Total Synthesis of the Latrunculins

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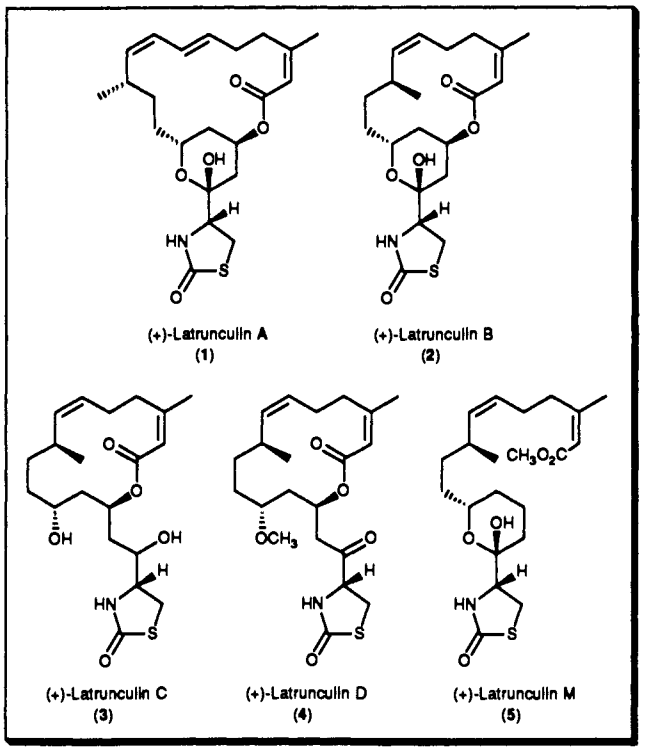
Abstract: The total syntheses of (+)-latrunculin A (**1**) and (+)-latrunculin B (**2**), two architecturally novel toxins isolated from the Red Sea sponge *Latrunculia magnifica* (Keller), have been achieved via highly convergent and stereocontrolled routes (longest linear sequences, 16 and 12 steps, respectively). Formal syntheses of scalemic latrunculins C (**3**) and M (**5**) also derive from the construction of **2**. Central features of the unified synthetic strategy include the aldol reaction of aldehyde (−)-**12** with methyl ketone (−)-**13**, a novel acid-catalyzed reorganization–equilibration of ortho ester (−)-**11**, and Mitsunobu macrolide cyclization.

The sponge *Latrunculia magnifica* (Keller) enjoys remarkable freedom from predation, thriving in exposed colonies in the Red Sea.[1] As a defense mechanism, the sponge exudes a reddish fluid which causes many organisms to flee. Upon exposure to this secretion in an aquarium, fish suffer tremors and loss of balance, followed within minutes by hemorrhaging and death.[1] These intriguing observations by Kashman and co-workers led to a detailed investigation of *L. magnifica* metabolites, and in 1980 the Tel Aviv group reported the isolation and characterization of two toxins, latrunculins A and B (**1** and **2**).[2]

The structure of latrunculin A was elucidated through extensive ^1H and ^{13}C NMR studies, in conjunction with single-crystal X-ray analysis of the *O*-methyl derivative.[2,3] Degradation experiments revealed the absolute configuration, as shown.[3] More recently, **1** has been found in the Pacific nudibranch *Chromodoris elisabethina* and in the Fijian sponge *Spongia mycofijiensis*.[4,5] The structure and absolute stereochemistry of B were then determined by spectroscopic comparison with **1**.[2] Latrunculins A and B appear to be the first macrolides isolated from a marine species and the first natural products to embody the 2-thiazolidinone moiety. Kashman subsequently described several additional toxins, including latrunculins C (**3**) and D (**4**) in 1985[3c] and latrunculin M (**5**) in 1989.[3f] It should be noted that the structures originally reported for C and D were reversed.[3c]

Sub-micromolar quantities of **1** and **2** induce striking, reversible changes in cell morphology, disrupt the organization of microfilaments, and suppress microfilament-mediated processes during cell reproduction.[3a,6] Latrunculin A also binds reversibly to the cytoskeletal protein actin and inhibits actin polymerization.[6c] Accordingly, this family of toxins may serve as specific probes of actin microfilament structure and function, complementing the characteristic behavior of cytochalasin D.[6c] Their remarkable biological profiles and novel architecture have established the latrunculins as significant targets for total synthesis. In this full account, we describe experiments culminating in their construction in scalemic form.[7,8]



Retrosynthetic Analysis: Development of a Unified Synthetic Strategy. From the outset, we sought to devise a unified strategy for the preparation of latrunculins A and B as well as other congeners. Our retrosynthetic analysis thus led to a common advanced intermediate **6** via cleavage of the macrocyclic ester moiety and scission of the cis olefin (Scheme I). In the synthetic direction, union of the northern and southern hemispheres would occur via a Wittig reaction[9] followed by macrolactonization.

(1) Neeman, I.; Fishelson, L.; Kashman, Y. *Mar. Biol.* **1975**, *30*, 293.
(2) Kashman, Y.; Groweiss, A.; Shueli, U. *Tetrahedron Lett.* **1980**, *21*, 3929.
(3) (a) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493. (b) Groweiss, A.; Shueli, U.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3512. (c) Kashman, Y.; Groweiss, A.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron* **1985**, *41*, 1905. (d) Kashman, Y.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron Lett.* **1986**, *27*, 1367. (e) Blasberger, D.; Green, D.; Carmely, S.; Spector, I.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 459. (f) Blasberger, D.; Carmely, S.; Cojocaru, M.; Spector, I.; Shochet, N. R.; Kashman, Y. *Liebigs Ann. Chem.* **1989**, 1171.
(4) Okuda, R. K.; Scheuer, P. J. *Experientia* **1985**, *41*, 1355.
(5) Kakou, Y.; Crews, P.; Bakus, G. J. *J. Nat. Prod.* **1987**, *50*, 482.
(6) For leading references, see: (a) Cone, M.; Breuner, S. L.; Spector, I.; Kom, E. D. *FEBS Lett.* **1987**, *13*, 316. (b) Schatten, G.; Schatten, H.; Spector, I.; Cline, C.; Paweletz, N.; Simerly, C.; Petzelt, C. *Exp. Cell Res.* **1986**, *166*, 191. (c) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell Motil. Cytoskeleton* **1989**, *13*, 127.
(7) (a) Zibuck, R.; Liverton, N. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2451. (b) Smith, A. B., III; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Org. Chem.* **1990**, *55*, 3977. (c) Also see: 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.
(8) Concurrent with our work, White and Kawasaki (Oregon State University) also completed a total synthesis of (+)-latrunculin A: White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991. For an approach to the pyran unit of the latrunculins, see: Hirama, M.; Sugi, K.; Itô, S. *Abstracts of Papers*, International Chemical Congress of Pacific Basin Societies, Honolulu, HI; American Chemical Society: Washington, DC, 1984; ORGN 10E104.
(9) (a) For a recent review on Wittig olefination, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. Also see: (b) Schaaf, T. K.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 2921. (c) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977.

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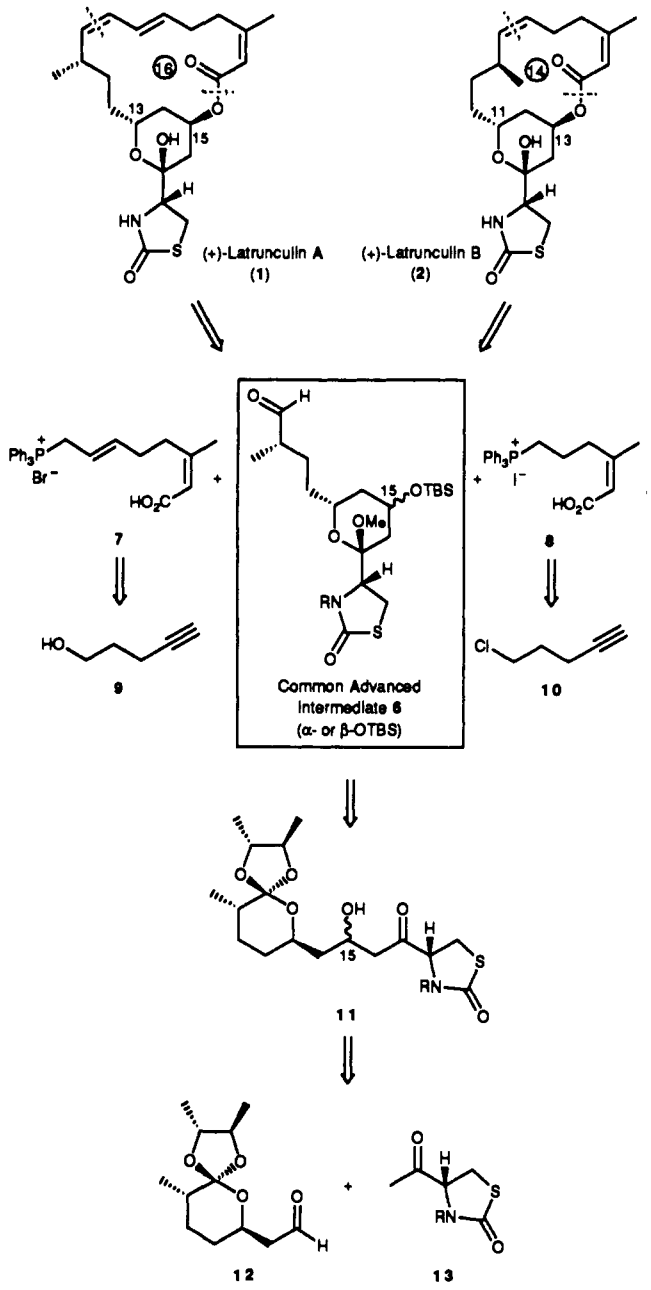
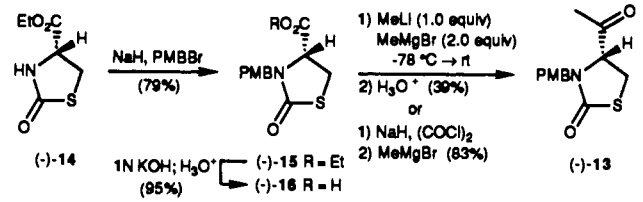
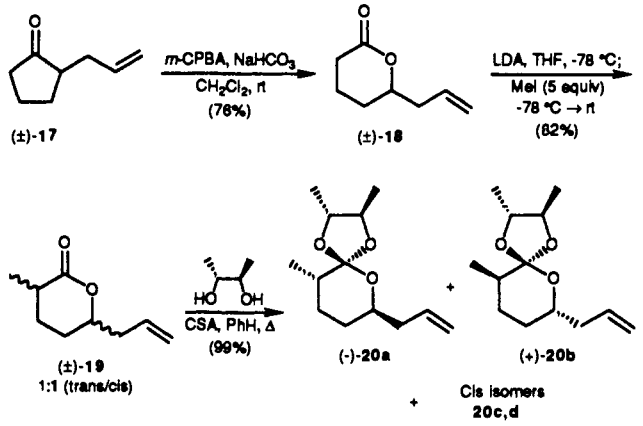
Scheme I



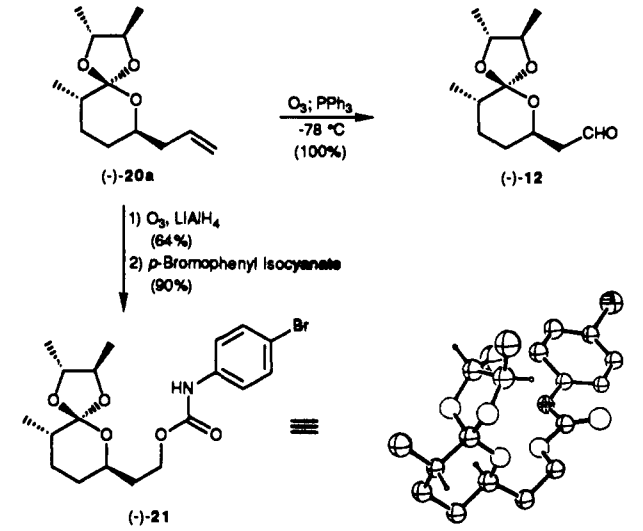
Scheme II



Scheme III



Scheme IV



The northern hemisphere phosphonium salts (**7** and **8**) would be available from the acetylenes **9** and **10**, whereas aldehyde **6** was envisioned to arise from hydrolysis and reorganization of **11**, the aldol derived from aldehyde **12** and methyl ketone **13**. We recognized that aldol reactions of methyl ketone enolates frequently suffer from poor stereoselectivity,[10] Accordingly, we designed alternative modes of macrocyclization which would accommodate both C(15) configurations (latrunculin A numbering) in **11**. If the α epimer predominated, ring closure would be effected with inversion of configuration via the Mitsunobu reaction,[11] whereas the β isomer could be lactonized with retention via carboxy activation,[12] Finally, the requisite enantiomer of ketone **13** would be secured by elaboration of L-cysteine ethyl ester, and aldehyde **12** would derive from (±)-2-allylcyclopentanone and (+)-(*R*,*R*)-2,3-butanediol,

Preparation of Aldehyde (−)-12 and Ketone (−)-13, Key Building Blocks for the Latrunculins. As our point of departure, L-cysteine ethyl ester was converted to ethyl 2-oxo-4-thiazolidinecarboxylate (**14**, Scheme II) via a published procedure,[13] Unbeknown to us, the selection of a protecting group for the amide nitrogen was critical (vide infra); the 4-methoxybenzyl derivative[14] ultimately proved to be satisfactory, Hydrolysis of the resultant ester (−)-**15** then afforded carboxylic acid (−)-**16**, We initially transformed **16** to the requisite methyl ketone **13** via the method of Rapoport,[15] However, the modest 39% yield for the latter process prompted us to devise an alternative protocol, whereby reaction of the derived acid chloride with methylmagnesium bromide[16] furnished (−)-**13** (R = PMB) in 83% yield (63% overall from **14**).

Aldehyde (−)-**12** was prepared in four steps from (±)-2-allylcyclopentanone (**17**).[17] Baeyer–Villiger oxidation generated

(10) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, p 111 and references cited therein.

(11) Mitsunobu, O. *Synthesis* **1981**, 1. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455.

(12) See, for example: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. Back, T, G. *Tetrahedron* **1977**, *33*, 3041.

(13) Kubodera, N.; Nagano, H.; Takagi, M.; Matsunaga, I. *Heterocycles* **1982**, *18*, 259.

(14) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.

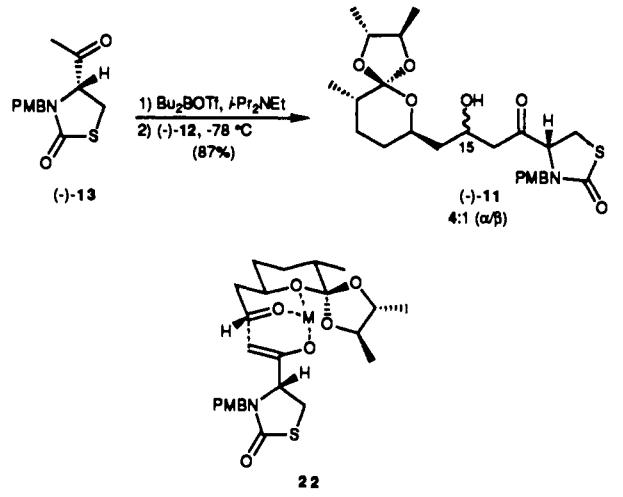
(15) Knudsen, C.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260.

(16) Shirley, D. A. *Org. React.* (*N.Y.*) **1954**, *8*, 28.

