Total Synthesis of (+)-A83543A [(+)-Lepicidin A]

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Abstract: The first synthesis of the macrolide insecticide A83543A (lepicidin A) has been completed using a Diels–Alder strategy to construct the carbocyclic framework. Diene synthesis through Pd-catalyzed Stille coupling of a macrocyclic vinylstannane and suitably functionalized vinyl iodide was followed by a diastereoselective Lewis acid-mediated intramolecular Diels–Alder reaction to construct the *trans* hydrindene subunit. Refunctionalization and intramolecular aldol condensation afforded the differentially protected (+)-lepicidin A aglycon. Successive glycosidations with 2,3,4-tri-*O*-methyl-D-rhamnose and *N*-protected L-forosamine followed by deprotection and methylation completed the synthesis of the enantiomer of the natural product.

The tetracyclic macrolide A83543A (lepicidin A) was isolated in 1990 from the fermentation broth of the soil microbe *Saccharopolyspora spinosa* by Eli Lilly and Company researchers (Figure 1).[1] To date, nine analogues, differing in the degree of N, O, and C methylation on the aglycon and sugar constituents, have been isolated. Of this family of macrolides, lepicidin A is the most abundant member accounting for 85–90% of the isolated material. The pseudoaglycon lacking the forosamine moiety has also been isolated from the culture. Projected commercial interest in this natural product stems from its exhibited insecticidal activity, particularly against lepidoptera larvae. Based on this biological activity, the name lepicidin has been suggested for this macrolide.[2]

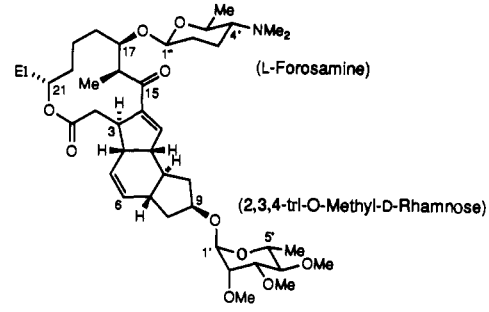

Figure 1. (+)-A83543A [(+)-lepicidin A].

Structure. The lepicidin structure is comprised of a 12-membered macrocyclic lactone fused to a 5,6,5-*cis-anti-trans* carbocyclic ring system. The carbon skeleton contains nine stereogenic centers, two of which bear hydroxyl groups that serve as anchors for the sugar residues. The C_9 α-linked sugar is 2,3,4-tri-*O*-methylrhamnose while the C_{17} β-linked, acid-labile aminosugar is forosamine. The lepicidin carbotricyclic subunit bears a close resemblance to the related tricyclic component found in the *Streptomyces* antibiotics ikarugamycin[3] and capsimycin4[4] (Figure 2). In the early stages of this project, the similarly between these three structures prompted us to assume that they might be biogenetically related and would possess the same absolute configuration. It was under this assumption that we undertook the synthesis of (+)-lepicidin A.

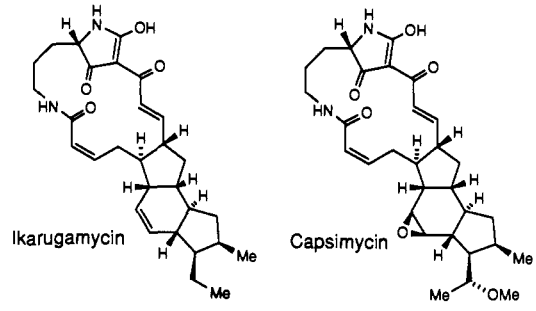

Figure 2. Structurally related antibiotics.

The initial structure assigned to lepicidin was based on the single crystal X-ray analysis of the pseudoaglycon obtained by removal of the acid-labile forosamine.[5] Subsequently, the X-ray structure of lepicidin A was obtained, which established the absolute stereochemical assignment by comparison of the C_{17}-derived forosamine to a sample of natural forosamine. D-(+)-Forosamine is readily obtained from the antibiotic spiramycin[6] and was shown to be identical to the sample obtained from lepicidin A.[7] This correlation thus established the absolute stereochemistry of the natural product to be enantiomeric to that shown in Figure 1.

Synthesis Plan. The aldol and Diels–Alder retrons are prominent features of the lepicidin aglycon, and several synthesis plans based on these reactions were considered (Scheme I). In the first route ($\mathbf{A}_1 \rightarrow \mathbf{A}_5$), the critical cycloaddition is staged from intermediate $\mathbf{A}_3$ containing the intact 12-membered lactone. The advantage inherent to this route is its convergency while the accompanying liability is linked to the uncertainty associated with the stereochemical outcome of the cycloaddition process. In particular, it is not clear what influence the resident stereocenters at C_3 and C_9 (lepicidin numbering) might play in either reinforcing or opposing the dienophile facial bias imposed by the chiral imide auxiliary in $\mathbf{A}_3$.

Through a 1,3-oxygen transposition ($\mathbf{A}_1 \rightarrow \mathbf{B}_1$), a complementary set of disconnections may be created. In this plan, the cycloaddition ($\mathbf{B}_4 \rightarrow \mathbf{B}_3$) is carried out on a less complex substrate carrying fewer heteroatoms as well as potentially interfering stereogenic centers. On the other hand, the liability associated with this route is that the macrocyclic lactone must then be constructed from the tricyclic intermediate $\mathbf{B}_2$. Irrespective of the route, it was our intention to assemble either diene moiety through a convergent Stille coupling[8] of vinylstannane and vinyl halide precursors.

The precedent for both cycloaddition processes came from our earlier studies on auxiliary-controlled asymmetric [4 + 2] Diels–Alder reactions.[9] Included among the cases studied was the illustrated acid-catalyzed intramolecular process, which proceeded in good yield and stereoselectivity (eq 1).

In the following discussion, we describe the asymmetric synthesis of lepicidin through the more convergent $\mathbf{A}_1 \rightarrow \mathbf{A}_5$ route outlined in Scheme I.

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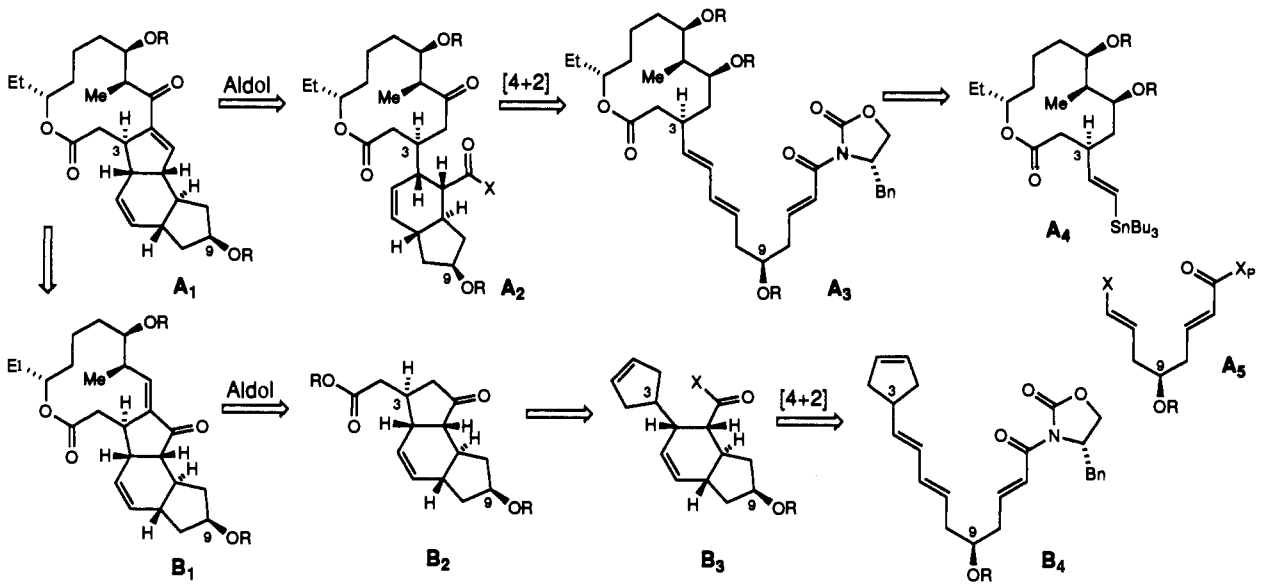
Scheme I

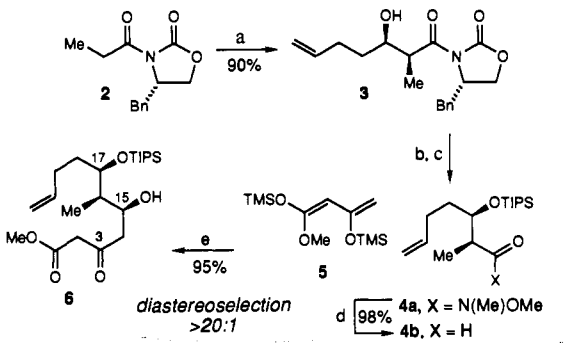


Results and Discussion

Synthesis of the Macrocyclic Fragment. The synthesis was initiated with the assemblage of the C_{15}–C_{17} *syn* stereotriad. We envisioned that these stereocenters could be produced by well-established asymmetric aldol[10] and carbonyl addition methodology and, once in place, could be used to control the stereochemical course of the C_3 bond construction.

Treatment of the boron enolate derived from imide **2** with 4-pentenal[11] provided a 90% yield of the diastereomerically pure aldol adduct **3**. Removal of the oxazolidinone auxiliary by transamination (Me_3Al, MeONHMe·HCl)[12] followed by protection of the alcohol as its triisopropylsilyl (TIPS) ether and DIBAL-H reduction of the *N*-methoxy-*N*-methylamide afforded the enantiomerically pure aldehyde **4b** in 98% yield for the three-step sequence (Scheme II). The Lewis acid-promoted reaction of this aldehyde with 1,3-bis((trimethylsilyl)oxy)-1-methoxybuta-1,3-diene (**5**)[13] ($TiCl_2(OiPr)_2$, −78 °C, 95%) afforded the desired Felkin adduct **6** in very high diastereoselectivity. It should be noted that although this stereogenic center is destined to be removed through oxidation in the natural product, its configuration is crucial to the establishment of the proper configuration of the C_3 appendage (*vide infra*).

Scheme II[a]



[a] (a) Bu_2BOTf, Et_3N, 4-pentenal, CH_2Cl_2, −78 °C; H_2O_2; (b) MeONHMe·HCl, Me_3Al, CH_2Cl_2, −20 °C to room temperature; (c) iPr_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) DIBAL-H, THF, −78 °C; (e) $TiCl_2(OiPr)_2$, CH_2Cl_2, −78 °C.

This highly stereoselective version of an acetoacetate aldol addition, developed by Chan and co-workers,[13] has only seen limited application in addition to chiral α-substituted aldehydes.[14] However, precedents from related acid-catalyzed Mukaiyama aldol reactions with aldehydes suggested that this system should

(1) Boeck, L. D.; Chio, H.; Eaton, T. E.; Godfrey, O. W.; Michel, K. H.; Nakatsukasa, W. M.; Yao, R. C. (Eli Lilly) Eur. Pat. Appl. EP 375 316, **1990**; *Chem. Abstr.* **1991**, *114*, 80066.

(2) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260–2262.

(3) Isolation, see: Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271. Structure, see: Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813–1820. Total syntheses, see: (a) Boeckman, R. K.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036–8037. (b) Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037–8039. Partial syntheses, see: (c) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403–6408. (d) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31–34. (e) Boeckman, R. K.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486–5489. (f) Kurth, M. J.; Burns, D. H.; O'Brien, M. J. *J. Org. Chem.* **1984**, *49*, 731–733. (g) Boeckman, R. K.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152–4154.

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(5) Kirst, H. A., Eli Lilly and Co., personal communication.

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(8) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817. (b) Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989**, *30*, 3645–3648.

(9) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

(10) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83–91.

(11) (a) Mamdapur, V. R.; Subramaniam, C. S.; Chadha, M. S. *Indian J. Chem., Sect. B* **1979**, *18B*, 75–76. (b) Whittaker, M.; McArthur, C. R.; Leznoff, C. C. *Can. J. Chem.* **1985**, *63*, 2844–2852.

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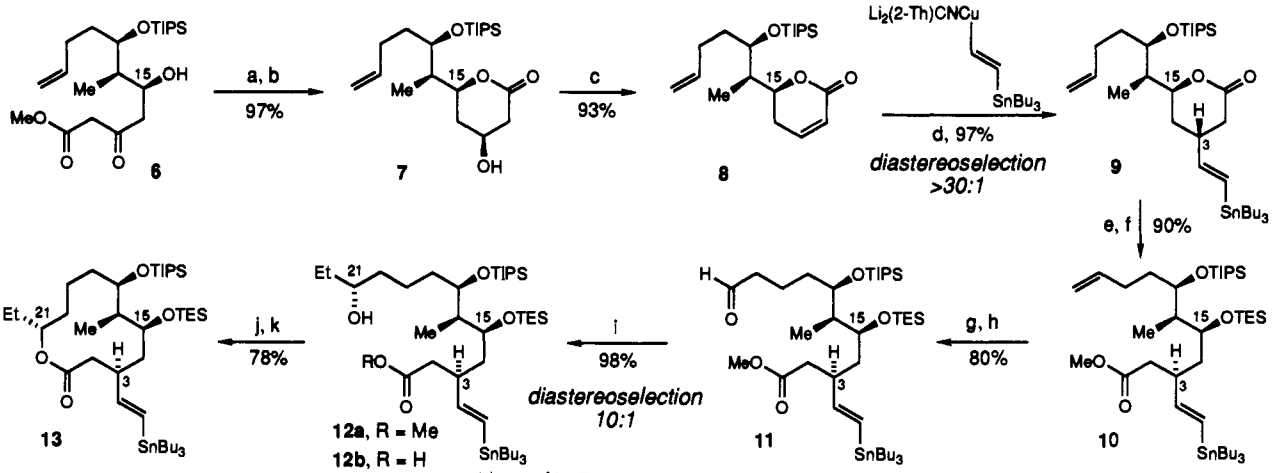
(13) (a) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578–579. (b) Brownbridge, P.; Chan, T.-H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688–693. See also: (c) Yamamoto, K.; Suzuki, S.; Tsuji, J. *Chem. Lett.* **1978**, 649–652.

(14) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 693–700.

Scheme III[a]



[a] (a) $Me_4NBH(OAc)_3$, CH_3CN, HOAc, −40 °C; (b) PPTS, C_6H_6, reflux; (c) MsCl, Et_3N, CH_2Cl_2, room temperature; (d) $BF_3{\cdot}OEt_2$, THF, −78 °C; (e) LiOH, THF; CH_2N_2; (f) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (g) Sia_2BH, THF, 0 °C; H_2O_2, $NaHCO_3$, THF, 0 °C; (h) pyr·SO_3, DMSO, iPr_2NEt, CH_2Cl_2, 0 °C; (i) Et_2Zn, (+)-*N,N*-dibutylnorephedrine, hex, 0 °C; (j) LiOH, *t*-BuOH, 35 °C; (k) 2,4,6-trichlorobenzoyl chloride, iPr_2NEt, THF, room temperature; DMAP, $PhCH_3$, 110 °C.

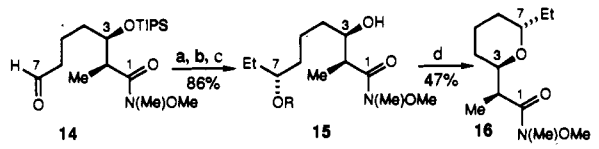
exhibit good levels of Felkin selectivity,[15] a prediction that was confirmed by the formation of **6**.

The elaboration of **6** into the fully functionalized macrocyclic lactone is summarized in Scheme III. The principal stereochemical issue in this phase of the synthesis was the selective generation of the C_3 stereocenter and associated vinylstannane appendage. It was anticipated that proper stereocontrol in the construction of this center would be achieved through conjugate addition to α,β-unsaturated δ-lactone **8**, a reaction which is well precedented in the literature.[16,17] Directed reduction of β-keto ester **6** with tetramethylammonium triacetoxyborohydride[18] afforded the derived diol as a 10:1 mixture of *anti:syn* diastereomers which was lactonized (PPTS) to δ-lactone **7** in 97% yield for the two-step sequence.

Conjugate addition of the illustrated vinylstannane to lactone **8** was accomplished using a higher order cuprate reagent under Lewis acid conditions. Treatment of **8** with dilithium(tributylstannyl)vinyl-2-thienyl(cyano)cuprate[19] ($BF_3{\cdot}OEt_2$, −78 °C, 97%) provided adduct **9** in excellent yield and complete stereoselectivity for the desired C_3 diastereomer. Hydrolysis of the lactone with LiOH in THF proceeded to give the desired hydroxy acid which was immediately esterified (CH_2N_2) to prevent protodestannylation.[20] Since the stannane moiety in the resulting hydroxy methyl ester was sensitive to silica gel chromatography, further protection as the C_{16} triethylsilyl ether was carried out on the unpurified material to provide **10** in 90% combined yield. At this point, **10** was sufficiently stable to normal methods of purification.

Selective hydroboration of **10** with disiamylborane followed by oxidation of the resulting alcohol under Parikh–Doering conditions[21] provided aldehyde **11** in 80% yield. The C_{21} stereocenter was next introduced using the (+)-*N,N*-dibutylnorephedrine-catalyzed diethylzinc addition recently described by Soai and co-workers.[22] Treatment of **11** with diethylzinc in the presence of 5 mol % of (+)-*N,N*-dibutylnorephedrine (hexane, 0 °C, 98%) provided the desired ethylcarbinol **12a** as an inseparable 10:1 mixture of C_{21} diastereomers. The stereochemical assignment of this adduct, initially made on the basis of a relevant Soai analogy, was reinforced by converting the adduct of model aldehyde **14** to ethylcarbinol **15** (R = H) through the analogous catalyzed diethylzinc addition (C_7 diastereoselection, 7:1) (Scheme IV). The stereocenters at the C_7 and C_3 were then correlated by base-catalyzed cyclization of the derived tosylate **15** (R = Ts) to the *trans* 2,6-disubstituted tetrahydropyran **16**. The observance of NOEs between C_7-H and C_2-H and between C_3-H and the ethyl group confirmed the indicated stereochemical assignment. In both reactions, the illustrated sense of asymmetric induction is consistent with that reported by Soai.[22]

Scheme IV[a]



[a] (a) (+)-*N,N*-Dibutylnorephedrine, Et_2Zn, hex, 0 °C; (b) Ts_2O, DMAP, pyr, CH_2Cl_2, reflux; (c) 48% aqueous HF, CH_3CN, room temperature; (d) pyr, reflux.

As a prelude to macrolactonization, base hydrolysis (LiOH, *t*-BuOH) of methyl ester **12a** afforded the derived acid without the destannylation that accompanied hydrolysis in other solvents. Macrolactonization was then accomplished using an optimized version of the method of Yamaguchi.[23] Treatment of the unpurified acid **12b** with 2,4,6-trichlorobenzoyl chloride and Hunig's base afforded the corresponding mixed anhydride which was then syringe pumped into excess DMAP in refluxing toluene. This procedure afforded 78% of the desired 12-membered lactone **13** along with 9% of the readily separable C_{21} diastereomeric lactone derived from the C_{21} diastereomeric alcohol impurity introduced during the diethylzinc addition step.

(15) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. For the seminal study on Felkin-selective additions of silyl enol ethers see: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668.

(16) (a) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619–3622. (b) Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. *Tetrahedron* **1990**, *46*, 1767–1782. (c) Takano, S.; Shimazaki, Y.; Moriya, M.; Ogasawara, K. *Chem. Lett.* **1990**, 1177–1180.

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 221–231.

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

(19) (a) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959–5962. (b) Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Elsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27–30. (c) Burke, S. D.; Strickland, S. M. S.; Organ, H. M.; Silks, L. A., III. *Tetrahedron Lett.* **1989**, *30*, 6303–6306.

(20) In the following reactions, it was noticed that protodestannylation often accompanied acidic aqueous workup using 1 M $NaHSO_4$; however, by using 1 M NaH_2PO_4 (pH 4.2), this mode of decomposition could be avoided.

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

(22) (a) Soai, K.; Yokoyama, S.; Ebihara, K.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690–1691. (b) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *Chem. Lett.* **1988**, 843–846.

(23) (a) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

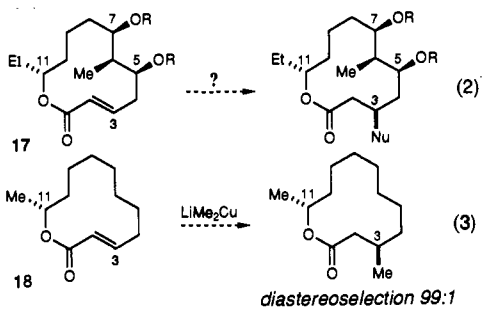
Table I. Optimization of Yamaguchi Macrocyclization (**12b** → **13**)[a]

T (°C)	addn time (h)	macrocycle prod (%)	destannylated monomer (%)	dimer (%)
25	0.5	13	–	33
70	0.5	63	7	10
110	10	10	63	1
110	**1**	**78**	**3**	**3**

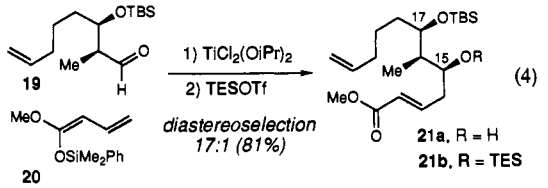
[a] Final cyclization concentration was 0.007 M in toluene.

The initial macrocyclization attempts were not encouraging. When lactonization was performed at room temperature, although a rapid reaction ensued, the major products were dimers and other oligomers (Table I). An increase in the reaction temperature to 70 °C reduced the amount of dimer to 10% and allowed the isolation of 63% of the desired macrocycle. When the reaction was carried out at 110 °C using slow addition of the mixed anhydride to the DMAP–toluene solution, monomeric products were obtained almost exclusively. Unfortunately, the long reaction time (10 h) led to substantial amounts of the destannylated monomer. Under optimal conditions, when rapid addition and high temperature were combined, macrocyclization to **13** was realized in 78% yield.

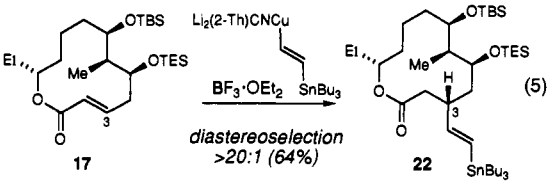
An Earlier Route to the Macrocyclic Fragment. Prior to the successful development of the preceding route to macrocyclic fragment **13**, we explored the illustrated conjugate addition (eq 2) to establish the desired stereochemical relationship and vinylstannane appendage at C_3. This route was appealing in that it postponed the introduction of the labile vinylstannane moiety until later in the synthesis. A relevant analogy for this conjugate addition[24] documents that (*E*)-unsaturated lactone **18** undergoes a highly stereoselective methylcuprate addition to afford the illustrated *anti* diastereomer with excellent selectivity (eq 3). This same study also indicates that the analogous (*Z*)-unsaturated lactone might provide access to the corresponding *syn* diastereomer. Based on this literature precedent and on our own computational efforts,[25] we anticipated that macrocyclic lactone **17** would afford the required facial selectivity in the conjugate addition if diastereoselection could be related to lactone conformation.



