Total Synthesis of (+)-Carbonolide B[1]

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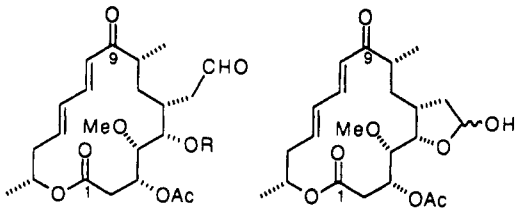
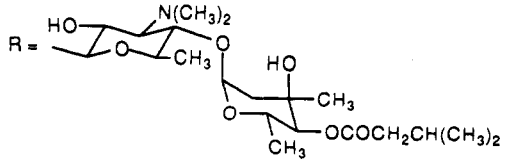
The macrolide (+)-carbonolide B, the aglycon of the antibiotic carbomycin B, was synthesized *via* a convergent sequence. A key step of the approach is the union of aldehyde **6** with stannane **7** in the presence of $MgBr_2{\cdot}OEt_2$ as Lewis acid to afford the C_1–C_9 fragment **26**. This chelation-controlled process uses resident stereochemistry at C_4 to control stereochemistry at C_5 and C_6. Elaboration of this fragment at both ends and incorporation of a C_{11}–C_{15} fragment (hydroxy enal **4**) *via* esterification and intramolecular Emmons reaction was used to complete the synthesis.

Introduction

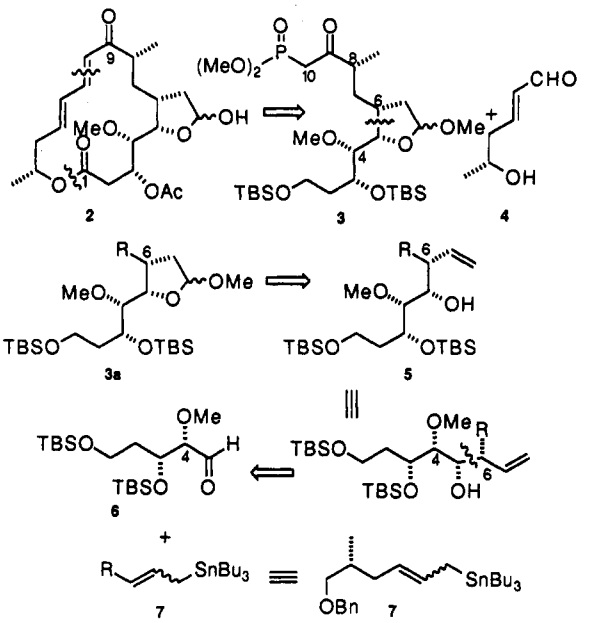
Carbomycin B (**1**), isolated from *Streptomyces halstedii* in 1954,[2] is representative of the now well known family of medicinally important 16-membered macrolide antibiotics.[3] The chemical structure of carbomycin, established by degradative studies in 1965, contains most of the synthetically challenging structural features common to this class of highly oxygenated compounds.[4]

The first total synthesis of carbomycin B and the aglycon carbonolide B (**2**) was reported by Tatsuta in 1980, starting from D-glucose.[5] The following year, Nicolaou reported a highly efficient carbohydrate-based approach to carbonolide B using an intramolecular Horner–Emmons coupling to close the 16-membered macrocycle.[6] More recently, Yonemitsu synthesized a number of macrolide aglycons (niddanolide, carbonolide, and platenolide) stereoselectively from D-glucose by an approach utilizing Yamaguchi's esterification followed by a modified intramolecular Horner–Emmons-type cyclization.[7] A strategy common to all of these syntheses is a carbohydrate-based construction of the C_1–C_{10} right-hand portion of the lactone structure, followed by coupling with an intermediate representing the C_{11}–C_{17} subunit. We record herein the first non-carbohydrate-based convergent synthesis of the macrolide carbonolide B. The key element of this approach is the use of a chelation-controlled addition of a complex allylstannane to a chiral aldehyde for assembly of the C_1–C_9 subunit.





Scheme 1



Retrosynthetic Analysis

Our retrosynthetic analysis of carbonolide B is outlined in Scheme 1. Relying on a recent improvement in the Steglich esterification developed in our lab,[8] and its successful use by us and others,[9] we selected the macrolactonization of the seco acid as the penultimate step. A second disconnection at C_{10}–C_{11} was envisioned *via* Horner–Emmons coupling[10] of a keto phosphonate such as **3** with hydroxy enal **4**.

For the synthesis of the C_1–C_{10} subunit, an approach in which the C_6 substituent was elaborated from a vinyl unit as in intermediate **5** was considered. A consideration of the structure and stereochemistry of this fragment sug-

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(3) Omura, S. *Macrolide Antibiotics*; Academic Press: Orlando, FL, 1984; pp 3–35.

(4) Carbomycin A: Woodward, R. B.; Weiler, L. S.; Dutta, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 4662.

(5) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837.

(6) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1222. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327.

(7) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. *Chem. Pharm. Bull.* **1991**, *39*, 64.

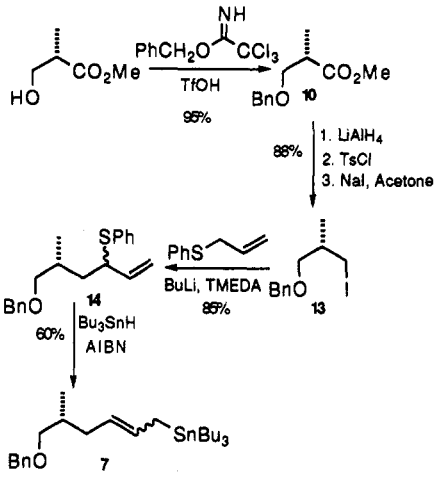
(8) (a) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394. (b) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896.

(9) (a) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896. (b) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606. (c) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. (d) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

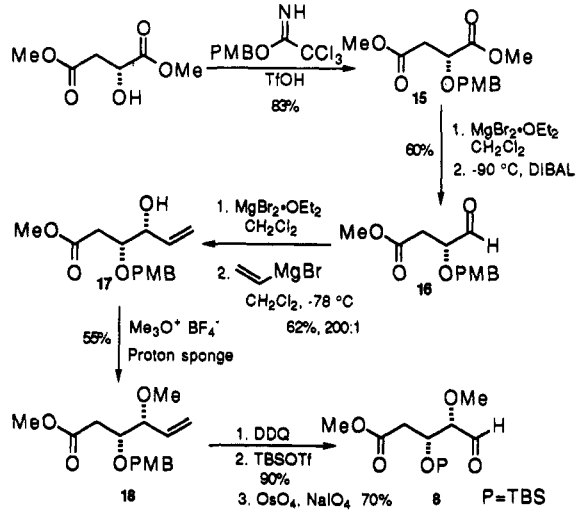
(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

0022-3263/94/1959-3113$04.50/0

Scheme 2



Scheme 3

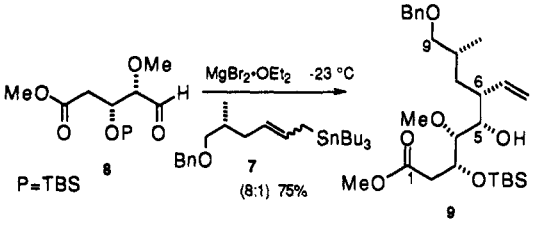


gested a connective approach *via* reaction of an allylstannane of general structure **7** with aldehyde **6**, which would be expected to afford the requisite *all-syn* stereochemistry embodied in **5** if "chelation control" from the α-methoxy substituent in **6** were realized. The chiral aldehyde **6** corresponding to subunit C_1–C_5 should be obtained by a chelation-controlled addition of vinyl Grignard to an appropriately protected malic acid derivative, whereas the allylstannane **7** should be readily accessible in a few steps from commercially available (*S*)-3-hydroxy-2-methylpropionate.

Results and Discussion. Our synthetic approach began with the synthesis of chiral allylstannane **7** (Scheme 2). Benzylation of (*S*)-3-hydroxy-2-methylpropionate according to the general procedure of Widmer[11] provided the benzyl ether **10** in 95% yield. $LiAlH_4$ reduction of **10** followed by tosylation and treatment of the resulting tosylate with NaI gave iodide **13** in 88% overall yield. The displacement of the iodide **13** with allyl phenyl sulfide anion gave sulfide **14**, with only a trace of γ-alkylated product, in 85% yield.[12] It should be noted that the use of the intermediate tosylate in place of iodide **13** in the alkylation reaction gave a very low yield of the desired product. The allyl sulfide **14** was then subjected to Ueno's free radical procedure[13] to give the required allylstannane **7** in 60% yield as a mixture of *trans* and *cis* isomers (75:25).

The first approach to the synthesis of aldehyde **8** is shown in Scheme 3. Starting with malic acid dimethyl ester, protection of the free alcohol using Yonemitsu's procedure gave the ester **15** in 83% yield.[14] The next step utilized methodology recently developed in our laboratory,[15] namely the regioselective DIBAL reduction of ester **15** in the presence of $MgBr_2$·OEt_2 at −90 °C, followed by the chelation-controlled addition of vinylmagnesium bromide to the resulting aldehyde, to provide **17** in 62% yield. Methylation of the resultant alcohol using Meerwein's salt in the presence of Proton sponge gave the methyl ester **18** in 55% yield.[16] Deprotection of the PMB group using DDQ,[17] followed by TBS protection provided the TBS ether **20** in 92% yield. This change of protecting group proved necessary since the PMB group was found to be optimal for the vinyl addition but not for the subsequent stannane addition.[18] Oxidative cleavage of the terminal olefin using the Lemieux procedure[19] then gave the aldehyde **8** in 70% yield.

With aldehyde **8** and stannane **7** in hand, we next examined the chelation-controlled coupling of these two pieces (eq 1).[20] After complexation of aldehyde **5** at 0 °C for 1 h with $MgBr_2$·OEt_2, the stannane **7** was added at −23 °C to give a 75% yield of the homoallylic alcohol **9** as a 8:1 mixture of two diastereomers.



After the successful synthesis of this subunit, we encountered a serious problem upon its attempted elaboration. Specifically, and quite surprisingly, the methyl ester at C_1 was found to interfere with nucleophilic addition to a C_9 aldehyde carbonyl. Thus, in reaction with lithium salt of dimethyl methylphosphonate, the C_1 ester moiety and the C_9 aldehyde underwent nucleophilic addition at essentially the same rate, leading to a poor yield for the desired β-hydroxy phosphonate and a complex product mixture. To avoid this complication, it was decided that the C_1 carbon would be carried through the sequence at the oxidation state of a protected alcohol.

Thus, we turned our attention to an alternative synthesis of the aldehyde **6** with the C_1 carbon present as a protected alcohol and incorporating the TBS protecting group optimal for the allylstannane addition (Scheme 4). This second approach began with an Evans' aldol condensation of (*S*)-4-(phenylmethyl)-2-oxazolidinone (**21**) with alde-

(11) Widmer, U. *Synthesis* **1987**, 568.
(12) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573.
(13) Ueno, Y.; Ohta, M.; Okawara, M. *J. Organomet. Chem.* **1980**, *197*, C1–C4.
(14) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(15) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.
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(17) Oikawa, Y.; Yoshioka, T; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(18) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281.
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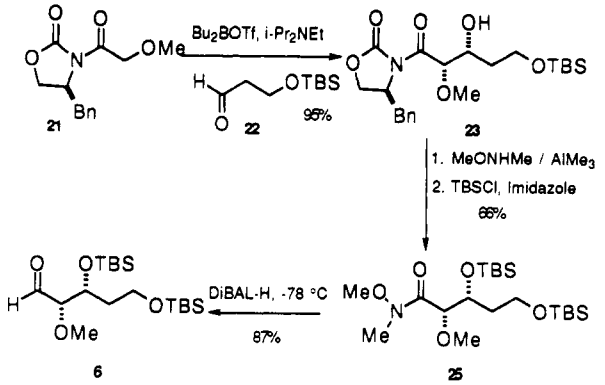
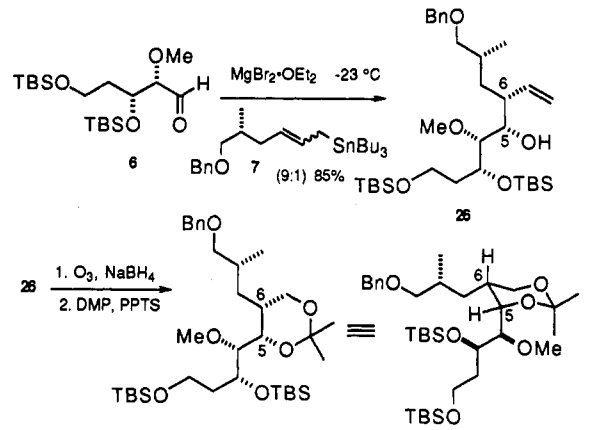
(20) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139.

