Total Synthesis of the Ansamycin Antibiotic (+)-Thiazinotrienomycin E

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The first total synthesis of (+)-thiazinotrienomycin E (**1**), member of a novel class of cytotoxic ansamycin antibiotics, has been achieved. Key features of the synthetic strategy include (a) the efficient construction of sulfone **7** incorporating TBS protection of the aniline, (b) an improved synthesis of allyl chloride (−)-**6**, the advanced intermediate employed in our trienomycins A and F total syntheses, (c) application of the Kocienski modified Julia protocol to elaborate the *E*,*E*,*E*-triene subunit in a stereo-controlled fashion, (d) an efficient union of sulfone **7** with advanced iodide **62**, and (e) Mukaiyama macrolactamization to access the thiazinotrienomycin macrocyclic ring.

In 1995, Hosokawa and co-workers reported the isolation and planar structures of the (+)-thiazinotrienomycins (A−E, Figure 1),[1] novel ansamycin antibiotics produced by *Streptomyces* sp. MJ672-m3, displaying significant in vitro cytotoxicity against human cancer cell lines derived from the cervix, stomach, colon, and breast.[1,2] Our interest in the chemistry and biology of the ansamycin antibiotics, particularly the structurally similar trienomycins,[3] led us to consider the synthesis of thiazinotrienomycin E. As a prelude to this venture, we, in collaboration with Hosokawa and co-workers,[4] assigned the complete relative and absolute stereochemistries of (+)-thiazinotrienomycin E (**1**) exploiting both degradation and chemical correlation. In this, a full account, we describe the first total synthesis of (+)-thiazinotrienomycin E.[5] We anticipate that our synthetic strategy will not only provide access to other members of the thiazinotrienomycin family but also to potentially bioactive analogues.

Synthetic Analysis. From the retrosynthetic perspective, we envisioned installation of the C(29−38) side chain late in the synthesis (Scheme 1), thereby permitting construction of thiazinotrienomycins C, D, and E from a common advanced intermediate (e.g., **2**). A similar tactic was employed to good advantage in our trienomycin syntheses. Further disconnections of **2** led to aniline **3**, acetylenic acid **4**, and phosphonate **5**. Assembly of the requisite macrocyclic lactam would entail coupling of **3** with **4** to furnish the amide, followed by Horner−Emmons union with **5** and macrocyclization exploiting Stille cross-coupling reaction. Alternatively, the last two operations could be reversed. Advanced aniline **3** in turn was envisioned to derive via alkylation of allyl chloride (−)-**6** with sulfone **7**, the former prepared during our earlier trienomycin syntheses.[3]

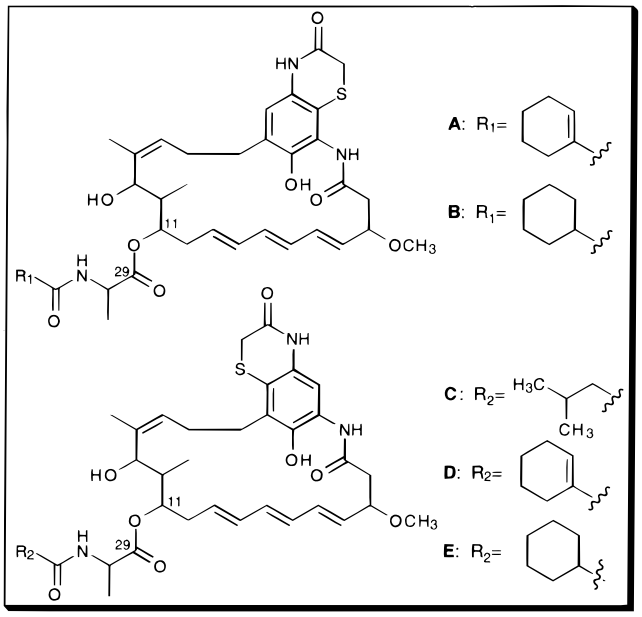

Figure 1. Planar structures of the (+)-thiazinotrienomycins A−E.

Allyl Chloride (−)-6: An Improved Synthesis. We are pleased to report here a significant improvement in the construction of allyl chloride (−)-**6** (Scheme 2), begining with known homoallyl alcohol (+)-**8**,[6] prepared in three steps from 3-buten-1-ol. Protection as the tri-

(1) Hosokawa, N.; Naganawa, H.; Inuma, H.; Hamada, M.; Takeuchi, T.; Kanbe, T.; Hori, M. *J. Antibiot.* **1995**, *48*, 471−478.

(2) Hosokawa, N.; Yamamoto, S.; Uehara, Y.; Hori, M.; Tsuchiya, K. S. *J. Antibiot.* **1999**, *52*, 485−490. Hosokawa, N.; Inuma, H.; Takeuchi, T.; Sato, S.; Yamori, T.; Tsuchiya, K. S.; Hori, M. *J. Antibiot.* **2000**, *53*, 306−308.

(3) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Komiyama, K.; Ōmura, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308−8315. Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316−8328. Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777−10778. Smith, A. B., III; Wood, J. L.; Gould, A. E.; Ōmura, S.; Komiyama, K. *Tetrahedron Lett.* **1991**, *32*, 1627−1630. Smith, A. B., III; Wood, J. L.; Ōmura, S. *Tetrahedron Lett.* **1991**, *32*, 841−842. Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Funayama, S.; Ōmura, S. *J. Am. Chem. Soc.* **1990**, *112*, 7425−7426. For other synthetic approaches to the trienomycins and related mycotrienins, see: Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4123−4134. Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965−2968. Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541−8560. Schoning, K. U.; Hayashi, R. K.; Powell, D. R.; Kirschning, A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 817−820. Schoning, K. U.; Wittenberg, R.; Kirschning, A. *Synlett* **1999**, 1624−1626.

(4) Smith, A. B., III; Barbosa, J.; Hosokawa, N.; Naganawa, H.; Takeuchi, T. *Tetrahedron Lett.* **1998**, *39*, 2891−2894.

(5) Preliminary communication: Smith, A. B., III; Wan, Z. *Org. Lett.* **1999**, *1*, 1491−1494.

(6) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318−333.

10.1021/jo991958j CCC: $19.00
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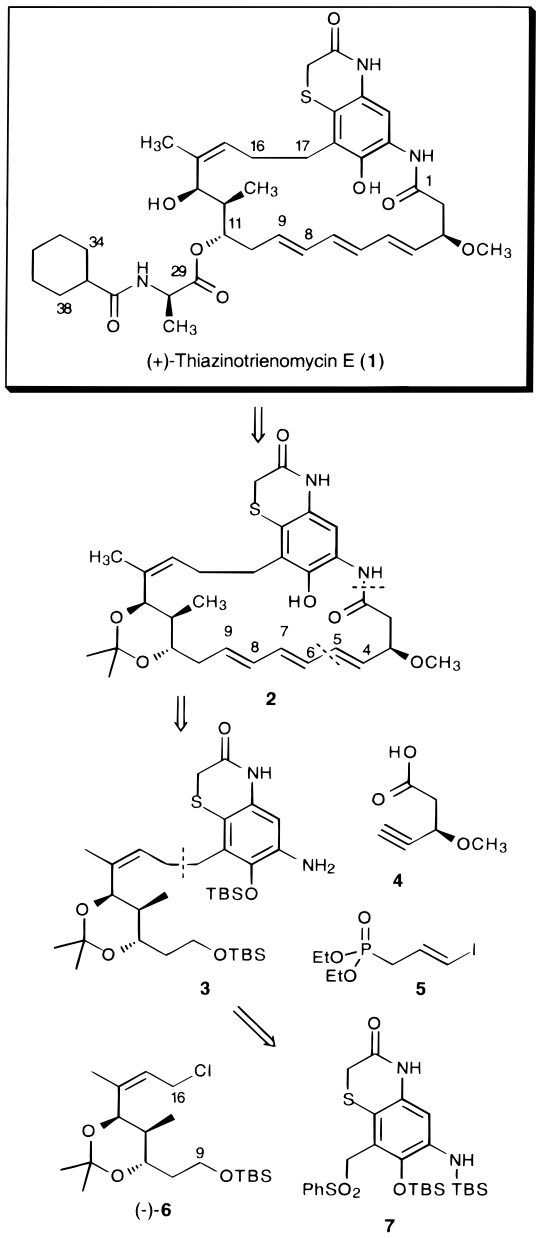
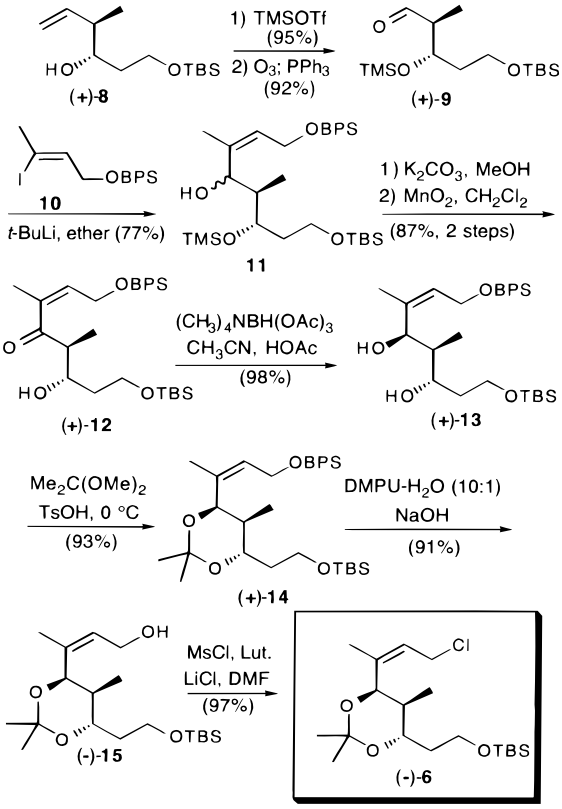
Scheme 1



Scheme 2

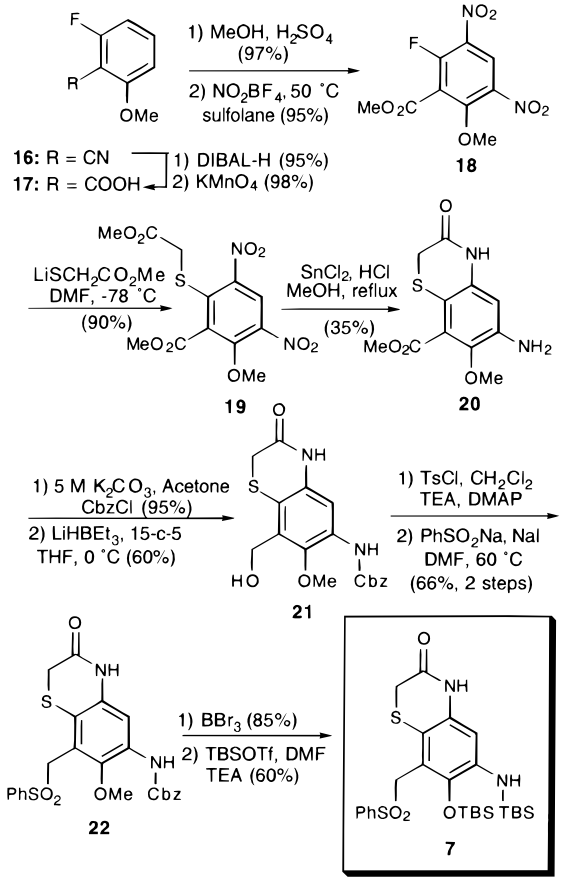


methylsilyl ether followed by reductive ozonolysis to furnish aldehyde (+)-**9** and then addition of the vinyl anion derived from vinyl iodide **10**,[7] the latter available in two steps from 2-butyn-1-ol, afforded a mixture of alcohols (**11**; ca. 2:1). After removal of the TMS group, selective oxidation of the allylic hydroxyl with manganese(IV) oxide provided ketone (+)-**12**. Completion of (−)-**6** entailed directed reduction[8] of the β-hydroxyl ketone with tetramethylammonium triacetoxyborohydride (95% de), generation of the 1,3-acetonide, selective removal of the primary BPS moiety in the presence of the primary TBS,[9] and conversion of the resultant allylic hydroxyl to the corresponding chloride. Allyl chloride (−)-**6**, identical in all respects to that prepared previously, was thus available in nine steps and 48% overall yield, compared to our previous route of 16 steps and 24% overall yield.

Construction of Sulfone 7. Our point of departure for sulfone **7** was commercially available 2-fluoro-6-methoxybenzonitrile (**16**, Scheme 3). Reduction with diisobutylaluminum hydride (DIBAL) and oxidation ($KMnO_4$) of the resultant aldehyde provided known acid **17**.[10] Esterification with methanol followed by bisnitration with nitronium tetrafluroborate (NO_2BF_4)[11] furnished **18**. Displacement of the fluorine with the lithium salt of methyl thioglycolate[12] to provide phenylthioether **19** followed by tin(II)-mediated reduction of the nitro groups with concomitant cyclization[13] then led to benzolactam **20** albeit in modest yield. Other reduction protocols such as hetero- or homogeneous hydrogenation[14,15] did not improve the yield. Protection of the aniline as benzyloxy carbamate (Cbz) and reduction of the benzoate with super hydride produced benzyl alcohol **21**. Initially, this reduction was also troublesome due to the unexpected ease with which the amide functionality was reduced over the ester (Scheme 4). This difficulty was eliminated by using a combination of super hydride and 15-crown-5 ether. Although the mechanistic details of this reduction remain unknown, we speculate that the amide is first converted to the lithium enolate via the basic combination of super hydride and 15-c-5, thereby rendering the amide carbonyl unreactive. Completion of sulfone **7** entailed tosylation

(7) Takemoto, T.; Sdeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477−8478.
(8) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(9) To the best of our knowledge, this is the first example of such selectivity.
(10) Horne, S.; Rodrigo, R. *J. Org. Chem.* **1990**, *55*, 4520−4522.
(11) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571−4580.
(12) Teulade, J. C.; Grassy, G.; Escale, R.; Chapat, J. P. *J. Org. Chem.* **1981**, *46*, 1026−1030.
(13) Kelly, T. R.; Kim, M. H.; Gurtis, A. D. M. *J. Org. Chem.* **1993**, *58*, 5855−5857.
(14) Sleath, P. R.; Noar, J. B.; Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 3328−3338.
(15) Entwistle, I. D. *Tetrahedron Lett.* **1979**, *20*, 555−558.

Scheme 3



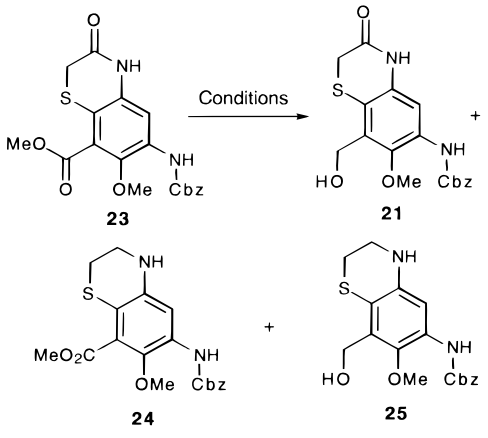
of **21** (Scheme 3), displacement with sodium benzenesulfinate, removal of methyl and Cbz groups,[16] and TBS protection of both the amine and hydroxyl groups.

Acid (+)-4 and Phosphonate 5. The synthesis of acid (+)-**4** began with (+)-**26**,[17] readily prepared from propargyl alcohol in two steps (Scheme 5). Methylation of the hydroxyl provided (+)-**27**; selectivity vis-à-vis the hydroxyl and alkyne was 10:1. Ozonolysis of the terminal alkene in the presence of the alkyne,[18] followed by reduction with triphenyl phosphine and oxidation with pyridinium dichromate (PDC) completed the synthesis of acid (+)-**4**.

Phosphonate **5** was readily prepared from known alcohol **29**,[19] the latter available from propargyl alcohol in one step (Scheme 6). Three steps were required: bromination, displacement of bromide with the sodium salt of diethyl phosphite, and titration with iodine; the overall yield was 78%.

Construction of the Macrocyclic Lactam. We turned next to the union of the four fragments (Scheme 7). Allyl chloride (−)-**6** was first converted to the iodide (**32**) by treatment with sodium iodide in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. Without isolation, the iodide was added to the anion derived from sulfone **7** (NaHMDS, THF, −78 °C); a diastereomeric mixture resulted. Reductive removal of the sulfone moiety with

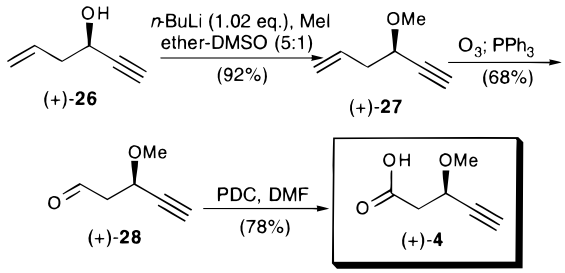
Scheme 4



Conditions	21	24	25
DIBAL / Toluene / 0 °C	0	0	50%
$LiBH_4$ / CH_2Cl_2 / 0 °C	17%	18%	35%
$LiBH_4$ / THF / 0 °C	35%	30%	0
n-BuLi/DIBAL / Toluene / -78 °C	23%	17%	0
n-BuLi / $LiHBEt_3$ / THF / -78 °C	20%	19%	0
$LiHBEt_3$ / 15-c-5 / THF / 0 °C	60%	0	0

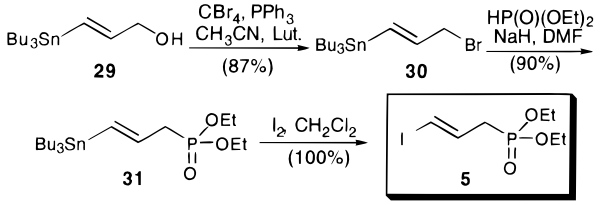
sodium amalgam, followed by treatment with silica gel in chloroform to remove the silyl group then furnished aniline (−)-**3** in 38% yield for the three steps. The acid chloride derived from acid (+)-**4** was next added to produce amide (+)-**35** in 80% overall yield.

