Total Synthesis of the Macrolide Antitumor Antibiotic Lankacidin C

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Abstract: The first total synthesis of natural (−)-lankacidin C (**1**) has been achieved by a convergent, enantioselective sequence starting from D-arabinose and L-aspartic acid, proceeding through the tricyclic carbamate **15** as an advanced relay intermediate. Specifically, the β-lactam diene intermediate **41** is acylated by the thiopyridyl ester **34c**. The resulting β-ketolactam **42** is stereospecifically reduced by KEt_3BH to carbinol **43**, which on desilylation undergoes acid-catalyzed N → O acyl migration to yield the δ-lactone **44**. The derived iodo aldehyde **46** undergoes Stille coupling to give tetraene **54a**, which upon Stork−Takahashi cyclization to ketone **56** and CBS reduction gives the key relay **15**. N-acylation of the latter, and then regioselective carbamate scission followed by Dess−Martin oxidation, produces the target antibiotic (−)-lankacidin C (**1**).

Introduction

The antitumor antibiotic lankacidin C (**1**), also referred to as bundlin A or T-2636 C in the Japanese literature, is the parent member of a group of 17-membered macrocyclic tetraenes (Figure 1) isolated independently from various species of *Streptomyces* by researchers in Switzerland[1] and Japan.[2,3] The polyfunctional nature and stereochemical details of the lankacidin C structure, including the absolute configuration, have been firmly established by an extensive degradative chemistry[4] and by the single-crystal X-ray determination of its 2′-[(*p*-bromophenyl)sulfonyl]hydrazone.[5] Other members of the group are interrelated by the presence or absence of an acetyl function at the C(14) oxygen as well as by a variable oxidation level at C(2′). Proof of these structures has come from interconversions of the family members by oxidation, reduction, and acetylation.[4]

The lankacidins show strong antimicrobial activities against a variety of Gram-positive bacteria, including several strains resistant to the conventional macrolide antibiotics.[6] More importantly, these antibiotics are well tolerated and show weak toxicities in mice.[7] Unlike most other antibacterial substances, lankacidin C and its C(8) and C(14) acyl derivatives show considerable *in vivo* antitumor activity against L1210 leukemia, B16 melanoma, and 6C3 HED/OG lymphosarcoma.[8] It is of added interest that the lankacidins show good antibacterial

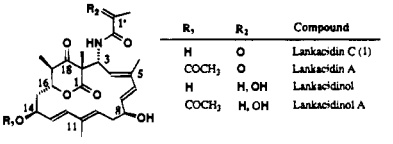

Figure 1.

activity against "Shirahagara disease" in rice, suggesting a use in control of this agricultural pathogen. The biological mode of activity is believed to involve the inhibition of protein synthesis, although the exact mechanism is unknown.[6] The effect on growth of *Streptomyces aureus* FDA 209 P shows that protein synthesis is completely and immediately inhibited after addition of 10 μg/mL to the culture medium, but DNA and RNA syntheses were not significantly altered at the same concentration.

The possible role of a biogenetic "Favorskii rearrangement" in the biosynthesis of the lankacidins has been postulated.[9] Chemical transformations of intact lankacidin antibiotics have been severely limited by their instability to even mild acids and bases.[4,10] The combination of the potential chemotherapeutic value and the stereochemically complex structure makes the lankacidins attractive synthetic targets, and several reports have appeared describing approaches to their total syntheses.[11] Herein, we describe in detail the first enantioselective total synthesis of lankacidin C.[12]

[⊗] Abstract published in *Advance ACS Abstracts*, July 15, 1995.

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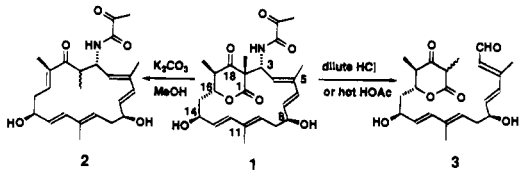
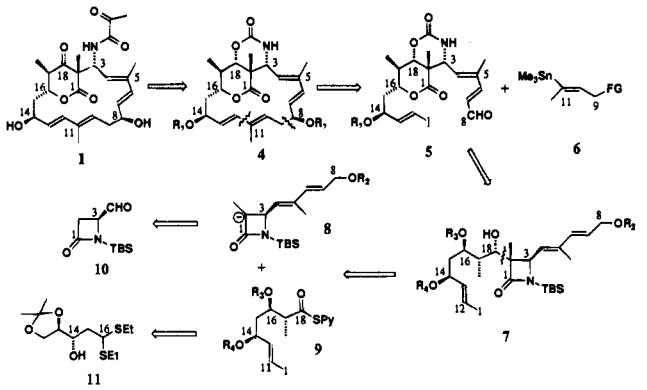


Figure 2.

Scheme 1



Synthetic Plan

At the outset of the project, we carefully reviewed the literature on the chemical stability of lankacidin C because such information is extremely important for designing a viable synthetic plan for a complex molecule like **1**. For our purposes it is sufficient to note that the pyrandione moiety of the lankacidins is reported to undergo ready degradation to the lankacidinol series **2** by base (pH above 10), and the macrocycle is cleaved by acid (pH below 3) to aldehyde **3** through an apparent "retro-Mannich" hydrolysis of the bond from C(3) to the pyrandione C(2) center (Figure 2).[4]

Since the instability of lankacidin C is the mechanistic consequence of the 1,3-dicarbonyl array at C(1) and C(18), we postulated that the structure **4** (Scheme 1), in which the C(18) ketone is reduced and the amino group temporarily protected, would serve as a stable advanced precursor and potential relay toward **1**. We elected to carry this portion of the molecule in reduced oxidation state until late in the synthesis.

Construction of the macrocycle was to be achieved by a linchpin closure in which the "acyclic" iodovinyl aldehyde **5** would be cyclized employing the vinylstannane synthon **6**, comprising the missing C(9) to C(11) carbons of the chain plus the C(11) methyl group. We reasoned that this approach would allow us maximum flexibility in the key macrocyclization step. The unidentified functional group (FG) in the synthon **6** could be either a removable electron-withdrawing group or a good leaving group. With FG as an electron-withdrawing group, the bidentate reactivity of **6** would permit intermolecular anion addition of the future C(9) to the C(8) aldehyde of **5**, to be followed by mild, stereospecific, intramolecular Stille coupling[13] of the vinylstannane C(11) to the iodomethylene C(12) of **5**, or we could do the reverse of this two-step sequence. In the case where FG is a leaving group, Stille coupling would form the C(11)–C(12) single bond stereospecifically, followed by a Stork–Takahashi cyanohydrin procedure to form the macrocycle.[14]

Aldehyde **5** was therefore identified as a pivotal synthetic target. We elected to explore a novel strategy whereby the δ-lactone system of **5** would arise from an intramolecular N-to-O acyl migration of the β-lactam derivative **7** under acid catalysis. Analogous intramolecular nucleophilic openings of the β-lactam ring by amino nitrogen, ureido nitrogen, and amide oxygen are well documented in the penicillin series,[15] and N-to-O acyl migrations under mild conditions are well precedented.[16] The relief of the ring strain[17] associated with the β-lactam system and the less negative entropic effect for intramolecular ring closure would provide an adequate driving force for the desired rearrangement. More importantly, model studies in our lab demonstrated the viability of this β-lactam to lactone approach,[18] as will be detailed later in this paper.

In the interest of convergence, the C(2)–C(18) bond in **7** was retrosynthetically cut to divide the molecule into two approximately equal segments. In the synthetic direction, coupling of the β-lactam enolate **8** with the acylating reagent **9** would generate the key C(2) quaternary center. Acylation would be expected to take place from the less hindered face of the β-lactam **7** away from the bulky side chain at C(3) to give the desired configuration at the C(2) chiral center. Further simplification of **8** led to the known β-lactam aldehyde **10**,[19] and **9** would in turn be made from the known dithioacetal **11**.[20]

Results and Discussions

Synthesis of 4 through Degradation. We recognized from the beginning of our project that the main source of lankacidin C instability, namely, the ultimate C(18) carbonyl, must be masked until near the end of the synthesis. An important premise underlying this strategy is that we would be able to selectively hydrolyze the cyclic carbamate in the presence of the δ-lactone at the stage of the advanced intermediate **4** and oxidize the resulting free C(18) hydroxyl group to give the labile pyrandione moiety of the target molecule. The fragile nature of **1** also dictated that the choice of protecting group R_1 will be critical to success. R_1 should be stable enough to allow the manipulation of **4** and removable under mild reaction conditions that the natural product could survive. To test the viability of **4** as our advanced intermediate and a potential relay, we elected to make this compound through the degradation of natural lankacidin C.[21]

Toward this end, natural **1** was silylated under standard conditions ((TBS)Cl, imidazole, DMF) and then reduced with

(12) For our preliminary report, see: Kende, A. S.; Koch, K.; Dorey, G.; Kaldor, I.; Liu, K. *J. Am. Chem. Soc.* **1993**, *115*, 9842.

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(17) For a discussion of the acid-catalyzed hydrolysis of lactams, see: Wan, P.; Modro, T. A.; Yates, K. *Can. J. Chem.* **1980**, *58*, 2423.

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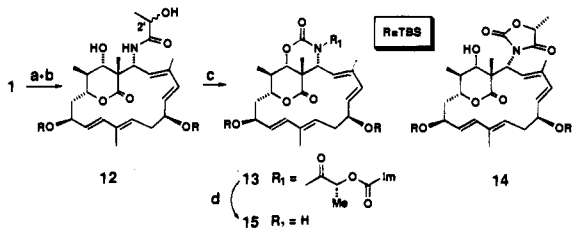
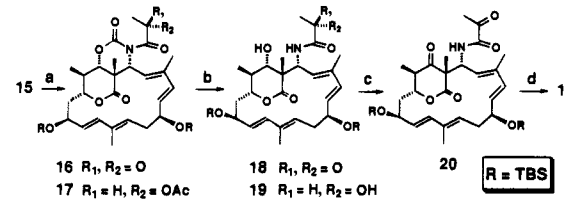
(21) A sample of lankacidin C was kindly provided by Takeda Chemical Industries.

Scheme 2[a]



[a] Conditions: (a) imidazole, (TBS)Cl, DMF, rt, 100%; (b) $NaBH_4$, MeOH, rt, 99%; (c) 1,1′-carbonyldiimidazole, LiHMDS, THF, −78 °C, 92% (from the less polar isomer); (d) LiOOH, THF−H_2O (3:1), 98%.

Scheme 3[a]



[a] Conditions: (a) LiHMDS, THF, −78 °C, and then RCOCl, 91% for **16** and 85% for **17**; (b) LiOH, THF−H_2O, 0 °C, 30% for **18** and 82% for **19**; (c) Dess−Martin periodinane, CH_2Cl_2, rt, 96% (from **19**); (d) HCOOH, THF−H_2O, rt, 3 h, 82%.

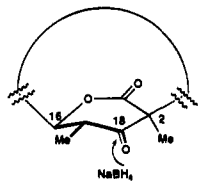
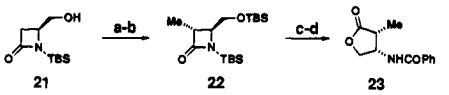


Figure 3.

$NaBH_4$ in MeOH to give a 1:1 mixture of the C(2′) epimeric diol **12** (Scheme 2).[22] The C(2′) stereochemistry of the chromatographically separable less polar isomer was subsequently shown to be *S* by establishing the identity of this material with our hydroxy amide **19**, prepared from relay **15** by synthesis as described later (Scheme 3). Treatment of this less polar diol with lithium bis(trimethylsilyl)amide and 1,1′-carbonyldiimidazole gave the biscarbamate **13** in 92% yield. When the more polar diol was subjected to the same reaction conditions, no desired cyclic carbamate but rather a product in 88% yield that was identified as **14** based on its NMR characteristics was isolated. Selective deacylation of **13** with LiOOH in aqueous THF according to the Evans protocol[23] gave a 98% yield of the desired tricyclic carbamate **15** as a crystalline solid, mp 186−187 °C, $[\alpha]^{22}_D = -68.3°$.

The C(18) *S* configuration was assigned on the basis of NOE studies on **15**. In particular, irradiation of the C(2) Me in **15** revealed a NOE of 8% on the *cis* C(18) H and one of 11% on the *cis* C(3) H; irradiation of C(18) H gave a NOE of 1.1% on the *cis* C(17) Me and one of 1.7% on the *cis* C(2) Me. Further support for the *anti* stereochemical relationship between the centers at C(17) and C(18) was the observed vicinal proton coupling constant of $J_{17,18} = 11.0$ Hz, indicating an *anti* axial−axial coupling. X-ray analysis of lankacidin C 2′-[(*p*-bromophenyl)sulphonyl]hydrazone[5a] showed that the pyrandione moiety of the molecule took the conformation shown in Figure 3. It is quite clear that the upper face of the pyrandione ring is completely shielded by the macrocyclic ring. The C(18) carbonyl can only be attacked from below to generate the assigned (*S*)-carbinol.

Scheme 4[a]



[a] Conditions: (a) (TBS)Cl, imidazole, DMF, 95%; (b) LDA, THF, −78 °C, MeI, 97%; (c) HCl, MeOH−H_2O; (d) PhCOCl, DMAP, pyridine, CH_2Cl_2, 76% (two steps).

