Total Synthesis of the Macrolide Antibiotic Rutamycin B

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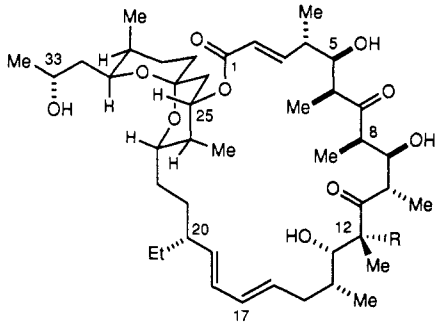
Received July 26, 1993®

Abstract: A convergent asymmetric synthesis of the macrolide antibiotic rutamycin B has been achieved through the synthesis and coupling of its spiroketal and polypropionate subunits. Both fragments were constructed utilizing auxiliary-based asymmetric aldol and alkylation reactions to control the absolute stereochemical relationships. The polypropionate fragment was assembled from its C_1–C_8 and C_9–C_{17} subunits, which were joined through a diastereoselective, mismatched, double-stereodifferentiating aldol reaction. Union of the spiroketal and polypropionate subunits was accomplished through a Suzuki coupling, providing direct access to the rutamycin seco acid, which was cyclized in high yield to the protected macrolide.

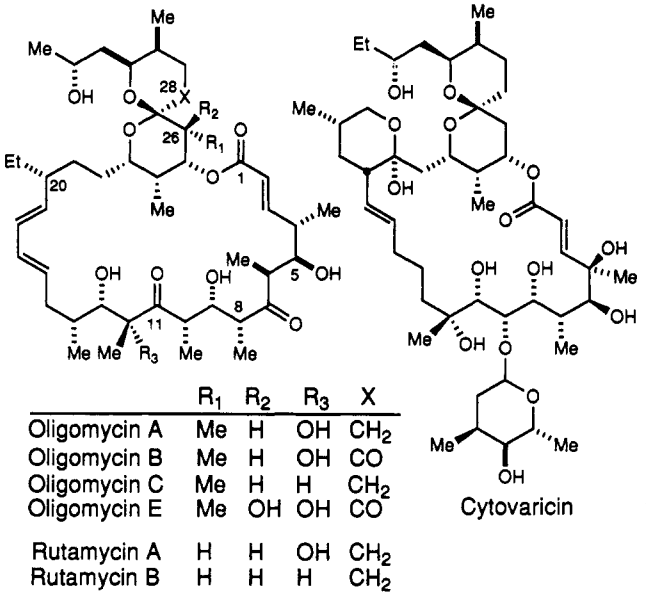
The molecular architecture associated with the macrolide antibiotics[1] has posed some of the greatest challenges for chemical synthesis, and this family of natural products has provided the stimulus for the development of a broad selection of highly stereoselective bond constructions.[2] In this study we describe the first synthesis of rutamycin B, a representative of the oligomycin/rutamycin family of macrolides.[3]

Rutamycin A (**1a**) was isolated by Thompson and co-workers in 1961 from cultures of *Streptomyces griseus*.[4] Its structure and relative stereochemistry were elucidated by X-ray diffraction.[5]



1a, R = OH: Rutamycin A
1b, R = H: Rutamycin B

The discovery of this natural product was followed by the isolation of a close structural analogue, rutamycin B (**1b**), from *Streptomyces aureofaciens* by Keller-Schierlein,[6] who assigned its relative stereostructure by NMR spectroscopy. The absolute stereochemical assignment of the rutamycins has recently been determined in this laboratory by comparing the spiroketal fragment obtained from degradation of the rutamycins with the identical fragment prepared through asymmetric synthesis.[7] This stereochemical assignment is in agreement with the absolute stereochemistry of cytovaricin, whose synthesis has also been accomplished in this laboratory.[8]



	R_1	R_2	R_3	X
Oligomycin A	Me	H	OH	CH_2
Oligomycin B	Me	H	OH	CO
Oligomycin C	Me	H	H	CH_2
Oligomycin E	Me	OH	OH	CO
Rutamycin A	H	H	OH	CH_2
Rutamycin B	H	H	H	CH_2

Cytovaricin

Figure 1. Structures of the oligomycins and cytovaricin.

The rutamycins are members of the oligomycin family of macrolide antibiotics[9] sharing a common 1,7-dioxaspiro[5.5]-undecanyl ring system which is integrated into a 26-membered macrolactone ring biosynthesized largely from propionate units (Figure 1). The individual members of this family represent variations in the degree of oxidation at C_{28} and the substitution pattern at C_{26}. This family of structures also shares important structural similarities with cytovaricin and the closely related macrolides phthoramycin[10] and kaimonolide.[11]

Like cytovaricin, the rutamycins are cytotoxic in nature, preventing oxidative phosphorylation in mitochondria by inhibiting H^+–ATPase.[12] This may be explained in part by similarities in their natural conformation. The superposition of the the atoms in the 26-membered lactone ring and integrated spiroketal of

* Abstract published in *Advance ACS Abstracts,* November 1, 1993.

(1) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.

(2) (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (b) Boeckman, R. K.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 1–139.

(3) For a preliminary account of aspects of this study, see: Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229–2232.

(4) Thompson, R. Q.; Hoehn, M. M.; Higgins, C. E. *Antimicrob. Agents Chemother.* **1961**, 474–480.

(5) Arnoux, B.; Garcia-Alvarez, M. C.; Marazano, C.; Bhupesh, C. D.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1978**, 318–319.

(6) Wuthier, v. D.; Keller-Schierlein, W. *Helv. Chim. Acta* **1984**, *67*, 1208–1216.

(7) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260–6268.

(8) Evans, D. A.; Kaldor, S. W.; Jones, T. K. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

(9) For leading references, see: (a) ref 1, pp 520–521. (b) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Shiobara, Y.; Nishimoto, N. *J. Antibiot.* **1987**, *40*, 1053–1057.

(10) Nakagawa, A.; Miura, S.; Imai, H.; Imamura, N.; Omura, S. *J. Antibiot.* **1989**, *42*, 1324–1327.

(11) Hirota, A.; Okada, H.; Kanza, T.; Nakayama, M.; Hirota, H.; Osagai, A. *Agric. Biol. Chem.* **1989**, *53*, 2831–2833.

(12) Pedersen, P. L.; Carafoli, E. *TIBS* **1987**, *12*, 146–150.

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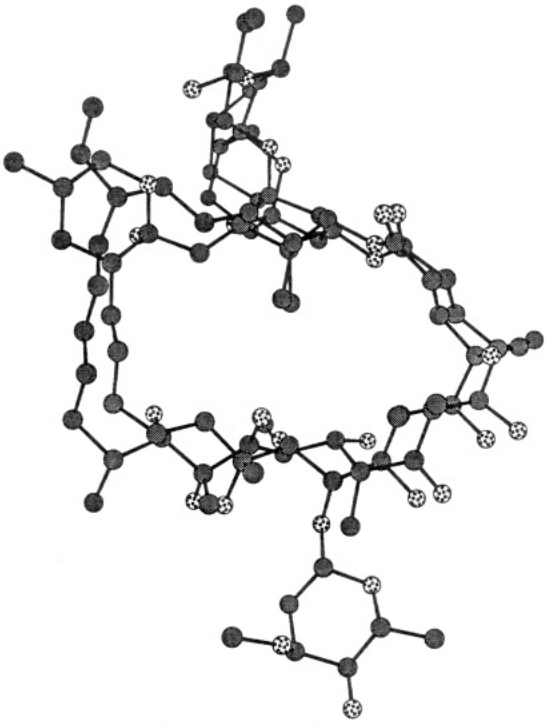
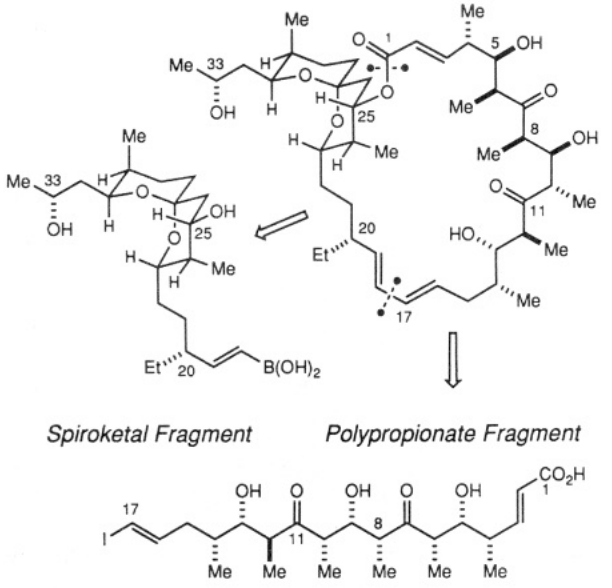


Figure 2. Superposition of rutamycin A and cytovaricin X-ray structures.

Scheme I



rutamycin onto the 22-membered cytovaricin macrocycle reveals a striking three-dimensional homology for the two structures (Figure 2).

As a continuation of our efforts directed toward the development of methodology relevant to the syntheses of macrolide and polyether antibiotics, we have addressed the synthesis of rutamycin B. The following discussion describes the first total synthesis of this natural product.

Principal Fragments

The rutamycin skeleton was partitioned into the illustrated spiroketal and polypropionate fragments of comparable complexity through disconnection of the C_{17}–C_{18} and the acyl oxygen bonds (Scheme I). In the synthetic direction, each of these analogous bond constructions is based on reactions which are known to function reliably with complex substrates. For example, the synthesis of dienes through the Pd(0)-catalyzed coupling of vinyl iodides and either vinylstannanes (Stille)[13] or vinyl boronates (Suzuki)[14] is documented to work well with highly functionalized coupling partners. Finally, with the highly evolved methods for macrolactonization which are currently available,[15] this process has become a more reliable, although system-dependent, transformation. In the following discussion, the syntheses and assemblage of the illustrated spiroketal and propionate fragments are described.

Synthesis of the Spiroketal Fragment

The synthesis of the rutamycin spiroketal fragment, although paralleling the plan used for the construction of the related cytovaricin moiety,[8] included a number of simplifying steps (Scheme II). Since this aspect of the synthesis has appeared in print,[7] the highlights of the successful route are summarized.

The illustrated synthesis of spiroketal **2** involves no more than 10 linear steps and proceeds in an overall yield of 25%. With the exception of the C_{33} and C_{27} stereocenters, all stereochemical relationships are controlled through the use of the illustrated *(S)*- and *(R)*-phenylalanine-derived imide chiral auxiliaries[16] in their derived aldol[17] and alkylation[18] reactions. As in the synthesis of cytovaricin, triethylsilyl (TES) protection of the C_{23} hydroxyl group ensured that epimerization of the C_{24} methyl group did not occur during the deprotection/spiroketalization cascade. Finally, one of the major improvements in the efficiency of the synthesis plan hinged on the consecutive alkylation and acylation of acetone dimethylhydrazone to assemble the carbon skeleton in good overall yield.

Based on the success of the Suzuki coupling in the Kishi palytoxin synthesis,[19] we elected to utilize this process for the union of the spiroketal and polypropionate subunits. Accordingly, spiroketal **2** was elaborated with a TES C_{25} alcohol protecting group (Scheme III), with the expectation that selective desilylation of this functional group could be achieved in the staging of the macrolactonization. Subsequent deprotection of the C_{19} *p*-methoxybenzyl (PMB) protecting group and Swern oxidation[20] of the derived primary alcohol afforded aldehyde **3** (95% over three steps), which was homologated to the vinylboronic acid **4** with lithiated bis(1,3,2-dioxaborin-2-yl)methane according to the Matteson procedure.[21] Although the yields for the Matteson homologation appear to be high, during execution of the synthesis,, vinylboronic acid **4** was carried directly into the Suzuki coupling step without purification. The acceptable combined yield (77%) for this two-step sequence (*vide infra*) attests to the viability of both bond constructions.

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(14) For leading references, see: (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980.

(15) For references on macrolactonization in macrolide synthesis, see ref 2.

(16) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83–91.

(17) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

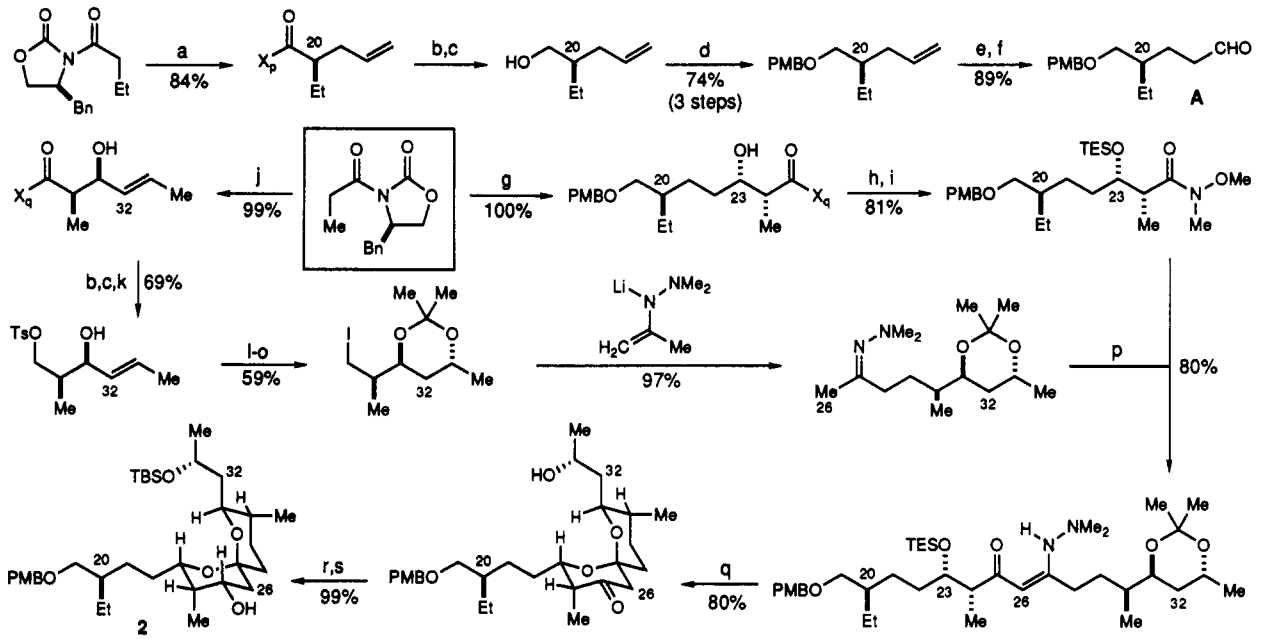
(18) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(19) (a) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorther, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530. (b) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorther, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7530–7533.

(20) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

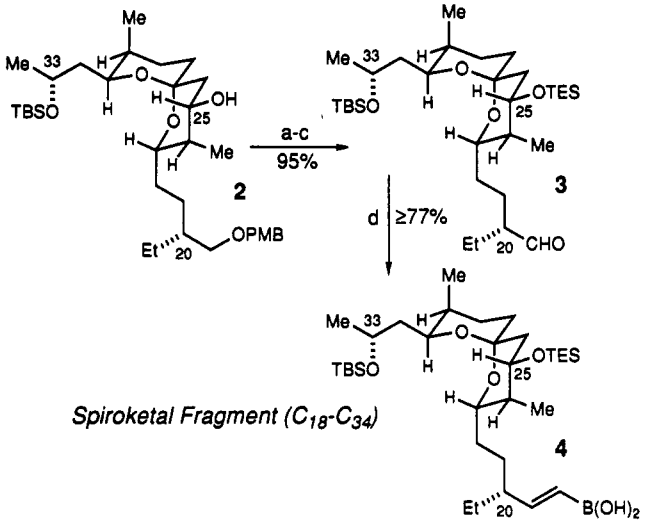
(21) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20–28.

Scheme II[a]



[a] (a) NaNTMS2, allyl iodide, THF, −78 °C. (b) LiOOH, THF–H_2O, 0 °C. (c) $LiAlH_4$, Et_2O, 0 °C. (d) PMB–Br, NaH, THF–DMF, 0 °C. (e) 9-BBN, THF, 23 °C; NaOOH. (f) Swern oxidation. (g) *n*-Bu_2BOTf, Et_3N, A, CH_2Cl_2, −78 °C. (h) $AlMe_3$, MeONHMe–HCl, THF, 0 °C. (i) TES–Cl, imidazole, DMF, 23 °C. (j) *n*-Bu_2BOTf, Et_3N, crotonaldehyde, CH_2Cl_2, −78 → 0 °C. (k) TsCl, Et_3N, DMAP, CH_2Cl_2, 23 °C. (l) I_2, THF–H_2O, KH_2PO_4, THF, 5 → 10 °C. (m) *n*-Bu_3SnH, AIBN, benzene, reflux. (n) $Me_2C(OMe)_2$, TsOH, 23 °C. (o) NaI, acetone, 23 °C. (p) LDA, THF, −78 °C. (q) HF, MeCN–H_2O, 23 °C. (r) TBSCl, Et_3N, CH_2Cl_2, 23 °C. (s) SmI_2, Me_2CHOH, THF, 23 °C.

Scheme III[a]



[a] (a) TESOTf, lutidine, CH_2Cl_2, 0 °C. (b) DDQ, CH_2Cl_2, 5 °C. (c) Swern oxidation. (d) $LiCH[B(-OCH_2CH_2CH_2O-)_2]_2$, H_3O^+.

Synthesis of the Polypropionate Fragment

Aldol Disconnection. The presence of carbonyl groups at C_7 and C_{11}, along with the associated hydroxyl functions at C_5, C_9, and C_{13} in the propionate fragment, provides the retrons for four possible aldol disconnections (Scheme I). The two "interior" aldol bond constructions that afford the highest level of convergency with regard to fragment complexity are illustrated in Scheme IV. By inspection, each of these projected reactions is a *syn* aldol construction, and each reaction is double-stereodifferentiating[22] in nature. Of the two options, the stereochemical outcome of the projected C_9–C_{10} aldol reaction is unprecedented in the literature (eq 1). On the other hand, precedent for the C_8–C_9 *syn* aldol variant (eq 2) with achiral aldehydes has been established in this laboratory for titanium enolates (eq 3)[23] and by Paterson for boron enolates.[24] Based on this precedent, the C_8–C_9 aldol bond construction was adopted for the synthesis plan. The major uncertainty associated with the successful execution of this reaction concerns the influence that the chiral aldehyde might have on the stereochemical outcome of this double-stereodifferentiating process. Numerous examples document the fact that *(Z)*-enolates belong to a special class of nucleophiles that exhibit selectivity for the *anti* Felkin aldehyde diastereoface,[25] a π-facial bias which is incompatible with the desired stereochemical outcome of the projected aldol process. As a consequence, the chiral elements in the aldehyde and enolate fragments are stereochemically "mismatched" in the desired bond construction (eq 2). In spite of this stereochemical uncertainty, we felt that the C_9–C_{17} aldehyde might be manipulated at the C_{11} hydroxyl center, in both configuration and selection of protecting groups, so as to engineer the desired stereochemical outcome.

