A Synthesis of C(16),C(18)-Bis-*epi*-cytochalasin D via Reformatsky Cyclization

E. Vedejs*,† and S. M. Duncan

Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

edved@umich.edu

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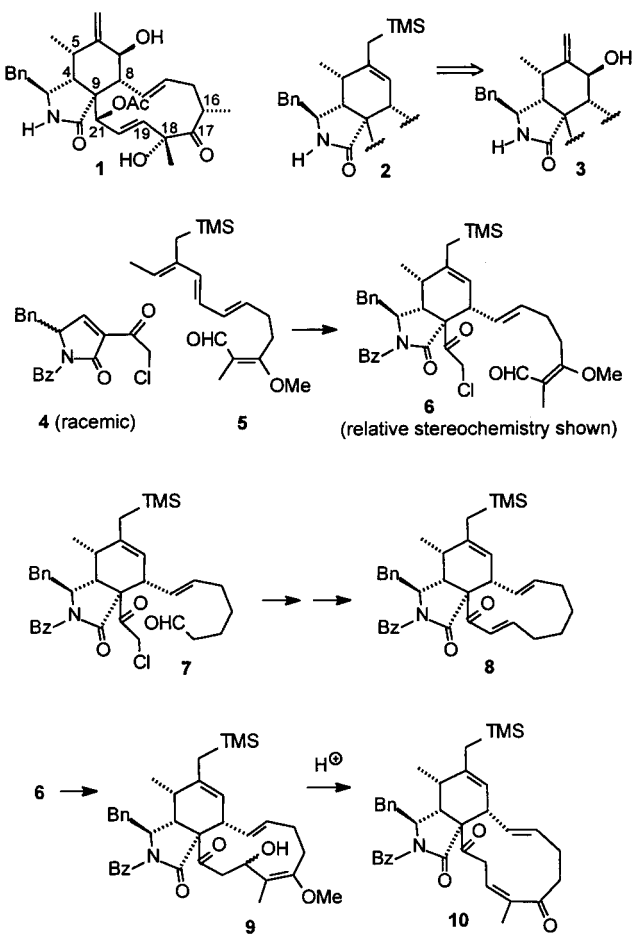
Triene **5** has been prepared by the *E*-selective olefination of aldehyde **12** with the ylide **11**. Several alternative syntheses of **12** were evaluated, and the successful route involved conversion of **22** into the vinyl ether **23** by Petasis olefination, followed by Claisen rearrangement. Diels−Alder cycloaddition of **5** with **4** gave the adduct **6** in 77% yield, and Reformatsky cyclization under dilution conditions afforded **10** (67%). After conversion to enol silane **32**, oxidation with dimethyldioxirane produced **34**. Conversion to a key intermediate **38** using electrophilic selenenylation and selenoxide rearrangement, followed by enolate alkylation and deprotection, gave **43**. The X-ray crystal structure of **43** was determined to prove the stereochemistry.

The cytochalasins have attracted interest because of their broad spectrum of biological effects,[1] and several total syntheses of macrocyclic lactone or carbocycle members of this family have been completed.[2−5] In general, the synthetic approaches have relied on the combination of two chiral, enantiomerically pure subunits to solve the problem of remote stereocontrol. Cytochalasin D (**1**) is representative of the carbocyclic series in this regard (total synthesis: Thomas et al.),[2] and it has been among the most intensively studied of the cytochalasins from the biological, as well as the synthetic perspectives. Our own interest in this and related structures was based in part on the possibility that remote stereocenters might be introduced under the control of medium ring conformational preferences such that only one of the subunits would need to be chiral.[6] The work outlined below details this effort and describes a stereocontrolled synthesis of C(16),C(18)-bis-*epi*-cytochalasin D using this strategy.

Prior efforts have devised ways to convert cyclohexene intermediates of general structure **2** into the required allylic alcohol **3**. Disconnection of the chiral tetrahydroisoindolone subunit in **2** at C(4),C(5) and C(8),C(9) then leads to a diene component and a chiral dienophile for a well-precedented Diels−Alder synthesis.[2−5] Further disconnection at C(19),C(20) results in the pivotal structures **4** and **5** as shown in Scheme 1. Structure **5** incorporates all but one of the carbons that is required in the eventual target (missing the C(16) methyl group). The C(18) methyl is present early in the synthesis and is attached to an sp^2-hybridized carbon. In principle, this allows construction of the target using a single chiral component **4** in the Diels−Alder step if stereocontrol at C(16) and C(18) is possible later in the scheme by

Scheme 1



† Current address: Department of Chemistry, University of Michigan, Ann Arbor, MI 48109.

(1) Tannenbaum, S. W., Ed. *Cytochalasins: Biochemical and Cell Biological Aspects*; North-Holland, Amsterdam, 1978. Kapadi, A. H.; Dev, S. In *Recent Advances in Cytochalasans*; Pendse, G. S., Ed.; Chapman-Hall: New York, 1986; Chapter 2.

(2) Merifield, E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1990**, 464. Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Chem. Commun.* **1990**, 467. Merifield, E.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3269.

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(5) (a) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376. (b) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.

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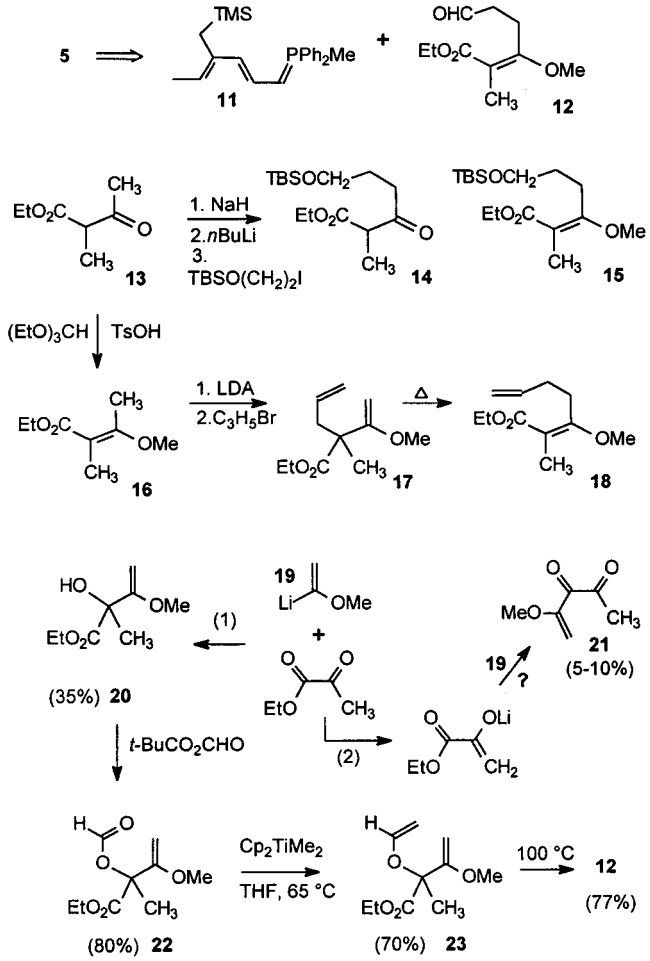
exploiting the conformational preferences of the 11-membered ring.[6,7] The Diels−Alder adduct **6** is preactivated for Reformatsky cyclization, as in a model study reported earlier where the simplified analogue **8** was assembled from **7**.[8] Conversion of **6** to **9** and **10** would afford a versatile ring environment having differentiated functionality in place to selectively activate the C(16) and C(18) positions. As already indicated, it was expected that these sites would also be differentiated sterically because of conformational preferences.

The enol ether functionality in **5** was chosen to simultaneously mask the C(17) ketone and to place the C(18) methyl group in an achiral environment. Logical precursors of **5** were therefore identified as **11** and **12**, based on *E*-selective olefination chemistry,[9] but a practical synthesis of the aldehyde **12** would prove to be one of the most difficult obstacles in this project. The initial approach to **12** assumed that **14** would be easy to convert to the O-methylated derivative **15** in view of the extensive literature on C- vs O-alkylation of stabilized enolates.[10] No problems were encountered in the preparation of **14** by dianion alkylation of **13**,[11,12] but enolate methylation of **14** under a variety of conditions afforded mixtures of C- and O-alkylation products. This route was not pursued further.[13]

In an alternative approach, **13** was treated with methyl orthoformate/TsOH to give an enol ether **16**. Conversion of **16** to the dienolate with LDA followed by allylation provided the C-allylation product **17** in excellent yield. Thermal Cope rearrangement produced the isomer **18**, but oxidative cleavage to the desired aldehyde **12** did not succeed despite much effort. In most attempts, the results were too complex to interpret, but the ozonolysis of **18** with a deficiency of ozone gave ethyl pyruvate and methyl 4-pentenoate as well as unreacted starting material. The products are derived from cleavage of the tetrasubstituted double bond. Evidently, the vinylogous carbonate environment does not provide sufficient stabilization to direct oxidants to the terminal double bond.

An alternative route was devised that would incorporate the terminal carbon of **12** at the correct aldehyde oxidation state using Claisen rearrangement. A suitable allyl vinyl ether might be obtained by vinylation of the tertiary alcohol **20**, a structure that corresponds to the adduct of ethyl pyruvate and α-methoxyvinyllithium (**19**), eq 1 (Scheme 2).[14] The desired addition of **19** did take place in THF at low temperature and the alcohol **20** was obtained in 35% yield. Deprotonation of ethyl pyruvate by **19** probably occurs as well, as evidenced by starting material recovery, and by the formation of an enone

Scheme 2



byproduct tentatively identified as **21** (5−10%). This product probably is formed by the addition of **19** to the enolate of ethyl pyruvate, as shown in eq 2 (Scheme 2). Purification of **20** was initially hampered by similarities in chromatographic properties and volatility compared to **21**. However, separation of **20** by chromatography was accomplished easily if the crude reaction mixture was first treated with $NaBH_4$/EtOH to destroy **21**.

