Total Synthesis of the Polyether Antibiotic Lonomycin A (Emericid)

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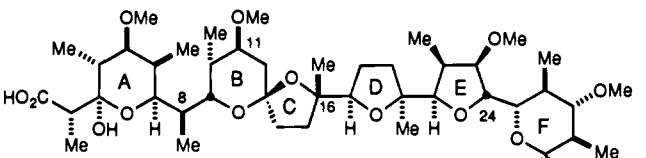
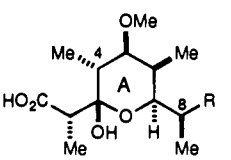
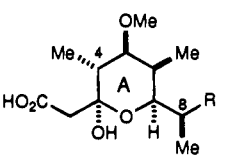
Abstract: The first asymmetric synthesis of the polyether antibiotic lonomycin has been achieved. The skeleton is assembled through the synthesis and union of two subunits comprising the C_1-C_{11} and $C_{12}-C_{30}$ portions of the structure. These fragments were constructed utilizing auxiliary-based asymmetric aldol and acylation reactions to control the absolute stereochemical relationships in the structure. The majority of the 1,2-dioxygen relationships in the polyether portion of the molecule were established through a succession of epoxidation reactions which were transformed through intramolecular heterocyclization to establish rings D, E, and F. The major subunits were coupled through a highly diastereoselective aldol reaction to construct the $C_{11}-C_{12}$ bond. Spiroketalization followed by selective methylation of the C_{11} hydroxyl provided the protected ionophore in high yield.

The polyether antibiotics[1] have provided the chemical community with a family of structures that have been instrumental in stimulating the development of reactions which address the issue of acyclic stereocontrol.[2] Advances in the use of allylic strain concepts introduced by Kishi,[3] the concept of macrocyclic stereocontrol promoted by Still,[4] and the development of chiral enolate bond constructions[5] are representative of the important contributions which have emerged from the synthesis activities in this area. In the present investigation, the incorporation of these advances into the first synthesis of lonomycin A (**1a**) is presented.[6]

Lonomycin A (**1a**), also known as emericid, was isolated and characterized by X-ray crystallography by two groups in 1975. Otake and co-workers[7] isolated **1a** from *Streptomyces ribosidificus* and reported the X-ray structure of the thallium(I) salt (Figure 1). Riche[8] independently isolated the same material from *S. ribosidificus* and proposed the name emericid for this natural product. In subsequent studies, the lonomycin A structure has been fully assigned using ^1H NMR and ^{13}C NMR spectroscopy, and its absolute configuration has been determined by X-ray crystallography.[9] Otake and Omura have reported that *Streptomyces hygroscopicus* also produces lonomycins B (**1b**) and C (**1c**).[10] The structures of these analogs were determined through spectroscopic analyses and chemical interconversion.







The lonomycins are members of a large class of polyether antibiotics which include monensin, nigericin, X-206, and septamycin.[1] All of these antibiotics show monovalent ionophoric activity. As is evident from the crystal structure (Figure 1), the metal cation is encapsulated within the interior of the ligand, while the exterior hydrocarbon backbone forms a hydrophobic shell which facilitates cation transport across biological membranes.[11] Such transport is the basis for lonomycin's biological activity. Lonomycin and its derivatives have

[⊗] Abstract published in *Advance ACS Abstracts*, March 1, 1995.

(1) For an excellent review of the chemistry and biology of this family of natural products, see: *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vols. 1 and 2.

(2) For an important early review of this subject, see: Bartlett, P. A. *Tetrahedron* **1981**, *36*, 3−72.

(3) (a) The introduction of allylic strain concepts to the design of complex synthesis targets appeared in the Kishi monensin synthesis: (i) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259−260. (ii) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260−262. (iii) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262−263. (b) A review of aspects of this topic has appeared: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(4) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.

(5) (a) Evans, D. A. *Asymmetric Synth.* **1984**, *3*, 2−110. (b) Heathcock, C. H. *Asymmetric Synth.* **1984**, *3*, 111−212.

(6) For previous publications in ionophore synthesis from this laboratory, see the following. (a) Calcimycin (A23187): Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789−6791. (b) X-206: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526. (c) Ionomycin: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5313. (d) Ferensimycin B: Evans, D. A.; Polniaszek, R. P.; DeVries, K. E.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613−7630.

(7) (a) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, 4147−4150. (b) Omura, S.; Shibata, M.; Machida, S.; Sawada, J.; Otake, N. *J. Antibiot.* **1976**, *29*, 15−20.

(8) Riche, C.; Pascard-Billy, C. *J. Chem. Soc., Chem. Commun.* **1975**, 951.

(9) (a) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *J. Chem. Soc., Perkin Trans. 2* **1977**, 494−496. (b) Rodios, N. A.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 447−457. (c) Rodios, N. A.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1979**, *88*, 37−41. (d) Seto, H.; Mizoue, K.; Otake, N. *J. Antibiot.* **1980**, *33*, 979−988. (e) Beloeil, J. C.; Le Cocq, C.; Michon, V.; Lallemand, J. Y. *Tetrahedron* **1981**, *37*, 1943−1949.

(10) (a) Seto, H.; Mizoue, K.; Otake, N.; Yamagishi, M.; Mizutani, T.; Hara, H.; Omura, S. *J. Antibiot.* **1978**, *31*, 929−932. (b) Mizutani, T.; Yamagishi, M.; Hara, H.; Omura, S.; Ozeki, M.; Mizoue, K.; Seto, H.; Otake, N. *J. Antibiot.* **1980**, *33*, 1224−1230.

(11) Mitani, M.; Otake, N. *J. Antibiot.* **1978**, *31*, 750−755.

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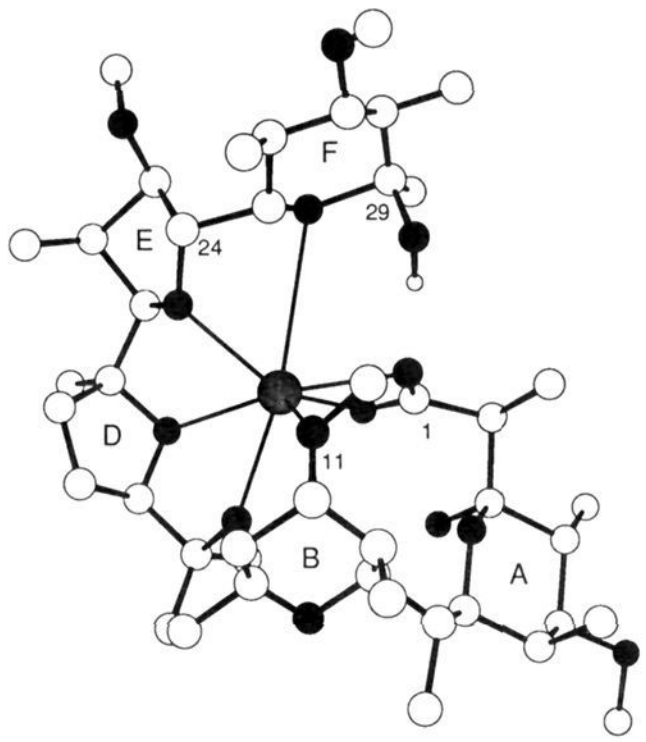
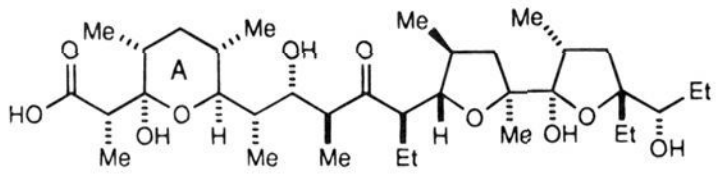


Figure 1. X-ray structure of Lonomycin A thallium(I)salt.[7]

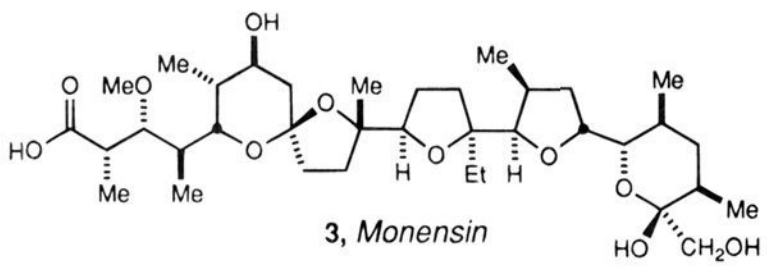
shown antibacterial, antiviral, and antiprotozoic activity[12] and are effective in the treatment of coccidiosis.[13] Miyagami has shown that lonomycin also exhibits potent activity against toxoplasma in mice and human kidneys.[14] Intracoronary administration of lonomycin A produces coronary vasodilation in the presence of pindolol. It is thought that lonomycin affects either the influx of Ca^{2+} or stimulation of Na^+/K^+ ATPase.[15]

Synthesis Plan

Prominent aspects of the lonomycin structure include an array of 23 stereogenic centers and a latent β-keto acid moiety masked as an internal hemiketal. This structural motif, which is also found in the lysocellin–ferensimycin polyether subgroup,[1d] renders the free ligand prone toward successive ring–chain tautomerism and subsequent decarboxylation. In addition to the structural similarities between lonomycin A and ferensimycin B (**2**) in the region of the carboxyl terminus, the polyether portion of **1a** is similar to the comparable region of monensin (**3**);[16] however, lonomycin differs from both of these structures in complexity due to its more highly oxygenated backbone.



2, *Ferensimycin B*



3, *Monensin*

As with most target structures of this complexity, the element of convergency is essential, and such considerations are highlighted in the terminal phase of the synthesis plan (Scheme 1). In direct analogy to the published approaches to the syntheses of monensin,[16] opening of the B/C spiroketal reveals a β-hydroxy ketone that can be sectioned at C_{11}–C_{12} by an aldol disconnection. This operation conveniently divides the molecule into two fragments of comparable complexity. In the corresponding assemblage process, related Felkin-selective aldol reactions of metal enolates have been employed in the synthesis of both monensin[16] and premonensin.[17] The liability associated with this strategy is that, in contrast to monensin, the C_{11} oxygen in lonomycin is disposed as its methyl ether. Accordingly, our most attractive plan for fragment coupling hinged on the union of dimethyl acetal $\mathbf{C_1}$ with enol silane **B** through an acid-catalyzed addition to give the methylated aldol adduct **A** (R = Me) directly. In this fragment-coupling strategy, it is also possible to consider merging the aldol and spiroketalization steps through the proper choice of protecting groups at the C_9 and C_{16} hydroxyl groups. In the alternative plan, the conventional aldol union between **B** and $\mathbf{C_1}$ could be entertained. The decision to pursue this option would have to be followed by an obligatory post-aldol methylation either before or after spiroketalization, a reaction that we viewed as highly speculative due to the large number of oxygen-bearing functional groups resident in advanced intermediate **A** or its derived spiroketal.

Synthesis of the C_1–C_{11} Polypropionate Fragment[18]

The two principal aldol bond constructions to be used for the C_1–C_{11} fragment are illustrated (Scheme 2). On the basis of recently developed methodology,[19] we anticipated that β-keto imide **4**, through its derived Sn(II) enolate, might afford the two successive aldol bond constructions illustrated in eqs 1a and 1b. The successful implementation of these reactions would allow **4** to be employed for eight of the eleven carbons and seven of the eight stereocenters in the polypropionate backbone. Furthermore, since the oxazolidinone chiral auxiliary reduces the kinetic lability of the C_2 methyl-bearing stereocenter in β-keto imides such as **4**,[20] it was anticipated that this auxiliary would be similarly advantageous as a stabilized C_1 carboxylic acid equivalent. Finally, we elected to incorporate the remaining C_{10} stereocenter and requisite oxygenation at C_{11} through a diastereoselective hydroboration. The development of these reactions is summarized in Schemes 3 and 4.

Stannous triflate-mediated aldol coupling between **4** and methacrolein ($Sn(OTf)_2$, Et_3N, **4**, −20 °C; RCHO, −78 °C, 85%) afforded **5** as a 95:5 mixture of diastereomers (Scheme

(12) (a) Yamagishi, M.; Mizoue, K.; Mizutani, T.; Hara, H.; Omura, S.; Seto, H.; Otake, N., Taisho Pharmaceutical Co., Ltd. Jpn. Belg. Patent BE 874687, Sep 10, 1978, 15 pp. AI JP Appl. 78/30187, Mar 16, 1978. (b) Hara, H.; Mizoue, K.; Mizutani, T.; Omura, S.; Otake, N.; Seto, H.; Yamagishi, M., Taisho Pharmaceutical Co., Ltd., Jpn. U. S. Patent. 4199515, Apr 22, 1980, 5 pp JP Appl. 78/30187, Mar 16, 1978.

(13) (a) Taisho Pharmaceutical Co., Ltd., Jpn. Jpn. Kokai Tokkoyo Koho JP 55/66584 [80/66584], May 20, 1980, 4 pp. JP Appl. or Pr. 78/140574, Nov 15, 1978. (b) Cruthers, L. R.; Szanto, J.; Linkenheimer, W. H.; Maplesden, D. C.; Brown, W. E. *Poult. Sci.* **1978**, *57*, 1227–1233.

(14) Miyagami, T.; Takei, Y.; Matsumoto, Y.; Otake, N.; Mizoue, K.; Mizutani, T.; Omura, S.; Ozeki, M.; Suzuki, N. *J. Antibiot.* **1981**, *34*, 218–223.

(15) (a) Tsuchida, K.; Kaneko, K.; Aihara, H.; Chiba, S. *Jpn. J. Pharmacol.* **1985**, *38*, 109–112. (b) Tsuchida, K.; Aihara, H. *Jpn. J. Pharmacol.* **1986**, *41*, 353–361.

(16) For syntheses of monensin, see: (a) Reference 3a. (b) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117–2118, 2118–2120, 2120–2121. (b) Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152–7165. (c) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166–7172.

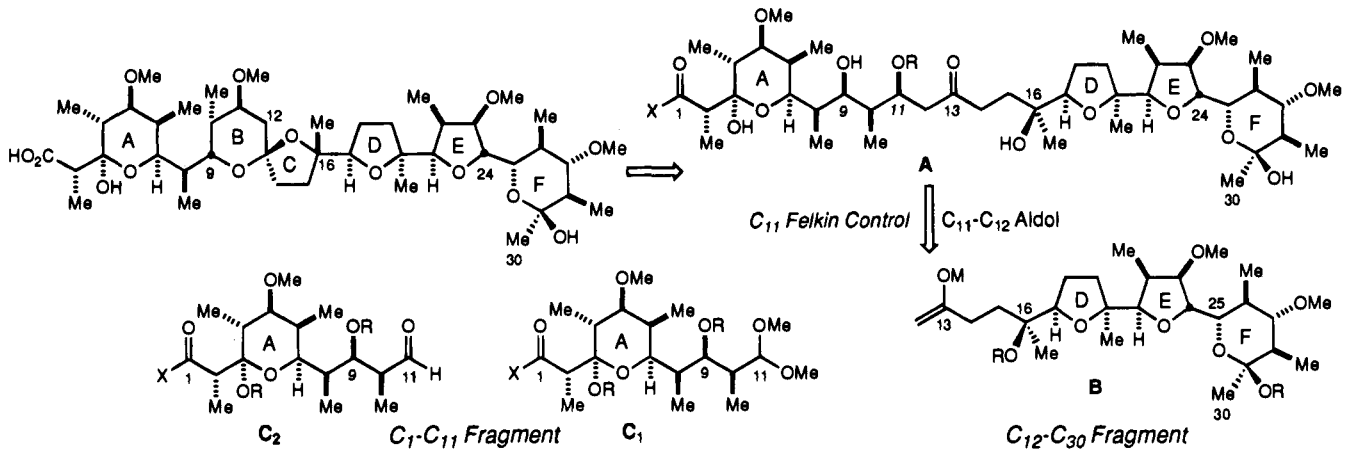
(17) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476–2478.

(18) For a preliminary communication from this laboratory on this subject, see: Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192–5194.

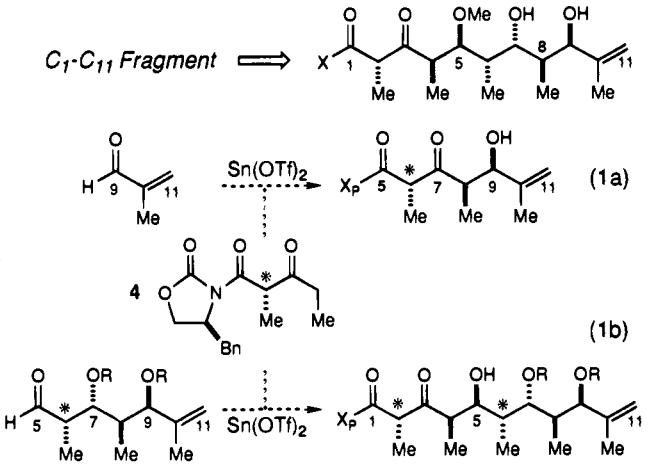
(19) Evans, D. A.; Clark, J. S.; Metternich, R.; Novak, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.

(20) Evans, D. A.; Ng, H. P.; Clark, S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.

Scheme 1



Scheme 2



3). In accordance with established precedent,[21] directed *anti* reduction of the C_7 ketone with $NaBH(OAc)_3$ formed the lactonization-prone 1,3-diol as a single diastereomer which was immediately protected as its derived acetonide in 93% overall yield. ^{13}C NMR spectral analysis of acetonide **6** established that the reduction had proceeded with the expected *anti* diastereocontrol.[22] Reductive removal of the chiral auxiliary ($LiBH_4$, EtOH, Et_2O)[23] afforded the primary alcohol in 86% yield along with 90% recovery of the auxiliary. Swern oxidation[24] under the standard conditions provided aldehyde **7** in quantitative yield. The second β-keto imide aldol reaction employing **4** and aldehyde **7** proceeded with exceptional diastereoselection (>95:5) to give the *anti* Felkin aldol adduct **8** in 86% yield. We attribute the high diastereoselection in this reaction to the fact that the intrinsic *anti* Felkin bias for the (*Z*) Sn(II) enolate establishes a "matched" relationship between the chiral reacting partners in this double stereodifferentiating process.[25] This assumption has been verified in the analogous reaction with *ent*-**4** which affords a poorly diastereoselective process.

At this stage, we were faced with the task of methylating the hindered β-hydroxy ketone **8** without promoting either epimerization of the C_2 stereocenter, retro-aldol cleavage, or dehydration. Several procedures were investigated, including Ag_2O/MeI[26] and various catalyzed diazomethane variants;[27] however, these attempts were met with limited success. Meerwein's salt (Me_3OBF_4)[28] in the presence of excess Proton Sponge (Aldrich) rapidly methylated the C_5 hydroxyl moiety, but accompanying epimerization at the C_2 stereocenter was observed along with products derived from competing alkylation of the oxazolidinone auxiliary. It was ultimately discovered that treatment of **8** with methyl triflate (15 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (30 equiv)[29] ($CHCl_3$, 60 °C, 6.5 h) smoothly promoted methylation to give **9** in 88% yield without any accompanying C_2 epimerization.

At this juncture, the decision was made to reconfigure acetonide **9** (Dowex 50, $MeOH/CH_2Cl_2/CH(OMe)_3$, 98% yield) to give **10**, the protected A ring analog of lonomycin A. This transformation added significant stability to the epimerization-prone C_2 center while exposing the C_9 hydroxyl moiety for needed differential protection. Unfortunately, the liability associated with this transformation was that **10** proved to be more acid sensitive than anticipated. For example, acids such as camphorsulfonic acid and trichloroacetic acid facilitated methanol elimination to give the ring A dihydropyran which could not be efficiently rehydrated. In spite of the acid sensitivity of **10**, the decision was made to employ this intermediate in the synthesis.

The final reaction required to complete the synthesis of the C_1–C_{11} fragment was the *re* face-selective hydroboration of olefin **10** (Scheme 4). In independent studies on the hydroboration of related 1,1-disubstituted allylic alcohols, we have documented that the required *syn* reaction diastereoselection appears to be an attribute of the Rh(I)-catalyzed process,[30] a stereochemical outcome which is opposite to the uncatalyzed hydroboration of the same substrates with dialkylboranes.[31]

(21) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(22) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

(23) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307–312.

(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(25) For a discussion of (*Z*) enolate additions to chiral α-substituted aldehydes, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.

(26) Greene, A. E.; Drian, C. L.; Crabbe, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583–7584.

(27) (a) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, 4405–4406. (b) Smith, A. B., III; Hale, K. J.; Laakso, L. M.; Chen, K.; Rieva, A. *Tetrahedron Lett.* **1989**, *30*, 6963–6966.

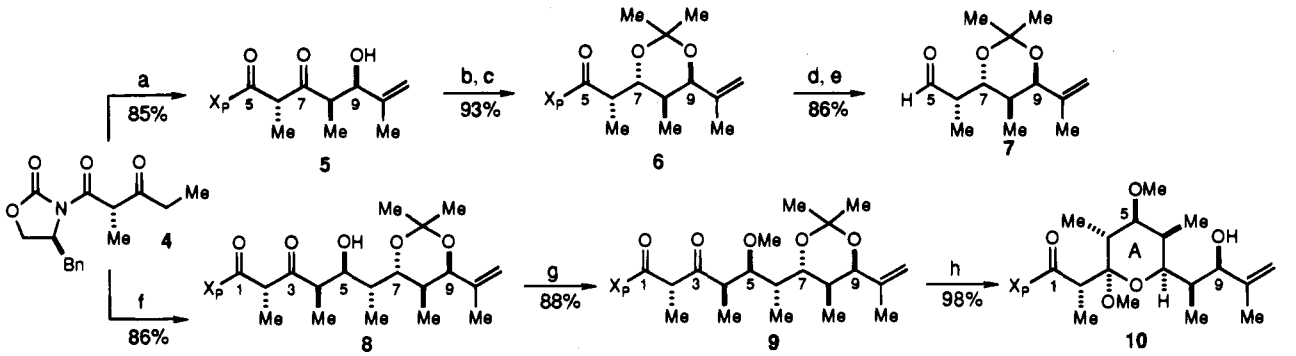
(28) Meerwein, H.; Hinz, G.; Hofmann, P.; Kronig, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257.

(29) For a precedent for this transformation, see: Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046–1056.

(30) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917–6918. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 2280–2282. (c) Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett.* **1989**, *30*, 395–398.

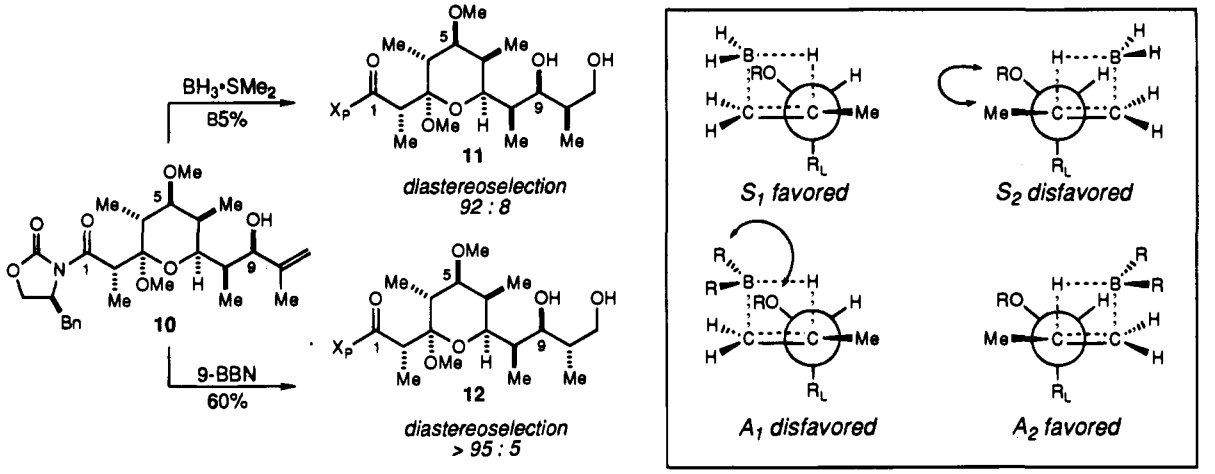
(31) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489.

Scheme 3[a]



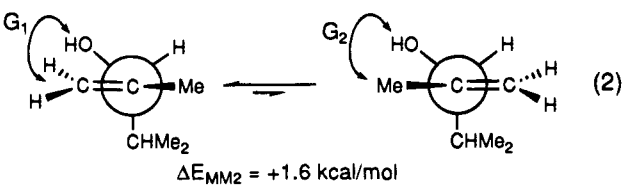
[a] (a) $Sn(OTf)_2$, Et_3N, methacrolein; (b) $NaBH_4$, HOAc; (c) 2,2-dimethoxypropane, Dowex 50, CH_2Cl_2; (d) $LiBH_4$, EtOH, Et_2O, −10 °C; (e) oxalyl chloride, DMSO, Et_3N, −78 to −20 °C; (f) $Sn(OTf)_2$, Et_3N, **7**; (g) MeOTf, 2,6-di-*tert*-butylpyridine, $CHCl_3$, Δ; (h) Dowex 50, MeOH, CH_2Cl_2, $CH(OMe)_3$, 23 °C.

