A Unified Total Synthesis of the Immunomodulators (−)-Rapamycin and (−)-27-Demethoxyrapamycin: Assembly of the Common C(1−20) Perimeter and Final Elaboration

Amos B. Smith, III,* Stephen M. Condon, John A. McCauley, Johnnie L. Leazer, Jr., James W. Leahy, and Robert E. Maleczka, Jr.

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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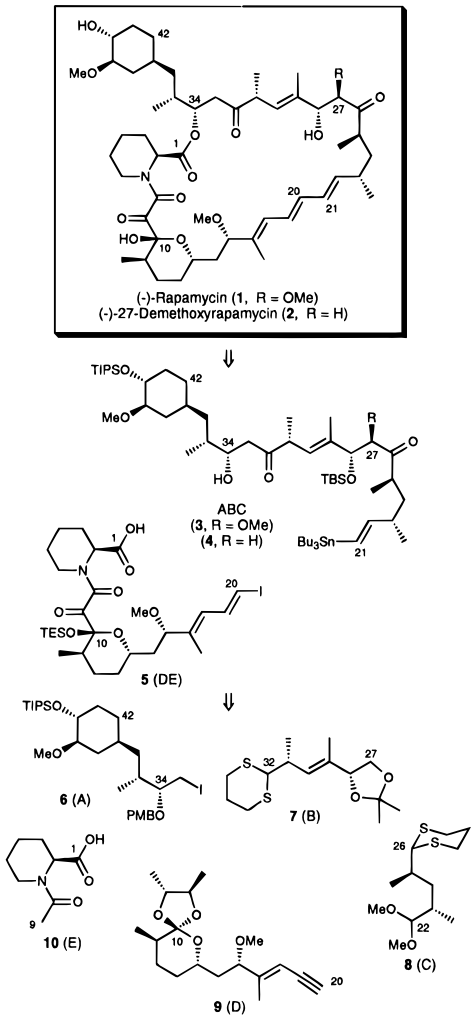
Abstract: The potent, naturally occurring immunomodulators (−)-rapamycin (**1**) and (−)-27-demethoxyrapamycin (**2**) have been synthesized via a unified and highly convergent strategy. In the preceding paper we discussed the construction of common building blocks A−C and their linkage to provide the C(21−42) segments of **1** and **2**. Herein we describe model studies of triene generation and hydroxyl deprotection, the preparation and coupling of building blocks D and E, a two-step protocol for macrocycle formation via union of the ABC and DE subtargets, and completion of the total syntheses. The synthesis of 27-demethoxyrapamycin (**2**) confirmed the assigned structure.

In this two-part full account,[1] we present a unified, highly convergent synthetic route to the potent immunosuppressant rapamycin (**1**)[2] and its naturally occurring 27-demethoxy congener **2**.[3] Our second-generation analysis of the rapamycin problem, discussed in the preceding paper,[1] generated the C(21−42) ABC perimeters **3** and **4** and the common C(1−20) DE perimeter **5** as key subtargets (Scheme 1). The macrocycles could then be elaborated by intermolecular acylation at C(34) and intramolecular Pd(0)-catalyzed Stille coupling,[4,5] or alternatively via initial formation of the triene seco acids followed by macrolactonization. Although we have also made considerable progress in exploring the lactonization strategy,[6] it was the former approach which we successfully employed for the total syntheses of **1** and **2**.[7,8] The previous reports detailed the construction of common subunits A, B, and C[9] and the assembly of the ABC segments **3** and **4**.[1] Herein we describe model studies of triene formation and macrolide deprotection, the

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1997.

(1) Part 1: Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leahy, J. W.; Leazer, J. L., Jr.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 0000 (preceding paper in this issue).

(2) (a) Vézina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721. (b) Sehgal, S. N.; Baker, H.; Vézina, C. *Ibid*. **1975**, *28*, 727. (c) Baker, H.; Sidorowicz, A.; Sehgal, S. N.; Vézina, C. *Ibid*. **1978**, *31*, 539. (d) Singh, K.; Sun, S.; Vézina, C. *Ibid*. **1979**, *32*, 630. (e) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491. (f) McAlpine, J. B.; Swanson, S. J.; Jackson, M.; Whittern, D. N. *J. Antibiot.* **1991**, *44*, 688. (g) McAlpine, J. B.; Swanson, S. J.; Jackson, M.; Whittern, D. N. *Ibid*. **1991**, *44*, C-3 (correction). (h) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579. (i) Findlay, J. A.; Radics, L. *Ibid.* **1981**, *59*, 49 (erratum).

(3) (a) Sehgal, S. N.; Baker, H.; Eng, C.; Singh, K.; Vézina, C. *J. Antibiot.* **1983**, *36*, 351. (b) Findlay, J. A.; Liu, J. S.; Burnell, D. J.; Nakashima, T. T. *Can. J. Chem.* **1982**, *60*, 2046. (c) Caufield, C. E.; Musser, J. H. *Annu. Rep. Med. Chem.* **1989**, *25*, 195.

(4) To our knowledge, Stille was the first to employ his palladium-catalyzed coupling for macrolide construction: Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785. See also: Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883. The Nicolaou synthesis of rapamycin[5] elegantly extended this methodology by using a Stille−type "stitching−cyclization" to install the C(19,20) vinyl unit and close the macrocycle in 28% yield.

(5) (a) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318. (b) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

(6) Condon, S. M. Ph.D. Thesis, University of Pennsylvania, 1995.

(7) Preliminary communication: 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.

(8) The intramolecular Stille coupling remains an effective protocol for natural product synthesis. See for example: (a) Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215. (b) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Org. Chem.* **1996**, *61*, 685.

(9) Preliminary communications: (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leahy, J. W.; Leazer, J. L., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1994**, *35*, 4907. (b) Smith, A. B., III; Maleczka, R. E., Jr.; Leazer, J. L., Jr.; Leahy, J. W.; McCauley, J. A.; Condon, S. M. *Ibid.* **1994**, *35*, 4911.

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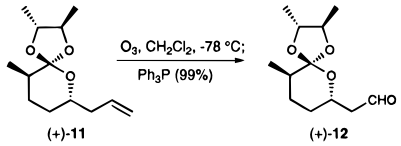
preparation and union of fragments D and E to furnish **5**, and completion of the synthetic venture.

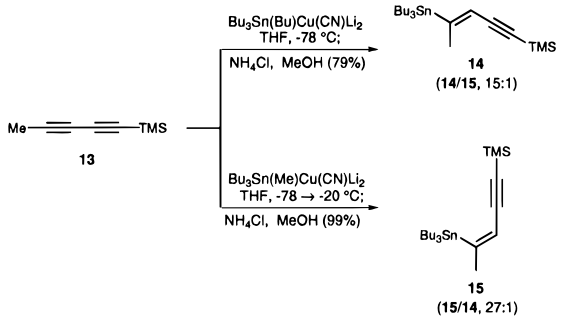
Preparation of Subunit D. The key element of the common DE fragment **5** was building block D, the enyne ortho ester **9**. Retrosynthetically, **9** was expected to derive from organometallic addition of an enyne moiety to aldehyde **12**, the latter readily available from alkene (+)-**11** (Scheme 2), an intermediate in

Scheme 2



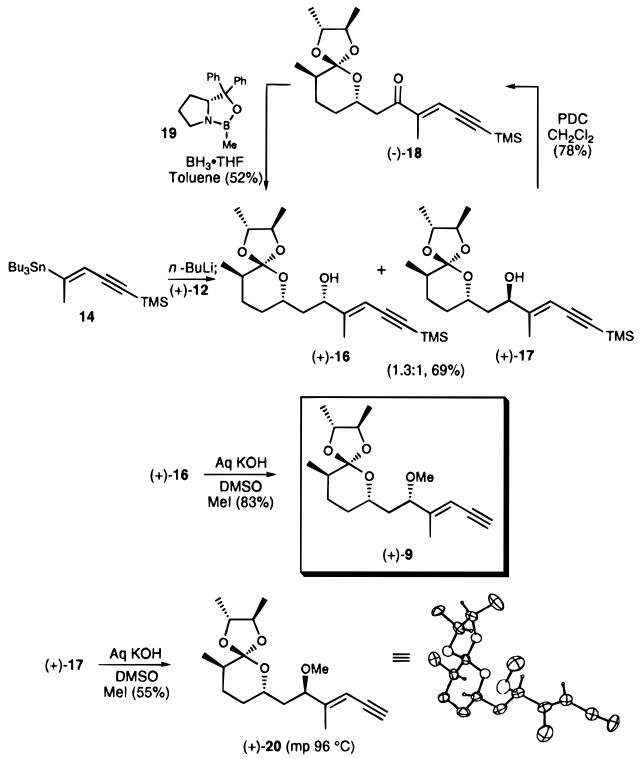
our latrunculin synthesis.[10] Hydrostannylation of the known silyl diyne **13**[11] was viewed as an expedient approach to vinylstannane **14**, precursor to the desired lithio derivative.[12] In the event, reaction of **13** with conventional stannyl cuprates afforded unacceptable mixtures of regio- and stereoisomers, but both the (*E*)- and (*Z*)-enynes **14** and **15** could be selectively generated in quantity via higher-order cuprates (Scheme 3).[13]

Scheme 3



For installation of the all *trans*-triene of rapamycin, we initially focused on the (*E*)-vinylstannane **14**. Transmetalation (*n*-BuLi, THF, −78 °C) and addition to aldehyde (+)-**12** (Scheme 4) afforded a 1.3:1 mixture of the diastereomeric alcohols (+)-**16** and (+)-**17** in 69% yield. Fortuitously, we observed that the (*Z*)-organolithium, present in minor amounts, reacted with much higher diastereoselectivity; substitution of **15** (>98% Z) for **14** led to epimers (+)-**25** and (+)-**26** in a 5.6:1 ratio (65%, Scheme 6). At this juncture, however, it was unclear whether the (*Z*)-enyne could serve as a viable precursor to the triene moiety in **1**; the configurations of the new carbinol stereocenters in both pairs of adducts also remained to be elucidated. Following chromatographic separation, the *E* isomers **16** and **17** were *O*-methylated with concurrent removal of the trimethylsilyl groups, affording ethers (+)-**9** and (+)-**20** in good yield. Single-crystal X-ray analysis revealed that **20** embodied the undesired (*R*) stereochemistry. We then optimized the formation of (+)-**16** via an oxidation/asymmetric reduction sequence, employing the Corey chiral oxaborolidine catalyst[14]

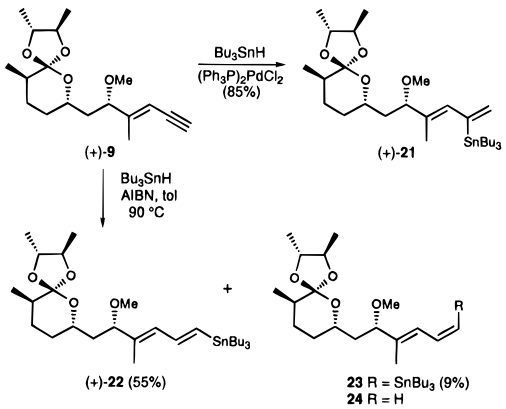
Scheme 4



to provide the pure (*S*)-alcohol in 30% yield overall from aldehyde **12**.

Triene Formation: Model Studies with Fragments C and D. Including *N*-acetylpipecolinic acid (E), a known compound,[15] we now had in hand all five subunits.[1] As outlined above, we envisioned from the outset that palladium-mediated σ-bond coupling of the ABC and DE subtargets would install the potentially sensitive (*E*,*E*,*E*)-triene in regio- and stereocontrolled fashion.[16] Before proceeding with elaboration of the subtargets, we decided to model the Stille cross-coupling with partners derived from fragments C with D. To generate the desired dienylstannane, we first investigated palladium-catalyzed hydrostannylation. Reaction of **9** with tributyltin hydride in the presence of $(Ph_3P)_2PdCl_2$[17] (5 mol %) gave exclusively the internal stannane (+)-**21** (Scheme 5). In contrast, treatment of

Scheme 5



9 with *n*-Bu_3SnH and AIBN in toluene at reflux furnished the

(10) The (−)-antipode of **11**, obtained by resolution, was required for the latrunculins: (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. *Ibid.* **1992**, *114*, 2995.

(11) Holmes, A. B.; Jones, G. E. *Tetrahedron Lett.* **1980**, *21*, 3111.

(12) (a) Zweifel, G.; Leong, W. *J. Am. Chem. Soc.* **1987**, *109*, 6409. (b) Stacker, E. C.; Zweifel, G. *Tetrahedron Lett.* **1991**, *32*, 3329.

(13) (a) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Ibid.* **1989**, *30*, 2065. (c) Singer, R. D.; Hutzinger, M. W.; Oehlschager, A. C. *J. Org. Chem.* **1991**, *56*, 4933.

(14) (a) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835. (b) Corey, E. J.; Bakshi, R. K. *Ibid.* **1990**, *31*, 611.

(15) (a) Rodwell, V. W. *Methods Enzymol.* **1971**, *17*, Part B, 174. (b) Toone, E. J.; Jones, J. B. *Can. J. Chem.* **1987**, *65*, 2772. (c) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

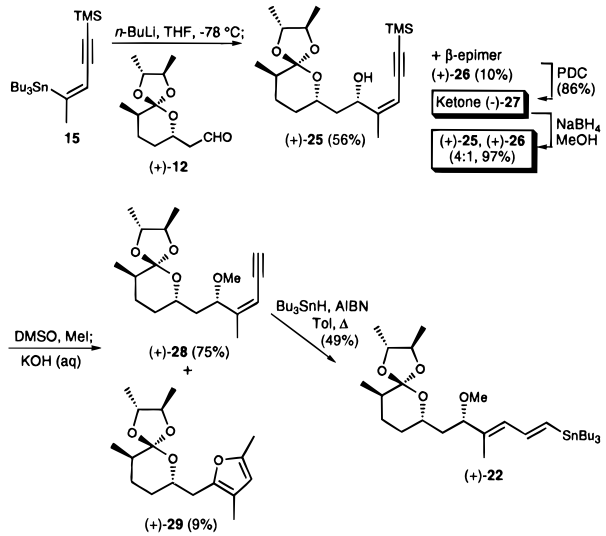
(16) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(17) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

E,E linear isomer (+)-**22** in 55% yield, readily separable from a small amount of (*E,Z*)-stannane **23** (9%).[18] *This reversal of hydrostannylation regiochemistry appears to be quite general for enynes.*[19] Resubmission of **23** to the reaction conditions resulted in partial isomerization to **22**.