The complete retrosynthesis of the polypropionate fragment is illustrated in Scheme V. This plan relies on the utilization of the illustrated β-ketoimide **7**[26] for seven of the 10 stereogenic centers which will be constructed by both aldol- and acylation-based bond constructions. The reduction of this plan to practice is described in the following discussion.

C_9–C_{17} Subunit. Synthesis of the C_9–C_{17} subunit began with Swern oxidation of the *(R)*-alcohol **5** previously prepared in conjunction with our synthesis of ionomycin.[27] The resulting aldehyde **6** was treated with the *(E)*-boron enolate[28] derived from the β-ketoimide **7** to provide the desired *anti* aldol adduct **8** in

(22) For a leading reference to double diastereodifferentiating reactions, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.

(23) Evans, D. A.; Rieger D. L; Bilodeau M. T; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049.

(24) The analogous *syn* aldol face selectivity has also been observed for boron enolates: Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229–1232.

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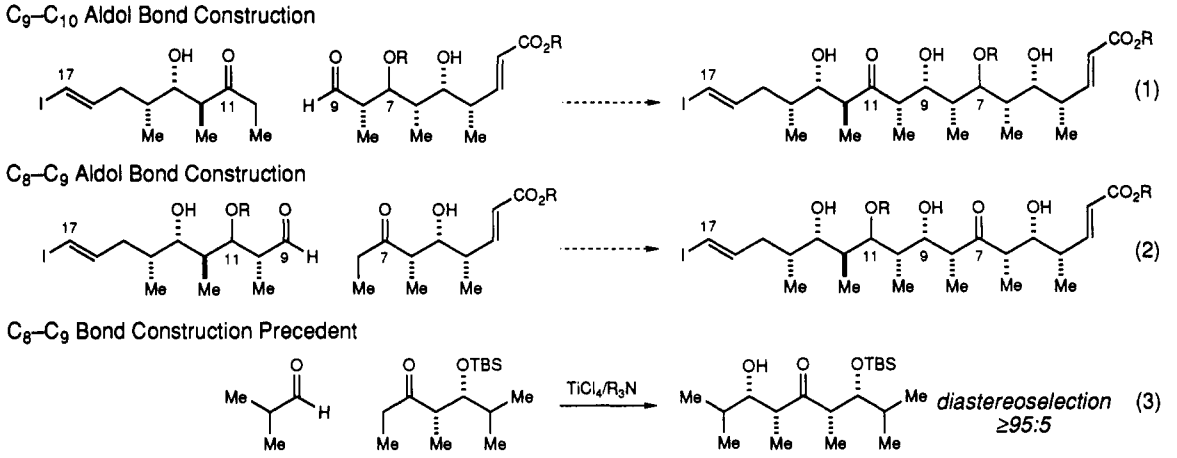
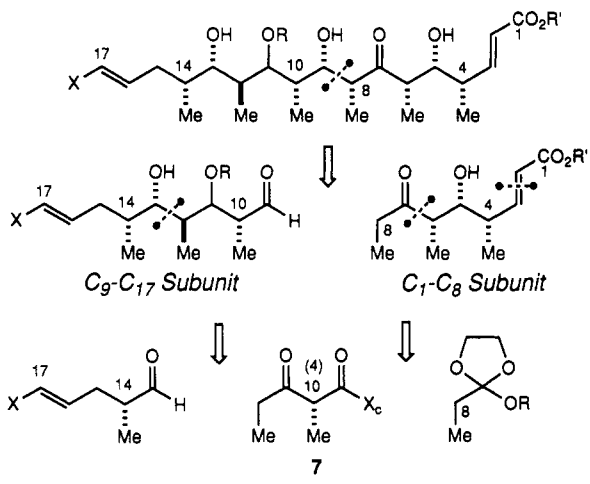
(26) For a leading reference to β-ketoimides, see: Evans, D. A., Clark, J. S.; Metternich, R.; Novak, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868 and references cited therein.

(27) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.

Scheme IV



Scheme V



excellent yield (84%) and diastereoselectivity (97:3)[29] (Scheme VI). Although the stereochemical outcome of these aldol addition reactions had previously been established for achiral aldehydes, confirmation of the stereochemical outcome of this reaction was undertaken. Consistent with established precedent,[30] chelate-controlled reduction of ketone **8** with zinc borohydride[31] afforded the *syn* diol **9** in 56% yield with 4:1 diastereoselection. Subsequent ketalization afforded acetonide **10**. Analysis of the vicinal coupling constants in the ^{1}H NMR spectrum of **10** confirmed that the aldol reaction had indeed established the *anti* relationship between C_{12} and C_{13} and that the reduction had generated the *syn* 1,3-diol relationship between C_{11} and C_{13}.

Since the C_{11} hydroxyl-bearing stereocenter was viewed as a potential variable in the C_8–C_9 bond construction (Scheme IV, eq 2), the reduction of **8** to the corresponding *anti* diol **11** was also undertaken. This reaction was carried out with complete selectivity using sodium triacetoxyborohydride ($NaBH(OAc)_3$),[32] and the derived acetonide **12** was analyzed by ^{13}C NMR spectroscopy to establish that the reduction had proceeded as expected.[33]

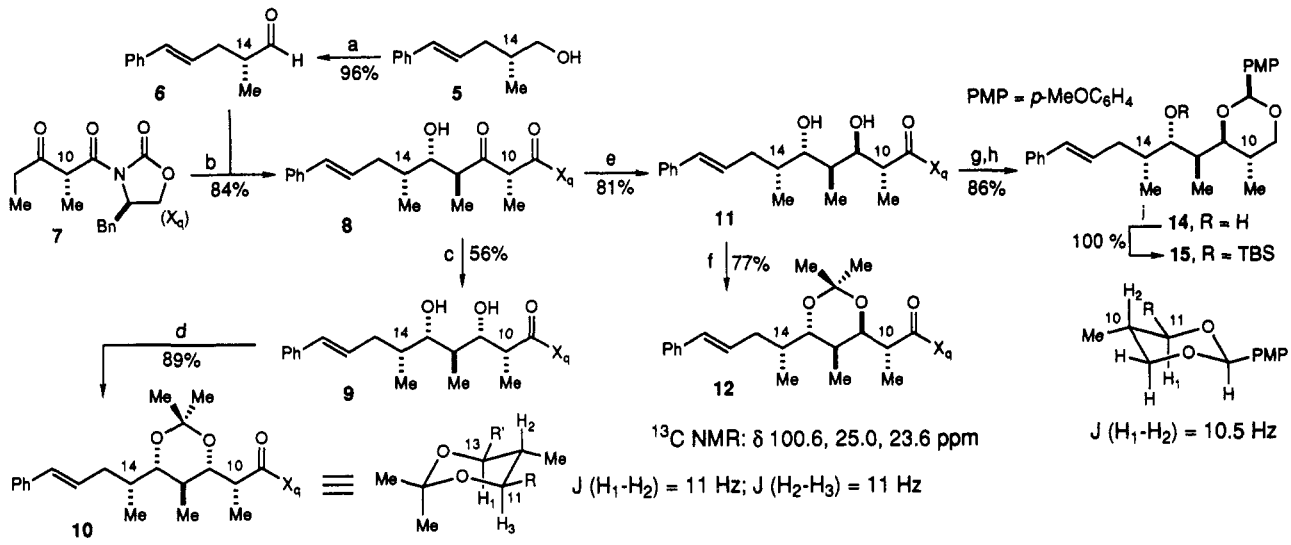
The absolute stereochemical relationships associated with the C_{11}–C_{13} stereotriad were determined by correlation with the C_{10} stereocenter, the configuration of which was secure. Sequential reduction of **11** to the corresponding triol **13** by the procedure of Penning ($LiBH_4$, MeOH, THF, 94%)[34] and regioselective protection with *p*-anisaldehyde dimethyl acetal afforded the *p*-methoxybenzylidene acetal **14** in 91% yield.[35] Following silylation, analysis of the vicinal coupling constants in the ^{1}H NMR spectrum of **15** confirmed the relative stereochemical relationship between C_{10} and C_{11}. This sequence of experiments established that the critical aldol reaction (**7** → **8**) had proceeded in the expected fashion and that both the *syn* and *anti* diol intermediates **9** and **11**, respectively, could be constructed in a stereoselective fashion.

At this juncture, the impact of the C_{11} stereocenter on the critical C_8–C_9 bond construction had yet to be evaluated. The decision to carry the *anti* diol **11** (rather than the *syn* diastereomer **9**) forward in the synthesis was based on the greater selectivity associated with the *anti* reduction process to give **11**. Accordingly, acetal **15** was transformed to the fully functionalized C_9–C_{17} subunit by regioselective acetal cleavage with diisobutylaluminum hydride (DIBAL-H)[36] to give alcohol **16** in quantitative yield (Scheme VII). The cinnamyl moiety was transformed to the corresponding vinyl iodide by oxidation of the olefin (OsO_4, *N*-methylmorpholine *N*-oxide)[37] followed by diol cleavage ($NaIO_4$, buffered with $NaHCO_3$). The resultant aldehyde was homologated to the desired vinyl iodide **17** by employing a modification of Takai's chromous chloride procedure ($CrCl_2/CHI_3$)[38] to give a 14:1 (*E*/*Z*) mixture of olefins, separable by preparative HPLC (79% yield over two steps). In independent studies conducted in this laboratory, it has been observed that a significant solvent effect exists in this reaction and that the (*E*/*Z*) olefin selectivity can be altered by manipulating this reaction parameter.[39] High yields and modest selectivities (*ca.* 4:1) were obtained when THF was employed as the solvent as prescribed by Takai. Optimum yields and improved selectivities (14:1) for the present reaction were obtained by using 6:1 dioxane/THF. Finally, Swern oxidation afforded the target aldehyde **18** in an overall yield of 33% over nine steps from β-ketoimide **7**.

C_1–C_8 Subunit. Synthesis of the C_1–C_8 subunit was initiated by acylation[40] of the titanium enolate derived from β-ketoimide

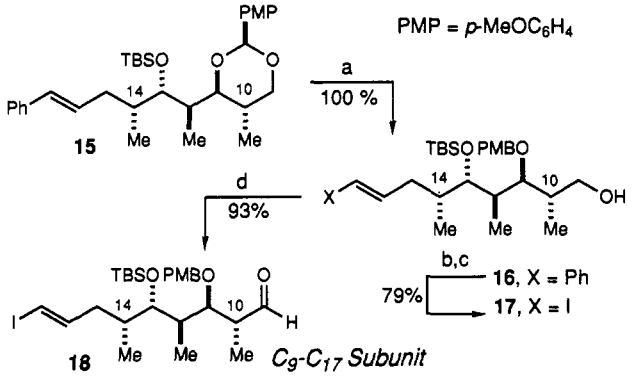
(28) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.
(29) The unusually high facial preference of this particular *anti* aldol coupling is the result of the Cram preference of chiral aldehyde **6**, *i.e.*, this is a "matched" diastereodifferentiating reaction.
(30) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.
(31) Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5385–5386.
(32) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
(33) (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.
(34) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307–312.
(35) The other possible acetals formed from derivatization of the C_{11} and C_{13} alcohols were also observed but in no more than 5% yield.
(36) For other examples of the regioselective reductive cleavage of benzylidine acetals, see: Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593–1596.
(37) VanRheenen, V.; Kelley, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973-1976.
(38) Takai, K.; Nitta, K.; Ulimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
(39) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260–2262.

Scheme VI[a]



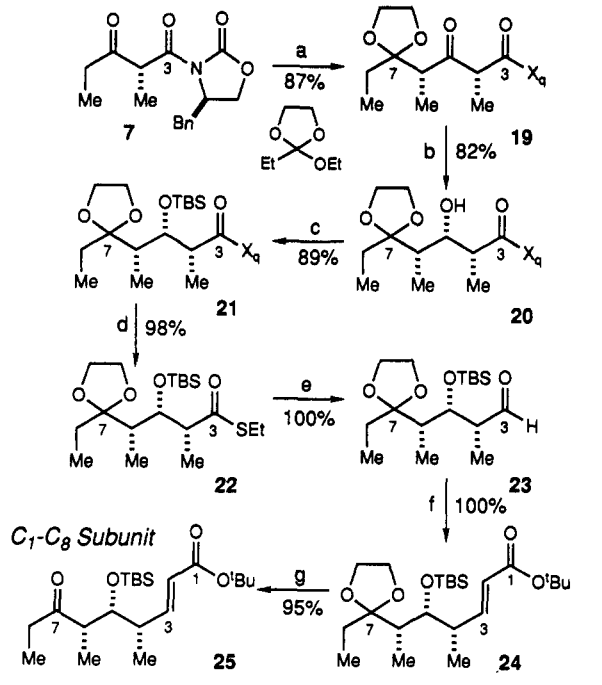
[a] (a) Swern oxidation. (b) $(c\text{-hex})_2BCl$, EtNMe2, Et_2O, 0 °C. (c) $Zn(BH_4)_2$, CH_2Cl_2, −78 °C. (d) $Me_2C(OMe)_2$, CSA, 23 °C. (e) $NaBH(OAc)_3$, AcOH, 23 °C. (f) $Me_2C(OMe)2$, CSA, 23 °C. (g) $LiBH_4$, MeOH, THF, 0 °C. (h) $ArCH(OMe)_2$, CSA, DMF, 23 °C. (i) TBSOTf, lutidine, CH_2Cl_2, 0 °C.

Scheme VII[a]



[a] (a) DIBAL-H, CH_2Cl_2, 0 °C. (b) (i) OsO_4, NMO, t-BuOH/THF/H_2O, 23 °C. (ii) $NaIO_4$, $NaHCO_3$, 23 °C. (c) $CrCl_2$, CHI_3, dioxane/THF, 23 °C. (d) Swern oxidation.

Scheme VIII[a]



[a] (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C. (b) $Zn(BH_4)_2$, CH_2Cl_2, −20 °C. (c) TBSOTf, lutidine, CH_2Cl_2, 0 °C. (d) EtSLi, THF, −78 °C → 0 °C. (e) Et_3SiH, Pd/C, acetone, 23 °C. (f) $(EtO)_2P(O)CH_2CO_2$-*t*-Bu, *n*-BuLi, THF, 23 °C. (g) $FeCl_3$·SiO_2, acetone, 23 °C.

7 with the illustrated propionate-derived ortho ester[41] to give ketal **19** in good yield (87%) and diastereoselectivity (93:7) (Scheme VIII). The facial bias exhibited in this reaction is that anticipated from electrophilic attack from the more accessible face of the chelated (*Z*)-titanium enolate. The final stereocenter in this fragment was introduced through the selective chelate-controlled reduction of ketone **19** with zinc borohydride (>97:3) to afford alcohol **20**, which was protected (TBSOTf/lutidine) to afford imide **21**.

In anticipation of elaborating **21** to the C_1–C_8 synthon, the terminal imide moiety was reduced to the corresponding alcohol, albeit in low yield. However, this problem was circumvented by transesterification of the imide to the thioester **22** (EtSH/*n*-BuLi) according to the excellent procedure reported by Damon.[42] Reduction of this ester according to the Fukuyama procedure (Et_3SiH/Pd(C), acetone)[43] afforded aldehyde **23** in excellent yield (98% over two steps). It is noteworthy that this reaction sequence has proven to be attractive for other challenging imide → aldehyde transformations which we have recently encountered.[39] The completion of this subunit was achieved by Horner–Emmons olefination[44] to **24** (>95:5 *E*:*Z*) followed by deketalization ($FeCl_3$·SiO_2, acetone)[45] to provide ketone **25** in 59% overall yield from β-ketoimide **7**.

Assemblage of Subunits

The critical C_8–C_9 bond construction was achieved through reaction of aldehyde **18** with the titanium enolate[23] derived from ketone **25**, providing the *syn* adduct **26** in high yield (83%) and diastereoselectivity (97:3) (Scheme IX). *Although the factors*

(40) For an analogous acylation, see: Evans, D. A.; Urpí, F; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. The analogy for the **7** → **10** transformation was provided by Dr. Brett Huff from this laboratory.

(41) Soulier, J.; Farines, M.; Authier, R.-M.; Fournier, M. *J. Heterocyc. Chem.* **1976**, *13*, 1125–1128.

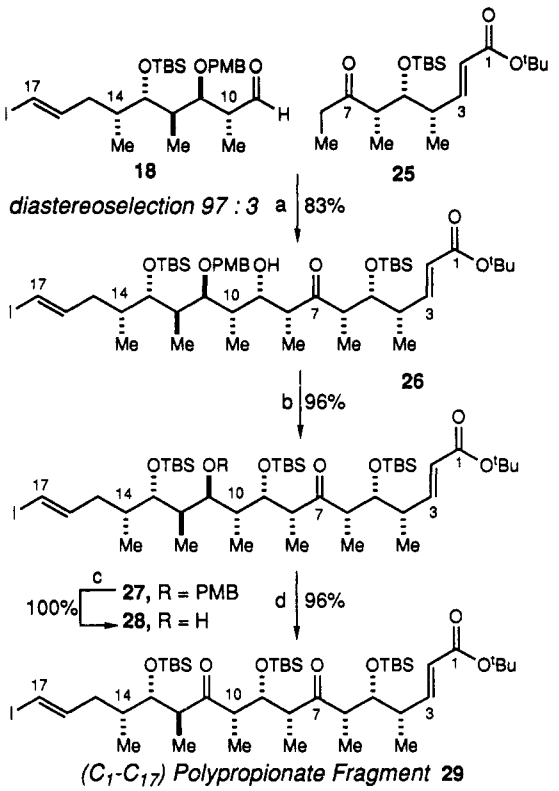
(42) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849–2852.

(43) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.

(44) For a lead reference, see: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386–3388.

(45) Kim. K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404–407.