The next step was to incorporate the vinyl ether moiety. Attempts to perform vinyl exchange in this system failed, so a two-step vinylation method was explored on the basis of O-formylation followed by olefination of the presumably more reactive formate carbonyl group. When the alcohol **20** was deprotonated with *n*-BuLi at 0 °C and treated with acetic formic anhydride, the formate ester **22** was obtained in 60% yield, but some of the acetate ester was also formed. The selectivity problem was solved and the yield improved by using the easily purified *tert*-butyl formic anhydride in a similar reaction.[15] Thus, **20** was reacted with *n*-BuLi followed by *tert*-butyl formic anhydride at 0 °C to afford **22** in 80% yield. The subsequent olefination of **22** was challenging, but good results were obtained with the Petasis reagent (Cp_2TiMe_2)[16] in refluxing THF to give the vinyl ether **23** in 70% yield. The Claisen rearrangement

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(8) (a) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705.

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(10) (a) Kurts, A. L.; Macias, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4759−67. (b) Kurts, A. L.; Dem'yanov, P. I.; Macias, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4769. (c) Kurts, A. L.; Genkina, N. K.; Macias, A.; Beletskaya, I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4777.

(11) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (b) Wolfe, J. F.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3249.

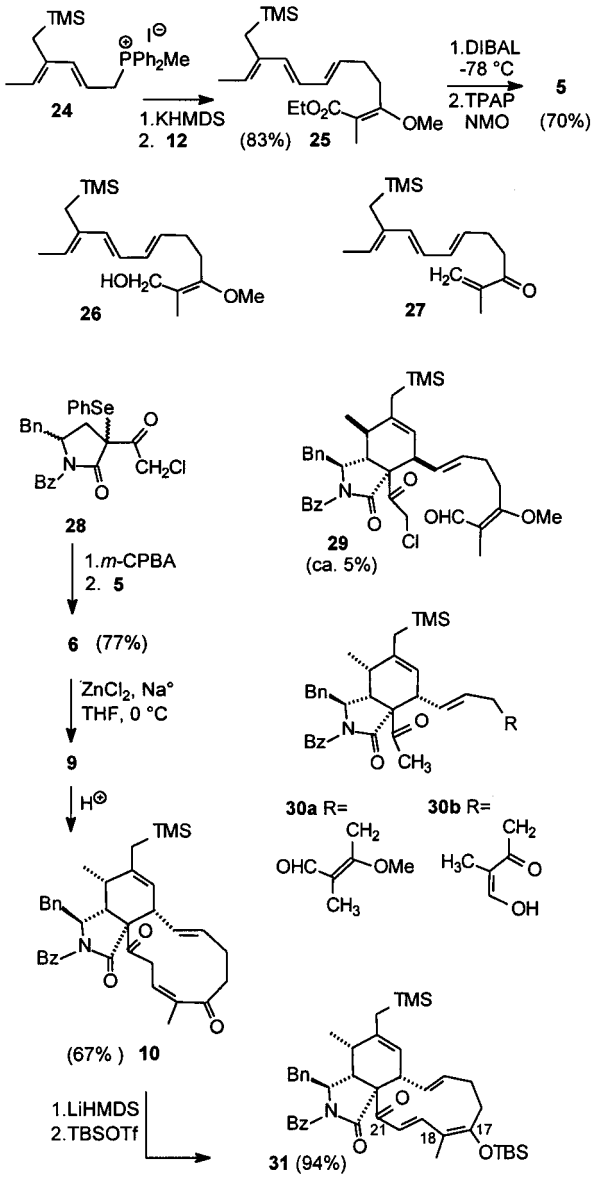
(12) The alkylating agent was made in two steps from 2-chloroethanol (80% yield) according to Moody's procedure: Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.

(13) An *O*-silylated analogue of **15** could be prepared, but it proved unsuitable for the intended synthesis because the corresponding derivative of **5** (replace methoxy by *tert*-butyldimethylsiloxy) undergoes facile silatropic rearrangement to an isomeric ketone enol silane under a variety of conditions, including exposure to silica gel.

(14) (a) Soderquist, J. A.; Hsu, G. J. H. *Organometallics* **1982**, *1*, 830. (b) Baldwin, J. E.; Hoefle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(15) Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *Recl.: J. R. Neth. Chem. Soc.* **1982**, *101*, 460.

Scheme 3



of **23** could be effected by refluxing in THF overnight or by heating several hours in refluxing toluene. The moderately stable aldehyde **12** was obtained in 77% yield, provided that **23** had been purified prior to the thermal rearrangement step to remove titanium contaminants.

With the elusive aldehyde **12** finally in hand, conversion to the conjugated triene **5** could be performed using a Wittig reaction and a reduction/oxidation sequence. The Wittig reaction with the *E*-selective ylide **11** was carried out as previously reported for a simpler aldehyde,[8a] and the ester **25** (Scheme 3) was obtained in 83% yield as an inseparable mixture of E/Z isomers (ca. 87:13) at the C(8),C(9) and C(10),C(11) double bonds. Ester **25** was sensitive to extended storage or to prolonged exposure to silica gel and was used promptly in the next step to prepare the triene aldehyde **5**. This involved the reduction of **25** with DIBAL/CH_2Cl_2/−78 °C and reoxidation of **26**, but the reaction required careful control due to the risk of conversion of **26** to an enone **27**. Treatment of **26** with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO)[17] and 4A molecular sieves afforded the aldehyde **5** in 70% yield. Like its precursors, **5** was also sensitive to chromatography and storage.

Reaction of an excess of **5** with the *N*-acylpyrrolinone dienophile **4** (generated in situ from selenide **28** and *m*-CPBA)[4] afforded the Diels−Alder adduct **6** in 77% yield. The stereochemical assignment for the main product **6** was guided by precedent from earlier work in the cytochalasin series,[4,5] and the detailed structure was eventually confirmed by X-ray crystallography after cyclization to the 11-membered ring. Regioisomeric Diels−Alder adducts were not detected, but an isomer **29** (resulting from the alternative exo transition state with respect to the dienophile) crystallized from more polar chromatography fractions, and the structure was solved by X-ray crystallography.[18] The strong regiochemical preference in the Diels−Alder process is a consequence of the directing effect of a trimethylsilylmethyl substituent in the triene environment according to prior work in our laboratory.[5]

As reported in a model study, intramolecular Reformatsky reaction can be used for the macrocyclization of chloromethyl ketones containing an aldehyde at C(19) (cytochalasin numbering).[8a] The Diels−Alder adduct **6** has a similar substitution pattern compared to the model, but the aldehyde is a vinylogous formate ester. This difference did not cause complications, and the cyclization could be carried out effectively by following a variation of the original procedure. Best results were obtained with activated Rieke zinc[19a] prepared by the reduction of $ZnCl_2$ in THF with sodium naphthalide at room temperature,[19b] and slow addition of a dilute solution of **6** over 5−6 h (300 mg scale) to the suspension of finely divided zinc metal at 0 °C. The initially formed cyclization product **9** proved to be unstable to acid and afforded the elimination product **10** (structure proof by X-ray crystallography: see Supporting Information). Traces of DCl in $CDCl_3$ were initially responsible for this elimination, but the more reliable procedure was to stir the crude reaction mixture with 10% H_2SO_4 and ether for several hours. The reaction also gave a second product tentatively identified as **30b** based on a signal at δ 15.19 ppm for the enolic proton, and the absence of methoxy and aldehyde signals. This substance is derived from protonation of the zinc enolate to give **30a** followed by enol ether hydrolysis. Isolation of **30a** was possible from an experiment where the H_2SO_4 step was omitted. Due to the heterogeneous nature of the Reformatsky cyclization, the yield of **10** was variable and somewhat dependent on the scale. Reactions performed with 200−300 mg of starting material **6** appeared to be in the optimum range and could be controlled to produce **10** in 60−67% yield.

It was now necessary to differentiate the two ketone carbonyl groups in the 11-membered ring. Treatment of **10** with lithium hexamethyldisilazide gave a dienolate that reacted with TBSOTf to form a single product **31**. The yield of this reaction was very sensitive to any excess of the silyl triflate, so the experiment was performed as a titration, with the silyl triflate added dropwise until the yellow color of the enolate had disappeared. The

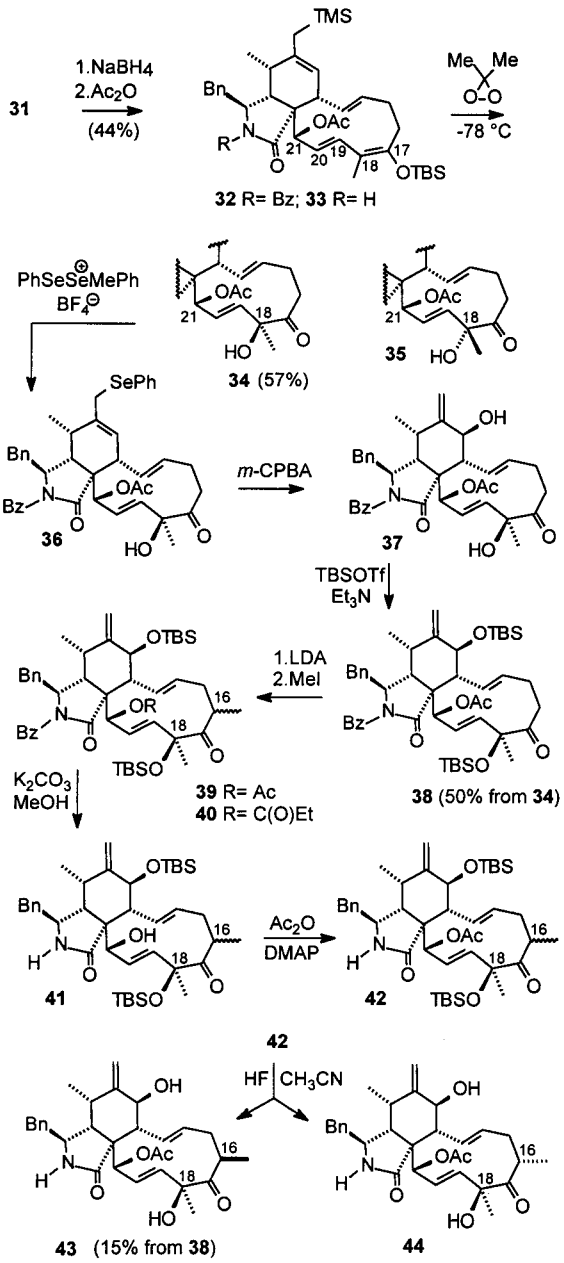
(16) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−4.