Resynthesis of Lankacidin C from Relay 15. To further explore our planned synthetic strategy, the relay conversion of **15** into **1** was examined. Direct alkaline hydrolysis of **15** gave only lactone cleavage, and then eventual decomposition. It has been documented in the literature that secondary lactams or cyclic carbamates could be hydrolyzed under mild conditions when they were activated by N-acylation.[24] Therefore, relay **15** was reacted with excess lithium bis(trimethylsilyl)amide, followed by acylation with pyruvic acid chloride as shown in Scheme 3 to give the *N*-acylcarbamate **16** in 91% yield. Reaction of **16** with 3 equiv of aqueous LiOH at 0 °C gave in 30% yield the desired hydroxy amide **18**, along with 60% of the *exo*-ring cleavage product, *i.e.*, the starting relay **15**. We reasoned that a more sterically demanding pyruvic derivative should improve the ratio of the hydrolysis products in favor of the desired *endo*-ring cleavage.[23,24] Relay **15** was then acylated with *O*-acetyl-(*S*)-lactoyl chloride to form the *N*-acylcarbamate **17** in 85% yield. Hydrolysis of **17** with aqueous LiOH under the same reaction conditions as those for **16** gave in 82% yield the hydroxy amide **19** along with 10% of recovered relay **15**. Dess−Martin[25] oxidation of **19** gave 97% of diketone **20**, identical in all respects with the bis(TBS ether) obtained from the direct silylation of natural **1** as described before. The delicate desilylation of **20** failed with all variants of F^- or HF, but was finally achieved using aqueous formic acid at 20 °C for 3 h to produce in 82% yield the target molecule **1**, identical in all respects with the natural antibiotic.

Model Studies on the Construction of the Pyrandione Ring System.[18] Another tactical premise of our synthetic strategy was that a β-lactam having a suitable hydroxyl-bearing side chain α to the carbonyl will undergo rapid N-to-O transacylation with lactam cleavage and formation of a lactone. Before attempting a synthesis of the actual system, we felt that it would be prudent to demonstrate our proposal by a model study. Thus, the TBS ether of the known (hydroxymethyl)azetidinone **21**[19b] was monomethylated (LDA, MeI, −78 °C) to give exclusively the α-methyl adduct **22** as a single diastereomer in 97% yield (Scheme 4). Treatment of **22** with aqueous methanolic HCl overnight followed by benzoylation led to a 76% yield of the known γ-lactone **23**[26] (IR 1770 cm^{-1}).

With the feasibility of our N-to-O acyl migration established, we set out to model the stereochemically correct pyrandione ring system of lankacidin C. It is known in the patent literature that the aldol reactions of 3-alkyl-substituted β-lactams lead to a mixture of all four possible products in roughly equal proportions.[27] In model studies using the azetidinone **22** and isobutyraldehyde, the aldol reaction led to a 3:1 mixture of

(22) Formation of both C(2′) carbinols on controlled reduction has been reported in ref 4a.

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

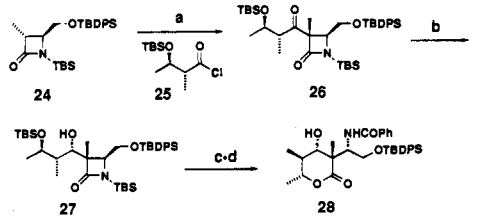
(24) (a) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424. (b) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

(25) For the preparation, use, and possible hazards of the Dess−Martin periodinane, see: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(26) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

(27) Christensen, B. G.; Ratcliffe, R. W. Eur. Pat. Appl. EP 38,869, Nov 4, 1981; *Chem. Abstr.* **1982**, *96*, 199398w. See also: Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.

Scheme 5[a]



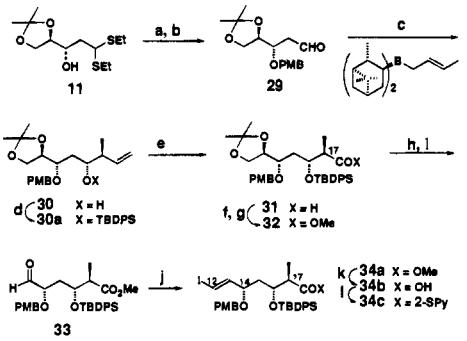
[a] Conditions: (a) LDA, THF, −78 °C, then **25**, 79%; (b) KEt_3BH, Et_2O, 0 °C, 87%; (c) MeOH−H_2O−HCl (90:10:2), 8 equiv, rt, 16 h; (d) PhCOCl, DMAP, pyridine, CH_2Cl_2, 47% (two steps).

β-methyl and α-methyl epimers as well as a 1:1 mixture of hydroxyl epimers. With these data in hand, we sought another method of controlling the stereochemistry of the key quaternary center. It has been shown that an acylation−reduction sequence can substitute for a single aldol reaction[28] and this protocol can be highly selective.[29] With this in mind, the anion of **24** (LDA, −78 °C) was cannulated into a solution of the chiral acid chloride **25** at −78 °C to form the acylated β-lactam **26** in 79% yield (Scheme 5). Examination of the crude ^1H NMR revealed no evidence of another diastereomer. The acylation was expected to take place from the less hindered face of the lactam *trans* to the TBDPS ether side chain, which was supported by the observation of a 10% NOE on the siloxymethylene hydrogens when the quaternary methyl group was irradiated. The origin of this enhanced face selectivity is unclear since one might expect the more reactive acid chloride to give poorer face selectivity than the corresponding aldehyde. Evans has proposed that acid chlorides are sterically more demanding than corresponding aldehydes,[30] thus increasing the face selectivity on reaction with the chiral azetidinone.

Fortunately, treatment of the acylazetidinone **26** with potassium triethylborohydride in Et_2O at 0 °C again gives a single product, **27**, in 87% yield. After several unsuccessful attempts, N-to-O acyl migration was observed by treatment of **27** with aqueous methanolic HCl (MeOH−H_2O−HCl (90:10:2), 8 equiv, rt, 16 h). Benzoylation of the crude amine gave an overall yield of 47% for the amide **28**. Irradiation of the quaternary methyl group gave an 8% NOE for the hydrogen on the newly formed carbinol chiral center, leading to our tentative assignment of the reduction stereochemistry in **27**. The origin of this stereoselection is discussed later.

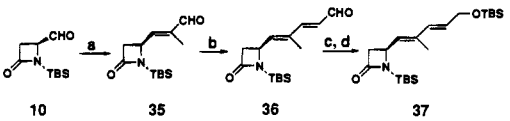
Synthesis of Fragment 9. With the success of our model studies we undertook the synthesis of the fully functionalized C(12)−C(18) portion of lankacidin C (Scheme 6). Starting from the known dithioacetal **11**, made in four steps (43% overall yield) from D-arabinose,[20] hydroxyl protection, followed by dithioacetal cleavage,[20b] produced aldehyde **29** in 70% yield. This underwent addition of the Brown (*E*)-crotyldiisopinocampheylborane reagent derived from (+)-α-pinene to give 58% of the anticipated adduct **30**.[31] Subsequent protection of the hydroxyl group as its *tert*-butyldiphenylsilyl ether followed by ozonolysis of the terminal olefin provided the unstable aldehyde **31**. The C(17) chiral center underwent facile epimerization during silica gel chromatography. Owing to its fragile nature, crude aldehyde **31** was directly subjected to Lindgren oxidation[32] followed by reaction with CH_2N_2[33] to give ester **32**. Difficulties were then encountered in removing the acetonide protecting

Scheme 6[a]



[a] Conditions: (a) NaH, (PMB)Cl, DMF, rt, 91%; (b) $HgCl_2$/HgO, MeCN−H_2O (5:1), 0 °C, 77%; (c) chiral borane reagent, NaOH, H_2O_2, THF, 58%; (d) (TBDPS)Cl, imidazole, DMF, rt, 48 h, 84%; (e) O_3, Sudan III, Me_2S, CH_2Cl_2−CH_3OH (1:1), −78 °C; (f) $NaClO_2$, NaH_2PO_4, MeCN−DMSO−H_2O, rt, 78% (two steps); (g) CH_2N_2, Et_2O, 87%; (h) $CuCl_2$, MeOH, reflux for 1 h, 97%; (i) $Pb(OAc)_4$, THF, 0−5 °C; (j) $CrCl_2$, CHI_3, THF, 62% (two steps); (k) LiOH, THF−H_2O−MeOH (6:3:2), rt, 12 h; (l) $(2\text{-PyS})_2$, Ph_3P, THF, rt, 15 h, 79% (two steps).

Scheme 7[a]



[a] Conditions: (a) *t*-BuN=CHCH(Me)$SiEt_3$, *sec*-BuLi, Et_2O, −78 °C; silica gel, CH_2Cl_2, 1 h; AIBN, PhSSPh, benzene, reflux for 7 days, 50%; (b) *t*-BuN=$CHCH_2SiEt_3$, *sec*-BuLi, Et_2O, −78 °C, 78%; (c) $LiBH_4$, THF, −30 °C, 100%; (d) (TBS)Cl, imidazole, DMF, 85%.

group. Acidic hydrolysis under different reaction conditions (HCl, CSA, pTSA) failed to give clean cleavage. After considerable experimentation, the deprotection was finally achieved using 5 equiv of $CuCl_2{\cdot}2H_2O$ in refluxing MeOH for 1 h to give the deprotected diol in 97% yield.[34] $Pb(OAc)_4$ cleavage[35] then gave the unstable noraldehyde **33**, directly converted by the Takai method[36] to the iodoalkene ester **34a** in 62% yield. Saponification gave the acid **34b**, which was activated as its 2-thiopyridyl ester **34c**[37] in good yield (79% for two steps).

Synthesis of Fragment 8. The C(1)−C(8) segment of lankacidin C was in turn available starting from the known β-lactam **10**,[19] prepared from L-aspartic acid. In our preliminary report,[12] compound **37** was made by two successive modified Peterson sequences[38] as shown in Scheme 7. Condensation of β-lactam aldehyde **10** with *t*-BuN=CH(Me)$SiEt_3$, followed by imine hydrolysis and $(PhS)_2$/AIBN equilibration of the resulting crude enals, produced the *E*-unsaturated aldehyde **35** in 50% yield. A second condensation of **35** with *t*-BuN=$CHCH_2SiEt_3$ gave on workup a 78% yield of the (*E,E*)-dienal **36**, which was sequentially reduced with lithium borohydride and O-silylated to gave **37** in 85% yield.

This approach suffered from several drawbacks: (1) the moderate yield and nonstereospecificity of the first Schlessinger−Peterson condensation; (2) the long reaction time (7 days in

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(31) Cf.: Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 283.
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(34) Iwata, M.; Ohrui, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2837.
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(36) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
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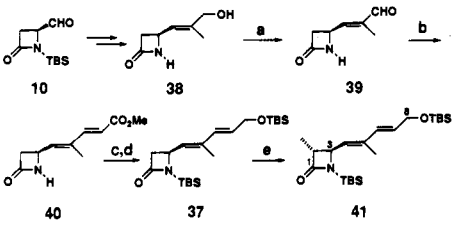
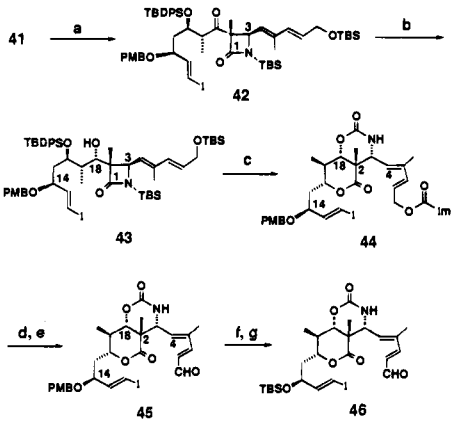
Scheme 8[a]



[a] Conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, 86%; (b) $Ph_3P{=}CHCO_2Me$, toluene, 50 °C, 1 h; (c) DIBAL-H, THF, −78 to 0 °C; (d) TBSOTf, Et_3N, CH_2Cl_2, 75% from **39**; (e) LDA, THF, −78 °C, and then MeI, 82%.

Scheme 9[a]



[a] Conditions: (a) LDA, THF, −78 °C, and then **34c**, 85%; (b) KEt_3BH, Et_2O, −78 °C, 85%; (c) Bu_4NF, THF, rt, 2 h; MsOH, rt, 2 h; Et_3N, 1,1′-carbonyldiimidazole, rt, 12 h, 85%; (d) HCl (0.14 M), H_2O−dioxane (1:1), rt, 8 h, 70%; (e) Dess−Martin periodinane, CH_2Cl_2, 85%; (f) CAN, MeCN−H_2O, 97%; (g) (TBS)Cl, imidazole, DMF, 79%.

refluxing benzene) required by $(PhS)_2$/AIBN equilibration of the crude enals; (3) commercial unavailibilities of reagents *t*-BuN=CHCH($SiEt_3$)CH_3 and *t*-BuN=$CHCH_2SiEt_3$. As a result, an alternative and more expedient route to **37** was developed (Scheme 8). Again starting from β-lactam **10**, alcohol **38** was conveniently made according to the reported procedure.[11e] Swern oxidation gave in 86% yield the unsaturated aldehyde **39**, which was reacted with commercial methyl (triphenylphosphoranylidene)acetate (toluene, 50 °C, 1 h) to produce stereospecifically the *E,E*-unsaturated ester **40**. Reduction of **40** with diisobutylaluminum hydride, followed by reaction with excess *tert*-butyldimethylsilyl trifluoromethanesulfonate, generated **37** in 75% overall yield from **39**. Finally, C-methylation (LDA, MeI, −78 °C) produced the C(1)−C(8) synthon **41** in 82% yield as a single diastereomer.

