was added dropwise to a cooled (0 °C) solution of 106.2 g (0.92 mol) of diacetone alcohol and 202 g (2 mol) of dry (KOH) triethylamine in 1 L of diethyl ether. After completed addition, the white slurry was warmed to room temperature and filtered. The filtrate was refluxed for 24 h, generating additional amounts of precipitate which were filtered. The filtrate was concentrated on a rotary evaporator and the residue distilled on a Kugelrohr apparatus [Aldrich Chemical Co.; bp 130–190 °C (0.5 mm)] to give 50 g of a part crystalline, part liquid product: ^{31}P NMR δ 64.5 (D), 61.2 (Ib) (about equal intensity). The ^{31}P NMR chemical shifts as measured in the mixture differ slightly from those of the pure compounds. The crystalline material was separated to give 21.3 g of product which upon crystallization from toluene (in which solvent NEt_3·HCl present as an impurity is insoluble) gave 15 g (8.3%) of colorless crystals, mp 97 °C. For analyses see Table I: IR (KBr) 3000 (m), 2980 (s), 2930 (m), 2870 (w), 1445 (m), 1420 (m), 1380 (m), 1365 (m), 1300 (s), 1280 (m), 1222 (vs), 1163 (s), 1150 (s), 1100 (m), 1050 (m), 983 (m), 928 (vs), 880 (s), 842 (m), 785 (s), 735 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 198 (3, M^+ (^{37}Cl)), 196 (9, M^+ (^{35}Cl)), 183 (3) and 181 (10) $M^+ - CH_3$, 161 (20, $M^+ - Cl$), 145 (7, $M^+ - (CH_3, HCl)$), 141 (3) and 139 (10) $M^+ - (CH_3, C_3H_6)$, 121 (12, $M^+ - (C_3H_4, Cl)$), 120 (13, $M^+ - (C_3H_5, Cl)$), 118 (35, $M^+ - (C_3H_7, Cl)$), 105 (10, $(CH_3)_2CPO_2^+$), 103 (22, $M^+ - (C_3H_7, Cl, CH_3)$), 83 (100, $M^+ - (CH_3PO_2, Cl)$), 67 (11, $C_5H_7^+$), 55 (12, $C_4H_7^+$), 43 (15, $C_3H_7^+$).

Acknowledgment. We thank Dr. J. J. Freeman for the FT IR spectra, Professor W. H. Urry, University of Chicago, for the 270-MHz proton NMR spectrum of D, and R. C. Scheibel for the mass spectra.

Registry No. Ia, 32503-56-3; Ib, 80754-28-5; IIa, 4529-76-4; IIb, 80754-29-6; D, 80754-30-9; methylphosphonous dichloride, 676-83-5; diacetonealcohol, 123-42-2; phenylphosphonous dichloride, 644-97-3.

Synthesis of the Cytochalasin D Isoindolone Unit: Solutions to the Problem of Regiochemistry in *N*-Benzoylpyrrolinone Diels–Alder Reactions

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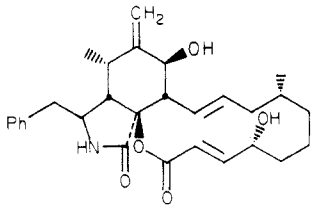
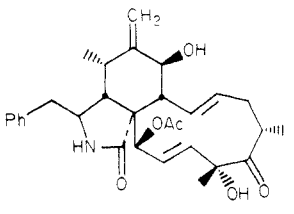
The bicyclic isoindolone portion of cytochalasin D with the correct relative stereochemistry has been prepared via a Diels–Alder sequence. Condensation of trienyl acetate **51** with doubly activated dienophile **4b** affords a single bicyclic adduct **52**. After oxidation to a sulfoxide, sulfenate–sulfoxide interconversion affords the key allylic alcohol **54a** with cytochalasin functionality. A related series of adducts has been prepared from monoactivated dienophile **4a** and various dienes or trienes. In all cases, the endo rule is obeyed although regioisomer mixtures are formed with unsymmetrical dienes. The (trimethylsilyl)methyl diene **37** reacts with much improved 3.5:1 regiochemistry due to the directive influence of silicon. Treatment of the major adduct **38** with MCPBA affords an allylic alcohol, **57**, having the cytochalasin D substitution pattern but the undesired hydroxyl stereochemistry. Oxidation appears to occur from the more congested face of **38**, apparently due to stereoelectronic factors involving silicon. An osmylation–deoxysilation approach affords the correct stereoisomer. A new Horner–Emmons reagent $Ph_2PO^-CHCH{=}CHCH_2O^-,2Li^+$ is described and is used for synthesis of trienol **24** from 2-[(trimethylsilyl)-methyl]acrolein **22**.

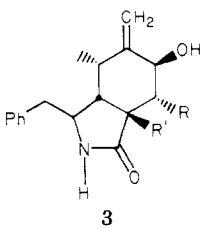
Derivatives of the "cytochalasan" nucleus have been isolated from a variety of molds and microorganisms[1] and include groups of structurally similar substances such as the cytochalasins,[2] chaetoglobosins,[2] and aspochalasins.[3] Cytochalasin B (phomin, 1, a 24-oxa[14]cytochalasan) was the first cytochalasin to be identified and remains the most important member of the series due to its fascinating biological properties. Cytochalasin D (2, an [11]cytochalasan) is also highly potent and like cytochalasin B has been used extensively as a tool to probe diverse aspects of cell metabolism.[1] The most highly active natural products have an exocyclic double bond in the isoindolone unit and an allylic alcohol function as in **1** and **2**. We will focus on the synthesis of structures **3** which duplicate the isoindolone substitution of **1** and **2** and allow for variation of groups R and R′ for eventual incorporation of the macrocycle.



1 (cytochalasin B)



2 (cytochalasin D)

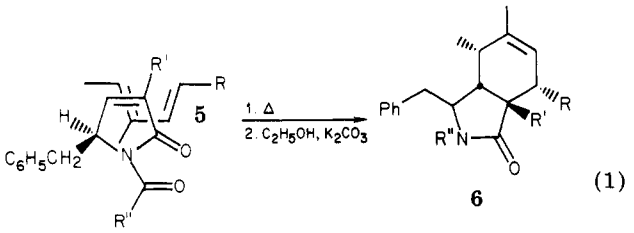


3

As described in a preliminary paper,[4] our approach is based on the Diels–Alder reaction between an *N*-benzoylpyrrolinone, **4**, and a diene, **5**. Assuming the classical endo transition state with the diene approaching from the less hindered face of the dienophile, one would predict control of five assymetric centers in a single step. A conceptually similar approach was first described by Weinreb et al. using an enol lactone analogue of **4** in an intramolecular Diels–Alder process.[5] More recently, Weinreb et al. have shown that maleimide-derived Diels–Alder adducts can be selectively converted to structures similar to **6**[6] (eq 1). Other variations of the Diels–Alder

(1) S. W. Tanenbaum, Ed., "Frontiers of Biology", North-Holland Publishing Co., New York, 1980, Vol. 46.
(2) C. Tamm, ref 1, Chapter 2.
(3) W. Keller-Shierlein and E. Kupfer, *Helv. Chim. Acta*, **62**, 1501, 1525 (1979).
(4) E. Vedejs and R. C. Gadwood, *J. Org. Chem.*, **43**, 376 (1978).
(5) J. Auerbach and S. W. Weinreb, *J. Org. Chem.*, **40**, 3311 (1975).
(6) M. Y. Kim and S. M. Weinreb, *Tetrahedron Lett.*, 579 (1979).

0022-3263/82/1947-1534$01.25/0

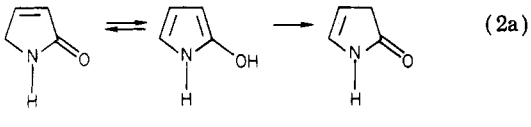


(1)

4a, R′ = H; R″ = C_6H_5
b, R′ = $CO_2C_2H_5$; R″ = C_6H_5
c, R′ = H; R″ = CH_2Cl

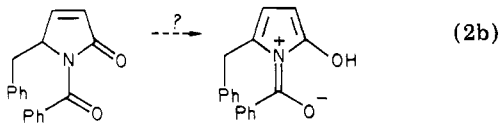
strategy have appeared,[7] but the only method to date which simultaneously controls benzyl stereochemistry as well as six-membered-ring stereochemistry is by the use of *N*-acetylpyrrolinones **4**. Stork et al. have subsequently adapted this technique for the total synthesis of cytochalasin B[8a] and related dienophiles have also been studied by Tamm et al. in an intramolecular Diels–Alder approach.[8b]

Preparation of Dienophiles. The choice of *N*-acylpyrrolinones as dienophiles was based on the known tendency of the parent lactam **7** and its derivatives to undergo facile tautomerization as in **7** → **9**[9] (eq 2). An



(2a)

7 **8** **9**



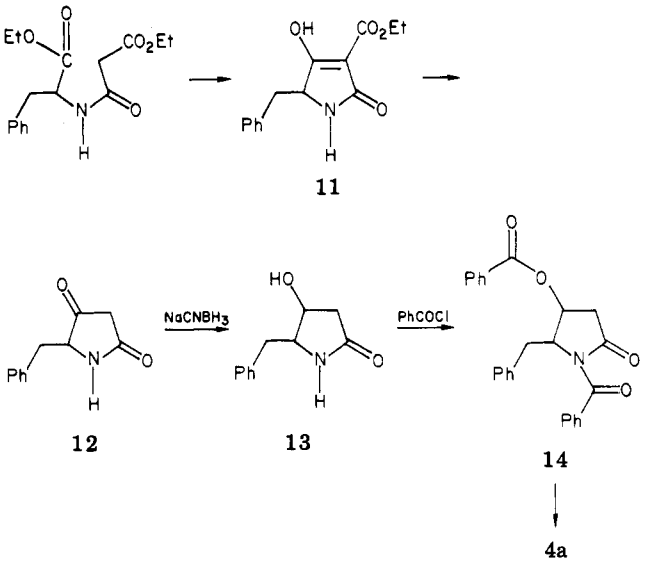
(2b)

4a **10**

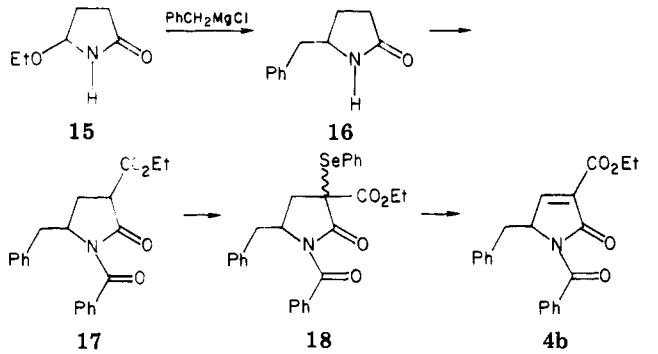
intermediate hydroxypyrrole **8** is responsible for the ease of this transformation. We expected that *N*-acyl derivatives of **7** would resist the tautomerization since the corresponding intermediate **10** can be viewed as a destabilized 4-π-electron system. One example of a thermally stable *N*-acyl-3-pyrrolin-2-one had already been described prior to our work.[10]

The dienophile **4a** can be obtained from the known **11**, which in turn is easily available from phenylalanine (Scheme I).[11] Decarboxylation of **11** to **12** is achieved in high yield (improved over a recent literature report)[11] simply by heating **11** in aqueous ethanol. The reduction of **12** to lactam alcohol **13** with conventional reducing agents is troublesome, apparently due to enolate formation. However, reduction with $NaCNBH_3$ in THF plus $ClCH_2CO_2H$ works well. After O,N-benzoylation and base-induced elimination, the *dl* dienophile **4a** can be isolated in good yield as a stable crystalline solid. The molecule does not undergo observable tautomerization, even after

Scheme I



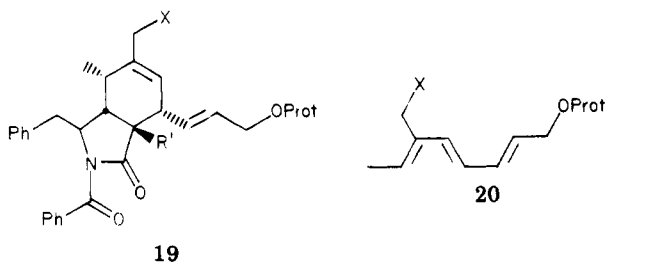
Scheme II



prolonged heating at 150 °C.

The doubly activated dienophile **4b** is available according to Scheme II by starting from the known **15**. In contrast to **4a**, **4b** is a very sensitive molecule. Samples which appear to be pure by NMR analysis have been obtained after HPLC separation of the selenoxide elimination product mixture. However, **4b** has not been obtained crystalline despite extensive efforts, and significant decomposition to complex products occurs within a few hours at room temperature.[12] The decomposition process is accelerated by silica gel and also by impurities carried over from the selenoxide elimination.

Diene Components. Trienes. Our plans for macrocycle attachment require isoindolones having a substituted allylic sidechain as in **19**. In principle, **19** might be



available by condensation between **4a** or **4b** with functionalized trienes **20**. Alternatively, dienes **5** could be used to prepare the adducts **6** which might be transformed into

(7) S. Bailey, E. J. Thomas, B. W. Turner, and J. A. J. Jarvis, *J. Chem. Soc., Chem. Commun.*, 474 (1978); C. Owens and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1504 (1978); R. Brettle and D. P. Cummings, *ibid.*, 2385 (1977); S. G. Pyne, M. J. Hensel, S. R. Byrn, A. T. McKenzie, and P. L. Fuchs, *J. Am. Chem. Soc.*, **102**, 5960 (1980).

(8) (a) G. Stork, Y. Nakahara, Y. Nakahara, and W. J. Greenlee, *J. Am. Chem. Soc.*, **100**, 7775 (1978). (b) T. Schmidlin and C. Tamm, *Helv. Chim. Acta*, **61**, 2096 (1978); T. Schmidlin, W. Zurcher, and C. Tamm, *ibid.*, **64**, 235 (1981).

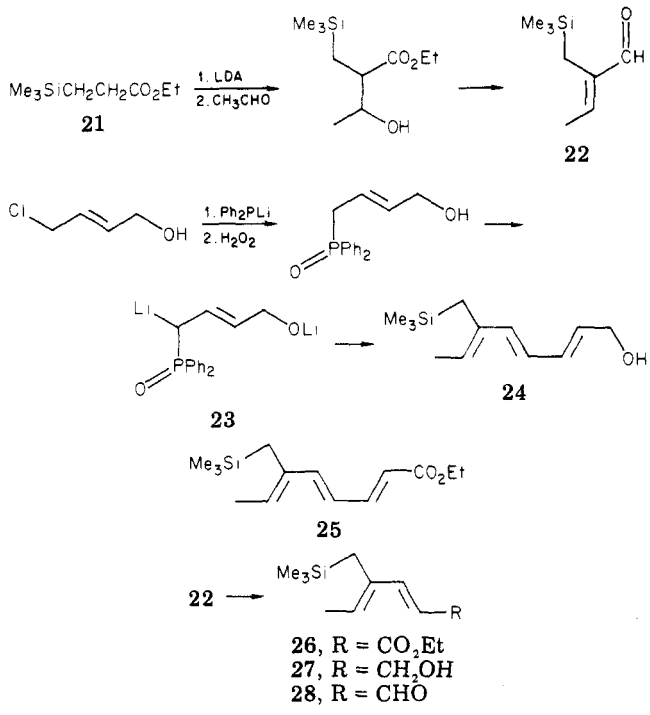
(9) R. Mondelli, V. Bucchi, G. P. Gardini, and L. Chierici, *Org. Magn. Reson.*, **3**, 7 (1971); J. T. Baker and S. Sifniades, *J. Org. Chem.*, **44**, 2798 (1979); T. Schmidlin and C. Tamm, *Helv. Chim. Acta*, **63**, 121 (1980).

(10) T. W. Guentert, H. H. A. Linde, M. S. Ragab, and S. Spengel, *Helv. Chim. Acta*, **59**, 2138 (1976).