The synthesis of macrocycle **17** was highlighted by the utilization of the γ-selective[26] crotonate aldol reaction methodology developed by Fleming and co-workers (eq 4).[27] Although the literature precedent for reactions of this nucleophile with chiral aldehydes is lacking, we found that under the influence of a mild Lewis acid catalyst, good γ-selectivity and Felkin stereocontrol may be achieved at low temperatures. Thus, the addition of silyl ketene acetal **20** to aldehyde **19** ($TiCl_2(OiPr)_2$, CH_2Cl_2, –50 °C) followed by silylation provided the desired adduct **21b** in 81% yield along with only 5% of the corresponding *anti* Felkin adduct.[28]



Unsaturated ester **21b** was elaborated to the desired macrocycle in accord with the general route outlined in Scheme III, providing **17** in 10 steps and 21% overall yield. With this substrate in hand, we attempted the conjugate addition of the vinylcuprate illustrated in eq 5. The reaction proceeded rapidly at –90 °C to provide **22** as a single diastereomer. *Unfortunately, the new stereocenter was found to be opposite of that desired.*[29] At the present time, the origin of the control elements which are manifest in the divergent stereochemical course of the cuprate addition to unsaturated lactones **17** (eq 5) and **18** (eq 3) remain undefined. In the aftermath of this setback, the less ambiguous route to the suitably functionalized lactone intermediate **13** was successfully developed (Scheme III).

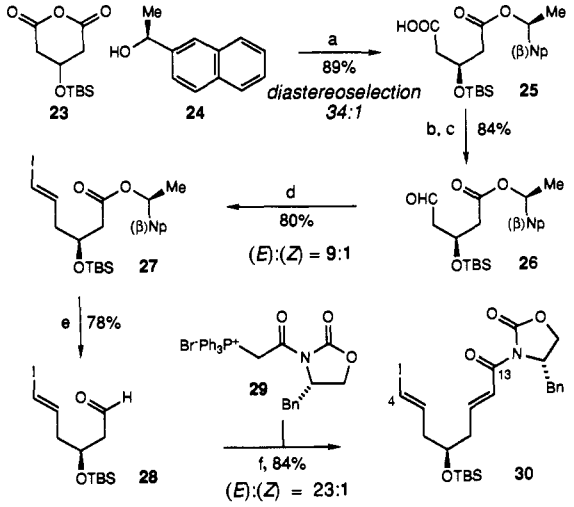


Diene Fragment. Stereoselective olefin formation was one of the dominant stereochemical issues in the projected synthesis of the iodo diene fragment (the C_4–C_{13} lepicidin subunit). We envisioned both of these olefins arising from aldehyde precursors, which necessitated the formation of a differentiated 3-hydroxy 1,5-dicarboxylate synthon (Scheme V). The symmetry-breaking enantioselective transesterification study of Heathcock and coworkers seemed particularly well-suited to this task.[30] In a slight modification of the literature method, *meso* anhydride **23** was opened with commercially available (*S*)-2-naphthylethanol to provide a 34:1 mixture of diastereomeric silyl ethers **25**. Borane reduction of the acid followed by Swern oxidation[31] then afforded aldehyde **26**. In an improvement on the Takai vinyl iodide synthesis,[32] this aldehyde was treated with iodoform and chromous chloride in a 6:1 mixture of dioxane:THF. This solvent mixture afforded (*E*)-vinyl iodide **27** as a 9:1 mixture of olefin isomers, which could be separated after the next step. Reductive cleavage of the ester moiety to aldehyde **28** (DIBAL-H, toluene, –78 °C, 78%) was followed by a Wittig reaction with phosphonium salt **29**[33] (DMAP, $CHCl_3$, 25 → 60 °C, 84%) to selectively afford the (*E*)-unsaturated imide **30** (*E*:*Z* = 23:1). These reaction conditions were specifically designed to promote olefin formation and subsequent equilibration of the initial 1.6:1 *E*:*Z* mixture of α,β-

(24) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981–3996.
(25) All calculations were performed with an MM2 forcefield on structures generated by a Multiconformer search using MacroModel (Version 3.5) provided by Professor W. Clark Still, Columbia University.
(26) For leading references, see: Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288–5302.
(27) (a) Fleming, I. *Bull. Soc. Chim. Fr.* **1981**, II.7–II.13. (b) Fleming, I.; Lee, T. V. *Tetrahedron Lett.* **1981**, *22*, 705–708. (c) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *20*, 3205–3208, 3209–3212. (d) Fleming, I.; Iqbal, J. *Tetrahedron Lett.* **1983**, *24*, 2913–2916.
(28) Proof of stereochemsitry for **21** was obtained by desilylation followed by conversion of the diol to a cyclic formal. NOEs were observed between the C_{15}-H and C_{17}-H, confirming the *syn* relationship.
(29) Proof of stereochemistry was obtained by removal of the C_{15} silyl group followed by hydrolysis of the macrocycle and subsequent cyclization to the δ-lactone. NOE analysis showed this lactone to be *cis*-substituted and hence the undesired stereochemistry at C_3.
(30) (a) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374–2378. (b) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733.
(31) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
(32) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
(33) This phosphonium salt was prepared from the corresponding (bromoacetyl)oxazolidinone (Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595–4602) in 82% yield. The analogous stabilized phosphonate has recently been reported; see: Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907–5910.

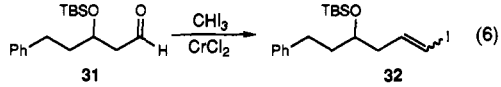
unsaturated imides. The previously observed nucleophilic equilibration of α,β-unsaturated carboxylic acid derivatives with DMAP[34] formed the basis for the design of this Wittig reaction. It is noteworthy that in the present instance, acid catalysis by DMAP·HBr, generated in conjunction with phosphonium salt deprotonation, is also required for the equilibration process.

Scheme V[a]



[a] (a) DMAP, CH_2Cl_2, −60 °C; (b) BH_3·Me_2S, THF, room temperature; (c) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C; (d) CHI_3, $CrCl_2$, dioxane/THF, room temperature; (e) DIBAL-H, $PhCH_3$, −78 °C; (f) DMAP, $CHCl_3$, 25 → 60 °C.

The solvent modifications employed in the Takai vinyl iodide synthesis (**26** → **27**) were prompted by the poor olefin selectivity obtained under the standard THF conditions. When aldehyde **26** was treated with iodoform and chromous chloride (THF, 0 °C), a disappointing 4:1 mixture of (*E*) and (*Z*) olefins was obtained.[35] In an attempt to improve this selectivity, a range of solvents was screened on model aldehyde **31** (eq 6). When dioxane was employed, the reaction was extremely sluggish but afforded a remarkable 22:1 mixture of olefin isomers. Optimal reaction conditions were realized by using a 6:1 mixture of dioxane:THF which afforded a 13:1 mixture of olefins **32**. Subsequent studies from this laboratory have shown this solvent effect to be general for other substrates as well.



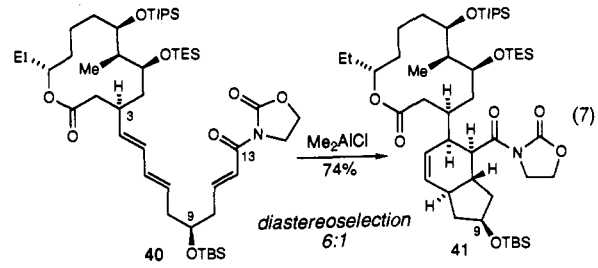
(6)

Solvent	Time	Yield	(*E*):(*Z*)
THF	4h	73%	4:1
Dioxane	4d	40%	22:1
6:1 Dioxane:THF	8h	69%	13:1

Assemblage of the Lepicidin Aglycon. Initial attempts at the Pd-catalyzed Stille coupling[8,36] of the two principal fragments **13** and **30** were complicated by protodestannylation, loss of the triethylsilyl ether, and formation of homodimers derived from both **13** and **30**. A number of steps were taken to address these problems. First, the reaction was buffered by the addition of the noncoordinating base *i*-Pr_2NEt, a modification which prevented desilylation and markedly reduced the amount of protodestannylation. Second, the use of a Pd(0) catalyst, $Pd_2(dba)_3$·$CHCl_3$,[37] prevented the initial loss of vinylstannane (the limiting reagent) through reductive dimerization. A disadvantage of this approach was the short lifetime of this catalyst in solution; however, continuous syringe pump addition of fresh $Pd_2(dba)_3$·$CHCl_3$ over the course of the reaction circumvented this problem. Third, the oxidative dimerization of the vinyl iodide was minimized by maintaining a low concentration of **30** in the reaction flask. This was accomplished by addition of the vinyl iodide *via* a second syringe pump to a concentrated solution of vinylstannane. Finally, a Lewis acid was added to act as a transmetalation cocatalyst.[38] Zinc chloride has been used for this purpose in the Stille reaction on several occasions,[39] and while $ZnCl_2$ did improve our coupling reaction, a more dramatic effect was observed with $CdCl_2$. In the presence of 30 mol % of this additive, homodimerization was eliminated, allowing the isolation of 69% of the desired triene **33** (Scheme VI). Curiously, despite the large effect of $CdCl_2$ on the product distribution, only a small rate acceleration was observed.

With the requisite triene in hand, the critical Diels–Alder reaction assembling the carbocyclic portion of lepicidin A was attempted. Although little reaction was observed under the standard conditions (1.4 equiv of Me_2AlCl, −30 °C),[9] with 5 equiv of Lewis acid and higher temperatures (25 °C), the reaction afforded a 71% yield of the desired cycloadduct **34** along with small amounts of three minor diastereomers which were readily removed during chromatographic purification. Very little loss of the acid-labile TES ether was observed under these conditions.

Although it appeared that the chiral imide auxiliary was responsible for the observed stereoinduction, we were interested in determining the direction of the intrinsic bias imparted by the resident triene chirality on the cycloaddition. To answer this question, triene **40** equipped with an *achiral imide auxiliary* at C_{13} was prepared. When the reaction of this substrate was carried out under the conditions of the previous cycloaddition, a 6:1 mixture of diastereomers was obtained in 74% yield (eq 7). *The major product, **41**, from this reaction proved to be the endo diastereomer with the opposite sense of induction to that observed with the chiral imide auxiliary (**33** → **34**).* The minor diastereomer from this reaction was found to be stereochemically analogous to **34**, a point which was confirmed by its transformation of thioester **35**. The fact that the stereochemical course of the Diels–Alder reaction could be regulated by the chiral oxazolidinone auxiliary in the presence of the opposing internal bias imposed by the stereogenic centers at C_3 and C_9 was indeed fortunate.



(7)

The stereochemical assignments of the newly generated stereocenters in Diels–Alder adducts **34** and **41** were established by observing NOEs within the bicyclic nucleus (Figure 3). In

(34) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709–710.

(35) By comparison, *n*-octanal reacts under these conditions to give an *E*/*Z* ratio of 5:1 in 82%. See ref 32.

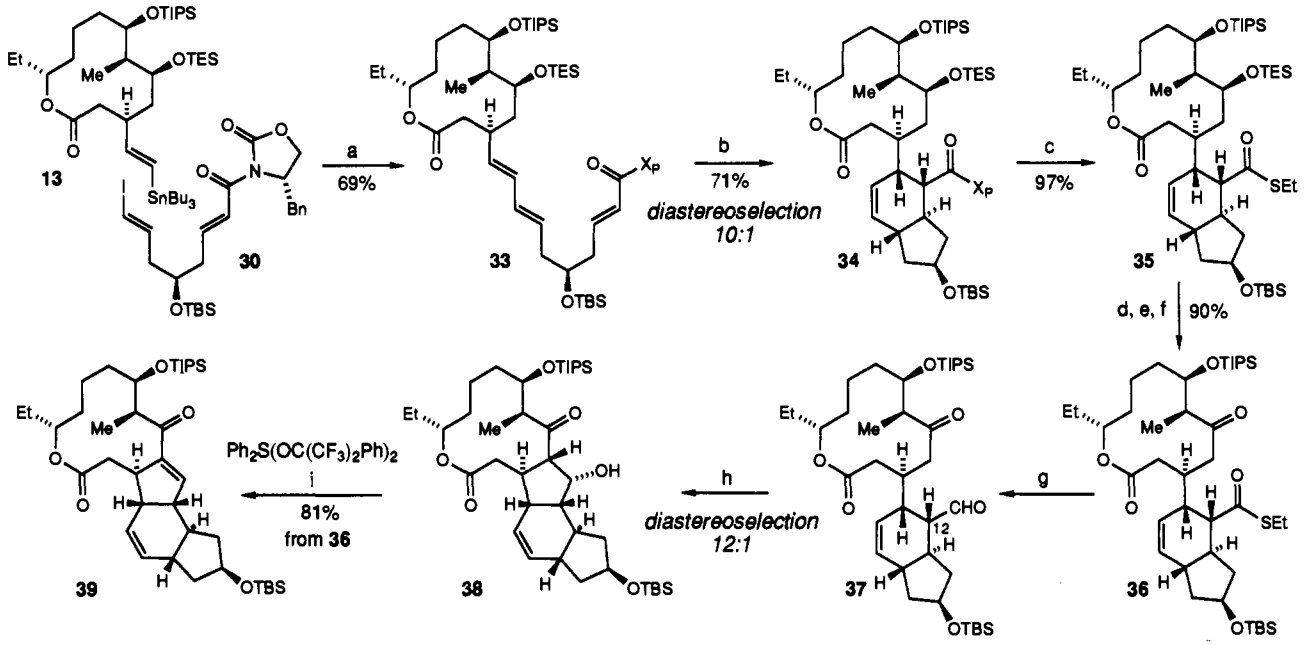
(36) For a discussion on the mechanism of this reaction, see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(37) Tris(dibenzylideneacetone)dipalladium(0) is an air-stable Pd(0) compound that is commercially available from Aldrich Chemical Co. See: (a) Takahashi, Y.; Ito, T.; Sakai, S.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **1970**, 1065–1066. (b) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–266.

(38) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256.

(39) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040. See also: Harada, T.; Kotani, Y.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1573–1576.

Scheme VI[a]



[a] (a) $Pd_2(dba)_3 \cdot CHCl_3$, $CdCl_2$, iPr_2NEt, 1-methyl-2-pyrrolidinone, 45 °C; (b) Me_2AlCl, CH_2Cl_2, 0 °C → room temperature; (c) LiSEt, THF, room temperature; (d) HOAc, THF/H_2O, room temperature; (e) TBSCl, ImH, CH_2Cl_2, room temperature; (f) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (g) Et_3SiH, 5% $Pd/CaCO_3/PbO$, acetone, room temperature; (h) NaHMDS, THF, -78 °C; (i) Martin sulfurane, CH_2Cl_2, 0 °C.

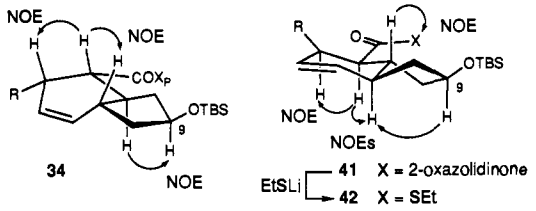


Figure 3. Proof of stereochemistry in Diels–Alder adducts **34** and **41**.

these stereochemical assignments, the C_9 stereocenter of known configuration served as an important reference point.

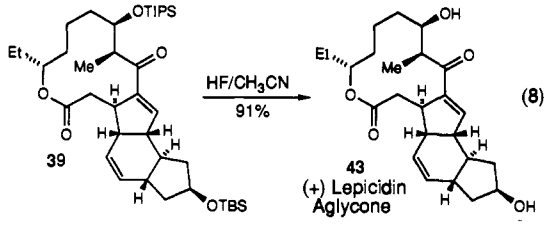
The intramolecular aldol cyclization was the remaining bond construction linking the Diels–Alder adduct with the aglycon. In pursuing the refunctionalization of **34** to set up this transformation, hydrolytic removal of the chiral auxiliary from this substrate was found to be extremely sluggish, and the normally dependable lithium hydroperoxide conditions[40] failed due to competing hydrolytic breakdown of the oxazolidinone heterocycle. However, the utilization of Damon's recently reported lithio mercaptide method of oxazolidinone removal (LiSEt, THF, room temperature)[41] afforded thioester **35** in exceptional yield (Scheme VI). This result provides convincing evidence of the value of using mercaptide nucleophiles in the selective cleavage of *N*-acyloxazolidinones.

Transformations directed toward setting up the intramolecular aldol closure from the C_{15} ketone and C_{13} aldehyde were then undertaken. Unfortunately, deprotection of the sterically hindered C_{15} TES ether was accompanied by removal of the much less hindered C_9 TBS ether; however, monoprotection of this diol (TBSCl, imidazole) proceeded with complete selectivity for the C_9 position. A subsequent Swern oxidation then afforded the desired C_{15} ketone **36** in good yield. The final manipulation preceding the aldol cyclization was the required transformation of the C_{13} thioester moiety to the derived aldehyde. This transformation was conveniently achieved through the application of Fukuyama's recently reported hydrosilylation-based reduction of thioesters (Et_3SiH, Pd/C).[42] Reduction of **36** did proceed according to the precedent but with accompanying reduction of the resident disubstituted olefin as well. However, by conducting this reduction in the presence of Lindlar's catalyst ($Pd/CaCO_3$/PbO), olefin reduction was completely suppressed, affording aldehyde **37** in 96% yield. This compound was carried on directly to the aldol reaction as chromatographic purification led to some epimerization at the C_{12} stereocenter. Treatment of keto aldehyde **37** with sodium hexamethyldisilazide at low temperature afforded a 12:1 mixture of two *syn* aldol adducts in high yield. Although the minor diastereomer could be dehydrated through its derived mesylate, the major adduct **38** proved to be inert to these conditions. Fortunately, after screening a number of dehydrating reagents and alternative elimination strategies, it was found that the dehydration of both aldol diastereomers could be effected in >90% yield using bis[α,α-bis(trifluoromethyl)benzenemethanolato]-diphenylsulfur (Martin sulfurane).[43] By performing the three-reaction sequence of thioester reduction, aldol reaction, and dehydration, unsaturated ketone **39** was obtained in an 81% overall yield from thioester **36**. This successful aldol condensation completed the synthesis of the differentially protected lepicidin A aglycon in 25 steps and 14% overall yield.

Both silyl groups were removed at this juncture by treatment with aqueous HF/acetonitrile to provide a 91% yield of lepicidin A aglycon (**43**) (eq 8). The analytical properties (^1H NMR, ^{13}C NMR, IR, TLC) of the synthetic material proved to be identical in all respects to those of the natural aglycon with the exception of the optical rotation, which was equal in magnitude but opposite in sign.[44] This confirmed that the absolute configuration of the natural product is opposite that shown in Figure 1.

2,3,4-Tri-*O*-methyl-D-rhamnose. In light of the known lability of the C_{17} forosamine residue in lepicidin, we elected to pursue the introduction of the C_9 sugar prior to attempting the C_{17} glycosidation. Although D-rhamnose is not a readily available

(40) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
(41) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849–2852.
(42) Fukuyama, T.; Lin, S. C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.
(43) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.
(44) Optical rotation of natural lepicidin aglycon: $[\alpha]^{23}_D$ -129° (*c* 0.27, $CHCl_3$). Optical rotation of synthetic lepicidin aglycon: $[\alpha]^{22}_D$ +131° (*c* 0.18, $CHCl_3$).



sugar, a C_6 deoxygenation of D-mannose can provide the required rhamnose derivatives. Using this approach, 2,3,4-tri-*O*-methyl-D-rhamnose (**48**) was synthesized without incident by the route illustrated in Scheme VII. Treatment of this sugar with acetic anhydride afforded the corresponding glycosyl acetate **49**, a suitably activated intermediate for use in the subsequent glycosidation.

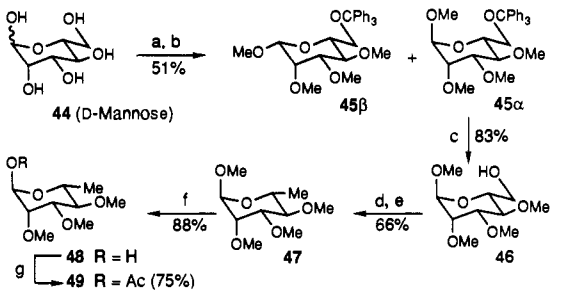
Selective deprotection of aglycon **39** (HOAc/THF/H_2O) afforded the C_9 alcohol **50** required for glycosidation (Scheme VIII). Acid-catalyzed glycosidation of **50** with glycosyl acetate **49** in the presence of catalytic quantities of trityl perchlorate (PhMe, room temperature)[45] selectively provided protected pseudoaglycon **51** in 87% yield, along with 5% of the undesired β-anomer. Deprotection of the C_{17} TIPS ether with aqueous HF cleanly afforded the pseudoaglycon **52**. Correlation of this material with an authentic sample, which has also been isolated as a natural product, showed the two compounds to be identical in all respects with the exception of their optical rotations, which were of opposite sign.

L-Forosamine. When planning the construction and appendage of L-forosamine[46] to the C_{17} alcohol, the formation of the difficult 2″-deoxy-β-glycoside linkage was an important consideration. A number of methods have been developed to overcome the problems presented by 2-deoxy-β-glycosidations.[47] We opted for a variant of the Koenigs–Knorr procedure in which controlled inversion of an α-glycosyl halide provides the desired β-glycoside.[48] A suitable protecting group for the forosamine was also required. An electron-withdrawing group such as a carbamate at the $C_{4'}$ position was considered advantageous as it would be expected to increase β-selectivity.[49] Since lepicidin has a low tolerance both to acid and to catalytic reduction, we chose an Fmoc group which could be removed by treatment with mild base.[50] The synthesis of the requisite forosamine derivative is outlined in Scheme IX.

Acylation of the (*R*)-phenylalanine-derived oxazolidinone **53**[10] with glutaric anhydride was followed by methylation of the resulting acid to provide imide **54** in 86% yield. The boron enolate of this imide reacted with acetaldehyde to provide a hydroxy ester which was lactonized (PPTS, benzene, reflux) to **55** in 79% overall yield. Hydrolysis of the imide with lithium hydroperoxide[40] followed by continuous extraction and chromatographic separation of the recovered oxazolidinone **53** afforded the desired acid **56** in 88% yield. The completion of the L-forosamine synthesis was achieved through Curtius rearrangement[51] of lactone acid **56**. Accordingly, formation of Fmoc-protected amine **57** was accomplished by treating the triethylammonium salt of **56** with diphenyl phosphorazidate followed by *in situ* trapping of the intermediate isocyanate with 9-fluorenylmethanol (72% yield). DIBAL-H reduction of lactone **57** cleanly provided Fmoc-protected forosamine, an intermediate which proved to be very difficult to manipulate due to its insolubility in all available solvents with the exception of THF and DMSO. As a result, this troublesome lactol was transformed directly to glycosyl acetate **58** (Ac_2O, pyr, 94% for two steps).