Scheme 5



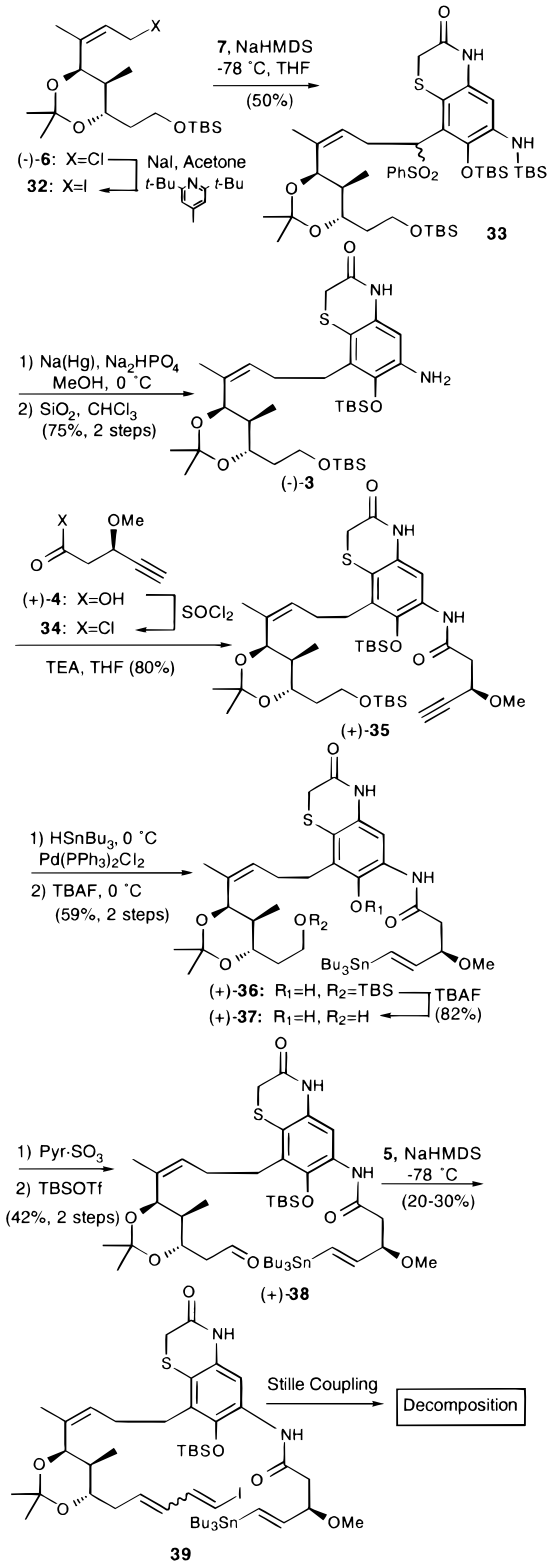
With union of three of the key components complete, palladium(0)-promoted hydrostannylation[20] afforded the *trans*-vinylstannane, accompanied by a small amount of the internal vinylstannane (ca. 4:1). Without purification, removal of the phenolic TBS moiety with TBAF at 0 °C furnished phenol (+)-**36** in 59% yield (two steps). It was at this stage that the desired *trans*-vinylstannane could be separated from the internal vinylstannane. Treatment of (+)-**36** with TBAF at room temperature, oxidation of the resultant alcohol to the aldehyde employing the Parikh−Doering protocol,[21] and reprotection of the phenol led to aldehyde (+)-**38**. Intermolecular Horner−Emmons

Scheme 6



(16) Combes, S.; Finet, J.-P. *Synth. Commun.* **1997**, *27*, 3769−3778.
(17) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095−13096.
(18) Chen, S.-Y.; Joullié, M. M. *Synth. Commun.* **1984**, *14*, 591−597.
(19) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854.

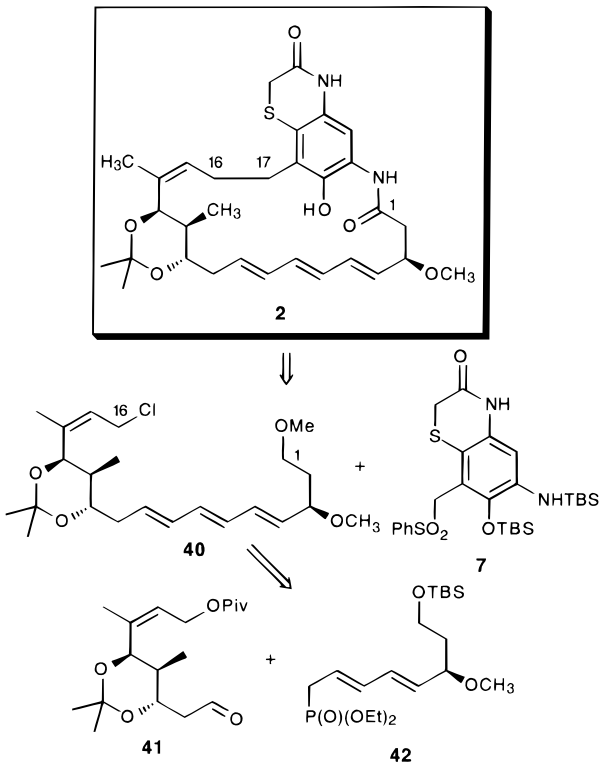
Scheme 7



reaction of (+)-**38** with phosphonate **5** then afforded a 1:1 mixture of olefins **39** in modest yield. Unfortunately, all attempts at this point to effect macrocyclization, employing a variety of Stille[22] protocols, led only to rapid decomposition of the olefins.[23]

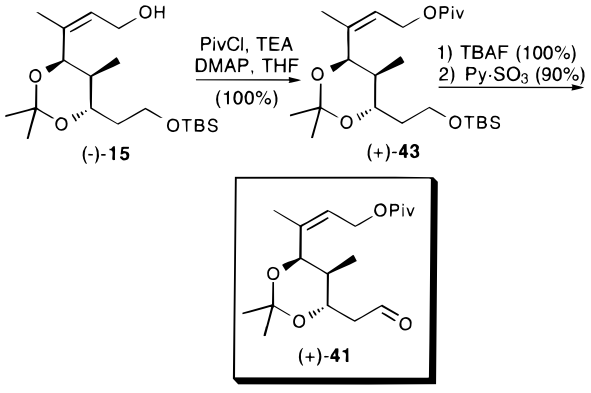
A Second Generation Strategy. Our inability to install the *E,E,E*-triene with simultaneous macrocyclization via an intramolecular Stille reaction led us to consider a second generation strategy for macrocyclic lactam assembly, which called for alkylation of sulfone **7** with triene **40** followed by a Mukaiyama macrolactamization (Scheme 8).[24] Advanced triene **40** in turn was envisioned to derive from aldehyde **41** and phosphonate **42**.

Scheme 8



Construction of Aldehyde (+)-41 and Phosphonate (+)-42. Aldehyde (+)-**41** was prepared from allylic alcohol (−)-**15** in three steps (Scheme 9): pivalation (PivCl) of the hydroxyl, removal of the TBS group (TBAF), and Parikh−Doering oxidation.

Scheme 9



Construction of phosphonate (+)-**42** began with radical-promoted (AIBN) hydrostannylation of alkyne (+)-**28** (Scheme 10); *trans*-vinylstannane (+)-**44** was obtained,

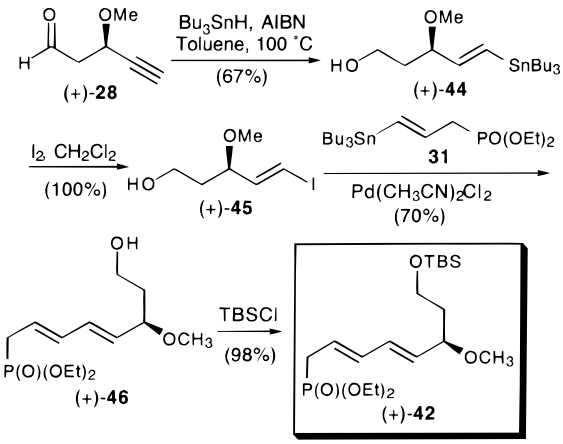
(20) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(21) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(22) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817.

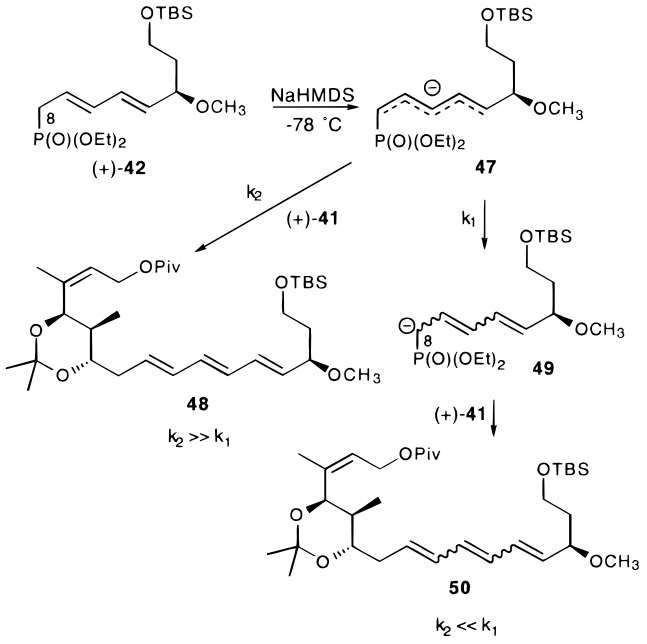
contaminated with ca. 6% of the cis isomer.[25] Separation of the isomers via flash chromatography, followed by treatment with iodine, afforded alcohol (+)-**45**. Preparation of (+)-**42** was then completed via a palladium-catalyzed Stille cross-coupling reaction with **31**, followed by TBS protection of the primary hydroxyl.

Scheme 10



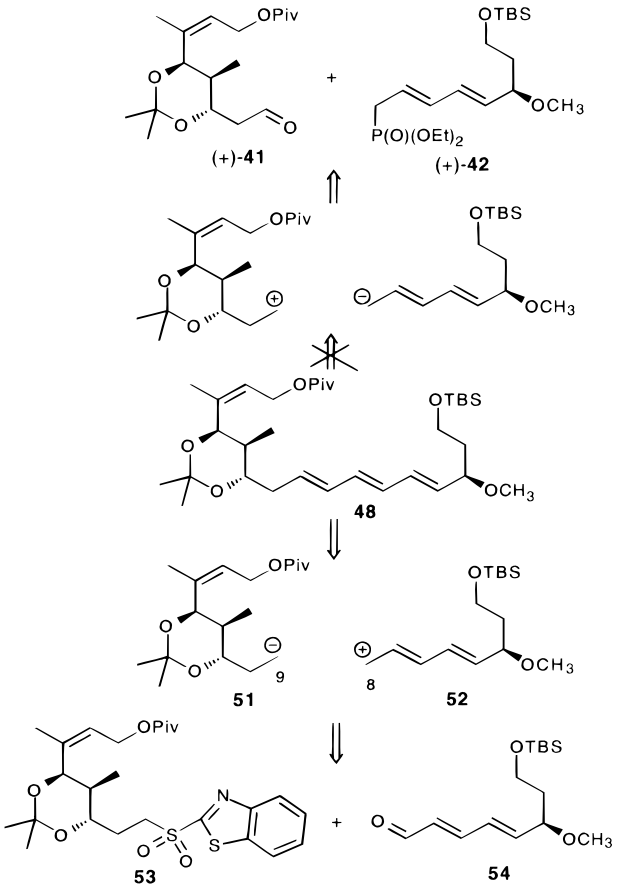
Horner−Emmons Construction of the Triene. With both aldehyde (+)-**41** and phosphonate (+)-**42** in hand, Horner−Emmons reaction (Scheme 11) led to an inseparable mixture of trienes **50** in at best modest yield (25−30%). A variety of bases, solvents, and reaction temperatures did not improve either the selectivity or yield. The lack of selectivity can be rationalized as depicted in Scheme 11. Treatment of (+)-**42** with NaHMDS produces anion **47**, which can either react with (+)-**41** to give the desired all-trans triene **48** or isomerize to a mixture of anions **49**, which in turn would afford a mixture of olefins. Presumably, isomerization (k_1) is faster than olefination (k_2).

Scheme 11



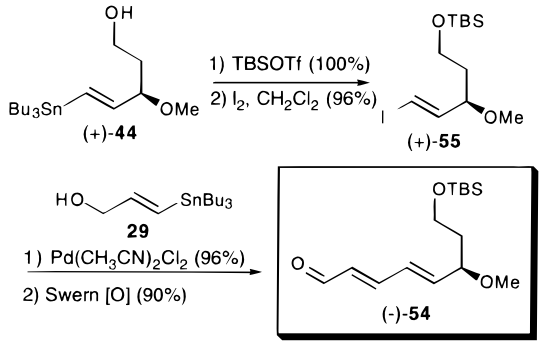
Julia Olefination: An Alternate Approach to Triene 40. To avoid anion isomerization, we considered reversal of the coupling functionality (e.g., **51** and **52**; Scheme 12). Julia olefination[26] of sulfone **53** with aldehyde **54** appeared to be the obvious choice.

Scheme 12



Toward this end, construction of aldehyde (−)-**54** (Scheme 13) entailed protection of alcohol (+)-**44** as the TBS ether followed in turn by treatment with iodine, Stille cross-coupling with vinylstannane **29** and Swern[27] oxidation of the derived alcohol led to aldehyde (−)-**54** in 83% overall yield for the four steps.

Scheme 13



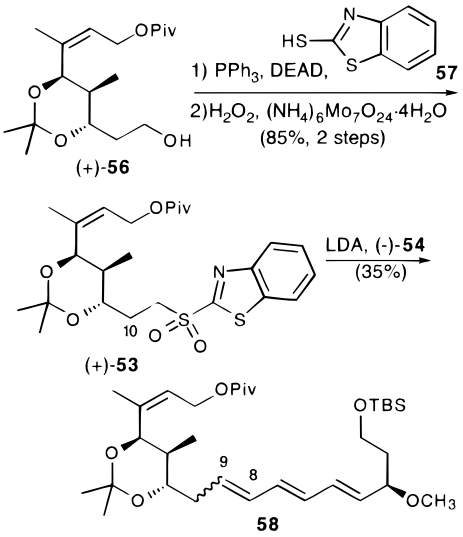
Synthesis of the requisite sulfone (+)-**53** began with alcohol (+)-**56** (Scheme 14). Mitsunobu reaction[28] with

(23) For an example of macrocyclization employing Stille coupling, see: 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.* **1997**, *119*, 947−973.

(24) For an example of Mukaiyama macrolactamization of a free aniline, see: Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331−11332.

(25) Interestingly, the aldehyde was also reduced under these conditions.

Scheme 14



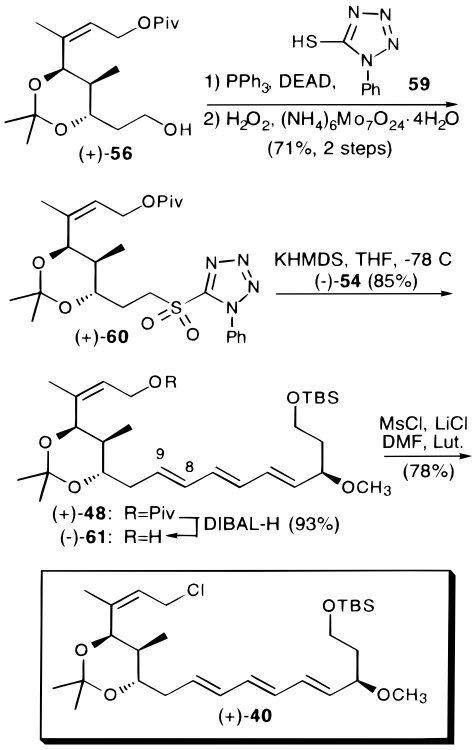
2-mercaptobenzothiazole (**57**) followed by oxidation with hydrogen peroxide and ammonium heptamolybdate tetrahydrate [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] furnished sulfone (+)-**53** in 85% yield (two steps). Julia coupling then afforded triene **58**, with the newly formed C(8,9) olefin obtained as a cis/trans mixture (ca. 1:1.5). Importantly no isomerization at either the C(4,5) or C(6,7) olefins was observed.

The Kocienski−Julia Protocol: Construction of the All-Trans Triene. In 1998, Kocienski[29] and coworkers introduced an important modification of the Julia olefination reaction, leading to high trans selectivity. The protocol calls for the construction of the 1-phenyl-1*H*-tetrazole-5-yl sulfone. Toward this end, Mitsunobu reaction of (+)-**56** with 1-phenyl-1*H*-tetrazole-5-thiol (**59**) followed by oxidation of the resultant sulfide furnished (+)-**60** (Scheme 15). Addition of aldehyde (−)-**54** to the derived anion provided triene (+)-**48**; importantly, the newly formed C(8,9) olefin was predominantly trans (ca. 10:1). In addition, no isomerization at C(4,5) or C(6,7) was observed. Reductive removal of the pivaloate moiety[30] and halogenation of the resultant allylic alcohol completed the construction of (+)-**40**.

With the *E*,*E*,*E*-triene available, we proceeded with the alkylation of sulfone **7**. The allyl chloride moiety in (+)-**40** was first converted to the corresponding iodide (**62**, Scheme 16). Addition to the anion derived from **7** (1.05 equiv) then afforded a diastereomeric mixture (ca. 2:1) of sulfones **63**. Although the iodide was completely consumed, approximately 30% of sulfone **7** was recovered (e.g., 95% based on the conversion of **7**). Attempts to improve the conversion of this coupling procedure went unrewarded. Notwithstanding this event, we turned to functional group manipulation in anticipation of macrolactamization.