(17) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(18) The NMR signals of **29** slowly appeared if purified **6** was heated to 85 °C for several hours.

(19) (a) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (b) Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.

Scheme 4



presence of a new *E*-disubstituted double bond in **31** was deduced from the NMR spectrum, so the silylation must have occurred at the C(17) enolate oxygen. Direct evidence for the geometry of the resulting enol ether at C(17),C(18) was not obtained, but the isomeric enol silane (not shown) would have an *E*-double bond with respect to the 11-membered ring to make a total of three *E*-double bonds as well as a trans-ring fusion. Based on ring strain considerations, the product shown (**31**) is the more likely isomer.

With the C(21) and C(17) carbonyls differentiated, the next step was the reduction of the C(21) carbonyl group in ketone **31** (Scheme 4). The reduction was carried out with $NaBH_4$ in ethanol at 0 °C, and the expected changes in the NMR spectrum were observed. However, the NMR integrals for the olefinic region of the main product fraction could not be fully reconciled with the expected structure, and it became clear that the material was contaminated with an alcohol derived from a competing 1,4-reduction of the starting enone. Separation of the sideproduct was difficult on preparative scale, and could only be done after conversion to the acetate **32**. The low overall yield (44%) reflects the separation problem, but there are other complications, apparently due to competing cleavage of the *N*-benzoyl group according to NMR integration. This would result in the lactam **33**, but the C(19),C(20) dihydro derivative of **33** would presumably form as well, and the polar fractions could not be separated or fully characterized. The 1,4-reduction could be avoided using $NaBH_4/CeCl_3 \cdot 7H_2O$ in ethanol at room temperature, but these conditions gave extensive cleavage of the *N*-benzoyl group.

We had expected that the conversion to **32** would closely resemble a similar enone reduction in the cytochalasin D synthesis of Thomas et al. and that the stereochemistry of the major product could be safely assigned by analogy.[2] In view of the selectivity and yield problems in the case of **32**, and of several structural differences compared to the Thomas enone,[2] the possibility remained that the C(21) configuration may not be correct. However, it was clear that a single diastereomer had been isolated after chromatography, and that the NMR characteristics of **32** were consistent with those reported by Thomas et al. for a related allylic acetate. The stereochemistry shown for **32** was therefore assumed and was eventually confirmed.

The next step desired in the synthesis is the incorporation of the C(18) hydroxyl by oxidation of the silyl enol ether to the ketol **35** (Scheme 4). Osmylation is one attractive option for this conversion,[20] but several attempts failed to produce either diastereomer (**34** or **35**) cleanly. Oxidation with *m*-CPBA was more promising.[21] The procedure afforded diastereomer mixtures in preliminary experiments using dichloromethane or chloroform as the solvent and the product ratio was in the range of 1:3−4 when the reaction was performed in the presence of sodium carbonate. A similar experiment was then carried out using a solution of dimethyldioxirane [22,23] in acetone/chloroform. The optimum procedure was to treat the enol silane **32** in $CHCl_3$ at −78 °C with dimethyldioxirane/acetone solution and to allow the reaction mixture to warm to room temperature before quenching with dimethyl sulfide to destroy excess oxidant. The crude product was then treated with acetic acid in aqueous THF to ensure conversion of the intermediate epoxide to ketols. This provided a single isomeric ketol (>20:1 diastereomer ratio) in 57% yield, corresponding to the minor product of the *m*-CPBA oxidation.

According to the NMR spectrum, the dimethyldioxirane product could be either the desired structure **35**, or the C(18) diastereomer **34**. Some evidence bearing on the issue was available from NOE studies,[24] but the interpretation was uncertain because of the conformational mobility of the 11-membered ring, and because of the uncertainty regarding the configuration at C(21). A decision was therefore made to proceed with the single isomer obtained from the relatively clean dimethyldioxirane oxidation in the hope that a crystalline intermediate would be encountered in subsequent steps that could

(20) McCormick, J. P.; Tomasik, Witold; Johnson, Mark W. *Tetrahedron Lett.* **1981**, *22*, 607.
(21) Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 3783; Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
(22) Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* **1994**, *59*, 2358.
(23) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

be used to establish the configuration at C(21) as well as at C(18). In the event, suitable crystals were not encountered until the last step in the intended synthesis (structure **43**). According to the X-ray structure of **43**, the dimethyldioxirane product is **34**, the isomer that would correspond to a C(18)-*epi*-cytochalasin D. The X-ray evidence also confirmed that the correct C(21) configuration had been formed in the troublesome borohydride reduction, but neither the C(21) nor the C(18) assignments were clear when our limited material had to be committed to a sequence of seven additional synthetic steps.

The precedented conversion from **34** to **38** was performed with minimal purification of intermediates prior to the last step so that the challenging enolate alkylation of **38** could be evaluated. Excess LDA conditions did produce enolates from **38**, and treatment with iodomethane gave a complex mixture of products. New methyl doublets were seen in the NMR spectrum, but the C(21) acetate methyl signal was greatly diminished, suggesting that the enolization may have occurred at C(21) as well as at the C(16) position adjacent to ketone carbonyl. Support for competing C(21)-acetate enolization and methylation was found in the NMR spectrum of the crude product in the form of C-ethyl quartets near 3 ppm, consistent with the presence of C(21) propionate esters such as **40**. Acetate enolization could not be avoided at partial conversion, and other bases were not helpful. No single isomer corresponding to the desired structure **39** could be isolated. Therefore, the mixture of alkylation products was treated with methanolic potassium carbonate to cleave the *N*-benzoyl blocking group as well as to remove the undesired C(21)-propionate. This gave the lactam alcohol **41** as a mixture of isomers that could not be separated efficiently. The material was taken through the last two steps (re-acylation at C(21); silyl protecting group cleavage with HF/acetonitrile) that would lead to the cytochalasin D substitution pattern. Chromatographic purification then afforded a fraction consisting of a 5:1 ratio of two substances that closely resembled cytochalasin D (**1**) in TLC behavior, but neither was identical to the natural product. When the route was repeated with the remainder of material, the combined final product fractions were successfully separated (10−15% overall from **38**). The major isomer crystallized from acetone and was shown by X-ray crystallography to have the structure **43**, corresponding to C(16),C(18)-bis-*epi*-cytochalasin D. By inference, the minor isomer is probably the epimeric alkylation product **44**, but this substance was not obtained in sufficient quantity or purity for characterization.

Summary

The synthetic work described above has established an effective Diels−Alder/Reformatsky cyclization strategy for the synthesis of the key intermediate **10**. Uncertainties regarding the configuration of products obtained by the reduction of **31** and the dimethyldioxirane oxidation of **32** have been resolved by the X-ray structure of **43**. The stereochemistry of the borohydride reduction is the same as in the cytochalasin D synthesis of Thomas et al., as had been expected.[2] However, further work will be needed to reach the goal of control over stereochemistry in the 11-membered ring at C(16) and C(18). The C(18) configuration resulting from the dimethyldioxirane oxidation of **32** is shown to be epimeric compared to that of cytochalasin D. A plausible geometry for the preferred pathway can be proposed as shown in Figure 1, with bonding from above to set the new C−O bonds. This would produce a labile epoxide **45** that is converted into **34** by treatment with acid. If the C(18) stereocenter controls the final enolate alkylation at C(16), then it may be possible to achieve the desired configuration at C(16) in the enolate alkylation step using a precursor that has the correct C(18) stereochemistry. Experiments designed to test this proposition are under way and will be reported in a later publication.

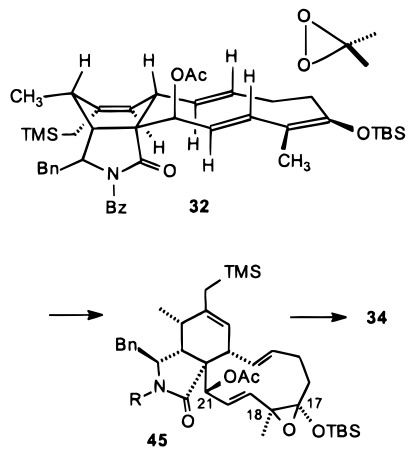


Figure 1. Dimethyldioxirane oxidation of **32**.

Experimental Section

General Methods. Dry solvents were obtained as follows: Et_2O and THF were distilled from sodium−benzophenone ketyl; CH_2Cl_2 was distilled from P_2O_5; CH_3CN was distilled from P_2O_5, redistilled from K_2CO_3, and stored over 4 Å molecular sieves; benzene was distilled from sodium−benzophenone ketyl and stored over 4 Å molecular sieves. Methyl triflate and *tert*-butyldimethylsilyl triflate were distilled and stored under N_2 and kept in the dark at −10 °C.