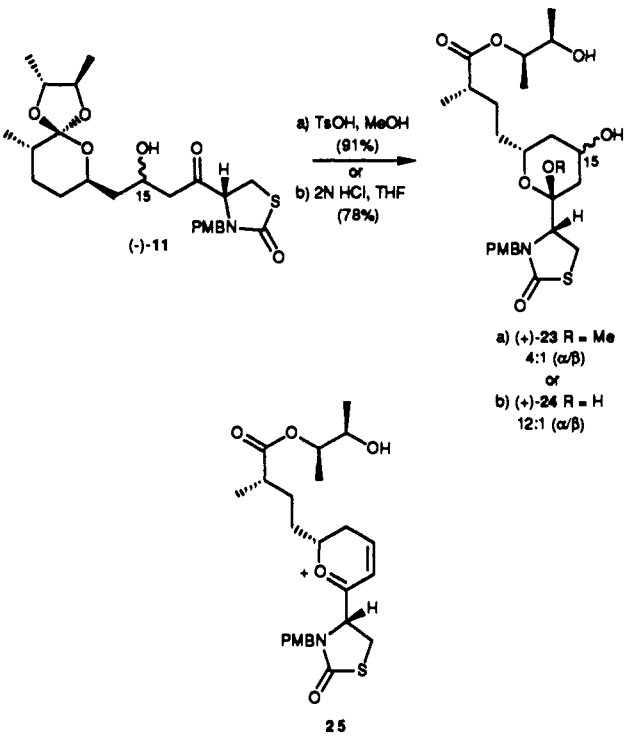
lactone (±)-**18** (Scheme III), which in turn was methylated with lithium diisopropylamide and methyl iodide to furnish (±)-**19** as a 1;1 mixture of diastereomers, Ortho ester formation with (+)-(*R*,*R*)-2,3-butanediol effected both resolution and equilibration; the trans;cis ratio improved to 6;1 (**20a,b**;**20c,d**) (99% yield), presumably reflecting the more advantageous conformational bias of the ortho esters vis-â-vis the starting lactones.[18,19] Moreover, the diastereomers were very readily separated by preparative HPLC, affording the trans isomers **20a** and **20b** in 40–42% yields, To ascertain the absolute configurations of the major products, (−)-**20a** was converted to the *p*-bromophenyl carbamate derivative (−)-**21** via a two-step sequence (Scheme IV; ozone, lithium aluminum hydride followed by *p*-bromophenyl isocyanate; 57% yield overall), Single-crystal X-ray analysis of (−)-**21**, in conjunction with the known absolute stereochemistry of the butanediol moiety, then revealed that (−)-**20a** was in fact the requisite diastereomer. Ozonolysis of the ortho ester furnished enantiomerically pure aldehyde (−)-**12** almost quantitatively,

The Aldol Reaction; Union of Aldehyde (−)-12 and Ketone (−)-13. The aldol reaction was initially effected via deprotonation of **13** with lithium bis(trimethylsilyl)amide (1,1 equiv, THF, −78 °C) followed by addition of **12** (1,2 equiv), affording (−)-**11** (R = PMB) in ca, 35% yield as an inseparable 4;1 mixture of diastereomers (Scheme V), The C(15) α configuration of the major isomer was initially assigned via NMR and X-ray analyses of related compounds,[20] Use of the zinc enolate derived from **13** [lithium bis(trimethylsilyl)amide (1,1 equiv), zinc chloride (1,5 equiv), and THF][21] increased the yield of **11** to ca, 58%. Optimal results were realized by employing boron enolate technology [i,e,, treatment of (−)-**13** with dibutylboron triflate (2.5 equiv) and Hunig's base (3.0 equiv) at −78 °C, followed by addition of (−)-**12**];[22a–c] the latter protocol furnished (−)-**11** in 87% yield, Interestingly, the 4;1 diastereomer ratio remained essentially invariant despite significant changes in reaction conditions and yields, Transition-state model **22** may account for selective generation of the C(15) α epimer observed with the lithium and zinc enolates (Scheme V), A rationale for the boron enolate selectivity, however, remains obscure,[22d]

Scheme V



Scheme VI

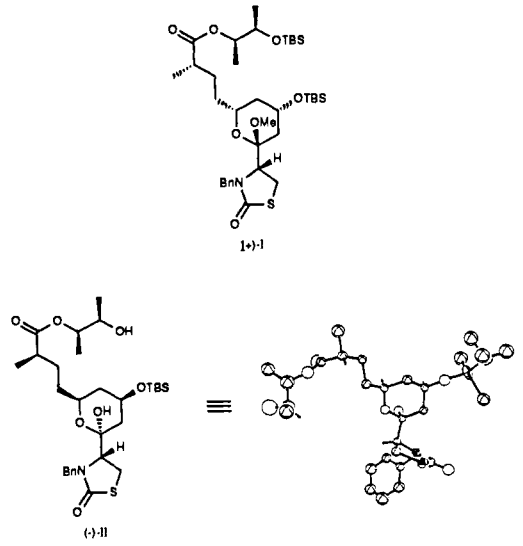


(17) Bernstein, P. R. *Tetrahedron Lett.* **1979**, 1015. 2-Allylcyclopentanone is also readily available via modification of the *Organic Synthesis* procedure: Howard, H. L.; Lorette, N. B. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 25.

(18) The parent δ-valerolactone adopts half-chair and boat conformations of nearly equal energy [see: Lambert, J. B.; TeVrucht, M. L. E. *Org. Magn. Reson.* **1984**, *22*, 613. Philip, T.; Cook, R. L.; Malloy, T. B., Jr.; Allinger, N. L.; Chang, S.; Yuh, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2151]. Similar conformational preferences probably account for the ineffectiveness of our efforts to equilibrate the diastereomeric α-methyl lactones (±)-**19**, which furnished a 60:40 mixture at best. Mechanistically, the epimerization that accompanies ortho ester formation would appear to occur via ketene acetal intermediates. We also note that poor stereoselectivity in alkylations of substituted δ-valerolactones has been observed previously: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Florida, 1984; Vol. 3, pp 54–56. Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978**, *43*, 378.

(19) J. D. White et al. exploited a similar enhancement in their boromycin synthesis: White, J. D.; Avery, M. A.; Choudry, S. C.; Dhingra, O. P.; Kang, M.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517.

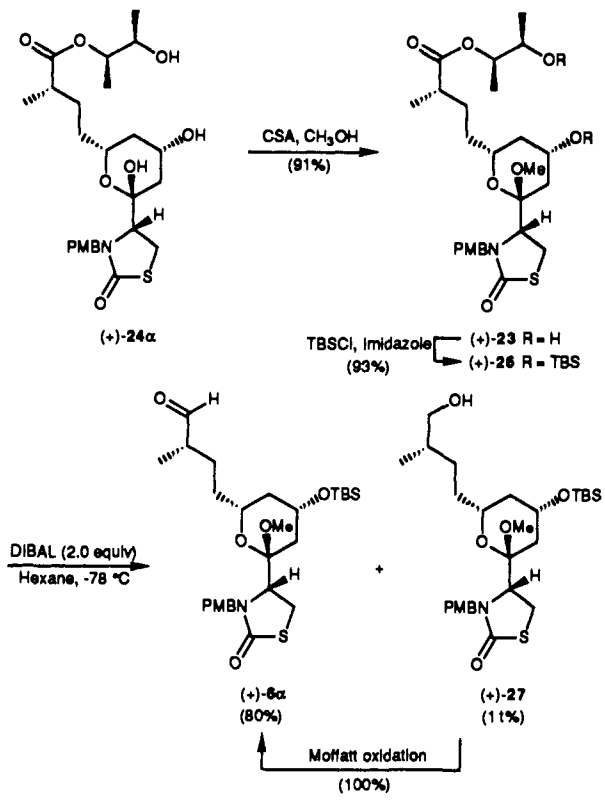
(20) NMR analysis of the *N*-benzyl analogue (vide infra) of the major epimer of (+)-**26** [i.e., (+)-**l**] furnished a tentative assignment of the C(15) α configuration. This conclusion was buttressed by the X-ray structure of (−)-**ll**, prepared from the aldol product of aldehyde (+)-**12** [available from ortho ester (+)-**20b**] with the *N*-benzyl analogue of (−)-**13**, followed by NMR comparison of **ii** and **l**. For details, see: Zibuck, R. Ph.D. Thesis, University of Pennsylvania, 1986 (available from University Microfilms Int., Order No. DA8624044). See also ref 7c. The stereochemistry of the major epimer of **11** was ultimately verified via X-ray analyses of (+)-**41** and (+)-**46** and the total syntheses of latrunculins A and B.



(21) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(22) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, Chapter 1. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, pp 1–116. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (d) Masamune, S. In *Organic Synthesis Today and Tomorrow*; Trost, B. M., Ed.; Pergamon Press: New York, 1981; pp 204–6.

Scheme VII

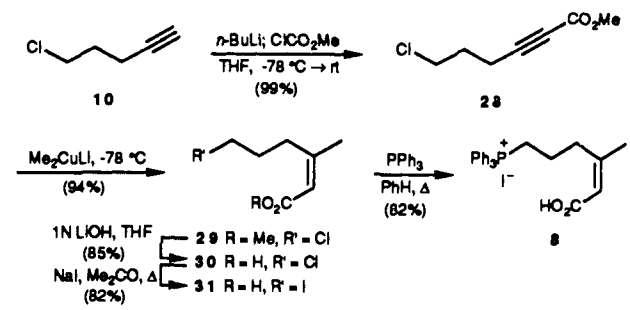


Reorganization of Ortho Ester (−)-11 via a Novel Acid-Catalyzed Equilibration; Cornerstone of the Latrunculin Synthetic Venture. With an efficient route to the aldols (−)-**11** in hand, we turned our attention to the proposed ortho ester reorganization, Rearrangement catalyzed by *p*-toluenesulfonic acid in methanol did furnish the methyl acetals **23** as the corresponding 4:1 mixture of C(15) diastereomers (91% yield; Scheme VI), Much to our delight, exposure of the aldols to 2 N aqueous hydrochloric acid in THF (1:5, room temperature, 24 h) effected C(15) equilibration as well, furnishing hemiacetal (+)-**24** as a 12:1 mixture of easily separable α and β epimers in 78% yield. Oxonium ion **25** presumably serves as a template for introduction of the equatorial C(15) hydroxyl, whereas the hemiacetal stereochemistry is governed by the anomeric effect, We previously observed a similar equilibration in our total synthesis of the talaromycins.[23] In preparative experiments, the aldol reaction and subsequent reorganization were performed as a single operation, without isolation of **11**, Reequilibration of the minor isomer **24**β further enhanced the overall yield,

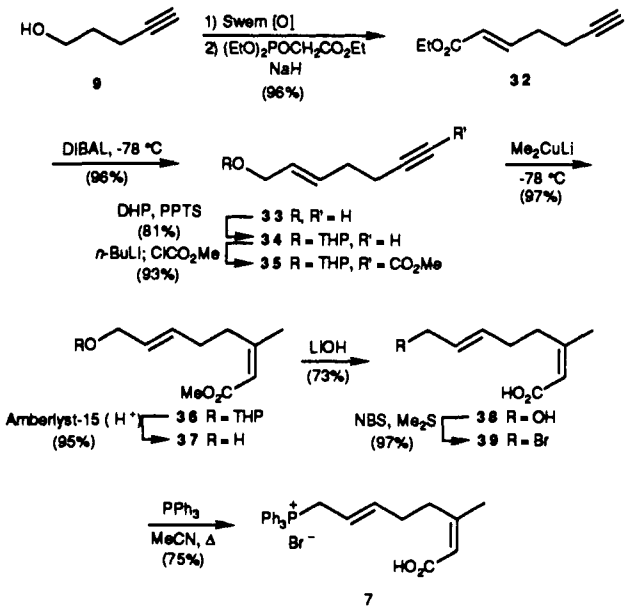
Methanolysis of (+)-**24**α (camphorsulfonic acid, methanol/toluene; Scheme VII) provided methyl acetal (+)-**23** as a single diastereomer, whereupon hydroxyl protection furnished bis(*tert*-butyldimethylsilyl) ether (+)-**26** in 81% yield for the two steps, The common advanced intermediate (+)-**6**α (R = PMB) was then prepared in 80% yield by DIBAL reduction in hexane at −78 °C, Alcohol (+)-**27**, a minor byproduct, afforded **6**α quantitatively upon Moffatt oxidation,

Preparation of Northern Hemisphere Wittig Reagents 8 and 7. The phosphonium salt **8**, required for the synthesis of latrunculin B, was generated from 5-chloro-1-pentyne (**10**), as outlined in Scheme VIII, Carbalkoxylation of **10** (*n*-butyllithium, methyl chloroformate) provided **28**, which underwent stereoselective[24] lithium dimethylcuprate addition to afford **29**. Saponification with lithium hydroxide followed by Finkelstein reaction[25] of chloro

Scheme VIII



Scheme IX



acid **30** gave iodide **31**, and reaction with triphenylphosphine then furnished **8**, The overall yield for this five-step sequence was 53%,

The northern hemisphere phosphonium salt for latrunculin A (**7**) was prepared in a similar fashion from 4-pentyn-1-ol (**9**) (Scheme IX), Swern oxidation followed by Wadsworth–Emmons olefination led to unsaturated ester **32**, Chemoselective reduction with DIBAL and protection of the resultant alcohol **33** afforded tetrahydropyranyl ether **34**, The terminal alkyne was then converted to unsaturated ester **36** in the manner described above. Acidic depyranylation of the latter and saponification of **37** with lithium hydroxide gave hydroxy acid **38**. After bromination with *N*-bromosuccinimide, the requisite salt **7** was secured via addition of **39** to triphenylphosphine (34% yield, 10 steps).

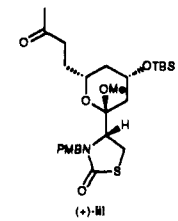
Final Elaboration of (+)-Latrunculin B (2). Wittig coupling[9] of (+)-**6**α with the dianion derived from **8** [potassium bis(trimethylsilyl)amide (5,8 equiv), THF] furnished the cis alkene (−)-**40** in 86% yield (Scheme X), Successful olefination required careful removal of oxygen from the reaction medium,[26] The

(23) Smith, A. B., III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469. See also: Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schönberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489. Similar C(15) epimerizations observed by Kashman et al.[3f] probably proceed via analogous pathways.

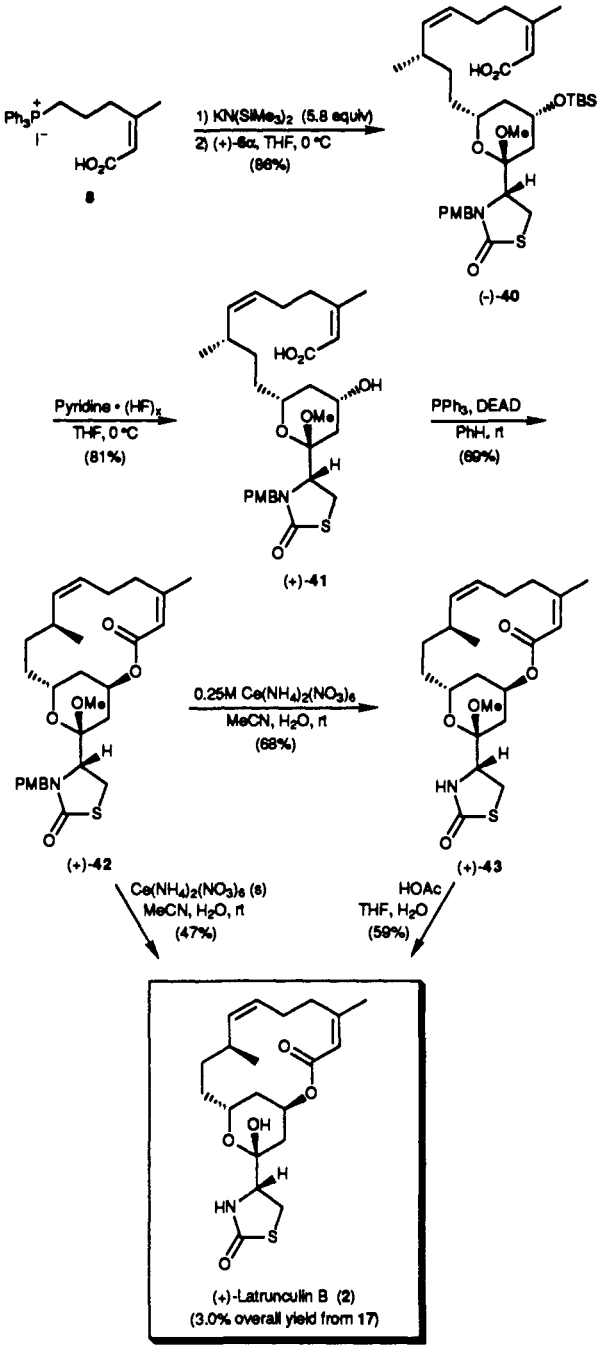
(24) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

(25) Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528.

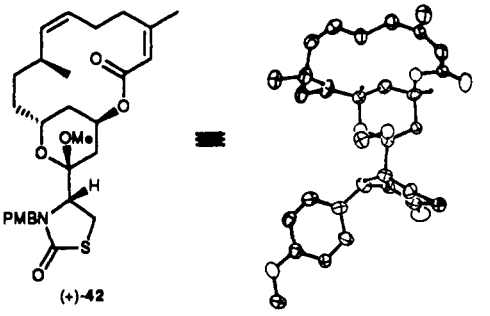
(26) Under standard conditions (i.e., without scrupulous deoxygenation), methyl ketone (+)-**iii** was produced as the only isolable product, presumably via fragmentation of an α-hydroperoxide. For precedent, see: Barton, D. H. R.; Faulkner, D. J.; Templeton, J. F. *J. Chem. Soc. C* **1962**, 4743. We thank Professor Barton for kindly informing us of the latter study.