Reductive desulfonylation of **63** followed by treatment with silica gel in chloroform to liberate selectively the

Scheme 15



aniline moiety furnished (+)-**64**. Treatment with allyl chloroformate (AllocCl) followed by selective removal of the phenolic TBS with HOAc-TBAF and reprotection of the resultant phenol with chloromethyl methyl ether (MOMCl)[31] then afforded MOM ether (+)-**65**. After unmasking of the primary alcohol, a two-step oxidation protocol (Parikh−Doering and $NaClO_2$[32]) led to acid (+)-

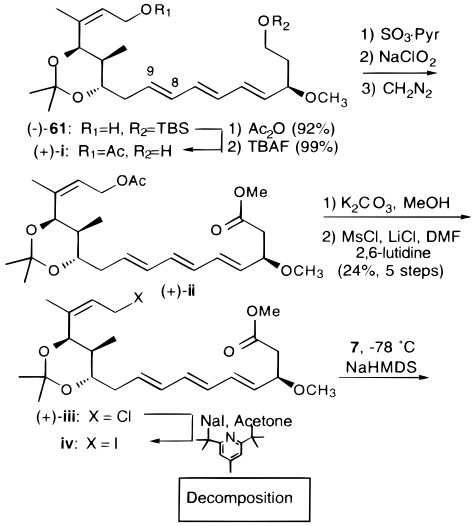
(26) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178.

(27) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(28) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(29) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *1*, 26−28. For recent applications of this reaction in synthesis, see: Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955−968. Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925. Williams, D. R. Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291−2294. Metternich, R.; Denni, D.; Thai, B.; Sedrani, R. *J. Org. Chem.* **1999**, *64*, 9632−9639.

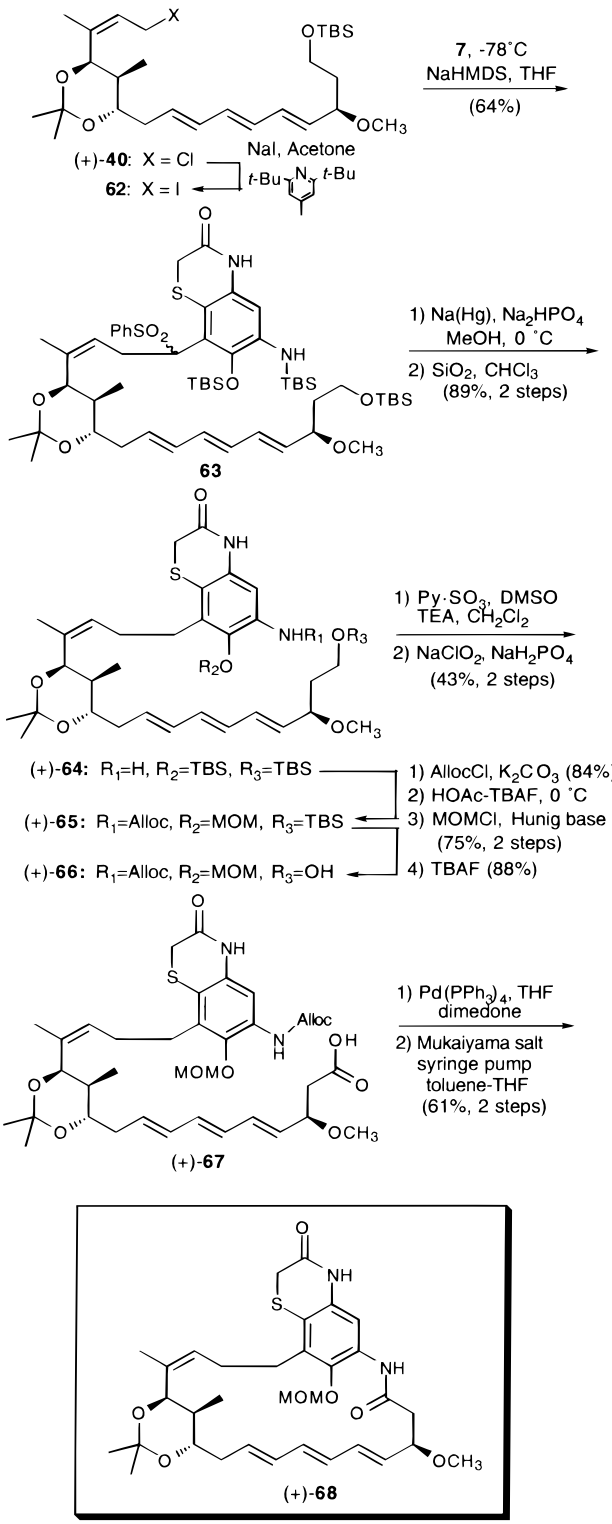
(30) This strategy should give us the option to oxidize the C(1) alcohol to acid before coupling with sulfone **7**. This route although more convergent, is highly risky. To this end, (−)-**61** was converted to **iv** as outlined below. Unfortunately, coupling with **7** proved impossible; only recovery of sulfone **7** was observed. We reasoned that initial deprotonation of C(2) in **iv** by the sulfone anion leads to elimination of C(3) methoxy followed by decomposition. To avoid this problem, we introduced the carboxylic acid functionality after union with sulfone **7**.



(31) Protecting group exchange proved very important for the macrolactamization step: unpublished result of Z.W.

(32) Crimmins, M. T.; Al-awar, R. S.; Vallin, I. M.; Hollis, W. G., Jr.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 7513−7528.

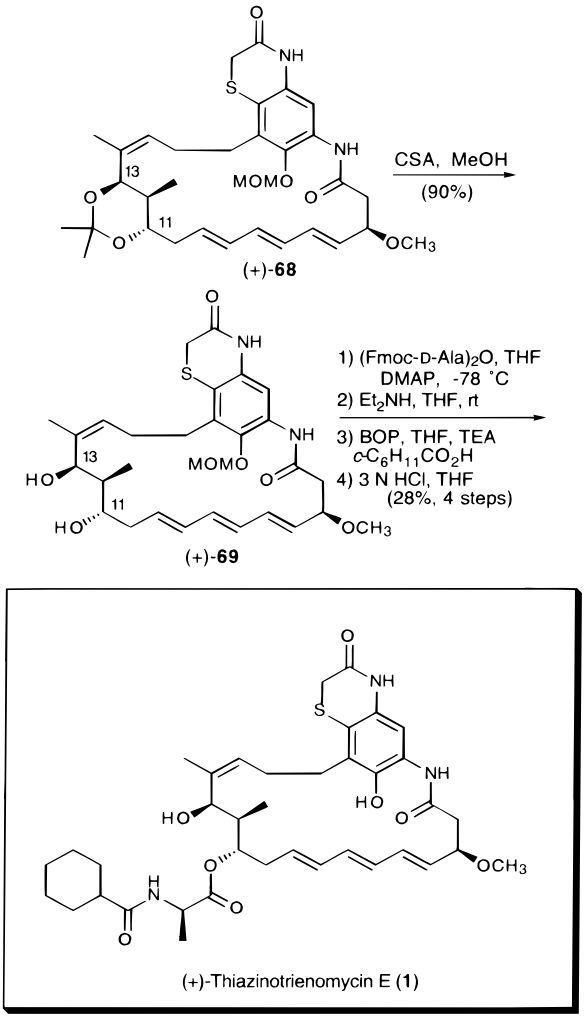
Scheme 16



67 as a mixture of rotamers (ca. 4:1); removal of the Alloc group provided an unstable amino acid. Without purification, slow addition of this acid via syringe pump to a mixture of 2-chloro-1-methylpyridinium iodide (Mukaiyama salt)[33] and TEA in toluene furnished macrocyclic lactam (+)-**68** in 61% yield for the two steps.

Side Chain Attachment: Completion of the Total Synthesis. All that remained to complete the synthesis of (+)-thiazinotrienomycin E (**1**) was removal of the acetonide, installation of the acylated amino acid side chain, and final deprotection (Scheme 17). To this end, treatment of (+)-**68** with acidic methanol and the symmetrical anhydride derived from FMOC-D-alanine led to an inseparable mixture of monoacylated products in a ratio of 2:1 favoring acylation at C(11). A small amount (<7%) of bis-acylated material was also observed. Liberation of the primary amine by exposure of the mixture to diethylamine in THF, followed by BOP-mediated coupling with cyclohexanecarboxylic acid, removal of the MOM group, and separation (HPLC) furnished (+)-thiazinotrienomycin E (**1**), identical in all respects with the natural material (^{1}H and ^{13}C NMR, HRMS, optical rotation, and TLC in three solvent systems).

Scheme 17



Summary. The first total synthesis of (+)-thiazinotrienomycin E (**1**) has been achieved. Importantly, the synthesis confirms the previously reported relative and absolute stereochemistries. Particularly noteworthy features of the synthesis include the efficient assembly of the *E,E,E*-triene and the improved synthesis of advanced allyl chloride (−)-**6**. Exploitation of this synthetic strategy, as currently underway, should provide access to other members of the thiazinotrienomycin family, as well as a variety of potentially bioactive analogues. Finally, the efficient construction of (−)-**6** constitutes an improved total synthesis of the closely related (+)-trienomycins A and F.

(33) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166.

Experimental Section[34]

Aldehyde (+)-9. To a solution of (+)-**8** (200 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (0.382 mL, 3.28 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.297 mL, 1.64 mmol). After 10 min, the resultant mixture was added to brine (50 mL) and extracted with ether (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) provided the corresponding TMS ether (246 mg, 95% yield) as a colorless oil: $[\alpha]^{23}_D$ −14.8° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2960 (s), 2920 (s), 2850 (m), 1550 (w), 1470 (w), 1250 (s), 1217 (s), 1090 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82−5.78 (m, 1 H), 5.03−4.94 (m, 2 H), 3.80 (m, 1 H), 3.70−3.60 (m, 2 H), 2.30−2.21 (m, 1 H), 1.68−1.50 (m, 2 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.12 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 115.2, 73.0, 60.3, 43.9, 37.2, 26.1, 18.4, 15.6, 0.4, −5.3; high-resolution mass spectrum (CI, NH_3) *m/z* 315.2182 [(M − H)$^+$; calcd for $C_{16}H_{35}O_2(Si)_2$ 315.2175].

Ozone was bubbled through a solution of the above TMS ether (100 mg, 0.316 mmol) in CH_2Cl_2 (20 mL) at −78 °C until a blue color persisted. Argon was then bubbled through the solution until it became colorless, and triphenylphosphine (124 mg, 0.474 mmol) was added. The mixture was stirred at ambient temperature for 12 h and then concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 100:1) afforded (+)-**9** (93 mg, 92% yield) as a colorless oil: $[\alpha]^{23}_D$ +11.7° (*c* 0.6, $CHCl_3$); IR (plate) 2960 (s), 2920 (s), 2850 (s), 1725 (s), 1470 (m), 1460 (m), 1250 (s), 1100 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, J = 2.2 Hz, 1 H), 4.13 (dt, J = 4.8, 7.1 Hz, 1 H), 3.72−3.68 (m, 2 H), 2.50−2.43 (m, 1 H), 1.80−1.64 (m, 2 H), 1.09 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 70.4, 59.0, 51.7, 37.8, 25.9, 18.1, 10.4, 0.2, −5.5; high-resolution mass spectrum (ES, Na) *m/z* 341.1954 [(M + Na)$^+$; calcd for $C_{15}H_{34}O_3(Si)_2Na$ 341.1944].

Ketone (+)-12. To a solution of vinyl iodide **10** (746 mg, 1.7 mmol) in ether (20 mL) at −78 °C was added dropwise *t*-BuLi (1.7 M in pentane, 2 mL, 3.4 mmol). After 30 min, a solution of (+)-**9** (150 mg, 0.47 mmol) in ether (3 mL) was introduced via cannula. The solution was then warmed to 0 °C over 2 h. The reaction was quenched with saturated NH_4Cl (10 drops), poured into brine (30 mL), and extracted with ether (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 50:1−20:1) afforded an inseparable (2:1) mixture of diastereomers as a colorless oil **11** (228 mg, 77% yield).

To a solution of **11** (85 mg, 0.135 mmol) in anhydrous MeOH (5 mL) was added K_2CO_3 (187 mg, 1.35 mmol). The resultant suspension was stirred at room temperature for 3 h, added to brine (25 mL), and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) provided an inseparable (2:1) mixture of diastereomeric diols as a colorless oil (75 mg, 100% yield).

To a solution of the above diols (75 mg, 0.135 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (235 mg, 2.7 mmol). After 12 h, the solution was filtered through a pad of Celite and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**12** (65 mg, 87% yield) as a colorless oil: $[\alpha]^{23}_D$ +10.8° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3490 (m), 3065 (m), 3010 (m), 3000 (s), 2955 (s), 2900 (s), 2847 (s), 1675 (m), 1600 (m), 1470 (m), 1420 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4 H), 7.42−7.37 (m, 6 H), 6.03 (t, J = 5.6 Hz, 1 H), 4.58−4.47 (m, 2 H), 3.92 (m, 1 H), 3.83 (m, 1 H), 3.76 (m, 1 H), 3.37 (d, J = 4.1 Hz, 1 H), 2.95 (m, 1 H), 1.98 (s, 3 H), 1.68−1.54 (m, 2 H), 1.05 (s, 9 H), 0.96 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 142.9, 135.5, 133.68, 133.65, 133.60, 129.5, 127.64, 127.59, 72.7, 63.0, 61.8, 48.0, 35.8, 26.8, 25.8, 20.6, 19.1, 16.9, 13.0, −5.6; high-resolution mass spectrum (ES, Na) *m/z* 577.3143 [(M + Na)$^+$; calcd for $C_{32}H_{50}O_4(Si)_2Na$ 577.3145].

Anal. Calcd for $C_{32}H_{50}O_4(Si)_2$: C, 69.31; H, 9.03. Found: C, 69.70; H, 9.24.

Diol (+)-13. Tetramethylammonium triacetoxyborohydride (47.6 mg, 0.181 mmol) was dissolved in CH_3CN and HOAc (1 mL each), and the resulting solution was cooled to −20 °C. A solution of (+)-**12** (10 mg, 0.0181 mmol) in CH_3CN (0.25 mL) was then added. The reaction mixture was stirred at −20 °C for an additional 16 h and quenched with MeOH (0.2 mL). The mixture was warmed to room temperature, poured into a saturated $NaHCO_3$ solution (20 mL), and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) afforded (+)-**13** (10 mg, 98% yield) as a colorless oil: $[\alpha]^{23}_D$ +15.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3460 (s), 3005 (s), 2960 (s), 2920 (s), 2850 (s), 1725 (s), 1470 (m), 1420 (s), 1250 (s), 1100 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73−7.70 (m, 4 H), 7.45−7.37 (m, 6 H), 5.50 (m, 1 H), 4.57 (d, J = 3.0 Hz, 1 H), 4.28 (ddd, J = 13.0, 7.4, 1.2 Hz, 1 H), 4.21 (ddd, J = 13.0, 5.6, 1.1 Hz, 1 H), 3.91 (br s, 1 H), 3.85 (m, 1 H), 3.77 (m, 2 H), 3.17 (br s, 1 H), 1.79 (s, 2 H), 1.74 (m, 1 H), 1.52 (m, 1 H), 1.36 (m, 1 H), 1.08 (s, 9 H), 0.93 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 135.6, 135.5, 133.8, 133.7, 129.5, 127.6, 127.5, 126.0, 76.3, 71.7, 63.2, 60.2, 42.7, 35.9, 26.8, 25.7, 20.3, 19.1, 18.0, 11.4, −5.61, −5.63; high-resolution mass spectrum (ES, Na) *m/z* 579.3304 [(M + Na)$^+$; calcd for $C_{32}H_{52}O_4(Si)_2Na$ 579.3302].

Acetonide (+)-14. A solution of (+)-**13** (10 mg, 0.018 mmol) in 2,2-dimethoxypropane (1 mL) at 0 °C was treated with TsOH (two crystals). After 5 min, the mixture was poured into a saturated $NaHCO_3$ solution (10 mL) and extracted with ether (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**14** (10 mg, 93% yield) as a colorless oil: $[\alpha]^{23}_D$ +4.1° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2970 (s), 2930 (s), 2860 (m), 1517 (w), 1465 (m), 1420 (s), 1380 (s), 1250 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.69 (m, 4 H), 7.48−7.39 (m, 6 H), 5.50 (t, J = 5.6 Hz, 1 H), 4.51 (d, J = 6.0 Hz, 1 H), 4.32 (dd, J = 13.4, 7.1 Hz, 1 H), 4.28 (dd, J = 13.4, 4.8 Hz, 1 H), 3.68−3.62 (m, 2 H), 3.42 (dt, J = 9.7, 3.0 Hz, 1 H), 1.71 (s, 3 H), 1.70 (m, 1 H), 1.63−1.55 (m, 2 H), 1.22 (s, 6 H), 1.08 (s, 9 H), 0.90 (s, 9 H), 0.77 (d, J = 7.1 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 134.7, 134.04, 133.97, 129.4, 127.5, 126.3, 100.4, 71.0, 70.1, 60.6, 59.4, 40.9, 37.7, 26.8, 25.9, 24.6, 23.9, 20.9, 19.1,

(34) **Materials and Methods.** All 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. Triethylamine (TEA) and diisopropylethylamine (DIPEA) were distilled from calcium hydride and stored over potassium hydroxide. Anhydrous pyridine, *N*,*N*-dimethylformamide (DMF), toluene, and dimethyl sulfoxide (DMSO) were purchased from Aldrich and used without purification. *n*-Butyllithium (*n*-BuLi) and *tert*-butyllithium (*t*-BuLi) were purchased from Aldrich and standardized by titration with diphenylacetic acid or *N*-pivaloyl-*o*-toluidine. 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 column chromatography was performed using silica gel 60 (particle size 0.023−0.040 mm) supplied by E. Merck. High-performance liquid chromatography (HPLC) was performed with a Waters component analytical system. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All melting points were obtained on 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 AM250 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00), chloroform (δ 7.26), methanol (δ 4.78), pyridine (δ 7.55), or benzene (δ 7.15) for ^1H and chloroform (δ 77.0), methanol (δ 49.0), pyridine (δ 149.9), 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, or at the University of Pennsylvania. Single-crystal X-ray structure determinations were performed at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer.