Ethyl 2-Methyl-6-*tert*-butyldimethylsiloxy-3-oxohexanoate 14. Under an inert atmosphere, a THF (90 mL) solution of ethyl acetopropionate (Aldrich, 15 mL, 100 mmol) was added dropwise to a suspension of NaH (Aldrich, 60%, 137 mmol) in THF (180 mL) at 0 °C. After being stirred for 30 min at 0 °C, the reaction was treated with *n*-BuLi (1.64 M in hexanes, 68 mL, 111 mmol) and stirred for an additional 30 min. The dianion was treated with a THF (40 mL) solution of 2-*tert*-butyldimethylsiloxyethyl iodide (37 g, 129 mmol). After the reaction was warmed to room temperature and stirred for 1 h, it was quenched with NH_4Cl and extracted with ether. The organic layer was treated with brine and $MgSO_4$. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 × 5 cm), 1:9 ether/hexane eluent (21.15 g, 70%): analytical TLC on silica gel, 1:4 ether/hexane, R_f = 0.39; HRMS for $C_{15}H_{30}O_4Si$ M + 1 303.1986, error = 0 ppm, base peak = 171 amu; IR ($CDCl_3$, cm^{-1}) 1745, 1720, 1270; 300 MHz NMR ($CDCl_3$, ppm) δ 4.15 (2H, q, J = 7.0 Hz), 3.57 (2H, t, J = 6.2 Hz), 3.49 (1H, q, J = 7.4 Hz), 2.7−2.5 (2H, m), 1.80−1.72 (2H, m), 1.3 (3H, d, J = 7.4 Hz), 1.23 (3H, t, J = 7.0 Hz), 0.85 (9H, s), 0.0 (6H, s).

(24) Irradiation of the C(18) methyl group in **34** gave a strong NOE enhancement of the C(20) vinylic hydrogen, while the corresponding experiment with a sample enriched in **35** resulted in the enhancement of the C(19) hydrogen signal. This evidence is consistent with an extended conformation of the 11-membered ring where the C(18) methyl is pseudoaxial in **34**, but pseudoequatorial in **35**, and could have been interpreted to make the correct assignment of C(18) configuration.

C/O Alkylation of 14. Under an inert atmosphere, a suspension of KH (Aldrich, 25% oil suspension washed twice with ether, 118 mg, 0.73 mmol) in HMPA (1.0 mL) at room temperature was stirred 45 min with the ketoester **14** (148 mg, 0.49 mmol) in HMPA (1.5 mL). The reaction mixture was treated with MeOTf (Aldrich, 0.1 mL, 0.88 mmol) and stirred for 30 min. The reaction was quenched with water (5 mL) and diluted with ether. The organic layer was washed with brine and treated with $MgSO_4$. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 × 1.5 cm), 1:9 ether/hexane eluent, to afford the *O*-alkylated isomer **15** (31 mg, 20%): analytical TLC on silica gel, 3:1:1 hexane/ether/dichloromethane, $R_f = 0.64$; molecular ion calcd for $C_{16}H_{32}O_4Si$ 316.20691, found *m/e* = 316.2080, error = 3 ppm, base peak = 259 amu; IR (CCl_4, cm^{-1}) 1735, 1697, 1280; 300 MHz NMR ($CDCl_3$, ppm) δ 4.13 (2H, q, J = 7.0 Hz), 3.71 (3H, s), 3.66 (2H, t, J = 5.4 Hz), 2.82 (2H, dd, J = 7.7, 10.9 Hz), 1.78 (3H, s), 1.78−1.69 (2H, m), 1.27 (3H, t, J = 7.0 Hz), 0.88 (9H, s), 0.04 (6H, s); followed very closely by the *C*-alkylated isomer, ethyl 2,2-dimethyl-6-*tert*-butyldimethylsiloxy-3-oxohexanoate (30 mg, 20%); analytical TLC on silica gel, 3:1:1 hexane/ether/dichloromethane, R_f = 0.62; HRMS $C_{16}H_{32}O_4Si$, M − 57, 259.1374, error = 3 ppm, base peak = 185 amu; IR (CCl_4, cm^{-1}) 1739, 1716, 1257; 300 MHz NMR ($CDCl_3$, ppm) δ 4.15 (2H, q, J = 7.0 Hz), 3.57 (2H, t, J = 6.2 Hz), 2.52 (2H, t, J = 7.0 Hz), 1.75 (2H, p, J = 7.0 Hz), 1.33 (6H, s), 1.23 (3H, t, J = 7.0 Hz), 0.86 (9H, s), 0.0 (6H, s).

Allylation of 16 to 17. Under an inert atmosphere, an LDA solution in THF (1.0 M, 7.2 mL, 7.2 mmol) at −78 °C was treated with **16** (1.1 g, 6.95 mmol) in THF (10 mL). After the solution was stirred for 45 min at −78 °C, the anion was treated with allyl bromide (0.8 mL, 9.25 mmol), allowed to warm to room temperature, and stirred for 3 h. The reaction was quenched with water and diluted with ether. The organic layer was washed with brine and treated with $MgSO_4$. After solvent removal (aspirator), distillation of the product gave a clear liquid: bp 60−63 °C, 1 mm, Vigreux column (1.31 g, 96%); analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.50; molecular ion calcd for $C_{11}H_{18}O_3$ 198.12555, found *m/e* = 198.1260, error = 2 ppm, base peak = 125 amu; IR (CCl_4, cm^{-1}) 1738, 1650, 1246; 300 MHz NMR ($CDCl_3$, ppm) δ 5.74−5.6 (1H, m), 5.1−5.05 (1H, m), 5.04−5.02 (1H, m), 4.14 (1H, q, J = 6.0 Hz), 4.15 (1H, q, J = 6.0 Hz), 4.06 (2H, s), 3.53 (3H, s), 2.60−2.45 (2H, m), 1.23 (3H, t, J = 6.0 Hz), 1.29 (3H, s).

Cope Rearrangement to 18. In a sealed tube under vacuum **17** (460 mg, 2.3 mmol) was heated at 210 °C for 34 h. The reaction was subjected to flash chromatography (SiO_2, 15 × 2 cm) 1:19 ether/hexane eluent (240 mg, 52%): analytical TLC on silica gel, 3:1:1 hexane/ether/dichloromethane, R_f = 0.6; molecular ion calcd for $C_{11}H_{18}O_3$ 198.12555, found *m/e* = 198.1251, error = 2 ppm, base peak = 129 amu; IR (CCl_4, cm^{-1}) 1735, 1720, 1620; 300 MHz NMR ($CDCl_3$, ppm) δ 5.87 (0.95H, ddt, J = 16.8, 10.0, 6.6 Hz), 5.75−5.58 (0.05H, m), 5.11−5.04 (1H, m), 5.00 (1H, dd, J = 10.0, 1.5 Hz), 4.16 (2H, q, J = 7.2 Hz), 3.7 (2.85H, s), 3.53 (0.15H, s), 2.86 (1.9H, br t, J = 7.8 Hz), 2.53 (0.1H, t, J = 6.6 Hz), 2.37−2.23 (2H, m), 1.81 (3H, s), 1.23 (0.15H, t, J = 6.9 Hz), 1.28 (2.85H, t, J = 7.2 Hz).

Ethyl 3-Methoxy-2-methyl-2-hydroxybut-3-enoate (20). The procedure of Soderquist[14a] was used as follows. Under a nitrogen atmosphere, a THF (90 mL) solution of methyl vinyl ether (Aldrich, 11 g, 190 mmol) at −78 °C was treated with *t*-BuLi (Aldrich, 1.7 M, 110 mL, 187 mmol). The solution was warmed to 0 °C over a 15 min period. The α-methoxyvinyllithium (**19**) was cooled to −78 °C and added dropwise over a 90 min period via a cold cannula to a THF (90 mL) solution of ethyl pyruvate (Aldrich, 18 mL, 164 mmol) at −78 °C. After being stirred for 20 min at −78 °C, the dark red solution was quenched with NH_4Cl (satd, 50 mL). The reaction mixture was poured into ether and water, and the organic layer was washed with water and brine. After the aqueous layers were washed with ether, the combined ether layers were treated with $MgSO_4$. After solvent removal, the crude oil was diluted with EtOH (95%, 50 mL) and treated at room temperature with $NaBH_4$ (Aldrich, 400 mg, 10 mmol) to destroy **21**. The reaction was quenched after 20 min with water (5 mL) and extracted with Et_2O, and the organic layer was dried with $MgSO_4$. After removal of solvent and ethyl pyruvate (aspirator), the residue was purified in two batches by flash chromatography on silica gel (20 × 5 cm), 1:4 EtOAc/hexane eluent, 20 mL fractions. The fractions were analyzed by TLC (1:4 EtOAc/hexane, I_2 detection). The nonpolar byproducts resulting from the decomposition of the cross-condensation products eluted first (R_f = 0.5, 1:4 EtOAc/hexane) and were discarded. Fractions containing the product (R_f = 0.29) eluted next and were combined. The fractions following the product (R_f = 0.2−0.1) contained minor products and were discarded. The solvent was removed (aspirator) from the combined fractions to give **20** (10 g, 35%) as a colorless oil: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.29; molecular ion calcd for $C_8H_{14}O_4$ 174.08914, found *m/e* = 174.0888, error = 2 ppm, base peak = 101 amu; IR ($CDCl_3$, cm^{-1}) 1733, 3547, 1249; 200 MHz NMR ($CDCl_3$, ppm) δ 4.39 (1H, d, J = 3.0 Hz) 4.24 (2H, q, J = 7.1 Hz) 4.12 (1H, d, J = 3.0 Hz) 3.57 (3H, s) 3.53 (1H, s) 1.56 (3H, s) 1.27 (3H, t, J = 7.1 Hz).