Scheme 4



However, as a correction to our preliminary report,[18] the Rh(I)-catalyzed hydroboration of olefin **9** was found to be unexpectedly capricious when applied to highly complex olefin substrates. This problem was circumvented with the observation that the uncatalyzed hydroboration of **10** with BH_3·DMS (THF, 0 °C) resulted in a 92:8 ratio of diastereomeric primary alcohols **11** and **12**, respectively, in a combined yield of 92%.[32] In contrast, hydroboration of **10** with 9-BBN displayed the anticipated opposite olefin facial bias, affording a 60% yield of **12** as the only detectable diastereomer. The stereochemical assignments of these two hydroboration products were secured by conversion of the respective diols to the derived acetonides **13** and **14** (structures not shown) from which the ^1H NMR vicinal coupling constants for the protons on carbons 9−11 could be readily extracted.

The diastereoselective hydroboration of allylic alcohols with dialkylboranes has been well-documented both experimentally and theoretically.[31,33] Given the Houk assertion that non-eclipsed transition states are preferred in these and related reactions, transition state $\mathbf{A_2}$ for this reaction is favored over the diastereomeric transition state $\mathbf{A_1}$ which is destabilized by nonbonding interactions between the boron substituents and the allylic hydroxyl moiety (or its derived borinate ester). Why does the face selectivity of the hydroboration process reverse when the less sterically demanding borane reagent is employed? We propose that transition state $\mathbf{S_1}$ is favored over transition state $\mathbf{S_2}$. The argument supporting this proposal follows: in the absence of the dominant steric effect imposed on the reaction from the boron carbon ligands, the subtle difference in the destabilizing A(1,2) interactions between the allylic OR substituent and either Me (in $\mathbf{S_2}$) or $=CH_2$ in the olefin (in $\mathbf{S_1}$) could be the major contributor to the difference in the heat of formation of the two transition states. The relative magnitude of these two A(1,2) interactions may be evaluated by molecular mechanics (MM2 force field).[34] In the two illustrated constrained conformations of 3-hydroxy-2,4-dimethyl-4-pentene, the A(1,2) interaction G_2 is destabilizing by 1.6 kcal/mmol relative to the competing A(1,2) interaction G_1 (eq 2). For this reason,



$$\Delta E_{MM2} = +1.6 \text{ kcal/mol} \quad (2)$$

we would like to suggest that the reaction of **10** with BH_3·DMS likely proceeds predominantly through $\mathbf{S_1}$ to give **11** with good stereoselectivity.

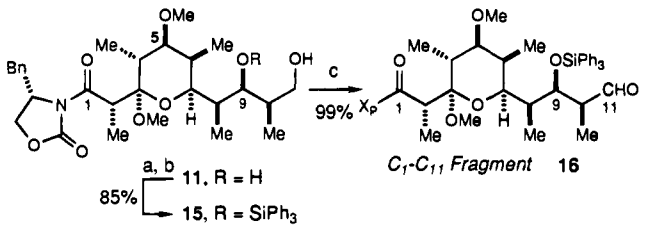
Completion of the synthesis of the C_1-C_{11} synthon from diol **11** is illustrated (Scheme 5). Bis-silylation with chlorotri-

(32) Precedent for the stereochemical course of this reaction can be found in the following two studies: (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797−800. (b) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2974−2991.

(33) Houk, K. N.; Rondan, N. G.; Wu, Y. D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257−2274.

(34) All calculations were performed with an MM2 force field on structures generated by a Multiconformer search using MacroModel (Version 3.5) provided by Professor W. Clark Still, Columbia University.

Scheme 5[a]



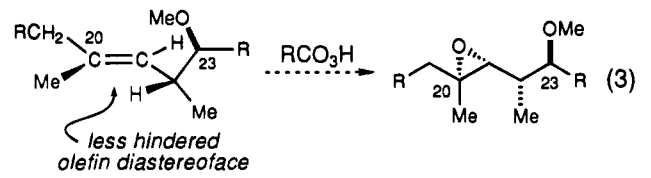
[a] (a) Ph_3SiCl, imidazole, DMAP, 23 °C; (b) HF·pyr, pyridine, THF, −45 °C; (c) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C.

phenylsilane followed by monodeprotection with HF·pyr afforded **15** in 85% yield for the two steps. Oxidation of the liberated primary alcohol with the Dess−Martin periodinane[35] (pyridine, CH_2Cl_2, 0 °C, 99% yield) provided the C_1-C_{11} fragment **16** in 36% overall yield from β-keto imide **4**. This general procedure may be employed with equal efficiency to incorporate a range of C_9 trialkylsilyl protecting groups. In studies to be described (*vide infra*), it has been observed that the steric requirements of this protecting group have a significant impact on the stereochemical outcome of aldol reactions with the C_{11} aldehyde.

As previously discussed (Scheme 1), the options of employing either an acetal- or aldehyde-based aldol union of the C_1-C_{11} and $C_{12}-C_{30}$ fragments had been raised. In the most attractive option, the use of the dimethyl acetal derived from **16** would obviate the need to face the speculative post-aldol methylation of the C_{11} hydroxyl moiety (see **A**, Scheme 1). Unfortunately, all attempts to transform aldehyde **16** into its derived dimethyl acetal were thwarted by the intrinsic acid lability of this intermediate. The ramifications of this change in the synthesis plan will be addressed at a later point.

Synthesis of the $C_{12}-C_{30}$ Polyether Subunit

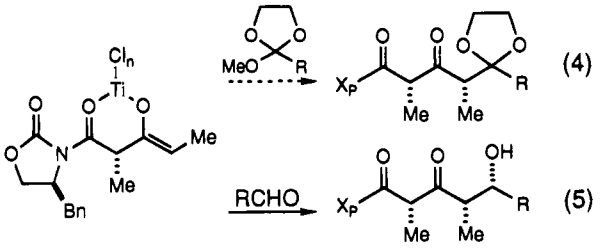
Our approach to the synthesis of the $C_{12}-C_{30}$ polyether fragment is based on the Cane−Celmer−Westley postulate[36] for the biosynthesis of lonomycin A. This postulate provides the inspiration that rings D, E, and F might be formed from triepoxide precursor **D** (Scheme 6). This strategy hinges on the feasibility of stereoselectively synthesizing the required triepoxide precursor for the eventual "epoxide cascade" to the polyether subunit. Of the three epoxidations, the $C_{20}-C_{21}$ olefin epoxidation would be expected to proceed with the desired sense of asymmetric induction based on A(1,3) conformational control[3b] (eq 3). In contrast, the $C_{16}-C_{17}$ olefin affords the most



challenging of the three epoxidations as a consequence of its isolation from other stereogenic centers which might influence the stereochemical outcome of the reaction. One solution to this problem, an outgrowth of Still's macrocyclic stereocontrol strategy,[37] is to consider the multiple epoxidation of conformationally constrained olefinic precursors of **D**. Suitable equivalents such as lactones $\mathbf{E_1}-\mathbf{E_4}$ might be constructed by linking the C_{13} acyl moiety to one of the pendant oxygen substituents positioned along the carbon backbone at either C_{23}, C_{27}, or C_{29} with the goal of determining which of these lactones orient the requisite olefin diastereofaces for the obligatory stereoselective epoxidations.

An analysis of the four illustrated lactones resulted in the selection of the 12-membered lactone $\mathbf{E_4}$ as the synthesis target based on the confidence level of the projected epoxidation reactions. Independently, Schreiber has found that a lactone similar to our $C_{13}-C_{24}$ subunit was epoxidized with good stereoselectivity in the desired sense.[37b] The decision to employ the $C_{24}-C_{25}$ (*Z*) olefin that would eventually require an inversion of the C_{25} oxygen substituent was offset by the strong facial bias that would secure the stereochemical course of the final epoxidation. This compromise conveniently led to the use of the Wittig reaction to couple the $C_{13}-C_{24}$ lactone and the $C_{25}-C_{30}$ phosphonium salt fragments. The reduction of this plan to practice is described in the following discussion.

$C_{25}-C_{30}$ Polypropionate Subunit. Consideration of potential routes to the synthesis of this fragment led us to develop the ortho ester acylation of the titanium enolate derived from β-keto imide **4** (eq 4). The precedent for the stereochemical course of this reaction was anticipated from the related aldol process (eq 5)[10] while other studies had demonstrated the utility of the ortho ester acylation of titanium enolates.[38]

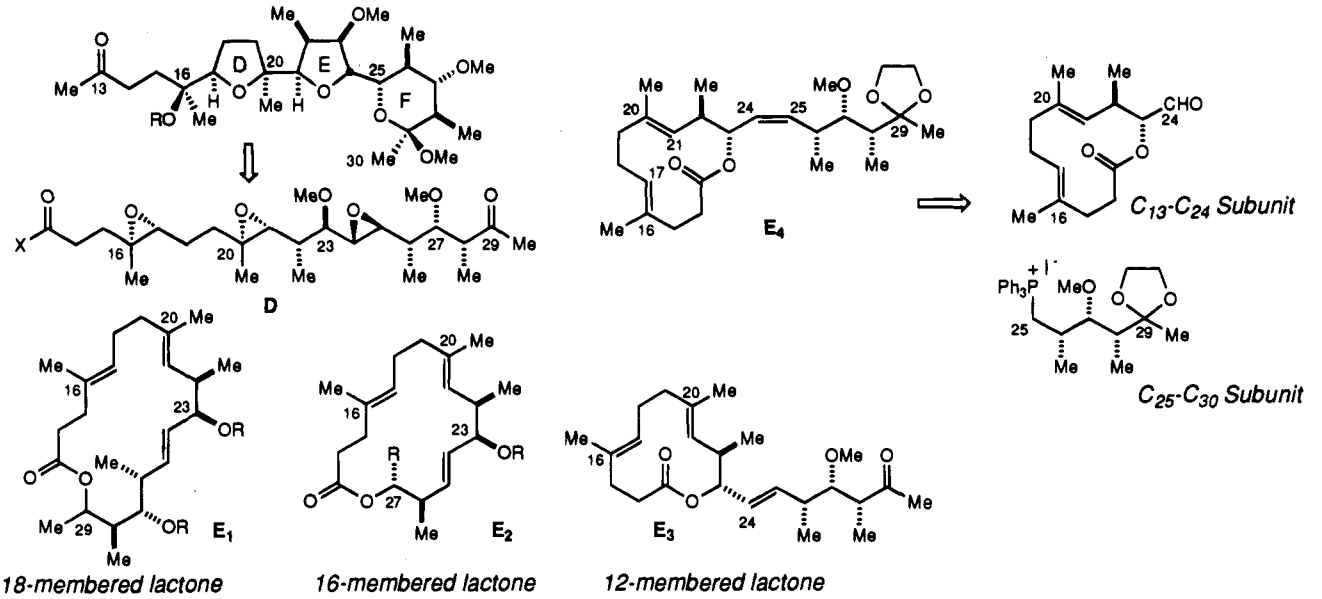


Acylation of β-keto imide **4** with the illustrated ortho ester[39] afforded ketal **17** in 86% yield and good diastereoselectivity (93:7) (Scheme 7). Chelate-controlled reduction with zinc borohydride provided the alcohol **18** (70% yield) as a single diastereomer,[40] while methylation of the derived secondary alcohol (Me_3OBF_4, Proton Sponge, CH_2Cl_2, 23 °C) proceeded smoothly to afford **19** in 82% yield. Reductive removal of the oxazolidinone auxiliary with $LiBH_4$ was followed by mesylation ($MeSO_2Cl$, Et_3N, 0 °C) to give **20** in 86% overall yield. The completion of this subunit was achieved by iodide displacement of mesylate **20** and subsequent formation of the phosphonium salt **21** (Ph_3P, MeCN, 16 h, 80 °C) in 98% yield.

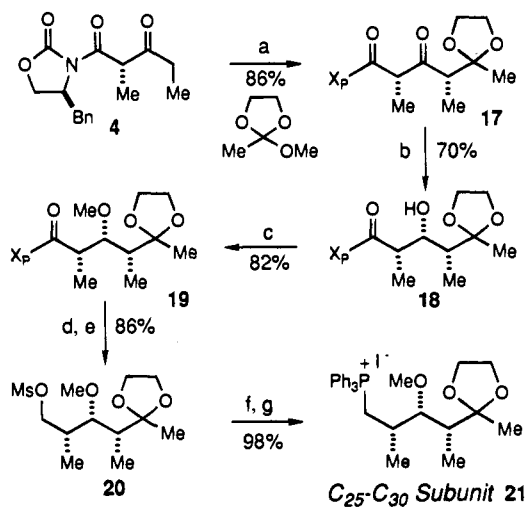
The final displacement step in this reaction sequence is noteworthy for the absence of the competing intramolecular alkylation by the C_{29} ketal oxygen. In an earlier rendition of the synthesis of a related phosphonium salt, the decision had been made to carry the C_{29} oxygen through the bulk of the synthesis as a protected secondary alcohol. In attempting to implement the phosphine alkylation, we were unable to suppress

(35) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(36) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594−3600.
(37) This concept has been articulated and tested in several instances: (a) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105−2106. (b) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106−2108. (c) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058−5061.
(38) For analogous ortho ester acylations, see: (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459.
(39) Soulier, J.; Farines, M.; Authier, R.-M.; Fournier, M. *J. Heterocycl. Chem.* **1976**, *13*, 1125−1128.
(40) The stereochemical assignment of **18** was made through relevant NOE interactions of a δ-lactone formed by removal of the ketal (PPTS, acetone), chelate-controlled reduction of the methyl ketone ($Zn(BH_4)_2$, CH_2Cl_2, −78 °C), and silica gel-promoted lactonization.

Scheme 6

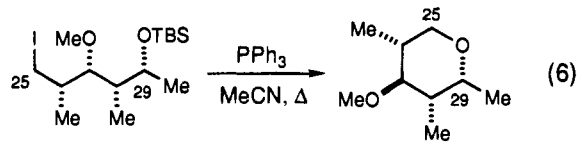


Scheme 7[a]



[a] (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C; (b) $Zn(BH_4)_2$, CH_2Cl_2, −20 °C; (c) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 23 °C; (d) $LiBH_4$, EtOH, Et_2O, −10 °C; (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (f) NaI, K_2CO_3, acetone, Δ; (g) PPh_3, MeCN, Δ.

competing intramolecular oxygen alkylation (eq 6). A comparison of the two attempted phosphine alkylations (**20** → **21** *vs* eq 6) suggests that inductive deactivation of the ketal oxygen appears to be sufficient to suppress this side reaction.



(6)

$C_{13}-C_{24}$ Subunit. The synthesis of the $C_{13}-C_{24}$ subunit was initiated with a diastereoselective imide-derived aldol reaction which established the required C_{22} and C_{23} stereocenters (Scheme 8).[41] Addition of the boron enolate derived from the propionyloxazolidinone **22** to α-(benzyloxy)acetaldehyde provided the aldol adduct **23** in 74% yield as a 98:2 mixture of diastereomers. Transamidation of **23** to the derived *N*-methoxy-*N*-methylamide[42] ($AlMe_3$, MeO(Me)NH·HCl, THF) followed by protection of the C_{23} hydroxyl function as its *tert*-butyldimethylsilyl (TBS) ether afforded amide **24** in 95% yield. Successive reduction of **24** with diisobutylaluminum hydride and addition of 2-propenyllithium to the derived aldehyde **25** provided the alcohol **26** in 83% overall yield as an inseparable 3:1 mixture of diastereomers.

The first of the two Claisen rearrangements was then implemented to establish the required (*E*)-trisubstituted $C_{20}-C_{21}$ olefin geometry. Upon heating allylic alcohol **26** with *N,N*-dimethylacetamide dimethyl acetal (toluene, 110 °C), (*E*)-trisubstituted olefin **27** was obtained in 95% yield as a single isomer.[43] Reduction of the dimethylamide with freshly prepared lithium triethoxyaluminum hydride ($LiAlH_4$, 1.5 equiv, EtOAc, Et_2O) proceeded smoothly to afford the aldehyde **28** in 93% yield.[44] The process was then repeated to append the $C_{13}-C_{16}$ (*E*)-trisubstituted olefin subunit. Propenyllithium addition to **28** afforded a mixture of allylic alcohols **29** which were subjected to the Johnson ortho ester Claisen rearrangement ($MeC(OEt)_3$, propionic acid, 140 °C) to afford **30** in 89% yield.[37] The required hydroxy acid **31** was then prepared in 89% overall yield by successive fluoride ion deprotection and subsequent saponification. Macrolactonization was effected under Mitsunobu conditions[45] (diisopropyl azodicarboxylate (DIAD), PPh_3, toluene, −10 °C, 15 min) to give the 12-membered macrocycle **32** in excellent yield (95%). In developing this macrocyclization process, the selection of the proper reaction conditions proved to be critical. Important variables were found to include selection of both the proper reagent (DIAD *vs* diethyl azodicarboxylate (DEAD)) and solvent. When DEAD was employed in THF at 25 °C, the DEAD substrate acylation product was obtained in 85% yield with no detectable macrocyclization. When the same reaction was carried out in benzene at 25 °C, the desired product **32** was obtained in 47% yield. The use of hindered azodicarboxylate reagent (DIAD) in

(41) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–91.

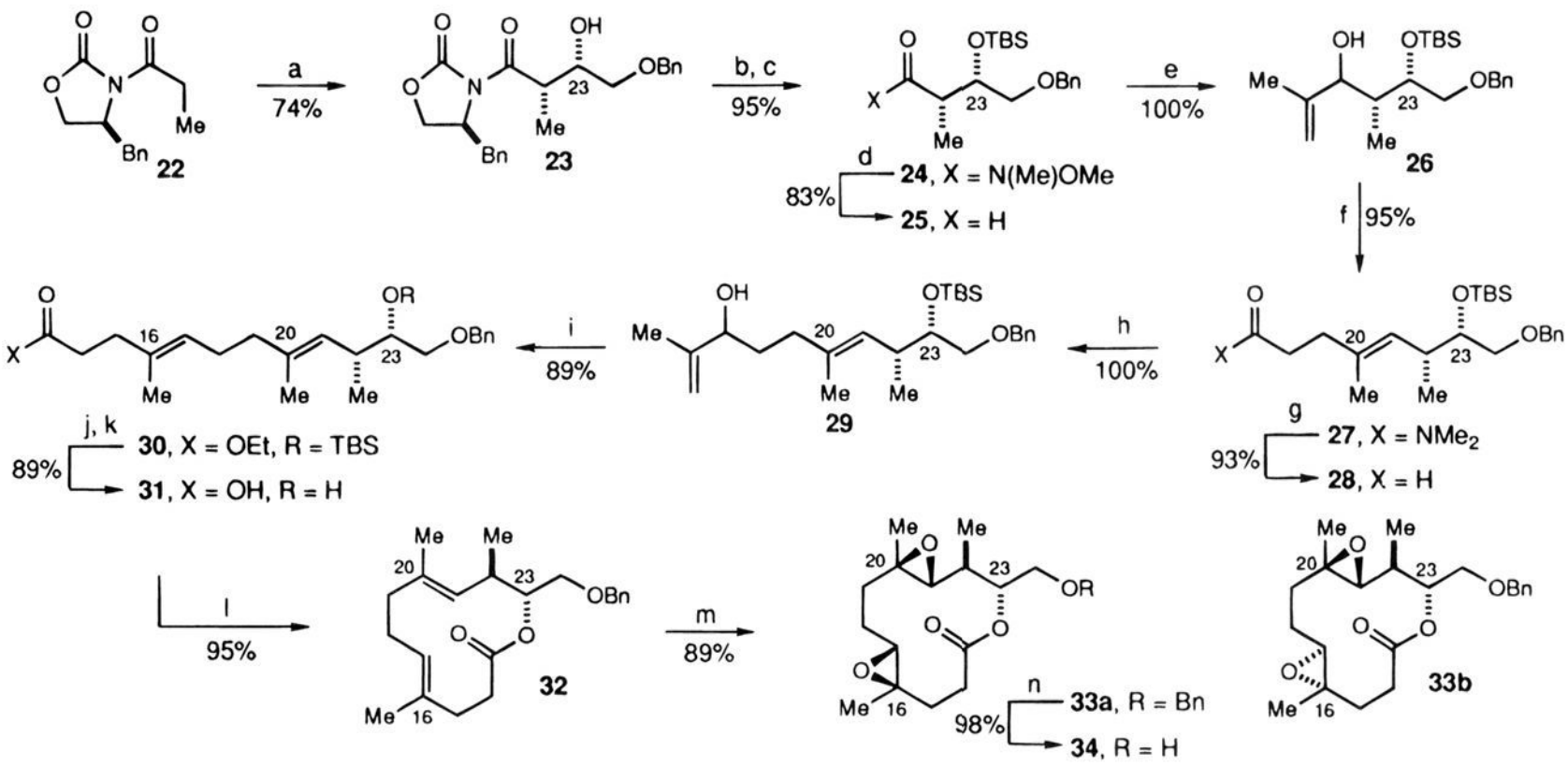
(42) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993. (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.

(43) For a review of Claisen rearrangements, see: Bennett, G. B. *Synthesis* **1977**, 589–606.

(44) Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079–1085.

(45) (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.

Scheme 8[a]



[a] (a) (1) Bu_2BOTf, Et_3N, 0 °C; (2) $BnOCH_2CHO$, CH_2Cl_2, −78 °C; (b) Me_3Al, MeONHMe·HCl, THF, 0 °C; (c) TBSCl, imidazole, DMAP, 23 °C; (d) DIBAlH THF, −78 °C; (e) 2-lithiopropene, THF, −78 °C; (f) $Me_2NC(OMe)_2Me$, toluene, 110 °C; (g) $Li(EtO)_3AlH$, Et_2O, −10 °C; (h) 2-lithiopropene, THF, −78 °C; (i) $MeC(OEt)_3$, propionic acid, 140 °C; (j) TBAF, THF 23 °C; (k) (1) KOH, MeOH, H_20; (2) HCl; (l) DIAD, PPh_3, toluene, −10 °C; (m) *m*-CPBA, CH_2Cl_2, −78 to 0 °C; (n) Pd/C, H_2 (300 psi), EtOAc, 23 °C.

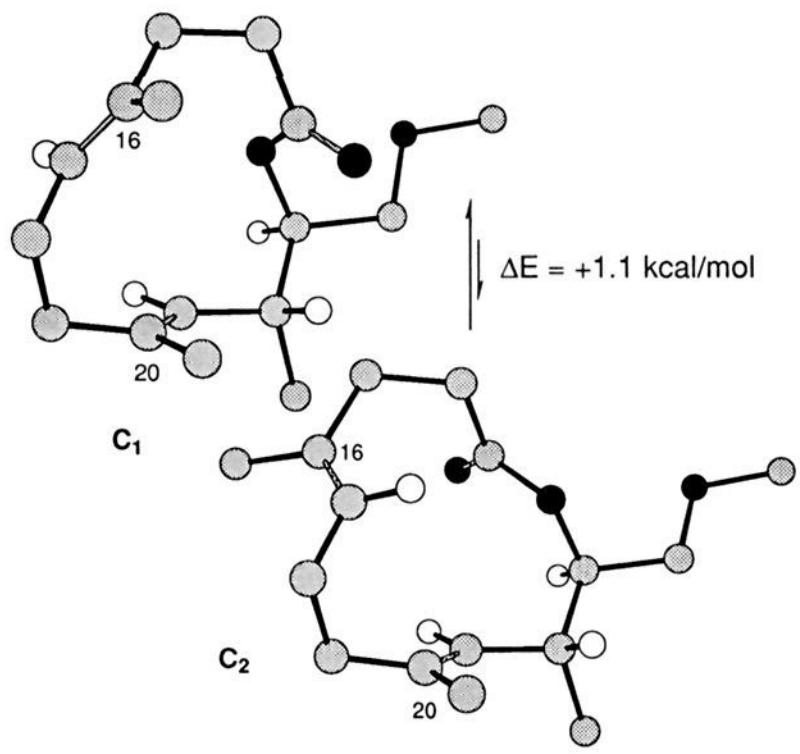


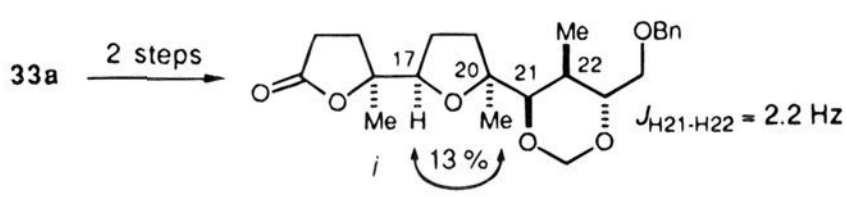
Figure 2. Molecular mechanics minimization of the macrocyclic diene **32**.

conjunction with a nonpolar solvent such as toluene transforms the initially marginal reaction into a high-yield macrolactonization.