Scheme 4



Scheme 5

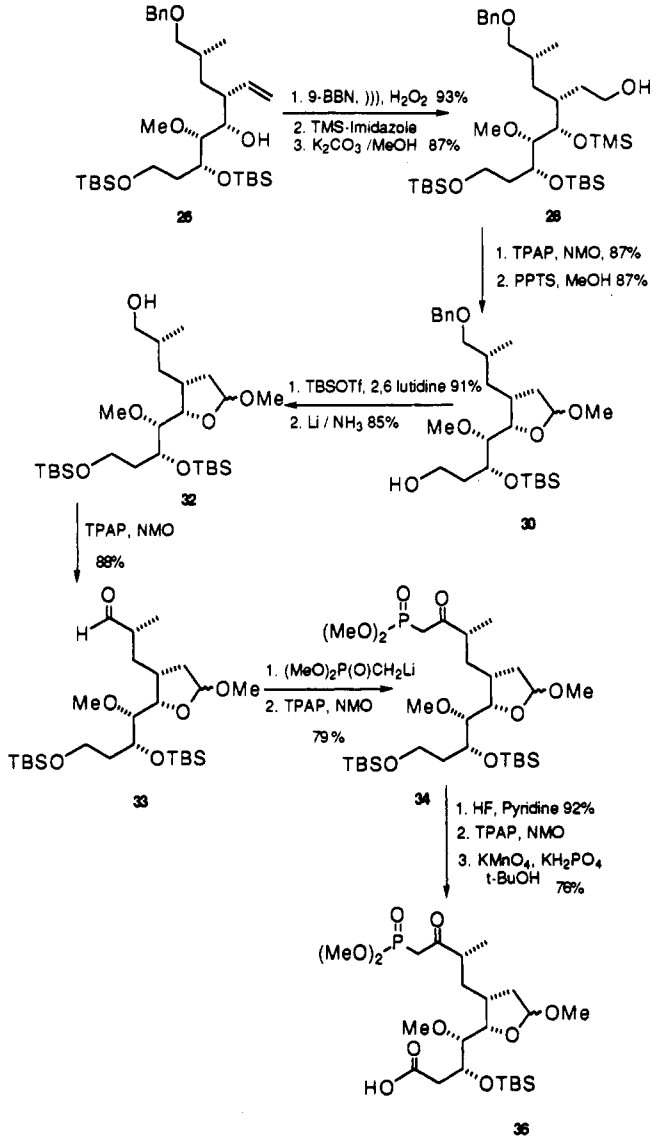


hyde **22**,[21] which afforded the desired aldol product **23** as a single diastereoisomer in 95% yield.[22] Weinreb transamidation followed by TBS protection gave the amide **25** in 66% yield.[23] DIBAL reduction of the resultant amide in toluene afforded the aldehyde **6** in excellent overall yield (Scheme 4).[24] As with the previous aldehyde **8**, the chelation-controlled allylstannane addition to aldehyde **6** was very successful. The aldehyde **6** was first complexed with $MgBr_2{\cdot}OEt_2$ for 1 h at 0 °C and treated with allylstannane **7** at −23 °C to give an 85% yield of the homoallylic alcohol as a 9:1 mixture of diastereomers (Scheme 5).

The two isomers were readily separated by chromatography. The stereochemistry of the major isomer was confirmed by converting **26** into a dioxolane as shown in Scheme 5. A small coupling of 2 Hz was observed for the methine protons at C_5 and C_6, indicative of a *syn* relationship in the major isomer.

Having established the correct stereochemistry at C_5 and C_6, the elaboration of suitable functionality for the Horner–Emmons coupling and macrolactonization was then required (Scheme 6), in addition to formation of the lactol moiety at C_5–C_6. Hydroboration of the vinyl group with 9-BBN was extremely sluggish under standard conditions; however, use of ultrasound resulted in a rapid reaction which gave the desired diol in good yield after oxidation with hydrogen peroxide.[25] TMS protection of the diol followed by selective removal of the primary TMS group produced the primary alcohol **28** in 87% yield.

Scheme 6



TPAP oxidation of the primary alcohol afforded 87% of the aldehyde,[26] which was then subjected immediately to acidic methanol to give the methoxy lactol **30** in 87% yield. Protection of the alcohol as the TBS ether (91%) followed by removal of the benzyl group using lithium in liquid ammonia produced the alcohol **32** in 85% yield. TPAP oxidation gave the aldehyde **33**, which was treated with the lithio derivative of dimethyl methylphosphonate followed by TPAP oxidation to give the β-keto phosphonate **34** in excellent overall yield. Selective removal of the primary TBS ether was effected cleanly with HF–pyridine, leaving the secondary TBS ether intact.[27] Direct oxidation of the primary alcohol to an acid proved to be problematic with PDC in DMF;[28] however, employing a two-step protocol gave the acid **36** in 76% yield.[29]

The C_{11}–C_{15} subunit was prepared from (*R*)-ethyl β-hydroxybutyrate (Scheme 7) as outlined below. The

(21) Prepared in two steps (1. TBSCl/imidazole, 2. OsO_4/$Pb(OAc)_4$) from 3-buten-1-ol.

(22) (a) Evans, D. A.; Gage, J. R. *Org. Synth.* **1990**, *68*, 83. (b) Evans, D. A.; Gage, J. R.; Leighton, J. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(23) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(24) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958.

(25) (a) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187. (b) Crimmins, M. T.; O'Mahony, R. *Tetrahedron Lett.* **1989**, *30*, 5993.

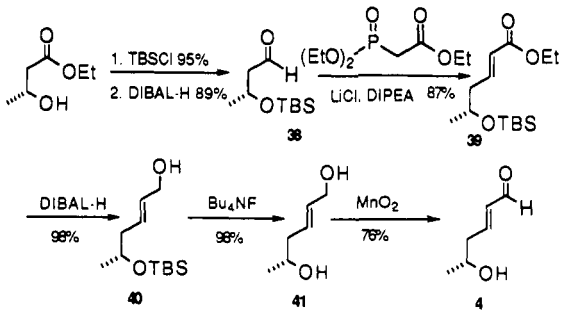
(26) (a) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13. (b) Cherif, A.; Farquhar, D. *J. Med. Chem.* **1992**, *35*, 3208.

(27) Evans, D. A.; Gage, J. R.; Leighton, J. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

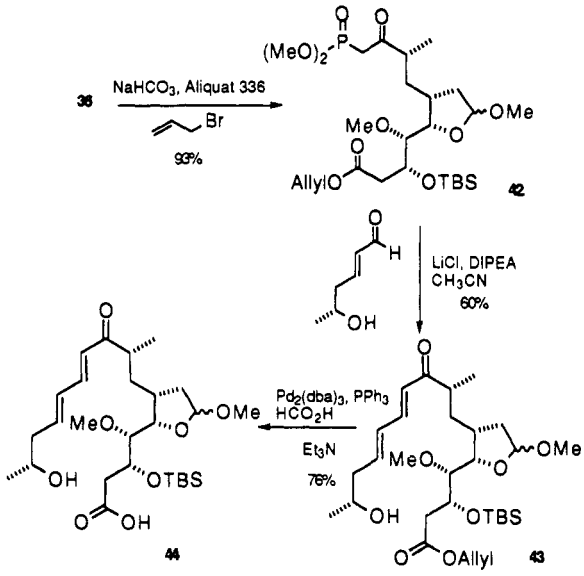
(28) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(29) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

Scheme 7



Scheme 8

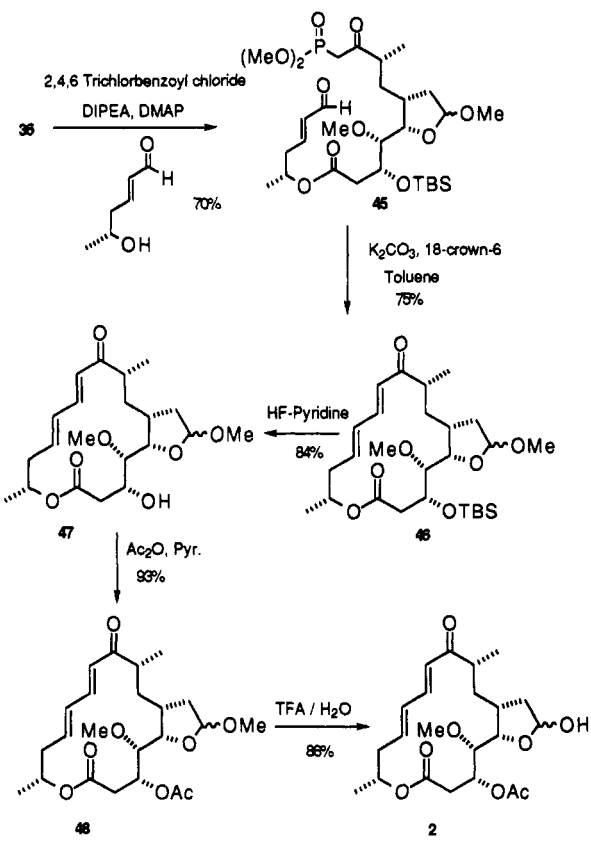


hydroxy ester was protected as the TBS ether in 95% yield, followed by reduction to give aldehyde **38** in 89% yield. Roush–Masamune coupling of triethyl phosphonoacetate with aldehyde **38** gave an 87% yield of α,β-unsaturated ester **39**.[10] DIBAL reduction of **39** followed by deprotection of the TBS ether and selective oxidation with MnO_2 gave the hydroxy enal **4** in good overall yield.

Having synthesized the acid and the enal, we next examined the coupling of these two pieces. Coupling of the keto phosphonate **36** with enal **4** under Roush–Masamune conditions produced the seco acid, although in very low yield.

After considerable investigation, it was found that the free acid was not compatible with the coupling conditions (Scheme 8). Although the reasons for this observation were not clear, successful Emmons reactions could be realized using ester derivatives of acid **36**. Thus, conversion of the acid to the allyl ester **42**,[30] followed by Roush–Masamune coupling with enal **4**, gave a 60% yield of the coupled product **43**. Palladium-catalyzed deprotection of the allyl ester **43** afforded the seco acid **44** in good yield.[31] An attempted macrolactonization of the seco acid **44** under our modified Steglich esterification conditions resulted in elimination to afford a trienone as the major product. Control experiments revealed the pronounced sensitivity of this compound to the mild acid (DMAP·HCl) used in the procedure.