Importantly, the AIBN reaction not only delivered the requisite regiochemistry, but also proceeded via a freely rotating[20] allylic radical intermediate which permitted *Z*-to-*E* isomerization of the C(17,18) trisubstituted olefin. We thus could consider (*Z*)-enyne **25** as a building block for the diene moiety. Although **25** was formed with enhanced stereoselectivity (5.6:1, Scheme 6) vis-á-vis **16** (1.3:1, Scheme 4), the

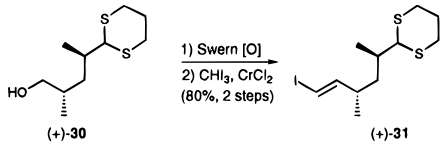
Scheme 6



configuration of the C(16) carbinol stereocenter remained to be determined. To this end (+)-**25** was *O*-methylated, furnishing ether (+)-**28** (75% yield) and furan (+)-**29** (9%).[21] We were not disappointed when treatment of **28** with *n*-Bu_3SnH and AIBN (toluene, at reflux) gave key dienylstannane (+)-**22** in 50% yield, identical to the material derived from **9**. This result established that the cis-to-trans isomerization had indeed occurred and that the earlier addition step had produced the desired (*S*)-alcohol as the major isomer. Alcohol (+)-**26**, the unwanted *R* epimer of **25**, was readily converted to a separable 4:1 mixture of **25** and **26** via PDC oxidation and $NaBH_4$ reduction (83% yield, two steps).

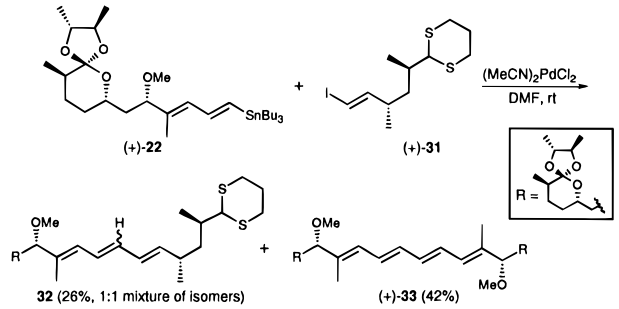
Preparation of the second cross-coupling partner began with Swern oxidation of hydroxy dithiane **30**.[1] Without purification, the resultant aldehyde was subjected to Takai−Nozaki olefination,[22] affording the desired vinyl iodide (+)-**31** (80% overall, Scheme 7). Unfortunately, coupling with **22** mediated by

Scheme 7



$(MeCN)_2PdCl_2$ furnished the desired triene **32** in low yield as a 1:1 mixture of *E* and *Z* isomers, accompanied by significant quantities of the homocoupled tetraene (+)-**33**[23] (Scheme 8).

Scheme 8

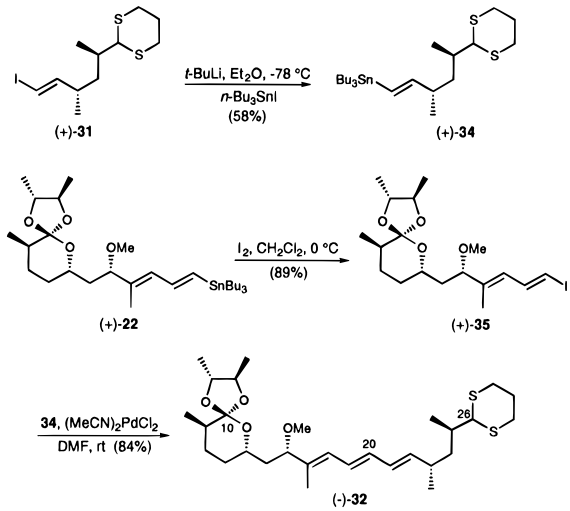


No meaningful improvement was achieved by variation of the metal oxidation state [$(Ph_3P)_4Pd(0)$], ligand (Ph_3As),[24] solvent, and temperature, or by the addition of CuI.[25]

The rapid appearance of **33** did demonstrate efficient turnover of the catalyst. Accordingly, the problematic step seemed likely to be oxidative addition of the vinyl iodide to palladium; this process might be inhibited by ligation of the proximal dithiane group in **31**. Crisp and co-workers previously observed that *(E)*-3-iodoallyl glycinate[26] generally gave low-to-moderate yields of products in Pd(0)-catalyzed Stille couplings. The latter finding may reflect ligation of the amide or ester to palladium, in accord with our interpretation of the behavior of **31**.

Crisp et al. enjoyed greater success with the analogous stannane *(E)*-3-(tributylstannyl)allyl glycinate.[27] Moreover, transposition of the vinylic functionalities dramatically influenced the product distribution for a Stille reaction in the Julia total synthesis of avermectin.[28] We therefore converted vinyl iodide (+)-**31** to the corresponding stannane (+)-**34** via metalation (*t*-BuLi, ether, −78 °C) followed by treatment with freshly distilled *n*-Bu_3SnI (58% yield, Scheme 9). Dienylstannane (+)-

Scheme 9



22 furnished the iodide (+)-**35** in near quantitative yield upon

(18) Le Ménez, P.; Berque, I.; Fargeas, V.; Ardisson, J.; Pancrazi, A. *Synlett* **1994**, 998.

(19) Maleczka, R. E., Jr.; Condon, S. M. (University of Pennsylvania). These results will be described elsewhere.

(20) The rotation barrier for [1-^{2}H]allyl radical is 15.7 kcal/mol: Korth, H.−G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483.

(21) Methylation of (+)-**25** furnished furan (+)-**29** as the major product when MeI was introduced after KOH; cf. Bonnet, P. H.; Bohlmann, F. *Chem. Ber.* **1971**, *104*, 1616. For more recent work, also see: Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435−3443. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966−5968.

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

(23) For examples of palladium-mediated homocoupling of vinyl stannanes, see: (a) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. A.; Spirkhin, L. V. *Synthesis* **1989**, 633. (b) Borzilleri, R. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 9789. (c) McDermott, T. S.; Mortlock, A. A.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 700.

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

(25) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (b) Liebeskind, L. S.; Fengl, R. W. *Ibid.* **1990**, *55*, 5359.

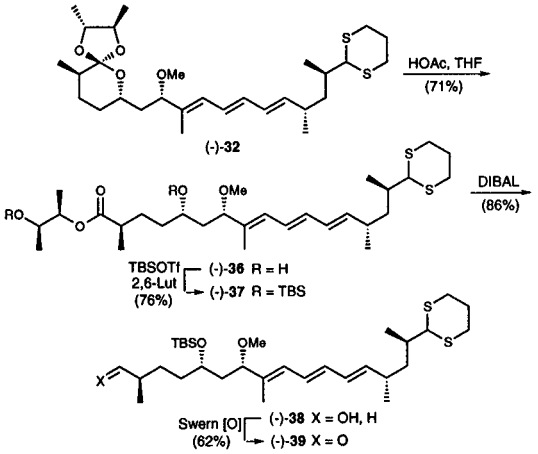
(26) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 2623.

(27) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213.

titration with a solution of I_2 in dichloromethane. This seemingly minor change afforded dramatic improvements in the yield and isomeric purity of the CD triene (−)-**32** (Scheme 9). Support for the requisite all *trans*-triene structure derived from the $^1H-^1H$ coupling constants at C(19,20) (14.5 Hz) and C(21,22) (14.8 Hz). Although a homocoupled product derived from **34** was also observed (18%, not shown), the reaction could be driven to completion by employing a slight excess of this reactant.

Prompted by an earlier report from the Danishefsky laboratories which noted the "poor 'shelf life' under essentially neutral conditions" of their triene intermediates, it seemed prudent at this point to explore the stability of the triene system.[29] We began with hydrolysis of ortho ester (−)-**32**, which provided dihydroxy ester (−)-**36** in 71% yield (Scheme 10). DIBAL

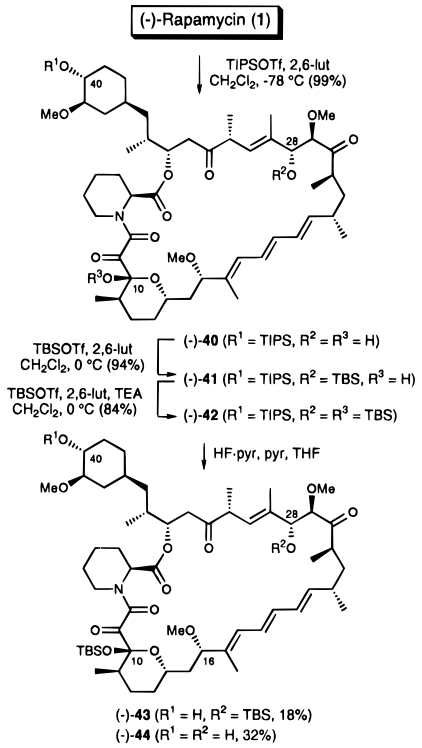
Scheme 10



reduction of the derived bis(TBS ether) (−)-**37** gave alcohol (−)-**38** as a single isomer. Swern oxidation then furnished aldehyde (−)-**39** in 62% yield. We were pleased to discover that all of these compounds were relatively stable, with characteristic ^1H NMR spectra for the triene.[6]

Evaluation of Endgame Protective Groups. A generous sample of natural rapamycin, kindly provided by Wyeth-Ayerst Laboratories (Princeton, NJ), enabled us to test our strategy for protection of the three hydroxyl groups in **1** and **2**. Via a highly chemoselective three-step sequence, we installed a TIPS ether at C(40)[30] followed by TBS ethers at C(28) and C(10) to generate (−)-**42** (Scheme 11). However, subsequent experiments immediately revealed that the regeneration of rapamycin by unmasking of **42** would not be a trivial operation. Treatment of **42** with TBAF or HF·MeCN gave mixtures of unidentifiable materials. Exposure to HF·pyridine in pyridine/THF (1:1) at 0 °C[31] led to two isolable products, the C(40) alcohol (−)-**43** (18% yield) and the C(28,40) diol (−)-**44** (32%), but extended reaction times or elevated temperatures resulted in decomposition of both the products and starting material. No rapamycin was detected. In their FK506 analog program, the Merck group cleaved a related C(10) TBS ether by exposure to neat trifluoroacetic acid at 0 °C for 5 min.[32] However, upon application of this protocol to an analogous rapamycin derivative at Wyeth-Ayerst, rapid solvolysis of the C(16) methoxy group generated an extended

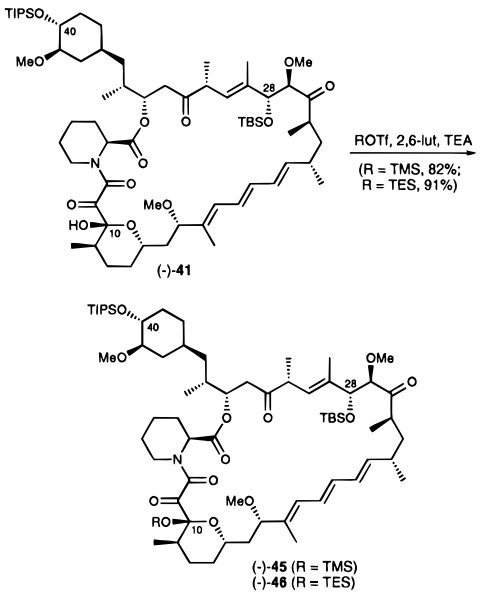
Scheme 11



heptatrienyl cation[33] which has been exploited in the construction of analogs.[34]

These findings mandated an alternative tactic for protection of the C(10) hemiketal hydroxyl. Speculating that steric hindrance was interfering with removal of the C(10) TBS moiety in **42**, we installed less bulky trimethylsilyl (TMS) and triethylsilyl (TES) groups at this position in (−)-**45** and (−)-**46**, respectively (Scheme 12). In the TMS protection reaction the

Scheme 12



use of toluene as solvent proved to be unexpectedly critical;

(28) Férézou, J. P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A. *Synlett* **1991**, 53.

(29) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826.

(30) Yohannes, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1992**, *33*, 7469.

(31) (a) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453. (b) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906.

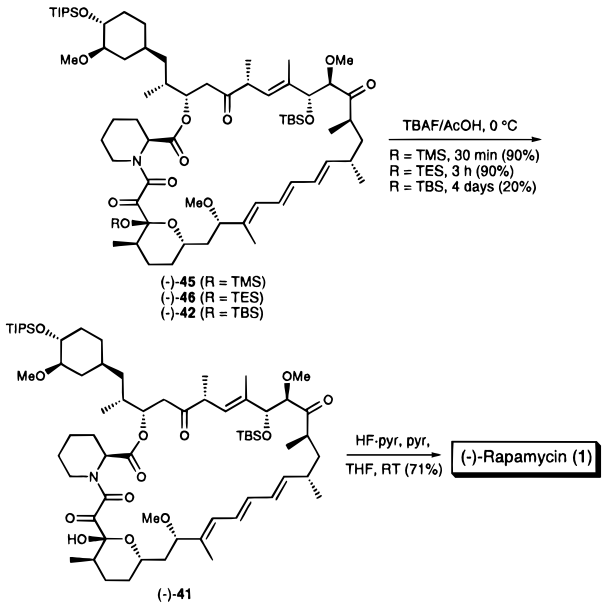
(32) Goulet, M. T.; Hodkey, D. W. *Tetrahedron Lett.* **1991**, *32*, 4627.

(33) (a) Grinfeld, A. A.; Caufield, C. E.; Schiksnis, R. A.; Mattes, J. F.; Chan, K. W. *Tetrahedron Lett.* **1994**, *35*, 6835. (b) Luengo, J. I.; Konialian-Beck, A.; Rozamus, L. W.; Holt, D. A. *J. Org. Chem.* **1994**, *59*, 6512.

(34) Luengo, J. I.; Yamashita, D. S.; Dunnington, D.; Konialian-Beck, A.; Rozamus, L. W.; Yen, H.-K.; Bossard, M. J.; Levy, M. A.; Hand, A.; Newmann-Tarr, T.; Badger, A.; Faucette, L.; Johnson, R. K.; D'Alessio, K.; Porter, T.; Shu, A. Y. L.; Heys, R.; Choi, J.; Kongsaeree, P.; Clardy, J.; Holt, D. A. *Chem. Biol.* **1995**, *2*, 471.

other choices such as dichloromethane led to varying amounts of byproducts, tentatively identified as isomeric six- and seven-membered-ring mixed silyl ether ketals.[35] TBAF/AcOH chemoselectively removed the TMS and TES groups, affording the bis(silyl ether) **41** (Scheme 13).[36,37] Interestingly, even the

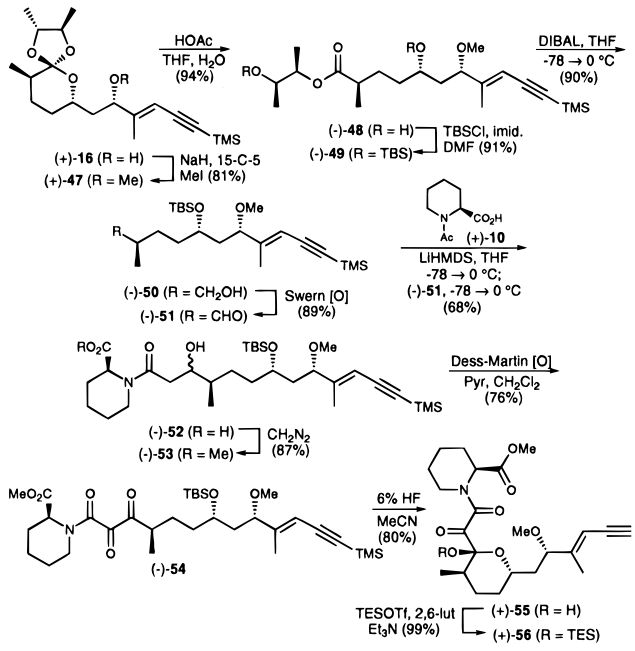
Scheme 13



C(10) TBS ether was cleaved under these conditions, although the alcohol was isolated in only 20% yield as the remaining material decomposed. The C(28) and C(40) hydroxyls were then unmasked with HF·pyridine to generate semisynthetic rapamycin. We selected the C(10) TES moiety for the construction of **1** and **2** because the TMS group seemed unlikely to survive all of the required synthetic operations.