Scheme IX[a]



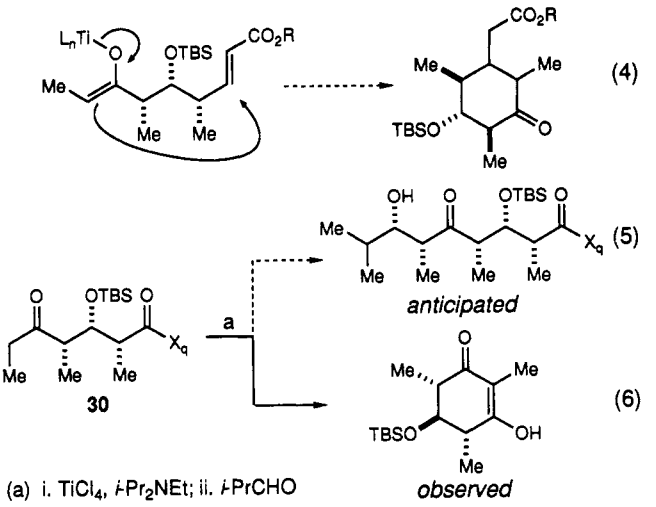
(C$_1$-C$_{17}$) Polypropionate Fragment **29**

[a] (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C. (b) TBSOTf, lutidine, CH_2Cl_2, −30 °C. (c) DDQ, CH_2Cl_2, 5 °C. (d) Dess–Martin periodinane, pyridine, CH_2Cl_2, 23 °C.

controlling this exceptionally diastereoselective reaction have not yet been unambiguously determined, the illustrated C_{11} hydroxyl configuration and protecting group are both critical to the stereochemical outcome (vide infra).[46]

Silylation of alcohol **26** under carefully defined conditions (TBSOTf, lutidine, −30 °C, 24 h) afforded ester **27**. A complicating aspect of this transformation was the competitive Lewis acid-catalyzed cleavage of the *tert*-butyl ester, a side reaction which can be avoided with careful temperature control. Oxidative removal of the *p*-methoxybenzyl (PMB) protective group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded alcohol **28**, which was immediately transformed to the completed polypropionate fragment **29** through Dess–Martin oxidation[47] (76% yield over four steps).

It was surprising to observe the propensity of ketone **25** to undergo *intermolecular* aldol addition rather than *intramolecular* Michael addition (eq 4), in view of the fact that such reactions are well documented with these titanium enolates.[48] In an earlier rendition of the synthesis, other observations which reinforced this concern were associated with the attempted aldol addition of imide **30** (eq 5). In attempting to execute this reaction, we observed competing intramolecular acylation (eq 6), which proceeded to the exclusion of the desired process. We therefore explored the aldol reactions of ketone **25** with some apprehension and were pleasantly surprised when these reactions performed so superbly.



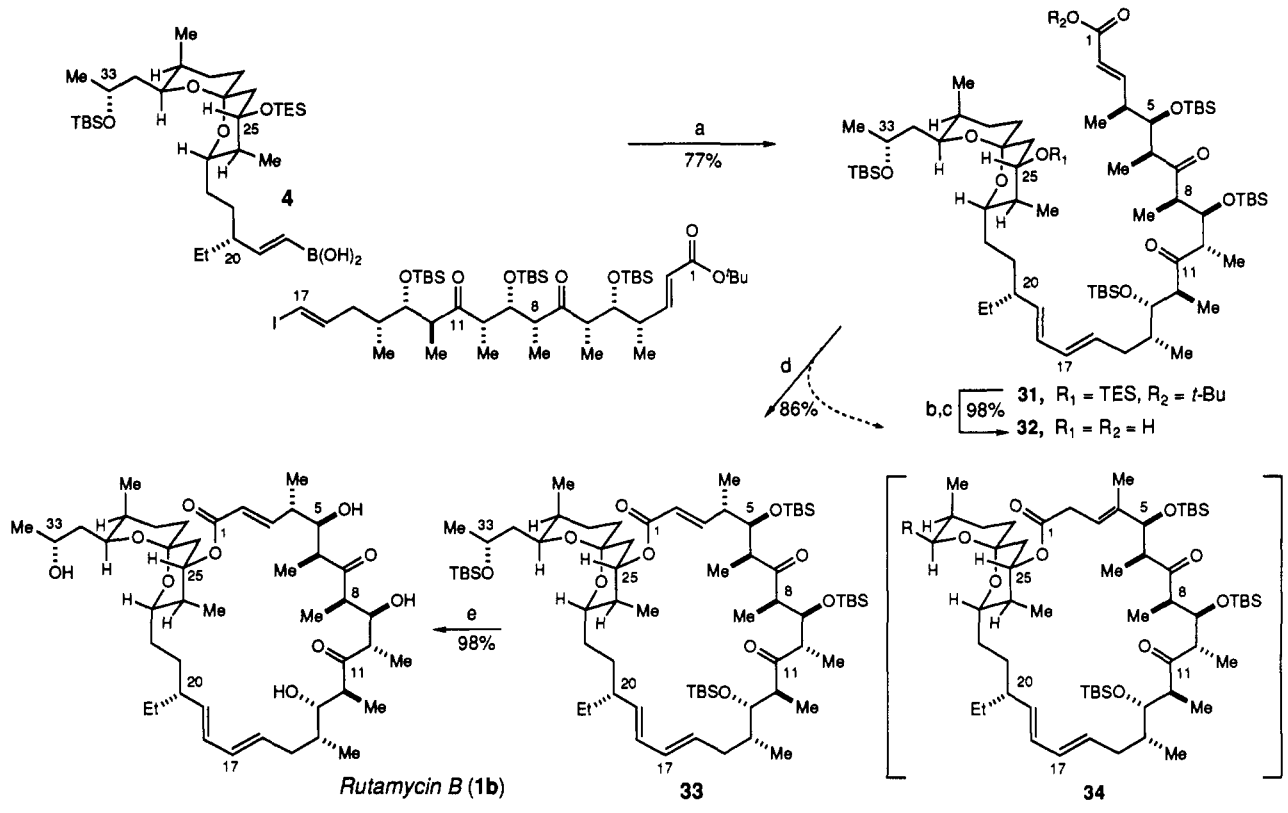
Fragment Coupling and Deprotection

According to our synthesis plan, the spiroketal and polypropionate fragments were now joined by employing Kishi's modification[49] of the Suzuki coupling[14] (aqueous solution of thallium hydroxide/$Pd(PPh_3)_4$[50] in degassed THF) to give diene **31** in 77% yield (Scheme X). At this juncture, deprotection of the C_{25} alcohol and *tert*-butyl ester moieties was required for macrolactonization. Unfortunately, the C_{33} *tert*-butyldimethylsilyl (TBS) protecting group was found to be more labile than anticipated.[51] In initial deprotection experiments designed to set up macrocyclization, the *tert*-butyl ester and C_{25} TES-protected alcohol protecting group could not be deprotected without concomitant loss of the C_{33} TBS ether. In addressing this problem, we elected to exploit the observed side reaction (cleavage of the *tert*-butyl ester) noted in the silylation of alcohol **26**. Thus, we found the optimum conditions for deprotection to be initial treatment of **31** with trimethylsilyl triflate (TMSOTf)/lutidine at 0 °C to remove the *tert*-butyl group from the ester, followed by treatment with pyridinium hydrofluoride (buffered with excess pyridine) to selectively remove the C_{25} triethylsilyl (TES) group to afford the desired hydroxy acid **32** in 98% yield.

Macrolactonization of seco acid **32** proved to be exceptionally challenging. The Keck macrolactonization procedure (DCC, DMAP, and DMAP·HCl in refluxing chloroform)[52] that performed so well in our cytovaricin synthesis[8] afforded a 2:1 mixture of lactones, of which the major product was the *deconjugated* lactone **34**. In an effort to avoid this side reaction, macrolactonization procedures described by Mukaiyama,[53] Corey,[54] and Yamaguchi[55] were evaluated with similar results. In all instances, **34** was formed in significant amounts. Of these methods, the most promising was the Yamaguchi macrolactonization, which afforded a 1:1 mixture of lactones **33** and **34**. Control experiments indicated that double-bond migration did not occur after macrolactonization. By default, it was concluded that this critical isomerization was probably occurring at the active ester stage of the lactonization process prior to ring closure. We postulated that this problem could be overcome by investigating lower temperatures for the macrolactonization process. To explore this possibility, we submitted the seco acid to conditions first reported by Yonemitsu (DMAP, Et_3N, trichlorobenzoyl chloride, and the seco acid in benzene at ambient temperature).[56] We were pleased

(46) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L., manuscript in preparation. (b) Also see later discussion.
(47) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(48) Evans, D. A; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750–5752.
(49) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.
(50) Prepared according to published procedures: Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121–124.
(51) In a control study, significant desilylation of ketal **2** was observed when shaken with 0.3 M $NaHSO_4$ for 2 min. A survey of acidic conditions for desilylation showed that only HF–pyridine (buffered with excess pyridine) used under very closely monitored conditions was effective in removing the TES group of ester **31** without also removing the C_{33} TBS group.
(52) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.
(53) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50.
(54) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616. (b) Also see: Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409–3412.
(55) Inanagana, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

Scheme X[a]



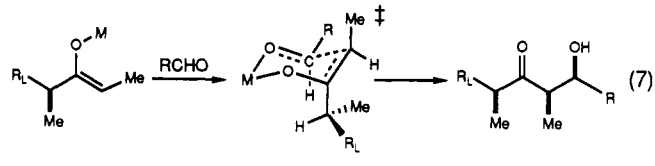
[a] (a) $Pd(P(Ph_3)_4$, TlOH, THF, 23 °C. (b) TMSOTf, lutidine, CH_2Cl_2, 0 °C. (c) HF·pyridine, THF, 23 °C. (d) $Cl_3C_6H_2COCl$, DMAP, Et_3N, benzene, 23 °C. (e) HF (aqueous), CH_3CN, CH_2Cl_2, 23 °C.

to obtain exclusively lactone **33** from this reaction in 86% yield. Final deprotection with hydrofluoric acid/acetonitrile[57] afforded synthetic rutamycin [mp 128–130 °C; $[\alpha]^{23}_D$ –72.0° (*c* 0.47, $CHCl_3$)] in 98% yield which coeluted by TLC and HPLC analysis with natural rutamycin B [mp 129–130 °C; $[\alpha]^{23}_D$ –72.8° (*c* 1.21, $CHCl_3$)] in a number of solvent systems. In addition, the synthetic and natural samples were spectroscopically indistinguishable (IR, ^1H and ^{13}C NMR, HRMS). This correlation thus confirms the Keller-Schierlein stereochemical assignment for this natural product.[6]

Double-Stereodifferentiating C_8–C_9 Aldol Bond Construction

The aldol fragment coupling of aldehyde **18** with the titanium enolate of ketone **25** (Scheme IX) is striking, and conventional wisdom suggested that this "mismatched" reaction should not have been so highly diastereoselective.[25] Initial studies indicated that the enolate's π-facial preference is compatible with the desired stereochemical outcome (Scheme IV, eq 3), and a stereochemical model for the reaction had been proposed by us (eq 7).[23] However, detailed studies of these aldol reactions with chiral aldehydes had not yet been reported.

Literature examples of double-stereodifferentiating aldol reactions with chiral aldehydes have established the modest trend that (*Z*)-enolates are typically more selective for the *anti*-Felkin aldehyde diastereoface.[25a] Since enolate addition to the Felkin aldehyde diastereoface was desired, literature analogies led us to anticipate poor selectivity for this reaction. The unanticipated stereoselectivity observed in the C_8–C_9 aldol bond construction provided the stimulus to examine the complete set of related reactions shown below. In these reactions, the configuration and



protecting group on the β-oxygen-bearing stereocenter of the aldehyde constituent were systematically varied (Scheme XI).[58]

As is evident from these cases, only one of the four possible permutations of the β-stereocenter and associated protecting group combinations on the aldehyde leads to a stereoselective aldol bond construction. As noted earlier, the more selective reduction of ketone **8** to the *anti* diol **11** (Scheme VI) led us to synthesize the aldehyde analogous to aldehyde **37b**. Had we proceeded forward in the synthesis with the *syn* diol **9** (Scheme VI), the corresponding aldehyde, analogous to aldehyde **36b**, probably would have delivered a much less diastereoselective aldol coupling. Our choice of the C_{11} *p*-methoxybenzyl protective group also proved to be crucial, as demonstrated by the low selectivity in the analogous aldol reaction of aldehyde **37a**. Again, the selection of this protecting group was predicated upon the need to differentiate this hydroxyl group during the course of the synthesis (Scheme IX). The present aldol reaction (Scheme X) reveals a level of complexity which is not covered in the recent Roush analysis of double-stereodifferentiating aldol processes,[25a] and further speculation on those factors contributing to reaction sterreoselectivity are premature. In an independent study, White and co-workers[59] have carried out a very similar C_8–C_9 aldol bond construction under the conditions previously reported by us for the generation of titanium enolates.[23] Their results are in full agreement with the present investigation.

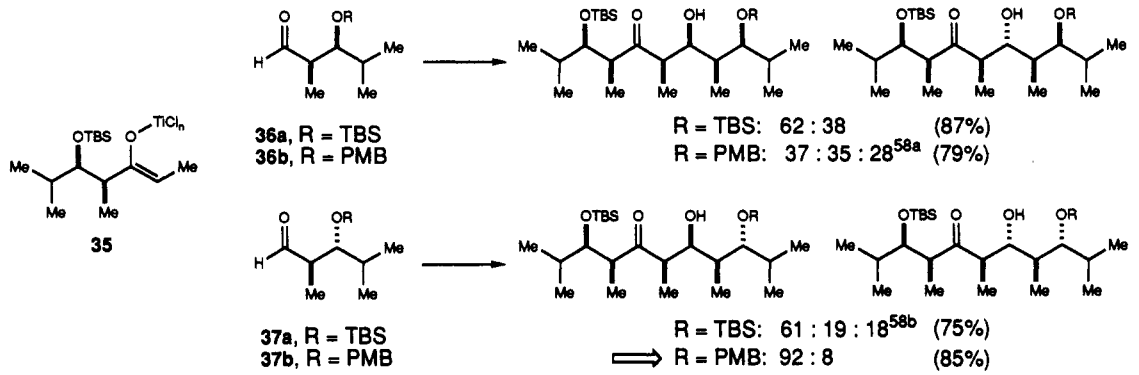
(56) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367–6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9.

(57) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981–3982.

(58) (a) The third unpictured isomer is the other *syn* aldol adduct in Scheme XI. (b) The third unpictured isomer is the other *anti* aldol adduct in Scheme XI.

(59) White, J. D.; Porter, W. J.; Tiller, T. *Synlet.* **1993**, 535–538.

Scheme XI



Conclusions

Complex synthesis projects provide the stimulus for reaction development. The continued development of β-ketoimide-based bond constructions and their use in complex reactions (Schemes VI, VIII) are good illustrations of this point. This dipropionyl synthon which has recently been employed in the synthesis of calyculin[60] is proving to be a useful building block in the syntheses of propionate natural products. In a related area, when the synthesis of rutamycin was undertaken, our parallel investigations into double-stereodifferentiating aldol reactions were in the early stages of development. At that time, the projected C_8–C_9 aldol coupling reaction was viewed as a serious uncertainty in the synthesis plan. The fact that the reaction has proven to be so highly stereoselective has strongly influenced our subsequent methodological studies in this area. The present investigation illustrates the importance of aldehyde structure, at both the α and β stereocenters, in contributing to the overall stereoselectivities in these reactions and provides a cautionary note to those attempting to employ the simple stereoinduction models for predicting π-facial selectivities.

Experimental Section

General.[60] Organolithium reagents were titrated according to the method of Brown.[61] 4-Methoxybenzaldehyde dimethyl acetal,[62] 2-ethyl-2-ethoxy-1,3-dioxalane,[41] zinc borohydride $Zn(BH_4)_2$,[63] ferric chloride/silica gel complex ($FeCl_3$-SiO_2),[45] *tert*-butyl diethylphosphonoacetate,[64] bis(1,3,2-dioxaborin-2-yl)methane,[21] and tetrakis(triphenylphosphine)-palladium(0)[50] were all prepared according to literature procedures. The Dess–Martin periodinane was formed using a modification of the literature procedure[47] in which the hydroxiodinane oxide intermediate was heated to 80 °C with acetic anhydride and acetic acid only until dissolution was complete (*ca.* 10 min). Typically, all nonorganometallic, commercially obtained reagents were purified by distillation or recrystallization prior to use.

When NMR data are given, all *J* values are in hertz. **[2*S*,2-(3*R*),3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*]-3,9-Dimethyl-8-(2-((1,1-dimethylethyl)dimethylsiloxy)propyl)-2-(3-ethyl-3-formylpropyl)-4-(triethylsiloxy)-1,7-dioxaspiro[5.5]undecane (3).** To a solution of 200 mg (0.34 mmol) of alcohol **2** in 4.4 mL of CH_2Cl_2 at 0 °C was added 60 μL (55 mg; 0.51 mmol) of 2,6-lutidine and 92 μL (108 mg; 0.41 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After the mixture was stirred at 0 °C for 90 min, 30 mL of 0.3 M aqueous $NaHSO_4$ was added. This was extracted with three 40-mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 235 mg (98%) of the silyl ether as a clear, colorless oil: $[\alpha]^{23}_D$ –45° (*c* 0.92, CH_2Cl_2); IR (film) 2957, 2877, 1614, 1587, 1514, 1462, 1384, 1248, 1181, 1016, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.7, 2H, ArH), 6.87 (d, *J* = 6.7, 2H, ArH), 4.42 (s, 2H, $ArCH_2$), 4.14 (m, 1H, C_4-H), 3.80–3.75 (m, 4H, C_8-H, $ArOCH_3$), 3.72 (m, 1H, C_2-H), 3.48 (m, 1H, C_8–$C_{2'}$-H), 3.33 (d, *J* = 5.7, 2H, C_2–$C_{4'}$-H_2), 2.06 (m, 1H, C_{10}-H_{ax}), 1.69 (m, 1H, C_5-H_{ax}), 1.62–1.24 (m, 15H, C_2–$C_{1'}$-H_2, C_2–$C_{2'}$-H_2, C_2–C_3-H, C_2–C_3-$C_{1''}$-H_2, C_3-H, C_5-H_{eq}, C_8–$C_{1'}$-H_2, C_9-H, C_{10}-H_{eq}, C_{11}-H_2), 1.19 (d, *J* = 6.0, 3H, C_8–$C_{3'}$-H_3), 0.97–0.91 (m, 12H, C_9-CH_3, $SiCH_2CH_3$), 0.88–0.86 (m, 12H, C_2–C_3'–$C_{2''}$-H_3, $SiC(CH_3)_3$), 0.81 (d, *J* = 6.9, 3H, C_3-CH_3), 0.57 (q, *J* = 8.0, 6H, $Si(CH_2CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 131.0, 129.0, 113.7, 97.4, 72.8, 72.6, 71.2, 69.2, 67.81, 67.77, 55.2, 53.3, 43.6, 39.9, 39.8, 39.1, 30.0, 29.7, 27.9, 26.5, 25.9, 24.6, 23.7, 18.1, 11.2, 11.0, 6.8, 5.0, 4.2, –4.4, –4.6. Anal. Calcd for $C_{40}H_{74}O_6Si_2$: C, 67.94; H, 10.55. Found: C, 67.85; H, 10.62.