18.1, 12.1, −5.38, −5.42; high-resolution mass spectrum (ES, Na) *m/z* 619.3619 [(M + Na)$^+$; calcd for $C_{35}H_{56}O_4(Si)_2Na$ 619.3614].

Anal. Calcd for $C_{35}H_{56}O_4(Si)_2$: C, 70.47; H, 9.40. Found: C, 70.25; H, 9.21.

Alcohol (−)-15. A solution of (+)-**14** (10 mg, 0.0168 mmol) in DMPU (1 mL) was treated with NaOH (16.8 mg, 0.42 mmol) in water (0.1 mL). The mixture was stirred for 1 h, poured into a saturated NH_4Cl solution (20 mL) and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) afforded (−)-**15** (5.5 mg, 91% yield) as a colorless oil that was spectroscopically and analytically identical to that prepared in the trienomycin project.

Bis-Nitro Benzoate 18. To a white suspension of 2-fluoro-6-methoxybenzonitrile (**16**, 10 g, 66.2 mmol) in toluene (250 mL) at −78 °C was added DIBAL (1 M in hexanes, 70 mL) via addition funnel. After the addition, the ice bath was removed, and the mixture was stirred at ambient temperature for 12 h. The reaction was then quenched by slow addition of MeOH (50 mL) at 0 °C and the resultant precipitate dissolved in HCl (1 N, 300 mL). The organic part was separated, and the aqueous part was extracted with ether (3 × 300 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 1:3) afforded the corresponding aldehyde (9.7 g, 95% yield) as a light yellow solid: mp 60−61 °C (hexane/ethyl acetate); IR ($CHCl_3$) 3010 (m), 1695 (s), 1615 (s), 1575 (m), 1477 (s), 1440 (m), 1400 (m), 1290 (m), 1250 (m), 1180 (m), 1090 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1 H), 7.47−7.50 (m, 1 H), 6.72−6.80 (m, 2 H), 3.95 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2, 164.4, 162.4, 162.2, 162.1, 136.0, 135.9, 114.3, 114.2, 108.7, 108.6, 107.3, 107.2, 56.4; high-resolution mass spectrum (CI, NH_3) *m/z* 172.0772 [(M + NH_4)$^+$; calcd for $C_8H_{11}FNO_2$ 172.0774].

A solution of the above aldehyde (35 g, 0.227 mol) in acetone (100 mL) was added to a mechanically stirred suspension of $KMnO_4$ (53.9 g, 0.34 mol) in water (400 mL). After addition, the mixture was heated at reflux for 3 h, cooled to room temperature, and added to a NaOH solution (3.5 M, 100 mL, 0.35 mol). The resultant black precipitate was removed by filtration, and the filtrates were extracted with ethyl acetate (300 mL). The aqueous part was then treated with HCl (5 M, 70 mL) and extracted with ethyl acetate (3 × 400 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford **17** (37.9 g, 98% yield) as a yellow solid.

A solution of **17** (29 g, 0.171 mol) and concentrated H_2SO_4 (1 mL) in MeOH (150 mL) was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and concentrated to dryness in vacuo. The residue was dissolved in ethyl acetate (1 L) and washed in turn by NaOH (1 N, 100 mL) and brine (2 × 500 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to provide the corresponding methyl benzoate (30.4 g, 97% yield) as a brown oil that was used without further purification: IR ($CHCl_3$) 3020 (m), 2960 (w), 1730 (s), 1620 (s), 1600 (m), 1585 (m), 1475 (s), 1435 (s), 1310 (s), 1290 (s), 1270 (s), 1240 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.31 (m, 1 H), 6.74−6.71 (m, 2 H), 3.93 (s, 3 H), 3.86 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 161.3, 159.3, 158.2, 158.1, 131.8, 131.7, 112.1, 111.9, 108.4, 108.2, 107.0, 106.9, 56.3, 52.5; high-resolution mass spectrum (CI, NH_3) *m/z* 185.0608 [(M + H)$^+$; calcd for $C_9H_{10}FO_3$ 185.0613].

A solution of the above methyl benzoate (15 g, 81.5 mmol) and NO_2BF_4 (25 g, 179 mmol) in sulfolane (240 mL) was heated to 50 °C for 15 h. The solution was then cooled to room temperature, diluted with ethyl acetate (1 L), and washed in turn with saturated $NaHCO_3$ (500 mL) and brine (3 × 500 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) afforded **18** (21.2 g, 95% yield) as a yellow oil: IR ($CHCl_3$) 3100 (w), 3040 (w), 2960 (w), 1700 (s), 1610 (s), 1550 (s), 1350 (s), 1310 (s), 1270 (s), 1155 (s), 1080 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 7.7 Hz, 1 H), 4.09 (s, 3 H), 4.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 156.6, 156.5, 154.4, 138.6, 132.0, 124.9, 120.9, 120.8, 64.0, 53.9.

Anal. Calcd for $C_9H_7FN_2O_7$: C, 39.42; H, 2.55; N, 10.27. Found: C, 39.80; H, 2.76; N, 9.93.

Sulfide 19. To a solution of methyl thioglycolate (0.755 mL, 8.0 mmol) in DMF (40 mL) was added LiOH (161.4 mg, 6.7 mmol). The mixture was stirred until all the LiOH was dissolved (3 h). The resultant yellow solution was then added to **18** (1.68 g, 6.13 mmol) in DMF (20 mL) at −78 °C via cannula. The mixture was stirred at room temperature for an additional 3 h. The resultant dark red solution was diluted with ethyl acetate (300 mL), washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) provided **19** (2.2 g, 90% yield) as a yellow foam: IR ($CHCl_3$) 3025 (w), 2960 (w), 1745 (s), 1590 (s), 1540 (s), 1440 (m), 1400 (w), 1350 (s), 1270 (s), 1160 (m), 1140 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 4.04 (s, 3 H), 4.03 (s, 3 H), 3.74 (s, 2 H), 3.72(s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 163.8, 152.9, 149.0, 142.5, 140.5, 131.9, 122.6, 64.3, 53.5, 52.8, 38.6; high-resolution mass spectrum (CI, NH_3) *m/z* 378.0601 [(M + NH_4)$^+$; calcd for $C_{12}H_{16}N_3O_9S$ 378.0607].

Aniline 20. To a yellow suspension of **19** (1.776 g, 4.93 mmol) in MeOH (25 mL) was added $SnCl_2$ (3.74 g, 19.73 mmol) in HCl (2 M, 25 mL, 50 mmol). The mixture was heated at reflux for 14 h. The resultant dark green solution was cooled to room temperature, treated with a solution of NaOH (5 M, 8 mL, 40 mmol), and mixed with a saturated $NaHCO_3$ solution (25 mL). The resultant precipitate was removed by filtration and the filtrate extracted with ethyl acetate (4 × 200 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Gradient flash chromatography (ether/hexanes, 4:1; ether/ethyl acetate, 1:1; ethyl acetate) provided **20** (462 mg, 35% yield) as a yellow oil: IR ($CHCl_3$) 3400 (w), 3200 (w), 3000 (w), 1730 (m), 1680 (s), 1620 (m), 1480 (m), 1435 (m), 1365 (m), 1260 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 6.39 (s, 1 H), 3.99 (s, 3 H), 3.82 (s, 3 H), 3.33 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.3, 141.7, 139.7, 133.5, 126.7, 107.6, 106.0, 61.3, 52.6, 30.5; high-resolution mass spectrum (CI, NH_3) *m/z* 286.0868 [(M + NH_4)$^+$; calcd for $C_{11}H_{16}N_3O_4S$ 286.0862].

***N*-Cbz Amide 23**. A solution of **20** (520 mg, 1.94 mmol) in acetone (15 mL) was treated with aqueous K_2CO_3 (5 M, 1.55 mL, 7.76 mmol) and CbzCl (1.166 mL, 7.76 mmol). The mixture was stirred for 4 h, diluted with ethyl acetate (50 mL), and washed in turn with saturated $NaHCO_3$ (30 mL) and brine (30 mL). The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1 to 1:1) afforded **23** (741 mg, 95% yield) as a yellow solid: mp 174−176 °C (hexane/ethyl acetate); IR ($CHCl_3$) 3400 (m), 3020 (w), 1730 (s), 1690 (s), 1600 (m), 1515 (s), 1460 (m), 1370 (m), 1260 (m), 1195 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1 H), 8.02 (s, 1 H), 7.42−7.29 (m, 6 H), 5.23 (s, 2 H), 3.99 (s, 3 H), 3.80 (s, 3 H), 3.35 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.8, 153.2, 142.7, 135.6, 133.7, 130.7, 128.7, 128.6, 128.5, 125.6, 113.8, 109.6, 67.7, 62.6, 52.7, 30.0; high-resolution mass spectrum (CI, NH_3) *m/z* 420.1238 [(M + NH_4)$^+$; calcd for $C_{19}H_{22}N_3SO_6$ 420.1229].

Anal. Calcd for $C_{19}H_{18}N_2SO_6$: C, 56.72; H, 4.48; N, 6.97. Found: C, 56.35; H, 4.49; N, 6.60.

Alcohol 21. A solution of **23** (11.2 g, 27.9 mmol) and 15-crown-5 ether (46 g, 209 mmol) in THF (100 mL) at 0 °C was treated with super hydride (1 M in THF, 209 mL, 209 mmol). The resultant mixture was stirred at ambient temperature for an additional 12 h and then recooled to 0 °C and quenched with HCl (1 N, 20 mL). The mixture was diluted with ethyl acetate (1 L) and washed with brine (5 × 500 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 1:1 to 3:1) afforded **21** (6.25 g, 60% yield) as a white solid: mp 189−190 °C (hexane/methanol); IR ($CHCl_3$) 3400 (m), 2960 (m), 1730 (m), 1680 (s), 1600 (m), 1520 (s), 1510 (m), 1375 (m), 1240 (s), 1115(m), 1060 (m), 1000(s) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.65−7.30 (m, 6 H), 5.21 (s, 2 H), 4.73 (s, 2 H), 3.74 (s, 3 H), 3.35 (s, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.2,

154.3, 145.0, 136.6, 133.6, 131.6, 130.4, 128.2, 127.8, 127.7, 116.8, 109.7, 66.5, 61.7, 56.2, 29.3; high-resolution mass spectrum (CI, NH_3) *m*/*z* 392.1292 [(M + NH_4)$^+$; calcd for $C_{18}H_{22}N_3O_5S$ 392.1281].

Sulfone 22. To a solution of **21** (1.02 g, 2.73 mmol) in CH_2Cl_2 (60 mL) were added triethylamine (5.7 mL, 41 mmol), 4-(dimethylamino)pyridine (333 mg, 2.73 mmol), and *p*-toluenesulfonyl chloride (2.6 g, 13.64 mmol). The mixture was stirred for 6.5 h, diluted with CH_2Cl_2 (300 mL), and washed with brine (200 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The resultant dark residue was dissolved in DMF (50 mL) and treated with NaI (2.05 g, 13.64 mmol) and $PhSO_2Na$ (4.48 g, 27.3 mmol). The mixture was then stirred at 60 °C for 13 h. The solution was next cooled to room temperature, diluted with ethyl acetate (200 mL), and washed in turn with saturated $NaHCO_3$ (100 mL) and brine (100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 1:1 to 2:1) provided **22** (0.90 g, 66% yield) as a light yellow solid: mp 184−186 °C (hexane/chlorofom); IR ($CHCl_3$) 3500 (m), 3300 (m), 3000 (s), 2900 (m), 1770 (m), 1720 (w), 1670 (m), 1600 (w), 1450 (w), 1340 (m), 1240 (m), 1175 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (m, 2 H), 7.73 (br s, 1 H), 7.65 (m, 1 H), 7.53 (m, 2 H), 7.44 (m, 5 H), 7.01 (s, 1 H), 5.25 (s, 2 H), 4.64 (s, 2 H), 3.75 (s, 3 H), 3.19 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 153.0, 144.8, 139.1, 135.5, 134.0, 133.8, 130.9, 129.1, 128.8, 128.67, 128.65, 128.5, 120.9, 117.4, 108.9, 67.7, 61.8, 56.2, 30.5; high-resolution mass spectrum (ES, Na) *m*/*z* 521.0811 [(M + Na)$^+$; calcd for $C_{24}H_{22}N_2O_6S_2Na$ 521.0817].

Anal. Calcd for $C_{24}H_{22}N_2O_6S_2$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.43; H, 4.17; N, 5.37.

TBS Aniline 7. A suspension of **22** (80 mg, 0.16 mmol) in CH_2Cl_2 at 0 °C was treated with BBr_3 (1 M in CH_2Cl_2, 1.6 mL, 1.6 mmol). The mixture was stirred at ambient temperature for 12 h and then quenched with MeOH (1 mL). The solution was concentrated to dryness in vacuo. The crude dark residue was dissolved in ethyl acetate (25 mL), treated with HCl (1 N, 5 mL), and washed with brine (25 mL). After separation, the aqueous phase was mixed with saturated $NaHCO_3$ (25 mL) and washed with ethyl acetate (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to provide the corresponding phenol-aniline (47.8 mg, 85% yield) as a glassy solid that was used without any further purification: IR (Plate) 3400 (m), 2940 (s), 2920 (s), 2850 (s), 1675 (s), 1590 (s), 1463 (s), 1357 (s), 1340 (m), 1250 (s) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.83−7.81 (m, 2 H), 7.76−7.72 (m, 1 H), 7.62−7.58 (m, 2 H), 7.12 (s, 1 H), 4.95 (s, 2 H), 3.05 (s, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 166.6, 146.2, 138.3, 134.3, 131.8, 129.2, 128.4, 125.7, 119.1, 116.5, 113.3, 55.5, 29.2; high-resolution mass spectrum (ES, Na) *m*/*z* 373.0295 [(M + Na)$^+$; calcd for $C_{15}H_{14}N_2O_4S_2Na$ 373.0293].

To a solution of the above phenol-aniline (180 mg, 0.51 mmol) in DMF (10 mL) were added triethylamine (1.075 mL, 7.71 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.24 mL, 5.14 mmol). After 2 h, the reaction was quenched with brine (40 mL). The resultant mixture was extracted with ether (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) provided **7** (178 mg, 60% yield) as a light yellow oil: IR ($CHCl_3$) 3400 (m), 2940 (s), 2880 (m), 1680 (s), 1600 (m), 1470 (s), 1350 (m), 1320 (w), 1260 (s), 1140 (m), 1090 (m), 940 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (m, 2 H), 6.94−6.82 (m, 3 H), 6.76 (s, 1 H), 4.74 (s, 2H), 3.50 (s, 1 H), 2.82 (s, 2 H), 0.98 (s, 9 H), 0.87 (s, 9 H), 0.27 (s, 6 H), −0.03 (s 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.0, 139.6, 139.2, 132.7, 132.6, 129.1, 128.2, 128.0, 118.9, 109.5, 105.1, 57.2, 30.7, 26.4, 25.5, 18.4, 18.1, −3.9, −4.6; high-resolution mass spectrum (ES, Na) *m*/*z* 579.2220 [(M + H)$^+$; calcd for $C_{27}H_{43}N_2O_4S_2(Si)_2$ 579.2202].

Methyl Ether (+)-27. A solution of (+)-**26** (1.013 g, 10.55 mmol) in diethyl ether−DMSO (5:1, 48 mL) at 0 °C was treated with *n*-BuLi (2.5 M in hexanes, 4.3 mL, 10.75 mmoL) and methyl iodide (0.985 mL, 15.82 mmol). The mixture was heated to reflux for 1 h, cooled to room temperature, diluted with ether (100 mL), and washed with ice-cold water (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford (+)-**27** (1.07 g, 92% yield) as a colorless oil: $[\alpha]^{23}_D$ +50.2° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 3300 (s), 3080 (w), 3000 (w), 2940 (s), 2820 (w), 1650 (m), 1450 (m), 1360 (s), 1260 (w), 1100 (s), 990 (m), 920 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1 H), 5.15 (m, 2 H), 4.05 (ddd, *J* = 6.5, 6.4, 2.0 Hz, 1 H), 3.41 (s, 3 H), 2.52 (m, 2 H), 2.49 (d, *J* = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 117.8, 82.0, 74.2, 70.6, 56.4, 39.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 128.1076 [(M + NH_4)$^+$; calcd for $C_7H_{14}NO$ 128.1074].

Aldehyde (+)-28. Ozone was bubbled through a solution of (+)-**27** (0.5 g, 4.54 mmol) in diethyl ether (40 mL) at −78 °C. The reaction was closely monitored by TLC, and the O_3 bubbling was immediately stopped when the starting material disappeared. The solution was then treated with triphenylphosphine (1.43 g, 5.46 mmol) and allowed to warm to room temperature. After being stirred at ambient temperature for 12 h, the mixture was concentrated in vacuo. Flash chromatography (ether/pentane, 1:1) afforded (+)-**28** (346 mg, 68% yield) as a light yellow oil: $[\alpha]^{23}_D$ +57.3° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 2940 (s), 2920 (s), 2840 (s), 1721 (m), 1463 (m), 1432 (w), 1390 (w), 1360 (m), 1255 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.0 Hz, 1 H), 4.47 (m, 1 H), 3.47 (s, 3 H), 2.86 (ddd, *J* = 2.1, 7.1, 17.2 Hz, 1 H), 2.78 (ddd, *J* = 1.8, 5.1, 17.2 Hz, 1 H), 2.55 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 80.8, 75.2, 65.7, 56.8, 48.7; high-resolution mass spectrum (CI, NH_3) *m*/*z* 130.0860 [(M + NH_4)$^+$; calcd for $C_6H_{12}NO_2$ 130.0868].

