Articles

Total Synthesis of (+)-Latrunculin A, an Ichthyotoxic Metabolite of the Sponge *Latrunculia magnifica*, and Its C-15 Epimer

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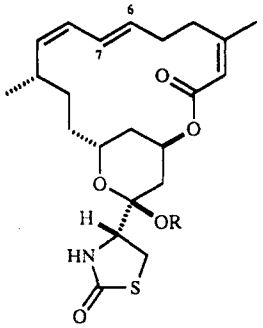
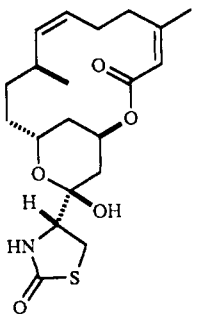
Received May 8, 1992

Latrunculin A (1), an icthyotoxic metabolite of the sponge *Latrunculia magnifica* with potent inhibitory action on microfilament-mediated processes involved in cell division, was synthesized via a convergent approach. Construction of a major segment of the latrunculin backbone was accomplished by means of a three-component coupling of aldehyde **24**, β-keto ester **27**, and phosphonium salt **26**, which established the conjugated *E,Z*-diene moiety of **31**. The thiazolidinone subunit of **1** was elaborated in the form of **39** from L-cysteine and was linked to **35** without nitrogen protection. Final lactonization of **47** was carried out using the Mitsunobu protocol. A parallel sequence employing the epimeric seco acid **48** produced 15-epilatrunculin A.

The ability of marine animals, notably nudibranchs and sponges, to emit defensive secretions is widely known.[1] However, the discovery that a sponge, *Latrunculia magnifica* (Keller), exudes a fluid with very powerful icthyotoxic properties[2] proved to be an event of special significance to the natural products community as well as marine biologists. *L. magnifica* colonizes the Gulf of Aquaba and parts of the Red Sea and is conspicuously immune to predation in its natural habitat, apparently relying on its reddish-colored exudate to ensure its continued survival. Subsequent investigation of the chemical constituents present in *L. magnifica* by a group at Tel Aviv University led to the characterization of two substances, latrunculin A (**1**) and B (**2**),[3] both of which manifest the toxic action associated with the sponge. Latrunculins A and B induce disorientation, hemorrhaging, and eventually death of fish exposed to these substances in a confined environment.[4] Latrunculin A (**1**) has more recently been found in the Pacific nudibranch *Chromodoris elisabethina*[5] and in a species *Spongia mycofijiensis*[6] present in Fijian waters. The isolation of **1** from contrasting marine environments presents an intriguing biological paradox.



1, R = H
3, R = Me



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Chemical degradation of latrunculin A in conjunction with spectroscopic studies and an X-ray crystallographic analysis of ketal **3** resulted in its designation (including absolute configuration) as the macrolide structure **1**.[7] The presence of macrolides in marine organisms was previously unknown and is still exceptional. However, following the discovery of **1** and **2**, several additional members of the latrunculin family were isolated,[8] including 6,7-epoxylatrunculin A.[9] In every case the latrunculins have been found to contain a thiazolidinone moiety derived from L-cysteine.

Studies of the biological action of **1** at the cellular level have revealed that it exerts a profound effect on the morphology of nonmuscle cells. This occurs by disruption of the microfilament organization without affecting the microtubular system.[10] Latrunculin A has been shown to be an especially potent inhibitor of microfilament-mediated processes involved in fertilization and in cell division.[11] As with certain cytochalasins, this activity appears to be associated with formation of a 1:1 complex with the cytoskeletal protein actin,[12] thereby inhibiting actin polymerization. The unusual constitution and biological profile of **1** and its congeners have drawn attention to their chemical properties[13] and, recently, to their synthesis.[14] We now describe a complete account of our studies leading to the total synthesis of (+)-latrunculin A (**1**) and (+)-15-epilatrunculin A (**50**).[15]

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551.
(2) Neeman, I.; Fishelson, L.; Kashman, Y. *Marine Biol.* **1975**, *30*, 293.
(3) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3929.
(4) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493.
(5) Okuda, R. K.; Scheuer, P. J. *Experientia* **1985**, *41*, 1355.
(6) Kakou, Y.; Crews, P.; Bakus, G. J. *J. Nat. Prod.* **1987**, *50*, 482.
(7) Groweiss, A.; Shmueli, U.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3512.
(8) Kashman, Y.; Groweiss, A.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron* **1985**, *41*, 1905.
(9) Blasberger, D.; Carmely, S.; Cojocaru, M.; Spector, I.; Shochet, N. R.; Kashman, Y. *Justus Liebigs Ann. Chem.* **1989**, 1171.
(10) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell Mobil. Cytoskl.* **1989**, *13*, 127.
(11) Schatten, G.; Schatten, H.; Spector, I.; Cline, C.; Paweletz, N.; Simerly, C.; Petzelt, C. *Exptl. Cell Res.* **1986**, *166*, 191.
(12) Cone, M.; Brenner, S. L.; Spector, I.; Koru, E. D. *FEBS Lett.* **1987**, *213*, 316.
(13) Blasberger, D.; Green, D.; Carmely, S.; Spector, I.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 459.
(14) (a) Kashman, Y.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron Lett.* **1986**, *27*, 1367. (b) Zibuck, R.; Liverton, N. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2451. (c) Smith, A. B., III; Zibuck, R.; Liverton, N. J. In *New Synthetic Methodology and Functionally Interesting Compounds*; Yoshida, Z., Ed.; Kodansha: Tokyo, 1986; Series in Organic Chemistry 25, pp 183-202. (d) Smith, A. B., III; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Org. Chem.* **1990**, *55*, 3977. (e) Smith, A. B., III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995.

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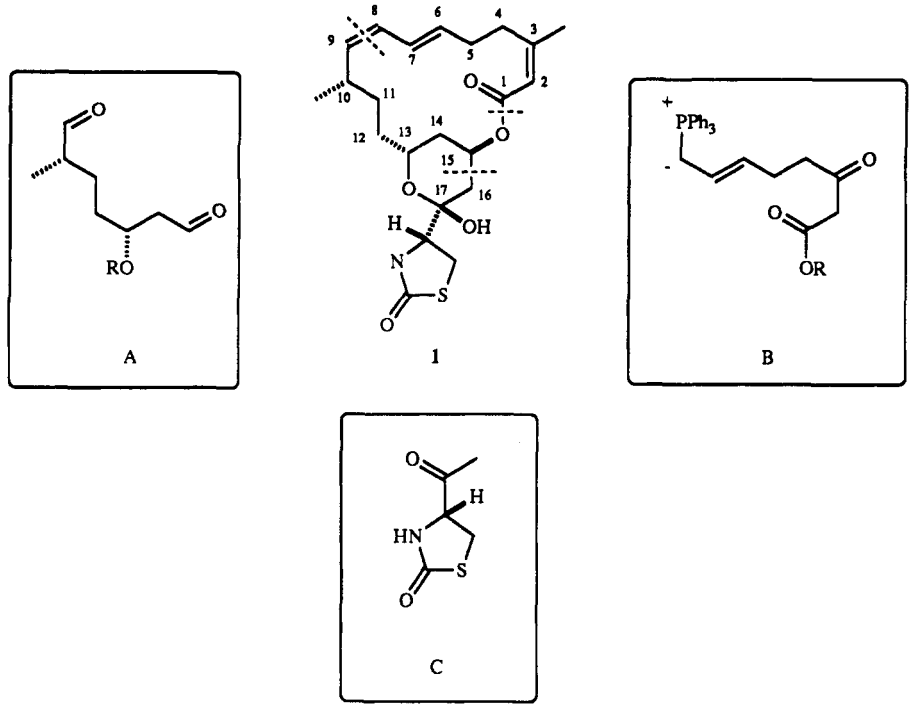
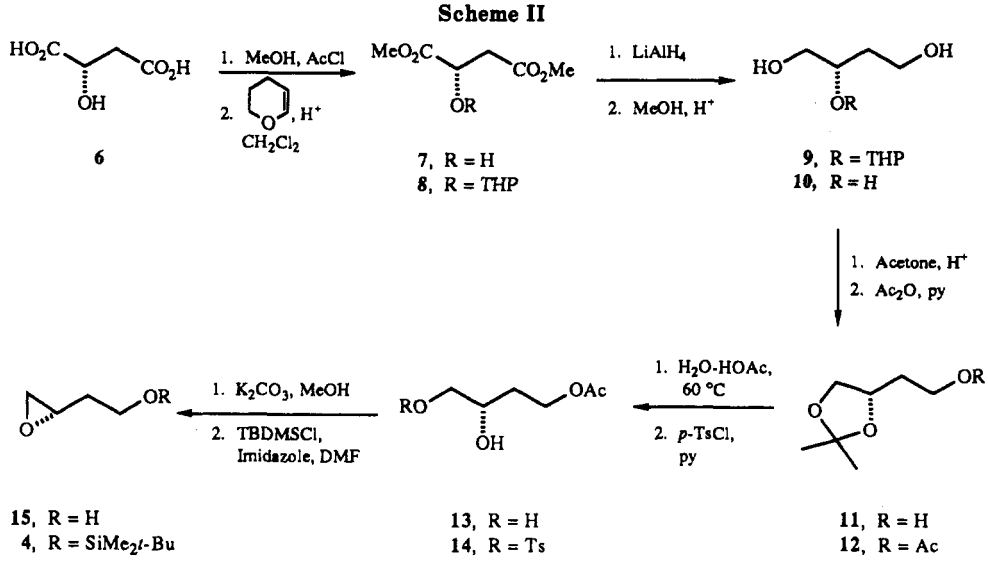
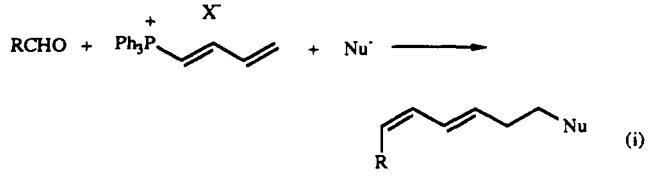
Scheme I



