Total Syntheses of (+)-Trienomycins A and F via a Unified Strategy

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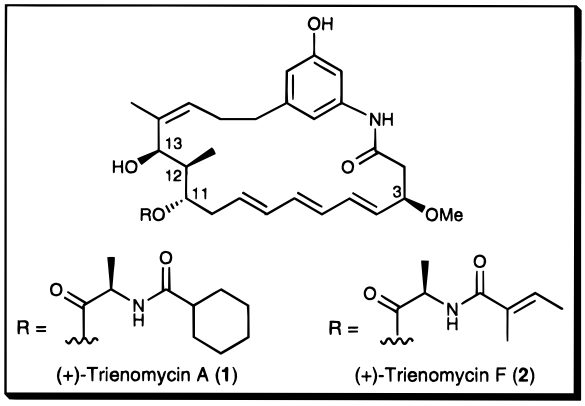
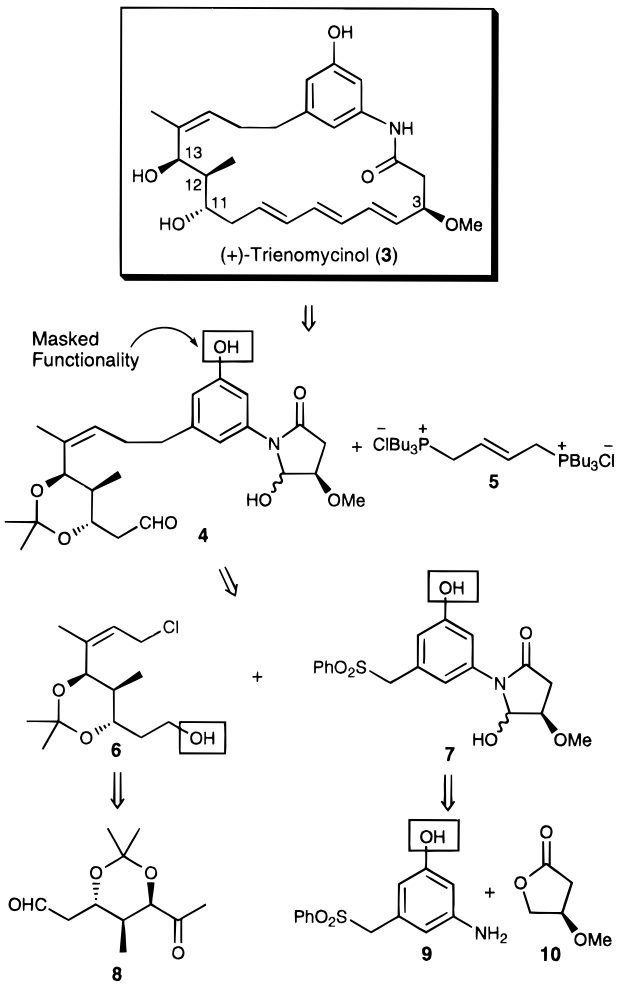
Abstract: The first total syntheses of (+)-trienomycins A and F, representative members of a new class of cytotoxic ansamycin antibiotics, have been achieved. Key features of the unified synthetic scheme included incorporation of the (*E*,*E*,*E*)-triene unit with concomitant macrocyclization via a novel bis-Wittig olefination and the use of (2,2,2-trichloroethoxy)methyl protecting group for the secondary amide.

The (+)-trienomycins A−E, novel ansamycin antibiotics isolated from the culture broth of *Streptomyces* sp. No. 83−16,[1] were first reported by Umezawa and co-workers in 1985. Trienomycin A (**1**), the most active compound, demonstrated potent in vitro cytotoxicity against the HeLa S_3,[2] L-5178Y murine leukemia, and human PLC hepatoma cell lines.[3] The initial studies defined a common connectivity for the trienomycins but the stereochemistries remained unknown except for the side-chain D-alanine in **1**, which was identified via chemical degradation. As prelude to the construction of (+)-**1**, we collaborated with Ōmura et al. at the Kitasato Institute (Tokyo) in elucidation of the complete relative and absolute stereochemistry.[4] The latter investigation led to the discovery and characterization of a previously unknown congener, (+)-trienomycin F (**2**)[5] and also established that trienomycins A−F are differentiated by variation of the acyl residue in the C(11) side chain. In this full account we describe the first (and to date only) total syntheses of (+)-trienomycins A and F.[6,7] Our unified strategy should readily accommodate the entire family of natural products and also provide access to potentially bioactive trienomycin analogs.



Analysis of the Trienomycin Problem. From the retrosynthetic perspective (Scheme 1), we envisioned that (+)-trienomycinol (**3**), or a protected version thereof, would serve as a common advanced precursor of (+)-**1** and (+)-**2**. To install the (*E*,*E*,*E*)-triene moiety and simultaneously effect macrocy-

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

(1) (a) Funayama, S.; Okada, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1107. (b) Funayama, S.; Okada, K.; Iwasaki, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1677. (c) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, K.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 479.

(2) (a) Umezawa, I.; Funayama, S.; Okada, K.; Iwasaki, K.; Satoh, J.; Masuda, K.; Komiyama, K. *J. Antibiot.* **1985**, *38*, 699. (b) Funayama, S.; Anraku, Y.; Mita, A.; Yang, Z.-B.; Shibata, K.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1988**, *41*, 1223.

(3) Hiramoto, S.; Sugita, M.; Andō, C.; Sasaki, T.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1103.

(4) (a) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Funayama, S.; Omma, S. *J. Am. Chem. Soc.* **1990**, *112*, 7425. (b) Also see: Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Funayama, S.; Komiyama, K.; Omma, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308.

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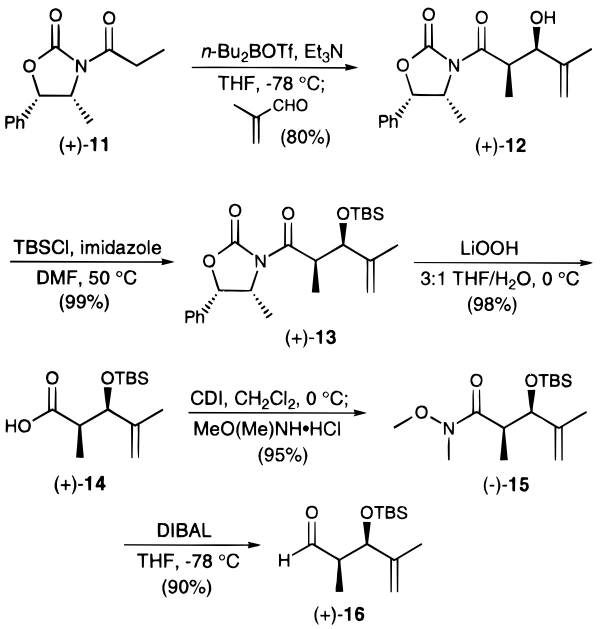
clization, we planned to employ a novel bis-olefination reaction of hemiaminal aldehyde **4** with bis-Wittig reagent **5**.[8] We had discovered earlier that 1,4-amido aldehydes readily cyclize to form five-membered-ring hemiaminals such as **4**.[9] We initially believed that this cyclization would eliminate the need for potentially troublesome protection of the amide nitrogen.[10] Aldehyde **4** would in turn arise via alkylation of sulfone **7** with chloride **6**. Keto aldehyde **8**,[11] which we had isolated via degradation of (+)-**1**, was considered to be an ideal intermediate for the elaboration of **6**. Finally, acylation of aniline **9** with the known γ-lactone **10**[12] was expected to provide sulfone **7**.

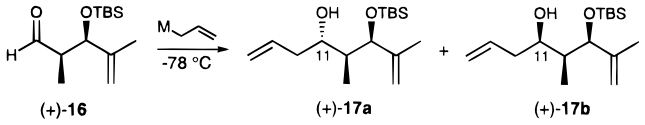
Preparation of Keto Aldehyde (+)-8. Our synthesis of keto aldehyde (+)-**8** began with an Evans aldol addition of (+)-**11**[13] to methacrolein, which furnished a single product as a crystalline solid (80% yield, Scheme 2). X-ray analysis confirmed the desired syn aldol structure (+)-**12**. Protection of the alcohol as a *tert*-butyldimethylsilyl (TBS) ether followed by removal of the chiral auxiliary (LiOOH, 3:1 THF/H_2O, 2 h)[14] afforded acid (+)-**14** in 97% yield for the two steps. The Weinreb amide (−)-**15** was generated via activation of the acid with 1,1′-carbonyldiimidazole (CDI) followed by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride.[15] DIBAL reduction[16] then afforded aldehyde (+)-**16** (90%).

Scheme 2



The conversion of aldehyde (+)-**16** to (+)-**8** entailed installation of the C(11) stereocenter (trienomycin numbering) and two-carbon chain extension. To this end, reaction of (+)-**16** with allylmagnesium bromide (Et_2O or toluene, −78 °C) furnished a 1:2 mixture of the requisite alcohol **17a** and the undesired C(11) epimer **17b** (Table 1). Dissatisfied with this result, we explored the Roush allylborane protocol[17] (toluene, 4-Å molecular sieves, −78 °C), which led to a 1:1 diastereomer

Table 1. Stereoselective Generation of (+)-**17a** via Allylmetallic Addition to Aldehyde (+)-**16**



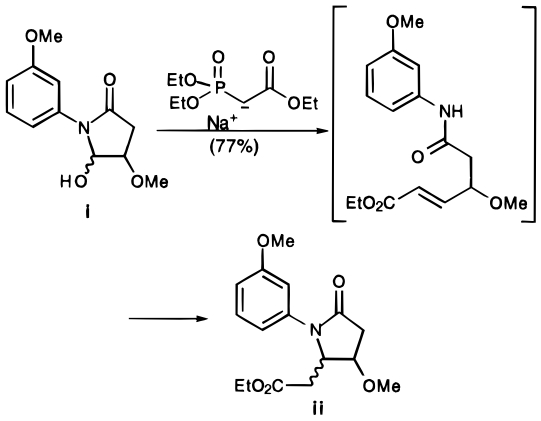
entry	M	solvent	yield (%)	**17a**:**17b**
1	BrMg	Et_2O	79	1:2
2	BrMg	toluene	66	1:2
3	*i*-PrO$_2$C, O, B, O, *i*-PrO$_2$C	toluene, 4-Å MS	76	1:1
4	$)_2$B	Et_2O	77	1:2
5	$)_2$B	CH_2Cl_2	73	2:1
6	$)_2$B	toluene, 4-Å MS	98	9:1

(5) Smith, A. B., III; Wood, J. L.; Gould, A. E.; Ōmura, S.; Komiyama, K. *Tetrahedron Lett.* **1991**, *32*, 1627. See also ref 4b.

(6) Preliminary communication: Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777.

(7) For other synthetic approaches to the trienomycins and the related mycotrienins, see: (a) Yadav, J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965, 2969. (b) Panek, J. S.; Yang, M.; Solomon, J. *Tetrahedron Lett.* **1995**, *36*, 1003.

(8) (a) The bis-Wittig macrocyclic ring construction was initially developed by John Wood in our laboratory.[9] (b) For intermolecular reactions of bis-Wittig reagent **5** with substituted benzaldehydes and cinnamaldehydes leading to *all-E* α,ω-diphenyl polyenes, see: Spangler, C. W.; McCoy, R. K.; Dembeck, A. A.; Sapochak, L. S.; Gates, B. D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 151. (c) For a review of bis-Wittig olefinations employed in the synthesis of nonbenzenoid aromatic systems, see: Vollhardt, K. P. C. *Synthesis* **1975**, 765. (d) For an alternative approach to a macrolide containing an (*E*,*E*,*E*)-triene unit, see: Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318. (e) That hemiaminals can participate in Wittig olefinations was demonstrated by the model study (**i** → **ii**)



(9) Wood, J. L. Ph.D. Thesis, University of Pennsylvania, Philadelphia, PA, 1991.

(10) Complications involving the protection of amide nitrogens arose in our earlier syntheses of the (+)-latrunculins and (+)-hitachimycin: (a) Smith, A. B., III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995. (b) Smith, A. B., III; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.

(11) We have also synthesized the (−) enantiomer of **8**.[4b]

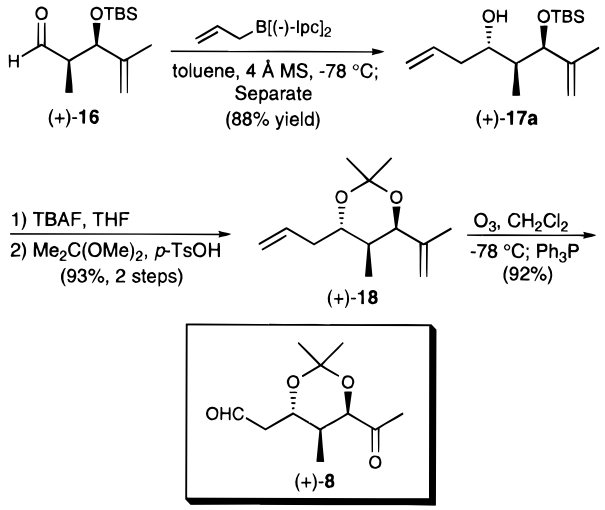
(12) Doyle, M. P.; Van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am Chem. Soc.* **1991**, *113*, 8982.

(13) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127, and references cited therein.

(14) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

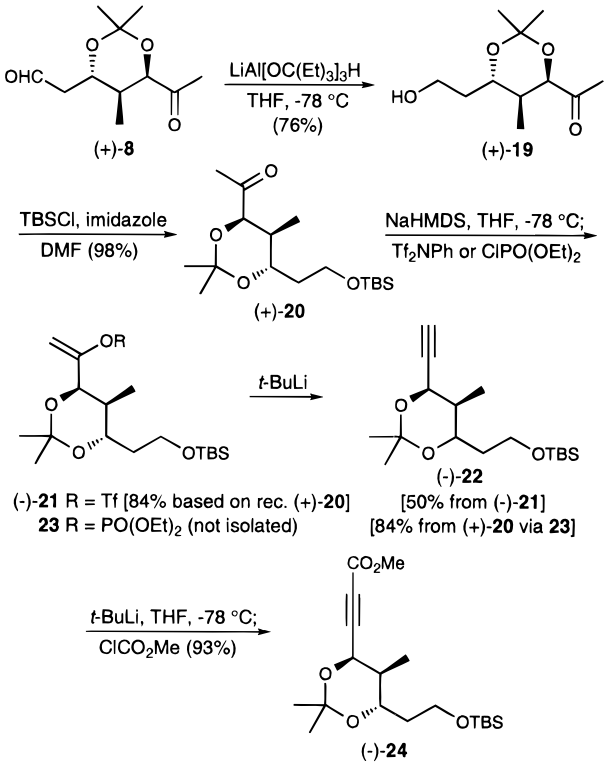
mixture (76%). After considerable experimentation, we found that the allylboration sequence developed by Brown[18] gave the best results (98% yield, 9:1 epimer ratio) with toluene as solvent and inverse addition (Scheme 3). The alcohols were separated by flash chromatography, and the major diastereomer (+)-**17a** was desilylated with TBAF. Protection of the resultant 1,3-diol as the acetonide then provided (+)-**18**[19] in 93% yield [two steps from (+)-**17a**]. Finally, ozonolysis[20] of (+)-**18** followed by reductive workup with Ph_3P afforded keto aldehyde (+)-**8** in 92% yield, identical to a sample obtained by degradation of (+)-trienomycin A (**1**).