Acid (+)-4. To a suspension of PDC (1.13 g, 3 mmol) in DMF (2 mL) was added (+)-**28** (110 mg, 1 mmol) in ether (3.5 mL). The resultant mixture was stirred for 19 h, poured into water (60 mL), and extracted with ether (4 × 20 mL). The combined organic phases were washed twice with brine (40 mL, with 5 mL of 1 N HCl), dried over $MgSO_4$, filtered, and concentrated to provide (+)-**4** (98 mg, 78% yield) as a colorless oil: $[\alpha]^{23}_D$ +53.4° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3300 (m), 3000 (br s), 1715 (s), 1410 (m), 1340 (w), 1290 (s), 1105 (s), 905 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (ddd, *J* = 8.3, 5.1, 3.2 Hz, 1 H), 3.46 (s, 3 H), 2.84 (dd, *J* = 16.1, 8.3 Hz, 1 H), 2.78 (dd, *J* = 16.1, 5.1 Hz, 1 H), 2.52 (d, *J* = 2.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 80.7, 74.7, 66.9, 56.8, 40.8; high-resolution mass spectrum (CI, NH_3) *m*/*z* 146.0825 [(M + NH_4)$^+$; calcd for $C_6H_{12}NO_3$ 146.0817].

Allyl Bromide 30. A solution of **29** (3 g, 8.65 mmol) and triphenylphosphine (4.53 g, 17.3 mmol) in acetonitrile (80 mL) was treated with carbon tetrabromide (3.44 g, 10.38 mmol) and 2,6-lutidine (0.201 mL, 1.73 mmol). After 10 min, the mixture was added to saturated $NaHCO_3$ (100 mL) and extracted with hexanes (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 100:1) provided **30** (3.08 g, 87% yield) as a colorless oil: IR ($CHCl_3$) 2980 (s), 2930 (s), 2880 (s), 2860 (s), 1590 (w), 1460 (m), 1380 (m), 1200 (m), 1070 (m), 990 (s), 860 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 18.6, 1.0 Hz, 1 H), 6.17 (dt, *J* = 18.6, 6.7 Hz, 1 H), 3.98 (dd, *J* = 6.7, 1.0 Hz, 2 H), 1.55 (m, 6 H), 1.35 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 135.1, 35.8, 29.1, 27.2, 13.7, 9.6.

Anal. Calcd for $C_{15}H_{31}BrSn$: C, 43.94; H, 7.62. Found: C, 43.67; H, 7.59.

Phosphonate 31. To a solution of **30** (120 mg, 0.29 mmol) in DMF (2 mL) were added NaH (60% in mineral oil, 83 mg, 1.45 mmol) and diethyl phosphite (0.185 mL, 1.45 mmol) in DMF (2 mL). The resultant clear mixture was stirred for 3 h, added to water (25 mL) and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded **31** (123 mg, 90% yield) as a colorless oil: IR ($CHCl_3$) 2995 (m), 2960 (m), 2930 (m), 2580 (w), 2860 (w), 1600 (m), 1460 (m), 1395 (w), 1250 (s), 1060 (s), 960 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6,15 (ddt, *J* = 18.8, 4.5, 1.2 Hz, 1 H), 5.91 (m, 1 H), 4.10 (m, 4 H), 2.73 (ddd, *J* = 21.6, 6.9, 1.2 Hz, 2 H), 1.49 (m, 6 H), 1.32 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 136.4, 135.4, 135.3, 61.81, 61.76, 36.3, 35.2,

29.0, 27.2, 16.43, 16.38, 13.7, 9.5; high-resolution mass spectrum (ES, Na) *m/z* 491.1705 [(M + Na)$^+$; calcd for $C_{19}H_{41}O_3PSnNa$ 491.1713].

Vinyl Iodide 5. To a solution of **31** (40 mg, 0.086 mmol) in CH_2Cl_2 (1 mL) was added I_2 in CH_2Cl_2 until a purple color persisted. The mixture was stirred for an additional 30 min and then was quenched with saturated Na_2SO_3 (1 mL). The mixture was poured into brine (20 mL) and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) provided **5** (26 mg, 100% yield) as a light yellow oil: IR ($CHCl_3$) 3000 (s), 2930 (w), 1650 (w), 1445 (w), 1250 (s), 1025 (s), 970 (s), 940 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (m, 1 H), 6.30 (ddt, J = 14.5, 4.9, 1.2 Hz, 1 H), 4.13 (m, 4 H), 2.63 (ddd, J = 21.5, 7.6, 1.2 Hz, 2 H), 1.40 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 134.6, 79.6, 79.5, 62.3, 62.2, 34.5, 33.4, 16.49, 16.45; high-resolution mass spectrum (CI, NH_3) *m/z* 305.3102 [(M + H)$^+$; calcd for $C_7H_{15}IO_3P$ 305.3118].

Sulfone 33. A solution of (−)-**6** (120 mg, 0.32 mmol) in acetone (4 mL) was treated with 2,6-di-*tert* -butyl-4-methylpyridine (4 mg, 0.0192 mmol) and sodium iodide (192 mg, 1.28 mmol). The resultant cloudy solution was stirred for 1 h and then filtered through a short plug of neutral alumina. The filtrate was concentrated to dryness in vacuo to afford the corresponding unstable allyl iodide as a yellow oil. The allyl iodide was used immediately in the following step.

A solution of **7** (185 mg, 0.32 mmol) in THF (2 mL) at −78 °C was treated with sodium bis(trimethylsilyl)amide (1 M in THF, 1.28 mL, 1.28 mmol). After 5 min, the above allyl iodide in THF (2 mL) was introduced via cannula. The resultant yellow solution was stirred at −78 °C for 1.5 h, quenched with methanol (0.5 mL), added to brine (25 mL), and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1 to 1:1) gave recovered **7** (88 mg) and afforded **33** (147 mg, 50% yield or 95% yield based on recovered **7**) as a yellow foam: IR ($CHCl_3$) 3400 (m), 2960 (s), 2940 (s), 2860 (s), 1682 (s), 1600 (s), 1460 (s), 1362 (s), 1260 (s), 1145 (s), 1088 (s), 830 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.68−7.60 (complex series of m, 2 H), 6.97−6.90 (complex series of m, 1 H), 6.86−6.79 (complex series of m, 2 H), 6.78, 6.76 (diastereomers, s, s, 1 H), 5.82, 5.63 (diastereomers, t, t, J = 6.1 Hz, 1 H), 5.28−5.22 (complex series of m, 1 H), 5.17, 5.03 (diastereomers, d, d, J = 5.4 Hz, 1 H), 4.24−3.61 (complex series of m, 5 H), 3.37, 3.28 (diastereomers, s, s, 1 H), 3.08−2.90 (complex series of m, 2 H), 2.09−1.97 (complex series of m, 1 H), 1.86, 1.84 (diastereomers, s, s, 3 H), 1.82−1.73 (complex series of m, 2 H), 1.51−1.40 (overlapping s, 6 H), 1.06−0.90 (overlapping s, 30 H), 0.30−0.02 (overlapping s, 18 H); ^{13}C NMR (125 MHz, C_6D_6) δ169.4, 169.3, 140.2, 139.8, 139.5, 139.4, 139.2, 137.4, 136.8, 134.0, 133.9, 132.8, 129.5, 128.62, 128.61, 128.5, 128.3, 123.5, 123.2, 122.7, 122.2, 109.0, 105.9, 105.7, 100.9, 99.0, 71.4, 71.3, 70.5, 70.3, 69.7, 65.43, 65.38, 59.9, 59.7, 41.5, 41.4, 38.5, 38.3, 31.3, 30.4, 26.9, 26.79, 26.75, 26.18, 26.16, 26.10, 25.6, 25.2, 25.1, 24.5, 24.3, 21.6, 21.4, 19.04, 19.01, 18.9, 18.6, 18.5, 18.4, 12.72, 12.68, −3.2, −3.4, −3.6, −3.7, −4.1, −4.3, −4.4, −5.1, −5.2; high-resolution mass spectrum (ES, Na) *m/z* 941.4641 [(M + Na)$^+$; calcd for $C_{46}H_{78}N_2O_7S_2(Si)_3Na$ 941.4660].

Aniline (−)-3. A suspension of **33** (145 mg, 0.158 mmol) and Na_2HPO_4 (217 mg, 1.58 mmol) in anhydrous methanol (5 mL) at 0 °C was treated with excess sodium amalgam (5%, ca. 1.2 g). After 2 h, the mixture was filtered through a plug of silica gel with ethyl acetate as eluant, and the filtrate was concentrated to dryness in vacuo. The crude residue was then dissolved in chloroform (15 mL) and added to silica gel (ca. 2 g). After 20 min, the silica gel was removed by filtration, and the filtrate was concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1 to 1:1) afforded (−)-**3** (79 mg, 75% yield for two steps) as a yellow foam: $[\alpha]^{23}_D$ −2.5° (*c* 1.5, benzene); IR ($CHCl_3$) 3400 (m), 3000 (s), 2960 (s), 2935 (s), 2860 (s), 1680 (s), 1615 (s), 1470 (s), 1380 (s), 1360 (s), 1240 (s), 1090 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.22 (s, 1 H), 5.43 (t, J = 7.1 Hz, 1 H), 5.02 (d, J = 5.7 Hz, 1 H), 3.81 (m, 1 H), 3.70 (m, 2 H), 3.15 (br s, 2 H), 3.03 (s, 2 H), 2.98 (m, 2 H), 2.52 (m, 1 H), 2.36 (m, 1 H), 1.91 (s, 3 H), 1.85 (m, 2 H), 1.71 (m, 1 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.00 (s, 9 H), 0.97 (s, 9 H), 0.87 (d, J = 7.0 Hz, 3 H), 0.12 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.2, 138.1, 137.6, 135.3, 132.3, 131.0, 124.9, 108.2, 103.3, 100.5, 70.9, 69.2, 59.4, 41.6, 38.0, 30.1, 29.3, 27.9, 25.9, 25.8, 24.6, 24.1, 20.9, 18.4, 18.1, 12.3, −3.62, −3.64, −5.49, −5.54; high-resolution mass spectrum (ES, Na) *m/z* 687.3872 [(M + Na)$^+$; calcd for $C_{34}H_{60}N_2O_5S(Si)_2$-Na 687.3863].

Anal. Calcd for $C_{34}H_{60}N_2O_5S(Si)_2$: C, 61.44; H, 9.04; N, 4.22. Found: C, 61.54; H, 9.03; N, 3.82.

Amide (+)-35. A solution of (+)-**4** (20 mg, 0.156 mmol) in chloroform (3 mL) was treated with thionyl chloride (0.04 mL, 0.548 mmol). The resultant mixture was heated to reflux for 8 h and then concentrated to dryness in vacuo to afford the corresponding acid chloride as a yellow oil. The acid chloride was used immediately in the following step.

A solution of (−)-**3** (15 mg, 0.0226 mmol) and triethylamine (0.080 mL, 0.574 mmol) in THF (3 mL) was treated with the above acid chloride in THF (1 mL). The resultant mixture was stirred for 30 min, added to brine (20 mL), and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) afforded (+)-**35** (14 mg, 80% yield) as a white foam: $[\alpha]^{23}_D$ +4.8° (*c* 0.5, benzene); IR ($CHCl_3$) 3300 (w), 2960 (s), 2920 (s), 2860 (s), 1630 (s), 1600 (s), 1510 (s), 1440 (s), 1380 (m), 1250 (m), 1220 (m), 1100 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 8.12 (br s, 1 H), 7.70 (br s, 2 H), 5.38 (t, J = 7.6 Hz, 1 H), 5.01 (d, J = 5.5 Hz, 1 H), 4.42 (dt, J = 6.0, 1.9 Hz, 1 H), 3.83 (m, 1 H), 3.68 (m, 2 H), 3.20 (s, 3 H), 2.90−2.80 (m, 2 H), 2.85 (s, 2 H), 2.76 (d, J = 6.0 Hz, 2 H), 2.44 (m, 1 H), 2.32 (m, 1 H), 2.06 (d, J = 1.9 Hz, 1 H), 1.90 (s, 3 H), 1.73 (m, 2 H), 1.70 (m, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 0.98 (s, 9 H), 0.94 (s, 9 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.5, 167.1, 164.3, 138.5, 136.0, 133.2, 131.1, 124.9, 115.5, 108.1, 101.1, 81.7, 75.1, 71.3, 69.7, 68.2, 59.7, 56.8, 44.7, 41.9, 38.2, 30.0, 29.4, 27.9, 25.9, 25.8, 24.8, 24.2, 21.1, 18.4, 18.2, 12.4, −3.9, −4.0, −5.5, −5.6; high-resolution mass spectrum (ES, Na) *m/z* 797.4045 [(M + Na)$^+$; calcd for $C_{40}H_{66}N_2O_7S(Si)_2$-Na 797.4027].

Phenol (+)-36. A solution of (+)-**35** (385 mg, 0.50 mmol) in methylene chloride (10 mL) at 0 °C was treated with bis-(triphenylphosphine)palladium(II) chloride (40 mg, 0.05 mmol) and tributyltin hydride (0.88 mL, 3.27 mmol). After 30 min, the mixture was filtered through a short plug of silica gel with ethyl acetate as eluant, and the filtrate was concentrated to dryness in vacuo. The crude residue was then dissolved in THF (10 mL), cooled to 0 °C, and treated with tetrabutylammonium fluoride (1 M in THF, 1 mL, 1 mmol). After 5 min, the resultant mixture was poured into brine (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) provided (+)-**36** (280 mg, 59% yield for two steps) as a yellow oil: $[\alpha]^{23}_D$ +5.0° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3400 (w), 2950 (s), 2920 (s), 2840 (m), 1670 (s), 1590 (w), 1520 (w), 1450 (s), 1370 (s), 1240 (m), 1080 (s), 830 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.78 (s, 1 H), 9.52 (s, 1 H), 8.33 (s, 1 H), 6.48 (s, 1 H), 6.28 (d, J = 19.1 Hz, 1 H), 5.90 (dd, J = 19.1, 6.7 Hz, 1 H), 5.41 (t, J = 7.4 Hz, 1 H), 5.05 (d, J = 5.6 Hz, 1 H), 3.86−3.79 (m, 2 H), 3.74−3.65 (m, 2 H), 3.17 (s, 3 H), 3.20−3.08 (m, 2 H), 3.03 (s, 2 H), 2.56−2.48 (m, 2 H), 2.42−2.37 (m, 2 H), 1.91 (s, 3 H), 1.90−1.78 (m, 3 H), 1.70−1.50 (m, 6 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.45−1.30 (m, 6 H), 0.99−0.93 (m, 27 H), 0.072 (s, 3 H), 0.067 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 166.8, 146.4, 144.5, 135.5, 133.1, 131.4, 130.1, 125.6, 125.5, 119.0, 109.4, 100.8, 82.0, 71.4, 69.7, 59.8, 56.4, 42.9, 42.0, 38.4, 30.1, 29.5, 27.6, 26.1, 25.0, 24.4, 21.3, 18.4, 17.3, 13.9, 12.7, 9.8, −5.15, −5.20; high-resolution mass spectrum (ES, Na) *m/z* 975.4375 [(M + Na)$^+$; calcd for $C_{46}H_{80}N_2O_7S(Si)(Sn)Na$ 975.4390].

Alcohol (+)-37. A solution of (+)-**36** (130 mg, 0.137 mmol) in THF (5 mL) was treated with tetrabutylammonium fluoride (1 M in THF, 0.5 mL, 0.50 mmol). After 8 h, the resultant

mixture was added to brine (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 4:1) afforded (+)-**37** (93.8 mg, 82% yield) as a yellow oil: $[\alpha]^{23}_D$ +4.6° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3500−2500 (br s), 3040 (w), 2960 (s), 2920 (s), 2860 (m), 1660 (s), 1580 (w), 1520 (w), 1450 (s), 1370 (s), 1060 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.52 (br s, 1 H), 9.01 (br s, 1 H), 8.37 (s, 1 H), 6.30 (s, 1 H), 6.28 (d, J = 19.1 Hz, 1 H), 5.92 (dd, J = 19.1, 6.7 Hz, 1 H), 5.50 (t, J = 7.6 Hz, 1 H), 5.02 (d, J = 5.6 Hz, 1 H), 3.84−3.70 (m, 3 H), 3.50 (dt, J = 8.1, 3.7 Hz, 1 H), 3.17 (s, 3 H), 3.19−3.04 (m, 2 H), 3.02 (s, 2 H), 2.52−2.34 (m, 5 H), 1.90 (s, 3 H), 1.91−1.82 (m, 1 H), 1.64−1.58 (m, 6 H), 1.43−1.21 (m, 8 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.02−0.91 (m, 15 H), 0.79 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.6, 166.8, 146.7, 144.6, 135.3, 133.0, 132.6, 131.2, 130.0, 125.8, 119.0, 109.8, 100.9, 82.2, 74.5, 69.3, 61.0, 56.5, 43.0, 41.6, 37.1, 30.2, 29.5, 27.6, 24.9, 24.2, 21.1, 17.3, 13.9, 13.7, 12.8, 9.8; high-resolution mass spectrum (ES, Na) *m/z* 861.3510 [(M + Na)$^+$; calcd for $C_{40}H_{66}N_2O_7S(Sn)Na$ 861.3527].

Aldehyde (+)-38. A solution of (+)-**37** (27 mg, 0.032 mmol) in DMSO (1.5 mL) was treated with triethylamine (0.5 mL) and pyridine·SO_3 complex (103 mg, 0.64 mmol). The solution was stirred for 1 h, poured into ethyl acetate (20 mL), and washed with brine (10 mL). After separation, the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo to provide the corresponding aldehyde. The aldehyde was used immediately in the following step.