Scheme II



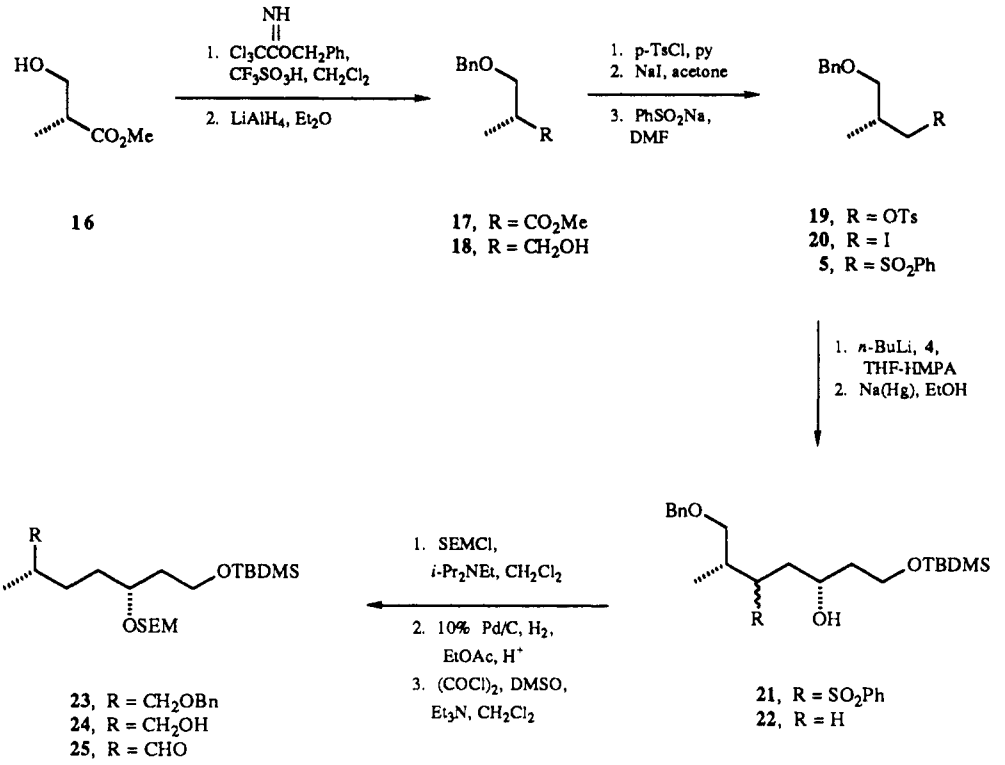
A structural feature that distinguishes **1** from other members of the latrunculin family is the presence of a conjugated diene. Our synthetic plan took cognizance of this in the form of a new approach to acyclic dienes of *E,Z* configuration which has been shown to afford general access to this functional grouping.[16] Specifically, a nucleophile is added to butadienyltriphenylphosphonium bromide to produce an ylide of *E* configuration which undergoes stereoselective Wittig reaction with an aldehyde in situ to yield an *E,Z*-diene (eq i). Experimentation revealed that β-dicarbonyl dianions and α-branched aldehydes are especially effective partners in this diene synthesis. With this precept at the center of our plan, a route to **1** was designed which sectioned the target into three principal subunits, A, B, and C (Scheme I).



Synthesis of the C9–C15 Aldehyde. The aldehyde segment representing A was prepared by linking the two four-carbon units, **4** and **5**. Epoxide **4** was obtained from (*S*)-(−)-malic acid (**6**) by modification of a known procedure[17] (Scheme II). Thus, **6** was first converted to its dimethyl ester **7**, the hydroxyl function was protected as its tetrahydropyranyl ether **8**, and the ester groups were reduced to yield diol **9**. Acid-catalyzed methanolysis of **9** afforded triol **10** which was selectively protected as acetonide **11**. Acetylation of this alcohol gave **12**, from which the acetonide was removed upon acidic hydrolysis. Selective tosylation of the primary alcohol **13** furnished **14** in an overall 30% yield from **6**. Treatment of **14** with

(15) Preliminary report: White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991.
(16) White, J. D.; Jensen, M. S. *Tetrahedron Lett.* **1992**, *33*, 577.
(17) Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471.

Scheme III



methanolic potassium carbonate simultaneously cleaved the acetate and effected epoxide formation. Final protection of **15** as its *tert*-butyldimethylsilyl ether gave **4**.

The sulfone **5** was acquired in five steps from methyl (*R*)-3-hydroxy-2-methylpropionate (**16**) by the sequence shown in Scheme III. Conversion of **16** to its ether **17** with benzyl trichloroacetimidate[18] was followed by reduction of the ester to yield alcohol **18**. The derived tosylate **19** was transformed efficiently to **5** by displacement of iodide **20** with sodium benzenesulfinate in DMF. Coupling of the lithium anion of **5** with **4** produced **21**, from which the sulfone was excised reductively to give optically pure **22**. Protection of this alcohol as its SEM ether **23** was followed by hydrogenolysis. A Swern oxidation of **24** finally gave aldehyde **25**.

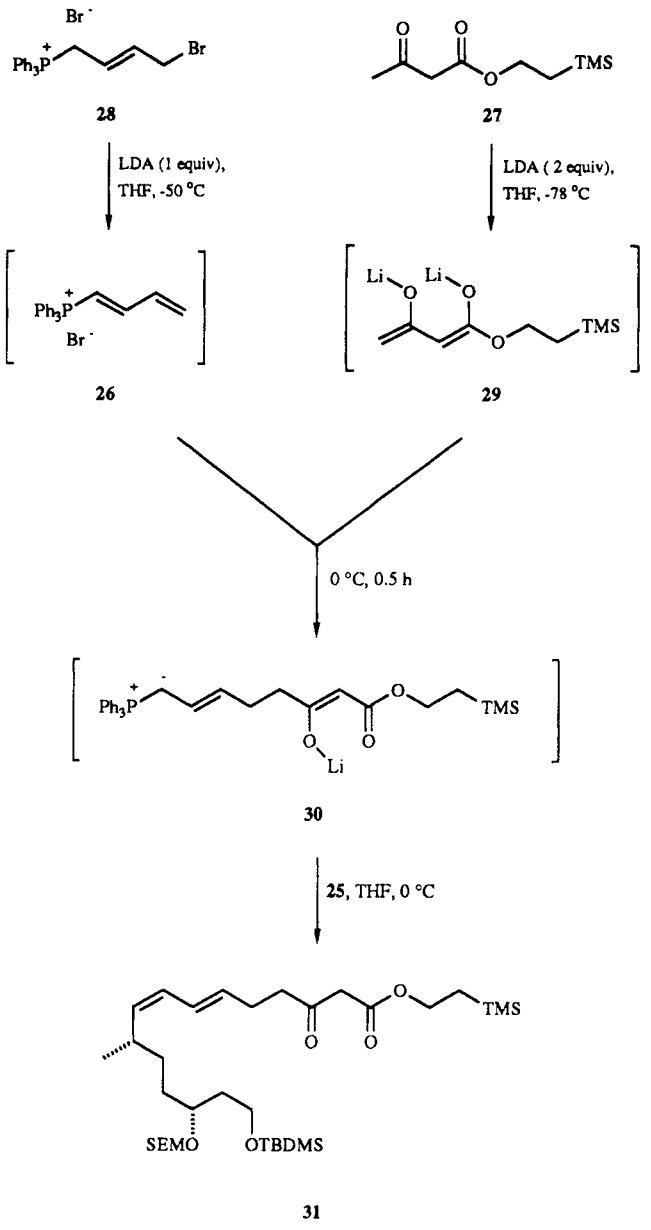
Assembly of the Upper Perimeter by a Three-Component Coupling. Implementation of our plan for assembling the C1–C15 segment of **1** hinged on the coupling of butadienyltriphenylphosphonium bromide (**26**) with a nucleophile which embodied C1–C4 of **1** and then with aldehyde **25**. The *dianion* **29** of β-keto ester **27** was selected as the nucleophile, in part to ensure alkylation at the γ carbon,[19] but also to suppress subsequent attack at the ketone (Scheme IV). It was also reasoned that the (trimethylsilyl)ethyl ester grouping in **27** would facilitate our plan by release of the carboxyl function under nonhydrolytic conditions at a late state of the synthesis. Diene **26**,[20] generated from phosphonium bromide **28**[21] with one equivalent of base, is a reasonably stable species which is conveniently used in situ. Its reaction with dilithio dianion **29** is characterized by formation of a yellow-orange color characteristic of allylic phosphorane **30**. The color slowly disappeared after addition of **25**, and diene **31** was isolated in 60% yield along with a trace of the *E,E*-diene. The exclusive formation of *E* phosphorane **25** in this sequence is noteworthy, as is its Wittig reaction to produce a new double bond of *Z* configuration.[22] This is to be contrasted with a published report describing the reaction of **26** with a ketone enolate to yield a cyclohexa-1,3-diene,[23] a process that must have involved a *Z* allylic phosphorane.

Completion of our route to the C1–C15 portion of **1** required elaboration of β-keto ester **31** into a β-methyl-substituted *Z*-unsaturated ester and refunctionalization of C15 as an aldehyde. The first of these transformations was effected by converting **31** to *E* enol phosphate **32**[24] (Scheme V) which underwent clean substitution with retention of configuration when reacted with the magnesiocuprate from methylcopper and methylmagnesium chloride.[25] The resulting ester **33** could also be prepared directly by coupling of the *Z* dianion of senecioic acid[26] with **26** followed by addition of **25**, but the yield was inferior and the product was contaminated with stereoisomeric olefins. For the final manipulation of **33** the *tert*-butyldimethylsilyl ether was selectively removed with acidic methanol and the resulting alcohol **34** was subjected to a Swern oxidation to yield **35**.

Synthesis and Coupling of the Thiazolidinone Subunit. The third segment C needed for assembling the skeleton of **1** was prepared from methyl (*R*)-cysteinate (**36**) as shown in Scheme VI. The latter was converted with CO and O_2 in the presence of selenium to thiazolidinone **37**,[27] from which the ester was cleaved by hydrolysis.[28]

(18) Iverson, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
(19) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(20) Büchi, G.; Pawlak, M. *J. Org. Chem.* **1975**, *40*, 100.
(21) Buchta, E.; Andrée, F. *Justus Liebigs Ann. Chem.* **1961**, *640*, 29.
(22) For a discussion of the stereochemistry of the Wittig reaction of allylic phosphoranes, see: Barlow, L.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1029.
(23) Fuchs, P. L. *Tetrahedron Lett.* **1974**, 4055.
(24) Alderdice, M.; Spino, C.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1643.
(25) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731.
(26) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1981**, *46*, 2437.
(27) Sonoda, N.; Yamameto, G.; Natsukawa, K.; Kondo, K.; Murai, S. *Tetrahedron Lett.* **1975**, 1969.
(28) Maclaren, J. A. *Aust. J. Chem.* **1968**, *21*, 1891.