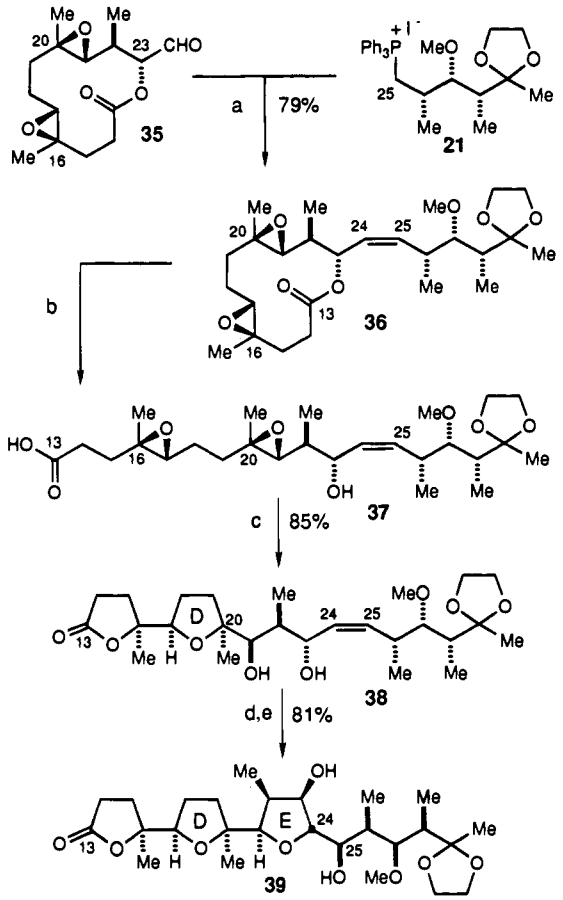
The preceding synthesis plan was predicated on the diastereoselective bis-epoxidation of macrolactone **32**. This plan had been fortified by a molecular mechanics analysis of the low-energy conformations of macrolactone **32**[34] which revealed that lowest-energy conformation was $\mathbf{C_1}$ while conformer $\mathbf{C_2}$ was found to be 1.1 kcal/mol higher in energy (Figure 2). In conformation $\mathbf{C_1}$, the requisite π faces of both trisubstituted double bonds are exposed in the desired fashion to allow bis-epoxidation to take place with the desired stereochemical outcome. As expected, the $C_{20}-C_{21}$ olefin possesses a well-defined facial bias imposed by the conformation of the macrolactone and by an allylic (1,3) strain control element due to the C_{22} stereocenter. This study suggests that the major point of conformational flexibility in **32** is in the region of the $C_{16}-C_{17}$ olefin and that epoxidation of this olefin should be the less diastereoselective of the two oxidations. In the event, epoxidation of **32** with *m*-CPBA afforded a 9:1 mixture of bisepoxide isomers **33a** and **33b** in 99% yield. It is noteworthy that these results are in accord with prediction and that the $C_{20}-C_{21}$ olefin was epoxidized with excellent stereocontrol (97:3) while the $C_{16}-C_{17}$ olefin afforded a 9:1 mixture of diastereomeric epoxides.[46] These results are in agreement with observations reported by Schreiber.[37b] The stereochemical assignment of bisepoxide **33a** was made on a rearranged intermediate.[46b] Synthesis of the $C_{13}-C_{24}$ subunit was completed by hydrogenolytic cleavage of the C_{24} benzyl protecting group (Pd/C, H_2 (300 psi), EtOAc, 98%) followed by oxidation of the primary alcohol **34** with the Dess−Martin periodinane[35] (pyridine, CH_2Cl_2, 0 °C, 88%) to give the derived aldehyde **35**.

Assemblage of the $C_{12}-C_{30}$ Subunit. With the macrolactone aldehyde and phosphonium salt fragments in hand, the Wittig coupling was investigated (Scheme 9). It was found that the optimal contitions for ylide formation involved treatment of a THF solution of the phosphonium salt **21** (1.4 equiv) with freshly prepared lithium hexamethyldisilazide (LiHMDS, −78 °C). Slow addition of a concentrated solution of aldehyde **35** to the ylide resulted in the exclusive formation of the (*Z*) olefin

(46) (a) In the epoxidation of **32**, the $C_{16}-C_{17}$ olefin reacts first. We were able to isolate the major monoepoxide diastereomer and subsequently transformed it into bisepoxide **33a** with 97:3 diastereoselectivity. From these experiments, we conclude that the $C_{16}-C_{17}$ olefin exhibits the lower facial bias upon epoxidation. (b) The stereochemistry of **33a** was shown to have the C_{17}-(*R*) and C_{20}-(*S*) configuration through NOE and coupling constant analysis of the formalin derivative *i*. This compound was formed through basic hydrolysis of the macrolactone, followed by an acid-promoted epoxide ring opening cascade reaction. The product diol was protected using formaldehyde and *p*-TsOH.



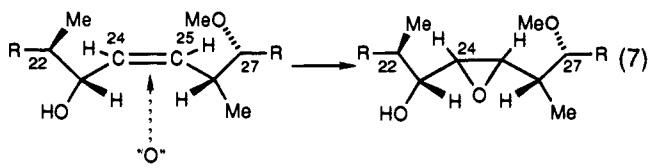
Scheme 9[a]



[a] (a) LiHMDS, THF, −78 to 0 °C; (b) (1) KOH, 3:1 MeOH/H_2O, 23 °C, (2) AcOH; (c) 4 Å mol. sieves, CH_2Cl_2, 23 °C; (d) MMPP, 4 Å molecular sieves, CH_2Cl_2, 0 °C; (e) AcOH, CH_2Cl_2, 23 °C.

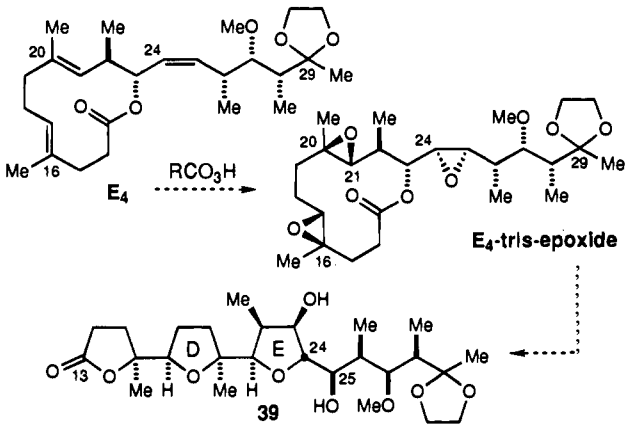
36 (79%). Lactone hydrolysis (KOH, MeOH/H_2O, 120 h, 23 °C) then afforded the hydroxy acid **37**, the substrate required for the epoxide cascade.[47] Unfortunately, this reaction proved to be problematic due to the acid sensitivity of the substrate. For example, use of external acid catalysts such as camphorsulfonic acid promoted the desired cascade reaction but also caused partial hydrolysis of the C_{29} ketal protecting group. In addition, other isomeric tetrahydrofurans were also detected, perhaps formed *via* some competing nonstereoregulated epoxide cleavage pathway. Fortunately, these problems were solved by stirring a methylene chloride solution of carboxylic acid **37** in the presence of 4 Å molecular sieves (120 h, 25 °C), allowing the carboxylic acid within the fragment to catalyze the reaction. This procedure consistently afforded lactone **38** as the only detectable isomer in 85% yield for the two steps.

The diastereoselective hydroxyl-directed epoxidation of the $C_{24}-C_{25}$ olefin remained as the last of the three obligatory olefin oxidations to be executed. We anticipated that π-facial selectivity in this oxidation would be governed by A(1,3) strain (eq 7).



It should be noted that the allylic stereocenters at C_{23} and C_{26} act in concert to shield the top face of the olefin leaving the bottom face open for epoxidation. Directed epoxidation reactions of this type are well-known,[48] with the best selectivities being achieved with reagents such as *m*-CPBA and $VO(acac)_2$/*t*BuOOH. In attempted epoxidations of **38** with *m*-CPBA, low yields of the desired epoxide were obtained due to extensive decomposition of both the starting olefin and the desired product by the benzoic acid byproduct. Alternatively, in metal-catalyzed epoxidation attempts, olefin oxidation was sluggish and complicated by the preferential oxidation of the C_{23} alcohol to the derived ketone. After considerable effort, it was discovered that the desired transformation could be achieved with the buffered oxidant magnesium monoperoxyphthalate (MMPP). Subsequent treatment of this labile epoxide with acetic acid induced the desired hydroxyl-mediated heterocyclization to diol **39** in 81% yield for the two steps. The overall diastereoselectivity for the merged oxidation and cyclizations steps, determined to be 98%, reflects the good level of stereocontrol in the epoxidation step.

Scheme 10



In retrospect, the synthesis of the $C_{13}-C_{30}$ fragment could be refined through the direct epoxidation of lactone **E**$_4$ (Scheme 10) which is now precedented to proceed with the required stereochemical outcome at all three olefinic centers. The subsequent saponification and epoxide cascade would lead to the previously constructed intermediate **39** (Scheme 9).

Prior to formation of the ring F lactol, inversion of the C_{25} hydroxyl stereocenter was required. Unfortunately, the level of steric hindrance flanking the C_{25} carbinol precludes the use of the Mitsunobu reaction.[45a,49] For this reason, we chose to use the two-step oxidation/reduction sequence (Scheme 11) to effect the desired transformation. Selective protection of the less hindered C_{23} hydroxyl moiety in **39** (TESCl, imidazole, DMAP, CH_2Cl_2, −78 °C), followed by oxidation of the C_{25} alcohol using the Dess−Martin periodinane,[35] gave ketone **41** in 96% overall yield. Chelate-controlled reduction of this ketone with $Zn(BH_4)_2$ provided the needed alcohol **42** in quantitative yield as a single diastereomer. We had anticipated the desired stereochemical outcome based on the premise that the five-membered chelate between the ketone carbonyl and the ring E tetrahydrofuran oxygen would dictate the course of the reduction. The alternate six-membered chelate between the C_{25} ketone and the C_{27} methoxyl was excluded likely on the basis of chelate ring size.[50]

Assemblage of the ring F lactol was executed by transketalization of **42** with PPTS in MeOH and concomitant removal

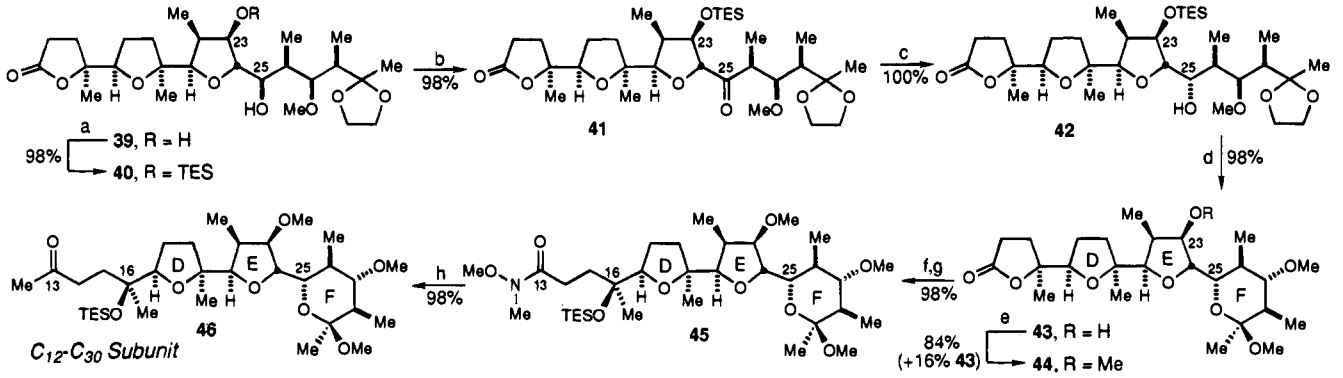
(47) For an analogous acid-catalyzed epoxide cascade reaction, see: Paterson, I.; Boddy, I. *Tetrahedron Lett.* **1988**, *29*, 5301−5304.

(48) For a general review of hydroxyl-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(49) For a recent example, see: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(50) For a detailed discussion of chelate-controlled carbonyl addition, see: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

Scheme 11[a]



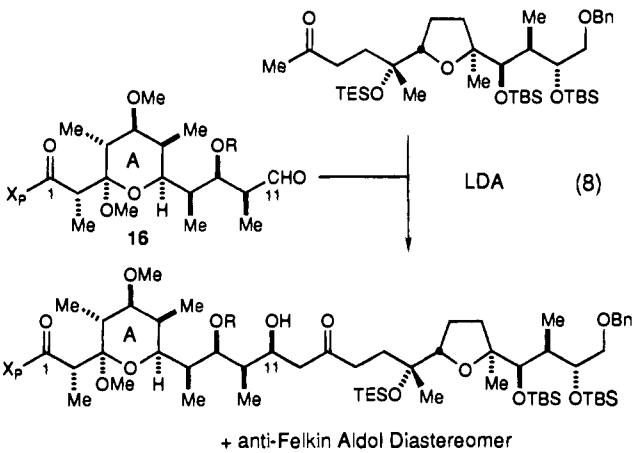
[a] (a) TESCl, imidazole, DMAP, CH_2Cl_2, −78 °C; (b) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C; (c) $Zn(BH_4)_2$, CH_2Cl_2, −25 °C; (d) PPTS, MeOH, 23 °C; (e) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 0 °C; (f) $AlMe_3$, MeNH(OMe)·HCl, THF, 0 °C; (g) TESCl, imidazole, DMF, 23 °C; (h) MeMgBr, THF, 0 °C.

of the triethylsilyl group to afford **43** in 98% yield. Methylation under carefully controlled conditions (Me_3OBF_4, Proton Sponge, CH_2Cl_2, 0 °C) produced **44** in 84% yield along with 16% recovered alcohol **43**. The selective methylation of the hydroxyl residue in **43** without attendant methylation of either ring D or E tetrahydrofuran rings is noteworthy. Completion of the synthesis of the $C_{12}-C_{30}$ subunit by transamidation of lactone **44** using Weinreb conditions[42] ($AlMe_3$, MeNH(OMe)·HCl, THF, 0 °C) and subsequent silylation of the tertiary alcohol provided amide **45** in 98% overall yield. Addition of MeMgI (THF, 0 °C) to this amide afforded the desired methyl ketone **46** in 98% yield (overall yield from **22**, 12%).

Aldol Model Studies

Since the acetal-based aldol union of the principal fragments was no longer an option (see C_1, Scheme 1), the projected aldol reaction needed for the union of the lonomycin subunits was executed on model compounds to identify a C_9 protecting group that would provide high reaction diastereoselectivity. The added requirement for this protecting group is that its removal must be accomplished in the presence of the acid sensitive functionality associated with the lonomycin skeleton.

The lithium enolate of the model methyl ketone[51] was treated with several silyl-protected C_1-C_{11} aldehydes (THF, −78 °C; eq 8). As summarized in Table 1, the size of the protecting



group was found to play a significant role in the diastereoselectivity of the aldol reaction. The smaller protecting groups, trimethylsilyl and triethylsilyl, displayed only modest Felkin selectivity which ranged from approximately 2:1 to 4:1, respectively. Use of the larger *tert*-butyldimethylsilyl group dramatically increased both the yield (83%) and diastereoselectivity (92:8) of the reaction. However, the conditions needed for the removal of the TBS group (H_2O−MeCN, HF, 3 days, 25 °C) caused elimination of the ring A lactol as well as epimerization at the C_2 stereocenter. Use of the triphenylsilyl protecting group provided both the steric bulk necessary for a selective reaction (71% yield, >95:5 diastereoselectivity) and the acid lability required for deprotection under mild conditions. For example, HF·pyr at room temperature efficiently removed the silicon protecting groups, forming a 1:1 mixture of spiroketals.

Table 1. Model Aldol Reactions (eq 8)

R	yield (%)	selectivity
Me_3Si	35	71:29
Et_3Si	62	80:20
tBuMe$_2$Si	83	92:8
Ph_3Si	71	>95:5

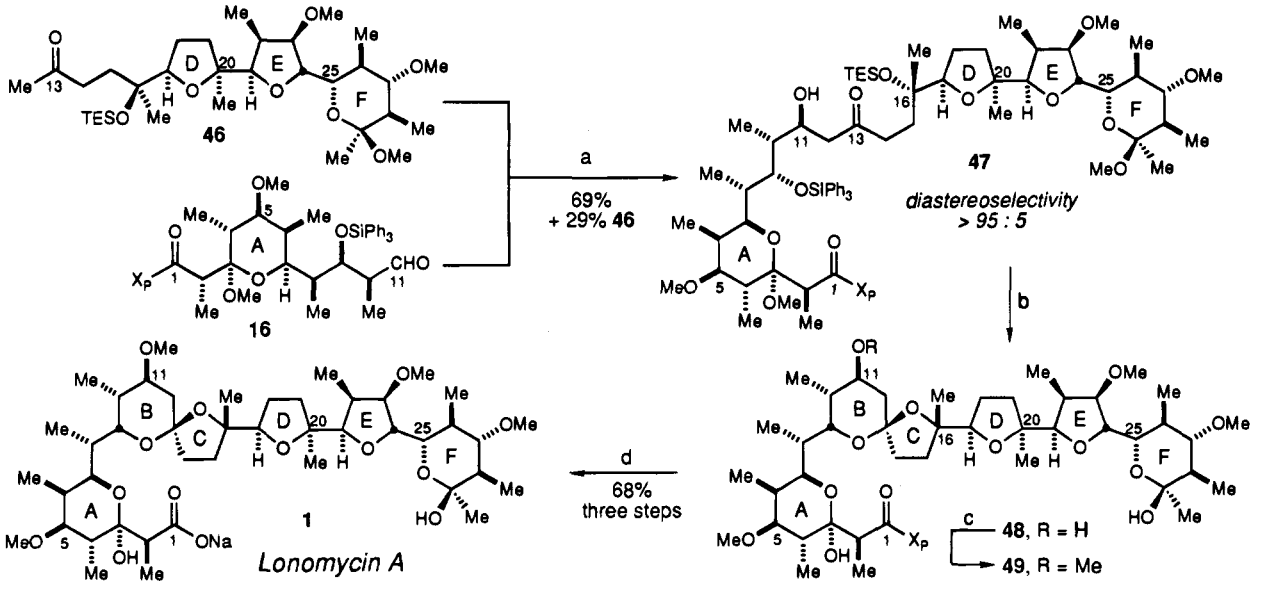
Fragment Coupling

Formation of the lithium enolate of ketone **46** (1.0 equiv) with lithium diisopropylamide (1.1 equiv, THF) at −78 °C followed by dropwise addition of the triphenylsilyl-protected aldehyde **16** (1.5 equiv) afforded the aldol adduct **47** in 69% yield, uncontaminated with the C_{11} diastereomer, along with 29% recovered ketone (Scheme 12). Deprotection of this aldol adduct was not as simple as suggested by the model studies. Treatment of **47** with excess HF·pyr in THF removed the triphenylsilyl group leaving the tertiary TES-protected alcohol at C_{16} unaffected. Removal of both silyl groups required aqueous HF in MeCN at 0 °C for 6 h. Under these conditions, a cascade of transformations was initiated: the silicon protecting groups were removed, spiroketalization to a single spiroketal diastereomer was effected, and finally, the lactol methyl ethers at C_3 and C_{29} were hydrolyzed. By maintaining the reaction temperature at 0 °C, the acid-catalyzed elimination and epimerization side reactions observed earlier in the synthesis were prevented.

The next transformation to be accomplished was methylation of the ring B C_{11} hydroxyl function. Earlier attempts at incorporation of the methoxyl residue into the skeleton *via* the dimethyl acetal aldol-based Mukaiyama aldol reaction had failed (*vide supra*), as had an abortive attempt to methylate the aldol adduct **47**. Fortunately, conditions were found that effected the desired transformation on the fully assembled lonomycin

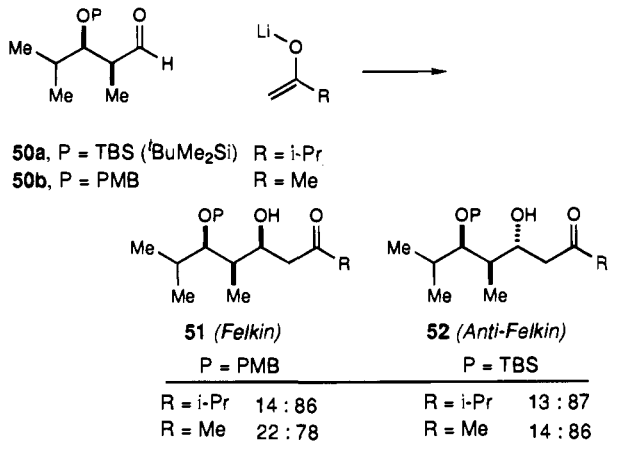
(51) This ketone was prepared from the minor diepoxide diastereomer **33b**.

Scheme 12[a]



[a] (a) (1) **46**, LDA, THF, −78 °C; (2) **16**, THF, −78 °C to −45 °C; (b) 5:86:9 48% aqueous HF/CH_3CN/H_2O, 0 °C; (c) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 23 °C; (d) LiOOH, THF, H_2O, 0 °C.

Scheme 13



structure. Treatment of **48** with MeOTf (25 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 (25 °C, 18 h) selectively installed the ring B methyl ether at C_{11} without methylation at either the C_3 or C_{29} lactols. Hydrolysis of the oxazolidinone with LiOOH in THF at 0 °C for 15 min and subsequent treatment of the carboxylic acid with 0.5 M NaOH provided the sodium salt of synthetic lonomycin A in 68% yield for the three-step sequence (overall yield for synthesis, 6%). This material proved to be identical in all respects ($[\alpha]_D$, ^1H and ^{13}C NMR, IR, TLC, HRMS) with natural lonomycin A sodium salt, thus confirming the stereochemical assignment of this natural product.

Commentary on the $C_{11}-C_{12}$ Aldol Coupling

The stereochemical outcome of this and the related $C_{11}-C_{12}$ aldol reactions found in the published syntheses of monensin,[16] although predicted by the Felkin–Anh paradigm,[52] cannot be extrapolated from simpler substrates. For example, the related aldol reactions illustrated in Scheme 13 all afford principally the *anti* Felkin adducts **52** with the lithium enolates derived from either acetone or 3-methyl-2-butanone, irrespective of the nature of the β-alkoxy protecting group.[53] We have recently provided evidence that the substituent β to the aldehyde moiety can play a significant role, in concert with the α-stereocenter, to define a bias for carbonyl addition. For substrates such as **50** where the α- and β-substituents are in the *syn* stereochemical relationship, the two stereocenters are nonreinforcing in nature.[54] In such instances, the *anti* Felkin product diastereomer can become the major reaction product. The fact that the principal aldol adduct in the $C_{11}-C_{12}$ aldol bond construction conforms to the Felkin–Anh model is purely serendipitous. The identification of the relevant control elements for this reaction are not possible at this time.

Stereochemical Inventory

The most noteworthy aspect of the synthesis has been the successful use of the β-keto imide building block **2** from which the bulk of the stereochemical relationships in lonomycin (Scheme 14) evolved through both aldol and ortho ester acylation reactions. This paper provides a good illustration of the utility of these building blocks for the synthesis of polypropionate natural products.[55]

Experimental Section[56]

[3(2*S*,4*R*,5*R*),4*S*]-3-(1,3-Dioxo-5-hydroxy-2,4,6-trimethyl-6-heptenyl)-4-(phenylmethyl)-2-oxazolidinone (5). To a suspension of 3.03 g (7.26 mmol) of stannous triflate in 30 mL of CH_2Cl_2 at 25 °C was added 1.01 mL (735 mg, 7.26 mmol) of triethylamine, and the pale yellow slurry was immediately cooled to −25 °C. After 5 min, a solution of 2.00 g (6.90 mmol) of imide **4** in 7 mL of CH_2Cl_2 was added *via* cannula (3 mL of CH_2Cl_2 rinse), and the resultant solution was stirred at −25 °C for 1 h. The enolate was cooled to −78 °C, 2.85 mL (2.42 g, 34.50 mmol) of freshly distilled methacrolein was added, and the resulting solution was stirred at −78 °C for 30 min.

(52) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70.

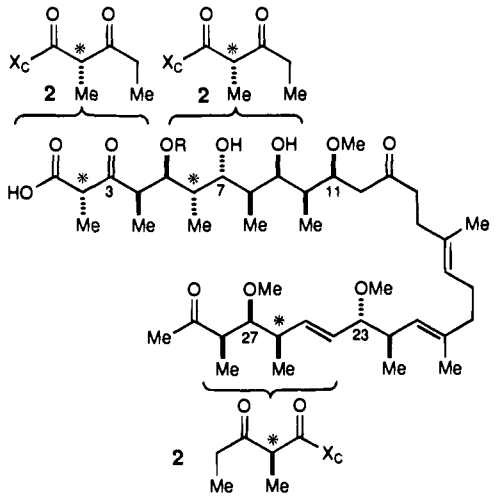
(53) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. Unpublished results.

(54) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537–8540.

(55) For other instances where these dipropionyl synthons have been employed in natural products synthesis, see: (a) Reference 38b. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.

(56) For a general discussion of the spectrometers employed and solvent-drying procedures, see: Reference 55b.

Scheme 14



The reaction mixture was added rapidly *via* cannula to an ice-cooled beaker containing 350 mL of CH_2Cl_2 and 350 mL of aqueous 1 M $NaHSO_4$. After the solution was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 layers were washed with 350 mL of saturated aqueous $NaHCO_3$, 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 95:5 mixture of diastereomers. Purification by flash chromatography (5% EtOAc/hexane) afforded 2.11 g (85%) of **5** as a clear oil: $[\alpha]^{23}_D$ +108.4° (*c* 1.1, CH_2Cl_2); IR (neat) 3526, 2984, 2941, 1779, 1714, 1693, 1454, 1391, 1359, 1214, 1119, 1008, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H, Ar*H*), 5.11 (m, 1H, C_{11}-*H*), 4.97 (m, 1H, C_{11}-*H*), 4.89 (q, *J* = 7.3 Hz, 1H, C_6-*H*), 4.76 (m, 1H, C*H*N), 4.46 (br s, 1H, C_9-*H*), 4.27 (dd, *J* = 8.9, 8.1 Hz, 1H, OCH_2), 4.20 (dd, *J* = 9.1, 2.9 Hz, 1H, OCH_2), 3.31 (dd, *J* = 13.3, 9.6 Hz, 1H, $ArCH_2$), 2.94 (m, 1H, C_8-*H*), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1H, $ArCH_2$), 2.63 (d, *J* = 2.6 Hz, 1H, C_9-O*H*), 1.71 (s, 3H, C_{10}-CH_3), 1.50 (d, *J* = 7.3 Hz, 3H, C_6-CH_3), 1.18 (d, *J* = 7.2 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.2, 170.2, 153.6, 143.5, 135.0, 129.4, 129.0, 127.4, 112.0, 73.6, 66.5, 55.3, 51.8, 46.6, 37.9, 19.4, 13.0, 9.6. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01. Found: C, 66.81; H, 7.09.

