Total Syntheses of (−)-Macrolactin A, (+)-Macrolactin E, and (−)-Macrolactinic Acid: An Exercise in Stille Cross-Coupling Chemistry

Amos B. Smith, III* and Gregory R. Ott

Contribution from the Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received January 20, 1998

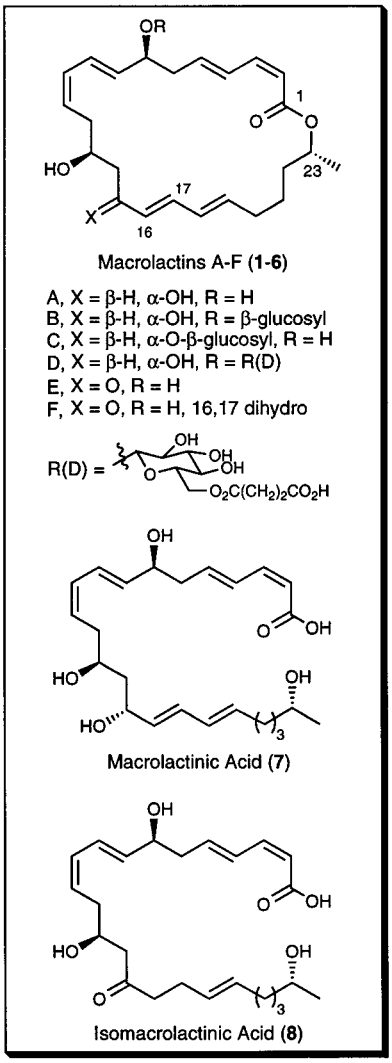
Abstract: The total syntheses of the potent antiviral agent (−)-macrolactin A (**1**) and two related family members, (+)-macrolactin E (**5**) and (−)-macrolactinic acid (**7**), have been achieved, exploiting a unified, convergent, and highly stereocontrolled strategy. Extensive use of the palladium-catalyzed Stille cross-coupling reaction for the stereospecific construction of the three isolated dienes including macrocyclization formed the cornerstone of the successful strategy. The total syntheses of these natural products, no longer available via fermentation, confirm their relative and absolute stereochemistries and provide access to possible analogues for further biological study.

In 1989 Fenical and co-workers reported the isolation and planar structures of macrolactins A−F, macrolactinic acid, and isomacrolactinic acid (**1**−**8**, Scheme 1), new secondary metabolites produced in culture by a taxonomically unclassifiable deep-sea bacterium.[1] The parent aglycone, macrolactin A [(−)-**1**], inhibits type I and type II *Herpes simplex* virus with IC_{50} values of 5.0 and 8.3 μg/mL, respectively. Comparison of the cytotoxicity of **1** against the Hep-2 and MA-104 carrier cell lines revealed a potential therapeutic index range of 10−100.[1] Macrolactin A also inhibits replication of B16-F10 murine tumor cells in vitro (IC_{50} 3.5 μg/mL). Most importantly, **1** protects human T-lymphoblasts against the HIV-1 virus, with optimum effectiveness observed at 10 μg/mL.[1] Further investigation of the molecular mechanism of both T-lymphoblast protection and cytotoxicity was, however, precluded by lack of natural material.

The relative and absolute stereochemistries of macrolactins B and F were subsequently assigned by Rychnovsky et al. via a combination of NMR analysis, degradation, and chemical correlation.[2] The extreme scarcity of natural material precluded elucidation of the three-dimensional architecture of the other macrolactins, although it has reasonably been assumed that the configurations of congeners B and F are maintained throughout the macrolactin family (Scheme 1).[2]

The unique pharmacological properties of (−)-**1** juxtaposed with the absence of natural material presented the synthetic community with a challenge of considerable importance.[3,4] Herein we describe a full account of the design and execution of the first total synthesis of macrolactin A (−)-**1**, exploiting as the cornerstone of the successful strategy the palladium-catalyzed Stille cross-coupling reaction.[5] The approach proved highly convergent, economic (i.e., short), and highly stereocontrolled. Extension of this strategy to other members of the macrolactin family has recently led to the total synthesis of (+)-macrolactin E (**5**) and (−)-macrolactinic acid (**7**). The culmination of this synthetic venture not only confirms the relative and absolute stereochemistries of (−)-macrolactin A, (+)-macrolactin E, and (−)-macrolactinic acid but also provides a versatile route to these natural products no longer available via fermentation.

Scheme 1



(1) Gustafson, K.; Roman, M.; Fenical, W. *J. Am. Chem. Soc.* **1989**, *111*, 7519.

(2) Rychnovsky, S. D.; Skalitzky, D. J.; Pathirana, C.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671.

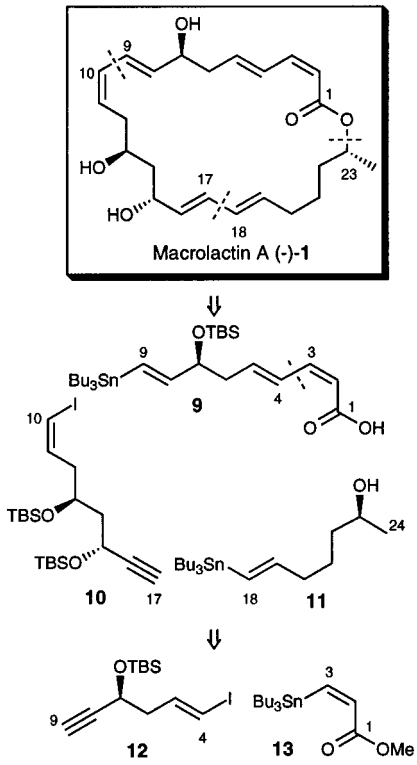
(3) For a synthesis of 13,15-dimethoxymacrolactin A, which also exploits Stille and Suzuki cross-coupling chemistry for key bond constructions, see: Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501.

S0002-7863(98)00203-0 CCC: $15.00
Published on Web 04/14/1998

Retrosynthetic Analysis of (−)-Macrolactin A. The multiple diene motif of (−)-macrolactin (**1**) led us to consider a σ-bond construction approach,[6] wherein we would generate the medial σ-bond of each diene via a stereospecific palladium-catalyzed Stille cross-coupling reaction.[7] Although the precise conditions that deliver optimal results are often highly system dependent, the Stille reaction has become a powerful tool in the area of macrolide total synthesis.[8,9] We reasoned that the unique architecture of the macrolactins would present an ideal opportunity to extend the effectiveness of this tactic for both diene construction and macrocycle formation. We also anticipated that the recently introduced accelerating ligands,[10] stoichiometric additives,[11] cocatalysts,[12] and copper(I)-coupling reagents,[13] which improve the overall efficiency of the Stille process, might prove particularly useful during this synthetic enterprise.

From the retrosynthetic perspective disconnections at the lactone, the C(9,10) and the C(17,18) diene linkages led to advanced subtargets **9**, **10**, and **11** (Scheme 2). The most convergent route would then entail construction of the C(1−17) fragment via Stille cross-coupling of **9** and **10** followed either by Mitsunobu esterification[14] of the C(1−17) and C(18−24) fragments and Stille macrocyclization, or conversely, C(16−19) diene formation via a Stille reaction followed by Mitsunobu macrolactonization.[15] Similar σ-bond disconnection at C(3,4) of fragment **9** led to subtargets **12** and **13**, further revealing the extent to which the Stille reaction could be utilized for key-bond constructions.

Scheme 2



Synthesis of the C(1−9) Subunit (9). As our point of departure, propynal[16] was treated with *B*-allyldiisopinocampheylborane, derived from commercially available (−)-*B*-methoxydiisopinocampheylborane and allylmagnesium bromide, to furnish known alcohol (−)-**15**[17] in 90% ee as determined by optical rotation and confirmed by Mosher analysis (Scheme 3).[18] Protection of the hydroxyl as the TBS ether, selective ozonolysis,[19] and Cr(II)-mediated olefination[20] then furnished vinyl iodide **12** as an inseparable mixture (ca. 4:1) of *E*- and *Z*-isomers. The known[21] vinyl stannane **13** was prepared in one step from commercially available methyl propiolate (**18**). Unfortunately, attempts to couple **12** and **13** did not lead to the desired *Z*,*E*-diene.

Failure of the Stille process was attributed to the presence of the *Z*-olefin in **12** which we believe undergoes oxidative addition followed by Pd(II) insertion into the pendant alkyne, thus halting the Stille catalytic cycle. Nuss and co-workers[22] demonstrated that intramolecular insertion into a terminal alkyne, forming a

(4) For other synthetic approaches to macrolactin A and related derivatives, see: (a) Rychnovsky, S. D.; Pickering, D. A. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society, San Diego, CA; American Chemical Society: Washington, DC, 1994; ORGN 209 (b) Benvegnu, T.; Schio, L.; Le Floc'h, Y.; Grée, R. *Synlett* **1994**, 505. (c) Benvegnu, T. J.; Toupet, L. J.; Grée, R. L. *Tetrahedron* **1996**, *52*, 11811. (d) Benvegnu, T. J.; Grée, R. L. *Ibid.* **1996**, *52*, 11821. (e) Donaldson, W. A.; Bell, P. T.; Wang, Z.; Bennett, D. W. *Tetrahedron Lett.* **1994**, *35*, 5829. (f) Prahlad, V.; Donaldson, W. A. *Tetrahedron Lett.* **1996**, *37*, 9169. (g) Tanimori, S.; Morita, Y.; Tsubota, M.; Nakayama, M. *Synth. Commun.* **1996**, *26*, 559. (h) González, Á.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949.

(5) Preliminary communication: Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095.

(6) A general theme of recent synthetic ventures of this laboratory exploits σ-bond constructions; for an overview see: Smith A. B., III; Condon S. M.; McCauley, J. A. Submitted for publication in *Acc. Chem. Res.*

(7) (a) Stille, J. K. *Angew. Chem., Int. Ed. Eng.* **1986**, *25*, 508. For a comprehensive review see: (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1997; Vol. 50, pp 1−652. See also: (c) Mitchell, T. N. *Synthesis* **1992**, 803.

(8) To our knowledge Stille was the first to employ his palladium-catalyzed coupling for macrolide construction: (a) Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785. See also: (b) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883. Nicolaou elegantly extended this methodolgy by using a Stille-type "stitching" cyclization in his synthesis of rapamycin. (c) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (d) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318. Recently, Paterson reported a novel Stille-type cyclodimerization using the stoichiometric coupling reagent copper(I) thiophene-2-carboxylate (CuTC),[13] see: (e) Paterson, I.; Man, J. *Tetrahedron Lett.* **1997**, *38*, 695.

(9) (a) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Org. Chem.* **1996**, *61*, 685. (b) McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.*, **1996**, *61*, 700. (c) Pattenden, G.; Thom, S. M. *Synlett*, **1993**, 215. (d) Boden, C.; Pattenden, G. *Synlett* **1994**, 181. (e) Kende, A. S.; Liu, K.; Kaldor, I.; Dorey, G.; Koch, K. *J. Am. Chem. Soc.* **1995**, *117*, 8258. (f) Kende, A. S.; Koch, K.; Dorey, G.; Kaldor, I.; Liu, K. *J. Am. Chem. Soc.* **1993**, *115*, 9842 (g) Evans, D. A.; Black, W. C.; *J. Am. Chem. Soc.* **1992**, *114*, 2260. (h) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407. (i) Smith, A. B., III.; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *Ibid.* **1997**, *119*, 947. (j) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *Ibid.* **1997**, *119*, 962.

(10) Farina, V.; Krishnan, B.; *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(11) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

(12) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. See also: Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C. Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(13) For the use of stoichiometric copper(I) thiophene-2-carboxylate (CuTC) to effect Stille-type couplings see: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

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

(15) (a) Zibuck, R.; Liverton, N. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2451. (b) Smith, A. B., III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995.

(16) Sauer, J. C. *Organic Syntheses*; Wiley: New York, 1963; Coll. Vol. IV, p 813.

(17) (*S*)-5-Hexen-1-yn-3-ol has been resolved by lyophilized-yeast hydrolysis of the racemic acetate. Blänzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron* **1987**, *43*, 5791.

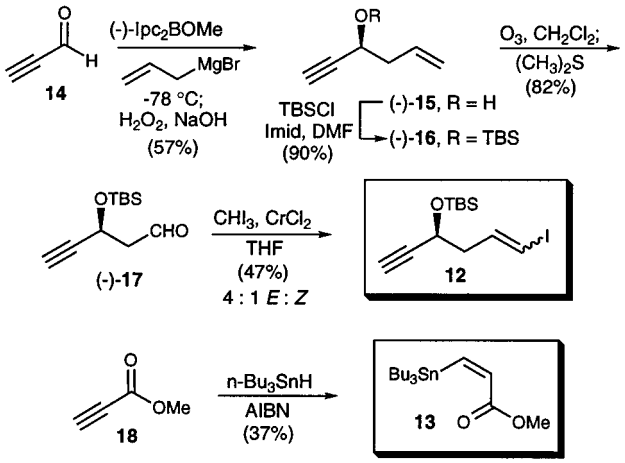
(18) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(19) Chen, S.-Y.; Joullié, M. M. *Synth. Commun.* **1984**, *14*, 591.

(20) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(21) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5194.

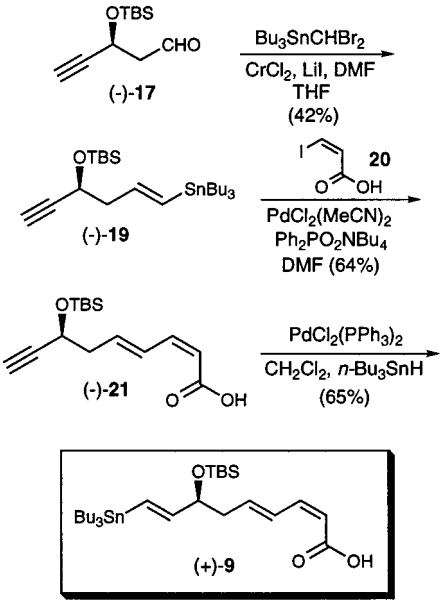
Scheme 3



five-membered ring, is competetive with intermolecular transmetalation. Similar processes have been exploited in cascade cyclizations leading to five- and six-membered rings.[23] To circumvent the problem we explored the tactic of vinyl substituent interchange; we also chose to forego carboxylic acid protection.

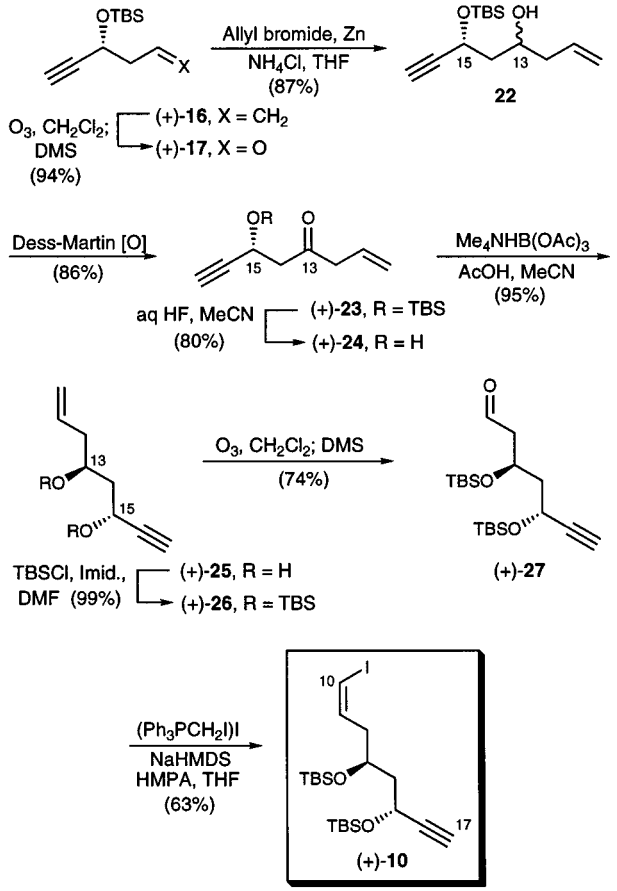
Construction of transposed Stille component **19** (Scheme 4) entailed chromium(II)-mediated one-carbon homologation[24] of (−)-**17**; a single isomer was produced in 42% yield. To our delight the Pd-catalyzed cross-coupling of (−)-**19** with known vinyl iodide **20**[25] employing the standard Stille conditions [cf., $PdCl_2(MeCN)_2$, DMF][26] furnished the *Z,E*-diene (−)-**21** in 64% yield; $Ph_2PO_2NBu_4$ was added to facilitate removal of tin contaminants.[11] Pd(0)-catalyzed hydrostannylation[27] completed construction of (+)-**9** (six steps from propynal; 10% overall yield).