To a solution of 220 mg (0.311 mmol) of the above *p*-methoxybenzyl ether in 4 mL of 18:1 CH_2Cl_2/water at 5 °C was added 92 mg (0.404 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). After the mixture was stirred vigorously for 2 h, 10 mL of saturated aqueous $NaHCO_3$ solution was added, and the mixture was poured into 20 mL of deionized water and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 180 mg (99%) of the alcohol as a clear, colorless oil: $[\alpha]^{23}_D$ –57.8° (*c* 1.20, CH_2Cl_2); IR (film) 3428 (b), 2957, 2878, 1462, 1385, 1250, 1075, 1007, 978, 835, 774, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 1H, C_4-H), 3.80 (m, 1H, C_8-H), 3.73 (m, 1H, C_2-H), 3.56–3.50 (m, 3H, C_8–$C_{2'}$-H, C_2–$C_{4'}$-H_2), 2.05 (m, 1H, C_{10}-H_{ax}), 1.69 (m, 1H, C_5-H_{ax}), 1.59–1.30 (m, 15H, C_2–$C_{1'}$-H_2, C_2–$C_{2'}$-H_2, C_2–C_3-H, C_2–C_3-$C_{1''}$-H_2, C_3-H, C_5-H_{eq}, C_8–$C_{1'}$-H_2, C_9-H, C_{10}-H_{eq}, C_{11}-H_2), 1.20 (d, *J* = 6.0, 3H, C_8–$C_{3'}$-H_3), 0.97–0.89 (m, 15H, C_9-CH_3, C_2–C_3– $C_{2''}$-H_3, $SiC(CH_3)_3$), 0.88 (d, *J* = 6.9, 3H, C_3-CH_3),0.82 (d, *J* = 6.9, 3H, C_3-CH_3), 0.57 (q, *J* = 8.0, 6H, $Si(CH_2CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.5, 71.2, 69.2, 67.8, 67.7, 65.1, 43.6, 42.3, 39.8, 39.2, 30.0, 29.9, 29.7, 27.5, 26.5, 25.9, 24.6, 23.4, 18.1, 11.1, 11.0, 6.8, 5.0, 4.2, –4.4, -4.6; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 609.4346, found 609.4361.

To a solution of 32 μL (48 mg; 0.37 mmol) of oxalyl chloride in 1.0 mL of CH_2Cl_2 at –78 °C was added 52 μL (57 mg; 0.74 mmol) of DMSO. This was stirred at –78 °C for 20 min, and then 180 mg (0.307 mmol) of the above alcohol in 1.0 mL of CH_2Cl_2 was added dropwise *via* cannula. After 15 min, 102 μL (74 mg; 0.74 mmol) of Et_3N was added. The cloudy mixture was allowed to warm to –10 °C over 1 h and then was poured into 15 mL of 1:1 brine/water solution and 20 mL of Et_2O. The organic layer was separated and washed further with 15 mL of 1:1 brine/water solution and then 15 mL of brine. The combined aqueous washes were back-extracted with two 20-mL portions of Et_2O. The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 176 mg (98%) of a clear, colorless oil: $[\alpha]^{23}_D$ –57° (*c* 0.53, CH_2Cl_2); IR (film) 2958, 2879, 1730, 1460, 1384, 1249, 1074, 1004, 978, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, *J* = 2.8, 1H, CHO), 4.11 (dt, *J* = 4.9, 11.4, 1H, C_4-H), 3.79 (m, 1H, C_8-H), 3.68 (dt, *J* = 2.4, 7.0, 1H, C_2-H), 3.51 (dq, *J* = 2.0, 9.0, 1H, C_8–$C_{2'}$-H), 2.17 (m, 1H, C_2–C_3-H), 2.02 (m, 1H, C_{10}-H_{ax}), 1.87 (m, 1H, C_5-H_{ax}), 1.69–1.31 (m, 14H, C_2–$C_{1'}$-H_2, C_2–$C_{2'}$-H_2, C_2–C_3–$C_{1''}$-H_2, C_3-H, C_5-H_{eq}, C_8–$C_{1'}$-H_2, C_9-H, C_{10}-H_{eq}, C_{11}-H_2), 1.18 (d, *J* = 4.0, 3H, C_8–$C_{3'}$-H_3), 0.95–0.89 (m, 15H, C_9-CH_3, C_2–C_3– $C_{2''}$-H_3, $SiC(CH_3)_3$), 0.78 (d, *J* = 6.9, 3H, C_3-CH_3), 0.55 (q, *J* = 8.0, 6H, $Si(CH_2CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR

(60) For a general discussion of the spectrometers employed and solvent drying procedures, see: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.
(61) Brown, C. A. *Synthesis* **1974**, 427–428.
(62) Kloosterman, M.; Slaghek, T.; Hermans, J. P. G.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 335–341.
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(125 MHz, $CDCl_3$) δ 204.8, 97.5, 70.8, 69.2, 67.8, 67.6, 53.4, 43.6, 39.7, 39.2, 30.2, 30.0, 29.6, 26.5, 25.9, 25.6, 24.6, 21.6, 18.1, 11.3, 11.2, 6.8, 5.0, 4.2, –4.4, –4.5; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 607.4190, found 607.4199.

[2S,2(3R),3R,4S,6R,8S,8(2R),9S]-3,9-Dimethyl-8-(2-((1,1-dimethylethyl)dimethylsiloxy)propyl)-2-(3-ethyl-5-(dihydroxyboryl)-4-pentenyl)-4-(triethylsiloxy)-1,7-dioxaspiro[5.5]undecane (4). To a solution of 261 mg (1.85 mmol) of 2,2,6,6-tetramethylpiperidine in 4.0 mL of THF at 0 °C was added 1.03 mL (1.54 mmol) of 1.50 M *n*-butyllithium in hexane. The mixture was stirred at 0 °C for 15 min and then at ambient temperature for 30 min. It was recooled to –78 °C, and 340 mg (1.85 mmol) of bis(1,3,2-dioxaborin-2-yl)methane[21] in 1 mL of THF was added, followed by 279 μL (215 mg; 1.85 mmol) of TMEDA. The mixture was stirred at –78 °C for 40 min and then at 0 °C for 30 min. Aldehyde **3** (90 mg; 0.154 mmol) in THF (1.0 mL + 0.5 mL wash) was added *via* cannula, and the mixture was stirred at 0 °C for 15 min and then at ambient temperature for 10 min. The mixture was diluted with 60 mL of EtOAc and washed sequentially with 40 mL of brine, 40 mL of 1:9 1.0 N aqueous HCl solution/brine solution, 40 mL of deionized water, 40 mL of saturated aqueous $NaHCO_3$ solution, and finally 40 mL of brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 100 mg (103%) of the vinyl boronic acid as a clear, slightly yellow oil. The product oil was not purified but was rather used immediately after preparation.

[3(2R,3S,4S,5S,6R,8E),4R]-3-(3,5-Dihydroxy-2,4,6-trimethyl-1-oxo-9-phenyl-8-nonenyl)-4-(phenylmethyl)-2-oxazolidinone (9). To a solution of 138 mg (0.300 mmol) of ketone **8**[28] in 15 mL of CH_2Cl_2 at –78 °C was added 1.7 mL (0.45 mmol) of 0.2 M zinc borohydride ($Zn(BH_4)_2$) in Et_2O. This was allowed to warm to 0 °C over 3 h, and then 5 mL of saturated aqueous NH_4Cl solution was added. The mixture was stirred at 0 °C for 10 min and then poured into 25 mL of CH_2Cl_2 and 10 mL of brine. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 20 mL), and the organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Analysis of the unpurified mixture by ^1H NMR (400 MHz) showed a 4:1 ratio of diols **9** to **11**. Purification by flash chromatography on silica gel produced 78 mg (56%) of **9** as a clear, colorless oil: $[\alpha]_D$ –63.5° (*c* 0.89, CCl_4); IR (CH_2Cl_2) 3490 (b), 2975, 2930, 1783, 1699, 1385, 1240, 1041, 968, 645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 10H, ArH), 6.42 (d, *J* = 15.8, 1H, C_9-H), 6.25 (m, 1H, C_8-H), 4.68 (m, 1H, H_3), 4.20–4.15 (m, 3H, H_4, H_5, C_3-H), 3.94 (d, *J* = 7.9, 1H, C_5-H), 3.62 (dd, *J* = 1.9, 8.9, 1H, C_2-H), 3.26 (dd, *J* = 3.3, 13.4, 1H, H_1), 2.77 (dd, *J* = 9.5, 13.5, 1H, H_4), 2.35 (m, 1H, C_7-H), 2.26 (m, 1H, C_7-H), 1.86-1.72 (m, 2H, C_4-H, C_6-H), 1.27 (d, *J* = 6.9, 3H, C_2-CH_3), 0.92 (d, *J* = 6.8, 3H, C_4-CH_3), 0.78 (d, *J* = 6.9, 3H, C_6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 153.9, 137.7, 134.9, 131.1, 129.7, 129.4, 128.9, 128.4, 127., 126.8, 125.9, 76.7, 66.2, 55.1, 39.6, 38.0, 37.8, 37.7, 36.6, 35.6, 12.7, 11.9, 9.6; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 488.2413, found 488.2414.

[4R,4(1R,2(4R)),5S,6S,6(1R)]-4-(1-Methyl-2-oxo-2-(2-oxo-4-(phenylmethyl)-*N*-oxazolidinyl)ethyl)-6-(1-methyl-4-phenyl-3-butenyl)-2,2,5-trimethyl-1,3-dioxane (10). To a solution of 17 mg (0.036 mmol) of diol **9** in 1 mL of 2,2-dimethoxypropane and 1 mL of anhydrous acetone was added 3.0 mg (0.013 mmol) of anhydrous camphorsulfonic acid (CSA). This mixture was stirred at ambient temperature for 10 h, and then two drops of triethylamine were added, and the solution was stirred for 5 min. All volatiles were then removed *in vacuo*, and the resultant residue was taken up in 2 mL of deionized water and 3 mL of CH_2Cl_2. The aqueous layer was separated and extracted further with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel produced 16 mg (89%) of the acetonide **10** as a colorless oil: $[\alpha]_D$ –72.1° (*c* 0.67, CCl_4); IR (CCl_4) 3015, 2980, 2940, 1785, 1715, 1600, 1455, 1380, 1355, 1200 (b), 1015, 700, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10H, ArH), 6.35 (d, *J* = 15.8 ,1H, C_6–$C_{4'}$-H), 6.17 (m, 1H, C_6–$C_{3'}$-H), 4.55 (m, 1H, C_4–$C_{2'}$-H_3), 4.17–4.09 (m, 2H, C_4–$C_{2'}$-H_4, C_4–$C_{2'}$-H_5), 4.00 (m, 1H, C_4–$C_{1'}$-H), 3.85 (dd, *J* = 4.5, 10.0, 1H, C_4-H), 3.48 (dd, *J* = 5.7, 16.6, 1H, C_6-H), 3.37 (dd, *J* = 5.7, 16.6, 1H, C_4–$C_{2'}$-H_1), 2.74 (dd, *J* = 9.4, 13.5, 1H, C_4–$C_{2'}$-H_4), 2.30–2.10 (m, 2H, C_6–$C_{2'}$-H_2), 1.85 (m, 1H, C_6–$C_{1'}$-H), 1.64 (m, 1H, C_5-H), 1.34 (s, 3H, C_2-CH_3), 1.27 (s, 3H, C_2-CH_3), 1.20 (d, *J* = 6.9, 3H, C_4–$C_{1'}$-CH_3), 0.90 (d, *J* = 6.8, 3H, C_6–$C_{1'}$-CH_3), 0.79 (d, *J* = 6.7, 3H, C_5-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 153.4, 137.8, 135.5, 131.2, 129.6, 129.5, 128.9, 128.5, 127.3, 126.8, 125.9, 97.9, 75.1, 74.3, 66.2, 56.3, 40.2, 37.7, 37.5, 33.6, 33.0, 29.9, 19.5, 12.5, 10.8, 8.9; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 528.2726, found 528.2746.

[3(2R,3R,4S,5S,6R,8E),4R]-3-(3,5-Dihydroxy-2,4,6-trimethyl-1-oxo-9-phenyl-8-nonenyl)-4-(phenylmethyl)-2-oxazolidinone (11). To 8.5 mL of glacial acetic acid in a cold water bath was slowly added 197.0 mg (5.20 mmol) of sodium borohydride in small portions. At the end of the addition, another 8.0 mL of glacial acetic acid was added, and the mixture was stirred for 1 h at ambient temperature. In a separate flask, ketone **8** (220 mg; 0.47 mmol) was azeotropically dried with toluene (2 × 5 mL) and dissolved in 3.3 mL of glacial acetic acid. The borohydride solution was then rapidly tranferred to this solution *via* cannula. The mixture was stirred at ambient temperature for 1 h, whereupon all volatiles were removed *in vacuo*. Toluene was used to azeotropically remove residual acetic acid. The resultant residue was dissolved in 30 mL of CH_2Cl_2 and 30 mL of 5% aqueous $NaHCO_3$ solution. The organic layer was separated and shaken vigorously for 10 min with saturated aqueous sodium potassium tartrate solution. The combined aqueous washes were back-extracted with three 20-mL portions of CH_2Cl_2, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel produced 179 mg (81%) of a clear, colorless oil: $[\alpha]_D$ –69.3° (*c* 0.98, CCl_4); IR (CH_2Cl_2) 3490 (b), 2975, 2930, 1783, 1699, 1385, 1240, 1041, 968, 645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.17 (m, 10H, ArH), 6.39 (d, *J* = 15.8, 1H, C_9-H), 6.20 (m, 1H, C_8-H), 4.70 (m, 1H, H_3), 4.30 (m, 1H, C_3-H), 4.20–4.01 (m, 3H, H_4, H_5, C_2-H), 3.51 (d, *J* = 5.5, 1H, C_5-H), 3.23 (dd, *J* = 5.7, 16.6, 1H, H_1), 2.77 (dd, *J* = 9.4, 13.4, 1H, H_4), 2.35–2.30 (m, 1H, C_7-H), 2.18–2.14 (m, 1H, C_7-H), 1.91–1.84 (m, 2H, C_4-H, C_6-H), 1.15 (d, *J* = 6.9, 3H, C_2-CH_3), 0.99–0.94 (q, 6H, C_4-CH_3, C_6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 153.5, 135.1, 131.4, 129.3, 128.8, 128.7, 128.4, 127.2, 127.0, 126.9, 125.9, 77.0, 73.2, 66.1, 55.1, 41.0, 37.8, 37.7, 35.8, 35.6, 14.3, 13.5, 10.0; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 488.2413, found 488.2414. Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58. Found: C, 71.81; H, 7.66.

[4S,4(1R,2(4R)),5S,6S,6(1R)]-4-(1-Methyl-2-oxo-2-2-oxo-4-(phenylmethyl)-*N*-oxazolidinyl)ethyl)-6-(1-methyl-4-phenyl-3-butenyl)-2,2,5-trimethyl-1,3-dioxane (12). To a solution of 28 mg (0.060 mmol) of diol **11** in 1 mL of 2,2-dimethoxypropane and 1 mL of anhydrous acetone was added 3.0 mg (0.013 mmol) of anhydrous CSA. This mixture was stirred at ambient temperature for 15 h, and then two drops of triethylamine were added, and the solution was stirred for 5 min. All volatiles were then removed *in vacuo*, and the resultant residue was taken up in 2 mL of deionized water and 3 mL of CH_2Cl_2. The aqueous layer was separated and extracted further with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative TLC (0.5-mm plate, 30% ethyl acetate/hexane) produced 23 mg (77%) of the acetonide **12** as a colorless oil: $[\alpha]_D$ –61.7° (*c* 0.81, CCl_4); IR (CCl_4) 3030, 2980 (b), 2940, 1790, 1705, 1600, 1500, 1455, 1380, 1350, 1240, 1225, 1190, 1020, 970, 880, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.10 (m, 10H, ArH), 6.23 (d, *J* = 12.6, 1H, C_6–$C_{1'}$-H), 6.11 (m, 1H, C_6–$C_{1'}$-H), 4.56 (m, 1H, C_4–$C_{2'}$-H_5), 4.07 (m, 2H, C_4–$C_{2'}$-H_4, C_4–$C_{2'}$-H_5), 3.92 (m, 2H, C_4–$C_{1'}$-H, C_6–$C_{1'}$-H), 3.17 (m, 2H, C_4–$C_{2'}$-H, C_6-H), 2.72 (dd, *J* = 9.6, 13.4, 1H, C_4–$C_{2'}$-H_4), 2.26 (m, 1 H, C_6–$C_{2'}$-H), 2.08 (m, 1H, C_6–$C_{2'}$-H), 1.83 (m, 1H, C_5-H), 1.64 (m, 1H, C_6–$C_{1'}$-H), 1.20 (s, 3H, C_2-CH_3), 1.16 (s, 3H, C_2-CH_3), 1.07 (d, *J* = 6.0, 3H, C_4–$C_{1'}$-CH_3), 0.90 (d, *J* = 6.8, 3H, C_5-CH_3), 0.83 (d, *J* = 6.7, 3H, C_6–$C_{1'}$-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 153.3, 137.8, 135.4, 131.3, 129.5, 129.4, 128.9, 128.5, 127.3, 126.8, 125.9, 100.6, 77.2, 71.5, 66.0, 55.4, 38.0, 37.8, 37.3, 36.5, 34.2, 25.0, 23.6, 14.0, 13.1, 12.3; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 528.2726, found 528.2714.