Scheme 9



After the unexpected result of the attempted macrolactonization, we turned to an alternative sequence (Scheme 9) which was well documented by Nicolaou and Yonemitsu in their carbonolide syntheses. Bimolecular esterification of the acid **36** with hydroxy enal **4** utilizing the Yamaguchi procedure[32] afforded a 70% yield of ester **45**. Intramolecular Horner–Emmons coupling of **45** under Nicolaou's conditions[33] provided the macrolactone **46** in excellent yield. Removal of the TBS ether, acetylation of the resulting alcohol, and acidic hydrolysis of the methoxy lactol provided carbonolide B (**2**) in good overall yield. This compound was identical in all respects (^{1}H NMR, IR, MS, R_f, $[\alpha_D]$) to the compound previously reported by Yonemitsu and co-workers.[7]

The chemistry described herein provides an indication of the utility of substrate-directed additions of allylstannanes as a method for constructing acyclic subunits of macrolide antibiotics in a convergent manner. In this particular case, a five-ring chelated intermediate was used to control facial selectivity in the addition of allylstannane **7** to aldehyde **6**. *Syn* selectivity for the bond construction itself then led to the *all-syn* arrangement of stereocenters at C_4, C_5, and C_6.[34] In addition, five-ring chelates were employed to control the regioselectivity of reduction of **15** and the stereochemistry for addition of a vinyl moiety to aldehyde **16**. Marshall has recently reported a synthetic approach to the C_1–C_9 fragment of the related antibiotic tylosin using an optically active γ-alkoxy stannane for construction of the C_5–C_6 bond.[35] Our own studies using

(30) Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 751.
(31) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 71.
(32) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(33) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.
(34) For an excellant recent review of reactions of allylstannanes and allylsilanes, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(35) Marshall, J. A.; Yashunsky, D. V. *J. Org. Chem.* **1991**, *56*, 5493.

stannane 7 for this purpose *via* a substrate-controlled addition pathway will be reported separately.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Reagent grade AcOH, MeOH, and acetone were purchased and used without further purification. Yields were calculated for material judged homogeneous by TLC and NMR. TLC was performed on Merck kieselgel 60 F_{254} plates, visualizing with a 254-nm UV lamp and staining with an ethanol solution of 12-molybdophosphoric acid. Column chromatography was performed with W.G. Grace Davisil 62 silica gel, slurry packed in glass columns. Melting points are uncorrected. Radial preparative-layer chromatography (radial PLC) was performed on a chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with a 1-, 2-, or 4-mm thickness of kiesegel 60 PF_{254} containing gypsum. Proton nuclear magnetic resonance (^{1}H NMR) were recorded on Varian XL-300 or Unity-300 (300 MHz) instruments. The chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz on Varian XL-300 or Unity-300 instruments and are reported (ppm) relative to the center line of a triplet at 77.0 ppm for $CDCl_3$. Infrared (IR) spectra were measured with Perkin-Elmer 298 or Mattson FTIR 3000 infrared spectrophotometer. Mass spectra were determined on a Finnigan MAT 95 high-resolution gas chromatograph/mass spectrometer with a Finnigan MAT ICIS II operating system. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

Preparation of Methyl (*S*)-3-(Benzyloxy)-2-methylpropionate (10). To a stirring solution of methyl (*S*)-3-hydroxy-2-methylpropionate (Aldrich) (5.00 g, 42.3 mmol) and freshly distilled benzyl trichloroacetimidate (16.03 g, 63.49 mmol) in CH_2Cl_2 (40 mL) was added triflic acid (0.190 g, 1.26 mmol). The solution was allowed to stir at rt for 30 min, and then the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was washed three times with 50-mL portions of CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4, concentrated, and chromatographed over a silica gel column (15 × 3 cm), eluting with a solvent gradient from hexanes through 5% EtOAc/hexanes to yield 8.4 g (95%) of a colorless oil: $[\alpha]_D$ +11.7° (*c* 5.04, $CHCl_3$); R_f 0.39 (20% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.52 (s, 2 H), 3.68 (s, 3 H), 3.64 (dd, *J* = 7.3, 9.1 Hz, 1 H), 3.49 (ddd, *J* = 0.8, 5.9, 9.1 Hz, 1 H), 2.78 (sextet, *J* = 7.1 Hz, 1 H), 1.17 (d, *J* = 7.1 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 175.2, 138.1, 128.3, 127.5, 127.5, 73.0, 71.9, 51.6, 40.1, 13.9; IR (neat) cm^{-1} 3120, 2980, 2950, 2860, 1740 (br), 1500, 1455, 1360, 1250, 1200, 1175, 1100, 1030, 990, 735, 700. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.19; H, 7.73.

Preparation of (*S*)-3-(Benzyloxy)-2-methylpropan-1-ol (11). To a stirring solution of compound 10 (15.0 g, 72.1 mmol) in Et_2O was added lithium aluminum hydride (2.73 g, 72.1 mmol) portionwise. The solution was stirred for 30 min, and the reaction was quenched with Na_2SO_4·10H_2O/Celite. After being stirred for 2–3 h, the slurry was filtered through Celite, and the cake was washed several times with ether. The filtrate was concentrated and chromatographed over a silica gel column (20 × 5 cm), eluting with a solvent gradient from hexanes through 50% EtOAc/hexanes. The product-containing fractions were concentrated to yield 10.8 g (85%) of colorless oil: $[\alpha]_D$ +15.7° (*c* 6.38, $CHCl_3$); R_f 0.1 (20% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 4.50 (s, 2 H), 3.58 (dd, *J* = 4.8, 6.3 Hz, 2 H), 3.51 (dd, *J* = 4.9, 9.0 Hz, 1 H), 3.41 (dd, *J* = 7.8, 9.1 Hz, 1 H), 2.82 (bs, 1 H), 2.05 (m, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.0, 128.3, 127.6, 127.5, 75.0, 73.2, 67.4, 35.6, 13.5; IR (neat) cm^{-1} 3400 (br), 3015, 2960, 2880, 1490, 1450, 1360, 1205, 1090, 1040, 740, 690. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.17; H, 8.84.

Preparation of (*S*)-3-(Benzyloxy)-2-methyl-1-(4-methylbenzenesulfonyl)propane (12). To a stirring solution of 11 (5.65 g, 31.4 mmol) in dry pyridine (50 mL) were added 4-methylbenzenesulfonyl chloride (11.9 g, 62.8 mmol) and DMAP (0.300 g, 1.57 mmol). The solution was stirred at rt for 3 h. The mixture was poured into water (400 mL) and extracted three times with 200-mL portions of methylene chloride. The combined organic layers were washed with 3% hydrochloric acid (300 mL), water (300 mL), and saturated aqueous $NaHCO_3$ (300 mL). The organic phase was dried with Na_2SO_4, concentrated, and chromatographed over silica gel, eluting with 25% EtOAc/hexanes. The product-containing fractions were combined and concentrated to yield 9.2 g (88%) of a colorless oil: $[\alpha]_D$ +5.28° (*c* 6.86, $CHCl_3$); R_f 0.20 (20% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.77 (m, 2 H), 7.27 (m,7 H), 4.38 (s, 2 H), 4.04 (dd, *J* = 5.6, 9.4 Hz, 1 H), 3.98 (dd, *J* = 5.7, 9.4 Hz, 1 H), 3.35 (dd, *J* = 4.2, 8.1 Hz, 1 H), 3.30 (dd, *J* = 6.7, 9.3 Hz, 1 H), 2.40 (s, 3 H), 2.08 (m, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 144.6, 138.1, 132.9, 129.7, 128.2, 127.8, 127.5, 127.3, 72.9, 72.2, 70.9, 33.6, 21.5, 13.5; IR (neat) cm^{-1} 3040, 2980, 2860, 1600, 1490, 1450, 1360, 1190, 1175, 1100, 975, 940, 830, 810, 730, 700, 665. Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63. Found: C, 64.79; H, 6.67.

Preparation of (*S*)-3-(Benzyloxy)-2-methyl-1-iodopropane (13). A solution of tosylate 12 (10.7 g, 32.0 mmol) and dry sodium iodide (12.0 g, 80.1 mmol) in acetone (120 mL) was stirred for 2 days. The mixture was poured into a separatory funnel containing water (50 mL) and methylene chloride (50 mL). The aqueous layer was extracted two times with 15-mL portions of methylene chloride. The combined organic phase was dried with Na_2SO_4, concentrated via rotary evaporation, and flash chromatographed through a silica gel column (3 × 18 cm), eluting with 5% EtOAc/hexanes. The product-containing fractions were collected and concentrated to yield 8.69 g (98%) of a colorless oil: $[\alpha]_D$ +12.3° (*c* 0.440, $CHCl_3$); R_f 0.56 (20% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.51 (s, 2 H), 3.38 (dd, *J* = 9.3, 5.2 Hz, 1 H), 3.29 (m, 2 H), 3.27 (dd, *J* = 9.4, 7.3 Hz, 1 H), 1.77 (m, 1 H), 0.98 (d, *J* = 6.7 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.2, 128.3, 128.4, 127.5, 74.0, 73.1, 35.1, 17.6, 13.8; IR (neat) cm^{-1} 3060, 3030, 2960, 2860, 1495, 1455, 1360, 1200, 1100, 1025, 735, 695. Anal. Calcd for $C_{11}H_{15}IO$: C, 45.54; H, 5.21. Found: C, 45.21; H, 5.24.

Preparation of (5*R*)-6-(Benzyloxy)-5-methyl-3-(phenylthio)-1-hexene (14). To a stirring solution of allyl phenyl sulfide (3.50 g, 23.5 mmol) in dry tetrahydrofuran (100 mL) at −78 °C was added a 2.5 M solution of *n*-butyllithium in hexanes (9.40 mL, 23.5 mmol) *via* syringe over 20 min followed by tetramethylethylenediamine (2.72 g, 23.5 mmol). After 30 min, a solution of 13 (4.60 g, 16.8 mmol) in tetrahydrofuran (50 mL) was added dropwise via addition funnel. After 1 h, the reaction was quenched with saturated $NaHCO_3$ (25 mL), and the mixture was allowed to warm to rt. The mixture was poured into water (100 mL) and methylene chloride (100 mL). The aqueous phase was extracted three times with 50-mL portions of methylene chloride. The combined organic phase was dried with Na_2SO_4, concentrated, and chromatographed over silica gel, eluting with a solvent gradient from hexanes through 5% EtOAc/hexanes. The product-containing fractions were concentrated to yield 4.7 g (90%) of colorless oil (60:40 mixture of diastereomers epimeric at C_3 and 5% γ-alkylated regioisomer): $[\alpha]_D$ +1.46° (*c* 3.55, $CHCl_3$); R_f 0.46 (20% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 10 H), 5.66 (m, 1 H), 4.86 (m, 2 H), 4.50 (s, 2 H), 3.69 (q, *J* = 8.3 Hz, 1 H), 3.33 (m, 2 H), 2.12 (m, 1 H), 1.82 (m, 1 H), 1.50 (m, 1 H), 1.00 (d, *J* = 6.7 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 139.1, 132.8, 128.7, 128.6, 128.7, 128.3, 127.5, 126.9, 115.3, 75.2, 72.9, 50.2, 38.2, 31.1, 17.5; IR (neat) cm^{-1} 3160, 3120, 2910, 2850, 1580, 1480, 1450, 1360, 1090, 1020, 980, 910, 740, 690. Anal. Calcd for $C_{20}H_{24}OS$: C, 76.88; H, 7.74. Found: C, 76.78; H, 7.80.

Preparation of (5*R*)-6-(Benzyloxy)-5-methyl-1-(tri-*n*-butylstannyl)-2-hexene (7). A stirring solution of allyl sulfide 14 (2.00 g, 6.43 mmol), Bu_3SnH (3.93 g, 13.5 mmol), and 2,2′-azobis-(2-methylpropionitrile) (0.105 g, 0.640 mmol) in dry toluene (60 mL) was degassed with nitrogen for 30 min. The mixture was heated to 90 °C for 2 h and then cooled to rt. The mixture was concentrated *via* rotary evaporation with saturated aqueous NaOCl (~100 mL) placed in the receiving flask. The residue was then poured into a separatory funnel containing Et_2O (50 mL) and 3 M NaOH (50 mL). The layers were separated, and the aqueous layer was extracted two times with 50-mL portions

of 3 M NaOH and H_2O. The combined organic phase was dried with Na_2SO_4 and concentrated in vacuo. Purification by radial PLC (silica gel, hexanes–5% EtOAC/hexanes) afforded 1.52 g (50%) of a clear colorless oil (3:1, *E:Z* inseparable mixture of olefin isomers): $[\alpha]_D$ −3.26° (*c* 0.95, $CHCl_3$); R_f 0.55 (5% EtOAc/hexanes); capillary GC (DX-4, 175–250 °C, 3 °C/min) (major) 21.45 min, (minor) 20.92 min; 300-MHz ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 5.54 (dt, *J* = 14.9, 8.3 Hz, 1 H), 5.20 (dt, *J* = 14.9, 7.1 Hz, 1 H), 4.51 (s, 2 H), 3.35 (dd, *J* = 9.0, 5.4 Hz, 1 H), 3.25 (dd, *J* = 9.0, 6.3 Hz, 1 H), 2.13 (m, 1 H), 1.81 (m, 2 H), 1.70 (d, *J* = 8.3 Hz, 2 H), 1.48 (m, 6 H), 1.31 (m, 6 H), 0.90 (m, 15 H), 0.84 (d, *J* = 8.1 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.6, 130.8, 128.3, 127.5, 127.4, 123.4, 75.6, 72.9, 36.8, 34.2, 29.1, 27.4, 16.8, 14.2, 13.7, 9.1; IR (neat) cm^{-1} 3060, 2960, 2920, 2850, 1580, 1455, 1375, 1095, 960, 740, 695. Anal. Calcd for $C_{23}H_{46}OSn$: C, 63.30; H, 9.40. Found: C, 63.23; H, 9.43.