A solution of the above aldehyde in DMF (2 mL) was treated with triethylamine (0.089 mL, 0.64 mmol) and TBSOTf (0.073 mL, 0.32 mmol). After 20 min, the mixture was added to ether (20 mL) and washed with brine (2 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Preparative TLC (ethyl acetate/hexanes, 1:1) afforded (+)-**38** (13 mg, 42% yield for two steps) as a yellow oil: $[\alpha]^{23}_D$ +10.6° (*c* 1.01, EtOAc); IR ($CHCl_3$) 2920 (s), 2840 (m), 1680 (s), 1590 (m), 1510 (m), 1430 (m), 1360 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.42 (m, 1 H), 9.05 (s, 1 H), 8.51 (s, 1 H), 8.18 (s, 1 H), 6.37 (d, J = 19 Hz, 1 H), 6.10 (dd, J = 19.0, 6.8 Hz, 1 H), 5.33 (t, J = 7.4 Hz, 1 H), 4.89 (d, J = 5.7 Hz, 1 H), 4.10 (m, 1 H), 3.72 (ddd, J = 8.8, 8.7, 3.0 Hz, 1 H), 3.20 (s, 3 H), 3.00−2.83 (m, 3 H), 2.89 (s, 2 H), 2.74 (dd, J = 14.5, 8.5 Hz, 1 H), 2.32−2.17 (m, 4 H), 1.99−1.95 (m, 1 H), 1.80 (s, 3 H), 1.62−1.47 (m, 6 H), 1.41−1.18 (m, 12 H), 1.03−0.82 (m, 24 H), 0.63 (d, J = 6.9 Hz, 3 H), 0.06 (s, 3 H), −0.06 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 169.3, 164.6, 146.8, 138.3, 135.0, 133.0, 131.7, 130.5, 129.9, 124.8, 115.0, 108.1, 100.8, 82.0, 70.0, 68.9, 56.2, 47.3, 44.7, 40.9, 29.8, 29.7, 29.2, 27.4, 27.3, 25.8, 24.1, 23.7, 20.7, 18.3, 13.6, 12.1, 9.5, −3.5, −4.3; high-resolution mass spectrum (ES, Na) *m/z* 973.4211 [(M + Na)$^+$; calcd for $C_{46}H_{78}N_2O_7S(Si)(Sn)Na$ 973.4200].

Pivaloate (+)-43. To a solution of (−)-**15** (150 mg, 0.42 mmol) in THF (5 mL) were added triethylamine (0.584 mL, 4.2 mmol), DMAP (5.1 mg, 0.042 mmol), and trimethylacetyl chloride (0.18 mL, 2.1 mmol). The resulting white suspension was stirred for an additional 30 min, added to brine-saturated $NaHCO_3$ (1:1, 40 mL), and extracted with ether (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 8:1) afforded (+)-**43** (186 mg, 100% yield) as a colorless oil: $[\alpha]^{23}_D$ +0.9° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2880 (m), 1809 (s), 1713 (s), 1460 (m), 1380 (m), 1280 (m), 1210 (s), 1160 (s), 1130 (m), 1095 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37−5.31 (m, 1 H), 4.72−4.68 (m, 1 H), 4.63−4.59 (m, 2 H), 3.66−3.62 (m, 2 H), 3.49−3.47 (td, J = 9.3, 2.8 Hz, 1 H), 1.80−1.60 (m, 3 H), 1.69 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.17 (s, 9 H), 0.87 (s, 9H), 0.80 (d, J = 6.9, 3 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 138.6, 121.0, 100.7, 71.1, 70.6, 61.2, 59.4, 41.0, 38.7, 37.8, 27.2, 25.9, 24.7, 24.0, 21.2, 18.2, 12.0, −5.33, −5.37; high-resolution mass spectrum (ES, Na) *m/z* 465.3000 [(M + Na)$^+$; calcd for $C_{24}H_{46}O_5SiNa$ 465.3012].

Aldehyde (+)-41. To a solution of (+)-**43** (160 mg, 0.36 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1 M in THF, 1.5 mL, 1.5 mmol). The resultant yellow solution was stirred for 12 h, poured into brine (20 mL), and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded the corresponding alcohol (119 mg, 100% yield) as a colorless oil: $[\alpha]^{23}_D$ +11.2° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3510 (s), 2990 (s), 2930 (m), 1715 (s), 1480 (m), 1452 (m), 1380 (s), 1281 (s), 1205 (s), 1160 (s), 1120 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40−5.38 (m, 1 H), 4.72−4.56 (m, 3 H), 3.79−3.70 (m, 2 H), 3.50 (dt, J = 9.1, 2.9 Hz, 1 H), 2.52 (br s, 1 H), 1.83−1.62 (m, 3 H), 1.70 (s, 3 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.17 (s, 9 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 138.2, 121.3, 101.0, 75.0, 70.5, 61.6, 61.0, 40.8, 38.7, 36.2, 27.2, 24.6, 24.0, 21.1, 12.2; high-resolution mass spectrum (ES, Na) *m/z* 351.2146 [(M + Na)$^+$; calcd for $C_{18}H_{32}O_5Na$ 351.2147].

A solution of the above alcohol (22 mg, 0.067 mmol) in dimethyl sulfoxide (1.5 mL) was treated with triethylamine (0.5 mL) and Py·SO_3 complex (106 mg, 0.67 mmol). After 20 min, the resultant yellow mixture was added to brine (20 mL) and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) provided (+)-**41** (20 mg, 90% yield) as a yellow oil: $[\alpha]^{23}_D$ +12.6° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 2990 (s), 2940 (s), 2880 (m), 1720 (s), 1450 (m), 1380 (s), 1282 (m), 1210 (s), 1160 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (m, 1 H), 5.41−5.35 (m, 1 H), 4.80−4.70 (m, 2 H), 4.66−4.57 (m, 1 H), 3.83 (dt, J = 9.2, 8.7 Hz, 1 H), 2.60 (ddd, J = 16.3, 9.3, 2.6 Hz, 1 H), 2.50 (ddd, J = 16.3, 3.7, 1.7 Hz, 1 H), 1.86−1.82 (m, 1 H), 1.71 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 1.17 (s, 9 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 178.5, 138.0, 121.5, 101.2, 70.3, 70.1, 61.0, 47.6, 40.5, 38.7, 27.2, 24.3, 23.9, 21.1, 12.1; high-resolution mass spectrum (ES, Na) *m/z* 349.1993 [(M + Na)$^+$; calcd for $C_{18}H_{30}O_5Na$ 349.1991].

Alcohol (+)-44. A solution of (+)-**28** (100 mg, 0.89 mmol) and tributyltin hydride (1.2 mL, 4.45 mmol) in toluene (10 mL) was immersed in a preheated oil bath (90 °C) for 5 min before AIBN (36.5 mg, 0.225 mmol) was added in one portion. The solution was then heated to 100 °C for 12 h. The mixture was cooled to room temperature and then concentrated to dryness in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1) afforded (+)-**44** (242 mg, 67% yield) as a colorless oil: $[\alpha]^{23}_D$ +17.7° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3500 (br s), 2960 (s), 2930 (s), 2880 (m), 2860 (m), 1600 (w), 1450 (m), 1100 (m), 1070 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (d J = 19.1 Hz, 1 H), 5.80 (dd, J = 19.1, 7.2 Hz, 1 H), 3.72 (m, 3 H), 3.21 (s, 3 H), 2.53 (dd, J = 6.3, 4.5 Hz, 1 H), 1.75 (m, 2 H), 1.48 (m, 6 H), 1.24 (m, 6 H), 0.95 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 131.9, 85.5, 60.9, 56.17, 37.7, 29.1, 27.2, 13.7, 9.5; high-resolution mass spectrum (CI, NH_3) *m/z* 349.1192 [(M − C_4H_9)$^+$; calcd for $C_{14}H_{29}O_2Sn$ 349.1189].

Anal. Calcd for $C_{18}H_{38}O_2Sn$: C, 53.33; H, 9.38. Found: C, 53.44; H, 9.45.

Vinyl Iodide (+)-45. To a solution of (+)-**44** (110 mg, 0.272 mmol) in CH_2Cl_2 (2 mL) was added I_2 in CH_2Cl_2 until purple color persisted. The solution was stirred for an additional 30 min, then quenched with a saturated Na_2SO_3 solution (1 mL). The mixture was added to brine (20 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) provided (+)-**45** (66 mg, 100% yield) as a light yellow oil: $[\alpha]^{23}_D$ +46.8° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3500 (br m), 3040 (m), 2990 (s), 2930 (s), 2820 (m), 1610 (s), 1440 (s), 1350 (m), 1260 (s), 1170 (m), 1100 (s), 950 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (dd, J = 14.6, 7.4 Hz, 1 H), 6.36 (d, J = 14.6 Hz, 1 H), 3.75 (m, 3 H), 3.30 (s, 3 H), 2.57 (dd, J = 6.1, 4.5 Hz, 1 H), 1.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 82.8, 78.7, 59.8, 56.7, 37.2; high-resolution mass spectrum (CI, NH_3) *m/z* 260.0156 [(M + NH_4)$^+$; calcd for $C_6H_{15}INO_2$ 260.0148].

Alcohol (+)-46. To a solution of (+)-**45** (108.4 mg, 0.448 mmol) in DMF (3 mL) was added bis(acetonitrile)palladium(II) chloride (11.6 mg, 0.0448 mmol). After 2 min, **31** (230 mg, 0.49 mmol) in DMF (1 mL) was added via a syringe. The resultant

dark red solution was stirred at room temperature for 21 h, poured into brine (20 mL), and extracted with ether (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (methanol/ethyl acetate, 1:10) provided (+)-**46** (91.6 mg, 70% yield) as a yellow oil: $[\alpha]^{23}_D$ +10.7° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3400 (br s), 3000 (s), 2920 (m), 2820 (w), 1720 (w), 1400 (m), 1230 (s), 1160 9m), 1100 (m), 920 (s), 890 (m), 860 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.18−6.11 (m, 2 H), 5.63−5.54 (m, 1 H), 5.49−5.42 (m, 1 H), 4.07−4.02 (m, 4 H), 3.81−3.75 (m, 1 H), 3.72−3.64 (m, 2 H), 3.24 (s, 3 H), 2.73−2.61 (br s, 1 H), 2.60−2.55 (dd, *J* = 22.3, 7.4 Hz, 2 H), 1.81−1.66 (m, 2 H), 1.27 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 134.0, 132.64, 132.60, 131.99, 131.96, 122.9, 122.8, 81.4, 62.02, 61.97, 60.4, 56.3, 37.9, 31.2, 30.1, 16.44, 16.39; high-resolution mass spectrum (ES, Na) *m/z* 315.1340 [(M + Na)$^+$; calcd for $C_{13}H_{25}O_5PNa$ 315.1337].

TBS Ether (+)-42. To a solution of (+)-**46** (25 mg, 0.086 mmol) in DMF (2 mL) were added imidazole (11.7 mg, 0.17 mmol) and *tert*-butyldimethylsilyl chloride (19.3 mg, 0.13 mmol). The solution was stirred for 10 min, added to brine (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 5:1) afforded (+)-**42** (34 mg, 98% yield) as a colorless oil: $[\alpha]^{23}_D$ +2.1° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3000 (s), 2960 (s), 2940 (s), 1460 (m), 1390 (m), 1250 (s), 1210 (s), 1100 (s), 1060 (s), 1030 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17−6.14 (m, 2 H), 5.64−5.60 (m, 1 H), 5.48−5.44 (m, 1 H), 4.11−4.05 (m, 4 H), 3.74−3.66 (m, 2 H), 3.61−3.57 (m, 1 H), 3.22 (s, 3 H), 2.60 (dd, *J* = 22.3, 7.1 Hz, 2 H), 1.75−1.60 (m, 2 H), 1.29 (t, *J* = 6.7 Hz, 6 H), 0.87 (s, 9 H), 0.020 (s, 3 H), 0.013 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 134.3, 133.6, 133.5, 131.69, 131.65, 122.4, 122.3, 78.6, 62.02, 61,97, 59.3, 56.3, 38.8, 31.3, 30.2, 25.9, 18.3, 16.5, 16.4, −5.34, −5.36; high-resolution mass spectrum (ES, Na) *m/z* 429.2210 [(M + Na)$^+$; calcd for $C_{19}H_{39}O_5PSiNa$ 429.2202].

Vinyl Iodide (+)-55. A solution of (+)-**44** (210 mg, 0.568 mmol) in CH_2Cl_2 (6 mL) was treated with triethylamine (0.3 mL, 2.1 mmol) and TBSOTf (0.2 mL, 0.86 mmol). After 5 min, the solution was added to brine-saturated $NaHCO_3$ (1:1, 20 mL) and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 15:1) afforded the corresponding TBS ether (295 mg, 100% yield) as a colorless oil: $[\alpha]^{23}_D$ +7.7° (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3001 (m), 2960 (s), 2930 (s), 2860 (s), 1460 (m), 1250 (m), 1200 (s), 1080 (s), 990 (m), 920 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 19.0, 0.8 Hz, 1 H), 5.75 (dd, *J* = 19.0, 7.6 Hz, 1 H), 3.72−3.60 (m, 3 H), 3.22 (s, 3 H), 1.82−1.78 (m, 1 H), 1.68−1.61 (m, 1 H), 1.54−1.47 (m, 6 H), 1.30−1.21 (m, 6 H), 1.89−1.81 (m, 24 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 131.2, 82.5, 59.5, 56.1, 38.5, 29.2, 27.3, 25.9, 18.1, 13.7, 9.51, −5.3; high-resolution mass spectrum (CI, NH_3) *m/z* 538.3100 [(M + NH_4)$^+$; calcd for $C_{24}H_{56}NO_2SnSi$ 538.3102].

A solution of the above TBS ether (290 mg, 0.559 mmol) in CH_2Cl_2 was treated dropwise with a CH_2Cl_2 solution of I_2 until the purple color persisted. The reaction was then quenched with saturated Na_2SO_3 solution (10 mL), poured into brine (20 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (+)-**55** (191 mg, 96% yield) as a colorless oil: $[\alpha]^{23}_D$ +10.4° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3005 (s), 2960 (s), 2930 (s), 2860 (s), 1601 (s), 1470 (m), 1250 (s), 1210 (s), 1100 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 14.5, 7.8 Hz, 1 H), 6.24 (d, *J* = 14.5, 1 H), 3.73−3.68 (m, 2 H), 3.64−3.59 (m, 1 H), 3.23 (s, 3 H), 1.78−1.72 (m, 1 H), 1.68−1.62 (m, 1 H), 0.87 (s, 9 H), 0.03 (s 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 80.7, 77.9, 58.8, 56.7, 37.9, 25.9, 18.3, −5.36, −5.40; high-resolution mass spectrum (CI, NH_3) *m/z* 357.0746 [(M + H)$^+$; calcd for $C_{12}H_{26}IO_2Si$ 357.0746].

Aldehyde (−)-54. A solution of **29** (25 mg, 0.07 mmol) in DMF−THF (2:1, 0.6 mL) was treated with bis(acetonitrile)-palladium(II) chloride (1.82 mg, 0.007 mmol) in DMF (0.3 mL). After 2 min, a solution of (+)-**55** (26.8 mg, 0.077 mmol) in THF (0.5 mL) was added. The resultant dark green solution was stirred at room temperature for an additional 12 h. The mixture was then added to brine (20 mL) and extracted with ether (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) provided the corresponding alcohol (19.3 mg, 96% yield) as a yellow oil: $[\alpha]^{23}_D$ +4.0° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3604 (m), 3050 (s), 2960 (s), 2930 (s), 2860 (s), 1460 (m), 1250 (s), 1205 (s), 1090 (s), 990 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.30−6.21 (m, 2 H), 5.85−5.79 (m, 1 H), 5.56−5.52 (dd, *J* = 14.9, 7.9 Hz, 1 H), 4.15 (d, *J* = 6.0 Hz, 2 H), 3.82−3.69 (m, 2 H), 3.64−3.58 (m, 1 H), 3.21 (s, 3 H), 1.70−1.62 (m, 2 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 132.2, 131.6, 130.6, 78.7, 63.1, 59.3, 56.2, 38.7, 25.9, 18.3, −5.34, −5.36; high-resolution mass spectrum (CI, NH_3) *m/z* 269.1935 [(M − OH)$^+$; calcd for $C_{15}H_{29}O_2Si$ 269.1937].

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.13; H, 10.70.

To a solution of oxalyl chloride (2 M in CH_2Cl_2, 0.148 mL, 0.296 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added dimethyl sulfoxide (0.042 mL, 0.592 mmol). After 5 min, to the mixture was added the above alcohol (18 mg, 0.063 mmol) in CH_2Cl_2 (0.4 mL) and triethylamine (0.206 mL, 1.48 mmol). The resultant light yellow solution was stirred for an additional 5 min, poured into brine-saturated $NaHCO_3$ (10 mL each), and extracted with ether (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (−)-**54** (16.1 mg, 90% yield) as a yellow oil: $[\alpha]^{23}_D$ −11.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3002 (s), 2950 (s), 2930 (s), 2860 (s), 2820 (m), 1675 (s), 1640 (s), 1460 (m), 1250 (s), 1205 (s), 1160 (m), 1100 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 8.2 Hz, 1 H), 7.04 (dd, *J* = 15.3, 11.0 Hz, 1 H), 6.44 (dd, *J* = 15.3, 11.0 Hz, 1 H), 6.10 (m, 2 H), 3.96 (m, 1 H), 3.73−3.68 (m, 1 H), 3.64−3.59 (m, 1 H), 3.27 (s, 3 H), 1.82−1.71 (m, 2 H), 0.91 (s, 9 H), 0.025 (s 3 H), 0.018 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 151.1, 145.5, 131.8, 129.1, 78.1, 58.9, 57.0, 38.3, 25.9, 18.3; high-resolution mass spectrum (CI, NH_3) *m/z* 285.2250 [(M + H)$^+$; calcd for $C_{15}H_{29}O_3Si$ 285.2245].