[3(2*S*(4*R*,5*S*,6*R*)),4*S*]-3-[1-Oxo-2-[2,2,5-trimethyl-4-(1-methylethenyl)-1,3-dioxan-6-yl]propyl]-4-(phenylmethyl)-2-oxazolidinone (6). To 42 mL of glacial acetic acid in a cold water bath was slowly added 1.05 g (27.83 mmol) of $NaBH_4$ in small portions. At the end of the addition, another 42 mL of acetic acid was added, and the solution was stirred at ambient temperature for 1 h. In a separate flask, 2.00 g (5.57 mmol) of ketone **5** was dissolved in 30 mL of acetic acid. The borohydride solution was then added rapidly to this solution *via* cannula. The homogeneous solution was stirred at ambient temperature for 1 h, at which time the volatiles were removed *in vacuo*. The resultant oil was dissolved in 250 mL of CH_2Cl_2 and was carefully washed with saturated aqueous $NaHCO_3$ (2 × 250 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* without heating. The unpurified viscous oil was azeotroped with MeOH (3 × 50 mL) and used without further purification.

To a solution of the unpurified diol in 13.5 mL of CH_2Cl_2 and 13.5 mL of 2,2-dimethoxypropane at ambient temperature was added 60 mg of Dowex 50 × 8-200 resin. After the mixture was stirred for 12 h, the resin was removed by filtration through a short column of Celite with CH_2Cl_2. The filtrate was washed with 100 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with 100 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc/hexane) afforded 2.07 g (93%) of **6** as a clear oil: $[\alpha]^{23}_D$ +104.0° (*c* 1.0, CH_2Cl_2); IR (neat) 2983, 2936, 1781, 1702, 1455, 1380, 1352, 1223, 1116, 1013, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H, Ar*H*), 4.99 (m, 1H, C_{11}-*H*), 4.87 (m, 1H, C_{11}-*H*), 4.65 (m, 1H, C*H*N), 4.21−4.14 (m, 3H, OCH_2, C_9-*H*), 4.06 (m, 1H, C_6-*H*), 3.63 (dd, *J* = 6.9, 5.0 Hz, 1H, C_7-*H*), 3.33 (dd, *J* = 13.3, 3.2 Hz, 1H, $ArCH_2$), 2.77 (dd, *J* = 13.3, 9.8 Hz, $ArCH_2$), 2.04 (m, 1H, C_8-*H*), 1.66 (br s, 3H, C_{10}-CH_3), 1.34 (s, 3H, one $C(CH_3)_2$), 1.32 (s, 3H, one $C(CH_3)_2$), 1.30 (d, *J* = 6.9 Hz, 3H, C_6-CH_3), 0.80 (d, *J* = 6.9 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.7, 153.1, 142.0, 135.3, 129.4, 128.9, 127.3, 110.2, 100.6, 75.4, 71.4, 66.0, 55.7, 41.2, 37.3, 35.4, 25.1, 23.8, 19.8, 12.4, 11.8. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 66.80; H, 7.78. Found: C, 66.56; H, 7.76.

[4*R*,5*S*,6*S*,(1*R*)]-4-(1-Methylethenyl)-6-(2-hydroxy-1-methylethyl)-2,2,5-trimethyl-1,3-dioxane (7a). To a solution of 1.55 g (3.86 mmol) of imide **6** in 77 mL of Et_2O at −10 °C were added 272 μL (214 mg, 4.64 mmol) of EtOH and 2.32 mL (4.64 mmol, 2.0 M in THF) of $LiBH_4$. The solution was stirred at −10 °C for 1.5 h, and the reaction mixture was quenched by addition of 10 mL of aqueous 1 M NaOH. After the cloudy mixture was stirred for 15 min at 0 °C, it was poured into 100 mL of Et_2O and 200 mL of saturated aqueous NaCl. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (17% EtOAc/hexane) afforded 757 mg (86%) of **7a** as a clear oil: $[\alpha]^{23}_D$ +35.1° (*c* 1.2, CH_2Cl_2); IR (neat) 3321, 2972, 2906, 1452, 1380, 1224, 1175, 1147, 1070, 1033, 1009, 896, 702 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.34 (m, 1H, C_{11}-*H*), 4.94 (m, 1H, C_{11}-*H*), 4.24 (d, *J* = 4.5 Hz, 1H, C_9-*H*), 3.58 (m, 1H, C_5-*H*), 3.51 (dd, *J* = 7.8, 2.9 Hz, 1H, C_7-*H*), 3.47 (m, 1H, C_5-*H*), 1.88 (m, 1H, C_6-*H*), 1.62 (m, 1H, C_8-*H*), 1.50 (s, 3H, C_{10}-CH_3), 1.34 (s, 3H, one $C(CH_3)_2$), 1.28 (s, 3H, one $C(CH_3)_2$), 0.96 (d, *J* = 7.0 Hz, 3H, C_6-CH_3), 0.73 (d, *J* = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (125.8 MHz, C_6D_6) δ 142.3, 110.5, 100.9, 76.1, 72.1, 66.2, 38.7, 35.6, 25.2, 23.7, 19.8, 12.7, 11.0. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.49; H, 10.65.

(4*S*)-4-Benzyl-3-[(2*S*,4*R*,5*S*,6*R*)-5-hydroxy-6-[(4*S*,5*R*,6*R*)-6-isopropenyl-2,2,5-trimethyl-1,3-dioxan-4-yl]-2,4-dimethyl-3-oxoheptanoyl]-2-oxazolidinone (8). To a solution of 145 μL (211 mg, 1.66 mmol) of oxalyl chloride in 5.5 mL of CH_2Cl_2 at −78 °C was added 236 μL (259 mg, 3.32 mmol) of dimethyl sulfoxide (gas evolution). After 10 min, a solution of 315 mg (1.38 mmol) of alcohol **7a** in 1.0 mL of CH_2Cl_2 was added *via* cannula (0.5 mL rinse). The resultant white slurry was stirred at −78 °C for 15 min, and 963 μL (700 mg, 6.90 mmol) of triethylamine was then added. The heterogeneous mixture was warmed to −20 °C over a period of 45 min and was quenched by addition of 5.0 mL of saturated aqueous NH_4Cl. The mixture was poured into 40 mL each of CH_2Cl_2 and saturated aqueous NH_4Cl. The layers were separated, and the organic layer was washed with 40 mL of cold H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow oil. The aldehyde was used without further purification.

To a suspension of 1.21 g (2.90 mmol) of stannous triflate in 11.6 mL of CH_2Cl_2 was added 404 μL (293 mg, 2.90 mmol) of triethylamine. The resulting pale yellow slurry was immediately cooled to −25 °C. After 5 min, a solution of 800 mg (2.76 mmol) of imide **4** in 4.0 mL of CH_2Cl_2 was added *via* cannula (2.8 mL of CH_2Cl_2 rinse), and the resultant solution was stirred at −25 °C for 1 h. The enolate was cooled to −78 °C, and the aldehyde **7**, as a solution in 2.5 mL of CH_2Cl_2, was added by cannula (1.0 mL of CH_2Cl_2 rinse). The resulting solution was stirred at −78 °C for 30 min, at which time the reaction mixture was added rapidly *via* cannula to an ice-cooled beaker containing 200 mL of CH_2Cl_2 and 250 mL of aqueous 1 M $NaHSO_4$. After the solution was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were washed with 250 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified reaction mixture showed only one diastereomer. Purification by flash chromatography (7% EtOAc/CH_2Cl_2) afforded 612 mg (86%) of **8** as a clear oil: $[\alpha]^{23}_D$ +85.8° (*c* 0.95, CH_2Cl_2); IR (neat) 3526, 2982, 2938, 1780, 1713, 1692, 1454, 1381, 1359, 1224, 1173, 1026, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.15 (m, 5H, Ar*H*), 4.99 (br s, 1H, C_{11}-*H*), 4.95 (q, *J* = 7.3 Hz, 1H, C_2-*H*), 4.86 (br s, 1H, C_{11}-*H*), 4.73 (m, 1H, C*H*N), 4.26 (dd, *J* = 9.1, 7.5 Hz, OCH_2), 4.19 (dd, *J* = 9.2, 3.0 Hz, 1H, OCH_2), 4.17 (d, *J* = 8.2 Hz, 1H, C_9-*H*), 3.94 (app dt, *J* = 8.3, 3.3 Hz, 1H, C_5-*H*), 3.73 (dd, *J* = 7.9, 1.7 Hz, 1H, C_7-*H*), 3.31 (dd, *J* = 13.3, 3.4 Hz, $ArCH_2$), 3.02 (d, *J* = 3.4 Hz,

1H, C_5-O*H*), 2.92 (m, 1H, C_4-*H*), 2.77 (dd, J = 13.3, 9.7 Hz, 1H, ArCH_2), 1.69 (m, 1H, C_8-*H*), 1.67 (s, 3H, C_{10}-CH_3), 1.65 (m, 1H, C_6-*H*), 1.50 (d, J = 7.3 Hz, C_2-CH_3), 1.36 (s, 3H, C(CH_3)$_2$), 1.30 (s, 3H, C(CH_3)$_2$), 1.24 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.93 (d, 3H, J = 7.1 Hz, 3H, C_6-CH_3), 0.72 (d, J = 6.8 Hz, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.6, 170.4, 153.5, 142.2, 135.0, 129.4, 129.0, 127.4, 110.1, 100.8, 73.7, 72.0, 71.8, 66.4, 55.4, 51.4, 46.4, 37.9, 35.1, 25.1, 23.7, 19.9, 13.2, 12.4, 10.6, 9.6. Anal. Calcd for $C_{29}H_{41}NO_7$: C, 67.55; H, 8.01. Found: C, 67.26; H, 8.17.

(4*S*)-4-Benzyl-3-[(2*S*,4*R*,5*S*,6*R*)-5-methoxy-6-[(4*S*,5*R*,6*R*)-6-isopropenyl-2,2,5-trimethyl-1,3-dioxan-4-yl]-2,4-dimethyl-3-oxoheptanoyl]-2-oxazolidinone (9). To a solution of 145 mg (0.283 mmol) of aldol adduct **8** in 2.83 mL of $CHCl_3$ (EtOH free) were added 1.75 g (8.5 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine and 481 μL (4.25 mmol) of methyl triflate. The reaction mixture was heated at reflux for 6.5 h. After the mixture was cooled to ambient temperature, 1 mL of MeOH was slowly added (gas evolution). The heterogeneous mixture was poured into 30 mL of CH_2Cl_2 and was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The aqueous layer was back-extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) afforded 132 mg (88%) of **9** as a clear oil: $[\alpha]^{23}_D$ +30.7° (*c* 1.90, CH_2Cl_2); IR (neat) 2981, 1782, 1716, 1692, 1454, 1379, 1359, 1225, 1174, 1027, 866, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 5H, Ar*H*), 5.06 (q, J = 7.1 Hz, 1H, C_2-*H*), 4.99 (br s, 1H, C_{11}-*H*), 4.85 (br s, 1H, C_{11}-*H*), 4.74 (m, 1H, C*H*N), 4.26 (app t, J = 8.8 Hz, OCH_2), 4.20 (dd, J = 11.8, 2.8 Hz, 1H, OCH_2), 4.13 (d, J = 4.4 Hz, 1H, C_9-*H*), 3.61 (m, 2H, C_5-*H*, C_7-*H*), 3.29 (dd, J = 13.0, 3.2 Hz, ArCH_2), 3.29 (s, 3H, C_5-OCH_3), 2.89 (dq, J = 5.7, 1.4 Hz, 1H, C_4-*H*), 2.79 (dd, J = 13.4, 9.6 Hz, 1H, ArCH_2), 1.88 (m, 1H, C_6-*H*), 1.65 (s, 3H, C_{10}-CH_3), 1.55 (m, 1H, C_8-*H*), 1.49 (d, J = 7.1 Hz, C_2-CH_3), 1.36 (s, 3H, C(CH_3)$_2$), 1.30 (s, 3H, C(CH_3)$_2$), 1.17 (d, J = 7.0 Hz, 3H, C_4-CH_3), 0.87 (d, 3H, J = 7.0 Hz, 3H, C_8-CH_3), 0.70 (d, J = 6.8 Hz, C_6-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.6, 171.4, 153.2, 142.4, 135.0, 129.4, 127.4, 109.9, 100.6, 81.0, 72.8, 71.7, 66.2, 59.7, 55.3, 50.5, 46.4, 39.8, 37.9, 35.6, 25.1, 23.8, 19.9, 13.4, 12.2, 10.4, 9.1. Anal. Calcd for $C_{30}H_{43}NO_7$: C, 68.03; H, 8.18. Found: C, 68.07; H, 8.22.

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-tetrahydro-6-[(1*R*,2*R*)-2-hydroxy-1,3-dimethyl-3-butenyl]-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (10). To a solution of 115 mg (0.217 mmol) of methyl ether **9** in 1.0 mL of CH_2Cl_2 and 1.5 mL of MeOH at ambient temperature were added 150 μL of trimethylorthoformate and 25 mg of Dowex 50 × 8-200 resin. After the mixture was stirred for 4 h, the resin was removed by filtration through a short column of Celite with CH_2Cl_2. The filtrate was washed with 50 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc/hexane) afforded 107 mg (98%) of **10** as a clear oil: $[\alpha]^{23}_D$ +157.4° (*c* 1.00, CH_2Cl_2); IR (film) 3524, 2974, 2923, 1781, 1696, 1456, 1387, 1348, 1246, 1211, 1098, 1016, 986, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (m, 5H, Ar*H*), 4.99 (br s, 1H, C_{11}-*H*), 4.92 (br s, 1H, C_{11}-*H*), 4.84 (q, J = 7.1 Hz, 1H, C_2-*H*), 4.58 (m, 1H, C*H*N), 4.55 (s, 1H, C_9-*H*), 4.13 (dd, J = 9.1, 1.8 Hz, OCH_2), 4.02 (dd, J = 9.1, 7.5 Hz, 1H, OCH_2), 3.69 (dd, J = 10.1, 1.9 Hz, 1H, C_7-*H*), 3.31 (dd, J = 13.4, 3.3 Hz, ArCH_2), 3.31 (s, 3H, C_3-OCH_3), 3.30 (s, 3H, C_5-OCH_3), 3.18 (dd, J = 10.8, 4.6 Hz, 1H, C_5-*H*), 2.75 (dd, J = 13.2, 9.5 Hz, 1H, ArCH_2), 2.10 (m, 2H, C_4-*H*, C_6-*H*), 1.68 (s, 3H, C_{10}-CH_3), 1.59 (m, 1H, C_8-*H*), 1.30 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.15 (d, J = 6.4 Hz, 3H, C_4-CH_3), 0.66 (d, J = 7.0 Hz, 3H, C_6-CH_3), 0.61 (d, J = 6.8 Hz, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.5, 153.2, 147.6, 135.5, 129.5, 128.9, 127.3, 109.3, 103.2, 82.9, 71.9, 70.9, 65.6, 56.5, 56.3, 47.8, 41.4, 38.0, 36.3, 35.7, 30.6, 19.8, 13.2, 12.2, 7.2, 4.3. Anal. Calcd for $C_{28}H_{41}NO_7$: C, 66.78; H, 8.21. Found: C, 66.84; H, 8.33.

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*,2*S*,3*R*)-2,4-dihydroxy-1,3-dimethylbutyl]tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (11). To a solution of 160 mg (0.318 mmol) of alcohol **10** in 6.4 mL of THF at 0 °C was added 477 μL (954 mmol, 2.0 M in THF) of BH_3·DMS. After 15 min, the reaction mixture was warmed to ambient temperature with continued stirring for 4 h. The mixture was recooled to 0 °C and quenched with 400 μL each of 1:1 EtOH/THF, aqueous pH 7 phosphate buffer, and 30% aqueous hydrogen peroxide. After 15 min, the solution was again warmed to ambient temperature where it stirred for 3 h. Saturated aqueous Na_2SO_3 (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified reaction mixture showed a 92:8 mixture of diastereomers. Purification by flash chromatography (linear gradient of 45−60% EtOAc/hexane) afforded 141 mg (85%) of **11** as a clear oil: $[\alpha]^{23}_D$ +146.0° (*c* 1.0, CH_2Cl_2); IR (film) 3476, 2974, 1777, 1692, 1453, 1390, 1245, 1099, 1016, 984, 735, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (m, 5H, Ar*H*), 4.74 (q, J = 7.3 Hz, 1H, C_2-*H*), 4.58 (m, 1H, C*H*N), 4.15 (dd, J = 9.1, 2.0 Hz, 1H, OCH_2), 4.08 (m, 2H, C_9-*H*, OCH_2), 3.61 (dd, J = 10.0, 1.9 Hz, 1H, C_7-*H*), 3.60 (m, 1H, C_{11}-*H*), 3.49 (m, 1H, C_{11}-*H*), 3.30 (s, 3H, C_3-OCH_3), 3.29 (m, 1H, ArCH_2), 3.28 (s, 3H, C_5-OCH_3), 3.16 (dd, J = 10.8, 4.7 Hz, 1H, C_5-*H*), 2.76 (dd, J = 13.4, 9.9 Hz, 1H, ArCH_2), 2.61 (m, 1H, O*H*), 2.05 (m, 1H, C_6-*H*), 1.96 (m, 1H, C_4-*H*), 1.70 (m, 1H, C_8-*H*), 1.55 (m, 1H, C_{10}-*H*), 1.30 (d, J = 7.3 Hz, C_2-CH_3), 1.13 (d, J = 6.5 Hz, 3H, C_4-CH_3), 1.05 (d, J = 6.9 Hz, 3H, C_6-CH_3), 0.80 (d, J = 7.0 Hz, 3H, C_{10}-CH_3), 0.62 (d, J = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3, 153.8, 135.3, 129.4, 128.9, 127.3, 103.2, 82.7, 71.7, 70.0, 65.9, 65.2, 56.6, 56.3, 47.9, 41.9, 39.6, 38.1, 37.7, 36.0, 30.3, 13.1, 13.0, 12.0, 8.4, 4.3; exact mass calcd for $C_{28}H_{43}NO_8Na$ 544.2886, found 544.2893 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*,2*S*,3*S*)-2,4-dihydroxy-1,3-dimethylbutyl]tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (12). To a solution of 40 mg (0.080 mmol) of alcohol **10** in 1.3 mL of THF at 0 °C was added 29 mg (0.120 mmol) of 9-BBN in 300 μL of THF. After 15 min, the reaction mixture was warmed to ambient temperature with stirring for 24 h. The mixture was recooled to 0 °C and quenched with 100 μL each of 1:1 EtOH/THF, aqueous pH 7 phosphate buffer, and 30% aqueous hydrogen peroxide. After 15 min, the solution was again warmed to ambient temperature and stirred for 3 h. Saturated aqueous Na_2SO_3 (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified reaction mixture showed a >95:5 mixture of diastereomers. Purification by flash chromatography (linear gradient of 45−60% EtOAc/hexane) afforded 25 mg (60%) of **12** as a clear oil: $[\alpha]^{23}_D$ +168.8° (*c* 0.65, CH_2Cl_2); IR (film) 3430, 2929, 1782, 1692, 1453, 1384, 1246, 1099, 1017, 735, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 5H, Ar*H*), 4.82 (q, J = 7.3 Hz, 1H, C_2-*H*), 4.58 (m, 1H, C*H*N), 4.12 (dd, J = 9.0, 1.8 Hz, 1H, OCH_2), 4.01 (m, 2H, C_9-*H*, OCH_2), 3.78 (m, 1H, C_{11}-*H*), 3.72 (m, 1H, C_{11}-*H*), 3.63 (dd, J = 9.9, 1.9 Hz, 1H, C_7-*H*), 3.30 (s, 6H, C_3-OCH_3, C_5-OCH_3), 3.29 (dd, J = 14.0, 3.3 Hz, 1H, ArCH_2), 3.17 (dd, J = 10.8, 4.7 Hz, 1H, C_5-*H*), 2.77 (dd, J = 13.3, 9.8 Hz, 1H, ArCH_2), 2.51 (m, 1H, O*H*), 2.08 (m, 2H, C_4-*H*, C_6-*H*), 1.81 (m, 1H, C_{10}-*H*), 1.54 (m, 1H, C_8-*H*), 1.30 (d, J = 7.4 Hz, C_2-CH_3), 1.13 (d, J = 6.4 Hz, 3H, C_4-CH_3), 0.78 (d, J = 7.1 Hz, 3H, C_6-CH_3), 0.73 (d, J = 7.1 Hz, 3H, C_{10}-CH_3), 0.62 (d, J = 6.8 Hz, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.5, 153.2, 135.4, 129.5, 128.9, 127.3, 103.1, 82.8, 74.2, 70.6, 69.4, 65.5, 56.4, 56.3, 47.9, 41.3, 38.1, 37.9, 36.4, 35.7, 30.5, 13.2, 12.4, 12.2, 7.7, 4.4; exact mass calcd for $C_{28}H_{43}NO_8Na$ 544.2886, found 544.2896 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*)-[(4*S*,5*R*)-2,2,5-trimethyldioxan-4-yl]ethyl]-(2*S*,3*S*)-tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (13). To a solution of 20 mg (0.038 mmol) of diol **11** in 300 μL each of CH_2Cl_2 and 2,2-dimethoxypropane at ambient temperature was added 5 mg of Dowex 50 × 8-200 resin. After the mixture was stirred for 45 min, the resin was removed by filtration through a short column of Celite with CH_2Cl_2. The filtrate was washed with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc/hexane) afforded 21 mg (100%) of **13** as a clear oil: $[\alpha]^{23}_D$ +159.7° (*c* 0.60, CH_2Cl_2); IR (film) 2976, 1781, 1695, 1454, 1389, 1242, 1196, 1100, 1012, 734, 701 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5H, Ar*H*), 4.82 (q, J = 7.4 Hz, 1H, C_2-*H*), 4.60 (m, 1H, C*H*N), 4.29 (app t, J = 2.4 Hz, 1H, C_9-*H*), 4.21 (dd, J = 11.4, 2.6 Hz, 1H, C_{11}-*H*), 4.14 (dd, J = 9.0, 1.9 Hz, 1H, OCH_2), 4.03 (app t, J = 7.6 Hz, 1H, OCH_2), 3.50 (dd, J = 11.5, 1.4 Hz, 1H, C_{11}-*H*), 3.34 (dd, J = 10.1, 1.9 Hz, 1H, C_7-*H*), 3.29 (s, 3H, C_3-OCH_3), 3.28 (m, 1H, ArCH_2), 3.27 (s, 3H, C_5-OCH_3), 3.13 (dd, J = 10.9, 4.6 Hz, 1H, C_5-*H*), 2.80 (dd, J = 13.3, 9.5 Hz, 1H, ArCH_2), 2.15 (m, 1H, C_4-*H*), 2.05 (m, 1H, C_6-*H*), 1.45 (m, 2H, C_8-*H*, C_{10}-*H*), 1.39 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.30 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.13 (d, J = 6.4 Hz, 3H, C_4-CH_3), 1.09 (d, J = 7.0 Hz, 3H, C_6-CH_3), 0.83 (d, J = 6.9 Hz, 3H, C_{10}-CH_3), 0.64 (d, J = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2, 153.2, 135.3, 129.5, 128.9, 127.3, 103.4, 98.4, 82.6, 72.8, 69.2, 67.5, 65.6, 56.3, 56.1, 48.2, 41.0, 38.5, 38.1, 35.5, 33.9, 29.8, 19.7, 13.4, 12.7, 12.2, 10.3, 4.4; exact mass calcd for $C_{31}H_{47}NO_8Na$, 584.3199, found 584.3187 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*)-[(4*S*,5*S*)-2,2,5-trimethyldioxan-4-yl]ethyl]-(2*S*,3*S*)-tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (14). To a solution of 15 mg (0.028 mmol) of diol **12** in 300 μL each of CH_2Cl_2 and 2,2-dimethoxypropane at ambient temperature was added 5 mg of Dowex 50 × 8-200 resin. After the mixture was stirred for 45 min, the resin was removed by filtration through a short column of Celite with CH_2Cl_2. The filtrate was washed with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc/hexane) afforded 16 mg (100%) of **14** as a clear oil: $[\alpha]^{23}_D$ +173.4° (*c* 0.50, CH_2Cl_2); IR (film) 2974, 1783, 1694, 1456, 1386, 1236, 1195, 1100, 1067, 1014, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 5H, Ar*H*), 4.83 (q, J = 7.3 Hz, 1H, C_2-*H*), 4.56 (m, 1H, C*H*N), 4.13 (dd, J = 9.1, 1.8 Hz, 1H, OCH_2), 4.00 (app t, J = 9.2 Hz, 1H, OCH_2), 3.98 (dd, J = 12.5, 1.3 Hz, 1H, C_9-*H*), 3.64 (dd, J = 11.4, 5.7 Hz, 1H, C_{11}-*H*), 3.60 (app t, J = 11.3 Hz, 1H, C_{11}-*H*), 3.52 (dd, J = 10.2, 1.9 Hz, 1H, C_7-*H*), 3.30 (s, 3H, C_3-OCH_3), 3.28 (dd, J = 13.4, 3.2 Hz, 1H, ArCH_2), 3.23 (s, 3H, C_5-OCH_3), 3.18 (dd, J = 10.8, 4.5 Hz, 1H, C_5-*H*), 2.79 (dd, J = 13.3, 9.6 Hz, 1H, ArCH_2), 2.05 (m, 2H, C_4-*H*, C_6-*H*), 1.81 (m, 1H, C_{10}-*H*), 1.56 (m, 1H, C_8-*H*), 1.40 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.30 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.14 (d, J = 6.4 Hz, 3H, C_4-CH_3), 0.80 (d, J = 6.9 Hz, 3H, C_6-CH_3), 0.68 (d, J = 6.7 Hz, 3H, C_{10}-CH_3), 0.62 (d, J = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.6, 153.1, 135.4, 129.5, 128.9, 127.3, 103.2, 98.0, 82.4, 71.9, 70.1, 65.9, 65.5, 56.4, 56.3, 48.1, 41.3, 37.9, 35.8, 35.4, 30.6, 30.0, 19.8, 13.4, 12.0, 11.8, 8.2, 4.2; exact mass calcd for $C_{31}H_{47}NO_8Na$ 584.3199, found 584.3193 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*,2*S*,3*R*)-1,3-dimethyl-4-hydroxy-2-triphenylsiloxybutyl]tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (15). To a solution of 79 mg (0.152 mmol) of diol **11** in 1.5 mL of DMF at ambient temperature were added 103 mg (1.52 mmol) of imidazole, 223 mg (0.758 mmol) of triphenylsilyl chloride, and 8 mg of DMAP. The heterogeneous reaction mixture was stirred for 16 h and was poured into 40 mL each of Et_2O and saturated aqueous NaCl. The aqueous layer was extracted with Et_2O (2 × 40 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil which was used without further purification.