Preparation of (4*S*)-3-(2-Methoxy-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (21). To a stirring solution of (4*S*)-4-benzyl-2-oxazolidinone (0.100 g, 0.560 mmol) in THF (2 mL) at −78 °C was added a 2.5 M solution of *n*-butyllithium in hexanes (0.35 mL, 0.57 mmol) dropwise *via* syringe over 5 min. After complete addition and 30 min, a solution of freshly distilled 2-methoxyacetyl chloride in THF (2 mL) was added dropwise via cannula. The mixture was stirred for 30 min at −78 °C and 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and water (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. Purification by radial PLC (slilica gel, 50% ethyl acetate/hexanes) gave 0.110 g (80%) of **21** as a white solid: mp 52 °C; $[\alpha]_D$ +72.3° (*c* 1.48, $CHCl_3$); R_f 0.49 (50% ethyl acetate/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.31–7.12 (m, 5 H), 4.62 (m, 1 H), 4.55 (s, 2 H), 4.19 (m, 2 H), 3.44 (s, 3 H), 3.29 (dd, *J* = 13.4, 3.2 Hz, 1 H), 2.76 (dd, *J* = 13.4, 9.5 Hz, 1 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 169.9, 153.3, 134.8, 129.3, 128.9, 127.4, 72.2, 67.3, 59.5, 54.7, 37.7; IR (neat) cm^{-1} 2984, 2930, 1778, 1712, 1393, 1265, 1226, 702. Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.60; H, 6.09; N, 5.63.

Preparation of (2*S*,3*R*)-3-[3-Hydroxy-2-methoxy-5-[(*tert*-butyldimethylsilyl)oxy]pentanoyl]-4-(phenylmethyl)-2-oxazolidinone (23). To a stirring solution of **21** (0.600 g, 2.41 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a freshly prepared 1.0 M solution of *n*-Bu_2BOTf in CH_2Cl_2 (2.89 mL, 2.89 mmol) dropwise *via* syringe followed by Hunig's base (0.470 mL, 3.61 mmol), and the mixture was stirred for 1 h at 0 °C. This mixture was cooled to −78 °C and a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-propanal (0.490 g, 2.65 mmol) in CH_2Cl_2 (2 mL) was added *via* cannula. The resulting solution was then stirred for 5 h while gradually being warmed to rt. An aqueous phosphate buffer solution (pH = 7, 10 mL) was added and the mixture was stirred for 1.5 h. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. Purfication by radial PLC (silica gel, 40% ethyl acetate/hexanes) afforded 1.10 g (95%) of **23** as a yellow oil: $[\alpha]_D$ +16.6° (*c* 0.800, $CHCl_3$); R_f 0.52 (50% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 4.93 (d, *J* = 3.3, 1 H), 4.68 (m, 1 H), 4.12 (m, 1 H), 3.77 (m, 2 H), 3.43 (s, 1 H), 3.32 (dd, *J* = 13.4, 3.2 Hz, 1 H), 1.91 (m, 1 H), 1.75 (m, 1 H), 0.83 (s, 9 H), 0.01 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 170.4, 153.4, 135.1, 129.4, 128.9, 127.4, 82.1, 71.3, 66.9, 61.4, 58.7, 55.7, 37.8, 35.6, 25.9, 18.3, −5.4; IR (neat) cm^{-1} 3489, 2955, 2931, 1778, 1737, 1388, 1244, 1213, 1099, 837, 777. Anal. Calcd for $C_{22}H_{35}O_6NSi$: C, 60.62; H, 8.06; N, 3.20. Found: C, 60.43; H, 8.10; N, 3.19.

Preparation of (2*S*,3*R*)-*N*,2-Dimethoxy-3,5-bis[(*tert*-butyldimethylsilyl)oxy]-*N*-methylpentanamide (25). To a 0 °C suspension of *N,O*-dimethylhydroxylamine hydrochloride (0.702 g, 7.20 mmol) in THF (5 mL) at 0 °C was added a 2.0 M solution of trimethylaluminum in toluene (3.60 mL, 7.20 mmol) dropwise *via* syringe. The resulting colorless solution was allowed to warm to rt and stirred for 1 h. It was then recooled to 0 °C and a solution of the aldol adduct **23** (1.05 g, 2.40 mmol) in THF (2 mL) was added dropwise *via* syringe. The reaction mixture was then allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous Rochelle salts (50 mL), and the mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted three times with CH_2Cl_2 (75 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. This material was taken on directly to the next step without further purification.

To a stirring solution of the total sample of unpurified alcohol **24** (0.676 g, 2.39 mmol) in dry *N,N*-dimethylformamide (2 mL) was added imdazole (0.325 g, 4.78 mmol) and *tert*-butyldimethylsilyl chloride (0.540 g, 3.60 mmol). The solution was stirred overnight, and the reaction was quenched with methanol (0.5 mL). The mixture was poured into a separatory funnel containing water (10 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted twice with CH_2Cl_2 (50 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was then chromatographed over a 1.5 × 15 cm silica gel column (slurry packed with hexanes), eluting with 100-mL portions of 5%, 10%, 15%, 20%, and 25% ethyl acetate/hexanes. The product was found in fractions 16–41 (8-mL fractions), which were combined and concentrated to yield 0.690 g of a colorless oil (66% from aldol adduct): $[\alpha]_D$ −7.65° (*c* 1.02, $CHCl_3$); R_f 0.71 (50% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.16 (m, 1 H), 4.02 (d, *J* = 5.65, 1 H), 3.74 (s, 3 H), 3.69 (m, 2 H), 3.37 (s, 3 H), 3.24 (s, 3 H), 1.65 (q, *J* = 6.4 Hz 2 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 6 H), 0.05 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 171.5, 83.6, 70.2, 61.2, 57.9, 59.6, 36.4, 26.0, 25.8, 18.3, 18.2, −4.1, −4.9, −5.2, −5.3; IR (neat) cm^{-1} 2955, 2931, 2856, 1670, 1472, 1253, 1105, 837, 777. Anal. Calcd for $C_{20}H_{45}NO_5Si_2$: C, 55.13; H, 10.41; N, 3.21. Found: C, 55.11; H, 10.36; N, 3.23.

Preparation of (2*S*,3*S*)-2-Methoxy-3,5-bis[(*tert*-butyldimethylsilyl)oxy]pentanal (6). To a stirring solution of **25** (0.750 g, 1.72 mmol) in 4 mL of toluene at −78 °C was added a 1.5 M solution of diisobutylaluminum hydride in toluene (5.7 mL) *via* syringe pump over 30 min. After complete addition, the reaction mixture was stirred for 10 min; then ethyl acetate (4 mL) was slowly added followed by saturated Rochelle salts (20 mL) and CH_2Cl_2 (50 mL). The mixture was warmed to rt and stirred for 1 h. The layers were separated and the aqueous phase was extracted three times with CH_2Cl_2 (30 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was then chromatographed over a 1.5 × 12 cm silica gel column (slurry packed with hexanes), eluting with 100-mL portions of 5%, 10%, and 20% EtOAc/hexanes. The product was found in fractions 8–23 (8-mL fractions), which were combined and concentrated to yield 0.563 g (87%) of a colorless oil: $[\alpha]_D$ +4.5° (*c* 0.53, $CHCl_3$); R_f 0.65 (25% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.78 (d, *J* = 1.5 Hz, 1 H), 4.24 (m, 1 H), 3.66 (m, 3 H), 3.45 (s, 3 H), 1.90 (m, 1 H), 1.59 (m, 1 H), 0.89 (s, 18 H), 0.10 (s, 6 H), 0.05 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 203.3, 88.1, 69.3, 59.0, 58.7, 36.1, 29.1, 25.9, 25.8, 18.2, 18.1, −4.6, −4.66, −5.3; IR (neat) cm^{-1} 2955, 2931, 2858, 1736, 1471, 1255, 1101, 837, 777, 734. Anal. Calcd for $C_{18}H_{40}O_4Si_2$: C, 57.38; H, 10.70. Found: C, 57.49; H, 10.70.

Preparation of (8*R*,6*R*,5*S*,4*S*,3*R*)-9-(Benzyloxy)-8-methyl-6-ethenyl-5-hydroxy-4-methoxy-1,3-bis[(*tert*-butyldimethylsilyl)oxy]nonane (26). To a stirring solution of **6** (0.075 g, 0.199 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added magnesium bromide etherate (0.154 g, 0.598 mmol). The solution was stirred for 1 h at 0 °C and cooled to −23 °C. To this solution was added **4** (75:25 *E:Z*, 0.196 g, 0.398 mmol) dissolved in CH_2Cl_2 (2 mL) dropwise *via* syringe. The solution was slowly warmed to rt over a period of 5 h, and then the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was poured into a separatory funnel containing water (10 mL) and the aqueous phase was extracted three times with CH_2Cl_2 (50 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by radial PLC (silica gel, hexanes–5% EtOAc/hexanes) gave 0.098 g (85%) of the major isomer and 0.012 g (11%) of the minor isomer as colorless oils.

Major isomer: $[\alpha]_D$ −0.058° (*c* 0.955, $CHCl_3$); R_f 0.16 (5% EtOAc/haxanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 5.47 (m, 1 H), 5.05 (m, 2 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.40 (d, *J* = 12.2 Hz, 1 H), 4.05 (ddd, *J* = 8.7, 5.3, 3.0 Hz, 1 H), 3.64 (m, 3 H), 3.45 (m, 1 H), 3.39 (s, 3 H), 3.20 (ddd, *J* = 10.7, 5.4, 2.2 Hz, 2 H), 2.23 (d, *J* = 9.6 Hz, 1 H), 2.16 (d, *J* = 4.3 Hz, 1 H), 1.59–1.90 (m, 4 H), 1.07 (m, 1 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 0.88 (s, 18 H), 0.06 (s, 3H), 0.04 (s, 3 H), 0.03 (s, 6 H); 75-MHz ^{13}C NMR δ 140.3,

138.8, 128.2, 127.4, 127.3, 116.9, 80.9, 74.9, 72.9, 71.8, 67.5, 59.5, 58.6, 47.9, 35.8, 35.3, 30.9, 29.1, 25.9, 19.2, 18.3, 18.0, -4.2, -4.8, -5.2, -5.2; IR (neat) cm^{-1} 3560, 2955, 2930, 1471, 1462 1255, 1099, 910, 837, 734; mass spectrum (CI, isobutane), *m/z* (rel intensity) (M + 1) 581 (100.0), 523 (2), 467 (11). Anal. Calcd for $C_{32}H_{60}O_5Si$: C, 66.15; H, 10.41. Found: C, 66.22; H, 10.45.

Minor isomer $[\alpha]_D$ +18.8° (*c* 1.02, $CHCl_3$); R_f 0.12 (5% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 5.57 (m, 1 H), 5.00 (m, 2 H), 4.43 (d, *J* = 12.3 Hz, 1 H), 4.38 (d, *J* = 12.3 Hz, 1 H), 4.02 (ddd, *J* = 8.8, 4.1, 3.8 Hz, 1 H), 3.59 (m, 3 H), 3.33 (s, 3 H), 3.20 (ddd, *J* = 9.8, 4.2, 2.3 Hz, 2 H), 3.03 (m, 1 H), 2.27 (d, *J* = 7.0 Hz, 1 H), 2.13 (m, 1 H), 1.53–1.80 (m, 4 H), 1.07 (m, 1 H), 0.83 (d, *J* = 5.1 Hz, 3 H), 0.81 (s, 18 H), 0.09 (s, 3 H), 0.01 (s, 3 H), -0.03 (s, 6 H); 75-MHz ^{13}C NMR δ 138.7, 138.4, 128.2, 127.4, 127.3, 116.7, 82.3, 76.5, 72.9, 71.6, 67.6, 59.4, 58.7, 47.1, 35.6, 35.1, 30.8, 25.9, 18.3, 18.1, 16.3, -4.3, -4.6, -5.1, -5.2; IR (neat) cm^{-1} 3557, 2955, 9230, 1471, 1255, 1099, 910, 837, 734. Anal. Calcd for $C_{32}H_{60}O_5Si$: C, 66.15; H, 10.41. Found: C, 66.29; H, 10.39.