Elaboration of the DE Subtarget 5. Although we anticipated that the (*E*,*E*)-dienyl iodide in **5** could be derived from a (*Z*)-enyne precursor, we nonetheless elected to carry forward both the *E* and *Z* isomers. In the *E* series, alcohol (+)-**16** was *O*-methylated under conditions that retained the TMS group protecting the terminal alkyne, affording (+)-**47** (Scheme 14).

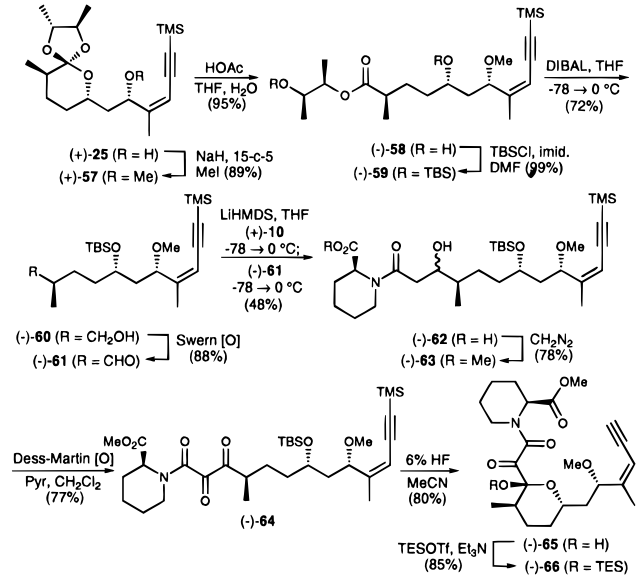
Scheme 14



Hydrolysis of the ortho ester moiety gave dihydroxy ester (−)-**48** which in turn was bissilylated, furnishing (−)-**49**. DIBAL reduction provided alcohol (−)-**50** and also regenerated the TBS-protected chiral auxiliary. Swern oxidation then delivered aldehyde (−)-**51**; the overall yield for this five-step sequence was 55%.

The dilithio derivative of the E subunit, *N*-acetyl-L-pipecolinic acid (**10**),[15] added smoothly to aldehyde **51**, generating (−)-**52** as an inconsequential mixture of aldol diastereomers (Scheme 14). Diazomethane esterification proved surprisingly sluggish, but after exposure to a large excess of the reagent for 24-48 h, ester (−)-**53** could be isolated in good yield (87%). Dess−Martin oxidation (5 equiv) then gave the desired tricarbonyl species (−)-**54** via the procedure of Golec et al.[38] Removal of the *O*- and *C*-silyl groups produced (+)-**55**, a single hemiketal as evidenced by the ^{13}C NMR spectrum.[35] Although ^{1}H NMR analysis initially suggested the presence of a mixture of products, amide rotamers apparently were responsible for the multiple resonances, consistent with high-temperature NMR studies of later synthetic intermediates. Both our own observations and those of Danishefsky[39] had indicated that the C(10) hemiketal would require protection during the couplings with the advanced ABC intermediates **3** and **4**. To this end, we prepared the C(10) TES ether (+)-**56** under the conditions previously described. Via an analogous sequence (Scheme 15), the (*Z*)-enyne alcohol

Scheme 15

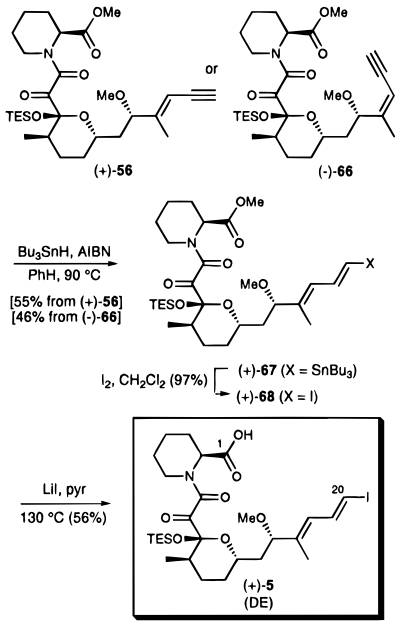


(+)-**25** furnished the protected hemiketal (−)-**66**.

We could now attempt the critical hydrostannylations of the fully elaborated (*E*)- and (*Z*)-enynes (+)-**56** and (−)-**66**. As foreshadowed by the successful model experiments, treatment of either compound with *n*-Bu_3SnH and AIBN in oxygen-free benzene[40] at reflux gave the desired (*E*,*E*)-dienyl stannane (+)-**67** in 55−60% yield (Scheme 16). Exposure to I_2 (CH_2Cl_2, 0 °C) then furnished the corresponding dienyl iodide (+)-**68**. For the final methyl ester cleavage, standard hydrolytic methods

(35) Hughes, P.; Musser, J.; Conklin, M.; Russo, R. *Tetrahedron Lett.* **1992**, *33*, 4739.
(36) Smith, A. B., III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013.
(37) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345.
(38) (a) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, *34*, 167. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (c) Meyer, S. D.; Schreiber, S. L. *Ibid.* **1994**, *59*, 7549.
(39) Yohannes, D.; Myers, C. D.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 2075.

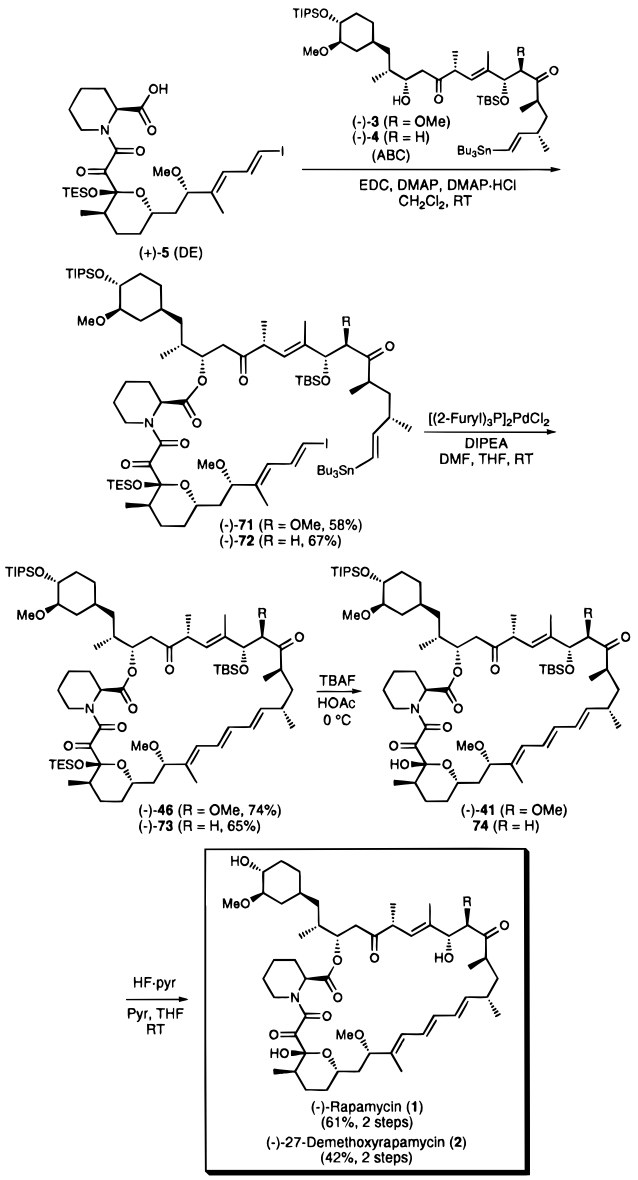
Scheme 16



and a number of aprotic alternatives led to decomposition.[41] Demethylation of **68** was ultimately achieved with LiI (20 equiv) in anhydrous pyridine[42] at reflux, affording the DE subtarget (+)-**5** in 56% yield.

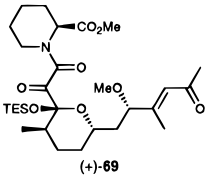
Final Assembly of Rapamycin and 27-Demethoxyrapamycin. With the fully elaborated C(21−42) ABC fragments **3** and **4**[1] and C(1−20) DE subunit **5** in hand, we were well positioned to consummate the total syntheses of rapamycin and demethoxyrapamycin. Our highly flexible approach would, in principle, permit assembly of the macrocycle either by intermolecular acylation at C(34) and intramolecular Pd(0)-catalyzed Stille coupling or alternatively via initial formation of the triene seco acid followed by macrolactonization. Concurrent studies of both options suggested that bimolecular esterification and Stille cyclization would provide superior results.[6] Union of the common DE carboxylic acid (+)-**5** with the ABC alcohols (−)-**3** (R = OMe) and (−)-**4** (R = H) was mediated by EDC [1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DMAP, DMAP·HCl],[43] affording (−)-**71** and (−)-**72** in 58% and 67% yields, respectively (Scheme 17). The successful generation of the esters in the presence of the C(32) carbonyl group was notable in view of the well-documented propensity of rapamycin to undergo base-induced β-elimination at the C(32−34) aldol linkage.[44] Moreover, in our ^{1}H NMR study of amide rotamers, the seco rapamycin intermediate (−)-**71** was heated to 102 °C in nitrobenzene-d_5 without observable decomposition.[45]

Scheme 17



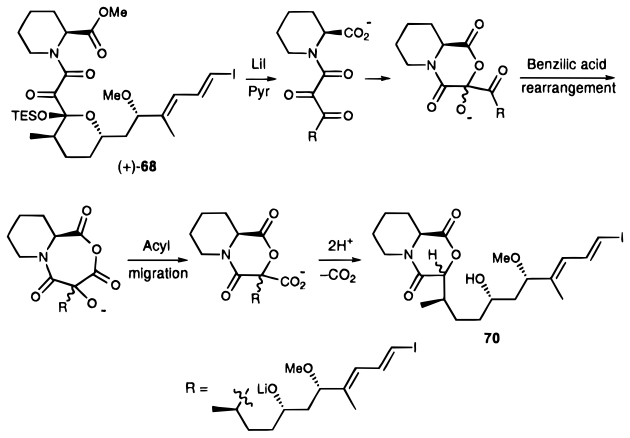
The Stille macrocyclization of (−)-**72** was investigated first. To our surprise, none of the desired product was produced under

(40) Failure to exclude oxygen (e.g., via freeze/thaw degassing) resulted in the formation of ketone (+)-**69** in yields approaching 30%, presumably by reaction of an intermediate radical with adventitious O_2.



(41) Limited success was achieved with bis(tributyltin) oxide. See: Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *34*, 4239.

(42) McMurry, J. *Org. React.* **1976**, *24*, 187. The concentration of **68** was 0.017 M. At higher concentrations, or when the C(10) hemiketal hydroxyl was protected as a TMS ether, rearrangement product **70** was produced as a partially separable 1:1 mixture of isomers. A plausible sequence leading to **70** involves cleavage of both the methyl ester and TES (or TMS) ether, benzilic acid rearrangement, acyl migration, protonation, and decarboxylation.



(43) DMAP·HCl suppressed formation of the *N*-acylurea derived from **5**. See: Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(44) (a) Luengo, J. I.; Konialian, A. L.; Holt, D. A. *Tetrahedron Lett.* **1993**, *34*, 991. (b) Steffan, R. J.; Kearney, R. M.; Hu, D. C.; Failli, A. A.; Skotnicki, J. S.; Schiksnis, R. A.; Mattes, J. F.; Chan, K. W.; Caufield, C. E. *Ibid.* **1993**, *34*, 3699.

(45) McCauley, J. A. Ph.D. Thesis, University of Pennsylvania, 1996.

the conditions developed earlier for coupling of **34** with **35** (Scheme 9). Other protocols also failed, including those utilized in our previous series of intermolecular cross-couplings[6] and in the Nicolaou rapamycin synthesis.[5] However, exposure of **72** to the Farina−Scott catalyst $[(2\text{-furyl})_3P]_2PdCl_2$[46,47] in DMF/THF at room temperature cleanly generated (−)-10-*O*-TES-28-*O*-TBS-40-*O*-TIPS-27-demethoxyrapamycin (**73**) in 65% yield as a ca. 3:1 mixture of rotamers (Scheme 17). Trifurylphosphine ligands are known to accelerate the Stille reaction.[47]

Treatment of **73** with TBAF in THF buffered with AcOH (0 °C, 10 min) provided an inseparable 3:1 mixture of the desired C(10) hemiketal **74** and a byproduct tentatively identified as the oxepane **75** (Figure 1) based upon ^{13}C NMR analysis (125

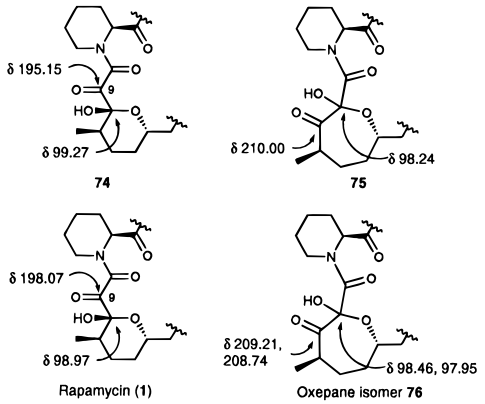


Figure 1. Comparison of selected ^{13}C NMR resonances for **74** and **75** with Hughes data for rapamycin and the isomeric oxepane **76**.[35]

MHz, C_6D_6). Hughes reported that C(9) and C(10) of rapamycin (major rotamer) resonate at δ 198.07 and 98.97 in DMSO-d_6.[35] For the isomeric rapamycin oxepane **76**, a 1:1 mixture of amide rotamers, Hughes assigned signals at δ 208.74 and 209.21 to the C(10) ketone, whereas the C(9) hemiketal carbon appeared at δ 98.46 and 97.95.[35] Carbons 9 and 10 of the trissilylated demethoxyrapamycin intermediate **73** (major rotamer) resonate at δ 197.8 and 102.5; after removal of the C(10) TES group, the major product **74** displays ^{13}C signals at δ 195.15 and 98.27, consistent with the six-membered-ring hemiketal structure. Resonances at δ 98.24 and 210.00 for the putative oxepane isomer **75** have been assigned to C(9) and C(10), respectively, fully in accord with the published data for the rapamycin oxepane **76**.[35]

The demethoxyrapamycin bis(silyl ether) **74** and isomer **75** were unmasked with HF·pyridine and excess pyridine in THF (Scheme 17). Synthetic (−)-27-demethoxyrapamycin (**2**) proved to be identical in all respects (^1H and ^{13}C NMR, IR, UV, optical rotation, HRMS, TLC in three solvent systems) to an authentic sample generously provided by Professor Koji Nakanishi (Columbia University).