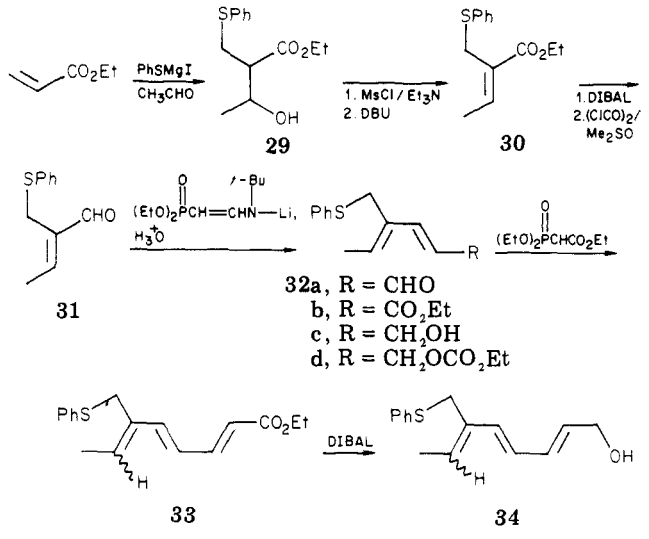
(11) R. C. F. Jones and S. Sumaria, *Tetrahedron Lett.*, 3173 (1978), describe preparation of optically pure **11**. Our compounds start with *dl*-phenylalanine.

(12) An analogous 3-acylpyrrolin-3-en-2-one lacking an *N*-acyl substituent is also highly unstable: C. Tamm, *Helv. Chim. Acta*, **63**, 121 (1980).

Scheme III



Scheme IV



20. Stork et al. had already shown that trienes similar to **20** prefer to react with maleimide dienophiles at the more substituted end of the triene,[13] so the triene route appeared most promising.

Two general approaches have been pursued where the group X in **20** is chosen to facilitate eventual conversion into the exocyclic methylene alcohol functionality present in cytochalasins 1 or 2. If X = SPh, the desired conversion would be achieved by allyl sulfoxide–sulfenate interconversion with thiophilic capture of the sulfenate.[14] For X = $Si(CH_3)_3$, an epoxidation–fragmentation sequence achieves the same result.[15,16]

Both types of substituted trienes can be prepared from appropriately functionalized tiglaldehyde derivatives. The starting material **22** for the silicon series is available from **21**[17] by an aldol condensation–elimination sequence (Scheme III). Direct conversion of **22** into the triene alcohol **24** is possible by using the new Horner–Emmons reagent **23**. However, the optimized yield of **24** from **23** is only 37% after much effort. The loss of material is apparently characteristic of **23** rather than of any unusual reactivity of **22** since benzaldehyde gives a similar yield of $C_6H_5CH{=}CHCH{=}CHCH_2OH$ upon reaction with **23**. Both reactions using **23** show a strong solvent dependence and work best in the presence of HMPA.

Direct conversion of **22** into the conjugated triene ester **25** has proved considerably more difficult. Only traces of **25** can be detected upon treatment of **22** with $Bu_3P{=}CHCH{=}CHCO_2Et$, and the conjugated Wadsworth–Emmons reagent $(EtO)_2POC^-HCH{=}CHCO_2C_2H_5$ gives a maximum of 18% of **25** under a variety of conditions. The most efficient overall conversion of **22** into **25** is the multistep sequence via **26** (Wadsworth–Emmons, 94%), **27** (DIBAL, 87%), **28** (Swern oxidation, 91%), and a second Wadsworth–Emmons reaction from **28** to give **25** (80%). DIBAL reduction of **25** affords the same alcohol **24** obtained by direct condensation of **23** with **22**.

Sulfur-substituted dienes and trienes are available from enal sulfide **31** which is conveniently prepared by using the "one-step joining reaction".[18] The overall yield for aldol coupling (to **29**) and elimination (to **30**) is 87%.

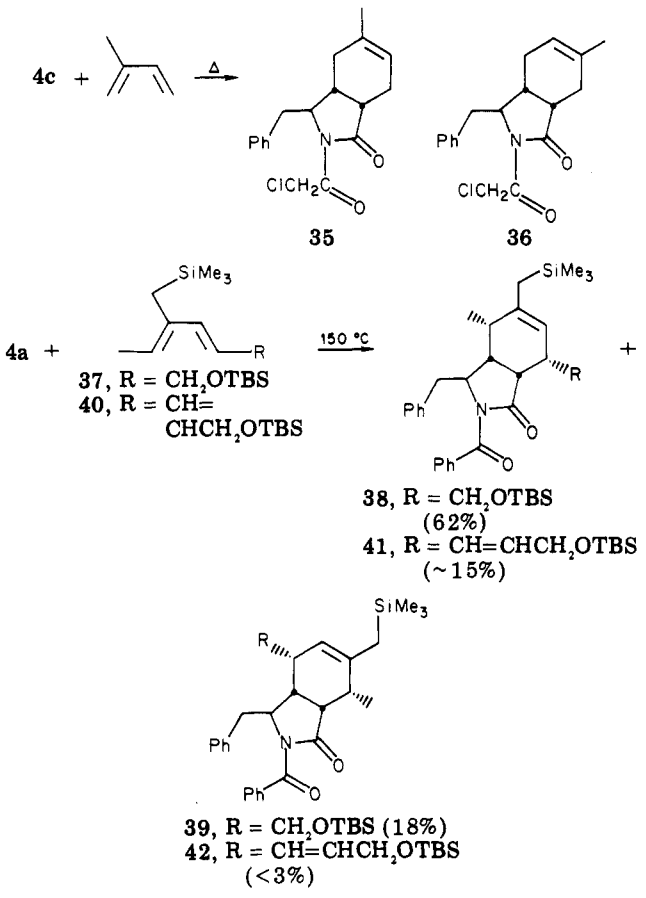
Attempted direct conversion of **31** into the desired triene alcohol **34** with Horner–Emmons reagent **23** results in a complex mixture containing no recognizable **34**. A multistep Wadsworth–Emmons sequence via the dienal **32a** (method of Meyers et al.[19]) does work. Chromatographic separation affords dienal **32a** (*E,E* isomer) which is then converted by Wadsworth–Emmons reaction into **33** (Scheme IV). In the course of this reaction, the trisubstituted double bond is equilibrated to an *E/Z* mixture. Both disubstituted double bonds clearly retained their geometry according to 270-MHz NMR analysis of the relevant coupling constants. Since this isomerization process has not been observed in the analogous silicon series, we conclude that *E,Z* isomerization is due to the presence of an allylic phenylthio group. A reversible 1,3-shift of this group provides a mechanism for unusually facile loss of double bond geometry.[20] A similar Wadsworth–Emmons reaction with ethyl phosphonoacetate can be used to prepare dienoate **32b** (47%) which is converted into diene carbonate **32d** by standard methods. Both **32b** and **32d** are likewise obtained as *E,Z* mixtures at the trisubstituted olefin.

Although the *E,Z* equilibration makes product characterization in the sulfur series more difficult, fortunately it causes no complications in the Diels–Alder step. The undesired isomer is apparently less reactive as might be expected, and no Diels–Alder products from this isomer have been detected.

Diels–Alder Adducts. Regiochemistry. We have already reported that various derivatives of the parent diene **5** react with **4** to give mixtures no better than 2.5:1 in favor of the correct adduct regioisomer **6**.[4] The best

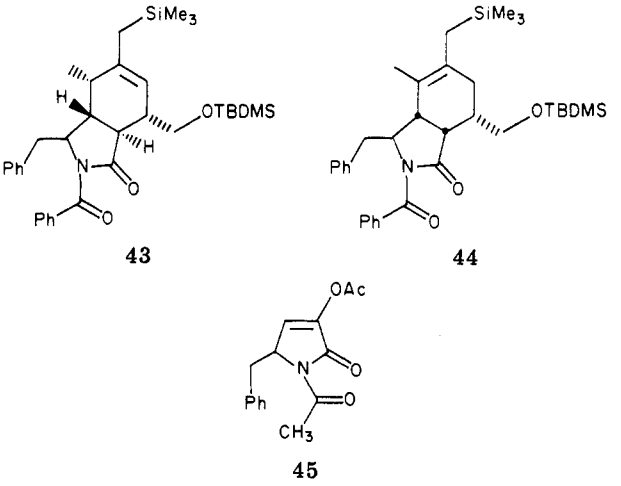
(13) Private communication from Professor Stork; see also ref 8.
(14) R. W. Hoffmann and N. Maak, *Tetrahedron Lett.*, 2237 (1976).
(15) B.-W. Au-Yeung and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 79, 81 (1977). See also: M. J. Carter and I. Fleming, *ibid.*, 679 (1976); I. Gailiunas, E. M. Tsyrlina, N. I. Solov'eva, N. G. Komalenkova, and V. P. Yur'ev, *Zh. Obshch. Khim.*, 47, 2394 (1977).
(16) I. Gailiunas, E. M. Tsyrlina, N. I. Solov'eva, N. G. Komalenkova, and V. P. Yur'ev, *Zh. Obshch. Khim.*, 47, 2394 (1977); J. G. Richer, M. A. Poisier, Y. Maroni, and G. Manuel, *Can. J. Chem.*, 58, 29 (1980).
(17) J. Dunognes, A. Konya, R. Calas, J. P. Picard, and N. Duffant, *J. Organomet. Chem.*, 66, C39 (1974).
(18) T. Shono, Y. Matsumura, S. Kashimura, and K. Hatanaka, *J. Am. Chem. Soc.*, 101, 4752 (1979).
(19) A. I. Meyers, K. Tomioka, and M. P. Fleming, *J. Org. Chem.*, 43, 3788 (1978).
(20) Previous examples of facile 1,3-phenylthio shifts in allylic systems: H. Kwart and N. A. Johnson, *J. Am. Chem. Soc.*, 99, 3441 (1977); P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1131 (1977).

Scheme V



result is obtained with a carbonate ester (**5**, R = $CH_2OCO_2C_2H_5$) while use of ether protecting groups (**5**, R = CH_2OSiMe_2-*t*-Bu, etc.) affords 1:1 mixtures. This result is somewhat surprising since isoprene gives **35** without significant amounts of a regioisomer **36** (Scheme V). Evidently, the directive effects of an alkyl substituent at each terminus of the diene do not simply "cancel out" as we had hoped. Fortunately, the directive effect of the internal diene substituent can be enhanced by a trimethylsilyl group. Thus, condensation of the silyl-substituted dienyl ether **37** with **4a** affords a much improved regioisomer ratio of 3.5:1 in favor of the desired **38** (62% isolated affter chromatography). Similar directive effects of the (trimethylsilyl)methyl group on Diels–Alder regioselectivity have been observed independently by Wilson et al. and Sakurai et al.[21] Attempts to condense **4a** with the silicon-containing triene analogue **40** have been largely unsuccessful due to competing decomposition of **40** at Diels–Alder temperatures (>120 °C). Although the yield of **41** is no better than 15%, the reaction appears to be highly regioselective (no **42** detected).

In some Diels–Alder experiments, unknown impurities have caused cis/trans isomerization of the initial adducts. A simple thermodynamic equilibration is involved, as shown by conversion of **38** into a mixture containing mostly the trans-fused isomer **43** by DBU. A double bond shifted isomer, **44**, has also been obtained in a few experiments due to adventitious catalysis. However, in no case have we ever detected stereoisomers which might be due to an alternative Diels–Alder transition state. The less hindered endo transition state as postulated previously can be assumed safely since Stork et al. have already shown that closely related adducts derived from the dienophile **45** have cytochalasin stereochemistry.[8] All of our Diels–Alder adducts (including the "wrong" regioisomers **39**, **42**, etc.) are in the same "endo" stereochemical series as evidenced by virtually identical vicinal coupling constants at all five methine proton sites.



The best regiochemical results have been obtained by using the doubly activated dienophile **4b**. In principle, this substance might be capable of Diels–Alder addition via conflicting endo transition states (ester π system vs. imide π system). However, the effect of a constrained imide π system appears to dominate completely over the freely rotating ester. Thus, freshly made (unstable) **4b** reacts with 1,4-dimethylbutadiene to give a single major adduct, **46** (Scheme VI). After saponification and decarboxylation, **46** is converted into a mixture of cis- and trans-fused **47**, identical with material prepared independently from **4a**.[22] In the case of the unsymmetrical dienes **32d** or **48**, two regioisomers **49** and **50** are formed in each case, with **49** predominating in a ratio 2.5:1. Again, no indications of any competing alternative endo transition state can be found. The NMR coupling parameters of **49** and **50** compare closely with those of all of the previous adducts of the correct stereochemical series.

Reaction of **4b** with the triene derivative **51** gives a large improvement in regioisomer ratio. Only the desired **52** can be detected, although the yield is modest (28%). Triene decomposition is not a serious problem since the doubly activated **4b** reacts at temperatures as low as 60–80 °C (vs. 150 °C for **4a**), but extensive dienophile self-destruction has proved unavoidable to date.

No products from Diels–Alder addition at the less substituted diene subunit of **51** have been detected. This finding was expected from the work of Stork et al.[8,13] and has some support in early Diels–Alder literature.[23] However, there is one reported example where the less substituted end of a triene reacts [CH_2=C(Br)CHO + CH_2=CHCH=CHC(CH_3)=$CHCH_2CH_2CO_2Me$] preferentially.[24]

Conversion to the Cytochalasin Isoindolone Substitution Pattern. Current plans for cytochalasin D synthesis require introduction of the correct isoindolone functionality near the end of the synthesis. To determine

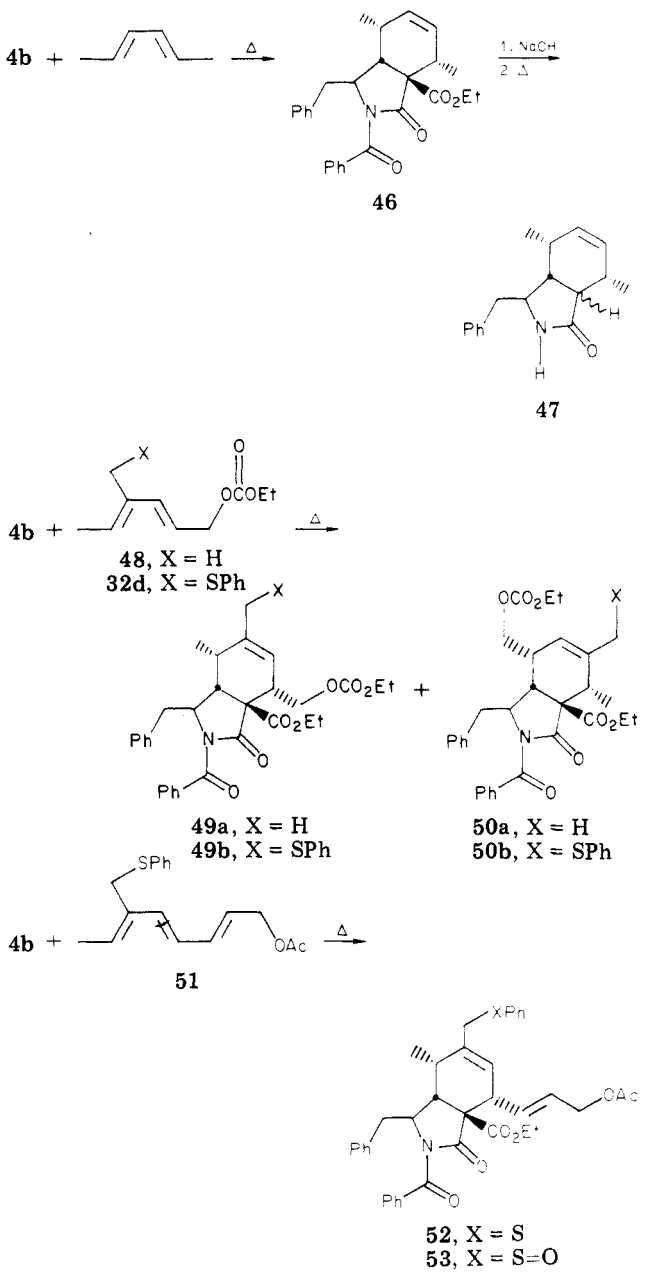
(21) S. R. Wilson, L. R. Phillips, and K. J. Natalie, Jr., *J. Am. Chjem. Soc.*, **101**, 3340 (1979); A. Hosomi, M. Saito, and H. Sakurai, *Tetrahedron Lett.*, 355 (1980).

(22) R. G. Gadwood, Ph.D. Dissertation, University of Wisconsin, 1978.