[2S,3S,4S,5S,6R,8E]-2,4,6-Trimethyl-9-phenyl-non-8-ene-1,3,5-triol (13). To a solution of 190 mg (0.408 mmol) of imide **11** in 9.0 mL of THF and 36 μL (28 mg; 0.90 mmol) of methanol at 0 °C was added 0.45 mL (0.90 mmol) of 2.0 M lithium borohydride ($LiBH_4$) in THF. Gas evolution was observed. After the solution was stirred at 0 °C for 1 h, the reaction was quenched by careful addition of 6 mL of 1.0 M aqueous NaOH solution. The resulting mixture was stirred at 0 °C for 5 min and then poured into 20 mL of Et_2O and 20 mL of deionized water. The ethereal layer was separated and washed with 10 mL of brine. The combined aqueous washes were back-extracted with Et_2O (2 × 20 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant oil was purified by flash chromatography to give 112 mg (94%) of a clear, colorless oil: $[\alpha]^{23}_D$ 13.4° (*c* 0.64, CH_2Cl_2); IR (film) 3350 (b), 2966, 2931, 1598, 1494, 1460, 1028, 968, 742, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H, ArH), 6.39 (d, *J* = 15.8, 1H, C_9-H), 6.20 (m, 1H, C_8-H), 4.11 (q, *J* = 7.1, 1H, C_5-H), 3.95 (d, *J* = 9.6, 1H, C_3-H), 3.65 (q, *J* =

8.6, 1H, C_1-H), 3.46 (t, J = 5.6, 1H, C_1-H), 2.31 (m, 1H, C_7-H), 2.11 (m, 1H, C_7-H), 1.90–1.79 (m, 3H, C_2-H, C_4-H, C_6-H), 0.98 (d, J = 6.7, 3H, C_2-CH_3), 0.94 (d, J = 7.0, 3H, C_4-CH_3), 0.75 (d, J = 6.9, 3H, C_6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.4, 128.7, 128.4, 126.9, 125.9, 77.8, 76.7, 68.9, 37.6, 37.1, 36.1, 35.8, 13.9, 13.1, 10.1; HRMS (FAB) m/z calcd for $[M + Na]^+$ 315.1936, found 315.1931.

[2*S*,4*S*,4(1*R*,2*S*,3*R*,5*E*),5*S*]-2-(4-Methoxyphenyl)-5-methyl-4-(2-hydroxy-1,3-dimethyl-6-phenyl-5-hexenyl)-1,3-dioxane (14). To a solution of 75 mg (0.256 mmol) of triol **13** in 3.0 mL of DMF were added 70 mg (0.384 mmol) of 4-methoxybenzaldehyde dimethyl acetal and 5 mg (21 mmol) of anhydrous CSA. This was stirred at ambient temperature for 12 h and then diluted with 10 mL of 10:1 hexanes/CH_2Cl_2 solution. The resultant mixture was washed with deionized water (3 × 5 mL) and then brine (2 × 5 mL). The combined aqueous washes were back-extracted with 10:1 hexanes/CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 96 mg (91%) of a clear, colorless oil: $[\alpha]^{23}_D$ 31.2° (*c* 0.87, CCl_4); IR (CCl_4) 3320, 2970, 2840, 1620, 1520, 1460, 1390, 1300, 1250, 965 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.17 (m, 7H, ArH), 6.80 (d, J = 8.7, 2H, ArH), 6.40 (d, J = 15.8, 1H, C_4–$C_{6'}$- H), 6.22 (m, 1H, C_4–$C_{5'}$-H), 5.45 (s, 1H, C_2-H), 4.10 (m, 1H, C_6-H), 3.88 (dd, J = 1.0, 9.8, 1H, C_4-H), 3.75 (s, 3H, $ArOCH_3$), 3.60 (m, 1H, C_4–$C_{2'}$-H), 3.50 (t, J = 11.1, 1H, C_6-H), 2.32 (m, 1H, C_4–$C_{4'}$-H), 2.17–2.08 (m, 3H, C_4–$C_{4'}$-H, OH, C_5-H), 1.92 (dt, J = 1.6, 7.4, 1H, C_4–$C_{1'}$-H), 1.82 (m, 1H, C_4–$C_{3'}$-H), 0.99 (d, J = 7.0, 3H, C_4–$C_{1'}$-H), 0.96 (d, J = 6.7, 3H, C_4–$C_{3'}$-CH_3), 0.75 (d, J = 6.7, 3H, C_5-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 137.3, 131.2, 131.0, 129.1, 128.4, 127.1, 126.8, 125.9, 113.4, 100.8, 82.5, 75.4, 73.1, 55.1, 38.0, 36.0, 35.7, 30.3, 12.9, 11.9, 10.6. Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.14; H, 8.29.

[2*S*,4*S*,4(1*R*,2*S*,3*R*,5*E*),5*S*]-2-(4-Methoxyphenyl)-5-methyl-4-(1,3-dimethyl-6-phenyl-2-((1,1-dimethylethyl)dimethylsiloxy)-5-hexenyl)-1,3-dioxane (15). To a solution of 900 mg (1.72 mmol) of alcohol **14** in 20 mL of CH_2Cl_2 was at 0 °C were added 275 μL (253 mg; 2.36 mmol) of 2,6-lutidine and 542 μL (624 mg; 2.36 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. This was stirred at 0 °C for 1 h and then quenched by addition of 10 mL of saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 20 mL of 0.5 M aqueous $NaHSO_4$ solution. The aqueous wash was back-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 1.03 g (100%) of a clear, colorless oil: $[\alpha]^{23}_D$ 12.1° (*c* 0.92, CCl_4); IR (CCl_4) 2960, 2940, 2860, 1620, 1520, 1465, 1390, 1305, 1250, 1100, 1045, 970, 835, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.19 (m, 7H, ArH), 6.85 (d, J = 8.7, 2H, ArH), 6.38 (d, J = 15.8, 1H, C_4–$C_{6'}$-H), 6.20 (quin, 1H, C_4–$C_{5'}$-H), 5.47 (s, 1H, C_2-H), 4.13 (dd, J = 4.7, 11.1, 1H, C_6-H), 3.81–3.77 (m, 5H, Ar-OCH_3, C_4-H, C_4–$C_{2'}$-H), 3.50 (t, J = 11.1, 1H, C_6-H), 2.28–2.06 (m, 3H, C_4–$C_{4'}$-H_2, C_5-H), 1.86–1.84 (m, 2H, C_4–$C_{1'}$-H, C_4–$C_{3'}$-H), 0.97–0.91 (m, 15H, C_4–$C_{1'}$-CH_3, C_4–$C_{3'}$-CH_3, $SiC(CH_3)_3$), 0.75 (d, J = 6.7, 3H, C_5-CH_3), 0.01 (s, 3H, $SiCH_3$), –0.2 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 137.8, 131.6, 130.8, 130.3, 128.5, 127.3, 126.8, 125.9, 113.5, 100.6, 81.0, 75.8, 73.3, 55.2, 38.8, 38.6, 36.4, 30.3, 26.4, 18.6, 12.4, 12.3, 10.0, -2.7, –3.8. Anal. Calcd for $C_{32}H_{48}O_4Si$: C, 73.23; H, 9.22. Found: C, 73.14; H, 9.11.

[2*S*,3*S*,4*R*,5*S*,6*R*,8*E*]-2,4,6-Trimethyl-9-phenyl-5-((1,1-dimethylethyl)-dimethylsiloxy)-3-((4-methoxyphenyl)methoxy)-1-non-8-enol (16). To a solution of 1.60 g (3.0 mmol) of acetal **15** in 18 mL of CH_2Cl_2 at 0 °C was added 9.0 mL (9.0 mmol) of 1.0 M diisobutylaluminum hydride (DIBAL-H) solution in toluene. The resultant solution was stirred at 0 °C for 6 h and then quenched by careful addition of 1.3 mL of methanol, followed by 45 mL of saturated aqueous sodium potassium tartrate solution and 27 mL of CH_2Cl_2. This was stirred vigorously for 10 h at ambient temperature to give a clear, biphasic mixture. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 1.62 g (100%) of a clear, colorless oil: $[\alpha]^{23}_D$ –0.57° (*c* 1.05, CCl_4); IR (CCl_4) 3330 (b), 2960, 2930, 2860, 1615, 1515, 1460, 1250, 1040, 965, 905, 830, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 7H, ArH), 6.86 (d, J = 8.5, 2H, ArH), 6.44 (d, J = 15.8, 1H, C_9-H), 6.20 (m, 1H, C_8-H), 4.61 (q, J = 8.3, 2H, $ArCH_2$), 3.80–3.75 (m, 5H, $ArOCH_3$, C_3-H, C_5-H), 3.65 (m, 2H, C_1-H_2), 2.35 (m, 1H, C_7-H), 2.18 (m, 1H, C_7-H), 2.00–1.86 (m, 3H, C_4-H, C_2-H, C_6-H), 1.07 (d, J = 7.1, 3H, C_2-CH_3), 1.06–1.00 (m, 15H, C_4-CH_3, C_6-CH_3, $SiC(CH_3)_3$), 0.18 (s, 6H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 137.4, 131.1, 130.3, 129.5, 128.9, 128.3, 126.8, 125.7, 113.7, 84.8, 77.0, 74.7, 65.7, 55.0, 42.0, 38.4, 38.2, 36.4, 26.0, 18.4, 15.1, 13.9, 11.4, –3.2, –3.9. Anal. Calcd for $C_{32}H_{50}O_4Si$: C, 72.96; H, 9.56. Found: C, 72.86; H, 9.45.

[2*S*,3*S*,4*R*,5*S*,6*R*,8*E*]-9-Iodo-2,4,6-trimethyl-3-((4-methoxyphenyl)-methoxy)-5-((1,1-dimethylethyl)dimethylsiloxy)-1-non-8-enol (17). To a solution of 250 mg (0.470 mmol) of olefin **16** in 11 mL of 10:3:1 *tert*-butyl alcohol/THF/water solution were added 111 mg (0.950 mmol) of 4-methylmorpholine *N*-oxide and 320 μL (0.050 mmol) of 0.15 M aqueous OsO_4 solution. This was stirred at ambient temperature for 1 h, and then 3.3 mL of deionized water was added, followed by 200 mg (2.4 mmol) of $NaHCO_3$ and 305 mg (1.4 mmol) of $NaIO_4$. After being stirred at ambient temperature for 2 h, the mixture was concentrated to half its volume *in vacuo*. The residue was then dissolved in 40 mL of saturated aqueous Na_2SO_3 solution and extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 210 mg (98%) of the aldehyde as a clear, colorless oil: $[\alpha]^{23}_D$ –6.3° (*c* 0.59, CH_2Cl_2); IR (film) 3431 (b), 2957, 2931, 2856, 1724, 1613, 1514, 1463, 1250, 1039, 834 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H, CHO), 7.20 (d, J = 8.6, 2H, ArH), 6.82 (d, J = 8.6, 2H, ArH), 4.51 (q, J = 10.4, 2H, $ArCH_2$), 3.74 (s, 3H, $ArOCH_3$), 3.64–3.56 (m, 4H, C_8-H_2, C_4-H, C_6-H), 2.50 (q, J = 10.4, 1H, C_2-H), 2.33–2.31 (m, 2H, C_2-H, C_5-H), 1.84–1.81 (m, 2H, C_3-H, C_7-H), 0.97 (d, J = 7.2, 3H, C_3-CH_3), 0.94 (d, J = 6.9, 3H, C_7-CH_3), 0.91 (d, J = 6.3, 3H, C_5-CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 159.3, 130.5, 129.0, 113.9, 84.4, 77.4, 74.6, 66.0, 55.2, 49.0, 41.9, 38.6, 31.0, 26.1, 18.5, 15.2, 14.5, 11.3, –3.1, –3.9; HRMS (FAB) m/z calcd for $[M + Na]^+$ 475.2856, found 475.2847.

To a slurry of 325 mg (3.04 mmol) of flame-dried chromous chloride in 0.7 mL of THF was added a solution of 120 mg (0.304 mmol) of the above aldehyde and 312 mg (0.912 mmol) of iodoform in dioxane (4.2 mL + 1.0 mL wash) *via* cannula. The resultant brown suspension was stirred at room temperature for 20 h and then diluted with 200 mL of Et_2O and poured into 200 mL of 1:1 brine/water. The aqueous layer was separated, saturated with NaCl, and extracted with Et_2O (2 × 200 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Analysis of the unpurified reaction mixture by ^{1}H NMR (500 MHz) showed a 14:1 ratio of (*E*)- to (*Z*)-olefins. Purification by flash chromatography gave 121 mg (80%) of a clear, colorless oil:[65] $[\alpha]^{23}_D$ –2.2° (*c* 0.90, CH_2Cl_2); IR (film) 3438 (b), 2957, 2929, 2852, 1612, 1514, 1462, 1249, 1037, 835, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, J = 1.9, 4.3, 2H, ArH), 6.88 (dd, J = 2.0, 6.6, 2H, ArH), 6.45 (m, 1H, C_8-H), 6.01 (d, J = 14.3, 1H, C_9-H), 4.55 (q, J = 4.2, 2H, $ArCH_2$), 3.79 (s, 3H, $ArOCH_3$), 3.71 (m, 1H, C_1-H), 3.65–3.62 (m, 2H, C_1-H, C_5-H), 3.55 (dd, J = 3.9, 6.3, 1H, C_3-H), 2.11 (m, 1H, C_7-H), 1.99 (m, 1H, C_7-H), 1.89–1.83 (m, 2H, C_2-H, C_4-H), 1.70 (m, 1H, C_6-H), 0.99 (t, J = 7.4, 6H, C_2-CH_3, C_4-CH_3), 0.91–0.89 (m, 12H, C_6-CH_3, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 145.6, 130.5, 129.1,1 114.0, 84.8, 77.2, 75.4, 74.8, 65.9, 55.3, 42.1, 41.5, 38.5, 35.8, 26.2, 18.5, 15.3, 13.9, 11.4, –3.1, –3.8. Anal. Calcd for $C_{26}H_{45}IO_4Si$: C, 54.16; H, 7.87. Found: C, 54.08; H, 8.04.

[2*R*,3*R*,4*R*,5*S*,6*R*,8*E*]-9-Iodo-2,4,6-trimethyl-5-((1,1-dimethylethyl)-dimethylsiloxy)-3-((4-methoxyphenyl)methoxy)-8-nonenal (18). To a solution of 67 μL (98 mg; 0.77 mmol) of oxalyl chloride in 1.5 mL of CH_2Cl_2 at -78 °C was added 109 μL (121 mg; 1.55 mmol) of DMSO. This was stirred at –78 °C for 20 min, and then 340 mg (0.645 mmol) of alcohol **17** in CH_2Cl_2 (0.8 mL + 0.4 mL wash) was added dropwise *via* cannula. After 15 min, 214 μL (156 mg; 1.55 mmol) of Et_3N was added. The resultant cloudy mixture was allowed to warm to -10 °C over 1 h and was then poured into 30 mL of 1:1 brine/water solution and 30 mL of Et_2O. The organic layer was separated and washed further with 30 mL of 1:1 brine/water solution and then 30 mL of brine. The combined aqueous washes were back-extracted with Et_2O (2 × 30 mL), and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 310 mg (93%) of a clear, colorless oil: $[\alpha]^{23}_D$ –7.3° (*c* 0.87, CH_2Cl_2); IR (film) 2955, 2930, 2884, 2956, 1723, 1613, 1586, 1514, 1462, 1249, 1039, 836, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, J = 2.6, 1H, CHO), 7.22 (d, J = 8.5, 2H, ArH), 6.88 (d, J = 8.6 , 2H, ArH), 6.42 (m, 1H, C_8-H), 6.00 (d, J = 14.3, 1H, C_9-H), 4.49 (s, 2H, $ArCH_2$), 3.81–3.79 (m, 4H, C_3-H, $ArOCH_3$), 3.67 (dd, J = 1.7, 6.8, 1H, C_5-H), 2.67 (m, 1H, C_2-H), 2.10 (m, 1H, C_7-H), 1.98 (m, 1H, C_7-H), 1.82 (m,

(65) Trace amounts of the (*Z*)-olefin may be removed by preparative HPLC.

1H, C_4-H), 1.72 (m, 1H, C_6-H), 1.10 (d, J = 7.0, 3H, C_2-CH_3), 0.98 (d, J = 7.1, 3H, C_4-CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.88 (d, J = 6.8, 3H, C_6-CH_3), 0.09 (s, 3H $SiCH_3$), 0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 159.2, 145.5, 130.4, 128.8, 113.8, 80.8, 76.8, 75.5, 73.7, 55.2, 50.0, 42.0, 41.6, 35.7, 26.1, 18.4, 13.8, 11.6, 11.2, -3.3, -3.9; HRMS (FAB) m/z calcd for $[M + Na]^+$ 597.1875, found 597.1901.

[3(2*R*,4*R*),4R]-3-(2,4,-Dimethyl-1,3-dioxo-4-(2-ethyl-1,3-dioxan-2-yl)-butyl)-4-(phenylmethyl)-2-oxazolidinone (19). To a solution of 8.08 g (28 mmol) of imide **7** in 120 mL of CH_2Cl_2 at -10 °C were added 3.36 mL (5.84 g; 30.8 mmol) of $TiCl_4$ and 5.36 mL (4.00 g; 30.8 mmol) of i-Pr_2NEt. Enolization was allowed to occur for 1 h at -78 °C before 12.3 mL (12.3 g; 84 mmol) of 2-ethyl-2-ethoxy-1,3-dioxalane[41] was added. The mixture was then allowed to warm to -50 °C over 3.5 h and stirred at -50 °C for 15 h before being quenched with 50 mL of aqueous pH 7 phosphate buffer solution. The mixture was warmed to ambient temperature and then poured into 200 mL of deionized water and 600 mL of CH_2Cl_2. The organic layer was separated and washed further with 200 mL of saturated aqueous $NaHCO_3$ solution and then 200 mL of deionized water. The combined aqueous washes were back-extracted with CH_2Cl_2 (2 × 200 mL) and the organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Analysis of the unpurified reaction mixture by HPLC (25% EtOAc/hexane, flow rate 2 mL/min, 254 nm) showed a 12:1 ratio of **19** to an unidentified diastereomer. Purification by flash chromatography gave 9.49 g (87%) of a clear, colorless oil: $[\alpha]^{23}_D$ -90.0° (c 0.90, CCl_4); IR (CCl_4) 2980, 2940, 2880, 1790, 1595, 1455, 1355, 1275, 1245, 1180, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.13 (m, 5H, ArH), 5.01 (q, J = 7.1, 1H, C_2-H), 4.63 (m, 1H, H_3), 4.16–4.09 (m, 2H, H_4, H_5), 3.93–3.86 (m, 4H, OCH_2CH_2O), 3.22 (dd, J = 3.2, 13.4, 1H, H_1), 3.15 (q, J = 7.0, 1H, C_4-H), 2.72 (dd, J = 9.6, 13.4, 1H, H_2), 1.61 (q, J = 7.4, 2H, CH_2CH_3), 1.41 (d, J = 7.1, 3H, C_2-CH_3), 1.07 (d, J = 7.0, 3H, C_4-CH_3), 0.79 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 170.6, 153.4, 135.2, 129.4, 128.9, 127.3, 112.2, 66.2, 65.6, 65.2, 55.6, 52.2, 50.6, 38.0, 27.6, 13.9, 12.3, 7.1; HRMS (FAB) m/z calcd for $[M + Na]^+$ 412.1736, found 412.1762. Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99. Found: C, 64.38; H, 7.26.