For the synthesis of rapamycin, Stille cyclization of **71** with $[(2\text{-furyl})_3P]_2PdCl_2$ in DMF/THF readily provided the protected macrolide (−)-**46** in 74% yield (Scheme 17). Removal of the C(10) triethylsilyl group (TBAF, AcOH, THF, 0 °C, 1 h; 88% yield) uneventfully furnished (−)-**41** without interference from oxepane formation. Treatment with HF·pyridine and excess pyridine in THF then cleaved the C(40) TIPS and C(28) TBS ethers to give synthetic (−)-rapamycin (**1**) in 69% yield, identical in all respects with the natural material.

Summary. We have devised and executed a unified, highly convergent total synthesis of (−)-rapamycin (**1**) and (−)-27-demethoxyrapamycin (**2**), confirming the latter structure. For rapamycin, the longest linear sequence from the first point of convergence is 14 steps. The macrocyclic framework was assembled in only two steps via union of fully functionalized ABC and DE intermediates, demonstrating the effectiveness of Stille macrocyclization mediated by $[(2\text{-furyl})_3P]_2PdCl_2$. The preparation of linear (*E*,*E*)-dienylstannanes by free-radical hydrostannylation of enynes, complemented by palladium-catalyzed internal stannylation, should prove valuable in the generation of a wide range of substituted 1,3-dienes. The successful route to rapamycin exploited both dithiane couplings of complex intermediates and stereocontrolled σ-bond olefin constructions. We anticipate that the ready accessibility of the five subtargets, their adaptability toward structural modification, and the highly convergent nature of the approach will significantly facilitate the rational synthesis of rapamycin analogs.

Experimental Section[48]

Aldehyde (+)-12. A solution of allyl ortho ester (+)-**11** (9.39 g, 41.5 mmol) in dichloromethane (500 mL) was cooled to −78 °C and treated with ozone until a faint blue color persisted. The reaction mixture was purged with argon, and the resultant colorless solution was treated with triphenylphoshine (12.0 g, 45.7 mmol) portionwise, warmed to ambient temperature, stirred for 17.5 h, and concentrated. Flash chromatography (gradient elution, hexanes/ethyl acetate, 10:1 → 5:1) provided (+)-**12** (9.47 g, 99% yield) as a pale yellow oil: $[\alpha]_D^{23}$ +43.3° (*c* 3.33, $CHCl_3$); IR ($CHCl_3$) 1710 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, J = 2.0 Hz, 1 H), 4.32 (m, 1 H), 3.87 (dq, J = 8.2, 6.1 Hz, 1 H), 3.63 (dq, J = 8.2, 6.1 Hz, 1 H), 2.63 (ddd, J = 11.3, 9.0, 2.3 Hz, 1 H), 2.39 (ddd, J = 16.4, 4.1, 2.3 Hz, 1 H), 1.85 (m, 1 H), 1.69 (m, 1 H), 1.62−1.52 (m, 2 H), 1.36 (m, 1 H), 1.25 (d, J = 6.3 Hz, 3 H), 1.24 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 120.8, 80.6, 77.2, 69.3, 49.0, 35.9, 30.9, 29.2, 18.6, 16.5, 15.0; high-resolution mass spectrum (CI, NH_3) *m/z* 228.1361 [M^+; calcd for $C_{12}H_{20}O_4$, 228.1361]. *The air-sensitive aldehyde was used immediately in the next reaction.*

(*E*)-Enynylstannane 14. A slurry of dried CuCN (3.16 g, 35.2 mmol) in THF (400 mL) was cooled to −35 °C, and *n*-BuLi (1.6 M in hexanes, 44.0 mL, 70.4 mmol) was added dropwise over 30 min. The resultant clear yellow solution was stirred for 30 min at −35 °C, cooled to −78 °C, treated dropwise with tributyltin hydride (18.8 mL, 70.4 mmol), and stirred 30 min further. A solution of diyne **13** (4.00 g,

(46) Hettrick, C. M.; Scott, W. *J. Am. Chem. Soc.* **1991**, *113*, 4903.
(47) Farina, V.; Baker, S. R.; Benigni, D.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739.

(48) **Materials and Methods.** Reactions were carried out in oven- 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. Dichloromethane, benzene, diisopropylamine, and hexamethylphosphoramide (HMPA) were freshly distilled from calcium hydride. Triethylamine and diisopropylethylamine were distilled from calcium hydride and stored over potassium hydroxide. Anhydrous pyridine, *N*,*N*-dimethylformamide, and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium and *tert*-butyllithium were purchased from Aldrich and standardized by titration with diphenylacetic acid. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin layer chromatography with Whatman 0.25-mm precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.023−0.040 mm) supplied by E. Merck. Radial chromatography was performed with a Chromatotron (Harrison Research, Inc., Palo Alto, CA) and silica gel rotors supplied by Analtech (Newark, DE). High-performance liquid chromatography (HPLC) was performed with a Ranin component analytical/semiprep system. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrometer with polystyrene as external standard. Proton NMR spectra were recorded on a Bruker AM-500 spectrometer. Carbon-13 NMR spectra were recorded on a Bruker AM-500 or AM-250 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00) for ^1H and chloroform (δ 77.0) or benzene (δ 128.0) for ^{13}C. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center with either a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, NJ. Single-crystal X-ray structure determinations were performed at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer.

29.4 mmol) in THF (10 mL) was cooled to −78 °C and added to the cuprate via a cannula. The reaction mixture was stirred overnight (15 h) at −78 °C and then carefully quenched with methanol and saturated aqueous NH_4Cl (100 mL each), maintaining the internal temperature below −60 °C. The clear, dark brown solution was allowed to warm to ambient temperature, stirred for an additional 1.5 h, and then extracted with hexanes (500 mL). The organic phase was washed with brine (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes) gave **14** (9.8 g, 79% yield, 15:1 *E*:*Z*) as a pale yellow oil: bp 162 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (q, J = 1.6 Hz, 1 H), 2.12 (d, J = 1.8 Hz, 3 H), 1.51−1.43 (series of m, 6 H), 1.33−1.25 (series of m, 6 H), 0.99−0.85 (series of m, 15 H), 0.19 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 160.9, 118.3, 102.0, 97.7, 29.1, 27.4, 23.0, 13.6, 9.3, 0.1; high-resolution mass spectrum (CI, NH_3) *m/z* 429.1976 [(M + H)$^+$; calcd for $C_{20}H_{41}SiSn$, 429.1999].

(*Z*)-Enynylstannane 15. A slurry of dried CuCN (7.89 g, 88.1 mmol) in THF (1 L) was cooled to −50 °C, and MeLi−LiBr (1.5 M in ether, 117 mL, 176 mmol) was added dropwise over 30 min. The resultant clear yellow solution was stirred for 30 min, cooled to −78 °C, and treated dropwise with tributyltin hydride (47.0 mL, 176 mmol). After an additional 30 min, a solution of diyne **13** (10.0 g, 73.4 mmol) in THF (10 mL) at ambient temperature was introduced via a cannula. The reaction mixture was allowed to warm to −20 °C over 4 h and then carefully quenched with methanol and saturated aqueous NH_4Cl (100 mL each), warmed to ambient temperature, stirred 1.5 h further, and partitioned between methyl *tert*-butyl ether (1.5 L) and water (500 mL). The organic phase was washed with water and brine (500 mL each), dried over $MgSO_4$, filtered through a pad of Celite 545, and concentrated. Flash chromatography (hexanes) furnished **15** (31.4 g, 99% yield, 27:1 *Z*:*E*) as a pale yellow oil: bp 164 °C (0.1 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (q, J = 1.8 Hz, 1 H), 1.99 (d, J = 1.7 Hz, 3 H), 1.55−1.49 (series of m, 6 H), 1.35−1.28 (series of m, 6 H), 1.04−0.99 (series of m, 6 H), 0.89 (t, J = 7.3 Hz, 9 H), 0.19 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 161.4, 119.8, 106.2, 92.2, 29.2, 27.4, 27.3, 13.7, 9.8, −0.1; high-resolution mass spectrum (CI, NH_3) *m/z* 371.1231 [(M − Bu)$^+$; calcd for $C_{16}H_{31}SiSn$, 371.1217].

Alcohol (+)-16. A. From 14 and (+)-12. A solution of enynylstannane **14** (16.0 g, 37.4 mmol, 14:1 *E*:*Z*) in THF (250 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M in hexanes, 25.7 mL, 41.2 mmol) was added dropwise. The dark red mixture was stirred for 45 min, treated dropwise with a solution of aldehyde (+)-**12** (5.7 g, 25.0 mmol) in THF (50 mL), and stirred for an additional 1 h at −78 °C. The reaction mixture was warmed to 0 °C, quenched with saturated aqueous NH_4Cl (100 mL), and partitioned between ethyl acetate (500 mL) and water (300 mL). The organic phase was washed with brine (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes/ether, 50:1 → 4:1) provided (+)-**16** (3.53 g, 39% yield) and (+)-**17** (2.73 g, 30% yield) as colorless oils.

(+)-16: $[\alpha]_D^{23}$ +9.3° (*c* 9.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (t, J = 1.1 Hz, 1 H), 4.24 (dd, J = 9.2, 2.8 Hz, 1 H), 3.99 (tt, J = 11.5, 2.4 Hz, 1 H), 3.91 (ddt, J = 8.6, 6.0, 6.0 Hz, 1 H), 3.70 (br s, 1 H), 3.64 (ddt, J = 8.5, 6.1, 6.1 Hz, 1 H), 1.86 (d, J = 1.1 Hz, 3 H), 1.85 (m, 1 H), 1.73−1.64 (series of m, 3 H), 1.55−1.46 (series of m, 2 H), 1.35 (m, 1 H), 1.28 (d, J = 6.1 Hz, 3 H), 1.26 (d, J = 6.0 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 153.7, 120.6, 105.1, 102.8, 98.1, 80.6, 77.3, 75.5, 74.9, 40.7, 36.2, 31.4, 29.0, 18.3, 16.2, 15.4, 15.0, 0.2; high-resolution mass spectrum (CI, NH_3) *m/z* 366.2209 [M$^+$; calcd for $C_{20}H_{34}O_4Si$, 366.2226].

(+)-17: $[\alpha]_D^{23}$ +39.1° (*c* 14.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (t, J = 1.3 Hz, 1 H), 4.25 (br s, 1 H), 3.94 (m, 1 H), 3.89 (ddt, J = 8.4, 6.1, 6.1 Hz, 1 H), 3.62 (ddt, J = 8.4, 6.1, 6.1 Hz, 1 H), 2.94 (d, J = 3.8 Hz, 1 H), 1.83 (s, 3 H), 1.81 (m, 2 H), 1.65 (m, 2 H), 1.51−1.29 (series of m, 3 H), 1.27 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.1 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.15 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 120.7, 105.1, 102.9, 98.3, 80.5, 77.4, 72.9, 71.5, 39.4, 36.2, 31.2, 29.2, 18.6, 16.3, 16.1, 15.1, 0.0; high-resolution mass spectrum (CI, NH_3) *m/z* 366.2215 [M$^+$; calcd for $C_{20}H_{34}O_4Si$, 366.2226].

Methyl Ether (+)-9 (D). A solution of alcohol (+)-**16** (354 mg, 0.966 mmol) in dimethyl sulfoxide (20 mL) was cooled to 0 °C and treated with potassium hydroxide (1.37 g, 24.4 mmol) dissolved in water (5 mL). After 1 h methyl iodide (5.0 mL, 74 mmol) was added, and the reaction mixture was warmed to ambient temperature over 4 h and then partitioned between ether (100 mL) and water (50 mL). The organic phase was washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 4:1) provided (+)-**9** (246 mg, 83% yield) as a colorless oil: $[\alpha]_D^{23}$ +52.8° (*c* 3.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 3.83 (dq, J = 8.4, 6.0 Hz, 1 H), 3.66 (dd, J = 8.4, 6.1 Hz, 1 H), 3.61 (m, 1 H), 3.58 (dq, J = 8.3, 6.0 Hz, 1 H), 3.11 (s, 3 H), 3.05 (d, J = 2.3 Hz, 1 H), 1.90 (m, 1 H), 1.80 (m, 1 H), 1.76 (d, J = 0.9 Hz, 3 H), 1.72 (m, 1 H), 1.65 (m, 1 H), 1.58−1.41 (series of m, 3 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.8 MHz, C_6D_6) δ 152.5, 121.3, 107.7, 82.8, 81.7, 80.9, 80.7, 77.4, 70.7, 55.9, 40.1, 36.9, 31.5, 29.8, 19.0, 16.7, 15.6, 13.9; high-resolution mass spectrum (CI, NH_3) *m/z* 309.2065 [(M + H)$^+$; calcd for $C_{18}H_{29}O_4$, 309.2066]. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.09; H, 9.15. Found: C, 70.22; H, 9.53.

Alcohol (+)-25. A. From 15 and (+)-12. Via the procedure described above for the preparation of (+)-**16**, reaction of stannane **15** (2.14 g, 5.0 mmol, 17:1 *Z*:*E*) in THF (50 mL) with *n*-BuLi (1.25 M in hexanes, 4.0 mL, 5.0 mmol), addition to aldehyde (+)-**12** (0.76 g, 3.3 mmol) in THF (2 mL), workup, and flash chromatography (gradient elution, hexanes/ether, 50:1 → 4:1) gave (+)-**25** (685 mg, 56% yield) and (+)-**26** (131 mg, 10%) as colorless oils.

(+)-25: $[\alpha]_D^{23}$ +22.5° (*c* 5.08, $CHCl_3$); IR ($CHCl_3$) 3620−3300 (br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (t, J = 0.7 Hz, 1 H), 5.00 (d, J = 10.3 Hz, 1 H), 4.07 (m, 1 H), 3.95 (ddt, J = 8.5, 6.0, 6.0 Hz, 1 H), 3.67 (br s, 1 H), 3.65 (ddt, J = 8.5, 6.1, 6.1 Hz, 1 H), 1.84 (m, 1 H), 1.81 (m, 1 H), 1.79 (d, J = 1.3 Hz, 3 H), 1.71 (m, 1 H), 1.59 (m, 1 H), 1.54 (m, 1 H), 1.36 (ddd, J = 11.8, 11.8, 4.3 Hz, 1 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.23 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 155.9, 120.7, 104.9, 102.0, 98.5, 80.7, 77.3, 75.8, 72.6, 40.5, 36.3, 31.4, 29.1, 18.5, 17.5, 16.3, 15.1, 0.0; high-resolution mass spectrum (CI, NH_3) *m/z* 366.2221 [M$^+$; calcd for $C_{20}H_{34}O_4Si$, 366.2226].