Scheme 4



Construction of C(10−17) Vinyl Iodide (10) and Attempted Stille Coupling. Preparation of vinyl iodide **10** (Scheme 5) began with selective ozonolysis[19] of (+)-**16**.[28] Luche allylation[29] followed by Dess−Martin oxidation[30] of the resultant diastereomeric alcohols (**22**, ca. 1:1) furnished ketone (+)-**23**. Removal of the silyl group followed by hydroxyl-directed reduction[31] to introduce the C(13) stereocenter led to *anti*-diol (+)-**25**.[32] Protection, selective ozonolysis,[19] and one-

Scheme 5



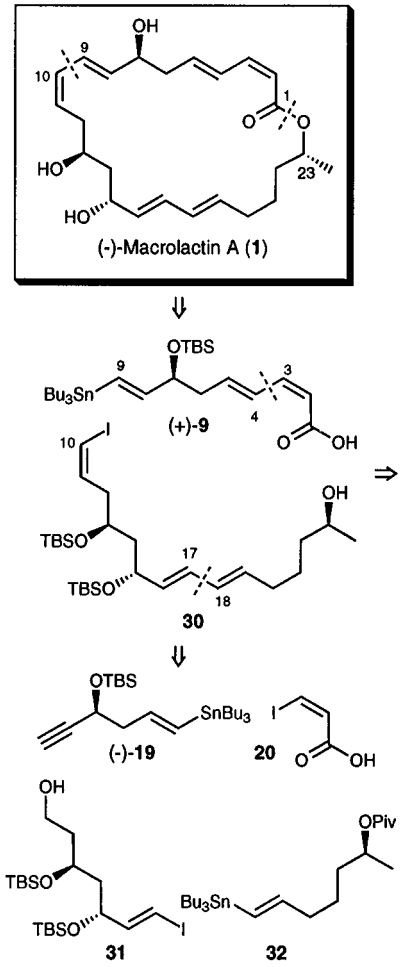
carbon Wittig olefination of the resultant aldehyde (+)-**27** exploiting the Stork/Zhao protocol[33] led to (+)-**10** as a single olefinic isomer in 63% yield. The 10-step sequence from propynal furnished **10** in 12% overall yield, with an average yield of 81% per step. Unfortunately, all attempts to couple (+)-**9** and (+)-**10** failed to generate the desired *E,Z*-diene. Again, failure of the Stille process was attributed to possible intramolecular carbopalladation of the pendant alkyne.[22,23]

A Second Generation Retrosynthetic Analysis. Our inability to effect cross-coupling of **9** and **10**, or to convert **10** to the corresponding stannane to explore Stille coupling with the transposed substituents, led us to revise our approach. The

(22) Nuss, J. M.; Levine, B. H.; Rennels, R. A.; Heravi, M. M. *Tetrahedron Lett.* **1991**, *32*, 5243.
(23) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
(24) (a) Hodgson, D. M. *Tetrahedron Lett.* **1992**, *33*, 5603. (b) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Ibid.* **1994**, *35*, 2231. See also: (c) Cliff, M. D.; Pyne, S. G. *Ibid.* **1995**, *36*, 763.
(25) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.
(26) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(27) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(28) (+)-**16** was prepared in an analogous fashion as (−)-**16** except that the opposite enantiomer (+)-*B*-methoxydiisopinocampheylborane was employed.
(29) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910.
(30) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Reagent preparation: Ireland, R. E.; Liu, L. *Ibid.* **1993**, *58*, 2899.
(31) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287. For a review of $NaBH_4$ reductions in carboxylic acid media see (c) Gribble, G. W.; Nutaitis, C. F. *Org. Proc. Prepr. Int.* **1985**, *17*, 317.

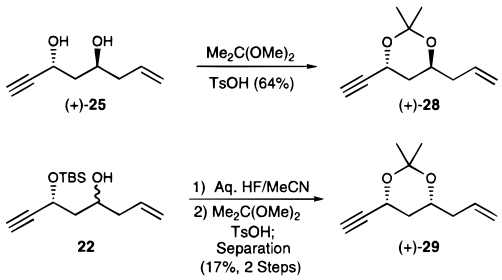
revised strategy (Scheme 6), also permitting considerable flexibility, called for assembly of the macrocycle through Mitsunobu esterification of (+)-**9** with **30**, followed by intramolecular Stille coupling, or alternatively, formation of the C(9,10)

Scheme 6



diene linkage and then Mitsunobu macrolactonization. Subtarget **30** was anticipated to arise via Stille coupling of **31** and **32**. Importantly, no revisions in the key bond disconnections were necessary; only the order of the steps leading to the diene was altered, thus again demonstrating the inherent versatility of the Stille approach to the macrolactins.

(32) The relative stereochemistry of (+)-**25** was assigned by ^{13}C NMR chemical shift analysis of the derived *anti*-acetonide (+)-**28**. For comparison, the corresponding *syn*-acetonide (+)-**29** was prepared from **22**.

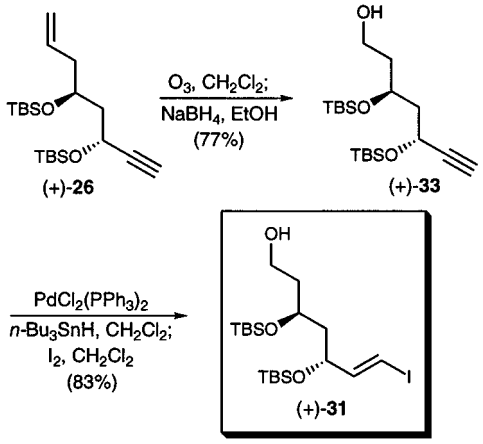


For a complete discussion of ^{13}C NMR analysis for assignment of 1,3-diol relative stereochemistry see: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Ibid*. **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem*. **1993**, *58*, 3511. (d) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *Ibid*. **1993**, *58*, 5251.

(33) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

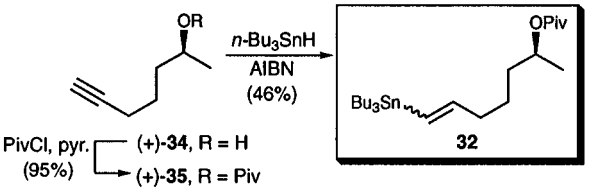
Synthesis of the C(10−24) Subunit (30). Construction of subtarget **31** (Scheme 7) began with selective ozonolysis[19] of (+)-**26** followed by in situ reduction of the derived ozonide ($NaBH_4$) to furnish (+)-**33**. Pd(0)-catalyzed hydrostannylation[27] of the alkyne followed by halogen−tin exchange afforded (+)-**31** in 10 steps and 16% overall yield from propynal.

Scheme 7



Subtarget **32** (Scheme 8) was prepared in two steps from the known acetylenic alcohol (+)-**34**;[34] protection of the secondary hydroxyl followed by radical-induced hydrostannylation of the alkyne gave **32** as an inseparable mixture of *E*- and *Z*-isomers (ca. 4.1:1).

Scheme 8

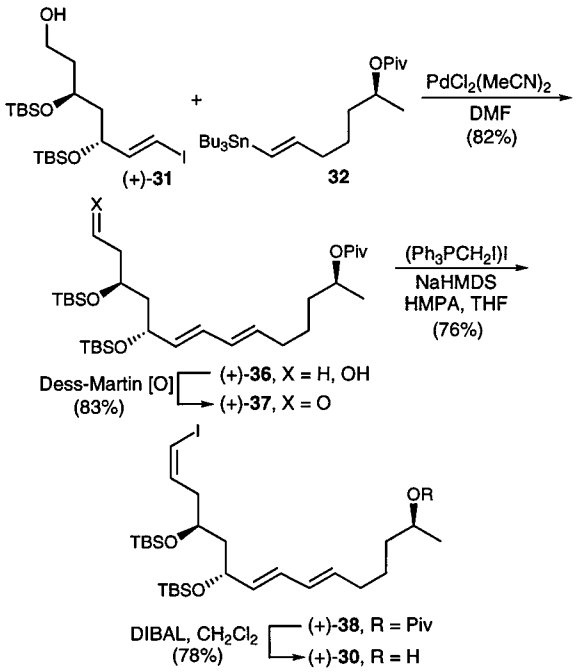


Pd-catalyzed cross-coupling of (+)-**31** and **32**, again using the standard Stille protocol [$PdCl_2(MeCN)_2$, DMF],[26] afforded the pure *E*,*E*-diene (+)-**36** in 82% yield following flash chromatography (Scheme 9). Importantly, the reaction was amenable to multigram production of (+)-**36.** Completion of **30** required oxidation of the primary alcohol with the Dess−Martin periodinane[30] followed by our second use of the Stork/Zhao one-carbon Wittig homologation.[33] This protocol generated *Z*-vinyl iodide (+)-**38** again as a single isomer in 63% yield (two steps). Reductive removal of the pivaloyl protecting group then afforded (+)-**30**, poised for either Stille cross-coupling or Mitsunobu esterification. The synthesis of **30** required 14 steps from propynal and proceeded in 7% overall yield.

Macrocycle Construction via Mitsunobu Esterification Followed by Intramolecular Stille Cross-Coupling. Previous experience in the rapamycin/demethoxyrapamycin[6,9h−j] area suggested that esterification followed by an intramolecular Stille cross-coupling process would provide superior results. To this end (+)-**9** and (+)-**30** (Scheme 10) were subjected to Mitsunobu esterification to furnish (+)-**39** in 74% yield.

The Stille macrocyclization of (+)-**39** to afford (−)-**40** proved quite challenging. Use of Pd(II) precatalysts which required in situ reduction to the Pd(0) catalytic species, such as $PdCl_2(MeCN)_2$,[26] $PdCl_2(PPh_3)_2$,[35] or $PdCl_2[P(2\text{-furyl})_3]_2$,[10] led predominantly to slow protodestannylation, even in the presence of 10 equiv of Hunig's base, added to minimize stannane

Scheme 9

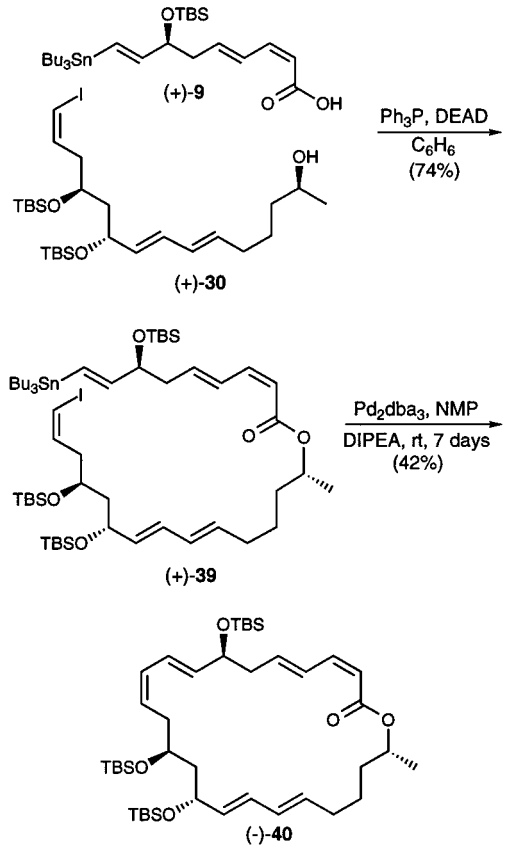


degradation by adventitious acid.[36] Best results were obtained with Pd_2dba_3 employing *N*-methyl-2-pyrrolidinone (NMP) as solvent in the absence of phosphine ligands.[37] Addition of copper(I) iodide as an accelerating cocatalyst[12] or ligands of reduced donicity[10] [e.g., triphenylarsine or tri(2-furyl)phosphine] proved ineffective. A typical reaction employed 10 mol % catalyst and 10 equiv of Hunig's base. Under these conditions, (−)-**40** was obtained in 42% yield. Although elevated temperatures accelerated the coupling process, reactions performed at room temperature furnished cleaner products. Unfortunately, the macrocyclizations were not reproducible; competing protodestannylation proved particularly problematic upon scale-up.

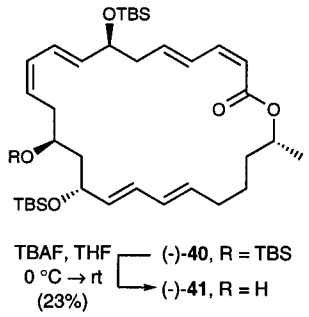
Despite these problems, a sufficient quantity of macrocycle (−)-**40** was eventually prepared to explore the unmasking of the three hydroxyl groups required to complete the total synthesis of macrolactin A. The unfortunate lack of natural macrolactin A however precluded effective systematic screening of various desilylation conditions via TLC analysis. The only approach to endgame development was therefore product analysis employing (−)-**40**. To this end, (−)-**40** was subjected to a variety of acidic conditions. Surprisingly, desilylation conditions known to be effective with allylic TBS ethers in highly unsaturated systems (e.g., HCO_2H/THF/H_2O; HF-pyr/pyridine)[9e−f,38] led either to no reaction or to decomposition. Dowex resins[39] or protic acids (e.g., TsOH or HCl, MeOH) proved too harsh for the highly unsaturated system. Even mild acidic conditions such as H_2SiF_6 (MeCN/*t*-BuOH) were incompatible with the macrolide.[40]

Our inability to effect desilylation with a variety of acids, coupled with fact that macrolactinic acid (**7**), the open chain form of macrolactin A, was known to be stable to base[41] led us to attempt deprotection with fluoride ion. Treatment of (−)-**40** with tetrabutylammonium fluoride (TBAF) in THF at 0 °C followed by warming to room temperature (Scheme 11) led on a single occasion to bis-TBS-protected macrocycle **41** in 23%. Further exposure of **41** to fluoride ion or mild acid resulted only in decomposition.

Scheme 10



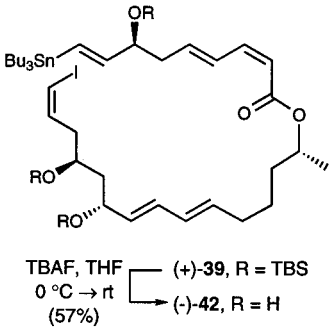
Scheme 11



The difficulty associated with removal of the TBS ethers led us to focus on removal of the silyl groups prior to macrocyclization, in anticipation that intramolecular Stille coupling might be effected on triol **42**. Toward this end, treatment of (+)-**39** with an excess of TBAF (Scheme 12) led to complete desilylation to furnish (−)-**42**, although significant isomerization of the C(2,3) olefin and protodestannylation were also observed. More significant, however, all attempts to effect cyclization,

(34) Millar, J. G.; Oehlschlager, A. C. *J. Org. Chem.* **1984**, *49*, 2332.
(35) Catalyst prepared according to: Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: New York, 1985; p 18.
(36) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
(37) Complete omission of ligands for Stille cross-couplings has been noted previously see: Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.
(38) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
(39) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, *21*, 137.
(40) (a) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492. (b) Pilcher, A. S.; DeShong, P. *Ibid.* **1993**, *58*, 5130.
(41) Macrolactin A was converted to macrolactinic acid using KOH/MeOH. See reference 1.

