3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 135.8, 135.7, 134.1, 133.8, 133.5, 129.9, 129.8, 127.7, 118.1, 99.3, 81.7, 77.9, 75.2, 74.1, 70.7, 66.8, 62.5, 45.6, 40.8, 38.1, 35.0, 34.3, 27.0, 25.8, 22.3, 19.1, 18.2, 13.2, -4.01, -5.25; high-resolution mass spectrum (CI, NH_3) m/z 756.3742 [(M + NH_4)$^+$; calcd for $C_{40}H_{62}NO_7SSi_2$: 756.3786].

(±)-Breynolide (3). Allyl ether **79** (3.1 mg, 4.2 μmol) was dissolved in 90% EtOH. DABCO (2 mg, 17.8 μmol, 4.2 equiv) was added, and the mixture was warmed to 80 °C. Following the introduction of $RhCl(PPh_3)_3$ (1.0 mg, 1.0 μmol, 0.26 equiv), the reaction mixture was stirred for 15 min, cooled to room temperature, and quenched with pH 7.0 buffer solution. The aqueous phase was extracted with diethyl ether (3 × 10 mL), and the combined organic solutions were concentrated in vacuo. The crude enol ether was taken up in methanol (1 mL), and concentrated HCl (300 μL) was added. The resultant mixture was stirred at ambient temperature for 18 h and then concentrated in vacuo. HPLC with 1:11.5 methanol/chloroform as eluant furnished (±)-breynolide (3) (1.1 mg, 76% yield) as an oil: IR (KBr) 3369 (br, s), 2960 (m), 2932 (s), 1782 (s), 1607 (m), 1464 (m), 1429 (m), 1412 (m), 1389 (m), 1339 (m), 1236 (m), 1163 (s), 1126 (s), 1086 (s), 1056 (s), 1045 (s), 1031 (s), 1018 (s), 982 (s), 868 (s) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 4.65 (s, 1 H), 4.40-4.39 (m, 1 H), 4.33 (s, 1 H), 4.15 (d, J = 5.5 Hz, 1 H), 4.12 (d, J = 5.2 Hz, 1 H), 4.08 (d, J = 3.3 Hz, 1 H), 4.00 (br s, 1 H), 3.86-3.85 (m, 1 H), 3.77 (apparent t, J = 11.2 Hz, 1 H), 3.43 (dd, J = 4.4, 11.2 Hz, 1 H), 3.11 (dd, J = 4.0, 11.4 Hz, 1 H), 3.08 (d, J = 8.0 Hz, 1 H), 2.82-2.73 (m, 2 H), 1.95 (dd, J = 3.9, 14.1 Hz, 1 H), 1.88 (dd, J = 3.5, 14.1 Hz, 1 H), 1.84-1.81 (m, 1 H), 1.71 (td, J = 13.6, 2.2 Hz, 1 H), 1.50 (dt, J = 3.8, 13.5 Hz, 1 H), 0.87 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 211.8, 160.1, 80.4, 77.0, 75.4, 71.0, 67.1, 62.6, 46.2, 40.9, 38.4, 35.3, 34.6, 27.9, 13.0; high-resolution mass spectrum (CI, NH_3) m/z 364.1417 [(M + NH_4)$^+$; calcd for $C_{15}H_{26}NO_7S$: 364.1430].

Acknowledgment. We are pleased to acknowledge support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant CA-19033. In addition, we thank Drs. George Furst and Patrick J. Carroll and Mr. John M. Dykins of the University of Pennsylvania Spectroscopic Service Centers for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra. Dr. Christopher S. Shiner and Mr. Paul Sprengeler provided helpful suggestions and critical comments.

Supplementary Material Available: Tables of experimental details, positional parameters, and thermal parameters for X-ray analyses of **20b**, **27**, **40**, **44**, **49**, and **65** (41 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Calyculin A

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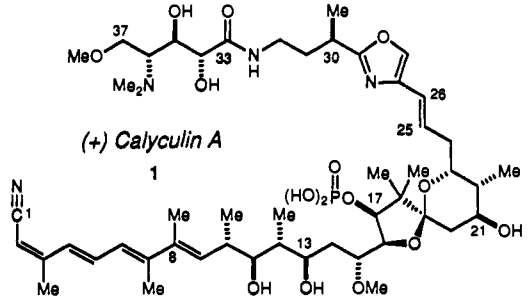
Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received July 1, 1992*

Abstract: A convergent asymmetric synthesis of the marine natural product calyculin A has been accomplished through the union of the two subunits comprising the C_1-C_{25} and C_{26}-C_{37} portions of the molecule. These fragments were constructed utilizing auxiliary-based asymmetric aldol, alkylation, hydroxylation, and Michael reactions to establish 10 of the 15 stereogenic centers. The remaining chirality was incorporated through internal asymmetric induction. Stereoselective Wittig coupling of the two fragments and subsequent deprotection provided synthetic calyculin A. The spectral properties of the synthetic material were in complete agreement with those of the natural material except for the optical rotation which was equal and opposite in sign to that of the natural material. The absolute configuration of (-)-calyculin A has thus been shown to be opposite to that illustrated in structure **1**.

Calyculin A (**1**) was isolated in 1986 by Fusetani and co-workers from the marine sponge *Discodermia calyx*.[2] Its relative stereostructure was determined by X-ray analysis. Degradation



of the natural product by acidic hydrolysis allowed the isolation of a fragment corresponding to the C_{33}-C_{37} γ-amino acid.[3] Comparison of the circular dichroism spectrum of this fragment to those of simple (*S*)-α-hydroxy acids led to a tentative assignment of the absolute configuration of (-)-calyculin A as being enantiomeric to that illustrated in structure **1**. A recent unambiguous synthesis of this degradation product by Shioiri and co-workers confirmed the Fusetani absolute configuration assignment.[4]

Interest in *D. calyx* and its active components was prompted by its activity in the anti-cell-division assay using fertilized starfish eggs and in cytotoxicity tests against P388 and L1210 leukemia cells.[5] It has since been demonstrated that calyculin A is a potent inhibitor of protein phosphatases 1 and 2a, two of the four major protein-serine/threonine phosphatases, with IC_{50} values on the order of 1 nM.[6] This activity profile was shown to be similar to that of the marine natural product okadaic acid.[7] The activity of both compounds is fully complementary to and equipotent with that of the phorbol ester class of protein kinase C activators in

(1) Taken, in part, from the Ph.D. Thesis of J. R. Gage, Harvard University, 1991.
(2) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780-2781.
(3) Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1991**, *32*, 5605-5606.
(4) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983-5986.
(5) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930-3932.
(6) Ishihara, H.; Martin, B. L.; Brautigan, D. L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, K.; Uemura, D.; Hartshorne, D. J. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871-877.
(7) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469-2471.

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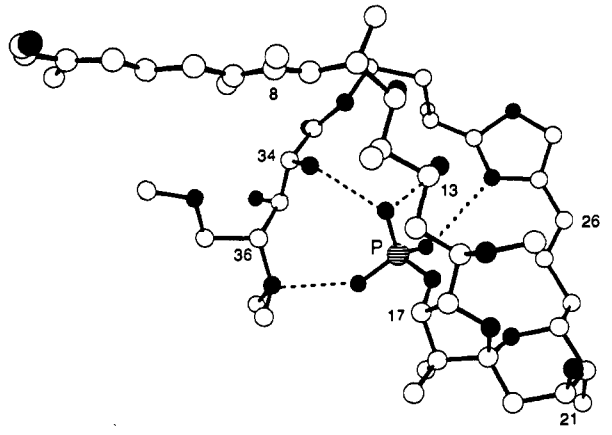


Figure 1. X-ray structure of calyculin A.[2]

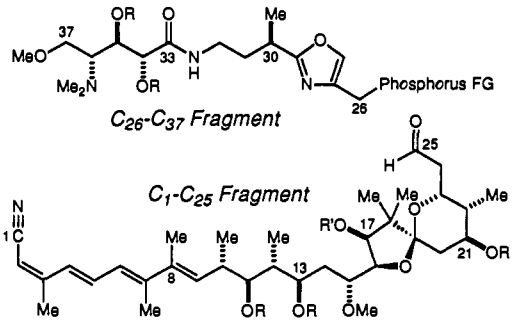
tumor promotion assays, and both compounds are proving invaluable in identifying those cellular processes which are regulated by protein-serine/threonine phosphatases.[8]

In subsequent studies, Fusetani and co-workers have reported the isolation of seven closely related calyculin-derived analogues (calyculins B–H) from the same organism.[5,9] Since X-ray crystal structures have not been obtained for any of these compounds, structural assignments rest primarily on spectroscopic analysis and chemical interconversion. Four of the new calyculins, C, D, G, and H, have an additional methyl group at C_{32}, the configuration of which was deduced from NOE data. The only other difference among the eight calyculins lies in the double-bond geometries of the conjugated tetraenes, and these have also been assigned on the basis of NOE data. Calyculins A, B, E, and F can be interconverted by exposure to light, as can calyculins C, D, G, and H. Of the eight, calyculin A appears to be the most abundant, but the possibility that double-bond isomerism is an artifact of the isolation has not been ruled out. The presence of an additional methyl group at C_{32} in calyculins C, D, G, and H and changes of geometry in the tetraene portion of the molecule are reported to have a negligible effect on the biological activity.

Solid-State Structure. The phosphate moiety in calyculin A provides the organizational focal point for the solid-state tertiary structure. This polar functionality forms an array of hydrogen bonds to the illustrated heteroatoms located on both side chains (Figure 1). As a consequence, the C_{17} phosphate ester is encapsulated within the interior of the molecule, exposing a relatively hydrophobic exterior. This lipophilicity is apparent in its solution behavior. Calyculin A was isolated by partitioning crude ethanol extracts from the sponge between water and dichloromethane and was purified from the organic extract by silica gel chromatography ($MeOH/CH_2Cl_2$). Hence, this formally zwitterionic structure behaves like a neutral structure. Having the benefit of the X-ray structure, it is quite apparent why calyculin resists hydrolysis of the phosphate moiety under either acidic or enzymatic conditions.[2]

Synthesis Plan. The calyculin A phosphate and tetraene moieties were two architectural elements to which we paid close attention. Although it was known that the phosphate ester is stable to hydrolysis in the natural product, its presence in partially assembled intermediates was viewed as a liability due to the extra reactivity that such an appendage might confer on the system. We were also concerned with the photolability and presumed oxygen sensitivity of the conjugated tetraenic portion of the structure. The instability of this natural product can probably be linked to this structural component. For these reasons, the decision was made to incorporate both the phosphate and tetraene moieties late in the assemblage process to simplify the execution of the synthesis plan.

Calyculin A may be conveniently sectioned at the C_{25}–C_{26} olefin into two fragments of comparable complexity. A phosphorus-based olefination procedure appeared attractive in this setting due to the relatively mild conditions needed for the desired bond construction. Given the presence of the diverse functionality in calyculin A, we wanted to retain flexibility with respect to the timing of fragment coupling. As an example, cyanotetraene installation after the C_{25}–C_{26} olefin construction was considered a viable scenario.



Protecting-group strategy inevitably becomes a major consideration in a synthetic undertaking of this size. We elected to adopt what could be termed the *cumulative silicon strategy*, an approach successfully demonstrated in the recent total synthesis of cytovaricin.[10] That is, hydroxyl groups to be protected until the end of the synthesis are masked with silicon-based protecting groups, while hydroxyl groups requiring only temporary protection before undergoing some chemical operation during the course of the synthesis are masked with appropriate, orthogonal, non-silicon protecting groups.

In the following discussion, we describe the first total synthesis of this structurally unique marine natural product.[11,12]

Results and Discussion

Synthesis of the C_1–C_{25} Subunit. We chose to incorporate the spiroketal ring system early in the synthesis in order to simplify the problems associated with hydroxyl group protection. This decision dictated that major bond disconnections be made on either side of this segment. Truncation of this subunit at the three indicated sites fulfills this requirement and provides four smaller fragments which served as our immediate goals for synthesis (Scheme I). The synthesis and assemblage of each of these calyculin subunits is described in the following discussion.

C_{13}–C_{20} Subunit. It was anticipated that the absolute stereochemical relationships in this subunit might be controlled through auxiliary-based enolate oxygenation to establish the C_{17} center. From this stereogenic center, the adjacent centers at C_{15} and C_{16} might be relayed through chelate-controlled aldehyde addition

(8) For a review on the biology of okadaic acid and calyculin A, see: Cohen, P.; Holmes, C. F. B.; Tsukitani, Y. *Trends Biochem. Sci.* **1990**, *15*, 98–102.

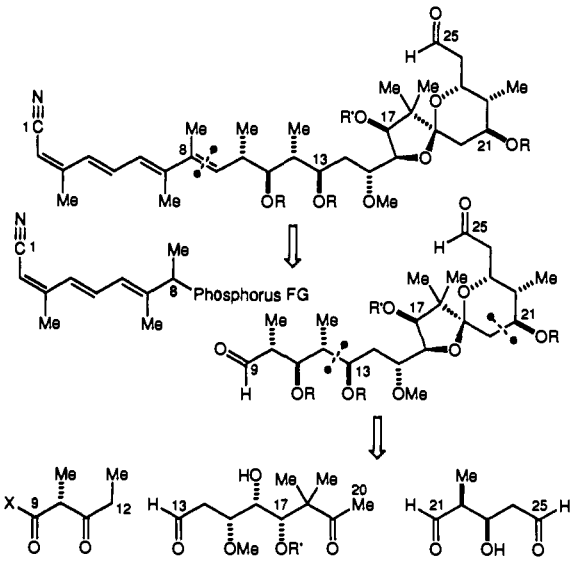
(9) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999–3006.

(10) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

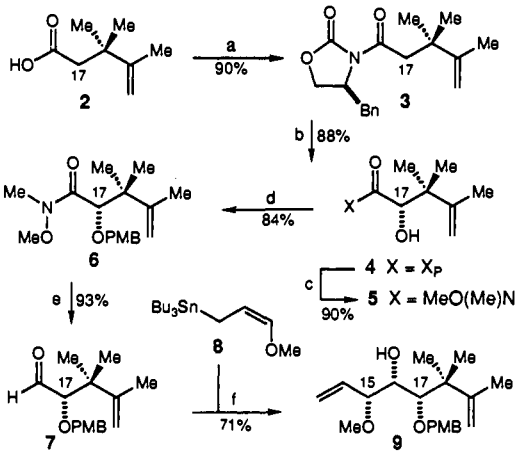
(11) For preliminary communications from this laboratory on this subject, see: (a) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. (b) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958–1961. (c) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961–1963. (d) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964–1966.

(12) For other efforts directed toward the synthesis of the calyculins, see: (a) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357–7360. (b) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937–1940. (c) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett.* **1991**, 283–284, 285–286. (d) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett.* **1992**, 149–150, 151–152, 153–155. (e) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609–1612. (f) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749–5752. (g) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855–4858. (h) Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859–4862. (i) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243–5245. (j) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1236–1238. (k) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238–1240. (l) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Malecha, J. W.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1240–1242.

Scheme I



Scheme II[a]

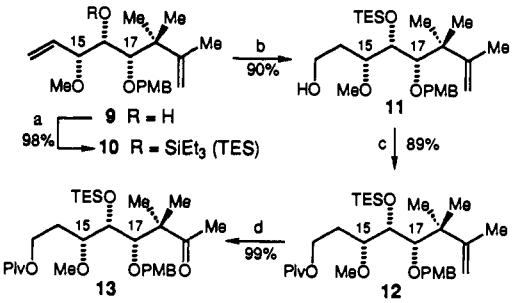


[a] (a) Pivaloyl chloride, Et_3N, Et_2O; X_PLi, THF, −78 °C to 0 °C. (b) NaHMDS, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C. (c) $AlMe_3$, MeNH(OMe)·HCl, CH_2Cl_2, reflux. (d) NaH, *p*-methoxybenzyl bromide, THF/DMF, 0 °C. (e) DIBAl-H, toluene, −78 °C. (f) $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −40 °C.

of alkoxyallylstannanes according to the precedent reported independently by Keck and Koreeda.[13]

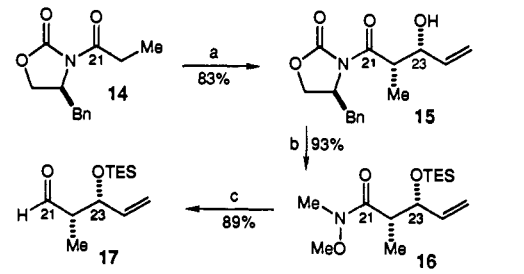
The synthesis was initiated by acylation of the (*S*)-phenylalanine-derived oxazolidinone (X_PH)[14] with the known 3,3,4-trimethyl-4-pentenoic acid (**2**)[15] under mixed anhydride conditions (pivaloyl chloride, Et_3N, 90%) to afford **3** (Scheme II). Application of the auxiliary-controlled asymmetric hydroxylation reaction resulted in formation of alcohol **4** as a single diastereomer in 88% yield.[16] Chiral auxiliary removal ($AlMe_3$, MeO(Me)NH·HCl, 90%) afforded amide **5**,[17] which was protected as its *p*-methoxybenzyl (PMB) ether (NaH, PMB-Br, 84%) to provide amide **6** in good yield. It is noteworthy that the transamination

Scheme III[a]



[a] (a) TES-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C. (b) $Rh(PPh_3)_3Cl$, catecholborane, THF; H_2O_2; $NaBH_4$, EtOH. (c) Pivaloyl chloride, DMAP, pyridine, CH_2Cl_2. (d) OsO_4, NMO, *tert*-butyl alcohol/THF/H_2O; $NaIO_4$.

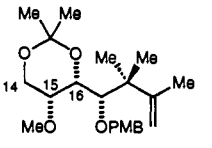
Scheme IV[a]



[a] (a) *n*-Bu_2BOTf, *i*-Pr_2NEt, acrolein, CH_2Cl_2, −78 °C. (b) MeNH(OMe)·HCl, $AlMe_3$, THF; TES-Cl, Et_3N, CH_2Cl_2. (c) DIBAl-H, THF, −90 °C.

of **4** is critically assisted by the free hydroxyl group, as its derived Al(III) alcoholate, which serves to activate the acyl-transfer step through chelation with the exocyclic imide carbonyl moiety. Diisobutylaluminum hydride reduction of **6** afforded aldehyde **7** (93%), which was directly treated with the (methoxyallyl)stannane **8** and magnesium bromide etherate to provide alcohol **9** along with a minor product diastereomer in a 7.5:1 ratio. These diastereomers were readily separated by chromatography to afford a 71% isolated yield of diene **9** in a 40% overall yield from acid **2**.

The stereochemical outcome of the allylstannane addition reaction was determined by two sets of experiments. Oxidation of **9** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under anhydrous conditions gave the derived *p*-methoxybenzylidene acetal.[18] The C_{16}–C_{17} relationship was shown to be syn by NOE experiments. The C_{15}–C_{16} relationship was established by degradation of **9** to the illustrated 1,3-diol acetonide from which the vicinal coupling constants for the protons on carbons 14–16 could be readily extracted.



Coupling constants	
J_{ab} = 13.0 Hz	
J_{ac} = 1.9 Hz	
J_{bc} = 1.6 Hz	
J_{cd} = 1.5 Hz	

At this stage we were faced with the prospect of olefin differentation in diene **9**. Since the C_{20}–C_{21} bond construction was to precede C_{12}–C_{13} bond formation, we attempted to selectively convert the 1,1-disubstituted olefinic moiety to the derived methyl ketone. Epoxidation of this hindered but relatively electron-rich olefin proceeded selectively in good yield. Unfortunately, all attempts at oxidative cleavage[19] of this epoxide led to decomposition, principally through loss of the *p*-methoxybenzyl ether. Alternatively, osmylation resulted in the undesired selective

(13) (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139–142. (b) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143–146.

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

(15) Andersen, N. H.; Hadley, S. W.; Kelley, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144–4151.

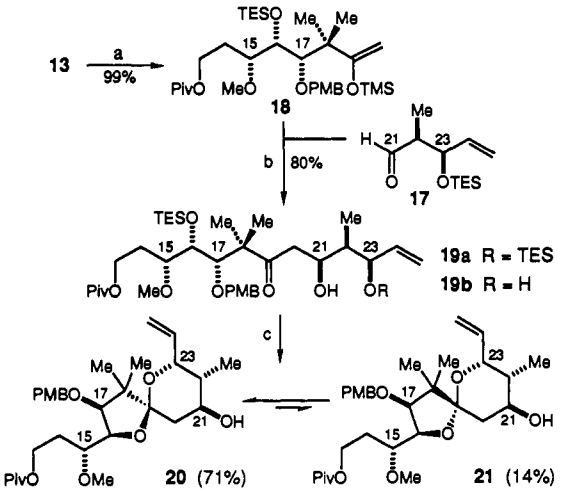
(16) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348. (b) Morrissey, M. M. Ph.D. Thesis, Harvard University, 1986.

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

(18) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889–892.

(19) For a typical procedure for oxidative cleavage of an epoxide to a ketone, see: Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599–4600.

Scheme V[a]



[a] (a) TMS-OTf, Et_3N, CH_2Cl_2, 0 °C. (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C. (c) 48% aqueous HF, CH_3CN, H_2O.

functionalization of the monosubstituted olefin. Regioselective olefin differentiation was finally achieved through Rh-catalyzed hydroboration of **10** with catecholborane (Scheme III).[20] With this reagent system, no competitive hydroboration of the more hindered olefin was detected. By comparison, the analogous hydroboration with 9-borabicyclononane (9-BBN) did not proceed to completion and resulted in a 2:1 mixture of **11** and the products derived from hydroboration at the 1,1-disubstituted olefin.