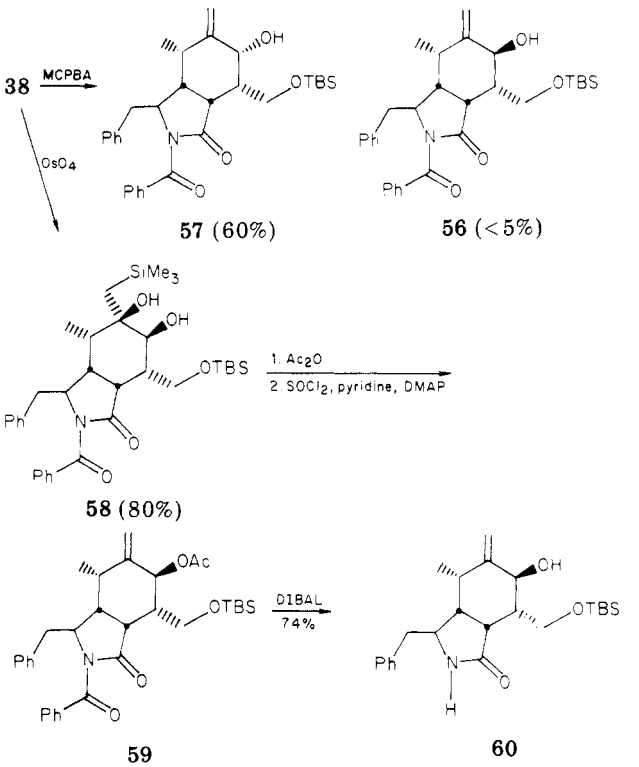
(23) H. Fleischacker and G. F. Woods, *J. Am. Chem. Soc.*, **78**, 3436 (1956); K. Alder and H. von Brachel, *Justus Liebigs Ann. Chem.*, **608**, 195 (1957); K. Alder, A. Dricke, H. Eipenbach, and U. Wicker, *ibid.*, **609**, 1 (1957); Y. Chretien-Bessiere, *Ann. Chim. (Rome)*, **2**, 301 (1957); A. S. Onischenko, "Diene Synthesis", D. Davey and Co., 1964, p 238.

(24) E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, **94**, 2549 (1972).

Scheme VI

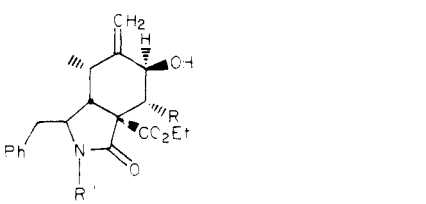


Scheme VII



whether this conversion is feasible, the key Diels–Alder adducts **38**, **49b**, and **52** have been carried through the steps which introduce the exocyclic methylene group and allylic hydroxyl.

The necessary transformations are easily performed by starting from the sulfides **49b** or **52**. After conversion to sulfoxide (MCPBA, mixture of diastereomers) the usual sulfoxide–sulfenate equilibration can be intercepted with trimethyl phosphite to give a single allyl alcohol diastereomer in each case (**54a**, 62%; **54b**, 57%), nonoptimized yield. According to molecular models, the conformation of **54** has little flexibility and closely resembles the isoindolone geometry of natural cytochalasins with the allylic hydroxyl group in an equatorial orientation. In **54a**, the axial methine proton α to oxygen appears as a doublet at 4.03 ppm (J = 8.8 Hz). In deoxaphomin (a 13-membered carbocyclic cytochalasin) the corresponding proton is a doublet at 3.97 ppm (J = 10 Hz).[25] Apparently, only the "correct" β-sulfenate diastereomer has been intercepted by phosphite. This result was expected in view of the steric congestion on the α face of the cis-fused bicyclic skeleton present in sulfoxide **53**.



54a, R = CH=CHCH$_2$OAc; R″ = COC$_6$H$_5$
b, R = CH$_2$OCO$_2$Et; R″ = COC$_6$H$_5$
55a, R = CH=CHCH$_2$OH; R″ = H
b, R = CH$_2$OH; R″ = H

For final verification, the O- and N-protecting groups have been removed from **54a** and **54b**. A highly crystalline diol lactam **55a** is obtained in good yield upon reaction of **54a** with $NaOC_2H_5/C_2H_5OH$ and a similar product **55b** can be prepared from **54b** by treatment with DIBAL. The NMR parameters of **55** compare favorably with analogous signals in cytochalasin D and related compounds[25] (**55b**: CHOH, δ 4.34, d, J = 10 Hz).

In the silicon series, transformation of **38** into an exocyclic methylene alcohol occurs smoothly upon treatment with MCPBA at 0 °C. Much to our surprise, the only substantial (>5%) product of this reaction has proved to be **57** (60% after chromatography) and not the expected diastereomer **56** (Scheme VII)! Two characteristic broadened singlets for the C=CH$_2$ protons are present as required, but the methine proton α to hydroxyl is a broadened doublet with a vicinal J no larger than 5 Hz. In the desired isomer **56**, the corresponding proton would be axial, and the J value would be large, as it is in **54** and **55**.

The stereochemical result of the MCPBA reaction is remarkable. While it is conceivable that the trimethylsilyl group might shield the β face of the molecule sufficiently

(25) Reference 2, p 26, 31 (cyto B, D); M. Binder and C. Tamm., *Helv. Chim. Acta*, **56**, 966 (1973) (deoxaphomin).

to favor α-epoxidation on steric grounds alone, we believe that this rationale is incorrect. Thus, treatment of **38** with OsO_4 results in a single diol **58** (80% yield). The product is clearly formed by β-face attack and has the expected doublet of 10 Hz for the axial proton α to secondary hydroxyl. Since osmylation occurs with "normal" stereochemistry, we can only conclude that a stereoelectronic effect involving the trimethylsilyl group dominates with the sterically less demanding MCPBA. Since the trimethylsilyl group probably prefers an orientation with $(CH_3)_3Si$ above the β face, MCPBA approach from the α direction corresponds to anti attack on the allyl silane. Other studies of allyl silane epoxidation have found no clear stereochemical evidence for silicon participation[15,16] and report isolation of epoxides which fragment to allyl alcohols upon mineral acid catalysis.[15] These findings may be due to substrate conformations where the allyl C–Si bond lies near the olefin plane rather than occupying a perpendicular orientation with respect to the double bond. The latter geometry is quite reasonable for **38**.

The desired cytochalasin substitution pattern can be obtained from **58** by a sequence of acetylation and deoxysilation ($SOCl_2$, DMAP, pyridine) to give acetate **59** (82%). After protecting group cleavage by treatment with DIBAL, **60** can be isolated in 74% yield. Both **59** and **60** have the appropriate coupling constants J(CH(OH)CH) of 9.6 Hz, indicating natural cytochalasin stereochemistry at the allylic hydroxyl group.

In conclusion, the cytochalasin D isoindolone functionality has been assembled with correct stereochemistry. Subsequent publications will deal with the problem of attaching an 11-membered carbocycle to Diels–Alder-derived isoindolone precursors.

Experimental Section

NMR spectra were recorded by using a JEOL MH-100 or a Bruker 270-MHz superconducting instrument. Infrared spectra were obtained with a Perkin-Elmer Model 267 spectrometer. Melting points are uncorrected (hot-stage microscope apparatus). Analytical HPLC separations were done by using an LDC Constametric pump and conventional UV/RI detection while preparative work was done on the Waters Prep 500 LC system. Tetrahydrofuran was dried over sodium–benzophenone and was distilled freshly prior to use. Dry chlorocarbons were obtained by distillation from P_2O_5. Routine workup procedures are abbreviated and refer to the following techniques. The reaction mixture was diluted with 2–4 volumes of water and extracted three times with an equal volume of organic solvent. after the combined organic phase was washed once with water, the combined organics were dried ($MgSO_4$), filtered, and evaporated (aspirator).

Sequence Leading to Dienophile 4a. *N*-(3-Ethoxy-1,3-dioxopropyl)-DL-phenylalanine Ethyl Ester. A 500-mL, three-necked, round-bottomed flask, fitted with a mechanical stirrer and two addition funnels, was charged with phenylalanine ethyl ester (23.4 g, 0.121 mol) in 75 mL of ether and chilled in an ice bath. With vigorous stirring, ethyl malonyl chloride (16.3 mL, 0.133 mol) in 75 mL of ether and K_2CO_3 (18.4 g, 0.133 mol) in 75 mL of water were added simultaneously at a moderate rate. After the addition was complete, the layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and condensed (aspirator) to leave 37.2 g (100%) of the amide as a colorless oil which was pure by NMR: IR ($CHCl_3$) 3430 (w), 3360 (w), 3010 (m), 1740 (s), 1680 (s), 1530 cm^{-1} (s); NMR ($CDCl_3$) δ 7.41 (1 H, d, J = 8 Hz), 7.17 (5 H, m), 4.77 (1 H, dt, J = 8, 6 Hz), 4.11 (2 H, q, J = 7 Hz), 4.09 (2 H, q, J = 7 Hz), 3.23 (2 H, s), 3.07 (2 H, d, J = 6 Hz), 1.19 (3 H, t, J = 7 Hz), 1.16 (3 H, t, J = 7 Hz).

5-Benzyl-3-(carboethoxy)-1,5-dihydro-4-hydroxy-2*H*-pyrrol-2-one (11). Sodium (4.60 g, 0.200 mol) was dissolved in 110 mL of absolute ethanol and this was added to 250 mL of anhydrous ether (Mallinckrodt) in a 1-L, three-necked flask fitted with a mechanical stirrer. The crude amide from above (49.4 g, 0.161 mol) was added to 125 mL of anhydrous ether at room temperature with vigorous stirring. Approximately midway through the addition, the sodium enolate of the product began to precipitate, and this precipitation continued during the rest of the addition. After the addition was complete, the reaction was stirred an additional 15 min at room temperature, 150 mL of hexane was added, and the mixture was chilled in an ice bath. The solid was removed by filtration, washed with anhydrous ether, and dried (aspirator).

The sodium salt thus prepared was dissolved in 200 mL of 95% ethanol and 35 mL of water, and this solution was chilled in an ice bath. With good stirring, 6 N HCl (29.5 mL, 0.177 mol) was added dropwise, and after removal of the solvent (aspirator) the crude product was dissolved in 150 mL of $CHCl_3$ and 150 mL of water. The layers were shaken and separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), condensed (aspirator) to a volume of approximately 50 mL, and then treated with 150 mL of anhydrous ether. Crystallization began rapidly, and the solution was chilled and allowed to crystalline. The product (32.7 g, 78%) was isolated in two crops: mp 102–105 °C dec; IR ($CHCl_3$) 3450 (w), 3010 (w), 1710 (s), 1655 (m), 1625 (m), 1240 cm^{-1} (m); NMR ($CDCl_3$) δ 10.0 (1 H, br s), 7.20 (5 H, m), 6.46 (1 H, s), 4.34 (3 H, m), 3.25 (1 H, dd, J = 14, 4 Hz), 2.74 (1 H, dd, J = 14, 9 Hz), 1.24 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 187.7, 170.0, 167.2, 135.6, 129.4, 128.6, 127.0, 61.2, 58.2, 37.6, 14.3; mass spectrum, m/e 261 (M^+), 189, 91 (base), 59; calcd for $C_{14}H_{15}NO_4$ m/e 261.100 10, obsd 261.099 08 (3.9 ppm error).

5-Benzyl-2,4-pyrrolidinedione (12). The ester **11** (40.1 g, 0.154 mol) was dissolved in 150 mL of reagent grade acetonitrile (Aldrich), water (5.53 mL, 0.307 mol) was added, and the solution was heated at 70 °C until gas evolution ceased (~2 h). The solvent was removed (aspirator), and the residue was crystallized from $CHCl_3/CCl_4$ to yield 26.2 g of product in two crops: 90%; mp 126–127 °C; IR (KBr) 3210 (w), 2930 (w), 1770 (m), 1690 (s), 1660 (s), 1360 (m), 1280 (m), 775 (m), 640 cm^{-1} (m); NMR ($CDCl_3$) δ 7.24 (6 H, m), 4.24 (1 H, dd, J = 7, 4 Hz), 3.16 (1 H, dd, J = 14.4 Hz), 2.96 (1 H, dd, J = 14, 7 Hz), 2.76 (2 H, AB q, J = 22 Hz); ^{13}C NMR ($CDCl_3$) δ 206.9, 171.4, 135.5, 129.6, 128.8, 127.2, 65.2, 40.8, 38.2; mass spectrum, m/e 189 (M^+), 92, 91 (base), 65; calcd for $C_{11}H_{11}NO_2$ m/e 189.078 98, obsd 189.078 89 (0.4 ppm error).

5-Benzyl-4-hydroxy-2-pyrrolidinone (13). To 260 mL of anhydrous CH_3OH (Mallinckrodt) containing 13.0 g (0.206 mol) of sodium cyanoborohydride (Aldrich) and 26.0 g (0.275 mol) of chloroacetic acid (recrystallized from CCl_4) was added 26.0 g (0.138 mol) of the ketone **12**. After being stirred for 1 h at room temperature, the solution was made basic with $NaOCH_3$ in CH_3OH (litmus), filtered, and condensed (aspirator). Saturated aqueous NaCl (250 mL) was added to the residue, followed by extraction with $CHCl_3$ (3 × 250 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and solvent was removed (aspirator). EtOAc (200 mL) was added to the residue, and the solution was chilled and allowed to crystallize. The title compound was isolated in three crops; 19.7 g (75%).

The material thus prepared (a mixture of diastereomers) is sufficiently pure for further transformations. One recrystallization from EtOAc led to isolation of a single diastereomer which gave the following data: mp 135–137 °C; IR (KBr) 3470 (s), 3200 (s), 3070 (m), 2965 (m), 1685 (s), 1045 (s), 765 (m), 700 cm^{-1} (s); NMR (Me_2SO-d_6) δ 7.51 (1 H, br s), 7.31 (5 H, s), 5.15 (1 H, d, J = 6 Hz), 4.18 (1 H, m), 3.73 (1 H, ddd, J = 8, 6, 4 Hz), 3.03 (1 H, dd, J = 14, 8 Hz), 2.70 (1 H, dd, J = 14, 6 Hz), 2.45 (1 H, dd, J = 17, 6 Hz), 2.00 (1 H, dd, J = 17, 3 Hz); mass spectrum, m/e 191 (M^+), 100 (base), 91, 83, 57; calcd for $C_{11}H_{13}NO_2$ m/e 191.094 63, obsd 191.093 79 (−4.4 ppm error).

Dienophile 4a. A solution of the hydroxypyrrolidinone **13** (mixture of diastereomers; 0.877 g, 4.58 mmol) in 50 mL of dry THF was cooled to −78 °C. To the cooled solution was added dropwise 5.46 mL of *n*-BuLi (Foote; 9.17 mmol, 1.68 M in hexane). Following the addition, the reaction was stirred 30 min at −78 °C. Benzoyl chloride (freshly distilled; 1.16 mL, 10.1 mmol) in 1 mL of THF was added quickly followed by stirring for 30 min. The solution was warmed slowly to 25 °C, and triethylamine (distilled from CaH_2; 0.84 mL, 5.96 mmol) was added. After the mixture was stirred overnight (16 h), 50 mL of ether was added, and the mixture was filtered through a short silica gel plug. TLC

(ethyl acetate/hexane) revealed three major spots: R_f 0.1 for the starting hydroxypyrrolidinone, R_f 0.17 for **4a**, and R_f 0.44 for benzoic anhydride. The pure product was isolated by preparative liquid chromatography (Waters Prep 500) with 20% ethyl acetate in hexane (250 mL/min): 0.80 g (63%, after crystallization from 25% ethyl acetate–hexane); mp 99–100 °C; IR (CCl_4) 3070 (w), 3040 (w), 1740 (s), 1675 (s), 1300 cm^{-1} (s); NMR (270 MHz, CCl_4) δ 7–8 (11 H, m), 5.84 (1 H, dd, J = 6, 2 Hz), 5.12 (1 H, m), 3.36 (1 H, dd, J = 14, 4 Hz), 2.92 (1 H, dd, J = 14, 9 Hz); mass spectrum, m/e 277 (M^+), 122, 105 (base), 91, 77; calcd for $C_{18}H_{15}NO_2$ m/e 277.110 28, obsd 277.109 04 (−4.5 ppm error).

Sequence to Dienophile 4b. 5-Benzyl-2-pyrrolidinone (16). To a solution of benzyl magnesium chloride [prepared from magnesium turnings (12.0 g, 0.50 mol) and benzyl chloride (Aldrich; 57.3 mL, 0.50 mol) according to the method of Gilman[26] in dry ether (300 mL) was added a solution of 5-ethoxy-2-pyrrolidinone (prepared by the method of Speckamp;[27] 16.0 g, 0.124 mol) in dry tetrahydrofuran (400 mL) at such a rate that a brisk reflux was maintained. After the addition was completed, reflux was maintained for 0.5 h. The solution was cooled, and saturated aqueous ammonium chloride was added dropwise until a heavy precipitate formed. Filtration and evaporation of the solvent left a yellow oil which was distilled [bp 159–164 °C (0.07 mmHg)] to a pale yellow oil which crystallized from ether as a white solid: mp 59–61 °C; yield 69%; IR ($CHCl_3$) 3240 (m), 2995 (m), 1743 cm^{-1} (s); NMR ($CDCl_3$) δ 7.2 (6 H, m), 3.9 (1 H, m), 2.82 (2 H, d, J = 7 Hz), 1.6–2.4 (4 H, m); mass spectrum, m/e 175 (M^+), 84 (base); calcd for $C_{11}H_{13}NO$ m/e 175.0994, obsd 175.0995 (0.3 ppm error).