Formate Ester 22. Under a nitrogen atmosphere, a THF (90 mL) solution of the alcohol **20** (11.5 g, 66 mmol) at −78 °C was treated with *n*-BuLi (Aldrich, 1.51 M, 47 mL, 71 mmol) dropwise over a 25 min period. The resulting yellow solution was stirred at −78 °C for 30 min, warmed to 0 °C, and stirred for an additional 30 min. The *tert*-butyl formic anhydride[15] (11.2 mL, 86 mmol) was added dropwise over a 15 min period. The solution was stirred for 45 min at 0 °C, warmed to room temperature, and stirred for an additional 4.5 h. The reaction was quenched with water and diluted with ether. The organic layer was washed with water and brine. The aqueous layers were combined and washed with ether, and the ethereal layers were combined and dried ($MgSO_4$). After removal of solvent (N_2 stream), the residue was purified by flash chromatography on silica gel (5 × 16 cm), 6:1:1 hexane/ether/dichloromethane (300 mL), 5:1:1 hexane/ether/dichloromethane (250 mL), 4:1:1 hexane/ether/dichloromethane (300 mL) eluent, 20 mL fractions. The fractions were analyzed by TLC (1:4 EtOAc/hexane, I_2 detection). The initial fractions contained the product resulting from the addition of BuLi to the ester (R_f = 0.5, 1:4 EtOAc/hexane) followed by the *tert*-butyl ester product (R_f = 0.45) derived from pivaloyl transfer and were discarded. The fractions immediately following these contain the product (R_f = 0.4) and were combined. The fractions that eluted after the product contained the starting alcohol **20** (R_f = 0.29) and a minor product that was not characterized. The solvent was removed (aspirator) from the combined fractions to give **22** (10.7 g, 80%) as a colorless oil: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.4; molecular ion calcd for $C_9H_{14}O_5$ 202.08404, found *m/e* = 202.0850, error = 5 ppm, base peak = 101 amu; IR ($CDCl_3$, cm^{-1}) 1737, 1756, 1631; 300 MHz NMR ($CDCl_3$, ppm) δ 8.06 (1H, s), 4.52 (1H, d, J = 3.3 Hz), 4.25 (1H, q, J = 7.2 Hz), 4.24 (1H, q, J = 7.2 Hz), 4.21 (1H, d, J = 3.3 Hz), 3.60 (3H, s), 1.80 (3H, s), 1.27 (3H, t, J = 7.2 Hz).

Allyl Vinyl Ether 23. A THF solution of dimethyltitanocene[16] (0.5 M, 3 mL) was added to the neat formate **22** (205 mg, 1.01 mmol) and heated under a nitrogen atmosphere at 70 °C for 25 h. The dark red solution was filtered through Celite (5 × 1.5 cm) with hexane as eluent. The solution was concentrated and the filtration performed again. After removal of solvent (aspirator), the residue was purified by plug filtration chromatography on silica gel (10 × 1.5 cm), 8:92 EtOAc/hex eluent, 5 mL fractions. The fractions were analyzed by TLC (1:4 EtOAc/hexane, I_2 detection). The fractions corresponding to the top spot on the TLC plate contained titanium byproducts (R_f = 0.6, 1:4 EtOAc/hexane) that are yellow and were discarded. These fractions were followed closely by fractions containing the product **23** (R_f = 0.5), and those were combined. The fractions directly after the product contained the formate **22** (R_f = 0.4) and those were followed by fractions containing the impure alcohol **20** (R_f = 0.29). The solvent was removed (aspirator) from the combined fractions to provide **23** (140 mg, 70%): analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.5; molecular ion calcd for $C_{10}H_{16}O_4$ 200.10470, found *m/e* = 200.1041, error = 4 ppm, base peak = 129 amu; IR ($CDCl_3$, cm^{-1}) 1742, 1637, 1253; 200 MHz NMR ($CDCl_3$, ppm) δ 6.35 (1H, dd, J = 13.6, 6.4 Hz), 4.59 (1H, dd, J = 13.6, 1.3

Hz), 4.44 (1H, d, J = 3.3 Hz), 4.26 (1H, d, J = 3.3 Hz), 4.24 (2H, q, J = 7.2 Hz), 4.14 (1H, dd, J = 6.4, 1.3 Hz), 3.58 (3H, s), 1.62 (3H, s), 1.28 (3H, t, J = 7.2 Hz).

Claisen Rearrangement of 23 to 12. A toluene (40 mL) solution of the allyl vinyl ether **23** (3.9 g, 19.5 mmol) was refluxed for 2 h. After solvent removal (aspirator), the residue was purified by flash chromatography on silica gel (10 × 3 cm), 1:4 EtOAc/hexane eluent, 15 mL fractions. Due to the instability of the aldehyde toward silica gel the flow rate for the chromatography was increased with gentle air pressure to minimize the contact time. The fractions were analyzed by TLC (1:4 EtOAc/hexane, UV detection). The fractions containing the desired (UV active) material eluted first and were combined. The decomposition products corresponding to the baseline material were never removed from the column. The solvent was removed (aspirator) from the combined fractions to give **12** (3 g, 77%) as a colorless oil: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.2; molecular ion calcd for $C_{10}H_{16}O_4$ 200.10470, found m/e = 200.1048, error = 0 ppm, base peak = 125 amu; IR (CCl_4, cm^{-1}) 1699, 1728, 1622; 300 MHz NMR ($CDCl_3$, ppm) δ 9.82 (1H, s), 4.15 (2H, q, J = 7.0 Hz), 3.67 (3H, s), 3.06 (2H, t, J = 7.9 Hz), 2.69 (2H, t, J = 7.9 Hz), 1.81 (3H, s), 1.27 (3H, t, J = 7.0 Hz).

Triene Ester 25. Solutions and solvents used in the workup procedure were deoxygenated (N_2 bubbled in for 20 min) prior to use. All transfers were done under a nitrogen atmosphere via cannula into flame dried flask cooled under a stream of nitrogen for 30 min at room temperature.

A THF solution (20 mL) of *E*,*E*-4-(trimethylsilylmethyl)hexa-2,4-dien-1-ol (**5**)[5b] (6 g, 32.5 mmol) at −78 °C was treated with *n*-BuLi (Aldrich, 1.05 M, ca. 30 mL) under nitrogen until the endpoint was reached as indicated by 1,10-phenathroline. After being stirred for 5 min, the alkoxide was treated with ClP(O)(OEt)$_2$ (5.0 mL, 34.4 mmol), the cooling bath was removed, and the reaction was stirred at room temperature for 4 h. The dienyl phosphate solution was cooled to −78 °C and treated dropwise with a freshly made solution of lithiodiphenylphosphide prepared by addition of *n*-BuLi (Aldrich, 1.05 M, 28 mL) to a THF solution (20 mL) of freshly distilled diphenylphosphine (Aldrich, 5.0 mL, 28.7 mmol) at −78 °C (nitrogen atmosphere). The reaction was diluted with ether (200 mL) and quenched with Na_2CO_3 (100 mL). The ethereal layer was removed and washed with brine, dried over K_2CO_3, transferred to another flask and the solvent was removed using a N_2 stream. The viscous residue of the air-sensitive phosphine was dissolved in ether (75 mL) at room temperature and treated with methyl iodide (Aldrich, 12 mL, 192 mmol) for 10 h. The resulting suspension was filtered to provide the dienyl phosphonium salt **24** (10.9 g, 77%) as an off-white powder. The phosphonium salt was moderately stable, but over extended periods of time would slowly decompose and was used without purification.

Under a nitrogen atmosphere a suspension of the phosphonium salt **24**[8a] (8 g, 16.7 mmol) in THF (50 mL) at −78 °C was treated with KHMDS (Aldrich, 0.8 M, 21 mL, 16.8 mmol). The solution was warmed to 0 °C over a 30 min period and then cooled to −78 °C and a THF solution (50 mL) of the aldehyde **12** (3 g, 15 mmol) was added dropwise. After the addition was complete, the reaction was warmed to room temperature and stirred for 1 h. The reaction was quenched with Na_2CO_3 (saturated, 25 mL) and diluted with ether, and the organic layer was washed with brine and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (10 × 4 cm), 1:9 ether/hexane eluent, 20 mL fractions. Due to instability of the triene product toward silica gel the flow rate for the chromatography was increased using gentle air pressure to minimize the contact time with the silica. The fractions were analyzed by TLC (1:4 EtOAc/hexane, UV detection). The initial fractions (R_f = 0.7, 1;4 EtOAc/hexane) contained hexamethyldisilazane and were discarded. These fractions were followed by the product (R_f = 0.57). The solvent was removed (aspirator) from the combined fractions to give triene ester **25** (4.52 g, 83%) as an inseparable mixture of *E*/*Z* isomers, with an estimated ratio of 87:13 at both the C(8),C(9) and C(10),C(11) double bonds (NMR assay): analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.57; molecular ion calcd for $C_{20}H_{34}O_3Si$ 350.22769, found m/e = 350.2261, error = 4 ppm; IR ($CDCl_3$, cm^{-1}) 1690, 1617, 1285; 300 MHz NMR ($CDCl_3$, ppm) δ 6.55 (0.12H, d, J = 15.3 Hz), 6.28−5.97 (2.88H, m), 5.71 (1H, dt, J = 15.3, 6.9 Hz), 5.47 (0.88H, q, J = 6.9 Hz), 5.26 (0.12H, q, J = 6.9 Hz), 4.18 (2H, q, J = 6.9 Hz), 3.72 (3H, s), 2.91−2.85 (2H, m), 2.37−2.30 (2H, m), 1.83 (3H, s), 1.78−1.65 (5H, m), 1.30 (3H, t, J = 6.9), 0.03 (9H, s).