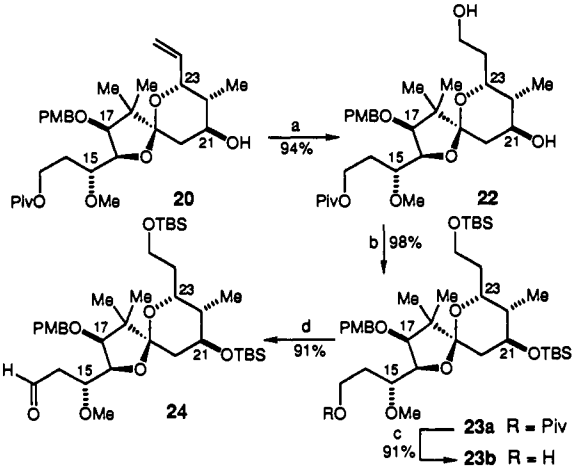
With the monosubstituted olefin successfully functionalized, oxidation of the 1,1-disubstituted olefin was uneventful. Esterification of primary alcohol **11** (pivaloyl chloride, pyridine), osmylation,[21] and in situ periodate cleavage afforded the desired methyl ketone **13** in 88% overall yield.

C_{21}–C_{25} Subunit. Addition of acrolein to the boron enolate derived from carboximide **14**[14] afforded the corresponding aldol adduct **15** in good yield (Scheme IV). Transamination ($AlMe_3$, MeO(Me)NH·HCl, THF)[17] and silylation of the unpurified amide/oxazolidinone mixture with chlorotriethylsilane produced amide **16** (93% overall), which was smoothly reduced to aldehyde **17** in 89% yield on treatment with diisobutylaluminum hydride at low temperature.[22]

Coupling and Spiroketal Formation. The original plan called for the aldol union of the C_{13}–C_{20} methyl ketone and C_{21}–C_{25} aldehyde subunits with attendant control of the newly generated C_{21} hydroxyl-bearing stereocenter being derived from Felkin–Anh selection on the aldehyde coupling partner. To our surprise, the requisite lithium enolate exhibited an unanticipated level of anti-Felkin diastereoselectivity (~5:1) in this reaction. Fortunately, the desired stereochemical outcome could be achieved when the Mukaiyama aldol variant of this coupling process was employed.[11a] The basis for this experiment was suggested by the Heathcock–Flippin study which demonstrated that the boron trifluoride etherate promoted addition of silyl enol ethers to 2-phenylpropanal provides enhanced levels of Felkin selectivity relative to those of the addition of the corresponding lithium enolate.[23]

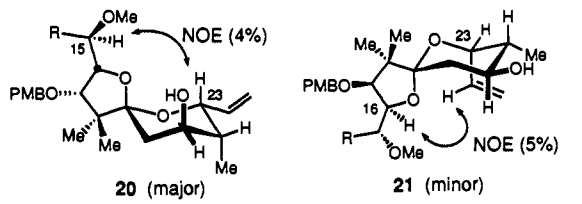
As illustrated in Scheme V, the aldol addition of silyl enol ether **18** and aldehyde **17** under Lewis acidic conditions affords alcohol **19a** in 80% yield as a single diastereomer. The stereochemistry of this adduct was proven by conversion of **19b** to its acetonide and measurement of the relevant coupling constants and NOE's.

Scheme VI[a]



[a] (a) 9-BBN, ultrasound, THF; H_2O_2. (b) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C. (c) DIBAl-H, CH_2Cl_2, −78 °C. (d) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 °C.

When this aldol adduct was subjected to HF/MeCN/H_2O (room temperature, 4 h), the diastereomeric spiroketals **20** and **21** were



formed in a 5:1 ratio in a combined yield of 85%. The use of triethylsilyl (TES) blocking groups on those oxygens integral to the spiroketal skeleton proved to be essential, since the presence of a more robust protecting group (e.g. TBS) at either site resulted in low product yields and extensive decomposition. During the reaction, it appears that the monodesilylated intermediate **19b** forms first and is converted preferentially to the minor spiroketal diastereomer **21**. Over time, the desired spiroketal **20** forms at the expense of **21**. The two spiroketals were readily separated by chromatography, and submission of either diastereomer to the reaction conditions resulted in >90% recovery of the diastereomer pair as the 5:1 equilibrium mixture. The stereochemical assignments at the spiroketal junctions of both diastereomers were determined by NOE measurements, two of the most informative of which are illustrated in the structures of **20** and **21**.

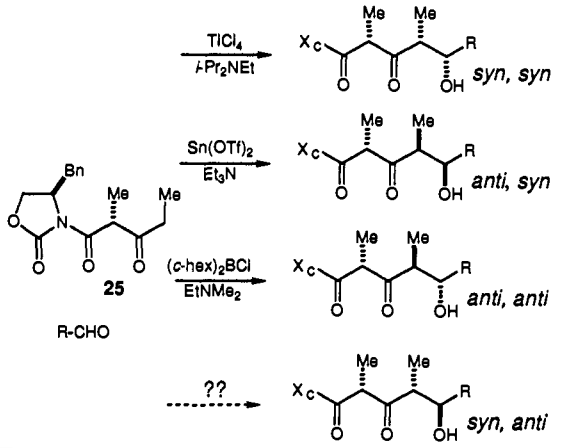
The origin of the kinetic preference for formation of the less stable spiroketal **21** is not readily apparent from the available data. The principal uncertainty which prevents a more thorough analysis is the lack of information pertaining to the ordering of the ring-forming steps during the spirocyclization process.

Spiroketal **20** was then transformed into the derived C_{13} aldehyde, the appendage point for the C_{10}–C_{13} dipropionate subunit (Scheme VI). Hydroboration of the vinyl group with 9-BBN was extremely sluggish under normal conditions, and attempted hydroboration with the borane/dimethylsulfide complex reduced the spiroketal moiety. However, the application of ultrasound to the 9-BBN reaction resulted in a clean, rapid transformation, affording diol **22** (94% yield),[24] which was converted to aldehyde **24** in 81% overall yield by silylation (TBS-OTf, 2,6-lutidine), reductive removal of the ester blocking group (DIBAl-H), and Swern oxidation.[25]

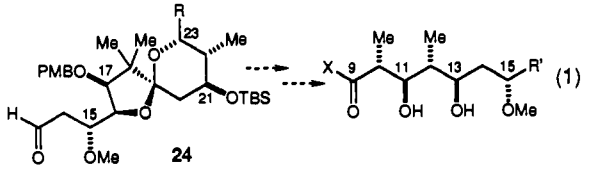
Dipropionate Synthesis. The next stage in the synthesis was concerned with the incorporation of the C_9–C_{13} dipropionate

(20) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917–6918. (b) Fu, G. C. Ph.D. Thesis, Harvard University, 1991.
(21) VanRheenen, V.; Kelley, R. C.; Cha, D. *Tetrahedron Lett.* **1976**, 1973–1976.
(22) A significant amount of over-reduction to the hydroxylamine ether occurred at −78 °C. Reduction at −90 °C circumvented this problem.
(23) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668.
(24) (a) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187–2190. (b) Crimmins, M. T.; O'Mahony, R. *Tetrahedron Lett.* **1989**, *30*, 5993–5996.
(25) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

Scheme VII



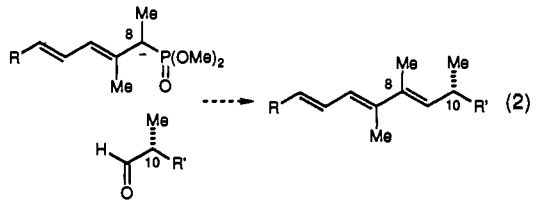
segment and its accompanying four stereocenters into the spiroketal fragment **24** (eq 1).



A promising point of departure for this construction was provided by several studies recently reported from these laboratories on the use of chiral β-ketoimides in aldol addition reactions (Scheme VII).[26] Thus, imide **25**, via its kinetic enolate, may be manipulated through selection of the appropriate metal to provide three of the four possible diastereomeric aldol adducts. *Unfortunately, the only variant which has not yet been discovered is the one required for the calyculin synthesis.* Of the available options, we speculated that the desired C_{10} and C_{12} methyl-bearing stereocenters might be established through the titanium enolate mediated aldol reaction and that the derived syn–syn aldol adduct might be transformed into the desired stereochemical array through a subsequent directed anti reduction followed by a selective inversion of the C_{13} alcohol.

The implementation of this strategy is illustrated in Scheme VIII. Addition of aldehyde **24** to the titanium enolate derived from **25** resulted in formation of aldol **26** in 93% yield as a single diastereomer. Directed reduction with $Me_4NBH(OAc)_3$ stereoselectively afforded diol **27** uncontaminated by its C_{11} diastereomer.[27] All that remained was to carry out the necessary hydroxyl inversion of the C_{13} alcohol. Examples from the literature document that the Mitsunobu reaction is very sensitive to steric effects.[28] In particular, secondary alcohols branched on both sides are unreactive.[29] It therefore appeared possible that the C_{13} alcohol might be selectively inverted without attendant protection of the hydroxyl group at C_{11}. Indeed, this proved to be the case: the Mitsunobu reaction (di-*tert*-butyl azodicarboxylate, Ph_3P, acetic acid, benzene) proceeded in 72% yield to afford acetate **28** along with 14% recovered **27**. Reduction of **28** ($LiBH_4$) afforded triol **29a** in 84% yield.[30] Selective esterification of the primary alcohol with pivaloyl chloride in pyridine, followed by bis-silylation of the derived diol afforded **30** in 76% overall yield.

Synthesis of the Cyano Tetraene. The C_8–C_9 bond construction which was chosen for the initiation of the synthesis of the tetraene portion of calyculin A is shown in eq 2. This particular Horner–Emmons trisubstituted olefin synthesis does not appear to have been precedented prior to the present study.



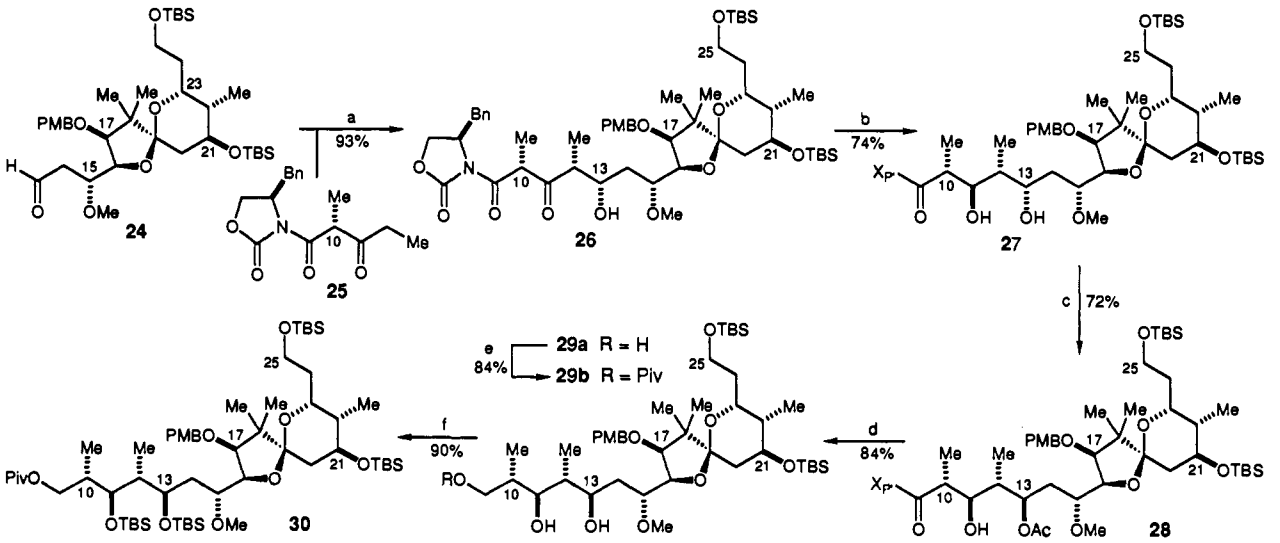
The synthesis began with the known vinylstannane **31**[31] (Scheme IX), which was most conveniently prepared by reduction of the readily available methyl (*E*)-3-(tributylstannyl)-2-propenoate.[32] Swern oxidation afforded aldehyde **32** (95%),[25] which was added to the lithium anion of triethyl 2-phosphonopropionate (THF, 20 °C) to give dienoate **33** as a 19:1 (*E*):(*Z*) mixture of olefin isomers in 96% yield. Reduction with diisobutylaluminum hydride (CH_2Cl_2, −78 °C → −50 °C) afforded alcohol **34a** (91%), which was transformed to the derived bromide (CBr_4, Ph_3P, 2,6-lutidine, MeCN).[33] This latter transformation was invariably accompanied by some allylic transposition, affording **34b** and its isomeric C_6 bromide as an inseparable 6:1 mixture. Upon heating this mixture in the presence of trimethyl phosphite, the desired phosphonate **35a** was obtained in very low (<15%) yield, as destannylation appeared to be a major side reaction. The Michaelis–Becker reaction was then used as a mild alternative.[34] Thus, treatment of the bromide mixture with a solution of the sodium conjugate of dimethyl phosphite in THF afforded **35a** in 46% yield from alcohol **34a**. Finally, treatment of **35a** with *n*-butyllithium (1.0 equiv, THF, −78 °C) resulted in the immediate formation of a deep-red solution which afforded the desired methylated phosphonate **35b** in 92% yield upon quenching with iodomethane. This transformation was remarkable in that no destannylation was observed during the deprotonation process.

In principle, phosphonate **35b** could be elaborated in either of two ways to complete the construction of the cyano tetraene moiety. Metal-catalyzed sp^2–sp^2 coupling of an appropriate C_1–C_3 synthon could give the completed tetraene synthon, ready for coupling to the spiroketal fragment. Alternatively, Horner–Emmons reaction of **35b** with the spiroketal-derived aldehyde could precede final elaboration of the tetraene. Stille coupling[32] of **35b** with the known vinyl iodide **36**[35] ($(Ph_3P)_2PdCl_2$, DMF) gave phosphonate **37** in 73% yield (Scheme X). The metalation (*n*-BuLi, THF, −78 °C) and subsequent condensation of **37** with isobutyraldehyde was, as expected, sluggish even at 20 °C due to anion stabilization by the cyano group. When this reaction was quenched, the starting phosphonate was recovered as a 1:1.2 mixture of olefin isomers. In the more attractive option, metalation of **35b** and condensation with isobutyraldehyde (20 °C, 5 min) afforded stannyl triene **38** as a 5:1 mixture of (*E*) and (*Z*) olefins at the newly formed double bond. NOE measurements on this compound established the olefin geometry. Stille coupling of the unpurified olefin mixture with iodide **36** ($(Ph_3P)_2PdCl_2$, DMF) gave cyano tetraene **39** as a 5:1 mixture of olefin isomers in 59% overall yield from **35b**. These studies thus substantiated that the sequential application of the Horner–Emmons and Stille bond constructions was viable for the synthesis.

Removal of the C_{17} *p*-methoxybenzyl[36] and C_9 pivaloyl protecting groups from the C_9–C_{25} fragment **30** proceeded smoothly to provide diol **40b** in 92% overall yield (Scheme XI). Selective oxidation of the primary alcohol proved to be unexpectedly straightforward. Thus, treatment of **40b** with the Dess–Martin periodinane[37] (pyridine, CH_2Cl_2) afforded aldehyde **41** in 88%

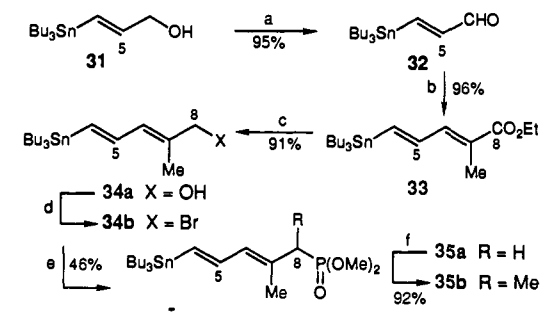
(26) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.
(27) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
(28) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(29) For a recent example, see: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.
(30) Penning, T. D.; Djurić, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307–312.
(31) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.
(32) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817.
(33) Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139–2141.
(34) Michaelis, A.; Becker, T. *Chem. Ber.* **1897**, *30*, 1003–1009.
(35) Chalchat, J.-C.; Thêron, F.; Vessière, R. *C. R. Acad. Sci. Paris Sér. C* **1971**, *273*, 763–764.
(36) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.
(37) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156–4158.

Scheme VIII[a]



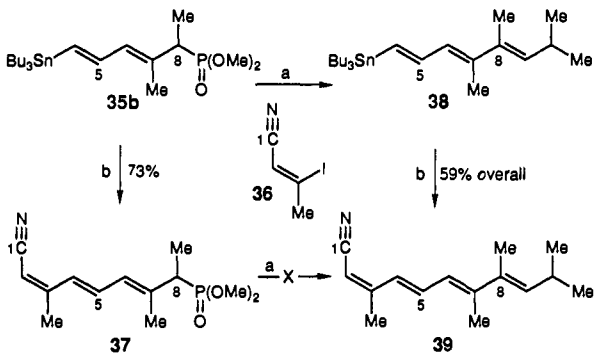
[a] (a) **25**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −20 °C; **24**, −78 °C. (b) $Me_4NBH(OAc)_3$, MeCN/AcOH, −20 °C. (c) Di-*tert*-butyl azodicarboxylate, Ph_3P, AcOH, benzene. (d) $LiBH_4$, MeOH, THF, 0 °C. (e) Pivaloyl chloride, pyridine. (f) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

Scheme IX[a]



[a] (a) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 °C to −35 °C. (b) Triethyl 2-phosphonopropionate, *n*-BuLi, THF; (c) DIBAl-H, CH_2Cl_2, −78 °C to −50 °C. (d) CBr_4, Ph_3P, 2,6-lutidine, MeCN. (e) NaH, $(MeO)_2P(O)H$, THF. (f) *n*-BuLi, MeI, THF, −78 °C to 0 °C.

Scheme X[a]

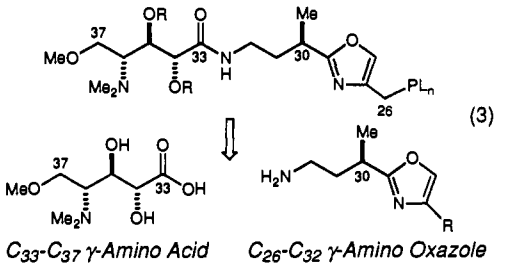


[a] (a) *n*-BuLi, *i*-PrCHO, THF, −78 °C to +20 °C. (b) $(Ph_3P)_2PdCl_2$, DMF, **36**.

yield with complete selectivity for the primary alcohol. Despite the large number of documented applications of this mild oxidation, no study has yet addressed its potential for selective oxidations of sterically differentiated diols.[38] We surmise that the C_{17} alcohol is too hindered to allow us to draw any general conclusions about the inherent selectivity of this oxidant.

In the application of the preceding methodology to the synthesis, addition of aldehyde **41** to the metalated phosphonate **35b** (2 equiv) afforded the stannyl triene **42** as a 7:1 mixture of olefin isomers, accompanied by some recovered phosphonate **35b**. Submission of this unpurified mixture to Stille coupling with vinyl iodide **36** afforded cyano tetraene **43a** accompanied by its C_8–C_9 olefin isomer as well as phosphonate **37**. Importantly, **43a** and its (*Z*) olefin isomer are chromatographically separable, leading to the isolation of the desired (*E*) trisubstituted olefin in 64% overall yield from aldehyde **41**. In an early rendition of the synthesis of this calyculin fragment, the C_{17} PMB protecting group was retained throughout the assemblage of the cyano tetraene to provide the C_1–C_{25} fragment **43b**.[11b] However, it was discovered that the olefin isomer separation of this intermediate could not be achieved, and the even more serious problem of PMB removal from **43b** was encountered. At best, only modest yields of deprotection using DDQ could be achieved, and other methods of cleaving this protecting group fared no better.

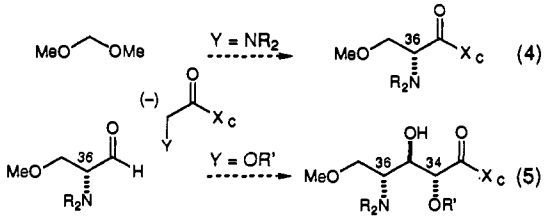
Synthesis of the C_{26}–C_{37} Subunit. In contrast to the stereochemical complexity of the C_1–C_{25} subunit, the abundance of heteroatom functionality in this fragment contributes to the challenge of its construction. Disconnection of this fragment at the amide junction affords the C_{33}–C_{37} γ-amino acid and C_{26}–C_{32} γ-amino oxazole structures (eq 3) whose syntheses are described in the following discussion.



(3)

C_{33}-C_{37} γ-Amino Acid *C_{26}-C_{32} γ-Amino Oxazole*

C_{33}–C_{37} γ-Amino Acid. The synthesis of this densely functionalized amino acid was predicated on the development of the two enolate-based bond constructions illustrated in eqs 4 and 5.