1-Benzoyl-5-benzyl-2-pyrrolidinone. Sodium hydride (Alpha; 50% dispersion in oil, 2.62 mmol) was freed of oil by washing with dry tetrahydrofuran (THF) (2 × 5 mL) and suspended in dry THF. After the mixture was cooled (0 °C), a solution of **16** (0.42 g, 2.38 mmol) in dry THF (2 mL) was added dropwise. After 0.5 h at 0 °C, benzoyl chloride (0.305 mL, 2.62 mmol) in dry THF (1 mL) was added dropwise. Stirring was continued for an additional 0.5 h, and the reaction mixture was added to water (10 mL). Routine ether workup left an orange oil which crystallized (ether/hexane) to give a white solid (0.51 g) having a melting range of 84–86 °C: yield 77%; IR ($CHCl_3$) 3010 (m), 1740 (s), 1675 cm^{-1} (s); NMR ($CDCl_3$) δ 7.1–7.117 (10 H, m), 4.70 (1 H, m), 3.3 (1 H, dd, J = 12.5, 3 Hz), 2.9 (1 H, dd, J = 12.5, 8 Hz), 2.4 (2 H, m), 2.0 (2 H, m); mass spectrum, m/e 279 (M^+), 105 (base); calcd for $C_{18}H_{17}NO_2$ m/e 270.125 65, obsd 279.125 93 (1.0 ppm error).

1-Benzoyl-5-benzyl-3-(carboethoxy)-2-pyrrolidinone (17). Lithium diisopropylamide (LDA) was generated in situ by the addition of n-butyllithium (Alpha; 1.67 M, 3.86 mL, 6.44 mmol) to a cooled (0 °C) solution of diisopropylamine (0.90 mL, 6.44 mmol) in tetrahydrofuran (THF, 15 mL). After being stirred for 10 min, the solution was cooled to −78 °C, and a solution of 1-benzoyl-5-benzyl-2-pyrrolidone (802 mg, 2.87 mmol) and hexamethylphosphoramide (Aldrich; 50 mL, 2.87 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred for 45 min. Ethyl chloroformate (Aldrich; 288 μL, 3.01 mmol) in THF (5 mL) was added dropwise, and stirring was containued for an additional 0.5 H. The solution was warmed to −25 °C (0.5 h) and finally to room temperature (1 h). The base was destroyed by the addition of a 1 M solution of acetyl chloride and methanol in ether (10 mL). The reaction mixture was then added to aqueous 10% hydrochloric acid (10 mL). Routine ether workup was followed by liquid chromatography (Porasil, 20% ethyl acetate/hexane) to give the product, a 1:1 mixture of diastereomers, as a pale yellow oil: 0.72 g (72%); IR ($CHCl_3$) 3000 (m), 1760 (s), 1735 (s), 1688 cm^{-1} (s); NMR ($CDCl_3$) δ 7.4 (10 H, m), 4.7 (1 H, m), 4.1 (2 H, m), 2.0–3.5 (5 H, m), 1.21 and 1.18 (3 H, 2 overlapping t, J = 6, 6 Hz); mass spectrum, m/e 351 (M^+), 105 (base); calcd for $C_{21}H_{21}NO_4$ m/e 351.1469, obsd 351.1468 (0.3 ppm error).

1-Benzoyl-5-benzyl-3-(phenylseleno)-3-(carboethoxy)-2-pyrrolidinone (18). Lithium diisopropylamine (LDA) was generated in situ by the addition of n-butyllithium (Alpha; 1.50 M, 0.65 mL, 0.97 mmol) to diisopropylamine (10 mL) as mentioned previously. A solution of 17 (180 mg, 0.512 mmol) and hexamethylphosphoramide (Aldrich; 89 μL, 0.512 mmol) in THF (4 mL) was added dropwise to the cooled (−78 °C) LDA solution. The resulting solution was stirred at −78 °C for 45 min. Phenylselenyl chloride (164 mg, 0.855 mmol) in THF (3 mL) was added dropwise, and stirring was continued at −78 °C (0.5 h). The solution was warmed to −25 °C (0.5 h) and finally to room temperature (1 h). After the addition of a solution of 1 M acetyl chloride and methanol in ether (3 mL), the solution was added to 1 M aqueous hydrochloric acid (5 mL). A routine ether workup followed by liquid chromatography on a Porasil column (18% ethyl acetate/hexane) afforded the product, a mixture of diastereomers in about a 7:2 ratio, as a yellow oil (149 mg). In addition, some unreacted starting material (58 mg) was recovered: yield (based on recovered starting material) 84%; IR ($CHCl_3$) 2980 (m), 1748 (s), 1687 cm^{-1} (s); NMR ($CDCl_3$) δ 7.0–7.8 (15 H, m), 4.5 (1 H, m), 4.2 (2 H, 2 overlapping q), 3.25 (1 H, m), 2.7 (2 H, m), 2.28 and 2.12 (1 H, 2 d, $J_{downfield}$ = 8 Hz, $J_{upfield}$ = 7 Hz), 1.21 and 1.61 (3 H, 2 t, J = 8, 7 Hz); mass spectrum, m/e 507 (M^+), 105 (base); calcd for $C_{27}H_{25}NO_4Se$ m/e 507.0937, obsd 507.0932 (1.6 ppm error).

***N*-Benzoyl-5-benzyl-3-(carboethoxy)-3-pyrrolin-2-one (4b).** Hydrogen peroxide (Alpha; 340 mg of a 30% solution in water, 2.98 mmol) was dissolved in water (0.5 mL) and added dropwise to a cooled (0 °C) solution of 18 (0.252 g, 0.497 mmol) and glacial acetic acid (4 drops) in tetrahydrofuran (5 mL). The resulting solution was stirred at 0 °C for 2 h and was then poured into water (10 mL). This solution was extracted with ether (3 × 10 mL). The combined organic layers were washed with water (2 × 15 mL), and these aqueous layers were in turn combined and washed with ether (1 × 10 mL). The organic layers were dried ($MgSO_4$), filtered, and evaporated to an unstable yellow oil (129 mg) which, in most cases, was sufficiently pure to carry on with no additional purification. While **4b** was usually used immediately, it was found that, if stored in ether in a refrigerator, it was stable for at least several hours.

If purification was desired, crude **4b** was quickly passed through a very short plug of silica gel with ether as the eluent (contact time <15 s). This was done solely to remove very polar materials. Final purification was possible via HPLC only if a μ-CN adsorbent (Waters) was used. With 10% ethyl acetate–hexane as the eluent, a very pale yellow oil (111 mg) was obtained: 111 mg (64%); IR ($CHCl_3$) 2980 (m), 1763 (s), 1725 (s), 1682 cm^{-1} (m); 270-MHz NMR ($CDCl_3$) δ 8.0 (1 H, d, J = 2 Hz), 7.0–7.7 (10 H, m), 5.3 (1 H, ddd, J = 8, 4, 2 Hz), 4.22 (2 H, q, J = 7 Hz), 3.43 (dd, J = 14, 4 Hz), 3.07 (1 H, dd, J = 14, 8 Hz), 1.29 (3 H, t, J = 7 Hz). Upon being allowed to stand, the oil began to develop a finely divided precipitate, and TLC analysis indicated the formation of numerous products.

Dienes and Trienes. (*E*,*E*)-4-Methyl-2,4-hexadien-1-ol was prepared in 49% overall yield from tiglaldehyde by the procedure of Auerbach and Weinreb;[5] bp 89–91 °C (14 mmHg) [lit. bp 40–45 °C (0.2 mmHg)].

(*E*,*E*)-1-(*tert*-Butyldimethylsiloxy)-4-methyl-2,4-hexadiene. To 2 mL of DMF (distilled from CaH_2) were added (*E*,*E*)-4-methyl-2,4-hexadien-1-ol (1.09 mL, 8.93 mmol) and imidazole (Aldrich, 1.52 g, 22.3 mmol). *tert*-Butyldimethylsilyl chloride (Aldrich, 1.61 g, 10.7 mmol) was added to this solution, and the reaction mixture was stirred for 10 min at room temperature. The DMF solution was extracted with hexane (2 × 10 mL), the combined hexane phases were concentrated (aspirator), and the residue was distilled to yield product: 1.66 g (82%); bp 61 °C (0.4 mmHg); NMR (CCl_4) δ 6.04 (1 H, d, J = 16 Hz), 5.40 (2 H, m), 4.08 (2 H, d, J = 7 Hz), 1.68 (6 H, m), 0.98 (9 H, s), 0.04 (6 H, s); mass spectrum, m/e 226 (m^+), 169, 95, 75 (base); calcd for $C_{13}H_{26}OSi$ m/e 226.175 26, obsd 226.176 03 (3.3 ppm error).

(*E*,*E*)-4-Methyl-2,4-hexadien-1-yl Ethyl Carbonate. The alcohol (0.54 mL, 4.46 mmol) was added to 15 mL of pyridine (distilled from CaH), and to this solution at room temperature was added ethyl chloroformate (freshly distilled; 0.51 mL, 5.35 mmol). After being stirred at room temperature for 1 h, the reaction mixture was poured into 30 mL of water and then extracted with ether (3 × 25 mL). The combined ether phases were washed with 25 mL of 3 N HCl and with 10 mL of saturated aqueous Na_2CO_3 solution. After the mixture was dried ($MgSO_4$) and filtered, solvent was removed (aspirator), and the residue was

(26) H. Gilman, "Organic Syntheses", Collect. Vol. I, Wiley, New York, 1941, p 471.
(27) J. C. Hubert, J. B. P. A. Wynberg, and W. C. Speckamp, *Tetrahedron*, 31, 1437 (1975).

distilled to yield product: 0.60 g (73%); bp 63 °C (0.05 mmHg)]; NMR (CCl_4) δ 6.24 (1 H, d, J = 16 Hz), 5.56 (2 H, m), 4.54 (2 H, d, J = 7 Hz), 4.10 (2 H, q, J = 7 Hz), 1.72 (6 H, m), 1.28 (3 H, t, J = 7 Hz); mass spectrum, m/e 184 (M^+), 95, 79 (base); calcd for $C_{10}H_{16}O_3$ m/e 184.109 94, obsd 184.109 52 (−2.3 ppm error).

Sequence to Silyl-Substituted Dienes and Trienes. Ethyl 2-[(Trimethylsilyl)methyl]-3-hydroxybutanoate. A dry 250-mL flask cooled under a stream of N_2 was charged with 18.54 mL (132.3 mmol) of diisopropylamine (distilled from CaH_2) and 150 mL dry THF. After the mixture was cooled to −78 °C, n-BuLi (76.0 mL, 126.0 mmol, 1.65 M in hexane) was added dropwise. After the mixture was stirred 15 min at −78 °C, a solution of ethyl 3-(trimethylsilyl)propanoate **21**[1b] (20.74 g, 119.0 mmol) in 30 mL of THF was added over a period of 2 h. The resulting yellow solution was stirred 1 h at −78 °C. Freshly distilled acetaldehyde (10.14 mL, 180.0 mmol) in 20 mL of THF was then added over a period of 15 min. After the mixture was stirred 1.5 h at −78 °C, the cooling bath was removed and the solution stirred 30 min. The reaction was quenched by pouring the mixture into 300 mL of 0.5 N HCl at 0 °C. The aqueous phase was saturated with NaCl followed by separation of the layers and extraction of the aqueous phase with ether (3 × 50 mL). The combined organic layer was washed once with 100 mL of brine, followed by drying over anhydrous Na_2SO_4. The solvents were removed by rotary evaporation, with the residual liquid being distilled to yield 22.31 g (102.3 mmol, 86%) of the colorless ester: bp 72–75 °C (10.2 mmHg); TLC R_f 0.29 (25% ethyl acetate/hexane); ^1H NMR ($CDCl_3$) δ 4.08 (2 H, q, J = 7 Hz), 3.79 (1 H, q, J = 6 Hz), 2.64 (1 H, br s), 2.41 (1 H, m), 1.23 (3 H, t, J = 7 Hz), 1.12 (3 H, d, J = 6 Hz), 0.85 (2 H, m), −0.02 (9 H, s); IR (neat) 3443 (m), 2960 (s), 1743 (s), 1377 (w), 1253 (s), 1191 (m), 1149 (w), 853 cm^{-1} (s).

Ethyl 2-[(Trimethylsilyl)methyl]-2-butenoate. To an ice bath cooled (0 °C) solution of ethyl 2-[(trimethylsilyl)methyl]-3-hydroxybutanoate (21.8 g, 100.0 mmol) in 140 mL of ether was added 8.13 mL of methanesulfonyl chloride (distilled, 105.0 mmol). Immediately, triethylamine (distilled from CaH_2; 14.8 mL, 105.0 mmol) was added. The white suspension was stirred 30 min at 0 °C followed by dilution with 150 mL of hexane. The mixture was filtered through a Celite plug by using several portions of 1:1 ether/hexane. The solvent was removed by rotary evaporation while the temperature was maintained below ~35 °C. The resulting crude yellow oil was taken up in 180 mL of dry THF, and 35.9 mL of DBU (1,5-diazabicyclo[5.4.0]undec-5-ene, Aldrich, 240.0 mmol) was added all at once. The reaction mixture was warmed to 40 °C and stirred 30 h. After the mixture cooled, ether (100 mL) and H_2O (100 mL) were added. The layers were separated, and the organic phase was washed with saturated $CuSO_4$ (2 × 150 mL) to remove the excess DBU. After a final wash with 150 mL of brine, drying ($MgSO_4$), and removal of the solvents, the residual liquid was distilled to give 18.10 g (90.5 mmol, 90.5%) of a colorless oil: bp 44–46 °C (0.1 mmHg); TLC R_f 0.60 (25% ethyl acetate/hexane); ^1H NMR ($CDCl_3$) δ 6.68 (1 H, q, J = 7 Hz), 4.13 (2 H, q, J = 7 Hz), 1.80 (2 H, s,), 1.69 (3 H, d, J = 7 Hz), 1.26 (3 H, t, J = 7 Hz), 0.0 (9 H, s); IR (neat) 2955 (s), 2900 (m), 1721 (s), 1648 (w), 1383 (w), 1277 (s), 1250 (s), 1178 (s), 1119 (w), 1051 (m), 852 cm^{-1} (s).

2-[(Trimethylsilyl)methyl]-2-buten-1-ol. To a −78 °C solution of ethyl 2-[(trimethylsilyl)methyl]-2-butenoate (4.09 g, 20.46 mmol) in 50.0 mL of dry THF was added dropwise 37.8 mL of diisobutylaluminum hydride (Aldrich, 45.0 mmol, 1.19 M in hexane). After being stirred 2 h at −78 °C and 1 h at 0 °C, the solution was poured with stirring into excess 0 °C 1 N H_2SO_4. The mixture was stirred 30 min, followed by saturating the aqueous phase with NaCl and adding 50 mL of ether. The layers were separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined ether layer was dried (Na_2SO_4) and condensed, and the crude alcohol was distilled to yield the product: 2.93 g (18.62 mmol, 91%); bp 45–48 °C (0.1 mmHg); TLC R_f 0.21 (25% ethyl acetate/hexane); ^1H NMR ($CDCl_3$) δ 5.21 (1 H, q, J = 7 Hz), 3.79 (2 H, s), 2.57 (1 H, br s), 1.52 (3 H, d, J = 7 Hz), 1.50 (2 H, s), 0.0 (9 H, s); IR (neat) 3328 cm^{-1} (s).