Scheme IV



Treatment of the resulting carboxylic acid with methyllithium and methylmagnesium chloride afforded ketone **39**.

It was assumed initially that protection of the nitrogen atom of thiazolidinone **39** would be required in order to effect aldol coupling with **35** and, to this end, the thiazolidinone **37** was converted to methoxymethyl (MOM) ether **38**. Careful treatment of the latter with methyllithium gave **40**. Exposure of **35** to the enolate of **40**, prepared with LDA and cerium trichloride, resulted in smooth aldol condensation to give a 81% yield of hydroxy ketone **41** as a 1:1 mixture of stereoisomers (Scheme VII). Although this lack of stereoselectivity was disappointing, a more serious problem appeared at the next step. Our protecting group strategy had been planned with the aim of removing the SEM ether of **41** at this stage by acidic hydrolysis in anticipation of a spontaneous ring closure to the δ hemiketal moiety of **1**. This transformation indeed occurred but, unfortunately, was followed by a second cyclization in which the formaldehyde unit of the MOM ether participated. The resulting *N,O*-acetal **42** illustrates a feature of latrunculin chemistry that had been encountered previously,[9] and as expected, this acetal proved to be exceptionally resistant to hydrolysis. Thus, although **42** could be lactonized to the latrunculin A derivative **43**, no means could be found for converting this substance to **1**. Several other protecting groups were attached to the nitrogen atom of thiazolidinone **39**, but in all cases they were either impossible to remove after lactonization or their cleavage impacted on the integrity of the macrocycle.[14e]

The solution to this problem proved to be surprisingly straightforward; protection of the thiazolidinone nitrogen was, in fact, unnecessary. The *dianion* of **39** was found to be quite compatible with **35** and led to the crossed aldol product **44** as a 1:1 mixture of epimers in good yield. Thus, by employing its mixed lithio–cerio dianion the route from **39** to **1** was considerably simplified. The stereoisomers of **44** were inseparable and consequently the mixture was taken forward to methyl ketals **45** and **46** as indicated in Scheme VIII by selective cleavage of the SEM ether followed by treatment with methanol in the presence of an acidic catalyst. The less polar alcohol **45** was now easily separated by chromatography from its more polar stereoisomer **46**. Since only the latter showed an internally hydrogen-bonded hydroxyl proton in its ^{1}H NMR spectrum, this property enabled confident stereochemical assignment to be made based on the diaxial relationship of 15β-hydroxy and 17β-methoxy substituents.

Cleavage of the (trimethylsilyl)ethyl ester from **45** proceeded efficiently to yield carboxylic acid **47** but, in the case of **46**, seco acid **48** was accompanied by a small quantity of an anhydro product containing a dihydropyran which resulted from elimination of methanol. Lactonization of 15α alcohol **47** using the Mitsunobu protocol[29] gave in good yield the methyl ketal **3** of latrunculin A, a substance whose properties had already been described in the literature.[7] Final hydrolysis of **3** afforded synthetic latrunculin A (**1**), identical in all respects including optical rotation with a sample of the natural material. Analogous Mitsunobu lactonization of 15β alcohol **48** gave in somewhat poorer yield ketal **49** which, upon acidic hydrolysis, furnished 15-epilatrunculin A (**50**).

Experimental Section

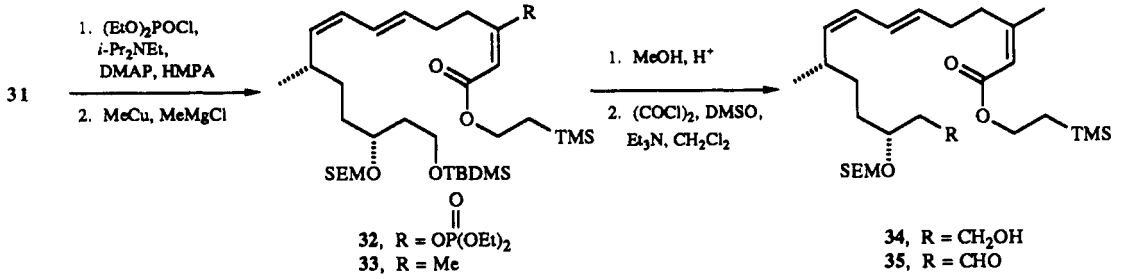
Solvents were dried by distillation shortly before use from an appropriate drying agent. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on 2.5- × 7.0-cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Flash chromatography was carried out with E. Merck silica gel 60 (230–400-mesh ASTM). High-pressure liquid chromatography (HPLC) was performed with a Waters M-45 solvent delivery system equipped with two Waters semipreparative silica columns and a refractive index detector.

Melting points were measured on a Büchi melting points apparatus and are uncorrected. Infrared spectra (IR) were recorded on either a Perkin-Elmer 727B or a Nicolet 5DXB FT-IR spectrometer. Optical rotations were measured in 1-dm cells (1-mL capacity) on a Perkin-Elmer Model 243 polarimeter at ambient temperature. Nuclear magnetic resonance spectra (NMR) were recorded on either a Bruker AM-300 or a Bruker AM-400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from internal Me_4Si on the δ scale. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were determined on a Kratos MS-50. Elemental analyses were performed by Desert Analytics (formerly MicAnal), Tucson, AZ.

Methyl (2*R*)-3-(Benzyloxy)-2-methylpropionate (17). To a solution of **16** (18.8 g, 0.158 mol) in 370 mL of cyclohexane and

(29) Mitsunobu, O. *Synthesis* **1981**, 1.