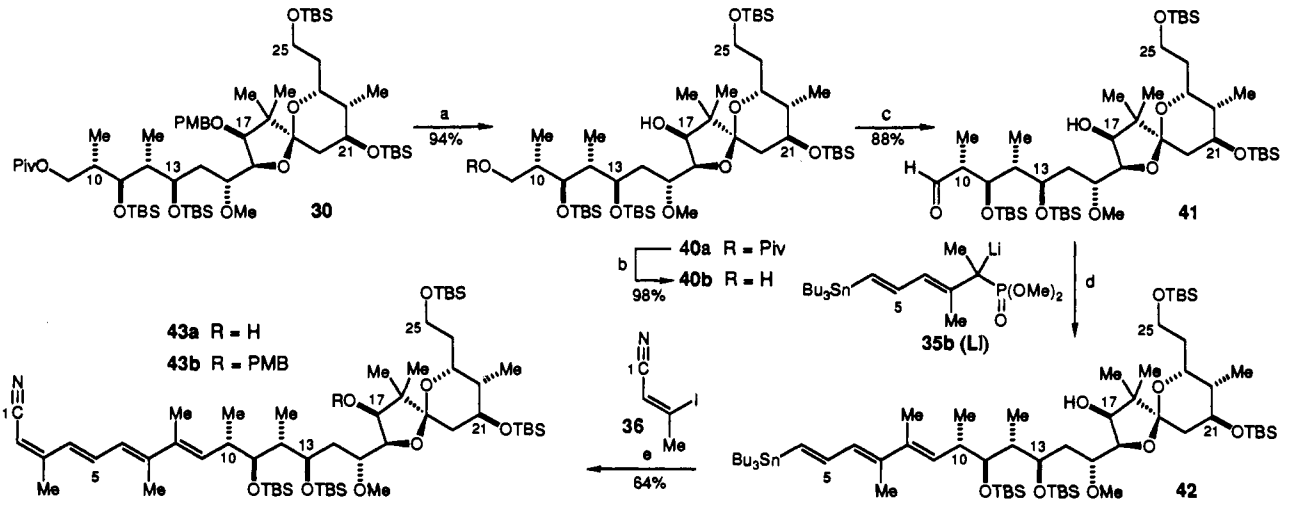
(4)

(5)

Neither of these enantioselective bond constructions is directly

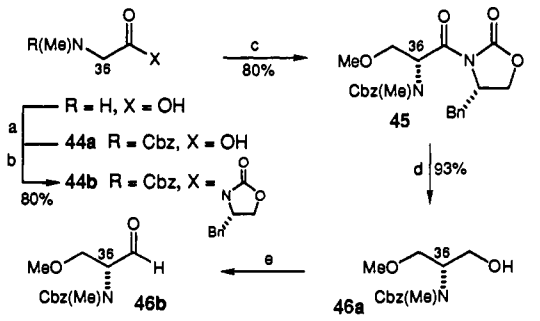
(38) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287 and their ref 41.

Scheme XI[a]



[a] (a) DDQ, CH_2Cl_2, H_2O. (b) DIBAl-H, CH_2Cl_2, −78 °C. (c) Dess–Martin periodinane, pyridine, CH_2Cl_2. (d) THF, 0 °C. (e) $(MeCN)_2PdCl_2$, 1-methyl-2-pyrrolidinone.

Scheme XII[a]

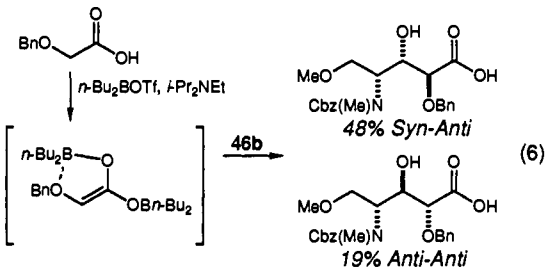


[a] (a) Aqueous NaOH, BnOCOCl, 0 °C. (b) Pivaloyl chloride, Et_3N, THF, −78 °C to +20 °C; X_PLi, −78 °C to +20 °C. (c) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; $(MeO)_2CH_2$, $BF_3{\cdot}OEt_2$, 20 °C. (d) $LiBH_4$, MeOH, THF, 0 °C. (e) Oxalyl chloride, DMSO, *i*-Pr_2NEt, −78 °C to −50 °C.

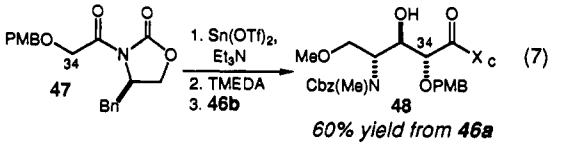
precedented in the literature. The development of these reactions and their application to the synthesis is detailed below.

N-Protection of sarcosine as its benzyl carbamate afforded acid **44a**, which was used to N-acylate the (*S*)-phenylalanine-derived oxazolidinone, affording the chiral glycine derivative **44b** in 80% overall yield (Scheme XII). Lewis acid promoted alkylation of the titanium enolate derived from **44b** ($TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C) with dimethoxymethane (10 equiv) in the presence of $BF_3{\cdot}OEt_2$ (10 equiv, 20 °C, 2 h) provided **45** in good yield (80%) and diastereoselectivity (98:2). The stereochemical assignment of **45** was made in analogy to the reactions of related titanium enolates.[39] Reductive removal of the chiral auxiliary ($LiBH_4$, MeOH, THF, 0 °C) proceeded smoothly to afford alcohol **46a** in 93% yield along with a 92% recovery of the auxiliary.[30] Swern oxidation of **46a** under the standard conditions (oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −60 to −40 °C)[25] provided aldehyde **46b**, which had been substantially racemized (~30%) as judged by reduction to **46a** (DIBAl-H) and ^1H NMR analysis of the derived Mosher ester.[40] The use of Hunig's base in place of triethylamine in the Swern oxidation cleanly circumvented this problem. Although this building block could also have been synthesized from D-serine, the route illustrated in Scheme XII is competitive with this alternative.

In the next bond construction, the anti aldol reaction illustrated in eq 5 was required. Some years ago we reported that the boron enediolate of benzyloxyacetic acid undergoes an anti-selective aldol addition reaction with aldehydes.[41] With this reaction serving as a precedent, this reaction was applied to aldehyde **46b** in the hope that the N(Me)Cbz substituent would act as the "large" group in a Felkin-selective[42] transformation, thus affording the desired all-anti stereotriad. In fact, enolization of benzyloxyacetic acid with 2 equiv of *n*-Bu_2BOTf (*i*-Pr_2NEt, Et_2O, 0 °C) followed by addition of **46b** afforded a 2.6:1 mixture of anti aldol adducts favoring the *undesired* syn–anti product (eq 6). No explanation can be provided for this unexpected stereochemical outcome.



Following this result, the incorporation of external control in the aldol reaction via a chiral enolate was pursued. On the basis of a lead that (*Z*) tin(II) enolates exhibit anti aldol diastereoselectivity when complexed with chelating diamines,[43] we found that the addition of TMEDA to the tin(II) enolate of glycolate imide **47** led to acceptable anti diastereoselectivity in the desired aldol reaction. Thus, the sequential enolization of 1.5 equiv of imide **47** ($Sn(OTf)_2$, Et_3N, CH_2Cl_2, −10 °C, 45 min), addition of TMEDA (−78 °C, 5 min) and addition of 1.0 equiv of aldehyde **46b** (−78 °C, 4 h) afforded the desired anti aldol adduct **48** in 60% isolated yield accompanied by a total of 24% of other diastereomers (eq 7).[11c,44] A detailed understanding of the details of this reaction awaits further study.



(39) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

(40) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

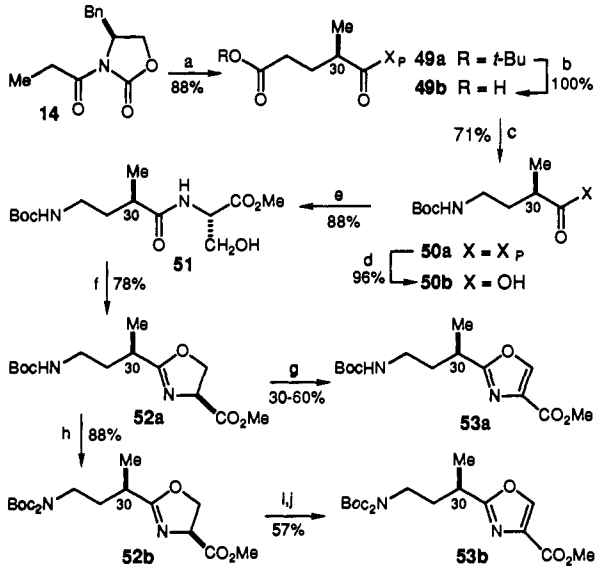
(41) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

(42) There was some precedent for this notion. See, for example: (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Eng.* **1987**, *26*, 1141–1143. (b) Raczko, J.; Golebiowski, A.; Krajewski, J. W.; Gluzinski, P.; Jurczak, J. *Tetrahedron Lett.* **1990**, *31*, 3797–3800.

(43) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753–756.

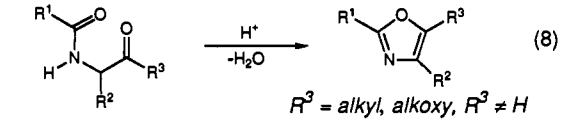
(44) The relative stereochemistry of **48** was proven by its conversion into an *N*-methylpyrrolidinone derivative and measurement of the relevant coupling constants and NOE's. See the supplementary material for details.

Scheme XIII[a]

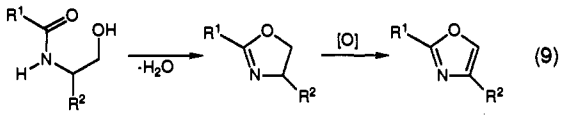


[a] (a) Ti(O-*i*-Pr)Cl_3, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; *tert*-butyl acrylate. (b) 3:1 CH_2Cl_2/TFA. (c) DPPA, Et_3N, *tert*-butyl alcohol, reflux. (d) LiOOH, 4:1 THF/H_2O, 0 °C. (e) *i*-BuOCOCl, NMM, THF, −25 °C; L-serine methyl ester·HCl, NMM, 20 °C. (f) $SOCl_2$, pyridine, 9:1 Et_2O/THF, 0 °C. (g) Nickel peroxide, C_6H_6, reflux. (h) Boc_2O, DMAP, MeCN. (i) KHMDS, PhSeCl, THF, −78 °C. (j) 30% Aqueous H_2O_2, CH_2Cl_2, pyridine, 0 °C.

C_{26}–C_{32} γ-Amino Oxazole. The two challenges posed by this fragment are associated with the construction of a suitable 2,4-disubstituted oxazole[45] and the asymmetric synthesis of the requisite carboxylic acid precursor. One of the oldest and most frequently used oxazole syntheses, the Robinson–Gabriel cyclodehydration of keto amides and ester amides,[46] does not extend to the cyclodehydration of aldehydo amides (eq 8). We therefore



(8)

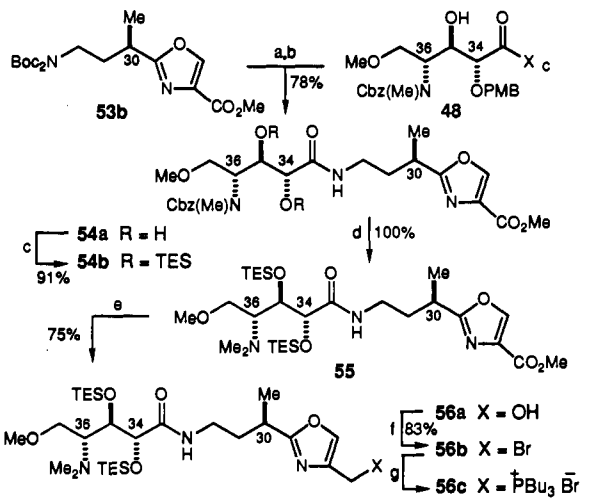


(9)

turned to the conceptually related cyclodehydration of appropriately activated amide alcohols to oxazolines, which upon dehydrogenation furnish oxazoles (eq 9).

The synthesis was initiated with the illustrated Michael reaction of *N*-propionyloxazolidinone **14**[14] with *tert*-butyl acrylate to afford ester **49a** as a single diastereomer (>95:5) in 88% yield (Scheme XIII).[47] Acid-catalyzed cleavage of the *tert*-butyl ester afforded the derived acid **49b**, which was submitted to the Curtius rearrangement[48] with diphenylphosphoryl azide (Et_3N, *tert*-butyl alcohol, reflux, 15 h) to efficiently install the C_{32} amino group in protected form, giving **50a** in 71% yield. Hydrolytic removal of the chiral auxiliary with basic hydrogen peroxide[49] produced the protected (*R*)-γ-amino acid **50b** in 96% yield.[50] Mixed

Scheme XIV[a]



[a] (a) HCl(g), EtOAc, 0 °C. (b) $AlMe_3$, CH_2Cl_2, 20 °C. (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. (d) H_2 (1 atm), 10% Pd/C, aqueous formaldehyde, MeOH, AcOH. (e) $LiAlH_4$, Et_2O, −78 °C. (f) CBr_4, Ph_3P, 2,6-lutidine, MeCN. (g) Bu_3P, DMF, 20 °C.

anhydride coupling of this acid with L-serine methyl ester·HCl cleanly provided dipeptide **51** (88%), which was cyclized in a single step to the desired oxazoline **52a** ($SOCl_2$, pyridine, 0 °C, 78%).

The usual reagent for the oxidative aromatization of oxazolines is "nickel peroxide", an uncharacterized black powder produced by treatment of nickel(II) sulfate with sodium hypochlorite.[51] Oxidation of oxazoline **52a** according to this procedure did indeed provide the desired oxazole **53a**, but in variable and often low yields (30%–60%). We therefore developed a more reproducible alternative for this transformation. Enolization of **52b** with KHMDS (1.1 equiv, THF, −78 °C) followed by reaction with phenylselenenyl chloride cleanly provided a 1:1 mixture of diastereomeric selenides, which, without purification, was submitted to oxidative elimination with hydrogen peroxide to afford oxazole **53b** in 57% overall yield.[52] Despite the more involved nature of this procedure, it was found to be the method of choice for larger-scale reactions.

Assemblage of the C_{26}–C_{37} Subunit. With the amino acid and oxazole fragments in hand, a practical coupling and protection sequence was developed (Scheme XIV). Nitrogen deprotection (HCl, EtOAc, 0 °C) of oxazole **53b** (1.25 equiv) afforded the derived solid hydrochloride salt. To a suspension of this salt in CH_2Cl_2 were sequentially added $AlMe_3$ (2.50 equiv, 2.5 M in toluene) and imide **48** (1.0 equiv, 20 °C, 2 h) to give the expected amide coupling product[17] *along with the analogous product* ***54a***, *having unexpectedly lost the C_{34} PMB ether protecting group.* Since this deprotection step was to be faced in subsequent steps, the in situ removal of the protecting group was promoted by the introduction of an additional 3.75 equiv of $AlMe_3$ to the reaction to provide diol **54a** in 78% yield. Once optimized, this transformation accomplished not only the removal of the chiral auxiliary and formation of the desired amide bond but also the removal of the *p*-methoxybenzyl ether protecting group in a single operation. At this juncture, the C_{34} and C_{35} hydroxyl protecting groups were incorporated into diol **54a**. Prior experience alerted us to the fact that acid-promoted silicon deprotection in the environment of a basic nitrogen would be strongly attenuated by amine protonation. Accordingly, triethylsilyl protecting groups were selected

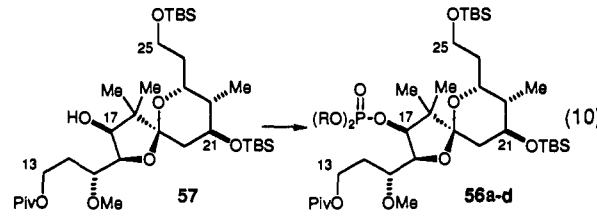
(45) For a review of the synthesis and chemistry of oxazoles, see: Turchi, I. J. *The Chemistry of Heterocyclic Compounds, 45*; John Wiley & Sons: New York, 1986; pp 1–341.
(46) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167–2174.
(47) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750–5752.
(48) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
(49) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
(50) The absolute configuration of **50b** was assigned by analogy; see ref 47.
(51) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497–501.
(52) Several other oxidants were screened, giving similar results, and in all cases the same byproduct was formed, as indicated by TLC analysis. ^1H NMR analysis of this compound indicated that it is a decomposition product of the selenenate ester formed by competing [2,3] rearrangement of the intermediate selenoxides.

for these alcohol functional groups.[53] Protection of this diol afforded the derived bis(triethylsilyl) ether **54b** in 91% yield, while subsequent removal of the Cbz N-protecting group and in situ reductive methylation afforded dimethylamine **55** in quantitative yield. Finally, the carbomethoxyl moiety in **55** was transformed smoothly into the tributylphosphonium salt **56c** in preparation for the Wittig union with the C_1–C_{25} fragment.

Phosphate Model Studies. In order to minimize the number of transformations through which the labile phosphate moiety would be carried, the decision was made to incorporate this group just prior to the C_{25}–C_{26} olefination step. This decision placed the following constraints on the phosphodiester substituents: these substituents would have to withstand the conditions for selective removal of the primary TBS ether at C_{25} (HF·pyridine, pyridine), would have to be stable to the conditions of the Wittig coupling (metal amide base), and would have to be removed under conditions compatible with the functionality present in the fully assembled calyculin A skeleton.

Given the lack of information in the literature regarding protecting groups for the synthesis of phosphate monoesters, alcohol **57** was chosen as a model for the monophosphorylation studies. With this substrate, it was discovered that, while dialkyl phosphorochloridates and phosphorus oxychloride are unreactive toward either **57** or its derived lithium alkoxide, the more electrophilic dialkyl phosphorochloridites react smoothly to furnish, after oxidation, phosphotriesters in good overall yield.[11d] Subsequently, a convenient one-pot procedure for the synthesis of dialkyl phosphate derivatives of **57** was developed. In a representative procedure, treatment of **57** with PCl_3 (2 equiv, pyridine, 10 min, 20 °C), followed by the addition of 3-hydroxypropionitrile (6 equiv, 20 min) and in situ oxidation (30% aqueous H_2O_2, CH_2Cl_2), provided the desired phosphate **58a** in 88% yield (eq 10, R = $NCCH_2CH_2$). These conditions were also employed to synthesize the phosphotriesters **58b–58d** in comparable yields (Table I). The success of this procedure is perhaps due to the steric hindrance in the vicinity of the C_{17} alcohol, and it is unclear whether this method would be applicable to less hindered alcohols.

The stability of these phosphate esters to the reaction conditions to be encountered during the terminal stages of the synthesis was evaluated (Table I). The base-labile 2-cyanoethyl group, a common protecting group in polynucleotide synthesis,[54] has been shown to be useful for the synthesis of phosphate monoesters.[11d] However, **58a** suffers partial deprotection during attempted Wittig coupling of the derived C_{25} aldehyde, rendering product isolation and characterization difficult. The 2-(trimethylsilyl)ethyl group (**58b**) did not suffer from this liability, but proved to be quite difficult to remove. This phosphate was completely stable to aqueous HF/MeCN and underwent loss of only one TMS ethyl group upon prolonged exposure to tetrabutylammonium fluoride, conditions which are destructive to the natural product.[55] We turned next to benzyl protecting groups with the expectation that their acid lability could be regulated by selection of the appropriate aromatic substituent. The benzyl and *p*-methoxybenzyl (PMB) protected phosphates **58c** and **58d** were prepared and tested for acid lability.[56] In each case, selective removal of the primary TBS ether was effected cleanly with HF·pyridine, leaving the phosphate and the secondary TBS protecting groups intact. When **58c** was exposed to aqueous HF (HF, MeCN/H_2O), the dibenzyl phosphate moiety was unaffected although both TBS groups were removed. Finally, the ideal characteristics of the PMB derivative were revealed when it was found that exposure of **58d** to the same conditions resulted in the removal of both silicon and PMB phosphate groups. Since these were the conditions that were anticipated for the final deprotection step in the synthesis, the PMB moiety met all of the necessary conditions for the phosphate protecting group.



Conditions: PCl_3, pyridine; ROH; 30% aq H_2O_2, CH_2Cl_2.

Table I. Stability of Phosphate Protecting Groups

cmpd	R	HF·Pyr[a]	HF, CH_3CN[b]	KHMDS[c]
58a	$NCCH_2CH_2$	yes	yes	no
58b	$Me_3SiCH_2CH_2$	yes	yes	yes
58c	$C_6H_5CH_2$	yes	yes	
58d	*p*-$MeOC_6H_4CH_2$	yes	no	

[a] HF·pyridine, pyridine, THF. [b] 48% aqueous HF, CH_3CN, H_2O. [c] Stability checked during attempted Wittig coupling of derived C_{25} aldehyde with **56c**.

Assemblage of Subunits. The phosphorylation conditions described above, as applied to **43a**, resulted in the isolation of the desired PMB-protected phosphate **59a** in 84% yield (Scheme XV). As with the model compound **58d**, selective removal of the primary TBS ether proved to be straightforward (HF·pyridine, pyridine, THF), affording alcohol **59b** in 76% yield, along with 10% recovered **59a**. Oxidation of **59b** with the Dess–Martin periodinane (pyridine, CH_2Cl_2, 87%) provided aldehyde **60** and set the stage for the C_{25}–C_{26} Wittig olefination.

We had previously expended some effort on the C_{25}–C_{26} olefination,[11d] concentrating initially on phosphonate-based olefinations. However, the anions derived from these phosphonates proved to be too basic and caused β-elimination in aldehydes related to **60**. We then turned to the derived phosphonium salts which had been the subject of a model study reported by Armstrong.[12e] As was disclosed, the stabilized ylides derived from these salts were found to be highly (*E*) selective in Wittig reactions with aldehydes. Addition of aldehyde **60** (1.0 equiv, DMF) to a cooled (0 °C) solution of phosphonium salt **56c** (1.5 equiv, DMF) was followed by the addition of a solution of lithium diisopropylamide (1.5 equiv, THF, 0 °C), to produce the fully protected calyculin A structure **61** in 65% yield along with 20% of recovered aldehyde **60** (Scheme XV). No evidence for the (*Z*) C_{25}–C_{26} olefin isomer could be detected by ^1H NMR spectroscopy. Optimal results were obtained with the in situ formation of phosphonium salt **56c** in DMF directly preceding the Wittig reaction. Treatment of **61** with aqueous HF in MeCN for 92 h afforded synthetic calyculin A in 70% yield (Scheme XV). This material proved to be identical in all respects (^1H and ^{13}C NMR; IR; TLC; UV; HRMS) with natural calyculin A except for its optical rotation, which was equal in magnitude and opposite in sign to that of the natural material.[57] This study thus confirms the absolute configuration of calyculin A to be enantiomeric to that illustrated in structure **1**.

Several aspects of the final deprotection procedure deserve comment. TLC analysis of the ongoing reaction indicates that the PMB groups on the phosphate are removed within 12 h, as judged by the appearance of *p*-methoxybenzyl alcohol. After 24 h, a compound that coelutes with natural calyculin A is formed. Upon product isolation at this stage of the reaction, ^1H NMR and mass spectroscopic analyses reveal the presence of synthetic calyculin A as well as a mono-TBS-protected calyculin A deriv-

(53) Model studies confirmed that TBS protecting groups could not be removed from these functional groups under the acidic conditions (HF, MeCN/HOH) which would be employed for the final deprotection step in the synthesis.