Preparation of (8*R*,6*R*,5*S*,4*S*,3*R*)-9-(Benzyloxy)-8-methyl-6-(2-hydroxyethyl)-5-hydroxy-4-methoxy-1,3-bis[(*tert*-butyldimethylsilyl)oxy]nonane (27). To a solution of **26** (0.405 g, 0.697 mmol) in tetrahydrofuran (8 mL) was added a 0.5 M solution of 9-BBN in tetrahydrofuran (9.70 mL, 4.87 mmol). The resulting solution was then placed in a water bath and sonicated at 60 Hz for 90 min. The flask was removed from the sonication bath. Aqueous pH 7 phosphate buffer (2 mL) was added. The resulting solution was stirred for 48 h. The volatiles were removed on a rotary evaporator and the resulting white slurry was diluted with water (20 mL) and extracted three times with methylene chloride (30 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by radial PLC (silica gel, 100-mL portions of 5%, 10%, 15%, 20%, and 25% EtOAc/hexanes) afforded 0.389 g (93%) of **27** as a colorless oil: $[\alpha]_D$ +5.53° (*c*, 1.53, $CHCl_3$); R_f 0.34 (25% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 4.41 (s, 2 H), 4.04 (dd, *J* = 8.1, 3.8 Hz, 1 H), 3.61 (m, 3 H), 3.35 (s, 3 H), 3.32 (dd, *J* = 8.3, 3.8 Hz, 1 H), 3.27 (dd, *J* = 8.3, 3.8, 1 H), 3.18 (ddd, *J* = 8.8, 6.2, 2.7 Hz, 1 H), 3.03 (dd, *J* = 4.8, 1.7 Hz, 1 H), 2.5 (br(s), 1 H), 1.90–1.36 (m, 7 H), 1.14 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.82 (s, 9 H), 0.81 (s, 9 H), 0.02 (s, 6 H), -0.02 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.5, 128.2, 127.4, 127.4, 84.2, 75.4, 70.5, 66.9, 60.5, 59.4, 57.9, 39.3, 35.3, 33.4, 31.3, 25.9, 25.9, 19.0, 18.2, 18.0, -4.2, -4.7, -5.2, -5.3; IR (neat) cm^{-1} 3426, 2955, 2930, 1471, 1256, 1097, 837, 775. Anal. Calcd for $C_{32}H_{62}O_6Si_2$: C, 64.12; H, 10.43. Found: C, 64.28; H, 10.48.

Preparation of (8*R*,6*R*,5*S*,4*S*,3*R*)-9-(Benzyloxy)-8-methyl-6-(2-hydroxyethyl)-5-[(trimethylsilyl)oxy]-4-methoxy-1,3-bis[(*tert*-butyldimethylsilyl)oxy]nonane (28). To a stirring solution of diol **27** (0.089 g, 0.140 mmol) in methylene chloride (2 mL) were added DMAP (0.005 g, 0.040 mmol) and (trimethylsilyl)imidazole (0.042 g, 0.297 mmol). The reaction mixture was stirred for 24 h, and the reaction was quenched with H_2O (2 mL). The reaction mixture was then poured into a separatory funnel containing H_2O (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. This material was then taken on directly to the next step without purification.

To a stirring solution of the total sample of unpurified TMS-protected diol in MeOH (1 mL) was added K_2CO_3 (0.003 g, 0.015 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, and the reaction was quenched with ice-cold 1 M AcOH (0.1 mL) and ice-cold H_2O (2 mL). The resulting cloudy solution was poured into a separatory funnel containing methylene chloride (20 mL) and water (5 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (4 × 20 mL). The combined organic phase was then dried with Na_2SO_4 and concentrated. The resulting oil was then chromatographed over a (0.5 × 8 cm) silica gel column (slurry packed with hexanes), eluting with 50-mL portions of hexanes and 2%, 4%, 6%, 8%, and 10% EtOAc/hexanes; 7-mL fractions were collected. The product-containing fractions (36–54) were concentrated to yield 0.087 g (87%) of a colorless oil: $[\alpha]_D$ +6.56° (*c* 1.25, $CHCl_3$); R_f 0.27 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 4.42 (s, 2 H), 4.01 (ddd, *J* = 7.5, 4.9, 2.5 Hz, 1 H), 3.84 (t, *J* = 3.8 Hz, 2 H), 3.61 (m, 3 H), 3.33 (s, 3 H), 3.26 (dd, *J* = 9.0, 5.3 Hz, 1 H), 3.15 (dd, *J* = 8.9, 6.5 Hz, 1 H), 3.00 (dd, *J* = 5.3, 2.9 Hz, 1 H), 2.30 (m, 3 H), 1.71–1.95 (m, 4 H), 1.40 (m, 3 H), 1.10 (m, 1 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.83 (s, 9 H), 0.82 (s, 9 H), 0.07 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H), -0.02 (s, 6 H); 75-MHz ^{13}C NMR δ 138.5, 128.2, 127.5, 127.4, 82.3, 75.9, 73.1, 72.9, 67.9, 62.1,, 59.6, 59.0, 38.7, 36.6, 36.5, 34.3, 31.5, 26.1, 25.9, 25.8, 18.5, 18.3, 18.1, 0.9, -3.9, -4.4, -5.2, -5.3; IR (neat) cm^{-1} 2955, 2940, 1471, 1090, 910, 839, 777, 734. Anal. Calcd for $C_{35}H_{68}O_6Si_3$: C, 62.82; H, 10.24. Found: C, 62.07; H, 10.13.

Preparation of (8*R*,6*R*,5*S*,4*S*,3*R*)-9-(Benzyloxy)-8-methyl-6(1-oxoethyl)-5-[(trimethylsilyl)oxy]-4-methoxy-1,3-bis[(*tert*-butyldimethylsilyl)oxy]nonane (29). To a solution of **28** (0.131 g, 0.195 mmol) in methylene chloride (3 mL) were added crushed 4-Å molecular sieves (0.13 g), *N*-methylmorpholine *N*-oxide (0.034 g, 0.293 mmol), and tetrapropylammonium perruthenate (0.004 g, 0.010 mmol). The reaction was stirred for 1 h and diluted with ether (20 mL). The mixture was filtered through Celite and silica gel on a sintered glass funnel, washing with ether (75 mL). The filtrate was concentrated and flash chromatographed through a silica gel column (0.5 × 8 cm), eluting with 50-mL portions of hexanes and 2%, 4%, 6%, and 8% EtOAc/hexanes; 8-mL fractions were collected. The product-containing fractions (17–35) were concentrated to yield 0.10 g (80%) of a colorless oil: $[\alpha]_D$ +8.35° (*c* 0.85, $CHCl_3$); R_f 0.43 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.72 (s, 1 H), 7.26 (m, 5 H), 4.45 (s, 2 H), 4.10 (ddd, *J* = 8.5, 5.7, 2.4 Hz, 1 H), 4.02 (dd, *J* = 4.2, 1.9 H z, 1 H), 3.66 (m, 2 H), 3.36 (s, 3 H), 3.25 (dd, *J* = 5.8, 2.2 Hz, 2 H), 3.10 (dd, *J* = 5.7, 2.0 Hz, 1 H), 2.36 (m, 3 H), 1.42–1.95 (m, 6 H), 1.12 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.11 (s, 6 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H); 75-MHz ^{13}C NMR δ 203.4, 138.6, 128.2, 127.4, 81.9, 75.7, 73.1, 70.9, 67.3, 59.5, 58.4, 45.7, 36.4, 36.3, 35.5, 30.8, 25.9, 25.9, 25.8, 18.2, 18.0, 17.6, 0.8, -4.1, -4.6, -5.2, -5.2; IR (neat) cm^{-1} 2955, 2930, 1724, 1471, 1253, 1093, 910, 839, 777, 734. Anal. Calcd for $C_{35}H_{69}O_6Si_3$: C, 62.82; H, 10.24. Found: C, 62.07; H, 10.13.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[3-(benzyloxy)-2(*R*)-methylpropyl]-5-[1(*S*)-methoxy-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxybutyl]tetrahydrofuran (30). To stirring solution of aldehyde **29** (0.200 g, 0.297 mmol) in methanol (2 mL) and methylene chloride (2 mL) was added PPTS (0.015 g, 0.061 mmol). The reaction mixture was stirred for 8 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was poured into a separatory funnel containing water (5 mL) and the aqueous layer extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed through a silica gel column (0.5 × 8 cm), eluting with 50-mL portions of hexanes and 5%, 10%, 15%, 20%, 25%, and 30% EtOAc/hexanes; 7-mL fractions were collected. The product-containing fractions (40–64) were concentrated to yield 0.128 g (87%) of a clear colorless oil (4:1 mixture of diastereomers epimeric at the methyl lactol): $[\alpha]_D$ +57.4° (*c* 0.93, $CHCl_3$); R_f 0.21 (25% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.21 (m, 5 H), 4.95 (dd, *J* = 7.9, 4.4 Hz, 1 H), 4.41 (s, 2 H), 4.32 (d, *J* = 7.9 Hz, 1 H), 4.04 (dd, *J* = 5.1, 1.8 Hz, 1 H), 3.64 (m, 2 H), 3.27 (s, 3 H), 3.30 (s, 3 H), 3.14 (d, *J* = 4.9 Hz, 1 H), 2.48 (m, 1 H), 2.14 (br(s), 1 H), 1.5–2.0 (m, 5 H), 1.13 (m, 2 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.82 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.5, 128.2, 127.5, 127.4, 104.7, 81.4, 77.4, 75.4, 73.1, 69.2, 60.4, 57.5, 54.7, 39.2, 36.9, 35.8, 33.9, 32.5, 25.8, 18.0, 17.9, -4.5, -4.6; IR (neat) cm^{-1} 3474, 2955, 2930, 1776, 1462, 1361, 1257, 1097, 1072, 910, 734. Anal. Calcd for $C_{27}H_{48}O_6Si$: C, 65.28; H, 9.74. Found: C, 65.51; H, 9.78.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[3-(benzyloxy)-2(*R*)-methylpropyl]-5-[1(*S*)-methoxy-2(*R*),4-bis[(*tert*-butyldimethylsilyl)oxy]butyl]tetrahydrofuran (31). To a stirring solution of **30** (0.128 g, 0.250 mmol) and 2,6-lutidine (0.140 g, 1.29 mmol) in methylene chloride (4 mL) at 0 °C was added *tert*-butyldimethylsilyl triflate (0.136 g, 0.516 mmol). After 20 min of stirring, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was poured into a separatory funnel containing methylene chloride (15 mL) and water (10 mL). The aqueous layer was extracted two times with methylene chloride (40 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and chromatographed over a silica gel

column (0.5 × 8 cm), eluting with 5% EtOAc/hexanes. The product-containing fractions were concentrated to yield 0.152 g (97%) of a colorless oil: $[\alpha]_D$ +51.2° (*c* 1.42, $CHCl_3$); R_f 0.73 (25% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.21 (m, 5 H), 4.94 (dd, *J* = 4.4, 1.7 Hz, 1 H), 4.41 (s, 2 H), 4.31 (d, *J* = 7.8 Hz, 1 H), 4.11 (ddd, *J* = 8.3, 5.0, 1.5 Hz, 1 H), 3.60 (m, 2 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 3.23 (m, 2 H), 3.08 (d, *J* = 4.9 Hz, 1 H), 1.45–1.80 (m, 5 H), 1.16 (m, 2 H), 0.82 (s, 9 H), 0.80 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H), –0.01 (s, 3 H), –0.03 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 138.6, 128.2, 127.4, 127.3, 104.6, 81.4, 77.2, 75.3, 73.1, 66.5, 59.5, 57.0, 54.6, 39.2, 36.9, 35.7, 34.1, 32.5, 25.9, 25.9, 18.2, 18.0, –4.5, –4.5, –5.2, –5.2; IR (neat) cm^{-1} 2955, 2930, 2858, 1471, 1257, 1097, 908, 837, 734. Anal. Calcd for $C_{33}H_{62}O_6Si_2$: C, 64.87; H, 10.23. Found: C, 64.92; H, 10.19.