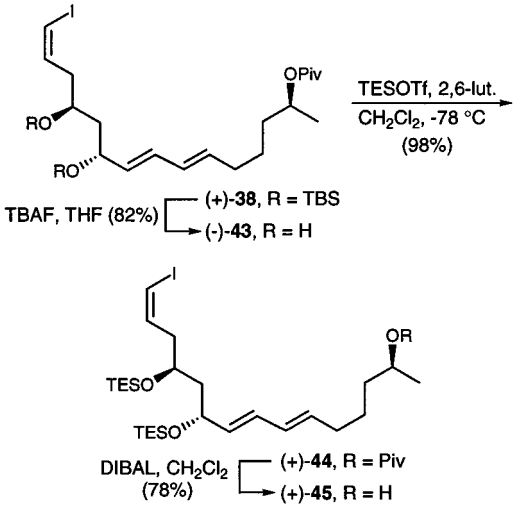
Scheme 12



including conditions that led to **40**, failed to produce macrolactin A (**1**); only slow decomposition of the starting material was observed. Our inability to effect macrocyclization of (−)-**42** in conjunction with the inefficient deprotection of (+)-**39** led us to abandon this approach.

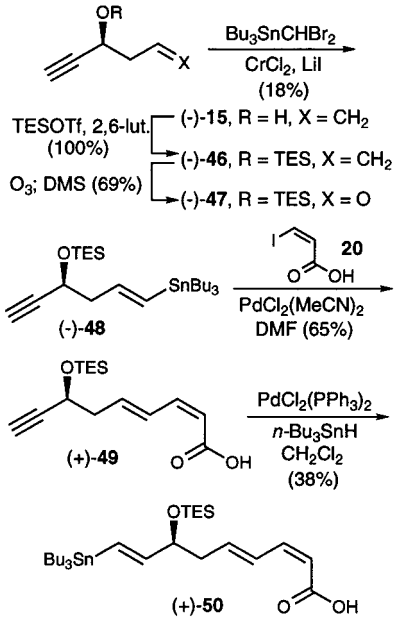
Protecting Group Modification: The Triethylsilyl Series. At this juncture it appeared that the reaction conditions required to remove the TBS groups were incompatible with macrolactin A. We reasoned that the more labile triethylsilyl (TES) group[42] might be removed employing TBAF buffered with acetic acid, the latter to modulate the basicity of the fluoride ion.[43] This tactic proved highly effective in the endgames of both our rapamycin/demethoxyrapamycin[9h−j] and acutiphycin[44] syntheses. Interestingly, (+)-**38** was readily deprotected with TBAF/THF furnishing diol (−)-**43** in 82% (Scheme 13). Diol **43** was then protected (TESOTf, 2,6-lut) and the pivaloyl moiety removed to furnish (+)-**45** in 63% overall yield for the three steps.

Scheme 13



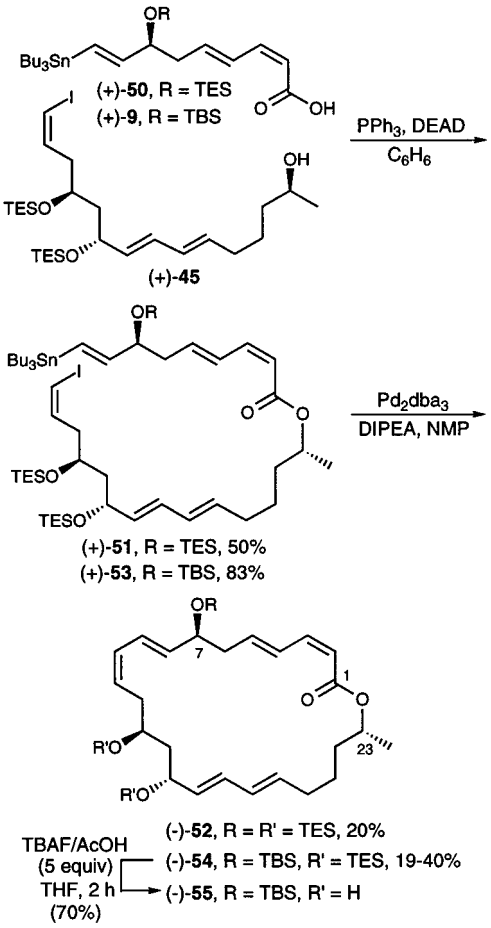
Construction of the requisite C(1−9) fragment (**50**, Scheme 14) with the C(7) hydroxyl protected as a TES ether, however, met with difficulty. Alcohol (−)-**15** was first converted to the TES ether (−)-**46**. Selective ozonolysis[19] followed by homologation[24] furnished vinyl stannane (−)-**48**, albeit in low yield. Stille coupling with (*Z*)-3-iodopropenoic acid (**20**)[25] proceeded without event, but the required Pd(0)-catalyzed hydrostannylation proceeded in only 38% yield accompanied by a number of unidentified products.

Scheme 14



Construction of TES protected macrocycle (−)-**52** (Scheme 15) was achieved in an analogous fashion to the TBS congener,

Scheme 15



(42) (a) Greene, T. W.; Wutz, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1991; p 73. (b) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: New York, 1994; p 31. (c) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

(43) To the best of our knowledge Otera and co-workers were the first to employ TBAF buffered with acetic acid to mitigate the basicity of fluoride to suppress β-elimination of a TBS ether. (a) Otera, J.; Niibo, Y.; Nozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3655.

(44) Smith, A. B., III.; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013. Danishefsky also exploited TBAF/HOAc in the synthesis of rapamycin; Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345.

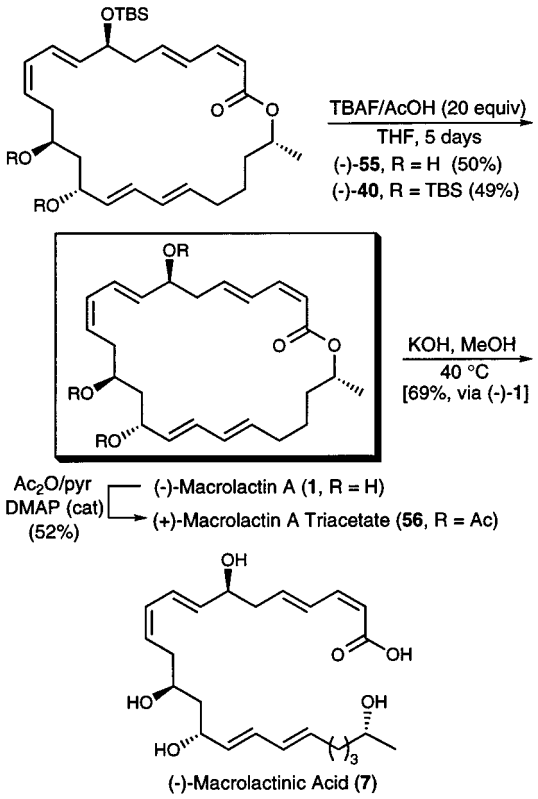
although here again, only modest yields prevailed. For example, Mitsunobu esterification of (+)-**45** and (+)-**50** afforded (+)-**51** in 50% yield (Scheme 15); the palladium-catalyzed macrocyclization also proved capricious, providing (−)-**52** in ca. 20% yield. A single attempt at deprotection employing buffered TBAF was carried out without success. Although unsuccessful, this approach did reveal important insights vis á vis future endgame strategies. Particularly noteworthy was the high yield obtained in the unmasking of the C(13) and C(15) hydroxyls in (+)-**38** (Scheme 13); this observation led us to speculate that the C(7) silyl ether and corresponding hydroxyl in the macrolide were prone to elimination.

Undaunted, we chose to explore a stepwise endgame. The apparent lability of the C(7) TES ether to both the coupling and deprotection protocols dictated use of the more robust TBS group at C(7). We therefore focused on unmasking the C(13) and C(15) TES moieties in the fully elaborated macrocycle. We anticipated that selective desilylation might be accomplished employing TBAF/AcOH, leaving the C(7) TBS ether intact. This approach, if successful, would prove advantageous for elaboration of other members of the macrolactin family (vide infra).

Construction of the differentially protected macrocycle (−)-**54** (Scheme 15) entailed Mitsunobu esterification of (+)-**9** with (+)-**45** followed by the now familiar Stille macrocyclization. Initially this process provided (−)-**54** in only 30% for the two steps (vide infra). More importantly, however, treatment with TBAF/AcOH furnished the monoprotected macrocycle (−)-**55** in 70% yield. With the successful unmasking of the 1,3-diol, all that remained to complete the total synthesis of macrolactin A was removal of a single TBS ether.

Although initial attempts to remove the TBS moiety employing TBAF/AcOH (ca. 3 equiv) were unsuccessful, treatment of (−)-**55** with a large excess (ca. 20 equiv) of TBAF/AcOH effected slow conversion (5 days) to furnish (−)-macrolactin A in 50% yield (Scheme 16).

Scheme 16



With synthetic macrolactin A in hand, we reexamined the deprotection of (−)-**40** (Scheme 16). Exposure of (−)-**40** to the more vigorous deprotection conditions led to the removal of the three TBS ethers over a 5 day period to furnish (−)-**1** in 49% yield. This deprotection venture reaffirmed the critical value of the availability of natural material for endgame development.

Comparison of the ^{1}H (d_5-pyr) and ^{13}C ($CDCl_3$, d_6-acetone) NMR spectra of synthetic (−)-**1**, as well as the ^{1}H NMR ($CDCl_3$) spectra of the derived triacetate[45] (**56**, Scheme 16), with the corresponding spectra kindly provided by Professor William Fenical (University of California, San Diego)[46] demonstrated that we had indeed completed the total synthesis of (−)-macrolactin A; the sign and magnitude of the optical rotation were also in good agreement with the reported value {lit.[1] $[\alpha]^{23}_D$ −9.6° (*c* 1.86, MeOH); obsd. $[\alpha]^{23}_D$ −8.9° (*c* 0.09, MeOH)}.

Synthesis of (−)-Macrolactinic Acid (7). Macrolactinic acid (−)-**7**, originally isolated from culture, was also prepared by Fenical et al. via opening the lactone of natural (−)-**1**.[1] In an analogous fashion, we found that treatment of synthetic (−)-**1** with KOH/MeOH furnished (−)-**7** in 69% yield (Scheme 16). The ^{1}H and ^{13}C NMR (CD_3OD) spectra were again identical to the corresponding spectra derived from natural material;[46] the optical rotation was of equal sign and of comparable magnitude with the reported value {lit.[1] $[\alpha]^{23}_D$ −13.9° (*c* 0.58, MeOH); obsd. $[\alpha]^{23}_D$ −13.0° (*c* 0.29, MeOH)}.

Reinvestigation of the Stille Macrocyclization. The syntheses of (−)-macrolactin A and macrolactinic acid, although victories, were somewhat bittersweet given the modest yield experienced in the macrocyclization. Additional optimization of the cyclization process employing the tributylstannyl moiety at C(9) appeared imprudent. Instead, our success with the interchange of the vinyl substituents and the reported enhanced reactivity of the trimethylvinyl tin moiety in the Stille cross-coupling process[26] suggested we explore these alternatives. To this end, palladium-catalyzed tin−iodine exchange furnished trimethylstannane (+)-**58** from (+)-**30** with complete retention of stereochemistry (Scheme 17);[47] vinyl stannane (+)-**9** (Scheme 17) was also converted to vinyl iodide (+)-**57** via halogen−tin exchange.

As before, assembly of the macrocycle entailed Mitsunobu esterification followed by Pd-catalyzed macrocyclization (Scheme 17). In this case the Stille coupling proved quite facile; reproducible yields (ca. 67%) of (−)-**40** were readily obtained on 100 mg scale. Importantly, the reaction time decreased to 45 min. Addition of $Ph_2PO_2NBu_4$,[11] rigorous deoxygenation, and high dilution (ca. 0.00025 M) to curtail substrate polymerization also facilitated the reaction.

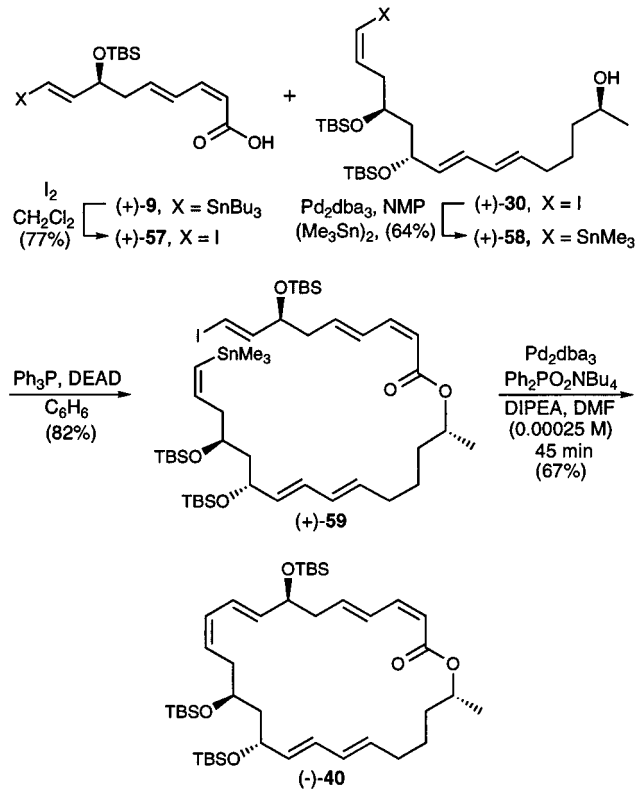
Synthesis of (+)-Macrolactin E (5). Having achieved the total synthesis of (−)-macrolactin A, we turned to other members of the macrolactin family. We envisioned that macrolactin E possessing the C(15) carbonyl could be prepared from diol (−)-**55**, generated from differentially protected macrocycle (−)-**54**. Our initial synthesis of (−)-**54**, employing tributylvinyl stannane (+)-**53** (Scheme 15), however, was not particularly efficient. We therefore chose, as in our macrolactin A synthesis, to interchange the tin and iodide vinyl substituents of the Stille coupling partners and to take advantage of the more reactive trimethylvinyl stannyl moiety.

(45) Fenical and co-workers prepared the triacetate derivative while performing the structure elucidation see ref 1.

(46) We thank Professor William Fenical at The Scripps Institution of Oceanography, University of California, San Diego for providing copies of the ^{1}H and ^{13}C spectra.

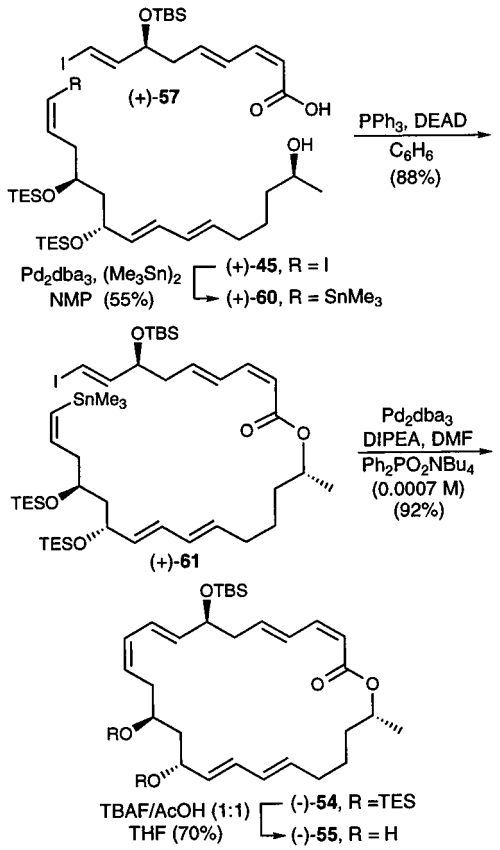
(47) Farina, V.; Hauck, S. I. *J. Org. Chem.* **1991**, *56*, 4317.