Coupling and Lactone Formation. With syntheses of C(12)−C(18) and C(1)−C(8) fragments **34c** and **41** in hand, their coupling was undertaken (Scheme 9). Treatment of a tetrahydrofuran solution of lactam **41** with lithium diisopropylamide (LDA) at −78 °C resulted in the formation of the lithium enolate. Subsequent addition of a solution of the 2-thiopyridyl ester **34c** followed by stirring at −78 °C for 10 min afforded the desired β-ketolactam **42** in 85% yield as a single diastereomer.[39] Once again we found that reduction of **42** by potassium triethylborohydride in Et_2O at −78 °C produced the single carbinol **43** with the desired stereochemical outcome. Deprotection, N-to-O transacylation, and subsequent protection of the hydroxy amine were achieved in a "one-pot" fashion as follows. All three silyl protecting groups were first removed with tetrabutylammonium fluoride. Subsequent addition of methanesulfonic acid to the reaction mixture catalyzed the N-to-O acyl migration. After 2 h at room temperature, triethylamine was added to quench the acid, followed by 1,1′-carbonyldiimidazole trapping to yield 85% of the bicyclic lactone carbamate **44**. Selective hydrolysis followed by Dess−Martin oxidation gave the conjugated dienal **45** in 60% overall yield. With the sensitive 4,6-diene now protected by the C(8) aldehyde, ceric ammonium nitrate (CAN) oxidative scission of the *p*-methoxybenzyl (PMB) group[40] and subsequent silylation gave the stable iodo aldehyde **46** in 76% yield.

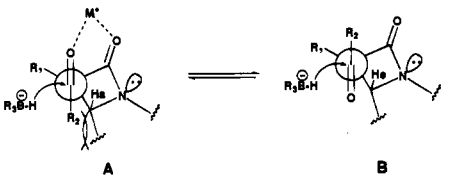


Figure 4.

The assignment of the C(18) *S* stereochemistry of **43** was corroborated by high-field NOE measurements on the derived carbamate **44** as well as on derivatives prepared subsequently. In particular, irradiation of the C(2) Me in **44** gave an NOE of 7% on the *cis* C(18) H and one of 9% on the *cis* C(3) H. Together with the observed vicinal proton coupling constant $J_{17,18}$ of 9.4 Hz, the above data indicate a half-chair conformation for the lactone ring in **44**. These findings were relevant as well to **45**, **46**, **54**−**56**, and **15**.

This C(18) *S* assignment implies that KEt_3BH−Et_2O reduction of our β-ketolactam **42** takes a steric course opposite that observed for a structurally related thienamycin precursor lacking the angular methyl substituent.[41] Bouffard postulated a mechanism suggesting that a *syn*-chelated conformer A was involved in their stereoselective reduction of a β-ketolactam system (R_1 = H, R_2 = CH_3) (Figure 4). Preferred attack of the borohydride anion on the β-face of the ketone carbonyl generates the (*R*)-carbinol. In our system where R_1 is the methyl group and R_2 is the long side chain, we tentatively concluded that the steric interference between the bulky R_2 and the β-lactam ring disfavored conformer A, driving the conformational equilibrium toward conformer B in which β-face attack on the ketone carbonyl generated the (*S*)-carbinol **43**. Attack on the face of the ketone carbonyl opposite that indicated is disfavored in both cases by steric interference due to H_a and electrostatic repulsion between the negatively charged borohydride anion and the lone pair electrons of the lactam nitrogen.[41] When the KEt_3BH reduction of **42** was carried out in CH_2Cl_2 instead of Et_2O, a 4:1 mixture of (*S*)- to (*R*)-carbinols was obtained. Consistent with the above mechanism, the poorer cationic solvating ability of CH_2Cl_2 relative to Et_2O should be expected to shift the conformational equilibrium to the *syn*-chelated conformer A which would give *R* product on β-face reduction.

Macrocyclization and Synthesis of Relay 4. With the C(12) through C(8) core of the target **1** correctly arrayed in **46**, we addressed the identity of linch-pin synthon **6**. We first designed this to be vinylstannane−sulfone **48**, prepared by us from the known alcohol **47**[42] (Scheme 10). The imidazolyl sulfone functional group was chosen in the hope that it would direct the nucleophilicity of its anion to the α-position.[43] In model studies, regiospecific anion addition of **48** to cinnamaldehyde produced in 86% yield the adduct **49** as a statistical mixture of diastereomers. Subsequent Stille coupling of **49** to the acyclic

(39) For an analogous C-acylation, see ref 11e.

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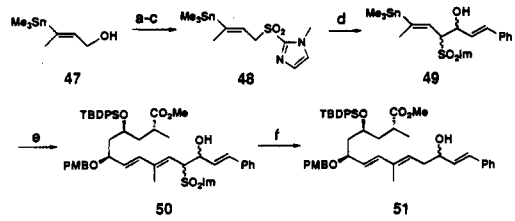
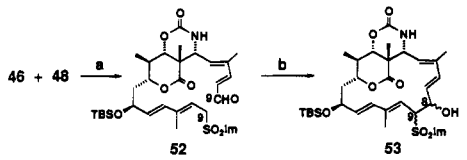
Scheme 10[a]



[a] Conditions: (a) NCS, Me_2S; (b) imidazolyl sulfide, Et_3N; (c) mCPBA, 54% overall; (d) NaHMDS, THF, −78 °C, and then cinnamaldehyde, 86%; (e) 5% $PdCl_2(MeCN)_2$, **34a**, DMF, rt, 2 h, 87%; (f) 5% $PdCl_2(MeCN)_2$, 1.0 equiv of $LiBH_4$, THF, 0 °C, 5 min, 80%.

Scheme 11[a]



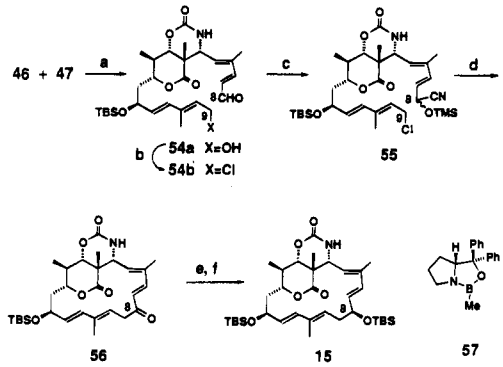
[a] Conditions: (a) 5% $PdCl_2(MeCN)_2$, DMF, rt, 92%; (b) LiHMDS, (TMS)Cl, THF, −78 °C; AcOH, aqueous THF, 63%.

iodovinyl ester **34a** efficiently yielded **50** (87%). As important, moreover, was our finding that, in the presence of $PdCl_2$ and $LiBH_4$ at 0 °C,[44] **50** was chemoselectively desulfurized to yield product **51**, in which the three double bonds and the ester were retained with no (*E*)/(*Z*)-alkene isomerization.

With the success of our model studies, we applied synthon **48** to the iodo aldehyde **46** (Scheme 11). Stille coupling of **48** and **46** gave in 92% yield the tetraenal **52**. Subsequent intramolecular anion addition of C(9) to C(8) aldehyde successfully formed the macrocycle product **53** in 57% yield as a mixture of C(8) epimeric alcohols, whose stereochemistry could not be determined by spectrometric methods. The addition of sulfone anion to aldehyde was a capricious process due to the potential equilibrium between product alkoxy sulfone and starting material. TMS trapping of the initial aldol product followed by acetic acid deprotection was found essential to drive the reaction to completion. Unfortunately, subsequent attempts to desulfurize **53**, including the Inomata method that worked quite well for our model system, only led to decomposition. In an attempt to circumvent this problem, we tried to oxidize the C(8) hydroxyl group to the carbonyl group before desulfurization. However, Dess−Martin oxidation of **53** only gave an 8,9-diketone product in low yield (20%).[45] The frustrating results of the desulfurization and the lack of stereocontrol at the C(8) center prompted us to change our tactics.

We turned our attention to the feasibility of Stork−Takahashi cyanohydrin chemistry. Despite its success in a number of natural product syntheses,[46] this method has never been applied to a highly functionalized system like lankacidin C. Stille coupling of iodo aldehyde **46** with the stannane−alcohol **47** gave in 90% yield the carbinol **54a**, which was converted to the chloride **54b** quantitatively by the Collington−Meyers procedure[47] (Scheme 12). The chloride **54b** was reacted with

Scheme 12[a]



[a] Conditions: (a) 5% $PdCl_2(MeCN)_2$, DMF, rt, 90%; (b) MsCl, 2,6-lutidine, LiCl, DMF, 0 °C; (c) (TMS)CN, catalytic KCN/18-crown-6 complex; (d) LiHMDS, THF, −78 °C; AcOH, THF−H_2O; 1% aqueous NaOH, 61% from **54a**; (e) BH_3−THF, 5% CBS reagent **57**, THF, −10 °C, 89%; (f) (TBS)Cl, imidazole, DMF, rt, 95%.

trimethylsilyl cyanide in the presence of a catalytic amount of KCN/18-crown-6 complex to produce the Stork−Takahashi intermediate **55**. The macrocyclization was immediately carried out by treating a dilute solution of **55** in tetrahydrofuran (0.02 M) with excess lithium bis(trimethylsilyl)amide at −78 °C for 30 min. After mild hydrolysis, we were gratified to obtain the desired macrocycle **56**, mp 155−157°, in 61% yield from **54a**.

The critical stereospecific reduction of C(8) ketone was now examined. The general method for 1,2-reduction of conjugated ketones developed by Luche,[48] which utilizes a combination of $NaBH_4$ and $CeCl_3$ in methanol, gave a complex mixture in our system. L-Selectride reduction gave a 1:1 mixture of the 1,4-reduction product and the epimeric 1,2-reduction products, with the undesired 8α-carbinol predominating.[49] The stereospecific reduction of the C(8) ketone was finally achieved by use of the (*R*)-oxazaborolidine-catalyzed CBS borane method.[50] This method was chosen on the basis of its excellent enantioselectivities, catalytic nature, short reaction time, high selectivity for 1,2-reduction of conjugated ketones,[50a] and documented success in the synthesis of MK-0417.[50b] Treatment of a solution of **56** in tetrahydrofuran with BH_3·THF (0.67 equiv) at −10 °C for 30 min in the presence of 10 mol % (*R*)-CBS catalyst **57** gave a 10:1 mixture of 8β- to 8α-carbinols in 89% yield.[49] When the (*S*)-CBS catalyst was used, the 8α-carbinol was produced exclusively in 91% yield.[49] Silylation of the desired 8β-carbinol ((TBS)Cl, imidazole, DMF) produced in 96% yield a crystalline tricyclic lactone carbamate, mp 187−188 °C, $[\alpha]^{22}_D = -69.9°$, having a mixed melting point, TLC properties, ^1H NMR, ^{13}C NMR, IR, and FAB-MS experimentally indistinguishable from those of authentic **15** prepared from lankacidin C.

Since we had already carried out the relay conversion of **15** to **1**, our synthesis of **15** thus completes the first total synthesis of lankacidin C.

Conclusion

A convergent, stereoselective synthesis of the macrolide antitumor antibiotic lankacidin C is described. The most noteworthy aspect of the synthesis has been the successful use

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(48) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(49) The C(8) stereochemistry of the reduction product was established by comparing the spectra of the corresponding TBS ether with those of the relay **15**.

(50) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Thomas, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

of the novel intramolecular N → O acyl migration strategy to construct the δ-lactone **44** from the β-lactam **43**. This paper also provides a good illustration for application of the Stork–Takahashi cyanohydrin methodology within a highly functionalized system. Our synthetic approach to lankacidin C allows easy access to other lankacidin family members by simple manipulation of protecting groups. Degradation chemistry on lankacidin C shown in this paper may lead to novel lankacidin derivatives with higher biological reactivities worthy of clinical development.

Experimental Section

General Procedures. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. *N,N*-Dimethylformamide, 2,6-lutidine, and dimethyl sulfoxide were distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves under argon. Dicholoromethane, diisopropylamine, triethylamine, benzene, and toluene were freshly distilled from calcium hydride. Oxalyl chloride was distilled at 760 Torr immediately prior to use. All reactions involving air- or moisture-sensitive reactants were performed in flame-dried glassware fitted with rubber septa under a positive pressure of dry nitrogen or argon. Flash chromatography was performed using silica gel 60 (230–400 mesh) with the indicated solvent. Thin-layer chromatography was performed using 250 μm (analytical) or 500 μm (preparative) silica gel (230–400 mesh) plates impregnated with a fluorescent indicator (254 nm). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a GE QE-300 (300 MHz) NMR spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$, δ 7.27). Data are presented as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonances), coupling constant in hertz (Hz), integration. IR spectra were recorded as solutions in chloroform ($CHCl_3$) and reported in wavenumbers (cm^{-1}).

2-Deoxy-3-*O*-[(4-methoxyphenyl)methyl]-4,5-*O*-(1-methylethylidene)-D-*erythro*-pentose (29). To a solution of 8.0 g (28.6 mmol) of alcohol **11**[20] in 400 mL of DMF was added 2.3 g (57.5 mmol) of NaH (60% mineral oil dispersion) in one portion, and the resulting suspension was stirred at ambient temperature for 3 h. The reaction was cooled to 0 °C, and 5.35 g (34.3 mmol) of *p*-methoxybenzyl bromide was added dropwise over a period of 15 min. The reaction was warmed to ambient temperature and stirred for 45 min. The mixture was poured into 800 mL of cold water and extracted with ethyl acetate (3 × 400 mL). The combined extracts were washed with water (4 × 150 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The pale yellow residue was purified by flash chromatography (8% EtOAc/hexane) to give 10.37 g (91%) of the PMB ether as a clear oil: $[\alpha]^{25}_D$ −14.4° (*c* 3.2, MeOH); IR ($CHCl_3$) 2940, 1630, 1520, 1225, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.17–3.88 (m, 5H), 3.81 (s, 3H), 2.70–2.55 (q, *J* = 8.0 Hz, 4H), 2.01–1.95 (m, 2H), 1.45 (s, 3H), 1.35 (s, 3H), 1.24 (t, *J* = 8.0 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.2, 130.6, 129.4, 113.7, 108.9, 78.4, 76.4, 73.0, 65.9, 55.0, 47.6, 38.8, 26.4, 25.2, 24.2, 23.3, 14.5, 14.4. Anal. Calcd for $C_{20}H_{32}O_4S_2$: C, 59.96; H, 8.05. Found: C, 59.80; H, 8.01.