To a solution of the yellow oil in 5.0 mL of THF, cooled to −45 °C, was added 500 mL of freshly prepared, buffered pyridinium hydrofluoride (stock solution prepared from 2.0 g of pyridinium hydrofluoride (Aldrich), 4.0 mL of pyridine, and 16.0 mL of THF). After 6 h at −40 °C, the mixture was poured into 30 mL each of CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient of 15−25% EtOAc/hexane) afforded 104 mg (85% for two steps) of **15** as a clear oil: $[\alpha]^{23}_D$ +102.0° (*c* 0.25, CH_2Cl_2); IR (film) 3424, 2974, 1774, 1699, 1456, 1428, 1388, 1243, 1211, 1114, 1062, 1013, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.60 (m, 6H, Ar*H*), 7.42−7.15 (m, 14H, Ar*H*), 4.61−4.50 (m, 3H, C_2-*H*, C_9-*H*, C*H*N), 4.15 (dd, J = 9.0, 1.8 Hz, 1H, OCH_2), 4.05 (dd, J = 9.0, 7.4 Hz, 1H, OCH_2), 3.50 (m, 1H, C_{11}-*H*), 3.38 (m, 1H, C_{11}-*H*), 3.24 (s, 3H, C_3-OCH_3), 3.22 (m, 1H, ArCH_2), 3.14 (dd, J = 10.0, 1.6 Hz, C_7-*H*), 2.85 (dd, J = 10.8, 4.5 Hz, C_5-*H*), 2.78 (dd, J = 13.4, 9.6 Hz, 1H, ArCH_2), 2.72 (s, 3H, C_5-OCH_3), 2.25−2.12 (m, 2H, C_4-*H*, O*H*), 1.71 (m, 2H, C_6-*H*, C_{10}-*H*), 1.58 (m, 1H, C_8-*H*), 1.20 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.05 (d, J = 6.4 Hz, 3H, C_4-CH_3), 0.94 (d, J = 7.0 Hz, 3H, C_6-CH_3), 0.74 (d, J = 7.1 Hz, 3H, C_8-CH_3), 0.56 (d, J = 6.7 Hz, 3H, C_{10}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2, 153.7, 135.8, 135.4, 135.3, 135.3, 129.8, 129.5, 128.9, 127.8, 127.4, 103.3, 82.7, 74.4, 74.0, 65.9, 65.2, 56.3, 56.2, 47.8, 43.8, 41.2, 39.0, 37.9, 35.3, 30.2, 13.6, 12.4, 11.8, 11.3, 4.4; exact mass calcd for $C_{46}H_{57}NO_8SiNa$ 802.3751, found 802.3755 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*R*)-6-[(1*R*,2*S*,3*R*)-1,3-dimethyl-4-oxo-2-triphenylsiloxybutyl]tetrahydro-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (16). To a suspension of 250 mg (0.590 mmol) of Dess−Martin periodinane in 1.5 mL of CH_2Cl_2 at 0 °C was added 234 μL (202 mg, 2.56 mmol) of pyridine. After 10 min, the alcohol **15** in 0.5 mL of CH_2Cl_2 was added *via* cannula (0.5 mL of CH_2Cl_2 rinse), and the mixture was warmed to ambient temperature. After 6 h, the solution was poured into 30 mL each of EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with 15 mL of aqueous 1 M $Na_2S_2O_3$. The aqueous layers were back-extracted with EtOAc (2 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc/hexane) afforded 114 mg (99%) of **16** as a clear oil: $[\alpha]^{23}_D$ +121.4° (*c* 1.40, CH_2Cl_2); IR (film) 3056, 2977, 1778, 1698, 1454, 1429, 1388, 1348, 1244, 1115, 1064, 1013, 740, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 1.7 Hz, 1H, C_{11}-*H*), 7.65−7.15 (m, 20H, Ar*H*), 4.77 (dd, J = 5.5, 1.7 Hz, 1H, C_9-*H*), 4.64−4.52 (m, 2H, C_2-*H*, C*H*N), 4.15−4.05 (m, 2H, OCH_2), 3.41 (dd, J = 10.1, 1.8 Hz, C_7-*H*), 3.30 (s, 3H, C_3-OCH_3), 3.22 (dd, J = 13.4, 3.1 Hz, 1H, ArCH_2), 3.02 (dd, J = 10.8, 4.5 Hz, C_5-*H*), 2.78 (dd, J = 13.3, 9.4 Hz, 1H, ArCH_2), 2.68 (s, 3H, C_5-OCH_3), 2.60 (m, 1H, C_{10}-*H*), 2.35 (m, 1H, C_4-*H*), 1.91 (m, 1H, C_6-*H*), 1.60 (m, 1H, C_8-*H*), 1.22 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.09 (d, J = 6.5 Hz, 3H, C_4-CH_3), 1.00 (d, J = 6.9 Hz, 3H, C_6-CH_3), 0.83 (d, J = 7.0 Hz, 3H, C_8-CH_3), 0.62 (d, J = 6.8 Hz, 3H, C_{10}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.3, 174.0, 153.1, 135.3, 135.2, 134.7, 130.1, 129.4, 128.8, 127.9, 127.3, 103.3, 82.6, 74.6, 72.6, 65.6, 56.2, 55.9, 52.7, 47.5, 41.0, 38.0, 37.7, 35.3, 30.5, 13.8, 12.2, 10.4, 10.1, 4.3; exact mass calcd for $C_{46}H_{55}NO_8SiNa$ 800.3594, found 800.3589 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[3(2*S*,4*S*),4*S*]-3-[2,4-Dimethyl-1,3-dioxo-4-(2-methyl-1,3-dioxan-2-yl)butyl]-4-(phenylmethyl)-2-oxazolidinone (17). To a solution of 7.3 g (25.33 mmol) of imide **4** in 63.0 mL of CH_2Cl_2 at −50 °C were added 3.1 mL (27.87 mmol) of $TiCl_4$ and 5.1 mL (29.19 mmol) of *i*-Pr_2NEt. Enolization was allowed to occur for 30 min before 7.84 g (66.36 mmol) of 2-methoxy-2-methyl-1,3-dioxolane was added, and the solution was stirred at −50 °C for 1 h. The reaction mixture was then warmed to −20 °C over 30 min, at which time it was added *via* cannula to an ice-cooled beaker containing 200 mL of EtOAc and 500 mL of saturated aqueous K_2CO_3. The aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with 500 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified mixture showed a 14:1 ratio of **17** to an unidentified diastereomer. Purification by flash chromatography (30% EtOAc/hexane) gave 8.55 g (86%) of **17** as a clear oil: $[\alpha]^{23}_D$ +99.4° (*c* 0.57, CH_2Cl_2); IR (neat) 2990, 2945, 2890, 1783, 1730, 1695, 1455, 1390, 1360, 1215, 1180, 1120, 1050, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28−7.20 (m, 5H, Ar*H*), 5.07 (q, J = 7.2 Hz, 1H, C_{26}-*H*), 4.70 (m, 1H, C*H*N), 4.18 (m, 2H, OCH_2), 3.93 (m, 4H, OCH_2CH_2O), 3.30 (dd, J = 13.4, 3.2 Hz, ArCH_2), 3.14 (q, J = 7.1 Hz, 1H, C_{28}-*H*), 2.76 (dd, J = 13.4, 9.6 Hz, 1H, ArCH_2), 1.46 (d, J = 7.2 Hz, 3H, C_{26}-CH_3), 1.28 (s, 3H, C_{30}-H_3), 1.14 (d, J = 6.9 Hz, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.2, 170.5, 153.2, 135.1, 129.2, 128.8, 127.2, 110.2, 66.1, 64.7, 64.3, 55.4, 52.2, 51.9, 37.8, 20.9, 123.8, 12.4. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.76; H, 6.86.

[3(2*S*,3*R*,4*S*)4*S*]-3-[2,4-Dimethyl-3-hydroxy-1-oxo-4-(2-methyl-1,3-dioxan-2-yl)butyl]-4-(phenylmethyl)-2-oxazolidinone (18). To a solution of 6.0 g (15.98 mmol) of ketone **17** in 160 mL of CH_2Cl_2 at −25 °C was added 120 mL (23.97 mmol, 0.20 M in Et_2O) of Zn-

$(BH_4)_2$. This solution was stirred for 3 h at −25 °C and was quenched by slow addition of 20 mL of saturated aqueous Na/K tartrate. The mixture was poured into 500 mL of Na/K tartrate, and the aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were washed with 300 mL of saturated aqueous NH_4Cl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (40% EtOAc/hexane) afforded 4.59 g (70%) of **18** as a clear oil: $[\alpha]^{23}_D$ +71.5° (*c* 0.40, CH_2Cl_2); IR (neat) 3615, 2980, 2940, 2885, 1785, 1690, 1450, 1300, 1350, 1208, 1120, 1040, 968, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (m, 5H, Ar*H*), 4.68 (m, 1H, C*H*N), 4.32 (dd, *J* = 8.9, 1.6 Hz, 1H, C_{27}-*H*), 4.26 (m, 2H, OCH_2), 4.01 (m, 5H, C_{26}-*H*, OCH_2CH_2O), 3.22 (dd, *J* = 13.4, 2.6 Hz, ArCH_2), 3.09 (br s, 1H, C_{27}-O*H*), 2.77 (dd, *J* = 13.3, 9.5 Hz, 1H, ArCH_2), 1.86 (dq, *J* = 7.2, 1.5 Hz, 1H, C_{28}-*H*), 1.38 (d, *J* = 6.8 Hz, 3H, C_{26}-CH_3), 1.36 (s, 3H, C_{30}-H_3), 0.98 (d, *J* = 7.2 Hz, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8, 152.6, 134.9, 129.3, 128.8, 127.3, 112.1, 70.9, 65.8, 64.8, 64.2, 54.9, 42.9, 41.3, 37.5, 21.9, 14.9, 7.8. Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21. Found: C, 63.46; H, 7.38.

[3(2*S*,3*R*,4*S*)4*S*]-3-[2,4-Dimethyl-3-methoxy-1-oxo-4-(2-methyl-1,3-dioxan-2-yl)butyl]-4-(phenylmethyl)-2-oxazolidinone (19). To a solution of 4.59 g (12.16 mmol) of alcohol **18** in 61 mL of CH_2Cl_2 at ambient temperature were added 13.03 g (60.80 mmol) of proton sponge and 8.99 g (60.80 mmol) of Me_3OBF_4, and the heterogeneous reaction mixture was stirred with protection from light for 48 h. The light brown reaction mixture was poured into 300 mL of CH_2Cl_2 and was washed with aqueous 1 M HCl (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography using 25% EtOAc/hexane afforded 3.88 g (82%) of **19** as a clear oil: $[\alpha]^{23}_D$ +48.4° (*c* 0.20, CH_2Cl_2); IR (neat) 2981, 1780, 1694, 1455, 1382, 1211, 1060, 971, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (m, 5H, Ar*H*), 4.63 (m, 1H, C*H*N), 4.16 (m, 3H, OCH_2, C_{26}-*H*), 3.94 (m, 4H, OCH_2CH_2O), 3.74 (dd, *J* = 7.4, 1.8 Hz, 1H, C_{27}-*H*), 3.45 (s, 3H, C_{27}-OCH_3), 3.26 (dd, *J* = 13.3, 2.2 Hz, 1H, ArCH_2), 2.77 (dd, *J* = 13.3, 9.7 Hz, 1H, ArCH_2), 1.78 (dq, *J* = 7.1, 1.6 Hz, 1H, C_{28}-*H*), 1.32 (s, 3H, C_{30}-H_3), 1.30 (d, *J* = 8.1 Hz, 3H, C_{26}-CH_3), 0.94 (d, *J* = 7.1 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8, 152.9, 135.2, 129.4, 128.9, 127.3, 111.7, 81.7, 66.0, 64.4, 64.3, 60.2, 55.6, 43.3, 41.2, 37.7, 20.8, 14.5, 9.3; exact mass calcd for $C_{21}H_{29}NO_6Na$ 414.1884, found 414.1884 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[(2*S*,3*R*,4*R*)-3-Methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-pentyl] Methanesulfonate (20). To a solution of 3.66 g (9.35 mmol) of **19** in 187 mL of Et_2O at −10 °C were added 658 μL (517 mg, 11.22 mmol) of EtOH and 5.61 mL (11.22 mmol, 2.0 M in THF) of $LiBH_4$. The solution was stirred at −10 °C for 1 h and was quenched by addition of 10 mL of aqueous 1 M NaOH. After the cloudy mixture was stirred for 15 min at 0 °C, it was poured into 100 mL of Et_2O and 200 mL of saturated aqueous NaCl. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting yellow oil was filtered through a small column of silica gel (40% EtOAc/hexane) to remove the oxazolidinone auxiliary. The filtrate was concentrated *in vacuo* to give 1.75 g (86%) of the alcohol as a clear oil which was used in the subsequent reaction without further purification: $[\alpha]^{23}_D$ +6.8° (*c* 0.10, CH_2Cl_2); IR (neat) 3880−3035, 2980, 2940, 1635, 1460, 1385, 1230, 1170, 1080, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (m, 4H, OCH_2CH_2O), 3.66 (dd, *J* = 10.8, 7.7 Hz, 1H, C_{25}-*H*), 3.55 (dd, *J* = 10.8, 4.9 Hz, 1H, C_{25}-*H*), 3.44 (m, 1H, C_{27}-*H*), 3.42 (s, 3H, C_{27}-OCH_3), 2.12 (m, 1H, C_{26}-*H*), 1.89 (dq, *J* = 7.2, 2.3 Hz, 1H, C_{28}-*H*), 1.28 (s, 3H, C_{30}-H_3), 1.05 (d, *J* = 7.2 Hz, 3H, C_{26}-CH_3), 0.89 (d, *J* = 7.0 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 112.0, 82.7, 66.2, 64.4, 64.3, 58.8, 41.9, 38.0, 20.4, 12.6, 10.6.

To a solution of 1.75 g (8.02 mmol) of the alcohol in 40 mL of CH_2Cl_2 at 0 °C were added 2.46 mL (1.78 g, 17.6 mmol) of Et_3N and 683 μL (1.01 g, 8.82 mmol) of methanesulfonyl chloride. After 2.5 h, 30 mL of saturated aqueous NH_4Cl was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (25% EtOAc/hexane) afforded 2.39 g (86%, for two steps) of **20** as a clear oil: $[\alpha]^{23}_D$ +10.6° (*c* 0.10, CH_2Cl_2); IR (neat) 2980, 2940, 1783, 1455, 1355, 1175, 1080, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (dd, *J* = 9.5, 6.6 Hz, 1H, C_{25}-*H*), 4.04 (dd, *J* = 9.5, 6.7 Hz, 1H, C_{25}-*H*), 3.96 (m, 4H, OCH_2CH_2O), 3.40 (s, 3H, C_{27}-OCH_3), 3.37 (app t, *J* = 4.1 Hz, 1H, C_{27}-*H*), 3.02 (s, 3H, OSO_2-CH_3), 2.21 (m, 1H, C_{26}-*H*), 1.86 (m, 1H, C_{28}-*H*), 1.28 (s, 3H, C_{30}-H_3), 1.01 (d, *J* = 7.2 Hz, 3H, C_{26}-CH_3), 0.98 (d, *J* = 6.9 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 111.6, 79.7, 72.4, 64.5, 64.2, 59.9, 53.4, 43.3, 37.8, 37.2, 20.7, 11.4, 10.7; exact mass calcd for $C_{12}H_{24}O_6SNa$ 319.1185, found 319.1208 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[(2*S*,3*R*,4*R*)-3-Methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-pentyl] Triphenylphosphonium Iodide (21). To a solution of 450 mg (1.52 mmol) of mesylate **20** in 8 mL of acetone were added 910 mg (6.09 mmol) of NaI and 5 mg of K_2CO_3. The heterogeneous mixture was heated at reflux for 16 h. After cooling to ambient temperature, the cloudy solution was poured into 50 mL each of Et_2O and H_2O. The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The yellow oil was filtered through a small column of silica gel (30% EtOAc/hexane). The filtrate was concentrated *in vacuo* to give 0.49 g (98%) of the iodide as a yellow oil which was used immediately without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (m, 4H, OCH_2CH_2O), 3.43 (s, 3H, C_{27}-OCH_3), 3.37 (dd, *J* = 4.9, 3.5 Hz, 1H, C_{27}-*H*), 3.34 (dd, *J* = 9.7, 5.8 Hz, 1H, C_{25}-*H*), 3.07 (dd, *J* = 9.6, 6.7 Hz, 1H, C_{25}-*H*), 1.91 (m, 1H, C_{26}-*H*), 1.81 (dq, *J* = 7.2, 3.5 Hz, 1H, C_{28}-*H*), 1.26 (s, 3H, C_{30}-H_3), 1.00 (d, *J* = 6.8 Hz, 3H, C_{26}-CH_3), 0.97 (d, *J* = 7.0 Hz, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 112.0, 82.5, 64.7, 64.3, 60.0, 43.2, 40.3, 20.9, 15.9, 13.2, 10.5; exact mass calcd for $C_{11}H_{21}IO_3$ 328.0537, found 328.0526 (EI).

To a solution of 1.30 g (3.97 mmol) of the iodide in 10 mL of acetonitrile was added 5.21 g (19.86 mmol) of PPh_3. The mixture was heated to 80 °C for 50 h. After the mixture was cooled to ambient temperature, the solvents were removed *in vacuo*. The residue was purified by flash chromatography (gradient of 100% EtOAc to 100% CH_3CN) to give 2.15 g (92%) of **21** as a white powder: $[\alpha]^{23}_D$ +11.7° (*c* 0.10, CH_2Cl_2); IR (neat) 3060, 2995, 2945, 2200, 1820, 1590, 1488, 1440, 1389, 1250, 1195, 1170, 920, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.68 (m, 15H, Ar*H*), 4.09 (m, 1H, C_{25}-*H*), 3.90 (m, 4H, OCH_2CH_2O), 3.61 (m, 1H, C_{25}-*H*), 3.43 (m, 1H, C_{27}-*H*), 3.27 (s, 3H, C_{27}-OCH_3), 2.28 (m, 1H, C_{26}-*H*), 2.05 (dq, *J* = 7.3, 2.8 Hz, 1H, C_{28}-*H*), 1.23 (s, 3H, C_{30}-H_3), 1.06 (d, *J* = 7.2 Hz, 3H, C_{26}-CH_3), 0.80 (d, *J* = 6.8 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.9, 133.5, 133.4, 131.8, 131.7, 130.4, 130.3, 128.4, 128.2, 118.6, 117.7, 111.2, 82.1, 82.0, 64.2, 64.1, 58.7, 41.6, 32.5, 32.4, 25.8, 25.3, 20.3, 15.6, 11.2. Anal. Calcd for $C_{29}H_{36}IO_3P$: C, 58.99; H, 6.15. Found: C, 58.68; H, 5.95.

[3(2*S*,3*R*),4*S*]-3-[2-Hydroxy-2-methyl-1-oxo-4-(phenylmethoxy)-butyl]-4-(phenylmethyl)-2-oxazolidinone (23). To a solution of 46.7 g (0.200 mol) of propionyl oxazolidinone **22** in 400 mL of CH_2Cl_2 at 0 °C were added 53.0 mL (0.210 mol) of *n*-Bu_2BOTf and 24.3 mL (0.240 mol) of Et_3N, keeping the internal temperature of the reaction below 5 °C. The resulting light yellow enolate was cooled to −78 °C, and a solution of 28.5 g (0.190 mol) of (benzyloxy)acetaldehyde in 25 mL of CH_2Cl_2 was added dropwise *via* cannula. The mixture was stirred at −78 °C for 0.5 h, slowly warmed to 0 °C, and stirred for an additional 1 h. The reaction was quenched by addition of 600 mL of 2:1 MeOH/aqueous pH 7 phosphate buffer, followed by careful addition of 600 mL of 2:1 MeOH/30% aqueous H_2O_2. The heterogeneous mixture was stirred at 0 °C for 1 h. Solvents were removed *in vacuo*. The resulting slurry was dissolved in 350 mL of EtOAc and washed with 350 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was back-extracted with EtOAc (2 × 300 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5% EtOAc/CH_2Cl_2) gave 53.9 g (74%) of **23** as a clear oil: $[\alpha]^{23}_D$ +71.2° (*c* 0.26, EtOH); IR (neat) 3500, 3010, 2900, 1780, 1700, 1500, 1460, 1390, 1210, 1110, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 10H, Ar*H*), 4.54 (m, 1H, C*H*N), 4.51 (s, 2H, $PhCH_2O$), 4.16 (dd, *J* = 11.0, 5.6 Hz, 1H, C_{23}-*H*), 4.08 (dd, *J* = 9.1, 2.6 Hz, 1H, OCH_2), 4.01 (app t, *J* = 8.2 Hz, 1H, OCH_2), 3.94 (app quint, *J* = 5.7 Hz, 1H, C_{22}-*H*), 3.53 (m, 2H, C_{24}-*H*), 3.19 (dd, *J* = 13.4, 3.2 Hz, 1H, ArCH_2), 2.80 (br s,

1H, C_{23}-O*H*), 2.74 (dd, J = 13.4, 9.4 Hz, 1H, ArC*H*$_2$), 1.27 (d, J = 7.0 Hz, 3H, C_{22}-C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 152.9, 137.8, 135.0, 129.3, 128.8, 128.3, 127.6, 127.2, 73.2, 71.7, 70.6, 65.9, 54.9, 40.2, 37.6, 12.1. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57. Found: C, 68.79; H, 6.67.

[2*S*,3*S*]-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-*N*-methoxy]-*N*,2-dimethyl-4-phenylmethoxybutanamide (24). To a suspension of 18.8 g (0.193 mol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 100 mL of THF at 0 °C was added dropwise 96.5 mL (0.193 mol, 2.0 M in toluene) of trimethylaluminum with concomitant evolution of gas. The resulting homogeneous solution was stirred for 30 min at 25 °C. A solution of 18.5 g (48.25 mmol) of carboximide **23** in 30 mL of THF was added *via* cannula to the aluminum amide solution at 0 °C. The resulting solution was stirred at 0 °C for 2 h, at which time it was added *via* cannula to an ice-cooled beaker containing 300 mL of CH_2Cl_2 and 200 mL of aqueous 0.5 M HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (60% EtOAc/hexane) gave 12.3 g (95%) of the amide as a clear oil: $[\alpha]^{23}_D$ +13.3° (*c* 0.30, EtOH); IR (neat) 3600−3300, 2980, 1750, 1655, 1455, 1390, 1200, 1180, 1100, 995, 910, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.13 (m, 5H, Ar*H*), 4.41 (br s, 2H, PhC*H*$_2$O), 3.93 (dd, J = 16.0, 5.5 Hz, 1H, C_{23}-*H*), 3.51 (s, 3H, NOC*H*$_3$), 3.40 (m, 2H, C_{24}-*H*$_2$), 3.03 (br s, 4H, N-C*H*$_3$, C_{22}-*H*), 1.08 (d, J = 7.0 Hz, 3H, C_{22}-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.4, 128.0, 127.9, 72.7, 71.4, 70.7, 66.5, 60.8, 36.7, 11.7. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 63.14; H, 7.83.