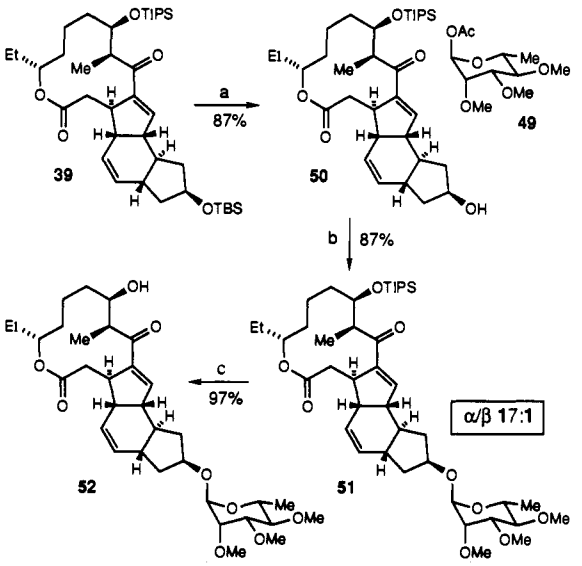
Attempted conversion of **58** to the corresponding glycosyl bromide (TMSBr, room temperature)[52] formed the bicyclic product **59**, resulting from intramolecular trapping of the

Scheme VII[a]



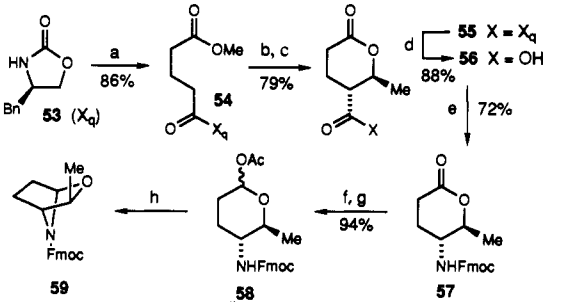
[a] (a) Ph_3CCl, pyr, 33 °C; (b) $Me_3O^+BF_4^-$, Proton Sponge, room temperature; (c) $TsOH{\cdot}H_2O$, $MeOH/CH_2Cl_2$, room temperature; (d) TsCl, pyr, CH_2Cl_2, room temperature; (e) $LiBHEt_3$, THF, 0 °C; (f) 2 M HCl, reflux; (g) Ac_2O, pyr, room temperature.

Scheme VIII[a]



[a] (a) HOAc/THF/H_2O; (b) Ph_3CClO_4, $PhCH_3$; (c) HF/CH_3CN.

Scheme IX[a]



[a] (a) *n*-BuLi, THF, −78 °C; glutaric anhydride; CH_2N_2; (b) Bu_2BOTf, Et_3N, MeCHO, CH_2Cl_2, −78 °C; (c) PPTS, PhH, reflux; (d) LiOOH, THF, 0 °C; (e) Et_3N, $Ph_2P(O)N_3$, 9-fluorenemethanol, PhH, reflux; (f) DIBAL-H, THF, −78 °C; (g) Ac_2O, pyr, room temperature; (h) TMSBr, CH_2Cl_2, room temperature.

(45) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031. This method represents a modification of a stoichiometric trityl perchlorate glycosidation developed by Mukaiyama and co-workers; see: Mukaiyama, T.; Kobayashi, S.; Shoda, S. *Chem. Lett.* **1984**, 907–910.

(46) For previous syntheses of forosamine and related aminosugars, see: (a) Albano, E. L.; Horton, D. *Carbohydr. Res.* **1969**, *11*, 485–495. (b) Guanti, G.; Banfi, L.; Narisano, E.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 2221–2222.

(47) For a summary of methods for the synthesis of 2-deoxy-β-glycosides, see: Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5–7.

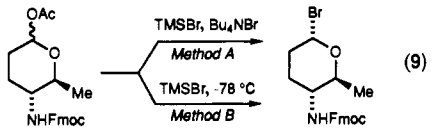
(48) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–224. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.

(49) (a) Van Boeckel, C. A. A.; Beetz, T.; Van Aelst, S. F. *Tetrahedron* **1984**, *40*, 4097–4107. (b) Van Boeckel, C. A. A.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 171–173. (c) Van Boeckel, C. A. A.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 174–176.

(50) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409.

(51) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.

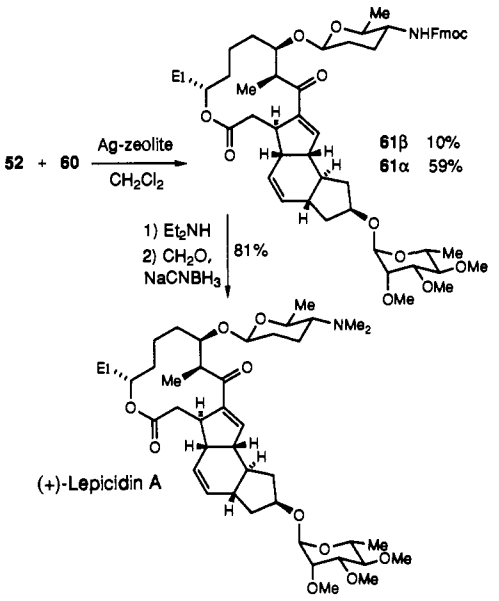
intermediate oxonium ion. This problem could be overcome by using external bromide ion to compete with the intramolecular process (eq 9, method A). Alternatively, the glycosyl bromide **60** could be prepared cleanly with TMSBr alone if the reaction temperature was lowered to −78 °C (eq 9, method B). In both cases, the extreme instability of **60** precluded its purification or characterization. NMR analysis of the unpurified glycosyl bromide showed it to exist exclusively as the α-anomer.



58 **60** (9)

Not unexpectedly, silver zeolite catalyzed glycosidation[53] of pseudoaglycon **52** with glycosyl bromide **60** suffered from competitive decomposition of **60** (Scheme X). The high reactivity of this species was also manifested in poor α/β-selectivity. When 2 equiv of **60** were used, a 41% yield of glycosidation product was obtained along with 58% recovered starting material. Unfortunately, the α/β ratio was 3:1 favoring the undesired α-anomer **61α**. In an attempt to increase the conversion, 4 equiv of the glycosyl bromide was added to the pseudoaglycon **52** in three separate portions. This resulted in a 69% yield of a 6:1 mixture of α/β-glycosides **61α** and **61β** along with 20% recovered **52**.

Scheme X



These glycosidation experiments provided sufficient quantities of the desired β-glycoside **61β** for the synthesis of lepicidin A to be completed. Treatment of **61β** with Et_2NH at room temperature cleanly removed the Fmoc protecting group without any apparent decomposition. The resulting primary amine (lepicidin C) was immediately methylated with formaldehyde and $NaCNBH_3$ to provide synthetic lepicidin A in 81% yield for the two steps (Scheme X). The analytical properties (^1H NMR, ^{13}C NMR, IR, TLC) of this material were identical in all respects to those of natural lepicidin with the exception of the optical rotation, which was equal in magnitude but opposite in sign.[54]

Conclusions

The first total synthesis of the macrolide insecticide lepicidin A (A83543A) in enantiomeric form has been completed, and the absolute configuration of the natural product has been confirmed to be opposite that shown in Figure 1. Numerous advances in reaction methodology of interest to this laboratory were made during the course of this investigation. Specifically, the successful chiral auxiliary-controlled intramolecular Diels–Alder reaction, the pivotal reaction in the synthesis, is the most complex example of such a reaction yet reported.

Experimental Section[55]

[3(2*S*,3*R*)4*S*]-3-[3-Hydroxy-2-methyl-6-heptenoyl]-4-benzyl-2-oxazolidinone (3). To a cooled (0 °C) solution of 17.4 g (74.4 mmol) of propionyloxazolidinone **2**[10b] in 150 mL of CH_2Cl_2 was added 20.6 mL (81.9 mmol) of di-*n*-butylboron triflate[56] followed by 14.0 mL (100 mmol) of Et_3N. After 10 min, the light yellow solution was cooled to −70 °C and a solution of 7.10 g (84.4 mmol) of 4-pentenal in 35 mL of CH_2Cl_2 was added *via* cannula. The resulting solution was stirred for 1.5 h at −70 °C and for 1 h at 0 °C and then quenched by addition of 80 mL of pH 7 phosphate buffer and 150 mL of methanol. After the solution was stirred for 10 min at 0 °C, a solution of 80 mL of 30% aqueous hydrogen peroxide in 200 mL of methanol was added slowly and the resulting mixture was stirred for 1 h at 0 °C and then concentrated *in vacuo*. The residue was extracted with one 400-mL and two 50-mL portions of EtOAc, and the combined organic extracts were washed with two 100-mL portions of 5% aqueous $NaHCO_3$ and 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (10 × 21 cm of silica gel, 30% EtOAc/hexanes) provided 21.2 g (66.9 mmol, 90%) of adduct **3** as a colorless oil: $[\alpha]^{24}_{546}$ +82° (*c* 0.83, CH_2Cl_2); IR (thin film) 3530 (br), 2940, 1780, 1695, 1645, 1390, 1210, 1110, 915, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.15 (m, 5H, Ar*H*), 5.80 (m, 1H, C_{20}-*H*), 5.03 (m, 1H, C_{21}-*H*(*Z*)), 4.94 (m, 1H, C_{21}-*H*(*E*)), 4.67 (m, 1H, BnC*H*N), 4.21–4.13 (m, 2H, CH_2O), 3.94 (m, 1H, C_{17}-*H*), 3.74 (dq, *J* = 7.0, 2.9 Hz, 1H, C_{16}-*H*), 3.21 (dd, *J* = 13.4, 3.3 Hz, 1H, one of $ArCH_2$), 2.95 (br s, 1H, O*H*), 2.76 (dd, *J* = 13.4, 9.4 Hz, 1H, one of $ArCH_2$), 2.25–2.07 (m, 2H, C_{19}-*H*), 1.61 (m, 1H, one of C_{18}-*H*), 1.48 (m, 1H, one of C_{18}-*H*), 1.23 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 152.9, 138.0, 134.9, 129.3, 128.8, 127.3, 114.9, 70.8, 66.1, 55.0, 42.1, 37.7, 32.9, 30.0, 10.5; TLC (30% EtOAc/hexanes) R_f 0.24. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30. Found: C, 68.22; H, 7.21.

(2*S*,3*R*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-6-heptenamide (3a). To a cooled (0 °C) suspension of 13.5 g (138 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 200 mL of CH_2Cl_2 was added 70 mL (140 mmol) of trimethylaluminum (2.0 M in hexanes) over a 40-min period. The resulting solution was allowed to warm to room temperature and stirred for 1 h. It was then recooled to −20 °C, and a solution of 20.9 g (66.0 mmol) of the aldol adduct **3** in 50 mL of CH_2Cl_2 was added slowly *via* cannula. The cloudy mixture was allowed to warm to room temperature over a 5-h period and then stirred overnight. The solution was transferred *via* cannula into 400 mL of 1 M aqueous tartaric acid at 0 °C and stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with three 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. This material was taken on directly to the next step but could be purified by flash chromatography on silica gel (50% EtOAc/hexanes) to give analytically pure amide **3a**: $[\alpha]^{19}_{546}$ +20° (*c* 1.64, CH_2Cl_2); IR (thin film) 3440 (br), 2940, 1640, 1460, 1390, 1180, 995, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H, C_{20}-*H*), 4.97 (m, 1H, C_{21}-*H*(*Z*)), 4.94 (m, 1H, C_{21}-*H*(*E*)), 3.88 (m, 1H, C_{17}-*H*), 3.77 (s, 1H, O*H*), 3.70 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.88 (m, 1H, C_{16}-*H*), 2.25 (m, 1H, one of C_{19}-*H*), 2.12 (m, 1H, one of C_{19}-*H*), 1.67 (m, 1H, one of C_{18}-*H*), 1.43 (m, 1H, one of C_{18}-*H*), 1.17 (d, *J* = 7.1 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 138.2, 114.6, 70.8, 61.4, 38.6, 33.0, 31.7, 30.0, 10.2; TLC (50% EtOAc/hexanes) R_f 0.25. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52. Found: C, 59.70; H, 9.42.

(2*S*,3*R*)-*N*-Methoxy-*N*,2-dimethyl-3-(triisopropylsiloxy)-6-heptenamide (4a). To a cooled (0 °C) solution of the total sample of unpurified alcohol **3a** (~66 mmol) in 300 mL of CH_2Cl_2 was added 31.2 mL (270

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(54) Optical rotation of natural lepicidin: $[\alpha]^{26}_D$ −139° (*c* 0.39, CH_2Cl_2); $[\alpha]^{26}_{546}$ −168° (*c* 0.39, CH_2Cl_2); $[\alpha]^{26}_{365}$ −24° (*c* 0.39, CH_2Cl_2). Optical rotation of synthetic lepicidin: $[\alpha]^{26}_D$ −133° (*c* 0.38, CH_2Cl_2); $[\alpha]^{26}_{546}$ +158° (*c* 0.38, CH_2Cl_2); $[\alpha]^{26}_{365}$ +25° (*c* 0.38, CH_2Cl_2).
(55) For a general discussion of the spectrometers employed and solvent drying procedures, see: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.
(56) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.

mmol) of 2,6-lutidine followed by 40.5 mL (150 mmol) of triisopropylsilyl trifluoromethanesulfonate. The reaction was stirred for 15 min at 0 °C and then warmed to room temperature. The excess triflate was consumed by addition of 5 mL of methanol; the solution was diluted with 300 mL of CH_2Cl_2 and washed with two 200-mL portions of saturated aqueous $NaHCO_3$. The combined aqueous layers were extracted with 100 mL of CH_2Cl_2, and the combined organic extracts were washed with three 200-mL portions of 1 M aqueous $NaHSO_4$. The organic extracts were then washed with brine, filtered through cotton, and concentrated *in vacuo* to give 46.6 g of a colorless oil. This material was used directly in the next reaction but could be purified by flash chromatography on silica gel (20% EtOAc/hexanes) to provide analytically pure silyl ether **4a**: $[\alpha]^{23}_{546}$ −14° (*c* 1.36, CH_2Cl_2); IR (thin film) 2950, 2870, 1670, 1465, 1390, 1255, 1120, 1055, 1000, 885, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H, C_{20}-*H*), 4.99 (m, 1H, C_{21}-*H*(*Z*)), 4.93 (m, 1H, C_{21}-*H*(*E*)), 4.18 (m, 1H, C_{17}-*H*), 3.69 (s, 3H, OCH_3), 3.17 (s, 3H, NCH_3), 2.98 (m, 1H, C_{16}-*H*), 2.17–2.03 (m, 2H, C_{19}-*H*), 1.70–1.57 (m, 2H, C_{18}-*H*), 1.20 (d, *J* = 6.9 Hz, 3H, C_{16}-CH_3), 1.08 (s, 21H, $SiCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 138.6, 114.2, 73.2, 61.3, 40.3, 35.0, 32.1, 28.4, 18.1, 13.7, 13.0; TLC (30% EtOAc/hexanes) R_f 0.51. Anal. Calcd for $C_{19}H_{39}NO_3Si$: C, 63.82; H, 10.99. Found: C, 63.82; H, 10.86.

(2*S*,3*R*)-2-Methyl-3-(triisopropylsiloxy)-6-heptenal (4b). To a cooled (−78 °C) solution of the total sample of unpurified amide **4a** (~66 mmol) in 500 mL of THF was added 195 mL (195 mmol) of DIBAL-H (1.0 M in toluene) over 1 h, and the resulting solution was stirred for an additional 15 min. The excess DIBAL-H was quenched by the addition of 10 mL of acetone followed by transfer of the solution *via* cannula into a vigorously stirred mixture of 700 mL of 1 M aqueous tartaric acid and 500 mL of hexane. After 1 h, 1 L of ether was added, the layers were separated, and the aqueous layer was extracted with two 400-mL portions of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (11 × 22 cm of silica gel, 4% EtOAc/hexanes) gaves 19.3 g (64.6 mmol, 98% from aldol adduct **3**) of aldehyde **4b** as a colorless oil: $[\alpha]^{22}_{546}$ +53° (*c* 1.62, CH_2Cl_2); IR (thin film) 2950, 2870, 2710, 1735, 1645, 1465, 1110, 1040, 885, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (d, *J* = 0.7 Hz, 1H, C_{15}-*H*), 5.79 (m, 1H, C_{20}-*H*), 5.00 (m, 2H, C_{21}-*H*), 4.35 (m, 1H, C_{17}-*H*), 2.49 (m, 1H, C_{16}-*H*), 2.05 (m, 2H, C_{19}-*H*), 1.68 (m, 2H, C_{18}-*H*), 1.08 (d, *J* = 6.9 Hz, 3H, C_{16}-CH_3), 1.05 (s, 21H, $SiCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 137.6, 115.1, 72.2, 50.8, 33.7, 29.9, 18.1, 12.8, 7.2; TLC (10% EtOAc/hexanes) R_f 0.50.

Methyl (5*S*,6*R*,7*R*)-5-Hydroxy-6-methyl-3-oxo-7-(triisopropylsiloxy)-10-undecenoate (6). To a cooled (0 °C) solution of 29 mL (97 mmol) of $Ti(OiPr)_4$ in 80 mL of CH_2Cl_2 was added 10.6 mL (96.7 mmol) of $TiCl_4$. After being stirring for 30 min at 0 °C, this solution was transferred slowly *via* cannula to a cooled (−75 °C) solution of 19.3 g (64.6 mmol) of aldehyde **4b** in 400 mL of CH_2Cl_2. The resulting cloudy mixture was stirred for 15 min at which time a solution of 34.0 g (131 mmol) of 1,3-bis((trimethylsilyl)oxy)-1-methoxybuta-1,3-diene (**5**)[13] in 20 mL of CH_2Cl_2 was added *via* cannula. The resulting yellow solution was stirred for 45 min at −78 °C and then quenched with 500 mL of pH 7 phosphate buffer solution. After the solution was stirred for 1 h, the layers were separated and the organic layer was washed with saturated aqueous NH_4Cl. The combined aqueous layers were extracted with 200 mL of CH_2Cl_2, and the combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (11 × 20 cm of silica gel, 10% EtOAc/hexanes) gave 25.4 g (61.1 mmol, 95%) of the desired adduct **6** as a colorless oil which existed as a 9:1 mixture of keto and enol tautomers: $[\alpha]^{24}_{546}$ −43° (*c* 0.78, CH_2Cl_2); IR (thin film) 3520 (br), 2900, 1730, 1645, 1465, 1325, 1240, 1100, 885, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H, C_{20}-*H*), 4.99 (m, 2H, C_{21}-*H*), 4.30 (m, 1H, C_{15}-*H*), 4.06 (m, 1H, C_{17}-*H*), 3.73 (s, 3H, OCH_3), 3.52 (s, 2H, C_2-*H*), 3.26 (s, 1H, O*H*), 2.79 (dd, *J* = 16.5, 8.4 Hz, 1H, one of C_{14}-*H*), 2.64 (dd, *J* = 16.5, 4.3 Hz, 1H, one of C_{14}-*H*), 1.98 (m, 2H, C_{19}-*H*), 1.75–1.60 (m, 3H, C_{16}-*H*, C_{18}-*H*), 1.07 (s, 21H, $SiCH(CH_3)_2$), 0.92 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 167.5, 137.7, 115.0, 71.0, 52.3, 49.7, 48.2, 41.0, 39.6, 33.5, 29.9, 18.2, 18.1, 13.3, 6.1; TLC (30% EtOAc/hexanes) R_f 0.43. Anal. Calcd for $C_{22}H_{42}O_5Si$: C, 63.72; H, 10.21. Found: C, 63.70; H, 10.08.

Methyl (3*S*,5*S*,6*R*,7*R*)-3,5-Dihydroxy-6-methyl-7-(triisopropylsiloxy)-10-undecenoate (6a). To a suspension of 528 mg (2.00 mmol) of tetramethylammonium triacetoxyborohydride[18] in 1 mL of acetonitrile was added 1 mL of glacial acetic acid, and the mixture was stirred for 20 min at room temperature until it became homogeneous. The solution was then cooled to −40 °C, and 119 mg (0.288 mmol) of β-keto ester **6** in 3 mL of acetonitrile was added *via* cannula. The reaction was stirred for 21 h at −40 °C and then quenched with 2 mL of 1 M aqueous disodium tartrate, warmed to room temperature, and diluted with 30 mL of CH_2Cl_2. Saturated aqueous $NaHCO_3$ was added until gas evolution ceased, and the layers were separated. The organic layer was washed with 20 mL of saturated aqueous $NaHCO_3$, and the combined aqueous layers were extracted with three 10-mL portions of CH_2Cl_2. The combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (1 × 19 cm of silica gel, 30% EtOAc/hexanes) gave 5.8 mg (0.015 mmol, 4%) of lactone **7**, along with 115 mg (0.275 mmol, 96%) of desired diol **6a** as a 10:1 mixture of *anti*:*syn* isomers: $[\alpha]^{23}_{546}$ −28° (*c* 0.46, CH_2Cl_2); IR (thin film) 3460 (br), 2950, 2880, 1735, 1645, 1465, 1440, 1100, 885, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H, C_{20}-*H*), 4.98 (m, 2H, C_{21}-*H*), 4.31 (m, 1H, C_3-*H*), 4.16 (m, 1H, C_{15}-*H*), 4.09 (m, 1H, C_{17}-*H*), 3.71 (s, 3H, OCH_3), 3.41 (s, 1H, one of O*H*), 3.41 (d, *J* = 4.8 Hz, 1H, one of O*H*), 2.54 (m, 2H, C_2-*H*), 2.04–1.87 (m, 2H, C_{19}-*H*), 1.79–1.45 (m, 5H, C_{14}-*H*, C_{16}-*H*, C_{18}-*H*), 1.09 (s, 21H, $SiCH(CH_3)_2$), 0.93 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 137.7, 115.0, 78.3, 72.3, 65.6, 51.7, 41.4, 41.2, 39.8, 33.7, 29.9, 18.2, 18.1, 13.4, 5.1; TLC (30% EtOAc/hexanes) R_f 0.20 (*anti*), R_f 0.25 (*syn*). Anal. Calcd for $C_{22}H_{44}O_5Si$: C, 63.42; H, 10.64. Found: C, 63.36; H, 10.68.

(4*S*,6*S*)-Tetrahydro-4-hydroxy-6-[(1*R*,2*R*)-1-methyl-2-(triisopropylsiloxy)-5-hexenyl]-2*H*-pyran-2-one (7). A solution of 107 mg (0.256 mmol) of diol **6a** and 13.2 mg (0.052 mmol) of pyridinium *p*-toluenesulfonate in 20 mL of benzene was heated at reflux for 1.5 h, then cooled, and concentrated *in vacuo*. Purification of the residue by flash chromatography (1.5 × 18 cm of silica gel, 40% EtOAc/hexanes) gave 95.2 mg (0.248 mmol, 97%) of desired hydroxy lactone **7** as a 10:1 mixture of alcohol diastereomers: $[\alpha]^{21}_{546}$ +30° (*c* 0.37, CH_2Cl_2); IR (thin film) 3440 (br), 2950, 2880, 1735, 1645, 1465, 1390, 1250, 1100, 1030, 885, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H, C_{20}-*H*), 4.98 (m, 2H, C_{21}-*H*), 4.35 (m, 1H, C_{15}-*H*), 4.24 (m, 1H, C_3-*H*), 3.91 (m, 1H, C_{17}-*H*), 2.88 (ddd, *J* = 17.0, 5.8, 1.1 Hz, 1H, equatorial C_2-*H*), 2.45 (dd, *J* = 17.0, 7.5 Hz, 1H, axial C_2-*H*), 2.31 (d, *J* = 4.0 Hz, 1H, O*H*), 2.29 (m, 1H, equatorial C_{14}-*H*), 2.04 (m, 2H, C_{19}-*H*), 1.80 (m, 1H, axial C_{14}-*H*), 1.77–1.56 (m, 3H, C_{16}-*H*, C_{18}-*H*), 1.05 (s, 21H, $SiCH(CH_3)_2$), 1.03 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 138.0, 114.9, 78.0, 72.9, 63.9, 42.4, 39.5, 36.3, 32.9, 30.1, 18.3, 13.0, 9.5; TLC (50% EtOAc/hexanes) R_f 0.33. Anal. Calcd for $C_{21}H_{40}O_4Si$: C, 65.58; H, 10.48. Found: C, 65.46; H, 10.62.