Scheme 3



Synthesis of Chloride 6. The transformation of (+)-**8** to chloride **6** first required chemoselective reduction of the aldehyde functionality, achieved by treatment of (+)-**8** with lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride[21] in THF at −78 °C (76% yield, Scheme 4). Protection of the resultant

Scheme 4

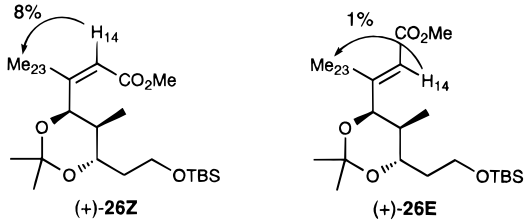


primary alcohol (+)-**19** as the TBS ether (TBS-Cl, imidazole, DMF, 1 h) then gave ketone (+)-**20** in 98% yield. The major challenge proved to be the installation of the *Z* olefin. Direct Horner−Emmons olefination of **20** failed to provide the requisite geometry.

We next explored cuprate addition to the derived acetylenic ester (−)-**24**.[10a] Trapping of the kinetic enolate of (+)-**20** with *N*-phenyltrifluoromethanesulfonimide[22] afforded enol triflate (−)-**21** in 38% yield. Elimination induced by *t*-BuLi provided the terminal alkyne (−)-**22** in 50% yield, accompanied by ketone (+)-**20** (10%), which presumably arose via nucleophilic attack on the triflate. To circumvent the low yield and side reaction, we employed the corresponding enol phosphate, generated via the one-pot procedure of Negishi[23] [sodium bis(trimethylsilyl)-amide, −78 °C, THF; diethyl chlorophosphate]. Elimination with *t*-BuLi then gave acetylene (−)-**22** in 84% yield with no trace of ketone (+)-**20**; the alkyne readily furnished acetylenic ester (−)-**24** (*t*-BuLi, THF, $ClCO_2Me$, −78 °C; 93%).

Addition of acetylenic ester (−)-**24** to solutions of Me_2CuLi gave only complex mixtures (Table 2),[24] presumably because the initial 1,4-adduct reacted further to give dimethylated products (**25**).[25] Inverse addition alleviated this problem but we then discovered that the *Z*/*E* selectivity varied dramatically with solvent. Diethyl ether provided predominantly (1:3 mixture) the undesired *E* isomer [(+)-**26*E***]; in tetrahydrofuran, however, we obtained exclusively the requisite *Z* enoate [(+)-**26*Z***] in 94% yield.

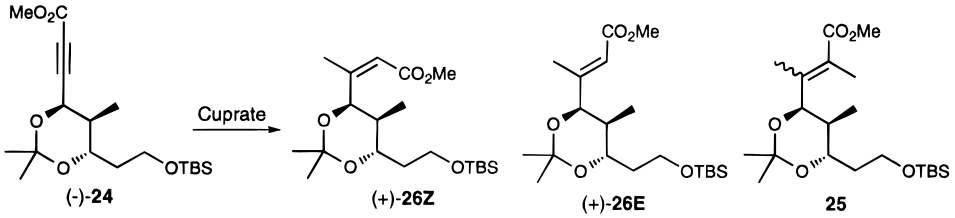
NOE experiments were employed to verify the stereochemical assigments for the olefin isomers. Irradiation of (+)-**26*Z*** at H(14) led to an 8% NOE enhancement at Me(23), whereas for (+)-**26*E***, only a 1% enhancement was observed. These data unambiguously confirmed the olefin geometries of (+)-**26*Z*** and (+)-**26*E***.



The final task was conversion of enoate **26*Z*** to an electrophile (i.e., **6** or derivative thereof) suitable for the sulfone coupling. DIBAL reduction (toluene, −78 °C) smoothly furnished allyl alcohol (−)-**27** (Scheme 5). We initially investigated the corresponding chloride as the electrophilic species, mainly to

(15) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.
(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(17) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953.
(18) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320, and references cited therein.
(19) The relative stereochemistry at C(13) was deduced from the ^{13}C chemical shifts of the acetonide carbons in (+)-**18** via the method of Rychnovsky and Evans: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
(20) For a review of ozonolysis, see: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1, Chapter 4, p 15.
(21) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628.
(22) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(23) (a) Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1986**, *64*, 44. (b) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526.
(24) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(25) Whitesides, G. M.; SanFilippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.

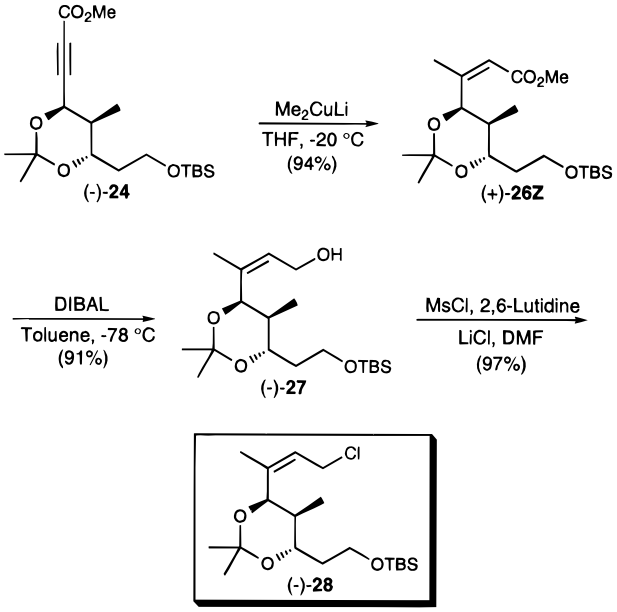
Table 2. Methyl Cuprate Additions to Alkynyl Ester (−)-**24**



entry	cuprate	solvent, temp (°C)	addition	product (yield)
1	Me_2CuLi	Et_2O, −78	normal	complex mixtures
2	Me_2CuLi	THF, −78	normal	complex mixtures
3	Me_2CuLi	Et_2O, −20	inverse	**26*Z*** (20%) + **26*E*** (62%) + **25** (trace)
4	Me_2CuLi	THF, −20	inverse	**26*Z*** (94%)

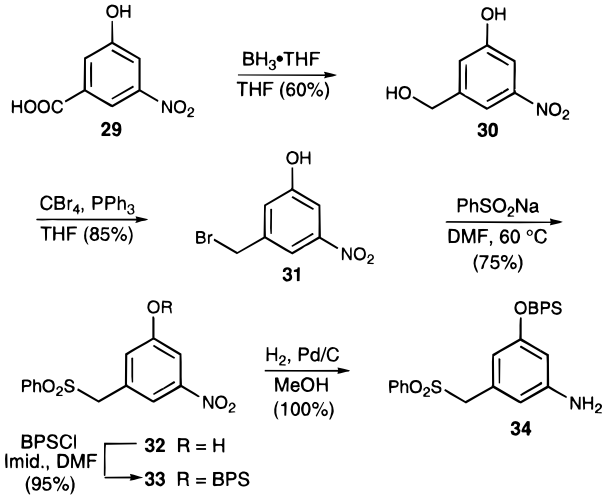
facilitate preparation and handling. In addition, the chloride would serve as pecursor to more reactive electrophiles if required. Treatment of (−)-**27** with methanesulfonyl chloride and LiCl in DMF provided *Z* allylic chloride (−)-**28** in 97% yield.[26]

Scheme 5



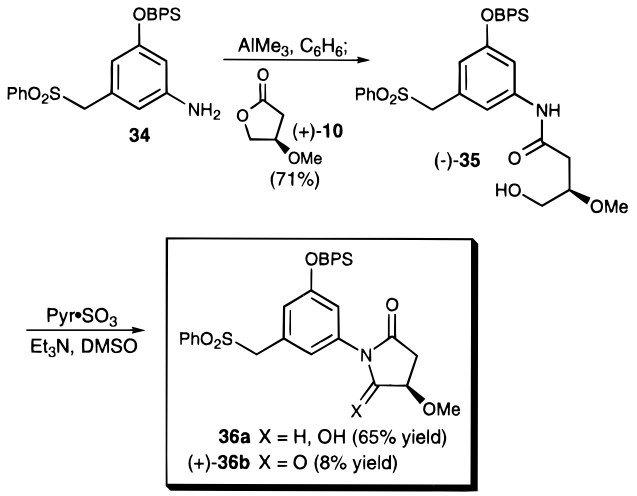
Construction and Coupling of Sulfone 7. Our point of departure was **29** (Scheme 6), readily available from 3,5-dinitrobenzoic acid in two steps.[27] Borane reduction provided benzylic alcohol **30** in 60% yield. Exposure to CBr_4 and PPh_3 in THF furnished bromide **31** (85%), which reacted with sodium benzenesulfinate (DMF, 60 °C, 75%) to afford sulfone **32**. We next addressed the issue of phenol protection. In our investigation of the stereochemistry of trienomycin A, we explored the use of methyl and MEM ethers as phenol protecting groups and found that their removal was problematic. The TBS ether proved far superior with respect to both introduction and removal; we therefore opted for a silyl protecting group in this case. Conversion of **32** to the *tert*-butyldiphenylsilyl (BPS) ether **33** followed by catalytic hydrogenolysis of the nitro group (H_2, 10% Pd/C, MeOH) gave aniline **34** (95% yield from **32**).

Scheme 6



Aniline **34** was coupled with the known γ-lactone (+)-**10** (available from D-malic acid in four steps[28]) via the Weinreb protocol,[29] providing alcohol (−)-**35** in 71% yield (Scheme 7).

Scheme 7



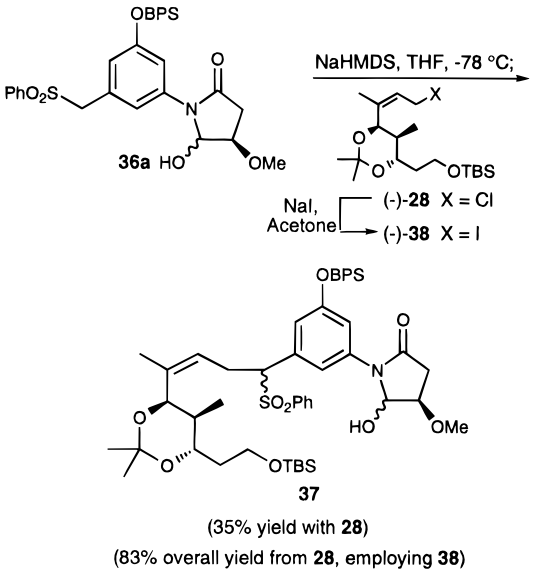
Parikh−Doering oxidation [pyridinesulfonate (pyr•SO_3), Et_3N, DMSO][30] then led to the N-acyl hemiaminal **36a** as a 1:1

(26) Meyers, A. I.; Collington, E. W. *J. Org. Chem.* **1971**, *36*, 3044.
(27) Herlt, A. J.; Kibby, J. J.; Rickards, R. W. *Aust. J. Chem.* **1981**, *34*, 1319.
(28) Preparation of the hydroxy γ-lactone: (a) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389. (b) Tanaka, A.; Yamashita, K. *Synthesis* **1987**, 570. Conversion to the *O*-methyl derivative: (c) Lardon, A; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003.

mixture of diastereomers in 65% yield along with 8% of the imide overoxidation product [(+)-**36b**].

We turned next to the union of chloride (−)-**28** with sulfone **36a**. Deprotonation of the latter (2 equiv) with NaHMDS (4 equiv) at −78 °C followed by addition of (−)-**28** (1 equiv) furnished the desired coupling product **37**; the presence of sulfone and hemiaminal diastereomers was inconsequential, but the yield was only 35% (Scheme 8). In an effort to improve the efficiency of the alkylation, chloride (−)-**28** was smoothly converted to the corresponding iodide (−)-**38** by treatment with NaI in acetone. The unstable iodide was immediately coupled with **36a** as described above, furnishing **37** in 83% overall yield from (−)-**28**.

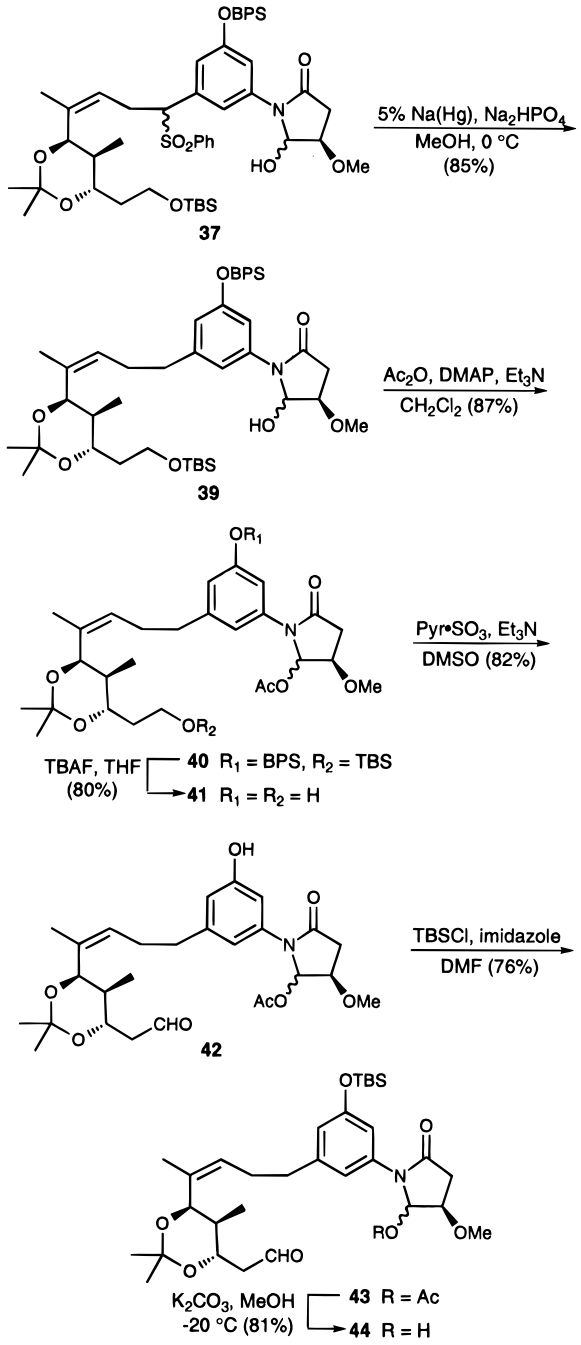
Scheme 8



Generation and Attempted Bis-Olefination of Hemiaminal Aldehyde 44. The successful coupling set the stage for elaboration of **37** to the bis-olefination substrate **44**. Desulfonylation of **37** [5% Na(Hg), MeOH, Na_2HPO_4, 0 °C] provided **39** as an 8−12:1 mixture of aminal diastereomers in 85% yield (Scheme 9).[31] The aminal hydroxyl was protected as the acetate (87% yield) to prevent oxidation to the imide in a subsequent step. Removal of both the TBS and BPS groups with TBAF then afforded hydroxy phenol **41** in 80% yield. Oxidation with pyr·SO_3[30] followed by reprotection of the phenol as the TBS ether (TBS-Cl, imidazole, DMF) provided aldehyde **43** in 62% yield for the two steps. Finally, deacetylation (K_2CO_3, MeOH, −20 °C, 81%) furnished hemiaminal aldehyde **44**, the bis-olefination substrate.