To a solution of 1.0 g (2.50 mmol) of the PMB ether in 35 mL of acetonitrile and 7 mL of water was added 1.15 g (11.5 mmol) of calcium carbonate and 2.71 g (9.98 mmol) of mercuric chloride. The heterogeneous reaction mixture was stirred at ambient temperature for 50 min and filtered through a pad of Celite with acetonitrile. The filtrate was concentrated *in vacuo*, and the residue was dissolved in 150 mL of ether. This ether solution was washed with 1 M KI solution (4 × 15 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% ethanol/hexane) gave 0.57 g (77%) of aldehyde **29** as a clear oil: $[\alpha]^{25}_D$ +15.2° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3000, 1725, 1615, 1510, 1380, 1225, 1070, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.10 (m, 2H), 3.96 (dd, *J* = 5.5, 5.8 Hz, 1H), 3.83 (m, 1H), 3.80 (s, 3H), 2.72 (dd, *J* = 5.5, 2.0 Hz, 2H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.3, 159.3, 129.8, 129.5, 113.7, 109.4, 77.2, 74.9, 72.0, 66.6, 55.0, 45.6, 26.4, 25.0. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.54; H, 7.49.

[4*R*-[4*R[α*R**(*S**),γ*S**]]]-γ-[(4-Methoxyphenyl)methoxy]-2,2-dimethyl-α-(1-methyl-2-propenyl)-1,3-dioxolane-4-propanol (30).** To a solution of 1.12 g (9.51 mmol) of potassium *tert*-butoxide in 9.0 mL of THF at −78 °C was added 5.0 mL (55 mmol) of *trans*-2-butene. A 3.88 mL (9.51 mmol, 2.45 M in hexane) sample of *n*-butyllithium was introduced at such a rate that the internal temperature was kept below −65 °C. The reaction was allowed to warm to −50 °C and stirred at that temperature for 15 min before it was cooled to −78 °C. (+)-*B*-Methoxydiisopinocampheylborane (9.51 mmol, 1.0 M in ethyl ether) was introduced at such a rate that the internal temperature was kept below −65 °C. After the reaction was stirred for 10 min at −78 °C, 1.75 g (12.36 mmol) of BF_3–Et_2O was added slowly, followed by a solution of 2.91 g (9.89 mmol) of aldehyde **29** in 11 mL of THF. The cloudy reaction mixture was stirred at −78 °C for 1.5 h. A 3 M NaOH aqueous solution (3.6 mL) was added to quench the reaction, and the mixture was allowed to warm to the ambient temperature. A 1.7 mL sample of 30% H_2O_2 aqueous solution was added carefully, and the mixture was stirred until the gas evolution ceased. The mixture was poured into 200 mL of ethyl ether and washed with water (2 × 10 mL) and brine (20 mL). The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2, 3% Et_2O/CH_2Cl_2, and finally 10% Et_2O/CH_2Cl_2) gave 2.03 g (58%) of the alcohol **30** as a clear oil: $[\alpha]^{25}_D$ −4.3° (*c* 2.37, MeOH); IR ($CHCl_3$) 3480, 2980, 1610, 1510, 1375, 1225, 1065, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.77 (m, 1H), 5.05 (m, 2H), 4.72 (d, 11.0 Hz, 1H), 4.55 (d, 11.0 Hz, 1H), 4.18 (m, 1H), 3.91–4.05 (m, 2H), 3.85 (m, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.08 (d, 1H, −O*H*), 2.23 (m, 1H), 1.50–1.69 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 140.2, 130.0, 129.6, 115.3, 113.8, 109.0, 78.2, 78.0, 73.0, 72.5, 65.8, 55.1, 43.8, 35.3, 26.4, 25.1, 15.6. Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.65.

[4*R*-[4*R[*S**(1*R**,2*S**)]]]-[[1-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-[(4-methoxyphenyl)methoxy]ethyl]-2-methyl-3-butenyl]oxy](1,1-dimethylethyl)diphenylsilane (30a).** To a solution of 9.0 g (25.68 mmol) of alcohol **30** in 25 mL of DMF at ambient temperature were added 8.7 g (128 mmol) of imidazole and 17.65 g (64.22 mmol) of (TBDPS)Cl. After 48 h, the solution was poured into 600 mL of Et_2O and washed with water (4 × 100 mL) and brine (100 mL). The ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (6% ethanol/hexane) gave 12.68 g (84%) of **30a** as a clear oil: $[\alpha]^{25}_D$ −13.6° (*c* 3.66, MeOH); IR ($CHCl_3$) 2940, 1610, 1510, 1225, 1110, 1065, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4H), 7.44–7.33 (m, 6H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.83 (m, 1H), 5.02 (m, 1H), 4.88 (m, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.29 (d, *J* = 11.0 Hz, 1H), 3.90–3.85 (m, 2H), 3.81 (s, 3H), 3.75 (m, 1H), 3.70 (m, 1H), 3.54 (m, 1H), 2.06 (m, 1H), 1.60–1.54 (m, 2H), 1.36 (s, 3H), 1.31 (s, 3H), 1.07 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H). Anal. Calcd for $C_{36}H_{48}O_5Si$: C, 73.43; H, 8.22. Found: C, 73.52; H, 8.15.

2,4-Dideoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-5-*O*-[(4-methoxyphenyl)methyl]-2-methyl-6,7-*O*-(1-methylethylidene)-D-*allo*-heptose (31). To a solution of 6.3 g (10.7 mmol) of **30a** in 60 mL of CH_2Cl_2 and 60 mL of MeOH was added 10 mg (0.03 mmol) of Sudan III dye. The solution was cooled to −78 °C, and a stream of oxygen–ozone was bubbled into the red-colored reaction mixture until the color turned yellow. The solution was immediately flushed with argon to remove excess ozone, and 7.6 g (105 mmol) of dimethyl sulfide was added at −78 °C. The reaction mixture was allowed to warm to ambient temperature slowly and concentrated *in vacuo* to give 6.9 g of crude aldehyde **31**, which was used immediately in the subsequent reaction without further purification because of partial racemization during silica gel chromatography: IR ($CHCl_3$) 2950, 1720, 1610, 1510, 1370, 1225, 1110, 1070, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.0 Hz, 1H), 7.70–7.64 (m, 4H), 7.50–7.35 (m, 6H),

7.02 (d J = 8.5 Hz, 2H), 6.79 (d J = 8.5 Hz, 2H), 4.46 (d, J = 11.0 Hz, 1H), 4.31 (d, J = 11.0 Hz, 1H), 4.14 (m, 1H), 3.91 (m, 1H), 3.80 (s, 3H), 3.84 (m, 1H), 3.65 (m, 1H), 3.58 (m, 1H), 2.30 (m, 1H), 1.73 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 1.06 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H).

2,4-Dideoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-5-*O*-[(4-methoxyphenyl)methyl]-2-methyl-6,7-*O*-(1-methylethylidene)-D-*allo*-heptaldonic Acid Methyl Ester (32). To a solution of 6.9 g (11.7 mmol) of crude aldehyde **31** in 30 mL of MeCN and 10 mL of DMSO were added 0.43 g (3.5 mmol) of NaH_2PO_4 as a solution in 5 mL of water and 2.35 g (19.9 mmol) of $NaClO_2$ (80%) as a solution in 15 mL of water. The reaction mixture was stirred at ambient temperature for 2 h and poured into 250 mL of EtOAc and 50 mL of water. The organic layer was washed with 30 mL each of water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5−15% ethanol/hexane) gave 5.65 g (78%, two steps) of the acid as a white foam: $[\alpha]^{25}_D$ −19.5° (*c* 2.63, MeOH); IR ($CHCl_3$) 2940, 1750, 1710, 1615, 1375, 1225, 1110, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76−7.62 (m, 4H), 7.49−7.35 (m, 4H), 7.03 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.49 (d, J = 11.0 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.02(m, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.77 (m, 1H), 3.65 (m, 1H), 2.42 (m, 1H), 1.72 (m, 2H), 1.35 (s, 3H), 1.27 (s, 3H), 1.07 (s, 9H), 1.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.9, 158.8, 135.8, 135.7, 133.4, 132.6, 130.3, 129.6, 129.5, 129.1, 127.4, 127.3, 113.4, 108.7, 77.7, 73.9, 72.3, 71.8, 64.7, 54.9, 43.7, 36.0, 26.8, 26.0, 24.9, 19.1, 13.2. Anal. Calcd for $C_{35}H_{46}O_7Si$: C, 69.27; H, 7.64. Found: C, 69.05, H, 7.25.

To a solution of 6.0 g (58 mmol) of *N*-nitrosomethylurea in 150 mL of Et_2O at 0 °C was carefully added 55 mL of a 3.0 M NaOH aqueous solution. After the addition was complete, the ether phase was aspirated with a smooth-tipped Pasteur pipet and introduced dropwise into a solution of 10.2 g (16.8 mmol) of the above acid in 100 mL of Et_2O until the yellow color persisted. The reaction mixture was stirred for 15 min at 0 °C, and anhydrous $MgSO_4$ was added to destroy the excess diazomethane. The mixture was filtered and concentrated *in vacuo*. Purification by flash chromatography (25% Et_2O/hexane) gave 9.11 g (87%) of the ester **32** as a clear oil: $[\alpha]^{25}_D$ −20.4° (*c* 2.33, MeOH); IR ($CHCl_3$) 2920, 1730, 1610, 1510, 1460, 1425, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.44−7.35 (m, 6H), 7.07 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.33 (d, J = 11.0 Hz, 1H), 4.10 (m, 1H), 3.78 (s, 3H), 3.75−3.63 (m, 4H), 3.60 (s, 3H), 2.53 (m, 1H), 1.62 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H), 1.04 (s, 9H), 1.00 (d, J = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.3, 159.1, 136.1, 134.2, 133.5, 130.7, 130.0, 129.7, 129.3, 127.6, 127.5, 113.7, 108.9, 78.3, 74.3, 72.6, 72.2, 64.9, 55.2, 51.3, 44.1, 36.0, 27.1, 26.3, 25.3, 19.4, 13.0. Anal. Calcd for $C_{36}H_{48}O_7Si$: C, 69.64; H, 7.79. Found: C, 69.32; H, 8.03.

3,5-Dideoxy-4-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-*O*-[(4-methoxyphenyl)methyl]-5-methyl-L-*ribo*-hexuronic Acid Methyl Ester (33). To a solution of 1.01 g (1.63 mmol) of **32** in 30 mL of MeOH was added 1.52 g (8.9 mmol) of $CuCl_2{\cdot}2H_2O$, and the green reaction mixture was refluxed for 1 h. The reaction was cooled to ambient temperature, and 2 g of $NaHCO_3$ was added. After the evolution of carbon dioxide ceased, 15 mL of water was added and the resulting blue precipitate was filtered off through a pad of Celite with EtOAc. The filtrate was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (6% ethanol/hexane) gave 0.92 g (97%) of the expected diol as a clear oil: $[\alpha]^{25}_D$ −13.5° (*c* 2.18, MeOH); IR ($CHCl_3$) 3445, 2940, 1725, 1610, 1510, 1460, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.68 (m, 4H), 7.46−7.37 (m, 6H), 7.07 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 4.53 (d, J = 10.1 Hz, 1H), 4.33 (d, J = 10.1 Hz, 1H), 4.13 (m, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.57−3.44 (m, 4H), 2.60 (m, 1H), 2.42 (d, J = 5.1 Hz, 1H, secondary −O*H*), 2.21 (m, 1H, primary −O*H*), 1.81−1.67 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.5, 159.2, 136.0, 133.8, 133.5, 130.2, 129.8, 129.4, 127.6, 127.5, 113.5, 76.7, 73.1, 72.5, 71.3, 62.9, 55.1, 51.4, 44.1, 35.4, 27.0, 19.4, 12.6. Anal. Calcd for $C_{33}H_{44}O_7Si$: C, 68.24; H, 7.64. Found: C, 68.27; H, 7.86.

To a solution of 0.92 g (1.58 mmol) of the diol in 15 mL of THF at 0 °C was added 1 g (2.14 mmol) of $Pb(OAc)_4$ as a solution in 15 mL of THF. The mixture was stirred at 0 °C for 40 min, and ethylene glycol was added to destroy the excess $Pb(OAc)_4$. After 10 min, the mixture was filtered through a pad of Celite with EtOAc. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine (20 mL each), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.02 g of the crude aldehyde **33** as a yellow oil, which was used without further purification because of partial racemization during silica gel chromatography: IR ($CHCl_3$) 2940, 1730, 1610, 1510, 1460, 1425, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J = 0.96 Hz, 1H), 7.70−7.66 (m, 4H), 7.45−7.36 (m, 6H), 7.15 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.26 (m, 1H), 3.85 (m, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 2.65 (m, 1H), 1.90−1.78 (m, 2H), 1.07 (d, J = 7.0 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.1, 174.5, 159.5, 136.0, 133.7, 133.2, 129.7, 129.6, 129.5, 129.3, 129.2, 127.7, 113.9, 113.8, 113.7, 79.5, 71.8, 71.7, 55.2, 51.4, 44.5, 33.6, 27.0, 19.4, 12.6.