(6*S*)-5,6-Dihydro-6-[(1*R*,2*R*)-1-methyl-2-(triisopropylsiloxy)-5-hexenyl]-2*H*-pyran-2-one (8). To a solution of 20.2 g (52.5 mmol) of hydroxy lactone **7** in 1 L of CH_2Cl_2 at room temperature was added 40 mL (290 mmol) of Et_3N followed by 9.0 mL (120 mmol) of methanesulfonyl chloride. The resulting yellow solution was stirred for 5 min, then quenched with 800 mL of water, and separated. The aqueous layer was extracted with two 300-mL portions of CH_2Cl_2, and the combined organic extracts were washed with two 1-L portions of 1 M aqueous $NaHSO_4$. The organic layer was washed with brine, filtered through cotton, and concentrated *in vacuo* to give a dark yellow oil. Purification by flash chromatography (11 × 20 cm of silica gel, 20% EtOAc/hexanes) gave 18.0 g (49.0 mmol, 93%) of desired unsaturated lactone **8** as a colorless oil: $[\alpha]^{19}_{546}$ −60° (*c* 0.51, CH_2Cl_2); IR (thin film) 2950, 2875, 1735, 1645, 1470, 1390, 1250, 1100, 1035, 885, 815, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (m, 1H, C_3-*H*), 6.01 (ddd, *J* = 9.7, 2.3, 1.2 Hz, 1H, C_2-*H*), 5.78 (m, 1H, C_{20}-*H*), 4.98 (m, 2H, C_{21}-*H*), 4.51 (m, 1H, C_{15}-*H*), 3.93 (m, 1H, C_{17}-*H*), 2.39 (m, 2H, C_{14}-*H*), 2.05 (m, 2H, C_{19}-*H*), 1.88 (m, 1H, C_{16}-*H*), 1.74 (m, 1H, one of C_{18}-*H*), 1.63 (m, 1H, one of C_{18}-*H*), 1.06 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 1.04 (s, 21H, $SiCH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 145.2, 138.0, 121.4, 114.9, 79.1, 72.8, 41.6, 32.9, 30.1, 27.9, 18.2, 18.2, 13.2, 9.7; MS (Na^+ FAB) *m*/*z* 389 (100, M + 23), 365 (5), 323 (13), 239 (35), 176 (16), 115 (14); TLC (30% EtOAc/hexanes) R_f 0.48. Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 68.92; H, 10.38.

(4*R*,6*S*)-Tetrahydro-6-[(1*R*,2*R*)-1-methyl-2-(triisopropylsiloxy)-5-hexenyl]-4-[(*E*)-2-(tributylstannyl)vinyl]-2*H*-pyran-2-one (9). To a cooled (−78 °C) solution of 0.38 mL (4.7 mmol) of thiophene in 5 mL of THF was added 1.9 mL (4.6 mmol) of *n*-BuLi (2.45 M in hexanes). This solution was stirred for 20 min at −78 °C and 30 min at −22 °C and then transferred *via* cannula to a −78 °C suspension of 416 mg (4.65 mmol) of cuprous cyanide in 5 mL of THF. The resulting slurry was stirred for 10 min and then warmed to −22 °C to provide a tan, homogeneous solution.

In a separate flask, a cooled (−78 °C) solution of 2.91 g (4.79 mmol) of 1,2-bis(tributylstannyl)ethylene[57] in 30 mL of THF was treated with 2.0 mL (4.9 mmol) of *n*-BuLi (2.45 M in hexanes) in one portion. The resulting solution was stirred for 1 h at −78 °C and then transferred *via* cannula into the −22 °C cuprate solution. This solution was allowed to warm to 0 °C, then cooled to −78 °C, treated with 0.60 mL (4.9 mmol) of boron trifluoride etherate, and stirred for 5 min. To this solution was added *via* cannula a solution of 800 mg (2.18 mmol) of unsaturated lactone **8** in 10 mL of THF. After being stirred for 20 min at −78 °C, the reaction mixture was poured into a rapidly stirred mixture of 100 mL of saturated aqueous NH_4Cl, 10 mL of concentrated NH_4OH, and 200 mL of ether. After the solution was stirred 20 min, the layers were separated and the aqueous layer was extracted with 100 mL of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 4.02 g of a colorless oil. Purification by flash chromatography (6 × 22 cm of silica gel, 10% EtOAc/hexanes) gave 1.45 g (2.13 mmol, 97%) of diastereomerically pure adduct **9**: $[\alpha]^{19}_{546}$ +6° (*c* 1.0, CH_2Cl_2); IR (thin film) 2950, 2880, 1750, 1645, 1600, 1465, 1380, 1250, 1040, 1000, 910, 885, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, *J* = 19.0 Hz, 1H, C_5-*H*), 5.92 (dd, *J* = 19.0, 5.4 Hz, 1H, C_4-*H*), 5.78 (m, 1H, C_{20}-*H*), 5.01 (dd, *J* = 17.1, 1.4 Hz, 1H, (*Z*)-C_{21}-*H*), 4.96 (dd, *J* = 10.1, 1.0 Hz, 1H, (*E*)-C_{21}-*H*), 4.46 (m, 1H, C_{15}-*H*), 3.89 (m, 1H, C_{17}-*H*), 2.74 (m, 1H, C_3-*H*), 2.53 (m, 2H, C_2-*H*), 2.04 (m, 2H, C_{19}-*H*), 1.92 (m, 1H, one of C_{14}-*H*), 1.85 (m, 1H, one of C_{14}-*H*), 1.76 (m, 2H, C_{16}-*H*, one of C_{18}-*H*), 1.60 (m, 1H, one of C_{18}-*H*), 1.47 (m, 6H, $SnCH_2CH_2CH_2$), 1.30 (m, 6H, $SnCH_2CH_2$), 1.06 (s, 21H, $SiCH(CH_3)_2$), 1.02 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 0.89 (m, 15H, $SnCH_2$-$CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 149.1, 138.9, 128.8, 114.9, 78.1, 73.1, 42.4, 37.2, 36.0, 34.3, 33.1, 31.7, 30.2, 29.1, 27.2, 18.4, 18.3, 13.7, 13.1, 9.4; TLC (10% EtOAc/hexanes) R_f 0.35. Anal. Calcd for $C_{35}H_{68}O_3SiSn$: C, 61.48; H, 10.02. Found: C, 61.50; H, 10.12.

Methyl (3*R*,4*E*)-3-[(2*S*,3*R*,4*R*)-2-Hydroxy-3-methyl-4-(triisopropylsiloxy)-7-octenyl]-5-(tributylstannyl)-4-pentenoate (9a). To a solution of 1.45 g (2.12 mmol) of δ-lactone **9** in 100 mL of THF at room temperature was added 15 mL of 2 M aqueous LiOH. The mixture was stirred vigorously for 17 h and then partitioned between 500 mL of EtOAc and 250 mL of 1 M aqueous NaH_2PO_4. The layers were separated; the aqueous layer was further acidified to pH 3.5 with 1 M aqueous phosphoric acid, saturated with NaCl, and extracted with 100 mL of EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to ~100 mL. This solution was cooled to 0 °C, and an ethereal solution of diazomethane was added until a yellow color persisted. The resulting solution was stirred for 30 min at room temperature and then concentrated *in vacuo* to give 1.54 g of hydroxy ester **9a** as a colorless oil. As this material was prone to protodestannylation, it was used directly in the next step without further purification. However, it could be purified by flash chromatography (5% EtOAc/CH_2Cl_2) to provide analytically pure hydroxy ester **9a** which had the following characteristics: $[\alpha]^{22}_{546}$ −11° (*c* 1.96, CH_2Cl_2); IR (thin film) 3530, 2960, 2870, 1745, 1645, 1595, 1460, 1100, 1090, 880, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, *J* = 18.9 Hz, 1H, C_5-*H*), 5.77 (m, 2H, C_4-*H*, C_{20}-*H*), 5.01 (dd, *J* = 17.1, 1.6 Hz, 1H, (*Z*)-C_{21}-*H*), 4.96 (dd, *J* = 10.1, 1.4 Hz, 1H, (*E*)-C_{21}-*H*), 3.98 (m, 1H, C_{15}-*H*), 3.87 (m, 1H, C_{17}-*H*), 3.63 (s, 3H, OCH_3), 3.32 (s, 1H, O*H*), 2.59 (m, 1H, C_3-*H*), 2.36 (m, 2H, C_2-*H*), 2.01 (m, 1H, one of C_{19}-*H*), 1.88 (m, 1H, one of C_{19}H-*H*), 1.76 (m, 1H, C_{16}-*H*), 1.65–1.40 (m, 8H, C_{18}-*H*, $SnCH_2$-CH_2CH_2), 1.28 (m, 6H, $SnCH_2CH_2$), 1.07 (s, 21H, $SiCH(CH_3)_2$), 0.88 (m, 15H, $SnCH_2CH_2CH_2CH_3$), 0.83 (d, *J* = 8.0 Hz, 3H, C_{16}-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 150.9, 137.7, 128.7, 115.0, 78.7, 73.4, 51.4, 41.2, 40.1, 38.9, 37.2, 33.8, 30.0, 29.0, 27.2, 18.2, 18.1, 13.7, 13.4, 9.4, 4.4; TLC (10% EtOAc/hexanes) R_f 0.21. Anal. Calcd for $C_{36}H_{72}O_4SiSn$: C, 60.41; H, 10.14. Found: C, 60.54; H, 10.17.

Methyl (3*R*,4*E*)-3-[(2*S*,3*R*,4*R*)-3-Methyl-2-(triethylsiloxy)-4-(triisopropylsiloxy)-7-octenyl]-5-(tributylstannyl)-4-pentenoate (10). To a cooled (−78 °C) solution of 1.54 g (~2.1 mmol) of unpurified methyl ester **9a** in 75 mL of CH_2Cl_2 was added 0.40 mL (3.4 mmol) of 2,6-lutidine followed by 0.62 mL (2.7 mmol) of triethylsilyl trifluoromethansulfonate. The reaction was stirred for 45 min at −78 °C, then 0.3 mL of methanol was added to consume the excess triflate, the stirring was continued for 5 min. The solution was then diluted with 300 mL of ether, washed with 50 mL of saturated aqueous $NaHCO_3$, three 100-mL portions of 1 M aqueous NaH_2PO_4, and brine, and then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography (6 × 22 cm of silica gel, 20% CH_2Cl_2/hexanes) gave 1.58 g (1.90 mmol, 90% from **9**) of silyl ether **10** as a colorless oil: $[\alpha]^{22}_{546}$ −0.1° (*c* 0.92, CH_2Cl_2); $[\alpha]^{22}_{365}$ −2.7° (*c* 0.92, CH_2Cl_2); IR (thin film) 2960, 2880, 1745, 1640, 1595, 1460, 1240, 1080, 1030, 880, 740, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, *J* = 18.9 Hz, 1H, C_5-*H*), 5.76 (m, 1H, C_{20}-*H*), 5.72 (dd, *J* = 18.9, 7.8 Hz, 1H, C_4-*H*), 4.97 (dd, *J* = 17.2, 1.6 Hz, 1H, (*Z*)-C_{21}-*H*), 4.91 (dd, *J* = 10.1, 1.6 Hz, 1H, (*E*)-C_{21}-*H*), 3.91 (m, 1H, C_{17}-*H*), 3.75 (m, 1H, C_{15}-*H*), 3.61 (s, 3H, OCH_3), 2.52 (m, 1H, C_3-*H*), 2.40 (dd, *J* = 14.7, 6.2 Hz, 1H, one of C_2-*H*), 2.25 (dd, *J* = 14.7, 8.4 Hz, 1H, one of C_2-*H*), 2.14 (m, 1H, one of C_{19}-*H*), 1.97 (m, 1H, one of C_{19}-*H*), 1.64 (m, 4H, C_{16}-*H*, C_{18}-*H*, one of C_{14}-*H*), 1.53 (m, 1H, one of C_{14}-*H*), 1.46 (m, 6H, $SnCH_2CH_2CH_2$), 1.27 (m, 6H, $SnCH_2CH_2$), 1.05 (s, 21H, $SiCH(CH_3)_2$), 0.96–0.85 (m, 24H, $SnCH_2CH_2CH_2CH_3$, $SiCH_2CH_3$), 0.82 (d, *J* = 8.0 Hz, 3H, C_{16}-CH_3), 0.57 (q, *J* = 7.2 Hz, 6H, $SiCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 151.0, 138.9, 128.7, 114.2, 72.9, 70.7, 51.3, 40.6, 40.1, 39.8, 33.7, 29.0, 27.9, 27.3, 18.4, 18.3, 13.7, 13.2, 9.4, 9.2, 7.0, 5.4; TLC (30% CH_2Cl_2/hexanes) R_f 0.38. Anal. Calcd for $C_{42}H_{86}O_4Si_2Sn$: C, 60.78; H, 10.44. Found: C, 60.63; H, 10.60.

Methyl (3*R*,4*E*)-3-[(2*S*,3*R*,4*R*)-8-Hydroxy-3-methyl-2-(triethylsiloxy-)4-(triisopropylsiloxy)octyl]-5-(tributylstannyl)-4-pentenoate (10a). To a cooled (0 °C) solution of 4.8 mL (45 mmol) of 2-methyl-2-butene in 60 mL of THF was added 2.2 mL (23 mmol) of a borane–dimethyl sulfide complex. The resulting solution was stirred for 2 h at 0 °C and then added *via* cannula to a 0 °C solution of 6.12 g (7.37 mmol) of olefin **10** in 90 mL of THF. After the solution was stirred for 1.2 h, the excess borane was quenched with 3 mL of ethanol and a mixture of 25 mL of saturated aqueous $NaHCO_3$ and 10 mL of 30% aqueous hydrogen peroxide was added. The mixture was allowed to warm to room temperature over 2 h with vigorous stirring and then partitioned between 1 L of ether and 250 mL of saturated aqueous Na_2SO_3. The aqueous layer was extracted with 100 mL of ether, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (8 × 22 cm of silica gel, 15% EtOAc/hexanes) gave 5.65 g (6.66 mmol, 90%) of alcohol **10a** as a colorless oil: IR (thin film) 3450 (br), 2960, 2880, 1745, 1595, 1460, 1375, 1240, 1100, 1030, 880, 740, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, *J* = 19.0 Hz, 1H, C_5-*H*), 5.76 (dd, *J* = 19.0, 7.3 Hz, 1H, C_4-*H*), 3.93 (m, 1H, C_{17}-*H*), 3.76 (m, 1H, C_{15}-*H*), 3.63 (m, 2H, C_{21}-*H*), 3.62 (s, 3H, OCH_3), 2.57 (m, 1H, C_3-*H*), 2.51 (dd, *J* = 14.6, 5.6 Hz, 1H, one of C_2-*H*), 2.26 (dd, *J* = 14.6, 8.7 Hz, 1H, one of C_2-*H*), 1.69 (m, 1H, C_{16}-*H*), 1.65–1.50 (m, 9H, O*H*, C_{14}-*H*, C_{18}-*H*, C_{19}-*H*, C_{20}-*H*), 1.46 (m, 6H, $SnCH_2CH_2CH_2$), 1.30 (m, 6H, $SnCH_2CH_2$), 1.06 (s, 21H, $SiCH(CH_3)_2$), 0.96–0.85 (m, 24H, $SnCH_2CH_2CH_2CH_3$, $SiCH_2CH_3$), 0.83 (d, *J* = 8.0 Hz, 3H, C_{16}-CH_3), 0.57 (q, *J* = 7.4 Hz, 6H, $SiCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$), δ 173.0, 151.3, 128.0, 72.8, 71.2, 63.0, 51.3, 40.4, 40.4, 40.1, 39.5, 34.6, 33.3, 29.0, 27.3, 20.5, 18.4, 18.3, 13.7, 13.2, 9.4, 9.3, 7.0, 5.4; TLC (15% EtOAc/hexanes) R_f 0.24. Anal. Calcd for $C_{42}H_{88}O_5Si_2Sn$: C, 59.48; H, 10.46. Found: C, 59.35; H, 10.36.

Methyl (3*R*,4*E*)-3-[(2*S*,3*R*,4*R*)-7-Formyl-3-methyl-2-(triethylsiloxy)-4-(triisopropylsiloxy)heptyl]-5-(tributylstannyl)-4-pentenoate (11). To a solution of 5.63 g (6.64 mmol) of alcohol **10a** in 50 mL of CH_2Cl_2 at room temperature was added 4.6 mL (26 mmol) of diisopropylethylamine, and the resulting solution was cooled to 0 °C. A solution of 3.12 g (19.6 mmol) of a sulfur trioxide–pyridine complex[58] in 20 mL of dimethyl sulfoxide was then added *via* cannula. The solution was stirred for 1 h at 0 °C and then partitioned between 800 mL of 2:1 hexanes/ether and 250 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 100 mL of 2:1 hexanes/ether, and the combined organic extracts were washed with 500 mL of 1 M aqueous NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (8 × 21 cm of silica gel, 7% ether/hexanes) gave 5.02 g (5.93 mmol, 89%) of desired aldehyde **11** as a colorless oil: $[\alpha]^{20}_{546}$ −0.6° (*c* 0.99, CH_2Cl_2); $[\alpha]^{20}_{365}$ −2.7° (*c* 0.99, CH_2Cl_2); IR (thin film) 2960, 2870, 1745, 1595, 1460, 1375, 1240, 1100, 1030, 880, 740, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.7 Hz, 1H, C_{21}-*H*), 5.92 (d, *J* = 18.9 Hz, 1H, C_5-*H*), 5.77 (dd, *J* = 18.9, 7.5 Hz, 1H, C_4-*H*), 3.94 (m, 1H, C_{17}-*H*), 3.77 (m, 1H, C_{15}-*H*), 3.62 (s, 3H, OCH_3), 2.55 (m, 1H, C_3-*H*), 2.44 (dd, *J* = 14.7, 6.0 Hz, 1H, one of C_2-*H*), 2.38 (m, 2H, C_{20}-*H*), 2.27 (dd, *J* = 14.7, 8.5 Hz, 1H, one of C_2-*H*), 1.80–1.50 (m, 7H, C_{14}-*H*, C_{16}-*H*, C_{18}-*H*, C_{19}-*H*), 1.46 (m, 6H, $SnCH_2CH_2CH_2$), 1.29 (m, 6H, $SnCH_2CH_2$), 1.06 (s, 21H, $SiCH(CH_3)_2$), 0.96–0.84 (m, 24H, $SnCH_2CH_2CH_2CH_3$, $SiCH_2CH_3$), 0.83 (d, *J* = 8.0

(57) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581–5583. (b) Nesmeyanov, A. N.; Borisov, A. E. *Dokl. Akad. Nauk SSSR* **1967**, *174*, 96.

(58) Obtained from Aldrich Chemical Co.

Hz, 3H, C_{16}-CH_3), 0.57 (q, J = 7.4 Hz, 6H, $SiCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 151.2, 128.3, 72.8, 70.8, 51.3, 44.2, 40.7, 40.4, 39.6, 34.2, 29.0, 27.3, 18.4, 18.3, 16.9, 13.7, 13.2, 9.4, 9.3, 7.0, 5.4; TLC (10% EtOAc/hexanes) R_f 0.33.

Methyl (3*R*,4*E*)-3-[(2*S*,3*R*,4*R*,8*R*)-8-Hydroxy-3-methyl-2-(triethylsiloxy)-4-(triisopropylsiloxy)decyl]-5-(tributylstannyl)-4-pentenoate (12a). To a cooled (0 °C) solution of 72.4 mg (0.275 mmol) of (+)-*N*,*N*-di-*n*-butylnorephedrine[22] in 6 mL of hexane was added 2.1 mL (20.5 mmol) of diethylzinc. After being stirred for 45 min, this solution was transferred *via* cannula into a cooled (0 °C) solution of 4.86 g (5.74 mmol) of aldehyde **11** in 20 mL of hexane. The resulting solution was stirred for 20 h at 0 °C, then transferred *via* cannula into 200 mL of saturated aqueous NH_4Cl, and diluted with 400 mL of ether. The layers were separated, and the aqueous layer was extracted with 100 mL of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (8 × 22 cm of silica gel, 75% CH_2Cl_2/hexanes to 100% CH_2Cl_2) gave 4.93 g (5.63 mmol, 98%) of alcohol **12a** as a 10:1 mixture of diastereomers (determined by ^{13}C NMR): $[\alpha]^{20}_{546}$ −1.9° (*c* 1.00, CH_2Cl_2); $[\alpha]^{20}_{365}$ −6.1° (*c* 1.00, CH_2Cl_2); IR (thin film) 3500 (br), 2950, 2870, 1745, 1600, 1460, 1380, 1240, 1105, 1010, 880, 740, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, J = 19.0 Hz, 1H, C_5-*H*), 5.76 (dd, J = 19.0, 7.3 Hz, 1H, C_4-*H*), 3.94 (m, 1H, C_{17}-*H*), 3.78 (m, 1H, C_{15}-*H*), 3.62 (s, 3H, OCH_3), 3.50 (m, 1H, C_{21}-*H*), 2.59 (m, 1H, C_3-*H*), 2.55 (dd, J = 14.4, 5.3 Hz, 1H, one of C_2-*H*), 2.25 (dd, J = 14.4, 8.7 Hz, 1H, one of C_2-*H*), 1.71 (m, 1H, C_{16}-*H*), 1.65–1.40 (m, 16H, C_{14}-*H*, C_{18}-*H*, C_{19}-*H*, C_{20}-*H*, C_{22}-*H*, $SnCH_2CH_2CH_2$), 1.29 (m, 6H, $SnCH_2CH_2$), 1.06 (s, 21H, $SiCH(CH_3)_2$), 0.97–0.85 (m, 27H, C_{23}-CH_3, $SnCH_2CH_2CH_2CH_3$, $SiCH_2CH_3$), 0.83 (d, J = 8.0 Hz, 3H, C_{16}-CH_3), 0.57 (q, J = 7.4 Hz, 6H, $SiCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 151.4, 127.9, 73.3, 72.7, 71.4, 51.3, 40.6, 40.4, 39.9, 39.5, 37.5, 34.9, 30.1, 29.0, 27.3, 20.7, 18.4, 18.3, 13.7, 13.3, 9.9, 9.4, 9.3, 7.0, 5.4; TLC (15% EtOAc/hexanes) R_f 0.41. Anal. Calcd for $C_{44}H_{92}O_5Si_2Sn$: C, 60.32; H, 10.59. Found: C, 60.14; H, 10.54.

(3*R*,4*E*)-3-[(2*S*,3*R*,4*R*,8*R*)-8-Hydroxy-3-methyl-2-(triethylsiloxy)-4-(triisopropylsiloxy)decyl]-5-(tributylstannyl)-4-pentenoic Acid (12b). To a solution of 3.72 g (4.25 mmol) of methyl ester **12a** in 140 mL of *tert*-butyl alcohol was added 30 mL of 2 M aqueous LiOH, and the mixture was stirred rapidly for 36 h at 35 °C. The solution was then diluted with 800 mL of EtOAc. A mixture of 350 mL of 1 M aqueous NaH_2PO_4 and 30 mL of 1 M aqueous $NaHSO_4$ was saturated with NaCl, and the resulting solution was added to the reaction mixture. The aqueous layer (pH 4) was separated and extracted with 200 mL of EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting seco acid **12b** was azeotroped with toluene and used directly in the next step.