To a solution of 12.3 g (45.83 mmol) of the amide in 120 mL of CH_2Cl_2 at 0 °C were added 5.26 g (77.19 mmol) of imidazole, 100 mg of DMAP, and 10.91 g (72.37 mmol) of TBSCl. The mixture was warmed to 25 °C and stirred for 16 h, at which time it was poured into 500 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexane) gave 17.5 g (100%) of **24** as a clear oil: $[\alpha]^{23}_D$ −1.3° (*c* 0.60, CH_2Cl_2); IR (neat) 2965, 2940, 2900, 2860, 1785, 1665, 1465, 1390, 1255, 1100, 1000, 835, 780, 735, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.16 (m, 5H, Ar*H*), 4.41 (s, 2H, PhC*H*$_2$O), 4.06 (m, 1H, C_{23}-*H*), 3.61 (s, 3H, NOC*H*$_3$), 3.45 (m, 2H, C_{24}-*H*$_2$), 3.15 (m, 1H, C_{22}-*H*), 3.09 (s, 3H, NC*H*$_3$), 1.17 (d, J = 7.2 Hz, 3H, C_{22}-C*H*$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.07 (s, 3H, SiC*H*$_3$), 0.04 (s, 3H, SiC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3, 128.1, 127.6, 127.4, 73.4, 73.3, 72.8, 61.3, 38.9, 32.1, 25.9, 18.1, 14.2, −4.3, −4.8. Anal. Calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.24. Found: C, 62.98; H, 9.21.

[2*S*,3*S*]-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-4-(phenylmethoxy)butanal (25). To a solution of 36.88 g (96.7 mmol) of amide **24** in 240 mL of THF at −78 °C was added dropwise 145 mL (145 mmol, 1.0 M in THF) of DIBAL. After 1 h, 10 mL of acetone was added *via* syringe and the solution was stirred for 10 min. The reaction mixture was added rapidly *via* cannula to an ice-cooled beaker containing 200 mL of CH_2Cl_2 and 500 mL of aqueous 1 M HCl. After 30 min, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with 250 mL of saturated aqueous NH_4Cl and 250 mL of saturated aqueous Na/K tartrate, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 25.7 g (83%) of **25** as a clear oil: $[\alpha]^{23}_D$ +28.7° (*c* 0.31, CH_2Cl_2); IR (neat) 3035, 2960, 2940, 2900, 2860, 2720, 1730, 1495, 1470, 1465, 1360, 1250, 1100, 1005, 835, 775, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H, C_{21}-*H*), 7.39−7.25 (m, 5H, Ar*H*), 4.52 (d, J = 12.0 Hz, 1H, PhC*H*$_2$O), 4.49 (d, J = 12.0 Hz, 1H, PhC*H*$_2$O), 4.32 (m, 1H, C_{23}-*H*), 3.48 (dd, J = 9.5, 5.3 Hz, 1H, C_{24}-*H*) 3.41 (dd, J = 9.5, 6.6 Hz, 1H, C_{24}-*H*), 2.60 (m, 1H, C_{22}-*H*), 1.06 (d, J = 7.0 Hz, 3H, C_{22}-C*H*$_3$), 0.84 (s, 9H, SiC(C*H*$_3$)$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.04 (s, 3H, SiC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.2, 137.9, 128.4, 127.7, 127.6, 73.4, 71.8, 70.5, 50.0, 25.7, 18.0, 7.6, −4.3, −5.1. Anal. Calcd for $C_{18}H_{30}O_3$: C, 67.03; H, 9.38. Found: C, 67.16; H, 9.27.

[4*S*,5*S*]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methyl-6-(phenylmethoxy)-1-hexen-3-ol (26). To a solution of 4.95 g (40.93 mmol) of 2-bromopropene in 150 mL of THF at −78 °C was added dropwise 44.0 mL (75.03 mmol, 1.7 M in pentane) of *t*-BuLi, forming a bright yellow solution. A solution of 11.0 g (34.11 mmol) of aldehyde **25** in 20 mL of THF was added dropwise *via* cannula over a period of 10 min. The solution was stirred for 15 min and was warmed slowly to 0 °C. A 25 mL portion of saturated aqueous NH_4Cl was added, and the reaction mixture was warmed to ambient temperature. The mixture was poured into 200 mL of CH_2Cl_2 and 300 mL of saturated aqueous NH_4Cl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 12.4 g (100%) of **26** as a 3:1 mixture of inseparable diastereomers: IR (neat) 3480, 3070, 3060, 2950, 2860, 1655, 1500, 1475, 1455, 1380, 1365, 1210, 1100, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H, Ar*H*), 5.09−4.88 (4 br s, 2H, C_{19}-*H*$_2$), 4.57 (s, 2H, PhC*H*$_2$O), 4.21−3.91 (m, 2H, C_{21}-*H*, C_{23}-*H*), 3.56 (m, 2H, C_{24}-*H*$_2$), 1.94 (m, 1H, C_{22}-*H*), 1.72 (s, 3H, C_{20}-C*H*$_3$), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.89−0.76 (2 d, J = 7.1 Hz, 3H, C_{22}-C*H*$_3$), 0.01 (m, 6H, Si(C*H*$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.9, 145.7, 138.2, 137.8, 128.4, 127.5, 127.4, 113.3, 110.7, 78.9, 75.4, 74.8, 73.5, 73.2, 72.3, 72.1, 38.6, 38.6, 25.8, 19.6, 18.1, 16.2, 11.9, 7.0, 5.6, 5.3, 4.7, 4.5. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 68.94; H, 9.89.

***N*,*N*,4,6-Tetramethyl-[4*E*,6*S*,7*S*]-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-8-(phenylmethoxy)-4-octenamide (27).** To a solution of 26.6 g (72.9 mmol) of alcohol **26** in 182 mL of toluene was added 32.0 mL (196 mmol) of *N*,*N*-dimethylacetamide dimethyl acetal. The solution was heated at reflux for 20 h. After cooling to ambient temperature, the reaction mixture was poured into 250 mL of CH_2Cl_2 and 250 mL of saturated aqueous NH_4Cl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexane) gave 30.0 g (95%) of **27** as a clear oil: $[\alpha]^{23}_D$ +5.0° (*c* 0.10, CH_2Cl_2); IR (neat) 2960, 2940, 2860, 2820, 1655, 1500, 1455, 1400, 1255, 1140, 1090, 1030, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.20 (m, 5H, Ar*H*), 5.44 (dd, J = 9.6, 1.0 Hz, 1H, C_{21}-*H*), 4.52 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.46 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 3.61 (dd, J = 10.2, 5.7 Hz, 1H, C_{23}-*H*), 3.43 (dd, J = 9.7, 4.4 Hz, 1H, C_{24}-*H*), 3.33 (dd, J = 9.6, 5.7 Hz, 1H, C_{24}-*H*), 2.98 (s, 3H, NC*H*$_3$), 2.94 (s, 3H, NC*H*$_3$), 2.58 (m, 1H, C_{22}-*H*), 2.35 (m, 2H, C_{18}-*H*$_2$), 2.28 (m, 2H, C_{19}-*H*$_2$), 1.64 (d, J = 1.0 Hz, 3H, C_{20}-C*H*$_3$), 0.92 (d, J = 6.7 Hz, 3H, C_{22}-C*H*$_3$), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.01 (s, 3H, SiC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 138.3, 133.3, 128.4, 128.0, 127.4, 127.2, 75.3, 73.3, 73.0, 37.0, 35.5, 35.2, 34.8, 32.0, 25.8, 18.1, 16.3, 15.7, 5.1, 4.5. Anal. Calcd for $C_{25}H_{43}NO_3Si$: C, 69.23; H, 9.99. Found: C, 69.05; H, 9.86.

[4*E*,6*S*,7*S*]-4,6-Dimethyl-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-8-(phenylmethoxy)-4-octenal (28). To a solution of 76.0 mL (76.0 mmol, 1.0 M in Et_2O) of $LiAlH_4$ in 150 mL of Et_2O at −10 °C was added 11.13 mL (113.7 mmol) of dry EtOAc over a period of 30 min. The resulting cloudy solution was stirred for 30 min and then added *via* cannula to a solution of 30.0 g (69.1 mmol) of amide **27** in 200 mL of Et_2O at −10 °C. The mixture was stirred for 1 h at −10 °C and was quenched by slow addition of 200 mL of saturated aqueous Na/K tartrate. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 400 mL). The combined organics were washed with 400 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 25.1 g (93%) of **28** as a clear oil: $[\alpha]^{23}_D$ −0.7° (*c* 0.90, CH_2Cl_2); IR (neat) 3060, 3030, 2960, 2930, 2890, 2858, 2710, 1730, 1470, 1460, 1450, 1385, 1360, 1250, 1125, 1090, 1028, 835, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, J = 1.8 Hz, C_{17}-*H*), 7.33−7.27 (m, 5H, Ar*H*), 5.03 (dd, J = 9.7, 1.2 Hz, 1H, C_{21}-*H*), 4.51 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.46 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 3.60 (dd, J = 10.2, 5.7 Hz, 1H, C_{23}-*H*), 3.40 (dd, J = 9.7, 4.4 Hz, 1H, C_{24}-*H*), 3.31 (dd, J = 9.7, 5.6 Hz, 1H, C_{24}-*H*), 2.58 (m, 1H, C_{22}-*H*), 2.47 (m, 2H, C_{18}-*H*$_2$), 2.28 (app t, J = 7.3 Hz, 2H, C_{19}-*H*$_2$), 1.62 (d, J = 1.2 Hz, 3H, C_{20}-C*H*$_3$), 0.91 (d, J = 6.8 Hz, 3H, C_{22}-C*H*$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.04 (s, 6H, Si(C*H*$_3$)$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 202.3, 138.4, 132.4, 129.2, 128.1, 127.6, 127.4, 75.4, 73.3, 73.2, 42.0, 35.7, 31.8, 25.9, 18.2, 16.3, 15.9, −4.2, −4.8;

exact mass calcd for $C_{23}H_{38}O_3SiNa$ 413.2478, found 413.2502 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[6*E*,8*S*,9*S*]-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-(phenylmethoxy)-2,6,8-trimethyldeca-1,6-dien-3-ol (29). To a solution of 7.31 g (60.4 mmol) of 2-bromopropene in 250 mL of THF at −78 °C was added dropwise 71.0 mL (120.9 mmol, 1.7 M in pentane) of *t*-BuLi, forming a bright yellow solution. A solution of 19.7 g (50.4 mmol) of aldehyde **28** in 50 mL of THF was added dropwise *via* cannula over a period of 10 min. The solution was stirred for 15 min and was warmed slowly to 0 °C. A 25 mL portion of saturated aqueous NH_4Cl was added, and the reaction mixture was warmed to ambient temperature. The mixture was poured into 200 mL of CH_2Cl_2 and 300 mL of saturated aqueous NH_4Cl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 21.8 g (100%) of **29** as a clear oil: IR (neat) 3400, 2960, 2940, 2860, 1472, 1465, 1360, 1250, 1130, 1100, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H, Ar*H*), 5.04 (d, J = 9.5 Hz, 1H, C_{21}-*H*), 4.93 (t, J = 0.9 Hz, 1H, one C_{15}-*H*), 4.84 (t, J = 1.5 Hz, 1H, one C_{15}-*H*), 4.51 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.46 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.02 (t, J = 6.6 Hz, 1H, C_{17}-*H*), 3.60 (m, 1H, C_{23}-*H*), 3.44 (dd, J = 9.7, 4.4 Hz, 1H, C_{24}-*H*), 3.32 (dd, J = 9.8, 5.9 Hz, 1H, C_{24}-*H*), 2.58 (m, 1H, C_{22}-*H*), 2.00 (m, 2H, C_{18}-*H*$_2$), 1.72 (s, 3H, C_{16}-C*H*$_3$), 1.61 (s, C_{20}-C*H*$_3$), 1.60 (m, 2H, C_{19}-*H*$_2$), 0.92 (d, J = 6.9 Hz, 3H, C_{22}-C*H*$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.02 (s, 3H, SiC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.4, 138.4, 134.4, 128.4, 128.2, 127.6, 127.4, 111.0, 110.9, 75.6, 73.5, 73.2, 35.7, 33.1, 25.9, 18.2, 17.6, 16.3, 16.2, 16.1, 5.3, 4.6. Anal. Calcd for $C_{26}H_{44}O_3Si$: C, 72.17; H, 10.25. Found: C, 71.98; H, 10.11.

Ethyl [4*E*,8*E*,10*S*,11*S*]-11-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-12-(phenylmethoxy)-4,8,10-trimethyldodeca-4,8-dienoate (30). To a solution of 21.8 g (50.4 mmol) of alcohol **29** in 125 mL of triethyl orthoacetate was added 1.25 mL of propionic acid. The resulting solution was heated at reflux for 45 min. After cooling to ambient temperature, the mixture was poured into 500 mL of saturated aqueous NaCl and 250 mL of aqueous 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 22.6 g (89%) of **30** as a clear oil: $[\alpha]^{23}_D$ −6.6° (*c* 0.50, CH_2Cl_2); IR (neat) 2960, 2935, 2860, 1740, 1465, 1455, 1370, 1250, 1155, 1135, 1095, 1030, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (m, 5H, Ar*H*), 5.13 (app t, J = 6.6 Hz, 1H, C_{17}-*H*), 4.99 (d, J = 9.6 Hz, 1H, C_{21}-*H*), 4.51 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.46 (d, J = 12.1 Hz, 1H, PhC*H*$_2$O), 4.10 (q, J = 7.1 Hz, 2H, CH_3CH_2O), 3.61 (dd, J = 10.2, 5.7 Hz, 1H, C_{23}-*H*), 3.44 (dd, J = 9.7, 4.2 Hz, 1H, C_{24}-*H*), 3.33 (dd, J = 9.6, 5.8 Hz, 1H, C_{24}-*H*), 2.56 (m, 1H, C_{22}-*H*), 2.37 (m, 2H, C_{14}-*H*$_2$), 2.31 (m, 2H, C_{15}-*H*$_2$), 2.04 (app t, J = 7.9 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.95 (app t, J = 7.7 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.60 (s, 6H, C_{16}-C*H*$_3$, C_{20}-C*H*$_3$), 1.23 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 0.92 (d, J = 6.7 Hz, 3H, C_{22}-C*H*$_3$), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.03 (s, 3H, SiC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3, 138.5, 134.1, 128.4, 128.2, 127.5, 127.3, 124.9, 73.5, 73.2, 60.1, 39.6, 35.6, 34.6, 33.2, 26.5, 25.9, 18.2, 16.3, 16.0, 15.8, 14.2, −4.2, −4.8. Anal. Calcd for $C_{30}H_{50}O_4Si$: C, 71.66; H, 10.02. Found: C, 71.61; H, 10.03.

[4*E*,8*E*,10*S*,11*S*]-11-Hydroxy-12-(phenylmethoxy)-4,8,10-trimethyldodeca-4,8-dienoic Acid (31). To a solution of 22.6 g (45.0 mmol) of ester **30** in 100 mL of THF at 25 °C was added 90 mL (90.0 mmol, 1.0 M in THF) of TBAF, and the resulting yellow solution was stirred at ambient temperature for 24 h. The mixture was poured into 500 mL of CH_2Cl_2, and the organics were washed with aqueous 1 M HCl (3 × 100 mL). The aqueous layer was back-extracted with 200 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by filtering through a short column of silica gel (EtOAc) gave the alcohol as a clear oil: $[\alpha]^{23}_D$ +31.9° (*c* 0.25, CH_2Cl_2); IR (neat) 3500, 2980, 2920, 2860, 1735, 1455, 1370, 1280, 1250, 1155, 1095, 765, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H, Ar*H*), 5.11 (app t, J = 6.7 Hz, 1H, C_{17}-*H*), 4.91 (d, J = 10.8 Hz, 1H, C_{21}-*H*), 4.54 (d, J = 11.9 Hz, 1H, PhC*H*$_2$O), 4.50 (d, J = 11.9 Hz, 1H, PhC*H*$_2$O), 4.11 (q, J = 7.1 Hz, 2H, CH_3CH_2O), 3.52 (m, 2H, C_{24}-*H*$_2$), 3.34 (dd, J = 9.1, 7.4 Hz, 1H, C_{23}-*H*), 2.47 (m, 2H, C_{22}-*H*, C_{23}-O*H*), 2.38 (m, 2H, C_{14}-*H*$_2$), 2.28 (m, 2H, C_{15}-*H*$_2$), 2.04 (app t, J = 7.6 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.96 (app t, J = 7.3 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.60 (s, 3H, C_{16}-C*H*$_3$), 1.59 (s, 3H, C_{20}-C*H*$_3$), 1.24 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$O), 1.03 (d, J = 6.6 Hz, 3H, C_{22}-C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.4, 137.9, 135.5, 133.3, 128.3, 127.6, 126.9, 124.8, 74.5, 73.2, 73.0, 60.2, 39.5, 35.7, 34.6, 33.1, 26.3, 17.2, 16.2, 15.9, 14.2. Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.24.

To a solution of 17.5 g (45.0 mmol) of the alcohol in 450 mL of MeOH at 25 °C was added 225 mL (225 mmol, 1 M in H_2O) of KOH. The solution was stirred at ambient temperature for 16 h. The reaction mixture was neutralized with 225 mL of aqueous 1 M HCl and poured into 300 mL of CH_2Cl_2. The aqueous layer was saturated with solid NaCl and extracted with EtOAc (3 × 300mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient 10% EtOAc/CH_2Cl_2 to 100% EtOAc) gave 14.5 g (89% over two steps) of **31** as a clear oil: $[\alpha]^{23}_D$ +22.5° (*c* 0.10, CH_2Cl_2); IR (neat) 3450, 2960, 2920, 2865, 1710, 1450, 1380, 1090, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H, Ar*H*), 5.12 (dd, J = 6.8, 5.7 Hz, 1H, C_{17}-*H*), 4.93 (dd, J = 9.7, 0.9 Hz, 1H, C_{21}-*H*), 4.53 (d, J = 11.8 Hz, 1H, PhC*H*$_2$O), 4.50 (d, J = 11.8 Hz, 1H, PhC*H*$_2$O), 3.56 (m, 2H, C_{24}-*H*$_2$), 3.36 (dd, J = 9.8, 8.0 Hz, 1H, C_{23}-*H*), 2.48 (m, 1H, C_{22}-*H*), 2.42 (app t, J = 7.7 Hz, 2H, C_{14}-*H*$_2$), 2.29 (app t, J = 7.4 Hz, 2H, C_{15}-*H*$_2$), 2.06 (app t, J = 7.1 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.98 (app t, J = 6.7 Hz, 2H, C_{18}-*H*, C_{19}-*H*), 1.61 (s, 3H, C_{16}-C*H*$_3$), 1.58 (s, 3H, C_{20}-C*H*$_3$), 1.01 (d, J = 6.7 Hz, 3H, C_{22}-C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.1, 137.9, 135.5, 133.3, 127.7, 126.9, 124.9, 74.5, 73.3, 72.9, 51.2, 39.5, 35.6, 34.5, 33.1, 26.2, 25.1, 16.9, 16.3, 15.9. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.06; H, 9.10.

[4*E*,8*E*,10*S*,11*R*]-11-[(Phenylmethoxy)methyl]-4,8,10-trimethylcyclododeca-4,8-dienoate (32). To a solution of 1.24 g (3.43 mmol) of carboxylic acid **31** in 340 mL of toluene was added 3.60 g (13.71 mmol) of PPh_3. The solution was cooled to −10 °C, and 2.70 mL (13.71 mmol) of diisopropyl azodicarboxylate was added dropwise over a 10 min period, resulting in a dark orange solution which was stirred at −10 °C for 15 min. The mixture was warmed to ambient temperature, and the solvents were removed *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 1.1 g (95%) of **32** as a clear oil: $[\alpha]^{23}_D$ +115.1° (*c* 0.70, CH_2Cl_2); IR (neat) 2980, 2920, 2860, 1735, 1458, 1365, 1238, 1202, 1155, 1110, 1060, 1030, 850, 740, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H, Ar*H*), 4.94 (m, 2H, C_{17}-*H*, C_{23}-*H*), 4.78 (d, J = 10.3 Hz, 1H, C_{21}-*H*), 4.61 (d, J = 12.2 Hz, 1H, PhC*H*$_2$O), 4.45 (d, J = 12.2 Hz, 1H, PhC*H*$_2$O), 3.55 (d, J = 3.9 Hz, 2H, C_{24}-*H*$_2$), 2.66 (m, 1H, C_{22}-*H*), 2.40−1.80 (m, 8H, C_{14}-*H*$_2$, C_{15}-*H*$_2$, C_{18}-*H*$_2$, C_{19}-*H*$_2$), 1.56 (s, 3H, C_{16}-C*H*$_3$), 1.51 (s, 3H, C_{20}-C*H*$_3$), 0.87 (d, J = 6.8 Hz, 3H, C_{22}-C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2, 138.0, 133.4, 132.9, 129.5, 128.3, 127.6, 125.9, 75.8, 73.0, 70.0, 39.4, 36.0, 33.9, 33.4, 24.8, 17.3, 15.4, 14.9. Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.03; H, 8.76.

[1*R*,4*R*,6*R*,7*S*,8*R*,13*R*]-8-[(Benzyloxy)methyl]-4,7,13-trimethyl-5,9,14-trioxatricyclo[11.1.0.0^{4,6}]tetradecan-10-one (33a). To a solution of 6.3 g (18.4 mmol) of diene **32** in 190 mL of CH_2Cl_2 at −78 °C was added 15.9 g (91.9 mmol, 55%) of *m*-CPBA, and the heterogeneous mixture was stirred for 6 h. The reaction mixture was allowed to warm to −35 °C over a period of 4 h and was held at that temperature for 8 h. After warming to 0 °C over 6 h, the solution was diluted with 250 mL of Et_2O, and the organic layer was washed with aqueous 1 M NaOH (2 × 250 mL). The aqueous layer was back-extracted with Et_2O (2 × 250 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient 10% EtOAc/hexane to 25% EtOAc/hexane) gave 6.1 g (89%) of **33a** and 0.61 g (10%) of **33b**. Major diepoxide **33a**: $[\alpha]^{23}_D$ +11.6° (*c* 0.60, CH_2Cl_2); IR (neat) 2960, 2930, 2865, 1730, 1635, 1450, 1383, 1365, 1230, 1150, 1110, 1095, 1070, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H, Ar*H*), 4.99 (dt, J = 10.7, 3.4 Hz, 1H, C_{23}-*H*), 4.58 (d, J = 12.2 Hz, 1H, PhC*H*$_2$O), 4.43 (d, J = 12.2 Hz, 1H, PhC*H*$_2$O), 3.58 (d, J = 3.5 Hz, 2H, C_{24}-*H*$_2$), 2.88 (dd, J = 7.4, 4.2 Hz, 1H, C_{17}-*H*), 2.63 (d, J = 9.2 Hz, 1H, C_{21}-*H*), 2.32 (m, 2H, C_{14}-*H*$_2$), 2.14 (m, 2H, C_{15}-*H*, C_{19}-*H*), 1.96 (m, 2H, C_{15}-*H*, C_{22}-*H*), 1.75 (m, 1H, C_{18}-*H*), 1.65 (m, 1H, C_{18}-*H*),

1.31 (s, 3H, C_{16}-CH_3), 1.29 (m, 1H, C_{19}-*H*), 1.28 (s, 3H, C_{20}-CH_3), 1.01 (d, J = 6.8 Hz, 3H, C_{22}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 137.3, 128.4, 127.8, 127.6, 75.8, 73.1, 69.5, 68.8, 61.8, 61.5, 59.8, 35.7, 33.1, 32.3, 29.9, 23.3, 18.1, 16.6, 13.8; exact mass calcd for $C_{22}H_{30}O_5Na$ 397.1991, found 397.1985 (FAB, *m*-nitrobenzyl alcohol, added NaI). Minor diepoxide **33b**: $[\alpha]^{23}_D$ +37.2° (*c* 0.30, CH_2Cl_2); IR (neat) 2975, 2943, 2875, 1735, 1455, 1388, 1363, 1240, 1210, 1150, 1110, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H, Ar*H*), 5.12 (dt, J = 10.5, 3.5 Hz, 1H, C_{23}-*H*), 4.61 (d, J = 12.2 Hz, 1H, PhCH_2O), 4.48 (d, J = 12.2 Hz, 1H, PhCH_2O), 3.57 (d, J = 4.3 Hz, 2H, C_{24}-H_2), 3.05 (dd, J = 10.2, 2.2 Hz, 1H, C_{17}-*H*), 2.58 (d, J = 8.3 Hz, 1H, C_{21}-*H*), 2.25−1.96 (m, 8H, C_{14}-H_2, C_{15}-H_2, C_{18}-H_2, C_{19}-H_2), 1.45 (m, 1H, C_{22}-*H*), 1.34 (s, 3H, C_{16}-CH_3), 1.27 (s, 3H, C_{20}-CH_3), 1.00 (d, J = 6.9 Hz, 3H, C_{22}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.1, 137.7, 128.3, 127.7, 127.5, 76.6, 73.0, 69.7, 66.7, 60.9, 59.7, 58.1, 34.5, 32.1, 31.3, 28.6, 24.2, 18.6, 16.6, 13.8.