(+)-26: $[\alpha]_D^{23}$ +39.1° (*c* 14.9, $CHCl_3$); IR ($CHCl_3$) 3620 (br), 3600−3300 (s), 2135 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (s, 1 H), 4.95 (dd, J = 3.9, 3.7 Hz, 1 H), 3.98 (m, 1 H), 3.91 (dq, J = 8.0, 6.1 Hz, 1 H), 3.62 (dq, J = 7.8, 6.2 Hz, 1 H), 2.83 (br s, 1 H), 1.87−1.82 (m, 2 H), 1.81 (s, 3 H), 1.72-1.67 (m, 2 H), 1.55−1.47 (series of m, 3 H), 1.36 (m, 1 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.1 Hz, 3 H), 0.89 (dd, J = 6.6, 0.5 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 154.4, 120.7, 105.3, 101.7, 98.6, 80.3, 77.1, 71.7, 69.3, 40.0, 36.1, 30.7, 29.3, 18.8, 18.0, 16.4, 15.0, −0.2; high-resolution mass spectrum (CI, NH_3) *m/z* 366.2222 [M$^+$; calcd for $C_{20}H_{34}O_4Si$, 366.2226].

(*E*)-Methyl Ether (+)-47. At 0 °C a solution of alcohol (+)-**16** (1.40 g, 3.82 mmol) and 15-crown-5 (0.84 g, 3.82 mmol) in THF (50 mL) was treated with sodium hydride (60% oil dispersion; 0.55 g, 22.9 mmol) portionwise, followed by dropwise addition of methyl iodide (2.9 mL, 45.8 mmol). After 2 h at 0 °C, the reaction mixture was warmed to ambient temperature, stirred for 2 h further, and poured onto a mixture of ice (100 g), saturated aqueous NH_4Cl (100 mL), and ether (150 mL). The organic phase was washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 4:1) furnished (+)-**47** (1.17 g, 81% yield) as a colorless oil: $[\alpha]_D^{23}$ +55.4° (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 5.74 (apparent t, J = 0.8 Hz, 1 H), 3.94 (qd, J = 8.1, 2.0 Hz, 1 H), 3.85 (m, 1 H), 3.75 (dd, J = 7.8, 6.0 Hz, 1 H), 3.50 (dq, J = 8.1, 6.1 Hz, 1 H), 2.95 (s, 3 H), 2.05 (ddd, J = 14.1, 8.7, 6.1 Hz, 1 H), 1.94 (d, J = 1.3 Hz, 3 H), 1.91 (m, 1 H), 1.61 (ddd, J = 12.1, 7.9, 4.1 Hz, 1 H), 1.50 (ddd, J = 16.9, 12.8, 4.2 Hz, 1 H), 1.43 (m, 1 H), 1.23 (m, 1 H), 1.15 (m, 1 H), 1.18 (d, J = 6.1 Hz, 3 H), 1.09 (d, J = 6.0 Hz, 3 H), 1.03 (d, J = 6.7 Hz, 3 H), 0.21 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 120.9, 108.8, 102.1, 98.3, 82.7, 80.5, 77.3, 70.7, 56.2, 39.4, 36.5, 31.4, 29.3, 18.5, 16.3, 15.2, 13.7, 0.0; high-resolution mass spectrum (CI, NH_3) *m/z* 380.2392 [M$^+$; calcd for $C_{21}H_{36}O_4Si$, 380.2383].

(*E*)-Dihydroxy Ester (−)-48. Ortho ester (+)-**47** (1.07 g, 2.80 mmol) was dissolved in a mixture of THF (16 mL), AcOH (16 mL), and water (2 mL) at ambient temperature. The reaction mixture was stirred for 36 h and then partitioned between ethyl acetate and water (100 mL each). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine (50 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ether) gave (−)-**48** (1.07 g, 94%

yield) as a colorless oil: $[\alpha]_D^{23}$ −45.8° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3600−3300 (s), 2135 (m), 1730 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (s, 1 H), 4.72 (dq, J = 6.4, 6.4 Hz, 1 H), 3.81 (m, 1 H), 3.75 (dd, J = 10.1, 3.1 Hz, 1 H), 3.71 (dq, J = 6.4, 6.4 Hz, 1 H), 3.62 (br s, 1 H), 3.20 (s, 3 H), 2.62 (br s, 1 H), 2.42 (m, 1 H), 1.82 (d, J = 1.1 Hz, 3 H), 1.73−1.61 (series of m, 3 H), 1.49−1.42 (series of m, 3 H), 1.18 (d, J = 6.4 Hz, 3 H), 1.16 (d, J = 6.4 Hz, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 0.19 (s, 9 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 176.1, 151.0, 107.8, 101.9, 99.2, 86.7, 74.9, 71.1, 70.0, 56.4, 40.4, 39.4, 34.2, 28.4, 19.1, 16.9, 16.4, 14.4, 0.0; high-resolution mass spectrum (CI, NH_3) *m/z* 398.2478 [M^+; calcd for $C_{21}H_{38}O_5Si$, 398.2488].

(*E*)-Bis(TBS ether) (−)-49. At ambient temperature a solution of diol (−)-**48** (1.05 g, 2.60 mmol) in DMF (25 mL) was treated with imidazole (1.15 g, 16.9 mmol). After 10 min TBSCl (1.20 g, 7.96 mmol) was introduced in one portion. The reaction mixture was stirred for 16 h further and then partitioned between ether and saturated aqueous $NaHCO_3$ (100 mL each). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine (100 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 95:5) provided (−)-**49** (1.48 g, 91% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ −6.8° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2135 (m), 1730 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J = 0.9 Hz, 1 H), 4.78 (dq, J = 8.1, 6.5 Hz, 1 H), 3.83 (dq, J = 7.7, 6.3 Hz, 1 H), 3.73 (m, 1 H), 3.59 (dd, J = 8.3, 4.4 Hz, 1 H), 3.13 (s, 3 H), 2.35 (m, 1 H), 1.80 (d, J = 1.2 Hz, 3 H), 1.71 (m, 2 H), 1.50 (m, 2 H), 1.41 (m, 2 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.13 (d, J = 6.4 Hz, 3 H), 1.07 (d, J = 6.3 Hz, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.19 (s, 9 H), 0.05 (s, 6 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 152.3, 107.3, 102.4, 98.4, 82.4, 73.2, 69.2, 68.8, 56.3, 41.2, 40.0, 34.2, 29.0, 25.9, 25.8, 18.2, 18.0 (2 C), 17.4, 14.4, 14.2, 0.1, −4.4, −4.6 (2 C), −4.8; high-resolution mass spectrum (FAB, NBA) *m/z* 611.3962 [$(M - CH_3)^+$; calcd for $C_{32}H_{63}O_5Si_3$, 611.3984].

(*E*)-Alcohol (−)-50. At −78 °C a solution of ester (−)-**49** (1.32 g, 2.11 mmol) in THF (100 mL) was treated dropwise with DIBAL (1.0 M in hexanes, 10.5 mL, 10.5 mmol), stirred for 30 min, and warmed to 0 °C. After 5 min, the reaction was carefully quenched at −78 °C with saturated aqueous Rochelle's salt (50 mL), warmed to 0 °C, and extracted with ethyl acetate (200 mL). The organic phase was washed with 1 N HCl and brine (50 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 4:1) furnished (−)-**50** (814 mg, 90% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ −7.0° (*c* 4.3, $CHCl_3$); IR ($CHCl_3$) 3660−3600 (br), 3580−3350 (br), 2140 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (s, 1 H), 3.71 (qd, J = 5.6, 5.6 Hz, 1 H), 3.44 (dd, J = 8.0, 4.7 Hz, 1 H), 3.42 (ddd, J = 39.3,10.5, 6.1 Hz, 2 H), 3.13 (s, 3 H), 1.79 (d, J = 1.1 Hz, 3 H), 1.74 (ddd, J = 13.0, 8.0, 5.1 Hz, 1 H), 1.67 (br s, 1 H), 1.60−1.50 (series of m, 3 H), 1.44-1.34 (m, 2 H), 1.13 (m, 1 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.18 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 107.3, 102.4, 98.4, 82.5, 69.7, 68.0, 56.2, 41.0, 35.7, 33.5, 28.2, 25.9, 18.1, 16.6, 14.4, 0.0, −4.4 (2 C); high-resolution mass spectrum (CI, NH_3) *m/z* 427.3050 [$(M + H)^+$; calcd for $C_{23}H_{47}O_3Si_2$, 427.3064].

(*E*)-Aldehyde (−)-51. At −78 °C a solution of oxalyl chloride (0.30 mL, 3.44 mmol) in dichloromethane (22 mL) was slowly treated with dimethyl sulfoxide (0.50 mL, 7.03 mmol) in dichloromethane (3 mL). The mixture was stirred for 15 min further, and a solution of alcohol (−)-**50** (714 mg, 1.73 mmol) in dichloromethane (3 mL) was then added at a moderate rate. After an additional 15 min, diisopropylethylamine (2.4 mL, 13.7 mmol) was introduced dropwise. The reaction mixture was warmed to 0 °C, stirred for 15 min, and partitioned between ether and water (50 mL each). The organic phase was washed with 1.0 N HCl, water, and brine (30 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (pentane/ether, 4:1) gave (−)-**51** (650 mg, 89% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ −24.9° (*c* 2.81, CCl_4); IR ($CHCl_3$) 1725 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.31 (d, J = 1.7 Hz, 1 H), 5.68 (d, J = 0.8 Hz, 1 H), 3.78 (qd, J = 4.9, 1.4 Hz, 1 H), 3.59 (dd, J = 8.6, 4.1 Hz, 1 H), 2.93 (s, 3 H), 1.92 (d, J = 1.2 Hz, 3 H), 1.87 (ddd, J = 8.4, 6.9, 1.6 Hz, 1 H), 1.84 (dd, J = 8.9, 4.9 Hz, 1 H), 1.58 (m, 1 H), 1.52 (m, 1 H), 1.43 (m, 1 H), 1.37 (m, 1 H), 1.23 (m, 1 H), 0.95 (s, 9 H), 0.80 (d, J = 7.0 Hz, 3 H), 0.22 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.2, 152.4, 108.0, 103.1, 98.8, 82.6, 69.6, 56.0, 46.2, 41.6, 33.9, 26.1, 18.2, 14.7, 13.6, 0.1, −4.3, −4.4; high-resolution mass spectrum (CI, NH_3) *m/z* 424.2847 [M^+; calcd for $C_{23}H_{44}O_3Si_2$, 424.2847].

(*E*)-Hydroxy Acid (−)-52. LiHMDS (1.0 M in THF, 7.8 mL, 7.8 mmol) was cooled to −78 °C, and a solution of *N*-acetylpipecolinic acid [(+)-**10** (E)] (669 mg, 3.91 mmol) in THF (10 mL), precooled to −78 °C, was added via a cannula. The resultant solution was stirred for 15 min, warmed to 0 °C, stirred for an additional 15 min, and recooled to −78 °C. A solution of aldehyde (−)-**51** (166 mg, 0.39 mmol) in THF (1 mL) was then added, and the reaction was stirred for 30 min further, warmed to 0 °C, and quenched with saturated aqueous NH_4Cl (5 mL). The mixture was partitioned between ethyl acetate and water (20 mL each), and the organic phase was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (dichloromethane/MeOH, 9:1) gave (−)-**52** (158 mg, 68% yield) as an amorphous pale yellow solid: (mp 62−66 °C); $[\alpha]_D^{23}$ −10.3° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3600−3200 (br), 2130 (w), 1720 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2:1 mixture of isomers, δ 5.49 (s, 1 H), 5.36 (m, 1 H), 3.95 (dq, J = 4.5, 3.7 Hz, 1 H), 3.71 (m, 2 H), 3.63 (m, 1 H), 3.24 (br t, J = 10.8 Hz, 1 H), 3.14 (s, 3 H), 2.29 (br d, J = 11.1 Hz, 1 H), 1.80 (d, J = 0.9 Hz, 3 H), 1.77−1.66 (complex series of m, 3 H), 1.63−1.34 (complex series of m, 10 H), 1.15 (m, 1 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.18 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); minor isomer, δ 4.53 (m, 2 H), 3.89 (m, 1 H), 3.75 (m, 1 H), 0.90 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer, δ 174.7, 173.7, 152.3, 107.4, 102.4, 98.4, 82.5, 71.5, 69.8, 56.2, 51.8, 43.5, 41.1, 38.2, 37.1, 34.3, 28.2, 26.3, 25.9, 25.1, 20.8, 18.1, 14.8, 14.4, 0.0, −4.3, −4.4; minor isomer, δ 175.4, 173.4, 152.3, 107.3, 102.4, 98.4, 82.5, 71.5, 69.7, 56.2, 51.8, 43.3, 41.1, 38.1, 37.1, 34.2, 28.2, 26.3, 25.9, 25.1, 20.8, 18.1, 15.4, 14.4, 0.0, −4.3, −4.4; high-resolution mass spectrum (FAB, NBA) *m/z* 618.3664 [(M + Na)$^+$; calcd for $C_{31}H_{57}NO_6Si_2Na$, 618.3622]. Anal. Calcd for $C_{31}H_{57}NO_6Si_2$: C, 62.48; H, 9.64. Found: C, 62.17; H, 9.62.

(*E*)-Methyl Ester (−)-53. At 0 °C a solution of carboxylic acid (−)-**52** (963 mg, 1.62 mmol) in ether (20 mL) was treated with a large excess of diazomethane in ether (60 mL). The reaction mixture was warmed to ambient temperature over 3 h, stirred for 16 h, and concentrated. Flash chromatography (hexanes/ether, 2:1) afforded (−)-**53** (863 mg, 87% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ −10.3° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 2120 (w), 1733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2:1 mixture of isomers, δ 5.50 (s, 1 H), 5.37 (d, J = 5.2 Hz, 1 H), 3.94−3.86 (m, 2 H), 3.72 (s, 3 H), 3.63 (m, 1 H), 3.25−3.18 (m, 1 H), 3.13 (s, 3 H), 2.50−2.41 (m, 1 H), 2.28−2.24 (m, 2 H), 1.81 (d, J = 1.1 Hz, 3 H), 1.77−1.69 (m, 3 H), 1.65−1.51 (complex series of m, 6 H), 1.50-1.32 (complex series of m, 4 H), 1.16 (m, 1 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.19 (s, 9 H), 0.03 (s, 6 H); minor isomer, δ 5.50 (s, 1 H), 4.56 (m, 2 H), 3.72 (s, 3 H), 3.14 (s, 3 H), 2.40−2.31 (m, 2 H), 1.81 (d, J = 1.1 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.19 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer, δ 173.3, 171.6, 152.4, 107.3, 102.4, 98.4, 82.5, 71.4, 69.7, 56.3, 52.3, 51.8, 43.4, 41.2, 38.2, 36.9, 34.3, 28.2, 26.5, 25.9, 25.2, 20.9, 18.1, 15.3, 14.5, 0.0, −4.3, −4.4; minor isomer, δ 173.0, 171.7, 152.4, 107.3, 102.4, 98.4, 82.5, 71.3, 69.7, 56.3, 52.3, 51.8, 43.3, 41.2, 38.0, 36.1, 33.6, 27.9 26.5, 25.9, 24.5, 20.8, 18.1, 15.3, 14.8, 0.0, −4.3, −4.4; high-resolution mass spectrum (FAB, NBA) *m/z* 632.3771 [(M + Na)$^+$; calcd for $C_{32}H_{59}NO_6Si_2Na$, 632.3779].