Preparation of (4*R*, 5*S*)-2-Methoxy-4-2(*R*)-methyl-3-hydroxypropyl)-5-[1(*S*)-methoxy-2(*R*),4-bis[(*tert*-butyldimethylsilyl)oxy]butyl]tetrahydrofuran (32). To a stirring solution of **31** (0.118 g, 0.226 mmol) in tetrahydrofuran (15 mL) at –78 °C was added condensed ammonia (8 mL). To this solution were added lithium chips (4 × 0.005 g) until a homogenous deep blue solution was achieved (~10 min). The solution was stirred for an additional 10 min, and the reaction was quenched by slow addition of ammonium chloride (0.5 g). The mixture was slowly warmed to rt and was poured into a separatory funnel containing water (20 mL). The aqueous layer was extracted with methylene chloride (3 × 20 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by radial PLC (silica gel, 10% EtOAc/hexanes–15% EtOAc/hexanes) gave 0.083 (82%) of **32** as a colorless oil: $[\alpha]_D$ +45.0° (*c* 0.600, $CHCl_3$); R_f 0.17 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.98 (dd, *J* = 4.5, 1.7 Hz, 1 H), 4.35 (d, *J* = 7.8 Hz, 1 H), 4.17 (ddd, *J* = 8.8, 4.6, 1.1 Hz, 1 H), 3.64 (m, 2 H), 3.51 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.44 (dd, *J* = 9.7, 5.8 Hz, 1 H), 3.34 (s 3 H), 3.29 (s, 3 H), 3.11 (d, *J* = 4.7 Hz 1 H), 2.46 (m, 1 H), 1.89–1.40 (m, 5 H), 1.16 (m, 2 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.85 (s, 9 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.01 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 104.5, 81.5, 77.4, 67.6, 66.5, 59.5, 57.1, 54.6, 39.2, 37.0, 35.8, 34.4, 33.5, 25.9, 25.9, 18.2, 18.0, 17.7, –4.4, –4.5, –5.2, –5.2; IR (neat) cm^{-1} 3479, 2955, 2930, 2897, 1471, 1255, 1097, 1070, 1039, 837, 775; mass spectrum (CI, methane) *m/z* (rel intensity) (M – CH_3O) 489 (5), 375 (15), 343 (7), 211 (10); exact mass calcd for $C_{25}H_{53}O_5Si_2$ 489.3432, found 489.3401. Anal. Calcd for $C_{26}H_{56}O_6Si_2$: C, 59.95; H, 10.84. Found: C, 59.86; H, 10.80.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[2(*R*)-methyl-3-oxopropyl]-5-[1(*S*)-methoxy-2(*R*),4-bis[(*tert*-butyldimethylsilyl)oxy]butyl]tetrahydrofuran (33). To a stirring solution of **32** (0.082 g, 0.157 mmol) in methylene chloride (2 mL) were added crushed 4-Å molecular sieves (0.08 g), *N*-methylmorpholine *N*-oxide (0.036 g, 0.314 mmol), and tetrapropylammonium perruthenate (0.003 g, 0.008 mmol). The reaction was stirred for 30 min, and the solution was diluted with ether (20 mL). The mixture was filtered through silica gel and Celite on a sintered glass funnel, washing with ether (75 mL). The filtrate was concentrated and flash chromatographed through a silica gel column (0.5 × 8 cm), eluting with 50-mL portions of hexanes and 2%, 4%, 6%, and 8% EtOAc/hexanes; 8-mL fractions were collected. The product-containing fractions (18–35) were concentrated to yield 0.072 g (88%) of **33** as a colorless oil: $[\alpha]_D$ +71.1° (*c* 0.49, $CHCl_3$); R_f 0.18 (25% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.52 (d, *J* = 2.1 Hz, 1 H), 4.95 (dd, *J* = 4.0, 1.0 Hz, 1 H), 4.29 (d, *J* = 7.7 Hz, 1 H), 4.15 (dt, *J* = 8.9, 4.3 Hz, 1 H), 3.60 (m, 2 H), 2.30 (m, 2 H), 1.20–1.9 0 (m, 6 H), 1.06 (d, *J* = 7.2 Hz, 3 H), 0.85 (s, 18 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 204.2, 104.3, 81.4, 76.7, 66.4, 59.4, 57.1, 54.6, 45.1, 38.7, 37.4, 35.6, 31.2, 25.9, 25.8, 18.2, 18.0, 14.6, –4.4, –4.5, –5.2, –5.2; IR (neat) cm^{-1} 2955, 2930, 2858, 1730, 1471, 1464, 1255, 1099, 837, 775; mass spectrum (CI, methane) *m/z* (rel intensity) 519(15), 503 (100), 487 (19), 445(13), 371 (27), 353 (15); exact mass calcd for $C_{26}H_{54}O_6Si_2$ 519.3537, found 519.3151. Anal. Calcd for $C_{26}H_{54}O_6Si_2$: C, 60.19; H, 10.49. Found: C, 58.61; H, 10.33.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[2(*R*)-methyl-3-oxo-4-(*O*,*O*-dimethylphosphono)butyl]-5-[1(*S*)-methoxy-2(*R*),4-bis[(*tert*-butyldimethylsilyl)oxy]butyl]tetrahydrofuran (34). To a stirring solution of dimethyl methylphosphonate (0.028 g, 0.230 mmol) in tetrahydrofuran (2 mL) at –78 °C was added a 2.5 M solution of *n*-butyllithium in hexanes (0.087 mL, 0.228 mmol) by syringe. After 30 min, compound **33** (0.057 g, 0.109 mmol) in tetrahydrofuran (1 mL) was added *via* cannula. The reaction mixture was stirred for 1 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was allowed to warm to rt and poured into a separatory funnel containing water (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. This material was taken on directly to the next step without further purification.

To a stirring solution of the total sample of unpurified alcohol (0.072 g, 0.111 mmol) in methylene chloride (2 mL) were added crushed 4-Å molecular sieves (0.072 g), *N*-methylmorpholine *N*-oxide (0.026 g, 0.218 mmol), and tetrapropylammonium perruthenate (0.002 g, 0.005 mmol). The reaction mixture was stirred for 1 h and diluted with ethyl acetate (5 mL). The mixture was filtered through Celite and silica gel on a sintered glass funnel, washing with EtOAc (25 mL) and concentrated *in vacuo*. Purification by radial PLC (silica gel, 70% EtOAc/hexanes) gave 0.055 g (79%) of **34** as a white solid: mp 93 °C; $[\alpha]_D$ +76.1° (*c* 0.52, $CHCl_3$); R_f 0.52 (10% EtOH/EtOAc); 300-MHz ($CDCl_3$) δ 4.98 (t, *J* = 4.0 Hz, 1 H), 4.28 (d, *J* = 7.2 Hz, 1 H), 4.19 (dt, *J* = 8.0, 4.7 Hz, 1 H), 3.73 (d, *J* = 11.2 Hz, 6 H), 3.64 (m, 2 H), 3.35 (s, 3 H), 3.25 (s, 3 H), 3.22 (d, *J* = 7.9 Hz, 1 H), 3.20 (dd, *J* = 22.8, 13.7 Hz, 1 H), 2.98 (dd, *J* = 22.5, 13.7 Hz, 1 H), 2.78 (m, 1 H), 2.18 (m, 1 H), 1.62–1.91 (m, 4 H), 1.15–1.25 (m, 2 H), 1.11 (d, *J* = 7.0 Hz, 3 H), 0.85 (s, 9 H), 0.84 (s, 9 H), 0.06 (s, 6 H), 0.00 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 204.7 (*J* = 6.6 Hz), 104.3, 81.3, 76.7, 66.4, 59.4, 57.1, 54.6, 53.0 (*J* = 13.0 Hz), 52.8 (*J* = 6.6 Hz), 45.7, 40.0 (*J* = 130 Hz), 38.5, 37.6, 35.6, 33.0, 25.9, 18.2, 18.0, 17.9, –4.4, –4.6, –5.2, –5.3; IR (neat) cm^{-1} 2955, 2930, 2856, 1714, 1471, 1462, 1256, 1097, 1064, 1034, 837; mass spectrum (CI, methane) *m/z* (rel intensity) 640 (2), 609 (100), 583 (55), 445 (24), 261 (24), 89 (22), 61 (18); exact mass calcd for $C_{28}H_{58}O_8PSi_2$ 609.3641, found 609.3381. Anal. Calcd for $C_{29}H_{61}O_9PSi_2$: C, 54.35; H, 9.59. Found: C, 54.30; H, 9.63.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[2(*R*)-methyl-3-oxo-4-(*O*,*O*-dimethylphophono)butyl]-5-[1(*S*)-methoxy-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxybutyl]tetrahydrofuran (35). To a stirring solution of **34** (0.025 g, 0.038 mmol) in tetrahydrofuran (1.5 mL) in a Nalgene reaction vessel was added a stock solution (1.5 mL) of pyridinium hydrofluoride (2.5 g), pyridine (5 mL), and THF (20 mL). The resulting solution was stirred for 4 h, and the reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, concentrated, and chromatographed over a silica gel column (1 × 10 cm), eluting with 10-mL portions of 20%, 40%, 60%, 80%, and 100% EtOAc/hexanes. The product-containing fractions were concentrated to yield 0.019 g (92%) of **35** as a colorless oil: $[\alpha]_D$ +73.4° (*c* 1.75, $CHCl_3$); R_f 0.23 (10% EtOH/EtOAc); 300-MHz ^1H NMR ($CDCl_3$) δ 5.03 (t, *J* = 3.8 Hz, 1 H), 4.34 (dd, *J* = 7.3, 1.5 Hz, 1 H), 4.19 (dt, *J* = 6.8, 3.1 Hz, 1 H), 3.79 (d, *J* = 11.2 Hz, 3 H), 3.78 (d, *J* = 11.2 Hz, 3 H), 3.64 (m, 2 H), 3.45 (s, 3 H), 3.32 (s, 3 H), 3.28 (dd, *J* = 7.8, 6.1 Hz, 1 H), 3.04 (dd, *J* = 22.7, 13.8 Hz, 1 H), 2.88 (dd, *J* = 23.1, 13.8 Hz, 1 H), 2.86 (m, 1 H), 2.27 (m, 1 H), 1.75 (m, 4 H), 1.20 (m, 2 H), 1.11(d, *J* = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.13(s, 3 H), 0.12 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 204.7 (d, *J* = 6.3 Hz), 104.4, 81.3, 77.2, 69.5, 59.9, 57.8, 54.7, 53.1 (d, *J* = 6.2 Hz), 52.9 (d, *J* = 7.0 Hz), 45.7, 39.9 (d, *J* = 129.3 Hz), 38.5, 37.5, 35.7, 32.6, 25.8, 17.9, 17.8, 14.2, –4.4, –4.5; IR (neat) cm^{-1} 3472, 2957, 2931, 1713, 1265, 1037, 908, 735. Anal. Calcd for $C_{23}H_{47}O_9PSi$: C, 52.46; H, 8.99. Found: C, 52.30; H, 8.91

Preparation of (4*R*,5*S*)-2-Methoxy-4[2(*R*)-methyl-3-oxo-4-(*O*,*O*-dimethylphosphono)butyl]-5-[1(*S*)-methoxy-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4-oxopropyl]tetrahydrofuran (36). To a stirring solution of **35** (0.012 g, 0.022 mmol) in methylene chloride (1 mL) were added crushed 4-Å molecular sieves (0.012 g), *N*-methylmorpholine *N*-oxide (0.004 g, 0.340 mmol), and tetrapropylammonium perruthenate (0.001 g, 0.002 mmol). The reaction was stirred for 30 min and diluted with EtOAc (25 mL). The mixture was filtered through Celite and silica gel on a sintered glass funnel, washed with EtOAc (25 mL), and concentrated *in vacuo*. The material was taken on directly to the next step without further purification.