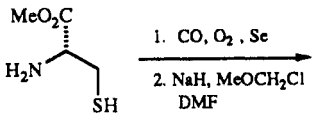
Scheme V



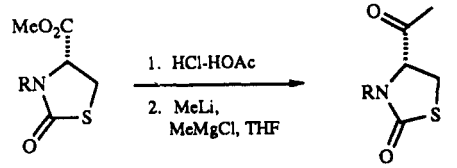
32, R = $OP(OEt)_2$
33, R = Me

34, R = CH_2OH
35, R = CHO

Scheme VI



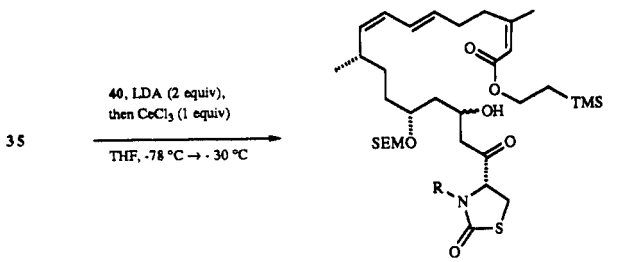
36



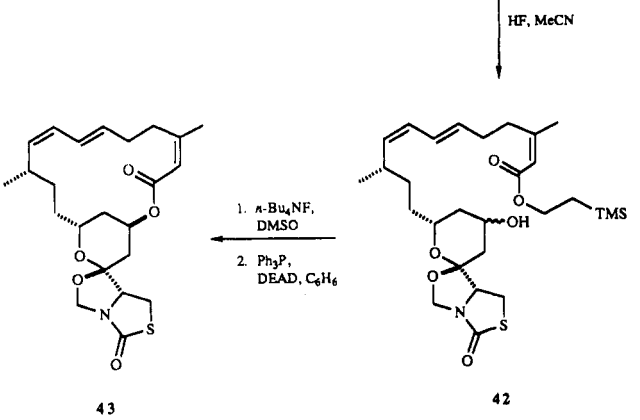
37, R = H
38, R = MOM

39, R = H
40, R = MOM

Scheme VII

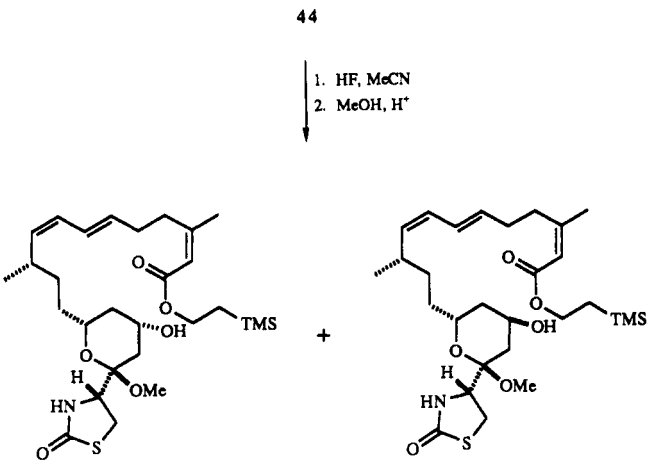


41, R = MOM
44, R = H

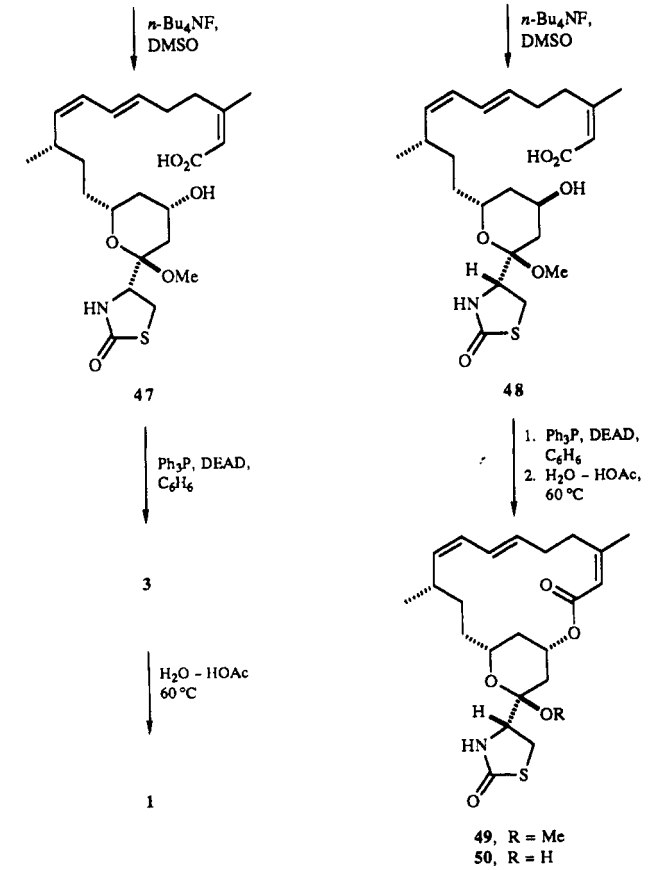


43 **42**

Scheme VIII



45 **46**



47 **48**

3

1

49, R = Me
50, R = H

190 mL of CH_2Cl_2 was added benzyl 2,2,2-trichloroacetimidate (50.0 g, 0.198 mol) followed by triflormethanesulfonic acid (2.40 g, 0.016 mol). The resulting solution was stirred overnight at room temperature. After 24 h the mixture was filtered, and the collected solid was washed with CH_2Cl_2. The filtrate was washed with H_2O, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). Purification of the residue after evaporation of the solvent on silica (hexane–EtOAc, 6:1) afforded 27.4 g (83%) of **17** as a colorless oil: $[\alpha]^{21}_D$ −11.8° (*c* 3.60, $CHCl_3$); IR (neat) 2979, 1742, 1455, 1201, 1097, 739, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.27 (5 H, m), 4.52 (2 H, s), 3.69 (3 H, s), 3.65 (1 H, dd, *J* = 1.7, 9.3 Hz), 3.49 (1 H, dd, *J* = 4.9, 9.3 Hz), 2.79 (1 H, m, *J* = 7.1 Hz), 1.18 (3 H, d, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 175.3, 138.1, 128.3, 127.6, 127.5, 73.0, 71.9, 51.7, 40.1, 13.9; MS *m/z* 208, 122, 107, 91, 77. Anal.

Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.99; H, 7.98.

(2*S*)-3-(Benzyloxy)-2-methyl-1-propanol (18). To a suspension of $LiAlH_4$ (5.0 g, 0.132 mol) of 130 mL of Et_2O at 0 °C was added a solution of **17** (27.4 g, 0.132 mol) in 130 mL of Et_2O dropwise with stirring. The mixture was warmed to room temperature, and after 30 min the excess $LiAlH_4$ was quenched by careful addition of 5.0 mL of H_2O, 5.0 mL of 15% aqueous NaOH, and then 15 mL of H_2O. After 15 min anhydrous $MgSO_4$ was added, and stirring was continued for 15 min. The mixture was filtered, the collected solid was washed with Et_2O, and the filtrate was concentrated under reduced pressure to give 23.9 g (98%) of **18** as a pale yellow oil of sufficient purity for the subsequent transformation. An analytical sample was obtained by chromatography on silica (hexane–EtOAc, 3:1) as a colorless oil: $[\alpha]^{21}_D$ −17.6° (*c* 4.53, $CHCl_3$); IR (neat) 3396, 3030, 2873, 1095, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.27 (5 H, m), 4.52 (2 H, s), 3.64–3.53 (3 H, m, *J* = 4.7, 9.1 Hz), 3.42 (1 H, dd, *J* = 8.2, 9.1 Hz), 2.62 (1 H, dd, *J* = 4.7, 6.7 Hz), 2.03 (1 H, m, *J* = 7.0 Hz), 0.88 (3 H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.4, 127.7, 127.6, 75.4, 73.3, 67.8, 35.5, 13.4; MS *m/z* 180, 165, 107, 91. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.28; H, 9.04.

(2*R*)-1-(Benzyloxy)-2-methyl-3-(*p*-toluenesulfonyloxy)-propane (19). To a solution of **18** (5.48 g, 30 mmol) in pyridine (120 mL) at 0 °C was added *p*-toluenesulfonyl chloride (7.53 g, 39 mmol). The mixture was allowed to warm to room temperature and was stirred for 20 h, after which is was poured on to a mixture of ice and 10% aqueous HCl. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The ethereal solution was washed with H_2O, saturated aqueous $CuSO_4$, and brine and dried ($MgSO_4$). Removal of the solvent under vacuum and purification of the residue on silica (hexane–EtOAc, 3:1) afforded 8.32 g (82%) of **19** as a colorless oil: $[\alpha]^{21}_D$ −4.75° (*c* 2.00, $CHCl_3$); IR (neat) 1598, 1360, 1176, 1116, 1098, 975, 942, 835, 814, 667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (2 H, s), 7.29 (7 H, m), 4.39 (2 H, s), 4.01 (2 H, dq, *J* = 14, 6 Hz), 3.33 (2 H, dq, *J* = 8, 1 Hz), 2.41 (3 H, s), 2.12 (1 H, m), 0.94 (3 H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 144.6, 138.2, 133.0, 129.8, 128.3, 127.9, 127.5, 127.4, 73.0, 72.2, 71.1, 33.6, 21.6, 13.6; MS *m/z* 334, 173, 162, 161, 91. Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63. Found: C, 64.24; H, 6.49.

(2*R*)-3-(Benzyloxy)-1-iodo-2-methylpropane (20). A solution of **19** (7.90 g, 24 mmol) and NaI (7.40 g, 49 mmol, dried under vacuum at 50 °C) in acetone (120 mL) was heated at reflux for 4 h. The mixture was diluted with Et_2O (200 mL) and filtered. The filtrate was washed with H_2O and saturated aqueous $Na_2S_2O_3$ and dried ($MgSO_4$). Removal of the solvent under vacuum and purification of the residue on silica (hexane–EtOAc, 6:1) yielded 5.12 g (72%) of **20** as a colorless oil: $[\alpha]^{22}_D$ −10.5° (*c* 3.35, $CHCl_3$); IR (neat) 1474, 1101, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (5 H, m), 4.51 (2 H, s), 3.34 (4 H, m), 1.78 (1 H, m), 0.98 (3 H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 138.3, 128.4, 127.6, 74.1, 73.2, 35.2, 17.7, 13.6; MS *m/z* 290, 91.

(2*R*)-3-(Benzyloxy)-2-methylpropyl Phenyl Sulfone (5). To a solution of **20** (9.9 g, 34 mmol) in 100 mL of DMF was added sodium benzenesulfinate (8.4 g, 51 mmol) at room temperature. The resulting white suspension was warmed to 35 °C and stirred for 16 h. The solution was then cooled, and 300 mL of Et_2O was added. The organic layer was evaporated and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a yellow oil which was purified by column chromatography on silica (hexane–EtOAc, 4:1–1:1) to give 8.1 g (78%) of **5** as a colorless oil: $[\alpha]^{21}_D$ −4.2° (*c* 1.35, $CHCl_3$); IR (neat) 2862, 2860, 1454, 1447, 1362, 1305, 1149, 1086, 740, 721, 698, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, d, *J* = 6.9 Hz), 2.34–2.46 (1 H, m), 2.93 (1 H, dd, *J* = 7.8, 14.3 Hz), 3.30 (1 H, dd, *J* = 6.6, 9.5 Hz), 3.41 (1 H, dd, *J* = 9.4, 4.5 Hz), 3.41, (1 H, dd, *J* = 14.1, 4.5 Hz), 4.40 (1 H, d, *J* = 10 Hz), 4.43 (1 H, d, *J* = 10 Hz), 7.23–7.36 (5 H, m), 7.52–7.58 (2 H, m), 7.61–7.67 (1 H, m), 7.89–7.94 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 17.0, 29.3, 59.1, 72.7, 73.4, 127.3 (2 C), 127.5, 127.6 (2 C), 128.2 (2 C), 129.1 (2 C), 133.4, 138.0; MS *m/z* 213, 198, 143, 91. Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62. Found: C, 66.88; H, 6.91.

(3*S*,6*R*)-7-(Benzyloxy)-3-hydroxy-6-methyl-5-(phenylsulfonyl)heptyl *tert*-Butyldimethylsilyl Ether (21). To a solution of **5** (304 mg, 1.0 mmol) in 3 mL of THF was added a solution of *n*-butyllithium in hexane (0.67 mL, 1.0 mmol) at −78 °C. The solution was stirred for 20 min, and then HMPA (0.21 mL, 1.2 mmol) in 2 mL of THF was added. The solution was stirred for an additional 10 min, and a solution of **4** (101 mg, 0.50 mmol) in 2 mL of THF was added. The resulting yellow solution was warmed to 0 °C and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2 × 50 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified by column chromatography on silica (hexane–EtOAc, 4:1) to give 226 mg (94%) of **21** as a colorless oil: IR (neat) 3460, 2954, 2930, 1303, 1292, 1146, 1084, 837, 779, 738 cm^{-1}; ^1H NMR ($CDCl_3$) mixture of two isomers (ca. 1:1) δ 0.87 (9 H, s), 1.01 and 1.15 (3 H, each a d, *J* = 7 Hz), 4.37 and 4.48 (2 H, each a s), all other signals m; ^{13}C NMR ($CDCl_3$) δ −5.6, 11.7, 15.1, 18.0, 25.8, 30.8, 31.9, 33.0, 34.4, 38.1, 38.8, 60.9, 61.7, 62.3, 63.0, 68.7, 69.7, 71.6, 72.6, 72.7, 72.9, 127.5, 127.6, 128.3, 128.4, 128.6, 128.8, 129.1, 133.4, 137.8, 138.4, 139.5; MS *m/z* 443, 341, 229, 217, 201, 185, 171, 157, 135, 105, 100, 91.

(3*R*,6*S*)-7-Benzyl-3-hydroxy-6-methylheptyl *tert*-Butyldimethylsilyl Ether (22). To a solution of **21** (48 mg, 0.10 mmol) in 3 mL of EtOH was added sodium amalgam (2.5%, 1.84 g) with stirring at room temperature. The mixture was stirred for 5 h, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (2 × 30 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to afford a yellow oil which was purified by column chromatography on silica (hexane–EtOAc, 4:1) to give 28 mg (83%) of **22** as a colorless oil: $[\alpha]^{21}_D$ +9.3° (*c* 1.50, $CHCl_3$); IR (neat) 3458, 2952, 2932, 2859, 1463, 1412, 1385, 1364, 1254, 1207, 1093, 1038, 1006, 979, 939, 906, 837, 778, 737, 699, 664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (6 H, s), 0.83 (s, 9 H), 0.88 (3 H, d, *J* = 7 Hz), 1.04–1.15 (1 H, m), 1.37–1.45 (2 H, m), 1.45–1.55 (1 H, m), 1.55–1.63 (2 H, m), 1.66–1.77 (1 H, m), 3.18 (1 H, dd, *J* = 7, 9 Hz), 3.28 (1 H, dd, *J* = 6, 9 Hz), 3.41 (1 H, d, *J* = 2 Hz), 3.69–3.78 (2 H, m), 3.83 (1 H, dt, *J* = 10, 5 Hz), 4.43 (2 H, s), 7.17–7.33 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −5.7, 17.1, 18.0, 25.7, 29.4, 33.4, 34.7, 38.0, 62.8, 72.5, 72.9, 75.7, 127.3, 127.4, 128.2, 138.7; MS *m/z* 366 (M^+), 308, 256, 216, 200, 188, 105, 100, 91, 75. Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 68.71; H, 10.33.