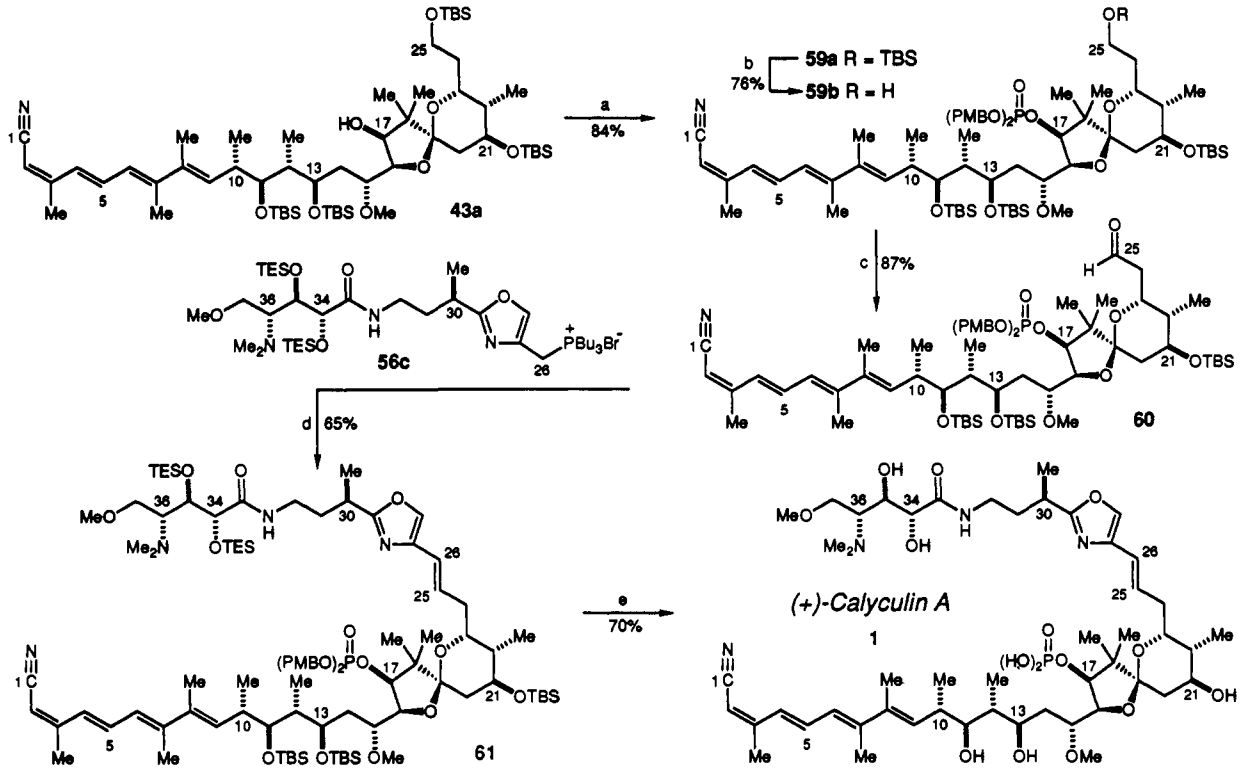
(54) For a review of phosphorous protection strategies for polynucleotide synthesis, see: Kossel, H.; Seliger, H. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 297–508.

(55) Our inability to remove both protecting groups under basic conditions was anticipated on the basis of our experience with the 2-cyanoethyl group.

(56) It has been reported that a *p*-methoxybenzyl ester can be hydrolyzed to the corresponding carboxylic acid with trifluoroacetic acid. See: Stewart, F. H. C. *Aust. J. Chem.* **1968**, *21*, 2543.

(57) In the original paper,[2] Fusetani reports the optical rotation of natural calyculin A as $[\alpha]_D$ +59.8° (*c* 0.12, EtOH). This value was later corrected[5] to $[\alpha]_D$ −60° (*c* 0.1, EtOH). The optical rotation of our synthetic material is $[\alpha]_D$ +60° (*c* 0.10, EtOH).

Scheme XV[a]



[a] (a) PCl_3, pyridine; *p*-methoxybenzyl alcohol; 30% aq H_2O_2, CH_2Cl_2. (b) HF·pyridine, pyridine, THF. (c) Dess–Martin periodinane, pyridine, CH_2Cl_2. (d) **56c**, **60**, DMF, 0 °C; LDA, THF, 0 °C. (e) 5:86:9 48% aqueous $HF/CH_3CN/H_2O$, 92 h.

ative tentatively assigned as the C_{11} silyl ether. The remarkable fact that these two compounds coelute on silica perhaps provides a clue as to why this last silyl group requires a total of 92 h to be completely removed, whereas the C_1–C_{25} fragment **43b** (Scheme XI) may be completely deprotected within 24 h when submitted to the same conditions. It is our belief that the C_{11} silyl ether, as the last protecting group to be removed, is rendered inaccessable to external reagents by the tertiary structure of the molecule enforced by the formation of the key hydrogen bonds between side chains and the phosphate moiety.

We also observe no equilibration of the spiroketal during the final deprotection, even though the conditions used were exactly the same as those which result in the independent equilibration of the spiroketals **20** and **21** to the same 5:1 mixture (Scheme V). We again speculate that the tertiary structure enforced by phosphate hydrogen bonding is responsible for the stability of the desired spiroketal.

Conclusion

The first total synthesis of (+)-calyculin A has been accomplished, and the absolute configuration of the natural product has been established. The synthesis plan is noteworthy in that 10 of the 15 stereogenic centers were established through enolate-based bond constructions. A number of these reactions (**24 + 25 → 26**, **44b → 45**, **46b + 47 → 48**, and **14 → 49a**) have been either developed or employed in a complex setting for the first time during the course of this project.

Experimental Section

General Methods. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AM-500, AM-400, AM-300, or AM 250 spectrometers. Calyculin numbering is used for assignments on all intermediates. Infrared spectra were recorded on a Perkin-Elmer 781 or Nicolet 5ZDX FT-IR spectrometer. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, MI). Mass spectra were obtained on a JEOL AX-505 or SX-102 spectrometer. Analytical chromatography was performed on EM reagents 0.25-mm silica gel 60-F plates. Flash chromatography was performed on EM reagents silica gel 60 (230–400 mesh). Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile, *tert*-butanol, diisopropylamine, triethylamine, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), diisopropylethylamine, pyridine, and 2,6-lutidine were distilled from calcium hydride. Dimethyl sulfoxide was distilled under reduced pressure from calcium hydride and stored over 4-Å molecular sieves. *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure and stored over 4-Å molecular sieves. Methanol was distilled from $Mg(OMe)_2$. Deuteriochloroform was stored over 4-Å molecular sieves. Acetic acid was distilled from acetic anhydride. Catecholborane, titanium tetrachloride, titanium tetraisopropoxide, dimethyl phosphite, and *p*-methoxybenzyl alcohol were distilled under reduced pressure, and oxalyl chloride, phosphorus trichloride, thionyl chloride, dimethoxymethane, and acrolein were distilled prior to use. All other commercially obtained reagents were used as received.

For brevity, experimental procedures for the following transformations have not been incorporated in this section: **6 → 7**, **9 → 10**, **11 → 12**, **15 → 16**, **22 → 23a**, **29a → 29b**, **29b → 30**, **31 → 32**, **40a → 40b**, **49a → 49b**, and **54a → 54b**. Full details for these procedures and complete analytical data can be found in the supplementary material.

[4*S*]-4-Benzyl-3-(3,3,4-trimethyl-4-pentenoyl)-2-oxazolidinone (3). To a mechanically stirred solution of 9.49 g (66.7 mmol) of 3,3,4-trimethyl-4-pentenoic acid[15] (**2**) in 725 mL of diethyl ether at −78 °C was added 9.77 mL (7.09 g, 70.1 mmol) of triethylamine followed by 8.63 mL (8.45 g, 70.1 mmol) of pivaloyl chloride. The resulting thick white precipitate was stirred for 1 h at 0 °C and then recooled to −78 °C. Meanwhile, a separate solution of 11.8 g (66.7 mmol) of [4*S*]-4-benzyl-2-oxazolidinone[14] in 150 mL of THF was prepared. Upon cooling this solution to −78 °C, 26.5 mL (66.7 mmol) of *n*-butyllithium (2.52 M in hexane) was added by syringe over 5 min. The resulting pale-red solution was transferred by cannula to the flask containing the mixed anhydride. The mixture was stirred for 15 min at −78 °C and 30 min at 0 °C before quenching by addition of 500 mL of saturated aqueous NH_4Cl. The layers were separated, and the organic layer was washed with 300 mL of brine, dried ($MgSO_4$), and concentrated, affording 22.2 g of a white solid. The solid was recrystallized from 100 mL of hot hexane to give 15.13 g of **3** as a crystalline solid. An additional 2.98 g of **3** was obtained by concentration and flash chromatographic purification of the mother liquor (5 × 15 cm, 10% EtOAc/hexane) for a total yield of 18.11 g (90%): mp 66–68 °C; $[\alpha]_D$ +59.0° (*c* 1.07, CH_2Cl_2); IR (solution in CH_2Cl_2) 3050, 2990, 1780, 1705, 1420, 895 cm^{-1}; ^1H

NMR ($CDCl_3$, 300 MHz) δ 7.33–7.20 (m, 5 H, Ar*H*), 4.80 (br s, 2 H, C=C*H*$_2$), 4.67 (m, 1 H, C*H*N), 4.13 (m, 2 H, OC*H*$_2$), 3.32 (dd, 1 H, *J* = 3.4 and 13.2 Hz, ArC*H*$_2$), 3.17 (d, 1 H, *J* = 16.0 Hz, C$_{17}$-*H*), 3.08 (d, 1 H, *J* = 16.0 Hz, C$_{17}$-*H*), 2.69 (dd, 1 H, *J* = 10.0 and 13.2 Hz, ArC*H*$_2$), 1.81 (s, 3 H, C$_{20}$-*H*), 1.24 (s, 6 H, C$_{18}$-(C*H*$_3$)$_2$; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.3, 153.5, 151.6, 135.4, 129.4, 128.9, 127.3, 109.4, 65.9, 55.3, 44.2, 38.7, 38.0, 27.4, 27.3, 19.7; TLC R_f = 0.26 (15% EtOAc/hexane). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.36; H, 7.71; N, 4.78.

[4*S*,3(2*S*)]-4-Benzyl-3-(2-hydroxy-3,3,4-trimethyl-4-pentenoyl)-2-oxazolidinone (4). To a solution of 30.3 mL (30.3 mmol) of NaHMDS (1.0 M in THF) and 45 mL of THF at −78 °C was added dropwise a solution of 7.63 g (25.3 mmol) of imide **3** in 45 mL of THF at a rate such that the internal temperature was kept below −70 °C (30 min). The resulting solution was stirred for 30 min at −78 °C and cooled to −92 °C. A solution of 9.25 g (35.4 mmol) of 2-(phenylsulfonyl)-3-phenyloxaziridine[58] in 30 mL of THF was prepared in a separate flask and cooled to −78 °C. This solution was transferred to the reaction flask by wide-bore cannula over 1 min. Upon completion of the addition, 7.5 mL of acetic acid in 150 mL of THF was added. The resulting mixture was poured into 1 L of 4:1 hexane/CH_2Cl_2 and washed with 500 mL each of 5% aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, aqueous 1 M $NaHSO_4$, 5% aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (11 × 35 cm, CH_2Cl_2 to elute the imine byproduct followed by 1% acetone/CH_2Cl_2) to afford 7.05 g (88%) of alcohol **4** as a viscous oil which solidified on standing. This compound was diastereomerically pure as judged by TLC, ^{1}H NMR, and ^{13}C NMR: mp 67.5–68.5 °C; $[\alpha]_D$ +92.0° (*c* 1.14, CH_2Cl_2); IR (thin film) 3520, 2990, 1780, 1690, 1355, 1210, 1105, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.20 (m, 5 H, Ar*H*), 5.39 (s, 1 H, C$_{17}$-*H*), 4.93 (br s, 1 H, C=C*H*$_2$), 4.86 (br s, 1 H, C=C*H*$_2$), 4.61 (m, 1 H, C*H*N), 4.18 (m, 2 H, OC*H*$_2$), 3.35 (dd, 1 H, *J* = 3.4 and 13.2 Hz, ArC*H*$_2$), 3.05 (br s, 1 H, C$_{17}$-O*H*), 2.82 (dd, 1 H, *J* = 10.0 and 13.2 Hz, ArC*H*$_2$), 1.81 (s, 3 H, C$_{20}$-*H*), 1.22 (s, 3 H, C$_{18}$-C*H*$_3$), 1.16 (s, 3 H, C$_{18}$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.6, 153.2, 150.0, 135.0, 129.4, 129.0, 127.4, 111.8, 73.2, 66.5, 56.0, 43.8, 37.5, 23.1, 22.3, 20.5; TLC R_f = 0.38 (1% acetone/CH_2Cl_2). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30. Found: C, 67.92; H, 7.27.

[2*S*]-2-Hydroxy-*N*-methoxy-*N*,3,3,4-tetramethyl-4-pentenamide (5). To a suspension of 24.8 g (254 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 200 mL of CH_2Cl_2 at 0 °C was added dropwise 127 mL (254 mmol, 2.0 M in toluene) of trimethylaluminum solution with the concomitant evolution of gas. The resulting homogeneous solution was stirred for 30 min at 25 °C. A solution of 16.1 g (50.8 mmol) of carboximide **4** in 100 mL of CH_2Cl_2 was added over 10 min accompanied by more gas evolution. The resulting solution was heated to reflux for 24 h. Upon cooling, it was cannulated rapidly into an ice-cooled beaker containing 1.5 L of aqueous 1 M HCl. The layers were separated, and the aqueous layer was extracted with two 500-mL portions of CH_2Cl_2. The combined organic layers were washed with 500 mL of 5% aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (11 × 32 cm, 50% EtOAc/hexane) to obtain 9.22 g (90%) of amide **5** as a white solid: mp 60–62 °C; $[\alpha]_D$ −11.8° (*c* 1.49, CH_2Cl_2); IR (solution in CH_2Cl_2) 3500, 2980, 1650, 1375, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.86 (br s, 1 H, C=C*H*$_2$), 4.81 (br s, 1 H, C=C*H*$_2$), 4.47 (d, 1 H, *J* = 9.8 Hz, C$_{17}$-*H*), 3.69 (s, 3 H, NOC*H*$_3$), 3.21 (s, 3 H, NC*H*$_3$), 2.99 (d, 1 H, *J* = 9.8 Hz, C$_{17}$-O*H*), 1.80 (s, 3 H, C$_{20}$-*H*), 1.12 (s, 3 H, C$_{18}$-C*H*$_3$), 1.05 (s, 3 H, C$_{18}$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.7, 111.6, 72.0, 61.0, 44.1, 23.0, 22.4, 20.5; TLC R_f = 0.19 (50% EtOAc/hexane). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.70; H, 9.60; N, 6.96.

[2*S*]-*N*-Methoxy-2-[(*p*-methoxybenzyl)oxy]-*N*,3,3,4-tetramethyl-4-pentenamide (6). A dry flask was charged with 3.40 g (85.1 mmol) of a 60% dispersion of sodium hydride in oil, and the oil was removed by washing with two 10-mL portions of pentane. The sodium hydride was suspended in 65 mL of DMF, and the resulting slurry was cooled to 0 °C. A solution of 5.71 g (28.4 mmol) of alcohol **5** in 65 mL of THF was added dropwise with gas evolution. After 15 min, the mixture was cooled to −7 °C, and 5.94 mL (8.56 g, 42.5 mmol) of 4-methoxybenzyl bromide was added over a 1-min period. After 5 min, 200 mL of aqueous 5% $NaHCO_3$ was added cautiously followed by 600 mL of 5:1 hexane/CH_2Cl_2. The resulting mixture was washed with five 500-mL portions of water and 300 mL of brine. The organic layer was dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (5 × 25 cm, 25% EtOAc/hexane) to afford 7.69 g (84%) of the desired ether **6** as a colorless oil: $[\alpha]_D$ −1.3° (*c* 0.53, CH_2Cl_2); IR (thin film) 2940, 1675, 1520, 1465, 1305, 1250, 1180, 1085, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, 2 H, *J* = 8.2 Hz, Ar*H*), 6.94 (d, 2 H, *J* = 8.2 Hz, Ar*H*), 4.94 (br s, 2 H, C=C*H*$_2$), 4.66 (d, 1 H, *J* = 11.9 Hz, C*H*$_2$Ar), 4.48 (br s, 1 H, C$_{17}$-*H*), 4.36 (d, 1 H, *J* = 11.9 Hz, C*H*$_2$Ar), 3.88 (s, 3 H, ArOC*H*$_3$) 3.59 (br s, 3 H, NOC*H*$_3$), 3.27 (br s, 3 H, C*H*$_3$N), 1.82 (s, 3 H, C$_{20}$-*H*), 1.32 (s, 3 H, C$_{18}$-C*H*$_3$), 1.17 (s, 3 H, C$_{18}$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.2, 150.2, 130.3, 129.1, 113.6, 111.5, 71.5, 60.7, 55.2, 43.4, 43.4, 23.2, 22.9, 20.5; TLC R_f = 0.15 (25% EtOAc/hexane). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.31; H, 8.57; N, 4.24.

[4*S*,5*S*,6*R*]-6-Methoxy-4-[(*p*-methoxybenzyl)oxy]-2,3,3-trimethyl-1,7-octadien-5-ol (9).[59] To a solution of 5.83 g (22.2 mmol) of aldehyde **7** in 220 mL of CH_2Cl_2 at −40 °C was added 6.03 g (23.3 mmol) of solid magnesium bromide etherate. The resulting suspension was warmed to −25 °C, and 8.60 mL (9.63 g, 26.7 mmol) of stannane **8** was added. An additional 3.00 g (11.6 mmol) of magnesium bromide etherate was introduced after 15 min, and the mixture was stirred at −20 °C for 1 h. A 200-mL portion of saturated aqueous NH_4Cl was added, and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (6 × 25 cm, benzene until the bulk of the tin-containing byproducts eluted followed by 15% EtOAc/hexane) afforded the minor diastereomer followed by 5.26 g (71%) of the major diastereomer **9** as a colorless oil. These compounds were diastereomerically pure as judged by TLC, ^{1}H NMR, and ^{13}C NMR. Data for major diastereomer **9**: $[\alpha]_D$ +6.1° (*c* 0.87, CH_2Cl_2); IR (thin film) 3510, 2960, 1615, 1520, 1250, 1115, 1080, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 6.88 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 5.79 (ddd, 1 H, *J* = 7.9, 10.3, and 17.3 Hz, C$_{14}$-*H*), 5.34 (d, 1 H, *J* = 10.3 Hz, C$_{13}$-*H*), 5.27 (d, 1 H, *J* = 17.3 Hz, C$_{13}$-*H*), 4.87 (s, 2 H, C=C*H*$_2$), 4.64 (d, 1 H, *J* = 10.4 Hz, C*H*$_2$Ar), 4.54 (d, 1 H, *J* = 10.4 Hz, C*H*$_2$Ar), 3.81 (s, 3 H, ArOC*H*$_3$), 3.60 (ddd, 1 H, *J* = 1.5, 5.3, and 7.3 Hz, C$_{16}$-*H*), 3.48 (d, 1 H, *J* = 1.5 Hz, C$_{17}$-*H*), 3.41 (dd, 1 H, *J* = 5.3 and 7.9 Hz, C$_{15}$-*H*), 3.33 (s, 3 H, C$_{15}$-OC*H*$_3$), 3.03 (d, 1 H, 7.3 Hz, C$_{16}$-O*H*), 1.76 (s, 3 H, C$_{20}$-*H*), 1.13 (s, 3 H, C$_{18}$-C*H*$_3$), 1.09 (s, 3 H, C$_{18}$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.2, 150.1, 135.8, 130.6, 129.3, 119.0, 113.8, 112.1, 86.0, 81.2, 72.5, 71.1, 56.6, 55.2, 44.5, 24.8, 21.5, 20.1; TLC R_f = 0.20 (15% EtOAc/hexane). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.65; H, 9.05.

[4*S*,5*S*,6*R*]-6-Methoxy-4-[(*p*-methoxybenzyl)oxy]-2,3,3-trimethyl-5-(triethylsiloxy)-1-octen-8-ol (11). To a solution of 6.27 g (13.9 mmol) of olefin **10** in 125 mL of THF under argon was added 388 mg (0.420 mmol) of tris(triphenylphosphine)rhodium(I) chloride. To the resulting red solution was added 3.29 mL (4.18 g, 34.9 mmol) of freshly distilled catecholborane, which led to the appearance of a yellow color. After the reaction mixture was stirred for 50 min, the flask was placed in an ice bath, and 30-mL portions of 1:1 THF/ethanol, 2 M aqueous NaOH, and 30% aqueous H_2O_2 were added. The cold bath was removed after 30 min, and 30 min later the mixture was partitioned between 700 mL of diethyl ether and 700 mL of water. The aqueous layer was saturated with NaCl and extracted with 300 mL of diethyl ether. The combined organic extracts were washed with three 300-mL portions of 1 M aqueous NaOH, dried ($MgSO_4$), filtered through a plug of Celite, and concentrated. The residue was purified by flash chromatography (5 × 25 cm, linear gradient of 10%–25% EtOAc/hexane) to afford two fractions: 3.74 g (57%) of alcohol **11** as an oil that crystallized on standing, R_f = 0.05 (15% EtOAc/hexane), and 2.10 g (32%) of the corresponding aldehyde as a colorless liquid, R_f = 0.33 (15% EtOAc/hexane).