Scheme 17



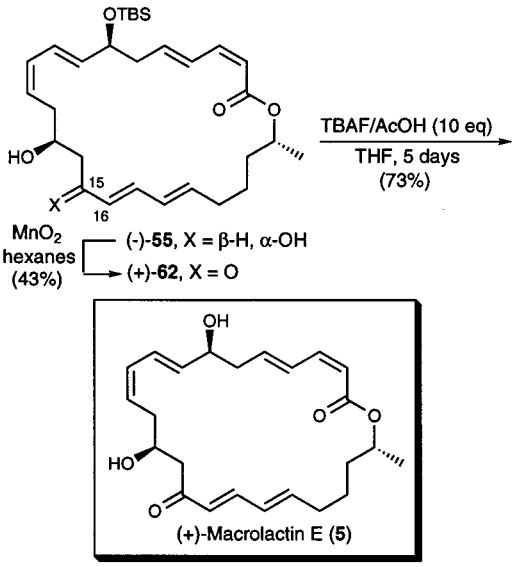
Palladium-catalyzed tin−iodine exchange[47] of vinyl iodide (+)-**45** generated *Z*-vinyl stannane (+)-**60** in 55% yield (Scheme 18). Assembly of the macrocycle was then achieved via Mitsunobu esterification of (+)-**57** with (+)-**60** to generate (+)-**61** (88%), followed by Stille macrocyclization employing the conditions optimized for the macrolactin A congener (Scheme 18). The latter transformation provided (−)-**52** in 92% yield which, to the best of our knowledge, represents the highest yield reported to date for a Stille macrocyclization. Conversion of (−)-**54** to (−)-**55** with TBAF and AcOH then proceeded in 70% yield.

Scheme 18



Macrocycle (−)-**55** was next subjected to MnO_2 oxidation[48] to generate (+)-**62** in 43% yield (Scheme 19); only unmasking of the C(7) hydroxyl remained to complete the total synthesis of macrolactin E. As in the case of macrolactin A, TBAF/AcOH (ca. 10 equiv) proved particularly well suited for the delicate desilylation of (+)-**62**, furnishing (+)-macrolactin E (**5**) in 73% yield over a 5 day period.[46]

Scheme 19



Summary. The total synthesis of the potent antiviral agent (−)-macrolactin A (**1**), and two related family members, (+)-macrolactin E (**5**) and (−)-macrolactinic acid (**7**), have been achieved. The approach proved highly convergent, economic (i.e., short), and highly stereocontrolled. The successful route not only confirmed the relative and absolute stereochemistries of all three natural products but also provides access to a variety of synthetic analogues for further biological analysis. For macrolactin A the longest linear sequence from propynal was 17 steps. The cornerstone of the successful strategy comprised the Pd-catalyzed Stille cross-coupling reaction for the rapid, stereospecific construction of the three dienes including macrocyclization. Particularly noteworthy was the use of the more reactive trimethylvinyl tin moiety and the $Ph_2PO_2NBu_4$ tin scavenger[11] for rapid, high-yielding Stille cross-couplings and macrocyclizations. Finally, the macrocyclic framework was assembled in only two steps via union of the functionalized intermediates (+)-**57** and (+)-**58**.

Experimental Section[49]

Alcohol (−)-15.[17] (−)-*B*-Methoxydiisopinocampheylborane (21.3 g, 67.3 mmol) was added to a tared flask in a glovebag under argon atmosphere. Anhydrous ether (25 mL) was added and the reaction mixture cooled to −78 °C. Allylmagnesium bromide (1 M in ether, 67.3 mL, 67.3 mmol) was added dropwise over 30 min, the resultant reaction mixture was stirred for 15 min at −78 °C and warmed to room

(48) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

temperature (1 h), and the magnesium salts were removed by filtration under argon. The reaction mixture was cooled to −78 °C, propynal[16] (2.33 g, 43.1 mmol) was added via cannula over 10 min, and the resultant mixture was stirred for 1 h at −78 °C and then warmed to room temperature (1 h). The reaction mixture was quenched with 30% hydrogen peroxide (30 mL) and 3 N NaOH (72 mL), heated to reflux for 1 h, and then stirred at room temperature for 12 h. The layers were separated, the aqueous layer was extracted with ether (5 × 200 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude alcohol was distilled (bp 67 °C, 35 mmHg) to afford (−)-**15** (3.77 g, 57% yield) as a colorless oil: $[\alpha]^{23}_D$ −36.4 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3600 (m), 3400 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90−5.84 (m, 1 H), 5.22−5.17 (m, 2 H), 4.41 (ddd, J = 6.1, 6.0, 2.0 Hz, 1 H), 2.49−2.41 (m, 1 H), 2.46 (d, J = 2.1 Hz, 1 H), 1.87 (d, J = 6.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 119.2, 84.2, 73.2, 61.4, 41.9.

TBS Ether (−)-16. A solution of alcohol (−)-**15** (1.97 g, 20.5 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (25 mL) was treated with imidazole (2.93 g, 43.0 mmol) and *tert*-butyldimethylsilyl chloride (3.25 g, 21.6 mmol) and stirred for 0.7 h. The reaction mixture was diluted with water (50 mL) and extracted with ether (3 × 50 mL), and the combined ether extracts were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane) provided (−)-**16** (3.87 g, 90% yield) as a colorless oil: $[\alpha]^{23}_D$ −26 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3300 (m), 2940 (s), 2880 (s), 1470 (m), 1250 (m), 1090 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.17−5.10 (m, 2 H), 4.36 (td, J = 6.5, 2.1 Hz, 1 H), 2.41 (tt, J = 6.8, 1.3 Hz, 2 H), 2.38 (d, J = 2.2 Hz, 1 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 117.7, 85.1, 72.4, 62.6, 43.1, 25.8, 18.2, −4.6, −5.1; high-resolution mass spectrum (CI, NH_3) m/z 211.1513 [(M + H)$^+$; calcd for $C_{12}H_{23}OSi$: 211.1518].

Aldehyde (−)-17. A solution of (−)-**16** (1.07 g, 5.07 mmol) in dichloromethane (5 mL) was cooled to −78 °C, and a stream of ozone bubbled through the solution until the starting material was consumed (TLC analysis). The reaction mixture was treated with dimethyl sulfide (7.9 mL, 10.14 mmol), warmed to room temperature, and stirred for 48 h. The mixture was then diluted with water (20 mL) and extracted with dichloromethane (3 × 25 mL). The combined dichloromethane extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/ethyl ether, 9:1) provided (−)-**17** (883.4 mg, 82% yield) as a colorless oil: $[\alpha]^{23}_D$ −56.9 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3310 (s), 2960 (s), 2875 (s), 1735 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (apparent t, J = 2.0 Hz, 1 H), 4.85 (ddd, J = 6.8, 4.9, 2.2 Hz, 1 H), 2.77 (ddd, J = 16.3, 6.8, 2.2 Hz, 1 H), 1.68 (ddd, J = 16.3, 4.8, 1.9 Hz, 1 H), 2.46 (d, J = 2.2 Hz, 1 H), 0.87 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 83.7, 73.7, 58.1, 51.3, 25.6, 18.0, −4.6, −5.2; high-resolution mass spectrum (CI, NH_3) m/z 230.1574 [(M + NH_4)$^+$; calcd for $C_{11}H_{24}NO_2Si$: 230.1579].

(*E*)-Vinyl Stannane (−)-19. A solution of chromium(II) chloride (2.47 g, 20.1 mmol) in anhydrous THF (32 mL) was stirred for 20 min and then treated with *N*,*N*-dimethylformamide (DMF) (1.48 mL, 20.1 mmol) dropwise via syringe over 20 min. The reaction mixture was stirred at room temperature for 15 min and cooled to 0 °C. A solution of aldehyde (−)-**17** (426.7 mg, 2.01 mmol) and tri-*n*-butylstannyldibromomethane[24a] (1.86 g, 4.02 mmol) in THF (6 mL) was added to the mixture via cannula (2 mL rinse) and stirred at 0 °C for 5 min. Lithium iodide (1.07 g, 8.04 mmol) in THF (6 mL) was transferred to the mixture via cannula (2 mL rinse). The flask was wrapped in aluminum foil, and the reaction mixture warmed to room temperature, stirred for 16 h, diluted with water (50 mL), and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/dichloromethane/triethylamine, 97:2:1) provided (−)-**19** (397.8 mg, 42% yield) and (−)-**16** (78 mg, 18% yield) as colorless oils: $[\alpha]^{23}_D$ −13 (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 3300 (m), 2950 (s), 1600 (w), 1085 (s), 830 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (m, 2 H), 4.36 (td, J = 6.4, 2.1 Hz, 2 H), 2.51−2.46 (m, 1 H), 2.36 (d, J = 2.2 Hz, 1 H), 1.49−1.45 (m, 6 H), 1.32−1.23 (m, 6 H), 0.91−0.81 (m, 15 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 131.8, 85.4, 72.2, 62.8, 47.0, 29.1, 27.3, 25.8, 18.2, 13.7, 9.4, −4.5, −5.0; high-resolution mass spectrum (CI, NH_3) m/z 443.1776 [(M − Bu)$^+$; calcd for $C_{20}H_{39}OSnSi$: 443.1792]. Anal. Calcd for $C_{24}H_{48}OSiSn$: C, 57.72; H, 9.69. Found: C, 57.81; H, 9.72.

(*Z*,*E*)-Diene (−)-21. A solution of (−)-**19** (1.43 g, 2.86 mmol), (*Z*)-3-iodopropenoic acid[25] (625 mg, 3.43 mmol), and tetrabutylammonium diphenylphosphonate[11] ($Ph_2PO_2NBu_4$) (1.71 g, 3.72 mmol) in *N*,*N*-dimethylformamide (DMF) (4 mL) was degassed with argon for 10 min, treated with bis(acetonitrile)palladium(II) chloride (20.0 mg, 0.07 mmol), and degassed 10 min further. The flask was wrapped in aluminum foil and stirred at room temperature for 18 h. Ethanol (10 mL) was added, and the mixture was stirred for 10 min and filtered through Celite to remove the phosphonate salts. The residue was concentrated, dissolved in ether (50 mL), filtered to remove the amine salts, washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution; hexanes/ethyl acetate, 9:1 → 3:1) afforded (−)-**21** (515 mg, 64% yield) as a colorless oil: $[\alpha]^{23}_D$ −7 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3400 (m), 3020 (s), 2950 (s), 2860 (s), 1695 (s), 1640 (m), 1605 (m), 1440 (m), 1250 (s), 1090 (s), 1000 (w), 960 (w), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 14.2, 11.5 Hz, 1 H), 6.65 (apparent t, J = 11.3 Hz, 1 H), 6.14 (dt, J = 14.8, 7.3 Hz, 1 H), 5.62 (d, J = 11.3 Hz, 1 H), 4.43−4.39 (m, 1 H), 2.58 (apparent t, J = 6.8 Hz, 2 H), 2.40 (d, J = 2.0 Hz, 1 H), 0.88 (s, 9 H) 0.12 (s, 3 H), 0.09 (s 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 146.9, 140.7, 129.7, 115.6, 84.6, 72.9, 62.2, 42.0, 25.7, 18.2, −4.6, −5.1; high-resolution mass spectrum (CI, NH_3) m/z 298.1839 [(M + NH_4)$^+$; calcd for $C_{15}H_{28}O_3Si_2N$: 298.1845].

(*E*)-Vinyl Stannane (+)-9. A solution of (−)-**21** (22.5 mg, 0.098 mmol) in dichloromethane (2 mL) at 0 °C was treated with bis(triphenylphosphine)palladium(II) chloride (3.4 mg, 0.005 mmol). Tributyltin hydride (34.3 mg, 0.118 mmol) was added dropwise over 2 min; the reaction mixture was then stirred at 0 °C for 10 min and warmed to room temperature (20 min). Concentration and flash chromatography (gradient elution; hexane → hexanes/ethyl acetate, 3:1) afforded (+)-**9** (35.4 mg, 65% yield) as a colorless oil: $[\alpha]^{23}_D$ +2 (*c* 0.54, CH_2Cl_2); IR ($CHCl_3$) 3000 (m), 2950 (s), 2860 (s), 1695 (m), 1620 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.65 (dd, J = 15.1, 11.7 Hz, 1 H), 6.29 (t, J = 11.4 Hz, 2 H), 6.22 (dd, J = 19.0, 1.1 Hz, 1 H), 6.06 (dd, J = 19.0, 5.5 Hz, 1 H), 5.97 (ddd, J = 15.2, 7.7, 7.6 Hz, 1 H), 5.52 (d, J = 11.2 Hz, 1 H), 4.10−4.07 (m, 1 H), 2.35−2.08 (m, 2 H), 1.72−1.59 (m, 6 H), 1.59−1.43 (m, 6 H), 1.10−0.90 (m, 24 H) 0.09 (s, 3 H), 0.06 (s 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 151.5, 147.3, 142.6, 129.6, 127.4, 115.5, 76.1, 42.0, 29.6, 27.8, 26.1, 18.5, 13.9, 9.8, −4.4, −4.6; high-resolution mass spectrum (CI, NH_3) m/z 573.2792 [(M + H)$^+$; calcd for $C_{27}H_{53}O_3SiSn$: 573.2792].

Alcohols 22. A solution of aldehyde (+)-**17** (2.07 g, 9.75 mmol) in THF (6.5 mL) at 0 °C was treated with allyl bromide (1.41 g, 11.7 mmol), saturated aqueous ammonium chloride (7.7 mL), and zinc dust (765 mg, 11.7 mmol). After 1 h, the reaction mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl ether/pentane, 1:1) provided **22** (2.17 g, 87% yield) as a colorless oil. ^1H NMR analysis revealed a mixture of diastereomers (ca. 1:1) which were inseparable by flash

(49) **Materials and Methods.** All reactions were carried out in oven-dried or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon before use. Dichloromethane, benzene, hexamethylphosphoramide (HMPA), and trimethylsilyl chloride (TMSCl) were freshly distilled from calcium hydride before use. Triethylamine, pyridine, and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. *N*,*N*-Dimethylformamide (DMF), *N*-methylpyrrollidinone (NMP), and 2,6-lutidine were freshly distilled and stored over 4 Å sieves. *n*-Butyllithium (*n*-BuLi) was purchased from Aldrich and standardized by titration with diphenylacetic acid. Deoxygenation was effected by bubbling argon through the reaction mixture for 15 min; the argon was deoxygenated by passing it through an "OXICLEAR" tube manufactured by Labclear, Oakland, CA. Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography using 0.25 mm Whatman precoated silica gel plates. Flash column chromatography was performed with the indicated solvents using silica gel-60 (particle size 0.023−0.040 mm) supplied by E. Merck.

chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84−5.79 (m, 2 H), 5.13−5.09 (m, 4 H), 4.70 (dt, J = 2.1, 5.2 Hz, 1 H), 4.59 (dt, J = 2.0, 6.7 Hz, 1 H), 4.18−4.12 (m, 1 H), 3.94−3.86 (m, 1 H), 2.94 (d, J = 1.9 Hz, 1 H), 2.79 (d, J = 1.5 Hz, 1 H), 2.45 (d, J = 2.0 Hz, 1 H), 2.43 (d, J = 2.1 Hz, 1 H), 2.27−2.23 (m, 4 H), 1.87−1.84 (m, 2 H), 1.80−1.78 (m, 2 H), 0.89 (s, 18 H), 0.17 (s, 3 H), 0.16 (s, 3 H); 0.15 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 134.4, 117.9, 117.5, 87.3, 54.4, 73.2, 73.1, 69.4, 67.8, 62.3, 61.6, 44.4, 43.4, 41.9, 41.8, 25.7, 25.7, 18.0, −4.4, −4.7, −5.1, −5.4; high-resolution mass spectrum (CI, NH_3) m/z 255.1780 [(M + H)$^+$; calcd for $C_{14}H_{27}O_2Si$: 255.1786].