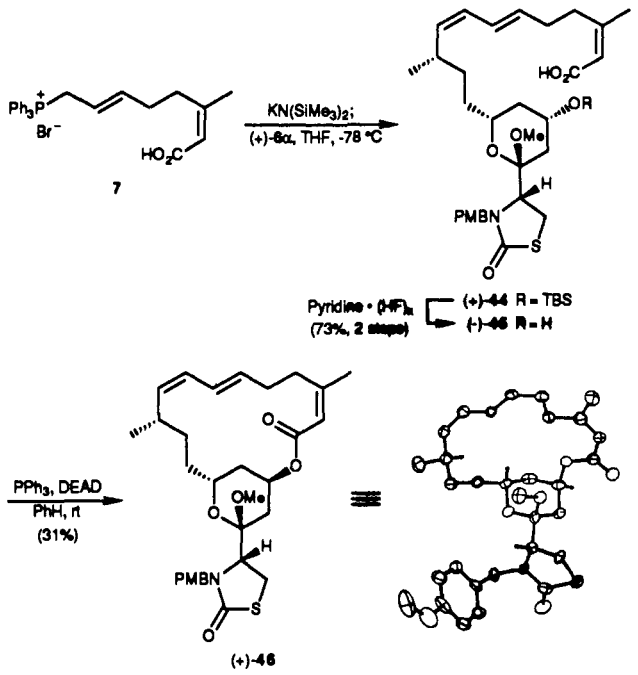
Scheme X



Scheme XI



Scheme XII



unwanted trans isomer could not be detected by 250-MHz ^{1}H NMR analysis, Deprotection with pyridine·$(HF)_x$[27] then provided hydroxy acid (+)-**41** (81%). The unnatural α configuration at C(15) dictated macrocyclization with inversion of configuration; the Mitsunobu protocol proved ideal, as exposure of **41** to diethyl azodicarboxylate and triphenylphosphine in benzene gave lactone (+)-**42** in 69% yield as the sole product, The relative configuration of **42** was confirmed by single-crystal X-ray analysis (Scheme XI).

All that remained to complete the total synthesis of (+)-latrunculin B was deprotection of the carbamate nitrogen followed by ketal hydrolysis, Earlier we had synthesized the *N*-benzyl and *N*-(3,4-dimethoxybenzyl) derivatives of latrunculin B, but were unable to remove either protecting group under a variety of conditions,[28] Other recent work further illustrates the striking robustness of N-benzylated amides, in contrast with the facile cleavage characteristic of benzylamines,[29] Finally we discovered that the 4-methoxybenzyl moiety of **42** could be cleaved readily upon exposure to ceric ammonium nitrate [CAN, 2,0 equiv, 0,25 M in acetonitrile/water (3;1)],[30] affording (+)-**43** in 68% yield (Scheme X), Acetal hydrolysis [acetic acid/THF/water (3;1;1), 60 °C] then furnished (+)-latrunculin B (**2**). A small amount (15%) of **2** was also generated in the oxidation of **42**; indeed, **2** could be directly obtained in 47% yield by addition of solid CAN to a solution of **42** in acetonitrile/water, Synthetic latrunculin B was identical in all respects with a sample of natural material,[31] Thus the first, and to date only, total synthesis of (+)-latrunculin B has been achieved in a highly convergent and stereocontrolled

(27) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

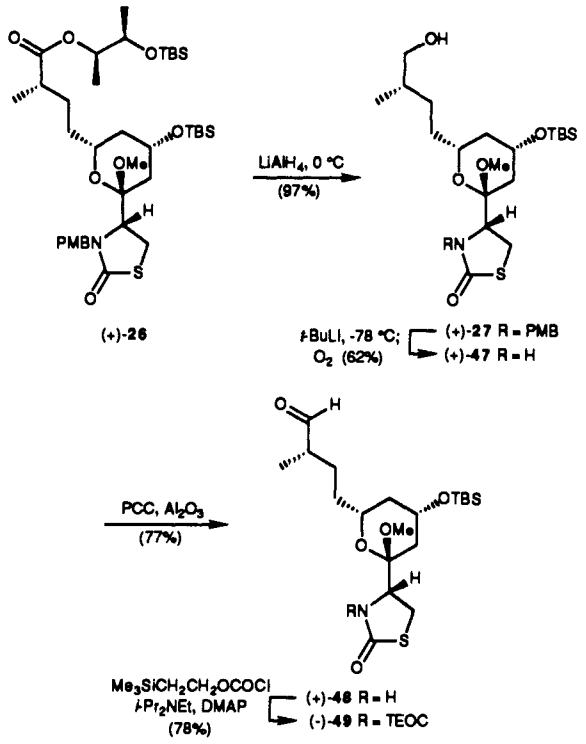
(28) The scarcity of the natural latrunculins precluded preliminary studies of nitrogen protection and deprotection. We initially completed a synthesis of *N*-benzyllatrunculin B, but were unable to debenzylate this material via transhydrogenation, direct hydrogenation, oxidation, or electrophile-assisted nucleophilic displacement (e.g., with trimethylsilyl iodide). We then synthesized *N*-(3,4-dimethoxybenzyl)latrunculin B (**iv**) only to find that this group likewise could not be removed via known methods. In fact, **iv** could be *stored* in DDQ, the reagent most commonly employed to cleave the dimethoxybenzyl moiety. It should be emphasized that only a highly economic (i.e., short) synthesis of latrunculin B could accommodate the development of a viable end-game in this fashion.

(29) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451 and references cited therein.

(30) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1011. Williams, R. M.; Armstrong, R. M.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733.

(31) We thank Professor Hirama (Tohoku University) for samples of natural latrunculin B and latrunculin A, originally provided by Professor Kashman (Tel Aviv University). We also thank Professor Kashman for high-field ^{1}H NMR spectra of latrunculins A and B.

Scheme XIII



fashion (longest linear sequence, 12 steps).

Formal Total Syntheses of (+)-Latrunculins C and M. Kashman et al. have converted natural latrunculin B to latrunculin C (**3**) and its C(15) epimer by reduction with sodium borohydride,[3c,f] They also prepared (+)-latrunculin M (**5**) from (+)-**2** via a four-step sequence,[3f] We have therefore completed formal syntheses of these two additional members of the latrunculin family.

A Revised End-Game for (+)-Latrunculin A (1). By analogy with the successful route to latrunculin B, the construction of A proceeded uneventfully to furnish crystalline *O*-methyl-*N*-(4-methoxybenzyl)latrunculin A [(+)-**46**, Scheme XII], Unfortunately, we were then unable to deprotect the carbamate nitrogen; the sensitive diene moiety apparently interfered with this critical operation, Single-crystal X-ray analysis of **46** did however establish that the macrocyclic lactone embodied the requisite relative stereochemistry,

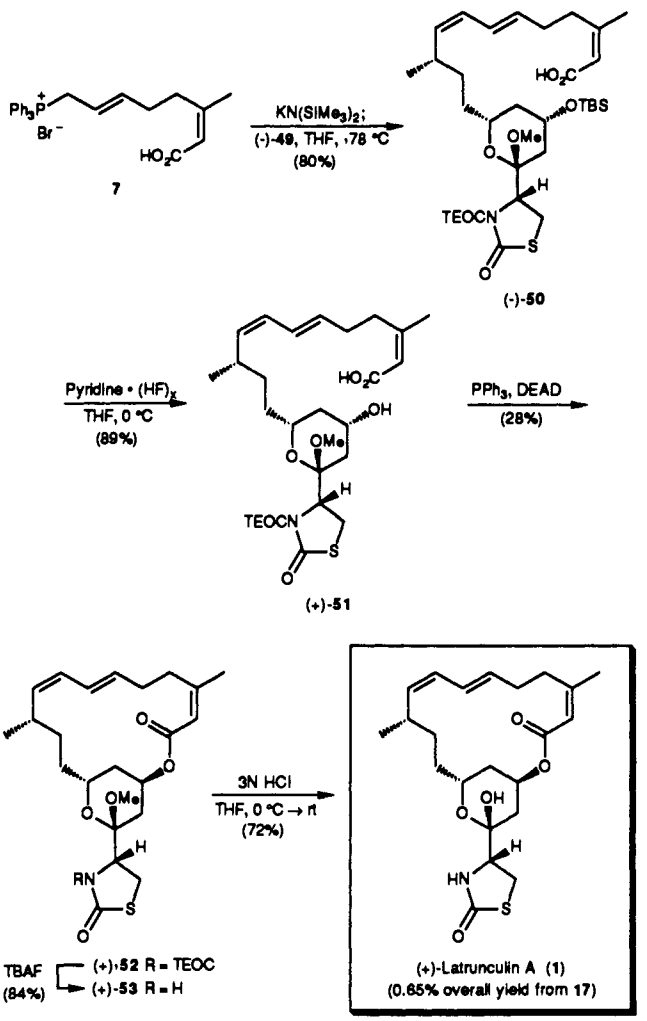
We circumvented this unanticipated difficulty by executing a protecting group interchange, To this end, lithium aluminum hydride reduction of ester (+)-**26** (Scheme XIII) followed by removal of the 4-methoxybenzyl group via the Williams protocol (*tert*-butyllithium, O_2, −78 °C) furnished (+)-**47** in 60% overall yield,[29] The modified southern hemisphere aldehyde (−)-**49** was then secured by oxidation (pyridinium chlorochromate, activated alumina)[32] and N-acylation with [β-(trimethylsilyl)ethoxy]-carbonyl (TEOC) chloride,[33] The yield for this two-step operation was 60%.

Wittig olefination proceeded as in the latrunculin B series with minor modifications: generation of the dianion of **7** (2.0 equiv) with sodium bis(trimethylsilyl)amide (3,8 equiv) followed by rapid addition of (−)-**49** furnished the desired cis,trans diene (−)-**50** with 7;1 stereoselectivity (80% yield; Scheme XIV), Desilylation and Mitsunobu macrocyclization then gave (+)-**52**, the *O*-methyl-*N*-TEOC derivative of latrunculin A, in 25% yield from **50**,

Final unmasking of (+)-latrunculin A (**1**) entailed removal of the TEOC group with tetrabutylammonium fluoride (84% yield) and acidic hydrolysis of the resultant methyl ketal (+)-**53** (49% yield, 72% based upon recovered starting material), Synthetic **1** proved to be identical with a sample of the natural product.[31]

(32) Cheng, Y.-S.; Liu, W.-L.; Chen, A. *Synthesis* **1980**, 223.
(33) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

Scheme XIV



Experimental Section[34]

***N*-(4-Methoxybenzyl)thiazolidinone (−)-15.** A suspension of sodium hydride (80% oil dispersion, 0.950 g, 31.7 mmol) in dry DMF (100 mL) was cooled to 0 °C, and **14**[13] (4.62 g, 26.4 mmol) dissolved in DMF (25

(34) **Materials and Methods.** Reactions were carried out in flame-dried glassware under an argon atmosphere, except where otherwise noted. All solvents were reagent grade. Ether and THF were distilled from sodium and benzophenone. Acetonitrile, benzene, and methylene chloride were distilled from calcium hydride. Dimethylformamide was dried over barium oxide and distilled. Diisopropylamine, triethylamine, and pyridine were distilled from KOH and stored over KOH. Acetone was dried over potassium carbonate prior to distillation. Analytical thin-layer chromatography was performed with E. Merck 250-μm precoated silica gel plates with fluorescent indicator. Preparative thin-layer chromatography was carried out with E. Merck 500-μm precoated silica gel plates. Flash chromatography[35] was performed with distilled solvents and E. Merck 230–400 mesh silica gel. Solutions of *n*-butyllithium and *tert*-butyllithium (Aldrich) were standardized by titration with diphenylacetic acid. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform with a Bruker WP200 (at 200 and 50.3 MHz, respectively), WP250 or AM250 (250 and 62.9 MHz), or AM500 (500 and 125 MHz) spectrometer; chemical shifts are reported in δ values relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were obtained by using either a Thomas-Hoover apparatus or a Bristoline hot-stage microscope and were corrected. Microanalyses were performed by the Rockefeller University Microanalytical Laboratories under the direction of S. T. Bella. High-resolution mass spectra were measured by the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi-Perkin-Elmer RMH-2 or a VG 70-70 Micromass spectrometer interfaced with a Kratos DS-50-s data system. Gas–liquid chromatography (GLC) analyses were performed on a Hewlett-Packard 5790A chromatograph equipped with a Hewlett-Packard 25 m × 0.2 mm × 0.33 μm Ultra 1 (cross-linked methyl silicone) column. Chromatograms were recorded on a Hewlett-Packard 3390a integrator. High-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500 HPLC with two PrepPak columns in series.

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

mL) was added slowly. The reaction was stirred for 30 min, and a solution of 4-methoxybenzyl bromide[14] (6,86 g, 34.3 mmol) in DMF (7 mL) was added. The mixture was stirred for 1,5 h at room temperature, poured into ether, and washed with water, The aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 4:1) gave **15** as a colorless oil (6.144 g, 78.9% yield): $[\alpha]^{25}_D$ −95.3° (*c* 1.16, absolute EtOH); IR ($CHCl_3$) 3000, 1740 (s), 1670 (s), 1610, 1510, 1245, 1170, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3 H), 3,33 (dd, J = 11.0, 3.0 Hz, 1 H), 3.48 (dd, J = 11.0, 8.0 Hz, 1 H), 3.80 (s, 3 H), 4.00 (d, J = 15,0 Hz, 1 H), 4.11 (dd, J = 8.0, 3.0 Hz, 1 H), 4.24 (q, J = 7,0 Hz, 2 H), 5.07 (d, J = 15.0 Hz, 1 H), 6.86 (d, J = 8,5 Hz, 2 H), 7,15 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 28,8, 47.1, 55.1, 59.1, 61.9, 114,0, 128.1, 129.5, 159.2, 169.7, 171.3; high-resolution mass spectrum (CI, NH_3) m/z 295.0870 [M^+, calcd for $C_{14}H_{17}NO_4S$ 295.0874]. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.81. Found: C, 57.25; H, 5.80.

Carboxylic Acid (−)-16. A stirred solution of **15** (5.30 g, 18.0 mmol) in THF (20 mL) at room temperature was treated with 1 N KOH (30.5 mL, 1.7 equiv). The reaction was stirred vigorously for 2 h and extracted with EtOAc, and the aqueous phase was then acidified with 3 N HCl and extracted with ether (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give **16** as a pale yellow oil (4.56 g, 94.9% yield), which was used without purification; $[\alpha]^{25}_D$ −55,2° (*c* 1.92, absolute EtOH); IR ($CHCl_3$) 3200–2400 (br), 1730 (s), 1675 (s), 1610, 1510 (s), 1250 (s), 1175, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (dd, J = 11.4, 2.6 Hz, 1 H), 3.54 (dd, J = 11.4, 8.5 Hz, 1 H), 3.80 (s, 3 H), 3.90 (d, J = 14,9 Hz, 1 H), 4.19 (dd, J = 8.5, 2.6 Hz, 1 H), 5.10 (d, J = 14.9 Hz, 1 H), 6,88 (d, J = 8.6 Hz, 2 H), 7.18 (d, J = 8.2 Hz, 2 H), 9,3–9.5 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 47.2, 55.1, 58.7, 114.2, 127.1, 129.7, 159.3, 171.9, 174.1; high-resolution mass spectrum (CI, NH_3) m/z 267.0546 [M^+, calcd for $C_{12}H_{13}NO_4S$ 267.0562].

Ketone (−)-13. Sodium hydride (80% oil dispersion, 0.633 g, 21.1 mmol) was added to a solution of carboxylic acid **16** (5.37 g, 20.1 mmol) in dry THF (250 mL) at 0 °C. The mixture was stirred at room temperature for 6 h and cooled to 0 °C, and oxalyl chloride (1,93 mL, 22.1 mmol) was added slowly. After 30 min at 0 °C, the reaction was warmed to room temperature and stirred for 14 h. The mixture was then cooled to −78 °C, treated with methyl magnesium bromide (2.8 M in ether, 14,2 mL, 40 mmol), stirred at −78 °C for 30 min, and poured into 3 N HCl (300 mL) with vigorous stirring. Following extraction with ether (3 × 100 mL), the combined organic layers were washed with 0.5 N KOH (100 mL) and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 2.5:1) afforded **13** as a white crystalline solid (4.40 g, 83% yield); mp 79–80 °C (recrystallized from hexane as white needles); $[\alpha]^{25}_D$ −38.8° (*c* 1.39, absolute EtOH); IR ($CHCl_3$) 3000 (m), 1730 (s), 1680 (br s), 1610 (s), 1510 (s), 1355 (s), 1250 (s), 1170 (s), 1030 (s), 655 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3 H), 3.12 (dd, J = 11,4, 4,0 Hz, 1 H), 3.51 (dd, J = 11.4, 9.2 Hz, 1 H), 3.80 (s, 3 H), 3,90 (d, J = 14.7 Hz, 1 H), 4.11 (dd, J = 9.2, 4.0 Hz, 1 H), 5.01 (d, J = 14.7 Hz, 1 H), 6,86 (d, J = 8.7 Hz, 2 H), 7.13 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 27.6, 47.3, 55.2, 65,3, 114,2, 127.1, 129.7, 159.3, 171,5, 204,3; high-resolution mass spectrum (CI, NH_3) m/z 265,0774 [M^+, calcd for $C_{13}H_{15}NO_3S$ 265.0769]. Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70. Found: C, 59.14; H, 5.82.