To a stirring solution of the total sample of unpurified aldehyde (0.009 g, 0.022 mmol) in *tert*-butyl alcohol (0.1 mL) were added a 1.25 M solution of potassium dihydrogen phosphate (0.2 mL) and a 1.0 M solution of aqueous potassium permanganate (0.3 mL). The reaction mixture was stirred for 1 h, and the reaction was quenched by the addition of saturated aqueous $NaHSO_3$ (0.2 mL). The mixture was then poured into a separatory funnel containing methylene chloride (10 mL) and saturated NH_4Cl (10 mL). The aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to yield 0.009 g (76%) of **36** as a colorless oil: $[\alpha]_D$ +80.2° (*c* 0.52, $CHCl_3$); R_f 0.16 (10% EtOH/EtOAc); 300-MHz ^1H NMR ($CDCl_3$) δ 5.00 (d, J = 4.3 Hz, 1 H), 4.44 (dt, J = 7.7, 3.3 Hz, 1 H), 4.35 (d, J = 8.1 Hz, 1 H), 3.77 (d, J = 10.7 Hz, 6 H), 3.40 (s, 3 H), 3.29 (s, 3 H), 3.28 (d, J = 7.7 Hz, 1 H), 3.22 (dd, J = 23.2, 13.7 Hz, 1 H), 3.02 (d, J = 22.7, 13.8 Hz, 1 H), 2.80 (m, 1 H), 2.75 (dd, J = 15.8, 4.3 Hz, 1 H), 2.64 (dd, J = 15.7, 7.7 Hz, 1 H), 2.30 (m, 1 H), 1.75–1.95 (m, 4 H), 1.21–1.27 (m, 1 H), 1.15 (d, J = 7.1 Hz, 3 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 204.6 (d, J = 6.3 Hz), 176.1, 104.6, 81.1, 77.2, 67.2, 57.5, 54.8, 53.2 (d, J = 6.5 Hz), 53.0 (J = 6.6 Hz), 45.8, 40.0 (d, J = 129.4 Hz), 38.6, 38.4, 37.4, 32.7, 25.8, 17.9, 17.8, -4.6, -4.7; IR (neat) cm^{-1} 3400–2830 (br), 2955, 1716, 1462, 1253, 1097, 1036, 835, 814, 779. Anal. Calcd for $C_{23}H_{45}O_{10}PSi$: C, 51.10; H, 8.39. Found: C, 50.98; H, 8.38.

Preparation of (*R*)-Ethyl 3-(*tert*-Butyldimethylsiloxy)butyrate (37). To a stirring solution of (*R*)-ethyl 3-hydroxybutyrate (8.98 g, 67.9 mmol) in *N,N*-dimethylformamide (9 mL) were added *tert*-butyldimethylsilyl chloride (12.3 g, 81.6 mmol) and imidazole (9.30 g, 67.9 mmol). The solution was stirred for 5 h at rt and then added to 40 mL of water, and the layers were separated. The aqueous layer was extracted three times with methylene chloride (40 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography over a 5 × 20 cm silica gel column, eluting with a solvent gradient of hexanes through 5% EtOAc/hexanes. The product-containing fractions were collected and concentrated to yield 15.9 g (95%) of a colorless oil: R_f 0.42 (10% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 4.27 (ddq, J = 11.6, 7.5, 5.6 Hz, 1 H), 4.11 (q, J = 7.1 Hz, 2 H), 2.46 (dd, J = 14.5, 7.6 Hz, 1 H), 2.35 (dd, J = 14.5, 5.4 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.19 (d, J = 6.1 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 171.7, 65.9, 60.3, 45.0, 25.8, 23.9, 17.9, spectrum (CI, methane) *m/z* (rel intensity) 540 (0.5), 509 (100), 491 (34), 477 (15), 451 (5); 14.2, -2.9, -4.5, -5.0; IR (neat) cm^{-1} 2925, 2830, 1728, 1450, 1290, 1240, 1170, 1055, 990, 820, 760. Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.64. Found: C, 58.22; H, 10.67.

Preparation of 3(*R*)-(*tert*-Butyldimethylsiloxy)butanal (38). A stirring solution of **37** (3.00 g, 12.2 mmol) in methylene chloride (122 mL) was cooled to -90 °C. To this solution was added a 1.5 M solution of diisobutylaluminum hydride in toluene (8.90 mL, 13.4 mmol) *via* syringe pump over 1 h. After complete addition, the reaction was quenched by the slow addition of methanol (4 mL), and the solution was allowed to warm to rt. The reaction mixture was added to saturated aqueous Rochelle salts (50 mL), and the resulting solution was stirred for 2 h. The layers were separated and the aqueous phase was extracted three times with methylene chloride (50 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. Purification by flash chromatography on a 20 × 5 cm column, eluting with a solvent gradient of 3% EtOAc/hexanes through 6% EtOAc/hexanes, gave 2.2 g (89%) of **38** as a colorless oil: R_f 0.39 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.78 (dd, J = 4.9, 2.6 Hz, 1 H), 4.33 (ddq, J = 11.9, 6.7, 5.2 Hz, 1 H), 2.51 (dd, J = 7.2, 2.7 Hz, 1 H), 2.47 (dd, J = 5.0, 2.0 Hz, 1 H), 1.22 (d, J = 6.2 Hz, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 202.3, 64.5, 52.9, 25.7, 24.2, 17.9, -4.4, -5.0; IR (neat) cm^{-1} 2920, 2840, 1715, 1450, 1355, 1240, 1080, 1010, 840, 760. Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 57.15; H, 10.55.

Preparation of (*R*)-Ethyl 5-(*tert*-Butyldimethylsiloxy)-2-hexenoate (39). To a stirring solution of triethyl phosphonoacetate (1.65 g, 7.92 mmol) in acetonitrile (79.0 mL) were added LiCl (0.483 g, 11.4 mmol), diisopropylethylamine (1.29 mL, 7.43 mmol), and **38** (1.00 g, 4.95 mmol). The reaction was stirred at rt for 18 h and then filtered through Celite. The filtrate was concentrated and purified by flash chromatography with a 20 × 4.5 cm silica gel column, eluting with a solvent gradient of hexanes through 10% EtOAc/hexanes. The product-containing fractions were concentrated to yield 1.17 g (87%) of a colorless oil: R_f 0.47 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 6.92 (ddd, J = 15.6, 8.1, 7.6 Hz, 1 H), 5.8 (d, J = 15.6 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.91 (ddq, J = 12.1, 6.1, 5.1 Hz, 1 H), 2.31 (dd, J = 2.9, 1.5 Hz, 1 H), 2.28 (dd, J = 7.6, 3.5 Hz, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.14 (d, J = 6.1 Hz, 3 H), 0.86 (s, 9 H), 0.03 (s, 6 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 166.5, 145.9, 123.1, 67.6, 60.1, 42.5, 25.8, 23.8, 14.3, -4.5, -4.8. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.63; H, 10.31.

Preparation of 5(*R*)-(*tert*-Butyldimethylsiloxy)-2-hexen-1-ol (40). To a stirring solution of **39** (0.200 g, 0.735 mmol) in methylene chloride (14.7 mL) at -40 °C was added a 1.5 M solution of diisobutylaluminum hydride in toluene (1.03 mL, 1.54 mmol) over 5 min. The reaction was quenched by slow addition of methanol (2 mL), and the solution was allowed to warm to rt. The mixture was allowed to stir with saturated aqueous Rochelle salts (40 mL) for 2 h. The layers were separated and the aqueous layer was extracted three times with methylene chloride (30 mL). The combined organic phase was dried with Na_2SO_4, concentrated, and purified by flash chromatography with a silica gel column (20 × 2 cm), eluting with a solvent gradient of hexanes through 10% EtOAc/hexanes. The product-containing fractions were concentrated to yield 0.165 g (98%) of a colorless oil: R_f 0.14 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 5.66 (m, 2 H), 4.08 (d, J = 3.3 Hz, 2 H), 3.82 (ddq, J = 12.1, 6.0, 5.1 Hz, 1 H), 2.18 (dd, J = 8.7, 5.9 Hz, 1 H), 2.16 (dd, J = 5.6, 2.8 Hz, 1 H), 1.37 (s, 1 H), 1.11 (d, J = 6.1 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 131.1, 129.7, 68.4, 63.8, 42.5, 25.9, 23.5, 18.2, -4.5, -4.6. Anal. Calcd for $C_{12}H_{28}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.28; H, 11.25.

Preparation of (5*R*)-2-hexene-1,5-diol (41). To a stirring solution of **40** (1.00 g, 4.38 mmol) in THF (6 mL) at 0 °C was added a 1 M THF solution of tetrabutylammonium fluoride (6.6 mL). The reaction mixture was warmed to rt overnight, and the reaction was quenched with saturated NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic phase was then dried over Na_2SO_4, concentrated, and chromatographed to yield 0.48 g (98%) of diol as a clear colorless oil: R_f 0.20 (75% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 5.29–5.74 (m, 2 H), 4.11 (d, J = 4.2 Hz, 2 H), 3.85 (m, 1 H), 2.30 (m, 2 H), 1.80 (s, 2 H), 1.20 (d, J = 7.2 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 132.4, 128.6, 67.2, 63.3, 41.9, 22.8; IR (neat) cm^{-1} 3360, 1550, 860, 740.

Preparation of 5(*R*)-Hydroxy-2-hexen-1-al (4). To a stirring solution of **41** (0.09 g, 0.79 mmol) in CH_2Cl_2 (5 mL) was added activated MnO_2. The reaction mixture was stirred for 1 h and diluted with EtOAc. The mixture was then filtered through Celite on a sintered glass funnel, washing with EtOAc (25 mL). The filtrate was concentrated and chromatographed to yield 0.066 g (76%) of enal as a colorless oil: R_f (0.32 EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 9.52 (d, J = 7.9 Hz, 1 H), 6.91 (dt, J = 16.0, 7.3 Hz, 1 H), 6.19 (ddt, J = 16.0, 7.9, 1.1 Hz, 1H), 4.04 (sextet, J = 6.2 Hz, 1 H), 2.5 (m, 2 H), 1.65 (s, 1 H), 1.27 (d, J = 6.3 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 193.8, 154.5, 134.8, 66.6, 42.1, 23.5; IR (neat) cm^{-1} 3350, 1680.

Preparation of (4*R*,5*S*)-2-Methoxy-4-[2(*R*)-methyl-3-oxo-4-(*O,O*-dimethylphosphono)butyl]-5-[1(*S*)-methoxy-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4-oxo-4-[(4-formyl-1(*R*)-methyl-3(*Z*)-butenyl)oxy]butyl]tetrahydrofuran (45). To a stirring solution of **36** (0.066 g, 0.121 mmol) in tetrahydrofuran (2 mL) were added triethylamine (0.010 mL, 0.157 mmol) and 2,4,6-trichlorobenzoyl chloride (0.025 mL, 0.146 mmol) at rt. After 2 h, the precipitated $Et_3N{\cdot}HCl$ was filtered on a sintered glass funnel, washing with THF (3 mL). The filtrate was concentrated and dissolved in toluene (3 mL). To this solution was added a mixture of **7** (0.017 g, 0.157 mmol) and DMAP (0.018 g, 0.746 mmol) via cannula. The mixture was stirred for 4 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was poured into a separatory funnel containing EtOAc (10 mL). The layers were separated and the aqueous layer was extracted two times with EtOAc (30 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*.