We next began to explore the critical bis-olefination, a process designed to incorporate the triene unit with concomitant macrocyclization. Treatment of bis-Wittig salt **5**[8b] with ethanolic sodium ethoxide (2 equiv) followed by slow addition of hemiaminal aldehyde **44** failed to produce the desired macrolactam **45** (Scheme 10). Although species similar to **5** are known to undergo facile elimination upon exposure to base,[32] some intermolecular bis-Wittig reactions have been effected via ylide generation from **5** in the presence of the carbonyl reactant.[33] Unfortunately, slow addition of 2 equiv of NaHMDS

Scheme 9



to a dilute solution of **5** and **44** (DMF, 0 °C) likewise provided none of the requisite macrolactam. We therefore elected to investigate an alternative bis-olefination tactic involving an N-protected dialdehyde substrate.

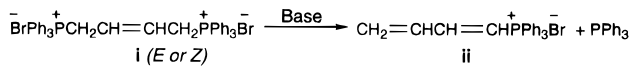
Synthesis of an N-Protected Bis-Olefination Substrate. To obtain a dialdehyde suitable for the bis-olefination reaction, a revised route was developed in order to incorporate a protecting group for the amide nitrogen, thereby blocking formation of

(29) (a) Basha, A.; Lipton, M. F.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.

(30) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

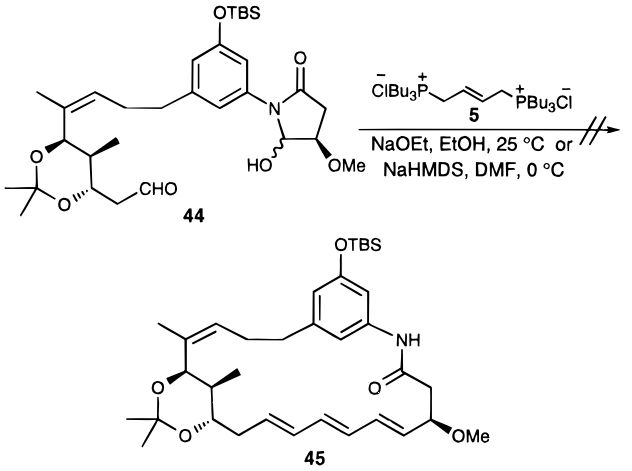
(31) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *17*, 3477.

(32) For example, **i** undergoes facile elimination of triphenylphosphine upon treatment with base to furnish **ii**; see: (a) Büchi, G.; Pawlak, M. *J. Org. Chem.* **1975**, *40*, 100. (b) McIntosh, J. M.; Seguin, F. P. *Can. J. Chem.* **1975**, *53*, 3526. (c) Ford, J. A., Jr.; Wilson, C. V. *J. Org. Chem.* **1961**, *26*, 1433. (d) McDonald, R. N.; Campbell, T. W. *J. Org. Chem.* **1959**, *24*, 1969.



(33) (a) Heitmann, H.; Sperna Weiland, J. H.; Huisman, H. O. *Koninkl. Ned. Akad. Wetenschap., Proc. Ser. B* **1961**, *64*, 165. (b) Pommer, H. *Agnew. Chem.* **1960**, *72*, 911.

Scheme 10



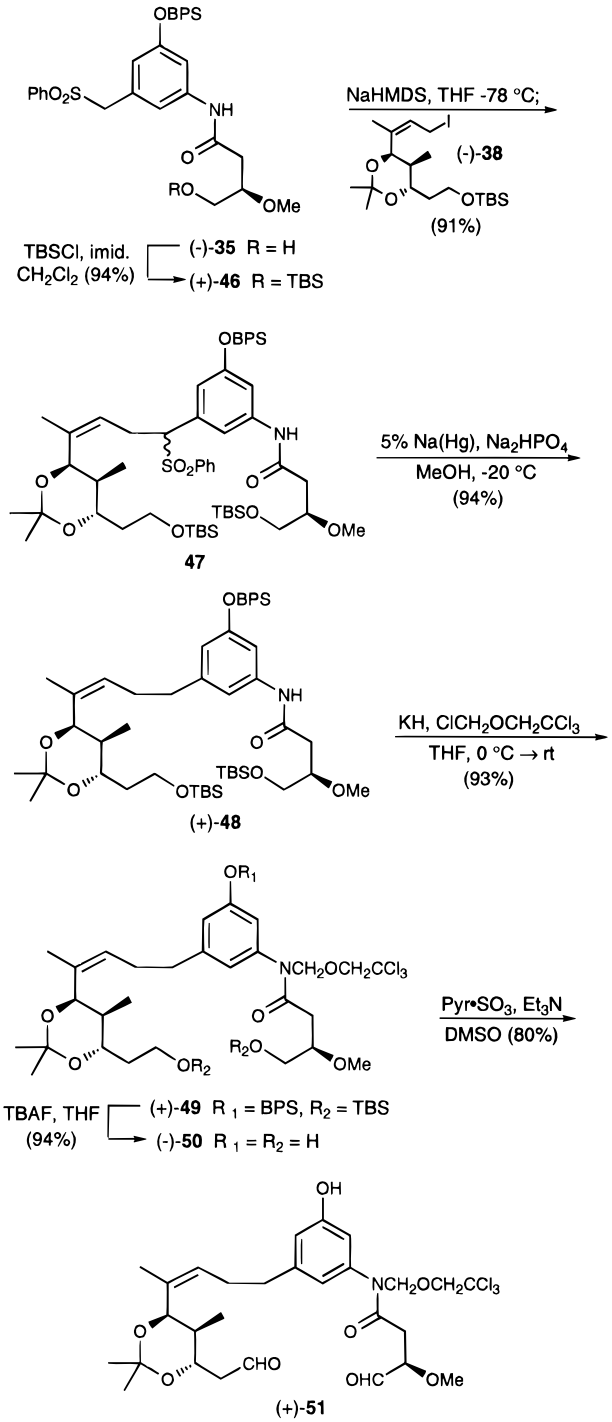
the unreacting *N*-acylhemiaminal. To that end, silylation of alcohol (−)-**35** (TBS-Cl, imidazole, CH_2Cl_2) gave (+)-**46** in 94% yield (Scheme 11). Coupling of (+)-**46** with iodide (−)-**38** (NaHMDS, THF, −78 °C) cleanly furnished **47** as a 1.5:1 mixture of diastereomers (91%, two steps from chloride **28**). Desulfonylation with Na(Hg) in buffered methanol then gave (+)-**48** (94%).[31]

The choice of amide protecting group proved to be unexpectedly critical. After considerable experimentation with other derivatives (BOC, PMB, SEM),[34] we discovered that the (2,2,2-trichloroethoxy)methyl unit was ideal. Evans had successfully employed this moiety for hydroxyl protection in his work on cytovaricin, demonstrating that it can be removed with Na(Hg).[35] Moreover, Solladié had established that (*E*,*E*,*E*)-trienes can survive exposure to similar reductive conditons.[36] Treatment of **48** with chloromethyl 2,2,2-trichloroethyl ether[37] and KH in THF provided tertiary amide (+)-**49** in 93% yield. Removal of the three silyl groups with TBAF followed by oxidation (pyr·SO_3, Et_3N, DMSO)[30] then furnished dialdehyde (+)-**51** in 75% yield for the two steps.

Bis-Olefination/Macrocyclization of Dialdehyde (+)-51: A Successful End Game. With dialdehyde (+)-**51** in hand, we again turned to the critical bis-olefination. Previous studies suggested that phenol protection would not be required. Indeed, slow addition of 3 equiv of NaHMDS to a dilute (∼0.01 M) mixture of bis-Wittig salt **5** and dialdehyde (+)-**51** (DMF, 0 °C) did effect macrocyclization (Scheme 12), affording the (*E*,*E*,*E*)-triene (+)-**52** in 21% yield as a complex mixture of amide rotamers.[38] Silylation (TBSOTf, 2,6-lutidine, CH_2Cl_2, 80%)[39] then gave (+)-**53**.

Deprotection of the amide was our next concern. Exposure of (+)-**53** to Na(Hg) in MeOH at −35 °C successfully

Scheme 11



fragmented the β-chloroethyl acetal to furnish **45** in 67% yield. This material proved identical in all respects to a sample prepared previously via degradation of natural (+)-**1**. Introduction of the side chains corresponding to (+)-trienomycins A (**1**) and F (**2**) was then achieved as reported in the accompanying paper.[4b] Syntheses of congeners B−E should proceed uneventfully via incorporation of the respective acyl moieties.

Summary. The first total syntheses of (+)-trienomycins A and F (**1** and **2**) have been achieved. A novel bis-olefination was utilized to generate the triene moiety and effect macrocyclization. This unified approach should likewise provide access to the remaining members of the trienomycin family as well as a variety of potentially bioactive analogs. In addition, the construction of (+)-**1** constitutes a formal total synthesis of the related mycotrienins I and II.[40]

(34) Attempted olefination of the BOC derivative led to β-elimination of methoxy, whereas *p*-methoxybenzyl and 2-(trimethylsilyl)ethoxymethyl (SEM) moieties could not be removed under oxidative (e.g., DDQ, CAN) or acidic conditions without extensive decomposition.

(35) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

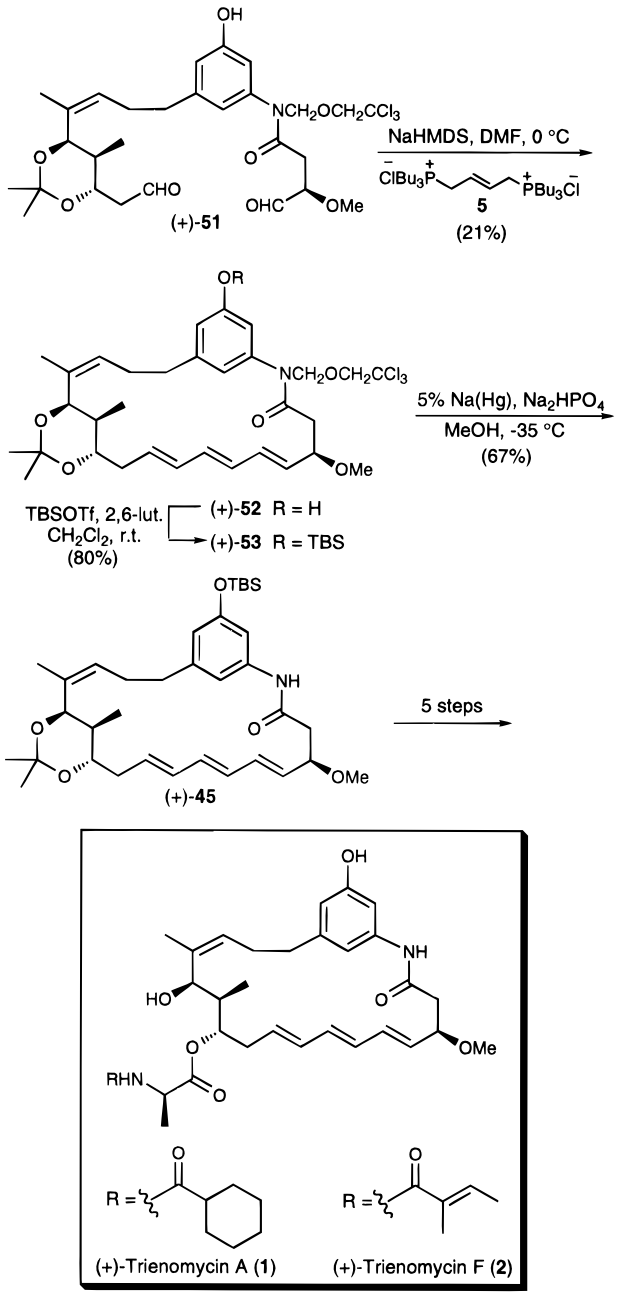
(36) Solladié, G.; Stone, G. B.; Andrés, J.-M.; Urbano, A. *Tetrahedron Lett.* **1993**, *34*, 2835.

(37) Chloromethyl 2,2,2-trichloroethyl ether was prepared by extension of the Boeckman protocol for BOM-Cl: Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. VI, p 101. Also see: Salomaa, P.; Linnantie, R. *Acta Chem. Scand.* **1960**, *14*, 777.

(38) An inseparable mixture of less polar materials believed to be triene isomers was also isolated in 34% yield. Attempts to isomerize this mixture to (+)-**52** both thermally and photochemically (e.g., *hν*, PhSSPh, benzene) were unsuccessful.

(39) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

Scheme 12



Experimental Section[41]

Alcohol (+)-12. A solution of oxazolidinone (+)-**11** (22.2 g, 90.6 mmol) in THF (500 mL) was cooled to −78 °C, and triethylamine (17.7 mL, 127 mmol) was added followed by di-*n*-butylboron triflate (25.5 g, 93.1 mmol) dropwise via a cannula. The reaction mixture was warmed to room temperature, stirred for 1.5 h, cooled to −78 °C, and treated with freshly distilled methacrolein (8.3 mL, 100 mmol). The resultant solution was stirred for 45 min, warmed to 0 °C, and stirred 1.5 h further. Phosphate buffer (pH 7, 500 mL) was added, the biphasic mixture was extracted with ether (1 L), and the organic layer was concentrated in vacuo. The residue was then dissolved in MeOH/H_2O (1:1, 400 mL), the resultant solution cooled to 0 °C, 30% H_2O_2 (103 mL, 906 mmol) introduced, and the mixture stirred at 0 °C for 1 h. Excess H_2O_2 was decomposed at 0 °C by slow addition of aqueous $NaHSO_3$ (2.7 M, 400 mL), the resultant mixture was extracted with ether (500 mL), and the organic solution was washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/hexanes) provided (+)-**12** (21.8 g, 80% yield) as a colorless solid: mp 97−99 °C (hexane/ethyl acetate); $[\alpha]_D^{23}$ +38° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3530 (w, br), 1780 (s), 1685 (m), 1370 (s), 1350 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44−7.37 (m, 3 H), 7.32−7.30 (m, 2 H), 5.69 (d, J = 7.2 Hz, 1 H), 5.14−5.13 (m, 1 H), 4.99−4.98 (m, 1 H), 4.80 (dt, J = 7.2, 6.7 Hz, 1 H), 4.44 (br s, 1 H), 3.98 (dt, J = 7.0, 3.3 Hz, 1 H), 2.96 (d, J = 3.2 Hz, 1 H), 1.77 (s, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 152.6, 143.8, 133.1, 128.8, 128.7, 125.6, 111.8, 78.9, 74.1, 54.9, 40.2, 19.4, 14.3, 9.8; high-resolution mass spectrum (Cl, NH_3) *m/z* 304.1575 [$(M + H)^+$; calcd for $C_{17}H_{22}NO_4$: 304.1549]. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.22; H, 6.85; N, 4.64.