Lactone (±)-18. A stirred solution of **17**[17] (0,250 g, 2.0 mmol) in CH_2Cl_2 (20 mL) containing sodium bicarbonate (0,252 g, 3.0 mmol) was treated dropwise with a solution of *m*-chloroperoxybenzoic acid (85%, 0.447 g, 2.2 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 14 h, poured into water (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water and saturated sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 4:1 → 3:1) furnished **18** as a colorless oil (0.197 g, 70.2% yield), accompanied by unreacted starting material (0.020 g, 8.0% yield). **18**; IR ($CHCl_3$) 3010 (w), 2960 (w), 1730 (s), 1250 (m), 1055 (m), 925 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.4–2.0 (m, 4 H), 2,25–2.6 (m, 4 H), 4.25–4.4 (m, 1 H), 5.0–5.2 (m, 2 H), 5.7–5.9 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 26.2, 28.5, 39.1, 78.9, 117.6, 131.7, 170.8; high-resolution mass spectrum (CI, CH_4) m/z 140.0838 [M^+, calcd for $C_8H_{12}O_3$ 140.0834].

Methylated Lactone (±)-19. A solution of diisopropylamine (2.96 mL, 21.1 mmol) in dry THF (40 mL) was stirred at −78 °C, and *n*-butyllithium (2.4 M in hexanes, 8.08 mL, 19.4 mmol) was added dropwise. The reaction mixture was stirred for 30 min, and a solution of **18** (2.47 g, 17.6 mmol) in dry THF (30 mL) was then introduced dropwise over 30 min. After the reaction was stirred for an additional 30 min at −78 °C, methyl iodide (5.48 mL, 88,0 mmol) was added in one portion. The mixture was stirred at −78 °C for 10 min, quenched with saturated NH_4Cl (5 mL), allowed to warm to room temperature, and concentrated at reduced pressure. Ether (100 mL) was added, and the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 4:1) gave a 1:1 mixture of diastereomers **19** as a colorless oil (2.230 g, 82.2% yield): IR ($CHCl_3$) 3010 (m), 2970 (m), 1730 (s), 1240 (m), 1045 (m), 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23, 1.30 (d, d, diastereomers, J = 7.0, 7.0 Hz, 3 H), 1.4–1.7 (m, 2 H), 1.9–2.1 (m, 2 H), 2.3–2.7 (m, 3 H), 4.3–4.4 (m, 1 H), 5.1–5.2 (m, 2 H), 5.7–5.9 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of diastereomers) δ 16.1, 17.3, 25.4, 26.0, 28.3, 28.4, 33.1, 36.0, 39.4, 40.3, 77.4, 80.9, 118.3, 118.4, 132.5, 132.7, 174.2, 176.0; high-resolution mass spectrum (CI, CH_4) m/z 155.1065 [$(M + H)^+$, calcd for $C_9H_{14}O_2$ 155.1063].

Ortho Esters (−)-20a and (+)-20b. A stirred solution of lactone **19** (1.586 g, 10.3 mmol) in benzene (30 mL) was treated with (*R,R*)-2,3-butanediol (1.110 g, 12.4 mmol) and a catalytic amount of camphorsulfonic acid. After the mixture was heated at reflux with azeotropic removal of water (Dean–Stark trap) for 72 h, capillary GC analysis showed the formation of four product diastereomers in a ratio of 6:6;1:1. The solution was cooled and washed with saturated sodium bicarbonate (2 × 100 mL), and the organic phase was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 10:1) furnished a mixture of ortho esters **20** (2.326 g, 99.9% yield). Purification by Waters Prep 500 HPLC using two PrepPak columns in series (hexane/EtOAc, 50:1) afforded **20a** (0.977 g, 42% yield) and **20b** (0.972 g, 42% yield) as colorless oils: **20a**: $[\alpha]^{25}_D$ −64.8° (*c* 2.48, $CHCl_3$); IR ($CHCl_3$) 3000, 2970, 2930, 1375, 1245, 1055, 960, 915 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0,92 (d, J = 6.5 Hz, 3 H), 1.28 (app t, J = 6.0 Hz, 6 H), 1.4–1.9 (m, 5 H), 2.1–2.4 (m, 2 H), 3,60–3.75 (m, 1 H), 3.78–3.90 (m, 1 H), 4.08–4.20 (m, 1 H), 5.00–5.15 (m, 2 H), 5,75–5.90 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.74, 16.69, 18.71, 29.16, 30.58, 35.52, 39.96, 72.82, 76.64, 79.87, 115.94, 120.47, 134.67; high-resolution mass spectrum (CI, NH_3) m/z 227.1641 [$(M + H)^+$, calcd for $C_{13}H_{23}O_3$ 227.1647].

(+)-**20b**: $[\alpha]^{26}_D$ +2.6° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 3080, 2990, 2960, 1450, 1380, 1250, 1050, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 3 H), 1.26 (d, J = 6.6 Hz, 3 H), 1.32 (d, J = 6.0 Hz, 3 H), 1.4–1.95 (m, 5 H), 2.1–2.4 (m, 2 H), 3.60–3.8 (m, 2 H), 3.9–4.0 (m, 1 H), 5.0–5.1 (m, 2 H), 5.75–5.90 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 16.3, 18.5, 29.1, 30.5, 35.8, 39.9, 73.3, 76.6, 80.0, 115.9, 120.5, 134.8; high-resolution mass spectrum (CI, NH_3) m/z 227.1654 [$(M + H)^+$, calcd for $C_{13}H_{23}O_3$ 227.1647].

Carbamate (−)-21. Ozone was bubbled into a solution of **20a** (50.0 mg, 0.220 mmol) in CH_2Cl_2 (20 mL) at −78 °C until a blue color persisted. Excess ozone was then removed by purging with argon, and a solution of $LiAlH_4$ (1.0 M in ether, 250 μL, 0.25 mmol) was added dropwise. The reaction was warmed to room temperature for 2 h and quenched with water (1 mL) and 3 N NaOH (0.25 mL). The resultant mixture was poured into ether, washed with brine, dried ($MgSO_4$), filtered, and concentrated. Preparative thin-layer chromatography (hexane/EtOAc, 1:1; 0.5 mm × 20 cm × 20 cm plate, E. Merck, 1 development) afforded the corresponding primary alcohol as a colorless oil (33.1 mg, 64% yield): IR ($CHCl_3$) 3520 (br), 2910 (m), 2860 (s), 1460 (m), 1450 (m), 1390 (m), 1260 (m), 1070 (s), 1020 (s), 980 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3 H), 1.26 (d, J = 6.0 Hz, 3 H), 1.30 (d, J = 6.0 Hz, 3 H), 1.40–1.90 (m, 7 H), 2,40–2.50 (br s, 1 H), 3.60–3.80 (m, 3 H), 4.00–4.10 (m, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 231.1596 [$(M + H)^+$, calcd for $C_{12}H_{23}O_4$ 231.1576].

A solution of the above alcohol (15.0 mg, 0.0651 mmol) in CH_2Cl_2 (2,5 mL) was treated with *p*-bromophenyl isocyanate (12.9 mg, 0.0651 mmol), and the resultant mixture was stirred at room temperature for 5 days. Concentration and preparative thin-layer chromatography (hexane/EtOAc, 1.5:1; 0.5 mm × 20 cm × 20 cm plate, E. Merck, 1 development) afforded **21** as a white solid (25.0 mg, 90% yield). Recrystallization of an analytical sample from hexane/ether gave a white solid; mp 76–78 °C; $[\alpha]^{25}_D$ −4.4° (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 3460 (w), 2920 (w), 1730 (s), 1600 (m), 1520 (m), 1400 (m), 1310 (m), 1080 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, J = 7.5 Hz, 3 H), 1.26 (d, J = 6.0 Hz, 6 H), 1.30–1.90 (m, 7 H), 3.60–3.75 (m, 2 H), 3.95–4.00 (m, 1 H), 4.05–4.15 (m, 1 H), 4.25–4.35 (m, 1 H), 6.60 (br s, 1 H), 7.27 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 427.0994 [M^+, calcd for $C_{19}H_{26}NO_5Br$ 427.0994].

Aldehyde (−)-12. Ozone was bubbled into a solution of **20a** (1.731 g, 7.655 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C until a blue color persisted. Argon was then bubbled into the reaction until the blue color dissipated. Triphenylphosphine (2.209 g, 8.421 mmol) was added in one portion, and the mixture was warmed to room temperature and stirred for 4 h. Concentration at reduced pressure and flash chromatography

(hexane/EtOAc, 7:1) gave **12** as a colorless oil (1.745 g, 100% yield); $[\alpha]^{25}_D$ −60.9° (*c* 1.82, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2950 (m), 2930 (m), 2830 (m), 1735 (m), 1660 (s), 1605 (s), 1510 (s), 1385 (m), 1240 (m), 1210 (m), 1030 (m), 975 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.5 Hz, 3 H), 1.28 (d, *J* = 8.0 Hz, 3 H), 1,30 (d, *J* = 8.0 Hz, 3 H), 1.35–1,90 (m, 5 H), 2.35–2.80 (m, 2 H), 3.4–3,7 (m, 1 H), 4.0–4,1 (m, 1 H), 4.3–4.4 (m, 1 H), 9.7 (t, *J* = 2.0 Hz, 1 H); ^{13}C NMR (50.3 Hz, $CDCl_3$) δ 14.9, 16.7, 18.8, 29.1, 30.9, 35.7, 49.2, 69.0, 78.1, 80.4, 120.6, 200,9; high-resolution mass spectrum (CI, NH_3) *m/z* 228.1359 [M^+, calcd for $C_{12}H_{20}O_4$ 228.1356].

Aldols (−)-11. A solution of **13** (1.30 g, 4.90 mmol) in dry CH_2Cl_2 (7 mL) was stirred at −78 °C and dibutylboron triflate (1.0 M in CH_2Cl_2, 6.27 mL, 6.3 mmol) was added dropwise. Diisopropylethylamine (1.02 mL, 5.86 mmol) was then introduced dropwise and the mixture stirred at −78 °C for 1 h. Following the dropwise addition of a solution of **12** (0,448 g, 1,96 mmol) in dry CH_2Cl_2 (2 mL), the reaction was stirred for an additional 2 h at −78 °C and quenched with saturated ammonium chloride. The mixture was diluted with CH_2Cl_2 and washed with cold 1 N HCl. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated to a volume of 10 mL and coevaporated with benzene (10 mL). Flash chromatography (hexane/EtOAc, 4:1 → 1:1) furnished an ca. 4;1 mixture of diastereomeric aldols **11** as a colorless oil (0,842 g, 87% yield); $[\alpha]^{25}_D$ −48° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3490 (br), 3000 (s), 2960 (s), 2930 (s), 1720 (s), 1675 (s), 1610 (s), 1510 (s), 1055 (m), 1030 (m), 960 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (mixture of diastereomers) δ 0.91 (d, *J* = 6.3 Hz, 3 H), 1,27 (d, *J* = 6,0 Hz, 3 H), 1.29 (d, *J* = 6.1 Hz, 3 H), 1.34–1,43 (m, 1 H), 1,47–1.65 (m, 4 H), 1.69–1.73 (m, 1 H), 1.78–1.83 (m, 1 H), 2,42 (dd, *J* = 16.4, 3,0 Hz, 1 H), 2.57–2.63 (m, 1 H), 3.01 (d, *J* = 3.9 Hz, 1 H), 3,15 (dd, *J* = 11.5, 3.8 Hz, 1 H), 3.41–3.48 (m, 1 H), 3.66–3.71 (m, 1 H), 3.79 (s, 3 H), 3,84 (dd, *J* = 14.7, 12.1 Hz, 1 H), 4.01–4.06 (*m*, 1 H), 4.06–4.11 (*m*, 1 H), 4.18 (dd, *J* = 9.4, 3.8 Hz, 1 H), 4.30–4.33 (m, 1 H), 5.01 (d, *J* = 14,7 Hz, 1 H), 6.84 (d, *J* = 8,5 Hz, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) major isomer δ 15.0, 16.8, 18.9, 27,1, 29,3, 31.0, 36.0, 41.8, 46.0, 47,4, 55,2, 65,2, 65.5, 70.7, 78.3, 80,5, 114,2, 120.9, 127.4, 129.9, 159.5, 171.7, 206,6, minor isomer δ 15.4, 16.8, 18,7, 27,1, 29.0, 31.5, 36.1, 41.7, 46.3, 47.2, 54.8, 65.2, 65.4, 74.5, 78.4, 80.7, 114.5, 120.8, 127.3, 130.0, 159.1, 178.4, 205,4; high-resolution mass spectrum (CI, NH_3) *m/z* 493,2072 [M^+, calcd for $C_{25}H_{35}NO_7S$ 493.2134].

Triols (+)-24α and (+)-24β. Method A. A stirred solution of **11** (0,630 g, 1.28 mmol) in THF (5 mL) was treated with 2 N HCl (1 mL), and the resultant mixture was stirred at room temperature for 24 h. Following the addition of saturated sodium bicarbonate, the mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 1;2) afforded **24α** (0.474 g, 72.5% yield) and **24β** (0.039 g, 6.0% yield) as colorless oils. **24α**: $[\alpha]^{25}_D$ +3.0° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3410 (br, m), 3000 (m), 2970 (m), 2950 (m), 2930 (m), 1725 (s), 1660 (s), 1610 (m), 1510 (s), 1445 (m), 1390 (m), 1380 (m), 1245 (s), 1185 (s), 1170 (s), 1100 (m), 1030 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6,6 Hz, 3 H), 1,19 (d, *J* = 7.0 Hz, 3 H), 1,22 (d, *J* = 6.4 Hz, 3 H), 1.43–1.65 (m, 4 H), 1.81–1,87 (m, 1 H), 1.97–2.01 (m, 1 H), 2.04–2,17 (m, 1 H), 2.22–2.25 (m, 1 H), 2.46–2.53 (m, 1 H), 2.82 (br m, 1 H), 3.29 (dd, *J* = 11.9, 9.4 Hz, 1 H), 3.37 (dd, *J* = 11.9, 1.8 Hz, 1 H), 3,56 (dd, *J* = 9.4, 1.8 Hz, 1 H), 3.71–3.76 (m, 1 H), 3.78 (s, 3 H), 3.82–3.89 (m, 1 H), 4.07–4.13 (m, 1 H), 4.27 (d, *J* = 14.6 Hz, 1 H), 4.74–4.79 (m, 1 H), 5.10 (d, *J* = 14.7 Hz, 1 H), 6,85 (d, *J* = 8,7 Hz, 2 H), 7.18 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16,4, 17.4, 19.2, 26,7, 29.8, 33.4, 37.3, 39.6, 40.6, 47.8, 55,3, 64.1, 64.5, 69,7, 70,0, 100,9, 114.1, 128.7, 129.6, 159.2, 173.1, 176,2; high-resolution mass spectrum (CI, CH_4) *m/z* 512.2303 [$(M + H)^+$, calcd for $C_{25}H_{38}NO_8S$ 512,2318].

24β: $[\alpha]^{25}_D$ +1.2° (*c* 0,39, $CHCl_3$); IR ($CHCl_3$) 3410 (br, m), 3000 (m), 2970 (m), 2915 (m), 1725 (s), 1655 (s), 1610 (m), 1510 (s), 1445 (m), 1395 (m), 1375 (m), 1300 (m), 1245 (s), 1190 (s), 1170 (s), 1050 (m), 1030 (m), 975 (m), 900 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6,2 Hz, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.22 (d, *J* = 6,2 Hz, 3 H), 1.43–1.58 (m, 4 H), 1.72–1.92 (m, 3 H), 2,04–2.10 (m, 1 H), 2.47–2.57 (m, 1 H), 3.07 (d, *J* = 3.5 Hz, 1 H), 3.21–3.39 (m, 2 H), 3.56–3.61 (m, 1 H), 3.71–3.78 (m, 1 H), 3.78 (s, 3 H), 4.20–4.29 (m, 1 H), 4,32 (d, *J* = 14.4 Hz, 1 H), 4,37–4,48 (m, 1 H), 4.69–4.78 (m, 1 H), 5.08 (d, *J* = 14.4 Hz, 1 H), 5.58 (s, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.20 (d, *J* = 8.6 Hz, 2 H); high-resolution mass spectrum (CI, CH_4) *m/z* 512.2371 [$(M + H)^+$, calcd for $C_{25}H_{38}NO_8S$ 512.2318].

Method B. A stirred solution of **13** (64,8 mg, 0.244 mmol) in dry CH_2Cl_2 (0.5 mL) was cooled to −78 °C, and dibutylboron triflate (1.0 M in CH_2Cl_2, 0,320 mL, 0.320 mmol) followed by diisopropylethylamine (60 μL, 0.34 mmol) were then added dropwise. The solution was stirred at −78 °C for 1 h, a solution of **12** (39,1 mg, 0,171 mmol) in dry dichloromethane (1 mL) was introduced, and the reaction was stirred for an additional 2 h at −78 °C. After the addition of saturated ammonium chloride (2 mL) and 3 N HCl (1 mL), the mixture was stirred at room temperature overnight and then extracted with ether (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated, Preparative thin-layer chromatography (hexane/EtOAc, 1;3; 2 mm × 20 cm × 20 cm plate, E. Merck, 1 development) gave **24α** (56.6 mg, 67% yield) and **24β** (7.0 mg, 8.3% yield) as colorless oils.