(*E*)-Tricarbonyl (−)-54. A solution of β-hydroxy amide (−)-**53** (420 mg, 0.685 mmol) in dichloromethane (20 mL) was treated with the Dess−Martin periodinane (1.66 g, 3.90 mmol) and pyridine (0.63 mL, 7.81 mmol) and stirred for 2 h at ambient temperature. Saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (10 mL each) were then added, and the biphasic mixture was stirred for 15 min and extracted with ether (30 mL). The organic phase was washed with brine (30 mL), saturated aqueous $CuSO_4$ (2 × 30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 9:1) furnished (−)-**54** (322 mg, 76% yield) as a clear, bright yellow oil: $[\alpha]_D^{23}$ −37.5° (*c* 2.05, $CHCl_3$); IR ($CHCl_3$) 2120 (w), 1740 (s), 1715 (s), 1640 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2:1 mixture of rotamers, δ 5.50 (s, 1 H), 5.24 (d, J = 5.3 Hz, 1 H), 3.77 (s, 3 H), 3.59 (dd, J = 8.6, 4.1 Hz, 1 H), 3.40 (m, 1 H), 3.39 (dq, J = 12.4, 9.2 Hz, 1 H), 3.21 (m, 1 H), 3.13 (s, 3 H), 2.31 (br d, J = 14.2 Hz, 1 H), 1.80 (s, 3 H), 1.78−1.65 (complex series of m, 5 H), 1.58−1.50 (m, 3 H), 1.49−1.39 (complex series of m, 4 H), 1.17 (d, J = 6.9 Hz, 3 H), 0.86 (s, 9

H), 0.19 (s, 9 H), 0.02 (s, 6 H); minor rotamer, δ 5.50 (s, 1 H), 4.43 (br d, J = 14.0 Hz, 1 H), 4.37 (d, J = 5.3 Hz, 1 H), 3.77 (s, 3 H), 3.63 (m, 1 H), 3.40 (m, 2 H), 3.13 (s, 3 H), 3.00 (m, 1 H), 2.25 (br d, J = 14.2 Hz, 1 H), 1.80 (s, 3 H), 1.16 (d, J = 6.9 Hz, 3 H), 0.86 (s, 9 H), 0.19 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer, δ 202.8, 185.2, 170.4, 165.6, 152.4, 107.2, 102.4, 98.4, 82.3, 69.1, 56.3, 52.6, 51.7, 44.1, 41.1, 40.2, 33.7, 27.0, 26.4, 25.9, 25.0, 20.9, 18.0, 15.1, 14.5, 0.0, −4.4, −4.5; minor rotamer, δ 152.4, 107.2, 102.4, 98.4, 82.3, 69.1, 56.3, 52.6, 51.7, 44.1, 41.1, 40.6, 39.7, 33.7, 27.0, 26.4, 25.9, 24.3, 20.8, 18.0, 14.8, 14.5, 0.0, −4.4, −4.5; high-resolution mass spectrum (FAB, NBA) *m/z* 644.3429 [(M + Na)$^+$; calcd for $C_{32}H_{55}NO_7Si_2Na$, 644.3415].

(*E*)-Hemiketal (+)-55. A solution of tricarbonyl TBS ether (−)-**54** (357 mg, 0.574 mmol) in 49% aqueous HF (0.5 mL) and acetonitrile (3.5 mL) was stirred for 4 h at ambient temperature. The reaction mixture was then partitioned between ether and brine (20 mL each), and the organic phase was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 8:1) provided (+)-**55** (200 mg, 80% yield) as a white amorphous solid: mp 111−114 °C; $[\alpha]_D^{23}$ +10.3° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3550−3310 (br), 3295 (m), 1740 (s), 1638 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 2:1 mixture of rotamers, δ 5.47 (m, 1 H), 5.28 (d, J = 5.4 Hz, 1 H), 4.31 (d, J = 1.4 Hz, 1 H), 3.86 (m, 1 H), 3.76 (s, 3 H), 3.65 (dd, J = 7.8, 6.4 Hz, 1 H), 3.24 (m, 1 H), 3.14 (s, 3 H), 3.10 (d, J = 2.0 Hz, 1 H), 2.33 (dd, J = 15.4, 1.8 Hz, 1 H), 2.10 (dq, J = 15.2, 6.6 Hz, 1 H), 1.81 (d, J = 1.0 Hz, 3 H), 1.78−1.30 (complex series of m, 11 H), 1.21 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H); minor rotamer, δ 5.53 (m, 1 H), 4.45 (m, 1 H), 4.35 (d, J = 1.3 Hz, 1 H), 3.77 (s, 3 H), 3.59 (dd, J = 7.2, 7.0 Hz, 1 H), 3.50 (br d, J = 15.3 Hz, 1 H), 3.15 (s, 3 H), 3.10 (s, 1 H), 2.98 (m, 1 H), 2.21−2.18 (m, 2 H), 1.80 (d, J = 0.7 Hz, 3 H), 1.78−1.30 (complex series of m, 11 H), 1.21 (m, 1 H), 0.90 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer, δ 195.1, 170.3, 166.6, 151.8, 107.6, 98.7, 82.4, 81.4, 80.6, 67.5, 56.2, 52.5, 51.4, 44.6, 39.4, 34.3, 31.2, 27.0, 26.5, 25.2, 21.0, 16.0, 13.7; minor rotamer, δ 195.9, 170.7, 165.9, 151.7, 107.7, 98.7, 82.3, 81.4, 80.6, 67.6, 56.4, 52.6, 51.4, 39.6, 39.1, 34.5, 31.2, 27.5, 26.9, 24.4, 20.9, 16.0, 13.6; high-resolution mass spectrum (CI, NH_3) *m/z* 436.2328 [(M + H)$^+$; calcd for $C_{23}H_{34}NO_7$, 436.2335].

(*E*)-TES Ketal (+)-56. At −78 °C a solution of hemiketal (+)-**55** (0.35 g, 0.80 mmol) in dichloromethane (12 mL) was treated with 2,6-lutidine (1.4 mL, 12 mmol) and triethylamine (0.56 mL, 4.0 mmol). After 5 min TESOTf (0.90 mL, 4.0 mmol) was added dropwise, and the reaction mixture was stirred for 5 h and then partitioned between ether and water (50 mL each). The organic phase was washed with 1.0 N HCl, water, and brine (25 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether, 2:1) gave (+)-**56** (0.44 g, 99% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ +16° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 1740 (s), 1645 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 2:1 mixture of rotamers, δ 5.60 (br s, 1 H), 5.32 (d, J = 4.6 Hz, 1 H), 4.61 (m, 1 H), 4.58 (m, 1 H), 3.97 (m, 1 H), 3.62−3.58 (m, 1 H), 3.24 (s, 3 H), 3.23 (m, 1 H), 2.95 (s, 3 H), 2.84 (br s, 1 H), 2.62 (m, 1 H), 2.05 (m, 1 H), 1.91 (m, 1 H), 1.88 (s, 3 H), 1.69 (ddd, J = 14.0, 6.9, 4.8 Hz, 1 H), 1.59 (dt, J = 12.4, 3.2 Hz, 1 H), 1.51−1.47 (m, 1 H), 1.41−1.31 (m, 3 H), 1.28−1.09 (m, 12 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.97−0.82 (m, 6 H); minor rotamer, δ 5.52 (br s, 1 H), 3.32 (s, 3 H), 2.89 (s, 3 H), 1.81 (s, 3 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) major rotamer, δ 197.5, 170.4, 167.1, 152.3, 106.5, 101.8, 82.0, 81.3, 80.5, 67.7, 56.1, 52.1, 51.4, 44.4, 40.1, 36.4, 30.9, 26.5, 26.4, 24.8, 21.1, 15.8, 14.2, 7.0, 6.5; minor rotamer, δ 197.3, 170.7, 166.2, 151.9, 106.9, 101.9, 82.3, 81.5, 80.3, 67.8, 56.0, 52.2, 40.5, 38.8, 36.4, 31.0, 27.4, 26.4, 24.3, 20.8, 15.8, 14.0, 6.4; high-resolution mass spectrum (FAB, NBA) *m/z* 572.3041 [(M + Na)$^+$; calcd for $C_{29}H_{47}NO_7SiNa$, 572.3020]. Anal. Calcd for $C_{29}H_{47}NO_7Si$: C, 63.36; H, 8.62; N, 2.55. Found: C, 63.37; H, 8.84; N, 2.46.

Dienylstannane (+)-67. A. From (+)-56. A solution of (*E*)-enyne (+)-**56** (303 mg, 0.55 mmol) in benzene (30 mL) was degassed five times via the freeze/thaw method (failure to employ the freeze/thaw degassing procedure resulted in the formation of ketone (+)-**69** in yields approaching 30%).[40] *n*-Bu_3SnH (1.7 mL, 5.5 mmol) was then added, and the flask was immersed in an oil bath preheated to 90 °C. After 5 min AIBN (11 mg, 0.060 mmol) was introduced in one portion, and the reaction mixture was stirred for an additional 1 h, cooled to ambient temperature, and concentrated. Flash chromatography (hexanes/ether, 3:1, containing 1% triethylamine) afforded (+)-**67** (254 mg, 55% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ +22° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 1740 (s), 1645 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 2:1 mixture of rotamers, δ 7.06 (dd, J = 18.6, 10.3 Hz, 1 H), 6.47 (d, J = 18.6 Hz, 1 H), 6.27 (d, J = 10.3 Hz, 1 H), 5.35 (d, J = 4.4 Hz, 1 H), 4.62 (m, 1 H), 4.05 (m, 1 H), 3.69 (m, 1 H), 3.27 (s, 3 H), 3.05 (s, 3 H), 2.65 (ddd, J = 12.0, 6.5, 3.9 Hz, 1 H), 2.19 (m, 1 H), 2.05 (ddd, J = 13.7, 7.4, 6.3 Hz, 1 H), 1.92 (br d, J = 11.8 Hz, 1 H), 1.77 (d, J = 0.7 Hz, 3 H), 1.76 (m, 1 H), 1.70−1.51 (m, 9 H), 1.49−1.29 (m, 8 H), 1.27−1.09 (m, 22 H), 1.01 (d, J = 6.4 Hz, 3 H), 0.98−0.87 (m, 12 H); minor rotamer, δ 6.50 (d, J = 18.6 Hz, 1 H), 6.24 (d, J = 10.3 Hz, 1 H), 4.68 (d, J = 5.2 Hz, 1 H), 3.60 (m, 1 H), 3.33 (s, 3 H), 3.01 (s, 3 H), 1.73 (d, J = 0.7 Hz, 3 H), 1.06 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) major rotamer, δ 198.2, 170.6, 167.4, 142.9, 136.5, 134.2, 131.2, 102.5, 83.9, 68.4, 55.8, 51.6, 44.6, 40.9, 36.8, 31.5, 29.5, 27.6, 27.0, 26.4, 25.0, 21.4, 16.4, 13.8, 11.6, 9.8, 7.5, 7.1; minor rotamer, δ 198.1, 170.8, 166.4, 142.7, 135.9, 134.8, 131.8, 102.6, 84.1, 68.3, 55.7, 51.8, 41.6, 39.0, 36.9, 31.6, 27.4, 26.9, 24.6, 21.1, 11.3, 7.1; high-resolution mass spectrum (FAB, NBA) *m/z* 864.4257 [(M + Na)$^+$; calcd for $C_{41}H_{75}NO_7SiSnNa$, 864.4233].

Dienylstannane (+)-67. B. From (−)-66. Via the procedure described above for conversion of (+)-**56** to (+)-**67**, treatment of (*Z*)-enyne (−)-**66** (0.37 g, 0.67 mmol) in benzene (30 mL) with *n*-Bu_3SnH (1.8 mL, 6.73 mmol) and AIBN (11 mg, 0.060 mmol) followed by workup and flash chromatography (hexanes/ether, 3:1, containing 1% triethylamine) afforded (+)-**67** (0.26 g, 46% yield) as a clear, colorless oil, identical to the material prepared from (+)-**56**.

Dienyl Iodide (+)-68. Via the procedure described above for the preparation of (+)-**35**, treatment of stannane (+)-**67** (136 mg, 0.16 mmol) in dichloromethane (5 mL) with iodine (41 mg, 0.16 mmol) in dichloromethane (3 mL) followed by workup and flash chromatography (hexanes/ether, 2:1) furnished (+)-**68** (107 mg, 97% yield) as a clear, colorless oil: $[\alpha]_D^{23}$ +25° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 1743 (s), 1648 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 2:1 mixture of rotamers, δ 7.19 (dd, J = 14.2, 11.1 Hz, 1 H), 6.06 (d, J = 14.2 Hz, 1 H), 5.83 (d, J = 11.1 Hz, 1 H), 5.34 (br d, J = 4.8 Hz, 1 H), 4.03 (m, 1 H), 3.65 (br d, J = 13.8 Hz, 1 H), 3.49 (dd, J = 8.5, 4.5 Hz, 1 H), 3.23 (s, 3 H), 2.96 (s, 3 H), 2.66 (m, 1 H), 2.09 (ddd, J = 14.0, 8.6, 5.1 Hz, 1 H), 1.89 (br d, J = 12.9 Hz, 1 H), 1.72−1.45 (m, 3 H), 1.41−1.04 (m, 8 H), 1.38 (d, J = 1.1 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.96−0.82 (m, 6 H); minor rotamer, δ 7.18 (dd, J = 14.2, 11.1 Hz, 1 H), 6.08 (d, J = 14.2 Hz, 1 H), 5.78 (d, J = 11.1 Hz, 1 H), 4.65 (br d, J = 5.3 Hz, 1 H), 4.61 (br d, J = 12.0 Hz, 1 H), 3.39 (dd, J = 8.1, 4.7 Hz, 1 H), 3.32 (s, 3 H), 2.92 (s, 3 H), 2.16 (br d, J = 13.6 Hz, 1 H), 1.95 (ddd, J = 13.7, 8.1, 5.3 Hz, 1 H), 1.32 (d, J = 1.1 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) major rotamer, δ 198.1, 170.6, 167.4, 141.5, 138.9, 127.0, 102.5, 83.3, 79.5, 68.3, 55.9, 51.6, 51.5, 44.5, 40.7, 36.8, 31.3, 27.0, 26.4, 24.9, 21.3, 16.3, 11.8, 7.4, 7.0; minor rotamer, δ 198.0, 170.7, 166.4, 141.2, 138.4, 127.5, 102.6, 83.5, 80.0, 68.2, 56.3, 55.8, 51.8, 41.1, 39.0, 36.9, 31.5, 27.9, 26.9, 24.6, 21.1, 11.6, 7.0; high-resolution mass spectrum (FAB, NBA) *m/z* 700.2130 [(M + Na)$^+$; calcd for $C_{29}H_{48}INO_7SiNa$, 700.2143]. Anal. Calcd for $C_{29}H_{48}INO_7Si$: C, 51.40; H, 7.14; N, 2.07. Found: C, 51.64; H, 7.28; N, 1.92.