TBS Ether (+)-13. A solution of alcohol (+)-**12** (18.4 g, 60.7 mmol) in *N*,*N*-dimethylformamide (250 mL) was treated with imidazole (8.3 g, 121 mmol) and chloro-*tert*-butyldimethylsilane (13.7 g, 91.0 mmol), heated to 50 °C, and stirred for 12 h. The reaction mixture was then cooled to room temperature, poured into brine (250 mL), and extracted with ether (600 mL); the organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (5% ethyl acetate/hexanes) furnished (+)-**13** (25.1 g, 99% yield) as a colorless solid: mp 62−64 °C (hexane/ethyl acetate); $[\alpha]_D^{23}$ +11° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 1780 (s), 1695 (m), 1365 (s), 1345 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5 H), 5.56 (d, J = 6.9 Hz, 1 H), 4.92 (br s, 1 H), 4.84 (br s, 1 H), 4.63 (apparent q, J = 6.9 Hz, 1 H), 4.33 (d, J = 6.6 Hz, 1 H), 4.01 (apparent q, J = 6.7 Hz, 1 H), 1.73 (br s, 3 H), 1.15 (q, J = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 152.7, 145.6, 133.2, 128.6, 125.5, 112.5, 78.8, 77.0, 55.2, 42.5, 25.7, 18.1, 17.7, 14.2, 12.1, −4.8, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 418.2377 [$(M + H)^+$; calcd for $C_{23}H_{36}NO_4Si$: 418.2413]. Anal. Calcd for $C_{23}H_{35}NO_4Si$: C, 66.15; H, 8.45; N, 3.35. Found: C, 66.12; H, 8.60; N, 3.32.

Acid (+)-14. A solution of acyl oxazolidinone (+)-**13** (51.9 g, 125 mmol) in THF/H_2O (3:1, 850 mL) was cooled to 0 °C and treated with 30% H_2O_2 (84.7 mL, 747 mmol) followed by $LiOH\cdot H_2O$ (10.5 g, 249 mmol). The resultant mixture was stirred for 3 h at 0 °C and then quenched with aqueous Na_2SO_3 (1.6 M, 500 mL). THF was removed in vacuo and the aqueous solution extracted with dichloromethane (1.5 L). The organic phase was washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, affording the chiral auxiliary (20.2 g, 92% recovery). The aqueous layer was acidified to pH 4 with aqueous HCl (1.0 M) and extracted with ethyl acetate (4 × 500 mL). The combined extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, providing analytically pure (+)-**14** (31.4 g, 98% yield) as a colorless oil: $[\alpha]_D^{23}$ +14° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3520−2400 (br), 2970 (s), 2945 (s), 2870 (s), 1760 (m), 1715 (s), 1655 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97−4.95 (m, 1 H), 4.90−4.87 (m, 1 H), 4.33 (d, J = 6.4 Hz, 1 H), 2.64 (q, J = 6.6 Hz, 1 H), 1.70 (s, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 144.5, 113.4, 77.6, 44.1, 25.7, 18.1, 17.7, 11.5, −4.7,

(40) Smith, A. B., III; Wood, J. L.; Ōmura, S. *Tetrahedron Lett.* **1991**, *32*, 841.

(41) **Materials and Methods**. Except as otherwise indicated, reactions were carried out under an argon atmosphere in flame- or oven-dried glassware, and solvents were freshly distilled. Diethyl ether and THF were distilled from sodium/benzophenone. Benzene and methylene chloride were distilled from calcium hydride. Pyridine, 2,6-lutidine, and triethylamine were distilled from calcium hydride and stored over potassium or sodium hydroxide. DMF and DMSO from freshly opened bottles were stored over 4-Å molecular sieves and used without purification. Toluene was distilled from sodium and methanol was distilled from $Mg(OMe)_2$ and stored over 4-Å molecular sieves. Reactions were monitored by thin-layer chromatography (TLC) with 0.25-mm E. Merck precoated silica gel plates. Silica gel for flash chromatography (particle size 0.040−0.063 mm) was supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Melting points were determined on a Bristoline heated-stage microscope or a Thomas-Hoover apparatus and are corrected. ^1H and ^{13}C spectra were recorded on a Bruker AM-500 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrometer with polystyrene as external standard. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center. Microanalyses were performed by Robertson Laboratories (Madison, NJ). Single-crystal X-ray analyses were carried out at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer. High-performance liquid chromatography (HPLC) was performed using a Ranin component analytical/semipreparative system.

−5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 259.1708 [(M + H)$^+$; calcd for $C_{13}H_{27}O_3Si$: 259.1729].

Amide (−)-15. A solution of acid (+)-**14** (18.4 g, 71.1 mmol) in dichloromethane (350 mL) was cooled to 0 °C, treated with 1,1′-carbonyldiimidazole (13.8 g, 85.3 mmol) and stirred for 30 min. *N*,*O*-Dimethylhydroxylamine hydrochloride (17.3 g, 178 mmol) was then added, and the resultant suspension was warmed to room temperature, stirred for 24 h, and filtered. The precipitate was washed with ether (750 mL), and the filtrate was washed with water and brine (250 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (12.5% ethyl acetate/hexanes) gave (−)-**15** (20.3 g, 95% yield) as a colorless oil: $[\alpha]_D^{23}$ −14° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 2986 (s), 1650 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85−4.83 (m, 1 H), 4.75−4.72 (m, 1 H), 4.21 (d, J = 8.6 Hz, 1 H), 3.62 (s, 3 H), 3.15−3.00 (m, 1 H), 3.09 (s, 1 H), 1.67 (br s, 1 H), 1.14 (d, J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 145.9, 112.7, 78.2, 61.4, 40.5, 32.0, 25.8, 18.2, 17.1, 14.3, −4.8, −5.1; high-resolution mass spectrum (Cl, NH_3) *m/z* 302.2098 [(M + H)$^+$; calcd for $C_{15}H_{32}NO_3Si$: 302.2151]. Anal. Calcd for $C_{15}H_{31}NO_3Si$: C, 59.80; H, 10.30; N, 4.65. Found: C, 59.75; H, 10.38; N, 4.42.

Aldehyde (+)-16. A solution of amide (−)-**15** (5.09 g, 16.9 mmol) in THF (200 mL) was cooled to −78 °C, DIBAL (1.0 M in hexane, 17.0 mL, 17.0 mmol) was added dropwise, and the resultant solution was stirred for 30 min and then quenched with methanol (5 mL) at −78 °C. The mixture was warmed to room temperature, diluted with ether (400 mL), and stirred vigorously with saturated aqueous Rochelle's salt (200 mL) until two clear phases were obtained. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:35 v/v)] afforded (+)-**16** (3.7 g, 90% yield) as an unstable colorless oil which was used immediately in the next reaction: $[\alpha]_D^{23}$ +2.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2930 (s), 2860 (s), 1725 (s), 1660 (w), 1255 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.48 (d, J = 1.4 Hz, 1 H), 4.94−4.91 (m, 1 H), 4.78−4.75 (m, 1 H), 4.23 (d, J = 4.7 Hz, 1 H), 2.14−2.07 (m, 1 H), 1.45 (s, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.4, 145.2, 112.7, 75.6, 50.4, 25.9, 18.4, 18.3, 8.2, −4.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 241.1770 [(M + H)$^+$; calcd for $C_{13}H_{27}O_2Si$: 241.1780].

Alcohol (+)-17a. In an argon-filled glovebag, four 50-mL centrifuge tubes were charged with (−)-*B*-methoxydiisopinocampheylborane (1.43 g each, 4.50 mmol) and capped with septa. The tubes were removed from the bag, toluene (10 mL each) was added, and the resultant solutions were cooled to −78 °C and treated with allylmagnesium bromide (1.0 M in ether, 4.5 mL, 4.5 mmol). The solutions were then warmed to room temperature and stirred for 3 h as white precipitates formed. The suspensions were centrifuged, and via a cannula, the clear supernatants were combined in one flask and added dropwise to a mixture of aldehyde (+)-**16** (3.49 g, 14.4 mmol), 4-Å molecular sieves (2.0 g), and toluene (100 mL) at −78 °C. The resultant solution was stirred for 1 h, warmed to room temperature, and stirred 1 h further. Aqueous NaOH (1.0 M, 40 mL) and 30% hydrogen peroxide (13 mL) were introduced, and the mixture was stirred at room temperature for 20 h, warmed to 50 °C, and stirred 3 h further. The layers were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:25 v/v)] gave (+)-**17a** (3.60 g, 88% yield) and (+)-**17b** (0.4 g, 10% yield). (+)-**17a**: less polar; colorless oil; $[\alpha]_D^{23}$ +15° (*c* 3.7, $CHCl_3$); IR ($CHCl_3$) 3440 (br, w), 2960 (s), 2930 (s), 1635 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91−5.83 (m, 1 H), 5.17−5.15 (m, 1 H), 5.13 (br s, 1 H), 4.95 (br s, 1 H), 4.90 (br s, 1 H), 4.30 (d, J = 3.5 Hz, 1 H), 3.60−3.54 (m, 1 H), 2.60 (d, J = 3.2 Hz, 1 H), 2.41−2.34 (m, 1 H), 2.14−2.08 (m, 1 H), 1.71 (br s, 3 H), 1.71−1.65 (m, 1 H), 0.91 (s, 9 H), 0.80 (d, J = 7.0 Hz, 3 H), 0.07 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 135.2, 117.9, 112.1, 71.8, 42.0, 39.3, 25.9, 19.5, 18.2, 10.6, −4.6, −5.2; high-resolution mass spectrum (Cl, NH_3) *m/z* 285.2253 [(M + H)$^+$; calcd for $C_{16}H_{33}O_2Si$: 285.2250].

(+)-**17b**: more polar; colorless oil; $[\alpha]_D^{23}$ +7° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3630 (br, w), 2980 (s), 2950 (s), 2880 (s), 1650 (w), 1265 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84−5.75 (m, 1 H), 5.14−5.06 (complex series of m, 2 H), 4.96−4.95 (m, 1 H), 4.90−4.88 (m, 1 H), 4.08 (d, J = 5.9 Hz, 1 H), 3.74−3.70 (m, 1 H), 2.33−2.27 (m, 1 H), 2.21−2.15 (m, 1 H), 2.14 (d, J = 2.7 Hz, 1 H), 1.66 (br s, 3 H), 1.66−1.62 (m, 1 H), 0.91 (s, 9 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.10 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 135.3, 117.3, 112.4, 80.1, 72.5, 40.1, 39.9, 25.9, 18.2, 18.1, 7.1, −4.5, −5.1; high-resolution mass spectrum (Cl, NH_3) *m/z* 285.2263 [(M + H)$^+$; calcd for $C_{16}H_{33}O_2Si$: 285.2250].

Diene Acetonide (+)-18. A solution of silyloxy alcohol (+)-**17a** (7.32 g, 25.9 mmol) in THF (150 mL) was treated with TBAF (1.0 M in THF, 26.0 mL, 26.0 mmol), and the reaction mixture was stirred at room temperature for 30 min and concentrated in vacuo. The residue was dissolved in ether (100 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant crude diol was dried azeotropically with benzene (3 × 20 mL) and used without purification in the next reaction.

The crude diol was dissolved in freshly distilled 2,2-dimethoxypropane (50 mL) and *p*-toluenesulfonic acid monohydrate (10.0 mg, 0.053 mmol) was added. The reaction mixture was then stirred at ambient temperature for 30 min, diluted with ether (100 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:35 v/v)] gave (+)-**18** (4.83 g, 93% yield) as a volatile colorless oil: $[\alpha]_D^{23}$ +39° (*c* 3.8, $CHCl_3$); IR ($CHCl_3$) 3010 (s), 1655 (w), 1640 (m), 1380 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, J = 17.1, 10.3, 6.8 Hz, 1 H), 5.13−5.08 (complex series of m, 1 H), 5.07−5.04 (complex series of m, 1 H), 5.00−4.98 (m, 1 H), 4.87−4.85 (m, 1 H), 4.24 (d, J = 4.9 Hz, 1 H), 3.34 (apparent q, J = 6.6 Hz, 1 H), 2.33−2.29 (m, 2 H), 1.84−1.76 (m, 1 H), 1.65 (br s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 0.72 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 135.2, 116.5, 110.0, 100.8, 74.6, 71.3, 39.1, 38.1, 25.1, 23.9, 19.9, 12.2; high-resolution mass spectrum (Cl, NH_3) *m/z* 211.1703 [(M + H)$^+$; calcd for $C_{13}H_{23}O_2$: 211.1698].

Keto Aldehyde (+)-8. At −78 °C a solution of diene (+)-**18** (5.44 g, 25.9 mmol) in dichloromethane (100 mL) was treated with ozone until a light blue color persisted (∼45 min). A solution of triphenylphosphine (13.6 g, 51.8 mmol) in THF (60 mL) was added, and the mixture was gradually warmed to room temperature and then concentrated in vacuo. Flash chromatography (25% ethyl acetate/hexanes) provided (+)-**8** (5.10 g, 92% yield) as a colorless oil: $[\alpha]_D^{23}$ +46° (*c* 5.9, $CHCl_3$); IR ($CHCl_3$) 1730 (s), 1390 (s), 1360 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.33−9.32 (m, 1 H), 4.08 (d, J = 5.5 Hz, 1 H), 3.60 (ddd, J = 9.5, 8.1, 3.1 Hz, 1 H), 2.10 (ddd, J = 16.6, 9.4, 2.6 Hz, 1 H), 1.92 (s, 3 H), 1.83−1.77 (m, 2 H), 1.24 (s, 3 H), 1.09 (s, 3 H), 0.59 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.6, 198.8, 101.4, 75.4, 69.9, 47.3, 39.0, 27.7, 24.5, 23.7, 12.0; high-resolution mass spectrum (Cl, NH_3) *m/z* 215.1283 [(M + H)$^+$; calcd for $C_{11}H_{19}O_4$: 215.1284].

Keto Alcohol (+)-19. A solution of keto aldehyde (+)-**8** (4.93 g, 23.0 mmol) in THF (80 mL) was cooled to −78 °C and treated dropwise with lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (0.5 M in THF, 46.1 mL, 23.1 mmol). The reaction mixture was stirred for 30 min and then diluted with ether (250 mL). Saturated aqueous Rochelle's salt (150 mL) was added and the mixture vigorously stirred until two clear layers were obtained. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (33% ethyl acetate/hexanes) furnished (+)-**19** (3.78 g, 76% yield) as a colorless oil: $[\alpha]_D^{23}$ +63° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3520 (m), 2990 (s), 2960 (s), 2940 (s), 1725 (s), 1710 (s), 1380 (s), 1355 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (d, J = 5.5 Hz, 1 H), 3.84−3.71 (m, 2 H), 3.57 (ddd, J = 8.5, 8.5, 3.2 Hz, 1 H), 2.30−2.24 (m, 1 H), 2.20−2.12 (m, 1 H), 2.17 (s, 3 H), 1.88−1.75 (m, 2 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 101.5, 75.5, 74.5, 61.1, 39.2, 36.1, 27.8, 24.8, 23.7, 12.2; high-resolution mass spectrum (Cl, NH_3) *m/z* 234.1793 [(M + NH_4)$^+$; calcd for $C_{11}H_{24}NO_4$: 234.1705].

TBS Ether (+)-20. A solution of alcohol (+)-**19** (3.50 g, 16.4 mmol) in *N*,*N*-dimethylformamide (150 mL) was treated with imidazole (2.22 g, 32.7 mmol) and chloro-*tert*-butyldimethylsilane (2.72 g, 18.0 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into ether (500 mL), washed with H_2O and brine (200 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (6.25% ethyl acetate/hexanes) gave (+)-**20** (5.29 g, 98% yield) as a colorless oil: $[\alpha]_D^{23}$ +21° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$)

2960 (s), 2930 (s), 1725 (s), 1710 (s), 1380 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.36 (d, J = 5.4 Hz, 1 H), 3.70−3.63 (m, 2 H), 3.52 (ddd, J = 8.8, 8.8, 2.8 Hz, 1 H), 2.16 (s, 3 H), 2.14−2.06 (m, 1 H), 1.78−1.65 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 101.3, 75.6, 71.1, 59.1, 39.3, 37.5, 27.8, 25.9, 24.9, 23.8, 18.2, 12.1, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 331.2311 [(M + H)$^+$; calcd for $C_{17}H_{35}O_4Si$: 331.2304]. Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.82; H, 10.41. Found: C, 62.01; H, 10.38.