To a solution of the aldehyde in 50 mL of absolute ethanol was added 342 mg (10.8 mmol) of sodium borohydride. The solution was stirred for 15 min, and 200 mL of saturated aqueous NH_4Cl was added. The mixture was extracted with three 100-mL portions of CH_2Cl_2. The combined organic extracts were dried ($NaSO_4$), filtered, and concentrated to afford an additional 2.10 g of alcohol **11** for a total yield of 5.84 g (90%). This compound was a single isomer as judged by ^{1}H NMR, ^{13}C NMR, and TLC: mp 57–59 °C; $[\alpha]_D$ −7.9° (*c* 0.66, CH_2Cl_2); IR (thin film) 3450, 2960, 1615, 1515, 1465, 1245, 1095, 820, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.86 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 4.85 (s, 1 H, C=C*H*$_2$), 4.83 (s, 1 H, C=C*H*$_2$), 4.68 (d, 1 H, *J* = 11.4 Hz, C*H*$_2$Ar), 4.55 (d, 1 H, *J* = 11.4 Hz, C*H*$_2$Ar), 3.93 (dd, 1 H, *J* = 2.8 and 4.4 Hz, C$_{16}$-*H*), 3.80 (s, 3 H, ArOC*H*$_3$), 3.71 (m, 2 H, C$_{13}$-*H*), 3.51 (d, 1 H, *J* = 2.8 Hz, C$_{17}$-*H*), 3.40 (s, 3 H, C$_{15}$-OC*H*$_3$), 3.29 (m, 1 H, C$_{15}$-*H*), 2.20 (br s, 1 H, C$_{13}$-O*H*), 1.90 (m, 1 H, C$_{14}$-*H*), 1.79 (s, 3 H, C$_{20}$-*H*), 1.72 (m, 1 H, C$_{14}$-*H*), 1.13 (s, 6 H, C$_{18}$-(C*H*$_3$)$_2$), 0.97 (t, 9 H, *J* = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.63 (q, 6 H, *J* = 8.0 Hz, SiC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 158.2, 151.6, 132.0, 128.4, 113.4, 111.3, 83.0, 81.0, 73.8, 71.3, 61.4, 58.0, 55.3, 45.0, 32.7,

(58) Vishwakarma, L. C.; Stringer, O. R.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203–210.

(59) This reaction was performed in accordance with Keck's method. See reference 13a.

25.7, 22.8, 20.3, 7.0, 5.7; TLC R_f = 0.05 (15% EtOAc/hexane). Anal. Calcd for $C_{26}H_{46}O_5Si$: C, 66.91; H, 9.93. Found: C, 66.98; H, 9.91.

[3*R*,4*S*,5*S*]-3-Methoxy-5-[(*p*-methoxybenzyl)oxy]-6,6-dimethyl-7-oxo-4-(triethylsiloxy)octyl Pivalate (13). To a solution of 6.33 g (11.5 mmol) of alkene **12** in 115 mL of 10:3:1 *tert*-butanol/THF/water were added 2.69 g (23.0 mmol) of *N*-methylmorpholine *N*-oxide and 7.66 mL (1.15 mmol) of a 0.15 M solution of osmium tetroxide in water. A dark orange-brown solution resulted, which faded to light orange after 20 h. TLC analysis indicated that the starting alkene was consumed at this time. To this solution was added 40 mL of water and 7.70 g (36.0 mmol) of sodium periodate, resulting in the gradual precipitation of a white solid. The mixture was stirred for an additional 20 h and filtered. The filtrate was reduced to half volume in vacuo, diluted with 250 mL of saturated aqueous Na_2SO_3, and extracted with three 250-mL portions of diethyl ether. The combined organic extracts were washed with 200 mL of brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5 × 15 cm, 15% EtOAc/hexane) yielded 6.30 g (99%) of ketone **13** as a colorless oil: $[\alpha]_D$ +2.7° (*c* 0.85, CH_2Cl_2); IR (thin film) 2960, 1735, 1715, 1620, 1520, 1465, 1360, 1290, 1250, 1160, 1100, 1040, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 6.85 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 4.70 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.46 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.14 (m, 2 H, C_{13}-*H*), 3.98 (dd, 1 H, *J* = 4.1 and 5.3 Hz, C_{16}-*H*), 3.80 (s, 3 H, ArOC*H*$_3$), 3.74 (d, 1 H, *J* = 4.1 Hz, C_{17}-*H*), 3.37 (s, 3 H, C_{15}-OC*H*$_3$), 3.33 (m, 1 H, C_{15}-*H*), 2.15 (s, 3 H, C_{20}-*H*), 2.08 (m, 1 H, C_{14}-*H*), 1.78 (m, 1 H, C_{14}-*H*), 1.19 (s, 9 H, C(C*H*$_3$)$_3$), 1.17 (br s, 6 H, C_{18}-(C*H*$_3$)$_2$), 0.95 (t, 9 H, *J* = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.62 (q, 6 H, *J* = 8.0 Hz, SiC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 212.6, 178.5, 158.9, 151.3, 131.0, 128.6, 113.6, 82.3, 80.1, 74.1, 71.6, 61.7, 58.8, 55.2, 52.4, 38.7, 29.1, 27.2, 22.6, 22.1, 7.0, 5.2; TLC R_f = 0.35 (15% EtOAc/hexane). Anal. Calcd for $C_{30}H_{52}O_7Si$: C, 65.18; H, 9.48. Found: C, 65.26; H, 9.44.

[4*S*,3(2*S*,3*R*)]-4-Benzyl-3-(3-hydroxy-2-methyl-4-pentenoyl)-2-oxazolidinone (15). To a solution of 5.00 g (21.4 mmol) of **14**[14] in 75 mL of CH_2Cl_2 at 0 °C were added dropwise 5.93 mL (6.46 g, 23.6 mmol) of dibutylboryl triflate[60] and 4.48 mL (3.32 g, 25.7 mmol) of diisopropylethylamine at a rate such that the internal temperature stayed below 3 °C. The resulting clear, colorless solution was cooled to −78 °C, and 7.16 mL (6.01 g, 107 mmol) of acrolein was added over 5 min. After 30 min, the solution was allowed to warm to 0 °C and quenched by addition of 30 mL of 1.5 M aqueous pH 7 phosphate buffer and 100 mL of methanol. To this was added 100 mL of 2:1 methanol/30% aqueous H_2O_2 carefully so as to keep the internal temperature below 5 °C. The volatiles were removed in vacuo, and 100 mL of water was added. The mixture was extracted with three 200-mL portions of ether. The combined organic extracts were washed with 50 mL of 5% aqueous $NaHCO_3$ and 50 mL of brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (6 × 25 cm, 35% EtOAc/hexane) afforded 5.17 g (83%) of aldol adduct **15** as a white, crystalline solid. The product was diastereomerically pure according to TLC, ^{1}H NMR, and ^{13}C NMR: mp 77–78 °C; $[\alpha]_D$ +92.6° (*c* 1.02, CH_2Cl_2); IR (solution in CH_2Cl_2) 3540, 3060, 2990, 1785, 1700, 1425, 1390, 985, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.18 (m, 5 H, Ar*H*), 5.85 (ddd, 1 H, *J* = 6.4, 10.2, and 17.2 Hz, C_{24}-*H*), 5.36 (d, 1 H, *J* = 17.2 Hz, C_{25}-*H*), 5.23 (d, 1 H, *J* = 10.2 Hz, C_{25}-*H*), 4.71 (m, 1 H, C*H*N), 4.50 (m, 1 H, C_{23}-*H*), 4.25–4.18 (m, 2 H, C*H*$_2$O), 3.88 (dq, 1 H, *J* = 6.4 and 7.1 Hz, C_{22}-*H*), 3.27 (dd, 1 H, *J* = 3.4 and 13.2 Hz, ArC*H*$_2$), 2.93 (d, 1 H, C_{23}-O*H*), 2.80 (dd, 1 H, *J* = 10.0 and 13.2 Hz, ArC*H*$_2$), 1.25 (d, 3 H, *J* = 7.1 Hz, C_{22}-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 176.5, 153.1, 137.4, 135.0, 129.4, 129.0, 127.4, 116.2, 72.6, 66.2, 55.1, 42.5, 37.8, 11.0; TLC R_f = 0.14 (25% EtOAc/hexane). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.42; H, 6.71.

[2*S*,3*R*]-2-Methyl-3-(triethylsiloxy)-4-pentenal (17). To a solution of 328 mg (1.14 mmol) of amide **16** in 1.0 mL of THF at −92 °C was added 3.04 mL (4.56 mmol) of DIBAL (2.0 M in toluene) dropwise. Upon completion of the addition, 1.5 mL of EtOAc was added dropwise. The cold bath was removed, and 7 mL of 1 M aqueous HCl and 7 mL of diethyl ether were added. The resulting mixture was stirred for 3 h at ambient temperature. The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (3 × 10 cm, 5% EtOAc/hexane) afforded 233 mg (87%) of aldehyde **17** as a colorless liquid: $[\alpha]_D$ +62.7° (*c* 0.95, CH_2Cl_2); IR (solution in CH_2Cl_2) 2960, 2890, 2710, 1725, 1460, 1415, 1240, 1155, 1080, 1030, 925, 820, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (d, 1 H, *J* = 1.3 Hz, C_{21}-*H*), 5.82 (ddd, 1 H, *J* = 6.3, 10.3, and 16.9 Hz, C_{24}-*H*), 5.24 (d, 1 H, *J* = 16.9 Hz, C_{25}-*H*), 5.16 (d, 1 H, *J* = 10.3 Hz, C_{25}-*H*), 4.51 (m, 1 H, C_{23}-*H*), 2.47 (m, 1 H, C_{22}-*H*), 1.05 (d, 3 H, *J* = 7.1 Hz, C_{22}-C*H*$_3$), 0.93 (t, 9 H, *J* = 7.9 Hz, SiCH$_2$C*H*$_3$), 0.58 (q, 6 H, *J* = 7.9 Hz, SiC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.5, 138.4, 115.9, 73.8, 52.6, 8.5, 6.7, 4.9; TLC R_f = 0.37 (5% diethyl ether/hexane).

[3*R*,4*S*,5*S*]-3-Methoxy-5-[(*p*-methoxybenzyl)oxy]-6,6-dimethyl-4-(triethylsiloxy)-7-(trimethylsiloxy)-7-octenyl Pivalate (18). To a solution of 6.65 g (12.0 mmol) of ketone **13** and 2.51 mL (1.82 g, 18.0 mmol) of triethylamine at 0 °C in 120 mL of CH_2Cl_2 was added 3.14 mL (3.61 g, 16.2 mmol) of trimethylsilyl trifluoromethanesulfonate dropwise. After 30 min, this solution was poured into 300 mL of saturated aqueous $NaHCO_3$ and extracted with 750 mL of 4:1 hexane/CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated, providing 7.45 g (99%) of the labile silyl enol ether **18** as a colorless oil which was used without further purification: IR (thin film) 2960, 1735, 1615, 1515, 1250, 1155, 1010, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 6.84 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 4.66 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.51 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.22 (s, 1 H, C_{20}-*H*), 4.12 (m, 2 H, C_{13}-*H*), 4.03 (s, 1 H, C_{20}-*H*), 3.90 (dd, 1 H, *J* = 4.1 and 5.3 Hz, C_{16}-*H*), 3.80 (s, 3 H, ArOC*H*$_3$), 3.68 (d, 1 H, *J* = 4.1 Hz, C_{17}-*H*), 3.40 (s, 3 H, C_{15}-OC*H*$_3$), 3.23 (m, 1 H, C_{15}-*H*), 2.01 (m, 1 H, C_{14}-*H*), 1.78 (m, 1 H, C_{14}-*H*), 1.18 (s, 9 H, C(C*H*$_3$)$_3$), 1.12 (s, 3 H, C_{18}-C*H*$_3$), 1.09 (s, 3 H, C_{18}-C*H*$_3$), 0.96 (t, 9 H, *J* = 8.0 Hz, SiCH$_2$C*H*$_3$), 0.62 (q, 6 H, *J* = 8.0 Hz, SiC*H*$_2$CH$_3$), 0.21 (s, 9 H, Si(C*H*$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 178.5, 164.5, 158.6, 131.9, 128.8, 113.4, 88.9, 80.3, 79.3, 73.6, 72.7, 61.9, 58.7, 55.2, 45.0, 38.7, 29.6, 27.2, 24.8, 21.2, 7.2, 5.6, 0.2; TLC R_f = 0.63 (15% EtOAc/hexane).

[3*R*,4*S*,5*S*,9*S*,10*R*,11*R*]-9-Hydroxy-3-methoxy-5-[(*p*-methoxybenzyl)oxy]-6,6,10-trimethyl-7-oxo-4,11-bis(triethylsiloxy)-12-tridecenyl Pivalate (19a). To a solution of 455 mg (1.99 mmol) of aldehyde **17** and 622 mg (1.00 mmol) of silyl enol ether **18** in 10 mL of CH_2Cl_2 at −78 °C was added dropwise 0.992 mL (1.14 g, 9.95 mmol) of boron trifluoride etherate. The resulting solution was stirred for 8 h at −78 °C and then quenched by the addition of 2.5 mL of triethylamine. The mixture was diluted with 30 mL of water and extracted with two 30-mL portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 18 cm, 10% EtOAc/hexane) afforded 625 mg (80%) of aldol adduct **19a** as a colorless oil. The product was diastereomerically pure by TLC, ^{1}H NMR and ^{13}C NMR: $[\alpha]_D$ −12.6° (*c* 0.89, CH_2Cl_2); IR (thin film) 3540, 2960, 1735, 1700, 1620, 1520, 1465, 1285, 1250, 1160, 1100, 1040, 1010, 825, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.83 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 5.81 (m, 1 H, C_{24}-*H*), 5.18 (d, 1 H, *J* = 17.2 Hz, C_{25}-*H*), 5.08 (d, 1 H, *J* = 10.2 Hz, C_{25}-*H*), 4.69 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.36 (d, 1 H, *J* = 11.1 Hz, C*H*$_2$Ar), 4.21–4.09 (m, 4 H, C_{13}-*H*, C_{21}-*H*, C_{23}-*H*), 3.95 (dd, 1 H, *J* = 5.1 and 5.1 Hz, C_{16}-*H*), 3.85 (d, 1 H, *J* = 5.1 Hz, C_{17}-*H*), 3.79 (s, 3 H, ArOC*H*$_3$), 3.37 (s, 3 H, C_{15}-OC*H*$_3$), 3.30 (m, 1 H, C_{15}-*H*), 3.14 (d, 1 H, *J* = 1.7 Hz, C_{21}-O*H*), 2.64 (d, 2 H, *J* = 6.0 Hz, C_{20}-*H*), 2.12–2.02 (m, 1 H, C_{14}-*H*), 1.85–1.77 (m, 1 H, C_{14}-*H*), 1.44 (m, 1 H, C_{22}-*H*), 1.19 (s, 12 H, C(C*H*$_3$)$_3$, C_{18}-C*H*$_3$), 1.13 (br s, 3 H, C_{18}-C*H*$_3$), 1.00–0.90 (m, 21 H, C_{22}-C*H*$_3$, SiCH$_2$C*H*$_3$), 0.68–0.55 (m, 12 H, SiC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 215.6, 178.5, 158.8, 139.8, 131.1, 128.6, 115.4, 113.5, 81.4, 80.3, 77.5, 74.1, 71.9, 68.5, 61.6, 59.0, 55.2, 52.4, 44.0, 43.3, 38.7, 28.9, 27.2, 22.3, 21.4, 8.8, 7.0, 6.8, 5.3, 5.0; TLC R_f = 0.40 (35% EtOAc/hexane). Anal. Calcd for $C_{42}H_{76}O_9Si_2$: C, 64.57; H, 9.81. Found: C, 64.71; H, 9.80.

[3*R*,3(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-3-[9-Hydroxy-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-7-vinyl-1,6-dioxaspiro[4.5]dec-2-yl]-3-methoxypropyl Pivalate (20). To a flask containing 7.95 g (10.2 mmol) of aldol adduct **19a** was added 200 mL of a premixed solution made up of 10 parts of 95:5 acetonitrile/48% aqueous HF to one part water, and the resulting solution was stirred for 3.5 h at room temperature. The mixture was poured into 1 L of 5% aqueous $NaHCO_3$ and extracted with three 250-mL portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The material was purified by flash chromatography (5 × 30, 35% EtOAc/hexane) to afford 0.75 g (14%) of spiroketal **21** and 3.86 g (71%) of spiroketal **20** as colorless oils. Data for major spiroketal **20**: $[\alpha]_D$ +64.4° (*c* 1.59, CH_2Cl_2); IR (thin film) 3540, 2970, 1730, 1615, 1520, 1465, 1285, 1250, 1150, 910, 825, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.82 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 5.71 (ddd, 1 H, *J* = 3.6, 10.8, and 17.2 Hz, C_{24}-*H*), 5.26 (d, 1 H, *J* = 17.2 Hz, C_{25}-*H*), 5.00 (d, 1 H, *J* = 10.8 Hz, C_{25}-*H*), 4.85 (m, 1 H, C_{23}-*H*), 4.60 (d, 1 H, *J* = 10.7 Hz, C*H*$_2$Ar), 4.32 (d, 1 H, *J* = 10.7 Hz, C*H*$_2$Ar), 4.21 (dd, 1 H, *J* = 5.8 and 9.3 Hz, C_{16}-*H*), 4.14 (m, 1 H, C_{13}-*H*), 4.09 (m, 1 H, C_{13}-*H*), 3.90–3.83 (m, 1 H, C_{21}-*H*), 3.70 (s, 3 H, ArOC*H*$_3$), 3.55 (d, 1 H, *J* = 5.8 Hz, C_{17}-*H*), 3.53–3.49 (m, 1 H, C_{15}-*H*), 3.47 (s, 3 H, C_{15}-OC*H*$_3$), 1.90–1.77 (m, 3 H, C_{20}-*H*), 1.62–1.52 (m, 3 H, C_{14}-*H*, C_{21}-O*H*), 1.22 (s, 3 H, C_{18}-C*H*$_3$), 1.09 (s, 9 H, C(C*H*$_3$)$_3$), 0.96 (s, 3 H, C_{18}-C*H*$_3$), 0.79 (d, 3 H, *J* = 7.1, C_{22}-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 178.4, 159.0, 137.2, 130.3, 128.7, 114.3, 113.5, 108.4, 86.5, 83.9, 78.7, 74.2, 70.7, 66.7, 60.7, 58.9,

(60) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.

55.2, 51.2, 38.6, 38.0, 29.7, 28.9, 27.1, 23.4, 17.1, 10.8; TLC R_f = 0.09 (35% EtOAc/hexane). Anal. Calcd for $C_{30}H_{46}O_8$: C, 67.39; H, 8.67. Found: C, 67.26; H, 8.70.

[3*R*,3(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-3-[9-Hydroxy-7-(2-hydroxyethyl)-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-3-methoxypropyl Pivalate (22). To a solution of 4.45 g (8.32 mmol) of spiroketal **20** in 83 mL of THF was added 4.06 g (16.6 mmol) of 9-borabicyclononane dimer. The resulting solution was stirred for 10 min and then placed in a water bath and sonicated at 60 Hz for 30 min. The flask was removed from the sonication bath. Aqueous pH 7 phosphate buffer (80 mL), methanol (170 mL), and 2:1 methanol/30% aqueous H_2O_2 (170 mL) were added sequentially. The resulting solution was stirred for 14 h. The volatiles were removed on a rotary evaporator, and the resulting slurry was diluted with 800 mL of water and extracted with three 400-mL portions of diethyl ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (5 × 20 cm, 75% EtOAc/hexane) provided 4.31 g (94%) of diol **22** as a colorless oil: $[\alpha]_D$ +62.8° (*c* 0.23, CH_2Cl_2); IR (thin film) 3500, 2970, 1730, 1615, 1515, 1470, 1285, 1240, 1110, 905, 870, 830, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.84 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 4.61 (d, 1 H, *J* = 11.8 Hz, CH_2Ar), 4.48 (m, 1 H, C_{23}-*H*), 4.33 (d, 1 H, *J* = 11.8 Hz, CH_2Ar), 4.12 (dd, 1 H, *J* = 5.0 and 9.2 Hz, C_{16}-*H*), 4.09–3.95 (m, 2 H, C_{13}-*H*), 3.85–3.80 (m, 2 H, C_{21}-*H*, C_{25}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.75–3.70 (m, 1 H, C_{25}-*H*), 3.58 (d, 1 H, *J* = 5.1 Hz, C_{17}-*H*), 3.55 (s, 3 H, C_{15}-OCH_3), 3.55–3.49 (m, 1 H, C_{15}-*H*), 1.96–1.90 (m, 1 H, C_{22}-*H*), 1.80 (dd, 1 H, *J* = 3.3 and 14.2 Hz, C_{20}-*H*), 1.70–1.52 (m, 5 H, C_{14}-*H*, C_{21}-O*H*, C_{24}-*H*, C_{25}-O*H*), 1.42–1.37 (m, 2 H, C_{20}-*H*, C_{24}-*H*), 1.21 (s, 9 H, C(CH_3)$_3$), 1.08 (s, 3 H, C_{18}-CH_3), 0.92 (s, 3 H, C_{18}-CH_3), 0.87 (d, 3 H, *J* = 7.1 Hz, C_{22}-CH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 178.4, 159.6, 130.9, 129.0, 113.7, 108.4, 86.2, 84.6, 78.3, 74.9, 70.6, 69.3, 63.0, 60.8, 59.6, 55.2, 50.9, 38.7, 38.1, 35.0, 29.8, 28.9, 27.2, 23.3, 17.8, 10.9; TLC R_f = 0.20 (75% EtOAc/hexane). Anal. Calcd for $C_{30}H_{48}O_9$: C, 65.19; H, 8.75. Found: C, 65.27; H, 8.82.