2-[(Trimethylsilyl)methyl]-2-butenal (22). A dry 100-mL three-necked flask equipped with an overhead mechanical stirrer was charged with 1.51 mL of oxalyl chloride (2.16 g, 17 mmol) and 30 mL of dry CH_2Cl_2. After the mixture was cooled to −78 °C, 2.42 mL of Me_2SO (2.66 g, 34.1 mmol) in 3 mL of CH_2Cl_2 was added over 30 s (**Caution**: vigorous gas evolution). After the mixture was stirred ca. 2 min, 2.45 g (15.5 mmol) of 2-[(trimethylsilyl)methyl]-2-buten-1-ol in 3 mL of CH_2Cl_2 was added over a 5-min period. The mixture was stirred 15 min at −78 °C followed by the addition of 8.74 mL (6.37 g, 62 mmol) triethylamine. The cooling bath was removed and the reaction mixture warmed to ambient temperature with stirring for 45 min. Water (25 mL) was added, and the layers were separated. The CH_2Cl_2 layer was washed sequentially with equal volumes of 5% HCl, saturated $NaHCO_3$, and brine. After the mixture was dried ($MgSO_4$), filtered, and condensed, the crude aldehyde was distilled, affording **22**: 2.09 g (13.4 mmol, 86.5%); bp 45–47 °C (0.5 mmHg); TLC R_f 0.56 (25% ethyl acetate/hexane); NMR ($CDCl_3$) δ 9.26 (1 H, s), 6.20 (1 H, q, J = 7 Hz), 1.82 (3 H, d, J = 7 Hz), 1.63 (2 H, s), −0.11 (9 H, s); IR (neat) 2958 (s), 2900 (m), 2808 (w), 2685 (w), 1691 (s), 1638 cm^{-1} (w); mass spectrum, calcd for $C_{10}H_{16}OSi$ m/e 156.097 04, obsd 156.0971; mp (2,4-dinitrophenylhydrazone) 156–158 °C.

Preparation of Horner–Emmons Precursors. Diphenyl[(*E*)-4-hydroxy-2-buten-1-yl]phosphine Oxide. To a −25 °C solution of freshly distilled (*E*)-4-chloro-2-buten-1-ol[16] (3.30 g, 31.0 mmol) in 50 mL of THF was added dropwise 19.1 mL of n-BuLi (30.0 mmol, 1.61 M in hexane). The slightly yellow solution was stirred 20 min at −25 °C followed by decantation dropwise via cannula into a 0 °C solution of lithium diphenylphosphide (30.0 mmol) in 40 mL of THF. After the addition was complete, the slightly orange solution was warmed to 25 °C and stirred for 30 min. The solution was recooled to 0 °C and quenched with 35 mL of 1 N HCl. The layers were separated, and the THF was removed by rotary evaporation. The residual oil was taken up in 50 mL of $CHCl_3$ followed by the dropwise addition of 20 mL of 15% H_2O_2. After the mixture was stirred for 30 min, 30 mL of saturated Na_2SO_3 was added, and the layers were separated. The $CHCl_3$ layer was washed with 30 mL of 1 N HCl and 30 mL of saturated K_2CO_3 and dried over anhydrous K_2CO_3. Removal of the solvent afforded 7.85 g of a slightly yellow viscous oil, 28.87 mmol (96%). One recrystallization from CH_2Cl_2/ether afforded white crystals: 76.6–78 °C; TLC R_f 0.17 (50/50 $CHCl_3$/THF); NMR ($CDCl_3$) δ 7.70 (4 H, m), 7.36 (6 H, m), 5.63 (2 H, m), 3.92 (2 H, t, J = 4 Hz), 3.74 (1 H, br s), 3.04 (2 H, dd, $J_{^{31}PH}$ = 14 Hz, J_{HH} = 6 Hz); IR (neat) 3358 (s), 2860 (w), 1617 (w), 1440 (m), 1175 (s), 1120 (s), 1099 (m), 718 cm^{-1} (s).

Horner–Emmons Reagent 23. Preparation of Trienol 24. A solution of diphenyl[(*E*)-4-hydroxy-2-buten-1-yl]phosphine oxide (1.59 g, 5.85 mmol) in 20 mL of dry THF and 5.0 mL of HMPA was cooled to −25 °C, and 7.3 mL of n-BuLi (11.2 mmol, 1.53 M in hexane) was added dropwise. The resulting dark red solution was stirred 20 min followed by the dropwise addition of 0.83 g (5.32 mmol) of aldehyde **22** in 5 mL of THF. The solution was then stirred 2 h at −25 °C followed by warming to ambient temperature and stirring overnight (ca 16 h). Aqueous 5% HCl was added dropwise with the pH adjusted to pH 8. Ether (20 mL) and 10 mL of H_2O were added and the layers separated. The ether layer was washed with an equal volume of saturated Na_2CO_3 solution and an equal volume of brine and dried over K_2CO_3. After concentration, the recovered yellow oil was chromatographed on silica gel (30 g) with 15% ethyl acetate/hexane as the eluant. There was obtained nearly pure trienol **24**: 0.42 g (2 mmol, 37%); TLC R_f 0.33 (25% ethyl acetate/hexane); NMR ($CDCl_3$) δ 6.29 (m, 1 H), 5.78–6.20 (m, 3 H), 5.58 (q, 1 H, J = 7 Hz), 4.21 (d, 2 H, J = 6 Hz), 1.77 (s, 2 H), 1.71 (d, 3 H, J = 7 Hz), 0.04 (s, 9 H); IR (neat) 3365 (s, br), 3025 (w), 1637 (w), 1608 (m), 1594 cm^{-1} (m); mass spectrum, calcd for $C_{12}H_{22}OSi$ m/e 210.143 99, obsd 310.1441.

Ethyl 4-[(Trimethylsilyl)methyl]-2,4-hexadienoate (26). To a dry 100-mL flask equipped with a septum side-arm inlet and a reflux condenser was added under N_2 NaH (0.44 g, 10.9 mmol, 57% in oil). The NaH was washed twice with dry THF to remove the oil and then suspended in 30 mL of fresh THF. Triethyl phosphonoacetate (2.10 mL, 2.38 g, 10.6 mmol) was added dropwise, with the mixture being stirred 45 min at room temperature. After the mixture was cooled in an ice–water bath, freshly distilled aldehyde **22** (1.60 g, 10.1 mmol) in 5 mL of THF was added dropwise via cannula. Following the addition, the cooling bath was removed, and the solution was heated to reflux (1.5 h). After the mixture was recooled to ambient temperature,

ether (25 mL) and water (25 mL) were added. The layers were separated, and the organic layer was washed with 30 mL of 5% HCl and 30 mL of brine. After the organic layer was dried ($MgSO_4$) and condensed, the yellow liquid was filtered through a silica gel column (~50 g) with 10% ether/hexane to give 2.24 g (9.5 mmol, 94%) of colorless liquid **26**: TLC R_f 0.60 (25% ethyl acetate/hexane); NMR ($CDCl_3$) δ 7.24 (d, 1 H, J = 15 Hz), 5.87 (q, 1 H, J = 7 Hz), 5.68 (d, 1 H, j = 15 Hz), 4.20 (q, 2 H, J = 7 Hz), 1.79 (d, 3 H, J = 7 Hz), 1.76 (s, 2 H), 1.33 (t, 3 H, J = 7 Hz), −0.05 (s, 9 H); IR (neat) 1725 cm^{-1} (s); mass spectrum, calcd for $C_{12}H_{22}O_2Si$ m/e 226.138 90, obsd 226.1390.

4-[(Trimethylsilyl)methyl]-2,4-hexadien-1-ol (27). To a 0 °C solution containing 2.86 g (12.6 mmol) of ester **26** in 20 mL of ether was added dropwise 23.2 mL of DIBAL (26.5 mmol, 1.14 M in hexane). Following the addition, the reaction mixture was stirred 30 min at 0 °C followed by warming to 25 °C and stirring an additional 1 h. After the mixture was recooled to 0 °C, a few drops of MeOH were added to quench unreacted hydride. The reaction mixture was then *slowly* poured with stirring into excess cold 5% H_2SO_4. After 30 min, excess NaCl was added to saturate the aqueous phase. The layers were separated, and the ether phase was washed with an equal volume of saturated $NaHCO_3$. After the ether phase was dried ($MgSO_4$), filtered, and condensed, there was obtained 2.36 g (12.8 mmol, >100% recovery) of the desired alcohol. Both TLC and NMR showed the material to be sufficiently pure (>95%) for further use. Kugelrohr distillation gave 2.01 g (10.9 mmol, 87%) of pure material: bp (pot temperature) 45–50 °C (0.03 mmHg). TLC R_f 0.35 (25% ethyl acetate/hexane). NMR ($CDCl_3$) δ 6.20 (d, 1 H, J = 16 Hz), 5.61 (dt, 1 H, J = 16, 6 Hz), 5.47 (q, 1 H, J = 7 Hz), 4.18 (d, 2 H, J = 6 Hz), 1.75 (s, 2 H), 1.70 (d, 3 H, J = 7 Hz), 0.06 (s, 9 H); IR (neat) 3330 cm^{-1} (s, br).

1-(*tert*-Butyldimethylsiloxy)-4-[(trimethylsilyl)methyl]-2,4-hexadiene (37). A 50-mL flask was charged with 1.58 g (10.4 mmol) of *tert*-butyldimethylsilyl chloride, 5 mL of dry DMF, and 1.77 g (26.1 mmol) of imidazole. To the resultant solution was added dienol **27** (1.73 g, 9.4 mmol) in 3 mL of DMF. After the mixture was stirred for 2 h at room temperature, 15 mL of ether and 15 mL of saturated $NaHCO_3$ solution were added. The layers were separated, and the ether layer was washed with an additional 15 mL of water followed by 15 mL of brine. After the ether layer was dried ($MgSO_4$) and condensed, the crude product was distilled: 2.36 g (7.9 mmol, 84%); bp 105–108 °C (0.1 mmHg); TLC R_f 0.75 (25% ethyl acetate/hexane); NMR ($CDCl_3$) δ 6.16 (d, 1 H, J = 16 Hz), 5.48 (dt, 1 H, J = 6, 16 Hz), 5.41 (q, 1 H, J = 7 Hz), 4.19 (d, 2 H, J = 6 Hz), 1.67 (s, 2 H), 1.62 (d, 3 H, J = 7 Hz), 0.83 (s, 9 H), 0.01 (s, 6 H), −0.07 (s, 9 H); mass spectrum, calcd for $C_{16}H_{34}OSi_2$ m/e 298.214 82, obsd 298.2148.

1-(*tert*-Butyldimethylsiloxy)-6-[(trimethylsilyl)methyl]-2,4,6-octatriene (40). To a solution of *t*-butyldimethylsilyl chloride (2.10 mmol, 0.316 g) and imidazole (0.323 g, 4.75 mmol) in 4 mL of DMF was added 0.41 g (1.90 mmol) of trienol **24** in 2 mL of DMF. After the mixture was stirred 1.5 h at room temperature, 10 mL of saturated $NaHCO_3$ was added followed by stirring for 5 min. Ether (15 mL) was added, and the layers were separated. The ether layer was washed with an equal volume of $NaHCO_3$ (saturated), dried over $MgSO_4$, filtered, and concentrated. The crude product was chromatographed on silica gel (40 g) with 5% ether/hexane as the eluant. The nearly colorless oil (0.473 g, 1.46 mmol, 77%) was >95% pure by NMR and TLC: TLC R_f 0.72 (20% ethyl acetate/hexane); NMR ($CDCl_3$) δ 6.25 (dd, 1 H, J = 10.1, 14.9 Hz), 6.15 (d, 1 H, J = 15.0 Hz), 6.01 (dd, 1 H, J = 10.1, 15.0 Hz), 5.69 (dt, 1 H, J = 5.4, 14.9 Hz), 5.46 (q, 1 H, J = 7.0 Hz), 4.21 (d, 2 H, J = 5.4 Hz), 1.71 (s, 2 H), 1.67 (d, 3 H, J = 7.0 Hz), 0.903 (s, 9 H), 0.063 (s, 6 H), 0.00 (s, 9 H); mass spectrum, calcd for $C_{18}H_{36}OSi_2$ m/e 324.230 47, obsd 324.2302.

Sulfur-Substituted Dienes and Trienes. (*Z*)-Ethyl 2-[(Phenylthio)methyl]-2-butenoate (30). To a 0 °C solution of freshly prepared (phenylthio)magnesium iodide (20 mmol) in ether (40 mL) was added dropwise a solution of ethyl acrylate (2.17 mL, 20.0 mmol) and acetaldehyde (1.12 mL, 20.0 mmol) in ether (20 mL)[18]. After the mixture was stirred at 0 °C for 3 h, the reaction was quenched by addition to saturated NH_4Cl. The organic layer was then extracted twice with 10% NaOH and once with saturated NaCl. After the mixture was dried with $MgSO_4$, the solvent was removed (aspirator), leaving **29** as a clear, colorless oil (4.94 g, 19.4 mmol, 97% yield) which was sufficiently pure for the next step. To a solution of this oil in 20 mL of ether was added methanesulfonyl chloride (1.70 mL, 22.0 mmol) at 0 °C, immediately followed by dropwise addition triethylamine (3.07 mL, 22.0 mmol). The resulting slurry was allowed to stir for 30 min at 0 °C. At this time the reaction mixture was diluted with hexane (20 mL) and filtered to remove amine salts. The solvent was removed (aspirator), and the crude mesylate was taken up in dry THF (40 mL). After addition of DBU (7.31 mL, 48 mmol), the reaction mixture was heated to 45 °C for 2 h. The reaction mixture was then extracted twice with water, twice with saturated $CuSO_4$, and once with brine. After the mixture was dried ($MgSO_4$), the solvent was removed (aspirator), leaving a viscous, reddish oil: 4.13 g (1m94 mmol, 87% yield overall); NMR indicates >95% of the desired **30**; IR (neat) 1704 (s), 1680 cm^{-1} (m); NMR ($CDCl_3$) δ 7.0–7.3 (m, 5 H), 6.77 (q, 1 H, J = 7 Hz), 4.09 (q, 2 H, J = 7 Hz), 3.72 (s, 2 H), 1.50 (d, 3 H, J = 7 Hz), 1.20 (t, 3 H, J = 7 Hz); mass spectrum, calcd for $C_{13}H_{16}O_2S$ m/e 236.0872; obsd 236.0872 (0.0 ppm error).

2-[(Phenylthio)methyl]-2-butenal (31). Diisobutylaluminum hydride (10.5 mL, 1 M in hexane) was added by syringe to a −78 °C solution of ester **30** (1.18 g, 4.99 mmol) in distilled CH_2Cl_2 (10 mL). After the mixture was stirred for 30 min at −78 °C, the reaction was quenched by addition to cold 10% H_2SO_4 (10 mL). After rapid stirring for 0.5 h, the aqueous layer was extracted three times with CH_2Cl_2. The combined organic fractions were then extracted with saturated $NaHCO_3$ and saturated brine, dried over $MgSO_4$, filtered, and evaporated (aspirator) to give crude 2-[(phenylthio)methyl]but-2-en-1-ol, 0.955 g (4.92 mmol, 99% yield).

Without further purification, the product alcohol was then oxidized by charging a dry 100-mL three-necked flask, equipped with a mechanical stirrer and addition funnel, with oxalyl chloride (0.960 mL, 11.0 mmol) and dry CH_2Cl_2 (30 mL). After the mixture was cooled to −78 °C, distilled Me_2SO (1.56 mL, 22.0 mmol) in CH_2Cl_2 (3 mL) was added over 30 s. After the mixture was stirred for 2 min, a solution of 2-[(phenylthio)methyl]but-2-en-1-ol (1.94 g, 10 mmol) in CH_2Cl_2 (3 mL) was added by an addition funnel over a 5-min period. The mixture was stirred for 15 min at −78 °C followed by addition of triethylamine (5.56 mL, 40.0 mmol). After the mixture was warmed to room temperature and stirred for 1 h, the reaction was quenched by addition of water (25 mL). The organic layer was separated, extracted with 5% H_2SO_4, saturated $NaHCO_3$, and brine, and dried with $MgSO_4$. After evaporation, a yellow oil remained which gave the desired **31** after vacuum distillation (Vigreux column) as a pale, yellow oil: 1.48 g (7.7 mmol); bp 96–101 °C (0.01 mmHg); 77% yield; IR (neat) 1680 (s), 1635 cm^{-1} (m); NMR ($CDCl_3$) δ 9.22 (s, 1 H), 7.1–7.5 (m, 5 H), 6.64 (q, 1 H, J = 7 Hz), 3.65 (s, 2 H), 1.76 (d, 3 H, J = 7 Hz); mass spectrum, calcd for $C_{1u}H_{12}OS$ m/e 192.0604, obsd 192.0609.