[2*R*-(2*R,3*R**,5*S**,6*E*)]-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-7-iodo-5-[(4-methoxyphenyl)methoxy]-2-methyl-6-heptenoic Acid Methyl Ester (34a).** To a suspension of 1.2 g (9.75 mmol) of $CrCl_2$ in 15 mL of THF were added 1.02 g (1.58 mmol) of the crude aldehyde **33** in 10 mL of THF and 1.25 g (3.17 mmol) of CHI_3. The reaction was sonicated for 1 h and quenched with 5 mL of water. The mixture was poured into 100 mL of Et_2O and 50 mL of a 10% $Na_2S_2O_3$ aqueous solution. The organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (6% EtOAc/hexane) gave 0.7 g (62% two steps) of **34a** as a clear oil: $[\alpha]^{25}_D$ −78.6° (*c* 1.57, MeOH); IR ($CHCl_3$) 2950, 1730, 1610, 1510, 1460, 1430, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.61 (m, 4H), 7.50−7.35 (m, 6H), 7.10 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.00 (dd, J = 16.0, 7.5 Hz, 1H), 5.33 (d, J = 16.0 Hz, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.05 (d, J = 11.0 Hz, 1H), 4.04 (m, 1H), 3.82 (s, 3H), 3.59 (s, 3H), 3.64−3.53 (m, 1H), 2.75 (m, 1H), 1.88 (m, 1H), 1.60 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 1.01 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.3, 159.2, 146.0, 136.1, 136.0, 133.7, 133.5, 130.0, 129.9, 129.3, 127.8, 127.7, 127.5, 113.8, 79.3, 77.8, 71.3, 69.8, 55.2, 51.6, 45.4, 39.0, 27.1, 26.9, 11.6. Anal. Calcd for $C_{33}H_{41}IO_5Si$: C, 58.92; H, 6.14. Found: C, 59.14; H, 6.24.

[2*R*-(2*R,3*R**,5*S**,6*E*)]-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-7-iodo-5-[(4-methoxyphenyl)methoxy]-2-methyl-6-heptenoic Acid (34b).** To a solution of 1.25 g (1.9 mmol) of **34a** in 35 mL of a mixture of THF−H_2O−MeOH (6:3:2) at ambient temperature was added 0.47 g (11.2 mmol) of $LiOH{\cdot}H_2O$. After 12 h, the reaction mixture was diluted with 20 mL of water and the pH value of the solution was adjusted to 4−5 by adding 0.1 N aqueous HCl. The aqueous phase was extracted with Et_2O (4 × 30 mL). The combined organic layers were washed with water and brine (40 mL each), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% ethanol/hexane) gave 0.94 g (75%) of **34b** as a white foam: $[\alpha]^{25}_D$ −70.5° (*c* 1.54, MeOH); IR ($CHCl_3$) 2920, 2860, 1720, 1610, 1510, 1460, 1425, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.50−7.35 (m, 6H), 7.07 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 6.06 (dd, J = 14.5, 8.0 Hz, 1H), 5.55 (d, J = 14.5 Hz, 1H), 4.32 (d, J = 7.3 Hz, 1H), 4.05 (d, J = 7.3 Hz, 1H), 4.07−4.01 (m, 1H), 3.81 (s, 3H), 3.66 (m, 1H), 2.67 (m, 1H), 1.91−1.63 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.2, 158.9, 145.4, 135.7, 133.2, 132.7, 129.7, 129.6, 129.0, 127.4, 113.5, 78.9, 77.4, 69.5, 55.0, 44.5, 38.9, 26.6, 12.1. Anal. Calcd for $C_{32}H_{39}IO_5Si$: C, 58.35; H, 5.97. Found: C, 57.97; H, 6.13.

[2*R*-(2*R,3*R**,5*S**,6*E*)]-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-7-iodo-5-[(4-methoxyphenyl)methoxy]-2-methyl-6-heptenoic Acid (*S*)-2-Pyridinyl Ester (34c).** To a solution of 60.3 mg (0.23 mmol) of Ph_3P and 50.3 mg (0.23 mmol) of $(2\text{-PyS})_2$ in 3 mL of THF was added at ambient temperature 0.10 g (0.15 mmol) of **34b** as a solution in THF (1.5 mL). After 15 h, the solvent was evaporated *in vacuo*. Purification by flash chromatography (20% EtOAc/hexane) gave 99 mg (89%) of **34c** as a yellow oil: $[\alpha]^{25}_D$ −139.8° (*c* 1.10, MeOH); IR ($CHCl_3$) 2940, 2860, 1700, 1610, 1575, 1510, 1450, 1420, 1225, 1110, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 3.9 Hz, 1H), 7.72−7.64 (m, 6H), 7.50−7.35 (m, 8H), 7.14 (d, J = 8.5 Hz, 1H),

6.86 (d, J = 8.5 Hz, 1H), 6.03 (dd, J = 14.6, 8.1 Hz, 1H), 5.43 (d, J = 14.6 Hz, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.18 (m, 1H), 4.09 (d, J = 11.2 Hz, 1H), 3.82 (s, 3H), 3.75 (m, 1H), 3.07 (m, 1H), 1.86−1.64 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.2, 159.2, 150.3, 145.9, 136.9, 136.1, 136.0, 133.6, 133.5, 130.1, 129.9, 129.5, 128.0, 127.8, 127.7, 123.4, 113.9, 79.6, 77.4, 71.6, 69.9, 55.3, 54.3, 38.3, 27.0, 12.3. Anal. Calcd for $C_{37}H_{42}INO_4SSi$: C, 59.11; H, 5.63. Found: C, 59.35; H, 5.37.

[3*S*-[3α(2*R,3*S**,5*R**,6*E*),4β(1*E*,3*E*)]-1-[(1,1-Dimethylethyl)-dimethylsilyl]-4-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1,3-pentadienyl]-3-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-7-iodo-5-[(4-methoxyphenyl)methoxy]-2-methyl-1-oxo-6-heptenyl]-3-methyl-2-azetidinone (42).** To a solution of lithium diisopropylamide (1.76 mmol) in 5 mL of THF (generated from 1.1 mL of 1.6 M *n*-BuLi in hexane and 0.27 mL of diisopropylamine at −78 °C) at −78 °C was added dropwise 0.55 g (1.34 mmol) of **41** in 5 mL of THF. The orange solution was stirred at −78 °C for 20 min, and then it was transferred *via* cannula to a solution of 1.0 g (1.33 mmol) of **34c** in 5 mL of THF at −78 °C. The reaction mixture was stirred at −78 °C for 10 min before it was quenched with 0.5 mL of saturated aqueous NH_4Cl. The mixture was warmed to ambient temperature, diluted with 50 mL of Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 1.17 g (85%) of **42** as a clear oil: $[\alpha]^{25}_D$ −57.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2960, 2930, 2860, 1735, 1280, 1225, 1110, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.4 (m, 6H), 7.14 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.26 (d, J = 15.6 Hz, 1H), 5.87 (dd, J = 8.3, 14.6 Hz, 1H), 5.77 (dt, J = 15.6, 5.1 Hz, 1H), 5.30 (d, J = 9.2 Hz, 1H), 5.14 (d, J = 15.6 Hz, 1H), 4.92 (d, J = 9.1 Hz, 1H), 4.27 (m, overlapping signals, 2H), 4.0 (m, overlapping signals, 2H), 3.82 (s, 3H), 3.62 (q, J = 4.3 Hz, 1H), 3.52 (t, J = 6.6 Hz, 1H), 1.84 (s, 3H), 1.82 (m, 2H), 1.75 (m, 1H), 1.15 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.93 (s, 9H), 0.23 (s, 3H), 0.12 (s, 3H), 0.09 (s, 6H). Anal. Calcd for $C_{54}H_{80}INO_6Si_3$: C, 61.75; H: 7.68. Found: C, 61.44; H, 7.88.

[3*S*-[3α(1*R,2*R**,3*S**,5*R**,6*E*),4β(1*E*,3*E*)]-1-[(1,1-Dimethylethyl)-dimethylsilyl]-4-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1,3-pentadienyl]-3-[3-[[(1,1-diphenylethyl)dimethylsilyl]oxy]-1-hydroxy-7-iodo-5-[(4-methoxyphenyl)methoxy]-2-methyl-6-heptenyl]-3-methyl-2-azetidinone (43).** To a solution of 0.765 g (0.738 mmol) of ketone **42** in 12 mL of Et_2O at −78 °C was added dropwise 1.0 mL (1.0 mmol, 1.0 M in Et_2O) of KEt_3BH. The reaction mixture was stirred for 10 min at −78 °C before it was quenched with 0.5 mL of saturated aqueous NH_4Cl. The mixture was warmed to ambient temperature, diluted with 50 mL of Et_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexane) gave 0.65 g (85%) of **43** as a clear oil: $[\alpha]^{25}_D$ −68.0° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 2960, 2930, 2860, 1735, 1280, 1225, 1110, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.4 (m, 6H), 7.14 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.26 (d, J = 15.6 Hz, 1H), 5.87 (dd, J = 8.3, 14.6 Hz, 1H), 5.77 (dt, J = 15.6, 5.1 Hz, 1H), 5.30 (d, J = 9.2 Hz, 1H), 5.14 (d, J = 15.6 Hz, 1H), 4.92 (d, J = 9.1 Hz, 1H), 4.27 (m, overlapping signals, 2H), 4.0 (m, overlapping signals, 2H), 3.82 (s, 3H), 3.62 (q, J = 4.3 Hz, 1H), 3.52 (t, J = 6.6 Hz, 1H), 1.84 (s, 3H), 1.82 (m, 2H), 1.75 (m, 1H), 1.15 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.93 (s, 9H), 0.23 (s, 3H), 0.12 (s, 3H), 0.09 (s, 6H). Anal. Calcd for $C_{54}H_{82}INO_6Si_3$: C, 61.63; H: 7.85. Found: C, 61.47; H, 7.58.

[4*R*-[4α(2*E*,4*E*),4aβ,7α(2*S,3*E*),8β,8aβ]-1*H*-Imidazole-1-carboxylic Acid 5-[Hexahydro-7-[4-iodo-2-[(4-methoxyphenyl)methoxy]-3-butenyl]-4a,8-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazin-4-yl]-4-methyl-2,4-pentadienyl Ester (44).** To a solution of 0.79 g (0.76 mmol) of **43** in 13 mL of THF at ambient temperature was added 4.5 mL (4.5 mmol, 1.0 M in THF) of Bu_4NF. After 2 h, 0.5 mL (7.7 mmol) of methanesulfonic acid was added. The reaction mixture was stirred at ambient temperature for 2 h before 1.6 mL (11.5 mmol) of triethylamine was added. After 20 min, 1.0 g (6.1 mmol) of 1,1′-carbonyldiimidazole was added. After 12 h, the reaction mixture was poured into 100 mL of EtOAc and 50 mL of water. The aqueous layer was extracted with 50 mL of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 0.45 g (85%) of **44** as a foam: $[\alpha]^{25}_D$ +78.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3420, 2990, 1755, 1720, 1398, 1295, 1095, 1000, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.42 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.07 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.44 (m, 2H), 6.33 (d, J = 15.6 Hz, 1H), 6.0 (br s, −N*H*, 1H), 5.89 (dt, J = 15.6, 6.6 Hz, 1H), 5.69 (d, J = 10.0 Hz, 1H), 4.91 (d, J = 6.6 Hz, 2H), 4.48 (d, J = 11.0 Hz, 1H), 4.3 (m, overlapping peaks, 2H), 4.11 (m, 1H), 4.04 (d, J = 9.4 Hz, 1H), 3.92 (m, 1H), 3.80 (s, 3H), 2.2 (m, 1H), 1.99 (m, 2H), 1.83 (s, 3H), 1.59 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.94, 159.28, 152.58, 148.43, 145.46, 139.47, 137.84, 137.10, 130.56, 129.67, 129.23, 129.13, 122.34, 117.14, 113.93, 84.37, 80.40, 77.76, 77.65, 70.40, 68.38, 55.88, 55.27, 45.64, 38.99, 37.84, 24.42, 14.18, 12.86. Anal. Calcd for $C_{31}H_{36}IN_3O_8$: C, 52.77; H, 5.14; N, 5.95. Found: C, 52.43; H, 5.22; N, 5.85.

[4*R*-[4α(2*E*,4*E*),4aβ,7α(2*S,3*E*),8β,8aβ]-5-[Hexahydro-7-[4-iodo-2-[(4-methoxyphenyl)methoxy]-3-butenyl]-4a,8-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazin-4-yl]-4-methyl-2,4-pentadienal (45).** To a solution of 0.76 g (1.08 mmol) of **44** in 30 mL each of 1,4-dioxane and water at ambient temperature was added 0.7 mL of concentrated hydrochloric acid (37% aqueous solution). After 8 h, the mixture was saturated with solid NaCl and layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 0.47 g (71%) of the expected alcohol as a white solid: mp 83−85 °C (from EtOAc); $[\alpha]^{25}_D$ +101.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 2990, 1725, 1398, 1295, 1095, 1000, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.44 (m, 2H), 6.19 (d, J = 15.7 Hz, 1H), 6.1 (br s, −N*H*, 1H), 5.89 (dt, J = 15.7, 5.5 Hz, 1H), 5.54 (d, J = 9.9 Hz, 1H), 4.48 (d, J = 11.1 Hz, 2H), 4.30 (m, overlapping peaks, 2H), 4.19 (d, J = 5.1 Hz, 1H), 4.12 (m, 1H), 4.02 (d, J = 9.7 Hz, 1H), 3.91 (m, 1H), 3.80 (s, 3H), 2.25 (m, 1H), 1.95 (m, 2H), 1.79 (s, 3H), 1.59 (s, 3H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.89, 159.28, 152.58, 145.44, 145.44, 138.64, 133.77, 130.13, 129.76, 129.23, 129.33, 126.51, 113.96, 84.42, 80.54, 77.81, 77.58, 70.41, 62.97, 55.99, 55.32, 45.53, 38.74, 37.85, 24.48, 14.16, 12.97. Anal. Calcd for $C_{27}H_{34}INO_7$: C, 53.03; H, 5.60; N, 2.29. Found: C, 53.31; H, 5.68; N, 2.39.