[3*R*,3(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*)]-3-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-3-methoxy-1-propanol (23b). To a solution of 2.83 g (3.62 mmol) of ester **23a** in 36 mL of CH_2Cl_2 at −78 °C was added dropwise 9.66 mL (14.5 mmol) of diisobutylaluminum hydride (1.5 M in toluene) at such a rate to maintain the internal temperature <−70 °C. The resulting solution was stirred for 1 h at −78 °C and quenched by the addition of 5 mL of EtOAc. The mixture was diluted with 60 mL of 0.5 M sodium potassium tartrate and 60 mL of CH_2Cl_2 and stirred at ambient temperature for 6 h. The layers were separated, and the aqueous layer was extracted with 80 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 20 cm, 25% EtOAc/hexane) afforded 2.29 g (91%) of alcohol **23b** as a colorless oil: $[\alpha]_D$ +81.4° (*c* 0.49, CH_2Cl_2); IR (thin film) 3460, 2960, 1615, 1515, 1470, 1385, 1360, 1340, 1300, 1250, 1110, 910, 830, 775, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.84 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 4.62 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.42 (m, 1 H, C_{23}-*H*), 4.19 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.14–4.10 (m, 2 H, C_{13}-*H*, C_{16}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.79 (s, 3 H, ArOCH_3), 3.70 (s, 3 H, C_{15}-OCH_3), 3.72–3.57 (m, 4 H, C_{13}-*H*, C_{15}-*H*, C_{25}-*H*), 3.43 (d, 1 H, *J* = 5.6 Hz, C_{17}-*H*), 2.78 (dd, 1 H, *J* = 3.5 and 7.4 Hz, C_{13}-O*H*), 1.76–1.67 (m, 1 H, C_{22}-*H*), 1.66 (dd, 1 H, *J* = 3.7 and 14.3 Hz, C_{20}-*H*), 1.62–1.36 (m, 5 H, C_{14}-*H*, C_{20}-*H*, C_{24}-*H*), 1.15 (s, 3 H, C_{18}-CH_3), 0.89 (s, 3 H, C_{18}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.85 (s, 9 H, SiC(CH_3)$_3$), 0.82 (d, 3 H, *J* = 7.1, C_{22}-CH_3), 0.04 (s, 3 H, SiCH_3), 0.00 (s, 3 H, SiCH_3), −0.03 (s, 3 H, SiCH_3), −0.04 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 159.0, 130.6, 128.7, 113.6, 107.2, 87.7, 84.9, 82.7, 74.3, 71.4, 63.4, 61.6, 61.2, 60.4, 55.2, 50.9, 38.6, 36.7, 33.6, 30.5, 26.0, 25.9, 23.2, 18.4, 18.2, 17.4, 10.5, −4.7, −5.0, −5.2, −5.3; TLC R_f = 0.19 (25% EtOAc/hexane). Anal. Calcd for $C_{37}H_{68}O_8Si_2$: C, 63.75; H, 9.83. Found: C, 63.61; H, 9.72.

[β*R*,2*S*,3*S*,5*S*,7*R*,8*S*,9*S*]-9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-β-methoxy-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane-2-propionaldehyde (24). To a solution of 322 μL (469 mg, 3.69 mmol) of oxalyl chloride in 25 mL of CH_2Cl_2 at −60 °C was added 572 μL (629 mg, 8.06 mmol) of dimethyl sulfoxide dropwise over a 5-min period with concomitant gas evolution. The resulting solution was stirred for 10 min at −60 °C. A solution of 2.34 g (3.36 mmol) of alcohol **23b** in 8 mL of CH_2Cl_2 was added by cannula and rinsed over with 1 mL of additional CH_2Cl_2, resulting in a cloudy solution which was stirred for 15 min at −60 °C. To this was added 2.34 mL (1.70 g, 16.8 mmol) of triethylamine. The mixture was allowed to warm to −30 °C over 45 min and quenched with 50 mL of water. This mixture was extracted with two 40-mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (5 × 18 cm, 20% EtOAc/hexane) to give 2.12 g (91%) of aldehyde **24** as a colorless oil: $[\alpha]_D$ +72.6° (*c* 0.76, CH_2Cl_2); IR (thin film) 2960, 1730, 1615, 1515, 1465, 1390, 1360, 1340, 1305, 1250, 1110, 905, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.60 (dd, 1 H, *J* = 1.6 and 3.2 Hz, C_{13}-*H*), 7.20 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 6.83 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 4.62 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.44 (m, 1 H, C_{23}-*H*), 4.19 (d, 1 H, *J* = 11.0 Hz, CH_2Ar), 4.13 (dd, 1 H, *J* = 5.6 and 9.0 Hz, C_{16}-*H*), 3.92 (ddd, 1 H, *J* = 3.3, 8.4, and 9.0 Hz, C_{15}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.73–3.62 (m, 2 H, C_{25}-*H*), 3.65 (s, 3 H, C_{15}-OCH_3), 3.43 (d, 1 H, *J* = 5.6 Hz, C_{17}-*H*), 2.33 (dd, 1 H, *J* = 1.6, 3.3, and 15.8 Hz, C_{14}-*H*), 2.27 (ddd, 1 H, *J* = 3.2, 8.4, and 15.8 Hz, C_{14}-*H*), 1.80–1.70 (m, 1 H, C_{22}-*H*), 1.67 (dd, 1 H, *J* = 3.8 and 14.3 Hz, C_{20}-*H*), 1.45–1.40 (m, 3 H, C_{20}-*H*, C_{24}-*H*), 1.17 (s, 3 H, C_{18}-CH_3), 0.89 (s, 3 H, C_{18}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.85 (s, 9 H, SiC(CH_3)$_3$), 0.83 (d, 3 H, *J* = 7.3, C_{22}-CH_3), 0.04 (s, 3 H, SiCH_3), 0.00 (s, 3 H, SiCH_3), −0.02 (s, 3 H, SiCH_3), −0.03 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 201.6, 159.0, 130.2, 128.8, 113.6, 107.3, 87.2, 84.1, 77.3, 74.0, 71.2, 63.4, 61.1, 60.2, 55.2, 51.0, 46.1, 38.5, 36.6, 30.4, 26.0, 25.8, 23.3, 18.4, 18.2, 17.4, 10.5, −4.7, −5.0, −5.2, −5.3; TLC R_f = 0.52 (25% EtOAc/hexane).

[4*R*,3(2*R*,4*R*,5*S*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*))]-4-Benzyl-3-[7-[9-(*tert*-butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-5-hydroxy-7-methoxy-2,4-dimethyl-3-oxoheptanoyl]-2-oxazolidinone (26). To a solution of 971 mg (3.35 mmol) of β-ketoimide **25** in 15 mL of CH_2Cl_2 at −20 °C was added 638 μL (665 mg, 3.51 mmol) of titanium tetrachloride dropwise by syringe. After 5 min, 638 μL (473 mg, 3.66 mmol) of diisopropylethyl amine was added dropwise to the yellow solution, resulting in a deep red color. The temperature was maintained between −20 and −10 °C for 1 h and then cooled to −78 °C. A solution of 2.12 g (3.05 mmol) of aldehyde **24** in 10 mL of CH_2Cl_2 was added by cannula at such a rate that the temperature in the reaction vessel stayed below −60 °C, and the aldehyde was rinsed over with an additional 5 mL of CH_2Cl_2. The resulting solution was allowed to warm to −50 °C over 1.5 h. The reaction was quenched by addition of 1.8 mL (16 mmol) of 2,6-lutidine and 50 mL of pH 7 phosphate buffer. The mixture was diluted with 100 mL of water and extracted with three 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 300 mL of aqueous 1 M $NaHSO_4$ and 300 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (5 × 16 cm, 25% EtOAc/hexane) afforded 2.79 g (93%) of aldol adduct **26** as a white foam. The product was diastereomerically pure by TLC, ^1H NMR, and ^{13}C NMR: $[\alpha]_D$ +21.8° (*c* 1.58, CH_2Cl_2); IR (thin film) 3540, 2930, 1780, 1715, 1615, 1515, 1460, 1385, 1360, 1245, 1110, 1080, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.19 (m, 7 H, Ar*H*), 6.83 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 4.93 (q, 1 H, *J* = 7.3 Hz, C_{10}-*H*), 4.72 (m, 1 H, C*H*N), 4.57 (d, 1 H, *J* = 10.8 Hz, OCH_2Ar), 4.42 (m, 1 H, C_{23}-*H*), 4.21 (d, 1 H, *J* = 10.8 Hz, OCH_2Ar), 4.18–4.09 (m, 4 H, CH_2OCN, C_{13}-*H*, C_{16}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.71 (s, 3 H, C_{15}-OCH_3), 3.73–3.63 (m, 2 H, C_{25}-*H*), 3.58 (m, 1 H, C_{15}-*H*), 3.48 (d, 1 H, *J* = 5.4 Hz, C_{17}-*H*), 3.29 (dd, 1 H, *J* = 3.4 and 13.6 Hz, CH_2Ar), 2.80–2.75 (m, 2 H, CH_2Ar, C_{12}-*H*), 1.78–1.70 (m, 1 H, C_{22}-*H*), 1.67 (dd, 1 H, *J* = 4.0 and 14.5 Hz, C_{20}-*H*), 1.61–1.57 (m, 1 H, C_{14}-*H*), 1.47–1.38 (m, 5 H, C_{13}-O*H*, C_{14}-*H*, C_{20}-*H*, C_{24}-*H*), 1.43 (d, 3 H, *J* = 7.3 Hz, C_{10}-CH_3), 1.14 (s, 3 H, C_{18}-CH_3), 0.92 (d, 3 H, *J* = 7.0 Hz, C_{12}-CH_3), 0.89 (s, 3 H, C_{18}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.84 (s, 9 H, SiC(CH_3)$_3$), 0.82 (d, 3 H, *J* = 7.3, C_{22}-CH_3), 0.04 (s, 3 H, SiCH_3), 0.00 (s, 3 H, SiCH_3), −0.05 (s, 3 H, SiCH_3), −0.05 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.6, 170.7, 158.8, 153.6, 135.2, 130.7, 129.4, 128.9, 128.4, 127.3, 113.5, 107.3, 87.3, 85.3, 82.4, 73.9, 71.4, 71.3, 66.3, 63.4, 61.1, 60.3, 55.4, 55.1, 51.6, 50.8, 49.4, 38.5, 37.9, 36.7, 34.3, 30.5, 26.0, 25.9, 23.2, 18.3, 18.2, 17.3, 13.2, 10.6, 10.4, −4.7, −5.0, −5.2, −5.3; TLC R_f = 0.43 (35% EtOAc/hexane). Anal. Calcd for $C_{53}H_{85}NO_{12}Si_2$: C, 64.67; H, 8.70. Found: C, 64.86; H, 8.54.

[4*R*,3(2*R*,3*R*,4*R*,5*S*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*))]-4-Benzyl-3-[7-[9-(*tert*-butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-3,5-dihydroxy-7-methoxy-2,4-dimethylheptanoyl]-2-oxazolidinone (27). Tetramethylammonium triacetoxy-borohydride[27] (4.40 g, 28.0 mmol) was transferred to a flask in a glovebag under N_2 and treated with 28 mL of acetic acid from a freshly opened bottle. The resulting solution was stirred for 1 h and then immersed in an ice bath. A solution of 2.76 g (2.80 mmol) of ketone **26** in 50 mL of acetonitrile (6 mL rinse) was added by cannula. The resulting solution was stirred for 6 h at −25 °C and 20 h at 0 °C. Water (20 mL) was added rapidly, resulting in a cloudy mixture. Methanol (75 mL) was added, and the volatiles were removed on a rotary evaporator. This step was repeated four more times to remove the bulk of the trimethylborate and acetic acid. The residue was carefully quenched with 150 mL of 5% aqueous $NaHCO_3$, and the mixture was extracted with three 80-mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and

purified by flash chromatography (5 × 18 cm, linear gradient of 35%–50% EtOAc/hexane) to afford 2.05 g (74%) of diol **27** as a white foam. The diol was diastereomerically pure by TLC, ^{1}H NMR, and ^{13}C NMR: $[\alpha]_D$ +28.4° (*c* 0.87, CH_2Cl_2); IR (solution in CH_2Cl_2) 3440, 2930, 1785, 1695, 1515, 1465, 1110, 1080, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.18 (m, 7 H, Ar*H*), 6.84 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 4.72 (m, 1 H, C*H*N), 4.68 (d, 1 H, *J* = 11.1 Hz, OCH_2Ar), 4.42 (m, 1 H, C_{23}-*H*), 4.24 (m, 1 H, C_{10}-*H*), 4.20–4.09 (m, 4 H, CH_2OCN, OCH_2Ar, C_{13}-*H*), 4.06 (dd, 1 H, *J* = 5.5 and 8.8 Hz, C_{16}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.74 (s, 3 H, C_{15}-OCH_3), 3.73–3.61 (m, 4 H, C_{11}-*H*, C_{15}-*H*, C_{25}-*H*), 3.45 (d, 1 H, *J* = 5.5 Hz, C_{17}-*H*), 3.27 (dd, 1 H, *J* = 3.2 and 13.3 Hz, CH_2Ar), 2.79 (dd, 1 H, *J* = 9.6 and 13.3 Hz, CH_2Ar), 1.78–1.70 (m, 1 H, C_{22}-*H*), 1.67 (dd, 1 H, *J* = 3.8 and 14.2 Hz, C_{20}-*H*), 1.46–1.41 (m, 6 H, C_{11}-O*H*, C_{13}-O*H*, C_{12}-*H*, C_{14}-*H*, C_{24}-*H*), 1.37 (m, 1 H, C_{20}-*H*), 1.17 (s, 3 H, C_{18}-CH_3), 1.03 (d, 3 H, *J* = 6.8 Hz, C_{10}-CH_3), 0.94 (d, 3 H, *J* = 7.0 Hz, C_{12}-CH_3), 0.90 (s, 3 H, C_{18}-CH_3), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.86 (s, 9 H, SiC(CH_3)$_3$), 0.83 (d, 3 H, *J* = 6.9, C_{22}-CH_3), 0.04 (s, 3 H, SiCH_3), 0.01 (s, 3 H, SiCH_3), 0.00 (s, 6 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 177.0, 158.9, 153.2, 135.5, 130.5, 129.4, 128.8, 128.5, 127.2, 113.7, 107.2, 87.7, 85.5, 83.5, 79.3, 74.4, 71.3, 71.1, 65.9, 63.5, 61.2, 60.6, 55.1, 50.9, 40.9, 38.5, 38.0, 37.8, 36.5, 35.6, 30.5, 26.0, 25.8, 23.2, 18.4, 18.2, 17.5, 14.3, 11.1, 10.5, −4.7, −5.0, −5.2; TLC R_f = 0.28 (50% EtOAc/hexane). Anal. Calcd for $C_{53}H_{87}NO_{12}Si_2$: C, 64.53; H, 8.89. Found: C, 64.83; H, 8.92.

[4*R*,3(2*R*,3*R*,4*S*,5*R*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*))]-4-Benzyl-3-[7-[9-(*tert*-butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-5-acetoxy-3-hydroxy-7-methoxy-2,4-dimethylheptanoyl]-2-oxazolidinone (28). To a solution of 2.05 g (2.08 mmol) of diol **27** and 1.91 g (7.29 mmol) of triphenylphosphine in 14 mL of benzene was added 131 μL (130 mg, 2.29 mmol) of acetic acid. In a separate flask, 1.58 g (6.87 mmol) of di-*tert*-butyl azodicarboxylate was dissolved in 6 mL of benzene. One-third of this yellow solution was added to the reaction flask by syringe, resulting in the dissipation of color within 10 s. Two additional equal portions of acetic acid and the di-*tert*-butyl azodicarboxylate solution were added after 30 min and 1 h. After being stirred for a total of 2.5 h, the solution was concentrated. Flash chromatography (5 × 20 cm, linear gradient of 25%–50% EtOAc/hexane) gave 1.54 g (72%) of ester **28** as a white foam along with 285 mg (14%) of returned diol **27**. Data for ester **28**, which was diastereomerically pure by TLC, ^{1}H NMR, and ^{13}C NMR: $[\alpha]_D$ +32.7° (*c* 1.31, CH_2Cl_2); IR (solution in CH_2Cl_2) 3520, 2930, 1785, 1735, 1615, 1515, 1465, 1385, 1210, 1110, 1080, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.25 (m, 5 H, Ar*H*), 7.19 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 6.83 (d, 2 H, *J* = 8.7 Hz, Ar*H*), 5.39 (m, 1 H, C_{13}-*H*), 4.70 (m, 1 H, C*H*N), 4.58 (d, 1 H, *J* = 10.9 Hz, OCH_2Ar), 4.43 (m, 1 H, C_{23}-*H*), 4.35 (d, 1 H, *J* = 10.9 Hz, OCH_2Ar), 4.25–4.15 (m, 2 H, CH_2OCN), 4.08 (dd, 1 H, *J* = 5.4 and 9.1 Hz, C_{16}-*H*), 3.94 (m, 1 H, C_{10}-*H*), 3.82 (m, 1 H, C_{21}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.75–3.69 (m, 1 H, C_{25}-*H*), 3.63–3.60 (m, 1 H, C_{15}-*H*), 3.61 (s, 3 H, C_{15}-OCH_3), 3.54–3.51 (m, 1 H, C_{25}-*H*), 3.43 (d, 1 H, *J* = 5.4 Hz, C_{17}-*H*), 3.36 (m, 1 H, C_{11}-*H*), 3.28 (d, 1 H, *J* = 9.6 Hz, C_{11}-O*H*), 3.23 (dd, 1 H, *J* = 3.2 and 13.3 Hz, CH_2Ar), 2.77 (dd, 1 H, *J* = 9.6 and 13.3 Hz, CH_2Ar), 1.99–1.96 (m, 1 H, C_{12}-*H*), 1.78–1.63 (m, 3 H, C_{14}-*H*, C_{20}-*H*, C_{22}-*H*), 1.68 (s, 3 H, OOCH_3), 1.55–1.41 (m, 4 H, C_{14}-*H*, C_{20}-*H*, C_{24}-*H*), 1.35 (d, 3 H, *J* = 7.0 Hz, C_{10}-CH_3), 1.14 (s, 3 H, C_{18}-CH_3), 0.89 (s, 3 H, C_{18}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.84 (s, 9 H, SiC(CH_3)$_3$), 0.87–82 (m, 6 H, C_{12}-CH_3, C_{22}-CH_3), 0.04 (s, 3 H, SiCH_3), 0.00 (s, 3 H, SiCH_3), −0.03 (s, 3 H, SiCH_3), −0.04 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 177.2, 170.7, 158.7, 152.8, 135.1, 131.2, 129.4, 128.9, 128.1, 127.4, 113.4, 107.2, 87.3, 85.3, 78.6, 76.5, 73.9, 71.5, 71.2, 66.2, 63.7, 61.1, 60.8, 55.2, 55.0, 50.9, 40.3, 40.0, 38.4, 37.7, 36.7, 2.4, 30.6, 25.9, 23.3, 20.8, 18.2, 18.1, 17.2, 15.8, 12.8, 10.4, −4.6, −5.0, −5.1; TLC R_f = 0.24 (35% EtOAc/hexane). Anal. Calcd for $C_{32}H_{80}NO_{10}Si_2$: C, 64.23; H, 8.72. Found: C, 64.27; H, 8.82.

[2*S*,3*S*,4*R*,5*R*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*)]-7-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[(*p*-methoxybenzyl)oxy]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-7-methoxy-2,4-dimethyl-1,3,5-heptanetriol (29a). To a solution of 708 mg (0.688 mmol) of imide **28** in 10 mL of THF at 0 °C were added 111 μL (88.0 mg, 2.75 mmol) of methanol and 1.72 mL of lithium borohydride (2.0 M in THF). The resulting solution was stirred for 2 d at room temperature. The reaction was quenched by addition of 30 mL of 0.5 M aqueous sodium potassium tartrate and 20 mL of diethyl ether. The mixture was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with two 40-mL portions of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (3 × 20 cm, 50% EtOAc/hexane) afforded 470 mg (84%) of triol **29a** as an oil: $[\alpha]_D$ +78.7° (*c* 1.34, CH_2Cl_2); IR (solution in CH_2Cl_2) 3400, 2930, 1615, 1515, 1465, 1385, 1250, 1080, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 6.84 (d, 2 H, *J* = 8.6 Hz, Ar*H*), 5.40 (s, 1 H, O*H*), 4.67 (d, 1 H, *J* = 10.9 Hz, OCH_2Ar), 4.44 (m, 1 H, C_{23}-*H*), 4.23 (dd, 1 H, *J* = 5.6 and 9.1 Hz, C_{16}-*H*), 4.18 (d, 1 H, *J* = 10.9 Hz, OCH_2Ar), 3.98 (m, 1 H, C_{11}-*H*), 3.94–3.91 (m, 1 H, C_{13}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.79 (s, 3 H, ArOCH_3), 3.79–3.63 (m, 3 H, C_9-*H*, C_{15}-*H*), 3.69 (s, 3 H, C_{15}-OCH_3), 3.56–3.51 (m, 3 H, C_{25}-*H*, O*H*), 3.45 (d, 1 H, *J* = 5.6 Hz, C_{17}-*H*), 1.75–1.63 (m, 6 H, C_{10}-*H*, C_{12}-*H*, C_{14}-*H*, C_{20}-*H*, C_{22}-*H*, O*H*), 1.49–1.42 (m, 4 H, C_{14}-*H*, C_{20}-*H*, C_{24}-*H*), 1.17 (s, 3 H, C_{18}-CH_3), 1.14 (d, 3 H, *J* = 7.1 Hz, C_{12}-CH_3), 0.91 (s, 3 H, C_{18}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.85 (s, 9 H, SiC(CH_3)$_3$), 0.84 (d, 3 H, *J* = 6.9 Hz, C_{22}-CH_3), 0.62 (d, 3 H, *J* = 6.8 Hz, C_{12}-CH_3), 0.05 (s, 3 H, SiCH_3), 0.01 (s, 3 H, SiCH_3), −0.02 (s, 3 H, SiCH_3), −0.03 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 159.1, 130.2, 128.6, 113.7, 107.2, 87.6, 84.1, 82.3, 80.7, 75.7, 74.2, 71.3, 64.9, 63.4, 60.9, 60.4, 55.2, 51.1, 41.6, 38.5, 36.7, 35.8, 35.4, 30.4, 25.9, 25.8, 23.3, 18.3, 18.2, 17.4, 15.4, 13.5, 10.5, −4.7, −5.0, −5.2, −5.2; TLC R_f = 0.26 (50% EtOAc/hexane). Anal. Calcd for $C_{55}H_{89}NO_{13}Si_2$: C, 63.51; H, 9.91. Found: C, 63.56; H, 9.91.