Ketone (+)-23. A solution of alcohols **22** (37.8 mg, 0.150 mmol) in anhydrous dichloromethane (4 mL) at room temperature was treated with the Dess−Martin periodinane[30] (76.3 mg, 0.180 mmol). After 12 h the reaction mixture was washed sequentially with 10% aqueous $Na_2S_2O_3$ (4 mL) and saturated aqueous $NaHCO_3$ (4 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (+)-**23** (32.3 mg, 86% yield) as a colorless oil: $[\alpha]^{23}_D$ +51 (c 0.5, $CHCl_3$); IR ($CHCl_3$) 1725 (s), 1480 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92−5.86 (m, 1 H), 5.19 (dd, J = 10.2, 1.4 Hz, 1 H), 5.13 (dd, J = 17.2, 1.5 Hz, 1 H), 4.83 (ddd, J = 10.5, 4.6, 2.1 Hz, 1 H), 3.21 (dd, J = 6.9, 1.1 Hz, 2 H), 2.93 (dd, J = 15.6, 8.4 Hz, 1 H), 2.68 (dd, J = 15.6, 4.6 Hz, 1 H), 2.40 (d, J = 2.1 Hz, 1 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 129.9, 119.2, 84.4, 72.7, 59.0, 50.3, 49.0, 25.6, 18.04, −4.8, −5.3; high-resolution mass spectrum (CI, NH_3) m/z 253.1631 [(M + H)$^+$; calcd for $C_{14}H_{25}O_2Si$: 253.1624]. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.36; H, 9.72.

***β*-Hydroxy Ketone (+)-24.** A 0 °C solution of 49% aqueous hydrofluoric acid/acetonitrile (4/96, 2 mL) was added to (+)-**23** (219.9 mg, 0.871 mmol) and stirred at 0 °C for 1 h. The reaction mixture was diluted with water (2 mL) and extracted with ether (5 × 5 mL). The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/ethyl ether, 1:1) provided (+)-**24** (95.5 mg, 83% yield) as a colorless oil: $[\alpha]^{23}_D$ +21 (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3320 (s), 3020 (s), 1715 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 5.21 (apparent dd, J = 10.2, 1.2 Hz, 1 H), 5.16 (apparent qd, J = 17.1, 1.5 Hz, 1 H), 4.77 (m, 1 H), 3.2 (d, J = 7.0 Hz, 2 H), 3.04 (d, J = 4.8 Hz, 1 H), 2.93 (dd, J = 17.6, 7.7 Hz, 1 H), 2.82 (dd, J = 17.6, 3.9 Hz, 1 H), 2.44 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 129.5, 119.7, 83.2, 73.1, 58.2, 48.5, 48.3; high-resolution mass spectrum (CI, NH_3) m/z 156.1025 [(M + NH_4)$^+$; calcd for $C_8H_{14}NO_2$: 156.1023].

Diol (+)-25. A solution of tetramethylammonium triacetoxyborohydride (620.0 mg, 2.336 mmol) in anhydrous acetonitrile (1.5 mL) and acetic acid (1.5 mL) was stirred at room temperature for 30 min and then cooled to −20 °C. A solution of ketone (+)-**24** (40.7 mg, 0.295 mmol) in anhydrous acetonitrile (0.75 mL) was added via cannula (0.75 mL rinse). The reaction mixture was stirred at −20 °C for 14 h and quenched with saturated aqueous Rochelle's salt (10 mL). The aqueous layer was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/ethyl ether, 3:2) provided (+)-**25** (39.3 mg, 95% yield) as a colorless oil: $[\alpha]^{23}_D$ +39 (c 0.49, $CHCl_3$); IR ($CHCl_3$) 3500 (br, s), 3310 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83−5.75 (m, 1 H), 5.14−5.10 (m, 2 H), 4.72−4.63 (m, 1 H), 4.28−4.23 (m, 1 H), 3.25−3.20 (br s, 1 H), 2.46 (d, J = 2.4 Hz, 1 H), 2.37−2.23 (m, 3 H), 1.95−1.84 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 118.7, 84.4, 73.2, 63.3, 60.7, 42.1, 41.9; high-resolution mass spectrum (CI, NH_3) m/z 141.0917 [(M + H)$^+$; calcd for $C_8H_{13}O_2$: 141.0915]. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.14; H, 8.50.

Bis(TBS) Ether (+)-26. A solution of diol (+)-**25** (288.3 mg, 2.057 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (4 mL) at room temperature was treated with imidazole (840.2 mg, 12.43 mmol) and stirred for 5 min. *tert*-Butyldimethylsilyl chloride (930.0 mg, 6.171 mmol) was added, and the reaction mixture was stirred for 12 h, diluted with water (20 mL), and extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 95:5) provided (+)-**26** (752.0 mg, 99% yield) as a colorless oil: $[\alpha]^{23}_D$ +44 (c 0.55 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, J = 12.4, 12.2, 9.8, 7.1 Hz, 1 H), 5.05−5.02 (m, 2 H), 4.45 (ddd, J = 8.2, 5.2, 2.1 Hz, 1 H), 3.92 (dq, J = 6.6, 5.0 Hz, 1 H), 2.38 (d, J = 2.1 Hz, 1 H), 2.29−2.18 (m, 2 H), 1.85 (ddd, J = 13.7, 8.2, 5.0 Hz, 1 H), 1.77 (ddd, J = 13.8, 7.1, 5.2 Hz, 1 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 117.1, 85.8, 72.6, 68.5, 59.6, 46.2, 42.1, 25.9, 25.8, 18.2, 18.1, −4.0, −4.2, −4.5, −4.7; high-resolution mass spectrum (CI, NH_3) m/z 369.2631 [(M + H)$^+$; calcd for $C_{20}H_{41}O_2Si_2$: 369.2645]. Anal. Calcd for $C_{20}H_{40}O_2Si_2$: C, 65.15; H, 10.95. Found: C, 65.00; H, 11.07.

Alcohol (+)-33. A solution of (+)-**26** (428.1 mg, 1.164 mmol) in anhydrous dichloromethane (3 mL) was cooled to −78 °C, and a stream of ozone was bubbled through the mixture until the starting material was consumed (TLC analysis). The reaction mixture was warmed to room temperature and transferred via cannula to a 0 °C mixture of sodium borohydride (220 mg, 5.82 mmol) in anhydrous ethanol (3 mL), warmed to room temperature, and stirred for 3 h. The mixture was poured into ice/brine (6 mL) and extracted with ether (2 × 40 mL), and the combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (+)-**33** (333.5 mg, 77% yield) as a colorless oil: $[\alpha]^{23}_D$ +18 (c 0.51, $CHCl_3$); IR ($CHCl_3$) 3500 (br w), 3410 (m), 2980 (s), 2900 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (td, J = 6.7, 2.2 Hz, 1 H), 4.13−4.08 (m, 1 H), 3.85−3.80 (m, 1 H), 3.72 (ddt, J = 11.2, 5.7, 5.5 Hz, 2 H), 2.41 (d, J = 2.2 Hz, 1 H), 1.96−1.86 (m, 1 H), 1.72−1.76 (m, 1 H), 0.882 (s, 9 H), 0.879 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.092 (s, 3 H), 0.087 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.2, 73.1, 60.0, 59.8, 45.8, 38.4, 25.8, 25.8, 18.2, 17.9, −4.2, −4.4, −4.6, −4.8; high-resolution mass spectrum (CI, NH_3) m/z 372.2607 [(M + H)$^+$; calcd for $C_{19}H_{41}O_3Si_2$: 373.2594]. Anal. Calcd for $C_{19}H_{40}O_3Si_2$: C, 61.23; H, 10.82. Found: C, 60.84; H, 10.54.

(*E*)-Vinyl Iodide (+)-31. A solution of (+)-**33** (185 mg, 0.496 mmol) in anhydrous dichloromethane (5 mL) was cooled to 0 °C, treated with bis(triphenylphosphine)palladium(II) chloride (35.0 mg, 0.049 mmol), and stirred for 5 min. The reaction mixture was treated with tributyltin hydride (0.21 mL, 0.74 mmol) dropwise via syringe, stirred 10 min further, and then concentrated. The residue was diluted with ethyl acetate/hexanes (4:1, 10 mL) and filtered through Celite to remove the palladium salts. The crude stannane was redissolved in anhydrous dichloromethane (4 mL) and cooled to 0 °C. A solution of iodine (126 mg, 0.496 mmol) in anhydrous dichloromethane (2 mL) was added dropwise via syringe over 2 min. Concentration and flash chromatography (hexanes/ethyl acetate, 4:1) provided (+)-**31** (205.6 mg, 83% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +11 (c 0.76, $CHCl_3$); IR ($CHCl_3$) 3500 (br, w), 3005 (m), 2950 (s), 2900 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, J = 14.5, 7.1 Hz, 1 H), 6.23 (dd, J = 14.4, 1.0 Hz, 1 H), 4.14−4.10 (m, 1 H), 3.96 (apparent tt, J = 5.8, 5.7 Hz, 1 H), 3.82−3.77 (m, 1 H), 3.72−3.67 (m, 1 H), 1.87−1.81 (m, 1 H), 1.80−1.75 (m, 1 H), 1.71−1.62 (m, 2 H), 0.87 (s, 9 H), 0.86 (m, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 76.6, 73.1, 68.6, 59.9, 45.2, 38.9, 25.9, 25.8, 18.2, 18.0, −4.1, −4.3, −4.4, −4.7; high-resolution mass spectrum (CI, NH_3) m/z 501.1723 [(M + H)$^+$; calcd for $C_{19}H_{42}IO_3Si_2$: 501.1719]. Anal. Calcd for $C_{19}H_{41}IO_3Si_2$: C, 45.59; H, 8.26. Found: C, 45.89; H, 8.25.

Pivalate (+)-35. A solution of (+)-**34**[34] (274.1 mg, 2.44 mmol) in dichloromethane (1 mL) was treated with pyridine (0.415 mL, 5.13 mmol) and cooled to 0 °C. Pivaloyl chloride (0.315 mL, 2.56 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 12 h, diluted with dichloromethane (10 mL), washed sequentially with 5% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/ethyl ether, 9:1) provided (+)-**35** (504.2 mg, 98% yield) as a colorless oil: $[\alpha]^{23}_D$ +7 (c 0.72, $CHCl_3$); IR ($CHCl_3$) 1710 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91−4.85 (m, 1H), 2.18 (td, J = 7.0, 2.6 Hz, 2H) 1.92 (t, J = 2.6 Hz, 1H), 1.70−1.45 (m, 4 H), 1.18 (d, J = 6.3 Hz), 1.16 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 84.0, 69.9, 68.6, 38.7, 34.9, 27.1, 24.3, 19.9, 18.3; high-

resolution mass spectrum (CI, NH_3) *m*/*z* 214.1812 $(M + NH_4)^+$; calcd for $C_{12}H_{24}NO_2$: 214.1807]

Vinyl Stannanes 32. Alkyne (+)-**35** (1.562 g, 7.92 mmol) was treated with tributyltin hydride (2.35 mL, 8.72 mmol) and 2,2′-azobis-(isobutyronitrile) (AIBN) (65.0 mg, 0.39 mmol), degassed with argon for 10 min, heated to 120 °C for 1 h, and then cooled to room temperature. Gradient flash chromatography (hexane → hexane/ethyl actetate, 95:5) afforded **32** (1.78 g, 46% yield) as a colorless oil. NMR analysis revealed a 4.1:1 mixture of *E*- and *Z*-isomers that were inseparable by flash chromatography. IR ($CHCl_3$) 1730 (s), 1180 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*E*-isomer) δ 5.90−5.83 (m, 2 H), 4.89−4.82 (m, 1 H), 2.15−2.09 (m, 2 H) 1.61−1.24 (m, 16 H), 1.18−1.08 (m, 12 H), 0.90−0.82 (m 15 H); (*Z*-isomer) δ 6.46 (td, J = 12.5, 7.0 Hz, 1 H), 5.78 (d, J = 12.4 Hz, 1 H) 4.89−4.82 (m, 1 H), 2.12−1.98 (m, 2 H), 1.61−1.24 (m, 16 H), 1.18−1.08 (m, 12 H), 0.90−0.82 (m 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) (*E*-isomer) δ 178.2, 149.0, 127.8, 70.4, 38.7, 37.4, 35.4, 29.1, 27.3, 27.2, 24.6, 19.9, 13.7, 9.4; (*Z*-isomer) δ 178.2, 148.6, 128.5, 70.5, 38.7, 36.8, 35.7, 29.2, 27.3, 27.2, 26.7, 19.8, 13.7, 10.2; high-resolution mass spectrum (CI, NH_3) *m*/*z* 431.1988 $[(M - Bu)^+$; calcd for $C_{20}H_{39}O_2Sn$: 431.1972].

(*E*,*E*)-Diene (+)-36. A solution of vinyl iodide (+)-**31** (1.41 g, 2.81 mmol) and vinyl stannane **32** (1.78 g, 3.66 mmol) in *N*,*N*-dimethylformamide (DMF) (5 mL) was treated with bis(acetonitrile)palladium(II) chloride (20 mg, 0.07 mmol). The flask was covered with aluminum foil, and the reaction mixture was stirred at room temperature. After 24 h another portion of bis(acetonitrile)palladium(II) chloride (10 mg, 0.035 mmol) was added, and the mixture was stirred an additional 24 h and then diluted with ether (75 mL), washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) gave (+)-**36** (1.32 g, 82% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +0.8 (*c* 2.05, $CHCl_3$); IR ($CHCl_3$) 2950 (s), 2900 (s), 2420 (w), 1720 (s) cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 6.04−5.93 (m, 2 H), 5.61 (dt, J = 14.2, 6.9 Hz, 1 H), 5.46 (dd, J = 14.5, 7.5 Hz, 1 H), 4.89−4.83 (m, 1 H), 4.12 (apparent q, J = 6.8 Hz, 1 H), 3.97−3.92 (m, 1 H), 3.84−3.78 (m, 1 H), 3.72−3.67 (m, 1 H), 2.30−2.29 (m, 1 H), 2.07 (q, J = 7.1 Hz, 1 H), 1.89−1.83 (m, 1 H), 1.83−1.78 (m, 1 H), 1.71−1.48 (m, 6 H), 1.17 (d, J = 6.1 Hz, 3 H), 1.17 (s, 9 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 6 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 134.4, 134.1, 130.3, 129.9, 71.3, 70.3, 69.3, 60.1, 45.9, 38.6, 35.4, 32.3, 27.1, 25.9, 25.8, 24.9, 19.9, 18.9, 18.2, 17.9, −3.8, −4.3, −4.53, −4.55; high-resolution mass spectrum (FAB, NBA) *m*/*z* 593.4036 $[(M + Na)^+$; calcd for $C_{31}H_{62}O_5Si_2Na$: 593.4034]. Anal. Calcd for $C_{31}H_{62}O_5Si_2$: C, 65.21; H, 10.94. Found: C, 65.07; H, 10.81.