4-[(Phenylthio)methyl]-2,4-hexadienal (32a). A solution of lithium diisopropylamide (LDA) was generated by the addition of diisopropylamine (0.25 mL, 1.8 mmol) to a cooled (−78 °C) solution of *n*-butyllithium (1.12 mL of a 1.60 M solution in hexane, 1.8 mmol) in dry tetrahydrofuran (THF, 2 mL). To this solution was added *N*-*tert*-butylethanimine according to the procedure of Meyers et al.[19] (78 mg, 0.90 mmol), and the mixture was stirred at −78 °C for 0.5 h. Diethyl chlorophosphate (130 μL, 0.90 mmol) was added dropwise, and stirring was continued for 2 h. The solution was warmed to −8 °C for 2 h and then recooled to −78 °C. A solution of **31** (125 mg, 0.65 mmol) in dry THF (1 mL) was added dropwise, and the mixture was stirred at −78 °C for 0.5 h and then warmed to room temperature overnight. A solution of oxalic acid (227 mg, 1.8 mmol) in water (4 mL) was added followed by 4 mL of toluene. After the mixture was stirred at room temperature for 7 h, the layers were separated, and the aqueous layer was extracted with ether (2 × 7 mL). The combined organic layers were washed successively with saturated oxalic acid (10 mL), saturated sodium bicarbonate (10 mL), and saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to a yellow oil. Preparative HPLC (10% ethyl acetate/hexane) afforded the product as a 2:1 mixture of isomers, 72% yield. The major isomer was isolated (HPLC, Porasil, 10% ethyl acetate/hexane) by carefully collecting the peak: colorless oil; IR (neat) 1672 (s), 1625 (s), 1605 (m), 1583 cm^{-1} (m); NMR

($CDCl_3$) δ 9.50 (d, 1 H, J = 6 Hz), 7.1–7.5 (m, 5 H), 6.99 (d, 1 H, J = 16 Hz), 6.0–6.4 (m, 2 H), 3.63 (s, 2 H), 1.62 (d, 3 H, J = 7 Hz); mass spectrum, m/e 218 (M^+), 109 (base).

Ethyl 4-[(Phenylthio)methyl]hexa-2,4-dienoate (32b). A 500-mL flask was charged with NaH (3.71 g, 77.4 mmol, prewashed with THF to remove the oil) and dry THF (200 mL). Triethyl phosphonoacetate (14.1 mL, 70.9 mmol, Aldrich) in THF (25 mL) was added dropwise to the stirred mixture (N_2 atmosphere). After H_2 evolution subsided (ca. 1.5 h, 20 °C), the mixture was cooled to 0 °C, and a solution of aldehyde **31** (12.4 g, 64.5 mmol) in THF (50 mL) was added dropwise. After an additional 1 h at 20 °C, the mixture was partitioned between 200 mL of saturated NH_4Cl and ether (2 × 300 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated (aspirator) to yield 17.7 g of yellow oil. The crude product was filtered over a 30 × 5 cm column of silica gel. Elution with hexane gave 1.6 g of sulfur-containing byproducts, and elution with 10% ether–hexane gave **32b** (7.6 g, 45%) as a mixture of Δ^4 isomers by NMR spectroscopy. The product was sufficiently pure for the next step.

Diene Carbonate 32d. A solution of 7.57 g (28.9 mmol) of **32b** in dry CH_2Cl_2 (200 mL) at −78 °C was treated dropwise with DIBAL (83 mL, 83 mmol) over 0.5 h. After 1 h, the mixture was cautiously added to stirred 10% H_2SO_4 at 0 °C by cannula. After 0.5 h, the aqueous phase was washed with CH_2Cl_2 (3 × 50 mL), and the organic layers were dried ($MgSO_4$) and evaporated. The crude oil was filtered over silica gel (2 × 20 cm) with 50% ether hexane to give alcohol **32c**, 6.01 g (94% yield).

A 1-g (4.54 mmol) protion of this product was dissolved in dry THF (12 mL) awt −78 °C and treated with n-C_4H_9Li (3.26 mL, 1.53 M in hexane). Ethyl chloroformate (0.48 mL, 4.99 mmol) was added dropwise by syringe to the orange solution of lithium alkoxide. After 15 min, the mixture was allowed to warm to 0 °C and was added to saturated NH_4Cl (30 mL). Partitioning between ether–brine, drying ($MgSO_4$), and evaporation of the organic layer (aspirator) gave 1.34 g of **32d** as a yellow oil: ca. 100% yield (mixture of Δ^4 isomers); NMR (partial, $CDCl_3$) minor isomer δ 6.52 (br d, J = 15.5 Hz, vinyl H_3), 1.68 (d, J = 7 Hz, CH_3), major isomer 6.16 (br d, J = 15 Hz, vinyl H_3), 1.60 (d, J = 7 Hz, CH_3). This material was used in the Diels–Alder reaction without additional purification or separation of isomers.

Ethyl 6-[(Phenylthio)methyl]-2,4,6-octatrienoate (33). Triethyl phosphonacetate (Aldrich, 9.9 mL, 50 mmol) was added to a stirred suspension of sodium hydride (Alpha; 2.4 g of a 50% dispersion in oil, 50 mmol) in dry tetrahydrofuran (200 mL) at such a rate that the temperature remained below 30 °C. After the addition was completed, the solution was stirred at room temperature for 1 h before a solution of **32** (9.5 g, 43.8 mmol) in dry THF (50 mL) was added such that the temperature remained between 20 and 30 °C. The resulting solution was heated to 60 °C for 15 min and then cooled (15–20 °C). A routine aqueous–ether workup left a yellow oil which was passed through a 1 × 15 cm silica gel plug (1:1 ether/hexane) to afford to pale yellow oil (9.57 g) which proved to be an inseparable isomer mixture of **33** in a ratio of 2:1. The product was sufficiently pure to use with no additional purification: yield 76%; IR (neat) 2986 (m), 1709 (s), 1613 cm^{-1} (s); NMR ($CDCl_3$) δ 7.1–7.4 (m, 5 H), 6.79 (d, 1 H, J = 16 Hz), 6.3–6.6 (m, 2 H), 5.6–5.9 (m, 2 H), 4.16 (q, 2 H, J = 7 Hz), 3.68 (2 overlapping s in a 2:1 ratio, 2 H), 1.73 and 1.64 (2 overlapping d in a 1:2 ratio, 3 H, J_A = J_B = 7 Hz), 1.22 (t, 3 H, J = 7 Hz).

6-[(Phenylthio)methyl]-2,4,6-octatrien-1-ol (34). Diisobutylaluminum hydride (DIBAL; Aldrich; 58.8 mL of a 1.14 M solution in hexane, 67 mmol) was added dropwise to a cooled (0 °C) solution of **33** (9.2 g, 31.9 mmol) in a mixture of hexane (120 mL) and methylene chloride (30 mL). After the mixture was stirred at 0 °C for 0.5 h, the reaction was quenched by the slow and careful addition of 5% aqueous hydrochloric acid until a thick, gelatinous precipitate formed. The solution was dried ($MgSO_4$) and filtered through a Celite plug. The filtrate was washed extensively with chloroform, and the combined organic layers were evaporated (aspirator) to a yellow oil (7.5 g) which was sufficiently pure to use with no further purification: IR (neat) 3380 (s), 2920 (m), 1593 (m), 991 cm^{-1} (s); NMR ($CDCl_3$) δ 7.0–7.5 (m, 5 H), 6.0–6.5 (m, 3 H), 5.4–6.0 (m, 2 H), 4.1 (m, 2 H), 3.63 and 3.61 (2 overlapping s in a 2:1 ratio, 2 H), 3.05 (br s, 1 H), 1.62 and 1.55 (2 overlapping d in a 1:2 ratio, 3 H, J_A = J_B = 8 Hz).

6-[(Phenylthio)methyl]-2,4,6-octatrienyl Acetate (51). Acetic anhydride (3.6 mL, 38.1 mmol) was added to a solution containing crude **34** from above, triethylamine (Aldrich; 6.1 mL, 44 mmol), and p-(dimethylamino)pyridine (Aldrich; 0.36 g, 2.9 mmol) in dry ether (100 mL). After being stirred at room temperature for 3 h, the solution was added to water (50 mL). The layers were separated, and the organic layer was extracted with saturated sodium bicarbonate (2 × 50 mL) followed by brine (50 mL). The combined aqueous layers were washed once with ether (50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to a yellow oil. Purification via preparative liquid chromatography (5% ethyl acetate/hexane) gave the product as a light yellow oil: 8.2 g (yield from alcohol **34** = 89%); IR (neat) 1755 cm^{-1} (s); NMR ($CDCl_3$) δ 7.0–7.3 (m, 5 H), 6.0–6.4 (m, 3 H), 5.6–5.8 (m, 2 H), 4.50 (2 partly overlapping d, 2 H, J_A = J_B = 6 Hz), 3.62 (2 partly overlapping s in a 2:1 ratio, 2 H), 1.94 (s, 3 H), 1.59 and 1.55 (2 partly overlapping d in a 2:1 ratio, 3 H, J_A = J_B = 8 Hz); mass spectrum, m/e 288 (M^+), 110 (base); calcd for $C_{17}H_{20}O_2S$ m/e 288.1180; obsd 288.1177 (0.4 ppm error).

Diels–Alder Reactions. Reaction of Ethyl 4-Methylhexadienyl Carbonate (48) with 4a; Preparation of 6a. The imide **4a** (0.186 g, 0.672 mmol), the diene carbonate **48** (0.378 mL, 2.01 mmol), and 2,5-di-*tert*-butylhydroquinone (Aldrich, 22 mg, 0.101 mmol) were added to a 1.3 × 1.5 cm thick-walled pyrex tube. Dry toluene (9.5 mL) was added, and the tube was cooled to −78 °C under vacuum and sealed. The contents were then heated at 150 °C for 82 h. The tube was opened, the solvent was removed (aspirator), and the residue was purified by HPLC (Porasil A, 0.78 × 122 cm, 10 mL/min, 20% EtOAc/hexane) to yield 55 mg of unreacted dienophile (k' = 4.0) and 65 mg of a mixture of regioisomeric adducts (k' = 1.5). This mixture was further purified by HPLC (Porasil A, 0.78 × 122 cm, 8 mL/min, 10% EtOAc/hexane) to yield 34 mg of isomer **6a** (16% based on recovered dienophile; k' = 4.5) and 17 mg of the undesired regioisomer (8% based on recovered dienophile; k' = 3.5).

Data for isomer **6a** (crystals from 10% EtOAc/hexane): mp 114–116 °C; IR (CCl_4) 1735 (s), 1680 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.36 (m, 10 H), 5.54 (br s, 1 H), 4.62 (dd, 1 H, J = 11, 7 Hz), 4.46 (dd, 1 H, J = 11, 8 Hz), 4.45 (obscured, 1 H), 4.16 (q, 2 H, J = 7 Hz), 3.22 (dd, 1 H, J = 13, 3 Hz), 3.04 (dd, 1 H, J = 9, 5 Hz), 2.89 (dd, 1 H, J = 13, 9 Hz), 2.60 (ddd, 1 H, J = 9, 7, 2 Hz), 2.52 (m, 1 H), 2.23 (m, 1 H), 1.75 (br s, 1 H), 1.29 (t, 3 H, J = 7 Hz), 0.93 (d, 3 H, J = 7 Hz); mass spectrum, m/e 461 (M^+), 371, 280, 105 (base); calcd for $C_{28}H_{31}NO_5$ m/e 461.220 22; obsd 461.219 60 (−1.3 ppm error).

Data for undesired regioisomer (crystals from 10% EtOAc/hexane): mp 79–80 °C; IR (CCl_4) 1735 (s), 1680 cm^{-1} (s); 270 MHz NMR ($CDCl_3$) δ 7.36 (m, 10 H), 5.49 (br s, 1 H), 4.41 (ddd, 1 H, J = 8, 3, 2 Hz), 4.25 (dd, 1 H, J = 11, 7 Hz), 4.18 (q, 2 H, J = 7 Hz), 3.99 (dd, 1 H, J = 11, 8 Hz), 3.16 (dd, 1 H, J = 13, 3 Hz), 2.99 (dd, 1 H, J = 13, 8 Hz), 2.80 (ddd, 1 H, J = 9, 7, 2 Hz), 2.66 (dd, 1 H, J = 9, 4 Hz), 2.48 (m, 1 H), 2.32 (m, 1 H), 1.75 (br s, 3 H), 1.35 (d, 3 H, J = 7 Hz), 1.30 (t, 3 H, J = 7 Hz); mass spectrum, m/e 461 (M^+), 402, 371, 370, 280, 105 (base), 91, 77; calcd for $C_{28}H_{31}NO_5$ m/e 461.220 20; obsd 461.221 00 (1.7 ppm error).

The experiment has not been optimized.

Silyl-Substituted Dienes. Preparation of Adducts 38, 39, 43, and 44. A 10-mL glass ampule filled with pH 7 phosphate buffer was heated overnight on a steam cone followed by rinsing throughly with distilled water and ethanol. After being dried 4 h in a 140 °C oven, the ampule was cooled under a stream of dry N_2 and charged with 0.180 g (0.65 mmol) of pyrrolinone **4a**, 0.52 mL of freshly distilled toluene, and 1.14 mL of **37** (TBS-protected diene; 1.05 g, 3.52 mmol, 5.4-fold excess). Also added was (0.017 g, 10%) 2,6-di-*tert*-butylhydroquinone as a radical inhibitor. The resultant solution was degassed by using two freeze–pump–thaw cycles and repurging with N_2. Following cooling to −78 °C, the ampule was quickly flame sealed and heated to 150 °C for 78 h. The ampule was cooled to ambient temperature, and the contents were concentrated. The excess diene was easily separated by passing the mixture through a short column of silica gel (50 g) with 10% ether/hexane as the eluant. The crude adducts were then separated on a Waters Prep 500 liquid chromatograph (Bondapak, 4% ether–hexane). The major product **38** (faster eluting) was obtained in 62% yield (0.210 g, 0.404 mmol) followed

by 0.069 g (0.119 mmol, 18%) of the regioisomer **39**.

38: mp 68–70 °C (from CH_3OH); 270-MHz NMR ($CDCl_3$) δ 7.1–7.8 (m, 10H), 5.324 (d, 1 H, J = 3.5 Hz), 4.423 (ddd, 1 H, J = 3, 1.7, 8.2 Hz), 4.059 (dd, 1 H, J = 9.9, 6.5 Hz), 3.824 (dd, 1 H, J = 9.9, 8.1 Hz), 3.184 (dd, 1 H, J = 3.0, 13.2 Hz), 2.913 (dd, 1 H, J = 9.2, 6.0 Hz), 2.908 (dd, 1 H, J = 13.2, 8.2), 2.522 (ddd, 1 H, J = 1.7, 6.0, 9.2 Hz), 2.392 (dddd, 1 H, J = 8.1, 6.5, 3.5, 6.0 Hz), 2.157 (dq, 1 H, J = 7.5, 6.0 Hz), 1.499 (s, 2 H), 0.882 (d, 3 H, J = 7.5 Hz), 0.850 (s, 9 H), 0.00 (s, 6 H), –0.055 (s, 9 H); IR ($CBrCl_3$) 1740 (s), 1672 (s), 1600 cm^{-1} (w); mass spectrum, calcd for $C_{34}H_{49}NO_3Si_2$ m/e 575.325 08; obsd 575.3252 (0.2 ppm error), m/e (relative intensity) 575 (weak), 523 (5), 521 (3), 520 (15), 519 (42), 518 (100), 443 (5), 430 (11), 278 (9).

39: mp 88–91 °C (from CH_3OH); 270-MHz NMR ($CDCl_3$) δ 7.1–7.8 (m, 10 H), 5.255 (br s, 1 H), 4.511 (ddd, J = 4.9, 13, 8 Hz), 3.684 (dd, 1 H, J = 6.6, 10.3 Hz), 3.548 (dd, 1 H, J = 10.3, 8.2 Hz), 3.101 (d, 1 H, J = 4.922 Hz), 2.786 (m, 1 H), 2.505 (dd, 1 H, J = 4.4, 9.7 Hz), 2.29 (m, 1 H), 1.28 (d, 3 H, J = 7.4 Hz), 0.902 (s, 9 H), 0.063 (s, 3 H), 0.045 (s, 3 H), –0.043 (s, 9 H); mass spectrum, calcd for $C_{34}H_{49}NO_3Si_2$ m/e 575.325 08, obsd 575.3259 (1.4 ppm error); m/e (relative intensity) 576 (0.9), 575 (1.9), 560 (1), 519 (4), 518 (13), 430 (17), 106 (6), 105 (100), 91 (6), 77 (19), 73 (58).