[2*E*,4*E*]-Ethyl 5-(Tributylstannyl)-2-methyl-2,4-pentadienoate (33). To a solution of 2.29 mL (2.55 g, 10.7 mmol) of triethyl 2-phosphonopropionate in 40 mL of THF at 0 °C was added 4.32 mL (10.2 mmol) of *n*-butyllithium (2.37 M in hexane) dropwise. After 10 min, the resulting solution was allowed to warm to ambient temperature. A solution of 3.21 g (9.30 mmol) of aldehyde **32** in 8 mL of THF (plus 2 mL rinse) was added by cannula. The bulk of the solvent was removed in vacuo, and 50 mL of water was added. The mixture was extracted with two 50-mL portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (5 × 18 cm, 5% EtOAc/hexane) afforded 3.83 g (96%) of ester **33** as a colorless liquid: IR (thin film) 2930, 1710, 1465, 1370, 1255, 1190, 1100, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, 1 H, *J* = 10.1 Hz, C_6-*H*), 6.89–6.73 (m, 2 H, C_4-*H*, C_5-*H*), 4.20 (q, 2 H, *J* = 7.1 Hz, OCH_2CH$_3$), 1.97 (s, 3 H, C_7-CH_3), 1.54–1.46 (m, 6 H, SnCH_2CH_2CH$_2$CH$_3$), 1.35–1.24 (m, 6 H, CH$_2$CH_2CH$_3$), 1.04–0.98 (m, 6 H, SnCH_2), 0.89 (t, 9 H, *J* = 7.2 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.9, 145.4, 141.8, 140.1, 125.6, 60.5, 29.0, 27.2, 14.3, 13.7, 12.7, 9.6; TLC R_f = 0.37 (5% EtOAc/hexane). Anal. Calcd for $C_{20}H_{38}O_2Sn$: C, 55.97; H, 8.92. Found: C, 56.06; H, 9.08.

[2*E*,4*E*]-5-(Tributylstannyl)-2-methyl-2,4-pentadien-1-ol (34a). To a solution of 3.82 g (8.90 mmol) of ester **33** in 45 mL of THF at −78 °C was added dropwise 17.8 mL of diisobutylaluminum hydride (1.5 M in toluene). Upon completion of the addition, the cold bath was removed, and the reaction was quenched by addition of 10 mL of methanol when the internal temperature reached −50 °C. An equal volume of saturated aqueous sodium potassium tartrate was added, and the mixture was stirred overnight at room temperature. The layers were separated, and the aqueous layer was extracted with two 50-mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (5 × 20 cm, 10% EtOAc/hexane) to afford 3.15 g (91%) of alcohol **34a** as a colorless liquid: IR (thin film) 3350, 2900, 1600 1465, 1375, 1070, 985, 875, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77 (dd, 1 H, *J* = 10.3 and 18.6 Hz, C_5-*H*), 6.24 (d, 1 H, *J* = 18.6 Hz, C_4-*H*), 6.06 (d, 1 H, *J* = 10.3 Hz, C_6-*H*), 4.07 (d, 2 H, *J* = 6.1 Hz, C_8-*H*), 1.83 (s, 3 H, C_7-CH_3), 1.54–1.46 (m, 6 H, SnCH_2CH_2CH$_2$CH$_3$), 1.35–1.24 (m, 6 H, CH$_2$CH_2CH$_3$), 1.04–0.98 (m, 6 H, SnCH_2), 0.89 (t, 9 H, *J* = 7.2 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.3, 135.9, 134.4, 128.1, 68.5, 29.1, 27.3, 14.2, 13.7, 9.5; TLC R_f = 0.23 (15% EtOAc/hexane). Anal. Calcd for $C_{18}H_{36}OSn$: C, 55.84; H, 9.37. Found: C, 55.34; H, 9.16.

[2*E*,4*E*]-5-(Tributylstannyl)-2-methyl-1-(dimethylphosphono)-2,4-pentadiene (35a). To a solution of 3.15 g (8.14 mmol) of alcohol **34a** and 4.27 g (16.3 mmol) of triphenylphosphine in 80 mL of acetonitrile were added 190 μL (174 mg, 1.63 mmol) of 2,6-lutidine and 5.40 g (16.3 mmol) of carbon tetrabromide. The resulting dark red solution was stirred for 10 min and then poured into 500 mL of 5% aqueous $NaHCO_3$. The mixture was extracted with two 500-mL portions of hexane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to about 100 mL volume. This was chromatographed (5 × 15 cm, 5% EtOAc/hexane) quickly to give bromide **34b** and the allylicly transposed C_6 bromide as a 6:1 mixture, which was used immediately.

In a separate flask, a suspension of 1.54 g (38 mmol) of a 60% dispersion of sodium hydride in mineral oil in 150 mL of THF was treated with 3.52 mL (4.23 g, 38 mmol) of freshly distilled dimethyl phosphite by syringe. The resulting mixture was gently warmed with a heat gun until a homogeneous solution formed. A 30-mL portion of this solution was added by syringe to a solution of the bromides in 50 mL of THF, resulting in the formation of a white precipitate. Two additional portions of the phosphite anion solution were added at 30-min intervals. The mixture was diluted with 500 mL of water and extracted with two 500-mL portions of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Rapid flash chromatography (5

× 20 cm, 60% EtOAc/hexane) afforded 1.78 g (46% from alcohol **34a**) of phosphonate **35a** as a colorless oil: IR (thin film) 2940, 1640, 1565, 1465, 1380, 1250, 1185, 1050, 990, 870, 845, 800, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.71 (dd, 1 H, J = 10.3 and 18.6 Hz, C_5-*H*), 6.18 (d, 1 H, J = 18.6 Hz, C_4-*H*), 5.96–5.90 (m, 1 H, C_6-*H*), 3.73 (d, 6 H, J = 10.7 Hz, $POCH_3$), 2.59 (d, 2 H, J = 22.7 Hz, C_8-*H*), 1.93 (s, 3 H, C_7-CH_3), 1.54–1.46 (m, 6 H, $SnCH_2CH_2CH_2CH_3$), 1.35–1.24 (m, 6 H, $CH_2CH_2CH_3$), 1.05–0.80 (m, 15 H, $SnCH_2$, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.2 (d, J_{CP} = 5 Hz), 133.4 (d, J_{CP} = 5 Hz), 132.9 (d, J_{CP} = 13 Hz), 126.7 (d, J_{CP} = 13 Hz), 52.7 (d, J_{CP} = 7 Hz), 36.8, 35.4, 29.1, 27.2, 17.9 (d, J_{CP} = 9 Hz), 13.7, 9.5; TLC R_f = 0.14 (50% EtOAc/hexane).

[2*E*,4*E*]-5-(Tributylstannyl)-1,2-dimethyl-1-(dimethylphosphono)-2,4-pentadiene (35b). To a solution of 1.25 g (2.61 mmol) of phosphonate **35a** in 25 mL of THF at −78 °C was added 1.79 mL (2.74 mmol) of *n*-butyllithium (1.53 M in hexane) dropwise, resulting in a dark red-brown solution. After 5 min, 195 μL (444 mg, 3.13 mmol) of iodomethane was added, and the cold bath was removed. The color faded to orange over 5 min, and the solution was poured into 50 mL of water and extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (5 × 12 cm, 50% EtOAc/hexane) afforded 1.19 g (92%) of phosphonate **35b** as a colorless oil. This phosphonate was a single isomer by TLC, ^1H NMR, and ^{13}C NMR: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.75 (dd, 1 H, J = 10.2 and 18.5 Hz, C_5-*H*), 6.20 (d, 1 H, J = 18.5 Hz, C_4-*H*), 6.01–5.96 (m, 1 H, C_6-*H*), 3.73 (d, 3 H, J = 10.6 Hz, $POCH_3$), 3.72 (d, 3 H, J = 10.6 Hz, $POCH_3$), 2.65 (dq, 1 H, J = 7.3 and 23.5 Hz, C_8-*H*), 1.91 (s, 3 H, C_7-CH_3), 1.54–1.46 (m, 6 H, $SnCH_2CH_2CH_2CH_3$), 1.37–1.24 (m, 9 H, C_8-CH_3, $CH_2CH_2CH_3$), 0.97–0.80 (m, 15 H, $SnCH_2$, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.3 (d, J_{CP} = 5 Hz), 133.9 (d, J_{CP} = 5 Hz), 132.7 (d, J_{CP} = 10 Hz), 131.6 (d, J_{CP} = 13 Hz), 53.0, 52.8 (d, J_{CP} = 20 Hz), 41.3, 40.0, 29.1, 27.3, 15.9 (d, J_{CP} = 3 Hz), 13.7, 9.5; TLC R_f = 0.29 (50% EtOAc/hexane).

[2*S*,3*S*,4*R*,5*R*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*)]-7-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-3,5-bis(*tert*-butyldimethylsiloxy)-7-methoxy-2,4-dimethylheptyl Pivalate (40a). To a solution of 865 mg (0.768 mmol) of *p*-methoxybenzyl ether **30** in 10 mL of CH_2Cl_2 was added 500 μL of H_2O. To this rapidly stirred biphasic mixture was added 350 mg (1.54 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in one portion, resulting in a green color which slowly faded to orange-brown. After 20 min, the reaction was quenched by the addition of 50 mL of saturated aqueous $NaHCO_3$ and the resultant mixture was extracted with 3 × 30 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 30 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (5.5 × 6.5 cm, linear gradient of 3%–5% EtOAc/hexane) afforded 726 mg (94%) of alcohol **40a** as a colorless oil: $[\alpha]^{21}_{577}$ +50.1° (*c* 0.76, CH_2Cl_2); IR (thin film) 3508, 2956, 2930, 2886, 2857, 1730, 1472, 1388, 1362, 1284, 1255, 1155, 1098, 1074, 1042, 1006, 978, 909, 874, 836, 775, 735, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.58 (m, 1 H, C_{23}-*H*), 4.26 (m, 1 H, C_{13}-*H*), 4.19 (dd, 1 H, J = 5.0 and 10.9 Hz, C_9-*H*), 3.97 (dd, 1 H, J = 4.0 and 8.9 Hz, C_{16}-*H*), 3.91 (dd, 1 H, J = 7.8 and 10.9 Hz, C_9-*H*), 3.82 (m, 1 H, C_{21}-*H*), 3.65 (s, 3 H, OCH_3), 3.61 (t, 2 H, J = 6.3 Hz, C_{25}-H_2), 3.55 (dd, 1 H, J = 4.7 and 6.4 Hz, C_{11}-*H*), 3.50 (dd, 1 H, J = 4.0 and 11.9 Hz, C_{17}-*H*), 3.47 (m, 1 H, C_{15}-*H*), 3.39 (d, 1 H, J = 12.0 Hz, C_{17}-O*H*), 2.11 (m, 1 H, C_{10}-*H*), 1.91 (m, 1 H, C_{12}-*H*), 1.74 (dd, 1 H, J = 3.9 and 14.4 Hz, C_{20}-*H*), 1.69–1.59 (m, 4 H, C_{14}-*H*, C_{22}-*H*, C_{24}-H_2), 1.49 (m, 1 H, C_{20}-*H*), 1.39 (m, 1 H, C_{14}-*H*), 1.20 (s, 9 H, $(CH_3)_3CCO$), 1.10 (s, 3 H, C_{18}-CH_3), 0.99 (d, 3 H, J = 6.9 Hz, C_{10}-CH_3), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.88–0.87 (m, 24 H, 2 $SiC(CH_3)_3$, C_{12}-CH_3, C_{18}-CH_3), 0.83 (d, 3 H, J = 7.1 Hz, C_{22}-CH_3), 0.12 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 6 H, 2 $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5, 108.5, 88.0, 80.2, 79.0, 75.9, 70.5, 68.2, 66.6, 65.2, 60.0, 60.0, 49.2, 43.0, 37.3, 36.9, 35.5, 34.4, 30.3, 27.3, 26.5, 26.3, 26.0, 25.9, 22.1, 18.2, 16.6, 14.5, 10.0, 10.1, −3.7, −3.9, −4.0, −4.3, −4.7, −5.0, −5.4; TLC R_f = 0.29 (5% EtOAc/hexane). Exact mass: calcd for $C_{52}H_{108}O_{10}Si_4Na$, 1027.6917; found, 1027.6890 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*S*,3*S*,4*R*,5*R*,7*R*,7(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*)]-7-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-3,5-bis(*tert*-butyldimethylsiloxy)-7-methoxy-2,4-dimethyl-1-heptanal (41). To a solution of 304 mg (0.330 mmol) of diol **40b** in 4 mL of CH_2Cl_2 was added 267 μL (261 mg, 3.30 mmol) of pyridine. Solid Dess–Martin periodinane[37] (154 mg, 0.363 mmol) was then added in one portion. After 20 min, the reaction was quenched by the addition of 30 mL each of 1.5 M Na_2SO_3 and saturated aqueous $NaHCO_3$, and the mixture was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 12 cm, 7% EtOAc/hexane) gave 268 mg (88%) of aldehyde **41** as a white foam: $[\alpha]^{21}_{577}$ +45.8° (*c* 0.36, CH_2Cl_2); IR (thin film) 3507, 2929, 2857, 2709, 1725, 1472, 1388, 1361, 1255, 1074, 1006, 978, 957, 938, 882, 836, 775, 739, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.79 (s, 1 H, C_9-*H*), 4.58 (m, 1 H, C_{23}-*H*), 4.24 (m, 1 H, C_{13}-*H*), 3.97 (m, 2 H, C_{11}-*H* and C_{16}-*H*), 3.83 (m, 1 H, C_{21}-*H*), 3.64 (s, 3 H, OCH_3), 3.62 (t, 2 H, J = 6.3 Hz, C_{25}-H_2), 3.52 (dd, 1 H, J = 4.0 and 12.0 Hz, C_{17}-*H*), 3.46 (m, 1 H, C_{15}-*H*), 3.40 (d, 1 H, J = 11.9 Hz, C_{17}-O*H*), 2.67 (m, 1 H, C_{10}-*H*), 1.95 (m, 1 H, C_{14}-*H*), 1.75 (dd, 1 H, J = 3.8 and 14.4 Hz, C_{20}-*H*), 1.68–1.62 (m, 3 H, C_{12}-*H*, C_{14}-*H*, C_{22}-*H*), 1.49 (m, 1 H, C_{20}-*H*), 1.30 (m, 2 H, C_{24}-*H*), 1.14 (d, 3 H, J = 7.0 Hz, C_{10}-CH_3), 1.10 (s, 3 H, C_{18}-CH_3), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 12 H, $SiC(CH_3)_3$, C_{18}-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.83 (d,3 H, J = 7.1 Hz, C_{22}-CH_3), 0.75 (d, 3 H, J = 7.1 Hz, C_{12}-CH_3), 0.15 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 6 H, 2 $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.1, 108.6, 87.9, 80.2, 79.0, 74.5, 70.5, 68.8, 65.2, 60.1, 60.0, 51.7, 49.3, 43.8, 37.4, 35.6, 34.4, 30.3, 26.0, 25.9, 22.1, 18.3, 18.2, 18.1, 16.6, 10.6, 10.1, 9.7, −3.9, −4.3, −4.3, −4.4, −4.7, −5.0, −5.4; TLC R_f = 0.44 (10% EtOAc/hexane). Exact mass: calcd for $C_{47}H_{98}O_9Si_4Na$, 941.6185; found, 941.6210 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*Z*,4*E*,6*E*,8*E*,10*S*,11*S*,12*R*,13*R*,15*R*,15(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (43a). To a solution of 307 mg (0.622 mmol) of phosphonate **35b** in 6 mL of THF at −78 °C was added dropwise 407 μL (0.622 mmol) of *n*-butyllithium (1.53 M in hexane), resulting in a deep red color. The solution was warmed to 0 °C, and 286 mg (0.311 mmol) of aldehyde **41** in 1.5 mL of THF (0.5 mL rinse) was added by cannula. After 30 min, the reaction was quenched by the addition of 25 mL each of saturated aqueous NH_4Cl and H_2O. The mixture was extracted with 3 × 40 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford stannyl triene **42**. ^1H NMR of **42** revealed an (*E*):(*Z*) ratio for C_8–C_9 of >7:1.

To a solution of **42** in 6 mL of 1-methyl-2-pyrrolidinone was added 99 μL (180 mg, 0.933 mmol) of vinyl iodide **36** followed by 0.8 mg of $(MeCN)_2PdCl_2$. After 24 h, another 0.5-mg portion of the Pd catalyst was added. After 48 h total, 33 μL (60 mg, 0.311 mmol) of vinyl iodide **36** and 0.5 mg of the Pd catalyst were added. After 76 h total, the reaction mixture was poured into 100 mL of saturated aqueous $NaHCO_3$ and extracted with 3 × 100 mL of Et_2O. The combined Et_2O layers were washed with 150 mL of H_2O, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (5 × 10 cm, slow linear gradient of 1%–4% EtOAc/hexane) afforded 212 mg (64%) of tetraene **43a** as a white foam: $[\alpha]^{21}_{577}$ +76.6° (*c* 0.59, CH_2Cl_2); IR (thin film) 3498, 2953, 2927, 2856, 2210, 1591, 1471, 1380, 1360, 1253, 1101, 1072, 1030, 1006, 960, 876, 835, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.02 (dd, 1 H, J = 11.2 and 14.9 Hz, C_5-*H*), 6.83 (d, 1 H, J = 15.0 Hz, C_4-*H*), 6.35 (d, 1 H, J = 11.1 Hz, C_6-*H*), 6.08 (d, 1 H, J = 9.1 Hz, C_9-*H*), 5.06 (s, 1 H, C_2-*H*), 4.58 (m, 1 H, C_{23}-*H*), 4.25 (m, 1 H, C_{13}-*H*), 3.96 (dd, 1 H, J = 4.1 and 8.8 Hz, C_{16}-*H*), 3.82 (m, 1 H, C_{21}-*H*), 3.63 (s, 3 H, OCH_3), 3.61 (m, 2 H, C_{25}-H_2), 3.53–3.46 (m, 3 H, C_{11}-*H*, C_{15}-*H*, C_{17}-*H*), 3.38 (d, 1 H, J = 12.0 Hz, C_{17}-O*H*), 2.75 (m, 1 H, C_{10}-*H*), 2.07 (s, 3 H, C_3-CH_3), 2.01 (s, 3 H, C_7-CH_3), 1.87 (s, 3 H, C_8-CH_3), 1.83 (m, 1 H, C_{12}-*H*), 1.75 (dd, 1 H, J = 3.8, 14.3 Hz, C_{20}-*H*), 1.69–1.58 (m, 4 H, C_{14}-*H*, C_{22}-*H*, C_{24}-H_2), 1.49 (m, 1 H, C_{20}-*H*), 1.29 (m, 1 H, C_{14}-*H*), 1.10 (s, 3 H, C_{18}-CH_3), 1.02 (d, 3 H, J = 7.0 Hz, C_{10}-CH_3), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 18 H, 2 $SiC(CH_3)_3$), 0.87 (s, 12 H, $SiC(CH_3)_3$, C_{18}-CH_3), 0.83 (d, 3 H, J = 7.1 Hz, C_{22}-CH_3), 0.77 (d, 3 H, J = 7.1 Hz, C_{12}-CH_3), 0.18 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 6 H, 2 $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 144.2, 134.4, 133.9, 133.4, 128.5, 124.0, 117.5, 108.5, 94.6, 87.9, 80.2, 78.9, 77.6, 70.5, 68.4, 65.3, 60.1, 60.0, 49.3, 45.1, 37.3, 37.3, 35.5, 34.1, 30.3, 26.4, 26.0, 26.0, 25.9, 22.1, 19.4, 18.6, 16.6, 14.5, 14.0, 10.3, 10.1, −3.5, −3.8, −3.8, −4.2, −4.7, −5.0, −5.4; TLC R_f = 0.46 (10% EtOAc/hexane). Exact mass: calcd for $C_{58}H_{111}NO_8Si_4Na$, 1084.7284; found, 1084.7275 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[4*S*]-3-[2-[*N*-[(Phenylmethoxy)carbonyl]-*N*-methylamino]-1-oxoethyl]-4-(phenylmethyl)-2-oxazolidinone (44b). To a solution of 7.00 g (78.6 mmol) of sarcosine in 30 mL of H_2O at 0 °C was added dropwise 15.7 mL (78.6 mmol) of 5 N NaOH over 5 min. Into a syringe clamped above the reaction flask was drawn 13.5 mL (16.1 g, 94.3 mmol) of benzyl chloroformate. This reagent and 47.2 mL (94.3 mmol) of 2 N NaOH were then added dropwise at an approximately equimolar rate such that both additions were complete in 1 h. The resultant heterogeneous solution was then warmed to 25 °C and stirred for 30 min. The

reaction mixture was then extracted with diethyl ether (3 × 60 mL). The aqueous layer was then acidified to pH 2 with 3 M HCl and extracted with ethyl acetate (5 × 60 mL). The combined ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated to afford acid **44a** as an oil which was used in the next reaction without further purification.