(4*R*,6*S*,7*R*,8*R*,12*R*)-12-Ethyl-7-methyl-4-[(*E*)-2-(tributylstannyl)-vinyl]-6-(triethylsiloxy)-8-(triisopropylsiloxy)oxacyclododecan-2-one (13). To a cooled (0 °C) solution of the entire sample of unpurified acid **12b** (~4.2 mmol) in 15 mL of THF was added 3.7 mL (21.2 mmol) of diisopropylethylamine followed by 2.0 mL (12.8 mmol) of 2,4,6-trichlorobenzoyl chloride. The resulting cloudy solution was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was suspended in ether and filtered through cotton to remove the amine hydrochloride salt. The filtrate was concentrated to a yellow oil, dissolved in 400 mL of toluene, and added over 1 h *via* a Hershberg dropping funnel to a refluxing solution of 11.2 g (91.3 mmol) of 4-(dimethylamino)-pyridine in 150 mL of toluene. The resulting suspension was cooled to room temperature and concentrated *in vacuo*. The residue was suspended in 500 mL of 4:1 hexane:ether, and 2.5 mL of DBU was added to precipitate excess benzoyl chloride. The suspension was stirred for 20 min and then filtered through cotton. The filtrate was washed with 500 mL each of water, 1 M aqueous NaH_2PO_4, saturated aqueous $NaHCO_3$, and brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (11 × 20 cm of silica gel, 30% CH_2Cl_2/hexanes to 40% CH_2Cl_2/hexanes) gave 338 mg (0.401 mmol, 9%) of the C_{21} epimeric macrocycle followed by 2.78 g (3.30 mmol, 78% from **12a**) of the desired macrocyclic lactone **13**: $[\alpha]^{21}_{546}$ −3.2° (*c* 1.02, CH_2Cl_2); IR (thin film) 2970, 2880, 1740, 1600, 1465, 1245, 1155, 1100, 1045, 885, 740, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (dd, J = 18.9, 8.2 Hz, 1H, C_4-*H*), 5.93 (d, J = 18.9 Hz, 1H, C_5-*H*), 4.79 (m, 1H, C_{21}-*H*), 3.86 (m, 1H, C_{17}-*H*), 3.80 (m, 1H, C_{15}-*H*), 2.66 (m, 1H, C_3-*H*), 2.63 (dd, J = 13.9, 5.0 Hz, 1H, one of C_2-*H*), 2.35 (dd, J = 13.9, 5.9 Hz, 1H, one of C_2-*H*), 1.87 (m, 1H, one of C_{20}-*H*), 1.75–1.65 (m, 3H, one of C_{14}-*H*, C_{16}-*H*, one of C_{19}-*H*), 1.65–1.40 (m, 13H, one of C_{14}-*H*, C_{18}-*H*, one of C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*, $SnCH_2CH_2CH_2$), 1.31 (m, 6H, $SnCH_2CH_2$), 1.07 (s, 21H, $SiCH(CH_3)_2$), 0.99–0.92 (m, 12H, $SiCH_2CH_3$, C_{16}-CH_3), 0.91–0.84 (m, 18H, C_{23}-CH_3, $SnCH_2CH_2$-CH_2CH_3), 0.60 (q, J = 7.9 Hz, 6H, $SiCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 152.4, 126.8, 73.1, 71.1, 70.5, 46.4, 43.4, 41.7, 39.5, 35.9, 32.4, 29.1, 28.0, 27.3, 19.0, 18.4, 18.3, 13.7, 13.1, 11.3, 9.5, 9.4, 7.1, 5.7; TLC (50% benzene/hexanes) R_f 0.36. Anal. Calcd for $C_{43}H_{88}O_4Si_2Sn$: C, 61.19; H, 10.51. Found: C, 61.25; H, 10.62.

Methyl (5*S*,6*R*,7*R*)-5-Hydroxy-6-methyl-7-(*tert*-butyldimethylsiloxy)-2,11-dodecadienoate (21a). To a cooled (0 °C) solution of 7.1 mL (24 mmol) of $Ti(OiPr)_4$ in 50 mL of CH_2Cl_2 was added 2.6 mL (24 mmol) of $TiCl_4$. The resulting colorless solution was transferred *via* cannula to a cooled (−70 °C) solution of 6.43 g (23.8 mmol) of aldehyde **19** in 200 mL of CH_2Cl_2. The mixture was warmed to −50 °C and stirred for 15 min. A solution of 7.02 g (29.9 mmol) of silyl dienyl ether **20**[27] in 25 mL of CH_2Cl_2 was then added *via* cannula. The resulting yellow solution was stirred at −50 °C for 1.5 h and then quenched by the addition of 400 mL of pH 7 phosphate buffer. The mixture was diluted with 250 mL of CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with three 150-mL portions of CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NH_4Cl and brine, then filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (11 × 20 cm of silica gel, 10% EtOAc/hexanes) gave 8.56 g of a colorless oil consisting of the desired adduct **21a** and byproduct phenyldimethylsilanol which was carried on to the next step without further purification. On a smaller scale reaction, the phenyldimethylsilanol could be removed under high vacuum to provide pure adduct **21a**: $[\alpha]^{14}_{546}$ −40° (*c* 1.55, CH_2Cl_2); IR (thin film) 3500 (br), 2960, 2860, 1730, 1660, 1440, 1255, 840, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (m, 1H, C_3-*H*), 5.90 (dd, J = 16.6, 1.0 Hz, 1H, C_2-*H*), 5.77 (m, 1H, C_{21}-*H*), 4.95 (m, 2H, C=CH_2), 3.90 (m, 1H, C_{15}-*H*), 3.84 (m, 1H, C_{17}-*H*), 3.72 (s, 3H, OCH_3), 2.91 (s, 1H, O*H*), 2.43 (m, 1H, one of C_{14}-*H*), 2.32 (m, 1H, one of C_{14}-*H*), 2.03 (q, J = 7.1 Hz, 2H, C_{20}-*H*), 1.60–1.25 (m, 5H, C_{16}-*H*, C_{17}-*H*, C_{18}-*H*), 0.88 (m, 12H, $SiC(CH_3)_3$, C_{16}-CH_3), 0.10 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.1, 138.3, 122.9, 114.8, 77.3, 73.8, 51.3, 39.7, 38.2, 34.0, 33.7, 25.8, 24.9, 18.0, 5.7, −3.7, −4.6; MS (Na^+ FAB) m/z 393 (100, M + Na), 199 (10), 173 (31), 133 (10), 115 (24); TLC (15% EtOAc/hexanes) R_f 0.18. Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.34. Found: C, 64.94; H, 10.32.

In addition, 0.40 g (1.08 mmol, 5%) of the *anti* adduct was recovered: $[\alpha]^{18}_{546}$ +30° (*c* 0.97, CH_2Cl_2); IR (thin film) 3480 (br), 2950, 2860, 1730, 1660, 1440, 1310, 1170, 1040, 840, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (M, 1H, C_3-*H*), 5.90 (d, J = 15.8 Hz, 1H, C_2-*H*), 5.79 (m, 1H, C_{21}-*H*), 5.00 (dd, J = 17.1, 1.6 Hz, 1H, (*Z*)-C=C*H*), 4.96 (dd, J = 10.2, 0.8 Hz, 1H, (*E*)-C=C*H*), 4.27 (s, 1H, O*H*), 3.78 (m, 2H, C_{15}-*H*, C_{17}-*H*), 3.72 (s, 3H, OCH_3), 2.46 (m, 1H, one of C_{14}-*H*), 2.27 (m, 1H, one of C_{14}-*H*), 2.06 (m, 2H, C_{20}-*H*), 1.74 (m, 1H, C_{16}-*H*), 1.57 (m, 2H, C_{18}-*H*), 1.51 (m, 1H, one of C_{19}-*H*), 1.30 (m, 1H, one of C_{19}-*H*), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.78 (d, J = 7.0 Hz, 3H, C_{16}-CH_3), 0.11 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 146.1, 138.4, 122.9, 114.7, 77.5, 72.7, 51.3, 42.1, 38.1, 33.6, 30.8, 25.8, 25.7, 17.9, 13.3, −4.4, −4.6; TLC (15% EtOAc/hexanes) R_f 0.24. Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.34. Found: 64.81; H, 10.21.

Methyl (5*S*,6*R*,7*R*)-6-Methyl-7-(*tert*-butyldimethylsiloxy)-5-(triethylsiloxy)-2,11-dodecadienoate (21b). To a cooled (−78 °C) solution of the total sample of unpurified adduct **21a** was added 4.3 mL (37 mmol) of 2,6-lutidine followed by 6.8 mL (30 mmol) of triethylsilyl trifluoromethanesulfonate. After the solution was stirred at −70 °C for 20 min, the reaction was quenched with 100 mL of saturated aqueous $NaHCO_3$ and diluted with 1 L of ether. The layers were separated, and the organic layer was washed with two 200-mL portions of 1 M aqueous $NaHSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (11 × 21 cm of silica gel, 3% EtOAc/hexanes) provided 9.36 g (19.3 mmol, 81% from **19**) of silyl ether **21b** as a colorless oil: $[\alpha]^{23}_{546}$ +2.3° (*c* 3.46, CH_2Cl_2); IR (thin film) 2960, 1735, 1660, 1460, 1435, 1255, 1100, 1035, 835, 770, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 1H, C_3-*H*), 5.83 (d, J = 15.8 Hz, 1H, C_2-*H*), 5.76 (m, 1H, C_{21}-*H*), 4.95 (m, 2H, C=CH_2), 3.89 (dt, J = 5.8, 5.5 Hz, 1H, C_{15}-*H*), 3.71 (s, 3H, OCH_3), 3.67 (dt, J = 6.0, 3.9 Hz, 1H, C_{17}-*H*), 2.43 (m, 2H, C_{14}-*H*), 2.01 (dt, J = 7.2, 7.0 Hz, 2H, C_{20}-*H*), 1.56 (m, 1H, C_{16}-*H*), 1.50–1.25 (m, 4H, C_{18}-*H*, C_{19}-*H*), 0.95 (t, J = 8.0 Hz, 9H, $SiCH_2CH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.86 (d, J = 5.0 Hz, 3H, C_{16}-CH_3), 0.59 (q, J = 8.0 Hz, 6H, $SiCH_2CH_3$), 0.03 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 146.2, 138.6, 122.9, 114.5, 72.6, 71.9, 51.3, 41.6, 38.2, 34.0, 33.8, 25.9,

24.6, 18.1, 9.5, 6.9, 5.2, -3.9, -4.5; TLC (10% EtOAc/hexanes) R_f 0.59. Anal. Calcd for $C_{26}H_{52}O_4Si_2$: C, 64.41; H, 10.81. Found: C, 64.47; H, 10.67.

Hydrogen (3*S*,1'*S*)-1-[1'-(2-Naphthyl)ethyl] 3-(*tert*-Butyldimethylsiloxy)pentanedioate (25). To a cooled (-78 °C) solution of 2.95 g (17.1 mmol) of (*S*)-1-(2'-naphthyl)ethanol (**24**) and 1.74 g (14.2 mmol) of 4-(dimethylamino)pyridine in 10 mL of CH_2Cl_2 was added a solution of 2.39 g (9.78 mmol) of 3-(*tert*-butyldimethylsiloxy)pentanedioic anhydride (**23**)[30] in 8 mL of CH_2Cl_2 *via* cannula. The resulting solution was stirred at -60 °C for 6 days and then partitioned between 125 mL of ether and 100 mL of 1 M aqueous phosphoric acid. The organic layer was washed with 50 mL of saturated aqueous $NaHCO_3$, and the combined aqueous layers were extracted with 50 mL of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting tan oil was partitioned between 40 mL of ether and 100 mL (10 mmol) of 0.1 M aqueous NaOH. The aqueous layer was acidified with 25 mL of 0.6 M aqueous HCl and extracted with three 20-mL portions of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide 3.64 g (8.73 mmol, 89%) of desired acid **25** as a light yellow oil: $[\alpha]^{20}_{546}$ -55° (*c* 0.94, CH_2Cl_2); IR (thin film) 3180 (v br), 2930, 2860, 1730, 1600, 1510, 1475, 1380, 1255, 1170, 1100, 1060, 970, 840, 780, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 4H, Np-*H*), 7.49 (m, 3H, Np-*H*), 6.07 (q, *J* = 6.6 Hz, 1H, NpC*H*), 4.58 (m, 1H, C_9-*H*), 2.64 (m, 4H, C_8-*H*, C_{10}-*H*), 1.64 (d, 3H, *J* = 6.6 Hz, NpCHCH_3), 0.81 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, one of SiCH_3), 0.02 (s, 3H, one of SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 170.1, 138.7, 133.1, 133.0, 128.4, 128.0, 127.6, 126.2, 126.0, 125.1, 124.0, 72.8, 66.0, 42.5, 42.0, 25.6, 22.2, 17.8, -4.9, -5.0; TLC (30% EtOAc/hexanes) R_f 0.06. Anal. Calcd for $C_{23}H_{32}O_5Si$: C, 66.31; H, 7.74. Found: C, 66.18; H, 7.82.

A cooled (0 °C) solution of 10.1 mg of acid **25** in 1 mL of ether was treated with an ethereal solution of diazomethane until a yellow color persisted. Analysis of this solution by gas chromatography (DB-1701 column, 235 °C) showed a 34:1 mixture of diastereomers with the major isomer at t_R = 7.3 min and the minor isomer at t_R = 7.69 min.

(*S*)-1-(2-Naphthyl)ethyl (3*S*)-5-Hydroxy-3-(*tert*-butyldimethylsiloxy)hexanoate (25a). To a cooled (0 °C) solution of 10.2 g (24.4 mmol) of acid **25** in 50 mL of THF was added 2.7 mL (28 mmol) of borane–dimethyl sulfide, and the solution was allowed to warm slowly to room temperature and stirred for 20 h. The excess borane was quenched by dropwise addition of 3 mL of water. The mixture was partitioned between 400 mL of ether and 100 mL of 1 M aqueous NaOH. The aqueous layer was extracted with 100 mL of ether, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (11 × 17 cm of silica gel, 30% EtOAc/hexanes) gave 8.69 g (21.6 mmol, 88%) of alcohol **25a** as a colorless oil: $[\alpha]^{22}_{546}$ -69° (*c* 1.07, CH_2Cl_2); IR (thin film) 3440 (br), 3060, 2940, 2860, 1740, 1510, 1470, 1360, 1255, 1165, 1060, 1020, 835, 775, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 4H, Np-*H*), 7.51 (m, 3H, Np-*H*), 6.06 (q, *J* = 6.6 Hz, 1H, NpC*H*), 4.37 (m, 1H, C_9-*H*), 3.78 (m, 1H, one of C_7-*H*), 3.72 (m, 1H, one of C_7-*H*), 2.61 (dd, *J* = 6.8, 2.7 Hz, 2H, C_{10}-*H*), 2.38 (br s, 1H, O*H*), 1.87 (m, 1H, one of C_8-*H*), 1.79 (m, 1H, one of C_8-*H*), 1.63 (d, *J* = 6.6 Hz, 3H, NpCHCH_3), 0.83 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 3H, one of SiCH_3), 0.02 (s, 3H, one of SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.7, 133.1, 133.0, 128.3, 127.9, 127.6, 126.2, 126.0, 125.1, 124.0, 72.6, 68.0, 59.5, 42.5, 38.7, 25.6, 22.1, 17.8, -4.8, -4.9; TLC (30% EtOAc/hexanes) R_f 0.21. Anal. Calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.70; H, 8.64.

(*S*)-1-(2-Naphthyl)ethyl (3*S*)-4-Formyl-3-(*tert*-butyldimethylsiloxy)pentanoate (26). To a cooled (-70 °C) solution of 3.7 mL (42 mmol) of oxalyl chloride in 130 mL of CH_2Cl_2 was added slowly 4.4 mL (62 mmol) of DMSO, and the resulting solution was stirred for 30 min. A solution of 8.39 g (20.8 mmol) of alcohol **25a** in 100 mL of CH_2Cl_2 was added *via* cannula over 30 min, and the mixture was stirred for an additional 15 min; 11.5 mL of Et_3N (82.5 mmol) was added, and the resulting slurry was stirred 15 min at -70 °C and then warmed slowly to 0 °C. The reaction was quenched with 500 mL of 1 M aqueous $NaHSO_4$ and diluted with 1 L of CH_2Cl_2. The aqueous layer was separated and extracted with 100 mL of CH_2Cl_2. The combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (8 × 16 cm of silica gel, 20% EtOAc/hexanes) gave 8.05 g (20.1 mmol, 96%) of the desired aldehyde **26** as a colorless oil: IR (thin film) 2960, 2860, 2715, 1735, 1600, 1510, 1470, 1380, 1255, 1170, 1060, 1000, 835, 775, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2 Hz, 1H, C_7-*H*), 7.84 (m, 4H, Np-*H*), 7.49 (m, 3H, Np-*H*), 6.06 (q, *J* = 6.6 Hz, 1H, NpC*H*), 4.65 (m, 1H, C_9-*H*), 2.67 (m, 2H, C_8-*H*), 2.62 (d, *J* = 6.1 Hz, 2H, C_{10}-*H*), 1.64 (d, 3H, *J* = 6.6 Hz, NpCHCH_3), 0.81 (s, 9H, SiC(CH_3)$_3$), 0.07 (s, 3H, one of SiCH_3), 0.02 (s, 3H, one of SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 169.9, 138.6, 133.1, 133.0, 128.4, 128.0, 127.6, 126.2, 126.1, 125.1, 124.0, 72.8, 64.8, 50.7, 42.6, 25.6, 22.1, 17.8, -4.8, -4.9; TLC (30% EtOAc/hexanes) R_f 0.44.

(*S*)-1-(2-Naphthyl)ethyl (3*S*,5*E*)-3-(*tert*-Butyldimethylsiloxy)-6-iodo-5-hexenoate (27). To a slurry of 159 mg (1.29 mmol) of flame-dried chromous chloride[58] in 0.5 mL of THF was added a solution of 69.5 mg (0.173 mmol) of aldehyde **26** and 126 mg (0.321 mmol) of iodoform in 3.0 mL of dioxane. The resulting brown suspension was stirred at room temperature for 7 h, then diluted with 20 mL of ether, and poured into 20 mL of water. The aqueous layer was separated, saturated with NaCl, and extracted with 20 mL of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (2 × 16 cm of silica gel, 60% CH_2Cl_2/hexanes) gave 72.4 mg (0.138 mmol, 80%) of vinyl iodide **27** as a 9:1 mixture of *E*:*Z* isomers: $[\alpha]^{23}_{546}$ -17° (*c* 0.66, CH_2Cl_2); IR (thin film) 3060, 2930, 2860, 1740, 1600, 1510, 1470, 1360, 1255, 1175, 1060, 950, 835, 775, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (m, 4H, Np-*H*), 7.49 (m, 3H, Np-*H*), 6.51 (dt, *J* = 14.4, 7.3 Hz, 1H, C_7-*H*), 6.06 (m, 2H, C_6-*H*, NpC*H*), 4.18 (m, 1H, C_9-*H*), 2.50 (m, 2H, C_{10}-*H*), 2.26 (m, 2H, C_8-*H*), 1.64 (d, 3H, *J* = 6.6 Hz, NpCHCH_3), 0.81 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, one of SiCH_3), -0.02 (s, 3H, one of SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 142.2, 138.8, 133.2, 133.0, 128.4, 128.0, 127.6, 126.2, 126.1, 125.1, 124.1, 77.5, 72.6, 68.0, 43.7, 42.4, 25.7, 22.2, 17.9, -4.6, -4.9; TLC (70% CH_2Cl_2/hexanes) R_f 0.50. Anal. Calcd for $C_{24}H_{33}IO_3Si$: C, 54.96; H, 6.34. Found: C, 54.90; H, 6.27.

(3*S*,5*E*)-3-(*tert*-Butyldimethylsiloxy)-6-iodo-5-hexenal (28). To a cooled (-78 °C) solution of 1.43 g (2.73 mmol) of **27** in 100 mL of toluene was added 2.0 mL (3.0 mmol) of DIBAl-H (1.5 M solution in toluene). After the solution was stirred for 45 min at -78 °C, the reaction was quenched with 30 mL of saturated aqueous NH_4Cl, and the solution was partitioned between 400 mL of ether and 200 mL of 1 M aqueous disodium tartrate. The organic layer was washed with 100 mL of 1 M aqueous disodium tartrate, and the combined aqueous layers were extracted with 100 mL of ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (6 × 20 cm of silica gel, 10% EtOAc/hexanes) gave 0.058 g (0.16 mmol, 6%) of (*Z*)-alkenyl aldehyde followed by 0.754 g (2.13 mmol, 78%) of desired aldehyde **28** as a 24:1 mixture of *E*:*Z* olefins: $[\alpha]^{25}_{546}$ +11° (*c* 0.79, CH_2Cl_2); IR (thin film) 3060, 2940, 2860, 2730, 1730, 1610, 1470, 1360, 1260, 1100, 1005, 950, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.9 Hz, 1H, C_{11}-*H*), 6.50 (ddd, *J* = 14.4, 7.9, 7.4 Hz, 1H, C_7-*H*), 6.10 (dt, *J* = 14.4, 1.2 Hz, 1H, C_6-*H*), 4.25 (m, 1H, C_9-*H*), 2.55 (m, 2H, C_{10}-*H*), 2.27 (m, 2H, C_8-*H*), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, one of SiCH_3), 0.05 (s, 3H, one of SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 141.8, 77.9, 66.7, 50.5, 44.0, 25.7, 17.9, -4.5, -4.8; TLC (10% EtOAc/hexanes) R_f 0.31.

(4*S*)-4-Benzyl-3-[2-(triphenylphosphonio)acetyl]-2-oxazolidinone Bromide (29). To a solution of 12.4 g (41.7 mmol) of (bromoacetyl)-oxazolidinone[59] in 125 mL of THF at room temperature was added a solution of 11.0 g (41.7 mmol) of triphenylphosphine in 75 mL of THF *via* cannula. The resulting suspension was stirred for 3.5 h and then filtered through a glass frit. The white solid was washed with hexane and dried under high vacuum to give 19.2 g (34.2 mmol, 82%) of the desired phosphonium salt **29**. This material was used without further purification but could be recrystallized from CH_2Cl_2/hexanes to provide analytically pure material: $[\alpha]^{25}_{546}$ +48° (*c* 1.58, CH_2Cl_2); $[\alpha]^{25}_{D}$ +41° (c 1.58, CH_2Cl_2); IR (mineral oil mull) 2700, 1780, 1690, 1440, 1380, 1230, 1115, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.9–7.6 (m, 15H, Ar*H*), 7.16 (m, 3H, Ar*H*), 6.97 (m, 2H, Ar*H*), 6.18 (m, 1H, one of PCH_2), 5.73 (m, 1H, one of PCH_2), 4.66 (m, 1H, BnC*H*N), 4.42 (m, 1H, one of BnCHCH_2O), 3.99 (m, 1H, one of BnCHCH_2O), 2.95 (dd, *J* = 13.4, 3.5 Hz, 1H, one of ArCH_2), 2.56 (dd, *J* = 13.4, 9.7 Hz, 1H one of ArCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (J_{C-P} = 5 Hz), 153.6, 134.9 (J_{C-P} = 2 Hz), 134.7, 133.8 (J_{C-P} = 11 Hz), 130.1 (J_{C-P} = 13 Hz), 129.1, 128.6, 127.1, 118.0 (J_{C-P} = 89 Hz), 66.7, 55.6, 37.3, 33.4 (J_{C-P} = 61 Hz);

(59) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42.

MS (FAB) *m/z* 480 (100, M^+), 329 (38), 303 (58), 289 (12), 275 (8); HR FABMS for $C_{30}H_{27}NO_3P^+$ requires *m/z* 480.1728, found *m/z* 480.1726.