To a solution of 0.25 g (0.40 mmol) of the above obtained alcohol in 10 mL of CH_2Cl_2 at ambient temperature was added 0.25 g (0.59 mmol) of Dess−Martin periodinane. After the resultant suspension was stirred for 20 min, 5.0 mL each of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added. The mixture was stirred vigorously at ambient temperature for 15 min before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 0.21 g (85%) of **45** as a white solid: mp 88−90 °C (from EtOAc); $[\alpha]^{25}_D$ +105.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2990, 1730, 1680, 1398, 1295, 1095, 1000, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 15.7 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.46 (m, 2H), 6.23 (dd, J = 15.7, 7.6 Hz, 1H), 6.08 (d, J = 9.9 Hz, 1H), 5.78 (br s, −N*H*, 1H), 4.49 (d, J = 11.1 Hz, 2H), 4.34 (dd, J = 10.1, 3.4 Hz, 1H), 4.27 (d, J = 11.0 Hz, 1H), 4.10 (m, overlapping peaks, 2H), 3.97 (m, 1H), 3.81 (s, 3H), 2.18 (m, 1H), 2.00 (m, 2H), 1.90 (s, 3H), 1.62 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 193.65, 170.67, 159.28, 152.74, 145.39, 137.90, 135.77, 129.69, 129.24, 113.96, 84.43, 80.48, 77.73, 70.39, 55.87, 55.30, 45.87, 39.40, 37.85, 24.18, 14.25, 12.87. Anal. Calcd for $C_{27}H_{32}INO_7$: C, 53.21; H, 5.29. Found: C, 53.17; H, 5.42.

[4*R*-[4α(2*E*,4*E*),4aβ,7α(2*S,3*E*),8β,8aβ]-5-[Hexahydro-7-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-iodo-3-butenyl]-4a,8-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazin-4-yl]-4-methyl-2,4-pentadienal (46).** To a solution of 0.22 g (0.32 mmol) of PMB ether **45** in 5.0 mL of acetonitrile at 0 °C was added 0.526 g (0.96 mmol) of CAN in 1.5 mL of water. The reaction mixture was warmed to ambient temperature and stirred for 15 min. The mixture was diluted with 20 mL of EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through a small column of silica gel (EtOAc) to remove the inorganic salt. The filtrate was concentrated *in vacuo* to give 0.15 g (97%) of the alcohol as a white solid which

was used in the subsequent reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 15.7 Hz, 1H), 6.57 (dd, J = 14.4, 6.4 Hz, 1H), 6.47 (d, J = 14.4 Hz, 1H), 6.25 (dd, J = 15.7, 7.5 Hz, 1H), 6.15 (d, J = 10.1 Hz, 1H), 5.56 (d, J = 2.4 Hz, 1H), 4.42 (m, 1H), 4.36 (dd, J = 10.1, 3.4 Hz, 1H), 4.10 (m, overlapping peaks, 2H), 2.35 (m, 1H), 2.2 (d, J = 2.7 Hz, 1H), 1.95 (m, 2H), 1.90 (s, 3H), 1.65 (s, 3H), 1.23 (d, J = 6.5 Hz, 3H).

To a solution of 0.14 g (0.286 mmol) of the alcohol in 2.0 mL of DMF at ambient temperature were added 0.2 g (2.9 mmol) of imidazole and 0.2 g (1.3 mmol) of (TBS)Cl. After 1 h, the mixture was poured into 20 mL of Et_2O and 10 mL of H_2O. The aqueous phase was extracted with 15 mL of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 0.12 g (79%) of **46** as a white solid: mp 90−91 °C (from EtOAc); $[\alpha]^{25}_D$ +274.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 3430, 2950, 2930, 2855, 1735, 1680, 1250 (br), 1330, 1075, 910, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 15.7 Hz, 1H), 6.51 (dd, J = 14.5, 6.1 Hz, 1H), 6.35 (d, J = 14.5 Hz, 1H), 6.24 (dd, J = 15.7, 7.6 Hz, 1H), 6.15 (d, J = 10.1 Hz, 1H), 5.5 (br s, 1H), 4.41 (q, J = 5.6 Hz, 1H), 4.35 (dd, J = 10.1, 3.3 Hz, 1H), 4.09 (d, J = 9.0 Hz, 1H), 3.95 (dt, J = 3.1, 10.4 Hz, 1H), 2.12 (m, 1H), 1.91 (s, 3H), 1.88 (m, 2H), 1.62 (s, 3H), 1.21 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 193.45, 170.33, 154.96, 152.52, 147.29, 138.11, 135.59, 129.90, 84.44, 77.91, 77.24, 71.78, 56.10, 45.78, 41.02, 39.53, 25.72, 23.93, 18.06, 14.47, 12.93, −4.52, −4.83. Anal. Calcd for $C_{25}H_{38}INO_6Si$: C, 49.75; H, 6.34; N, 2.32. Found: C, 49.93; H, 6.24; N, 2.39.

[4*R*-[4α(2*E*,4*E*),4a*β*,7α(2*S,3*E*,5*E*),8*β*,8a*β*]-5-[Hexahydro-7-[7-hydroxy-5-methyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,5-heptadienyl]-4a,8-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazin-4-yl]-4-methyl-2,4-pentadienal (54a).** To a solution of 120 mg (0.20 mmol) of **46** and 70 mg (0.25 mmol) of **47**[42] in 1.0 mL of DMF at ambient temperature was added 8.0 mg (0.03 mmol) of $PdCl_2(MeCN)_2$. The dark reaction mixture was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc) gave 98 mg (90%) of **54a** as a solid: mp 88−90 °C (from EtOAc); $[\alpha]^{25}_D$ +175.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2950, 1727, 1680, 1250, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 15.7 Hz, 1H), 6.43 (d, J = 2.9 Hz, 1H), 6.3−6.1 (m, overlapping signals, 3H), 5.77 (dd, J = 15.7, 7.7 Hz, 1H), 4.46 (q, J = 5.6 Hz, 1H), 4.33 (dd, J = 9.9, 3.1 Hz, 1H), 4.27 (d, J = 6.8 Hz, 2H), 2.12 (m, 1H), 1.91 (m, 1H), 1.89 (s, 3H), 1.78 (s, 3H), 1.60 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 193.51, 170.45, 154.98, 152.32, 138.07, 135.75, 135.21, 130.66, 130.63, 129.91, 84.44, 77.79, 70.23, 59.21, 56.15, 45.62, 42.00, 39.27, 25.78, 23.93, 18.06, 14.50, 12.93, 12.67, −4.24, −4.72. Anal. Calcd for $C_{29}H_{45}NO_7Si$: C, 63.59; H, 8.28; N, 2.32. Found: C, 63.12; H, 8.08; N, 2.37.

[4*R*-[4α(2*E*,4*E*),4a*β*,7α(2*S,3*E*,5*E*),8*β*,8a*β*]-5-[Hexahydro-7-[7-chloro-5-methyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,5-heptadienyl]-4a,8-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazin-4-yl]-4-methyl-2,4-pentadienal (54b).** To a solution of 83 mg (0.15 mmol) of **54a** in 2.0 mL of DMF was added 21 μL (0.18 mmol) of 2,6-lutidine and 12.7 mg (0.3 mmol) of LiCl. The mixture was cooled to 0 °C, and 14 μL (0.18 mmol) of methanesulfonyl chloride was added dropwise. After 3 h at 0 °C, the reaction mixture was partitioned between 10 mL each of Et_2O and cold water. The aqueous layer was extracted with 10 mL of Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give 85 mg of the crude **54b** which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 15.7 Hz, 1H), 6.3−6.1 (m, overlapping signals, 4H), 5.75−5.63 (m, overlapping signals, 2H), 4.48 (q, J = 5.9 Hz, 1H), 4.35 (dd, J = 10.0, 3.3 Hz, 1H), 4.40 (dd, J = 8.2, 2.2 Hz, 2H), 4.07 (d, J = 9.4 Hz, 1H), 3.94 (m, 1H), 2.15 (m, 1H), 1.93 (m, 2H), 1.89 (s, 3H), 1.84 (s, 3H), 1.60 (s, 3H), 1.19 (d, J = 6.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 193.36, 170.40, 154.81, 154.78, 138.12, 138.09, 135.53, 134.30, 132.14, 129.98, 126.59, 84.50, 77.64, 70.03, 56.23, 45.72, 41.92, 40.55, 39.42, 25.76, 24.05, 18.07, 14.47, 12.92, 12.40, −4.29, −4.72.

[1*S*,5*R*,5*E*,8*E*,12*E*,14*E*,16*S*,18*R*,21*S*,22*R*]-7,12,21,22-Tetramethyl-16-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,10,20-trioxo-2,19,4-dioxaazatricyclo[16.3.1.0^{5,21}]docosa-6,8,12,14-tetraene (56). To a solution of 85 mg (0.15 mmol) of **54b** in 0.5 mL of benzene at 0 °C were added 60 mg (0.6 mmol) of (TMS)CN and 0.5 mg of KCN/18-crown-6 complex. After 2.5 h at 0 °C, the solvent was removed *in vacuo*. Benzene (1.0 mL) was added, and the mixture was evaporated to dryness again *in vacuo*. The residue was dissolved in 7.5 mL of THF. To this solution at −78 °C was added dropwise 0.6 mL (0.6 mmol, 1 M in THF) of lithium bis(trimethylsilyl)amide. The resultant brown solution was stirred at −78 °C for 30 min and then quenched with 0.1 mL of saturated aqueous NH_4Cl. The mixture was warmed to ambient temperature, diluted with 10 mL of EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 2.0 mL of a mixture of THF−AcOH−H_2O (10:5:1). After 20 h at ambient temperature, the mixture was poured into 10 mL of Et_2O and 5 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 10 mL of Et_2O. The combined organic layers were washed with 10 mL of brine and concentrated *in vacuo* to a volume of 3 mL. This solution was shaken vigorously for 5 min with 5 mL of 1% NaOH aqueous solution. The layers were separated. The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 48.7 mg (61% from **54a**) of **56** as a white solid: mp 172−173 °C (from EtOAc); $[\alpha]^{25}_D$ −93.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3410, 2950, 1750, 1680, 1300, 970, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 16.4 Hz, 1H), 6.19 (d, J = 4.9 Hz, 1H), 6.13 (d, J = 15.5 Hz, 1H), 5.98 (d, J = 16.4 Hz, 1H), 5.81(t, J = 7.4 Hz, 1H), 5.69 (dd, J = 8.1, 15.4 Hz, 1H), 5.52 (d, J = 9.9 Hz, broad, 1H), 4.37 (m, 1H), 4.20 (dd, J = 4.9, 9.9 Hz, 1H), 4.08 (m, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.45 (dd, J = 17.5, 7.2 Hz, 1H), 3.24 (dd, J = 17.5, 7.8 Hz, 1H), 2.23 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.79 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.30 (d, J = 6.3 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.89, 171.39, 153.46, 146.48, 138.20, 137.81, 135.22, 131.74, 131.19, 126.10, 125.38, 85.87, 76.69, 71.06, 56.12, 47.31, 42.58, 39.17, 37.92, 28.03, 25.68, 17.94, 13.95, 13.09, 12.63, −3.98, −4.62; MS (EI) *m/e* 529 (M^+), 472, 397, 224, 197, 123; FAB HRMS (NBA) calcd for $C_{29}H_{44}NO_6Si$ (MH^+) 530.29384, found 530.29379.

[1*S*,5*R*,5*E*,8*E*,10*S*,12*E*,14*E*,16*S*,18*R*,21*S*,22*R*]-7,12,21,22-Tetramethyl-10,16-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,20-dioxo-2,19,4-dioxaazatricyclo[16.3.1.0^{5,21}]docosa-6,8,12,14-tetraene (15, Synthetic). To a solution of 48 mg (0.0906 mmol) of enone **56** in 1.0 mL of THF was added 9.0 μL (0.009 mmol, 1.0 M in toluene) of the oxazaborole catalyst **57**.[50] The mixture was cooled to −10 °C, and 63.5 μL (0.0635 mmol, 1.0 M in THF) of BH_3·THF was added dropwise. The resultant suspension was stirred at −10 °C for 30 min and quenched with 0.1 mL of methanol. The reaction mixture was warmed to ambient temperature and stirred for 2 h. The solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc) gave 43 mg of the 8β-carbinol product along with 3 mg of the 8α-carbinol product (89%): (8β-carbinol) mp 172−173 °C (from EtOAc); $[\alpha]^{25}_D$ −72.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 2930, 1730, 1250 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, J = 15.6 Hz, 1H), 5.70 (dd, J = 15.6, 9.0 Hz, 1H), 5.66 (d, J = 15.8 Hz, 1H), 5.49 (d, J = 4.7 Hz, 1H), 5.47 (dd, J = 15.8, 7.7 Hz, 1H), 5.27 (t, J = 8.0 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 4.34 (m, 1H), 4.21 (dd, J = 4.7, 10.8 Hz, 1H), 4.14 (m, 1H), 4.08 (m, 1H), 3.89 (d, J = 11.0 Hz, 1H), 2.40 (m, 2H), 2.22 (m, 1H), 2.05−1.90 (m, overlapping signals, 3H), 1.74 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.30, 153.47, 138.20, 136.95, 136.00, 133.37, 133.26, 131.87, 130.78, 126.57, 125.90, 85.70, 76.85, 71.06, 70.65, 56.05, 47.20, 39.40, 37.95, 28.25, 25.85, 18.10, 13.22, 12.65, 12.20, −3.98, −4.60; (8α-carbinol) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, J = 15.6 Hz, 1H), 6.02 (d, J = 16.0 Hz, 1H), 5.73−5.65 (m, overlapping signals, 2H), 5.60−5.45 (m, overlapping signals, 2H), 5.30 (br d, J = 10.6 Hz, 1H), 4.72 (br s, 1H), 4.35 (m, 1H), 4.22 (dd, J = 4.7, 10.8 Hz, 1H), 4.06 (m, 1H), 3.89 (d, J = 10.9 Hz, 1H), 2.50 (m, 2H), 2.40 (m, 1H), 2.22 (m, 1H), 2.10−1.97 (m, overlapping signals, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.47 (s, 3H), 1.25 (d, J = 5.6 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H).