Enol Triflate (−)-21. A solution of ketone (+)-**20** (94.1 mg, 0.285 mmol) in THF (20 mL) was cooled to −78 °C, treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.43 mL, 0.43 mmol), and stirred for 30 min. A solution of *N*-phenyltrifluoromethanesulfonimide (203.7 mg, 0.570 mmol) in THF (5 mL) was then added. The reaction mixture was stirred at −78 °C for 2 h, warmed gradually to room temperature, diluted with ether (60 mL), washed with H_2O and brine (30 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:35 v/v)] afforded (−)-**21** (50.7 mg, 38% yield) and unreacted (+)-**20** (51.0 mg). (−)-**21**: colorless oil; $[\alpha]_D^{23}$ −8° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 2930 (s), 1735 (s), 1675 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27 (dd, J = 3.4, 1.6 Hz, 1 H), 5.25 (dd, J = 3.4, 1.3 Hz, 1 H), 4.52 (ddd, J = 5.2, 1.4, 1.4 Hz, 1 H), 3.68−3.65 (m, 2 H), 3.49 (ddd, J = 9.1, 9.1, 3.2 Hz, 1 H), 1.94−1.86 (m, 1 H), 1.80−1.66 (m, 2 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 0.89 (s, 9 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 104.2, 101.7, 71.1, 68.3, 59.0, 38.4, 37.7, 25.9, 24.8, 23.5, 12.0, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 463.1824 [(M + H)$^+$; calcd for $C_{18}H_{34}F_3O_6SSi$: 463.1797].

Acetylene (−)-22. A solution of ketone (+)-**20** (2.38 g, 7.21 mmol) in THF (75 mL) was cooled to −78 °C, treated dropwise with sodium bis(trimethylsilyl)amide (1.0 M in THF, 7.57 mL, 7.57 mmol), and stirred for 30 min. Diethyl chlorophosphate (1.25 mL, 8.65 mmol) was added and the solution stirred at −78 °C for 1 h. Following the introduction of *tert*-butyllithium (1.7 M in pentane, 19.1 mL, 32.5 mmol), the reaction mixture was stirred 40 min further and then quenched by dropwise addition of methanol (20 mL). The resultant solution was poured into ether (200 mL), washed with H_2O and brine (100 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:25 v/v)] provided (−)-**22** (1.88 g, 84% yield) as a colorless oil: $[\alpha]_D^{23}$ −48° (*c* 5.7, $CHCl_3$); IR ($CHCl_3$) 3315 (m), 2965 (s), 2940 (s), 1260 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, J = 5.7, 2.4 Hz, 1 H), 3.78 (dt, J = 9.4, 2.6 Hz, 1 H), 3.69 (dd, J = 7.6, 4.7 Hz, 1 H), 2.49 (d, J = 2.4 Hz, 1 H), 1.87−1.76 (m, 2 H), 1.59−1.50 (m, 2 H), 1.54 (s, 3 H), 1.36 (s, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.5, 81.7, 75.8, 69.0, 64.3, 58.9, 38.1, 36.5, 28.2, 25.9, 23.5, 18.2, 13.0, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 313.2223 [(M + H)$^+$; calcd for $C_{17}H_{33}O_3Si$: 313.2199].

Acetylenic Ester (−)-24. A solution of alkyne (−)-**22** (1.88 g, 6.03 mmol) in THF (60 mL) was cooled to −78 °C, treated dropwise with *tert*-butyllithium (1.3 M in pentane, 5.1 mL, 6.63 mmol), and stirred for 1 h. Methyl chloroformate (0.70 mL, 9.1 mmol) was added, and the resultant solution was warmed to room temperature over 2 h and then stirred 2 h further. The reaction mixture was diluted with ether (200 mL), washed with saturated aqueous $NaHCO_3$, H_2O and brine (50 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:25 v/v)] gave (−)-**24** (2.08 g, 93% yield) as a colorless oil: $[\alpha]_D^{23}$ −34° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 1715 (s), 1255 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, J = 5.8 Hz, 1 H), 3.80 (ddd, J = 9.4, 9.4, 2.5 Hz, 1 H), 3.79 (s, 3 H), 3.69 (dd, J = 7.6, 4.8 Hz, 2 H), 1.95−1.88 (m, 1 H), 1.86−1.79 (m, 1 H), 1.61−1.53 (m, 1 H), 1.55 (s, 3 H), 1.36 (m, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.051 (s, 3 H), 0.050 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 100.6, 85.7, 79.1, 68.9, 64.6, 58.7, 52.7, 37.8, 36.3, 28.5, 25.9, 23.2, 18.2, 12.9, −5.3, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 371.2240 [(M + H)$^+$; calcd for $C_{19}H_{35}O_5Si$: 371.2254].

Ester 25: mixture of *E* and *Z* isomers; colorless oil; IR ($CHCl_3$) 2950 (s), 2920 (s), 1710 (s), 1375 (s) cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 145.1, 122.7, 100.7, 100.4, 71.1, 70.9, 70.8, 70.0, 59.5, 59.3, 51.4, 51.3, 40.6, 40.1, 37.6, 25.9, 24.7, 24.5, 24.3, 24.0, 18.2, 16.9, 16.2, 15.8, 15.3, 12.6, 12.1, −5.3, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 401.2701 [(M + H)$^+$; calcd for $C_{21}H_{41}O_5Si$: 401.2723].

Alkenyl Ester (+)-26*Z*. A suspension of copper(I) iodide[42] (209 mg, 1.10 mmol) in THF (6 mL) was cooled to 0 °C and treated with methyllithium (1.4 M in ether, 1.6 mL, 2.20 mmol). The resultant clear solution was stirred at 0 °C for 1 h, cooled to −20 °C, and then added dropwise via a cannula to a solution of alkynyl ester (−)-**24** (135 mg, 0.37 mmol) in THF (12 mL) at −20 °C. The reaction was monitored carefully by TLC; addition of the cuprate solution was terminated upon complete consumption of (−)-**24**. The resultant mixture was poured into saturated aqueous NH_4OH, saturated aqueous NH_4Cl and H_2O (1:1:1, 10 mL) and extracted with ether (2 × 50 mL); the combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate/hexanes (1:25 v/v)] furnished (+)-**26*Z*** (133 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}$ +10° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 2954 (s), 2936 (s), 1710 (s), 1634 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73−5.71 (m, 1 H), 5.53 (d, J = 5.9 Hz, 1 H), 3.69−3.66 (m, 2 H), 3.67 (s, 3 H), 3.49 (ddd, J = 8.8, 8.8, 3.2 Hz, 1 H), 2.27−2.20 (m, 1 H), 1.94 (dd, J = 1.4, 0.6 Hz, 3 H), 1.78−1.67 (m, 2 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 0.89 (s, 9 H), 0.78 (d, J = 7.2 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 160.3, 115.3, 100.4, 71.1, 69.5, 59.5, 50.9, 39.7, 37.5, 25.9, 24.7, 24.2, 18.2, 12.3, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 387.2531 [(M + H)$^+$; calcd for $C_{20}H_{39}O_5Si$: 387.2567]. Anal. Calcd for $C_{20}H_{38}O_5Si$: C, 62.11; H, 9.91. Found: C, 62.07; H, 9.84.

Alkenyl Ester (+)-26*E*: colorless oil; $[\alpha]_D^{23}$ +35° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s), 2860 (s), 1710 (s), 1655 (s), 1380 (s) $cm^{-1;}$ ^1H NMR (500 MHz, $CDCl_3$) δ 6.02−6.00 (m, 1 H), 4.33 (dd, J = 5.0, 1.3 Hz, 1 H), 3.72−3.64 (m, 2 H), 3.70 (s, 3 H), 3.44 (ddd, J = 8.4, 8.4, 3.1 Hz, 1 H), 2.06 (br s, 3 H), 1.96−1.88 (m, 1 H), 1.79−1.66 (m, 2 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 0.89 (s, 9 H), 0.69 (d, J = 6.8 Hz, 3 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 156.1, 114.4, 101.1, 72.3, 71.4, 59.3, 50.8, 39.1, 37.9, 25.9, 25.0, 23.7, 18.3, 16.2, 11.8, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 387.2549 [(M + H)$^+$; calcd for $C_{20}H_{39}O_5Si$: 387.2567].

Allylic Alcohol (−)-27. A solution of alkenyl ester (+)-**26*Z*** (1.16 g, 3.02 mmol) in toluene (15 mL) was cooled to −78 °C, treated dropwise with DIBAL (1.5 M in toluene, 4.3 mL, 6.3 mmol), and stirred for 10 min. The reaction mixture was then diluted with ether (60 mL), saturated aqueous Rochelle's salt (40 mL) was added, and the resultant mixture was stirred vigorously until two clear layers were obtained. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (18% ethyl acetate/hexanes) provided (−)-**27** (975 mg, 91% yield) as a colorless oil: $[\alpha]_D^{23}$ −18° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3460 (w), 2960 (s), 2935 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59−5.53 (m, 1 H), 4.52 (d, J = 5.4 Hz, 1 H), 4.16 (dd, J = 12.6, 6.7, 1 H), 4.04 (dd, J = 12.6, 7.2 Hz, 1 H), 3.68−3.61 (m, 2 H), 3.49 (ddd, J = 8.8, 8.8, 2.7 Hz, 1 H), 1.80−1.70 (m, 2 H), 1.68−1.60 (m, 1 H), 1.66 (br s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 0.87 (s, 9 H), 0.79 (d, J = 6.9 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 126.1, 101.0, 72.0, 71.3, 59.3, 58.8, 40.1, 37.8, 25.9, 24.8, 23.9, 21.8, 18.2, 12.2, −5.3, −5.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 341.2550 [(M − OH)$^+$; calcd for $C_{19}H_{37}O_3Si$: 341.2512].

Chloride (−)-28. A solution of alcohol (−)-**27** (49.2 mg, 0.137 mmol) in *N*,*N*-dimethylformamide (3.3 mL) was treated with lithium chloride (30 mg, 0.71 mmol), and the resultant suspension was stirred until all of the lithium chloride dissolved (10−20 min). 2,6-Lutidine (65 μL, 0.56 mmol) and methanesulfonyl chloride (22 μL, 0.28 mmol) were added, and the reaction was stirred at room temperature for 1 h, cooled to 0 °C, and then quenched with saturated aqueous $NaHCO_3$ (3 mL). The resultant mixture was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (9% ethyl acetate/hexanes) afforded (−)-**28** (50.0 mg, 97% yield) as a colorless oil: $[\alpha]_D^{23}$ −5.9° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2935 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.36−5.32 (m, 1 H), 4.65 (d, J = 5.6 Hz, 1 H), 4.09−4.02 (m, 2 H), 3.79−3.74 (m, 1 H), 3.69−3.65 (m, 1 H), 3.60−3.56 (m, 1 H), 1.76−1.64 (m, 2 H), 1.55 (br s, 3 H), 1.34 (s, 3

(42) Copper (I) iodide was purified via the method of Kauffman: Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1984**, *22*, 101.

H), 1.30 (s, 3 H), 0.98 (s, 9 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2, 123.1, 101.0, 71.3, 70.9, 59.6, 41.3, 40.7, 38.2, 26.1, 24.7, 24.0, 21.4, 18.4, 12.3, −5.2, −5.3; high-resolution mass spectrum (Cl, NH_3) *m/z* 377.2274 [(M + H)$^+$; calcd for $C_{19}H_{38}ClO_3Si$: 377.2279].

Benzylic Alcohol 30. A solution of acid **29** (11.0 g, 60.1 mmol) in THF (200 mL) was cooled to 0 °C, treated dropwise with BH_3/THF (1.0 M in THF, 300 mL, 300 mmol), stirred for 30 min, and then warmed to room temperature and stirred 15 h further. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of methanol (10 mL). The resultant solution was diluted with ether (1.5 L), washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (50% ethyl acetate/hexanes) provided **30** (6.0 g, 60% yield) as a yellow solid: mp 122−124 °C (hexane/chloroform); IR (KBr) 3470 (s), 3200 (s), 1520 (s), 1342 (s), 1280 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.16 (s, 1 H), 7.74−7.71 (m, 1 H), 7.53−7.50 (m, 1 H), 7.28−7.25 (m, 1 H), 4.71-4.68 (m, 2 H), 4.54−4.49 (m, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.9, 150.1, 147.0, 120.3, 112.8, 109.1, 63.5; high-resolution mass spectrum (Cl, NH_3) *m/z* 187.0730 [(M + NH_4)$^+$; calcd for $C_7H_{11}N_2O_4$: 187.0719].

Benzyl Bromide 31. A solution of alcohol **30** (5.90 g, 34.3 mmol) in THF (200 mL) was cooled to 0 °C, and triphenylphosphine (13.5 g, 51.5 mmol) and carbon tetrabromide (17.1 g, 51.5 mmol) were added. The resultant solution was stirred for 1 h, then warmed to room temperature, and stirred 1 h further. The resultant suspension was filtered, and the filtrate was diluted with ether (600 mL), washed with water and brine (200 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (25% ethyl acetate/hexanes) furnished **31** (6.88 g, 85% yield) as a light-yellow solid: mp 145−148 °C (hexane/chloroform); IR (KBr) 3400 (s), 3094 (s), 1516 (s), 1480 (s), 1352 (s), 1285 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.41 (s, 1 H), 7.84−7.81 (m, 1 H), 7.61−7.58 (m, 1 H), 7.38−7.36 (m, 1 H), 4.71 (s, 2 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.2, 150.4, 142.4, 123.2, 115.8, 110.7, 32.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 248.9852 [(M + NH_4)$^+$; calcd for $C_7H_{10}BrN_2O_3$: 248.9875].

Sulfone 32. Bromide **31** (4.10 g, 18.8 mmol) was dissolved in *N*,*N*-dimethylformamide (100 mL), sodium benzenesulfinate (6.24 g, 38.0 mmol) was added, and the resultant solution was stirred at 60 °C for 15 h. The reaction mixture was cooled to room temperature, diluted with ether (300 mL), washed with water and brine (100 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (50% ethyl acetate/hexanes) gave **32** (3.94 g, 75% yield) as a white solid: mp 219−221 °C (hexane/chloroform); IR (KBr) 3370 (m), 1535 (s), 1355 (s), 1295 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 9.41 (br s, 1 H), 7.80−7.70 (m, 3 H), 7.64−7.56 (m, 3 H), 7.54−7.52 (m, 1 H), 7.16−7.13 (m, 1 H), 4.66 (s, 2 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.8, 149.8, 139.4, 134.8, 133.1, 130.0, 129.3, 125.3, 117.7, 110.8, 61.5; high-resolution mass spectrum (Cl, NH_3) *m/z* 311.0722 [(M + NH_4)$^+$; calcd for $C_{13}H_{15}N_2O_4S$: 311.0702].