(3*R*,6*S*)-7-(Benzyloxy)-3-[[2-(trimethylsilyl)ethoxy]-methoxy]-6-methylheptyl *tert*-Butyldimethylsilyl Ether (23). To a solution of **22** (900 mg, 2.45 mmol) in 10 mL of CH_2Cl_2 was added i-Pr_2EtN (1.39 mL, 8.0 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (0.71 mL, 4.0 mmol) at room temperature. The solution was warmed to 40 °C and stirred for 5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O (2 × 50 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to afford a yellow oil which was purified by column chromatography on silica (hexane–EtOAc, 9:1) to give 1.11 g (91%) of **23** as a colorless oil: $[\alpha]^{25}_D$ −3.5° (*c* 2.3, $CHCl_3$); IR (neat) 2954, 2930, 2882, 2858, 1470, 1459, 1363, 1250, 1097, 1055, 1031, 938, 922, 859, 836, 776, 735, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24–7.37 (5 H, m), 4.69 (2 H, s), 4.49 (2 H, s), 3.53–3.74 (5 H, m), 3.33 (1 H, dd, *J* = 6, 9 Hz), 3.23 (1 H, dd, *J* = 7, 9 Hz), 1.64–1.83 (3 H, m), 1.43–1.64 (3 H, m), 1.07–1.22 (1 H, m), 0.94 (3 H, d, *J* = 7 Hz), 0.89 (9 H, s), 0.04 (6 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 138.7, 128.3, 127.5 (×2), 127.4 (×2), 93.9, 75.8, 74.9, 72.9, 65.1, 59.8, 37.6, 33.6, 32.0, 29.1, 25.9 (×3), 18.2, 18.1, 17.2, −1.4 (×3), −5.3 (×2); MS *m/z* 381 (M^+ − $C_6H_{15}Si$), 365 (M^+ − $C_6H_{15}OSi$), 354, 289, 257, 217, 201, 91, 73 (100).

(3*R*,6*S*)-7-Hydroxy-3-[[2-(trimethylsilyl)ethoxy]methoxy]-6-methylheptyl *tert*-Butyldimethylsilyl Ether (24). To a solution of **23** (610 mg, 12.3 mmol) in 10 mL of EtOAc was added 10 μL of 10% HCl and 100 mg of 10% Pd–C, and the mixture was stirred under H_2 for 30 min at room temperature. Et_3N (50 μL) was added, and the solution was filtered through Celite, concentrated, and purified by column chromatography on silica (hexane–EtOAc, 1:4) to give 472 mg (95%) of **24** as a colorless oil: $[\alpha]^{20}_D$ −5.5° (*c* 1.7, $CHCl_3$); IR (neat) 3428, 2954, 2932, 2884, 2863, 1467, 1410, 1383, 1253, 1193, 1097, 1053, 1031, 937, 856, 837, 776, 695, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.68 (2 H, s), 3.36–3.72 (7 H, m), 1.41–1.75 (7 H, m), 1.07–1.22 (1 H, m), 0.88–0.97 (5 H, m), 0.88 (9 H, s), 0.03 (6 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 93.9, 75.1, 68.1, 65.2, 59.8, 37.6, 35.9, 32.0, 28.5, 25.9 (×3), 18.2, 18.1, 16.6, −1.5 (×3), −5.3 (×3); MS *m/z* 289 (M^+ − $C_5H_{13}OSi$), 259 (M^+ − $C_6H_{15}O_2Si$), 231, 201, 187, 171, 168, 127, 109, 73 (100).

Anal. Calcd for $C_{20}H_{46}O_4Si_2$: C, 59.06; H, 11.40. Found: C, 58.82; H, 11.66.

(2*R*,5*R*)-2-Methyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-7-[(*tert*-butyldimethylsilyl)oxy]heptanal (25). To a solution of $(COCl)_2$ (0.35 mL, 4.0 mmol) in 8 mL of CH_2Cl_2 was added DMSO (0.57 mL, 8.0 mmol) in at −60 °C. After 2 min, a solution of **24** (472 mg, 1.16 mmol) in 8 mL of CH_2Cl_2 was added, and after 15 min Et_3N (2.23 mL, 16 mmol) was added. The resulting white suspension was warmed to −50 °C and stirred for 30 min. Saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O (2 × 50 mL). The organic layer was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated to give a yellow oil which was purified by column chromatography on silica (hexane–EtOAc, 1:9) to furnish 439 mg (93%) of **25** as a pale yellow oil: $[\alpha]^{20}_D$ +9.6° (*c* 1.7, $CHCl_3$); IR (neat) 2954, 2933, 2888, 2862, 1730, 1252, 1097, 1054, 1032, 936, 856, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.61 (1 H, d, *J* = 2 Hz), 4.68 (2 H, s), 3.52–3.77 (5 H, m), 2.27–2.41 (1 H, m), 1.32–1.90 (6 H, m), 1.10 (3 H, d, *J* = 7 Hz), 0.88–0.97 (2 H, m), 0.88 (9 H, s), 0.04 (6 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 204.9, 94.0, 74.7, 65.3, 59.6, 46.3, 37.5, 32.0, 26.1, 25.9 (×3), 18.1, 13.4, −1.4 (×3), −5.3 (×2). Anal. Calcd for $C_{20}H_{44}O_4Si_2$: C, 59.35; H, 10.96. Found: C, 58.92; H, 10.74.

(*trans*-4-Bromo-2-butenyl)triphenylphosphonium Bromide (28). To a solution of *trans*-1,4-dibromo-2-butene (20.0 g, 94 mmol) in 100 mL of C_6H_6 was added triphenylphosphine (24.5 g, 94 mmol) in 100 mL of C_6H_6 during 45 min at room temperature. The solution was stirred for 18 h. The deposited solid was collected by filtration and washed with 50 mL of C_6H_6 followed by 50 mL of hexane. After drying, 31.85 g (71%) of **28** was obtained as a white solid: mp 185–186 °C; ^1H NMR ($CDCl_3$) δ 7.76 (15 H, m), 6.50–5.45 (2 H, m), 4.95 (2 H, dd, *J* = 7, 16 Hz), 3.85 (2 H, dd, *J* = 3, 11 Hz). This material was used without further purification for preparation of **26**.

2-(Trimethylsilyl)ethyl Acetoacetate (27). To a mixture of diketene (1.68 g, 20 mmol) and 2-(trimethylsilyl)ethanol (2.37 g, 20 mmol) was added NaOAc (50 mg, 0.6 mmol). The mixture was heated to 50 °C, at which point a vigorous exothermic reaction started and the solution turned brown. After cooling, the brown oil was placed on a column of silica and eluted with hexane–EtOAc (9:1–4:1). The resulting yellow oil was further purified by bulb-to-bulb distillation (1 mmHg, 120 °C) to give 3.22 g (80%) of **27** as a colorless oil: IR (neat) 2956, 1743, 1720, 1361, 1317, 1251, 1176, 1152, 1044, 860, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16–4.27 (2 H, m), 3.42 (2 H, s), 2.26 (3 H, s), 0.94–1.05 (2 H, m), 0.03 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 200.7, 167.2, 63.7, 50.3, 30.1, 17.2, −1.6; MS *m*/*z* 187 ($M^+ - CH_3$), 159, 115, 73 (100). Anal. Calcd for $C_9H_{18}O_3Si$: C, 53.43; H, 8.97. Found: C, 53.61; H, 9.09.

2-(Trimethylsilyl)ethyl (10*S*,13*R*)-*trans*,*trans*-13-[[2-(Trimethylsilyl)ethoxy]methoxy]-10-methyl-3-oxo-15-[(*tert*-butyldimethylsilyl)oxy]-6,8-pentadecadienoate (31). To a suspension of **28** (1.43 g, 3.0 mmol) in 9 mL of THF was added LDA (3.0 mmol) in 6 mL of THF at −78 °C. The mixture was warmed to −50 °C and stirred for 30 min to give a brown solution of **26**. To a solution of **27** (607 mg, 3.0 mmol) in 6 mL of THF was added LDA (6 mmol) in 6 mL of THF at −78 °C, and the mixture was stirred for 5 min to give a pale yellow solution of **29**. This solution was transferred by cannula to the solution containing **26** at −50 °C. The resulting mixture was warmed to 0 °C and stirred for 30 min to give a deep red solution of the ylide **30**. To this solution was added a solution of **25** (439 mg, 1.1 mmol) in 6 mL of THF at 0 °C. After 3 min the solution was cooled to −30 °C, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (3 × 50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a brown oil. The oil was purified by column chromatography on silica (hexane–EtOAc, 9:1) to give 391 mg (56%) of **31** as a colorless oil: IR (neat) 2955, 2930, 2898, 2859, 1745, 1720, 1650, 1633, 1470, 1461, 1411, 1377, 1362, 1315, 1251, 1097, 1056, 1031, 860, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.15 (s), 6.35–6.25 (1 H, m), 5.92–5.83 (1 H, m), 5.64–5.54 (1 H, m), 5.09 (1 H, t, *J* = 10 Hz), 4.96 (s), 4.68 (2 H, s), 4.28–4.19 (2 H, m), 4.70–4.53 (5 H, m), 3.42 (s), 2.64 (1 H, t, *J* = 7 Hz), 2.54 (1 H, m), 2.41–2.23 (3 H, m), 1.74–1.61 (2 H, m), 1.50–1.25 (4 H, m), 0.98 (2 H, t, *J* = 7 Hz), 0.96 (3 H, d, *J* = 7 Hz), 0.93 (2 H, d, *J* = 7 Hz), 0.88 (9 H, s), 0.04 (6 H, s), 0.04 (9 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 202.0, 177.6, 172.8, 167.2, 137.1, 132.0, 131.8, 127.2, 127.1, 126.9, 126.8, 93.9, 89.5, 74.8, 65.1, 63.7, 62.2, 59.8, 49.5, 42.6, 37.7, 34.9, 32.8, 32.6, 32.3, 29.5, 26.6, 25.9, 21.4, 18.2, 18.1, 17.3, −1.4, −1.6, −5.3; MS *m*/*z* 630 (M^+), 613, 525, 481, 439, 409, 231, 185, 161, 147, 131, 73 (100). Anal. Calcd for $C_{32}H_{66}O_6Si_3$: C, 60.90; H, 10.54. Found: C, 61.06; H, 10.40.