Sulfone (+)-53. A solution of (+)-**56** (190 mg, 0.58 mmol) in THF (10 mL) was treated with triphenylphosphine (304.3 mg, 1.16 mmol), 2-mecaptobenzothiazole (262 mg, 1.57 mmol), and diethyl azodicarboxylate (0.22 mL, 1.39 mmol). After 5 min, the resultant mixture was added to saturated $NaHCO_3$ (25 mL) and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded the corresponding sulfide (310 mg, contaminated with a small amount of triphenylphosphine).

A solution of the above sulfide in ethanol (10 mL) at 0 °C was treated with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (143 mg, 0.116 mmol) in hydrogen peroxide (30%, 1.3 mL, 1.16 mmol). The resultant suspension was stirred at ambient temperature for 12 h, added to brine (25 mL), and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (+)-**53** (251 mg, 85% yield for two steps) as a colorless oil: $[\alpha]^{23}_D$ +2.3° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3009 (s), 2980 (s), 2930 (m), 1720 (s), 1465 (m), 1380 (m), 1330 (s), 1280 (m), 1200 (s), 1150 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.6 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 7.66−7.58 (m, 2 H), 5.34 (t, *J* = 5.6 Hz, 1 H), 4.71−4.65 (m, 1 H), 4.63−4.55 (m, 2 H), 3.79−3.71 (m, 1 H), 3.53−3.47 (m, 1 H), 3.42−3.37 (m, 1 H), 2.23−2.18 (m, 1 H), 2.04−1.97 (m, 1 H), 1.75−1.70 (m, 1 H), 1.64 (s, 3 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 1.16 (s, 9 H), 0.79 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 165.8, 152.8, 137.8, 136.8, 128.1, 127.7, 125.5, 122.4, 121.5, 101.1, 72.8, 70.4, 61.0, 52.0, 40.8, 27.2, 27.1, 24.4, 23.9, 21.1, 12.2; high-resolution mass spectrum (ES, Na) *m/z* 532.1806 [(M + Na)$^+$; calcd for $C_{25}H_{35}NO_6S_2Na$ 532.1803].

Sulfone (+)-60. A solution of (+)-**56** (1.83 g, 5.58 mmol) in THF (50 mL) was treated with triphenylphosphine (2.2 g, 8.39 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (1.99 g, 11.18 mmol), and

diethyl azodicarboxylate (1.584 mL, 10.06 mmol). After 5 min, the mixture was added to saturated $NaHCO_3$ (100 mL) and extracted with ether (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded the corresponding sulfide (3 g, contaminated with a small amount of triphenylphosphine).

A solution of the above sulfide in ethanol (40 mL) was cooled to 0 °C and treated with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.69 g, 0.558 mmol) in hydrogen peroxide (30%, 10 mL, 88 mmol). The resultant suspension was stirred at ambient temperature for 12 h, added to brine (100 mL), and extracted with ether (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (+)-**60** (2.06 g, 71% yield for two steps) as a colorless oil: $[\alpha]^{23}_D$ +5.4° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3005 (s), 2980 (s), 1720 (s), 1450 (m), 1380 (m), 1340 (s), 1150 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, 2 H), 7.62−7.51 (m, 3 H), 5.34 (t, J = 6.7 Hz, 1 H), 4.74−4.70 (m, 1 H), 4.63 (d, J = 5.6 Hz, 1 H), 4.59−4.56 (m, 1 H), 4.01−3.90 (m, 1 H), 3.80−3.72 (m, 1 H), 3.46−3.41 (m, 1 H), 2.30−2.21 (m, 1 H), 2.12−2.03 (m, 1 H), 1.82−1.76 (m, 1 H), 1.68 (s, 3 H), 1.31 (s, 6 H), 1.16 (s, 9 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 153.5, 137.8, 133.1, 131.5, 129.7, 125.1, 121.6, 101.2, 72.6, 70.4, 61.0, 53.2, 40.8, 38.7, 27.2, 26.9, 24.4, 24.0, 21.1, 12.2; high-resolution mass spectrum (ES, Na) *m*/*z* 543.2265 [(M + Na)$^+$; calcd for $C_{25}H_{36}N_4O_6SNa$ 543.2253].

Triene (+)-48. A solution of (+)-**60** (1.9 g, 3.65 mmol) in THF (20 mL) at −78 °C was treated with potassium bis(trimethylsilyl)amide (0.5 M in toluene, 9.5 mL, 4.75 mmol). The resultant yellow solution was stirred for 20 min before (−)-**54** (1.1 g, 3.84 mmol) in THF (10 mL) was introduced via cannula. The mixture was stirred for 1 h at −78 °C, warmed to room temperature, and stirred for an additional 1 h. The mixture was poured into brine (100 mL) and extracted with ether (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) provided (+)-**48** (1.8 g, 85% yield) as a colorless oil: $[\alpha]^{23}_D$ +9.0° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2970 (s), 2940 (s), 1720 (s), 1470 (m), 1380 (s), 1200 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.23−6.07 (m, 4 H), 5.79−5.70 (m, 1 H), 5.50 (dd, J = 14.5, 7.8 Hz, 1 H), 5.32 (t, J = 6.3 Hz, 1 H), 4.73−4.68 (m, 1 H), 4.66−4.57 (m, 2 H), 3.80−3.68 (m, 2 H), 3.64−3.57 (m, 1 H), 3.38−3.32 (m, 1 H), 3.23 (s, 3 H), 2.32−2.25 (m, 2H), 1.85−1.74 (m, 2 H), 1.67 (s, 3 H), 1.70−1.60 (m, 1 H), 1.27 (s, 6 H), 1.15 (s, 9 H), 0.87 (s, 9 H), 0.80 (d, J = 7.1 Hz, 3 H), 0.014 (s, 3 H), 0.008 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 138.4, 133.4, 133.0, 132.6, 132.2, 131.3, 130.3, 121.2, 100.8, 78.8, 74.5, 70.6, 61.1, 59.3, 56.2, 40.3, 38.9, 38.7, 37.8, 27.2, 25.9, 24.7, 23.9, 21.2, 18.3, 12.4, −5.33, −5.36; high-resolution mass spectrum (ES, Na) *m*/*z* 601.3899 [(M + Na)$^+$; calcd for $C_{33}H_{58}O_6SiNa$ 601.3900].

Anal. Calcd for $C_{33}H_{58}O_6(Si)$: C, 68.47; H, 10.10. Found: C, 68.25; H, 10.03.

Alcohol (−)-61. A solution of (+)-**48** (1.74 g, 3.01 mmol) in CH_2Cl_2 (20 mL) at −78 °C was treated with DIBAL (1 M in hexane, 6.02 mL, 6.02 mmol). The resultant solution was stirred for 10 min, quenched with methanol (5 mL), diluted with ether (150 mL), and then stirred vigorously with a saturated Rochelle salt solution (200 mL) until two clear layers appeared. After separation, the aqueous phase was extracted with ether (3 × 150 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) afforded (−)-**61** (1.38 g, 93% yield) as a colorless oil: $[\alpha]^{23}_D$ −6.1° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3500 (br s), 3004 (s), 2960 (s), 2930 (s), 1740 (s), 1380 (s), 1210 (s), 1190 (s), 1100 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21−6.10 (m, 4 H), 5.75−5.70 (m, 1 H), 5.56−5.40 (m, 2 H), 4.50 (d, J = 5.2 Hz, 1 H), 4.21−4.13 (m, 1 H), 4.09−4.01 (m, 1 H), 3.80−3.68 (m, 2 H), 3.64−3.57 (m, 1 H), 3.40−3.35 (m, 1 H), 3.19 (s, 3 H), 2.31−2.27 (m, 2 H), 2.18−2.12 (m, 1 H), 1.80−1.73 (m, 2 H), 1.67 (s, 3 H), 1.68−1.60 (m, 1 H), 1.36 (s, 3 H), 1.34(s, 3 H), 0.87 (s, 9 H), 0.79 (d, J = 7.4 Hz, 3 H), 0.020 (s, 3 H), 0.014 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.2, 133.5, 132.6, 132.4, 131.1, 130.6, 126.3, 101.0, 78.8, 74.6, 71.9, 59.3, 58.8, 56.2, 39.6, 38.9, 37.8, 25.9, 24.9, 23.9, 21.7, 18.3, 12.6, −5.33, −5.35; high-resolution mass spectrum (CI, NH_3) *m*/*z* 512.3770 [(M + NH_4)$^+$; calcd for $C_{28}H_{54}NO_5Si$ 512.3771].

Allyl Chloride (+)-40. A solution of (−)-**61** (185 mg, 0.374 mmol) in DMF (4 mL) was treated with 2,6-lutidine (0.175 mL, 1.5 mmol), lithium chloride (63.6 mg, 1.5 mmol), and mesyl chloride (0.058 mL, 0.75 mmol). The mixture was stirred at room temperature for 1 h and then added to brine and saturated $NaHCO_3$ (25 mL each). The resultant mixture was extracted with ether (3 × 50 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**40** (150 mg, 78% yield) as a colorless oil: $[\alpha]^{23}_D$ +2.9° (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3001 (s), 2940 (s), 2880 (m), 1470 (m), 1380 (s), 1210 (s), 1100 (s), 1000 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22−6.08 (m, 4 H), 5.82−5.76 (m, 1 H), 5.52−5.37 (m, 2 H), 4.65 (d, J = 5.6 Hz, 1 H), 4.22−4.17 (m, 2 H), 3.81−3.70 (m, 2 H), 3.67−3.55 (m, 1 H), 3.38−3.31 (m, 1 H), 3.22 (s, 3 H), 2.35−2.27 (m, 2 H), 1.90−1.81 (m, 2 H), 1.70−1.59 (m, 1 H), 1.68 (s, 3 H), 1.31 (s, 6 H), 0.87 (s, 9 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.020 (s, 3 H), 0.014 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 133.5, 133.0, 132.6, 132.3, 131.2, 130.4, 122.8, 100.9, 78.8, 74.5, 70.9, 59.3, 56.2, 41.1, 40.2, 38.9, 37.6, 26.0, 24.7, 23.9, 21.4, 17.6, 12.6, −5.33, −5.35; high-resolution mass spectrum (CI, NH_3) *m*/*z* 530.3427 [(M + NH_4)$^+$; calcd for $C_{28}H_{53}ClNO_4Si$ 530.3432].

Sulfone 63. A solution of (+)-**40** (530 mg, 1.03 mmol) in acetone (10 mL) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (12.8 mg, 0.062 mmol) and sodium iodide (186 mg, 1.24 mmol). The resultant cloudy solution was stirred for 1 h and filtered through a short pack of neutral alumina. The filtrate was concentrated and dried under high vacuum for 1 h to afford the corresponding unstable allyl iodide as a yellow oil. The allyl iodide was used immediately in the following step.

A solution of **7** (620 mg, 1.073 mmol) in THF (10 mL) at −78 °C was treated with sodium bis(trimethylsilyl)amide (1 M in THF, 4.29 mL, 4.29 mmol). To the resultant yellow solution was added the above allyl iodide in THF (5 mL) via cannula. The resultant mixture was stirred at −78 °C for an additional 1.5 h, quenched with methanol (1 mL), added to brine (50 mL), and extracted with ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded recovered **7** (220 mg) and provided **63** (695 mg, 64% yield or 95% yield based on recovered **7**) as a yellow foam. NMR analysis of **63** indicated a 2:1 mixture of diastereomers: IR ($CHCl_3$) 3390 (m), 2940 (s), 2920 (s), 2860 (s), 1670 (s), 1590 (s), 1450 (s), 1360 (m), 1352 (s), 1250 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50, 9.40 (diastereomers, s, s, 1 H), 7.51 (complex series of m, 2 H), 7.46 (complex series of m, 1 H), 7.23 (complex series of m, 2 H), 6.42, 6.39 (diastereomers, s, s, 1 H), 6.25−6.10 (complex series of m, 4 H), 5.79−5.72 (complex series of m, 1 H), 5.60−5.47 (complex series of m, 1 H), 5.35, 5.15 (diastereomers, t, t, J = 6.0 Hz, 1 H), 5.03−4.96 (complex series of m, 1 H), 4.78, 4.72 (diastereomers, d, d, J = 5.1 Hz, 1 H), 3.80−3.50 (complex series of m, 4 H), 3.42−3.39 (complex series of m, 2 H), 3.28−3.26 (complex series of s, 6 H), 2.45−2.33 (complex series of m, 2 H), 1.95 (m, 1 H), 1.76 (m, 1 H), 1.70 (overlapping s, 4 H), 1.32 (overlapping s, 6 H), 1.02−0.80 (complex series of s, 30 H), 0.21−0.0 (complex series of s, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.04, 167.99, 140.0, 139.6, 139.3, 138.1, 136.3, 133.3, 133.2, 133.09, 133.05, 132.98, 132.94, 132.88, 132.63, 131.96, 131.91, 131.5, 130.22, 130.18, 128.9, 127.9, 122.4, 122.0, 108.3, 108.2, 105.2, 105.0, 100.6, 78.8, 74.6, 69.9, 69.83, 69.78, 64.89, 64.80, 60.3, 59.3, 56.2, 56.1, 40.4, 40.3, 38.8, 37.9, 31.33, 31.27, 26.46, 26.43, 25.95, 25.87, 24.8, 24.7, 24.03, 24.00, 21.1, 18.6, 18.34, 18.30, 18.2, 12.6, −3.67, −3.72, −4.4, −4.51, −4.58, −5.40, −5.43; high-resolution mass spectrum (ES, Na) *m*/*z* 1077.5370[(M + Na)$^+$; calcd for $C_{55}H_{90}N_2O_8S_2(Si)_3Na$ 1077.5344].

Aniline (+)-64. A suspension of **63** (140 mg, 0.133 mmol) and Na_2HPO_4 (183 mg, 1.33 mmol) in anhydrous methanol (5 mL) at 0 °C was treated with excess sodium amalgam (5%, ca. 0.5 g). The mixture was stirred vigorously at 0 °C for 1.5 h, diluted with ethyl acetate (5 mL), and filtered through a

plug of silica gel with ethyl acetate as eluant. The filtrate was concentrated in vacuo; the crude residue was dissolved in chloroform (20 mL), added to silica gel (ca. 2 g), and stirred vigorously for 20 min. The silica gel was removed by filtration, and the filtrate was concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1 to 2:1) afforded (+)-**64** (95 mg, 89% yield for two steps) as a colorless oil: $[\alpha]^{23}_D$ +12.9° (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 3400 (m), 3010 (s), 2960 (m), 2940 (m), 1675 (s), 1615 (m), 1460 (s), 1380 (m), 1200 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 6.22−6.05 (m, 5 H), 5.79−5.70 (m, 1 H), 5.56−5.49 (m, 1 H), 5.22 (t, *J* = 7.4 Hz, 1 H), 4.82 (d, *J* = 4.5 Hz, 1 H), 3.79−3.60 (m, 5 H), 3.38−3.30 (m, 1 H), 3.32 (s, 2 H), 3.22 (s, 3 H), 2.70 (m, 2 H), 2.32−2.06 (m, 4 H), 1.82−1.66 (m, 3 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 1.78 (s, 3 H), 1.02 (s, 9 H), 0.88 (s, 9 H), 0.74 (d, *J* = 7.1 Hz, 3 H), 0.20 (s, 6 H), 0.027 (s, 3 H), 0.021 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 137.8, 136.3, 134.9, 133.5, 133.2, 133.0, 132.7, 132.6, 131.9, 131.8, 130.9, 124.9, 108.6, 102.9, 100.6, 78.8, 74.5, 72.7, 59.4, 56.2, 40.8, 38.9, 37.8, 30.6, 29.1, 27.6, 26.1, 26.0, 24.7, 24.4, 20.8, 18.7, 18.3, 12.6, −3.2, −3.3, −5.31, −5.34; high-resolution mass spectrum (ES, Na) *m*/*z* 823.4542 [$(M + Na)^+$; calcd for $C_{43}H_{72}N_2O_6S(Si)_2Na$ 823.4547].

Anal. Calcd for $C_{43}H_{72}N_2O_6S(Si)_2$: C, 64.45; H, 9.06; N, 3.50. Found: C, 64.70; H, 9.27; N, 3.83.

MOM Ether (+)-65. A solution of (+)-**64** (200 mg, 0.25 mmol) in acetone (5 mL) was treated with aqueous K_2CO_3 (5 M, 1.5 mL, 7.5 mmol) and allyl chloroformate (0.261 mL, 2.5 mmol). The resultant mixture was stirred for 1 h, poured into brine (50 mL), and extracted with ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded the corresponding amide (186 mg, 84% yield) as a colorless oil: $[\alpha]^{23}_D$ +11.7° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 2940 (s), 2960 (s), 1725 (s), 1680 (s), 1590 (m), 1514 (s), 1440 (m), 1380 (m), 1240 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.52 (s, 1 H), 6.81 (s, 1 H), 6.22−6.06 (m, 4 H), 5.98−5.92 (m, 1 H), 5.80−5.70 (m, 1 H), 5.58−5.50 (m, 1 H), 5.37 (dd, *J* = 17.1, 1.1 Hz, 1 H), 5.26 (dd, *J* = 10.8, 1.1 Hz, 1 H), 5.18 (t, *J* = 6.7 Hz, 1 H), 4.76 (d, *J* = 5.2 Hz, 3 H), 3.81−3.68 (m, 2 H), 3.66−3.52 (m, 1 H), 3.36−3.30 (m, 1 H), 3.32 (s, 2 H), 3.21 (s, 3 H), 2.72 (t, *J* = 7.4 Hz, 2 H), 2.33−2.04 (m, 4 H), 1.82−1.76 (m, 1 H), 1.72−1.59 (m, 2 H), 1.64 (s, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.03 (s, 9 H), 0.88 (s, 9 H), 0.71 (d, *J* = 7.1 Hz, 3 H), 0.026 (s, 6 H), 0.021 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 152.8, 138.6, 135.2, 133.3, 133.2, 133.1, 132.7, 132.29, 132.16, 131.29, 131.17, 130.2, 129.1, 124.5, 118.0, 114.7, 106.4, 100.6, 78.8, 74.5, 69.2, 66.0, 59.3, 56.2, 40.9, 38.9, 37.7, 30.2, 29.2, 27.5, 25.95, 25.92, 24.9, 24.2, 20.8, 18.6, 18.3, 12.7, −3.55, −3.63, −5.32, −5.35; high-resolution mass spectrum (ES, Na) *m*/*z* 907.4750 [$(M + Na)^+$; calcd for $C_{47}H_{76}N_2O_8S(Si)_2Na$ 907.4758].