Common DE Carboxylic Acid (+)-5. A solution of ester (+)-**68** (120 mg, 0.17 mmol) in pyridine (10 mL) was treated with LiI (470 mg, 3.52 mmol) in one portion, and the resultant solution was heated in an oil bath preheated to 130 °C. After 16 h the reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and saturated aqueous $CuSO_4$ (50 mL each). The organic phase was washed with aqueous $CuSO_4$ (30 mL), saturated aqueous $Na_2S_2O_3$ (2 × 30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, ethyl acetate → MeOH/ethyl acetate, 1:4) provided (+)-**5** (65 mg, 56% yield) as a white foam: $[\alpha]_D^{23}$ +28° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3015 (s), 2935 (s), 2880 (s), 2390 (m), 1732 (s), 1644 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 2:1 mixture of rotamers, δ 8.37 (br s, 1 H), 7.24 (dd, J = 14.2, 11.1 Hz, 1 H), 6.12 (d, J = 14.2 Hz, 1 H), 5.88 (d, J = 11.1 Hz, 1 H), 5.39 (d, J = 4.8 Hz, 1 H), 3.99 (m, 1 H), 3.62 (br d, J = 13.3 Hz, 1 H), 3.51 (dd, J = 8.1, 4.8 Hz, 1 H), 3.28 (m, 1 H), 2.99 (s, 3 H), 2.62 (m, 1 H), 2.07 (ddd, J = 14.0, 8.2, 5.3 Hz, 1 H), 1.99 (br d, J = 13.4 Hz, 1 H), 1.74−1.52 (m, 3 H), 1.44 (d, J = 1.0 Hz, 3 H), 1.42−1.05 (m, 7 H), 1.16−1.08 (m, 9 H), 1.04 (d, J = 6.5 Hz, 3 H), 0.95−0.78 (m, 6 H); minor rotamer, δ 7.19 (dd, J = 14.2, 11.1 Hz, 1 H), 6.10 (d,

J = 14.2 Hz, 1 H), 5.78 (d, J = 11.1 Hz, 1 H), 4.70 (d, J = 5.2 Hz, 1 H), 4.62 (br d, J = 11.7 Hz, 1 H), 3.40 (dd, J = 8.0, 4.9 Hz, 1 H), 2.93 (s, 3 H), 2.19 (br d, J = 13.5 Hz, 1 H), 1.33 (d, J = 1.0 Hz, 3 H), 1.01 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) major rotamer, δ 198.0, 175.4, 167.7, 141.4, 138.6, 127.2, 102.6, 83.5, 79.9, 68.2, 55.9, 51.6, 44.6, 40.6, 36.9, 31.3, 27.0, 26.3, 24.8, 21.3, 16.3, 11.9, 7.5, 7.1; minor rotamer, δ 198.1, 175.8, 166.5, 141.2, 138.3, 127.6, 102.6, 83.6, 80.1, 68.3, 55.8, 51.7, 41.1, 37.0, 31.5, 26.9, 24.6, 21.1, 16.4, 11.6, 7.5, 7.0; high-resolution mass spectrum (FAB, NBA) *m/z* 686.1971 [(M + Na)$^+$; calcd for $C_{28}H_{46}INO_7SiNa$, 686.1986].

Rapamycin ABCDE Iodo Stannane (−)-71. A solution of ABC alcohol (−)-**3** (4.9 mg, 0.0050 mmol) and DE carboxylic acid (+)-**5** (14 mg, 0.020 mmol) in dichloromethane (1 mL) was treated with a mixture of EDC (4 mg, 0.020 mmol), DMAP (4 mg, 0.030 mmol), and DMAP·HCl (3 mg, 0.020 mmol) in one portion at ambient temperature. The reaction mixture was stirred for 5 h and then partitioned between ether (20 mL) and water (10 mL). The organic phase was washed with 1 N HCl, water, and brine (10 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) furnished (−)-**71** (4.8 mg, 58% yield) as a viscous, colorless oil: $[\alpha]_D^{23}$ −32° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1730 (m), 1640 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 2:1 mixture of rotamers, δ 7.18 (dd, J = 14.1, 11.0 Hz, 1 H), 6.08 (d, J = 18.9 Hz, 1 H), 6.08 (d, J = 14.2 Hz, 1 H), 5.98 (dd, J = 18.9, 7.3 Hz, 1 H), 5.76 (d, J = 11.0 Hz, 1 H), 5.62 (dt, J = 9.8, 3.0, 1 H), 5.34 (m, 2 H), 4.71−4.65 (m, 1 H), 4.50 (d, J = 6.9 Hz, 1 H), 4.11 (m, 1 H), 4.01 (m, 1 H), 3.93 (d, J = 7.2 Hz, 1 H), 3.66−3.54 (m, 3 H), 3.40−3.32 (m, 2 H), 3.31 (s, 3 H), 3.25 (s, 3 H), 2.93−2.85 (m, 3 H), 2.92 (s, 3 H), 2.70 (d, J = 6.0 Hz, 1 H), 2.59 (dd, J = 8.9, 2.7 Hz, 1 H), 2.45 (m, 1 H), 2.31 (m, 1 H), 2.25 (m, 1 H), 2.15−1.83 (m, 5 H), 1.80 (d, J = 1.2 Hz, 3 H), 1.76−1.55 (m, 12 H), 1.52−1.27 (m, 15 H), 1.26−1.12 (m, 48 H), 1.11−0.74 (m, 30 H), 0.11 (s, 3 H), 0.04 (s, 3 H); minor rotamer, δ 7.24 (dd, J = 14.1, 11.0 Hz, 1 H), 6.13 (d, J = 14.2 Hz, 1 H), 5.92 (d, J = 11.0 Hz, 1 H), 5.58 (m, 1 H), 4.70 (br s, 1 H), 3.31 (s, 3 H), 3.03 (s, 3 H), 1.81 (d, J = 1.3 Hz, 3 H), 0.12 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) mixture of rotamers, δ 211.2, 211.1, 207.5, 206.8, 198.4, 198.2, 169.9, 167.4, 166.6, 154.5 (2 C), 141.6, 141.3, 139.1, 138.3, 138.1, 127.5, 127.4, 102.8, 102.5, 85.3 (2 C), 84.9, 84.8, 83.6, 83.3, 80.1, 79.5, 78.7, 78.5 (2 C), 75.8, 75.3 (2 C), 68.7, 68.4, 58.0, 57.1, 57.0, 56.9, 56.0, 55.9, 51.9, 47.0, 46.9, 44.5, 42.9, 42.8, 41.9, 41.2, 40.7, 40.2, 40.1, 39.7, 39.3, 38.9, 37.0, 36.9, 36.2, 36.0, 34.6, 34.5, 34.1, 33.5 (2 C), 33.3, 31.6, 31.5, 30.2, 29.6, 27.9, 27.7, 26.1, 24.9, 23.1, 21.5, 21.1, 18.5, 18.4, 16.5, 16.4, 16.2, 15.6, 15.5, 15.2, 14.3, 14.0, 13.1, 12.4, 11.5, 9.9, 7.6, 7.5, 7.2, 7.1, −4.3, −4.7; high-resolution mass spectrum (FAB, NBA) *m/z* 1738.8625 [(M + Na)$^+$; calcd for $C_{84}H_{154}INO_{13}Si_3SnNa$, 1738.8693].

10-*O*-TES-28-*O*-TBS-40-*O*-TIPS-rapamycin (−)-46. B. From (−)-71. A solution of iodo stannane (−)-**71** (8.6 mg, 0.0050 mmol) in THF and DMF (1:1, 0.6 mL) was treated with diisopropylethylamine (1 μL) and [(2-furyl)$_3$P]$_2$PdCl$_2$ (0.6 mg, 0.001 mmol)] at ambient temperature. The reaction mixture was stirred for 7 h and then partitioned between ether and water (10 mL each). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) furnished (−)-**46** (4.8 mg, 74% yield) as a colorless oil: $[\alpha]_D^{23}$ −86° (*c* 0.04, $CHCl_3$); IR ($CHCl_3$) 1730 (s), 1640 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 10:1 mixture of rotamers, δ 6.31 (dd, J = 14.8, 11.0 Hz, 1 H), 6.17 (dd, J = 14.8, 10.6 Hz, 1 H), 6.06 (d, J = 11.0 Hz, 1 H), 5.92 (dd, J = 15.0, 10.6 Hz, 1 H), 5.55 (d, J = 10.2 Hz, 1 H), 5.47 (d, J = 4.6 Hz, 1 H), 5.25 (dd, J = 15.0, 9.6 Hz, 1 H), 4.39 (d, J = 3.0 Hz, 1 H), 4.36 (d, J = 9.7 Hz, 1 H), 3.88 (d, J = 4.0 Hz, 1 H), 3.74−3.68 (m, 2 H), 3.62 (d, J = 10.0 Hz, 1 H), 3.52 (apparent t, J = 12.3 Hz, 1 H), 3.34 (s, 3 H), 3.20 (dd, J = 10.2, 6.6 Hz, 1 H), 3.17 (s, 3 H), 3.02 (s, 3 H), 2.93 (ddd, J =12.7, 8.3, 4.5 Hz, 1 H), 2.78 (ddd, J = 12.8, 7.5, 4.3 Hz, 1 H), 2.68 (dd, J = 17.7, 3.9 Hz, 1 H), 2.55 (dd, J = 17.7, 8.9 Hz, 1 H), 2.54 (m, 1 H), 2.35 (dt, J = 13.9, 3.4 Hz, 1 H), 2.13−2.02 (m, 2 H), 1.99 (dq, J = 12.9, 3.0 Hz, 1 H), 1.88 (d, J = 10.1 Hz, 1 H), 1.81 (dd, J = 12.9, 3.0 Hz, 1 H), 1.76 (s, 3 H), 1.69−1.59 (m, 2 H), 1.65 (s, 3 H), 1.50−1.26 (m, 6 H), 1.24−1.15 (series of m, 9 H), 1.20 (s, 21 H), 1.09 (d, J = 6.7 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.02 (s, 9 H), 0.99−0.84 (series of m, 27 H), 0.25 (s, 3 H), 0.11 (s, 3 H); minor rotamer, δ 3.09 (s, 3 H), 3.05 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) mixture of rotamers, δ 208.7, 206.1, 198.2, 170.0, 167.4, 139.5 (2 C),136.4, 132.5, 127.4, 127.2, 102.6, 87.1, 84.9, 83.6, 78.8, 75.9, 74.4, 68.1, 57.8, 57.3, 56.0, 51.8, 46.2, 44.3, 41.9, 41.4, 40.7, 40.6, 38.9, 37.2, 36.0, 35.9, 34.6, 34.5, 33.4, 32.2, 31.9, 30.7, 30.2, 27.1, 27.0, 26.1, 25.0, 22.2, 21.3, 18.5, 18.4, 16.4, 16.3, 16.0, 14.5, 14.0, 13.1, 11.1, 7.5, 7.0, −4.3, −4.5; high-resolution mass spectrum (FAB, NBA) *m/z* 1320.8505 [(M + Na)$^+$; calcd for $C_{72}H_{127}NO_{13}Si_3Na$, 1320.8513].

10-*O*-TES-28-*O*-TBS-40-*O*-TIPS-27-demethoxyrapamycin [(−)-73]. At ambient temperature a solution of iodo stannane (−)-**72** (9 mg, 5 μmol) in THF and DMF (3:1, 2 mL) was treated with an aliquot (1 mL) of a Pd catalyst stock solution, the latter freshly prepared by addition of DIPEA (5 μL) to a solution of [(2-furyl)$_3$P]$_2$PdCl$_2$ (3 mg, 4 μmol) in DMF (5 mL). The reaction mixture was stirred for 5 h and then partitioned between ether and water (20 mL each). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (−)-**73** (5.0 mg, 74% yield) as a colorless oil: $[\alpha]_D^{23}$ −77° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) 1740 (m), 1644 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 4:1 mixture of rotamers, major rotamer, δ 6.26 (dd, J = 14.8, 11.0 Hz, 1 H), 6.08 (dd, J = 14.8, 10.6 Hz, 1 H), 5.91 (d, J = 11.0 Hz, 1 H), 5.85 (dd, J = 14.9, 10.6 Hz, 1 H), 5.55 (apparent q, J = 5.0 Hz, 1 H), 5.43 (d, J = 10.8 Hz, 1 H), 5.40 (d, J = 5.1 Hz, 1 H), 5.33 (dd, J = 14.9, 9.8 Hz, 1 H), 4.71 (d, J = 8.5 Hz, 1 H), 4.38 (m, 1 H), 3.75 (m, 1 H), 3.68 (ddd, J = 11.0, 8.3, 4.7 Hz, 1 H), 3.51 (dd, J = 11.4, 1.6 Hz, 1 H), 3.36−3.23 (m, 2 H), 3.32 (s, 3 H), 2.99 (s, 3 H), 2.91 (ddd, J = 11.0, 8.1, 4.5 Hz, 1 H), 2.72−2.66 (m, 3 H), 2.34−1.50 (m, 12 H), 1.71 (s, 3 H), 1.62 (s, 3 H), 1.46−1.08 (m, 44 H), 1.04−0.72 (m, 32 H), 0.19 (s, 3 H), 0.09 (s, 3 H); minor rotamer, δ 3.31 (s, 3 H), 3.08 (s, 3 H), 1.74 (s, 3 H), 1.65 (s, 3 H), 0.22 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) mixture of rotamers, δ 209.6, 205.9, 197.8, 169.9, 167.5, 141.6, 141.1, 138.1, 133.4, 127.1, 124.0, 102.5, 84.8, 83.8, 75.8, 74.3, 72.3, 68.1, 57.1, 55.8, 52.1, 51.1, 46.5, 46.4, 44.3, 42.0, 41.2, 40.1, 39.9, 39.3, 37.2, 37.1, 35.9, 34.5, 34.1, 33.4, 31.9, 31.1, 30.1, 27.4, 26.7, 26.0, 24.9, 22.1, 21.2, 18.6, 18.4, 18.3, 17.8, 16.6, 16.4, 16.0, 15.6, 13.8, 13.0, 10.8, 7.5, 7.4, 7.1, 7.0, −4.2, −4.3, −4.6, −4.7; high-resolution mass spectrum (FAB, NBA) *m/z* 1290.8451 [(M + Na)$^+$; calcd for $C_{71}H_{125}NO_{12}Si_3Na$, 1290.8407].