Enol Phosphate 32. To a solution of **31** (380 mg, 0.55 mmol) in 5 mL of HMPA was added 5 mL of i-Pr_2NEt and 10 mg of DMAP at room temperature. The solution was cooled to 0 °C, $ClPO(OEt)_2$ (0.69 g, 4.0 mmol) was added, and the solution was stirred for 1 h. After dilution with 150 mL of Et_2O, the solution was washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated to give a yellow oil. This material was purified by column chromatography on silica (hexane–EtOAc, 9:1–4:1) to yield 290 mg (68%) of **32** as a colorless oil: $[\alpha]^{20}_D$ −31.4° (*c* 1.6, $CHCl_3$); IR (neat) 2954, 2931, 2899, 2859, 1717, 1648, 1389, 1363, 1293, 1279, 1250, 1171, 1121, 1098, 1031, 984, 968, 948, 922, 860, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.3 (1 H, dd, *J* = 11, 15 Hz), 5.87 (1 H, t, *J* = 11 Hz), 5.84 (1 H, d, *J* = 2 Hz), 5.63 (1 H, dt, *J* = 15, 7 Hz), 5.07 (1 H, t, *J* = 11 Hz), 4.67 (2 H, s), 4.13–4.24 (6 H, m), 3.55–3.69 (5 H, m); 2.85–2.95 (2 H, m), 2.47–2.60 (1 H, m), 2.32–2.45 (2 H, m), 1.63–1.75 (2 H, m), 1.20–1.55 (10 H, m), 0.88–1.05 (7 H, m), 0.87 (9 H, s), 0.03 (18 H, s), 0.00 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 166.2, 165.6 (d), 136.8, 132.3, 127.3, 126.7, 105.7 (d), 93.8, 74.8, 65.1, 64.8 (d), 62.3, 59.8, 37.7, 32.8, 32.6, 32.4, 31.5 (d), 30.0, 25.9 (×3), 21.4, 18.2, 18.1, 17.3, 16.1, 16.0, −1.4 (×3), −1.5 (×3), −5.3 (×2); MS *m*/*z* 779 ($M^+ + 1$), 778, 763, 749, 661, 519, 313, 269, 221 (100), 155, 127, 80, 73. This compound was used immediately in the preparation of **33**.

Triene 33. Methylcopper reagent was prepared by adding to a solution of CuI (210 mg, 1.1 mmol) in 10 mL of THF a solution of MeLi in Et_2O (0.79 mL, 1.1 mmol) followed by a solution of MeMgCl in THF (1.17 mL, 3.5 mmol). The mixture was stirred at 0 °C for 5 min. To a solution of **32** (272 mg, 0.35 mmol) in 20 mL of THF was added the reagent prepared above at −60 °C. The resulting suspension was warmed to −20 °C over 40 min, cooled to −60 °C, and quenched with saturated aqueous NH_4Cl. The solution was extracted with Et_2O (2 × 50 mL), and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography on silica (hexane–EtOAc, 19:1) to give 195 mg (87%) of **33** as a colorless oil: $[\alpha]^{20}_D$ −32.1° (*c* 1.1, $CHCl_3$); IR (neat) 2954, 2930, 2898, 2858, 1715, 1650, 1470, 1458, 1454, 1383, 1250, 1226, 1167, 1149, 1096, 1056, 1032, 985, 945, 941, 922, 860, 836, 776, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (1 H, dd, *J* = 11, 15 Hz), 5.88 (1 H, t, *J* = 11 Hz), 5.66 (1 H, dt, *J* = 15, 7 Hz), 5.65 (1 H, d, *J* = 1 Hz), 5.06 (1 H, t, *J* = 11 Hz), 4.68 (2 H, s), 4.12–4.20 (2 H, m), 3.51–3.70 (5 H, m), 2.68–2.74 (2 H, m), 2.46–2.63 (1 H, m), 2.18–2.23 (2 H, m), 1.88 (3 H, d, *J* = 1 Hz), 1.64–1.75 (2 H, m), 1.20–1.54 (5 H, m), 0.88–1.05 (7 H, m), 0.88 (9 H, s), 0.04 (9 H, s), 0.03 (6 H, s), 0.01 (9 H, s); ^{13}C NMR δ 166.5, 159.5, 136.4, 133.5, 127.5, 126.2, 116.6, 93.8, 74.8, 65.1, 61.6, 59.8, 37.7, 33.0, 32.8, 32.6, 32.3, 31.5, 25.9 (×3), 25.3, 21.4, 18.2, 18.1, 17.3, −1.4 (×3), −1.5 (×3), −5.3 (×2); MS *m*/*z* 437, 419, 354, 278, 244, 229, 199, 172, 73 (100). Anal. Calcd for $C_{33}H_{68}O_5Si_3$: C, 63.00; H, 10.89. Found: C, 62.71; H, 10.94.

Alcohol 34. To a solution of **33** (40 mg, 0.06 mmol) in 5 mL of MeOH was added 20 mL of pyridinyl *p*-toluenesulfonate, and the mixture was warmed to 40 °C for 2 h. The solution was diluted with 30 mL of EtOAc, washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography on silica (hexane–EtOAc, 3:1) to give 28 mg (85%) of **34** as a colorless oil: $[\alpha]^{20}_D$ −62.5° (*c* 2.5, $CHCl_3$); IR (neat) 3476, 2954, 1712, 1648, 1450, 1380, 1250, 1152, 1098, 1056, 1030, 986, 943, 859, 838, 763, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28 (1 H, dd, *J* = 11, 15 Hz), 5.89 (1 H, t, *J* = 11 Hz), 5.66 (1 H, dt, *J* = 15, 7 Hz), 5.64 (1 H, s), 5.04 (1 H, t, *J* = 11 Hz), 4.68 and 4.71 (2 H, two sets of AB d, *J* = 7 Hz), 4.10–4.21 (2 H, m), 3.53–3.83 (5 H, m), 2.44–2.76 (4 H, m), 2.17–2.33 (2 H, m), 1.87 (3 H, d, *J* = 1 Hz), 1.17–1.86 (6 H, m), 0.85–1.04 (7 H, m), 0.03 (9 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 166.5, 159.5, 136.1, 133.6, 127.6, 126.1, 116.6, 94.1, 76.3, 65.6, 61.6, 59.7, 36.7, 33.0, 32.9, 32.5, 32.1, 31.4, 25.3, 21.4, 18.0, 17.3, −1.5 (×6); MS *m*/*z* 395 ($M^+ - C_6H_{15}OSi$), 380, 307, 290, 244, 229, 147, 73 (100). Anal. Calcd for $C_{28}H_{54}O_5Si_2$: C, 63.83; H, 10.33. Found: C, 64.01; H, 10.40.

Aldehyde 35. To a solution of $(COCl)_2$ (9 μL, 0.1 mmol) in 0.4 mL of CH_2Cl_2 was added DMSO (14 μL, 0.2 mmol) at −60 °C,

the mixture was stirred for 10 min, and a solution of **34** (10 mg, 0.019 mmol) in 2 mL of CH_2Cl_2 was then added. The mixture was stirred for 15 min at −60 °C, after which Et_3N (56 μL, 0.4 mmol) was added. The solution was warmed to −50 °C, stirred for an additional 30 min, and quenched with saturated aqueous NH_4Cl. Extraction with Et_2O (2 × 20 mL), followed by washing of the organic layer with brine, drying ($MgSO_4$), and removal of the solvent, gave a pale yellow oil. This was purified by column chromatography on silica (hexane–EtOAc, 9:1) to afford 8.1 mg (81%) of **35** as a colorless oil: $[\alpha]^{20}_D$ −41.8° (*c* 0.40, $CHCl_3$); IR (neat) 2954, 2927, 1720, 1648, 1451, 1380, 1249, 1226, 1152, 1100, 1054, 1032, 986, 942, 859, 837, 762, 695, 669, 634, 620, 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (1 H, t, *J* = 2 Hz), 6.27 (1 H, dd, *J* = 11, 15 Hz), 5.90 (1 H, t, *J* = 11 Hz), 5.68 (1 H, dt, *J* = 15, 7 Hz), 5.65 (1 H, s), 5.04 (1 H, t, *J* = 11 Hz), 4.70 (2 H, s), 4.13–4.22 (2 H, m), 4.07 (1 H, quintet, *J* = 7 Hz), 3.54–3.64 (2 H, m), 2.49–2.76 (4 H, m). 2.18–2.33 (2 H, m), 1.88 (3 H, d, *J* = 1 Hz), 1.20–1.67 (4 H, m), 0.84–1.05 (7 H, m), 0.04 (9 H, s), 0.01 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 201.4, 166.4, 159.3, 135.7, 133.8, 127.7, 125.9, 116.5, 93.8, 72.8, 65.3, 61.5, 48.7, 32.9, 32.7 (×2), 32.0, 31.3, 25.2, 21.3, 17.9, 17.2, −1.6 (×6). Anal. Calcd for $C_{28}H_{52}O_5Si_2$: C, 64.07; H, 9.98. Found: C, 63.61; H, 10.11.