To a solution of the above amide (167 mg, 0.19 mmol) in THF (5 mL) at 0 °C were added tetrabutylammonium fluoride (1 M in THF, 0.56 mL, 0.56 mmol) and acetic acid (0.032 mL, 0.56 mmol). After 5 min, the mixture was poured into brine (25 mL) and extracted with ether (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The resultant residue was dissolved in CH_2Cl_2 and treated with *N*,*N*-diisopropylethylamine (0.33 mL, 1.9 mmol) and chloromethyl methyl ether (0.072 mL, 0.95 mmol). The resultant yellow solution was stirred for 30 min, added to brine-saturated $NaHCO_3$ (1:1, 40 mL), and extracted with ether (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded (+)-**65** (115 mg, 75% yield for two steps) as a white foam: $[\alpha]^{23}_D$ +12.6° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3680 (m), 3400 (m), 3010 (s), 2960 (s), 2940 (s), 1730 (s), 1680 (s), 1600 (s), 1515 (s), 1440 (m), 1380 (m), 1220 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 2 H), 7.61 (s, 1 H), 6.23−6.07 (m, 4 H), 5.98−5.92 (m, 1 H), 5.80−5.70 (m, 1 H), 5.57−5.49 (m, 1 H), 5.33 (d, *J* = 17.8 Hz, 1 H), 5.24 (m, 2 H), 4.93 (s, 2 H), 4.68 (m, 3 H), 3.80−3.68 (m, 2 H), 3.65−3.57 (m, 1 H), 3.60 (s, 3 H), 3.38−3.30 (m, 1 H), 3.34 (s, 2 H), 3.21 (s, 3 H), 2.72 (t, *J* = 7.1 Hz, 2 H), 2.34−2.10 (m, 4 H), 1.81−1.77 (m, 1 H), 1.74−1.62 (m, 2 H), 1.68 (s, 3 H), 1.30 (s, 3 H), 1.29 (s, 3 H), 0.87 (s, 9 H), 0.74 (d, *J* = 7.0 Hz, 3 H), 0.029 (s, 3 H), 0.023 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 153.2, 142.1, 135.3, 133.8, 133.7, 133.4, 133.1, 132.6, 132.4, 132.3, 132.0, 131.6, 131.0, 124.7, 118.0, 114.2, 106.4, 101.0, 100.6, 78.8, 74.5, 69.3, 65.9, 59.4, 57.6, 56.2, 40.8, 38.8, 37.8, 30.1, 29.2, 27.8, 26.0, 24.7, 24.0, 20.8, 18.3, 12.7, −5.32, −5.34; high-resolution mass spectrum (ES, Na) *m*/*z* 837.4184 [$(M + Na)^+$; calcd for $C_{43}H_{66}N_2O_9SSiNa$ 837.4156].

Alcohol (+)-66. A solution of (+)-**65** (115 mg, 0.141 mmol) in THF (3 mL) was treated with tetrabutylammonium fluoride (1 M in THF, 0.5 mL, 0.50 mmol). The resultant brown solution was stirred for 2.5 h, added to brine (40 mL), and extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 4:1) afforded (+)-**66** (87 mg, 88% yield) as a light yellow oil: $[\alpha]^{23}_D$ +17.6° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3700 (w), 3620 (w), 3405 (m), 3020 (s), 1730 (s), 1680 (s), 1600 (s), 1520 (s), 1450 (m), 1375 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.00 (s, 1 H), 7.74 (s, 1 H), 6.28−6.10 (m, 4 H), 6.05−5.97 (m, 1 H), 5.61−5.52 (m, 1 H), 5.43 (dd, *J* = 17.5, 1.5 Hz, 1 H), 5.34−5.28 (m, 2 H), 5.03 (s, 2 H), 4.72 (d, *J* = 5.6 Hz, 1 H), 4.70 (d, *J* = 5.6 Hz, 1 H), 3.91−3.88 (m, 1 H), 3.82−3.72 (m, 2 H), 3.69 (s, 3 H), 3.41 (m, 1 H), 3.40 (s, 2 H), 3.32 (s, 3 H), 2.80−2.70 (m, 2 H), 2.66 (br s, 1 H), 2.40−2.15 (m, 4 H), 1.92−1.82 (m, 1 H), 1.80−1.67 (m, 2 H), 1.72 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 0.78 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 153.5, 142.3, 135.6, 134.2, 134.0, 133.40, 133.37, 132.8, 132.6, 132.3, 132.2, 131.1, 130.2, 125.1, 118.3, 114.5, 107.0, 101.3, 101.0, 82.1, 74.8, 69.5, 66.3, 60.9, 57.9, 56.6, 41.2, 38.3, 37.9, 30.4, 29.6, 28.2, 25.0, 24.4, 21.2, 13.1; high-resolution mass spectrum (ES, Na) *m*/*z* 723.3277 [$(M + Na)^+$; calcd for $C_{37}H_{52}N_2O_9SNa$ 723.3291].

Anal. Calcd for $C_{37}H_{52}N_2O_9S$: C, 63.43; H, 7.43; N, 4.00. Found: C, 63.64; H, 7.57; N, 4.16.

Acid (+)-67. To a solution of (+)-**66** (20 mg, 0.0286 mmol) in CH_2Cl_2 (4 mL) were added triethylamine (0.3 mL, 2.15 mmol), dimethyl sulfoxide (0.1 mL, 1.43 mmol), and SO_3·Py complex (180 mg, 1.13 mmol). After 30 min, the solution was added to brine-saturated $NaHCO_3$ (1:1, 20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded the corresponding unstable aldehyde (20 mg) as a colorless oil. The aldehyde was used immediately in the following step.

To a solution of the above aldehyde in *tert*-butyl alcohol and 2-methyl-2-butene (1 mL each) were added sodium chlorite (26 mg, 0.277 mmol) and NaH_2PO_4·$2H_2O$ (33 mg, 0.212 mmol) in water (1 mL). After 20 min, the phases were separated, and the aqueous phase was mixed with brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate/hexanes, 3:1; CH_2Cl_2/MeOH, 20:1 to 10:1) provided (+)-**67** (8.8 mg, 43% yield for two steps) as a colorless oil: $[\alpha]^{23}_D$ +26.5° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3500 (br s), 2920 (s), 2840 (s), 1760 (m), 1740 (s), 1605 (s), 1505 (s), 1460 (m), 1370 (m), 1245 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 8.05 (overlapping s, 1H), 7.82 (s, 1 H), 6.42 (dd, *J* = 14.9, 10.1 Hz, 1 H), 6.23 (dd, *J* = 15.6, 11.2 Hz, 1 H), 6.15−5.38 (complex series of m, 6 H), 5.30 (m, 2 H), 5.06−4.81 (complex series of m, 2 H), 4.72 (m, 3 H), 4.17 (m, 1 H), 3.67 (overlapping s, 3 H), 3.51−3.32 (m, 3 H), 3.22−3.18 (m, 3 H), 2.88−2.77 (m, 2 H), 2.60−2.50 (m, 2 H), 2.38−2.10 (m, 3 H), 1.92−1.81 (m, 1 H), 1.73 (overlapping s, 3 H), 1.80−1.70 (m, 1 H), 1.40 (overlapping s, 6 H), 0.80 (overlapping d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 166.1, 153.7, 141.8, 136.3, 135.6, 134.4, 133.9, 133.6, 132.5, 132.4, 132.1, 131.6, 131.0, 130.7, 129.5, 123.7, 118.6, 118.1, 114.8, 107.3, 106.9, 101.0, 100.5, 78.8, 73.3, 69.2, 66.2, 66.0, 57.6, 57.5, 56.1, 40.5, 38.6, 36.3, 30.6, 29.3, 29.1, 28.6, 24.9, 24.1, 24.0, 20.74, 20.67, 12.7, 12.5; high-resolution mass spectrum (ES, Na) *m*/*z* 737.3082 [$(M + Na)^+$; calcd for $C_{37}H_{50}N_2O_{10}SNa$ 737.3084].

Macrolactam (+)-68. A solution of (+)-**67** (8 mg, 0.0112 mmol) in THF (2 mL) was treated with dimedone (16 mg, 0.112 mmol) and tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.0112 mmol). The resultant yellow solution was stirred for 1

h at room temperature and then concentrated in vacuo. Flash chromatography (ethyl acetate/hexanes, 1:1; CH_2Cl_2/MeOH, 20:1 to 1:1) afforded the corresponding unstable amino acid as a yellow solid. The acid was used immediately in the following step.

A solution of the above amino acid in THF−toluene (2:3, 5 mL) was treated with triethylamine (0.02 mL, 0.143 mmol). The resultant yellow solution was then added over a 2 h period via a syringe pump to a suspension of 2-chloro-1-methylpyridinium iodide (30 mg, 0.117 mmol) and triethylamine (0.03 mL, 0.215 mmol) in toluene (5 mL). After addition, the mixture was stirred for an additional 1 h. The resultant solid was then removed by filtration and the yellow filtrate concentrated in vacuo. Flash chromatography (ethyl acetate/hexanes, 3:1) provided (+)-**68** (4.2 mg, 61% yield for two steps) as a light yellow foam: $[\alpha]^{23}_D$ +43.2° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3400 (m), 2980 (s), 2920 (s), 2900 (s), 2850 (s), 1660 (s), 1611 (m), 1473 (s), 1380 (s), 1360 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.88 (s, 1 H), 7.51 (s, 1 H), 6.20−5.95 (m, 4 H), 5.81 (m, 1 H), 5.53 (dd, J = 15.0, 8.5 Hz, 1 H), 5.17 (t, J = 5.6 Hz, 1 H), 4.84 (d, J = 5.8 Hz, 1 H), 4.71 (d, J = 5.8 Hz, 1 H), 4.45 (d, J = 5.8 Hz, 1 H), 4.07 (m, 1 H), 3.62 (s, 3 H), 3.51 (m, 1 H), 3.34 (s, 2 H), 3.32 (s, 3 H), 2.90 (m, 2 H), 2.60 (dd, J = 12.9, 3.9 Hz, 1 H), 2.50 (m, 1 H), 2.31 (t, J = 11.1 Hz, 1 H), 2.20−2.02 (m, 3 H), 1.87−1.80 (m, 1 H), 1.72 (s, 3 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 0.91 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 165.4, 143.6, 143.0, 136.1, 133.8, 133.53, 133.50, 133.1, 132.6, 132.4, 131.2, 130.1, 129.9, 124.2, 108.1, 100.7, 100.5, 79.9, 73.1, 70.6, 68.8, 57.5, 56.4, 45.9, 36.0, 29.9, 29.1, 27.4, 24.5, 23.9, 20.0, 12.5; high-resolution mass spectrum (ES, Na) *m/z* 635.2785 [(M + Na)$^+$; calcd for $C_{33}H_{44}N_2O_7SNa$ 635.2767].

Diol (+)-69. A solution of (+)-**68** (4.2 mg, 0.00686 mmol) in methanol (2 mL) was treated with camphorsulfonic acid (three crystals). The mixture was stirred for 15 min and then quenched with triethylamine (three drops). After concentration to dryness, the residue was dissolved in ethyl acetate (5 mL), added to silica gel (ca. 0.2 g), and concentrated again. Flash chromatography (ethyl acetate) provided (+)-**69** (4 mg, 90% yield) as a white foam: $[\alpha]^{23}_D$ +16.1° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) 3390 (w), 2980 (m), 2940 (m), 2920 (s), 2850 (m), 1670 (s), 1610 (m), 1517 (s), 1372 (m), 1350 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.90 (s, 1 H), 7.52 (s, 1 H), 6.17−5.90 (m, 4 H), 5.73 (m, 1 H), 5.58 (dd, J = 15.2, 7.3 Hz, 1 H), 5.24 (t, J = 5.6 Hz, 1 H), 4.97 (d, J = 5.8 Hz, 1 H), 4.82 (m, 1 H), 4.81 (d, J = 5.8 Hz, 1 H), 4.14 (m, 1 H), 3.78 (m, 1 H), 3.62 (s, 3 H), 3.31 (overlapping s, 5 H), 2.86 (m, 2 H), 2.60 (dt, J = 12.4, 4.4 Hz, 1 H), 2.55 (m, 1 H), 2.36 (m, 2 H), 2.11−1.90 (m, 4 H), 1.82 (s, 3 H), 1.84−1.72 (m, 1 H), 0.95 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 150.4, 141.9, 139.6, 138.4, 132.1, 133.7, 133.2, 132.7, 132.6, 131.4, 130.5, 130.3, 129.2, 124.6, 107.3, 100.7, 96.1, 73.4, 70.1, 57.6, 56.6, 39.3, 29.9, 29.7, 29.5, 29.3, 20.3, 14.1, 11.0; high-resolution mass spectrum (ES, Na) *m/z* 595.2442 [(M + Na)$^+$; calcd for $C_{30}H_{40}N_2O_7SNa$ 595.2454].

(+)-Thiazinotrienomycin E (1). A solution of (+)-**69** (4 mg, 0.007 mmol) and DMAP (1 mg, 0.008 mmol) in THF (1 mL) at −78 °C was treated dropwise with a freshly prepared Fmoc-D-alanine anhydride (0.025 mM, 0.040 mmol) in CH_2Cl_2 (1.6 mL). The reaction solution was stirred for 2 at −78 °C and then quenched with pH 7 buffer solution (3 mL). The mixture was warmed to room temperature and extracted with ethyl acetate (6 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ethyl acetate) afforded the two inseparable monoacylation products as a white powder: high-resolution mass spectrum (ES, Na) *m/z* 888.3539 [(M + Na)$^+$; calcd for $C_{48}H_{55}N_3O_{10}SNa$ 888.3506].

A solution of the above acylation products in THF (2 mL) was treated with diethylamine (1 mL). After being stirred at room temperature for 1 h, the mixture was concentrated in vacuo to afford the corresponding primary amines.

A solution of the above amines in THF (1.5 mL) was treated with triethylamine (0.1 mL, 0.717 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (15 crystals, excess), and cyclohexanecarboxylic acid (2 drops, excess). After 1 h, the solution was added to $NaHCO_3$−brine (1:1, 4 mL), and extracted with ethyl acetate (6 × 4 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to provide the corresponding thiazinotrienomycin MOM ethers as a yellow powder; high-resolution mass spectrum (ES, Na) *m/z* 776.3563 [(M + Na)$^+$; calcd for $C_{40}H_{55}N_3O_9SNa$ 776.3557].

A solution of the above ethers in THF (0.5 mL) was treated with HCl (3 N, 0.5 mL). The resultant mixture was stirred at room temperature for 5.5 h, added to saturated $NaHCO_3$ (4 mL), and extracted with ethyl acetate (6 × 4 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. HPLC (3.9 × 300 mm analytical column, Waters Co. Ltd.; mobile phase, 95% ethyl acetate and 5% hexanes; flow rate, 1 mL/min.; detection, 254 nm; temperature, room temperature; retention time, 15.5−19 min) provided (+)-**thiazinotrienomycin E** (1.4 mg, 28% yield for four steps) as a white powder: $[\alpha]^{23}_D$ +195° (*c* 0.035, CH_3OH); ^1H NMR (500 MHz, pyridine-d_5) δ 11.82 (s, 1 H), 10.83 (s, 1 H), 9.74 (br s, 1 H), 9.10 (d, J = 6.1 Hz, 1 H), 7.63 (s, 1 H), 6.56 (dd, J = 15.6, 10.1 Hz, 1 H), 6.37 (dd, J = 15.0, 10.0 Hz, 1 H), 6.32 (dd, J = 15.0, 10.0 Hz, 1 H), 6.20 (dd, J = 15.3, 10.1 Hz, 1 H), 5.95 (m, 1 H), 5.75 (dd, J = 15.6, 8.9 Hz, 1 H), 5.56 (t, J = 4.6, 1 H), 5.41 (m, 1 H), 5.34 (m, 1 H), 5.23 (br s, 1 H), 4.78 (m, 1 H), 4.45 (m, 1 H), 3.60 (d, J = 14.6 Hz, 1 H), 3.54 (d, J = 14.6 Hz, 1 H), 3.27 (s, 3 H), 3.16 (dd, J = 12.2, 4.3 Hz, 1 H), 3.18−3.06 (m, 2 H), 2.95 (m, 1 H), 2.84−2.27 (m, 6 H), 2.03 (s, 3 H), 2.05−1.70 (m, 4 H), 1.58 (d, J = 7.3 Hz, 3 H), 1.55−1.17 (m, 6 H), 0.94 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, pyridine-d_5) δ 176.9, 173.1, 170.4, 165.9, 143.9, 140.6, 135.2, 134.8, 133.7, 131.6, 131.5, 130.8, 129.9, 129.6, 126.9, 124.2, 117.8, 109.4, 80.8, 75.4, 68.3, 56.2, 49.6, 44.4, 43.7, 39.0, 33.5, 30.7, 30.1, 29.8, 29.2, 27.3, 26.2, 26.1, 26.0, 21.2, 17.3, 10.3; high-resolution mass spectrum (ES, Na) *m/z* 732.3293 [(M + Na)$^+$; calcd for $C_{38}H_{51}N_3O_8SNa$ 732.3295].

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Supporting Information Available: Spectroscopic data for selected synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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