Aldehyde (+)-37. A solution of Dess−Martin periodinane[30] (438.0 mg, 1.034 mmol) in anhydrous dichloromethane (5 mL) at room temperature was treated with pyridine (0.17 mL, 2.07 mmol) dropwise via syringe. A solution of alcohol (+)-**36** (198.3 mg, 0.35 mmol) in anhydrous dichloromethane (3 mL) was transferred to the reaction mixture via cannula (2 mL rinse), and the resultant mixture was stirred for 2.5 h at room temperature. Following concentration, the residue was diluted with ether (50 mL) and washed with 10% aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layers were combined and back extracted with ether (2 × 50 mL). The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) provided (+)-**37** (164.2 mg, 83% yield) as a colorless oil: $[\alpha]^{23}_D$ +5 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 2970 (s), 1725 (s) cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, J = 2.2 Hz, 1 H), 6.00 (m, 2 H), 5.62 (ddd, J = 14.3, 7.2, 6.9 Hz, 1 H), 5.47 (dd, J = 14.8, 7.5 Hz, 1 H), 4.87−4.83 (m, 1 H), 4.29−4.25 (m, 1 H), 4.19 (apparent q, J = 6.6 Hz, 1 H), 2.57 (ddd, J = 15.6, 4.9, 2.1 Hz, 1 H), 2.49 (ddd, J = 15.6, 4.9, 3.1 Hz, 1 H), 2.07 (apparent q, J = 7.1 Hz, 2 H), 1.75−1.73 (m, 2 H), 1.60−1.49 (m, 4 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.17 (s, 9 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 9 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 178.1, 134.6, 134.1, 130.4, 129.8, 71.0, 70.3, 65.9, 51.5, 46.9, 35.4, 32.3, 27.2, 25.7, 25.8, 25.0, 19.9, 18.2, 18.0, −3.7, −4.2, −4.4, −4.5; high-resolution mass spectrum (CI, NH_3) *m*/*z* 568.3984 $[M^+$; calcd for $C_{31}H_{60}O_5Si_2$: 568.3979].

(*Z*)-Vinyl Iodide (+)-38. A solution of (iodomethyl)triphenylphosphonium iodide[33] $[(Ph_3PCH_2I)I]$ (4.59 g, 8.66 mmol) in anhydrous THF (60 mL) at room temperature was treated with sodium hexamethyldisilazide (NaHMDS) (1 M in THF, 8.49 mL, 8.49 mmol) dropwise via syringe over 5 min and stirred for 1 min. The reaction mixture was cooled to −60 °C, treated with hexamethylphosphoramide (HMPA) (2.6 mL, 14.1 mmol) dropwise via syringe over 1 min, and immediately cooled to −78 °C. A solution of aldehyde (+)-**37** (985 mg, 1.73 mmol) in THF (20 mL) was added to the ylide via cannula; the resultant mixture was stirred at −78 °C for 5 min and warmed to room temperature (30 min). The mixture was diluted with hexanes (200 mL) and washed with brine (100 mL). The aqueous layer was extracted with hexanes (2 × 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) provided (+)-**38** (982.4 mg, 82% yield) as a colorless oil: $[\alpha]^{23}_D$ +12 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 1720 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28−6.24 (m, 2 H), 6.11−5.95 (m, 2 H), 5.61 (ddd, J = 14.4, 7.4, 7.0 Hz, 1 H), 5.48 (dd, J = 15.8, 7.7 Hz, 1 H), 4.89−4.84 (m, 1 H), 4.18 (dd, J = 13.4, 7.1 Hz, 1 H), 3.90−3.81 (m, 1 H), 2.30−2.25 (m, 2 H), 2.07 (dd, J = 14.3, 7.2 Hz, 2 H), 1.70−1.33 (complex series of m, 6 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.17 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 137.9, 134.5, 134.2, 130.2, 130.0, 83.9, 71.0, 70.3, 68.0, 46.3, 42.8, 38.7, 35.4, 32.3, 27.2, 26.0, 25.9, 25.0, 19.9, 18.2, 18.1, −3.6, −4.1, −4.4, −4.5; high-resolution mass spectrum (FAB, NBA) *m*/*z* 715.3080 $[(M + Na)^+$; calcd for $C_{32}H_{61}IO_4Si_2Na$: 715.3051]. Anal. Calcd for $C_{32}H_{61}IO_4Si_2$: C, 55.47; H, 8.87. Found: C, 55.65; H, 8.99.

Alcohol (+)-30. A solution of (+)-**38** (310 mg, 0.447 mmol) in anhydrous dichloromethane (4 mL) was cooled to −78 °C and treated with diisobutylaluminum hydride (1 M in hexanes, 0.537 mL, 0.537 mmol). The reaction mixture was stirred for 2 min, quenched with methanol (1 mL) followed by saturated aqueous Rochelle's salt (2 mL), and warmed to room temperature. The aqueous phase was extracted with dichloromethane (5 × 15 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) furnished (+)-**30** (213.1 mg, 78% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +18 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 2940 (s), 1730 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28−6.23 (m, 2 H), 6.09−5.96 (m, 2 H), 5.64 (ddd, J = 14.3, 7.3, 7.0 Hz, 1 H), 5.48 (dd, J = 15.0, 7.7 Hz, 1 H), 4.18 (dd, J = 13.1, 7.2 Hz, 1 H), 3.92−3.87 (m, 1 H), 3.80−3.76 (m, 1 H), 2.30 (t, J = 5.2 Hz, 2 H), 2.11−2.07 (m, 2 H), 1.69−1.38 (m, 6 H), 1.17 (d, J = 6.2 Hz, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 134.5, 134.4, 134.3, 130.2, 83.9, 71.0, 68.0 (2 C), 46.3, 42.8, 38.8, 32.5, 26.0, 25.9, 25.4, 23.6, 18.2, 18.1, −3.6, −4.1, −4.4, −4.5; high-resolution mass spectrum (CI, NH_3) *m*/*z* 608.2564 $[M^+$; calcd for $C_{27}H_{53}IO_3Si_2$: 608.2578]. Anal. Calcd for $C_{27}H_{53}IO_3Si_2$: C, 53.27; H, 8.78. Found: C, 52.97; H, 8.49.

Iodo Stannane (+)-39. A solution of alcohol (+)-**30** (173.5 mg, 0.285 mmol) and acid (+)-**9** (200.3 mg, 0.350 mmol) in anhydrous benzene (10 mL) was cooled to 10 °C, treated with triphenylphosphine (449 mg, 1.71 mmol), and stirred for 5 min at 10 °C. Diethyl azodicarboxylate (DEAD) (271 μL, 1.71 mmol) was added dropwise via syringe, and the reaction mixture was stirred 20 min further, diluted with hexanes (10 mL), washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 94:5:1) afforded (+)-**39** (246.4 mg, 74% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +52 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2940 (s), 2880 (m), 1740 (m), 1710 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J = 15.3, 11.2 Hz, 1 H), 6.50 (t, J = 11.3 Hz, 1 H), 6.27−6.23 (m, 2 H), 6.08−6.05 (m, 3 H), 6.05 (d, J = 19.0 Hz, 1 H), 5.91 (dd, J = 19.0, 5.6 Hz, 1 H), 5.62 (ddd, J = 14.7, 7.4, 6.9 Hz, 1 H), 5.53 (d, J = 11.3 Hz, 1 H), 5.48 (dd, J = 14.9, 7.7 Hz, 1 H), 4.94 (m, 1 H), 4.17 (apparent dt, J = 13.0, 6.7 Hz, 1 H), 4.11 (apparent dt, J = 12.2, 6.5 Hz, 1 H), 3.90 (m, 1 H), 2.37 (m, 2 H), 2.32 (m, 2 H), 2.07 (q, J = 7.0 Hz, 2 H), 1.69−1.37 (m, 6 H), 1.49−1.43 (m, 6 H), 1.32−1.24 (m, 6 H), 1.22 (d, J = 6.3 Hz, 3 H), 0.88−0.84 (m, 42 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 150.8, 144.9, 141.6, 137.9, 134.5, 134.2, 130.2, 130.0, 128.8, 127.5, 116.3, 83.9, 78.4, 76.2, 71.0, 68.0, 46.3, 42.8, 41.8, 35.6, 32.4,

29.7, 29.1, 27.2, 26.0, 25.9, 25.1, 20.1, 18.3, 18.2, 18.1, 14.1, 13.7, −3.6, −4.1, −4.3, −4.5, −4.8; high-resolution mass spectrum (FAB, NBA) *m*/*z* 1185.5051 [(M + Na)$^+$; calcd for $C_{54}H_{103}IO_5Si_3SnNa$: 1185.5078].

7,13,15-Tris(*O*-TBS) Macrolactin A (−)-40. A solution of (+)-**39** (14.8 mg, 0.013 mmol) and diisopropylethylamine (0.25 mL, 0.13 mmol) in *N*-methyl 2-pyrrolidinone (1.3 mL) was treated with tris-(dibenzylideneacetone)dipalladium (0.6 mg, 0.0006 mmol). Another portion of catalyst was added after 24 and 48 h and the reaction mixture stirred for a total of 7 d. The reaction mixture was then diluted with ether (10 mL), washed with water (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 94:5:1) provided (−)-**40** (4.0 mg, 42% yield) as a colorless oil: $[\alpha]^{23}_D$ −10.7 (*c* 0.08, $CHCl_3$); IR ($CHCl_3$) 3020 (s), 1700 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (dd, *J* = 15.3, 11.3 Hz, 1 H), 6.67 (dd, *J* = 15.1, 11.3 Hz, 1 H), 6.32 (dd, *J* = 15.5, 10.3 Hz, 1 H), 6.27 (t, *J* = 11.5 Hz, 1 H), 6.13−6.08 (m, 2 H), 5.81 (dt, *J* = 15.2, 7.5 Hz, 1 H), 5.75−5.65 (m, 4 H), 5.59 (dd, *J* = 15.1, 5.7 Hz, 1 H), 5.08−5.06 (m, 1 H), 4.46−4.43 (m, 1 H), 4.18−4.15 (m, 1 H), 4.02−3.96 (m, 1 H), 2.66−2.60 (m, 1 H), 2.46−2.40 (m, 1 H), 2.38−2.25 (m, 2 H), 2.03−1.89 (m, 4 H), 1.40−1.30 (m, 4 H), 1.09 (d, *J* = 6.3 Hz, 3 H) 1.12 (s, 9 H), 1.01 (s, 9 H), 1.00 (s, 9 H), 0.18 (s, 3 H), 0.16 (s, 3 H), 0.13 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 142.8, 140.7, 136.5, 134.3, 134.0, 130.20, 130.16, 129.40, 129.38, 128.3, 124.5, 117.8, 72.8, 71.1, 71.0, 69.4, 46.1, 42.9, 35.7, 35.2, 32.3, 26.0, 25.9 (2C), 24.8, 20.0, 18.2 (2C), 18.1, −4.0, −4.1, −4.4 (2C), −4.6, −4.7; high-resolution mass spectrum (FAB, NBA) *m*/*z* 767.4862 [(M + Na)$^+$; calcd for $C_{47}H_{76}O_5Si_3Na$: 767.4898].

Diol (−)-43. A solution of (+)-**38** (153.2 mg, 0.221 mmol) in THF (2 mL) was treated with tetrabutylammonium fluoride (1 M in THF, 0.663 mL, 0.663 mmol) and stirred for 3 h. Concentration and flash chromatography (hexanes/ethyl acetate, 1:1) provided (−)-**43** (84.2 mg, 82% yield) as a colorless oil: $[\alpha]^{23}_D$ −7.2 (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3010 (s), 1710 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, *J* = 7.5 Hz, 1 H), 6.29−6.24 (m, 1 H), 6.19 (dd, *J* = 10.3, 4.9 Hz, 1 H), 6.00 (dd, *J* = 15.0, 10.4 Hz, 1 H), 5.66 (dt, *J* = 15.1, 7.0 Hz, 1 H), 5.62 (dd, *J* = 15.3, 6.4 Hz, 1 H), 4.88−4.82 (m, 1 H), 4.51−4.46 (m, 1 H), 4.08−4.03 (m, 1 H), 2.38−2.34 (m, 2 H), 2.09−2.01 (m, 2 H), 1.85−1.34 (complex series of m, 6 H), 1.161 (d, *J* = 5.2 Hz, 3 H), 1.160 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 137.5, 135.2, 132.8, 130.9, 129.7, 84.8, 70.7, 70.3, 67.9, 42.6, 42.1, 38.7, 35.4, 32.3, 27.2, 25.0, 19.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 482.1774 [(M + NH_4)$^+$; calcd for $C_{20}H_{37}IO_4N$: 482.1769].

Bis(TES) Ether (+)-44. A solution of (−)-**43** (84.6 mg, 0.182 mmol) and 2,6-lutidine (0.12 mL, 1.092 mmol) in dichloromethane (1.8 mL) was cooled to −78 °C, treated with TESOTf (0.125 mL, 0.547 mmol), and stirred for 2 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), warmed to room temperature, and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) afforded (+)-**44** (123.0 mg, 98% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +5.8 (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 2970 (s), 1720 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30−6.25 (m, 2 H), 6.16−5.94 (m, 2 H), 5.64−5.52 (m, 1 H), 5.49 (dd, *J* = 15.1, 7.8 Hz, 1 H), 4.97−4.86 (m, 1 H), 4.20−4.14 (m, 1 H), 3.93−3.80 (m, 1 H), 2.38−2.27 (m, 2 H), 2.16−1.95 (m, 2 H), 1.70−1.33 (complex series of m, 6 H), 1.17 (s, 9 H), 1.16 (d, *J* = 6.1 Hz, 3 H), 0.97−0.86 (m, 18 H), 0.63−0.48 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 137.9, 134.3, 134.2, 130.4, 130.0, 83.9, 70.8, 70.3, 67.9, 46.3, 42.8, 38.7, 35.4, 32.3, 27.2, 25.0, 19.9, 7.0, 6.9, 5.3, 5.2; high-resolution mass spectrum (FAB, NBA) *m*/*z* 715.3067 [(M + Na)$^+$; calcd for $C_{32}H_{61}IO_4Si_2Na$: 715.3051].

Bis(TES) Vinyl Iodide (+)-45. A solution of (+)-**44** (69.6 mg, 0.10 mmol) in anhydrous dichloromethane (1 mL) was cooled to −78 °C and treated with diisobutylaluminum hydride (1 M in hexanes, 0.15 mL, 0.15 mmol). The reaction mixture was stirred for 5 min, quenched with methanol (1 mL) followed by saturated aqueous Rochelle's salt (5 mL), and warmed to room temperature. The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) furnished (+)-**45** (47.8 mg, 78% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +7.9 (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 2950 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31−6.25 (m, 2 H), 6.07 (dd, *J* = 15.2, 10.4 Hz, 1 H), 6.02−5.46 (m, 1 H), 5.63 (dt, *J* = 14.5, 7.1 Hz, 1 H), 4.98 (dd, *J* = 15.1, 7.8 Hz, 1 H), 4.29 (apparent t, *J* = 6.7 Hz, 1 H), 4.18−4.14 (m, 1 H), 3.91−3.86 (m, 1 H), 3.83−3.75 (m, 1 H), 2.38−2.32 (m, 2 H), 2.11−2.06 (m, 2 H), 1.76−1.40 (complex series of m, 6 H), 1.17 (d, *J* = 6.1 Hz, 3 H), 0.98−0.90 (m, 18 H), 0.64−0.51 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 134.5, 134.1, 130.5, 129.9, 83.9, 70.8, 68.0, 67.9, 46.3, 42.8, 38.8, 32.5, 25.4, 23.6, 7.0, 6.9, 5.3, 5.2; high-resolution mass spectrum (CI, NH_3) *m*/*z* 626.2918 [(M + NH4)$^+$; calcd for $C_{27}H_{57}INO_3Si_2$: 626.2924].