Methyl (4*R*)-3-(Methoxymethyl)-2-oxo-4-thiazolidinecarboxylate (38). To a stirred solution of **37**[27] (162 mg, 1.0 mmol) in 3 mL of DMF at 0 °C was added NaH (60% mineral oil suspension, 40 mg, 1.0 mmol). After 10 min chloromethyl methyl ester (67 μL, 1.0 mmol) was added, and the resulting yellow solution was stirred at 0 °C for 0.5 h. Ice and then saturated aqueous NH_4Cl were added to the mixture which was extracted with EtOAc (3 × 20 mL). The extract was washed with brine and dried ($MgSO_4$), and the solvent was removed by evaporation. The residue was purified by column chromatography on silica ($CHCl_3$–EtOAc, 2:1) to yield 103 mg (50%) of **38** as a colorless oil: IR (neat) 1750, 1688, 1685, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.01 (1 H, d, *J* = 11 Hz), 4.63 (1 H, d, *J* = 11 Hz), 4.55 (1 H, dd, *J* = 9, 3 Hz), 3.82 (3 H, s), 3.65 (1 H, dd, *J* = 12, 9 Hz), 3.44 (1 H, dd, *J* = 12, 3 Hz), 3.33 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 172.4, 170.2, 75.1, 58.4, 56.4, 52.9, 29.1; MS *m/z* 205, 189, 176, 146, 119, 116. Anal. Calcd for $C_7H_{11}NO_4S$: C, 40.97; H, 5.40; N, 6.83. Found: C, 41.05; H, 5.51; N, 6.77.

(4*R*)-4-Acetyl-2-oxothiazolidine (39). To a solution of (4*R*)-2-oxothiazolidine-4-carboxylic acid[28] (0.50 g, 3.4 mmol) in 30 mL of THF was added a solution of methyllithium in Et_2O (3.0 mL, 4.2 mmol) at −78 °C. To the resulting white suspension was added a solution of methylmagnesium chloride in THF (10 mL, 30 mmol) at −20 °C followed by a further quantity of methyllithium in Et_2O (5 mL, 7 mmol). The resulting pale brown solution was warmed to room temperature and stirred for 2 h, cooled to −78 °C, and poured into to 50 mL of a mixture of MeOH–THF (2:3). The solution was treated with saturated NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The brown residue was purified by column chromatography on silica (hexane–EtOAc, 1:1) to give 249 mg (50%) of **39**: mp 54–55 °C; $[\alpha]^{20}_D$ −75.8° (*c* 1.7, $CHCl_3$); IR (neat) 3259, 1725, 1680, 1357, 1220, 1180, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.25 (1 H, br s), 4.39 (1 H, dd, *J* = 8, 7 Hz), 3.70 (1 H, dd, *J* = 11, 8 Hz), 3.50 (1 H, dd, *J* = 11, 7 Hz), 2.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 204.7, 175.3, 62.6, 31.2, 26.3; MS *m/z* 145 (M^+), 103, 102, 101, 74 (100); HRMS 145.0196 (calcd for $C_5H_7NO_2S$ 145.0198).

(4*R*)-4-Acetyl-3-(methoxymethyl)-2-oxothiazolidine (40). To a stirred solution of **38** (100 mg, 0.49 mmol) in 2 mL of THF at −78 °C was added a solution of MeLi (1.4 M in Et_2O, 0.35 mL, 0.5 mmol) in 1 mL of THF, and the mixture was stirred at −78 °C for 0.5 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc (2 × 20 mL). The extract was washed with brine and dried ($MgSO_4$). The residue after removal of the solvent was purified by column chromatography on silica ($CHCl_3$–EtOAc, 2:1) to furnish 60 mg (65%) of **40** as an off-white gum: IR (neat) 1725, 1681, 1676, 1381, 1226, 1176, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.91 (1 H, d, *J* = 11 Hz), 4.51 (1 H, d, *J* = 11 Hz), 4.49 (1 H, dd, *J* = 9, 4 Hz), 3.65 (1 H, dd, *J* = 11, 9 Hz), 3.30 (3 H, s), 3.22 (1 H, dd, *J* = 11, 4 Hz), 2.29 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 203.9, 172.7, 75.3, 64.7, 56.5, 28.0, 26.4; MS *m/z* 189, 157, 146, 116, 88. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40; S, 16.94. Found: C, 44.41; H, 5.80; N, 7.32; S, 17.16.

Hydroxy Ketone 44. Anhydrous $CeCl_3$ was prepared by heating $CeCl_3 \cdot 7H_2O$ (74 mg, 0.20 mmol) under vacuum at 140 °C for 2 h. After cooling 1 mL of THF was added. The resulting white suspension was stirred at room temperature for 1 h prior to use. To a solution of **39** (20 mg, 0.14 mmol) in 0.5 mL of THF was added a solution of LDA in THF (0.5 mL, 0.30 mmol) at −78 °C. The solution was stirred for 5 min, and the suspension of $CeCl_3$ in THF was added. The resulting mixture was stirred for an additional 10 min, and a solution of **35** (17 mg, 0.03 mmol) in 1.0 mL THF was added. The resulting pale brown solution was stirred at −78 °C for 1 h, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil which was purified by column chromatography on silica (EtOAc–hexane, 1:1) to furnish 13 mg (60%) of **44** as a colorless oil: IR (neat) 3237, 2953, 1704, 1683, 1448, 1413, 1380, 1331, 1282, 1249, 1152, 1055, 1029, 859, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.69 (1 H, s), 6.49 (1 H, s), 6.27 (1 H, dd, *J* = 15, 11 Hz), 6.03 (1 H, br s), 5.98 (1 H, br s), 5.90 (1 H, t, *J* = 11 Hz), 5.73–5.58 (2 H, m), 5.45–5.35 (m), 5.03 (1 H, t, *J* = 11 Hz), 4.73–4.63 (2 H, m), 4.41–4.29 (1 H, m), 4.19–4.08 (4 H, m), 3.93–3.49 (6 H, m), 3.39–3.27 (1 H, m), 3.00–2.92 (1 H, m), 2.76–2.09 (7 H, m), 1.88 (3 H, s), 1.86–1.19 (6 H, m), 1.02–0.89 (7 H, m), 0.04, 0.03, 0.02, 0.01 (18 H, each s); ^{13}C NMR ($CDCl_3$) δ 207.9, 206.4, 174.2, 173.9, 166.4, 159.4, 135.8, 133.8, 133.7, 127.8, 125.9, 116.4, 95.0, 94.8, 93.2, 75.9, 69.4, 66.0, 65.9, 65.7, 64.8, 62.9, 62.7, 61.6, 46.1, 45.5, 41.4, 41.0, 40.8, 33.0, 32.9, 32.1, 31.3, 31.1, 31.0, 30.8, 25.2, 21.3, 18.0, 17.9, 17.2, 4.2, −1.6, −1.9; MS (CI) *m/z* 667 ($M^+ - 2$), 606, 533, 519, 503 (100), 444, 332, 298, 269, 231.

Tetrahydropyrans 45 and 46. To a solution of **44** (21 mg, 0.031 mmol) in 1 mL of CH_3CN was added 0.1 mL of concentrated HF at room temperature. The mixture was stirred for 2 h and then poured into 30 mL of EtOAc. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give a pale yellow oil. This material was dissolved in 2 mL of MeOH, and camphorsulfonic acid (50 mg) was added. The solution was stirred at room temperature for 4 h and poured into 30 mL of Et_2O. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified by column chromatography on silica (hexane–EtOAc, 3:1–1:1) to give 6.3 mg (36%) of **45** and 5.2 mg (30%) of **46**, both as colorless oils.

45: $[\alpha]^{20}_D$ +23.1° (*c* 0.13, $CHCl_3$); IR (neat) 3460, 3225, 2952, 1684, 1451, 1381, 1245, 1228, 1151, 1108, 1035, 989, 948, 858, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (1 H, dd, *J* = 15, 11 Hz), 5.92 (1 H, t, *J* = 11 Hz), 5.74–5.62 (3 H, m), 5.04 (1 H, t, *J* = 10 Hz), 4.19–4.00 (4 H, m), 3.52 (1 H, m), 3.43–3.23 (2 H, m), 3.19 (3 H, s), 2.73 (1 H, m), 2.57 (1 H, m), 2.28 (2 H, q, *J* = 8 Hz), 2.05 (4 H, dd, *J* = 11, 4 Hz), 1.89 (3 H, d, *J* = 1 Hz), 1.60–1.33 (6 H, m), 1.16 (1 H, dd, *J* = 11, 7 Hz), 0.97 (3 H, d, *J* = 7 Hz), 0.04 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 174.1, 166.6, 159.5, 135.9, 133.9, 127.8, 125.9, 116.7, 101.4, 69.9, 64.6, 61.7, 56.2, 47.8, 40.4, 35.9, 33.3, 33.0, 32.9, 31.9, 31.3, 28.0, 25.3, 21.3, 17.3, −1.5; MS *m/z* 553 (M^+), 552, 551, 550, 532, 504, 478, 460, 434, 416, 404, 398, 386 (100), 352, 326, 312, 294, 256, 234, 215. Anal. Calcd for $C_{28}H_{47}NO_6SSi$: C, 60.72; H, 8.55. Found: C, 61.01; H, 8.29.

46: $[\alpha]^{20}_D$ +9.30° (*c* 0.30, $CHCl_3$); IR (neat) 3409, 3228, 2951, 2928, 1684, 1452, 1379, 1360, 1246, 1227, 1151, 1088, 1038, 990, 946, 858, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (1 H, dd, *J* = 15, 11 Hz), 5.92 (1 H, t, *J* = 11 Hz), 5.75–5.61 (2 H, m), 5.04 (1 H, t, *J* = 10 Hz), 4.19–4.06 (4 H, m), 3.54 (1 H, m), 3.50–3.29 (3 H, m), 3.22 (3 H, s), 2.71 (2 H, m), 2.58 (1 H, m), 2.27 (2 H, m), 2.16–1.78 (2 H, m), 1.88 (3 H, d, *J* = 1 Hz), 1.67–1.12 (6 H, m), 1.02–0.82 (2 H, m), 0.97 (3 H, d, *J* = 7 Hz), 0.04 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 174.4, 166.6, 159.5, 135.9, 133.9, 127.7, 125.9, 116.6, 100.9, 70.0, 64.4, 61.7, 56.6, 47.9, 40.3, 37.2, 33.2, 33.0, 31.9, 31.3, 29.7, 29.4, 25.3, 21.4, 17.3, 4.3, −1.5; MS *m/z* 553 (M^+), 532, 504, 478, 460, 444, 434, 416, 404, 386 (100), 326, 312, 294, 256, 234, 215. Anal. Calcd for $C_{28}H_{47}NO_6SSi$: C, 60.72; H, 8.55. Found: C, 60.94; H, 8.67.