[1*R*,4*R*,6*R*,7*S*,8*R*,13*R*]-8-(Hydroxymethyl)-4,7,13-trimethyl-5,9,-14-trioxatricyclo[11.1.0.0^{4,6}]tetradecan-10-one (34). To a solution of 330 mg (0.881 mmol) of diepoxide **33a** in 7 mL of EtOAc in a high-pressure vial was added 165 mg of 10% Pd/C. The mixture was placed in a bomb hydrogenator and was pressurized with 300 psi of H_2. The reaction mixture was stirred for 42 h, at which time the mixture was filtered through a small column of Celite with EtOAc and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (60% EtOAc/hexane) gave 246 mg (98%) of **34** as a clear oil: $[\alpha]^{23}_{577}$ −2.1° (*c* 0.62, CH_2Cl_2); IR (neat) 3452, 2960, 2929, 1729, 1456, 1387, 1370, 1233, 1202, 1152, 1090, 1064, 965, 892, 793 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (m, 1H, C_{23}-*H*), 3.86 (m, 1H, C_{24}-*H*), 3.73 (m, 1H, C_{24}-*H*), 2.93 (dd, J = 7.2, 4.6 Hz, 1H, C_{17}-*H*), 2.69 (d, J = 9.1 Hz, 1H, C_{21}-*H*), 2.38 (m, 2H, C_{14}-H_2), 2.16 (m, 2H, C_{15}-H_2), 2.02 (m, 1H, C_{18}-*H*), 1.93 (m, 1H, C_{19}-*H*), 1.77 (m, 1H, C_{19}-*H*), 1.66 (m, 1H, C_{18}-*H*), 1.55 (t, J = 3.8 Hz, 1H, C_{24}-O*H*), 1.33 (s, 3H, C_{16}-CH_3), 1.29 (s, 3H, C_{20}-CH_3), 1.10 (d, J = 6.8 Hz, 3H, C_{22}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1, 77.6, 68.5, 61.9, 61.4, 59.7, 35.7, 33.1, 32.8, 32.3, 29.9, 23.2, 18.1, 16.5, 13.9; exact mass calcd for $C_{15}H_{24}O_5Na$ 307.1521, found 307.1516 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[1*R*,4*R*,6*R*,7*S*,8*R*,13*R*]-8-Formyl-4,7,13-trimethyl-5,9,14-trioxatricyclo[11.1.0.0^{4,6}]tetradecan-10-one (35). To a suspension of 859 mg (2.03 mmol) of Dess−Martin periodinane in 17 mL of CH_2Cl_2 at 0 °C was added dropwise 548 μL (6.78 mmol) of pyridine. After 10 min, a solution of 320 mg (1.13 mmol) of alcohol **34** in 4.0 mL of CH_2Cl_2 was added *via* cannula (1.0 mL rinse). The mixture was stirred at 0 °C for 15 min and was warmed to ambient temperature, where it stirred for 3.5 h. The mixture was diluted with 30 mL of EtOAc and washed with 30 mL each of saturated aqueous $NaHCO_3$ and aqueous 1 M $Na_2S_2O_3$. The combined aqueous washes were back-extracted with 30 mL EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting yellow oil was filtered through a small column of silica gel (50% EtOAc/hexane), yielding 281 mg (88%) of **35** as a clear oil which was used without purification in the subsequent reaction: $[\alpha]^{23}_D$ +49.1° (*c* 0.46, CH_2Cl_2); IR (neat) 2963, 2928, 1740, 1460, 1386, 1359, 1239, 1148, 1101, 1062, 893, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, J = 0.9 Hz, 1H, C_{24}-*H*), 4.99 (app d, J = 11.2 Hz, 1H, C_{23}-*H*), 3.05 (app t, J = 6.0 Hz, 1H, C_{17}-*H*), 2.67 (d, J = 9.1 Hz, 1H, C_{21}-*H*), 2.38 (m, 2H, C_{14}-H_2), 2.20−2.00 (m, 4H, C_{15}-H_2, C_{19}-H_2), 1.90 (m, 1H, C_{22}-*H*), 1.65 (m, 2H, C_{18}-H_2), 1.29 (s, 3H, C_{16}-CH_3), 1.29 (s, 3H, C_{20}-CH_3), 1.10 (d, J = 6.8 Hz, 3H, C_{22}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.3, 172.1, 79.9, 68.1, 61.9, 61.5, 59.1, 35.4, 32.8, 32.0, 29.0, 23.0, 18.4, 16.5, 13.1.

(1*R*,4*R*,6*R*,7*S*,8*S*,13*R*)-8-[(1*Z*,3*R*,4*S*,5*R*)-4-Methoxy-3-methyl-5-(2-methyl-1,3-dioxolan-2-yl)-1-hexenyl]-4,7,13-trimethyl-5,9,14-trioxatricyclo[11.1.0.0^{4,6}]tetradecan-10-one (36). A solution of 0.3 M lithium hexamethyldisilazide was prepared as follows: To a solution of 653 μL (0.50 g, 3.10 mmol) of hexamethyldisilazane in 7.75 mL of THF at 0 °C was added 2.05 mL (3.10 mmol, 1.50 M in hexane) of *n*-butyllithium. The solution was stirred for 15 min at 0 °C.

To a solution of 802 mg (1.36 mmol) of phosphonium salt **21** in 15 mL of THF at −78 °C was added dropwise 4.53 mL (1.36 mmol) of the 0.3 M LIHMDS solution, resulting in a dark orange-colored mixture, which was stirred for 1 h. A solution of 275 mg (0.971 mmol) of the aldehyde **35** in 3 mL of THF was added dropwise *via* cannula, resulting in a bright yellow solution. This mixture was stirred at −78 °C for 2.5 h and was slowly warmed to 0 °C over 2 h where it was stirred for 30 min. The reaction was quenched by addition of 15 mL of aqueous pH 7 phosphate buffer, and the mixture was poured into 30 mL each of EtOAc and saturated aqueous NaCl. The phases were separated, and the aqueous layer was extracted with EtOAc (4 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified product showed >98:2 *Z*/*E* olefin geometry. Purification by flash chromatography (30% EtOAc/hexane) afforded 370 mg (79%) of **36** as a clear oil: $[\alpha]^{23}_D$ −33.3° (*c* 0.10, CH_2Cl_2); IR (film) 2967, 1728, 1457, 1384, 1233, 1196, 1148, 1092, 973, 948, 891, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2H, C_{23}-*H*, C_{24}-*H*), 5.23 (t, J = 10.5 Hz, 1H, C_{25}-*H*), 3.92 (m, 4H, OCH_2CH_2O), 3.41 (s, 3H, C_{27}-OCH_3), 3.21 (dd, J = 6.2, 1.8 Hz, 1H, C_{17}-*H*), 2.92 (m, 2H, C_{27}-*H*, C_{22}-*H*), 2.68 (d, J = 8.9 Hz, 1H, C_{21}-*H*), 2.29 (m, 2H, C_{14}-H_2), 2.16 (m, 2H, C_{15}-H_2), 1.97 (m, 1H, C_{19}-*H*), 1.81−1.64 (m, 5H, C_{19}-*H*, C_{18}-H_2, C_{26}-*H*, C_{28}-*H*), 1.32 (s, 3H, C_{29}-CH_3), 1.29 (s, 3H, C_{16}-CH_3), 1.28 (s, 3H, C_{20}-CH_3), 1.01 (d, J = 6.8 Hz, 3H, C_{26}-CH_3), 0.99 (d, J = 6.8 Hz, 3H, C_{22}-CH_3), 0.97 (d, J = 6.8 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1, 139.6, 126.2, 111.9, 83.8, 73.0, 68.8, 64.3, 64.3, 61.6, 61.5, 59.8, 59.7, 42.9, 37.1, 36.8, 35.7, 32.4, 30.0, 23.3, 20.5, 18.2, 17.1, 16.7, 13.9, 9.9; exact mass calcd for $C_{26}H_{42}O_7Na$ 489.2817, found 489.2826 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,5′*S*)-5′-[(1*R*,2*S*,3*S*,4*Z*,6*R*,7*S*,8*R*)-1,3-Dihydroxy-7-methoxy-2,6-dimethyl-8-(2-methyl-1,3-dioxolan-2-yl)-4-nonenyl]hexahydro-2,5′-dimethyl[2,2′-bifuran]-5(2*H*)-one (38). To a solution of 305 mg (0.654 mmol) of olefin **36** in 5 mL of 3:1 MeOH/H_2O at ambient temperature was added a solution of 1.85 g (32.70 mmol) of KOH in 1.5 mL of 3:1 MeOH/H_2O. After 120 h, the homogeneous solution was poured into 30 mL of CH_2Cl_2 and 2.62 mL (2.75 g, 45.78 mmol) of acetic acid was added. The organic layer was washed with 20 mL of saturated aqueous NaCl, and the aqueous layer was back-extracted with CH_2Cl_2 (4 × 25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The thick yellow oil was used immediately without further purification.

The yellow oil was dissolved in 5.0 mL of CH_2Cl_2, and 4 Å molecular sieves were added. After 120 h at ambient temperature, the solution was filtered through a short column of silica gel with EtOAc and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (70% EtOAc/hexane) afforded 265 mg (85% for two steps) of **38** as a clear oil: $[\alpha]^{23}_D$ +11.6° (*c* 0.86, CH_2Cl_2); IR (film) 3468, 2974, 2938, 2882, 1769, 1455, 1380, 1243, 1169, 1077, 1039, 945 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, J = 10.5, 9.0 Hz, 1H, C_{24}-*H*), 5.34 (app t, J = 10.4 Hz, 1H, C_{25}-*H*), 4.38 (m, 1H, C_{23}-*H*), 4.07 (s, 1H, C_{21}-*H*), 3.90 (m, 5H, C_{17}-*H*, OCH_2CH_2O), 3.39 (s, 3H, C_{27}-OCH_3), 3.21 (dd, J = 6.8, 1.3 Hz, 1H, C_{27}-*H*), 2.80−2.50 (m, 5H, C_{14}-H_2, C_{18}-*H*, C_{21}-O*H*, C_{26}-*H*), 2.23 (m, 2H, C_{19}-H_2), 2.05 (m, 1H, C_{15}-*H*), 1.86 (m, 1H, C_{18}-*H*), 1.71 (m, 3H, C_{22}-*H*, C_{23}-O*H*, C_{28}-*H*), 1.55 (m, 1H, C_{15}-*H*), 1.39 (s, 3H, C_{29}-CH_3), 1.25 (s, 3H, C_{16}-CH_3), 1.09 (s, 3H, C_{20}-CH_3), 1.05 (d, J = 6.7 Hz, 3H, C_{22}-CH_3), 0.98 (d, J = 7.1 Hz, 3H, C_{26}-CH_3), 0.91 (d, J = 7.1 Hz, 3H, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.6, 134.9, 131.7, 111.8, 87.4, 84.2, 80.3, 77.3, 75.0, 72.5, 64.3, 64.3, 59.8, 42.6, 39.0, 36.5, 31.2, 29.0, 27.7, 23.6, 22.8, 20.5, 17.8, 11.0, 9.7; exact mass calcd for $C_{26}H_{44}O_8Na$ 507.2934, found 507.2918 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*S*)-Decahydro-4″-hydroxy-5″-[(1*R*,2*R*,3*S*,4*R*)-1-hydroxy-3-methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)pentyl]-2,3″-trimethyl[2,2″:5′,2″-terfuran]-5(2*H*)-one (39). To a suspension of 530 mg (1.074 mmol) of magnesium monoperoxyphthalate in 10.0 mL of CH_2Cl_2 at ambient temperature were added 4 Å molecular sieves. After 30 min, the slurry was cooled to 0 °C, and a solution of 260 mg (0.537 mmol) of diol **38** in 2.5 mL of CH_2Cl_2 was added *via* cannula (1.0 mL rinse). The resultant heterogeneous mixture was stirred at 0 °C for 120 h. The reaction mixture was poured into 50 mL each of EtOAc and saturated aqueous $NaHCO_3$. The phases were separated, and the organic layer was washed with 50 mL each of H_2O and saturated aqueous NaCl. The combined aqueous layers were back-extracted with EtOAc (2 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a clear oil which was used without further purification.

To a solution of the unpurified epoxide in 10.0 mL of CH_2Cl_2 were added 3 Å molecular sieves and 150 μL of glacial acetic acid. After 48 h, the mixture was poured into 50 mL each of EtOAc and saturated aqueous $NaHCO_3$. The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (35% EtOAc/hexane) afforded 215 mg (81% over two steps) of **39** as a clear oil: $[\alpha]^{23}_D$ −24.7° (*c* 1.74, CH_2Cl_2); IR (film) 3442, 2977, 2940, 2884, 1767, 1452, 1381, 1218, 1149, 1061, 1015, 945, 884, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 6.6 Hz, 1H, C_{23}-*H*), 4.00−3.91 (m, 6H, C_{17}-*H*, C_{21}-*H*, OCH_2CH_2O), 3.75 (dd, *J* = 7.0, 5.6 Hz, 1H, C_{24}-*H*), 3.63 (m, 1H, C_{25}-*H*), 3.42 (dd, *J* = 5.3, 2.7 Hz, 1H, C_{27}-*H*), 3.37 (s, 3H, C_{27}-OCH_3), 2.71 (m, 1H, C_{14}-*H*), 2.55−2.38 (m, 4H, C_{14}-*H*, C_{15}-*H*, C_{23}-O*H*, C_{25}-O*H*), 2.27−2.21 (m, 2H, C_{18}-*H*, C_{22}-*H*), 1.99−1.86 (m, 3H, C_{18}-*H*, C_{26}-*H*, C_{28}-*H*), 1.79 (m, 1H, C_{15}-*H*), 1.67 (m, 1H, C_{19}-*H*), 1.59 (m, 1H, C_{19}-*H*), 1.33 (s, 3H, C_{30}-H_3), 1.29 (s, 3H, C_{16}-CH_3), 1.17 (s, 3H, C_{20}-CH_3), 1.00−0.97 (m, 9H, C_{22}-CH_3, C_{26}-CH_3, C_{28}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.3, 11.9, 87.6, 85.4, 84.6, 83.1, 82.0, 80.9, 74.7, 73.1, 64.5, 64.3, 59.2, 43.3, 40.2, 39.6, 32.1, 29.7, 28.5, 28.0, 23.6, 20.9, 9.8, 9.3, 8.5; exact mass calcd for $C_{26}H_{44}O_9Na$ 523.2833, found 523.2873 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*S*)-Decahydro-4″-(triethylsiloxy)-5″-[(1*R*,2*R*,3*S*,4*R*)-1-hydroxy-3-methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)pentyl]-2,3″,5′-trimethyl[2:2′,5′,2″-terfuran]-5(2*H*)-one (40). To a solution of 210 mg (0.420 mmol) of diol **39** in 8.4 mL of CH_2Cl_2 at −78 °C were added 71 mg (1.05 mmol) of imidazole, 10 mg of DMAP, and 78 μL (70 mg, 0.462 mmol) of chlorotriethylsilane. After 3 h at −78 °C, the reaction mixture was quenched by addition of 5 mL of saturated aqueous $NaHCO_3$ and warmed to ambient temperature. The mixture was poured into 25 mL each of EtOAc and saturated aqueous $NaHCO_3$. The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (45% EtOAc/hexane) afforded 253 mg (98%) of **40** as a clear oil: $[\alpha]^{23}_D$ −39.2° (*c* 0.95, CH_2Cl_2); IR (film) 3512, 2953, 2878, 1773, 1458, 1380, 1242, 1149, 1066, 1017, 945, 850, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (dd, *J* = 8.0, 6.1 Hz, 1H, C_{23}-*H*), 4.00 (d, *J* =4.2 Hz, 1H, C_{21}-*H*), 3.95 (m, 5H, C_{17}-*H*, OCH_2CH_2O), 3.76 (dd, *J* = 8.0, 2.3 Hz, 1H, C_{24}-*H*), 3.59 (m, 1H, C_{25}-*H*), 3.38 (dd, *J* = 5.6, 2.6 Hz, 1H, C_{27}-*H*), 3.37 (s, 3H, C_{27}-OCH_3), 2.70 (m, 1H, C_{14}-*H*), 2.45 (m, 2H, C_{14}-*H*, C_{15}-*H*), 2.25 (m, 1H, C_{18}-*H*), 2.05 (m, 2H, C_{22}-*H*, C_{25}-O*H*), 1.94 (m, 2H, C_{18}-*H*, C_{28}-*H*), 1.77 (m, 2H, C_{15}-*H*, C_{26}-*H*), 1.60 (m, 2H, C_{19}-H_2), 1.32 (s, 3H, C_{30}-H_3), 1.30 (s, 3H, C_{16}-CH_3), 1.15 (s, 3H, C_{20}-CH_3), 1.00−0.92 (m, 15H, C_{22}-CH_3, C_{26}-CH_3, $Si(CH_2CH_3)_3$), 0.91 (d, *J* = 7.1 Hz, 3H, C_{28}-CH_3), 0.61 (q, *J* = 7.7 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.2, 111.9, 87.8, 85.4, 85.2, 82.4, 81.9, 80.5, 74.3, 71.0, 64.4, 64.1, 59.4, 42.9, 41.6, 39.2, 31.7, 29.9, 28.4, 28.2, 23.4, 20.7, 9.8, 9.7, 8.6, 6.7, 4.7; exact mass calcd for $C_{32}H_{58}O_9SiNa$ 637.3748, found 637.3757 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*S*)-Decahydro-4″-(triethylsiloxy)-5″-[(1*R*,2*R*,3*S*,4*R*)-3-methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-oxopentyl]-2,3″,5′-trimethyl[2,2′:5′,2″-terfuran]-5(2*H*)-one (41). To a suspension of 490 mg (1.15 mmol) of Dess−Martin periodinane in 5.0 mL of CH_2Cl_2 at 0 °C was added 772 μL (755 mg, 9.55 mmol) of pyridine. After 10 min, 235 mg (0.382 mmol) of the alcohol **40** in 1.6 mL of CH_2Cl_2 was added *via* cannula (1.0 mL of CH_2Cl_2 rinse), and the mixture was warmed to ambient temperature. After 3.5 h, the solution was poured into 30 mL each of EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with aqueous 1 M $Na_2S_2O_3$. The combined aqueous layers were back-extracted with EtOAc (2 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (35% EtOAc/hexane) afforded 231 mg (98%) of **41** as a clear oil: $[\alpha]^{23}_D$ −2.5° (*c* 1.15, CH_2Cl_2); IR (film) 2952, 2878, 1775, 1458, 1381, 1241, 1150, 1073, 1017, 945, 862, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (app t, *J* = 6.2 Hz, 1H, C_{23}-*H*), 4.14 (d, *J* = 6.4 Hz, 1H, C_{24}-*H*), 3.90 (m, 6H, C_{17}-*H*, C_{21}-*H*, OCH_2CH_2O), 3.64 (dd, *J* = 6.8, 2.1 Hz, 1H, C_{27}-*H*), 3.42 (s, 3H, C_{27}-OCH_3), 3.40 (m, 1H, C_{26}-*H*), 2.65 (m, 1H, C_{14}-*H*), 2.45 (m, 2H, C_{14}-*H*, C_{28}-*H*), 2.28 (m, 1H, C_{18}-*H*), 2.16 (m, 1H, C_{22}-*H*), 1.90 (m, 1H, C_{18}-*H*), 1.75 (m, 1H, C_{15}-*H*), 1.63 (m, 3H, C_{15}-*H*, C_{19}-H_2), 1.33 (s, 3H, C_{30}-H_3), 1.27 (s, 3H, C_{16}-CH_3), 1.16 (s, 3H, C_{20}-CH_3), 1.09 (d, *J* = 7.0 Hz, 3H, C_{26}-CH_3), 0.93 (t, *J* = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.93 (d, J = 6.6 Hz, 3H, C_{22}-CH_3), 0.89 (d, *J* = 7.1 Hz, 3H, C_{28}-CH_3), 0.61 (q, *J* = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.9, 177.2, 111.6, 87.7, 86.3, 85.4, 85.0, 81.9, 80.7, 74.6, 64.4, 64.2, 59.5, 45.4, 42.8, 40.4, 32.7, 29.8, 28.4, 28.2, 23.5, 23.4, 20.6, 13.0, 9.6, 8.7, 6.8, 4.6; exact mass calcd for $C_{32}H_{58}O_9SiNa$ 635.3591, found 635.3579 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*S*)-Decahydro-4″-hydroxy-5″-[(1*S*,2*R*,3*S*,4*R*)-1-hydroxy-3-methoxy-2-methyl-4-(2-methyl-1,3-dioxolan-2-yl)pentyl]-2,3″,5′-trimethyl[2,2′:5′,2″-terfuran]-5(2*H*)-one (42). To a solution of 225 mg (0.368 mmol) of ketone **41** in 7.5 mL of CH_2Cl_2 at −25 °C were added 20 μL (15.1 mg, 0.184 mmol) of cyclohexene and 3.68 mL (0.552 mmol, 0.15 M in Et_2O) of $Zn(BH_4)_2$. After 1.5 h, 4.0 mL of saturated aqueous NH_4Cl was added and the mixture warmed to 0 °C, where it was stirred for 15 min. The reaction mixture was poured into 25 mL each of CH_2Cl_2 and saturated aqueous NH_4Cl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. NMR analysis of the unpurified product showed >98:2 diastereoselectivity. Purification by flash chromatography (40% EtOAc/hexane) afforded 226 mg (100%) of **42** as a clear oil: $[\alpha]^{23}_D$ −39.7° (*c* 0.40, CH_2Cl_2); IR (film) 3466, 2952, 2878, 1773, 1457, 1379, 1242, 1225, 1072, 1017, 945, 842, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (app t, *J* = 6.4 Hz, 1H, C_{23}-*H*), 3.92 (m, 6H, C_{17}-*H*, C_{21}-*H*, OCH_2CH_2O), 3.81 (dd, *J* = 6.7, 4.3 Hz, 1H, C_{24}-*H*), 3.71 (m, 1H, C_{25}-*H*), 3.63 (app t, *J* = 2.8 Hz, 1H, C_{27}-*H*), 3.50 (m, 1H, C_{25}-O*H*), 3.40 (s, 3H, C_{27}-OCH_3), 2.81 (m, 1H, C_{14}-*H*), 2.57 (m, 1H, C_{14}-*H*), 2.40 (m, 1H, C_{15}-*H*), 2.27 (m, 1H, C_{19}-*H*), 2.12 (m, 1H, C_{22}-*H*), 2.01 (m, 1H, C_{26}-*H*), 1.88 (m, 2H, C_{19}-*H*, C_{28}-*H*), 1.68 (m, 2H, C_{15}-*H*, C_{18}-*H*), 1.54 (m, 1H, C_{18}-*H*), 1.30 (s, 3H, C_{30}-H_3), 1.26 (s, 3H, C_{16}-CH_3), 1.14 (s, 3H, C_{20}-CH_3), 1.05 (d, *J* = 7.2 Hz, 3H, C_{22}-CH_3), 0.97 (t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.90 (d, *J* = 7.1 Hz, 3H, C_{26}-CH_3), 0.88 (d, *J* = 7.0 Hz, 3H, C_{28}-CH_3), 0.64 (q, *J* = 7.8 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.8, 111.9, 88.2, 85.4, 85.1, 82.0, 81.3, 77.2, 75.6, 73.4, 64.5, 64.4, 58.6, 43.0, 40.4, 37.7, 32.7, 30.1, 28.7, 28.0, 23.9, 20.6, 11.8, 10.6, 8.8, 6.9, 4.9; exact mass calcd for $C_{32}H_{58}O_9SiNa$ 637.3748, found 637.3777 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*R*)-Decahydro-4″-hydroxy-2,3″,5′-trimethyl-5″-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-4,6-dimethoxy-3,5,7-trimethyl-2*H*-pyran-2-yl][2,2′:5′,2″-terfuran]-5(2*H*)-one (43). To a solution of 216 mg (0.352 mmol) of alcohol **42** in 7.0 mL of MeOH at ambient temperature was added 13 mg of PPTS. After 32 h, the mixture was poured into 25 mL each of CH_2Cl_2 and saturated aqueous $NaHCO_3$, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (45% EtOAc/hexane) afforded 162 mg (98%) of **43** as a clear oil: $[\alpha]^{23}_D$ +4.9° (*c* 0.45, CH_2Cl_2); IR (film) 3448, 2975, 2935, 1772, 1457, 1377, 1215, 1166, 1086, 1063, 1020, 945 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (m, 1H, C_{23}-*H*), 4.08 (d, *J* = 4.3 Hz, 1H, C_{21}-*H*), 3.95 (dd, *J* = 8.3, 6.7 Hz, 1H, C_{17}-*H*), 3.70 (app t, *J* = 7.4 Hz, 1H, C_{24}-*H*), 3.42 (s, 3H, C_{29}-OCH_3), 3.28 (dd, *J* = 10.2, 6.9 Hz, 1H, C_{25}-*H*), 3.21 (s, 3H, C_{27}-OCH_3), 2.89 (t, *J* =10.2 Hz, 1H, C_{27}-*H*), 2.71 (m, 1H, C_{14}-*H*), 2.60 (d, *J* = 2.6 Hz, C_{23}-O*H*), 2.45 (m, 1H, C_{14}-*H*), 2.37 (m, 1H, C_{15}-*H*), 2.25 (m, 2H, C_{19}-*H*, C_{22}-*H*), 1.95 (m, 1H, C_{18}-*H*), 1.75−1.50 (m, 5H, C_{15}-*H*, C_{18}-*H*, C_{19}-*H*, C_{26}-*H*, C_{28}-*H*), 1.33 (s, 3H, C_{30}-H_3), 1.31 (s, 3H, C_{16}-CH_3), 1.16 (s, 3H, C_{20}-CH_3), 1.04 (d, *J* = 6.7 Hz, 6H, C_{26}-CH_3, C_{28}-CH_3), 0.96 (d, *J* = 7.2 Hz, C_{22}-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.4, 101.6, 87.7, 84.5, 84.1, 82.5, 80.3, 76.6, 75.4, 59.5, 47.9, 46.4, 42.5, 38.4, 31.6, 29.9, 28.4, 28.1, 23.4, 23.1, 21.7, 13.0, 12.1, 8.5; exact mass calcd for $C_{25}H_{42}O_8Na$ 493.2777, found 493.2726 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*S*,2′*R*,2″*R*,3″*S*,4″*R*,5′*S*,5″*R*)-Decahydro-4″-methoxy-2,3″,5′-trimethyl-5″-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-4,6-dimethoxy-3,5,7-trimethyl-2*H*-pyran-2-yl][2,2″:5′,2″-terfuran]-5(2*H*)-one (44). To a solution of 150 mg (0.319 mmol) of alcohol **43** in 16 mL of CH_2Cl_2 at 0 °C were added 478 mg (2.23 mmol) of proton sponge and 330 mg (2.23 mmol) of Me_3OBF_4. After 7 h, the heterogeneous mixture was poured into 20 mL each of CH_2Cl_2 and saturated aqueous $NaHCO_3$.