Careful collection of the lead zone of the peak containing **38** gave a small amount of material enriched in a third isomer assigned structure **43**. The substance could not be totally separated from **38** from Diels–Alder mixtures. However, crystalline **38** was converted into a mixture of ca. 93% **43** and 7% **38** by treatment with DBU. Thus, 0.03 g of **38** was dissolved in CH_3CN (1.0 mL), and DBU (0.01 g) was added. After 24 h at 20 °C the mixture was diluted with water (5 mL) and extracted with 1:2 ether–hexane (2 × 5 mL). After the extract was dried ($MgSO_4$) and evaporated (aspirator), a colorless oil was obtained which contained a single spot by TLC analysis which was indistinguishable by R_f from **38** in several systems. The 270-MHz NMR spectrum ($DCCl_3$) indicated a new major component, **43**: δ 7.25–7.74 (complex, 10 H), 5.18 (br s, 1 H), 4.51 (ddd, 1 H, J = 9.9, 6.5, 3.2 Hz), 3.90 (dd, 1 H, J = 9.5, 2.5 Hz), 3.71 (dd, 1 H, J = 9.5, 5.5 Hz), 3.29 (2 H, ABX, J_{AB} = 13.5 Hz, J_{AX} = 3.2 Hz, J_{BX} = 2.5 Hz), 2.1–2.5 (m, 4 H), 1.61 (d, 1 H, J = 14 Hz), 1.43 (d, 1 H, J = 14 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.90 (s, 9 H), 0.12 (s, 9 H), 0.03 (br s, 6 H). The spectrum also contained a minor signal at 5.32 ppm due to residual **38** and other appropriate but less resolved signals of **38**. By comparison of the heights of the olefinic hydrogens at ca. 5 ppm, 7% of **38** remains in the isomerized material. Assignment of the trans ring fusion to **43** follows from its similarity by NMR to the trans isomer **47** which has been analyzed completely.

In one experiment using the same conditions but a different and suspect batch of **4a**, a third (highly crystalline) isomer was obtained which was less polar on HPLC than **38**. This substance is assigned structure **44** on the basis of the presence of an olefinic methyl group in the NMR spectrum: mp 111–112 °C (from CH_3OH); IR ($CHCl_3$) 1790 (s), 1670 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.1–7.8 (m, 10 H), 4.52 (dd, 1 H, J = 9.6, 3.7 Hz), 3.88 (dd, 1 H, J = 9.5, 6.2 Hz), 3.63 (dd, 1 H, J = 9.5, 5.5 Hz), 3.19 (dd, 1 H, J = 13, 3.7 Hz), 2.97 (dd, 1 H, J = 7.4, 2.8 Hz), 2.78 (dd, 1 H, J = 13, 9.6 Hz), 2.61 (br d, J = 7.5 Hz), 1.69–1.80 (m, 3 H), 1.48 (d, 1 H, J = 13.4 Hz), 1.28 (d, tent, 1 H, J = 13.4 Hz, with a doublet upfield line obscured by methyl), 1.25 (s, 3 H), 0.80 (s, 9 H), –0.068 (s, 3 H), –0.074 (s, 3 H), –0.14 (s, 9 H), –0.068 (s, 3 H), –0.074 (s, 3 H), –0.14 (s, 9 H); mass spectrum, calcd for $C_{34}H_{49}NO_3Si_2$ m/e 575.325 08, obsd 575.3258 (1.2 ppm error).

Doubly Activated Dienophile 4b. Diels–Alder Condensation of 4b with 2,4-Hexadiene. Preparation of 46. Freshly prepared **4b** (195 mg, 0.385 mmol; via the previously described procedure) was added to a solution of 2,4-hexadiene (Aldrich; mixture of E,E and E,Z isomers; 439 μL, 3.85 mmol) in dry toluene (2 mL) and heated to reflux for 2.5 h. After the mixture cooled, the solvent and excess diene were evaporated (aspirator), and the residue was purified via HPLC (Porasil; 17% ethyl acetate/hexane). The product was recovered as a pale yellow oil: 64 mg (yield from selenide precursor 39%); IR ($CHCl_3$) 1740 (s), 1685 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 8.0–7.3 (m, 10 H), 5.69 (br s, 1 H), 4.37 (dt, 1 H, J = 8.7, 3.2 Hz), 4.3 (obscured q, 2 H), 4.3 (obscured, 1 H), 3.21 (dd, 1 H, J = 13, 8.8 Hz), 2.87 (dd, 1 H, J = 13, 3 Hz), 2.76 (dd, 1 H, J = 6.1, 3.1 Hz), 2.76 (m, 1 H), 2.33 (m, 1 H), 1.35 (t, 3 H, J = 7 Hz), 1.32 (d, 3 H, J = 5.4 Hz), 0.78 (d, 3 H, J = 6.6 Hz); mass spectrum, m/e 431 (M^+), 105 (base); calcd for $C_{27}H_{29}NO_4$ m/e 431.2096; obsd 431.2087 (1.0 ppm error).

Saponification and Decarboxylation: 47. Solid sodium hydroxide (6 mg, 0.16 mmol) was added to a solution of **46** (13 mg, 0.04 mmol) in ethanol (2 mL) and water (0.5 mL). The resulting solution was stirred at room temperature for 5 h and then at reflux for an additional 4 h. After the mixture cooled, the solvent was evaporated, and the residue was taken up in saturated sodium bicarbonate (2 mL) and extracted with chloroform (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to a white solid (11 mg). Complete hydrolysis was demonstrated by the total absence of an ethyl absorption in the NMR spectrum. The crude product was reacted directly with no attempt at purification.

The acid was dissolved in dry pyridine (4 mL) and heated to reflux for 5 h. The cooled solution was added to water (5 mL) and extracted with ether (3 × 7 mL). The combined organic layers were washed with 5% hydrochloric acid until the aqueous layer remained acidic. The organic layers were then washed with saturated sodium bicarbonate (10 mL), dried (Na_2SO_4), filtered, and evaporated to a white solid. Preparative layer chromatography (3:1 ethyl acetate/hexane) gave a white solid (9 mg) which proved to be a mixture of cis- and trans-fused **47** (ca. 1:1) by comparison with authentic samples.[22]

Reaction of 4b with Diene 48. Freshly prepared **4b** (crude material, 75 mg, 0.15 mmol; via the previously described selenoxide elimination) was added to a solution of (*E,E*)-4-methyl-2,4-hexadien-1-yl ethyl carbonate (102 mg, 0.55 mmol) in perdeuteriobenzene (0.5 mL). The solution was sealed in a Pyrex tube and heated at 125 °C for 1 h. After the mixture cooled, the solvent was evaporated, and the excess diene was removed via Kugelrohr distillation [40–50 °C 0.05 torr)]. The residue was purified via HPLC (Porasil, 17% ethyl acetate–hexane). The title compounds were separated as colorless oils in a ≥4:1 ratio of **49a**/**50a**, 17 and 4 mg, respectively (39% combined yield from selenide precursor). The minor isomer **50a** was not obtained completely free of **49a** and unknown impurities, and the structrual assignment is by spectral analogy to the corresponding regioisomer obtained from **4b**.

49a: IR ($CHCl_3$) 2930 (s), 1755 (s), 1690 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.0–7.8 (m, 10 H), 5.50 (br s, 1 H), 4.53 (dd, 1 H, J = 10.9, 8.4 Hz), 4.46 (dd, 1 H, J = 10.9, 5.7 Hz), 4.30 (obscured, 1 H), 4.13 (q, 2 H, J = 7 Hz), 4.11 (q, 2 H, J = 7 Hz), 3.11 (dd, 1 H, J = 13.3, 3 Hz), 2.96 (dd, 1 H, J = 13.3, 8.2 Hz). 2.92 (m, 1 H), 2.78 (dd, 1 H, J = 5.9, 3.5 Hz), 2.42 (m, 1 H), 1.74 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz)8 1.26 (t, 3 H, J = 7 Hz), 0.82 (d, 3 H, J = 7 Hz); mass spectrum, m/e 533 (M^+), 105 (base); calcd for $C_{31}H_{35}NO_7$ m/e 533.2523, obsd 533, 2414 (2.6 ppm error).

Reaction of 4b with Diene Carbonate 32d. Isolation of 49b and 50b. Freshly prepared **4b** (55 mg, 0.16 mol was added to a Pyrex tube containing a solution of **32d** (0.23 g, 0.79 mmol) in perdeuteriobenzene (0.5 mL). After being sealed, the system was heated to 130 °C for 1 h. The reaction mixture was then cooled and evaporated (aspirator) to a yellow oil. Liquid chromatography (LC; porasil, 15% ethyl acetate/hexane) gave the product as a mixture of regioisomers. Further purification via LC (μ-Porasil; 10% ethyl acetate/hexane) partially separated these isomers as colorless oils (ca. 5:2 ratio). The more abundant isomer (26 mg) proved to be the desired product **49b** while regioisomer **50b** was the minor product (11 mg). The combined yield was 37%.

49b: IR ($CHCl_3$) 1740 (s), 1682 (s); 270-MHz NMR ($CDCl_3$) δ 7.0–7.7 (15 H, m), 5.54 (1 H, dd, J = 2.9, 0.9 Hz), 4.1–4.7 (7 H, complex m), 3.52 (2 H, AB q, J = 13 Hz), 3.18 (1 H, dd, J = 13.4, 2.9 Hz), 2.95 (1 H, dd, J = 13.4, 8.5 Hz), 2.91 (1 H, m), 2.81 (1 H, dd, J = 6.0, 3.5 Hz), 2.50 (1 H, m), 1.33 (3 H, t, J = 7 Hz), 1.26 (3 H, t, J = 7 Hz), 0.92 (3 H, d, J = 7.5 Hz); mass spectrum, m/e 541 (M^+), 105 (base); calcd for $C_{37}H_{39}NO_7S$ m/e 641.2449, obsd. 641.2447 (0.2 ppm error).

50b: IR (neat) 1750 (s), 1682 cm^{-1} (m); 270-MHz NMR ($CDCl_3$) δ 7.0–7.7 (15 H, m), 5.52 (1 H, br s), 4.1–4.5 (7 H, complex m), 3.49 (2 H, br s), 3.03 (1 H, dd, J = 6.1, 3.7 Hz), 2.95 (1 H, dd, J = 7.0, 6.1 Hz), 2.94 (1 H, m), 2.82 (1 H, m), 2.59 (1 H, m), 1.43 (3 H, d, J = 7.5 Hz), 1.31 (3 H, t, J = 7 Hz), 1.25 (3 H, t, J = 7 Hz); mass spectrum, calcd for $C_{37}H_{39}NO_7S$ m/e 641.2449; obsd 641.2441 (0.6 ppm error).

Reaction of 4b with Triene Acetate 51. Isolation of 52. Freshly prepared crude **4b** (160 mg, 0.45 mmol) was added to a Pyrex tube containing a solution of **51** (1.3 g, 4.5 mmol) in benzene (1.0 mL). This solution was degassed by cooling (−78 °C) under a nitrogen atmosphere. After being cooled sufficiently, the solution was subjected to high vacuum (<0.1 torr) for 15 min, purged with nitrogen, and allowed to warm to room temperature. After this process was repeated a total of three times, the tube was sealed under vacuum, and the system was heated to 125 °C for 1 h. After the mixture cooled, the solvent was evaporated (aspirator) and the dark yellow residue was purified via high-pressure liquid chromatography (HPLC; Porasil, 15% ethyl acetate/hexane), collecting the major zone after unreacted triene. Further purification via HPLC (μ-CN; 10% ethyl acetate/hexane) gave a major zone of the pure product **52** as a pale yellow oil (81 mg); no other significant components which contained NMR signals due to both reactants could be found: yield 28%; IR (neat) 3050 (w), 2930 (m), 1750 (s), 1685 (s), 1230 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.3 (m, 15 H), 6.27 (dd, 1 H, J = 15.6, 9.0 Hz), 5.59 (m, 1 H), 5.58 (br s, 1 H), 4.52 (dt, 1 H, J = 8.5, 3.0 Hz), 4.43 (dd, 2 H, J = 6.4, 0.9 Hz), 4.15 (2 overlapping q, 2 H), 3.50 (br s, 2 H), 3.17 (dd, 1 H, J = 13.2, 3.1 Hz), 3.15 (m, 1 H), 2.84 (dd, 1 H, J = 13.2, 8.6 Hz), 2.82 (dd, 1 H, J = 6.4, 2.9 Hz), 2.50 (m, 1 H), 1.99 (s, 3 H), 1.30 (t, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7.4 Hz); mass spectrum, m/e 637 (M^+), 105 (base); calcd for $C_{38}H_{39}NO_6S$ m/e 637.2498, obsd 637.2513 (1.5 ppm error).

Conversion of 49b into 54b. A solution of 0.122 g of **49b** in 4 mL 9:1 CH_3OH/H_2O was stirred with 45 mg of $NaIO_4$ for 48 h at 23 °C. The product sulfoxide was partitioned between water and $CHCl_3$ (3 × 10 mL). After the mixture was dried ($MgSO_4$) and the $CHCl_3$ evaporated (aspirator), the resulting oil was dissolved in absolute ethanol (5 mL). Triethyl phosphite (72 μL) was added, and the reaction mixture was stirred for 24 h at 23 °C. The product was partitioned between ether and saturated $NaHCO_3$, and the organic layers were dried ($MgSO_4$) and evaporated (aspirator). The oil was purified by preparative TLC (silica gel, 3:1:2 hexane/CH_2Cl_2/ether, seven elutions). The major UV-active zone [R_f 0.53 (Et_2O)] was eluted to give **54b** as a clear oil which crystallized from ether–hexane: mp 118–119 °C; 0.059 g (57%); IR (neat oil) 1738, 1680 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 7.0–7.7 (10 H, complex), 5.10 (1 H, s), 5.02 (1 H, s), 4.3–4.7 (5 H, complex), 4.2 (s H, q, J = 7 Hz), 4.00 (1 H, d, J = 8.6 Hz), 3.11 (1 H, dd, J = 13.1, 3.5 Hz), 2.6–2.8 (3 H, m), 2.63 (1 H, dd, J = 13.9, 9.9 Hz), 2.08 (1 H, br s, D_2O exchangable), 1.34 (3 H, t, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz), 0.62 (3 H, d, J = 6.6 Hz); calcd, for $C_{31}H_{35}NO_8$ m/e 549.2363; obsd 549.2363.

Cytochalasin Functionality. Diisobutylaluminum hydride (300 μL, 1 M in hexane) was added over a period of 2 h to a −78 °C solution of isoindolone **54b** (22 mg, 40 μmol) in CH_2Cl_2 (10 mL). After being stirred for an additional hour at −78 °C, the reaction mixture was allowed to warm to room temperature and quenched by addition of 5% H_2SO_4 (10 mL). After rapid stirring for 0.5 h, the organic layer was separated, extracted three times with $CHCl_3$, dried with $MgSO_4$, and evaporated (aspirator) to give a pale yellow oil. Purification was achieved by using an 8 in. × 8 in. analytical TLC plate (50% EtOAc/Et_2O). The product **55b** was recovered as a pale yellow oil which crystalized when swirled in ether: mp 199–202 °C; 9.7 mg (26 μmol, 65% yield); 270-MHz NMR ($CDCl_3$) δ 7.14–7.37 (5 H, m), 5.82 (1 H, s, exchanged by D_2O), 5.39 (1 H, s), 5.11 (1 H, s), 4.34 (1 H, d, J = 10.0 Hz), 4.30 (2 H, q, J = 7.4 Hz), 4.02 (2 H, ABX, J_{AB} = 12.6 Hz, J_{AX} = 2.6 Hz, J_{BX} = 4.4 Hz), 3.40 (1 H, m), 2.94 (1 H, m), 2.78 (2 H, ABX, J_{AB} = 13.2 Hz, J_{AX} = 4.26 Hz, J_{BX} = 9.34 Hz), 2.65 (1 H, s, exchanged by D_2O), 2.61 (1 H, m), 1.63 (1 H, s, exchanged by D_2O), 1.36 (3 H, t, J = 7.4), 1.05 (3 H, d, J = 7 Hz).

Conversion of 52 to 54a. Sodium periodate (Ventron; 41 mg, 0.19 mmol) was added to a solution of **52** (110 mg, 0.17 mmol) in 90% methanol–water (10 mL). After being stirred at room temperature for 35 h, the reaction mixture was partitioned between $CHCl_3$ (25 mL) and water, and the organic layer was dried ($MgSO_4$) and evaporated to an oil. Preparative thin-layer chromatography (3:1 ether/hexane) gave the sulfoxide **53** as a colorless oil (90 mg; R_f 0.18). In addition, some starting material was also recovered (14 mg). The yield (based on recovered starting material) was 93%.