Methyl Ketal (+)-23. A solution of **24α** (1,25 g, 2.45 mmol) in toluene (7 mL) and methanol (1 mL) at room temperature was treated with camphorsulfonic acid (0.100 g) and stirred for 4.5 h. Triethylamine (1 mL) and water (25 mL) were added, and the resultant mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with 1 N HCl, saturated sodium bicarbonate, and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 3:5) gave **23** as a colorless oil (0,954 g, 74.6% yield) and unreacted starting material (0,235 g, 18,8% yield). **23**: $[\alpha]^{25}_D$ +24,1° (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 3580 (w), 3460 (br), 3000 (s), 2930 (m), 1720 (m), 1670 (s), 1610 (m), 1510 (m), 1245 (s), 1170 (m), 1030 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.5 Hz, 3 H), 1,19 (d, *J* = 6,9 Hz, 3 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 1.30–1,39 (m, 1 H), 1.43–1.64 (m, 4 H), 1,69–1.88 (m, 2 H), 1,91–2.03 (m, 1 H), 2.21 (dd, *J* = 11.3, 3.2 Hz, 1 H), 2.49–2.62 (m, 1 H), 3.08 (s, 3 H), 3.11–3.26 (m, 1 H), 3,24–3.29 (m, 1 H), 3.31–3.37 (m, 1 H), 3,52–3.65 (m, 1 H), 3.71–3.78 (m, 1 H), 3.80 (s, 3 H), 3.82–3.89 (m, 1 H), 3.99–4.11 (m, 1 H), 4.21 (d, *J* = 14,7 Hz, 1 H), 4.70–4.82 (m, 1 H), 5.10 (d, *J* = 14.7 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.4, 17.4, 19.2, 25,4, 30.0, 33.6, 37.0, 39,6, 40.4, 47.2, 47.5, 55.2, 58,8, 64.5, 70.0, 70.2, 74.6, 103.0, 114.0, 128.7, 129.8, 159.1, 172.8, 176.0; high-resolution mass spectrum (CI, NH_3) *m/z* 526.2471 [$(M + H)^+$, calcd for $C_{26}H_{40}NO_8S$ 526,2472],

Bis-silyl Ether (+)-26. A stirred solution of **23** (953 mg, 1.82 mmol) in dry DMF (4 mL) at room temperature was treated with imidazole (687 mg, 10.1 mmol) and *tert*-butyldimethylsilyl chloride (620 mg, 4,11 mmol). After 1 h, 4-(dimethylamino)pyridine (10 mg) was added and the mixture stirred for 14 h, The reaction was then quenched with water (25 mL) and extracted with ether (3 × 100 mL), The combined organic layers were washed with 1 N HCl, saturated sodium bicarbonate, and brine, dried (Na_2SO_4), filtered, and concentrated, Flash chromatography (hexane/EtOAc, 10;1) provided **26** as a colorless oil (1,28 g, 93% yield); $[\alpha]^{25}_D$ +15.2° (*c* 3.3, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (s), 2930 (s), 2850 (s), 1730 (s), 1665 (s), 1610 (m), 1510 (s), 1250 (s), 1115 (m), 1070 (s), 1035 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0,06 (s, 12 H), 0,88 (s, 18 H), 1,09 (d, *J* = 6.3 Hz, 3 H), 1.17 (d, *J* = 6,5 Hz, 3 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.23 (d, *J* = 11,8 Hz, 1 H), 1.47–1.53 (m, 3 H), 1,63–1.68 (m, 1 H), 1.81–1.84 (m, 1 H), 1.91–1.96 (m, 1 H), 2.03–2,06 (m, 1 H), 2.45–2.50 (m, 1 H), 3.05 (s, 3 H), 3,22–3.28 (m, 2 H), 3.53–3.57 (m, 1 H), 3.80 (s, 3 H), 3.80–3.87 (m, 2 H), 4.01–4,05 (m, 1 H), 4.22 (d, *J* = 14.4 Hz, 1 H), 4.82 (dq, *J* = 5,2, 6.4 Hz, 1 H), 5.10 (d, *J* = 14.4 Hz, 1 H), 6,87 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8,6 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −4.8, −4.6, −4.5, 14.7, 17.2, 18.0, 18.0, 18.5, 25.3, 25.7, 25.8, 30.1, 33,6, 37.1, 39.5, 41.0, 47.1, 47,4, 55.2, 58,9, 65.1, 69.0, 70.1, 73.7, 103.2, 114.0, 128.8, 129.8, 159.1, 172.8, 175.8; high-resolution mass spectrum (FAB, Cs ion gun, *m*-nitrobenzyl alcohol) *m/z* 753.4121 [M^+, calcd for $C_{38}H_{67}NO_8SSi_2$ 753,4108]. Anal. Calcd for $C_{38}H_{67}NO_8SSi_2$: C, 60.52; H, 8.96. Found; C, 60.74; H, 8,89.

Alcohol (+)-27. A solution of **26** (601 mg, 0.798 mmol) in dry THF (9 mL) was stirred at 0 °C, and lithium aluminum hydride (1.0 M in ether, 0.85 mL, 0.85 mmol) was added dropwise, The reaction was stirred for 5 min, silica gel (5 g) was added, and the resultant suspension was passed through a short silica gel column with ether as eluant, Concentration at reduced pressure and flash chromatography (hexane/EtOAc, 5:1 → 3;1) gave **27** as a white crystalline solid (427 mg, 96.7% yield). An analytical sample was obtained by recrystallization from hexane: mp 152.5–153.5 °C; $[\alpha]^{25}_D$ +12.2° (*c* 2.49, $CHCl_3$); IR ($CHCl_3$) 3460 (w), 3010 (m), 2960 (s), 2940 (m), 2910 (m), 2880 (s), 1665 (s), 1620 (m), 1520 (s), 1470 (m), 1410 (m), 1250 (s), 1180 (m), 1150 (m), 1120 (m), 1070 (m), 1040 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.84 (s, 9 H), 0,97 (d, *J* = 6,7 Hz, 3 H), 1.14–1.37 (m, 2 H), 1.51–1,69 (m, 4 H), 1.72–1.80 (m, 1 H), 1.83–1.86 (m, 1 H), 2.03–2.06 (m, 1 H), 3.06 (s, 3 H), 3.22–3.27 (m, 2 H), 3.50–3.56 (m, 3 H), 3.80 (s, 3 H), 3,82–3.86 (m, 1 H), 4.00–4.06 (m, 1 H), 4.25 (d, *J* = 14.4 Hz, 1 H), 5.11 (d, *J* = 14.4 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −4.6, −4,5, 16.5, 18.0, 25,3, 25.8, 29.3, 33.7, 35,9, 37.1, 41.0, 47.0, 47.4, 55.2, 58.9, 65,2, 68,1, 70.5, 103.1, 114.0, 128.9, 129.8, 159.1, 172.8; high-resolution mass spectrum (CI, NH_3) *m/z* 554,2995 [$(M + H)^+$, calcd for $C_{28}H_{48}NO_6SSi$ 554.2970]. Anal. Calcd for $C_{28}H_{47}NO_6SiS$: C, 60.70; H, 8.56. Found: C, 60.62; H, 8,44,

Aldehyde (+)-6α, Method A. A solution of **26** (0.193 g, 0,257 mmol) in hexane (20 mL) was cooled to −78 °C, and diisobutylaluminum hydride (1.0 M in hexanes, 0.514 mL, 0.51 mmol) was added dropwise. The reaction was stirred for 30 min and quenched at −78 °C with methanol (2 mL) followed by saturated sodium potassium tartrate (5 mL). The mixture was warmed to room temperature, poured into ether (75 mL), and washed with brine. The aqueous layer was extracted with ether (2 × 75 mL), and the combined organic solutions were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 4:1) afforded aldehyde **6α** as a white crystalline solid (63.5 mg, 44.8% yield) as well as starting material (85.1 mg, 44.0%) and alcohol **27** (8.8 mg, 6.2%). **6α**: mp 150–151 °C; $[\alpha]^{25}_D$ +26.0° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3000, 2950 (m), 2860, 1720 (m), 1660 (s), 1610, 1510 (m), 1400, 1250, 1175, 1150, 1120, 1075, 1030 (m), 835 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.2–2.1 (m, 8 H), 2.35–2.45 (m, 1 H), 3.06 (s, 3 H), 3.2–3.3 (m, 2 H), 3.5–3.6 (m, 1 H), 3.8 (s, 3 H), 3.8–3.9 (m, 1 H), 3.95–4.1 (m, 1 H), 4.22 (d, *J* = 14.4 Hz, 1 H), 5.11 (d, *J* = 14.4 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 8.6 Hz, 2 H), 9.67 (d, *J* = 2.0 Hz, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 551.2736 [M^+, calcd for $C_{28}H_{45}NO_6SSi$ 551.2734]. Anal. Calcd for $C_{28}H_{45}NO_6SSi$: C, 60.95; H, 8.23, Found: C, 61.11; H, 8.42.

Method B. A stirred solution of **27** (200 mg, 0.361 mmol) and dry DMSO (100 μL) in dry benzene (3 mL) was treated at room temperature with pyridine (30 μL) followed by trifluoroacetic acid (10 μL). After 15 min, dicyclohexylcarbodiimide (250 mg, 1.21 mmol) was added in one portion. The mixture was stirred at room temperature for 6 h, and then water (5 mL) and ether (5 mL) were added. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 4:1) furnished **6α** as a white crystalline solid (199 mg, 100% yield).

Ester 28. A solution of **10** (6.1 g, 6.3 mL, 59 mmol) in dry THF (100 mL) was stirred at −78 °C, and *n*-butyllithium (2.5 M in hexanes, 25 mL, 62 mmol) was added over 30 min. After 1 h at −78 °C, methyl chloroformate (6.5 mL, 84 mmol) was added in one portion. The mixture was allowed to warm to room temperature, stirred for 12 h, and then poured into water (150 mL). Following extraction with ether (4 × 150 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 9:1) gave **28** as a colorless oil (9.5 g, 94% yield): IR ($CHCl_3$) 3010 (m), 2980 (m), 2250 (s), 1710 (br s), 1440 (m), 1265 (br s), 1080 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.03 (m, 2 H), 2.55 (t, *J* = 7.0 Hz, 2 H), 3.64 (t, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H); high-resolution mass spectrum (CI, NH_3) *m/z* 161.0434 [$(M + H)^+$, calcd for $C_7H_{10}ClO_2$ 161.0369].

Alkene 29. A suspension of cuprous iodide (10.34 g, 54 mmol) in dry THF (125 mL) at −10 °C was treated with methyllithium (1.2 M in ether, 90 mL, 108 mmol) and stirred until the initially formed yellow precipitate redissolved to give a colorless solution. The reaction was cooled to −78 °C, and a solution of **28** (4.5 g, 28 mmol) in dry THF (10 mL) was added over 5 min. After the mixture was stirred at −78 °C for 1 h, ethanol (30 mL) was added rapidly. The mixture was poured into ether (250 mL) and washed with saturated ammonium chloride. The organic layer was washed with 5 M NH_4OH until the aqueous wash was colorless, and then it was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated, affording **29** as a pale yellow oil which was used without purification (4.6 g, 94% yield): IR ($CHCl_3$) 3075 (m), 2950 (m), 1710 (s), 1650 (m), 1440 (m), 1250 (br s), 1165 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.91 (d, *J* = 1.2 Hz, 3 H), 1.95 (m, 2 H), 2.74 (m, 2 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 3.67 (s, 3 H), 5.70 (br s, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 177.0686 [$(M + H)^+$, calcd for $C_8H_{14}ClO_2$ 177.0604].

Carboxylic Acid 30. A solution of **29** (2.55 g, 15 mmol) in THF (300 mL) at room temperature was treated with water (300 mL) and 1 N LiOH (110 mL). The resultant mixture was stirred vigorously at room temperature for 18 h. Following concentration at reduced pressure and acidification to pH 3 with 3 N HCl, the aqueous phase was extracted with ether (4 × 300 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Recrystallization from pentane gave **30** as a pale yellow solid (1.99 g, 85% yield): mp 55–56 °C; IR ($CHCl_3$) 3300–2400 (br, m), 1695 (s), 1640 (m), 1440 (m), 1410 (m), 1290 (m), 1250 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9 (m, 2 H), 1.95 (d, *J* = 1.2 Hz, 3 H), 2.74 (m, 2 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 5.74 (br s, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 163,0486 [$(M + H)^+$, calcd for $C_{11}H_{12}ClO_2$ 163.0447]. Anal. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.77. Found: C, 51.77; H, 6.78.

Iodide 31. Sodium iodide (28.2 g, 188 mmol) was dissolved in dry acetone (90 mL), and a solution of **30** (2.97 g, 18.3 mmol) in acetone (5 mL) was added. The mixture was heated at reflux under argon in the dark for 18 h, cooled to room temperature, and concentrated at reduced pressure. The residue was partitioned between ether and water, the phases were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Recrystallization from ether/hexane afforded **31** as a yellow crystalline solid (3.79 g, 82% yield): mp 81–82 °C; IR ($CHCl_3$) 3300–2400 (br, m), 1695 (s), 1645 (s), 1440 (m), 1410 (m), 1260 (m), 1220 (br, m), 1180 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.94 (d, *J* = 1.2 Hz, 3 H), 2.02 (m, 2 H), 2.71 (m, 2 H), 3.21 (t, *J* = 7.0 Hz, 2 H), 5.72 (br s, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 253–9791 [$(M + H)^+$, calcd for $C_7H_{12}IO_2$ 253.9805]. Anal. Calcd for $C_7H_{11}IO_2$: C, 33.07; H, 4.33. Found: C, 33.22; H, 4.35.

Phosphonium Iodide 8. A stirred solution of **31** (680 mg, 2.67 mmol) and triphenylphosphine (725 mg, 2.76 mmol) in dry benzene (4.5 mL) was heated at reflux for 17 h. The mixture was cooled to room temperature, diluted with ether (10 mL), and filtered. The solid was washed with ether (20 mL) and dried under reduced pressure to give **8** as a white powder (1.13 g, 82.0% yield): mp 163–165 °C; IR ($CHCl_3$) 3400–2500 (br, m), 2740 (s), 1690 (s), 1640 (m), 1440 (s), 1240 (br, s), 1110 (s), 720 (m), 690 (s), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.74 (br s, 3 H; m, 2 H), 2.95 (br m, 2 H), 3.72 (br m, 2 H), 5.75 (br s, 1 H), 7.8 (m, 15 H). Anal. Calcd for $C_{25}H_{26}IO_2P$: C, 58.13; H, 5.08. Found: C, 58,23; H, 5.12.

α,β-Unsaturated Ester 32. A solution of oxalyl chloride (4.40 mL, 6.65 g, 51.6 mmol) in THF (300 mL) was cooled to −78 °C, and a solution of DMSO (4.10 mL, 4.51 g, 57.8 mmol) in THF (20 mL) was added dropwise over 45 min. A white precipitate formed as the resulting mixture was stirred at −78 °C for 45 min. A solution of **9** (4.00 mL, 3.65 g, 43.4 mmol) in THF (15 mL) was then introduced dropwise over 40 min; during the addition, the precipitate thickened. After an additional 1 h at −78 °C, triethylamine (18.0 mL, 13.1 g, 0.129 mol) was added dropwise over 30 min. The reaction was stirred at −78 °C for 45 min, warmed to room temperature, and stirred for an additional 1 h. Finally, the mixture was filtered, the filtercake was washed with THF (30 mL), and the filtrate was stored under argon at 0 °C.

A suspension of sodium hydride (1.30 g, 54.2 mmol) in THF (100 mL) was cooled to 0 °C, and neat triethyl phosphonoacetate (11.0 mL, 12.4 g, 55.4 mmol) was added dropwise over 10 min. The resultant solution was stirred at 0 °C for 30 min and then added via a cannula to the filtrate described above. The solution was stirred at 0 °C for 1 h, diluted with ether (200 mL), and washed with saturated ammonium chloride, 1 N HCl, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, affording **32** as a pale yellow oil which was used without purification (6.344 g, 96% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 3:1): IR ($CHCl_3$) 3320 (s), 3025 (s), 3000 (s), 2980 (s), 2940 (s), 2115 (w), 1740 (s), 1670 (s), 1570 (m), 1555 (m), 1400 (m), 1350 (m), 1290 (s), 1160 (s), 1050 (s), 860 (w), 735 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.98 (t, *J* = 2.6 Hz, 1 H), 2.34 (m, 2 H), 2.42 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 5.88 (dt, *J* = 15.7, 1.5 Hz, 1 H), 6.96 (dt, *J* = 15.7, 6.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 17.4, 30.9, 60.2, 69.3, 82.6, 122.5, 146.2, 166.2; high-resolution mass spectrum (CI, NH_3) *m/z* 170.1175 [$(M + NH_4)^+$, calcd for $C_9H_{16}NO_2$ 170.1181].