The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient of 30−50% EtOAc/hexane) afforded 130 mg (84%) of **44** as a clear oil and 24 mg (16%) of recovered alcohol **43**: $[\alpha]^{23}_D$ +10.0° (*c* 0.95, CH_2Cl_2); IR (film) 2975, 2931, 1775, 1452, 1376, 1215, 1163, 1123, 1072, 1021, 945 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 7.2, 6.3 Hz, 1H, C_{23}-*H*), 4.03 (d, *J* = 3.9 Hz, 1H, C_{21}-*H*), 3.97 (dd, *J* = 7.4, 2.7 Hz, 1H, C_{24}-*H*), 3.92 (app t, *J* = 7.4 Hz, 1H, C_{17}-*H*), 3.48 (dd, *J* = 10.8, 2.6 Hz, 1H, C_{25}-*H*), 3.44 (s, 3H, C_{29}-OC*H*$_3$), 3.28 (s, 3H, C_{27}-OC*H*$_3$), 3.14 (s, 3H, C_{23}-OC*H*$_3$), 2.86 (t, *J* =10.2 Hz, 1H, C_{27}-*H*), 2.67 (m, 1H, C_{14}-*H*), 2.49 (m, 1H, C_{14}-*H*), 2.38 (m, 2H, C_{15}-*H*, C_{22}-*H*), 2.20 (m, 1H, C_{19}-*H*), 2.00 (m, 1H, C_{18}-*H*), 1.68 (m, 2H, C_{15}-*H*, C_{18}-*H*), 1.55 (m, 3H, C_{19}-*H*, C_{26}-*H*, C_{28}-*H*), 1.33 (s, 3H, C_{30}-*H*$_3$), 1.29 (s, 3H, C_{16}-C*H*$_3$), 1.14 (s, 3H, C_{20}-C*H*$_3$), 1.04 (d, *J* = 6.7 Hz, 3H, C_{28}-C*H*$_3$), 0.97 (d, *J* = 6.4 Hz, 3H, C_{26}-C*H*$_3$), 0.85 (d, *J* = 7.0 Hz, C_{22}-C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.1, 101.0, 87.7, 85.4, 84.8, 84.7, 81.4, 79.8, 79.0, 74.6, 60.0, 57.4, 47.5, 46.7, 38.9, 36.6, 31.8, 29.6, 28.9, 27.8, 23.0, 22.8, 21.9, 13.1, 12.3, 8.3; exact mass calcd for $C_{26}H_{44}O_8Na$ 507.2934, found 507.2914 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(γ*S*,2*S*,2′*R*,3′*S*,4′*R*,5*R*,5′*R*)-Octahydro-*N*,4′-dimethoxy-*N*,γ,2,3′-tetramethyl-5′-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-4,6-dimethoxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-γ-(triethylsiloxy)[2,2′-bifuran]-5-butyramide (45). To a suspension of 91 mg (0.930 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 1.0 mL of THF at 0 °C was added dropwise 372 μL (0.744 mmol, 2.0 M in toluene) of trimethylaluminum with concomitant evolution of gas. The resulting homogeneous solution was stirred for 30 min at 25 °C. A solution of 45 mg (0.093 mmol) of lactone **44** in 0.5 mL THF was added *via* cannula to the aluminum amide solution at 0 °C (0.5 mL of THF rinse). The resulting solution was stirred at 0 °C for 2 h, at which time it was added *via* cannula to an ice-cooled beaker containing 30 mL each of EtOAc and saturated aqueous Na/K tartrate. After 15 min, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The lactonization-prone amide thus produced was used immediately without further purification.

To a solution of the yellow oil in 0.5 mL of DMF at ambient temperature were added 158 mg (2.33 mmol) of imidazole and 312 μL (280 mg, 1.86 mmol) of TESCl. After 12 h, the solution was poured into 20 mL each of Et_2O and saturated aqueous NaCl. The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (22% EtOAc/hexane) afforded 60 mg (98%) of **45** as a clear oil: $[\alpha]^{23}_D$ +9.3° (*c* 0.75, CH_2Cl_2); IR (film) 2934, 1672, 1461, 1377, 1216, 1075, 1018, 875, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (app t, *J* = 6.7 Hz, 1H, C_{23}-*H*), 3.96 (dd, *J* = 7.4, 2.7 Hz, 1H, C_{24}-*H*), 3.96 (d, *J* = 4.0 Hz, 1H, C_{21}-*H*), 3.74 (app t, *J* = 7.1 Hz, 1H, C_{17}-*H*), 3.67 (s, 3H, NOC*H*$_3$), 3.50 (dd, *J* = 10.9, 2.7 Hz, 1H, C_{25}-*H*), 3.45 (s, 3H, C_{29}-OC*H*$_3$), 3.27 (s, 3H, C_{27}-OC*H*$_3$), 3.16 (s, 3H, NC*H*$_3$), 3.15 (s, 3H, C_{23}-OC*H*$_3$), 2.85 (t, *J* =10.2 Hz, 1H, C_{27}-*H*), 2.50 (m, 2H, C_{14}-*H*$_2$), 2.38 (m, 1H, C_{15}-*H*), 2.05 (m, 1H, C_{22}-*H*), 2.00−1.80 (m, 3H, C_{18}-*H*$_2$, C_{19}-*H*), 1.65 (m, 1H, C_{19}-*H*), 1.55 (m, 1H, C_{15}-*H*), 1.50 (m, 2H, C_{26}-*H*, C_{28}-*H*), 1.28 (s, 3H, C_{30}-*H*$_3$), 1.12 (s, 6H, C_{16}-C*H*$_3$, C_{20}-C*H*$_3$), 1.04 (d, *J* = 6.8 Hz, 3H, C_{26}-C*H*$_3$), 0.97 (d, *J* = 6.8 Hz, 3H, C_{28}-C*H*$_3$), 0.93 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.86 (d, *J* = 7.0 Hz, C_{22}-C*H*$_3$), 0.58 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 100.9, 85.1, 85.0, 84.4, 81.6, 80.3, 78.8, 77.2, 76.1, 74.6, 61.1, 60.1, 57.4, 47.5, 46.8, 38.9, 36.9, 35.0, 33.3, 26.8, 26.5, 22.7, 21.9, 12.9, 12.3, 8.3, 7.2, 6.8; exact mass calcd for $C_{34}H_{65}NO_9SiNa$ 682.4326, found 682.4322 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(γ*S*,2*S*,2′*R*,3′*S*,4′*R*,5*R*,5′*R*)-Octahydro-4′-methoxy-γ,2,3′-trimethyl-5′-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-4,6-dimethoxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-γ-(triethylsiloxy)[2,2′-bifuran]-5-pentan-2-one (46). To a solution of 60 mg (0.091 mmol) of amide **45** in 1.8 mL of THF at 0 °C was added 152 μL (0.455 mmol, 3.0 M in THF) of MeMgI. After 20 min, the reaction mixture was quenched with 0.5 mL of MeOH and was warmed to ambient temperature. The mixture was poured into 15 mL each of EtOAc and H_2O. The organic layer was washed with saturated aqueous Na/K tartrate. The combined aqueous layers were back-extracted with 15 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (17% EtOAc/hexane) afforded 60 mg (98%) of **46** as a clear oil: $[\alpha]^{23}_D$ +14.2° (*c* 0.50, CH_2Cl_2); IR (film) 2933, 2877, 1720, 1458, 1375, 1216, 1129, 1074, 1019, 952, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (app t, *J* = 6.8 Hz, 1H, C_{23}-*H*), 3.98 (d, *J* = 3.7 Hz, 1H, C_{21}-*H*), 3.96 (dd, *J* = 7.1, 2.6 Hz, 1H, C_{24}-*H*), 3.70 (app t, *J* = 6.9 Hz, 1H, C_{17}-*H*), 3.50 (dd, *J* = 10.8, 2.5 Hz, 1H, C_{25}-*H*), 3.45 (s, 3H, C_{29}-OC*H*$_3$), 3.28 (s, 3H, C_{27}-OC*H*$_3$), 3.14 (s, 3H, C_{23}-OC*H*$_3$), 2.85 (t, *J* =10.2 Hz, 1H, C_{27}-*H*), 2.50 (app t, *J* = 7.7 Hz, 2H, C_{14}-*H*$_2$), 2.35 (m, 1H, C_{15}-*H*), 2.13 (s, 3H, C_{12}-*H*$_3$), 2.04 (m, 1H, C_{22}-*H*), 1.98−1.70 (m, 3H, C_{18}-*H*$_2$, C_{19}-*H*), 1.67−1.40 (m, 4H, C_{15}-*H*, C_{19}-*H*, C_{26}-*H*, C_{28}-*H*), 1.28 (s, 3H, C_{30}-*H*$_3$), 1.11 (s, 3H, C_{16}-C*H*$_3$), 1.10 (s, 3H, C_{20}-C*H*$_3$), 1.04 (d, *J* = 6.8 Hz, 3H, C_{28}-C*H*$_3$), 0.97 (d, *J* = 6.4 Hz, 3H, C_{26}-C*H*$_3$), 0.92 (t, *J* = 8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.85 (d, *J* = 7.0 Hz, C_{22}-C*H*$_3$), 0.56 (q, *J* = 7.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.3, 100.9, 85.1, 84.7, 81.5, 79.9, 78.7, 76.1, 74.7, 60.1, 57.4, 47.5, 46.8, 38.9, 38.3, 36.9, 34.0, 32.6, 29.9, 26.9, 22.6, 22.4, 21.9, 12.9, 12.3, 8.2, 7.1, 6.8; exact mass calcd for $C_{33}H_{62}O_8SiNa$ 637.4111, found 637.4128 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(4*S*)-4-Benzyl-3-[(2*S*)-2-[(2*R*,3*R*,4*S*,5*R*,6*S*)-tetrahydro-6-[(1*S*,2*S*,3*R*,4*S*,9*S*)-4-hydroxy-1,3-dimethyl-9-[(2*S*,2′*R*,3′*S*,4′*R*,5*R*,5′*R*)-octahydro-4′-methoxy-2,3′-dimethyl-5′-[(2*S*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-4,6-dimethoxy-3,5,6-trimethyl-2*H*-pyran-2-yl][2,2′-bifuran]-5-yl]-6-oxo-9-(triethylsiloxy)-2-(triphenylsiloxy)decyl]-2,4-dimethoxy-3,5-dimethyl-2*H*-pyran-2-yl]propionyl]-2-oxazolidinone (47). To a solution of lithium diisopropylamide (0.122 mmol) in 0.5 mL of THF (generated from 80 μL of 1.52 M *n*-BuLi in hexane and 17 μL of diisopropylamine at −78 °C) at −78 °C was added dropwise 65 mg (0.106 mmol) of ketone **46** in 0.5 mL of THF *via* cannula (0.5 mL rinse). After the mixture was stirred for 25 min, a solution of 123 mg (0.159 mmol) of aldehyde **16** in 0.5 mL of THF was added *via* cannula. The homogeneous solution was stirred at −78 °C for 30 min and was warmed to −45 °C, where it was stirred for 10 min. The reaction mixture was quenched with 1.0 mL of saturated aqueous NH_4Cl and warmed to ambient temperature. The mixture was poured into 5 mL each of CH_2Cl_2 and saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient from 18% EtOAc/hexane to 25% EtOAc/hexane) afforded 100 mg (69%) of **47** as a clear oil, 19 mg of unreacted ketone **46** (29%), and 24 mg (20%) of aldehyde **16**. Data for **47**: $[\alpha]^{23}_D$ +61.9° (*c* 1.00, CH_2Cl_2); IR (film) 3531, 2974, 1779, 1700, 1456, 1429, 1378, 1215, 1073, 1014, 740, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.51 (m, 6H, Ar*H*), 7.40−7.10 (m, 14H, Ar*H*), 4.50 (m, 3H, C_2-*H*, C_9-*H*, C*H*N), 4.23 (m, 1H, C_{11}-*H*), 4.16 (app t, *J* = 6.6 Hz, 1H, C_{23}-*H*), 4.09 (m, 2H, OC*H*$_2$), 3.97 (m, 1H, C_{24}-*H*), 3.96 (d, *J* = 3.8 Hz, 1H, C_{21}-*H*), 3.65 (app t, *J* = 7.2 Hz, 1H, C_{17}-*H*), 3.50 (dd, *J* = 10.8, 2.5 Hz, C_{25}-*H*), 3.45 (s, 3H, C_{29}-OC*H*$_3$), 3.29 (m, 1H, C_7-*H*), 3.28 (s, 3H, C_3-OC*H*$_3$), 3.26 (s, 3H, C_{23}-OC*H*$_3$), 3.20 (m, 2H, C_5-*H*, ArC*H*$_2$), 3.12 (s, 3H, C_{27}-OC*H*$_3$), 2.88 (dd, *J* = 10.6, 4.5 Hz, 1H, C_{12}-*H*), 2.85 (app t, *J* = 10.2 Hz, 1H, C_{27}-*H*), 2.75 (dd, *J* = 13.4, 9.7 Hz, 1H, ArC*H*$_2$), 2.57 (s, 3H, C_5-OC*H*$_3$), 2.45 (dd, *J* = 17.2, 8.4 Hz, 1H, C_{12}-*H*), 2.35 (m, 4H, C_4-*H*, C_6-*H*, C_{14}-*H*$_2$), 2.05 (m, 1H, C_{22}-*H*), 1.88 (m, 4H, C_{10}-*H*, C_{18}-*H*, C_{19}-*H*$_2$), 1.65 (m, 1H, C_{15}-*H*), 1.60−1.40 (m, 5H, C_8-*H*, C_{15}-*H*, C_{18}-*H*, C_{26}-*H*, C_{28}-*H*), 1.26 (s, 3H, C_{30}-*H*$_3$), 1.19 (d, *J* = 7.4 Hz, 3H, C_2-C*H*$_3$), 1.11 (s, 3H, C_{20}-C*H*$_3$), 1.09 (s, 3H, C_{16}-C*H*$_3$), 1.04 (d, *J* = 6.4 Hz, 3H, C_4-C*H*$_3$), 0.97 (d, *J* = 6.5 Hz, 3H, C_8-C*H*$_3$), 0.92 (t, *J* = 8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 0.88 (d, *J* = 7.1 Hz, 3H, C_{10}-C*H*$_3$), 0.86 (d, *J* = 6.9 Hz, 3H, C_{26}-C*H*$_3$), 0.85 (d, *J* = 7.0 Hz, 3H, C_{28}-C*H*$_3$), 0.63 (d, *J* = 6.7 Hz, 3H, C_{22}-C*H*$_3$), 0.56 (q, *J* = 7.7 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.1, 174.2, 153.8, 135.6, 135.4, 129.8, 129.4, 128.9, 127.8, 127.3, 103.1, 100.9, 85.1, 84.8, 84.6, 82.9, 81.6, 80.0, 78.8, 77.3, 76.1, 75.9, 74.6, 73.0, 65.8, 65.2, 60.1, 57.4, 56.1, 48.1, 47.4, 47.4, 46.8, 42.9, 41.2, 38.9, 38.2, 37.7, 37.0, 36.9, 35.2, 33.9, 30.3, 26.8, 22.7, 22.4, 21.9, 13.8, 12.9, 12.4, 12.3, 10.1, 9.8, 8.3, 7.1, 6.8, 4.4; low-resolution mass calcd for $C_{79}H_{117}NO_{16}Si_2Na$ 1415, found 1415 (FAB, *m*-nitrobenzyl alcohol, added NaI).

Lonomycin A (1). To a solution of 20 mg (0.014 mmol) of aldol adduct **47** in 150 μL of acetonitrile at 0 °C was added 150 μL of freshly prepared HF solution (stock solution prepared from 0.50 mL of 48% aqueous HF, 8.6 mL of CH_3CN, and 0.90 mL of H_2O). Three additional 150 μL portions of the stock solution were added after 3, 6, and 9 h. After a total reaction time of 12 h, the solution was poured into 10 mL each of CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. NMR analysis of the unpurified reaction mixture showed only one spiroketal isomer. This very unstable product was used immediately without further purification.

To a solution of the yellow oil in 1.25 mL of CH_2Cl_2 at ambient temperature were added 288 mg (1.40 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine and 40 μL (0.35 mmol) of methyl triflate. The homogeneous solution was stirred for 18 h at ambient temperature and was quenched by addition of 0.50 mL of MeOH, forming a white precipitate. The heterogeneous mixture was poured into 15 mL each of CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Filtration through a short column of silica gel afforded an unstable light yellow oil; (low-resolution mass spec for $C_{54}H_{85}NO_{15}Na$ 1010, found 1010). This elimination-prone bis-lactol was used without further purification.

To a solution of the yellow oil in 1.0 mL of THF at 0 °C were added 200 μL of 30% aqueous hydrogen peroxide and 140 μL of LiOH (0.028 mmol, 0.2 M in H_2O). The mixture was stirred for 15 min at 0 °C and was quenched with 200 μL of aqueous 1.5 M Na_2SO_3. After 5 min, the reaction mixture was poured into 10 mL each of CH_2Cl_2 and H_2O. The aqueous layer was acidified to a pH of 3.0 with aqueous 0.1 M HCl and was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 5.0 mL of 3:1 acetone/H_2O, and aqueous 0.5 M NaOH was carefully added until the pH of the solution was 9.0. The solution was extracted with benzene (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (linear gradient from 30−40% EtOAc/hexane) afforded 8 mg (68% for three steps) of **1** as a white solid: $[\alpha]^{23}_D$ +57.5° (*c* 0.40, CH_2Cl_2); IR (film) 3172, 2975, 2936, 1594, 1454, 1387, 1076, 1043, 968 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.40 (br s, 1H, C_{29}-O*H*), 7.70 (br s, 1H, C_3-O*H*), 4.36 (d, *J* = 2.4 Hz, 1H, C_9-*H*), 4.21 (dd, *J* = 7.9, 6.5 Hz, 1H, C_{23}-*H*), 4.16 (d, *J* = 4.7 Hz, 1H, C_{21}-*H*), 4.05 (dd, *J* = 7.8, 2.0 Hz, 1H, C_{24}-*H*), 3.82 (dd, *J* = 10.8, 1.9 Hz, 1H, C_{25}-*H*), 3.66 (dd, *J* = 10.8, 2.1 Hz, 1H, C_7-*H*), 3.58 (dd, *J* = 9.9, 6.0 Hz, 1H, C_{17}-*H*), 3.42 (s, 3H, $COCH_3$), 3.34 (s, 3H, $COCH_3$), 3.26 (dd, *J* = 10.9, 4.8 Hz, 1H, C_5-*H*), 3.24 (s, 3H, $COCH_3$), 3.24 (s, 3H, $COCH_3$), 3.16 (m, 1H, C_{11}-*H*), 2.92 (t, *J* = 10.2 Hz, 1H, C_{27}-*H*), 2.44 (m, 1H, C_{22}-*H*), 2.36 (q, *J* = 7.1 Hz, 1H, C_2-*H*), 2.15−2.00 (m, 2H, C_6-*H*, C_{19}-*H*), 1.95−1.82 (m, 3H, C_4-*H*, C_{12}-*H*, C_{19}-*H*), 1.78−1.60 (m, 5H, C_{10}-*H*, C_{12}-*H*, C_{15}-*H*, C_{18}-*H*, C_{26}-*H*), 1.59−1.33 (m, 6H, C_8-*H*, C_{14}-*H*$_2$, C_{15}-*H*, C_{18}-*H*, C_{28}-*H*), 1.50 (s, 3H, C_{16}-CH_3), 1.25 (s, 3H, C_{30}-H_3), 1.12 (s, 3H, C_{20}-CH_3), 0.99 (d, *J* = 6.7 Hz, 3H, C_{28}-CH_3), 0.97 (d, *J* = 7.2 Hz, 3H, C_2-CH_3), 0.91 (d, *J* = 6.3 Hz, 3H, C_{26}-CH_3), 0.88 (d, *J* = 7.3 Hz, 3H, C_{10}-CH_3), 0.86 (d, *J* = 6.6 Hz, 3H, C_4-CH_3), 0.81 (d, *J* = 7.2 Hz, 3H, C_{22}-CH_3), 0.76 (d, *J* = 7.0 Hz, 3H, C_6-CH_3), 0.70 (d, *J* = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, C_6D_6) δ 181.3, 107.0, 101.0, 99.2, 85.8, 85.0, 84.8, 84.4, 82.7, 82.3, 81.4, 80.6, 80.2, 74.1, 71.1, 63.9, 59.6, 59.0, 56.8, 56.0, 47.8, 46.5, 39.4, 38.5, 38.2, 36.3, 36.2, 34.2, 33.8, 33.7, 31.9, 30.6, 29.5, 26.8, 26.0, 22.3, 14.0, 13.0, 12.2, 12.1, 11.8, 10.6, 9.3, 4.7; exact mass calcd for $C_{44}H_{75}O_{14}Na$ 873.4952, found 873.4935 (FAB, *m*-nitrobenzyl alcohol, added NaI).

Data for natural lonomycin A: $[\alpha]^{23}_D$ +58.8° (*c* 0.50, CH_2Cl_2); IR (film) 3170, 2975, 2930, 1591, 1454, 1386, 1091, 1042, 969 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.40 (br s, 1H, C_{29}-O*H*), 7.70 (br s, 1H, C_3-O*H*), 4.36 (d, *J* = 2.3 Hz, 1H, C_9-*H*), 4.21 (dd, *J* = 7.9, 6.5 Hz, 1H, C_{23}-*H*), 4.16 (d, *J* = 4.7 Hz, 1H, C_{21}-*H*), 4.05 (dd, *J* = 7.8, 2.0 Hz, 1H, C_{24}-*H*), 3.82 (dd, *J* = 10.8, 1.8 Hz, 1H, C_{25}-*H*), 3.66 (dd, *J* = 10.8, 2.1 Hz, 1H, C_7-*H*), 3.58 (dd, *J* = 9.9, 6.0 Hz, 1H, C_{17}-*H*), 3.42 (s, 3H, $COCH_3$), 3.34 (s, 3H, $COCH_3$), 3.26 (dd, *J* = 10.9, 4.8 Hz, 1H, C_5-*H*), 3.24 (s, 3H, $COCH_3$), 3.24 (s, 3H, $COCH_3$), 3.16 (m, 1H, C_{11}-*H*), 2.92 (t, *J* = 10.3 Hz, 1H, C_{27}-*H*), 2.44 (m, 1H, C_{22}-*H*), 2.36 (q, *J* = 7.1 Hz, 1H, C_2-*H*), 2.15−2.00 (m, 2H, C_6-*H*, C_{19}-*H*), 1.95−1.82 (m, 3H, C_4-*H*, C_{12}-*H*, C_{19}-*H*), 1.78−1.60 (m, 5H, C_{10}-*H*, C_{12}-*H*, C_{15}-*H*, C_{18}-*H*, C_{26}-*H*), 1.59−1.33 (m, 6H, C_8-*H*, C_{14}-*H*$_2$, C_{15}-*H*, C_{18}-*H*, C_{28}-*H*), 1.50 (s, 3H, C_{16}-CH_3), 1.25 (s, 3H, C_{30}-H_3), 1.12 (s, 3H, C_{20}-CH_3), 0.99 (d, *J* = 6.7 Hz, 3H, C_{28}-CH_3), 0.97 (d, *J* = 7.2 Hz, 3H, C_2-CH_3), 0.91 (d, *J* = 6.3 Hz, 3H, C_{26}-CH_3), 0.88 (d, *J* = 7.2 Hz, 3H, C_{10}-CH_3), 0.86 (d, *J* = 6.6 Hz, 3H, C_4-CH_3), 0.81 (d, *J* = 7.2 Hz, 3H, C_{22}-CH_3), 0.76 (d, *J* = 7.0 Hz, 3H, C_6-CH_3), 0.70 (d, *J* = 6.8 Hz, 3H, C_8-CH_3); ^{13}C NMR (100.6 MHz, C_6D_6) δ 181.3, 107.0, 101.0, 99.2, 85.8, 85.0, 84.8, 84.4, 82.7, 82.3, 81.4, 80.6, 80.2, 74.1, 71.1, 63.9, 59.7, 59.0, 56.8, 56.0, 47.8, 46.5, 39.4, 38.6, 38.2, 36.3, 36.2, 34.2, 33.8, 33.7, 31.9, 30.6, 29.5, 26.8, 26.0, 22.3, 14.0, 13.0, 12.2, 12.1, 11.8, 10.6, 9.3, 4.7; exact mass calcd for $C_{44}H_{75}O_{14}Na$ 873.4952, found 873.4977 (FAB, *m*-nitrobenzyl alcohol, added NaI).

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