The sulfoxide **53** from above (87 mg, 0.133 mmol) was stirred 18 h with trimethyl phosphite (34 μL, 0.29 mmol) and methanol (2 mL). The mixture was partitioned between ether (25 mL) and saturated $NaHCO_3$–H_2O, and the ether layer was dried ($MgSO_4$) and evaporated (aspirator). Liquid chromatography (Porasil; 35% ethyl acetate/hexane) afforded **54a** as a colorless oil: 45 mg (62%); IR (neat) 3430 (s), 2990 (m), 1748 (s), 1690 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.0–8.0 (m, 10 H), 6.30 (dd, 1 H, J = 15.4, 9.7 Hz), 5.73 (dt, 1 H, J = 15.4, 6.1 Hz), 5.15 (s, 1 H), 5.08 (s, 1 H), 4.50 (unresolved singlet with fine structure, 2 H), 4.42 (ddd, 1 H, J = 9.8, 3.5, 1.5 Hz), 4.25 (q, 2 H, J = 7 Hz), 4.03 (d, 1 H, J = 8.8 Hz), 3.10 (dd, 1 H, J = 13.1, 3.5 Hz), 2.88 (t, 1 H, J = 9.1 Hz), 2.80 (m, 2 H), 2.64 (dd, 1 H, J = 13.1, 9.8 Hz), 2.02 (s, 3 H), 1.72 (br s, 1 H), 1.38 (t, 3 Hz, J = 7 Hz), 0.67 (d, 3 H, J = 6.1 Hz); mass spectrum, m/e 545 (M^+), 105 (base); calcd for $C_{32}H_{35}NO_7$ m/e 545.2413; obsd 545.2405 (0.9 ppm error).

Cytochalasin Functionality: 55a. Sodium hydroxide (MCB; 7 mg, 0.17 mmol) was added to a solution of **54a** (42 mg, 0.077 mmol) in absolute ethanol (1 mL). After being stirred at room temperature for 1 h, the solution was poured into aqueous 5% sodium bicarbonate (5 mL), and a routine aqueous–ethyl acetate workup left a yellow solid. Recrystallization (methanol/hexane) afforded the product as white needles: 22 mg (72%); mp 201–202 °C; IR (CH_3CN) 3540 (m), 1745 (s), 1705 cm^{-1} (s); 270-MHz NMR ($CDCl_3$) δ 7.3 (m, 5 H), 6.0 (dd, 1 H, J = 15.7, 9.0 Hz), 5.85 (dt, 1 H, J = 15.7, 5.1 Hz), 5.81 (br s, 1 H), 5.28 (s, 1 H), 5.09 (s, 1 H), 4.24 (2 overlapping q, 2 H, J = 7 Hz), 4.2 (obscured, 1 H), 4.06 (m, 3 H), 3.36 (ddd, 1 H, J = 8.8, 8.6, 2.1 Hz), 315 (t, 1 H, J = 9 Hz), 2.97 (m, 1 H), 2.85 (dd, 1 H, J = 13.5, 4.5 Hz), 2.65 (dd, 1 H, J = 13.8, 9.0 Hz), 2.61 (br s, 1 H), 1.84 (br s, 1 H), 1.31 (t, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 6.8 Hz); mass spectrum, m/e 399 (M^+), 262 (base); calcd for $C_{23}H_{29}NO_5$ m/e 399.2045, obsd 399.2038 (0.7 ppm error).

Conversion of 38 into 57. A solution of **38** (0.10 g) in CH_2Cl_2 (distilled from P_2O_5, 5 mL) was cooled to 0 °C (ice bath). To the stirred solution was added excess 85% MCPBA (Aldrich) in small portions over 20 min (0.050 g total). Analysis by TLC (silica gel, 2:1:5 CH_2Cl_2/ether/hexane) indicated nearly total consumption of starting material (R_f 0.6), formation of a major product (R_f 0.45), and at least six minor products of greater polarity. After an additional 15 min of stirring at 20 °C, the mixture was diluted with ether (20 mL), and acids were removed by extraction with 5% NaOH at 5 °C (2 × 10 mL). After back-extraction of the aqueous layer (10 mL ether), the organics were dried ($MgSO_4$), evaporated (aspirator), and purified by preparative chromatography over silica gel as for the analytical probes. The R_f 045 zone was collected and gave 0.05 g of colorless, oily **57**: 270-MHz NMR ($CDCl_3$) δ 7.2–7.6 (10 H, complex), 5.25 (1 H, s), 4.93 (1 H, s), 4.53 (1 H, m), 4.31 (1 H, m, simplifies to br d with J = ca. 5 Hz after D_2O exchange), 3.94 (2 H, ABX, J_{AB} = 10.4 Hz, J_{AX} = 7.8 Hz, J_{BX} = 7.8 Hz), 2.94 (2 H, ABX, J_{AB} = 13.3 Hz, J_{AX} = 3.3 Hz, J_{BX} = 7.6 Hz), 2.77 (1 H, dd, J = 3.7, 9.8), 2.44 (1 H, br dd, J = 7.6, 7.9 Hz), 2.29 (1 H, m), 2.19 (1 H, m), 1.98 (1 H, d, J = 8.6 Hz, exchanged by D_2O), 0.86 (3 H, d, J = 7.0 Hz), 0.82 (9 H, s), −0.074 (6 H, 2 overlapping singlets).

Diol 58. A solution of **38** (24 mg) in 1 mL of pyridine (distilled from KOH) was stirred with OsO_4 (12 mg) for 1 h at 20 °C. A solution of $NaHSO_3$ (0.2 g) in 1:1 pyridine–H_2O (ca. 3 mL) was then added and stirred for 1 h at 20 °C. The initial deep red-brown color faded to orange within a few minutes. The mixture was diluted with ether (30 mL) and extracted with saturated $CuSO_4$ in water (2 × 15 mL). After back-extraction of the water layer (ether, 10 mL), the combined ether extracts were dried ($MgSO_4$) and evaporated to yield a solid. Recrystallization from CH_2Cl_2–hexane gave colorless needles: 21 mg (2 crops; 80%); mp 166–167.5 °C; 270-MHz NMR ($CDCl_3$) δ 7.24–7.51 (10 H, complex), 4.60 (1 H, dd, J = 5.3, 7.0 Hz), 4.55 (1 H, s, exchanged by D_2O), 4.46 (1 H, partly resolved dd, J = 10.6, 10.3 Hz), 3.76 (1 H, dd, J = 10.6, 3.0 Hz), 3.59 (1 H, d, J = 10.2 Hz), 3.05 (2 H, ABX, J_{AB} = 13.6 Hz, J_{AX} = 5.3 Hz, J_{BX} = 7.0 Hz), 2.86 (1 H, dd, J = 5.8, 7.4 Hz), 2.69 (1 H, J = 7.4, 6.9 Hz), 1.97–2.16 (2 H, m), 2.12 (1 H, s, exchangeable by D_2O), 1.31 (1 H, d, J = 15.4), 0.85 (9 H, s), 0.81 (3 H, d, J = 7.7 Hz, partly overlapping 1 H d, J = 15.4 Hz, at 0.76 ppm), 0.04 (3 H, s), 0.03 (3 H, s), 0.02 (9 H, s).

Allylic Acetate 59. The diol 58 (28 mg) was dissolved in pyridine (1.5 mL), and acetic anhydride (79 mg) was added. After

14 h at 20 °C, the product was partitioned between ether and saturated $CuSO_4$ solution (2×) and water (2×). After drying ($MgSO_4$) and ether evaporation (aspirator), a solid residue (14 mg) resulted which gave single spot on TLC (R_f 0.38; 2:1 hexane/ether, silica gel).

The crude solid acetate was dissolved in pyridine (1.1 mL) and cooled to 0 °C. Thionyl chloride (62 mg) and 4-(dimethylamino)pyridine (4 mg) were added in succession, and the mixture was stirred 1.5 h at 0 °C. The same workup as above gave a colorless oil. After preparative TLC (silica gel, 2:1 hexane/ether), 21 mg of pure **59** were obtained as a clear oil (82%) which crystallized from ether–hexane: mp 133.5–134 °C; 270-MHz NMR ($CDCl_3$) δ 7.2–7.6 (10 H, complex), 5.23 (1 H, d, J = 9.9 Hz), 5.21 (1 H, s), 5.00 (1 H, s), 4.51 (1 H, dd, J = 8.5, 3.3 Hz), 4.19 (1 H, dd, J = 9.9, 9.9 Hz), 3.50 (1 H, dd, J = 9.9, 4.6 Hz), 3.07 (1 H, dd, J = 13.5, 3.3 Hz), 2.97 (1 H, dd, J = 9.2, 3.7 Hz), 2.84 (1 H, dd, J = 13.5, 8.5 Hz), 2.60 (1 H, m), 2.47 (1 H, m), 2.21 (1 H, m), 1.92 (3 H, s), 0.83 (3 H, d, J = 6.6 Hz), 0.80 (9 H, s), −0.07 (3 H, s), −0.08 (3 H, s); IR ($CHCl_3$) 1740, 1674, 1659 cm^{-1}; mass spectrum, calcd for $C_{33}H_{43}NO_5Si$ m/e 561.291 02, obsd 561.2908.

Cytochalasin Functionality. Deprotection of 59 to 60. Acetate **59** (14.4 mg) was stirred in dry CH_2Cl_2 (1.5 mL) at −78 °C, and excess DIBAL in hexane (1 M, 0.25 mL) was added dropwise. After 5 h at −78 °C, CH_3OH (0.3 mL) was added dropwise, followed by aqueous H_2SO_4 (1 N, 0.4 mL). The dry ice bath was replaced by an ice bath, and the mixture was stirred 30 min. Solids were removed by filtration through a Celite plug ($CHCl_3$ rinse), and the organic phase was washed with water (3 × 10 mL). After the organic phase was dried ($MgSO_4$) and the solvent evaporated (aspirator), the residue was purified by preparative TLC over silica gel (5:1 ether/hexane) to give a major zone (R_f 0.31) containing 7.8 mg (74%) of **60** which crystallized from CH_2Cl_2–hexane: mp 122–123.5 °C; 270-MHz NMR δ 7.35–7.1 (5 H, complex), 5.29 (NH, br s), 5.23 (1 H, s) 5.01 (1 H, s), 4.47 (1 H, dd, J = 10.3, 10.0 Hz), 4.24 (1 H, d, J = 9.6 Hz), 3.99 (1 H, dd, J = 10.3, 4.0 Hz), 3.98 (OH, s), 3.40 (1 H, br dd, J = 5.1, 4.8 Hz), 2.81 (1 H, m, obscured), 2.76 (1 H, dd, J = 13.2, 4.8 Hz), 2.69 (1 H, dd, J = 10.3, 5.1 Hz), 2.59 (1 H, dd, J = 13.2, 8.8 Hz), 2.47 (1 H, ddd, J = 10.3, 6.2, 3.2 Hz), 2.20 (1 H, dddd, J = 10.0, 9.6, 5.1, 4.0 Hz), 1.00 (3 H, d, J = 7.0 Hz), 0.88 (9 H, s), 0.09 (3 H, s), 0.08 (3 H, s). IR ($CHCl_3$) 3425, 1690 cm^{-1}; mass spectrum, calcd for $C_{24}H_{37}NO_3Si$ m/e 415.254 25, obsd 415.2542.

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Registry No. (±)-**4a**, 80360-64-1; **4b**, 80360-65-2; (±)-**6a**, 80360-66-3; (±)-**11**, 80408-25-9; (±)-**12**, 80408-26-0; (±)-*cis*-**13**, 80360-67-4; (±)-*trans*-**13**, 80360-68-5; **15**, 39662-63-0; **16**, 14293-06-2; *cis*-**17**, 80360-69-6; *trans*-**17**, 80360-70-9; *cis*-**18**, 80360-71-0; *trans*-**18**, 80360-72-1; **21**, 17728-88-0; **22**, 80360-73-2; **22** 2,4-dinitrophenylhydrazone, 80360-74-3; (*E*)-**23**, 80360-75-4; **24**, 80360-76-5; **25**, 80360-77-6; **26**, 80360-78-7; **27**, 80360-79-8; **28**, 80360-80-1; **29**, 74457-20-8; **29** Mesylate, 80360-81-2; **30**, 80360-82-3; (*Z*)-**31**, 80360-83-4; (*E*,*E*)-**32a**, 80360-84-5; (*E*,*Z*)-**32a**, 80360-85-6; (*E*,*E*)-**32b**, 80360-86-7; (*E*,*Z*)-**32b**, 80360-87-8; (*E*,*E*)-**32c**, 80360-88-9; (*E*,*Z*)-**32c**, 80360-89-0; (*E*,*E*)-**32d**, 80360-90-3; (*E*,*Z*)-**32d**, 80360-91-4; **33**, 80360-92-5; **34**, 80360-93-6; **37**, 80360-94-7; (±)-**38**, 80360-95-8; (±)-**39**, 80360-96-9; **40**, 80360-97-0; (±)-41, 80360-98-1; (±)-**43**, 80360-99-2; (±)-**44**, 80361-00-8; **46**, 80361-01-9; **46** Acid, 80361-02-0; **47** (cis-fused), 80361-03-1; **47** (trans-fused), 80387-12-8; **48**, 80361-04-2; **49a**, 80361-05-3; **49b**, 80361-06-4; **50a**, 80361-07-5; **50b**, 80361-08-6; **51**, 80361-09-7; **52**, 80361-10-0; **53**, 80441-01-6; **54a**, 80361-11-1; **54b**, 80361-12-2; **55a**, 80361-13-3; **55b**, 80361-14-4; (±)-**57**, 80361-15-5; (±)-**58**, 80361-16-6; (±)-**58** diacetate, 80361-17-7; (±)-**59**, 80361-18-8; (±)-**60**, 80361-19-9; ethyl *N*-(3-ethoxy-1,3-dioxopropyl)-DL-phenylalanine, 80361-20-2; ethyl DL-phenylalanate, 1795-96-6; ethyl malonyl chloride, 36239-09-5; 1-benzoyl-5-benzyl-2-pyrrolidinone, 80361-21-3; (*E*,*E*)-4-Methyl-2,4-hexadien-1-ol, 57258-51-2; tiglaldehyde, 497-03-0; (*E*,*E*)-1-(*tert*-butyldimethylsiloxy)-4-methyl-2,4-hexadiene, 80361-22-4; ethyl 2-[(trimethylsilyl)methyl]-3-hydroxybutanoate, 80361-23-5; acetaldehyde, 75-07-0; ethyl 2-[(trimethylsilyl)methyl]-2-butenoate, 80361-24-6; 2-[(trimethylsilyl)methyl]-2-buten-1-ol, 80361-25-7; diphenyl [(*E*)-4-hydroxy-2-buten-1-yl]phosphine oxide, 80361-26-8; (*E*)-4-chloro-2-buten-1-ol, 1775-39-9; ethyl acrylate, 140-88-5; (*Z*)-2-[(phenylthio)methyl]but-2-en-1-ol, 80361-27-9; *N*-*tert*-butylethanimine, 7020-80-6; triethyl phosphonoacetate, 867-13-0; (*E*,*E*)-2,4-hexadiene, 5194-51-4; (*E*,*Z*)-2,4-hexadiene, 5194-50-3.

Photochemistry of 1,2-Distyrylbenzene Derivatives

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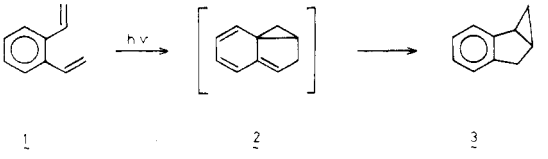
Photodimerization, accompanied by intramolecular, head to head [2 + 2] cycloaddition, which is observed with unsubstituted 1,2-distyrylbenzene (**12**), does not occur with derivatives containing an α or β substituent. α-Substituted 1,2-distyrylbenzenes yield benzobicyclo[2.1.1]hex-2-ene derivatives, at least when the substituent does not give rise to a new chromophoric system. Their photochemical behavior can be explained by assuming that such compounds (**22–24**) contain two formally conjugated but independently absorbing chromophores. The excitation energy is transferred to the chromophore with the lowest excitation energy, which determines the main route of the photoreaction. The formation of a photoelimination product as a second product from 1-(α-chlorostyryl)-2-(4-methylstyryl)benzene (**23**) but not from 1-(α-chloro-4-methylstyryl)-2-styrylbenzene (**24**) has been ascribed to the influence of the methyl substituent on the photocycloaddition. The concept used explains that the photoproduct of 1-(α-phenylstyryl)-2-styrylbenzene (**25**) arises via excitation of the triphenylethylene moiety. β-Substituted distyrylbenzene **26** is photostable due to steric hindrance.

About 15 years ago Pomerantz[1] and Meinwald[2] demonstrated that irradiation of 1,2-divinylbenzene (**1**) leads to benzobicyclo[3.1.0]hex-2-ene (**3**). The product arises via the initial formation of a [4 + 2] cycloaddition product (**2**), which undergoes a vinylcyclopropane–cyclopentene rearrangement (Scheme I). Several divinylbenzene derivatives, containing aliphatic substituents give similar results.[3,4] However, introduction of a phenyl group at the

Scheme I



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(2) J. Meinwald and P. H. Mazzocchi, *J. Am. Chem. Soc.*, **89**, 696 (1967).

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