Allylic Alcohol 33. A solution of **32** (6.520 g, 42.8 mmol) in THF (200 mL) was stirred at 0 °C, and diisobutylaluminum hydride (1 M in hexane, 95 mL, 95 mmol) was added dropwise over 1.5 h. The mixture was stirred at 0 °C for an additional 15 min, silica gel (25 g) was added, and the slurry was diluted with EtOAc. The mixture was then filtered and the filtercake washed with EtOAc (400 mL). Concentration at reduced pressure gave **33** as a pale yellow oil which was used without further purification (4.55 g, 96% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 3:1): IR ($CHCl_3$) 3450 (br, m), 3320 (s), 3010 (m), 2940 (m), 1440 (w), 1380 (w), 1210 (m), 980 (s), 910 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95 (t, *J* = 1.8 Hz, 1 H), 2.28 (m, 4 H), 4.12 (d, *J* = 4.2 Hz, 2 H), 5.74 (m, 2 H).

Tetrahydropyranyl Ether 34. At 0 °C, a stirred solution of **33** (4.55 g, 41.3 mmol) in CH_2Cl_2 (250 mL) was treated with dihydropyran (5.00 mL, 4,61 g, 54.8 mmol) and pyridinium *p*-toluenesulfonate (1.25 g, 4.97 mmol). The mixture was stirred at room temperature overnight and then washed with water, 1 N HCl, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, affording **34** as a yellow oil which was used without purification (6.49 g, 81% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 4:1): IR ($CHCl_3$) 3320 (s), 3020 (s), 2960 (s), 2860 (s), 2120 (w), 1470 (m), 1450 (m), 1370 (m), 1210 (m), 1130 (s), 1080 (s), 975 (s), 870 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.6 (m, 2 H), 1.70 (m, 2 H), 1.82 (m, 2 H), 1.94 (d, *J* = 2.3 Hz, 1 H), 2.27 (m, 4 H), 3.49 (m, 1 H), 3.86 (m, 1 H), 3.94 (dd, *J* = 12.2, 6.6 Hz, 1 H), 4.19 (dd, *J* = 12.2, 5.6 Hz, 1 H), 4.63 (t, *J* = 3.6 Hz, 1 H), 5.64 (m, 1 H), 5.75

(m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 19.5, 25.4, 30.6, 31.2, 62.1, 67.4, 68.6, 83.7, 97.7, 127.8, 137.7; high-resolution mass spectrum (CI NH_3) m/z 195.1380 [$(M + H)^+$, calcd for $C_{12}H_{19}O_2$ 195.1390].

Ester 35. A stirred solution of **34** (6.395 g, 32.9 mmol) in dry THF (250 mL) was cooled to −78 °C, and *n*-butyllithium (3.0 M in hexane, 12.6 mL) was added dropwise over 15 min. The reaction was stirred for an additional 1.5 h at −78 °C, and methyl chloroformate (3.60 mL, 4.40 g, 46.6 mmol) was then introduced dropwise. The mixture was stirred for an additional 1 h at −78 °C and at room temperature for 1 h. After dilution with ether (200 mL), the mixture was washed with saturated sodium bicarbonate and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated, furnishing **35** as a yellow oil which was used without purification (7.705 g, 93% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 9:1): IR ($CHCl_3$) 3310 (m), 3010 (m), 2980 (s), 2935 (m), 2260 (m), 1720 (s), 1450 (m), 1360 (w), 1220 (s), 1160 (w), 1080 (s), 980 (m), 820 (w), 640 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.51–1.84 (br m, 6 H), 2.37 (m, 4 H), 3.51 (m, 1 H), 3.75 (s, 3 H), 3.82–3.97 (m, 2 H), 4.21 (dd, J = 12.5, 4.5 Hz, 1 H), 4,63 (m, 1 H), 5.71 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 19,5, 25.4, 30.2, 30.6, 52.5, 62.2, 67.3, 73.2, 88.8, 97.8, 128.4, 130.8, 154.1; high-resolution mass spectrum (CI, NH_3) m/z 253.1460 [$(M + H)^+$, calcd for $C_{14}H_{21}O_4$ 253.1440].

Diene 36. A suspension of cuprous iodide (7.40 g, 38.9 mmol) in dry THF (250 mL) was stirred at 0 °C and treated with methyllithium (1.2 M in ether, 65 mL). After 30 min at 0 °C, the solution was cooled to −78 °C and a solution of **35** (7.01 g, 27.8 mmol) in dry THF (25 mL) was added over 10 min. A tan precipitate formed as the reaction was stirred at −78 °C for 2 h. After dilution with ether (200 mL), the mixture was poured into saturated ammonium chloride, and the organic layer was washed with 5 M NH_4OH until the aqueous phase was colorless. The organic solution was then washed with water and brine, dried ($MgSO_4$), filtered, and concentrated, affording **36** as a pale yellow oil which was used without purification (7.23 g, 97% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 9:1): IR ($CHCl_3$) 3020 (m), 2970 (s), 2860 (m), 1720 (s), 1660 (m), 1455 (s), 1390 (m), 1340 (w), 1220 (s), 1190 (s), 1090 (m), 980 (m), 910 (m), 820 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.52–1.91 (br m, 7 H), 1.88 (d, J = 1.4 Hz, 3 H), 2,33 (q, J = 7.2 Hz, 2 H), 2.72 (t, J = 7.8 Hz, 2 H), 3.50 (m, 1 H), 3.67 (s, 3 H), 3.92 (br s, 2 H), 4.19 (m, 1 H), 4.62 (m, 1 H), 5.67 (m, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 269.1760 [$(M + H)^+$, calcd for $C_{15}H_{25}O_4$ 269.1760].

Alcohol 37. Amberlyst-15 ion-exchange resin (H^+ form, 5.0 g) was added to a solution of **36** (7.00 g, 26.1 mmol) in methanol (100 mL), and the resultant mixture was stirred at room temperature for 3 h. After filtration, the solid cake was washed with ether. Saturated sodium bicarbonate (1 mL) was then added, the solution was concentrated at reduced pressure, and the residue was taken up in ether (70 mL). The solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give **37** as a yellow oil which was used without purification (4.64 g, 95% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 2:1): IR ($CHCl_3$) 3300 (br, m), 3020 (m), 2970 (s), 2860 (m), 1720 (s), 1660 (m), 1390 (m), 1340 (w), 1190 (m), 980 (m), 910 (m), 820 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (d, J = 1.3 Hz, 3 H), 2.23 (m, 2 H), 2.72 (t, J = 7.8 Hz, 2 H), 3.68 (s, 3 H), 4,08 (d, J = 5.0 Hz, 2 H), 5.71 (m, 3 H).

Hydroxy Acid 38. A suspension of **37** (4.29 g, 23.3 mmol) in saturated aqueous LiOH (75 mL) was stirred vigorously overnight at room temperature. The mixture was then cooled to 0 °C, acidified to pH 1 by dropwise addition of 6 N HCl, and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with water until the washings were neutral and then washed with brine. The aqueous solutions were combined with the acidic aqueous phase from the workup and saturated with salt. The resultant solution was continuously extracted with CH_2Cl_2 for 12 h. Finally, all of the organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated, furnishing **38** as a pale yellow oil which was used without purification (2.89 g, 73% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc, 1:1): IR ($CHCl_3$) 3200 (br, m), 3020 (m), 2940 (m), 2880 (m), 1700 (s), 1650 (m), 1450 (w), 1420 (w), 1290 (m), 1210 (s), 1120 (w), 980 (m), 670 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1,92 (d, J = 1.1 Hz, 3 H), 2.24 (m, 2 H), 2.72 (t, J = 7.7 Hz, 2 H), 4.09 (d, J = 4.2 Hz, 2 H), 5.68 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 30.6, 32.8, 63.5, 116.1, 129.6, 131.9, 159.7, 166.7; high-resolution mass spectrum (CI, NH_3) m/z 188.1280 [$(M + NH_4)^+$, calcd for $C_9H_{18}NO_3$ 188.1280].

Bromide 39. A solution of *N*-bromosuccinimide (2.244 g, 12.6 mmol) in CH_2Cl_2 (120 mL) was stirred at 0 °C, and dimethyl sulfide (1.10 mL, 0.931 g, 15.0 mmol) was added dropwise over 10 min, generating a yellow precipitate. The suspension was stirred at 0 °C for 15 min, cooled to −23 °C, and treated with a solution of **38** (1.423 g, 8.353 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at −23 °C for 15 min and then at room temperature for 2 h, during which time the precipitate dissolved. The mixture was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated, affording **39** as a yellow oil which was used without purification (1.894 g, 97% yield). An analytical sample was obtained by flash chromatography (hexane/EtOAc/*i*-PrOH, 40:10:1): IR ($CHCl_3$) 3450–2900 (br, m), 3010 (m), 2950 (m), 2870 (m), 1700 (s), 1650 (m), 1450 (m), 1300 (m), 1260 (s), 1210 (s), 1120 (w), 970 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (s, 3 H), 2.25 (q, J = 7.2 Hz, 2 H), 2.72 (t, J = 7.7 Hz, 2 H), 3.94 (d, J = 3.2 Hz, 2 H), 5.76 (m, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 252.0430 [$(M + NH_4)^+$, calcd for $C_9H_{17}NO_2Br$ 252.0420].

Phosphonium Bromide 7. A solution of **39** (2.44 g, 10.4 mmol) and triphenylphosphine (3.00 g, 11.4 mmol) in dry acetonitrile (150 mL) was heated at reflux for 12 h, cooled to room temperature, and concentrated to a volume of ca. 70 mL under reduced pressure. The residue was diluted with benzene (40 mL), and ether was added in portions (ca. 2 mL each) over a few hours until crystals began to form. This mixture was allowed to stand in the refrigerator overnight, and the crystals were then filtered, washed with ether, and dried under reduced pressure to give **7** as yellow needles (1.83 g, 35% yield). The filtrate was reduced in volume and the crystallization procedure repeated, furnishing a second crop (2.06 g, 40%). Recrystallization of an analytical sample from acetonitrile/ether gave colorless, cubic crystals: mp 91–93 °C; IR (Nujol) 3400 (br, m), 3060 (s), 3000 (s), 2940 (s), 1715 (s), 1650 (m), 1595 (w), 1490 (w), 1390 (w), 1240 (w), 1120 (s), 1000 (w), 730 (s), 695 (s) cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 1.74 (d, J = 1.2 Hz, 3 H), 2.14 (m, 2 H), 2.54 (t, J = 7.7 Hz, 2 H), 4.14 (dd, J = 15.2, 7.3 Hz, 2 H), 5.39 (m, 1 H), 5.68 (s, 1 H), 5.77 (m, 1 H), 7.72 (m, 12 H), 7.87 (m, 3 H); high-resolution mass spectrum (CI, NH_3) m/z 495.1060 [$(M + H)^+$, calcd for $C_{24}H_{29}O_2PBr$ 495.1090].

Carboxy Diene (−)-40. The THF employed in this reaction was freshly distilled and then degassed with argon for 30 min. A stirred suspension of **8** (94.9 mg, 0.184 mmol) in dry THF (1 mL) was cooled to 0 °C and treated with potassium bis(trimethylsilyl)amide (0.649 M in THF, 0.529 mL, 0.343 mmol). The mixture was stirred at 0 °C for 20 min, and a solution of **6α** (33.8 mg, 0.0613 mmol) in THF (1.5 mL) was added. The reaction was then stirred for 20 min and poured into ether (25 mL), and the resultant mixture was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 3:1) furnished **40** as a glass (34.8 mg, 86% yield): $[\alpha]^{25}_D$ −0.46° (*c* 3.26, $CHCl_3$); IR ($CHCl_3$) 3000, 2950 (s), 3000–2500 (br, w), 1690–1660 (br, s), 1610 (w), 1510 (m), 1440 (m), 1400 (m), 1245 (s), 1030, 830 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.87 (s, 9 H), 0.99 (d, J = 6.5 Hz, 3 H), 1.1–2.8 (m, 14 H), 1.90 (s, 3 H), 3.05 (s, 3 H), 3.2–3.3 (m, 2 H), 3.5–3.6 (m, 1 H), 3.80 (s, 3 H), 3.85–3.9 (m, 1 H), 3.95–4.1 (m, 1 H), 4.23 (d, J = 14.4 Hz, 1 H), 5.09 (d, J = 14.4 Hz, 1 H), 5,13–5.2 (m, 1 H), 5.3–5.5 (m, 1 H), 5.7 (s, 1 H), 6,83 (d, J = 8.6 Hz, 2 H), 7.20 (d, J = 8.6 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 662.3566 [$(M + H)^+$, calcd for $C_{35}H_{56}NO_7SSi$ 662.3544].

Methyl Ketone (+)-lii.[26] A solution of phosphonium salt **8** (115 mg, 0.223 mmol) in HMPA and THF (1:1, 1.0 mL) was treated with lithium bis(trimethylsilyl)amide (0.643 M in THF, 0.648 mL, 0.417 mmol) at 0 °C, and the resulting clear, red solution was stirred for 1 h. A solution of aldehyde **6α** (41.0 mg, 0.0744 mmol) in THF (1 mL) was added, and the reaction was then stirred for 40 min, quenched by the addition of THF/HOAc/H_2O (8:8:1), and extracted with ether (3 × 10 mL). Concentration and flash chromatography (hexane/EtOAc, 3:1) afforded *lii* as a white solid (5,6 mg, 14% yield): mp 153–154.5 °C; $[\alpha]^{25}_D$ +9.1° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (s), 2930 (s), 2860 (s), 1715 (m), 1660 (s), 1610 (m), 1510 (m), 1460 (m), 1440 (m), 1405 (m), 1360 (m), 1300 (m), 1250 (s), 1175 (m), 1145 (m), 1110 (m), 1070 (m), 1035 (s), 860 (m), 835 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.10–1.40 (m, 4 H), 1.24 (s, 3 H), 1.44–1.70 (m, 3 H), 1.80–1.95 (m, 1 H), 2.00–2.10 (m, 1 H), 2.50–2.70 (m, 1 H), 3.01 (s, 3 H), 3.20–3.30 (m, 1 H), 3.50–3.65 (m, 1 H), 3.79 (s, 3 H), 3.95–4.10 (m, 1 H), 4.20 (d, J = 14.8 Hz, 1 H), 5.13 (d, J − 14.9 Hz, 1 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.8 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 506.2363 [$(M - OMe)^+$, calcd for $C_{26}H_{40}NO_5SSi$ 506.2396].

Hydroxy Acid (+)-41. A solution of **40** (32.0 mg, 0.0484 mmol) in dry THF (4 mL) was cooled to 0 °C, pyridine·$(HF)_x$ (1.0 mL) was added, and the reaction was stirred at room temperature for 2 h. The mixture was then poured into ether and washed with water, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography ($CHCl_3$/MeOH, 97:3) gave **41** as a white solid (21.5 mg, 81.2% yield); mp 60–62 °C; $[\alpha]^{25}_D$ +19.0° (*c* 0.91, $CHCl_3$); IR ($CHCl_3$) 3500–2500 (br), 3000 (m), 2950 (m), 1730 (m), 1660 (br, s), 1610, 1510, 1445, 1405, 1250, 1175, 1035 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 3 H), 1.1–1.8

(m, 6 H), 1.90 (s, 3 H), 2.0–2.4 (m, 3 H), 2.4–2.8 (m, 4 H), 3.05 (s, 3 H), 3.2–3.3 (m, 2 H), 3.5–3.6 (m, 1 H), 3.80 (s, 3 H), 3.80–3.85 (m, 1 H), 4.0–4.2 (m, 1 H), 4.23 (d, J = 14,4 Hz, 1 H), 5.09 (d, J = 14.4 Hz, 1 H), 5.20 (m, 1 H), 5.3–5,45 (m, 1 H), 5.70 (s, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 7,20 (d, J = 8.6 Hz, 2 H); high-resolution mass spectrum (CI, NH_3) m/z 548,2678 [$(M + H)^+$, calcd for $C_{29}H_{42}NO_7S$ 548,2681]. Anal. Calcd for $C_{29}H_{41}NO_7S$: C, 63.59; H, 7.55, Found: C, 63.43; H, 7.32.

Lactone (+)-42. A stirred solution of **41** (19.5 mg, 0.0356 mmol) in dry benzene (4 mL) at room temperature was treated with triphenylphosphine (28.0 mg, 0.107 mmol) followed by diethyl azodicarboxylate (16.8 μL, 0.107 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated. Flash chromatography (hexane/EtOAc, 3,5:1) afforded **42** as a white crystalline solid (13.0 mg, 69% yield): mp 176–178 °C; $[\alpha]^{25}_D$ +104.3° (c 1.12, $CHCl_3$); IR ($CHCl_3$) 3000, 2960 (m), 1690, 1660 (s), 1610 (w), 1510 (m), 1400, 1380, 1350, 1280, 1250, 1175, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (d, J = 6,5 Hz, 3 H), 1.2–1.9 (m, 8 H), 1.90 (s, 3 H), 2.0–2.4 (m, 3 H), 2.6–2.85 (m, 2 H), 3.10 (s, 3 H), 3.18–3.25 (m, 2 H), 3.80 (s, 3 H), 3.78–3.82 (m, 1 H), 4.2–4.35 (m, 1 H), 4.29 (d, J = 14.4 Hz, 1 H), 5.09 (d, J = 14.4 Hz, 1 H), 5.05–5.2 (m, 2 H), 5.2–5.38 (m, 1 H), 5.60 (s, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 7.20 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (50.3 Hz, $CDCl_3$) δ 22.1, 24,4, 25.2, 26.5, 29.4, 29.8, 31.4, 32.4, 34.9, 35.5, 47.4, 47.5, 55.2, 59.0, 63.3, 67.4, 102,2, 113.9, 118.8, 127.9, 128.8, 129.9, 134.9, 154.2, 159.1, 166.0, 173.0; high-resolution mass spectrum (CI, NH_3) m/z 529.2496 [M^+, calcd for $C_{29}H_{39}NO_6S$ 529.2488]. Anal. Calcd for $C_{29}H_{39}NO_6S$: C, 65.75; H, 7.43. Found: C, 65.60; H, 7.53.