To a solution of 43 mg (0.08 mmol) of the 8β-carbinol product in 1.0 mL of DMF at ambient temperature were added 40 mg (0.58 mmol) of imidazole and 40 mg (0.26 mmol) of (TBS)Cl. After 1.5 h, the mixture was poured into 10 mL each of Et_2O and water. The aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 50 mg (96%) of **15** as a white solid: mp 187−188 °C (from EtOAc); $[\alpha]^{25}_D$ −69.9° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 3430, 2958, 2923, 2858, 1730, 1480, 1390, 1360, 1250, 1080,1060, 965, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, *J* = 15.6 Hz, 1H), 5.75 (d, *J* = 4.6 Hz, 1H, −N*H*), 5.68 (dd, *J* = 8.9, 15.6 Hz, 1H), 5.58 (d, *J* = 16.0 Hz, 1H), 5.45 (dd, *J* = 7.4, 16.0 Hz, 1H), 5.25 (dd, *J* = 5.1, 11.2 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 4.32 (m, 1H), 4.21 (dd, *J* = 4.7, 10.8 Hz, 1H), 4.05 (m, overlapping signals, 2H), 3.88 (d, *J* = 11.0 Hz, 1H), 2.42 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 2.00 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.50 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.06 (br s, overlapping signals, 9H), 0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.18, 153.33, 138.28, 136.75, 136.07, 133.32, 132.22, 130.87, 127.15, 124.65, 85.61, 76.99, 75.37, 70.63, 55.84, 47.14, 39.31, 37.93, 37.76, 28.21, 25.87, 25.80, 18.26, 18.05, 13.38, 12.67, 12.38, −3.87, −4.50, −4.77; MS (FD) *m/e* 645 (M^+), 514, 408, 322, 294, 133, 115, 78; FAB HRMS (NBA) calcd for $C_{35}H_{60}NO_6Si_2$ (MH^+) 646.3959, found 646.3968. Anal. Calcd for $C_{35}H_{59}NO_6Si_2$: C, 65.07; H, 9.21; N, 2.17. Found: C, 64.85; H, 9.35; N, 2.12.

[1*S*-(1*R,2*S**,3*E*,5*E*,7*R**,9*E*,11*E*,13*R**,15*S**,19*S**)]]-*N*-[18-Hydroxy-7,13-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,4,10,19-tetramethyl-17-oxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl]-2-hydroxypropanamide (12, from Natural 1).** To a solution of 230 mg (0.50 mmol) of lankacidin C (**1**) in 2.5 mL of DMF at ambient temperature were added 200 mg (2.9 mmol) of imidazole and 200 mg (1.3 mmol) of (TBS)Cl. After 0.5 h, the mixture was poured into 100 mL each of Et_2O and water. The aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 344 mg (100%) of the expected bis(TBS ether) as a white solid: mp 222−224 °C (from EtOAc); $[\alpha]^{25}_D$ −177.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3390, 2950, 2930, 2850, 1750, 1710, 1685, 1255, 1105, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 10.1 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 5.72 (dd, *J* = 9.4, 15.5 Hz, 1H), 5.5 (m, overlapping signals, 2H), 5.43 (t, *J* = 10.4 Hz, 1H), 5.25 (dd, *J* = 5.1, 11.2 Hz, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 4.35 (m, 1H), 4.31 (m, 1H), 4.00 (m, 1H), 2.47 (s, 3H), 2.46−2.40 (m, overlapping signals, 2H), 2.37−2.23 (m, overlapping signals, 2H), 2.2−2.1 (m, 1H), 1.9 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.14, 196.50, 169.73, 159.66, 139.51, 136.94, 136.31, 133.01, 132.59, 129.92, 127.87, 123.54, 75.61, 75.37, 70.73, 56.72, 51.77, 46.40, 38.32, 37.99, 25.81, 25.74, 24.40, 20.93, 18.19, 18.02, 12.80, 12.60, 9.56, −3.85, −4.46, −4.58, −4.83. Anal. Calcd for $C_{37}H_{61}NO_7Si_2$: C, 64.58; H, 8.94; N, 2.03. Found: C, 64.21; H, 8.96; N, 2.00.

To a solution of 130 mg (0.19 mmol) of the bis(TBS ether) in 4.0 mL of MeOH at ambient temperature was added 30 mg (0.75 mmol) of $NaBH_4$. The suspension slowly became homogeneous. After 1 h, the reaction was quenched with 0.2 mL of AcOH. Purification by flash chromatography (5% MeOH/EtOAc) gave 70 mg of less polar 2′-(*S*)-diol and 60 mg of more polar 2′-(*R*)-isomer (99% total): (less polar 2′-(*S*)-product) mp 226−228 °C (from EtOAc); $[\alpha]^{25}_D$ −85.9° (*c* 1.00, MeOH); IR ($CHCl_3$) 3410, 2950, 2930, 2855, 1722, 1660, 1500, 1460, 1250, 1050, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 19.6 Hz, 1H), 6.06 (d, *J* = 15.4 Hz, 1H), 5.70−5.59 (m, overlapping signals, 3H), 5.50−5.40 (m, overlapping signals, 2H), 5.28 (dd, *J* = 6.5, 11.6 Hz, 1H), 4.32 (m, 1H), 4.21 (m, 1H), 4.04 (m, 1H), 3.95 (br d, *J* = 10.4 Hz, 1H), 3.46 (br d, *J* = 10.0 Hz, 1H), 2.32 (m, 1H), 2.25 (m, 1H), 2.20−2.02 (m, overlapping signals, 2H), 1.85 (s, 3H), 1.50 (s, 3H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, overlapping signals, 6H), 0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.17, 174.62, 137.74, 137.20, 136.50, 134.04, 130.79, 129.37, 127.74, 127.05, 81.02, 78.07, 75.45, 71.22, 68.35, 52.98, 51.16, 39.10, 38.84, 38.08, 27.55, 25.89, 21.43, 18.26, 18.07, 13.37, 12.63, 12.42, −3.80, −4.44, −4.77. Anal. Calcd for $C_{40}H_{65}NO_9Si_2$: C, 64.21; H, 9.47; N, 2.02. Found: C, 64.35; H, 9.58; N, 2.06. (more polar 2′-(*R*)-diol) mp 210−211 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (br d, *J* = 8.9 Hz, 1H), 6.09 (d, *J* = 15.4 Hz, 1H), 5.62−5.59 (m, overlapping signals, 2H), 5.50−5.40 (m, overlapping signals, 3H), 5.30 (dd, *J* = 5.3, 10.9 Hz, 1H), 4.66 (br s, 1H), 4.33 (q, *J* = 7.6 Hz, 1H), 4.20 (q, *J* = 6.6 Hz, 1H), 4.06 (m, 1H), 3.93 (br d, *J* = 10.6 Hz, 1H), 3.40 (br d, *J* = 10.0 Hz, 1H), 2.42 (q, *J* = 11.3 Hz, 1H), 2.33 (m, 1H), 2.12 (br s, 2H), 1.79 (s, 3H), 1.78 (m, 1H), 1.48 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.28 (s, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.08 (s, overlapping signals, 6H), 0.07 (s, 3H), 0.03 (s, 3H).

[1*S*-[1*S*-(1*R,2*S**,3*E*,5*E*,7*R**,9*E*,11*E*,13*R**,15*S**,19*S**)]]-1*H*-Imidazole-1-carboxylic Acid 2-[7,12,21,22-Tetramethyl-10,16-bis-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,20-dioxo-2,19,4-dioxaazatricyclo[16.3.1.0^{5,21}]docosa-6,8,12,14-tetraen-4-yl]-2-oxo-1-methylethyl Ester (13).** To a solution of 70 mg (0.10 mmol) of **12** (less polar isomer) in 10 mL of THF was added 100 mg (0.61 mmol) of 1,1′-carbonyldiimidazole. The mixture was cooled to −78 °C, and 0.35 mL (0.35 mmol, 1.0 M in THF) of lithium bis(trimethylsilyl)-amide was added dropwise. After 10 min at −78 °C, the reaction was quenched with 0.2 mL of saturated aqueous NH_4Cl. The reaction mixture was warmed to room temperature, diluted with 20 mL of EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 76 mg (92%) of **13** as a white solid: mp 144−145 °C (from EtOAc); $[\alpha]^{25}_D$ −168.2° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2955, 2920, 2850, 1755, 1740, 1395, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.42 (s, 1H), 7.08 (s, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 5.86 (q, *J* = 6.6 Hz, 3H), 5.73 (d, *J* = 11.0 Hz), 1H), 5.65 (dd, *J* = 9.3, 15.6 Hz, 1H), 5.55 (m, overlapping signals, 2H), 5.26 (dd, *J* = 4.6, 11.0 Hz, 1H), 5.08 (d, *J* = 10.9 Hz, 1H), 4.30 (m, 1H), 4.08 (m, overlapping signals, 2H), 3.99 (d, *J* = 10.7 Hz, 1H), 2.42 (m, 1H), 2.30 (m, 1H), 2.22 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H), 1.84 (s, 3H), 1.76 (d, *J* = 6.5 Hz, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.87 (s, 9H), 1.85 (s, 9H), 0.40 (s, 3H), 0.35 (s, 3H), 0.34 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.66, 170.20, 150.22, 148.50, 141.76, 137.15, 136.69, 136.60, 133.11, 132.96, 130.89, 130.25, 127.56, 120.43, 117.09, 86.91, 76.40, 75.22, 74.11, 70.59, 55.21, 47.57, 38.33, 38.01, 37.81, 29.66, 27.48, 25.85, 25.79, 18.22, 18.06, 16.82, 13.54, 12.58, −3.78, −4.48, −4.77. Anal. Calcd for $C_{42}H_{65}N_3O_9Si_2$: C, 62.11; H, 8.07; N, 5.17. Found: C, 61.80; H, 8.25; N, 5.15.

[1*S*,5*R*,5*E*,8*E*,10*S*,12*E*,14*E*,16*S*,18*R*,21*S*,22*R*]-7,12,21,22-Tetramethyl-10,16-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,20-dioxo-2,19,4-dioxaazatricyclo[16.3.1.0^{5,21}]docosa-6,8,12,14-tetraene (15, Degradative Relay from Natural 1). To a solution of 73 mg (0.09 mmol) of **13** in 1.5 mL of THF and 0.5 mL of H_2O at 0 °C were added 80 μL (0.7 mmol, 30% aqueous solution) of H_2O_2 and 14.3 mg (0.35 mmol) of $LiOH·H_2O$. The reaction was warmed to ambient temperature. After 10 h, the reaction mixture was diluted with 15 mL of EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave 57 mg (98%) of **13** as a white solid: mp 186−187 °C (from EtOAc); $[\alpha]^{25}_D$ −68.3° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3430, 2958, 2923, 2858, 1730, 1480, 1390, 1360, 1250, 1080,1060, 965, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, *J* = 15.6 Hz, 1H), 5.68 (dd, *J* = 8.9, 15.6 Hz, 1H), 5.58 (d, *J* = 16.0 Hz, 1H), 5.57 (d, *J* = 4.6 Hz, 1H, −N*H*), 5.45 (dd, *J* = 7.4, 16.0 Hz, 1H), 5.25 (dd, *J* = 5.1, 11.2 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 4.32 (m, 1H), 4.21 (dd, *J* = 4.7, 10.8 Hz, 1H), 4.05 (m, overlapping signals, 2H), 3.88 (d, *J* = 11.0 Hz, 1H), 2.42 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 2.00 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.50 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.06 (br s, overlapping signals, 9H), 0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.21, 153.48, 138.24, 136.74, 136.08, 133.34, 132.17, 130.78, 127.15, 124.66, 85.62, 76.98, 75.37, 70.63, 55.78, 47.16, 39.28, 37.93, 37.75, 28.20, 25.87, 25.79, 18.25, 18.05, 13.39, 12.66, 12.38, −3.87, −4.50, −4.76; MS (FD) *m/e* 645 (M^+), 514, 408, 322, 294, 133, 115, 78; FAB HRMS (NBA) calcd for $C_{35}H_{60}NO_6Si_2$ (MH^+) 646.3959, found 646.3939. Anal. Calcd for $C_{35}H_{59}NO_6Si_2$: C, 65.07; H, 9.21; N, 2.17. Found: C, 65.40; H, 8.82; N, 2.16.