BPS Ether 33. A solution of phenol **32** (2.04 g, 7.00 mmol) in *N*,*N*-dimethylformamide (50 mL) was treated with imidazole (0.953 g, 14.0 mmol) and *tert*-butyldiphenylsilyl chloride (2.20 mL, 8.35 mmol) and then stirred at room temperature for 24 h. The reaction mixture was diluted with water (100 mL) and extracted with ether (2 × 200 mL); the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/hexanes) provided **33** (3.51 g, 95% yield) as a white solid: mp 118−121 °C (hexane/chloroform); IR (KBr) 1535 (s), 1450 (s), 1355 (s), 1320 (s), 1300 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4 H), 7.60−7.54 (m, 3 H), 7.49−7.45 (m, 3 H), 7.44−7.39 (m, 6 H), 7.31−7.29 (m, 1 H), 6.95−6.93 (m, 1 H), 4.16 (s, 2 H), 1.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 148.6, 137.4, 135.5, 134.1, 131.4, 130.7, 130.5, 129.1, 128.5, 128.3, 128.1, 118.3, 115.2, 62.0, 26.5, 19.5; high-resolution mass spectrum (Cl, NH_3) *m/z* 532.1631 [(M + H)$^+$; calcd for $C_{29}H_{30}NO_5SSi$: 532.1614]. Anal. Calcd for $C_{29}H_{29}NO_5SSi$: C, 65.51; H, 5.50; N, 2.63. Found: C, 65.84; H, 5.85; N, 2.58.

Aniline 34. A mixture of nitro derivative **33** (1.92 g, 3.61 mmol), 10% Pd/C (100 mg), and methanol (150 mL) was stirred under hydrogen (balloon) for 10 h. The mixture was then filtered through Celite, the filter pad was washed thoroughly with ethyl acetate, and the filtrate was concentrated in vacuo. Flash chromatography (67% ethyl acetate/hexanes) furnished **34** (1.80 g, 100% yield) as a pale yellow oil: IR ($CHCl_3$) 3500 (w), 3405 (w), 1620 (s), 1600 (s), 1475 (s), 1465 (s), 1355 (s), 1318 (s), 1312 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.61 (m, 4 H), 7.61−7.58 (m, 2 H), 7.55−7.50 (m, 1 H), 7.45−7.34 (m, 8 H), 6.04−6.01 (m, 1 H), 5.98−5.95 (m, 1 H), 5.87−5.84 (m, 1 H), 4.03 (s, 2 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 137.9, 135.5, 133.4, 132.8, 129.9, 129.8, 128.7, 128.6, 128.3, 127.8, 112.8, 110.6, 106.9, 62.8, 26.5, 19.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 502.1865 [(M + H)$^+$; calcd for $C_{29}H_{32}NO_3SSi$: 502.1872].

Hydroxy Amide (−)-35. A solution of aniline **34** (1.60 g, 3.19 mmol) in benzene (29 mL) was treated dropwise with trimethylaluminum (2.0 M in hexane, 1.92 mL, 3.83 mmol) and stirred for 20 min at room temperature. A solution of lactone **10** (450 mg, 3.87 mmol) in benzene (2 mL plus 2-mL rinse) was then added via a cannula. The reaction mixture was stirred at ambient temperature for 21 h, cooled to 0 °C, cautiously quenched with aqueous HCl (1.0 M, 15 mL), and extracted with ethyl acetate (100 mL). The organic phase was washed with water and brine (25 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (gradient elution, 50 → 75% ethyl acetate/hexanes) afforded (−)-**35** (1.4 g, 71% yield) as a white foam: $[\alpha]_D^{23}$ −5.9° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3340 (w), 1695 (s), 1610 (s), 1468 (s), 1434 (s), 1325 (s), 1314 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4 H), 7.59−7.50 (m, 3 H), 7.46−7.40 (m, 2 H), 7.39−7.33 (m, 6 H), 6.93−6.90 (m, 1 H), 6.86−6.83 (m, 1 H), 6.24−6.21 (m, 1 H), 4.07 (s, 2 H), 3.76 (dd, J = 11.7, 3.9 Hz, 1 H), 3.69−3.64 (m, 1 H), 3.53 (dd, J = 11.7, 4.2 Hz, 1 H), 3.37 (s, 3 H), 2.52 (dd, J = 14.8, 7.2 Hz, 1 H), 2.46 (dd, J = 14.8, 4.9 Hz, 1 H), 1.91 (br s, 1 H), 1.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 156.0, 138.8, 137.9, 135.5, 133.6, 132.5, 130.0, 129.6, 128.8, 128.5, 127.8, 118.0, 115.1, 111.6, 78.3, 62.9, 62.5, 57.5, 39.5, 26.5, 19.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 618.2297 [(M + H)$^+$; calcd for $C_{34}H_{40}NO_6SSi$: 618.2345].

Lactam Aminal 36a. A solution of hydroxy amide (−)-**35** (880 mg, 1.40 mmol) in DMSO (5 mL) was treated with triethylamine (1.60 mL, 11.4 mmol) followed by pyr·SO_3 (900.0 mg, 5.70 mmol). The resultant mixture was stirred for 1.5 h at room temperature, poured into water (20 mL), and extracted with ethyl acetate (2 × 60 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (33% ethyl acetate/hexanes) provided **36a** (571 mg, 65% yield) as an inseparable diastereomer mixture and imide **36b** (70.0 mg, 8% yield). **36a**: colorless oil; IR ($CHCl_3$) 3600−3100 (br, m), 3005 (s), 2950 (s), 2930 (s), 2855 (s), 1705 (s), 1600 (s), 1455 (s), 1445 (s), 1420 (s), 1400 (s), 1355 (s), 1315 (s), 1305 (s), 1255 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (m, 4 H), 7.55 (m, 2 H), 7.53 (m, 1 H), 7.52−7.33 (complex series of m, 8 H), 6.99, 6.80 (diastereomers, m, m, 1 H), 6.89, 6.79 (diastereomers, m, m, 1 H), 6.45, 6.35 (diastereomers, m, m, 1 H), 5.11, 5.00 (diastereomers, br apparent t, J = 5.1 Hz, br m, 1 H), 4.09 (br s, 2 H), 3.89, 3.68 (diastereomers, ddd, J = 7.3, 7.3, 5.2 Hz, m, 1 H), 3.41, 3.31 (diastereomers, s, s, 3 H), 2.87 (br s, 1 H), 2.79, 2.62 (diastereomers, dd, J = 17.7, 6.5 Hz, dd, J = 16.9, 7.5 Hz, 1 H), 2.53, 2.35 (diastereomers, dd, J = 16.9, 7.2 Hz, dd, J = 17.7, 1.9 Hz, 1 H), 1.07, 1.06 (diastereomers, s, s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 170.2, 156.1, 155.8, 138.2, 137.9, 137.8, 135.6, 133.6, 133.5, 132.5, 132.4, 130.1, 130.0, 129.7, 129.4, 128.9, 128.8, 128.5, 127.9, 127.8, 119.8, 119.5, 118.2, 117.7, 114.6, 114.4, 87.9, 82.9, 79.6, 73.5, 62.6, 62.5, 57.5, 56.8, 36.5, 35.8, 29.7, 26.6, 26.5, 19.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 633.2516 [(M + NH_4)$^+$; calcd for $C_{34}H_{41}N_2O_6SSi$: 633.2454]. Anal. Calcd for $C_{34}H_{37}NO_6SSi$: C, 66.31; H, 6.06; N, 2.27. Found: C, 65.91; H, 6.10; N, 2.17.

(+)-36b: colorless oil; $[\alpha]_D^{23}$ +38° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1725 (s), 1600 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.61 (m, 4 H), 7.54−7.49 (m, 3 H), 7.46−7.41 (m, 2 H), 7.40−7.34 (m, 6 H), 6.70−6.68 (m, 1 H), 6.59−6.57 (m, 1 H), 6.49−6.47 (m, 1 H), 4.22 (dd, J = 8.3, 4.2 Hz, 1 H), 4.10 (s, 2 H), 3.60 (s, 3 H), 3.04 (dd, J = 18.2, 8.3 Hz, 1 H), 2.66 (dd, J = 18.2, 4.2 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.8, 172.3, 156.0, 137.4, 135.5, 133.6, 132.2, 132.1, 130.1, 128.9, 128.5, 128.3, 127.9, 122.4, 121.3,

118.6, 74.6, 62.2, 58.9, 36.0, 26.5, 19.4; high-resolution mass spectrum (Cl, NH_3) *m/z* 631.2325 [(M + NH_4)$^+$; calcd for $C_{34}H_{39}N_2O_6SSi$: 631.2298].

Allylic Iodide (−)-38. A solution of chloride (−)-**28** (164 mg, 0.44 mmol) in acetone (4 mL) was treated with sodium iodide (262 mg, 1.76 mmol), and the resultant heterogeneous mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was filtered through a 1 cm × 2.5 cm plug of activity-I neutral alumina with 30% ethyl acetate/hexanes as eluant. Concentration in vacuo provided iodide (−)-**38** as an unstable colorless oil (∼85% pure by ^{1}H NMR) which was used immediately in the next reaction: $[\alpha]_D^{23}$ −40° (*c* 0.22, C_6H_6); IR (C_6H_6) 2960 (s), 2920 (s), 2860 (s), 1380 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6H_6) δ 5.34 (m, 1 H), 4.70 (d, J = 5.6 Hz, 1 H), 3.86 (apparent t, J = 9.3 Hz, 1 H), 3.77 (m, 1 H), 3.69 (m, 2 H), 3.62 (ddd, J = 8.7, 8.7, 2.9 Hz, 1 H), 1.78−1.68 (complex series of m, 3 H), 1.53 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 0.98 (s, 9 H), 0.80 (d, J = 6.9 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, C_6H_6) δ 139.1, 124.1, 101.0, 71.2, 70.6, 59.6, 40.8, 38.2, 26.1, 24.7, 24.1, 21.4, 18.4, 12.4, 2.7, −5.2; high-resolution mass spectrum (CI, NH_3) *m/z* 486.1904 [(M + NH_4)$^+$; calcd for $C_{19}H_{41}INO_3Si$: 486.1900].

Coupled Sulfone 37. At −78 °C a solution of sulfone **36a** (540 mg, 0.88 mmol) in THF (5 mL) was treated dropwise with sodium bis(trimethylsilyl)amide (0.9 M in THF, 1.8 mL, 1.6 mmol), and the resultant yellow solution was stirred for 5 min. A solution of iodide (−)-**38** (∼205 mg, 0.44 mmol) in THF (1 mL) was then added. The reaction mixture was stirred 5 min further at −78 °C, quenched with methanol (0.5 mL), poured into ether (20 mL), washed with water and brine (5 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (67% ethyl acetate/hexanes) afforded **37** (349 mg, 83% yield) as a complex diastereomer mixture: colorless oil; IR ($CHCl_3$) 3620−3100 (br, w), 2950 (s), 2930 (s), 1710 (s), 1595 (s), 1460 (s), 1380 (s), 1305 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.62 (complex series of m, 4 H), 7.49−7.24 (complex series of m, 11 H), 7.02−6.73 (m, 2 H), 6.51−6.35 (m, 1 H), 5.05, 5.03 (diastereomers, m, m, 1 H), 4.76 (apparent t, J = 6.7 Hz, 1 H), 4.49, 4.44 (diastereomers, d, J = 5.2 Hz, d, J = 5.4 Hz, 1 H), 3.91−3.61 (complex series of m, 3 H), 3.48−3.38 (complex series of m, 1 H), 3.42, 3.34, 3.33 (diastereomers, s, s, s, 3 H), 3.23, 3.07 (diastereomers m, m, 1 H), 2.80, 2.79 (diastereomers, dd, J = 17.7, 6.6 Hz, dd, J = 17.7, 6.5 Hz, 1 H), 2.66−2.41 (complex series of m, 2 H), 2.38 (dd, J = 17.6, 1.9 Hz, 1 H), 1.75−1.54 (complex series of m, 4 H), 1.50, 1.49, 1.48, 1.45 (diastereomers, s, s, s, s, 3 H), 1.33, 1.32 (diastereomers, s, s, 3 H), 1.27, 1.26 (diastereomers, s, s, 3 H), 1.08, 1.07, 1.06, 1.05 (diastereomers, s, s, s, s, 9 H), 0.90, 0.89 (diastereomers, s, s, 9 H), 0.73, 0.72, 0.63 (diastereomers, d, J = 6.9 Hz, d, J = 6.8 Hz, d, J = 6.9 Hz, 3 H), 0.05, 0.04 (diastereomers, s, s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.4, 156.0, 155.9, 155.7, 155.6, 139.9, 139.8, 138.1, 137.9, 137.8, 137.6, 137.5, 137.4, 137.2, 137.1, 137.0, 135.6, 135.5, 134.2, 134.1, 133.9, 133.8, 133.5, 133.3, 133.1, 132.7, 132.6, 130.1, 130.0, 129.9, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9, 127.8, 127.7, 121.1, 120.8, 120.3, 120.2, 120.1, 120.0, 119.0, 118.7, 118.6, 117.6, 117.3, 117.1, 116.4, 114.9, 114.8, 114.5, 114.4, 100.7, 100.6, 88.0, 87.9, 87.8, 87.5, 82.9, 80.1, 79.7, 79.5, 79.4, 73.6, 72.1, 71.8, 71.4, 71.3, 71.2, 71.1, 71.0, 70.7, 70.6, 70.3, 63.5, 63.4, 59.5, 59.4, 57.5, 56.9, 43.2, 42.5, 40.6, 40.5, 37.8, 36.9, 36.5, 35.9, 35.8, 35.5, 30.9, 29.7, 28.4, 27.7, 26.6, 26.1, 25.9, 25.8, 25.5, 25.3, 24.7, 24.0, 23.9, 21.3, 21.2, 20.9, 19.9, 19.5, 18.2, 18.1, 12.1, 12.0, 11.6, −5.3, −5.5, −5.6; high-resolution mass spectrum (FAB, NBA) *m/z* 898.3891 [(M − *t*-Bu)$^+$; calcd for $C_{49}H_{64}NO_9SSi_2$: 898.3840].

Desulfonylated Arene 39. A mixture of sulfones **37** (330 mg, 0.35 mmol), Na_2HPO_4 (200 mg, 1.4 mmol) and anhydrous MeOH (3 mL) was cooled to −20 °C, excess 6% Na(Hg) (ca. 750 mg) was added, and the resultant suspension was stirred until the starting material was completely consumed (∼15−30 min) as indicated by TLC analysis. The reaction mixture was then filtered through a short plug of silica with ethyl acetate as eluant, and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL), and the solution was washed with water and brine (5 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (33% ethyl acetate/hexanes) provided **39** (243 mg, 85% yield) as a mixture of diastereomers. HPLC gave the major isomer (+)-**39** as a colorless oil: $[\alpha]_D^{23}$ +9° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 2920 (s), 1700 (s), 1590 (s), 1460 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.87−7.81 (m, 4 H), 7.41−7.39 (m, 1 H), 7.32−7.29 (m, 1 H), 7.22−7.17 (m, 6 H), 6.68−6.66 (m, 1 H), 5.15−5.08 (m, 2 H), 4.82 (d, J = 5.7 Hz, 1 H), 3.85−3.79 (m, 1 H), 3.76−3.71 (m, 1 H), 3.69−3.64 (m, 1 H), 3.25−3.23 (m, 1 H), 2.46 (dd, J = 17.5, 6.2 Hz, 1 H), 2.39−2.35 (m, 1 H), 2.24 (dd, J = 17.5, 1.7 Hz, 1 H), 2.20−2.10 (m, 1 H), 2.10 (d, J = 6.7 Hz, 1 H), 1.82−1.68 (m, 3 H), 1.81 (s, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.20 (s, 9 H), 1.00 (s, 9 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 156.4, 144.3, 139.3, 136.0, 134.9, 130.3, 130.2, 125.5, 117.3, 115.9, 111.5, 100.8, 88.1, 80.0, 71.3, 69.8, 59.8, 56.2, 41.7, 38.3, 36.6, 36.4, 29.8, 26.8, 26.1, 24.8, 24.4, 21.2, 19.7, 18.4, 12.5, −5.2; high-resolution mass spectrum (FAB, NBA) *m/z* 758.3961 [(M − *t*-Bu)$^+$; calcd for $C_{43}H_{60}NO_7Si_2$: 758.3908]. Anal. Calcd for $C_{47}H_{69}NO_7Si_2$: C, 69.16; H, 8.52; N, 1.72. Found: C, 69.03; H, 8.56; N, 1.74.