[3(2*R*,3*S*,4*S*),4*R*]-3-(3-Hydroxy-2,4,-dimethyl-1-oxo-4-(2-ethyl-1,3-dioxan-2-yl)butyl)-4-(phenylmethyl)-2-oxazolidinone (20). To a solution of 730 mg (18.7 mmol) of ketone **19** in 93 mL of CH_2Cl_2 at -25 °C was added 18.7 mL (37.5 mmol) of 0.2 M $Zn(BH_4)_2$ in Et_2O.[66] This was allowed to warm to -12 °C over 3 h, and 30 mL of saturated aqueous NH_4Cl solution was added (T < 0 °C). The mixture was stirred at 0 °C for 10 min and then poured into 120 mL of CH_2Cl_2 and 60 mL of brine. The aqueous layer was back-extracted with CH_2Cl_2 (2 × 60 mL), and the organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 600 mg (82%) of a clear, colorless oil: $[\alpha]^{23}_D$ -37.3° (c 1.18, CCl_4); IR (CCl_4) 3550 (b), 2975, 2880, 1790, 1695, 1605, 1455, 1265, 1170, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H, ArH), 4.66 (m, 1H, H_3), 4.26 (d, J = 9.1, 1H, C_3-H), 4.21–4.15 (m, 2H, H_4, H_5), 4.03–3.96 (m, 5H, C_2-H, OCH_2CH_2O), 3.23 (dd, J = 3.2, 13.4, 1H, H_1), 2.76 (dd, J = 9.5, 13.4, 1H, H_2), 1.96 (dq, J = 1.3, 7.1, 1H, C_4-H), 1.77–1.69 (m, 2H, CH_2CH_3), 1.37 (d, J = 6.8, 3H, C_2-CH_3), 0.94–0.90 (m, 6H, C_4-CH_3, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 152.7, 135.0, 129.4, 128.9, 127.3, 114.4, 71.1, 65.9, 65.5, 64.8, 55.0, 41.4, 39.9, 37.6, 28.0, 15.2, 8.0, 7.3. Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47. Found: C, 64.04; H, 7.43.

[3(2*R*,3*S*,4*S*),4*R*]-3-(2,4,-Dimethyl-1-oxo-3-((1,1dimethylethyl)dimethylsiloxy)-4-(2-ethyl-1,3-dioxan-2-yl)butyl)-4-(phenylmethyl)-2-oxazolidinone (21). To a solution of 2.60 g (6.6 mmol) of alcohol **20** in 65 mL of CH_2Cl_2 at 0 °C were added 1.00 mL (0.92 g; 8.6 mmol) of 2,6-lutidine and 1.82 mL (2.09 g; 7.9 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. This was stirred at 0 °C for 1 h and then quenched by addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 20 mL of 0.5 M aqueous $NaHSO_4$ solution. The aqueous wash was back-extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 2.97 g (89%) of a colorless crystalline solid: mp 88–89 °C; $[\alpha]^{23}_D$ -62.0° (c 0.95, CH_2Cl_2); IR (CH_2Cl_2) 2957, 2935, 2884, 2857, 1780, 1698, 1463, 1383, 1210, 1050, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H, ArH), 4.62 (m, 1H, H_3), 4.18 (dd, J = 2.9, 6.3, 1H, C_3-H), 4.17–4.14 (m, 2H, H_4, H_5), 4.01 (quin, J = 6.6, 1H, C_2-H), 3.93–3.91 (m, 4H, OCH_2CH_2O), 3.25 (dd, J = 3.2, 13.4, 1H, H_1), 2.76 (dd, J = 9.7, 13.4, 1H, H_2), 2.09 (dq, J = 2.9, 7.2, 1H, C_4-H), 1.70 (dq, J = 5.8, 7.4, 2H, CH_2CH_3), 1.23 (d, J = 7.0, 3H, C_2-CH_3), 0.95 (d, J = 7.2, 3H, C_4-CH_3), 0.91–0.84 (m, 12H, CH_2CH_3, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.07 (, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 152.9, 135.4, 129.4, 128.9, 127.3, 113.7, 72.1, 65.8, 65.1, 64.9, 55.5, 44.2, 44.0, 37.8, 27.5, 26.1, 18.4, 14.4, 11.1, 7.5, -3.97, -4.00; HRMS (FAB) m/z calcd for $[M + Na]^+$ 528.2757, found 528.2753.

[2(1*S*,2*S*,3*R*)]-2-Ethyl-2-(1,3-dimethyl-2-((1,1-dimethylethyl)dimethylsiloxy)-4-(ethylthio)-4-oxobutyl)-1,3-dioxalane (22). To a solution of 237 μL (199 mg; 3.2 mmol) of ethanethiol in 12 mL of THF at -78 °C was added 1.73 mL (2.6 mmol) of 1.50 M n-butyllithium in hexane. The mixture was allowed to warm to 0 °C, at which time it became cloudy. A solution of imide **21** (600 mg; 1.17 mmol) in THF (10 mL + 10 mL wash) was added *via* cannula. The mixture was stirred at 0 °C for 30 min and then poured into 300 mL of Et_2O and 120 mL of 1 M aqueous NaOH solution. The organic layer was separated and washed with 120 mL of brine. The combined aqueous washes were back-extracted with 120 mL of Et_2O, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 448 mg (98%) of a clear, colorless oil: $[\alpha]^{23}_D$ -34.0° (c 0.86, CH_2Cl_2); IR (film) 2933, 2884, 2857, 1680, 1462, 1254, 1051, 960, 834, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (dd, J = 3.0, 4.8, 1H, C_2–$C_{2'}$-H), 3.95–3.87 (m, 4H, C_4-H_2, C_5-H_2), 2.83 (dt, J = 3.0, 7.0, 1H, C_2–$C_{3'}$-H), 2.77 (q, J = 7.5, 2H, CH_2S), 1.96 (m, 1H, C_2–$C_{1'}$-H), 1.58 (m, 2H, C_2-CH_2), 1.18 (t, J = 7.4, 3H, CH_3CH_2S), 1.07 (d, J = 7.0, 3H, C_2–$C_{3'}$-CH_3), 0.86–0.77 (m, 15H, C_2-CH_2CH_3, C_2–$C_{1'}$-CH_3, $SiC(CH_3)_3$), -0.01 (s, 3H, $SiCH_3$), -0.07 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 113.7, 72.2, 65.0, 64.9, 55.1, 42.4, 27.0, 26.1, 23.1, 18.4, 14.6, 11.5, 10.7, 7.4, -4.0, -4.3; HRMS (FAB) m/z calcd for $[M + Na]^+$ 413.2158, found 413.2156. Anal. Calcd for $C_{19}H_{38}O_4SSi$: C, 58.42; H, 9.80. Found: C, 58.58; H, 9.69.

[2(1*S*,2*S*,3*R*)]-2-Ethyl-2-(1,3-dimethyl-2-((1,1-dimethylethyl)dimethylsiloxy)-formylpropyl)-1,3-dioxalane (23). To a solution of 250 mg (0.64 mmol) of thioester **22** in 6 mL of acetone were added 34 mg (0.03 mmol) of 10% Pd/C and 204 μL (149 mg; 1.28 mmol) of triethylsilane. Gas evolution was immediately observed. After 15 min, TLC analysis indicated incomplete reaction, so another 102 μL (75 mg; 0.64 mmol) of triethylsilane was added. Thirty minutes later the mixture was filtered through a short column of silica gel with EtOAc. The filtrate was concentrated *in vacuo*, and the residue was chromatographed to give 211 mg (100%) of a clear, colorless liquid: $[\alpha]^{23}_D$ -58.0° (c 0.81, CH_2Cl_2); IR (film) 2936, 2885, 2858, 1723, 1463, 1254, 1048, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H, CHO), 4.25 (t, J = 3.8, 1H, C_2–$C_{2'}$-H), 3.94–3.89 (m, 4H, C_4-H_2, C_5-H_2), 2.63 (dt, J = 3.5, 6.8, 1H, C_2–$C_{1'}$-H), 1.68–1.58 (m, 2H, C_2-CH_2), 1.01 (d, J = 6.9, 3H, C_2–$C_{3'}$-CH_3), 0.90–0.81 (m, 15H, C_2-CH_2CH_3, C_2–$C_{1'}$-CH_3, $SiC(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 113.6, 71.2, 65.0, 64.9, 53.8, 41.6, 26.5, 26.0, 18.3, 11.2, 8.3, 7.1, -3.9, -4.4; HRMS (FAB) m/z calcd for $[M + Na]^+$ 353.2124, found 353.2101.

1,1-Dimethylethyl[2*E*,4*S*,5*R*,6*S*]-4,6-Dimethyl-5-((1,1-dimethylethyl)-dimethylsiloxy)-6-(2-ethyl-1,3-dioxan-2-yl)-2-hexenoate (24). To a solution of 520 μL (561 mg; 2.2 mmol) of *tert*-butyl diethylphosphonoacetate in 5 mL of THF was added 1.36 mL (2.1 mmol) of 1.54 M n-butyllithium in hexane over a 2-min period. The resultant solution was stirred at ambient temperature for 45 min, and then 210 mg (0.635 mmol) of aldehyde **23** in THF (3 mL + 1 mL wash) was added *via* cannula. After 30 min, the mixture was poured into 100 mL of EtOAc and 100 mL of aqueous pH 7 phosphate buffer. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered through a short column of silica gel with EtOAc, and concentrated *in vacuo*. Purification by flash chromatography gave 272 mg (100%) of a clear, colorless oil: $[\alpha]^{23}_D$ -28.0° (c 0.61, CH_2Cl_2); IR (film) 2965, 2935, 2884, 1714, 1650, 1463, 1367, 1254, 1158, 1049, 837, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dd, J = 6.1, 15.9, 1H, C_3-H), 5.60 (dd, J = 1.6, 15.8, 1H, C_2-H), 3.90–3.83 (m, 5H, C_5-H, OCH_2CH_2O), 2.44 (m, 1H, C_4-H), 1.76 (dq, J = 2.7, 7.2, 1H, C_6-H), 1.61–1.52 (m, 2H, CH_2CH_3), 1.42 (s, 9H, $OC(CH_3)_3$), 0.93 (d, J = 6.8, 3H, C_4-CH_3), 0.84–0.78 (m, 15H, C_6-CH_3, CH_2CH_3, $SiC(CH_3)_3$), 0.006 (s, 3H, $SiCH_3$), -0.005 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 150.7, 122.0, 113.9, 79.8, 73.4, 65.0, 64.9, 43.5, 41.1, 28.1, 26.5, 26.0, 18.3, 13.2, 11.0, 7.1, -3.8, -4.4;

(66) For optimum yields, this reaction requires that the zinc borohydride be freshly prepared and free of residual zinc chloride. See ref 62.

HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 451.2856, found 451.2878. Anal. Calcd for $C_{23}H_{44}O_5Si$: C, 64.44; H, 10.35. Found: C, 64.53; H, 10.73.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*]-4,6-Dimethyl-7-oxo-5-((1,1-dimethylethyl)dimethylsiloxy)-2-nonenoate (25). To a solution of 400 mg (0.93 mmol) of ketal **24** in 22 mL of acetone was added 100 mg of $FeCl_3$·SiO_2 complex. After being stirred at ambient temperature for 11 h, the mixture was filtered through a short column of silica gel with EtOAc. The filtrate was concentrated *in vacuo*, and the residue purified by flash chromatography to give 342 mg (95%) of a clear, colorless oil: $[\alpha]^{23}_D$ –12.6° (*c* 1.20, CH_2Cl_2); IR (film) 2933, 2858, 1714, 1652, 1462, 1367, 1254, 1154, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 7.4, 15.8, 1H, C_3-H), 5.63 (dd, *J* = 1.3, 15.7, 1H, C_2-H), 3.96 (dd, *J* = 4.9, 5.7, 1H, C_5-H), 2.56 (dt, *J* = 6.1, 7.0, 1H, C_6-H), 2.41 (q, *J* = 7.3, 2H, C_8-H_2), 2.33 (m, 1H, C_4-H), 1.42 (s, 9H, $OC(CH_3)_3$), 1.02 (d, *J* = 7.1, 3H, C_4-CH_3), 0.98–0.94 (m, 6H, C_6-CH_3, C_9-CH_3), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.00 (s, 3H, $SiCH_3$), –0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 165.8, 150.1, 122.8, 80.1, 75.5, 50.0, 41.4, 35.2, 28.1, 26.0, 18.3, 14.2, 13.1, 7.6, –4.1, –4.2; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 407.2594, found 407.2608. Anal. Calcd for $C_{21}H_{40}O_4Si$: C, 65.58; H, 10.48. Found: C, 66.13; H, 10.62.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*,8*R*,9*S*,10*S*,11*S*,12*R*,13*S*,14*R*,16*E*]-9-Hydroxy-17-iodo-4,6,8,10,12,14-hexamethyl-7-oxo-11-((4-methoxyphenyl)methoxy-5,13-bis((1,1-dimethylethyl)dimethylsiloxy)heptadeca-2,16-dienoate (26). To a solution of 136 mg (0.354 mmol) of ketone **25** in 1.75 mL of CH_2Cl_2 at –78 °C was added 43 μL (74 mg; 0.39 mmol) of $TiCl_4$ and 74 μL (55 mg; 0.42 mmol) of *i*-Pr_2NEt. The resultant deep red solution was stirred at –78 °C for 90 min before 176 mg (0.306 mmol) of aldehyde **18** dissolved in CH_2Cl_2 (0.4 mL + 0.3 mL wash) was added dropwise *via* cannula. The mixture was stirred at –78 °C for 2 h and then allowed to warm to –25 °C over a 3-h period. Aqueous pH 7 phosphate buffer solution (2 mL) was then added, and the mixture was allowed to warm to ambient temperature. The mixture was poured into 15 mL of CH_2Cl_2 and 15 mL of deionized water. The organic layer was separated and washed with 15 mL of saturated aqueous $NaHCO_3$ solution and then with 15 mL of deionized water. The combined aqueous extracts were back-extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Analysis of the unpurified reaction mixture by HPLC (7% EtOAc/hexane, flow rate 2 mL/min, 254 nm) showed a 97:3 ratio of **26** to an unidentified diastereomer. Purification by flash chromatography gave 240 mg (83%) of a clear, colorless oil: $[\alpha]^{23}_D$ –10.2° (*c* 1.03, CH_2Cl_2); IR (film) 3487 (b), 2956, 2931, 2857, 1712, 1653, 1613, 1515, 1462, 1368, 1252, 1037, 837, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5, 2H, ArH), 6.85 (d, *J* = 8.5, 2H, ArH), 6.78 (dd, *J* = 7.3, 15.8, 1H, C_3-H), 6.44 (m, 1H, C_{16}-H), 6.00 (d, *J* = 14.4, 1H, C_{17}-H), 5.67 (d, *J* = 15.8, 1H, C_2-H), 4.58 (d, *J* = 10.3, 1H, ArCH), 4.44 (d, *J* = 10.2, 1H, ArCH), 4.07 (d, *J* = 9.3, 1H, C_9-H), 4.02 (t, *J* = 4.8, 1H, C_5-H), 3.79 (s, 3H, $ArOCH_3$), 3.67 (dd, *J* = 2.1, 5.1, 1H, C_{11}-H), 3.42 (dd, *J* = 2.0, 7.4, 1H, C_{13}-H), 2.83 (dt, *J* = 7.0, 9.2, 1H, C_8-H), 2.65 (dt, *J* = 4.6, 7.2, 1H, C_6-H), 2.32 (dt, *J* = 5.9, 12.6, 1H, C_4-H), 2.13–2.10 (m, 2H, C_{12}-H, C_{15}-H), 1.97 (m, 1H, C_{15}-H), 1.51–1.47 (m, 11H, C_{10}-H, C_{14}-H, $OC(CH_3)_3$), 1.20 (d, *J* = 6.8, 3H, C_8-CH_3), 1.15 (d, *J* = 7.2, 3H, C_6-CH_3), 1.13 (d, *J* = 7.1, 3H, C_{12}-CH_3), 1.04–1.02 (m, 6H, C_4-CH_3, C_{14}-CH_3), 0.92–0.88 (m, 21H, C_{10}-CH_3, $SiC(CH_3)_3$), 0.15 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 165.6, 159.4, 150.1, 145.5, 130.1, 129.2, 122.9, 114.0, 87.0, 80.0, 75.8, 75.5, 74.0, 72.0, 55.2, 50.4, 48.8, 42.4, 42.3, 41.3, 37.6, 35.4, 33.6, 28.2, 26.1, 18.41, 18.36, 14.9, 14.3, 14.2, 12.9, 12.7, 11.9, –3.6, –3.9, –4.3, –4.4; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 981.4571, found 981.4600.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*,8*R*,9*S*,10*R*,11*R*,12*R*,13*S*,14*R*,16*E*]-17-Iodo-4,6,8,10,12,14-hexamethyl-7-oxo-11-((4-methoxyphenyl)methoxy)-5,9,13-tris((1,1-dimethylethyl)dimethylsiloxy)heptadeca-2,16-dienoate (27). To a solution of 157 mg (0.164 mmol) of alcohol **26** in 3.0 mL of CH_2Cl_2 at –50 °C were added 23 μL (21 mg; 0.20 mmol) of 2,6-lutidine and 41 μL (48 mg; 0.18 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. This was allowed to warm to –25 °C over 45 min and then kept at that temperature for 3 h. The reaction was stopped by addition of 0.5 mL of MeOH and stirring at –25 °C for 15 min. The mixture was then poured into 15 mL of 0.3 M aqueous $NaHSO_4$ solution and 15 mL of CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 169 mg (96%) of a clear, colorless oil: $[\alpha]^{23}_D$ –5.6° (*c* 0.68, CH_2Cl_2); IR (film) 2956, 2930, 2857, 1713, 1652, 1613, 1514, 1463, 1251, 1040, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6, 2H, ArH), 6.85 (d, *J* = 8.6, 2H, ArH), 6.80 (dd, *J* = 6.9, 15.8, 1H, C_3-H), 6.35 (m, 1H, C_{16}-H), 5.92 (d, *J* = 14.3, 1H, C_{17}-H), 5.60 (dd, *J* = 1.3, 15.8, 1H, C_2-H), 4.53 (d, *J* = 11.1, 1H, ArCH), 4.46 (d, *J* = 11, 1H, ArCH), 4.20 (t, *J* = 4.0, 1H, C_9-H), 4.08 (dd, *J* = 3.6, 5.4, 1H, C_5-H), 3.60 (dd, *J* = 1.4, 5.9, 1H, C_{11}-H), 3.37 (dd, *J* = 1.5, 7.7, 1H, C_{13}-H), 2.83 (dt, *J* = 4.7, 6.9, 1H, C_8-H), 2.77 (dt, *J* = 5.7, 2.2, 1H, C_6-H), 2.26 (m, 1H, C_4-H), 2.06 (m, 1H, C_{15}-H), 1.92 (m, 1H, C_{15}-H), 1.79–1.77 (m, 3H, C_{10}-H, C_{12}-H, C_{14}-H), 1.45 (s, 9H, $OC(CH_3)_3$), 1.08 (d, *J* = 2.6, 3H, C_8-CH_3), 1.07 (d, *J* = 2.8, 3H, C_6-CH_3), 0.94 (d, *J* = 6.8, 3H, C_4-CH_3), 0.91 (d, *J* = 7.2, 3H, C_{10}-CH_3), 0.88–0.83 (m, 30H, C_{12}-CH_3, $SiC(CH_3)_3$), 0.79 (d, *J* = 7.0, 3H, C_{14}-CH_3), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), –0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 165.8, 158.9, 150.8, 145.6, 131.1, 128.3, 122.3, 113.7, 81.2, 79.9, 78.4, 75.2, 74.2, 72.9, 72.4, 55.3, 50.9, 49.6, 42.0, 41.4, 40.3, 35.9, 28.2, 26.3, 26.2, 26.1, 18.6, 18.5, 18.4, 14.5, 13.6, 13.2, 12.9, 10.4, –3.2, –3.5, –3.6, –3.8, –4.0, –4.2; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 1095.5435, found 1095.5453.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*,8*R*,9*S*,10*R*,11*R*,12*R*,13*S*,14*R*,16*E*]-11-Hydroxy-17-iodo-4,6,8,10,12,14-hexamethyl-7-oxo-5,9,13-tris((1,1-dimethylethyl)dimethylsiloxy)-heptadec-2,16-dienoate (28). To a solution of 78 mg (0.073 mmol) of ester **27** in 2.4 mL of 18:1 CH_2Cl_2/water at 5 °C was added 20 mg (0.087 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). After the mixture was stirred vigorously for 1 h, 4 mL of saturated aqueous $NaHCO_3$ solution was added to the dark green solution, and the resultant orange mixture was poured into 10 mL of deionized water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 69 mg (100%) of a clear, colorless oil: $[\alpha]^{23}_D$ –6.7° (*c* 0.86, CH_2Cl_2); IR (film) 3486 (b), 2956, 2930, 2857, 1713, 1650, 1472, 1462, 1367, 1255, 1150, 990, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 7.2, 15.7, 1H, C_3-H), 6.34 (m, 1H, C_6-H), 5.92 (d, *J* = 14.6, 1H, C_{17}-H), 5.61 (dd, *J* = 1.2, 15.8, 1H, C_2-H), 4.29 (dd, *J* = 1.3, 6.2, 1H, C_9-H), 4.01 (dd, *J* = 3.5, 5.8, 1H, C_5-H), 3.64 (d, *J* = 10.1, 1H, C_{11}-H), 3.52–3.50 (m, 2H, C_{13}-H, OH), 2.81 (m, 1H, C_8-H), 2.70 (m, 1H, C_6-H), 2.22–2.16 (m, 2H, C_4-H, C_{15}-H), 1.81-1.70 (m, 2H, C_{14}-H, C_{15}-H), 1.57 (m, 1H, C_{12}-H), 1.47–1.40 (m, 10H, C_{10}-H, $OC(CH_3)_3$), 1.08 (d, *J* = 3.0, 3H, C_8-CH_3), 1.07 (d, *J* = 3.2, 3H, C_6-CH_3), 0.96 (d, *J* = 6.8, 3H, C_4-CH_3), 0.89–0.80 (m, 33H, C_{12}-CH_3, C_{14}-CH_3, $SiC(CH_3)_3$), 0.60 (d, *J* = 6.9, 3H, C_{10}-CH_3), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), –0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 165.8, 150.8, 145.0, 122.7, 81.3, 80.0, 75.3, 74.4, 72.4, 71.1, 49.8, 49.2, 41.4, 40.6, 40.3, 37.3, 36.1, 28.2, 26.2, 26.1, 18.4, 18.3, 15.6, 14.5, 13.7, 13.3, 11.4, 10.8, –3.7, –3.8, –3.9, –4.2, –4.4; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 975.4860, found 975.4887.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*,8*R*,9*R*,10*S*,12*S*,13*S*,14*R*,16*E*]-17-Iodo-4,6,8,10,12,14-hexamethyl-7,11-dioxo-5,9,13-tris((1,1-dimethylethyl)-dimethylsilyloxy)-heptadeca-2,16-dienoate (29). To a suspension of 237 mg (0.561 mmol) of Dess–Martin periodinane[47] in 3.0 mL of CH_2Cl_2 at 0 °C were added 227 μL (222 mg; 2.8 mmol) of pyridine, followed by 107 mg (0.112 mmol) of alcohol **28** in CH_2Cl_2 (0.5 mL + 0.2 mL wash). The mixture was stirred at ambient temperature for 30 h, diluted with 60 mL of EtOAc, and washed with 30 mL of saturated aqueous $NaHCO_3$ solution and 30 mL of saturated aqueous $Na_2S_2O_3$ solution. The combined aqueous washes were back-extracted with 30 mL of EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 103 mg (96%) of a clear, colorless oil: $[\alpha]^{23}_D$ –0.89° (*c* 0.67, CH_2Cl_2); IR (film) 2956, 2931, 2857, 1712, 1653, 1472, 1462, 1254, 1150, 994, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 7.0, 15.8, 1H, C_3-H), 6.49 (m, 1H, C_{16}-H), 6.05 (d, *J* = 14.4, 1H, C_{17}-H), 5.76 (dd, *J* = 1.3, 15.8, 1H, C_2-H), 4.34 (dd, *J* = 3.5, 6.6, 1H, C_9-H), 4.13 (dd, *J* = 3.8, 5.7, 1H, C_5-H), 3.96 (dd, *J* = 1.8, 7.8, 1H, C_{13}-H), 3.00 (m, 1H, C_{12}-H), 2.90 (m, 1H, C_6-H), 2.78–2.74 (m, 2H, C_8-H, C_{10}-H), 2.48 (m, 1H, C_4-H), 2.20 (m, 1H, C_{15}-H), 2.00 (m, 1H, C_{15}-H), 1.68 (m, 1H, C_{14}-H), 1.53 (s, 9H, $OC(CH_3)_3$), 1.15 (d, *J* = 7.1, 3H, C_6-CH_3), 1.11–1.08 (m, 9H, C_4-CH_3, C_8-CH_3, C_{10}-CH_3), 1.05 (d, *J* = 7.1, 3H, C_{12}-CH_3), 0.94–0.91 (m, 21H, C_{14}-CH_3, $SiC(CH_3)_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 9H, $SiCH_3$), 0.07 (s, 6H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 213.5, 165.8, 150.6, 145.4, 122.8, 80.0, 75.4, 74.7, 72.0, 50.44, 50.40, 49.7, 48.9, 41.4, 40.9, 36.3, 28.2,

26.2, 26.1, 18.5, 18.4, 13.8, 13.6, 13.4, 13.1, 12.2, -3.6, -3.8, -3.9, -4.1, -4.2, -4.5; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 973.4704, found 973.4692.

1,1-Dimethylethyl [2*E*,4*S*,5*R*,6*S*,8*R*,9*S*,10*S*,12*S*,13*S*,14*R*,16*E*,18*E*,-20*R*,22(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*)]-20-Ethyl-4,6,8,10,12,14-hexamethyl-7,11-dioxo-5,9,13-tris((1,1-dimethylethyl)dimethylsiloxy)-22-[3,9-dimethyl-4-(triethylsiloxy)-8-(2-((1,1dimethylethyl)dimethylsiloxy)propyl)-1,7-dioxaspiro[5.5]undec-2-yl]-2,16,18-docosatrienoate (31). To a solution of 100 mg (0.154 mmol) of vinylboronic acid **4** in 4.8 mL of freshly distilled, degassed THF was added 0.88 mL (0.40 mmol) of 10% aqueous TlOH solution. This was stirred for 5 min, and 52 mg (0.055 mmol) of vinyl iodide **29** in degassed THF (1.0 mL + 0.5 mL wash) was added *via* cannula, followed by 12.6 mg (0.011 mmol) of tetrakis(triphenylphosphine)palladium(0)[50] in 0.3 mL of degassed THF. After being stirring for 45 min, the cloudy green suspension was diluted with 30 mL of Et_2O, and anhydrous $MgSO_4$ was added. This was stirred for 15 min and then filtered through a short column of silica gel with EtOAc. The filtrate was concentrated *in vacuo* and purified by flash chromatography to give 59 mg (77%) of a clear, colorless oil: $[\alpha]^{23}_D$ -18.1° (*c* 1.19, CH_2Cl_2); IR (film) 2958, 2858, 1714, 1656, 1462, 1384, 1254, 1073, 989, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 7.0, 11.4, 1H, C_2-H), 6.01–5.92 (m, 2H, C_{17}-H, C_{18}-H), 5.70 (dd, *J* = 1.3, 8.3, 1H, C_3-H), 5.48 (m, 1H, C_{16}-H), 5.31 (dd, *J* = 5.0, 8.8, 1H, C_{19}-H), 4.28 (dd, *J* = 3.3, 6.8, 1H, C_9-H), 4.11 (ddd, *J* = 4.9, 4.9, 1.5, 1H, C_{25}-H), 4.07 (dd, *J* = 3.8, 5.7, 1H, C_5-H), 3.91 (dd, *J* = 1.8, 7.9, 1H, C_{13}-H), 3.79 (m, 1H, C_{33}-H), 3.70 (dt, *J* = 1.1, 6.0, 1H, C_6-H), 2.74 (quin, *J* = 7.2, 1H, C_8-H), 2.69 (dd, *J* = 3.3, 7.0, 1H, C_{10}-H), 2.33 (m, 1H, C_{24}-H), 2.16 (m, 1H, C_{15}-H), 2.05 (m, 1H, C_{29}-H_{ax}), 1.93 (m, 1H, C_{15}-H), 1.87 (m, 1H, C_{20}-H), 1.66 (m, 1H, C_{24}-H), 1.60–1.35 (m, 24H, $OC(CH_3)_3$, C_{14}-H, C_{20}-H_2, C_{21}-H_2, C_{22}-H_2, C_{26}-H_2, C_{28}-H_2, C_{29}-H, C_{30}-H, C_{32}-H_2), 1.19 (d, *J* = 6.0, 3H, C_{34}-H_3), 1.08 (d, *J* = 7.2, 3H, C_6-CH_3), 1.15–1.12 (m, 9H, C_4-CH_3, C_8-CH_3, C_{10}-CH_3), 1.00 (d, *J* = 7.1, 3H, C_{12}-CH_3), 0.93 (t, *J* = 8.0, 9H, $Si(CH_2CH_3)_3$), 0.90 (d, *J* = 7.1, 3H, C_{30}-CH_3), 0.88–0.86 (m, 39H, C_{14}-CH_3, $SiC(CH_3)_3$), 0.83 (t, *J* = 7.4, 3H, C_{20}-CH_2CH_3), 0.79 (d, *J* = 6.9, 3H, C_{24}-CH_3), 0.55 (q, *J* = 8.0, 6H, $Si(CH_2CH_3)_3$), 0.08 (s, 9H, $SiCH_3$), 0.07 (s, 6H, $SiCH_3$), 0.02 (s, 6H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 213.7, 165.8, 150.6, 136.6, 132.0, 130.5, 130.2, 122.8, 97.4, 79.9, 76.0, 74.6, 72.1, 71.0, 69.1, 67.84, 67.76, 50.5, 49.5, 48.7, 44.6, 43.6, 41.4, 39.7, 39.1, 37.5, 37.1, 32.1, 30.5, 30.0, 29.7, 28.1, 27.8, 26.5, 26.2, 26.13, 26.08, 25.9, 24.6, 18.41, 18.37, 18.1, 13.6, 13.3, 13.5, 13.2, 12.0, 11.6, 11.2, 6.8, 5.0, 4.2, -3.5, -3.9, -4.2, -4.3, -4.4, -4.5, -4.6; <HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 1428.0078, found 1428.0103.

[2*E*,4*S*,5*R*,6*S*,8*R*,9*S*,10*S*,12*S*,13*S*,14*R*,16*E*,18*E*,20*R*,22-(2*S*,3*R*,4*S*,6*R*,8*S*,8(2*R*),9*S*)]-20-Ethyl-4,6,8,10,12,14-hexamethyl-7,11-dioxo-5,9,13-tris((1,1-dimethylethyl)dimethylsiloxy)-22-[4-hydroxy-3,9-dimethyl-8-(2-((1,1dimethylethyl)dimethylsiloxy)propyl)-1,7-dioxaspiro[5.5]undec-2-yl]-2,16,18-docosatrienoic acid (32). To a solution of 33 mg (0.024 mmol) of ester **31** in 1.5 mL of CH_2Cl_2 at 0 °C were added 26 μL (24 mg; 0.24 mmol) of 2,6-lutidine and 22 μL (25 mg; 0.12 mmol) of trimethylsilyl trifluoromethanesulfonate. After being stirred at 0 °C for 90 min, the mixture was filtered through a short column of silica gel with 30% EtOAc/hexanes and concentrated *in vacuo* to give 33 mg (104%) of the unpurified carboxylic acid as a clear, colorless oil.

To a solution of the carboxylic acid in 0.5 mL of THF was added 29 μL (28 mg; 0.35 mmol) of pyridine and 290 μL (0.35 mmol) of a 1.2 M pyridinium hydrofluoride solution buffered with excess pyridine (stock solution prepared from 10 mL of THF, 7 mL of pyridine, and 2.0 g of Fluka pyridinium hydrofluoride). This was stirred at ambient temperature for 6 h and then diluted with 20 mL of CH_2Cl_2 and 15 mL of deionized water. The aqueous layer was acidifed to pH 2.5 by dropwise addition of 0.1 M aqueous $NaHSO_4$ solution with intermittent shaking. The aqueous layer was separated and extracted further with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 28.5 mg (98%) of a clear, colorless oil: $[\alpha]^{23}_D$ -12.0° (*c* 0.80, CH_2Cl_2); IR (film) 3360 (b), 2958, 2931, 2858, 1704, 1657, 1651, 1463, 1383, 1254, 989, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 7.0, 15.8, 1H, C_2-H), 6.04–5.92 (m, 2H, C_{17}-H, C_{18}-H), 5.82 (dd, *J* = 1.0, 15.3, 1H, C_3-H), 5.50 (quin, *J* = 6.7, 1H, C_{16}-H), 5.30 (dd, *J* = 8.8, 14.3, 1H, C_{19}-H), 4.28 (dd, *J* = 3.4, 6.6, 1H, C_9-H), 4.19 (dt, *J* = 11.8, 5.8, 1H, C_{25}-H), 4.10 (m, 1H, C_5-H), 3.91 (dd, *J* = 1.4, 7.8, 1H, C_{13}-H), 3.80 (m, 1H, C_{33}-H), 3.73 (dt, *J* = 2.2, 7.0, 1H, C_6-H), 3.56 (m, 1H, C_{31}-H), 2.96 (quin, *J* = 7.4, 1H, C_{12}-H), 2.84 (quin, *J* = 6.9, 1H, C_{12}-H), 2.78–2.70 (m, 2H, C_8-H, C_{10}-H), 2.42 (m, 1H, C_4-H), 2.17 (m, 1H, C_{15}-H), 2.03 (m, 1H, C_{29}-H_{ax}), 1.93 (m, 1H, C_{15}-H), 1.86 (m, 1H, C_{20}-H), 1.81 (m, 1H, C_{24}-H), 1.70 (dd, *J* = 6.2, 12.2, 1H, C_{26}-H_{ax}), 1.67–1.23 (m, 14H, C_{14}-H, C_{20}-H_2, C_{21}-H_2, C_{22}-H_2, C_{26}-H_{eq}, C_{28}-H_2, C_{29}-H_{eq}, C_{30}-H, C_{32}-H_2), 1.18 (d, *J* = 6.0, 3H, C_{34}-H_3), 1.10 (d, *J* = 7.1, 3H, C_6-CH_3), 1.07–1.03 (m, 9H, C_4-CH_3, C_8-CH_3, C_{10}-CH_3), 1.01 (d, *J* = 7.0, 3H, C_{12}-CH_3), 0.92 (d, *J* = 7.0, 3H, C_{30}-CH_3), 0.88–0.86 (m, 39H, C_{14}-CH_3, $SiC(CH_3)_3$), 0.85 (t, *J* = 7.4, 3H, C_{20}-CH_2-CH_3), 0.82 (d, *J* = 7.0, 3H, C_{24}-CH_3), 0.08 (s, 9H, $SiCH_3$), 0.05 (s, 6H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 213.8, 170.0, 154.4, 136.6, 132.0, 130.6, 130.4, 120.2, 97.6, 76.0, 74.4, 72.2, 71.1, 69.3, 67.5, 67.3, 50.7, 50.5, 49.6, 48.8, 44.6, 43.4, 41.9, 39.2, 38.1, 37.5, 37.2, 32.0, 30.3, 29.8, 29.7, 27.9, 26.5, 26.22, 26.18, 26.1, 25.9, 24.5, 18.5, 18.4, 18.1, 13.9, 13.5, 13.45, 13.38, 13.2, 12.1, 11.6, 11.0, 4.0, -3.5, -3.9, -4.2, -4.3, -4.5; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 1257.8588, found 1257.8606.