Purification by radial PLC (silica gel, 70% EtOAc/hexanes) gave 0.053 g (68%) of **45** as a colorless oil: $[\alpha]_D$ +81.6° (*c* 0.60, $CHCl_3$); R_f 0.49 (10% EtOH/EtOAc); 300-MHz ^1H NMR ($CDCl_3$) δ 9.50 (d, J = 7.8 Hz, 1 H), 6.78 (ddd, J = 15.5, 7.1, 1.3 Hz, 1 H), 6.14 (dd, J = 15.7, 7.9 Hz, 1 H), 5.06 (s, J = 6.1 Hz, 1 H), 5.00 (d, J = 4.3 Hz, 1 H), 4.50 (ddd, J = 7.7, 4.4, 3.3 Hz, 1 H), 4.34 (d, J = 7.7 Hz, 1 H), 3.80 (d, J = 1.3 Hz, 3 H), 3.76 (d, J = 1.1 Hz, 3 H), 3.39 (s, 3 H), 3.30 (s, 3 H), 3.28 (d, J = 7.7 Hz, 1 H), 3.23 (dd, J = 23.1, 13.7 Hz, 1 H), 3.02 (d, J = 22.7, 13.8 Hz, 1 H), 2.80 (m, 1 H), 2.74 (dd, J = 15.0, 3.3 Hz, 1 H), 2.60 (m, 2 H), 2.64 (dd, J = 15.6, 7.8 Hz, 1 H), 2.30 (m, 1 H), 1.75–1.95 (m, 4 H), 1.29 (d, J = 6.3 Hz, 3 H), 1.25 (m, 1 H), 1.16 (d, J = 7.2 Hz, 3 H), 0.86 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 204.6 (d, J = 6.4 Hz), 193.5, 172.4, 152.8, 135.0, 104.6, 80.8, 76.7, 68.7, 67.1, 57.3, 54.6, 53.1 (J = 6.5 Hz), 52.9 (d, J = 6.6 Hz), 45.8, 40.0 (d, J = 129.3 Hz), 38.9, 38.4, 38.2, 37.4, 32.8, 25.7, 19.9, 17.9, 17.8, -4.6, -4.7; IR (neat) cm^{-1} 2955, 2931, 2856, 1730, 1714, 1693, 1055, 1033. Anal. Calcd for $C_{29}H_{53}O_{11}SiP$: C, 54.71; H, 8.39. Found: C, 53.94; H, 8.44.

Preparation of 3-[(*tert*-Butyldimethylsilyl)oxy]carbonolide B 4-(Methoxy acetal) (46). To a stirring solution of **45** (0.021 g, 0.032 mmol) in toluene (32 mL) were added 18-crown-6 (0.113 g, 0.224 mmol) and K_2CO_3 (0.031 g, 0.224 mmol). The reaction mixture was stirred for 20 h, and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was poured into a separatory funnel containing EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layer was then washed with saturated aqueous KCl (2 × 20 mL). The combined organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. Purification by radial PLC (silica gel, 15% EtOAc/hexanes) afforded 0.012 g (75%) of **46** as a colorless oil: $[\alpha]_D$ +81.6° (*c* 0.65, $CHCl_3$); R_f 0.18 (20% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.06 (dd, J = 15.4, 8.9 Hz, 1 H), 6.27 (d, J = 15.4 Hz, 1 H), 6.08 (m, 2 H), 5.05 (ddq, J = 7.9, 6.1, 3.4 Hz, 1 H), 5.00 (dd, J = 6.9, 3.3 Hz, 1 H), 4.03 (dd, J = 7.0, 4.6 Hz, 1 H), 3.95 (ddd, J = 10.7, 7.3, 3.5 Hz, 1 H), 3.48 (s, 3 H), 3.30 (s, 3 H), 3.01 (dd, J = 6.9, 3.3 Hz, 1 H), 2.70 (dd, J = 16.7, 7.4 Hz, 1 H), 2.52 (m, 1 H), 2.50 (m, 1 H), 2.30 (dd, J = 16.6, 3.0 Hz, 1 H), 1.80–2.02 (m, 5 H), 1.7 (m, 1 H), 1.28 (d, J = 6.4 Hz, 3 H), 1.18 (d, J = 6.9 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 203.8, 170.8, 142.0, 139.6, 131.5, 124.8, 103.8, 82.2, 79.6, 70.1, 68.9, 59.4, 55.1, 45.6, 41.7, 41.2, 39.4, 38.5, 34.2, 26.2, 20.6, 18.4, 17.2, -4.2, -4.3; IR (neat) cm^{-1} 2953, 2932, 2857, 1738, 1686, 1597, 1251, 1174, 1099, 837, 733; mass spectrum (CI, methane) m/z (rel intensity) 51 (19), 497 (72), 479 (27), 411 (35), 177 (46), 154 (66), 133 (41), 97 (100), 84 (29), 75 (56); exact mass calcd for $C_{27}H_{46}O_7Si$ 511.3069, found 511.3091.

Preparation of Niddanolide Methoxy Acetal (47). To a stirring solution of **46** (0.021 g, 0.035 mmol) in tetrahydrofuran (0.1 mL) in a Nalgene reaction vessel was added a stock solution (0.88 mL) of pyridinium hydrofluoride (2.5 mL), pyridine (5 mL), and THF (10 mL). The resulting solution was stirred 6 h, and the reaction was quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and chromatographed over a silica gel column (1 × 8 cm), eluting with 50-mL portions of hexanes and 5%, 10%, 15%, 20%, 25%, 30%, and 35% EtOAc/hexanes; 8-mL fractions were collected. The product-containing fractions (39–53) were concentrated to yield 0.014 g (85%) of **47** as a white foam: $[\alpha]_D$ +72.0° (*c* 0.68, $CHCl_3$); R_f 0.50 (75% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.15 (dd, J = 15.1, 10.0 Hz, 1 H), 6.34 (d, J = 15.1 Hz, 1 H), 6.09 (m, 2 H), 5.22 (m, 1 H), 5.19 (dd, J = 5.8, 3.5 Hz, 1 H), 4.24 (dd, J = 9.2, 3.4 Hz, 1 H), 4.00 (s, 1 H), 3.64 (dd, J = 11.0, 1.5 Hz, 1 H), 3.55 (s, 3 H), 3.35 (s, 3 H), 3.04 (d, J = 9.2 Hz, 1 H), 2.85 (dd, J = 16.2, 11.0 Hz, 1 H), 2.53 (dt, J = 13.0, 3.0 Hz, 1 H), 2.44 (ddq, J = 13.8, 6.6, 2.6 Hz, 1 H), 2.16 (dd, J = 16.2, 1.8 Hz, 1 H), 2.00 (dd, J = 12.5, 5.7 Hz, 1 H), 1.89 (m, 2 H), 1.57 (m, 3 H), 1.32 (d, J = 6.3 Hz, 3 H), 1.20 (d, J = 7.0 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 203.1, 174.0, 141.9, 140.0, 131.9, 124.1, 103.9, 81.1, 80.4, 68.8, 67.7, 60.2, 55.2, 45.8, 41.9, 38.9, 38.2, 37.4, 33.7, 20.3, 17.6; IR (neat) cm^{-1} 3460, 2982, 2959, 2908, 1695, 1680, 1595, 1203, 1091; mass spectrum (CI, methane) m/z (rel intensity) 397 (28), 383 (23), 365 (23), 257 (17), 97 (100), 71 (28). Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.62; H, 8.14. Found: C, 63.72; H, 8.17.

Preparation of Carbonolide B Methoxy Acetal (48). To a stirring solution of **47** (0.012 g, 0.033 mmol) in CH_2Cl_2 (2 mL) were added triethylamine (0.047 mL, 0.330 mmol), DMAP (0.002 g, 0.015 mmol), and acetic anhydride (0.010 mL, 0.107 mmol). The reaction mixture was stirred for 6 h, and the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was poured into a separatory funnel containing CH_2Cl_2 (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and chromatographed through a silica gel column (1 × 5 cm), eluting with 50-mL portions of hexanes and 5%, 10%, 20%, 30%, and 40% EtOAc/hexanes; 7-mL fractions were collected. The product-containing fractions (32–44) were concentrated to yield 0.013 g (93%) of **48** as a colorless oil: $[\alpha]_D$ +80.9° (*c* 0.32, $CHCl_3$); R_f 0.42 (50% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.28 (dd, J = 15.3, 10.0 Hz, 1 H), 6.32 (d, J = 15.3 Hz, 1 H), 6.06 (ddd, J = 15.8, 10.5, 4.8 Hz, 1 H), 4.98–5.06 (m, 3 H), 3.87 (dd, J = 9.5, 3.7 Hz, 1 H), 3.58 (s, 3 H), 3.36 (s, 3 H), 3.19 (dd, J = 9.4, 1.4 Hz, 1 H), 2.96 (dd, J = 14.8, 11.5 Hz, 1 H), 2.53 (m, 1 H), 2.51 (dt, J = 13.5, 3.6 Hz, 1 H), 2.20 (dd, J = 14.9, 1.8 Hz, 1 H), 2.09 (dd, J = 12.7, 5.6 Hz, 1 H), 2.08 (s, 3 H), 2.10–1.90 (m, 1 H), 1.90–1.83 (m, 2 H), 1.63–1.55 (m, 2 H), 1.28 (d, J = 6.3 Hz, 3 H), 1.21 (d, J = 6.9 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 203.6, 170.2, 169.9, 142.9, 139.5, 132.3, 124.3, 103.9, 80.8, 80.1, 68.8, 68.2, 60.8, 55.4, 45.1, 41.1, 38.9, 38.5, 36.0, 33.8, 21.1, 20.4, 17.1; IR (neat) cm^{-1} 2933, 1739, 1683, 1693, 1599, 1448, 1373, 1340, 1307, 1236, 1178, 1149, 1099, 1070, 1053, 1022, 997, 966, 906, 734; mass spectrum (EI, 70 eV) m/z (rel intensity) 438 (7), 424 (24), 406 (12), 176 (28), 175 (37), 139 (36), 137 (45), 127 (51), 97 (100), 81 (34), 43 (58); exact mass calcd for $C_{23}H_{34}O_8$ 438.22235, found 438.22535.

Preparation of Carbonolide B Hemiacetal (2). To a stirring solution of **48** (0.006g, 0.013 mmol) in H_2O (0.1 mL) was added trifluroacetic acid (0.4 mL) at 0 °C. The resulting solution was stirred for 5 h at 0 °C, and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was poured into a separatory funnel containing CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted two times with CH_2Cl_2 (10 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and chromatographed over a silica gel column (1 × 3 cm), eluting with 10-mL portions of hexanes and 10%, 20%, 30%, and 40% EtOAc/hexanes. The product-containing fractions were concentrated to yield 0.005 g (86%) of **2** as an amorphous solid (2.5:1 mixture of isomers): $[\alpha]_D$ +37.6° (*c* 0.081, $CHCl_3$); R_f 0.20 (50% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 7.28 (dd, J = 15.4, 10.2 Hz, 1 H), 6.32 (d, J = 15.3 Hz, 1 H), 6.21–6.02 (m, 2 H), 5.56 (t, J = 4.6 Hz, 1 H). 5.15-4.97 (m, 2 H), 4.02 (dd, J = 9.5, 3.7 Hz, 1 H), 3.55 (s, 3 H), 3.16 (dd, J = 9.7, 1.4 Hz, 1 H), 2.95 (dd, J = 14.7, 11.5 Hz, 1 H), 2.62–2.47 (m, 2 H), 2.31 (dd, J = 15.6, 3.4 Hz, 1 H), 2.22 (dd, J = 14.7, 1.9 Hz, 1 H), 2.15–2.09 (m, 1 H), 2.07 (s, 3 H), 2.01–1.94 (m, 1 H), 1.90–1.71 (m, 2 H), 1.66–1.55 (m, 2 H), 1.28 (d, J = 6.3 Hz, 3 H), 1.21 (d, J = 6.9 Hz, 3 H); 75-MHz ^{13}C NMR ($CDCl_3$) δ 203.5, 170.2, 169.8, 142.9, 139.9, 132.3, 124.3, 97.5, 81.5, 80.2, 68.8, 68.2, 61.1, 45.1, 41.1, 40.1, 38.9, 36.0, 33.7, 21.1, 20.4, 17.2; IR (neat) cm^{-1} 3460, 3433, 2966, 2935, 1736, 1682, 1637, 1597, 1450, 1373, 1305, 1236, 1180, 1118, 1051, 999; mass spectrum (EI, 70eV) m/z (rel intensity) 424 (7), 406 (2), 345 (3), 279 (65), 167 (48), 149 (100), 97 (27), 84 (26), 57 (26), 43 (37); exact mass calcd for $C_{22}H_{32}O_8$ 424.2118, found 424.2097.

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Supplementary Material Available: Experimental procedures for all intermediates shown in eq 1 and Schemes 3 and 8 and ^1H and/or ^{13}C NMR spectra for compounds lacking combustion analysis (**2**, **4**, **41**, **46**, and **48**) (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.