Acetate 40. A solution of aminal **39** (170 mg, 0.21 mmol) in dichloromethane (2 mL) was treated sequentially with Et_3N (0.12 mL, 0.84 mmol), DMAP (2.5 mg, 0.20 mmol), and acetic anhydride (60 μL, 0.63 mmol). The reaction mixture was stirred at room temperature for 10 min, poured into ethyl acetate (10 mL), washed with saturated aqueous NH_4Cl (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/hexanes) afforded **40** (157 mg, 87% yield) as a diastereomer mixture: colorless oil; IR ($CHCl_3$) 1725 (s), 1595 (s), 1460 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.84−7.80 (m, 4 H), 7.40−7.38 (m, 1 H), 7.22−7.17 (m, 6 H), 6.70−6.68 (m, 1 H), 6.36 (s, 1 H), 5.09 (t, J = 7.5 Hz, 3 H), 4.84 (d, J = 5.8 Hz, 1 H), 3.87−3.81 (m, 1 H), 3.77−3.72 (m, 1 H), 3.67 (ddd, J = 9.0, 9.0, 2.6 Hz, 1 H), 3.28 (d, J = 5.7 Hz, 1 H), 3.04 (s, 3 H), 2.41 (dd, J = 17.6, 5.8 Hz, 1 H), 2.35 (apparent t, J = 7.5 Hz, 2 H), 2.28 (d, J = 17.6 Hz, 1 H), 2.15 (apparent q, J = 7.6 Hz, 2 H), 1.81 (s, 3 H), 1.81−1.72 (m, 3 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 1.18 (s, 9 H), 1.00 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2, 169.3, 156.4, 144.5, 139.0, 135.9, 134.9, 133.2, 133.0, 130.2, 125.4, 117.7, 115.4, 111.1, 100.8, 88.3, 77.3, 71.3, 69.8, 59.8, 56.7, 41.7, 38.3, 37.1, 36.4, 29.6, 26.7, 26.1, 24.8, 24.4, 21.3, 20.3, 19.7, 18.4, 12.5, −5.2; high-resolution mass spectrum (FAB, NBA) *m/z* 800.4042 [(M − *t*-Bu)$^+$; calcd for $C_{45}H_{62}NO_8Si_2$: 800.4014].

Hydroxy Phenol 41. Bis(silyl ether) **40** (123 mg, 0.144 mmol) was dissolved in THF (1.5 mL), and TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol) was added. The resultant solution was stirred at room temperature for 4 h and then poured into ether (20 mL), washed with water and brine (5 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (75% ethyl acetate/hexanes) gave **41** (58.0 mg, 80% yield) as a colorless oil: IR ($CHCl_3$) 3520−3040 (br), 1720 (s), 1600 (m) cm$^{-1;}$ ^{1}H NMR (500 MHz, C_6D_6) δ 7.34−7.32 (m, 1 H), 7.18−7.16 (m, 1 H), 6.77 (s, 1 H), 6.55−6.53 (m, 1 H), 5.29−5.24 (m, 1 H), 4.92 (d, J = 5.6 Hz, 1 H), 3.87−3.80 (m, 1 H), 3.78−3.72 (m, 1 H), 3.57 (ddd, J = 7.9, 7.9, 3.6 Hz, 1 H), 3.40 (d, J = 6.4 Hz, 1 H), 3.16 (s, 3 H), 2.58 (dd, J = 17.6, 5.9 Hz, 1 H), 2.59−2.46 (m, 1 H), 2.45 (d, J = 17.6 Hz, 1 H), 2.35−2.25 (m, 1 H), 1.91 (br s, 3 H), 1.81−1.71 (m, 3 H), 1.64 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 0.81 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.6, 169.6, 157.5, 144.7, 140.0, 135.1, 125.5, 113.6, 113.4, 107.3, 100.9, 88.2, 77.5, 74.6, 69.6, 60.9, 56.8, 41.0, 37.2, 36.5, 30.2, 24.7, 24.1, 21.1, 20.4, 12.7; high-resolution mass spectrum (FAB, NBA) *m/z* 528.2534 [(M + Na)$^+$; calcd for $C_{27}H_{39}NO_8Na$: 528.2573].

TBS Aldehyde 43. A solution of hydroxy phenol **41** (56.0 mg, 0.11 mmol) in DMSO (3 mL) was treated with triethylamine (1 mL) followed by pyr·SO_3 (145 mg, 0.44 mmol). The resultant mixture was stirred at room temperature for 1 h, poured into water (5 mL), and extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (67% ethyl acetate/hexanes) provided impure aldehyde **42**, which was used in the next reaction without further purification.

Aldehyde **42** was dissolved in DMF (0.5 mL), imidazole (25.0 mg, 0.33 mmol) and chloro-*tert*-butyldimethylsilane (33.0 mg, 0.22 mmol) were added; the resultant solution was stirred at room temperature for 2 h, poured into water (2 mL) and extracted with ethyl acetate (2 × 5 mL). The combined extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography

(25% ethyl acetate/hexanes) afforded **43** (39.2 mg, 62% yield) as a colorless oil: IR ($CHCl_3$) 1725 (s), 1590 (s), 1455 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.54 (dd, J = 2.9, 1.4 Hz, 1 H), 7.39−7.38 (m, 1 H), 7.29−7.28 (m, 1 H), 6.71 (s, 1 H), 6.70−6.67 (m, 1 H), 5.20−5.14 (m, 1 H), 4.77 (d, J = 5.8 Hz, 1 H), 3.76−3.72 (m, 1 H), 3.31 (d, J = 5.7 Hz, 1 H), 3.05 (s, 3 H), 2.52−2.07 (m, 8 H), 1.79 (br s, 3 H), 1.60 (s, 3 H), 1.32 (s, 3 H), 1.27 (s, 3 H), 1.00 (s, 9 H), 0.63 (d, J = 6.9 Hz, 3 H), 0.21 (s, 3 H), 0.20 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.7, 172.4, 169.4, 156.6, 144.5, 139.1, 134.7, 125.7, 118.2, 114.7, 111.4, 101.1, 88.0, 77.5, 70.2, 69.6, 56.7, 47.7, 41.0, 37.1, 36.4, 29.9, 25.8, 24.3, 24.1, 21.1, 20.4, 18.4, 12.3, −4.4; high-resolution mass spectrum (CI, NH_3) m/z 635.3744 [$(M + NH_4)^+$; calcd for $C_{33}H_{55}N_2O_8Si$: 635.3727].

Aminal 44. A solution of acetate **43** (30.0 mg, 0.05 mmol) in anhydrous MeOH (1 mL) was cooled to −20 °C, treated with anhydrous K_2CO_3 (7.0 mg, 0.05 mmol) stirred for 1 h, and then poured into ethyl acetate (10 mL). The resultant solution was washed with saturated aqueous NH_4Cl (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (50% ethyl acetate/hexanes) provided **44** (22.6 mg, 81% yield) as a 4:1 diastereomer mixture: colorless oil; IR ($CHCl_3$) 3610−3310 (br, w), 2930 (s), 1710 (s), 1590 (s), 1480 (s), 1400 (s) $cm^{-1;}$ ^1H NMR (500 MHz, C_6D_6) δ 9.47 (dd, J = 3.0, 1.5 Hz, 1 H), 7.57−7.55 (m, 1 H), 7.34−7.32 (m, 1 H), 6.80−6.78 (m, 1 H), 5.35 (d, J = 5.9 Hz, 1 H), 5.23−5.17 (m, 1 H), 4.77 (d, J = 5.8 Hz, 1 H), 3.67 (ddd, J = 8.6, 8.6, 3.5 Hz, 1 H), 3.31 (d, J = 5.6 Hz, 1 H), 2.87 (s, 3 H), 2.60−2.30 (complex series of m, 8 H), 1.81 (br s, 3 H), 1.62−1.55 (m, 1 H), 1.30 (s, 3 H), 1.25 (s, 3 H), 1.01 (s, 9 H), 0.63 (d, J = 6.9 Hz, 3 H), 0.25 (s, 3 H), 0.24 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.6, 200.1, 171.5, 169.8, 156.5, 156.4, 144.2, 144.0, 139.9, 139.7, 134.8, 134.7, 125.8, 117.8, 117.6, 115.0, 114.9, 111.9, 111.7, 101.1, 88.5, 83.1, 80.1, 73.5, 70.4, 70.3, 69.6, 69.5, 56.7, 56.2, 47.7, 41.0, 40.9, 36.6, 36.5, 36.0, 30.3, 30.2, 25.9, 24.5, 24.4, 24.1, 21.1, 21.0, 18.4, 12.3, −4.3; high-resolution mass spectrum (FAB, NBA) m/z 500.2495 [$(M - t\text{-Bu} - H_2O)^+$; calcd for $C_{27}H_{38}NO_6Si$: 500.2468].

TBS Ether (+)-46. A solution of alcohol (−)-**35** (329 mg, 0.53 mmol) in CH_2Cl_2 (5.3 mL) was treated with imidazole (94 mg, 1.38 mmol) and chloro-*tert*-butyldimethylsilane (105 mg, 0.69 mmol). The resultant heterogeneous mixture was stirred at room temperature for 20 min, diluted with ether (50 mL), and washed with water and brine (10 mL each). The combined aqueous phases were extracted with ether (50 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (25% ethyl acetate/hexanes) gave (+)-**46** (364 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}$ +1.2° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3430 (w), 3330 (w), 1713 (s), 1690 (s), 1605 (s), 1465 (s), 1430 (s), 1320 (s), 1310 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (br s, 1 H), 7.63 (dd, J = 8.0, 1.3 Hz, 4 H), 7.54 (dd, J = 8.2, 0.9 Hz, 2 H), 7.49 (apparent t, J = 7.4 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.36−7.32 (m, 6 H), 6.89 (br s, 1 H), 6.82 (br s, 1 H), 6.22 (br s, 1 H), 4.05 (s, 2 H), 3.65−3.61 (m, 2 H), 3.59−3.56 (m, 1 H), 3.35 (s, 3 H), 2.46 (dd, J = 14.9, 3.4 Hz, 1 H), 2.38 (dd, J = 14.9, 7.7 Hz, 1 H), 1.05 (s, 9 H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 155.9, 139.0, 137.9, 135.5, 133.4, 132.5, 129.9, 129.6, 128.7, 128.5, 127.8, 117.7, 115.0, 111.5, 78.8, 63.9, 62.6, 57.7, 39.8, 26.5, 25.8, 19.4, 18.2, −5.5; high-resolution mass spectrum (FAB, NBA) m/z 754.3035 [$(M + Na)^+$; calcd for $C_{40}H_{53}NO_6SSi_2Na$: 754.3030]. Anal. Calcd for $C_{40}H_{53}NO_6SSi_2$: C, 65.66; H, 7.25; N, 1.92. Found: C, 65.58; H, 7.36; N, 1.73.

Coupling Product 47. A solution of sulfone (+)-**46** (700 mg, 0.96 mmol) in anhydrous THF (10 mL) was cooled to −78 °C, and sodium bis(trimethylsilyl)amide (0.8 M in THF, 2.6 mL) was added dropwise. The resultant deep yellow solution was stirred at −78 °C for 10 min, and then freshly prepared iodide (−)-**38** (310 mg, 0.66 mmol) in THF (2.5 mL plus 2-mL rinse) was introduced via a cannula. After 10 min at −78 °C, the reaction mixture was transferred by cannula into a cold (0 °C), vigorously stirred mixture of pH 7 buffer and ether (1:1, 100 mL). The mixture was warmed to room temperature, the layers were separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (20% ethyl acetate/hexanes) provided **47** (645 mg, 91% yield) as a white foam. Further elution (30% ethyl acetate/hexanes) gave recovered (+)-**46** (123 mg). NMR analysis revealed a 1.5:1 diastereomer ratio: IR ($CHCl_3$) 3440 (w), 3340 (w), 2960 (s), 2940 (s), 2860 (s), 1690 (m), 1610 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (br s, 1 H), 7.66−7.61 (m, 4 H), 7.46−7.24 (complex m, 11 H), 7.03, 6.99 (diastereomers, br s, br s, 1 H), 6.74, 6.71 (diastereomers, br s, br s, 1 H), 6.30, 6.21 (diastereomers, br s, br s, 1 H), 4.72, 4.69 (diastereomers, t, J = 6.8 Hz, t, J = 7.1 Hz, 1 H), 4.52, 4.50 (diastereomers, d, J = 5.5 Hz, d, J = 5.6 Hz, 1 H), 3.76, 3.73 (diastereomers, dd, J = 11.1, 4.0 Hz, dd, J = 12.5, 3.9 Hz, 1 H), 3.71−3.56 (complex series of m, 6 H), 3.46, 3.42 (diastereomers, ddd, J = 9.1, 9.1, 2.7 Hz, ddd, J = 9.5, 9.5, 2.8 Hz, 1 H), 3.37, 3.35 (diastereomers, s, s, 3 H), 3.21, 3.07 (diastereomers, m, m, 1 H), 2.53−2.45 (m, 1 H), 2.38 (dd, J = 15.0, 7.7 Hz, 1 H), 1.75−1.59 (complex series of m, 3 H), 1.50, 1.47 (diastereomers, s, s, 3 H), 1.33, 1.28 (diastereomers, s, s, 3 H), 1.28, 1.27 (diastereomers, s, s, 3 H), 1.06, 1.05 (diastereomers, s, s, 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.71, 0.63 (diastereomers, d, J = 6.9 Hz, d, J = 6.9 Hz, 3 H), 0.05, 0.04 (diastereomers, s, s, 6 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 155.9, 138.9, 138.8, 137.6, 137.4, 136.8, 135.5, 133.8, 133.1, 132.7, 132.6, 129.9, 128.9, 128.5, 128.4, 127.7, 120.2, 120.1, 116.6, 114.4, 114.1, 111.5, 100.5, 78.8, 71.4, 71.2, 71.0, 70.9, 70.5, 70.1, 63.9, 59.4, 57.7, 40.5, 40.4, 39.9, 37.8, 37.7, 26.5, 26.1, 25.9, 25.8, 24.6, 23.9, 21.2, 21.1, 19.4, 18.2, 18.1, 12.1, 12.0, −5.3, −5.4, −5.5; high-resolution mass spectrum (FAB, NBA) m/z 1014.4825 [$(M - t\text{-Bu})^+$; calcd for $C_{55}H_{80}NO_9SSi_3$: 1014.4862]. Anal. Calcd for $C_{59}H_{89}NO_9SSi_3$: C, 65.98; H, 8.29; N, 1.30. Found: C, 65.97; H, 8.16; N, 1.25.