(4*S*)-4-Benzyl-3-[(2*E*,5*R*,7*E*)-5-(*tert*-butyldimethylsiloxy)-8-iodo-2,7-octadienoyl]-2-oxazolidinone (30). A solution of 0.707 g (2.00 mmol) of aldehyde **28**, 2.25 g (4.02 mmol) of phosphonium salt **29**, and 0.752 g (6.16 mmol) of 4-(dimethylamino)pyridine in 8 mL of chloroform was stirred at room temperature for 4 h and then heated to reflux for 1.5 h. The resulting orange solution was cooled to room temperature and partitioned between 200 mL of CH_2Cl_2 and 200 mL of 1 M aqueous $NaHSO_4$. The organic layer was washed with brine, filtered through cotton, and concentrated *in vacuo* to provide a viscous yellow oil. Purification by flash chromatography (6 × 21 cm of silica gel, 17% EtOAc/hexanes) gave 0.932 g (1.68 mmol, 84%) of unsaturated imide **30** as a colorless oil. HPLC analysis (Zorbax column, 10% EtOAc/hexanes, 2 mL/min, $t_R(Z)$ = 6.8 min, $t_R(E)$ = 8.7 min) showed the new olefin to be a 23:1 mixture of (*E*) and (*Z*) isomers: $[\alpha]^{22}_{546}$ +63° (*c* 0.86, CH_2Cl_2); IR (thin film) 2927, 1777, 1680, 1635, 1355, 1255, 1196, 1096, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.1–7.4 (m, 7H, Ar*H*, C*H*=C*H*CO), 6.50 (dt, *J* = 14.4, 7.7 Hz, 1H, C*H*=CHI), 6.09 (dt, *J* = 14.4, 1.1 Hz, 1H, CH=C*H*I), 4.73 (m, 1H, BnC*H*N), 4.19 (m, 2H, BnCHCH_2O), 3.88 (m, 1H, C*H*OSi), 3.33 (dd, *J* = 13.4, 3.2 Hz, 1H, one of ArCH_2), 2.80 (dd, *J* = 13.4, 9.6 Hz, 1H one of ArCH_2), 2.46 (m, 2H, CH_2CH=CHCO), 2.23 (m, 2H, CH_2CH=CHI), 0.90 (s, 9H, SiCCH_3), 0.07 (s, 6H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 153.4, 147.3, 142.5, 135.3, 129.4, 128.9, 127.3, 122.7, 77.5, 70.1, 66.1, 55.3, 43.7, 40.3, 37.8, 25.8, 18.0, –4.5, –4.6; TLC (30% EtOAc/hexanes) R_f 0.45. Anal. Calcd for $C_{24}H_{34}INO_4Si$: C, 51.89; H, 6.17. Found: C, 52.04; H, 6.16.

(4*S*)-4-Benzyl-3-[(2*E*,5*S*,7*E*,9*E*)-5-(*tert*-butyldimethylsiloxy)-10-[(4*R*,6*S*,7*R*,8*R*,12*R*)-12-ethyl-7-methyl-2-oxo-6-(triethylsiloxy)-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-2,7,9-decatrienoyl]-2-oxazolidinone (33). To a solution of 1.45 g (1.72 mmol) of vinylstannane **13** in 8.0 mL of *N*-methylpyrrolidinone (NMP) at 45 °C were added 0.06 mL (0.3 mmol) of diisopropylethylamine and 97.1 mg (0.530 mmol) of cadmium chloride. The reaction was protected from light, and a solution of 1.09 g (1.96 mmol) of vinyl iodide **30** in 10.0 mL of NMP was added *via* syringe pump over 42 h. Simultaneously, 53.8 mg (.0520 mmol) of tris(dibenzylideneacetone)dipalladium(0)–chloroform complex[37] in a total of 8.0 mL of CH_2Cl_2 was added in eight sequential 1-mL portions *via* a second syringe pump over 47 h. After the addition was complete, more catalyst (9.6 mg, .0093 mmol) was added and the solution stirred an additional 6 h. The resulting solution was partitioned between 300 mL of 1:1 ether:hexanes and 100 mL of 10% aqueous $CuSO_4$. The organic layer was washed with 100 mL of 1 M aqueous $NaHSO_4$ and brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (7 × 23 cm of silica gel, 12% EtOAc/hexanes) gave 1.16 g (1.19 mmol, 69%) of desired triene **33** as a colorless oil: $[\alpha]^{22}_{546}$ +39° (*c* 0.72, CH_2Cl_2); IR (thin film) 2950, 2870, 1785, 1730, 1685, 1635, 1455, 1350, 1245, 1190, 1090, 1000, 880, 830, 770, 740, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.20 (m, 7H, Ar-*H*, C_{11}-*H*, C_{12}-*H*), 6.05 (m, 2H, C_5-*H*, C_6-*H*), 5.83 (m, 1H, C_4-*H*), 5.58 (m, 1H, C_7-*H*), 4.81 (m, 1H, C_{21}-*H*), 4.73 (m, 1H, BnC*H*N), 4.17 (m, 2H, CH_2O), 3.83 (m, 3H, C_9-*H*, C_{15}-*H*, C_{17}-*H*), 3.33 (dd, *J* = 13.4, 3.2 Hz, 1H, one of ArCH_2), 2.80 (dd, *J* = 13.4, 9.6 Hz, 1H, one of ArCH_2), 2.66 (m, 2H, C_2-*H*), 2.42 (m, 3H, C_3-*H*, C_{10}-*H*), 2.26 (m, 2H, C_8-*H*), 1.85 (m, 1H, C_{16}-*H*), 1.73–1.51 (m, 9H, one of C_{14}-*H*, C_{18}-*H*, C_{19}-*H*, C_{20}-*H*, C_{22}-*H*), 1.30 (m, 1H, one of C_{14}-*H*), 1.07 (s, 21H, SiC*H*(CH_3)$_2$), 0.97 (t, *J* = 7.9 Hz, 9H, $SiCH_2CH_3$), 0.93 (d, *J* = 6.8 Hz, 3H, C_{16}-CH_3), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.86 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.59 (q, *J* = 7.9 Hz, 6H, Si$CH_2$$CH_3$), 0.06 (s, 6H, SiC$H_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 164.8, 153.3, 148.5, 136.5, 135.4, 133.1, 129.5, 128.9, 128.2, 127.3, 122.3, 73.5, 71.5, 70.0, 66.1, 55.3, 46.0, 43.2, 40.8, 40.1, 38.9, 37.9, 36.8, 35.8, 32.1, 28.1, 25.8, 18.8, 18.3, 18.3, 18.1, 13.1, 11.3, 9.6, 7.1, 5.8, –4.5, –4.6; TLC (20% EtOAc/hexane) R_f 0.35. Anal. Calcd for $C_{55}H_{95}NO_8Si_3$: C, 67.23; H, 9.75. Found: C, 67.24; H, 9.71.

(4*S*)-4-Benzyl-3-[[(2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-(*tert*-butyldimethylsiloxy)-5-[(4*R*,6*S*,7*R*,8*R*,12*R*)-12-ethyl-7-methyl-2-oxo-6-(triethylsiloxy)-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indanyl]-carbonyl]-2-oxazolidinone (34). To a cooled (–78 °C) solution of 1.10 g (1.12 mmol) of triene **33** in 100 mL of CH_2Cl_2 was added dropwise 0.47 mL (5.1 mmol) of dimethylaluminum chloride. The resulting bright yellow solution was warmed to 0 °C, stirred for 1 h, then warmed slowly to room temperature, and stirred for 1 h. The solution was cooled to 0 °C and then transferred *via* cannula into 200 mL of vigorously stirred 1 M aqueous tartaric acid at 0 °C along with 100 mL of CH_2Cl_2 rinse. The layers were separated, and the aqueous layer was washed with two 50-mL portions of CH_2Cl_2. The combined organics were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification by flash chromatography (7 × 22 cm of silica gel, 9% EtOAc/hexanes) gave 779 mg (0.792 mmol, 71%) of desired cycloadduct **34** as a colorless oil: $[\alpha]^{21}_{546}$ +77° (*c* 0.53, CH_2Cl_2); IR (thin film) 2960, 2870, 1790, 1730, 1700, 1460, 1385, 1350, 1250, 1175, 1100, 1050, 840, 740, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H, Ar-*H*), 5.98 (m, 1H, C_6-*H*), 5.78 (m, 1H, C_5-*H*), 4.85 (m, 1H, C_{21}-*H*), 4.67 (m, 1H, BnC*H*N), 4.38 (m, 1H, C_9-*H*), 4.14 (m, 2H, CH_2O), 3.97 (dd, *J* = 11.2, 7.1 Hz, 1H, C_{12}-*H*), 3.77 (m, 2H, C_{15}-*H*, one of ArCH_2), 3.70 (m, 1H, C_{17}-*H*), 3.17 (m, 1H, C_4-*H*), 2.84 (dd, *J* = 15.1, 4.3 Hz, 1H, one of C_2-*H*), 2.58 (dd, *J* = 12.7, 11.7 Hz, 1H, one of ArCH_2), 2.35 (m, 2H, one of C_2-*H*, C_{14}-*H*), 2.28 (m, 1H, C_7-*H*), 2.11 (m, 1H, C_3-*H*), 1.77 (m, 2H, one of C_8-*H*, one of C_{20}-*H*), 1.73–1.35 (m, 12H, one of C_8-*H*, one of C_{10}-*H*, C_{11}-*H*, one of C_{14}-*H*, C_{16}-*H*, C_{18}-*H*, C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*), 1.13 (m, 1H, one of C_{10}-*H*), 1.04 (s, 21H, SiC*H*(CH_3)$_2$), 0.94 (m, 12H, $SiCH_2CH_3$, C_{16}-CH_3), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.83 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.58 (m, 6H, $SiCH_2CH_3$), 0.03 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 173.6, 172.8, 153.0, 136.0, 131.2, 129.2, 129.0, 128.0, 127.3, 74.5, 72.8, 72.2, 66.3, 55.9, 48.0, 44.7, 43.5, 41.9, 41.5, 41.1, 40.5, 38.7, 37.8, 35.9, 35.1, 32.6, 28.1, 25.9, 18.3, 18.3, 18.1, 17.6, 13.0, 10.7, 9.8, 7.1, 5.8, –4.7, –4.8; TLC (20% EtOAc/hexanes) R_f 0.55. Anal. Calcd for $C_{55}H_{95}NO_8Si_3$: C, 67.23; H, 9.75. Found: C, 67.10; H, 9.96.

***S*-Ethyl (2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-(*tert*-Butyldimethylsiloxy)-5-[(4*R*,6*S*,7*R*,8*R*,12*R*)-12-ethyl-7-methyl-2-oxo-6-(triethylsiloxy)-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indancarbothioate (35).** To a cooled (–78 °C) solution of 0.20 mL (2.7 mmol) of ethanethiol in 10 mL of THF was added 1.3 mL (2.0 mmol) of *n*-BuLi (1.5 M solution in hexanes), and the resulting white suspension was warmed to 0 °C. To this mixture was added a solution of 779 mg (0.793 mmol) of imide **34** in 10 mL of THF *via* cannula along with three 5-mL portions of THF wash. The reaction mixture was stirred for 10 min at 0 °C where it slowly cleared; then the solution was warmed to room temperature and stirred for 1.3 h. The solution was partitioned between 150 mL of ether and 40 mL of 1 M aqueous NaOH solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (6 × 18 cm of silica gel, 5% ether/hexanes to 70% EtOAc/hexanes) gave 666 mg (0.768 mmol, 97%) of thioester **35** as a colorless oil followed by 125 mg (0.707 mmol, 89%) of recovered oxazolidinone. Analytical data for thioester **35**: $[\alpha]^{24}_{546}$ +52° (*c* 0.98, CH_2Cl_2); IR (thin film) 2950, 2860, 1730, 1690, 1460, 1380, 1250, 1150, 1100, 1040, 1000, 960, 890, 830, 770, 730, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (m, 1H, C_6-*H*), 5.73 (m, 1H, C_5-*H*), 4.85 (m, 1H, C_{21}-*H*), 4.35 (m, 1H, C_9-*H*), 3.79 (m, 1H, C_{15}-*H*), 3.71 (m, 1H, C_{17}-*H*), 3.02 (dd, *J* = 11.2, 7.6 Hz, 1H, C_{12}-*H*), 2.94 (m, 1H, one of SCH_2), 2.83 (m, 2H, C_4-*H*, one of SCH_2), 2.74 (dd, *J* = 14.7, 4.9 Hz, 1H, one of C_2-*H*), 2.31 (m, 2H, one of C_2-*H*, C_8-*H*), 2.21 (m, 1H, C_7-*H*), 2.14 (m, 1H, C_3-*H*), 1.84 (m, 1H, one of C_{20}-*H*), 1.76 (m, 1H, one of C_8-*H*), 1.71 (m, 2H, one of C_{14}-*H*, one of C_{18}-*H*), 1.61–1.45 (m, 8H, one of C_{10}-*H*, C_{11}-*H*, one of C_{14}-*H*, C_{16}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, C_{22}-*H*), 1.29 (m, 4H, one of C_{20}-*H*, SCH_2CH_3), 1.13 (m, 2H, one of C_{10}-*H*, one of C_{19}-*H*), 1.05 (s, 21H, SiC*H*(CH_3)$_2$), 0.97 (t, *J* = 8.0 Hz, 9H, $SciCH_2CH_3$), 0.92 (d, *J* = 6.9 Hz, 3H, C_{16}-CH_3), 0.89 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.61 (m, 6H, $SiCH_2CH_3$), 0.02 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 172.9, 131.5, 127.7, 76.9, 74.8, 72.4, 72.3, 58.1, 44.9, 43.4, 43.4, 43.1, 41.8, 40.6, 40.4, 37.4, 35.4, 35.0, 32.8, 28.1, 25.9, 23.4, 18.3, 18.3, 18.1, 17.7, 14.6, 13.0, 10.7, 9.6, 7.2, 5.9, –4.7, –4.8; TLC (5% ether/hexanes) R_f 0.37. Anal. Calcd for $C_{47}H_{90}O_6SSi_3$: C, 65.07; H, 10.46. Found: C, 65.19; H, 10.51.

***S*-Ethyl (2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-Hydroxy-5-[(4*R*,6*S*,7*R*,8*R*,12*R*)-12-ethyl-6-hydroxy-7-methyl-2-oxo-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indancarbothioate (35a).** To a solution of 660 mg (0.761 mmol) of thioester **35** in 30 mL of THF at room temperature were added 40 mL of glacial acetic acid and 13 mL of water, giving a cloudy solution which cleared over the course of the reaction. The solution was stirred for 17 h at room temperature and then diluted with 300 mL of ether and 150 mL of 1 M aqueous K_2CO_3 solution. Anhydrous K_2CO_3 was then added cautiously until gas evolution ceased. The aqueous layer was separated and extracted with 200 mL of ether, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This material was taken on directly to the next step but could be purified by flash chromatography on silica

gel (40% EtOAc/hexanes) to give analytically pure diol **35a** as a colorless oil: $[\alpha]^{25}_{546}$ +84° (*c* 1.10, CH_2Cl_2); IR (thin film) 3440, 2940, 2870, 1730, 1690, 1460, 1380, 1240, 1100, 1000, 955, 880, 815, 760, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (m, 1H, C_6-*H*), 5.75 (m, 1H, C_5-*H*), 4.79 (m, 1H, C_{21}-*H*), 4.45 (m, 1H, C_9-*H*), 3.80 (m, 1H, C_{15}-*H*), 3.67 (m, 1H, C_{17}-*H*), 3.04 (dd, *J* = 12.7, 5.3 Hz, 1H, C_{12}-*H*), 2.95 (m, 1H, one of SCH_2), 2.88 (m, 2H, C_4-*H*, one of SCH_2), 2.64 (dd, *J* = 14.0, 3.6 Hz, 1H, one of C_2-*H*), 2.43 (m, 1H, one of C_8-*H*), 2.24 (m, 3H, one of C_2-*H*, C_3-*H*, C_7-*H*), 1.81 (m, 1H, one of C_8-*H*), 1.72 (m, 1H, one of C_{20}-*H*), 1.69 (m, 1H, one of C_{18}-*H*), 1.67 (m, 1H, one of C_{14}-*H*), 1.64–1.48 (m, 10H, two O*H*, one of C_{10}-*H*, C_{11}-*H*, one of C_{14}-*H*, C_{16}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, C_{22}-*H*), 1.40 (m, 1H, one of C_{20}-*H*), 1.30 (dt, *J* = 7.3, 0.8 Hz, 3H, SCH_2CH_3), 1.26 (m, 1H, one of C_{19}-*H*), 1.07 (m, 1H, one of C_{10}-*H*), 1.05 (s, 21H, $SiCH(CH_3)_2$), 0.92 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 0.88 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 172.7, 130.8, 127.5, 76.8, 76.0, 73.8, 71.9, 58.1, 43.3, 43.2, 42.3, 41.8, 41.1, 40.3, 39.6, 37.5, 35.0, 34.1, 32.0, 27.7, 23.4, 19.2, 18.3, 18.2, 14.9, 12.9, 10.3, 9.7; TLC (40% EtOAc/hexanes) R_f 0.30. Anal. Calcd for $C_{35}H_{62}O_6SSi$: C, 65.78; H, 9.78. Found: C, 65.69; H, 9.61.

***S*-Ethyl (2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-(*tert*-Butyldimethylsiloxy)-5-[(4*R*,6*S*,7*R*,8*R*,12*R*)-12-ethyl-6-hydroxy-7-methyl-2-oxo-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indancarbothioate (35b).** A mixture of the total sample of unpurified diol **35a** (~0.76 mmol), 298 mg (1.98 mmol) of *tert*-butyldimethylsilyl chloride, and 156 mg (2.29 mmol) of imidazole was dissolved in 15 mL of CH_2Cl_2. A white suspension quickly formed, which was stirred at room temperature for 12.5 h and then quenched with 0.5 mL of methanol. After being stirred for 5 min, the reaction mixture was partitioned between 150 mL of CH_2Cl_2 and 50 mL of 1 M aqueous $NaHSO_4$. The aqueous layer was extracted with 50 mL of CH_2Cl_2, and the combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification by flash chromatography (4 × 16 cm of silica gel, 20% ether/hexanes) gave 559 mg (0.742 mmol, 98% from thioester **35**) of desired alcohol **35b** as a white foam: $[\alpha]^{24}_{546}$ +82° (*c* 0.74, CH_2Cl_2); IR (thin film) 3530, 2960, 2860, 1730, 1690, 1460, 1380, 1250, 1100, 1050, 1000, 965, 880, 830, 770, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (m, 1H, C_6-*H*), 5.70 (m, 1H, C_5-*H*), 4.79 (m, 1H, C_{21}-*H*), 4.35 (m, 1H, C_9-*H*), 3.80 (m, 1H, C_{15}-*H*), 3.66 (m, 1H, C_{17}-*H*), 3.00 (m, 2H, C_{12}-*H*, one of SCH_2), 2.89 (m, 1H, C_4-*H*), 2.86 (m, 1H, one of SCH_2), 2.63 (dd, *J* = 13.9, 3.5 Hz, 1H, one of C_2-*H*), 2.31 (m, 1H, one of C_8-*H*), 2.22 (m, 3H, one of C_2-*H*, C_3-*H*, C_7-*H*), 1.75 (m, 1H, one of C_8-*H*), 1.71 (m, 1H, one of C_{20}-*H*), 1.66 (m, 1H, one of C_{18}-*H*), 1.65 (m, 1H, one of C_{14}-*H*), 1.62–1.35 (m, 9H, one of C_{10}-*H*, C_{11}-*H*, one of C_{14}-*H*, C_{16}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*), 1.31 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.25 (m, 1H, one of C_{19}-*H*), 1.08 (m, 1H, one of C_{10}-*H*), 1.05 (s, 21H, $SiCH(CH_3)_2$), 0.92 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 0.88 (t, *J* = 7.4 Hz, 3H, C_{23}-*H*), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 172.7, 131.3, 127.1, 76.0, 73.9, 72.2, 58.1, 43.3, 41.9, 41.8, 41.1, 40.4, 40.3, 37.6, 35.1, 34.1, 32.0, 27.6, 25.9, 23.3, 19.2, 18.3, 18.2, 18.1, 14.9, 12.9, 10.2, 9.7, –4.7, –4.8; TLC (20% ether/hexanes) R_f 0.24. Anal. Calcd for $C_{41}H_{76}O_6SSi_2$: C, 65.37; H, 10.17. Found: C, 65.55; H, 10.13.

***S*-Ethyl (2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-(*tert*-Butyldimethylsiloxy)-5-[(4*R*,7*S*,8*R*,12*R*)-2,6-dioxo-12-ethyl-7-methyl-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indancarbothioate (36).** To a cooled (–78 °C) solution of 0.19 mL (2.2 mmol) of oxalyl chloride in 25 mL of CH_2Cl_2 was added 0.26 mL (3.7 mmol) of DMSO, and the resulting solution was stirred for 10 min. A solution of 556 mg (0.738 mmol) of alcohol **35b** in 10 mL of CH_2Cl_2 was added dropwise *via* cannula along with 5 mL of CH_2Cl_2 wash, and the mixture was stirred for 1 h at –78 °C. Et_3N (1.1 mL, 7.9 mmol) was then added, and the resulting solution was stirred for 15 min at –78 °C, then warmed slowly to 0 °C, and stirred for 30 min. The reaction was quenched with 75 mL of 1 M aqueous $NaHSO_4$ and was diluted with 100 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with 30 mL of CH_2Cl_2. The combined organic extracts were washed with brine, filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (4 × 19 cm of silica gel, 10% ether/hexanes) gave 509 mg (0.678 mmol, 92%) of ketone **36** as a viscous oil: $[\alpha]^{24}_{546}$ +87° (*c* 1.03, CH_2Cl_2); IR (thin film) 2940, 2870, 1730, 1690, 1460, 1370, 1300, 1260, 1100, 1040, 970, 935, 890, 835, 775, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (m, 1H, C_6-*H*), 5.56 (m, 1H, C_5-*H*), 4.74 (m, 1H, C_{21}-*H*), 4.33 (m, 1H, C_9-*H*), 3.82 (m, 1H, C_{17}-*H*), 3.07 (m, 2H, one of C_{14}-*H*, one of SCH_2), 3.03 (m, 1H, C_4-*H*), 2.75 (m, 2H, C_{12}-*H*, one of SCH_2), 2.68 (m, 1H, C_3-*H*), 2.59 (m, 2H, one of C_2-*H*, C_{16}-*H*), 2.51 (dd, *J* = 19.3, 3.3 Hz, 1H, one of C_{14}-*H*), 2.29 (m, 1H, one of C_{10}-*H*), 2.16 (m, 1H, C_7-*H*), 2.08 (dd, *J* = 14.0, 8.9 Hz, 1H, one of C_2-*H*), 1.75 (m, 1H, one of C_8-*H*), 1.61–1.39 (m, 8H, one of C_{10}-*H*, C_{11}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, C_{20}-*H*, C_{22}-*H*), 1.31 (m, 5H, one of C_{18}-*H*, one of C_{19}-*H*, SCH_2CH_3), 1.11 (d, *J* = 6.9 Hz, 3H, C_{16}-CH_3), 1.09 (m, 1H, one of C_{10}-*H*), 1.05 (s, 21H, $SiCH(CH_3)_2$), 0.86 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 200.6, 172.7, 132.3, 125.6, 75.0, 74.8, 72.2, 57.9, 53.6, 46.6, 42.2, 41.6, 40.8, 40.4, 40.4, 37.3, 37.1, 32.0, 31.8, 27.6, 25.9, 23.6, 20.0, 18.2, 18.2, 18.1, 16.1, 14.8, 12.8, 9.4, –4.8, –4.8; TLC (20% ether/hexanes) R_f 0.48. Anal. Calcd for $C_{41}H_{74}O_6SSi_2$: C, 65.55; H, 9.93. Found: C, 65.51; H, 9.81.