Iodo Stannane (+)-53. A solution of (+)-**9** (53.8 mg, 0.094 mmol) and (+)-**45** (47.8 mg, 0.078 mmol) in anhydrous benzene was treated with triphenylphosphine (123.8 mg, 0.47 mmol) and then diethyl azodicarboxylate (DEAD) (0.75 mL, 0.47 mmol) and stirred for 20 min. The reaction mixture was diluted with hexanes (20 mL), washed with water (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 89:10:1) furnished (+)-**53** (76.0 mg, 83% yield) as a viscous, colorless oil: $[\alpha]^{23}_D$ +7.5 (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 1710 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 15.2, 12.2 Hz, 1 H), 6.50 (t, *J* = 11.3 Hz, 1 H), 6.30−6.27 (m, 2 H), 6.10−5.95 (complex series of m, 4 H), 5.90 (dd, *J* = 19.1, 5.8 Hz, 1 H), 5.64−5.55 (m, 1 H), 5.53 (d, *J* = 11.3 Hz, 1 H), 5.49 (dd, *J* = 15.2, 7.9 Hz, 1 H), 4.94−4.92 (m, 1 H), 4.18−4.09 (m, 2 H), 3.90−3.87 (m, 1 H), 2.39−2.25 (m, 4 H), 2.10−2.04 (m, 2 H), 1.71−1.10 (complex series of m, 21 H), 1.00−0.80 (complex series of m, 42 H), 0.65−0.50 (m, 12 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 150.8, 145.0, 141.6, 137.9, 134.3, 130.4, 130.0, 128.8, 127.5, 124.2, 116.3, 83.9, 76.2, 70.8, 70.3, 67.9, 46.3, 46.3, 42.8, 41.8, 35.6, 32.4, 29.8, 27.2, 25.9, 25.1, 22.7, 18.3, 13.7, 9.5, 7.0, 6.9, 5.3, 5.2, −4.2, −4.3.

7-*O*-TBS-13,15-Bis(*O*-TES) Macrolactin A (−)-54. A solution of (+)-**53** (30.7 mg, 0.026 mmol) and diisopropylethylamine (DIPEA) (0.046 mL, 0.26 mmol) in *N*-methylpyrrolidinone (NMP) (1 mL) was treated with tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (0.6 mg, 0.0026 mmol). The flask was covered with aluminum foil, and the reaction mixture was stirred at room temperature for 7 d, diluted with ether (10 mL), washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) gave (−)-**54** (8.0 mg, 40% yield) as a colorless oil: $[\alpha]^{23}_D$ −11.3 (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 1710 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 15.2, 11.5 Hz, 1 H), 6.50 (t, *J* = 11.5 Hz, 1 H), 6.44 (dd, *J* = 15.0, 11.0 Hz, 1 H), 6.05−5.96 (m, 4 H), 5.66 (dd, *J* = 15.0, 5.8 Hz, 1 H), 5.65−5.60 (m, 1 H), 5.59 (dd, *J* = 14.1, 5.7 Hz, 1 H), 5.54 (d, *J* = 11.7 Hz, 1 H), 5.43 (dd, *J* = 14.8, 7.3 Hz, 1 H), 5.01−4.94 (m, 1 H), 4.26−4.26 (m, 1 H), 4.19−4.10 (m, 1 H), 3.72−3.69 (m, 1 H), 2.44−2.00 (complex series of m, 6 H), 1.76−1.31 (complex series of m, 6 H), 1.25 (d, *J* = 6.3 Hz, 3 H) 1.05−0.75 (m, 18 H), 0.89 (s, 9 H), 0.60−0.51 (m, 12 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 142.8, 140.7, 136.5, 134.2, 134.0, 130.4, 130.1, 129.5, 129.3, 128.1, 124.5, 117.8, 72.9, 71.1, 70.9, 69.4, 46.2, 43.0, 35.6, 35.2, 32.3, 25.9, 24.9, 20.0, 18.2, 6.9, 6.8, 5.12, 5.05, −4.1, −4.7; high-resolution mass spectrum (FAB, NBA) *m*/*z* 767.4881 [(M + Na)$^+$; calcd for $C_{47}H_{76}O_5Si_3Na$: 767.4898].

7-*O*-TBS Macrolactin A (−)-55. A solution of protected macrocycle (−)-**54** (6.2 mg, 0.008 mmol) in anhydrous THF (0.4 mL) was treated with a mixture of TBAF/AcOH (1:1, ca. 1 M in THF, 0.041 mL, 0.041 mmol). The flask was wrapped in aluminum foil, and the reaction mixture was stirred at room temperature for 2 h. Concentration and flash chromatography (hexanes/acetone/triethylamine, 50:49:1) furnished (−)-**55** (3.0 mg, 70% yield) as a colorless oil: $[\alpha]^{23}_D$ −9.6 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3600 (br w), 3010 (s), 2950 (s), 1700 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 15.0, 11.4 Hz,1 H), 6.49 (t, *J* = 11.4 Hz, 1 H), 6.48−6.46 (m, 1 H), 6.17 (dd, *J* = 15.3, 10.5 Hz, 1 H), 6.09 (t, *J* = 11.1 Hz, 1 H), 6.03−5.95 (m, 2 H), 6.69 (dd, *J* = 14.9, 5.1 Hz, 1 H), 5.65−5.57 (m, 2 H), 5.96 (dd, *J* = 15.3, 6.3 Hz, 1 H), 5.82 (dd, *J* = 17.5, 8.6 Hz, 1 H), 5.75 (d, *J* = 11.2 Hz, 1 H), 5.54 (d, *J* = 11.5 Hz, 1 H), 5.50−5.45 (m, 1 H), 5.02−4.97 (m, 1 H), 4.55−4.50 (m, 1 H), 4.31−4.27 (m, 1 H), 4.05−3.95 (m, 1

H), 2.60−2.00 (complex series of m, 6 H), 1.70−1.20 (complex series of m, 6 H), 1.25 (d, J = 6.2 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.0, 140.5, 137.0, 134.9, 132.7, 130.7, 130.6, 130.0, 129.3, 126.6, 124.0, 117.6, 72.1, 70.9, 70.6, 69.7, 42.8, 40.9, 35.6, 35.1, 32.1, 25.9, 24.4, 20.0, 18.2, −4.3, −4.7; high-resolution mass spectrum (FAB, NBA) *m*/*z* 539.3176 [(M + Na)$^+$; calcd for $C_{30}H_{48}O_5SiNa$: 539.3169].

Macrolactin A [(−)-1] via (−)-55. A solution of monoprotected macrocycle (−)-**55** (1.6 mg, 0.003 mmol) in anhydrous THF (0.25 mL) was treated with a mixture of TBAF/AcOH (1:1, ca. 1 M in THF, 0.06 mL, 0.0.06 mmol). The flask was wrapped in aluminum foil and the reaction mixture stirred at room temperature for 5 d. Concentration and flash chromatography ($CHCl_3$/MeOH, 9:1) furnished (−)-**1** (0.6 mg, 50% yield) as a white amorphous solid (mp 60−65 °C). All attempts to crystallize synthetic (−)-macrolactin A proved unsuccessful. $[\alpha]^{23}_D$ −8.9 (*c* 0.09, MeOH); IR ($CHCl_3$) 3300 (br w), 2950 (s), 1730 (s), 1640 (m), 1605 (m) cm $^{-1}$; ^{1}H NMR (500 MHz, pyridine-d_5) δ 7.58 (m, 1 H), 7.00 (dd, J = 15.6, 11.5 Hz, 1 H), 6.63 (t, J = 11.2 Hz, 1 H), 6.56 (dd, J = 15.6, 11.2 Hz, 1 H), 6.36 (dt, J = 15.2, 6.3 Hz, 1 H), 6.22 (dd, J = 17.4, 11.5 Hz, 1 H), 6.18 (dd, J = 14.5, 10.4 Hz, 1 H), 6.00 (dd, J = 14.9, 5.6 Hz, 1 H), 5.96 (dd, J = 15.3, 6.3 Hz, 1 H), 5.82 (dd, J = 17.5, 8.6 Hz, 1 H), 5.75 (d, J = 11.2 Hz, 1 H), 5.69 (ddd, J = 14.1, 6.7, 6.7 Hz, 1 H), 5.17−5.09 (m, 1 H), 4.95−4.90 (m, 1 H), 4.57−4.52 (m, 1 H), 4.49−4.45 (m, 1 H), 2.88−2.80 (m, 2 H), 2.71−2.56 (m, 4 H), 2.15−2.09 (m, 1 H), 2.04−1.97 (m, 2 H), 1.70−1.40 (m, 3 H), 1.20 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 142.7, 139.3, 136.0, 135.0, 132.8, 130.7, 130.4, 129.9, 128.3, 127.6, 125.0, 118.8, 71.3, 70.9, 70.4, 69.6, 41.5, 41.0, 35.5, 35.1, 32.0, 24.1, 19.9; (125 MHz, acetone-d_6) δ 166.4, 144.0, 142.0, 137.9, 135.9, 134.2, 131.4, 130.7, 130.0, 129.6, 128.3, 125.0, 117.9, 71.4, 71.0, 69.5, 69.1, 43.2, 42.9, 36.3, 35.7, 32.5, 25.4, 20.1; high-resolution mass spectrum (FAB, NBA) *m*/*z* 425.2318 [(M + Na)$^+$; calcd for $C_{24}H_{34}O_5$-Na: 425.2304].

Macrolactin A [(−)-1] via (−)-40. A solution of protected macrocycle (−)-**40** (18.2 mg, 0.024 mmol) in anhydrous THF (0.5 mL) was treated with a mixture of TBAF/AcOH (1:1, ca. 1 M in THF, 0.37 mL, 0.37 mmol). The flask was wrapped in aluminum foil and the reaction mixture stirred at room temperature for 5 d. Concentration and flash chromatography ($CHCl_3$/MeOH, 9:1) furnished (−)-**1** (4.9 mg, 49% yield) that was equivalent in all respects to synthetic (−)-**1** prepared via (−)-**55**.

Macrolactin A Triacetate (+)-56. Synthetic macrolactin A (−)-**1** (2.6 mg, 0.006 mmol) was treated with pyridine (0.1 mL), acetic anhydride (0.015 mL, 0.159 mmol), and a single crystal of *N*,*N*-(dimethylamino)pyridine (DMAP). The reaction mixture was stirred for 2 h, diluted with ethyl acetate (20 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/acetone, 3:2) gave (+)-**56** (1.8 mg, 54% yield). $[\alpha]^{23}_D$ +5.3 (*c* 0.15, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.22 (m, 1 H), 6.49 (t, J = 11.5 Hz, 1 H), 6.46 (dd, J = 15.2, 11.1 Hz, 1 H), 6.17−6.08 (m, 2 H), 6.00−5.91 (m, 2 H), 5.58 (d, J = 11.5 Hz, 1 H), 5.55−5.44 (m, 2 H), 5.42−5.35 (m, 1 H), 5.33−5.28 (m, 1 H), 5.04−5.01 (m, 1 H), 4.99−4.94 (m, 1 H), 2.59−2.39 (m, 4 H), 2.20−1.60 (complex series of m, 8 H), 2.06 (s, 3 H), 2.01 (s, 3 H), 1.98 (s, 3 H), 1.24 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 166.1, 142.9, 138.1, 135.9, 132.7, 131.7, 130.9, 129.8, 129.7, 128.3, 127.2, 127.1, 118.1, 73.3, 70.7, 70.6, 69.6, 38.8, 37.4, 34.9, 32.2, 31.8, 29.7, 24.4, 21.2, 21.1, 19.9.

Macrolactinic Acid (−)-7. A solution of synthetic macrolactin A (−)-**1** (3.9 mg, 0.01 mmol) in methanol (0.8 mL) was treated with KOH (1 N, 0.4 mL), stirred at 40 °C for 2 h, and then treated further with KOH (1 N, 0.2 mL) and stirred for 0.5 h. The reaction mixture was cooled to 0 °C, acidified with HCl (1 N, 0.6 mL), diluted with water (2 mL), and extracted with ethyl acetate (2 × 10 mL). The combined ethyl acetate extracts were dried with $MgSO_4$, filtered, and concentrated. Filtration (SiO_2 plug, ethyl acetate) and concentration afforded (−)-**7** (3.4 mg, 69% yield) as a yellow oil: $[\alpha]^{23}_D$ −13.03 (*c* 0.29, MeOH); IR ($CHCl_3$) 3600 (br w), 2950 (s), 1725 (s) cm $^{-1}$; ^{1}H NMR (500 MHz, MeOD) δ 7.37 (dd, J = 14.8, 11.6 Hz, 1 H), 6.57 (dd, J = 11.1, 11.0 Hz, 1 H), 6.52 (dd, J = 14.9, 11.3 Hz, 1 H), 6.16 (dd, J = 15.2, 10.8 Hz, 1 H), 6.08−5.99 (m, 3 H), 5.69 (dd, J = 14.9, 6.7 Hz, 1 H), 5.66−5.62 (m, 1 H), 5.58−5.47 (m, 3 H), 4.31−4.25 (m, 1 H), 4.22−4.15 (m, 1 H), 3.87−3.81 (m, 1 H), 3.69−3.63 (m, 1 H), 2.42−2.37 (m, 2 H), 2.34−2.30 (m, 2 H), 2.09−2.02 (m, 2 H), 1.58−1.19 (m, 6 H), 1.11 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 146.1, 137.0, 135.4, 135.36, 131.4, 131.1, 130.9, 130.4, 129.1, 126.9, 117.5, 72.7, 69.9, 39.1, 68.4, 45.0, 42.1, 39.7, 37.2, 33.6, 26.6, 23.5.

(*E*)-Vinyl Iodide (+)-57. A solution of (+)-**9** (7.3 mg, 0.013 mmol) in dichloromethane (0.25 mL) was treated with a solution of iodine (3.2 mg, 0.013 mmol) in dichloromethane (0.25 mL). Concentration followed by flash chromatography (hexanes/ethyl acetate, 3:1) furnished (+)-**57** (4.0 mg, 77% yield) as a yellow oil: $[\alpha]^{23}_D$ +5 (*c* 0.61, CH_2Cl_2); IR ($CHCl_3$) 3500 (w), 3150 (m), 2950 (s), 1690 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 15.3, 11.5 Hz, 1 H), 6.61 (t, J = 11.4 Hz, 1 H), 6.51 (dd, J = 14.4, 5.9 Hz, 1 H), 6.25 (d, J = 14.4 Hz, 1 H), 6.03 (apparent td, J = 15.0, 7.3 Hz, 1 H), 5.61 (d, J = 11.3 Hz, 1 H), 4.18−4.15 (m, 1 H), 2.39 (apparent t, J = 6.5 Hz, 2 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.9, 148.2, 146.8, 141.0, 129.6, 125.0, 115.5, 76.3, 41.1, 25.8, 18.2, −4.6, −4.9; high-resolution mass spectrum (FAB, NBA) *m*/*z* 431.0509 [(M + Na)$^+$; calcd for $C_{15}H_{25}IO_3SiNa$: 431.0516].