[1*S*,5*R*,6*E*,8*E*,10*S*,12*E*,14*E*,16*S*,18*R*,21*S*,22*R*]-*N*-[1,2-Dioxopropyl]-7,12,21,22-tetramethyl-10,16-bis[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3,20-dioxo-2,19,4-dioxaazatricyclo[16.3.1.0^{5,21}]docosa-6,8,12,14-

tetraene (16). To a solution of 30 mg (0.045 mmol) of relay **15** in 1.5 mL of THF at −78 °C was added dropwise 66 μL (0.066 mmol, 1.0 M in THF) of lithium bis(trimethylsilyl)amide. After 5 min, 90 μL (0.045 mmol, 0.5 M in THF) of pyruvoyl chloride was added. The reaction mixture was stirred at −78 °C for 15 min and then quenched with 60 μL of AcOH. The reaction was warmed to ambient temperature and purified directly by preparative TLC (50% EtOAc/hexane) to give 32 mg (91%) of **16** as a white solid: mp 233−234 °C (from EtOAc); $[\alpha]^{25}_D$ −142.1° (*c* 1.40, $CHCl_3$); IR ($CHCl_3$) 2950, 2920, 2855, 1738, 1158, 1060, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, *J* = 15.5 Hz, 1H), 5.65 (dd, *J* = 9.2, 15.4 Hz, 1H), 5.57 (m, 2H), 5.37 (d, *J* = 11.0 Hz, 1H), 5.27 (dd, *J* = 5.0, 11.2 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 4.29 (dt, J= 5.3, 10.1 Hz, 1H), 4.07 (m, overlapping signals, 2H), 3.99 (d, *J* = 10.9 Hz, 1H), 2.46 (s, 3H), 2.40 (m, 1H), 2.30 (m, 1H), 2.23 (m, 1H), 2.11 (m, 1H), 2.00 (m, 3H), 1.90 (s, 3H), 1.56 (s, 3H), 1.51 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, overlapping signals, 6H), 0.03 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.37, 169.96, 168.51, 150.59, 141.83, 136.79, 136.58, 133.18, 132.97, 130.19, 127.64, 120.00, 87.08, 76.56, 75.20, 70.54, 54.98, 47.39, 38.33, 37.99, 37.75, 29.65, 27.70, 25.85, 25.78, 18.23, 18.04, 13.40, 12.60, 12.65, −3.79, −4.49, −4.79. Anal. Calcd for $C_{38}H_{61}NO_8Si_2$: C, 63.74; H, 8.73; N, 1.96. Found: C, 63.96; H, 8.93; N, 1.91.

[2*S*-[1*S*-(1*R,2*S**,3*E*,5*E*,7*R**,9*E*,11*E*,13*R**,15*S**,19*S**)]]-*N*-[18-Hydroxy-7,13-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,4,10,19-tetramethyl-17-oxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl]-2-hydroxypropanamide (18).** To a solution of 30.0 mg (0.042) of **16** in 1.5 mL of a mixture of THF−H_2O (3:1) at 0 °C was added 6.0 mg (0.15 mmol) of LiOH·H_2O. After 5 min at 0 °C, the reaction mixture was diluted with 15 mL of EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to give 8.7 mg (30%) of **18** as a white solid along with 16.2 mg (60%) of **15**. Data for **18**: mp 149−150 °C (from EtOAc); $[\alpha]^{25}_D$ −195.0° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3400, 2950, 2930, 2855, 1722, 1680, 1250, 1050, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 10.2 Hz, −N*H*, 1H), 6.04 (d, *J* = 15.4 Hz, 1H), 5.65 (dd, *J* = 9.1, 15.4 Hz, 1H), 5.58 (d, *J* = 15.7 Hz, 1H), 5.57−5.40 (m, overlapping signals, 3H), 5.27 (dd, *J* = 5.1, 11.0 Hz, 1H), 4.30 (m, 1H), 4.03 (m, 1H), 3.95 (m, 1H), 3.50 (dd, *J* = 4.5 10.6 Hz, 1H), 2.59 (d, *J* = 4.6 Hz, −O*H*, 1H), 2.48 (s, 3H), 2.40 (m, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.87 (s, 3H), 1.50 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, overlapping signals, 6H), 0.01 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.65, 173.09, 159.49, 138.30, 137.60, 136.75, 133.76, 131.41, 129.56, 127.59, 125.92, 82.17, 77.05, 75.52, 71.20, 53.71, 50.81, 38.96, 38.75, 38.01, 27.85, 25.87, 25.80, 24.68, 18.24, 18.05, 13.33, 12.68, 12.41, −3.75, −4.45, −4.79. Anal. Calcd for $C_{37}H_{63}NO_7Si_2$: C, 64.40; H, 9.20; N, 2.03. Found: C, 64.65; H, 9.24; N, 1.96.

[1*S*,4(2*S*),5*R*,6*E*,8*E*,10*S*,12*E*,14*E*,16*S*,18*R*,21*S*,22*R*]-*N*-[2-Acetoxy-1-oxo-propyl]-7,12,21,22-tetramethyl-10,16-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-3,20-dioxo-2,19,4-dioxaazatricyclo[16.3.1.$0^{5,21}$]-docosa-6,8,12,14-tetraene (17). To a solution of 10 mg (0.015 mmol) of relay **15** in 0.5 mL of THF at −78 °C was added dropwise 22 μL (0.022 mmol, 1.0 M in THF) of lithium bis(trimethylsilyl)amide. After 5 min, 30 μL (0.015 mmol, 0.5 M in THF) of *O*-acetyl-(*S*)-lactoyl chloride was added. The reaction mixture was stirred at −78 °C for 15 min and then quenched with 20 μL of AcOH. The reaction was warmed to ambient temperature and purified directly by preparative TLC (50% EtOAc/hexane) to give 10.0 mg (85%) of **17** as a white solid: mp 252−253 °C (from EtOAc); $[\alpha]^{25}_D$ −195.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2950, 2920, 2855, 1735, 1370, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, *J* = 15.5 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.63−5.45 (m, overlapping signals, 4H), 5.27 (dd, *J* = 4.7, 11.2 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.32 (m, 1H), 4.06 (m, overlapping signals, 2H), 3.95 (d, *J* = 10.7 Hz, 1H), 2.43 (q, *J* = 11.7 Hz, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.11 (s + m, overlapping signals, 1H+3H), 1.86 (s, 3H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.54 (s, 3H), 1.41 (s, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, overlapping signals, 6H), 0.03 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.08, 170.98, 170.46, 150.31, 141.36, 136.64, 136.61, 133.20, 132.62, 130.28, 127.53, 120.90, 86.59, 76.35, 75.25, 70.78, 70.62, 54.83, 47.75, 38.35, 38.04, 37.81, 29.67, 27.40, 25.86, 25.79, 20.47, 18.23, 18.07, 16.64, 13.58, 12.58, −3.79, −4.48, −4.78. Anal. Calcd for $C_{40}H_{65}NO_9Si_2$: C, 63.20; H, 8.62. Found: C, 63.03; H, 8.83.

[2*S*-[1*S*-(1*R,2*S**,3*E*,5*E*,7*R**,9*E*,11*E*,13*R**,15*S**,19*S**)]]-*N*-[18-Hydroxy-7,13-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,4,10,19-tetramethyl-17-oxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl]-2-hydroxypropanamide (19, Synthetic from Relay 15).** To a solution of 10 mg (0.013) of **17** in 0.5 mL of a mixture of THF−H_2O (3:1) at 0 °C was added 2.0 mg (0.049 mmol) of LiOH·H_2O. After 30 min at 0 °C, the reaction mixture was diluted with 5 mL of EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to give 7.5 mg (82%) of **19** as a white solid: mp 226−228 °C (from EtOAc); $[\alpha]^{25}_D$ −85.1° (*c* 1.30, MeOH); IR ($CHCl_3$) 3410, 2950, 2930, 2855, 1722, 1660, 1500, 1460, 1250, 1050, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 19.6 Hz, 1H), 6.06 (d, *J* = 15.4 Hz, 1H), 5.70−5.59 (m, overlapping signals, 3H), 5.50−5.40 (m, overlapping signals, 3H), 5.28 (dd, *J* = 6.5, 11.6 Hz, 1H), 4.32 (m, 1H), 4.21 (m, 1H), 4.04 (m, 1H), 3.95 (br d, *J* = 10.4 Hz, 1H), 3.46 (br d, *J* = 10.0 Hz, 1H), 2.32 (m, 1H), 2.25 (m, 1H), 2.20−2.02 (m, overlapping signals, 2H), 1.85 (s, 3H), 1.50 (s, 3H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, overlapping signals, 6H), 0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.18, 174.62, 137.73, 137.21, 136.50, 134.04, 130.79, 129.37, 127.74, 127.05, 81.01, 78.06, 75.45, 71.22, 68.33, 52.98, 51.16, 39.10, 38.84, 38.09, 27.53, 25.89, 21.43, 18.26, 18.06, 13.37, 12.63, 12.43, −3.80, −4.44, −4.77. Anal. Calcd for $C_{40}H_{65}NO_9Si_2$: C, 64.21; H, 9.47; N, 2.02. Found: C, 64.21; H, 9.69; N, 2.08.

[1*S*-(1*R,2*S**,3*E*,5*E*,7*R**,9*E*,11*E*,13*R**,15*S**,19*S**)]-*N*-[7,13-Bis-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,4,10,19-tetramethyl-17,18-dioxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl]-2-oxo-propanamide (20, Synthetic from Relay 15).** To a solution of 7.5 mg (0.0108 mmol) of **19** in 0.5 mL of CH_2Cl_2 at ambient temperature was added 20 mg (0.047 mmol) of Dess−Martin periodinane. After the resultant suspension was stirred for 15 min, 0.5 mL each of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added. The mixture was stirred at ambient temperature for 15 min before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by preparative TLC (EtOAc) gave 7.2 mg (96%) of the expected alcohol as a white solid: mp 223−224 °C (from EtOAc); $[\alpha]^{25}_D$ −174.5° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3390, 2950, 2930, 2850, 1750, 1710, 1685, 1255, 1105, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 10.1 Hz, 1H), 6.00 (d, *J* = 15.5 Hz, 1H), 5.72 (dd, *J* = 9.4, 15.5 Hz, 1H), 5.5 (m, overlapping signals, 2H), 5.43 (t, *J* = 10.4 Hz, 1H), 5.25 (dd, *J* = 5.1, 11.2 Hz, 1H), 4.64 (d, *J* = 10.3 Hz, 1H), 4.35 (m, 1H), 4.31 (m, 1H), 4.00 (m, 1H), 2.47 (s, 3H), 2.46−2.40 (m, overlapping signals, 2H), 2.37−2.23 (m, overlapping signals, 2H), 2.2−2.1 (m, 1H), 1.9 (s, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.16, 196.50, 169.74, 159.65, 139.51, 136.94, 136.39, 133.02, 132.61, 129.92, 127.85, 123.54, 75.61, 75.35, 70.73, 56.74, 51.79, 46.40, 38.33, 38.00, 25.83, 25.74, 24.42, 20.93, 18.20, 18.02, 12.80, 12.60, 9.55, −3.85, −4.46, −4.58, −4.84. Anal. Calcd for $C_{37}H_{61}NO_7Si_2$: C, 64.58; H, 8.94; N, 2.03. Found: C, 64.32; H, 9.02; N, 2.06.

Lankacidin C (1) (Synthetic from Relay 15). A solution of 16 mg (0.023 mmol) of **20** in 2.0 mL of a mixture of THF−HCOOH−H_2O (6:3:1) was stirred at ambient temperature for 3 h. The mixture was cooled to 0 °C and neutralized with saturated aqueous $NaHCO_3$ (2 mL). The mixture was poured into 10 mL each of EtOAc and brine. The aqueous layer was extracted with 10 mL of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by preparative TLC (EtOAc) gave 8.7 mg (82%) of lankacidin C as a white solid: mp 199−201 °C dec; $[\alpha]^{22}_D$ −234.0° (*c* 0.70, EtOH); IR ($CHCl_3$) 3600, 3440, 2990, 1750, 1710, 1685, 1500, 1358, 1255, 1005, 965, 910 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, *J* = 10.0 Hz, 1H), 6.08 (d, *J* = 15.4 Hz, 1H), 5.52 (d, *J* = 16.0 Hz, 1H), 5.48 (dd, *J* = 15.4, 9.3 Hz, 1H), 5.36 (dd, *J* = 15.9, 8.0 Hz, 1H), 5.2 (m, overlapping signals, 2H), 5.00 (d, *J* = 3.5 Hz, 1H), 4.80 (d, *J* = 3.7 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.14 (m, 1H), 3.85 (m, 1H), 2.41 (m, 1H),

2.33 (s, 3H), 2.20 (m, 2H), 2.10 (m, 1H), 1.94 (m, 1H), 1.69 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H), 1.11 (d, J = 6.3 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 211.53, 197.01, 170.70, 160.08, 137.99, 136.41, 135.59, 133.05, 132.84, 130.85, 128.07, 124.55, 75.47, 73.44, 68.41, 56.72, 51.61, 46.34, 37.71, 24.91, 20.77, 12.82, 12.68, 9.59. Anal. Calcd for $C_{25}H_{33}NO_7$: C, 65.34; H, 7.24; N, 3.05. Found: C, 65.49; H,7.05; N, 3.01.

Data for Natural Lankacidin C: mp 199−200 °C dec; $[\alpha]^{22}_D$ −225.0° (c 1.00, EtOH); IR ($CHCl_3$) 3600, 3440, 2990, 1750, 1710, 1685, 1500, 1358, 1255, 1005, 965, 910 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 10.0 Hz, 1H), 6.08 (d, J = 15.4 Hz, 1H), 5.52 (d, J = 15.9 Hz, 1H), 5.48 (dd, J = 15.4, 9.3 Hz, 1H), 5.36 (dd, J = 15.9, 8.0 Hz, 1H), 5.2 (m, overlapping signals, 2H), 5.00 (d, J = 4.0 Hz, 1H), 4.80 (d, J = 4.2 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.14 (m, 1H), 3.85 (m, 1H), 2.41 (m, 1H), 2.33 (s, 3H), 2.20 (m, 2H), 2.10 (m, 1H), 1.94 (m, 1H), 1.69 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H), 1.11 (d, J = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 211.52, 197.01, 170.69, 160.08, 137.99, 136.41, 135.59, 133.05, 132.83, 130.85, 128.07, 124.55, 75.47, 73.43, 68.41, 56.72, 51.61, 46.34, 37.71, 24.91, 20.77, 12.82, 12.68, 9.59.

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Supporting Information Available: Text describing full experimental details and characterization for **37**, **39**−**41**, **48**, **52**, and **53** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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