(+)-*O*-Methyllatrunculin B (43). A suspension of **42** (9.0 mg, 0.017 mmol) in acetonitrile/water (3:1, 85 μL) was treated with ceric ammonium nitrate [0.25 M in acetonitrile/water (3:1), 136 μL, 0.034 mmol]. As the resulting mixture was stirred at room temperature for 25 min, it became homogeneous. The solution was poured into brine and extracted with chloroform (3 × 40 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Preparative thin-layer chromatography (hexane/EtOAc, 1:1; 0.25 mm × 20 cm × 20 cm plate, E. Merck, 1 development) afforded **43** as a colorless oil (3.3 mg, 48% yield) and latrunculin B (1.0 mg, 15% yield), **43**: $[\alpha]^{25}_D$ +94.2° (c 0.62, $CHCl_3$); IR ($CHCl_3$) 3410, 3000, 2950, 1690 (s), 1280, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H), 1.1–1.8 (m, 8 H), 1.90 (s, 3 H), 2.0–2.4 (m, 3 H), 2.6–2.9 (m, 2 H), 3.27 (s, 3 H), 3.2–3.4 (m, 2 H), 3.1–3.3 (m, 2 H), 4.0–4.3 (m, 3 H), 5.47 (s, 1 H), 5.66 (s, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 410.2000 [$(M + H)^+$, calcd for $C_{21}H_{32}NO_5S$ 410.2004],

(+)-Latrunculin B (2), Method A. A solution of **43** (7.0 mg, 0.017 mmol) in acetic acid/THF/water (3:1:1, 4 mL) was warmed to 60 °C for 2 h. The mixture was then cooled to room temperature, poured into water, and extracted with EtOAc (2 × 10 mL) followed by $CHCl_3$ (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Preparative thin-layer chromatography (hexane/EtOAc, 1:10; 0.25 mm × 20 cm × 15 cm plate, E, Merck, 2 developments) furnished latrunculin B (**2**) (4.0 mg, 59% yield): $[\alpha]^{25}_D$ +117° (c 1.99, $CHCl_3$) [lit.[2] $[\alpha]^{24}_D$ +112° (c 0.48, $CHCl_3$)]; IR ($CHCl_3$) 3560, 3400, 2960, 2920, 1690, (br, s), 1230 (w), 1050 (w), 900 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, J = 6.4 Hz, 3 H), 1.0–2.4 (m, 11 H), 1.90 (d, J = 1.5 Hz, 3 H), 2.6–2.8 (m, 2 H), 3.40 (dd, J = 11.0, 6.0 Hz, 1 H), 3.46 (dd, J = 11.0, 8.0 Hz, 1 H), 3.83 (app t, J = 8.0 Hz, 1 H), 3.85 (s, O*H*), 4.24 (br t, J = 10.0 Hz, 1 H), 5.06 (app t, J = 11.0 Hz, 1 H), 5.25 (dt, J = 11.0, 4.0 Hz, 1 H), 5.44 (br t, J = 3.0 Hz, 1 H), 5.70 (s, 1 H), 5.80 (s, N*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 22.2, 23.9, 26.8, 28.7, 28.9, 31.0, 31.1, 31.6, 35.3, 35.8, 61.5, 62.5, 68.7, 97.8, 117.8, 127.4, 135.8, 154.4, 165.4, 174.8; high-resolution mass spectrum (CI, NH_3) m/z 395.1764 [M^+, calcd for $C_{20}H_{29}NO_5S$ 395.1766].

Method B. A suspension of **42** (13.8 mg, 0.0260 mmol) in acetonitrile/water (2:1, 0.20 mL) was vigorously stirred at room temperature, and ceric ammonium nitrate (35.8 mg, 0.0650 mmol) was added in one portion. The flask was swirled to promote mixing. The mixture became homogeneous after 20 min and was stirred for an additional 20 min. The solution was then diluted with $CHCl_3$ (0.5 mL) and subjected to preparative thin-layer chromatography (hexane/EtOAc, 3;2; 0.25 mm × 20 cm × 15 cm plate, E. Merck, 2 developments), furnishing **2** (4.8 mg, 47% yield) and **43** (2.0 mg, 19%).

Triene (+)-44. The THF employed in this reaction was freshly distilled and then degassed with argon for 30 min. A suspension of **7** (254 mg, 0.514 mmol) in dry degassed HMPA (2 mL) was sonicated until the salt dissolved, diluted with THF (10 mL), and cooled to −78 °C. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.96 mL, 0.980 mmol) was added dropwise over 30 min, and the deep red solution was stirred at −78 °C for an additional 30 min. A solution of **6α** (202.2 mg, 0.367 mmol) in THF (4 mL) was added dropwise over 4 h, and the reaction was then stirred for an additional 1 h at −78 °C, warmed to room temperature, quenched with saturated NH_4Cl, and acidified with 4 N HCl. The resulting mixture was extracted with EtOAc (4 × 25 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 3:1) furnished **44** as a colorless oil (192 mg, 76% yield): $[\alpha]^{25}_D$ +5,3° (c 1.74, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2970 (s), 2940 (s), 2870 (m), 1700 (m), 1670 (s), 1620 (m), 1520 (s), 1410 (m), 1365 (m), 1260 (s), 1215 (s), 1180 (m), 1155 (m), 1125 (m), 1080 (m), 1040 (m), 985 (m), 930 (m), 840 (s), 760 (s), 670 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.03 (d, J = 6.7 Hz, 3 H), 1.20–1.33 (m, 4 H), 1.35–1.70 (m, 5 H), 1.73–1.79 (m, 1 H), 1.91 (s, 3 H), 2.00–2.10 (m, 1 H), 2.20–2.45 (m, 2 H), 2.60–2.78 (m, 2 H), 3.04 (s, 3 H), 3.24 (d, J = 6.0 Hz, 1 H), 3.45–3.60 (m, 1 H), 3.79 (s, 3 H), 3.92–4.10 (m, 1 H), 4.23 (d, J = 14.5 Hz, 1 H), 5.11 (d, J = 14.4 Hz, 1 H), 5,22–5.31 (m, 1 H), 5.41–5.55 (m, 1 H), 5.70 (br s, 1 H), 5.93 (t, J = 10.4 Hz, 1 H), 6.23–6.30 (m, 1 H), 6.60 (d, J = 8.9 Hz, 2 H), 7.20 (d, J = 8.8 Hz, 2 H).

Hydroxy Acid (−)-45. A stirred solution of **44** (180 mg, 0.262 mmol) in THF (8 mL) was treated with pyridine·$(HF)_x$ (400 μL) at 0 °C and then warmed to room temperature overnight. The reaction was quenched with saturated sodium bicarbonate and extracted with ethyl acetate (4 × 25 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 1:4) furnished **45** as a colorless oil (145 mg, 96% yield): $[\alpha]^{25}_D$ −5.4° (c 0.81, $CHCl_3$); IR ($CHCl_3$) 3610 (br), 3010 (m), 2940 (m), 1700 (m), 1670 (s), 1620 (s), 1520 (s), 1455 (m), 1410 (m), 1290 (m), 1255 (s), 1210 (s), 1180 (m), 1125 (m), 1040 (m), 990 (m), 730 (s), 670 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.01 (d, J = 6.3 Hz, 3 H), 1.10–1.28 (m, 4 H), 1.35–1.70 (m, 5 H), 1.92 (s, 3 H), 1.92–2.07 (m, 2 H), 2.15–2.45 (m, 3 H), 2.55–2.85 (m, 2 H), 3.08 (s, 3 H), 3.20–3.30 (m, 1 H), 3.79 (s, 3 H), 3.80–3.90 (m, 1 H), 3.95–4.15 (m, 1 H), 4.24 (d, J = 14.5 Hz, 1 H), 5.08 (d, J = 14.5 Hz, 1 H), 5.18–5.30 (m, 1 H), 5.38–5.50 (m, 1 H), 5.69 (br s, 1 H), 5.98 (t, J = 10.0 Hz, 1 H), 6.22–6.35 (m, 1 H), 6.85 (d, J = 8.4 Hz, 2 H), 7.18 (d, J = 8.5 Hz, 2 H).

Lactone (+)-46. A solution of **45** (57.8 mg, 0.101 mmol) and triphenylphosphine (35.0 mg, 0.133 mmol) in THF (10 mL) was cooled to −78 °C and treated with diethyl azodicarboxylate (21 μL, 0.133 mmol). The mixture was then warmed to room temperature for 3 h and concentrated. Flash chromatography (hexane/EtOAc, 9:1 → 1:1) furnished **46** as white needles (17.4 mg, 31% yield): mp 202–203 °C; $[\alpha]^{25}_D$ +151° (c 0.19, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2970 (m), 2940 (m), 2870 (m), 1690 (m), 1670 (s), 1620 (m), 1520 (m), 1460 (m), 1440 (m), 1410 (m), 1385 (m), 1360 (m), 1290 (m), 1255 (m), 1210 (s), 1130 (m), 1095 (s), 1035 (m), 990 (m), 725 (s), 665 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 3 H), 1.17–1.32 (m, 4 H), 1.39–1.55 (m, 4 H), 1.60–1.71 (m, 1 H), 1,86–2.05 (m, 1 H), 1.92 (d, J = 1.3 Hz, 3 H), 2.21–2.31 (m, 3 H), 2.75–2.90 (m, 1 H), 3.20 (s, 3 H), 3.23–3.26 (m, 1 H), 3.41–3.5 (m, 1 H), 3.82 (s, 3 H), 3.83–3.86 (m, 1 H), 4.10–4.25 (m, 1 H), 4.28 (d, J = 14.4 Hz, 1 H), 5.06 (t, J = 7.0 Hz, 1 H), 5.09 (d, J = 14.4 Hz, 1 H), 5.65 (d, J = 1.2 Hz, 1 H), 5.83 (dt, J = 15.2, 5.3 Hz, 1 H), 6.06 (t, J = 10.7 Hz, 1 H), 6.36 (dd, J = 14.9, 10.0 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.23 (d, J = 8.6 Hz, 2 H).

Thiazolidinone (+)-47. A solution of **27** (608 mg, 1.10 mmol) in dry THF (10 mL) was stirred at −78 °C, and *tert*-butyllithium (1.35 M in pentane, 1.64 mL) was added dropwise. The mixture was stirred for 5 min, and dry oxygen gas was then passed through the yellow solution until the color faded. Ammonium chloride (100 mg) and water (1 mL) were added, the mixture was extracted with ether (2 × 20 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 2:1) furnished **47** as a white crystalline solid (297 mg, 62.3% yield). An analytical sample was obtained by recrystallization from hexane/CH_2Cl_2: mp 156–158 °C; $[\alpha]^{25}_D$ +44.9° (c 1.36, $CHCl_3$); IR ($CHCl_3$) 3520 (m), 3400 (w), 3000 (s), 2950 (s), 2930 (s), 2890 (s), 2850 (s), 1670 (m), 1460 (m), 1385 (m), 1360 (m), 1250 (s), 1220 (m), 1210 (m), 1155 (s), 1115 (s), 1070 (s), 1035 (s), 850 (m), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.87 (s, 9 H), 0.92 (d, J = 6.7 Hz, 3 H), 1.10–1.14 (m, 1 H), 1.21 (q, J = 11.8 Hz, 1 H), 1.44–1.57 (m, 3 H), 1,55 (dd, J = 10.8, 12.6 Hz, 1 H), 1.59–1.64 (m, 1 H), 1.78–1.81 (m, 1 H), 1.86–1.89 (m, 1 H), 3.18 (s, 3 H), 3.29–3.38 (m, 2 H), 3.46–3.54 (m, 3 H), 3.97–4.03 (m, 1 H), 4.12 (dd, J = 8.1, 7.6 Hz, 1 H), 5.67 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −4.5, 16.6, 18.0, 25.8, 28.1, 28.8, 33.0, 35.8, 36.3, 40.7, 47.8, 56.4, 65.1, 67.9, 70.3, 101.4, 174.5; high-resolution mass spectrum (CI, NH_3) m/z 434.2441 [$(M + H)^+$, calcd for $C_{20}H_{40}NO_5SiS$ 434.2396]. Anal. Calcd for $C_{20}H_{39}O_5NSiS$: C, 55.40; H, 9.00. Found: C, 55.36; H, 8.98.

Aldehyde (+)-48. To a stirred solution of **47** (197 mg, 0.454 mmol) in dry CH_2Cl_2 (7 mL) at room temperature were added aluminum oxide (neutral, activated, Brockman 1, 150 mesh, 492 mg) and then pyridinium

chlorochromate (245 mg, 1.13 mmol). The mixture was stirred for 30 min and passed through a short silica gel column with ether as eluant. Concentration at reduced pressure and flash chromatography (hexane/EtOAc, 4:1) gave **48** as a colorless oil (150 mg, 76.8% yield): $[\alpha]^{25}_D$ +42.1° (*c* 1.80, $CHCl_3$); IR ($CHCl_3$) 3400 (s), 3190 (w), 2940 (s), 2920 (s), 2870 (s), 2850 (s), 2700 (m), 1720 (s), 1670 (s), 1455 (s), 1380 (s), 1350 (m), 1250 (s), 1150 (s), 1110 (s), 1070 (s), 1030 (s), 1000 (m), 985 (m), 950 (m), 890 (m), 850 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0,05 (s, 6 H), 0.87 (s, 9 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.22 (q, *J* = 11.7 Hz, 1 H), 1.33–1.41 (m, 1 H), 1.48–1.57 (m, 3 H), 1.76–1.79 (m, 1 H), 1.86–1.97 (m, 2 H), 2.31–2.39 (m, 1 H), 3,10 (dd, *J* = 11.4, 7.0 Hz, 1 H), 3.18 (s, 3 H), 3.34 (dd, *J* = 11.3, 8.6 Hz, 1 H), 3.50–3,56 (m, 1 H), 3.98–4.04 (m, 1 H), 4.10–4.13 (m, 1 H), 5.69 (br s, 1 H), 9.62 (d, *J* = 1.8 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –4.6, 13.4, 18.0, 25.8, 26.2, 28.1, 32.8, 36.3, 40.6, 46.1, 47.8, 56,4, 65.0, 69.8, 101.5, 174.5, 204.6; high-resolution mass spectrum (CI, NH_3) *m/z* 449.2470 [$(M + NH_4)^+$, calcd for $C_{20}H_{41}N_2O_5SSi$ 449.2506].

(Trimethylsilyl)ethyl Carbamate (–)-49. A solution of **48** (145 mg, 0.336 mmol) in dry CH_2Cl_2 (1.4 mL) was stirred at 0 °C and treated successively with diisopropylethylamine (70 μL, 0.402 mmol), [(trimethylsilyl)ethoxy]carbonyl chloride[33] (66 mg, 0.365 mmol), and 4-(dimethylamino)pyridine (7.0 mg, 57 μmol). The reaction was stirred at 0 °C for 2 h and then at room temperature for 1 h. Following the addition of saturated sodium bicarbonate (1 mL), the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with cold 1 N HCl, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 10:1 → 6:1) furnished **49** as a colorless oil (157 mg, 78.4% yield): $[\alpha]^{25}_D$ –18.6° (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2950 (s), 2930 (s), 2890 (m), 2850 (s), 1770 (s), 1720 (s), 1460 (m), 1370 (m), 1270 (m), 1260 (m), 1170 (s), 1150 (s), 1110 (s), 1070 (m), 1030 (s), 960 (m), 930 (s), 900 (m), 850 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.06 (s, 9 H), 0.86 (s, 9 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.07–1.17 (m, 2 H), 1.22 (q, *J* = 11.5 Hz, 1 H), 1.33–1.41 (m, 1 H), 1.42–1.48 (m, 2 H), 1.55 (dd, *J* = 11.3, 11.3 Hz, 1 H), 1.73–1.77 (m, 1 H), 1.90–1.96 (m, 1 H), 2.01 (ddd, *J* = 12.7, 4.7, 1.6 Hz, 1 H), 2.31 (dtq, *J* = 1.8, 6.8, 6.8 Hz, 1 H), 3.21 (s, 3 H), 3.22 (br m, 1 H), 3.47–3.52 (m, 1 H), 3.52 (dd, *J* = 11.6, 9.4 Hz, 1 H), 3.99 (ddt, *J* = 10.8, 10.8, 4.7 Hz, 1 H), 4.26 (ddd, *J* = 10.9, 10.3, 4.3 Hz, 1 H), 4.35 (ddd, *J* = 11.3, 10.9, 4,2 Hz, 1 H), 4.94 (d, *J* = 8.7 Hz, 1 H), 9.61 (d, *J* = 1.9 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –4.5, –1.6, 13.4, 17.6, 18,0, 25.2, 25.8, 26.1, 33,0, 37.5, 40.3, 46.2, 47.9, 58.7, 65.0, 66.0, 69.7, 102.4, 151.0, 170.7, 204,6; high-resolution mass spectrum (CI, NH_3) *m/z* 593.3091 [$(M + NH_4)^+$, calcd for $C_{26}H_{53}N_2O_7SSi_2$ 593.3112].