Trimethylvinyl Stannane (+)-58. A solution of (+)-**30** (25.5 mg, 0.042 mmol) in *N*-methyl-2-pyrrolidinone (NMP) (0.4 mL) was degassed with argon for 5 min, treated with tris(dibenzylideneacetone)-dipalladium (Pd_2dba_3) (3.7 mg, 0.004 mmol), and degassed with argon 5 min further. The reaction mixture was treated with hexamethylditin (12 μL, 0.055 mmol), stirred for 30 min, diluted with ether (20 mL), washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes → hexanes/ethyl acetate, 9:1) provided (+)-**58** (17.5 mg, 64% yield) as a colorless oil: $[\alpha]^{23}_D$ +13 (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 1730 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (apparent dt, J = 12.6, 6.5 Hz, 1 H), 6.05−5.95 (m, 2 H), 5.87 (dd, J = 12.6, 1.0 Hz, 1 H), 5.62 (dt, J = 14.5, 7.0 Hz, 1 H), 5.48 (dd, J = 14.5, 7.5 Hz, 1 H), 4.23−4.17 (m, 1 H), 3.89−3.84 (m, 1 H), 3.80−3.77 (m, 1 H), 2.25−2.21 (m, 2 H), 2.11−2.07 (m, 2 H), 1.70−1.40 (m, 6 H), 1.17 (d, J = 6.2 Hz, 3 H), 0.87−0.86 (m, 18 H), 0.14 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.025 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.8, 134.2, 130.9, 130.01, 129.97, 71.0, 69.2, 68.0, 46.7, 44.7, 38.8, 32.5, 25.97, 25.96, 25.4, 23.5, 18.2, 18.1, −3.5, −3.8, −4.2, −4.5, −8.6; high-resolution mass spectrum (FAB, NBA) *m*/*z* 669.3134 [(M + Na)$^+$; calcd for $C_{30}H_{62}O_3Si_2SnNa$: 669.3157].

Trimethylvinyl Stannane (+)-59. A solution of acid (+)-**57** (59.2 mg, 0.145 mmol) and alcohol (+)-**58** (85.1 mg, 0.132 mmol) in anhydrous benzene (3 mL) was cooled to 10 °C, treated with triphenylphosphine (208 mg, 0.792 mmol), and stirred for 5 min at 10 °C. Diethyl azodicarboxylate (DEAD) (0.125 mL, 0.792 mmol) was added dropwise via syringe, and the reaction mixture was stirred 20 min further and then diluted with hexanes (20 mL), washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) afforded (+)-**59** (112.2 mg, 83% yield) as a colorless oil: $[\alpha]^{23}_D$ +25 (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 1705 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 15.3, 11.2 Hz, 1 H), 6.50 (dd, J = 14.4, 5.7 Hz, 1 H), 6.50 (t, J = 12.0 Hz, 1 H), 6.43 (dt, J = 12.6, 6.8 Hz, 1 H), 6.24 (dd, J = 14.5, 1.1 Hz, 1 H), 6.05−5.94 (m, 3 H), 5.87 (d, J = 12.6 Hz, 1 H), 5.61 (dt, J = 12.3, 7.1 Hz, 1 H), 5.56 (d, J = 11.3 Hz, 1 H), 5.48 (dd, J = 14.6, 7.3 Hz, 1 H), 4.95−4.92 (m, 1 H), 4.22−4.14 (m, 1 H), 3.88−3.84 (m, 1 H) 2.37 (apparent t, J = 9.4 Hz, 2 H), 2.22 (apparent t, J = 6.6 Hz, 2 H), 2.10−2.05 (m, 2 H), 1.71−1.3 (m, 6 H), 1.22 (d, J = 6.3 Hz, 3 H), 0.870 (s, 9 H), 0.869 (s, 9 H), 0.86 (s, 9 H), 0.14 (s, 9 H), 0.05 (s, 3 H), 0.030 (s, 3 H), 0.026 (s, 3 H), 0.023 (s, 3 H), 0.019 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 148.2, 145.3, 144.4, 139.5, 134.9, 134.0, 130.9, 130.1, 129.9, 129.5, 128.3, 117.0, 74.7, 71.0, 70.4, 69.1, 46.7, 44.7, 41.1, 35.6, 32.4, 25.9 (2C), 25.8, 25.1, 20.1, 18.2 (2C), 18.1, −3.5, −3.8, −4.2, −4.5, −4.6, −4.9, −8.6 high-resolution mass spectrum (FAB, NBA) *m*/*z* 1059.3657 [(M + Na)$^+$; calcd for $C_{45}H_{85}IO_5Si_3SnNa$: 1059.3671].

7,13,15-Tris(*O*-TBS) Macrolacin A (−)-40 via (+)-59. A solution of (+)-**59** (123.8 mg, 0.119 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (0.21 mL, 1.19 mmol), and tetrabutylammonium diphenylphosphonate[11]

($Ph_2PO_2NBu_4$) (164 mg, 0.357 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (476 mL) was degassed with oxygen-free argon for 20 min. Tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (8.7 mg, 0.009 mmol) was then added and the reaction mixture degassed 30 min further. Another portion of catalyst (8.7 mg, 0.009 mmol) was added after 30 min and the reaction stirred 15 min further. The mixture was poured into ice/water (500 mL) and extracted with hexane (2 × 1 L). The combined ether extracts were washed with water (1 L) and brine (1 L), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 94:5:1) gave (−)-**40** (59.1 mg, 67% yield) as a colorless oil which was equivalent in all respects to (−)-**40** prepared from (+)-**39**.

Trimethylvinyl Stannane (+)-60. A solution of (+)-**45** (25.8 mg, 0.042 mmol) in *N*-methyl-2-pyrrolidinone (NMP) (0.5 mL) was degassed with argon for 5 min, treated with tris(dibenzylideneacetone)-dipalladium (Pd_2dba_3) (3.6 mg, 0.002 mmol), triphenylphosphine (PPh_3) (2.0 mg, 0.008 mmol), and degassed with argon 5 min further. The reaction mixture was heated to 50 °C, treated with hexamethylditin (0.5 mL, 0.225 mmol), stirred for 2.5 h, diluted with ether (20 mL), washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes → hexanes/ethyl acetate, 9:1) provided (+)-**60** (15.1 mg, 55% yield) as a colorless oil: $[\alpha]^{23}_D$ +8.4 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 1600 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.48 (dt, J = 13.0, 6.8 Hz, 1 H), 6.07−5.92 (m, 2 H), 5.87 (d, J = 12.6 Hz, 1 H), 5.65−5.58 (m, 1 H), 5.50 (dd, J = 14.7, 7.6 Hz, 1 H), 4.22−4.17 (m, 1 H), 3.89−3.82 (m, 1 H), 3.80−3.75 (m, 1 H), 2.29−2.17 (m, 2 H), 2.10−2.06 (m, 2 H), 1.72−1.37 (m, 6 H), 1.17 (d, J = 6.2 Hz, 3 H), 0.96−0.86 (m, 18 H), 0.61−0.53 (m, 12 H), 0.14 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.6, 134.2, 131.0, 130.1, 130.0, 70.8, 69.0, 68.0, 46.7, 44.6, 38.8, 32.5, 25.4, 23.6, 7.0, 6.9, 5.4, 5.3, −8.6; high-resolution mass spectrum (CI, NH_3) *m*/*z* 669.3142 [(M + Na)$^+$; calcd for $C_{30}H_{62}O_3Si_2SnNa$: 669.3157].

Trimethylvinyl Stannane (+)-61. A solution of (+)-**57** (15.0 mg, 0.036 mmol) and (+)-**60** (18.9 mg, 0.029 mmol) in anhydrous benzene (0.6 mL) was cooled to 10 °C, treated with triphenylphosphine (46.3 mg, 0.176 mmol), and stirred for 5 min at 10 °C. Diethyl azodicarboxylate (DEAD) (0.028 mL, 0.176 mmol) was added dropwise, and the reaction mixture was stirred 20 min further then diluted with hexanes (20 mL), washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 89:10:1) afforded (+)-**61** (23.6 mg, 78% yield) as a colorless oil: $[\alpha]^{23}_D$ +24.8 (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 1705 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.36 (m, 1 H), 6.51 (dd, J = 14.3, 5.8 Hz, 1 H), 6.52−6.58 (m, 1 H), 6.47 (dt, J = 12.6, 6.5 Hz, 1 H), 6.24 (dd, J = 14.3, 1.2 Hz, 1 H), 6.03−5.94 (m, 3 H), 5.87 (d, J = 12.6 Hz, 1 H), 5.58 (dt, J = 14.5, 7.4 Hz, 1 H), 5.56 (d, J = 11.2 Hz, 1 H), 5.50 (dd, J = 14.9, 7.6 Hz, 1 H), 4.94−4.91 (m, 1 H), 4.21−4.09 (m, 1 H), 3.89−3.80 (m, 1 H) 2.37 (apparent t, J = 6.2 Hz, 2 H), 2.31−2.27 (m, 2 H), 2.16−2.05 (m, 2 H), 1.72−1.20 (m, 6 H), 1.22 (d, J = 6.3 Hz, 3 H), 0.97−0.82 (m, 18 H), 0.86 (s, 9 H), 0.14 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 148.3, 145.3, 144.4, 139.5, 134.7, 134.0, 131.0, 130.2 (2C), 129.5, 117.0, 76.4, 74.7, 70.8, 70.4, 69.0, 46.7, 44.6, 41.1, 35.6, 32.4, 25.8, 25.1, 20.1, 18.2, 7.0, 6.6, 5.4, 5.3, −4.6, −4.9, −8.6; high-resolution mass spectrum (FAB, NBA) *m*/*z* 1059.3683 [(M + Na)$^+$; calcd for $C_{45}H_{85}IO_5Si_3SnNa$: 1059.3671].

7-*O*-TBS-13,15-Bis(*O*-TES) Macrolacin A (−)-54 via (+)-61. A solution of iodo trimethylstannyl ester (+)-**61** (23.6 mg, 0.023 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (0.04 mL, 0.23 mmol), and tetrabutylammonium diphenylphosphonate[11] ($Ph_2PO_2NBu_4$) (16.0 mg, 0.034 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (32.5 mL) was degassed with argon for 10 min. Tris(dibenzylideneacetone)-dipalladium (Pd_2dba_3) (2.1 mg, 0.0023 mmol) was added and the mixture degassed 10 min further. The flask was covered with aluminum foil and the reaction mixture stirred at room temperature for 10 min, diluted with ether (100 mL), washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 94:5:1) gave (−)-**54** (15.7 mg, 92% yield) as a colorless oil, equivalent in all respects to the sample prepared via (+)-**53**.

7-*O*-TBS Macrolactin E (+)-62. A solution of monoprotected macrocycle (−)-**55** (5.3 mg, 0.01 mmol) in anhydrous hexanes (0.5 mL) was treated with manganese(IV) oxide (MnO_2) (4.5 mg, 0.05 mmol). The flask was wrapped in aluminum foil and the reaction mixture stirred at room temperature. After 2.5 h the mixture was treated further with MnO_2 (4.5 mg, 0.05), stirred 2.5 h, diluted with ethyl acetate (10 mL), and filtered through Celite. Concentration and flash chromatography (hexanes/ethyl acetate/triethylamine, 50:49:1) furnished (+)-**62** (2.3 mg, 43% yield) as a colorless oil: $[\alpha]^{23}_D$ +29.2 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 1685 (s) cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J = 14.8, 10.6 Hz,1 H), 7.02 (dd, J = 15.8, 10.3 Hz, 1 H), 6.51 (t, J = 11.6 Hz, 1 H), 6.40 (dd, J = 15.0, 11.0 Hz, 1 H), 6.23−6.02 (m, 4 H), 5.97 (d, J = 15.9 Hz, 1 H), 5.73 (dd, J = 15.0, 5.3 Hz, 1 H), 5.55 (d, J = 11.5 Hz, 1 H), 5.54 (dd, J = 19.2, 8.43 Hz, 1 H), 5.03−5.01 (m, 1 H), 4.03−4.27 (m, 1 H), 4.13−4.10 (m, 1 H), 2.80 (dd, J = 16.9, 2.8 Hz, 2 H), 2.60 (dd, J = 16.9, 4.3 Hz, 2 H), 2.50−1.60 (complex series of m, 10 H), 1.26 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 166.3, 145.7, 144.9, 143.1, 140.9, 137.5, 131.0, 129.6, 129.1, 129.0, 126.7, 123.9, 117.6, 72.3, 70.6, 67.9, 43.2, 43.0, 35.1, 34.6, 32.4, 25.9, 24.6, 20.1, 18.2, −4.2, −4.7; high-resolution mass spectrum (FAB, NBA) *m*/*z* 537.3032 [(M + Na)$^+$; calcd for $C_{30}H_{46}O_5SiNa$: 537.3014].

Macrolactin E (+)-5. A solution of protected macrocycle (+)-**62** (2.1 mg, 0.005 mmol) in anhydrous THF (0.5 mL) was treated with a solution of TBAF/AcOH (1:1, ca. 1 M in THF, 0.05 mL, 0.05 mmol). The flask was wrapped in aluminum foil and the reaction mixture stirred at room temperature for 5 days. Concentration and flash chromatography (hexanes/ethyl acetate/triethylamine, 50:49:1) furnished (+)-**5** (1.2 mg, 73% yield): $[\alpha]^{23}_D$ +27 (*c* 0.12, MeOH); lit.[1] $[\alpha]^{23}_D$ +21.8 (*c* 0.44, MeOH);^1H NMR (500 MHz, C_6D_6) δ 7.50 (dd, J = 14.4, 11.5 Hz, 1 H), 6.94 (dd, J = 15.8, 10.4 Hz, 1 H), 6.35 (dd, J = 14.9, 11.2 Hz, 1 H), 6.23 (apparent t, J = 11.4 Hz, 1 H), 5.99 (t, J = 10.7 Hz, 1 H), 5.93 (d, J = 15.8 Hz, 1 H), 5.91−5.77 (m, 3 H), 5.64 (d, J = 11.4 Hz, 1 H), 5.53 (dt, J = 10.6, 8.6 Hz, 1 H), 5.43 (dd, J = 15.1, 6.0 Hz, 1 H), 5.08−5.03 (m, 1 H), 4.17−4.15 (m, 1 H), 3.87−3.80 (m, 1 H) 2.56−2.47 (m, 3 H) 2.38−2.33 (m, 1 H), 2.20−2.13 (m, 1 H), 2.12−2.07 (m, 1 H), 2.07−1.96 (m, 1 H), 1.72−1.68 (m, 1 H), 1.47−1.10 (m, 1 H), 1.29−1.10 (m, 3 H), 1.06 (d, J = 6.3 Hz, 3 H); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, J = 15.3, 11.2 Hz, 1 H), 7.03 (dd, J = 15.8, 10.0 Hz, 1 H), 6.53 (apparent t, J = 11.4 Hz, 1 H), 6.50 (dd, J = 15.2, 11.2 Hz, 1 H), 6.23−6.04 (m, 4 H), 5.973 (d, J = 15.8 Hz, 1 H), 5.78 (dd, J = 15.2, 6.0 Hz, 1 H), 5.58 (d, J = 11.6 Hz, 1 H), 5.54 (dd, J = 10.3, 10.2 Hz, 1 H), 5.05−5.02 (m, 1 H), 4.32−4.29 (m, 1 H), 4.15−4.12 (m, 1 H) 3.29 (d, J = 3.8 Hz, 1 H) 2.79 (dd, J = 16.8, 3.2 Hz, 1 H), 2.64 (dd, J = 16.8, 8.0 Hz, 1 H), 2.54−2.31 (m, 5 H), 2.18−2.11 (m, 1 H), 1.68−1.47 (m, 6H), 1.26 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 166.3, 145.9, 144.9, 142.7, 139.6, 136.2, 130.7, 129.6, 129.4, 129.1, 127.7, 125.1, 118.1, 71.5, 70.5, 68.0, 43.1, 41.5, 35.1, 34.5, 32.4, 24.5, 20.0; high-resolution mass spectrum (FAB, NBA) *m*/*z* 423.2159 [(M + Na)$^+$; calcd for $C_{24}H_{32}O_5Na$: 423.2147.

Acknowledgment. This article is dedicated to the memory of Professor John K. Stille, pioneer in the development and application of palladium cross-coupling reactions. Financial support was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033. In addition, we thank Drs. George T. Furst and Patrick J. Carroll and Mr. John Dykins of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra, respectively.

Supporting Information Available: Experimental procedures and characterization data for **10**, **12**, (+)-**15**, (+)-**16**, (+)-**17**, **27**−**29**, **42**, **46**−**52** (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980203B