Desulfonylated Arene (+)-48. A mixture of sulfone **47** (55 mg, 0.051 mmol), Na_2HPO_4 (29 mg, 0.21 mmol), and anhydrous methanol (1 mL) was cooled to −20 °C and stirred for 20 min. Excess 5% Na(Hg) (∼250 mg) was then added. The reaction mixture was stirred vigorously at −20 °C for 15 min, diluted with ethyl acetate (10 mL), and filtered through a plug of silica gel with ethyl acetate as eluant. After concentration in vacuo, the residue was dissolved in ethyl acetate (10 mL) and the solution was washed with water and brine (5 mL each), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (15% ethyl acetate/hexanes) afforded (+)-**48** (45 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}$ +2° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3340 (w), 2960 (s), 2860 (s), 1730 (m), 1685 (m), 1465 (s), 1430 (s), 1255 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (br s, 1 H), 7.71 (apparent d, J = 6.8 Hz, 4 H), 7.42−7.33 (complex series of m, 6 H), 6.99 (br s, 1 H), 6.76 (br s, 1 H), 6.28 (br s, 1 H), 5.10 (t, J = 6.6 Hz, 1 H), 4.64 (d, J = 5.7 Hz, 1 H), 3.69−3.62 (complex series of m, 5 H), 3.47 (apparent dt, J = 9.0, 9.0 Hz, 1 H), 3.40 (s, 3 H), 2.52 (dd, J = 14.9, 3.3, 1 H), 2.44 (dd, J = 15.0, 7.8, 1 H), 2.39 (t, J = 7.8 Hz, 2 H), 2.09 (m, 2 H), 1.80−1.60 (complex series of m, 3 H), 1.64 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.10 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.75 (d, J = 6.9 Hz, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 155.8, 143.8, 138.7, 135.5, 134.5, 132.9, 129.8, 127.7, 125.0, 115.6, 112.7, 108.7, 100.4, 78.9, 70.9, 69.3, 64.0, 59.5, 57.8, 41.0, 39.9, 37.7, 36.0, 29.2, 26.5, 25.9, 25.8, 24.6, 24.1, 20.8, 19.4, 18.2, 18.1, 12.2, −5.3, −5.4; high-resolution mass spectrum (FAB, NBA) m/z 954.5496 [$(M + Na)^+$; calcd for $C_{53}H_{85}NO_7Si_3Na$: 954.5532]. Anal. Calcd for $C_{53}H_{85}NO_7Si_3$: C, 68.31; H, 9.13; N, 1.50. Found: C, 68.41; H, 9.03; N, 1.39.

N-Protected Amide (+)-49. At 0 °C a solution of amide (+)-**48** (76 mg, 0.082 mmol) in anhydrous THF (1.6 mL) was treated with KH (65 mg, 1.63 mmol, washed with THF). After 5 min chloromethyl 2,2,2-trichloroethyl ether (16 μL, 0.12 mmol) was added, and the reaction mixture was then warmed to ambient temperature, stirred for 20 min, cooled to 0 °C, and slowly quenched with saturated aqueous $NaHCO_3$ (5 mL). The biphasic mixture was extracted with ether (20 mL), and the organic phase was washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (15% ethyl acetate/hexanes) furnished (+)-**49** (83.2 mg, 93% yield) as a colorless oil: $[\alpha]_D^{23}$ +4.0° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2920 (s), 2850 (s), 1720 (w), 1655 (m), 1585 (s), 1450 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.66 (m, 4 H), 7.41−7.33 (complex series of m, 6 H), 6.60 (m, 1 H), 6.58 (m, 1 H), 6.39 (m, 1 H), 5.16−5.08 (complex series of m, 3 H), 4.63 (d, J = 5.7 Hz, 1 H), 4.14 (m, 2 H), 3.68−3.65 (complex series of m, 3 H), 3.54 (m, 1 H), 3.49−3.47 (m, 2 H), 3.32 (s, 3 H), 2.44 (t, J = 7.8 Hz, 2 H), 2.19−2.10 (complex series of m, 4 H), 1.77−1.58 (complex series of m, 3 H), 1.64 (s, 3 H), 1.30 (s, 6 H), 1.09 (s, 9 H), 0.89 (s, 9 H), 0.84 (s, 9 H), 0.76 (d, J = 6.9 Hz, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 172.5, 156.3, 144.7, 141.6, 135.5, 134.9, 132.4, 130.1, 127.9, 124.7, 121.2, 119.9, 117.3, 100.5, 97.0, 81.6, 78.7, 78.4, 71.0, 69.5, 64.3, 59.5, 58.1, 41.1, 37.8, 36.5, 35.8, 28.9, 26.5, 25.9, 24.6, 24.1, 20.9, 19.4, 18.2, 12.2, −5.3, −5.4; high-resolution mass spectrum (FAB, NBA) *m/z* 1034.4162 [(M − *t*-Bu)$^+$; calcd for $C_{52}H_{79}Cl_3NO_8Si_3$: 1034.4179]. Anal. Calcd for $C_{56}H_{88}Cl_3NO_8Si_3$: C, 61.57; H, 8.13; N, 1.28. Found: C, 61.59; H, 8.39; N, 1.25.

Dihydroxy Phenol (−)-50. Tris(silyl ether) (+)-**49** (59.2 mg, 0.054 mmol) was dissolved in anhydrous THF (1.1 mL) and TBAF (1.0 M in THF, 0.18 mL, 0.18 mmol) was added. The mixture was stirred for 3 h at ambient temperature, diluted with ethyl acetate (10 mL), and washed with water and brine (5 mL each). The combined aqueous phases were extracted with ethyl acetate (2 × 20 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (gradient elution, 75 → 90% ethyl acetate/hexanes) afforded (−)-**50** (31.7 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}$ −1.9° (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3560−3100 (br), 2930 (s), 1660 (s), 1595 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (m, 1 H), 6.60 (m, 1 H), 6.58 (m, 1 H), 5.29 (d, *J* = 10.4 Hz, 1 H), 5.25 (d, *J* = 10.4 Hz, 1 H), 5.22 (t, *J* = 6.4 Hz, 1 H), 4.69 (d, *J* = 5.6 Hz, 1 H), 4.29 (s, 2 H), 3.82−3.69 (complex series of m, 4 H), 3.55 (ddd, *J* = 8.5, 8.5, 3.0 Hz, 1 H), 3.49 (dd, *J* = 11.6, 4.2 Hz, 1 H), 3.33 (s, 3 H), 2.56 (t, *J* = 7.7 Hz, 2 H), 2.52 (m, 1 H), 2.36 (dd, *J* = 15.8, 5.8 Hz, 1 H), 2.27 (m, 2 H), 1.88−1.69 (complex series of m, 3 H), 1.66 (s, 3 H), 1.34 (s, 3 H), 1.30 (s, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 157.4, 145.3, 141.9, 134.8, 124.9, 119.9, 115.7, 113.1, 100.9, 96.9, 82.0, 78.8, 78.3, 74.9, 69.3, 63.1, 61.4, 57.6, 40.6, 36.0, 35.9, 35.6, 29.5, 24.6, 24.1, 20.7, 12.4; high-resolution mass spectrum (FAB, NBA) *m/z* 648.1892 [(M + Na)$^+$; calcd for $C_{28}H_{42}Cl_3NO_8Na$: 648.1874]. Anal. Calcd for $C_{28}H_{42}Cl_3NO_8$: C, 53.74; H, 6.77; N, 2.24. Found: C, 53.65; H, 7.18; N, 2.14.

Dialdehyde (+)-51. A solution of diol (−)-**50** (25.3 mg, 0.040 mmol) in DMSO (0.8 mL) was treated with Et_3N (0.28 mL, 2.02 mmol) followed by pyr·SO_3 (96.5 mg, 0.61 mmol). The resultant mixture was stirred for 45 min at room temperature, diluted with ethyl acetate (10 mL), and washed with water and brine (5 mL each). The combined aqueous phases were extracted with ethyl acetate (20 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (gradient elution, 50 → 75% ethyl acetate/hexanes) gave (+)-**51** (20.1 mg, 80% yield) as a colorless oil: $[\alpha]_D^{23}$ +29° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 3580 (w), 3500−3180 (br), 1730 (s), 1670 (s), 1600 (s) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.57 (s, 1 H), 9.49 (m, 1 H), 6.56 (br s, 1 H), 6.53 (br s, 1 H), 6.48 (br s, 1 H), 5.85 (br s, 1 H), 5.14 (m, 2 H), 5.05 (m, 1 H), 4.73 (d, *J* = 5.7 Hz, 1 H), 4.33 (br s, 2 H), 3.80 (apparent t, *J* = 5.6 Hz, 1 H), 3.68 (ddd, *J* = 8.5, 8.5, 3.4 Hz, 1 H), 3.09 (s, 3 H), 2.52−2.07 (complex series of m, 8 H), 1.77 (s, 3 H), 1.63 (m, 1 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 0.62 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.1, 200.8, 170.8, 157.8, 145.4, 142.5, 135.0, 125.3, 120.5, 115.9, 113.3, 101.2, 97.7, 82.5, 82.4, 79.1, 70.5, 69.6, 58.4, 47.5, 40.8, 36.4, 36.0, 29.8, 24.4, 24.0, 21.1, 12.2; high-resolution mass spectrum (FAB, NBA) *m/z* 644.1567 [(M + Na)$^+$; calcd for $C_{28}H_{38}Cl_3NO_8Na$: 644.1561].

Macrolactam (+)-52. A solution of dialdehyde (+)-**51** (12 mg, 0.019 mmol) and bis-Wittig salt **5** (10.2 mg, 0.019 mmol) in anhydrous DMF (1.3 mL) was cooled to 0 °C, and sodium bis(trimethylsilyl)-amide (0.9 M in THF, 64 μL, 0.058 mmol) was added at a rate of 1 drop/10 min. The resultant deep red solution was stirred at 0 °C for 15 min and then warmed to room temperature, diluted with pH 7 buffer (5 mL), and extracted with ethyl acetate (20 mL). The organic phase was washed with brine (5 mL), and the combined aqueous layers were extracted with ethyl acetate (2 × 20 mL). The combined organic solutions were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (gradient elution, 30 → 50% ethyl acetate/hexanes) afforded a mixture of compounds believed to be triene isomers (4.2 mg, 34% yield) followed by (+)-**52** (2.6 mg, 21% yield) as an amorphous colorless solid [mp 134 °C dec]: $[\alpha]_D^{25}$ +257° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 3580 (w), 3500−3160 (br), 1730 (m), 1660 (s), 1590 (s), 1380 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) complex rotamer mixture: δ 6.61 (br s, 1 H), 6.53 (br s, 1 H), 6.40−6.10 (complex series of br m, 4 H), 6.02 (dd, *J* = 15.4, 10.1 Hz, 2 H), 5.86 (ddd, *J* = 15.2, 10.3, 4.9 Hz, 1 H), 5.61 (br s, 1 H), 5.23−5.21 (complex series of br m, 2 H), 4.87 (br s, 1 H), 4.58 (br d, *J* = 5.4 Hz, 1 H), 4.32−4.20 (complex series of br m, 3 H), 3.55 (br m, 1 H), 3.26 (br s, 3 H), 2.72 (br m, 1 H), 2.55 (br m, 3 H), 2.40 (br s, 1 H), 2.27 (br s, 1 H), 2.10 (br apparent t, *J* = 11.5 Hz, 1 H), 1.96−1.92 (br m, 2 H), 1.70 (br s, 3 H), 1.34 (br s, 3 H), 1.31 (br s, 3 H), 0.83 (br d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 156.4, 145.9, 142.4, 135.6, 134.1, 133.0, 131.4, 130.9, 130.0, 125.0, 119.3, 115.9, 112.3, 100.7, 96.8, 82.0, 79.9, 79.1, 73.8, 68.2, 56.4, 40.3, 37.3, 36.3, 35.2, 29.7, 24.9, 23.9, 20.5, 12.6; high-resolution mass spectrum (FAB, NBA) *m/z* 664.1978 [(M + Na)$^+$; calcd for $C_{32}H_{42}Cl_3NO_6Na$: 664.1975].

TBS Ether (+)-53. A solution of macrolactam phenol (+)-**52** (2.6 mg, 4.0 μmol) in CH_2Cl_2 (0.3 mL) was treated with 2,6-lutidine (5 μL, 40 μmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 μL, 20 μmol). After 30 min at ambient temperature, a second equal portion of silyl triflate was added and the solution was stirred 30 min further. The reaction mixture was then quenched with aqueous $NaHCO_3$ (5%, 3 mL) and extracted with ether (10 mL). The organic phase was washed with saturated aqueous $CuSO_4$ and brine (3 mL each), and the combined aqueous layers were extracted with ether (2 × 10 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (15% ethyl acetate/hexanes) afforded (+)-**53** (2.4 mg, 80% yield) as a colorless oil: $[\alpha]_D^{24}$ +305° (*c* 0.11, $CHCl_3$); UV (CH_3OH) λ_{max} 282 (25 500), 271 (33 000), 262 (25 300), 210 (31 100) nm; IR ($CHCl_3$) 2930 (s), 1660 (s), 1590 (s), 1460 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) complex rotamer mixture, δ 6.60 (br s, 1 H), 6.56 (br s, 1 H), 6.39−6.32 (br m, 2 H), 6.17 (br s, 1 H), 6.03 (dd, *J* = 15.3, 10.2 Hz, 2 H), 5.87 (ddd, *J* = 15.2, 10.3, 4.9 Hz, 1 H), 5.60 (br s, 1 H), 5.24−5.22 (complex series of br m, 2 H), 4.88 (br s, 1 H), 4.58 (br d, *J* = 5.3 Hz, 1 H), 4.31−4.21 (complex series of br m, 3 H), 3.55 (br m, 1 H), 3.26 (s, 3 H), 2.66 (br m, 1 H), 2.54 (br m, 3 H), 2.40 (br s, 1 H), 2.27 (br s, 1 H), 2.10 (br apparent t, *J* = 11.5 Hz, 1 H), 1.98−1.92 (complex series of m, 2 H), 1.70 (s, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 0.96 (s, 9 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 156.1, 145.6, 142.3, 135.6, 134.1, 132.8, 131.2, 130.9, 130.1, 125.0, 120.5, 117.0, 100.7, 96.9, 82.0, 79.8, 79.0, 73.9, 68.2, 56.4, 40.3, 37.3, 36.3, 35.1, 29.7, 25.6, 24.9, 23.9, 20.5, 18.2, 12.6, −4.4; high-resolution mass spectrum (FAB, NBA) *m/z* 778.2823 [(M + Na)$^+$; calcd for $C_{38}H_{56}Cl_3NO_6SiNa$: 778.2841].

Secondary Amide (+)-45. At −35 °C a mixture of N-protected amide (+)-**53** (2.4 mg, 3.1 μmol), Na_2HPO_4 (1.8 mg, 13 μmol), and anhydrous methanol (0.4 mL) was treated with excess 5% Na(Hg) (~50 mg) and stirred vigorously for 50 min. The reaction mixture was then filtered through a pad of silica gel with ethyl acetate as eluant. The filtrate was washed with water and brine (3 mL each), the combined aqueous phases were extracted with ethyl acetate (2 × 10 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (gradient elution, 30 → 50% ethyl acetate/hexanes) gave (+)-**45** (1.2 mg, 67% yield) as an amorphous colorless solid.[43]

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Supporting Information Available: X-ray coordinates for (+)-**12** (5 pages). See any current masthead page for ordering and Internet access instructions.

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(43) This material proved identical to that constructed in conjunction with our chemical degradation and stereochemistry elucidation work; see preceding article in this issue for characterization data.