(2*S*,3a*S*,4*R*,5*S*,7a*R*)-2-(*tert*-Butyldimethylsiloxy)-5-[(4*R*,7*S*,8*R*,12*R*)-2,6-dioxo-12-ethyl-7-methyl-8-(triisopropylsiloxy)-1-oxacyclododec-4-yl]-3a,4,5,7a-tetrahydro-4-indanal (37). To a vigorously stirred, room temperature mixture of 381 mg, 0.507 mmol) of thioester **36** and 3.39 g of Lindlar's catalyst (5% Pd/$CaCO_3$/PdO, 1.59 mmol of Pd) in 25 mL of acetone was added 1.2 mL (7.5 mmol) of triethylsilane dropwise *via* syringe pump over 1 h. The mixture was then filtered through Celite and washed with seven 20-mL portions of acetone. The filtrate was concentrated *in vacuo* and placed under high vacuum (5 mTorr) for 36 h to remove the volatile byproducts. The residue crystallized from hexane to give 373 mg of white crystals which were sufficiently pure for use in the next reaction. On a smaller scale (19.2 mg of thioester **36**, 0.0256 mmol), purification by flash chromatography was accompanied by some epimerization at the C_{12} center to provide a 96% yield (17.1 mg, 0.0247 mmol) of the desired aldehyde **37**: $[\alpha]^{23}_{546}$ +53° (*c* 0.85, CH_2Cl_2); IR (thin film) 2940, 2870, 2610, 1730, 1460, 1370, 1255, 1160, 1110, 1050, 965, 880, 835, 775, 680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (d, *J* = 1.6 Hz, 1H, C_{13}-*H*), 6.01 (m, 1H, C_6-*H*), 5.57 (m, 1H, C_5-*H*), 4.73 (m, 1H, C_{21}-*H*), 4.37 (m, 1H, C_9-*H*), 3.82 (m, 1H, C_{17}-*H*), 3.12 (m, 1H, C_4-*H*), 2.86 (ddd, *J* = 11.6, 7.8, 1.6 Hz, 1*H*, C_{12}-*H*), 2.60 (m, 4H, C_3-*H*, C_{14}-*H*, C_{16}-*H*), 2.54 (m, 1H, one of C_{10}-*H*), 2.43 (dd, *J* = 14.1, 1.8 Hz, 1H, one of C_2-*H*), 2.15 (m, 2H, one of C_2-*H*, C_7-*H*), 1.76 (m, 1H, one of C_8-*H*), 1.63–1.36 (m, 8H, one of C_8-*H*, C_{11}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, C_{20}-*H*, C_{22}-*H*), 1.25 (m, 2H, one of C_{18}-*H*, one of C_{19}-*H*), 1.12 (d, *J* = 6.8 Hz, 3H, C_{16}-CH_3), 1.06 (s, 21H, $SiCH(CH_3)_2$), 1.03 (m, 1H, one of C_{10}-*H*), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.83 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.02 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 203.5, 172.1, 132.7, 124.9, 75.4, 74.9, 72.3, 56.3, 53.7, 46.8, 41.8, 40.6, 40.0, 39.9, 38.8, 37.3, 37.0, 32.1, 31.9, 27.4, 25.9, 20.0, 18.2, 18.1, 16.0, 12.8, 9.6, –4.8, –4.8; mp 123–124 °C; TLC (10% EtOAc/hexanes) R_f 0.41.

(2*S*,3a*R*,5a*R*,5b*R*,9*R*,13*R*,14*S*,15a*S*,16*R*,16a*R*,16b*S*)-2-(*tert*-Butyldimethylsiloxy)-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,15a,16,16a,16b-hexadecahydro-16-hydroxy-14-methyl-13-(triisopropylsiloxy)-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione (38). To a cooled (–78 °C) solution of 2.6 mL (2.6 mmol) of sodium hexamethyldisilazide (1 M solution in THF) in 30 mL of THF was added 373 mg (~0.507 mmol) of unpurified keto aldehyde **37** in 15 mL of THF *via* cannula along with two 2-mL portions of THF wash. The resulting solution was stirred at –78 °C for 20 min, then quenched with 100 mL of saturated aqueous NH_4Cl, and diluted with 200 mL of ether. The organic layer was separated and washed with 75 mL of 5% aqueous HCl. The combined aqueous layers were extracted with 50 mL of ether, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 381 mg of a white foam. This material was used directly in the next reaction but could be purification by flash chromatography on silica gel (10% EtOAc/hexanes) to provide two analytically pure aldol adducts in a 12:1 ratio. Major adduct **38** had the following characteristics: $[\alpha]^{23}_{546}$ +33° (*c* 0.36, CH_2Cl_2); IR (thin film) 3510, 2940, 2860, 1730, 1460, 1385, 1370, 1250, 1110, 1055, 880, 835, 770, 670 cm^{-1}; ^1H NMR (500 MHz, 1:1 $C_6D_6/CDCl_3$) δ 5.89 (m, 1H, C_6-*H*), 5.70 (m, 1H, C_5-*H*), 4.82 (m, 1H, C_{21}-*H*), 4.35 (m, 2H, C_9-*H*), C_{13}-*H*), 4.11 (m, 1H, C_{17}-*H*), 3.01 (m, 1H, C_4-*H*), 2.93 (dd, *J* = 11.9, 5.2 Hz, 1H, C_{14}-*H*), 2.89 (dq, *J* = 8.9, 6.9 Hz, 1H, C_{16}-*H*), 2.54 (dd, *J* = 14.3, 5.2 Hz, 1H, one of C_2-*H*), 2.43 (dd, *J* = 14.3, 3.1 Hz, 1H, one of C_2-*H*), 2.35 (m, 1H, C_3-*H*), 2.31 (m, 1H, one of C_{10}-*H*), 2.25 (m, 2H, C_7-*H*, C_{12}-*H*), 1.84 (m, 1H, one of C_8-*H*), 1.75 (m, 2H, one of C_{18}-*H*, one of C_{19}-*H*), 1.66 (m, 1H, one of C_{20}-*H*), 1.52 (m, 2H, one of C_{18}-*H*, one of C_{22}-*H*), 1.41 (m, 2H, one of C_8-*H*, one of C_{20}-*H*), 1.29–1.12 (m, 4H, one of C_{10}-*H*, C_{11}-*H*, one of C_{19}-*H*, one of C_{20}-*H*), 1.25 (d, *J* = 6.8 Hz, 3H, C_{16}-CH_3), 1.12 (s, 21H, $SiCH(CH_3)_2$), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.81 (t, *J* = 7.6 Hz, 3H, C_{23}-*H*), 0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 172.2, 131.5, 128.1, 74.3, 74.1, 73.0, 62.7, 51.9, 48.2, 42.3, 40.8, 40.7, 40.4, 40.0, 36.5, 32.9, 31.3, 28.1, 25.9, 19.5, 18.3, 18.2, 17.7, 16.0, 12.9, 12.3, 9.4, 6.0, –4.7, –4.7; MS (Na^+ FAB) *m/z* 713

(53, M + Na), 647 (13), 517 (9), 387 (14), 269 (100), 255 (41), 243 (32), 213 (87); TLC (10% EtOAc/hexanes) R_f 0.27.

(2*S*,3a*R*,5a*S*,5b*R*,9*R*,13*R*,14*S*,16a*R*,16b*S*)-2-(*tert*-Butyldimethylsiloxy)-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-13-(triisopropylsiloxy)-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione (39). To a cooled (0 °C) solution of the total sample of unpurified aldol adduct **38** in 20 mL of CH_2Cl_2 was added a solution of 1.36 g (2.02 mmol) of Martin sulfurane[43,58] in 10 mL of CH_2Cl_2 *via* cannula. The resulting solution was stirred for 45 min at 0 °C, then quenched with 20 mL of saturated aqueous $NaHCO_3$, and diluted with 60 mL of CH_2Cl_2. The organic layer was separated, filtered through cotton, and concentrated *in vacuo*. Purification by flash chromatography (4 × 23 cm of silica gel, 4% ether/hexanes) gave 276 mg (0.410 mmol, 81% from thioester **36**) on the desired unsaturated ketone **39** as a viscous oil: $[\alpha]^{24}_{546}$ +89° (*c* 0.87, CH_2Cl_2); IR (thin film) 2950, 2870, 1730, 1710, 1670, 1615, 1460, 1370, 1255, 1150, 1100, 1055, 880, 835, 775, 705, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H, C_{13}-*H*), 5.86 (m, 1H, C_6-*H*), 5.76 (m, 1H, C_5-*H*), 4.65 (m, 1H, C_{21}-*H*), 4.35 (m, 1H, C_9-*H*), 4.05 (m, 1H, C_{17}-*H*), 3.47 (m, 1H, C_4-*H*), 3.22 (m, 1H, C_{16}-*H*), 3.08 (dd, *J* = 13.2, 5.0 Hz, 1H, one of C_2-*H*), 3.02 (m, 1H, C_3-*H*), 2.89 (m, 1H, C_{12}-*H*), 2.41 (dd, *J* = 13.2, 3.0 Hz, 1H, one of C_2-*H*), 2.24 (m, 2H, C_7-*H*, one of C_{10}-*H*), 1.82 (m, 1H, one of C_8-*H*), 1.67 (m, 2H, one of C_{18}-*H*, C_{20}-*H*), 1.59–1.33 (m, 6H, one of C_8-*H*, one of C_{18}-*H*, one of C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*), 1.27 (m, 1H, one of C_{10}-*H*), 1.24 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 1.08 (s, 21H, $SiCH(CH_3)_2$), 1.04 (m, 1H, one of C_{19}-*H*), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.86 (m, 1H, C_{11}-*H*), 0.82 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*), 0.03 (s, 6H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 172.5, 147.9, 143.3, 129.9, 128.8, 75.7, 74.5, 72.6, 49.6, 48.7, 47.7, 46.8, 41.5, 41.1, 40.8, 36.7, 34.7, 31.2, 27.9, 25.9, 19.4, 18.4, 18.3, 18.2, 18.1, 12.9, 9.4, –4.7; TLC (10% EtOAc/hexanes) R_f 0.48. Anal. Calcd for $C_{39}H_{68}O_5Si_2$: C, 69.59; H, 10.18. Found: C, 69.73; H, 10.08.

(+)-A83543A Aglycon (43). To a solution of 14.3 mg (0.0212 mmol) of protected aglycon **39** in 3 mL of acetonitrile and 2 mL of THF at room temperature was added 0.5 mL of hydrofluoric acid (48% aqueous solution). The resulting solution was stirred for 24 h and then partitioned between 30 mL of EtOAc and 15 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 10 mL of EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (2 × 17 cm of silica gel, 90% EtOAc/hexanes) gave 7.8 mg (0.019 mmol, 91%) of aglycon **43** as a viscous oil which gave white crystals on slow evaporation from ether/hexanes: $[\alpha]^{22}_{546}$ +150° (*c* 0.18, chloroform); $[\alpha]^{22}_{D}$ +131° (*c* 0.18, chloroform); IR (thin film) 3400, 2930, 2880, 1720, 1660, 1610, 1460, 1440, 1370, 1260, 1165, 1010, 905, 880, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H, C_{13}-*H*), 5.88 (m, 1H, C_6-*H*), 5.81 (m, 1H, C_5-*H*), 4.70 (m, 1H, C_{21}-*H*), 4.44 (m, 1H, C_9-*H*), 3.68 (m, 1H, C_{17}-*H*), 3.48 (m, 1H, C_4-*H*), 3.21 (m, 1H, C_{16}-*H*), 3.12 (dd, *J* = 13.6, 5.0 Hz, 1H, one of C_2-*H*), 3.02 (m, 1H, C_3-*H*), 2.90 (m, 1H, C_{12}-*H*), 2.42 (dd, *J* = 13.6, 3.2 Hz, 1H, one of C_2-*H*), 2.35 (m, 1H, one of C_{10}-*H*), 2.27 (m, 1H, C_7-*H*), 1.86 (m, 1H, one of C_8-*H*), 1.68–1.42 (m, 10H, one of C_8-*H*, C_9-O*H*, C_{17}-O*H*, C_{18}-*H*, one of C_{19}-*H*, C_{20}-*H*, C_{22}-*H*), 1.27 (m, 2H, one of C_{10}-*H*, one of C_{19}-*H*), 1.21 (d, *J* = 6.8 Hz, 3H, C_{16}-CH_3), 0.96 (m, 1H, C_{11}-*H*), 0.82 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 172.7, 147.6, 144.3, 129.4, 128.7, 76.9, 72.7, 72.3, 49.5, 48.1, 47.6, 46.6, 41.5, 41.1, 40.6, 39.9, 34.9, 34.0, 30.0, 28.4, 21.6, 15.7, 9.4; TLC (80% EtOAc/hexanes) R_f 0.19. MS (Na^+ FAB) *m/z* 425 (62, M + Na), 403 (21), 327 (38), 281 (97), 221 (100), 219 (89), 207 (100); HR FABMS for $C_{24}H_{34}NaO_5$ requires *m/z* 425.2302, found *m/z* 425.2296.

(2*S*,3a*R*,5a*S*,5b*R*,9*R*,13*R*,14*S*,16a*R*,16b*S*)-9-Ethyl-2-hydroxy-2,3,3a,-5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-13-(triisopropylsiloxy)-1*H*-*as*-indaceno[3,2-*d*]oxacyclododecin-7,15-dione (50). To a solution of 230 mg (0.342 mmol) of TBS ether **39** in 9 mL of THF at room temperature was added 9 mL of glacial acetic acid followed by 3 mL of water. The resulting solution was stirred for 21 h, then diluted with 50 mL of ether, and quenched with 10 mL of 1 M aqueous K_2CO_3. Anhydrous K_2CO_3 was then added cautiously until gas evolution ceased, and water was added periodically to dissolved precipitated solids. An additional 100 mL of ether was added, and the layers were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3 × 21 cm of silica gel, 30% EtOAc/hexanes) gave 12 mg (0.018 mmol, 5%) of recovered starting material **39** followed by 167 mg (0.299 mmol, 87%) of desired alcohol **50**: $[\alpha]^{20}_{546}$ +81° (*c* 0.89, CH_2Cl_2); IR (thin film) 3420 (br), 2940, 2870, 1725, 1660, 1610, 1455, 1365, 1230, 1095, 1000, 880, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H, C_{13}-*H*), 5.87 (d, *J* = 9.8 Hz, 1H, C_6-*H*), 5.76 (dt, *J* = 9.8, 2.8 Hz, 1H, C_5-*H*), 4.65 (m, 1H, C_{21}-*H*), 4.44 (m, 1H, C_9-*H*), 4.05 (m, 1H, C_{17}-*H*), 3.49 (m, 1H, C_4-*H*), 3.22 (m, 1H, C_{16}-*H*), 3.08 (dd, *J* = 13.1, 5.0 Hz, 1H, one of C_2-*H*), 3.04 (m, 1H, C_3-*H*), 2.90 (m, 1H, C_{12}-*H*), 2.42 (dd, *J* = 13.1, 2.9 Hz, 1H, one of C_2-*H*), 2.35 (dt, *J* = 12.9, 7.0 Hz, 1H, one of C_{10}-*H*), 2.26 (m, 1H, C_7-*H*), 1.86 (dd, *J* = 13.4, 7.0 Hz, 1H, one of C_8-*H*), 1.65 (m, 2H, one of C_{18}-*H*, C_{20}-*H*), 1.59–1.42 (m, 6H, one of C_8-*H*, one of C_{18}-*H*, one of C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*), 1.26 (m, 1H, one of C_{10}-*H*), 1.23 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 1.08 (s, 21H, $SiCH(CH_3)_2$), 1.04 (m, 1H, one of C_{19}-*H*), 0.93 (m, 1H, C_{11}-*H*), 0.82 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 172.5, 147.6, 143.5, 129.4, 129.1, 75.8, 74.6, 72.4, 49.6, 48.7, 47.1, 41.5, 41.0, 40.7, 40.0, 36.6, 34.7, 31.2, 27.9, 19.4, 18.4, 18.3, 18.2, 12.8, 9.4; TLC (50% ether/hexanes) R_f 0.17. Anal. Calcd for $C_{33}H_{54}O_5Si$: C, 70.92; H, 9.74. Found: C, 70.78; H, 9.63.

Triisopropylsiloxy-(+)-A83543A Pseudoaglycon (51). To a cooled (0 °C) solution of 156 mg (0.278 mmol) of monoprotected aglycon **50** and 100 mg (0.404 mmol) of acetylglycoside **49** in 15 mL of toluene was added 6.2 mg (0.18 mmol, 6 mol %) of trityl perchlorate.[60] The resulting suspension was stirred for 15 min at 0 °C and 1.3 h at room temperature and then partitioned between 50 mL of saturated aqueous $NaHCO_3$ and 80 mL of ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5 × 18 cm of silica gel, 50% ether/hexanes) gave 181 mg (0.242 mmol, 87%) of desired α-glycosidated material **51** followed by 11.2 mg (.015 mmol, 5%) of the corresponding β-anomer. Analytical data for the α-anomer **51**: $[\alpha]^{24}_{546}$ +146° (*c* 0.90, CH_2Cl_2); IR (thin film) 2930, 2870, 1720, 1660, 1610, 1455, 1340, 1230, 1100, 1030, 990, 910, 880, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 1H, C_{13}-*H*), 5.86 (d, *J* = 9.6 Hz, 1H, C_6-*H*), 5.78 (dt, *J* = 9.6, 2.7 Hz, 1H, C_5-*H*), 4.84 (d, *J* = 1.4 Hz, 1H, $C_{1'}$-*H*), 4.65 (m, 1H, C_{21}-*H*), 4.31 (m, 1H, C_9-*H*), 4.05 (m, 1H, C_{17}-*H*), 3.56 (M, 1H, $C_{2'}$-*H*), 3.55 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.48 (m, 2H, C_4-*H*, $C_{5'}$-*H*), 3.45 (dd, *J* = 9.2, 3.3 Hz, 1H, $C_{3'}$-*H*), 3.21 (m, 1H, C_{16}-*H*), 3.11 (t, *J* = 9.6 Hz, 1H, $C_{4'}$-*H*), 3.08 (dd, *J* = 13.3, 5.0 Hz, 1H, one of C_2-*H*), 3.03 (m, 1H, C_3-*H*), 2.88 (m, 1H, C_{12}-*H*), 2.41 (dd, *J* = 13.3, 3.0 Hz, 1H, one of C_2-*H*), 2.27 (dt, *J* = 12.8, 7.0 Hz, 1H, one of C_{10}-*H*), 2.15 (m, 1H, C_7-*H*), 1.92 (dd, *J* = 13.3, 7.0 Hz, 1H, one of C_8-*H*), 1.67 (m, 2H, one of C_{18}-*H*, C_{20}-*H*), 1.61–1.28 (m, 7H, one of C_8-*H*, one of C_{10}-*H*, one of C_{18}-*H*, one of C_{19}-*H*, one of C_{20}-*H*, C_{22}-*H*), 1.28 (d, *J* = 6.3 Hz, 3H, $C_{6'}$-*H*), 1.23 (d, *J* = 7.0 Hz, 3H, C_{16}-CH_3), 1.08 (s, 21H, $SiCH(CH_3)_2$), 1.04 (m, 1H, one of C_{19}-*H*), 0.89 (m, 1H, C_{11}-*H*), 0.82 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 172.5, 147.3, 143.6, 129.4, 129.2, 95.8, 82.4, 81.2, 77.9, 76.4, 75.8, 74.6, 68.1, 60.8, 59.0, 57.7, 49.6, 48.8, 47.8, 46.5, 41.6, 41.2, 37.6, 36.7, 36.5, 34.7, 31.3, 30.8, 27.9, 19.5, 18.4, 18.3, 18.2, 17.8, 12.9, 9.4; TLC (50% ether/hexanes) R_f 0.25. Anal. Calcd for $C_{42}H_{70}O_9Si$: C, 67.52; H, 9.44. Found: C, 67.60; H, 9.38.

(+)-A83543A Pseudoaglycon (52). To a solution of 147 mg (0.197 mmol) of silyl ether **51** in 12 mL of CH_3CN at room temperature was added 2.0 mL of 48% aqueous HF. The resulting solution was stirred for 2.5 h, then diluted with 70 mL of EtOAc, and washed with three 30-mL portions of saturated aqueous $NaHCO_3$ and 30 mL of brine. The combined aqueous layers were extracted with 20 mL of EtOAc, and the organic extract was washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3.5 × 10 cm of silica gel, 50% to 80% EtOAc/hexanes) gave 113 mg (0.192 mmol, 97%) of the desired pseudoaglycon **52**: $[\alpha]^{24}_{546}$ +215° (*c* 0.75, CH_2Cl_2); IR (thin film) 3500 (br), 2930, 1720, 1660, 1610, 1455, 1370, 1210, 1115, 1035, 1000, 910, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H, C_{13}-*H*), 5.88 (d, *J* = 9.7 Hz, 1H, C_6-*H*), 5.79 (dt, *J* = 9.7, 2.7 Hz, 1H, C_5-*H*), 4.85 (d, *J* = 1.6 Hz, 1H, $C_{1'}$-*H*), 4.69 (m, 1H, C_{21}-*H*), 4.31 (m, 1H, C_9-*H*), 3.69 (m, 1H, C_{17}-*H*), 3.56 (m, 1H, $C_{2'}$-*H*), 3.55 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.48 (m, 3H, C_4-*H*, $C_{5'}$-*H*, O*H*), 3.45 (dd, *J* = 9.4, 3.3 Hz, 1H, $C_{3'}$-*H*), 3.21 (m, 1H, C_{16}-*H*), 3.12 (m, 2H, one of C_2-*H*, $C_{4'}$-*H*), 3.02 (m, 1H, C_3-*H*), 2.87 (m, 1H, C_{12}-*H*), 2.41 (dd, *J* = 13.5, 3.2 Hz, 1H, one of C_2-*H*), 2.28 (dt, *J* = 12.8, 7.1 Hz, 1H, one of C_{10}-*H*), 2.16 (m, 1H, C_7-*H*), 1.92 (dd, *J* = 13.4, 7.0 Hz, 1H, one of C_8-*H*), 1.67–1.28 (m, 9H, one of C_8-*H*, one of C_{10}-*H*, C_{18}-*H*, C_{19}-*H*, C_{20}-*H*, C_{22}-*H*), 1.28 (d, *J* = 6.3 Hz, 3H, $C_{6'}$-*H*), 1.21 (d, *J* = 6.8 Hz, 3H, C_{16}-CH_3), 0.93 (m, 1H, C_{11}-*H*), 0.82 (t, *J* = 7.5 Hz, 3H, C_{23}-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 172.7, 147.4, 144.4, 129.4, 128.8,

(60) Dauben, H. J., Jr.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442–1445.

95.6, 82.3, 81.1, 77.8, 76.9, 76.2, 72.8, 68.0, 60.9, 60.0, 57.7, 49.5, 48.1, 47.7, 46.0, 41.6, 41.2, 37.4, 36.4, 35.0, 34.1, 30.1, 28.4, 21.5, 17.8, 15.7, 9.4; mp 169–170 °C; TLC (50% EtOAc/hexanes) R_f 0.14. Anal. Calcd for $C_{33}H_{50}O_9$: C, 67.09; H, 8.53. Found: C, 66.91; H, 8.56.