Rapamycin [(−)-1] via Hemiketal (−)-41. At 0 °C a solution of synthetic tris(silyl ether) (−)-**46** (7.5 mg, 6.0 μmol) in THF (1 mL) was treated with an aliquot (5 drops) of a solution prepared by addition of glacial AcOH (3 drops) to TBAF (1.0 M in THF, 0.5 mL). The reaction mixture was stirred for 1 h and then partitioned between ether and water (10 mL each). The organic phase was washed with water and brine (10 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) gave (−)-**41** (6.0 mg, 88% yield) as a colorless oil: $[\alpha]_D^{23}$ −83° (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3420 (br), 1720 (s), 1625 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 4:1 mixture of rotamers, δ 6.45 (dd, J = 12.0, 9.5 Hz, 2 H), 6.29 (d, J = 9.7 Hz, 1 H), 6.06 (dd, J = 15.0, 9.7 Hz, 1 H), 5.47 (dd, J = 15.0, 8.5 Hz, 1 H), 5.45−5.44 (m, 2 H), 5.40 (dt, J = 7.3, 4.4 Hz, 1 H), 4.90 (s, 1 H), 4.42 (d, J = 5.5 Hz, 1 H), 4.09 (m, 1 H), 3.89 (apparent t, J = 7.8 Hz, 1 H), 3.83 (d, J = 5.6 Hz, 1 H), 3.69−3.62 (m, 2 H), 3.43 (dd, J = 13.3, 3.6 Hz, 1 H), 3.38 (dd, J = 10.3, 6.7 Hz, 1 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.09 (s, 3 H), 2.89 (ddd, J = 11.0, 8.3, 4.4 Hz, 1 H), 2.77 (dd, J = 16.3, 7.4 Hz, 1 H), 2.71 (m, 1 H), 2.63 (dd, J = 16.3, 4.5 Hz, 1 H), 2.23−2.07 (m, 5 H), 1.99−1.95 (m, 2 H), 1.77 (d, J = 0.8 Hz, 3 H), 1.71 (s, 3 H), 1.70−1.44 (m, 6 H), 1.41−1.21 (m, 8 H), 1.22−1.20 (m, 24 H), 1.11 (apparent t, J = 6.8 Hz, 6 H), 1.06−1.01 (m, 3 H), 0.96 (s, 9 H), 0.95 (overlapped d, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.79 (q, J = 12.2 Hz, 1 H), 0.17 (s, 3 H), 0.06 (s, 3 H); minor rotamer, δ 6.11 (d, J = 10.2 Hz, 1 H), 4.39 (d, J = 7.4 Hz, 1 H), 3.17 (s, 3 H), 3.12 (s, 3 H), 0.13 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) mixture of rotamers, δ 209.2, 207.3, 194.1, 169.8, 167.0, 139.8, 137.9, 136.8, 133.5, 130.8, 99.2, 85.7, 84.8, 84.4, 79.2, 76.5, 75.8, 75.7, 67.4, 58.6, 57.1, 55.8, 51.8, 47.0, 44.3, 42.1, 42.0, 40.7, 38.7, 36.0, 35.5, 34.7, 34.5, 34.1, 33.4, 32.0, 31.6, 27.7, 26.9, 26.1, 25.2, 21.8, 20.7, 18.5, 16.5, 16.2, 15.6, 14.6, 13.1, 13.0, 10.5, −4.5, −4.7; high-resolution mass spectrum (FAB, NBA) *m/z* 1206.7635 [(M + Na)$^+$; calcd for $C_{66}H_{113}NO_{13}Si_2Na$, 1206.7648].

At 0 °C a solution of synthetic hemiketal (−)-**41** (5.1 mg, 4.3 μmol) in THF (0.5 mL) was treated with pyridine (0.5 mL) followed by HF·pyridine (0.5 mL). The reaction mixture was warmed to ambient temperature, stirred for 48 h, and then partitioned between ether and

water (10 mL each). The organic phase was washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, water, and brine (5 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1, then 1:3) provided synthetic (−)-**1** (2.7 mg, 69% yield) as a clear oil. Recrystallization (40% acetone/hexanes) gave (−)-**1** as a white solid: mp 183−184 °C; $[\alpha]_D^{23}$ −65° (*c* 0.21, MeOH); IR ($CHCl_3$) 3570 (w), 3460 (br), 3000 (s), 2970 (s), 2930 (s), 2870 (m), 1750 (s), 1720 (s), 1625 (s), 1455 (s), 1380 (m), 1330 (m), 1230 (s), 1190 (s), 1090 (s), 990 (s), 910 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4:1 mixture of rotamers, δ 6.38 (dd, J = 14.8, 10.5 Hz, 1 H), 6.31 (dd, J = 14.8, 10.1 Hz, 1 H), 6.14 (dd, J = 15.1, 10.1 Hz, 1 H), 5.95 (d, J = 10.5 Hz, 1 H), 5.54 (dd, J = 15.1, 8.8 Hz, 1 H), 5.41 (d, J = 9.9 Hz, 1 H), 5.28 (d, J = 4.9 Hz, 1 H), 5.17 (dd, J = 10.1, 6.0 Hz, 1 H), 4.81 (s, 1 H), 4.17 (d, J = 6.1 Hz, 1 H), 3.85 (m, 1 H), 3.70 (d, J = 6.1 Hz, 1 H), 3.66 (apparent t, J = 6.8 Hz, 1 H), 3.57 (d, J = 13.4 Hz, 1 H), 3.47−3.31 (m, 3 H), 3.40 (s, 3 H), 3.34 (s, 3 H), 3.14 (s, 3 H), 2.94 (ddd, J = 11.2, 8.7, 4.3 Hz, 1 H), 2.79−2.71 (m, 1 H), 2.74 (dd, J = 16.9, 5.9 Hz, 1 H), 2.59 (dd, J = 16.9, 6.3 Hz, 1 H), 2.36−2.30 (m, 2 H), 2.10 (m, 1 H), 2.01−1.96 (m, 3 H), 1.87−1.63 (m, 5 H), 1.74 (d, J = 1.0 Hz, 3 H), 1.65 (s, 3 H), 1.62−1.52 (m, 6 H), 1.50−1.31 (m, 5 H), 1.26−1.10 (m, 4 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.05 (d, J = 6.6 Hz, 3 H), 1.00 (m, 1 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.67 (q, J = 12.0 Hz, 1 H); minor rotamer, δ 6.23 (dd, J = 14.8, 10.1 Hz, 1 H), 5.89 (d, J = 10.5 Hz, 1 H), 5.47 (dd, J = 12.8, 9.5 Hz, 1 H), 5.11 (m, 1 H), 4.43 (d, J = 11.0 Hz, 1 H), 4.28 (d, J = 4.7 Hz, 1 H), 4.21 (d, J = 6.4 Hz, 1 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 1.74 (s, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 1 H); ^1H NMR (500 MHz, C_6D_6) 4:1 mixture of rotamers, δ 6.51 (dd, J = 14.9, 10.7 Hz, 1 H), 6.38 (dd, J = 14.9, 10.9 Hz, 1 H), 6.19 (d, J = 9.8 Hz, 1 H), 6.06 (dd, J = 15.2, 10.5 Hz, 1 H), 5.54 (dd, J = 15.2, 9.3 Hz, 1 H), 5.47 (d, J = 7.7 Hz, 2 H), 5.41 (m, 1 H), 5.17 (s, 1 H), 4.21 (d, J = 7.0 Hz, 1 H), 4.06 (m, 1 H), 3.86 (dd, J = 8.9, 6.4 Hz, 1 H), 3.60 (m, 1 H), 3.56 (d, J = 2.1 Hz, 1 H), 3.49−3.44 (m, 1 H), 3.41 (d, J = 6.7 Hz, 1 H), 3.19 (s, 3 H), 3.13 (s, 6 H), 3.12 (m, 1 H), 2.84−2.81 (m, 2 H), 2.75 (dd, J = 17.1, 6.7 Hz, 1 H), 2.62 (dd, J = 17.1, 5.8 Hz, 1 H), 2.47 (s, 1 H), 2.16−1.95 (m, 9 H), 1.71 (m, 1 H), 1.70 (d, J = 0.9 Hz, 3 H), 1.66−1.63 (m, 2 H), 1.60 (d, J = 1.2 Hz, 3 H), 1.56−1.52 (m, 2 H), 1.49−1.17 (m, 12 H), 1.16 (d, J = 6.6 Hz, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.67 (q, J = 11.8 Hz, 1 H); minor rotamer, δ 3.15 (s, 3 H), 3.14 (s, 3 H), 1.60 (d, J = 1.3 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer, δ 215.8, 208.2, 192.4, 169.2, 166.8, 140.3, 136.1, 135.5, 133.7, 130.2, 129.7, 126.9, 126.4, 98.5, 84.9, 84.4, 75.7, 74.0, 67.2, 59.5, 56.6, 55.9, 51.3, 46.6, 44.2, 41.4, 40.7, 40.2, 38.9, 38.4, 35.2, 34.2, 33.7, 33.2, 33.1, 31.7, 31.3, 27.3, 27.0, 25.3, 21.6, 20.6, 16.0, 15.8, 13.9, 13.0, 10.2; minor rotamer, δ 207.7, 170.0, 140.9, 133.5, 130.0, 129.4, 98.8, 86.4, 84.5, 75.8, 67.9, 59.4, 55.9, 46.1, 41.1, 40.9, 40.5, 38.5, 35.7, 34.6, 34.0, 32.9, 31.8, 31.1, 24.3, 21.8, 20.5, 16.3, 15.8, 15.0, 12.9, 10.3; ^{13}C NMR (125 MHz, C_6D_6) major rotamer, δ 215.5, 207.4, 192.8, 169.5, 167.5, 140.9, 137.0, 135.8, 134.4, 130.5, 130.2, 126.7, 99.1, 85.6, 84.9, 84.8, 77.8, 76.2, 74.3, 67.4, 59.6, 56.3, 55.8, 51.8, 46.7, 44.4, 41.3, 41.1, 40.5, 39.5, 38.8, 36.0, 34.8, 34.3, 33.8, 33.4, 32.0, 31.9, 31.8, 27.7, 26.9, 25.3, 21.9, 20.7, 16.6, 16.4, 16.1, 14.6, 12.7, 10.4; minor rotamer, δ 170.2, 141.3, 133.8, 99.3, 86.8, 77.7, 68.2, 59.2, 56.6, 56.4, 55.9, 46.2, 41.7, 40.8, 39.2, 39.0, 36.3, 35.1, 34.7, 33.5, 32.2, 31.4, 28.4, 27.3, 24.4, 22.0, 16.5, 15.5, 15.3, 12.5, 10.5; high-resolution mass spectrum (FAB, NBA) *m/z* 936.5463 [(M + Na)$^+$; calcd for $C_{51}H_{79}NO_{13}Na$, 936.5448].

27-Demethoxyrapamycin [(−)-2] via Hemiketal 74. At 0 °C a solution of tris(silyl ether) (−)-**73** (8.0 mg, 6.3 μmol) in THF (5 mL) was treated with an aliquot (2 drops) of a solution prepared by addition of glacial AcOH (3 drops) to TBAF (1.0 M in THF, 0.5 mL). After 10 min the reaction mixture was quenched with aqueous $NaHCO_3$ (5 mL) and partitioned between ether and water (10 mL each). The organic phase was washed with water and brine (10 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) furnished a 3:1 mixture of hemiketal **74** and the presumed C(9) oxepane hemiketal isomer **75** (6 mg).

A portion of the hemiketal mixture (3 mg, 2.6 μmol) was dissolved in THF (0.5 mL). The solution was cooled to 0 °C and treated with pyridine (0.2 mL) followed by dropwise addition of HF·pyridine (0.2 mL). The reaction mixture was warmed to ambient temperature, stirred for 3 h, and then partitioned between ether and water (10 mL each). The organic phase was washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and brine (10 mL each), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (gradient elution, hexanes/ethyl acetate, 1:1 → 0:1) followed by radial chromatography (1-mm layer, ether/ethyl acetate, 3:1) provided synthetic (−)-**2** (1.1 mg, 42% overall yield, 2 steps) as a colorless oil: $[\alpha]_D^{23}$ −148° (*c* 0.02, C_6H_6); IR ($CHCl_3$) 3685 (w), 3020 (s), 2935 (m), 2400 (m), 1728 (m), 1645 (m), 1525 (m), 1460 (m), 1230 (s), 1205 (s), 930 (m), 720 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) 4:1 mixture of rotamers, δ 6.31 (dd, J = 14.8, 10.9 Hz, 1 H), 6.20 (dd, J = 14.8, 10.4 Hz, 1 H), 6.05 (br d, J = 10.9 Hz, 1 H), 5.87 (dd, J = 15.0, 10.4 Hz, 1 H), 5.56 (d, J = 9.6 Hz, 1 H), 5.45 (m, 1 H), 5.35 (br d, J = 5.1 Hz, 1 H), 5.31 (dd, J = 15.0, 9.3 Hz, 1 H), 4.43 (br s, 1 H), 4.37 (m, 1 H), 3.71 (dd, J = 9.0, 5.0 Hz, 1 H), 3.57 (br d, J = 14.5 Hz, 1 H), 3.41 (ddd, J = 11.2, 8.6, 4.6 Hz, 1 H), 3.31 (d, J = 3.9 Hz, 1 H), 3.24 (m, 1 H), 3.13 (s, 3 H), 3.04 (s, 3 H), 2.81 (ddd, J = 11.2, 8.6, 4.2 Hz, 1 H), 2.69 (dd, J = 16.7, 3.9 Hz, 1 H), 2.69 (d, J = 5.5 Hz, 1 H), 2.58 (dd, J = 16.7, 8.0 Hz, 1 H), 2.47 (dd, J = 17.4, 9.2 Hz, 1 H), 2.39 (m, 1 H), 2.32 (dd, J = 17.4, 2.8 Hz, 1 H), 2.23−1.95 (m, 6 H), 1.91−1.48 (series of m, 8 H), 1.72 (d, J = 1.0 Hz, 3 H), 1.64 (d, J = 1.2 Hz, 3 H), 1.44−1.04 (series of m, 12 H), 1.19 (d, J = 6.8 Hz, 3 H), 1.15 (d, J = 6.6 Hz, 3 H), 0.95 (m, 1 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.88 (d, J = 6.1 Hz, 3 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.66 (apparent q, J = 11.6 Hz, 1 H); minor rotamer, δ 3.15 (s, 3 H), 3.12 (s, 3 H), 1.71 (d, J = 1.2 Hz, 3 H), 1.69 (d, J = 1.0 Hz, 3 H), 1.15 (d, J = 5.1 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) mixture of rotamers, δ 214.6, 207.0, 195.5, 169.7, 166.9, 141.0, 140.1, 137.3, 133.6, 124.5, 99.3, 84.8, 84.1, 75.2, 74.2, 72.9, 72.2, 68.0, 67.9, 56.2, 55.7, 52.1, 47.7, 46.6, 46.0, 44.4, 41.7, 40.6, 40.4, 38.6, 35.1, 34.5, 34.0, 33.6, 31.8, 31.7, 31.4, 27.5, 26.5, 25.1, 21.9, 20.9, 17.8, 16.5, 16.2, 15.7, 12.8, 10.6; UV (MeOH) λ_{max} 288.4, 277.6, 270.0 nm; high-resolution mass spectrum (FAB, NBA) *m/z* 906.5361 [(M + Na)$^+$; calcd for $C_{50}H_{77}NO_{12}Na$, 906.5343].

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Supporting Information Available: Experimental procedures and characterization data for **18**, **20**−**24**, **27**−**29**, **31**−**46**, **57**−**66**, **69**, **70**, and **72** and X-ray data for **20** (31 pages). See any current masthead page for ordering and Internet access instructions.

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