Conversion of Ester 25 to Aldehyde 5. Under a nitrogen atmosphere, DIBAL (Aldrich, 1.0 M, 25 mL) was slowly added via cannula over a 30 min period to a CH_2Cl_2 solution (50 mL) of the ester **25** (4.1 g, 11.3 mmol) at −78 °C. After the reaction was stirred for 30 min at −78 °C, Na_2SO_4·10 H_2O (40 g) was added portionwise to destroy the excess DIBAL, and the mixture was stirred for 2 h as it warmed to room temperature. The reaction mixture was filtered through Celite (5 × 4 cm) and the solvent removed (aspirator). The crude oil was diluted in dry CH_3CN (30 mL), cooled to 0 °C, and treated with 4-methylmorpholine *N*-oxide (Aldrich, 2 g, 17 mmol), 4 Å molecular sieves (6 g), and tetrapropylammonium perruthenate(VII) (Aldrich, 0.2 g, 0.56 mmol). The reaction was warmed to room temperature and stirred until consumption of starting material was complete by TLC (1:4, EtOAc/hexane), approximately 30 min. The reaction was filtered, the solvent removed (aspirator), and the residue was purified by flash chromatography on silica gel (15 × 4 cm), 1:4 EtOAc/hexane eluent, 15 mL fractions. Due to its instability toward silica gel the air flow rate for the chromatography was increased to minimize the contact time of the aldehyde with the silica. The fractions were analyzed by TLC (1:4 EtOAc/hexane, UV detection). The elimination product **27** (top spot) eluted first (R_f = 0.57, 1:4 EtOAc/hexane) and these fractions were discarded. The fractions containing the product (R_f = 0.19) followed and were combined. The solvent was removed (aspirator) from the combined fractions to give **5** (2.5 g, 70%) as an inseparable mixture of *E*/*Z* isomers, with a 87:13 ratio at both the C(8),C(9) and C(10),C(11) double bonds: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.19; molecular ion calcd for $C_{18}H_{30}O_2Si$ 306.20148, found m/e = 306.2002, error = 4 ppm; IR (CCl_4, cm^{-1}) 1641, 1615,1248; 300 MHz NMR ($CDCl_3$, ppm) δ 9.84 (1H, s), 6.53 (0.13H, d, J = 17.4 Hz), 6.15−5.91 (2.87H, m), 5.7−5.3 (1H, m), 5.45 (0.87H, q, J = 7.1 Hz), 5.24 (0.13H, q, J = 7.1 Hz), 3.82 (3H, s), 2.82−2.77 (2H, m), 2.37−2.29 (2H, m), 1.74−1.57 (8H, m), −0.02 (9H, s).

Diels−Alder Adduct 6. A CH_2Cl_2 solution (10 mL) of the selenide **28**[4] (335 mg, 0.65 mmol) at −78 °C was treated with a CH_2Cl_2 solution (5 mL) of *m*-CPBA (Aldrich 50−60%, 290 mg, 0.84 mmol). The reaction was stirred for 10 min at −78 °C, warmed to 0 °C by placing the reaction in an ice bath, stirred for 5 min, and then quenched with Me_2S (0.5 mL). The reaction should be worked up quickly due to the hydrolytic sensitivity of the α,β-unsaturated imide. The reaction was diluted with CH_2Cl_2, washed with Na_2CO_3, brine, and treated with $MgSO_4$. The organic layer was filtered directly into a flask containing the neat triene aldehyde **5** (300 mg, 0.94 mmol). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (10 × 2 cm), 1:4 EtOAc/hexane eluent, 5 mL fractions. The fractions were analyzed by TLC (7:3 ether/hexane, UV detection). The starting material **5** (top spot) eluted first (R_f = 0.6, 7:3 ether/hexane) followed by the desired Diels−Alder adduct **6** (R_f = 0.4), and then a zone (70 mg) containing relatively more of a minor isomer **29**, ca. 3:1 **29**:**6** as well as unknown impurities. All similar fractions were collected and the solvent was removed (aspirator) to afford the starting triene aldehyde (90 mg) and the product **6** as a white foam (300 mg, 77%): analytical TLC on silica gel, 7:3 ether/hexane, R_f = 0.40; HRMS for $C_{38}H_{46}ClNO_5Si$ M + 1 660.2912, error = 0 ppm, base peak = 660 amu; IR (CCl_4, cm^{-1}) 1726, 1681, 1658; 300 MHz NMR (C_6D_6, ppm) δ 9.79 (1H, s), 7.74−7.70 (2H, m), 7.15−7.08 (8H, m), 5.91 (1H, dd, J = 15.3, 9.6 Hz), 5.24 (1H, t, J = 2.7 Hz), 5.17 (1H, dt, J = 15.3, 6.6 Hz), 4.46−4.39 (1H, m), 4.43 (1H, d, J = 16.8 Hz), 3.27 (1H, dd, J = 13.5, 6.3 Hz), 3.2 (1H, d, J = 16.8 Hz), 3.14−3.08 (1H, m), 2.94 (3H, s), 2.94−2.68 (1H, m), 2.71 (1H, dd, J = 13.5, 2.7 Hz), 2.40−2.33 (1H, m), 2.15−2.06 (2H, m),

1.92 (3H, s), 1.75−1.65 (2H, m), 1.37 (2H, s), 0.78 (3H, d, J = 6.9 Hz), −0.06 (9H, s).

Fractions enriched in the minor diastereomer **29** from several experiments were combined and were stored in ether. This gave colorless crystals, mp 106 °C dec, suitable for X-ray crystallography, resulting in confirmation of the structure and of the double bond geometry assigned to the Diels−Alder diene component **5**: analytical TLC on silica gel, 7:3 ether/hexane, R_f = 0.3; HRMS for $C_{38}H_{46}ClNO_5Si$ M + 1 660.2904; IR (CCl_4, cm^{-1}) 1724, 1680, 1660; 300 MHz NMR (C_6D_6, ppm) δ 9.92 (1H, s), 7.8−7.7 (2H, m), 7.57 (2H, d, J = 7.7 Hz),7.30−7.15 (6H, m), 5.23−5.00 (3H, m), 4.67 (1H, br d, J = 12.8 Hz), 4.34 (2H, AB q, J = 16.5 Hz), 3.51 (1H, br t, J = 7.2 Hz), 3.36−3.22 (2H, m), 3.10 (3H, s), 2.67 (1H, dd, J = 13.4, 12.2 Hz), 2.36−2.24 (2H, m), 2.00 (3H, s), 1.87−1.71 (3H, m), 1.47 (1H, d, J = 14.6 Hz), 1.27 (1H, d, J = 14.6 Hz), 0.86 (3H, d, J = 8.0 Hz), −0.01 (9H, s).

Reformatsky Cyclization: Diketone 10. Under a nitrogen atmosphere, a THF solution (15 mL) of anhydrous $ZnCl_2$ (1.49 g, 10.93 mmol; fused under vacuum, 1 Torr) was added to a freshly prepared THF solution (45 mL) of sodium naphthalide (Na^0, 220 mg, 9.56 mmol; naphthalene, recrystallized from Et_2O, 1.4 g, 10.9 mmol) at 0 °C. The fine black suspension was stirred for 45 min and then a THF solution (45 mL) of the Diels−Alder adduct **6** (295 mg, 0.44 mmol) was added slowly over 6 h. After stirring for 5 min at 0 °C, the reaction was quenched with NH_4Cl (25 mL) and stirred for 20 min at room temperature. The reaction mixture was poured into ether, washed with brine, and dried with $MgSO_4$. After solvent removal (aspirator), the residue was diluted with ether (30 mL) and treated with 10% H_2SO_4 (5 mL) for two h at room temperature. The reaction was quenched with Na_2CO_3, diluted with ether, the organic layer was washed with brine, and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (10 × 3 cm), 4:1:1 hexane/Et_2O/dichloromethane eluent, 5 mL fractions. The initial fractions contained naphthalene (R_f = 0.9, 7:3 ether/hexane) and were discarded. The ensuing fractions contained the product **10** (R_f = 0.5) and were combined. These fractions were followed by the hydrolyzed reduction product **30b** (R_f = 0.3) and a minor unknown byproduct (R_f = 0.25). Solvent removal (aspirator) from the combined major fractions afforded **10** as a white powder (177 mg, 67%). Recrystallization from ether/hexane afforded X-ray quality crystals of **10**: mp 142.5−145 °C dec; analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.29, molecular ion calcd for $C_{37}H_{43}NO_4Si$, 593.29614, found m/e = 593.2991, error = 5 ppm, base peak = 105 amu; IR (CCl_4, cm^{-1}) 1734, 1696, 1677; 300 MHz NMR (C_6D_6, ppm) δ 7.78−7.75 (2H, m), 7.21−7.08 (8H, m), 6.12 (1H, t, J = 7.0 Hz), 5.71 (1H, dd, J = 15.6, 10.0 Hz), 5.25 (1H, s), 4.99 (1H, ddd, J = 15.6, 9.9, 5.4 Hz), 4.47−4.43 (1H, m), 3.35 (1H, dd, J = 13.8, 6.3 Hz), 3.16−3.11 (1H, m), 3.04 (1H, t, J = 10.0 Hz), 2.94 (1H, dd, J = 5.1, 3.3 Hz), 2.77−2.68 (2H, m), 2.56−2.47 (2H, m), 2.34 (1H, ddd, J = 9.3, 6.3, 3.0 Hz), 2.05−1.85 (2H, m), 1.93 (3H, s), 1.37 (2H, s), 0.88 (3H, d, J = 7.2 Hz), −0.05 (9H, s). The more polar fractions afforded 50 mg of material tentatively assigned as **30b** based on signals for an enol proton (δ15.19 ppm), the absence of methoxy and aldehyde signals, and a signal for the C(18) methyl group at δ 1.25 ppm. In a separate experiment where the sulfuric acid treatment was omitted, a third product **30a** was isolated from the more polar chromatography fractions in addition to **30b**. Characterization data for **30a**: analytical TLC on silica gel, 1.67:1:1 hexane/ether/dichloromethane, R_f = 0.27; HRMS for $C_{38}H_{47}NO_5Si$; M + 1, 626.3297, error = 1 ppm, base peak = 320 amu; IR (CCl_4, cm^{-1}) 1735, 1704, 1677; 300 MHz NMR (C_6D_6, ppm) δ 9.81 (1H, s), 7.83−7.79 (2H, m), 7.16−7.07 (8H, m), 6.10 (1H, dd, J = 15.3, 9.3 Hz), 5.27 (1H, br s), 5.22 (1H, dt, J = 15.3, 6.6 Hz), 4.51−4.46 (1H, m), 3.22−3.14 (1H, m), 3.13−3.05 (1H, m), 2.93 (3H, s), 2.95−2.75 (2H, m), 2.37−2.25 (1H, m), 2.21−2.12 (2H, m), 1.93 (3H, s), 1.83−1.73 (2H, m), 1.84 (3H, s), 1.36 (2H, br s), 0.75 (3H, d, J = 7.2 Hz), −0.05 (9H, s).