(4*R*)-3-[4-(Methoxycarbonyl)butanoyl]-4-benzyl-2-oxazolidinone (54). To a cooled (−78 °C) solution of 1.58 g (8.90 mmol) of oxazolidinone **53** in 20 mL of THF was added 5.9 mL (8.9 mmol) of a 1.5 M *n*-BuLi solution in hexanes, giving a light orange solution at the end of the addition. A solution of 1.05 g (9.19 mmol) of glutaric anhydride in 10 mL of THF was then added *via* cannula, giving a thick, white slurry, which was allowed to warm to room temperature with vigorous stirring. Five milliliters of 1 M aqueous $NaHSO_4$ was added, and the solution was concentrated *in vacuo*. The residue was partitioned between 50 mL of 1 M aqueous $NaHSO_4$ and 200 mL of CH_2Cl_2. The organic layer was washed with brine, filtered through cotton, and concentrated to give a colorless oil. This oil was dissolved in 50 mL of ether and treated with an ethereal solution of diazomethane until a yellow color persisted. The solution was stirred at room temperature for 15 min and then concentrated *in vacuo*. Purification by flash chromatography (5 × 19 cm of silica gel, 40% EtOAc/hexanes) provided 2.33 g (7.64 mmol, 86%) of the desired imide **54** as a colorless oil which crystallized on standing: $[\alpha]^{21}_{546}$ −73° (*c* 1.12, CH_2Cl_2); IR (thin film) 2950, 1765, 1725, 1690, 1500, 1435, 1400, 1370, 1330, 1210, 1155, 1115, 990, 760, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H, Ar-*H*), 7.25 (m, 1H, Ar-*H*), 7.18 (m, 2H, Ar-*H*), 4.64 (m, 1H, C*H*N), 4.15 (m, 2H, CH_2O), 3.66 (s, 3H, OCH_3), 3.26 (dd, *J* = 13.4, 3.3 Hz, 1H, one of CH_2Ph), 2.97 (m, 2H, C_4-*H*), 2.75 (dd, *J* = 13.4, 9.6 Hz, 1H, one of CH_2Ph), 2.41 (t, *J* = 7.4 Hz, 2H, C_2-*H*), 2.00 (m, 2H, C_3-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 172.3, 153.3, 135.2, 129.3, 128.8, 127.2, 66.2, 55.0, 51.4, 37.8, 34.6, 32.9, 19.4; mp 71–72 °C; TLC (30% EtOAc/hexanes) R_f 0.23. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27. Found: C, 62.71; H, 6.36.

(4*R*)-4-Benzyl-3-[[(5*R*,6*S*)-tetrahydro-2-oxo-6-methyl-2*H*-pyran-5-yl]-carbonyl]-2-oxazolidinone (55). To a cooled (0 °C) solution of 6.13 g (20.1 mmol) of imide **54** in 50 mL of CH_2Cl_2 was added 5.6 mL (22 mmol) of Bu_2BOTf followed by dropwise addition of 3.6 mL (26 mmol) of Et_3N. After being stirred for 5 min, the yellow solution was cooled to −78 °C and treated with 2 mL (35 mmol) of acetaldehyde. After 20 min at −78 °C, the solution was warmed to 0 °C and stirred for 1.5 h. Twenty-five milliliters of pH 7 phosphate buffer and 70 mL of methanol were then added followed by the slow addition of a mixture of 25 mL of 30% aqueous H_2O_2 in 50 mL of methanol. The resulting solution was stirred for 2 h at 0 °C and then concentrated *in vacuo*. The residue was extracted with three 100-mL portions of ether, and the combined extracts were washed with 100 mL of saturated aqueous $NaHCO_3$, 50 mL of 1 M aqueous $NaHSO_3$, and brine. The extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 6.74 g of a light yellow oil.

To a solution of this unpurified aldol adduct in 2 L of benzene was added 99.3 mg (0.395 mmol) of PPTS. The mixture was heated to reflux for 30 min, cooled to room temperature, and concentrated *in vacuo*. Purification by flash chromatography (7 × 19 cm of silica gel, 55% EtOAc/hexanes) provided 5.02 g (15.8 mmol, 79%) of the desired lactone **55** as a colorless oil: $[\alpha]^{25}_{546}$ −189° (*c* 1.25, CH_2Cl_2); IR (thin film) 2990, 1780, 1740, 1690, 1600, 1450, 1400, 1350, 1100, 940, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 3H, Ar-*H*), 7.21 (m, 2H, Ar-*H*), 4.80 (dq, *J* = 9.4, 6.3 Hz, 1H, C_5-*H*), 4.70 (m, 1H, C*H*N), 4.26 (m, 2H, CH_2O), 3.79 (dt, *J* = 9.4, 6.0 Hz, 1H, C_4-*H*), 3.23 (dd, *J* = 13.3, 3.3 Hz, 1H, one of CH_2Ph), 2.80 (dd, *J* = 13.3, 9.3 Hz, 1H, one of CH_2Ph), 2.69 (m, 1H, one of C_2-*H*), 2.61 (m, 1H, one of C_2-*H*), 2.29 (m, 1H, one of C_3-*H*), 1.99 (m, 1H, one of C_3-*H*), 1.40 (d, *J* = 6.3 Hz, 3H, C_6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 170.3, 152.9, 134.7, 129.0, 127.6, 76.5, 66.5, 55.1, 43.7, 37.8, 28.4, 23.4, 20.3; TLC (50% EtOAc/hexanes) R_f 0.38. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03. Found: C, 64.23; H, 6.38.

(5*R*,6*S*)-Tetrahydro-5-carboxy-6-methyl-2*H*-pyran-2-one (56). To a cooled (0 °C) solution of 2.54 g (8.02 mmol) of imide **55** in 60 mL of THF was added 8 mL of 30% aqueous H_2O_2 followed by 12 mL of 2 M LiOH. The resulting solution was stirred for 20 min at 0 °C, then quenched with 25 mL of 4 M aqueous $NaHSO_3$, and concentrated *in vacuo*. The residue was saturated with NaCl, transferred to a continuous extractor, and treated with 6 M HCl until the aqueous layer reached pH 1. After being extracted with CH_2Cl_2 for 2.5 d, the organic phase was concentrated *in vacuo* to give an off-white solid. Purification by flash chromatography (5.5 × 26 cm of silica gel, 25% EtOAc/CH_2Cl_2 to 5% HOAc/50% EtOAc/CH_2Cl_2 to 5% HOAc/EtOAc) provided 1.12 g (7.08 mmol, 88%) of the desired acid **56** as a hygroscopic, white, crystalline solid: $[\alpha]^{23}_{546}$ +69° (*c* 0.84, CH_2Cl_2); IR (mineral oil mull) 3300–2400 (v br), 1735, 1690, 1370, 1355, 1300, 1230, 1180, 1085, 1040, 850 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.8 (br s, 1H, COO*H*), 4.52 (dq, *J* = 9.3, 6.3 Hz, 1H, C_5-*H*), 2.51 (m, 3H, C_2-*H*, C_4-*H*), 1.98 (m, 2H, C_3-*H*), 1.27 (d, *J* = 6.3 Hz, 3H, C_6-*H*); ^{13}C NMR (100 MHz, d_6-DMSO) δ 173.9, 170.4, 76.2, 44.8, 28.0, 22.1, 20.2; mp 97–99 °C; TLC (5% HOAc to 45% EtOAc/hexanes) R_f 0.16. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.94; H, 6.51.

(5*R*,6*S*)-Tetrahydro-5-[[(9-fluorenylmethoxy)carbonyl]amino]-6-methyl-2*H*-pyran-2-one (57). To a suspension of 138 mg (0.869 mmol) of acid **56** in 5 mL of benzene at room temperature was added 0.12 mL (0.86 mmol) of Et_3N, giving a colorless solution. Diphenyl phosphorazidate (0.19 mL, 0.88 mmol) was then added, and the solution was warmed to 50 °C for 30 min, during which time gas was evolved. The solution was cooled to room temperature, treated with 341 mg (1.74 mmol) of 9-fluorenylmethanol,[58] and then heated to reflux for 3 h. The reaction mixture was then cooled, diluted with 25 mL of ether, and washed with 20 mL of water. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrate *in vacuo*. Purification by flash chromatography (3 × 18 cm of silica gel, 50% EtOAc/hexanes) provided 220 mg (0.625 mmol, 72%) of carbamate **57** as a rigid foam: $[\alpha]^{21}_{546}$ +44° (*c* 0.65, CH_2Cl_2); IR (thin film) 3500 (br), 3310, 3030, 2980, 2870, 1720, 1695, 1550, 1450, 1380, 1020, 760, 740 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.63 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.44 (m, 2H, Ar-*H*), 7.24 (m, 4H, Ar-*H*), 4.59 (dd, *J* = 10.9, 5.4 Hz, 1H, one of CH_2O), 4.49 (dd, *J* = 10.9, 5.4 Hz, 1H, one of CH_2O), 3.91 (m, 1H, C*H*Ar), 3.78 (d, *J* = 8.0 Hz, 1H, N*H*), 3.43 (m, 1H, C_5-*H*), 3.25 (m, 1H, C_4-*H*), 2.03 (m, 1H, one of C_2-*H*), 1.89 (m, 1H, one of C_2-*H*), 1.26 (m, 1H, one of C_3-*H*), 0.97 (d, 3H, *J* = 5.7 Hz, 3H, C_6-*H*), 0.86 (m, 1H, one of C_3-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.6, 152.8, 143.7, 141.4, 127.8, 127.1, 124.8, 120.0, 78.5, 66.6, 50.0, 47.3, 27.8, 25.0, 19.2; mp 57–58 °C; TLC (50% EtOAc/hexanes) R_f 0.22. MS (Na^+ FAB) *m/z* 374 (100, M + Na), 247 (8), 179 (60), 178 (62), 176 (35), 165 (20); HR FABMS for $C_{21}H_{21}NaNO_4$ requires *m/z* 374.1368, found *m/z* 374.1368. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02. Found: C, 71.68; H, 5.99.

Acetyl 2,3,4,6-Tetradeoxy-4-[[(9-fluorenylmethoxy)carbonyl]amino]-L-gluco-hexopyranoside (58). To a cooled (−78 °C) solution of 383 mg (1.09 mmol) of lactone **57** in 10 mL of THF was added 3.5 mL of DIBAL-H (1 M solution of THF). The solution was stirred for 15 min at −78 °C and then quenched with a mixture of 560 mg $Na_2SO_4 \cdot 10H_2O$ and 600 mg of Celite. The mixture was warmed to room temperature, then filtered through Celite, and washed with four 10-mL portions of THF. The organic filtrate was concentrated *in vacuo* to give a white solid which was immediately suspended in 15 mL of pyridine and 5 mL of acetic anhydride. The mixture was stirred for 12 h at room temperature, during which time it cleared to give a light yellow solution, and then the solution was concentrated *in vacuo*. The residue was partitioned between 100 mL of EtOAc and 50 mL of water. The organic phase was washed with two 50-mL portions of 5% aqueous HCl, and the combined aqueous layers were extracted with 50 mL of EtOAc. The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and then with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (3.5 × 11 cm of silica gel, 40% EtOAc/hexanes) provided 405 mg (1.03 mmol, 94%) of glycoside **58** as a 1:2 mixture of α- and β-anomers: $[\alpha]^{21}_{546}$ −36° (*c* 0.77, CH_2Cl_2); IR (thin film) 3500 (br), 3310, 2990, 2940, 2870, 1720 (br), 1530, 1450, 1370, 1300, 1230, 1050, 950, 740 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.45 (m, 2H, Ar-*H*), 7.22 (m, 4H, Ar-*H*), 6.16 (s, $^1/_3$H, $C_{1\alpha}$-*H*), 5.63 (dd, *J* = 8.6, 3.1 Hz, $^2/_3$H, $C_{1\beta}$-*H*), 4.62 (m, 1H, one of CH_2O), 4.49 (m, 1H, one of CH_2O), 3.94 (m, 1H, C*H*Ar), 3.63 (m, 1H, N*H*), 3.38 (m, 1H, C_4-*H*), 3.26 (m, $^1/_3$H, $C_{5\alpha}$-*H*), 2.67 (m, $^2/_3$H, one of $C_{5\beta}$-*H*), 1.70 (s, 1H, α-COCH_3), 1.64 (s, 2H, β-COCH_3), 1.54 (m, $^2/_3$H, one of $C_{2\beta}$-*H*), 1.44 (m, $^4/_3$H, $C_{3\beta}$-*H*), 1.33 (m, 1H, $C_{2\alpha}$-*H*, one of $C_{3\alpha}$-*H*), 1.17 (d, *J* = 6.0 Hz, 2H, $C_{6\beta}$-*H*), 1.13 (d, *J* = 6.1 Hz, 1H, $C_{6\alpha}$-*H*), 1.07 (m, $^1/_3$H, one of $C_{3\alpha}$-*H*), 0.72 (m, $^2/_3$H, one of $C_{2\beta}$-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.3, 155.8, 155.7, 143.8, 143.7, 141.4, 127.7, 127.0, 124.8, 120.0, 93.7, 91.0, 76.0, 70.9, 66.5, 60.3, 52.0, 51.6, 47.3, 29.2, 28.5, 25.3, 21.1, 20.0, 18.5, 18.2, 14.2; mp 107 °C (dec); TLC (30% EtOAc/hexanes) R_f 0.18. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.69; H, 6.48; N, 3.58.

***N*-[(9-Fluorenylmethoxy)carbonyl]-(+)-A83543C (61).** To a cooled (−78 °C) solution of 135 mg (0.344 mmol) of glycosyl acetate **58** in 1.5 mL of CH_2Cl_2 was added 0.045 mL (0.34 mmol) of TMSBr. The resulting solution was stirred at −78 °C for 1.5 h and then warmed to room

temperature. In a separate flask, a cooled (−78 °C) solution of 134 mg (0.342 mmol) of glycosyl acetate **58** in 1.5 mL of CH_2Cl_2 was treated with 0.045 mL (0.34 mmol) of TMSBr. The resulting solution was stirred at −78 °C for 2 h and then warmed to room temperature to generate a second batch of glycosyl bromide **60**. In a third flask, a room temperature mixture of 101 mg (0.171 mmol) of pseudoaglycon **52**, 250.8 mg of silver zeolite,[53] and 1.00 g of powdered 4-Å molecular sieves was stirred vigorously in 7 mL of CH_2Cl_2 while being protected from light. To this mixture was added the first solution of unpurified glycosyl bromide **60** dropwise *via* cannula. After the mixture was stirred for 30 min, one half of the second glycosyl bromide solution was added dropwise *via* cannula. After the mixture was stirred an additional 30 min, the remaining glycosyl bromide was added. The suspension was stirred for 1 h, then diluted with 15 mL of ether, and filtered through Celite. The solids were washed with four 10-mL portions of ether, and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (3.5 × 20 cm of silica gel, 70% ether/hexanes to 100% ether) followed by preparative TLC (8% THF/CH_2Cl_2) provided 93.8 mg (.101 mmol, 59%) of α-glycosidated product **61**α followed by 15.3 mg (.0165 mmol, 10%) of desired β-glycosidated product **61**β and 20.5 mg (.0347 mmol, 20%) of recovered pseudoaglycon **52**. Analytical data for β-anomer **61**β: $[\alpha]^{25}_{546}$ +123° (*c* 0.54, CH_2Cl_2); IR (thin film) 3520, 2930, 1720, 1660, 1610, 1530, 1450, 1370, 1290, 1230, 1120, 1070, 990, 910, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H, Ar-*H*), 7.58 (d, J = 7.5 Hz, 2H, Ar-*H*), 7.40 (t, J = 7.5 Hz, 2H, Ar-*H*), 7.32 (t, J = 7.5 Hz, 2H, Ar-*H*), 6.77 (s, 1H, C_{13}-*H*), 5.88 (d, J = 9.8 Hz, 1H, C_6-*H*), 5.80 (dt, J = 9.8, 2.7 Hz, 1H, C_5-*H*), 4.85 (d, J = 1.4 Hz, 1H, $C_{1'}$-*H*), 4.67 (m, 1H, C_{21}-*H*), 4.44 (m, 4H, CH_2O, $C_{1''}$-*H*, N*H*), 4.30 (m, 1H, C_9-*H*), 4.21 (m, 1H, C*H*Ar), 3.63 (m, 1H, C_{17}-*H*), 3.56 (s, 3H, OCH_3), 3.54 (m, 1H, $C_{2''}$-*H*), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.48 (m, 3H, C_4-*H*, C_3'-*H*, $C_{5'}$-*H*), 3.35 (m, 2H, C_{16}-*H*, $C_{5''}$-*H*), 3.11 (m, 2H, one of C_2-*H*, $C_{4''}$-*H*), 3.02 (m, 1H, C_3-*H*), 2.87 (m, 1H, C_{12}-*H*), 2.40 (dd, J = 13.4, 3.1 Hz, 1H, one of C_2-*H*), 2.26 (dt, J = 12.7, 6.9 Hz, 1H, one of C_{10}-*H*), 2.17 (m, 1H, C_7-*H*), 2.06 (m, 1H, $C_{4'''}$-*H*), 1.92 (m, 2H, one of C_8-*H*, one of $C_{2''}$-*H*), 1.77 (m, 2H, one of C_{19}-*H*, one of $C_{3''}$-*H*), 1.6–1.2 (m, 11H, one of C_8-*H*, one of C_{10}-*H*, C_{18}-*H*, one of C_{19}-*H*, C_{20}-*H*, C_{22}-*H*, one of $C_{2''}$-*H*, one of $C_{3'''}$-*H*), 1.28 (d, J = 6.3 Hz, 3H, $C_{6''}$-*H*), 1.18 (m, 6H, C_{16}-CH_3, $C_{6'''}$-*H*), 0.89 (m, 1H, C_{11}-*H*), 0.82 (t, J = 7.4 Hz, 3H, C_{23}-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 172.5, 155.8, 147.5, 144.2, 143.9, 143.8, 141.4, 129.4, 128.8, 127.7, 127.0, 124.9, 120.0, 103.1, 95.6, 82.3, 81.1, 80.8, 77.8, 76.1, 75.0, 68.0, 66.4, 60.9, 59.0, 57.7, 52.2, 49.5, 47.7, 47.6, 47.3, 46.0, 41.6, 41.2, 37.4, 36.3, 34.3, 34.2, 30.7, 30.2, 29.8, 28.4, 21.5, 18.4, 17.8, 16.2, 9.3; mp 108 °C dec; TLC (50% EtAOc/hexanes) R_f 0.32. MS (Na^+ FAB) m/z 948 (100, M + Na), 788 (8), 632 (10), 595 (9); HR FABMS for $C_{54}H_{71}NNaO_{12}$ requires m/z 948.4874, found m/z 948.4894.

(+)-A83543A (Lepicidin). A solution of 12.0 mg (0.0130 mmol) of Fmoc-protected A83543C **61**β in 2 mL of Et_2NH was stirred at room temperature for 9 h and then concentrated *in vacuo*. A buffered solution of formaldehyde was prepared by mixing 1.84 g (22.4 mmol) of NaOAc, 1.3 mL (1.3 g, 22 mmol) of acetic acid, 5 mL of water, and 7 mL of 30% aqueous formaldehyde solution. The unpurified A83543C residue was dissolved in 2 mL of CH_3OH and 1 mL of the buffered aqueous formaldehyde solution. After being stirred for 10 min at room temperature, the solution was treated with three 5-mg portions (0.2 mmol) of $NaCNBH_3$ over a 10-min period. The solution was stirred an additional 20 min and then partitioned between 30 mL of CH_2Cl_2 and 10 mL of saturated $NaHCO_3$. The organic phase was filtered through cotton and concentrated *in vacuo*. Purification by flash chromatography (2 × 16 cm of silica gel, 0.25% NH_4OH/2% CH_3OH/CH_2Cl_2 to 0.5% NH_4OH/3% CH_3OH/CH_2Cl_2) provided 7.7 mg (0.011 mmol, 81%) of (+)-A83543A: $[\alpha]^{27}_D$ +133° (*c* 0.38, CH_2Cl_2); $[\alpha]^{27}_{546}$ +158° (*c* 0.38, CH_2Cl_2); $[\alpha]^{28}_{365}$ +25° (*c* 0.38, CH_2Cl_2); IR (thin film) 2940, 1720, 1660, 1610, 1450, 1370, 1210, 1120, 1070, 990, 900 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H, C_{13}-*H*), 5.88 (d, J = 9.8 Hz, 1H, C_6-*H*), 5.79 (dt, J = 9.8, 2.8 Hz, 1H, C_5-*H*), 4.84 (d, J = 1.7 Hz, 1H, $C_{1'}$-*H*), 4.66 (m, 1H, C_{21}-*H*), 4.40 (d, J = 7.2 Hz, 1H, $C_{1'''}$-*H*), 4.31 (m, 1H, C_9-*H*), 3.62 (m, 1H, C_{17}-*H*), 3.55 (s, 3H, OCH_3), 3.54 (m, 1H, $C_{5''}$-*H*), 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.48 (m, 3H, C_4-*H*, $C_{2''}$-*H*, $C_{5''}$-*H*), 3.45 (dd, J = 9.3, 3.3 Hz, 1H, $C_{3'}$-*H*), 3.29 (m, 1H, C_{16}-*H*), 3.11 (m, 2H, one of C_2-*H*, $C_{4''}$-*H*), 3.01 (m, 1H, C_3-*H*), 2.86 (m, 1H, C_{12}-*H*), 2.40 (dd, J = 13.3, 3.2 Hz, 1H, one of C_2-*H*), 2.25 (m, 1H, one of C_{10}-*H*), 2.23 (s, 6H, NCH_3), 2.17 (m, 1H, C_7-*H*), 2.06 (m, 1H, $C_{4'''}$-*H*), 1.97 (m, 1H, one of $C_{2''}$-*H*), 1.92 (dd, J = 13.0, 6.8 Hz, 1H, one of C_8-*H*), 1.85 (m, 1H, one of $C_{3''}$-*H*), 1.77 (m, 1H, one of C_{19}-*H*), 1.6–1.2 (m, 11H, one of C_8-*H*, one of C_{10}-*H*, C_{18}-*H*, one of C_{19}-*H*, C_{20}-*H*, C_{22}-*H*, one of $C_{2''}$-*H*, one of $C_{3'''}$-*H*), 1.27 (d, J = 6.3 Hz, 3H, $C_{6''}$-*H*), 1.25 (d, J = 6.2 Hz, $C_{6'''}$-*H*), 1.17 (m, 3H, C_{16}-CH_3), 0.91 (m, 1H, C_{11}-*H*), 0.81 (t, J = 7.4 Hz, 3H, C_{23}-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 172.5, 147.4, 144.2, 129.4, 128.9, 103.5, 95.6, 82.3, 81.2, 80.7, 77.8, 77.3, 77.0, 76.7, 76.2, 73.7, 68.0, 64.9, 60.9, 59.0, 57.7, 49.5, 47.7, 47.6, 46.1, 41.6, 41.2, 40.7, 37.4, 36.3, 34.4, 34.2, 31.0, 30.2, 28.4, 21.6, 19.0, 18.5, 17.8, 16.2, 9.3; TLC (0.5% NH_4OH/7.5% CH_3OH/CH_2Cl_2) R_f 0.42. MS (Na^+ FAB) m/z 754 (40, M + Na), 732 (100, M + 1), 572 (5), 449 (8); HR FABMS for $C_{41}H_{65}NO_{10}$ requires m/z 754.4506, found m/z 754.4500.

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Supplementary Material Available: Experimental procedures for compounds **45–49**, Scheme VII (3 pages). Ordering information is given on any current masthead page.