[1*S*,4*E*,5′*S*,6*S*,6′*S*,6′(2*R*),7*R*,8*S*,10*R*,11*S*,12*S*,14*S*,15*S*,16*R*,18*E*,20*E*,-22*R*,25*S*,27*R*,29*R*]-7,11,15-Tris((1,1-dimethylethyl)dimethylsiloxy)-6′-(2-((1,1-dimethylethyl)dimethylsiloxy)propyl)-22-ethyltetrahydro-5′,6,8,-12,14,16,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-4,18,20-triene-27,2′-[2*H*]pyran]-3,9,13-trione (33). The seco acid **32** (27 mg; 0.022 mmol) was azeotropically dried with 5 mL of benzene and dissolved in 150 mL of benzene. Triethylamine (183 μL; 132 mg; 1.32 mmol), 2,4,6-trichlorobenzoyl chloride (135 μL, 213 mg; 0.87 mmol), and anhydrous 4-(dimethylamino)pyridine (DMAP) (27 mg, 0.22 mmol) were added. After the mixture was stirred for 1 h, another 27 mg (0.22 mmol) of anhydrous DMAP was added. The cloudy white mixture was stirred for 10 h more before it was diluted with 300 mL of CH_2Cl_2 and washed with 200 mL of 0.1 M aqueous $NaHSO_4$ solution. The aqueous layer was back-extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography gave a clear, colorless oil. Residual benzene was detected in the purified product and removed *in vacuo* (7 mT, 2 days) to give 23 mg (86%) of lactone **33**: $[\alpha]^{23}_D$ -38.5° (*c* 1.10, CH_2Cl_2); IR (film) 2956, 2931, 2858, 1718, 1651, 1463, 1385, 1256, 1063, 990, 836, 755, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 7.0, 15.8, 1H, C_3-H), 6.05–5.93 (m, 2H, C_{17}-H, C_{18}-H), 5.78 (dd, *J* = 1.2, 15.9, 1H, C_2-H), 5.40 (ddd, *J* = 4.6, 8.8, 13.9, 1H, C_{16}-H), 5.33–5.27 (m, 2H, C_{25}-H, C_{19}-H), 4.27 (dd, *J* = 1.4, 6.2, 1H, C_9-H), 4.15 (dd, *J* = 2.3, 7.5, 1H, C_{23}-H), 3.93 (d, *J* = 2.1, 7.0, 1H, C_{13}-H), 3.81 (q, *J* = 6.0, 1H, C_{33}-H), 3.72–3.67 (m, 2H, C_5-H, C_{31}-H), 2.96 (quin, *J* = 7.2, 1H, C_{12}-H), 2.81 (dq, *J* = 2.1, 7.0, 1H, C_6-H), 2.76 (quin, *J* = 7.3, 1H, C_8-H), 2.68 (q, *J* = 7.3, 1H, C_{10}-H), 2.48 (q, *J* = 6.2, 1H, C_4-H), 2.17 (dt, *J* = 15.1, 9.3, 1H, C_{15}-H), 2.09–1.96 (m, 4H, C_{14}-H, C_{15}-H, C_{20}-H, C_{24}-H), 1.81 (dd, *J* = 5.0, 12.5, 1H, C_{26}-H_{ax}), 1.68–1.50 (m, 8H, C_{20}-CH_2CH_3, C_{22}-H_2, C_{26}-H_{eq}, C_{30}-H, C_{32}-H_2), 1.44-1.25 (m, 6H, C_{21}-H_2, C_{28}-H_2, C_{29}-H_2), 1.19 (d, *J* = 6.0, 3H, C_{34}-CH_3), 1.086 (d, *J* = 6.8, 3H, C_4-CH_3), 1.079 (d, *J* = 6.3, 3H, C_{10}-CH_3), 1.008 (d, *J* = 7.2, 3H, C_6-CH_3), 1.006 (d, *J* = 3H, C_8-CH_3), 0.938 (d, *J* = 6.8, 3H, C_{30}-CH_3), 0.927 (d, *J* = 6.8, 3H, C_{12}-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 18H, $SiC(CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.84 (t, *J* = 7.4, 3H, C_{20}-CH_2CH_3), 0.81 (d, *J* = 6.9, 3H, C_{24}-CH_3), 0.13 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.05 (s, 6H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), -0.01 (s, 6H, $SiCH_3$), -0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 213.2, 165.4, 150.5, 136.1, 131.9, 131.5, 131.3, 128.3, 121.4, 97.4, 73.0, 72.8, 72.1, 70.4, 69.5, 69.3, 67.3, 51.8, 50.6, 47.4, 47.2, 44.1, 43.3, 42.7, 37.8, 35.8, 35.5, 34.9, 30.8, 29.8, 29.7, 28.7, 27.7, 26.5, 26.3, 26.1, 25.9, 24.5, 18.6, 18.4, 18.3, 18.0, 16.1, 14.7, 14.0, 13.0, 12.0, 11.4, 11.1, 11.0, 5.1, -3.3, -3.8, -4.07, -4.09, -4.2, -4.4, -4.6; HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 1239.8462, found 1239.8477.

[1*S*,5*E*,5′*S*,6′*S*,6′(2*R*),7*R*,8*S*,10*R*,11*S*,12*S*,14*S*,15*S*,16*R*,18*E*,20*E*,-22*R*,25*S*,27*R*,29*R*]-7,11,15-Tris((1,1-dimethylethyl)dimethylsiloxy)-6′-(2-((1,1-dimethylethyl)dimethylsiloxy)propyl)-22-ethyltetrahydro-5′,6,8,-12,14,16,29-octamethylspiro[2,26-dioxabicyclo[23.3.1]nonacosa-5,18,20-triene-27,2′-[2*H*]pyran]-3,9,13-trione (34). To a solution of 7.9 mg (0.031 mmol) of *N*-methyl-2-chloropyridinium iodide in 4.0 mL of refluxing CH_2Cl_2 were added a solution of 3.9 mg (0.0031 mmol) of the seco acid **32** and 8.6 μL (6.2 mg; 0.062 mmol) of Et_3N in 4.0 mL of CH_2Cl_2 over an 18-h period *via* syringe pump. The syringe was rinsed with 0.5 mL of CH_2Cl_2 and the rinse added to the refluxing mixture over 3 h. The mixture was cooled to ambient temperature and washed with 0.1 N aqueous $NaHSO_4$ solution (2 × 15 mL). The combined aqueous washes were back-extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 1.6 mg (43%) of a clear, colorless oil: $[\alpha]_D$ -36° (*c* 0.075, CCl_4); IR (film) 2957, 2931, 2858, 1738, 1711, 1472, 1463, 1386, 1255, 1066, 990, 836, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94–5.83 (m, 2H, C_{17}-H, C_{18}-H), 5.43 (t, *J* = 7.2, 1H, C_3-H), 5.30

(ddd, J = 6.7, 10.8, 14.9, 1H, C_{16}-H), 5.18 (dd, J = 10.2, 16.0, 1H, C_{19}-H), 5.16–5.12 (m, 1H, C_{25}-H), 4.22–4.21 (m, 2H, C_5-H, C_9-H), 3.90 (d, J = 7.0, 1H, C_{13}-H), 3.72 (q, J = 6.1, 1H, C_{33}-H), 3.64–3.61 (m, 2H, C_{23}-H, C_{31}-H), 2.98–2.85 (m, 3H, C_2-H_2, C_{12}-H), 2.74 (quin, J = 6.5, 1H, C_6-H), 2.68 (quin, J = 6.3, 1H, C_8-H), 2.56 (dd, J = 3.0, 7.3, 1H, C_{10}-H), 2.12–1.97 (m, 5H, C_{14}-H, C_{15}-H_2, C_{20}-H, C_{22}-H), 1.70–1.24 (m, 18H, C_4-CH_3, C_{20}-CH_2CH_3, C_{21}-H_2, C_{22}-H_2, C_{26}-H_2, C_{28}-H_2, C_{29}-H_2, C_{30}-H_2, C_{32}-H_2), 1.09 (d, J = 5.9, 3H, C_{34}-H_3), 1.00 (d, J = 7.0, 3H, C_{10}-CH_3), 0.91 (d, J = 7.4, 3H, C_8-CH_3), 0.90 (d, J = 7.5, 3H, C_4-CH_3), 0.85–0.74 (m, 48H, C_6-CH_3, C_{12}-CH_3, C_{20}-CH_3, C_{30}-CH_3, $Si(C(CH_3)_3)$), 0.72 (d, J = 6.9, 3H, C_{24}-CH_3), 0.02 (s, 3H, $SiCH_3$), –0.02-(–0.06) (m, 12H, $SiCH_3$), –0.09 (s, 3H, $SiCH_3$); HRMS (FAB) m/z calcd for $[M + Na]^+$ 1239.8462, found 1239.8431.

Rutamycin B (1b). To a solution of 15 mg (0.012 mmol) of lactone **33** in 2.5 mL of 1:1 CH_2Cl_2/CH_3CN was added 1.0 mL of concentrated aqueous hydrofluoric acid (47%). The resultant cloudy mixture was stirred at ambient temperature for 8 h and then diluted with 20 mL of deionized water and carefully quenched with 20 mL of saturated aqueous $NaHCO_3$ solution. This was extracted with EtOAc (3 × 50 mL), and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave 9.2 mg (98%) of a clear, colorless oil which solidified on standing. Recrystallization from ether did not noticeably increase the purity of the product (as determined by NMR and mp): mp 128–130 °C; $[\alpha]^{23}_D$ –72.0° (c 0.47, $CHCl_3$); IR (film) 3491 (b), 2964, 2931, 1705, 1644, 1456, 1380, 1280, 1227, 1188, 1098, 1057, 976, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, J = 9.9, 15.6, 1H, C_3-H), 6.04 (dd, J = 10.4, 13.6, 1H, C_{17}-H), 5.92 (dd, J = 10.4, 15.0, 1H, C_{18}-H), 5.81 (d, J = 15.7, 1H, C_2-H), 5.46 (ddd, J = 6.7, 10.8, 14.9, 1H, C_{16}-H), 5.29–5.26 (m, 1H, C_{25}-H), 5.23 (dd, J = 9.6, 15.0, 1H, C_{19}-H), 4.04 (dq, J = 2.9, 6.3, 1H, C_{33}-H), 4.01–3.97 (m, 2H, C_9-H, C_{23}-H), 3.83–3.79 (m, 2H, C_{13}-H, C_{31}-H), 3.77 (dd, J = 0.7, 10.0, 1H, C_5-H), 2.85–2.80 (m, 2H, C_8-H, C_{12}-H), 2.70 (dq, J = 1.5, 8.5, 1H, C_{10}-H), 2.66 (dq, J = 1.0, 7.4, 1H, C_6-H), 2.37 (m, 1H, C_4-H), 2.17–2.05 (m, 4H, C_{14}-H, C_{15}-H_2, C_{24}-H), 1.78 (m, 1H, C_{20}-H), 1.77 (dd, J = 5.1, 12.6, 1H, C_{26}-H_{ax}), 1.72–1.70 (m, 2H, C_{26}-H_{eq}, C_{30}-H), 1.67–1.26 (m, 12H, C_{20}-CH_2CH_3, C_{21}-H_2, C_{22}-H_2, C_{28}-H_2, C_{29}-H_2, C_{32}-H_2), 1.24-1.23 (m, 6H, C_{10}-CH_3, C_{34}-H_3), 1.17 (d, J = 6.5, 3H, C_4-CH_3), 1.09 (d, J = 7.3, 3H, C_6-CH_3), 1.04 (d, J = 7.0, 3H, C_8-CH_3), 0.91 (d, J = 7.1, 6H, C_{12}-CH_3, C_{14}-CH_3), 0.87 (d, J = 6.8, 3H, C_{30}-CH_3), 0.816 (t, J = 7.4, 3H, C_{20}-CH_2CH_3), 0.814 (d, J = 6.9, 3H, C_{24}-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.8, 216.1, 165.0, 148.4, 137.5, 132.3, 130.5, 129.7, 122.8, 97.4, 73.0, 71.4, 71.1, 70.8, 69.7, 67.5, 64.8, 49.4, 48.7, 47.4, 45.9, 45.7, 42.8, 40.0, 37.5, 35.6, 35.2, 33.5, 31.2, 30.8, 30.7, 29.9, 28.5, 26.6, 24.7, 17.7, 13.3, 12.8, 12.0, 11.3, 9.7, 8.3, 5.0; HRMS (FAB) m/z calcd for $[M + Na]^+$ 783.5023, found 783.5013.

Data for natural rutamycin B: mp 129–130 °C; $[\alpha]^{23}_D$ –72.8° (c 1.21, $CHCl_3$); IR (film) 3490 (b), 2966, 2936, 1704, 1642, 1456, 1384, 1283, 1226, 1188, 1096, 976, 912, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, J = 9.9, 15.6, 1H, C_3-H), 6.05 (dd, J = 10.1, 15.2, 1H, C_{17}-H), 5.92 (dd, J = 10.5, 15.0, 1H, C_{18}-H), 5.81 (d, J = 15.6, 1H, C_2-H), 5.46 (ddd, J = 6.7, 10.8, 14.9, 1H, C_{16}-H), 5.29-5.26 (m, 1H, C_{25}-H), 5.23 (dd, J = 9.6, 15.0, 1H, C_{19}-H), 4.05 (dq, J = 2.9, 6.3, 1H, C_{33}-H), 4.01–3.97 (m, 2H, C_9-H, C_{23}-H), 3.83–3.79 (m, 2H, C_{13}-H, C_{31}-H), 3.77 (d, J = 10.0, 1H, C_5-H), 2.85–2.80 (m, 2H, C_8-H, C_{12}-H), 2.70 (dq, J = 1.5, 8.5, 1H, C_{10}-H), 2.66 (dq, J = 1.0, 7.4, 1H, C_6-H), 2.37 (m, 1H, C_4-H), 2.17–2.05 (m, 4H, C_{14}-H, C_{15}-H_2, C_{24}-H), 1.78 (m, 1H, C_{20}-H), 1.77 (dd, J = 5.1, 12.6, 1H, C_{26}-H_{ax}), 1.72–1.70 (m, 2H, C_{26}-H_{eq}, C_{30}-H), 1.67–1.26 (m, 12H, C_{20}-CH_2CH_3, C_{21}-H_2, C_{22}-H_2, C_{28}-H_2, C_{29}-H_2, C_{32}-H_2), 1.24–1.23 (m, 6H, C_{10}-CH_3, C_{34}-H_3), 1.17 (d, J = 6.5, 3H, C_4-CH_3), 1.09 (d, J = 7.3, 3H, C_6-CH_3), 1.04 (d, J = 7.0, 3H, C_8-CH_3), 0.91 (d, J = 7.1, 6H, C_{12}-CH_3, C_{14}-CH_3), 0.87 (d, J = 6.8, 3H, C_{30}-CH_3), 0.820 (t, J = 7.4, 3H, C_{20}-CH_2CH_3), 0.816 (d, J = 6.9, 3H, C_{24}-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.7, 216.1, 165.0, 148.4, 137.5, 132.3, 130.4, 129.7, 122.8, 97.4, 72.9, 71.4, 71.1, 70.8, 69.7, 67.5, 64.7, 49.4, 48.7, 47.4, 45.9, 45.6, 42.7, 40.0, 37.4, 35.6, 35.2, 33.5, 31.2, 30.8, 30.7, 29.9, 29.7, 28.5, 26.5, 24.7, 17.7, 13.3, 12.8, 12.0, 11.2, 9.7, 8.3, 5.0; HRMS (FAB) m/z calcd for $[M + Na]^+$ 783.5023, found 783.5055.

Reported data[6] for rutamycin B: $[\alpha]_D$ –70.0° (c 1.22, $CHCl_3$); IR (KBr) 3490 (b), 2980 (s), 2930 (s), 2890 (m), 2860 (m), 1705 (s), 1690 (m), 1460 (m), 1380 (m), 1337 (w), 1305 (sh), 1278 (s), 1245 (w), 1228 (w), 1188 (m), 1170 (sh), 1130 (w), 1095 (br,m), 1056 (w), 1045 (w), 1015 (sh), 987 (s), 975 (s), 880 (w), 870 (w), 843 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.64 (dd, J = 10, 16, 1H), 6.08 (dd, J = 10, 15, 1H), 5.96 (dd, J = 10, 15, 1H), 5.83 (d, J = 16, 1H), 5.48 (ddd, J = 4, 11, 15, 1H), 5.26–5.34 (m, 2H), 4.0–4.1 (m, 3H), 3.78–3.86 (m, 3H), 2.82–2.89 (m, 2H), 2.71 (dq, J = 4, 11, 15, 1H), 2.39 (m, 1H), 2.02–2.23 (m, 4H), 1.2–1.9 (m, *ca.* 18H), 1.25 (d, J = 7, 3H), 1.24 (d, J = 6.5, 3H), 1.19 (d, J = 6.5, 3H), 1.11 (d, J = 7, 3H), 1.07 (d, J = 7, 3H), 0.93 (d, J = 7, 6H), 0.89 (d, J = 7, 3H), 0,84 (t, J = 7.5, 3H), 0.83 (d, J = 7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.41, 216.05, 164.92, 148.39, 137.43, 132.16, 130.39, 129.60, 122.69, 97.26, 72.79, 71.30, 71.02, 70.78, 69.65, 67.40, 64.54, 49.48, 48.77, 47.29, 45.77, 45.77, 40.11, 35.19, 33.43, 30.55, 42.58, 37.39, 35.52, 31.21, 30.84, 29.83, 28.49, 26.47, 24.71, 17.79, 13.48, 13.30, 12.79, 12.07, 11.27, 9.58, 8.27, 5.06; MS (FAB) m/z calcd for $[M + H]^+$ 761, found 761.

Acknowledgment. Support has been provided by the National Science Foundation and the National Institutes of Health. We are grateful to Eli Lilly and Co. for providing samples of natural rutamycin B. We thank Dr. Andrew Tyler of the Harvard Mass Spectrometry Facility for providing mass spectra and acknowledge the NIH BRS Shared Instrumentation Grant Program 1 S10 RR0174801A1 and NSF (CHE88-14019) for providing NMR facilities. Support from Eli Lilly and Merck is also acknowledged.