Hydroxy Acid 47. To a solution of **45** (4.3 mg, 0.008 mmol) in 0.5 mL of DMSO was added a solution of tetra-*n*-butylammonium fluoride in THF (30 μL, 0.03 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was poured into 30 mL of Et_2O and was washed with 1% aqueous

$NaHSO_4$. The solution was dried ($MgSO_4$), filtered, and concentrated to give a brown oil which was purified by column chromatography on silica (hexane–EtOAc–AcOH, 50:49:1) to afford 2.5 mg (71%) of **47** as a colorless oil: $[\alpha]^{20}_D$ +220° (*c* 0.25, $CHCl_3$); IR (neat) 3750, 3245, 2950, 1700, 1685, 1559, 1541, 1522, 1507, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (1 H, s), 6.37 (1 H, dd, J = 15, 11 Hz), 6.02 (1 H, t, J = 11 Hz), 5.82 (1 H, dt, J = 15, 5 Hz), 5.72 (1 H, s), 5.09 (1 H, t, J = 10 Hz), 4.19 (1 H, ddd, J = 10 Hz, J = 5, J = 1 Hz), 4.04 (1 H, m), 3.44 (1 H, dd, J = 12, 10 Hz), 3.38 (1 H, m), 3.29 (1 H, dd, J = 12, 5 Hz), 3.15 (3 H, s), 2.63–2.53 (2 H, m), 2.35–2.21 (2 H, m), 2.12–2.04 (2 H, m), 1.91 (3 H, d, J = 1 Hz), 1.76–1.08 (9 H, m), 1.01 (3 H, d, J = 7 Hz).

Hydroxy Acid 48. This substance was prepared from **46** (4.0 mg 0.007 mmol) in a manner analogous to that described for **47**. It was purified by column chromatography on silica (hexane–EtOAc–AcOH, 60:39:1) to give 1.9 mg (58%) of **48**: $[\alpha]^{20}_D$ +134° (*c* 0.19, $CHCl_3$); IR (neat) 3749, 3217, 2950, 1699, 1685, 1559, 1541, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71 (1 H, s), 6.33–6.22 (1 H, m), 5.94 (1 H, t, J = 11 Hz), 5.73–5.63 (2 H, m), 5.06–4.99 (1 H, m), 4.15–4.05 (2 H, m), 3.55 (1 H, m), 3.46–3.32 (2 H, m), 3.26 (3 H, s), 2.75 (1 H, m), 2.61 (2 H, m), 2.26 (2 H, m), 2.08–1.83 (2 H, m), 1.92 (3 H, d, J = 1 Hz), 1.70–1.16 (6 H, m), 0.98 (3 H, d, J = 7 Hz).

Latrunculin A Methyl Ketal (3). To a solution of Ph_3P (20 mg, 0.076 mmol) in 3 mL of benzene was added diethyl azodicarboxylate (8 mg, 0.046 mmol) at room temperature. The mixture was stirred for 5 min and then transferred to a solution of **47** (2.5 mg, 0.006 mmol) in 5 mL of benzene. The resulting solution was stirred at room temperature for 2 h. Concentration of the mixture, followed by column chromatography on silica (hexane–EtOAc 4:1–1:1), gave 1.6 mg (67%) of **3** as a white powder which was recrystallized from Et_2O–hexane: mp 142–147 °C; $[\alpha]^{20}_D$ +302° (*c* 0.16, $CHCl_3$); IR (KBr) 3416, 3250, 2951, 2931, 1698, 1659, 1459, 1436, 1379, 1279, 1222, 1133, 1091, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (1 H, dd, J = 15, 11 Hz), 6.04 (1 H, t, J = 11 Hz), 5.80 (1 H, dt, J = 15, 5 Hz), 5.64 (1 H, s), 5.43 (1 H, s), 5.16 (1 H, br s), 5.00 (1 H, t, J = 11 Hz), 4.17–4.12 (2 H, m), 3.47–3.35 (1 H, m), 3.34–3.27 (1 H, m), 3.32 (3 H, s), 2.80 (1 H, m), 2.34–2.12 (4 H, m), 1.94–1.81 (2 H, m), 1.92 (3 H, d, J = 1 Hz), 1.67 (1 H, d, J = 15 Hz), 1.48–1.32 (4 H, m), 1.15–0.95 (1 H, m), 1.01 (3 H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 174.5, 166.4, 157.8, 135.7, 132.2, 127.6, 124.9, 118.2, 99.8, 66.6, 63.1, 56.6, 47.9, 35.1, 32.1, 31.3, 31.0, 30.7, 29.6, 29.1, 28.0, 25.1, 21.6; MS m/z 436 (M^+ + 1), 435, 434 (100), 403, 360, 321.

Latrunculin A (1). A solution of **3** (1.0 mg, 0.002 mmol) in 0.6 mL of AcOH and 0.4 mL of H_2O was stirred at 60 °C for 2 h. The mixture was poured into 20 mL of EtOAc, and the solution was washed with saturated aqueous $NaHCO_3$ and brine. The solution was dried ($MgSO_4$), filtered, and concentrated, and the mixture was purified by column chromatography on silica (hexane–EtOAc, 2:1) to give 0.7 mg (72%) of **1** as a colorless oil: $[\alpha]^{20}_D$ +143° (*c* 0.07, $CHCl_3$); IR (neat) 3355, 2954, 2926, 1681, 1676, 1377, 1355, 1293, 1232, 1191, 1140, 1092, 1062, 990, 755, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (1 H, dd, J = 15, 12 Hz), 5.97 (1 H, t, J = 11 Hz), 5.73 (1 H, dt, J = 15, 6 Hz), 5.69 (1 H, s), 5.62 (1 H s), 5.43 (1 H, quintet, J = 3 Hz), 5.01 (1 H, t, J = 11 Hz), 4.25 (1 H, m), 3.89 (1 H, s), 3.85 (1 H, dd, J = 9, 6 Hz), 3.46 (1 H, dd, J = 12, 9 Hz), 3.44 (1 H, dd, J = 12, 6 Hz), 2.91–2.85 (1 H, m), 2.74–2.63 (2 H, m), 2.30–2.26 (2 H, m), 2.06 (1 H, dt, J = 15, 2 Hz), 1.92 (1 H, dd, J = 15, 4 Hz), 1.82 (3 H, d, J = 1 Hz), 1.79 (1 H, d, J = 14 Hz), 1.71 (1 H, m), 1.49–1.39 (3 H, m), 1.12–1.03 (1 H, m), 0.98 (d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 174.6, 165.3, 158.5, 136.5, 131.8, 127.1, 126.0, 117.3, 97.3, 68.2, 62.3, 61.2, 34.9, 32.6, 31.7, 31.4, 31.0, 30.4, 29.2, 28.7, 24.5, 21.6.

Epilatrunculin A Methyl Ketal (49). To a solution of Ph_3P (15 mg, 0.06 mmol) in 2 mL of benzene was added diethyl azodicarboxylate (5 mg, 0.03 mmol) at room temperature. The mixture was stirred for 5 min, transferred to a solution of **48** (1.9 mg, 0.004 mmol) in 3 mL of benzene, and stirred for 3 h at room temperature. Concentration of the solution, followed by column chromatography on silica (hexane–EtOAc, 3:1–1:1) gave 0.8 mg (44%) of **49** as a colorless oil: $[\alpha]^{20}_D$ +319° (*c* 0.08, $CHCl_3$); IR (neat) 3854, 3748, 3277, 2953, 2927, 2870, 1699, 1686, 1558, 1541, 1508, 1457, 1266, 1233, 1088, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.36 (1 H, dd, J = 15, 11 Hz), 6.04 (1 H, t, J = 11 Hz), 5.81 (1 H, dt, J = 15, 5 Hz), 5.65 (1 H, s), 5.41 (1 H, s), 5.15 (1 H, s), 5.00 (1 H, t, J = 11 Hz), 4.11 (1 H, m), 4.09 (1 H, t, J = 8 Hz), 3.47–3.23 (2 H, m), 3.37 (3 H, s), 2.79 (1 H, m), 2.35–2.12 (4 H, m), 1.92 (3 H, d, J = 1 Hz), 1.88–1.66 (3 H, m), 1.50–1.25 (4 H, m), 1.14–0.98 (1 H, m), 1.01 (3 H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 132.2, 127.7, 124.9, 118.2, 112.9, 80.1, 66.2, 63.1, 57.7, 48.2, 35.2, 32.1, 31.3, 30.8, 30.6, 29.6, 21.6, 19.3 (not all carbons shown).

Epilatrunculin A (50). A solution of **49** (0.6 mg. 0.001 mmol) in 0.6 mL of AcOH and 0.4 mL of H_2O was stirred at 60 °C for 1.5 h. The mixture was poured into Et_2O and washed with saturated aqueous $NaHCO_3$ and brine. The solution was dried ($MgSO_4$), filtered, and concentrated to leave a pale yellow oil which was purified by column chromatography on silica (hexane–EtOAc, 3:2) to give 0.4 mg (69%) of **50** as a colorless oil: $[\alpha]^{20}_D$ +333° (*c* 0.04, $CHCl_3$); IR (neat) 3427, 3414, 2955, 2925, 2855, 1685, 1292, 1279, 1091, 1062, 1051, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (1 H, dd, J = 15 Hz), 5.99 (1 H, t, J = 11 Hz), 5.74 (1 H, dt, J = 15, 6 Hz), 5.67 (1 H, s), 5.52 (1 H, s), 5.28 (1 H, br s), 4.99 (1 H, t, J = 11 Hz), 4.31 (1 H, m), 3.88 (1 H, dt, J = 8, 1 Hz), 3.43 (1 H, dd, J = 11, 8 Hz), 3.33 (1 H, d, J = 1 Hz), 3.31 (1 H, dd, J = 11, 8 Hz), 3.22–3.13 (1 H, m), 2.72 (1 H, m), 2.54–2.45 (1 H, m), 2.31–2.21 (2 H, m), 2.12 (1 H, dt, J = 15, 2 Hz), 1.93 (3 H, d, J = 1 Hz), 1.29–1.63 (3 H, m), 1.50–1.38 (3 H, m), 1.15–1.05 (1 H, m), 1.01 (1 H, d, J = 7 Hz); HRMS 421.1923 (calcd for $C_{22}H_{31}NO_5S$ 421.1923).

Acknowledgment. We are grateful to Professor Phillip Crews, University of California, Santa Cruz, and Professor Yoel Kashman, Tel Aviv University, for samples of natural latrunculin A. Financial support was provided by the National Institutes of Health (AI10964) and the National Science Foundation (CHE-9015466).