Triene (–)-50. A solution of **7** (238 mg, 0.464 mmol) in dry HMPA (1,4 mL) and THF (5.5 mL) was stirred at –78 °C, and sodium bis(trimethylsilyl)amide (1 M in THF, 910 μL) was added dropwise. The dark red solution was stirred for 30 min, and a solution of **49** (157.2 mg, 263 μmol) in THF (1.5 mL) was introduced via cannula. The mixture was then stirred for 30 min, poured into saturated ammonium chloride (25 mL), and extracted with ether (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 2;1) afforded **50** as a colorless oil (150 mg, 80% yield); $[\alpha]^{25}_D$ –32.1° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 3400–2700 (w), 2950 (s), 2920 (s), 2850 (s), 1770 (s), 1725 (s), 1690 (s), 1635 (s), 1450 (m), 1375 (m), 1265 (m), 1250 (m), 1215 (m), 1205 (m), 1170 (s), 1140 (s), 1110 (s), 1070 (s), 1030 (s), 940 (m), 930 (m), 850 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.06 (s, 9 H), 0.86 (s, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.08–1.22 (m, 4 H), 1.36–1.41 (m, 3 H), 1.53 (dd, *J* = 12.2, 11.0 Hz, 1 H), 1.69–1.75 (m, 1 H), 1.92 (s, 3 H), 1.99 (dd, *J* = 12.4, 3.7 Hz, 1 H), 2.28 (m, 2 H), 2.56 (br m, 1 H), 2.74 (m, 2 H), 3.19–3,23 (m, 1 H), 3.21 (s, 3 H), 3.44–3.50 (m, 1 H), 3.50 (dd, *J* = 11.4, 9.6 Hz, 1 H), 3.93–3.99 (m, 1 H), 4.27 (ddd, *J* = 11.0, 10.3, 6.3 Hz, 1 H), 4.35 (ddd, *J* = 11.1, 10.8, 6.4 Hz, 1 H), 4.91 (dd, *J* = 9.1, 4.9 Hz, 1 H), 5.07 (dd, *J* = 10.3, 10.3 Hz, 1 H), 5.66 (dt, *J* = 15.0, 7.5 Hz, 1 H), 5.70 (s, 1 H), 5.89 (dd, *J* = 11.0, 10,9 Hz, 1 H), 6.29 (dd, *J* = 14.4, 11.2 Hz, 1 H); ^{13}C NMR (62,9 MHz, $CDCl_3$) δ –4,5, –1.5, 17.5, 18.0, 21.5, 25.2, 25.6, 25.8, 31.3, 32.1, 32.8, 33.2, 37.5, 40.3, 47.8, 53.4, 58,8, 65.2, 65.9, 69.8, 102.3, 115,8, 126.3, 127.5, 133.3, 136.3, 150.8, 162.6, 170.3, 170.8; high-resolution mass spectrum (FAB, Cs ion gun, *m*-nitrobenzyl alcohol) *m/z* 734.3512 [$(M + Na)^+$, calcd for $C_{35}H_{61}NO_8SSi_2Na$ 734.3554].

Hydroxy Acid (+)-51. A solution of **50** (111 mg, 156 μmol) in dry THF (3 mL) was stirred at 0 °C and treated with pyridine·$(HF)_x$ (300 μL). After 1 h at 0 °C, the reaction was quenched with sodium carbonate (200 mg) and saturated sodium bicarbonate (2 mL). The resulting mixture was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/EtOAc, 3:1 → 2:1) gave **51** as a colorless oil (83.4 mg, 89.3% yield): $[\alpha]^{25}_D$ +5.7° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3550–2500 (w), 2960 (s), 2930 (s), 1765 (s), 1720 (s), 1690 (s), 1635 (m), 1440 (m), 1370 (s), 1260 (s), 1240 (s), 1210 (s), 1165 (s), 1105 (s), 1025 (s), 955 (m), 940 (m), 925 (s, m), 850 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0,06 (s, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.06–1.17 (m, 3 H), 1.31–1.58 (m, 5 H), 1.88–1.92 (m, 1 H), 1.92 (d, *J* = 1.3 Hz, 3 H), 2.13–2.20 (m, 1 H), 2,20–2.27 (m, 2 H), 2.53–2,64 (m, 2 H), 2.76–2.85 (m, 1 H), 3.22 (d, *J* = 11,5 Hz, 1 H), 3.23 (s, 3 H), 3.54 (dd, *J* = 11.6, 9.4 Hz, 1 H), 3.49–3.58 (m, 1 H), 4,00–4,12 (m, 1 H), 4.17–4.29 (m, 1 H), 4.31–4.42 (m, 1 H), 4,95 (d, *J* = 8.8 Hz, 1 H), 5.02 (dd, *J* = 10.5, 10,2 Hz, 1 H), 5,67 (dt, *J* = 14,8, 7.2 Hz, 1 H), 5.70 (s, 1 H), 5,91 (dd, *J* = 11.0, 10.9 Hz, 1 H), 6,25 (dd, *J* = 14.8, 10.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –1.5, 17.6, 21.5, 25,2, 25,4, 31.2, 32.0, 32.8, 33.0, 37.6, 40.2, 48.0, 53.4, 58.8, 65.5, 65,9, 69.9, 102.4, 115.8, 126.3, 127.6, 133.4, 136.3, 150,8, 162.6, 170,3, 170.9; high-resolution mass spectrum (FAB, Cs gun, *m*-nitrobenzyl alcohol) *m/z* 620.2750 [$(M + Na)^+$, calcd for $C_{29}H_{47}NO_8SSiNa$ 620.2690].

Lactone (+)-52. A solution of **51** (26.1 mg, 43.7 μmol) in dry benzene (3 mL) was stirred at 4 °C and treated with a solution of triphenylphosphine (22.9 mg, 87.4 μmol) in dry benzene (300 μL), followed by dropwise addition of diethyl azodicarboxylate (14,5 μL, 87.4 μmol), The mixture was warmed to room temperature, stirred for 2 days, and then passed through a short silica gel column (hexane/EtOAc, 2;1). Concentration at reduced pressure and preparative thin-layer chromatography (hexane/EtOAc, 3:1; 0.25 mm × 20 cm × 20 cm plate, E. Merck, 2 developments) gave **52** as a colorless oil (7.3 mg, 28% yield): $[\alpha]^{25}_D$ +196.7° (*c* 0.46, $CHCl_3$); IR ($CHCl_3$) 3050 (m), 2990 (m), 2940 (s), 2920 (m), 2860 (m), 2850 (m), 1765 (s), 1720 (s), 1685 (s), 1445 (m), 1370 (m), 1265 (s), 1230 (s), 1165 (m), 1080 (s), 1025 (m), 950 (m), 925 (m), 850 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0,06 (s, 9 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 1,10–1.13 (m, 2 H), 1.25–1.46 (m, 4 H), 1.55–1.62 (m, 1 H), 1.86–1.93 (m, 2 H), 1.92 (d, *J* = 1.0 Hz, 3 H), 2.10–2.17 (m, 1 H), 2.22–2.35 (m, 3 H), 2.80–2.83 (m, 1 H), 3.21 (d, *J* = 11.8 Hz, 1 H), 3.34 (s, 3 H), 3.42–3,47 (m, 1 H), 3,51 (dd, *J* = 11.7, 9,5 Hz, 1 H), 4.09–4,13 (m, 1 H), 4.20 (ddd, *J* = 11.6, 10,7, 6.5 Hz, 1 H), 4.39 (ddd, *J* = 11.5, 10.7, 6.6 Hz, 1 H), 4.91 (d, *J* = 9.2 Hz, 1 H), 5,00 (dd, *J* = 10,6, 10,6 Hz, 1 H), 5.13 (br s, 1 H), 5.63 (s, 1 H), 5.81 (ddd, *J* = 15.5, 5,1, 4.7 Hz, 1 H), 6,03 (dd, *J* = 10.7, 10.7 Hz, 1 H), 6.36 (dd, *J* = 15.4, 11.5 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ –1.6, 17.6, 21.7, 25.0, 25.1, 29,6, 29.8, 30.8, 31,2, 31,4, 32.3, 34.8, 47.9, 53,4, 58.9, 63,2, 66.0, 66.8, 101,0, 118.3, 125.0, 127.6, 132.1, 135.7, 150.8, 157.6, 166,4; high-resolution mass spectrum (Cl, NH_3) *m/z* 597,3002 [$(M + NH_4)^+$, calcd for $C_{29}H_{49}N_2O_7SSi$ 597.3030].

(+)-*O*-Methyllatrunculin A (53). A solution of **52** (3.5 mg, 6.0 μmol) in dry THF (600 μL) was stirred at room temperature, and tetrabutylammonium fluoride (1 M in THF, 50 μL) was added. After 3 min, the mixture was passed through a short silica gel column with ether as eluant. Concentration at reduced pressure followed by preparative thin-layer chromatography (hexane/EtOAc, 3:1; 0,25 mm × 20 cm × 20 cm plate, E. Merck, 2 developments) gave 2.8 mg of material. Recrystallization from hexane/CH_2Cl_2 then furnished **53** as colorless crystals (2.2 mg, 84% yield): mp 185–187 °C (authentic sample prepared from natural latrunculin A, mp 187–188 °C); $[\alpha]^{25}_D$ +297° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 3400 (s), 2980 (s), 2940 (m), 1685 (s), 1445 (m), 1370 (m), 1275 (s), 1260 (s), 1080 (m), 1015 (s), 975 (m), 940 (s), 895 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6,4 Hz, 3 H), 1.07–1.13 (m, 1 H), 1.36–1.46 (m, 3 H), 1.65–1.69 (m, 1 H), 1.81–1.88 (m, 1 H), 1,92 (d, *J* = 1.1 Hz, 3 H), 1,90–1.94 (m, 1 H), 2.14–2,17 (m, 2 H), 2.25–2,37 (m, 2 H), 2.77–2.83 (m, 1 H), 3.32 (s, 3 H), 3.24–3.37 (m, 1 H), 3.39–3.45 (m, 1 H), 4,12–4.17 (m, 2 H), 5.00 (dd, *J* = 10.7, 10.5 Hz, 1 H), 5.17 (br m, 1 H), 5.40 (br s, 1 H), 5.65 (br s, 1 H), 5,81 (ddd, *J* = 15.3, 5.7, 4.9 Hz, 1 H), 6.04 (dd, *J* = 10,8, 10.7 Hz, 1 H), 6,37 (dd, *J* = 15.5, 10,8 Hz, 1 H); ^{13}C NMR (62,9 MHz, $CDCl_3$) δ 21.6, 25,1, 28.0, 29.1, 29.6, 30.7, 31.0, 31.4, 32,1, 35,1, 47.9, 56,6, 63.1, 66.6, 99,8, 118.2, 124.9, 127,6, 132.2, 135.6, 157.8, 166.4, 174.5; high-resolution mass spectrum (Cl, NH_3) *m/z* 453,2446 [$(M + NH_4^+)$, calcd for $C_{23}H_{37}N_2O_5S$ 453.2424].

(+)-Latrunculin A (1). A solution of **53** (4.0 mg, 9.2 μmol) in THF (1 mL) was cooled to 0 °C, and 3 N HCl (0.3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, quenched with saturated sodium bicarbonate, and extracted with ether (5 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Preparative thin-layer chromatography (hexane/EtOAc, 2:1; 0.25 mm × 20 cm × 10 cm plate, E. Merck, 2 developments) afforded latrunculin A (**1**) (1.9 mg, 49% yield) and starting material (1.3 mg, 33%). Synthetic **1**: $[\alpha]^{25}_D$ +150° (*c* 0.19, $CHCl_3$) [lit.[2] $[\alpha]^{24}_D$ +152° (*c* 1.2, $CHCl_3$)]; IR ($CHCl_3$) 3510 (m), 3400 (m), 3310 (w), 2970 (m), 2910 (m), 1660 (s), 1430 (m), 1370 (s), 1310 (m), 1260 (m), 1225 (m), 1115 (s), 1080 (s), 1075 (m), 1040 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.3 Hz, 3 H), 1.06–1.11 (m,

1 H), 1.25-1.96 (m, 6 H), 1.93 (s, 3 H), 2.04-2.07 (m, 1 H), 2.23-2.28 (m, 2 H), 2.64-2.74 (m, 2 H), 2.86-2.92 (m, 1 H), 3.39-3.43 (m, 1 H), 3.46-3.51 (m, 1 H), 3.83-3.86 (m, 2 H), 4.22-4.26 (m, 1 H), 5.01 (dd, J = 10.7, 10.6 Hz, 1 H), 5.43 (m, 1 H), 5.62 (s, 1 H), 5.69 (s, 1 H), 5.74 (dt, J = 15.3, 5,7 Hz, 1 H), 5.97 (dd, J = 10.7, 10,7 Hz, 1 H), 6.40 (dd, J = 14.5, 11,4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 24.5, 28.7, 29.2, 30.4, 31.0, 31.4, 31.8, 32.7, 34.9, 61.3, 62.3, 68.2, 97.3, 117.3, 126,0, 127.2, 131.8, 136.5, 158.4, 165,3, 174.6; high-resolution mass spectrum (Cl, NH_3) m/z 439.2267 [($M + NH_4^+$), calcd for $C_{22}H_{35}N_2O_5S$ 439.2223].

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Supplementary Material Available: Tables of experimental details, positional parameters, and thermal parameters for the X-ray analyses of (-)-**21**, (+)-**42**, (+)-**46**, and (-)-**ii** (31 pages). Ordering information is given on any current masthead page.

Photochemical and ESR Spectral Evidence for a Stereoselective Rearrangement of Radical Cations Derived from Azoalkanes and Bicyclopentanes

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Abstract: Studies of the photosensitized electron transfer (PET) reactions of *anti/syn*-5-methylbicyclo[2.1.0]pentane (**1a,b**) and *syn/anti*-7-methyl-2,3-diazabicyclo[2,2.1]hept-2-ene (**2a,b**) have revealed a remarkable *stereochemical memory effect*. Thus, **1a** and **2a** furnished only 1-methylcyclopentene (**3a**) as the rearrangement product, while their isomers **1b** and **2b** afforded predominantly 3-methylcyclopentene (**3b**). The pathway responsible for the stereoselective olefin formation can be assigned to a radical cation rearrangement. This was established on the basis of direct ESR evidence showing that the 1,3-diyl radical cations **1a,b**$^{\bullet+}$ detected initially at 80-90 K following the radiolytic oxidation of **1a,b** in CF_3CCl_3 rearranged stereoselectively into the olefin radical cations **3a,b**$^{\bullet+}$ at 105 K. The ESR results further establish that, in the puckered conformations of **1a,b**$^{\bullet+}$, the pseudo-axial substituent on the methylene bridge is in almost perfect coplanar alignment with the radical cation 2p orbital lobes, thus facilitating its stereoselective migration. Also, in agreement with PET results, matrix ESR studies demonstrated that, on radiolytic oxidation of the azoalkanes **2a,b**, the olefin radical cations **3a,b**$^{\bullet+}$ were formed with high selectivity, although no precursor radical cations were detected in this case.

Azoalkanes[1] and strained hydrocarbons[2] serve as suitable electron donors in photosensitized electron transfer (PET) reactions carried out in liquid media at ambient temperature, and there is a considerable body of evidence which indicates that their transient radical cations can undergo fragmentation, rearrangement, or addition reactions.[1,2] A valuable underpinning in the rationalization of this diverse reactivity comes from direct studies of radical cations by matrix ESR spectroscopy.[1c,3] Thus, the chair cyclohexane-1,4-diyl and puckered cyclopentane-1,3-diyl radical cations formed by the respective oxidations of bicyclo[2,2,0]hexane[3d] and bicyclo[2,1,0]pentane[3c] were found to rearrange smoothly to the corresponding cyclohexene and cyclopentene radical cations by intramolecular hydrogen transfer at 90-100 K. In contrast, the structurally similar bicyclo[1.1,0]butane radical cation[3e] did not isomerize to the cyclobutene radical cation up to 160 K, the softening point of the matrix.

Taken at face value, these differing results would appear to suggest that the radical cation isomerization of cycloalkanediyls to the more stable cycloalkenes is facilitated by a 1,3- rather than a 1,2-hydrogen transfer since only the former process is excluded for the cyclobutane-1,3-diyl radical cation. However, the present work demonstrates inter alia that this quite reasonable conjecture[3c] is *incorrect*, at least for the cyclopentane-1,3-diyl radical cation, thereby illustrating the pitfalls of mechanistic conclusions based only on comparative studies of different reactants, even when these are done within the same family!

The dearth of information regarding the actual mechanism of

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