Conversion of 10 into the Silyl Dienyl Ether 31. A THF solution (20 mL) of diketone **10** (55 mg, 0.093 mmol) at −78 °C was treated with lithium hexamethyldisilazane (0.1 M, 1 mL, 0.1 mmol) and stirred for 30 min at −78 °C. The resulting dienolate was treated with *tert*-butyldimethyltrifluorosulfonate (Aldrich, 0.04 mL, 0.17 mmol) and stirred for 15 min before quenching with $NaHCO_3$ (saturated, 20 mL). The reaction was warmed to room temperature and poured into ether, washed with brine, and dried with K_2CO_3. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (5 × 1.5 cm), 3:7 ether/hexane eluent, 2 mL fractions. The initial fractions contained silicon byproducts and hexmethyldisilazane (R_f = 0.7, 3:1:1 hexane/ether/dichloromethane) and were discarded. These fractions were followed closely by the major spot (R_f = 0.64), the silyl enol ether **31** (62 mg, 94%) as a yellow foam: analytical TLC on silica gel, 3:1:1 hexane/ether/dichloromethane, R_f = 0.64; molecular ion calcd for $C_{43}H_{57}NO_4Si_2$ 707.38263, found m/e = 707.3847, error = 3 ppm, base peak = 105 amu; IR (CCl_4, cm^{-1}) 1638, 1728, 1682; 250 MHz (340 K) NMR (C_6D_6, ppm) δ 8.1 (1H, d, J = 16.5 Hz), 7.71 (2H, dd, J = 6.3, 1.7 Hz), 7.62 (2H, d, J = 7.0 Hz), 7.25−7.00 (6H, m), 6.42 (1H, d, J = 16.5 Hz), 5.99 (1H, dd, J = 15.4, 10.3 Hz), 5.17−5.02 (2H, m), 4.65−4.60 (1H, m), 3.63 (1H, dd, J = 5.4, 0.7 Hz), 3.25 (1H, dd, J = 12.4, 3.5 Hz), 3.09 (1H, dd, J = 12.7, 10.5 Hz), 2.90−2.87 (1H, m), 2.57−2.47 (1H, m), 2.17−1.97 (4H, m), 1.81 (3H, s), 1.42−1.25 (2H, m), 0.97−0.86 (3H, m), 0.93 (9H, s), 0.05 (6H, s), −0.13 (9H, s).

Reduction of 31: Conversion to the Acetate 32. An ethanolic solution (4 mL) of the dienone silyl enol ether **31** (39 mg, 0.055 mmol) at 0 °C was treated with $NaBH_4$ (Aldrich, 82 mg, 2.15 mmol) and stirred for 10 min. The reaction was quenched with water (1 mL), extracted with ether, and dried ($MgSO_4$), and the solvents were removed (aspirator). A CH_2Cl_2 solution (2 mL) of the crude alcohol was added to a mixture of triethylamine (0.4 mL), acetic anhydride (0.4 mL), and (dimethylamino)pyridine (Aldrich, 5 mg). After 1 h, the solution was quenched with $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$). After evaporation (aspirator), the residue was purified by flash chromatography on silica gel (10 × 1.5 cm), 6:1:1 hexane/ether/dichloromethane eluent, 2 mL fractions. The less polar fractions (R_f = 0.6, 3:1:1 hexane/ether/dichloromethane) were assayed by NMR and were found deficient in the integral for alkenyl protons (6.87 and 6.15 ppm), as expected for the C(19), C(20) dihydro derivative of **32** (11 mg). Characteristic signals for the less polar fraction were seen for H(13) (δ 6.29 ppm), C(21) acetate (δ 1.93 ppm), and C(5) methyl (δ 0.86 ppm). Careful separation of increasingly polar fractions afforded material (18 mg, 44%) having the correct integral for the C(19), C(20) hydrogens of **32** as a foam after solvent removal: analytical TLC on silica gel, 3:1:1 hexane/ether/dichloromethane, R_f = 0.54; molecular ion calcd for $C_{45}H_{61}NO_5Si_2$ 751.40881, found m/e = 751.4088, error = 0 ppm, base peak = 105 amu; IR (neat, cm^{-1}) 1747, 1679; 1282; 250 MHz (340 K) NMR (C_6D_6, ppm) δ 7.74−7.70 (2H, m), 7.52−7.46 (2H, m), 7.27−7.07 (6H, m), 6.87 (1H, d, J = 15.5 Hz), 6.36 (1H, dd, J = 15.4, 9.6 Hz), 6.15 (1H, d, J = 7.0 Hz), 5.45−5.30 (3H, m), 4.80−4.60 (1H, m), 3.50−3.44 (1H, m), 3.05−2.96 (1H, m), 2.78−2.69 (1H, m), 2.39−2.04 (4H, m), 1.88 (3H, s), 1.83 (3H, s), 1.40 (2H, br s), 1.35−1.20 (1H, m), 0.94 (9H, s), 0.95−0.85 (1H, m), 0.53 (3H, d, J = 7.3 Hz), 0.07 (3H, s), 0.06 (3H, s), −0.1 (9H, s).

Dimethyldioxirane Oxidation of 32: Isolation of Ketol 34. A $CHCl_3$ solution (Fisher, 12 mL) of silyl enol ether **32** (73 mg, 0.097 mmol) at −78 °C was treated with dimethyldioxirane (0.05 M, 3.0 mL, 0.15 mmol), prepared according to a known procedure,[23] and stirred for 15 min. The reaction was warmed to room temperature over a 20 min period and quenched with dimethyl sulfide (Aldrich, 0.5 mL). After removal of solvent (aspirator), the crude product was diluted with THF/HOAc/water (8:8:1, 8 mL) and stirred at room temperature for 5 h. The mixture was quenched with $NaHCO_3$ (10 mL) and extracted with ether. The ethereal layer was washed with water, brine, and treated with $MgSO_4$. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (10 × 1.5 cm), 4:1:1 ether/hexane eluent, 2 mL fractions. The initial fractions (R_f = 0.7, 2:1:1 hexane/ether/dichloromethane) contained silicon byproducts and were discarded. These fractions were followed much later by the major fraction followed closely by two minor unidentified contami-

nants (R_f = 0.2−0.3; 6.5 mg total). Solvent removal (aspirator) from the major fraction provided the α-ketol **34** (>20:1 diastereomer ratio, NMR assay; 36 mg, 57%) as a white powder: analytical TLC on silica gel, 2:1:1 ether/hexane/dichloromethane, R_f = 0.4; molecular ion calcd for $C_{39}H_{47}NO_6$-Si 653.31726, found *m/e* = 653.3172, error = 9 ppm, base peak = 105 amu; IR (CCl_4, cm^{-1}) 3462, 1736, 1706; 300 MHz NMR (C_6D_6, ppm) δ 7.70−7.60 (2H, m), 7.50−7.40 (2H, m), 7.30−7.05 (6H, m), 6.39 (1H, dd, *J* = 15.6, 2.1 Hz), 6.06 (1H, dd, *J* = 2.4, 2.1 Hz), 6.04 (1H, dd, *J* = 15.6, 10.2 Hz), 5.23−5.19 (1H, m, *J* = 1.0 Hz), 5.16 (1H, dd, *J* = 15.6, 2.4 Hz), 5.09 (1H, ddd, *J* = 15.6, 10.2, 4.8 Hz), 4.47−4.40 (1H, m), 4.06 (1H, br s), 3.34−3.25 (2H, m), 2.84 (1H, dd, *J* = 12.9, 9.6 Hz), 2.46 (1H, dd, *J* = 5.1, 2.7 Hz), 2.41−2.25 (2H, m), 2.18−1.80 (3H, m), 1.82 (3H, s), 1.30 (2H, br s), 1.25 (3H, s), 0.52 (3H, d, *J* = 7.5 Hz), −0.11 (9H, s).

Conversion of Ketol 34 to Bis-TBS Ether 38. Under an inert atmosphere, a CH_2Cl_2 solution (3 mL) of allylsilane **34** (30 mg, 0.046 mmol, 30:1 mixture of diastereomers by HPLC) at −78 °C was treated with $PhSeSe^+MePh\ BF_4^-$ (0.2 M, 0.28 mL solution in CH_2Cl_2, 0.056 mmol), prepared as previously described.[4b] The reaction was stirred for 10 min at −78 °C, warmed to 0 °C, stirred for 5 min, and then quenched with $NaHCO_3$ (saturated, 5 mL). After extraction with CH_2Cl_2 (3 × 20 mL) and solvent removal (aspirator), the residue was filtered through a column of silica gel (10 × 0.5 cm) with hexane eluent to remove a nonpolar fraction containing PhSeMe and then ether to recover the crude selenide **36** (R_f = 0.6). A CH_2Cl_2 solution (5 mL) of the selenide at −78 °C was treated with a, *m*-CPBA (Aldrich, 55%, 25 mg, 0.08 mmol) dissolved in CH_2Cl_2 (2 mL). After being stirred for 30 min, dimethyl sulfide (0.5 mL) was added, and the mixture was warmed to room temperature, quenched with Na_2CO_3 (saturated, 5 mL), extracted with CH_2Cl_2, and dried ($MgSO_4$). After solvent removal (aspirator), the residue was filtered through a column of silica gel (10 × 0.5 cm), hexane eluent, to remove nonpolar selenium byproducts and then EtOAc to recover the crude diol **37**. A CH_2Cl_2 solution (3 mL) of the diol at room temperature was treated successively with 4 Å molecular sieves (0.5 g), Et_3N (0.5 mL), and TBSOTf (0.4 mL) and stirred for 5 h. The reaction was quenched with $NaHCO_3$ (saturated, 5 mL), extracted with CH_2Cl_2 (3 × 25 mL), and dried ($MgSO_4$). After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 × 1 cm), 3:1:1 hexane/ether eluent, 2 mL fractions. The initial fractions contained silicon byproducts (R_f = 0.7, 3:1:1 hexane/ether/dichloromethane) and were discarded. These fractions were followed closely by the major fraction. Solvent removal (aspirator) afforded the bis-silyl ether **38** (19 mg, 50%, R_f = 0.61) as an oil: analytical TLC on silica gel, 3:1:1 ether/hexane/dichloromethane, R_f = 0.61; molecular ion calcd for $C_{48}H_{67}$-NO_7Si_2 825.44556, found *m/e* = 825.4456, error = 7 ppm, base peak = 105 amu; IR (CCl_4, cm^{-1}) 1748, 1730, 1712; 300 MHz NMR (C_6D_6, ppm) δ 7.68−7.63 (2H, m), 7.39 (2H, br d, *J* = 6.9 Hz), 7.23−6.99 (6H, m), 6.35 (1H, dd, *J* = 15.3, 1.8 Hz), 6.14 (1H, t, *J* = 1.8 Hz), 6.02 (1H, dd, *J* = 15.3, 9.6 Hz), 5.50 (1H, dt, *J* = 15.9, 6.6 Hz), 4.97 (1H, br s), 4.93 (1H, br s), 4.90 (1H, dd, *J* = 15.3, 1.8 Hz), 4.60−4.53 (1H, m), 3.94 (1H, d, *J* = 8.1 Hz), 3.35−3.21 (1H, m), 3.17 (1H, dd, *J* = 12.3, 2.5 Hz), 3.00 (1H, dd, *J* = 9.3, 8.4 Hz), 2.80 (1H, dd, *J* = 12.3, 11.1 Hz), 2.72−2.63 (1H, p, *J* = 6.0 Hz), 2.49−2.36 (1H, m), 2.20−2.10 (1H, m), 1.95 (1H, dddd, *J* = 15.9, 8.1, 5.4, 2.7 Hz).

Alkylation of 38: Isolation of 16,18-Bis-*epi*-cytochalasin D (43). Under a nitrogen atmosphere, a THF solution (2 mL) of **38** (11 mg, 0.013 mmol) at −78 °C was treated with freshly prepared LDA (0.11 M in THF/hexane, 0.58 mL, 0.06 mmol) for 1 h. The enolate was treated with methyl iodide (filtered over alumina and stored over 4 Å molecular sieves for 1 h prior to use, 1 mL, 16 mmol) for 10 min. The reaction was quenched with water and extracted with ether. After solvent removal (aspirator), the residue was purified by flash chromatography on silica gel (8 × 0.6 cm) hexane/ether/dichloromethane 4:1:1 eluent, 1 mL fractions and fractions were analyzed by TLC (silica gel, 3:1:1 hexane/dichloromethane/THF, UV detection). The first fraction (5.6 mg, R_f = 0.65, 3:1:1 hexane/ether/dichloromethane) had NMR characteristics as expected for the product **40** (no acetate methyl signal; poorly resolved C-ethyl signals for the propionyl group). The next fraction (1.4 mg, R_f = 0.65−0.60) contained **40** and a minor sideproduct, and the rest of the material from the column (R_f < 0.55) was combined in fraction three (3.9 mg). The combined material from the first two fractions (7 mg) was dissolved in MeOH/THF (5:1, 3 mL) and treated with K_2CO_3 (100 mg) for 7 h, the mixture diluted with CH_2Cl_2 (20 mL), washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). After solvent removal (aspirator), the residue was purified by flash chromatography on silica gel (6 × 0.6 cm) with hexane/ether/dichloromethane 1:1:1 eluent, 1 mL fractions. The major spot contained **41** (4.3 mg, R_f = 0.6, 1:1:1 hexane/ether/dichloromethane) after solvent removal (aspirator). The material was used directly in the next reaction. Diagnostic NMR signals: (300 MHz, $CDCl_3$, ppm) δ 6.55 (H_{19}, dd), 5.66 (H_{13}, dd), 5.42 (H_{12a}, br s), 5.1 (H_{21}, br s), 5.1−4.95 (H_{14}, m), 4.9 (H_{12b}, br s), 4.85 (H_{20}, dd), 1.13 and 1.11 (C_5 and C_{16} methyls; overlapping doublets).

The fractions containing alcohol **41** (4.3 mg, 0.006 mmol) in CH_2Cl_2 (2 mL) were treated with triethylamine (0.5 mL, 3.6 mmol), acetic anhydride (0.4 mL, 4.2 mmol), and a catalytic amount of (dimethylamino)pyridine for 30 min (rt, nitrogen atmosphere). The reaction was quenched with water, extracted with CH_2Cl_2, dried ($MgSO_4$), and solvents evaporated (aspirator) to afford the crude acetate **42**. The products were used directly in the next step without purification.

An acetonitrile solution (2 mL) of the acetates **42** was treated with 48% HF (0.1 mL) at 0 °C for 15 min and then warmed to room temperature and stirred for 1 h. The reaction was quenched with water and diluted with ethyl acetate, and the organic layer was washed with $NaHCO_3$. After drying ($MgSO_4$) and solvent removal (aspirator), the residue was purified by flash chromatography on silica gel (5 × 0.6 cm). The column was eluted with hexane/ether/dichloromethane 1:1:1 to remove a high R_f product and then the column was flushed with ethyl acetate to remove the polar products. The polar residue was dissolved in a minimal amount of acetone and hexane was added until the solution became cloudy. This solution was placed in the refrigerator (−10 °C) overnight. The precipitate (ca. 2 mg) consisted of a 5:1 ratio of **43** to **44** by ^1H NMR assay. Major product **43**: analytical TLC on silica gel, 5:3 acetone/hexane, R_f = 0.53; molecular ion calcd for $C_{30}H_{37}$-NO_6 507.26202, found *m/e* = 507.2657, error = 7 ppm; 300 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.24 (3H, m), 7.15−7.12 (2H, m), 6.51 (1H, dd, *J* = 15.9, 2.3 Hz), 5.76 (1H, dd, *J* = 15.1, 8.9 Hz), 5.56 (1H, br s), 5.45 (1H, br s), 5.41−5.32 (1H, m), 5.16 (1H, br s), 4.82 (1H, dd, *J* = 15.9, 2.3 Hz), 3.83 (1H, br d, *J* = 11.2 Hz), 3.53−3.42 (1H, m), 3.34−3.28 (1H, m), 2.94 (1H, dd, *J* = 14.0, 4.2 Hz), 2.85−2.74 (2H, m), 2.57 (1H, dd, *J* = 14.4, 10.1 Hz), 2.20 (3H, s), 2.22−1.92 (3H, m), 1.47 (3H, s), 1.19 (3H, d, *J* = 6.4 Hz), 1.11 (3H, d, *J* = 6.6 Hz), 1.10 (3H, d, 6.6 Hz). The products from this reaction were combined with the corresponding fractions from a second experiment and **43** (R_f = 0.53, 5:1 EtOAc/hexane) and **44** (R_f = 0.30) were separated by flash chromatography (silica gel, 5 × 0.5 cm) 3:1 EtOAc/hexane eluent, 1 mL fractions. The latter isomer was not obtained free of contaminants, but several of the NMR shifts were resolved, including δ 6.19 (H_{19}) 5.63 (H_{21}), 5.07 (H_{20}), 1.19 (C_{16} methyl) and 0.97 (C_5 methyl). Slow evaporation of acetone from **43** provided X-ray quality crystals. The crystal structure confirms the stereochemical assignment of the C(16) center incorporated in this sequence along with the C(21), C(18), C(7) centers established in earlier experiments.

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Supporting Information Available: NMR spectra of isolated intermediates; X-ray data tables for **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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