Acylation of 13.9 g (78.6 mmol) of the [4*S*]-4-(phenylmethyl)-2-oxazolidinone[14] with acid **44a** was performed using the procedure outlined in the conversion of **2** to **3** (12.1 mL, 86.5 mmol of Et_3N; 10.2 mL, 82.5 mmol of pivaloyl chloride; 39.3 mL, 78.6 mmol (2.50 M in hexane) of *n*-butyllithium; THF as solvent). The reaction was quenched by the addition of 300 mL of saturated aqueous NH_4Cl. The bulk of the THF was removed on the rotovap, and the residue was poured onto 300 mL of CH_2Cl_2. After mixing, the layers were separated and the aqueous layer was extracted with 150 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 250 mL each of saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (11 × 22 cm, linear gradient of 25%–35% EtOAc/hexane) afforded an oil. Concentration from toluene and drying gave 24.0 g (80%, 2 steps) of **44b** as a white powder: mp 94–95 °C; $[\alpha]^{18}_{577}$ +81.1° (*c* 0.65, CH_2Cl_2); IR (thin film) 3065, 3035, 2960, 1780, 1705, 1480, 1453, 1395, 1361, 1267, 1225, 1154, 1115, 1075, 995, 978, 731, 700, 654 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 100 °C) δ 7.37–7.18 (m, 10 H, Ar*H*), 5.12 (AB quartet, ν_B = 5.13, ν_A = 5.11, 2 H, J_{AB} = 12.7 Hz, OCH_2Ph), 4.69 (m, 1 H, C*H*N), 4.55 (AB quartet, ν_B = 4.59, ν_A = 4.52, 2 H, J_{AB} = 18.4 Hz, CH_2NMe), 4.40 (apparent t, 1 H, *J* = 8.6 Hz, one of OCH_2), 4.22 (dd, 1 H, *J* = 8.9, 3.3 Hz, one of OCH_2), 3.06 (dd, 1 H, *J* = 13.7, 3.3 Hz, one of CH_2Ph), 2.95 (s, 3 H, NCH_3), 2.94 (dd, 1 H, *J* = 13.5, 5.9 Hz, one of CH_2Ph); TLC R_f = 0.47 (50% EtOAc/hexane). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80. Found: C, 66.03; H, 5.81.

[3(2*R*),4*S*]-3-[2-[*N*-[(Phenylmethoxy)carbonyl]-*N*-methylamino]-3-methoxy-1-oxopropyl]-4-(phenylmethyl)-2-oxazolidinone (45). To a solution of 4.02 g (10.5 mmol) of imide **44b** in 40 mL of CH_2Cl_2 at 0 °C was added 1.21 mL (2.09 g, 11.0 mmol) of titanium tetrachloride. The resulting yellow solution was stirred for 5 min, and then 1.92 mL (1.42 g, 11.0 mmol) of diisopropylethylamine was added. The dark purple solution was stirred for 3 h at 0 °C, and then 9.29 mL (7.99 g, 105 mmol) of dimethoxymethane was added followed immediately by 12.9 mL (14.9 g, 105 mmol) of boron trifluoride etherate. The resulting brown solution was stirred for 2 h at 25 °C, during which time the color faded to a light orange. The mixture was then added by cannula to a vigorously stirred mixture of 500 mL of saturated aqueous $NaHCO_3$ and 250 mL of CH_2Cl_2 at 0 °C. The layers were separated, and the aqueous layer was extracted with 200 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 300 mL of brine, dried (Na_2SO_4), filtered, and concentrated. GLC analysis of the unpurified reaction mixture (DB-1, 240 °C) gave a 2(*R*) (t_r = 15.69 min) to 2(*S*) (t_r = 22.25 min) diastereomer ratio of 51:1. Flash chromatography (8 × 15 cm, 25% EtOAc/hexane) afforded 3.57 g, (80%) of imide **45** as a viscous, colorless oil: $[\alpha]^{18}_{577}$ +74.7° (*c* 0.73, CH_2Cl_2); IR (thin film) 3065, 3032, 2930, 1780, 1700, 1454, 1388, 1351, 1212, 1195, 1157, 1114, 823, 736, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 100 °C) δ 7.37–7.19 (m, 10 H, Ar*H*), 5.84 (dd, 1 H, *J* = 4.2, 8.2 Hz, C_{36}-*H*), 5.08 (s, 2 H, OCH_2Ph), 4.67 (m, 1 H, C*H*N), 4.32 (apparent t, 1 H, *J* = 8.6 Hz, one of CH_2OCO), 4.21 (dd, 1 H, *J* = 8.9, 3.7 Hz, one of CH_2OCO), 3.81 (dd, 1 H, *J* = 10.8, 8.2 Hz, C_{37}-*H*), 3.71 (dd, 1 H, *J* = 10.8, 4.2 Hz, C_{37}-*H*), 3.31 (s, 3 H, OCH_3), 3.06 (dd, 1 H, *J* = 13.8, 3.6 Hz, one of CH_2Ph), 3.02 (s, 3 H, NCH_3), 2.93 (dd, 1 H, *J* = 13.9, 7.8 Hz, one of CH_2Ph); TLC R_f = 0.65 (50% EtOAc/hexane). Exact mass: calcd for $C_{23}H_{26}N_2O_6Na$, 449.1689; found, 449.1684 (FAB, *m* = nitrobenzyl alcohol, added NaI).

[2*S*]-2-[*N*-[(Phenylmethoxy)carbonyl]-*N*-methylamino]-3-methoxy-1-propanol (46a). To a solution of 9.97 g (23.4 mmol) of imide **45** in 100 mL of THF at 0 °C were added 948 μL (750 mg, 23.4 mmol) of methanol and 11.7 mL (23.4 mmol) of $LiBH_4$ (2.0 M in THF) accompanied by gas evolution. The solution was stirred at 0 °C for 40 min. The reaction was quenched by the addition of 300 mL of 1.0 M sodium potassium tartrate and stirring for 10 min at 0 °C. The mixture was poured onto 400 mL of CH_2Cl_2 and mixed well. The layers were separated, and the aqueous layer was extracted with 250 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 200 mL of brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (11 × 15 cm, linear gradient of 10%–40% acetone/CH_2Cl_2) gave 3.81 g (92%) of recovered auxiliary followed by 5.49 g (93%) of alcohol **46a** as a colorless oil: $[\alpha]^{20}_{577}$ −6.8° (*c* 0.75, CH_2Cl_2); IR (thin film) 3440 (br), 2940, 2895, 1690, 1456, 1410, 1335, 1215, 1155, 1050, 770, 736, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz at 100 °C) δ 7.36–7.29 (m, 5 H, Ar*H*), 5.09 (s, 2 H, OCH_2Ph), 4.28 (br s, 1 H, O*H*), 4.15 (m, 1 H, C_{36}-*H*), 3.53 (m, 2 H, CH_2OH), 3.51 (dd, 1 H, *J* = 10.6, 7.6 Hz, C_{37}-*H*), 3.44 (dd, 1 H, *J* = 10.5, 5.3 Hz, C_{37}-*H*), 3.25 (s, 3 H, OCH_3), 2.83 (s, 3 H, NCH_3); TLC R_f = 0.25 (10% acetone/CH_2Cl_2). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56. Found: C, 61.55; H, 7.43.

[3(2*R*,3*R*,4*R*),4*R*]-3-[4-[*N*-[(Phenylmethoxy)carbonyl]-*N*-methylamino]-3-hydroxy-5-methoxy-2-[(4-methoxyphenyl)methoxy]-1-oxopentyl]-4-(phenylmethyl)-2-oxazolidinone (48). To a solution of 1.65 mL (2.41 g, 19.0 mmol) of oxalyl chloride in 40 mL of CH_2Cl_2 at −78 °C was added 2.69 mL (2.96 g, 37.9 mmol) of dimethyl sulfoxide (gas evolution). After 10 min, a solution of 4.00 g (15.8 mmol) of alcohol **46a** in 15 mL of CH_2Cl_2 was added by cannula (5 mL CH_2Cl_2 rinse). The resultant white slurry was stirred at −78 °C for 15 min, and 13.8 mL (10.2 g, 79.0 mmol) of diisopropylethylamine was then added, affording a clear solution. The mixture was warmed to −50 °C over 10 min and stirred at that temperature for 1 h. The reaction was quenched by the addition of 100 mL of saturated aqueous NH_4Cl and stirring for 5 min. The mixture was poured onto 100 mL of saturated aqueous NH_4Cl and 50 mL of CH_2Cl_2. The layers were separated, and the CH_2Cl_2 layer was washed with 150 mL of cold H_2O, dried (Na_2SO_4), filtered, and concentrated to afford a pale-yellow oil. The racemization-prone aldehyde **46b** thus produced was used immediately without further purification.

To a suspension of 9.88 g (23.7 mmol) of stannous triflate[61] in 100 mL of CH_2Cl_2 was added 3.30 mL (2.40 g, 23.7 mmol) of triethylamine, and the pale-yellow slurry was immediately cooled to −15 °C (ice/acetone). After 5 min, a solution of 8.42 g (23.7 mmol) of imide **47** in 15 mL CH_2Cl_2 was added by cannula (5 mL CH_2Cl_2 rinse), and the resultant homogeneous solution was stirred at −15 °C for 45 min. After the reaction mixture was cooled to −78 °C, 3.58 mL (2.75 g, 23.7 mmol) of TMEDA was added. After 5 min, the aldehyde **46b**, as a solution in 15 mL of CH_2Cl_2, was added by cannula (5 mL CH_2Cl_2 rinse) and the resulting solution was stirred at −78 °C for 4 h. The reaction mixture was poured onto a vigorously stirred, 0 °C mixture of 1 L of 1.0 M $NaHSO_4$ and 500 mL of CH_2Cl_2. After being stirred for 5 min, the layers were separated and the aqueous layer was extracted with 200 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 600 mL each of saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (11 × 15 cm, linear gradient of 25%–50% EtOAc/hexane) afforded 5.78 g (60% for 2 steps from **46a**) of imide **48** as a viscous, colorless oil: $[\alpha]^{20}_{577}$ −21.6° (*c* 0.37, CH_2Cl_2); IR (thin film) 3420 (br), 2930, 1784, 1702, 1615, 1515, 1455, 1390, 1249, 1211, 1110, 1030, 821, 734, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz at 125 °C) δ 7.36–7.21 (m, 12 H, Ar*H*), 6.87 (m, 2 H, two of anisyl Ar*H*), 5.35 (d, 1 H, *J* = 6.9 Hz, C_{34}-*H*), 5.08 (AB quartet, ν_B = 5.09, ν_A = 5.07, 2 H, J_{AB} = 12.9 Hz, OCH_2Ph), 4.64 (m, 1 H, C*H*N), 4.44 (AB quartet, ν_B = 4.46, ν_A = 4.42, 2 H, J_{AB} = 11.4 Hz, OCH_2ArOMe), 4.34 (m, 1 H, C_{36}-*H*), 4.28 (dd, 1 H, *J* = 8.9, 8.0 Hz, one of CH_2OCO), 4.19 (dd, 1 H, *J* = 8.9, 3.0 Hz, one of CH_2OCO), 4.02 (dd, 1 H, *J* = 6.9, 5.2 Hz, C_{35}-*H*), 3.76 (s, 3 H, ArOCH_3), 3.68 (dd, 1 H, *J* = 10.9, 8.6 Hz, C_{37}-*H*), 3.62 (dd, 1 H, *J* = 10.9, 4.6 Hz, C_{37}-*H*), 3.22 (s, 3 H, OCH_3), 3.11 (dd, 1 H, *J* = 13.9, 3.7 Hz, one of CH_2Ph), 2.94 (dd, 1 H, *J* = 13.9, 8.1 Hz, one of CH_2Ph), 2.86 (s, 3 H, NCH_3); TLC R_f = 0.31 (50% EtOAc/hexane). Anal. Calcd for $C_{33}H_{38}N_2O_9$: C, 65.33; H, 6.31. Found: C, 65.20; H, 6.37.

[4*S*,3(2*R*)]-4-Benzyl-3-[4-(*tert*-butoxycarbonyl)-2-methylbutanoyl]-2-oxazolidinone (49a). Titanium(IV) isopropoxide (7.74 mL, 7.40 g, 26.0 mmol) and 8.66 mL (15.0 g, 79.0 mmol) of titanium tetrachloride were added by syringe to 390 mL of CH_2Cl_2 at 0 °C. After 10 min, 18.8 mL (14.0 g, 108 mmol) of diisopropylethylamine was added. The resulting brown solution was stirred for 10 min, and 23.3 g (100 mmol) of **14**[14] was added as a solid. The resulting deep red solution was stirred at 0 °C for 1 h, and 22.0 mL (19.2 g, 150 mmol) of *tert*-butyl acrylate was added dropwise by syringe. The solution gradually turned brown. After 4 h at 0 °C, 1 L of saturated aqueous NH_4Cl was added. The layers were separated, and the aqueous layer was extracted with 500 mL of CH_2Cl_2. The combined organic layers were washed with 1 L of saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (11 × 20 cm, 35% EtOAc/hexane) afforded 31.8 g (88%) of ester **49a** as a viscous oil. This compound was diastereomerically pure according to TLC, ^1H NMR, and ^{13}C NMR spectroscopy: $[\alpha]_D$ +32.1° (*c* 1.26, CH_2Cl_2); IR (thin film) 2980, 1785, 1730, 1700, 1455, 1390, 1150, 975, 845, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.20 (m, 5 H, Ar*H*), 4.66 (m, 1 H, C*H*N), 4.20–4.13 (m, 2 H, CH_2O), 3.76 (m, 1 H, C_{30}-*H*), 3.32 (dd, 1 H, *J* = 3.3, 13.3 Hz, CH_2Ar), 2.73 (dd, 1 H, *J* = 9.8, 13.3 Hz, CH_2Ar), 2.34–2.23 (m, 2 H, C_{32}-*H*), 2.06 (m, 1 H, C_{31}-*H*), 1.77 (m, 1 H, C_{31}-*H*), 1.45 (s, 9 H, C(CH_3)$_3$), 1.19 (d, 3 H, *J* = 6.8 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 176.5, 172.3, 153.0, 135.3, 129.4, 128.9, 127.3, 80.3, 66.0, 55.4, 38.1, 36.9, 33.1, 28.7, 28.1, 16.9; TLC R_f = 0.42 (35% EtOAc/hexane). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53. Found: C, 66.38; H, 7.42.

(61) (a) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aube, F. *Inorg. Chem.* **1977**, *16*, 1414. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.

[4S,3(2R)]-4-Benzyl-3-[4-((*tert*-butoxycarbonyl)amino)-2-methylbutanoyl]-2-oxazolidinone (50a). To a solution of 10.1 g (33.1 mmol) of acid **49b** in 330 mL of *tert*-butyl alcohol were added 5.07 mL (3.70 g, 36.4 mmol) of triethylamine and 7.84 mL (10.0 g, 36.4 mmol) of diphenylphosphoryl azide. The resulting solution was heated to reflux for 15 h. Upon cooling, the mixture was diluted with 1 L of diethyl ether and washed with 1 L each of 1 M aqueous HCl and 1 M aqueous NaOH and 300 mL of brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (8 × 20 cm, 30% EtOAc/hexane) to afford 8.90 g (71%) of carbamate **50a** as an oil: $[\alpha]_D$ +20.0° (*c* 0.77, CH_2Cl_2); IR (thin film) 3400, 2980, 1785, 1700, 1510, 1390, 1200, 1115, 1020, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.17 (m, 5 H, Ar*H*), 4.72 (br s, 1 H, C_{32}-N*H*), 4.63 (m, 1 H, C*H*N), 4.17–4.11 (m, 2 H, CH_2O), 3.73 (m, 1 H, C_{30}-*H*), 3.36–3.29 (m, 1 H, CH_2Ar), 3.17 (m, 2 H, C_{32}-*H*), 2.69 (dd, 1 H, *J* = 10.1, 13.3 Hz, CH_2Ar), 1.94 (m, 1 H, C_{31}-*H*), 1.56 (m, 1 H, C_{31}-*H*), 1.37 (s, 9 H, $C(CH_3)_3$), 1.16 (D, 3 h, *j* = 6.8 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 176.7, 155.9, 153.1, 135.4, 129.4, 128.9, 127.3, 79.0, 66.1, 55.5, 38.2, 37.9, 35.1, 33.8, 28.4, 16.8; TLC R_f = 0.38 (35% EtOAc/hexane). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50. Found: C, 63.90; H, 7.42.

[2R]-4-((*tert*-Butoxycarbonyl)amino)-2-methylbutanoic Acid (50b). To a solution of 8.50 g (20.6 mmol) of imide **50a** in 225 mL of 4:1 THF/water at 0 °C were added 9 mL of 30% aqueous H_2O_2 and 1.52 g (36.1 mmol) of lithium hydroxide monohydrate. After 30 min, the solution was diluted with 150 mL of 1 M aqueous NaOH and 50 mL of saturated aqueous Na_2SO_3 and extracted with two 300-mL portions of CH_2Cl_2. Drying (Na_2SO_4), filtration, and concentration of these extracts afforded the free oxazolidinone. The aqueous layer was acidified with 3 M aqueous HCl and extracted with three 100-mL portions of EtOAc. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to afford 4.69 g (96%) of acid **50b** as an oil: $[\alpha]_D$ −14.0° (*c* 0.31, CH_2Cl_2); IR (thin film) 3430, 2980, 1710, 1525, 1370, 1250, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.70 (br s, 1 H, C_{32}-N*H*), 3.18 (m, 2 H, C_{32}-*H*), 2.52 (m, 1 H, C_{30}-*H*), 1.87 (m, 1 H, C_{31}-*H*), 1.65 (m, 1 H, C_{31}-*H*), 1.44 (s, 9 H, $C(CH_3)_3$), 1.21 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 37.0, 33.9, 28.4, 16.9. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81. Found: C, 54.91; H, 8.74.

[2S,2(2R)]-Methyl 2-[(4-((*tert*-Butoxycarbonyl)amino)-2-methyl-1-oxobutyl)amino]-3-hydroxypropanoate (51). To a solution of 124 mg (0.573 mmol) of acid **50b** in 5.7 mL of THF at −23 °C were added 66 μL (61 mg, 0.60 mmol) of *N*-methylmorpholine and 78 μL (82 mg, 0.60 mmol) of isobutyl chloroformate, resulting in the formation of a white precipitate. After 15 min, 94 mg (0.60 mmol) of L-serine methyl ester hydrochloride was added as a solid. The mixture was allowed to warm gradually to room temperature and stirred overnight. The mixture was diluted with 15 mL of 5% aqueous $NaHCO_3$ and extracted with five 15-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (2 × 10 cm, 75% EtOAc/hexane) to afford 160 mg (88%) of amide **51** as a white crystalline solid. This compound was diastereomerically pure as determined by TLC, ^1H NMR, and ^{13}C NMR: mp 85–86 °C; $[\alpha]_D$ +22.8° (*c* 0.76, CH_2Cl_2); IR (solution in CH_2Cl_2) 3450, 2980, 1750, 1700, 1675, 1520, 1370, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), δ 6.68 (d, 1 H, NH), 4.76 (m, 1 H, C_{32}-N*H*), 4.69 (m, 1 H, C_{27}-*H*), 4.23 (m, 1 H, O*H*), 4.02 (m, 1 H, C_{28}-*H*), 3.93 (m, 1 H, C_{28}-*H*), 3.78 (s, 3 H, OCH_3), 3.31 (m, 1 H, C_{30}-*H*), 2.98 (m, 2 H, C_{32}-*H*), 2.38 (m, 1 H, C_{31}-*H*), 1.88 (m, 1 H, C_{31}-*H*), 1.42 (s, 9 H, $C(CH_3)_3$), 1.15 (d, 3 H, *J* = 6.9 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.4, 171.0, 156.9, 80.2, 63.1, 55.0, 52.5, 38.2, 37.9, 35.6, 28.4, 18.3; TLC R_f = 0.23 (75% EtOAc/hexane). Anal. Calcd for $C_{14}H_{26}N_2O_6$: C, 52.82; H, 8.23. Found: C, 52.69; H, 8.35.

[4S,2(1R)]-2-[3-((*tert*-Butoxycarbonyl)amino)-1-methylpropyl]-2-oxazoline-4-carboxylic Acid Methyl Ester (52a). To a solution of 3.23 mL (3.16 g, 39.9 mmol) of pyridine in 48 mL of diethyl ether at 0 °C was added 1.09 mL (1.78 g, 15.0 mmol) of thionyl chloride, resulting in the formation of a white precipitate. To this was added dropwise by cannula a solution of 1.59 g (4.99 mmol) of amide **51** in 24 mL of 2:1 diethyl ether/THF and 8 mL of diethyl ether rinse. The mixture was stirred at 0 °C for 2 h, then quenched by addition of 100 mL of saturated aqueous $NaHCO_3$ and 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with five 50-mL portions of EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (5 × 9 cm, 70% EtOAc/hexane) afforded 1.17 g (78%) of oxazoline **52a** as a colorless oil: $[\alpha]_D$ +71.7° (*c* 1.47, CH_2Cl_2); IR (thin film) 3360, 2980, 1745, 1715, 1660, 1520, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.81 (br s, 1 H, C_{32}-N*H*), 4.71 (dd, 1 H, *J* = 7.8, 10.6 Hz, C_{27}-*H*), 4.41 (m, 2 H, C_{28}-*H*), 3.77 (s, 3 H, OCH_3), 3.15 (m, 2 H, C_{32}-*H*), 2.60 (m, 1 H, C_{30}-*H*), 1.80 (m, 1 H, C_{31}-*H*), 1.70 (m, 1 H, C_{31}-*H*), 1.41 (s, 9 H, $C(CH_3)_3$), 1.19 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.6, 171.8, 155.8, 79.2, 69.4, 67.8, 52.6, 38.4, 34.0, 31.4, 28.4, 17.6; TLC R_f = 0.26 (75% EtOAc/hexane). Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.99; H, 8.05. Found: C, 55.67; H, 8.06.

[4S,2(1R)]-2-[3-(Bis(*tert*-Butoxycarbonyl)amino)-1-methylpropyl]-2-oxazoline-4-carboxylic Acid Methyl Ester (52b). To a solution of 1.00 g (3.33 mmol) of oxazoline **52a** in 15 mL of CH_3CN at 25 °C were added 919 μL (873 mg, 4.00 mmol) of di-*tert*-butyl dicarbonate and 20 mg (0.16 mmol) of 4-(dimethylamino)pyridine. The resultant clear solution was stirred for 20 h, during which time it gradually turned yellow. To this yellow solution were then added 459 μL (437 mg, 2.00 mmol) of di-*tert*-butyl dicarbonate and 10 mg (0.082 mmol) of 4-(dimethylamino)pyridine. After being stirred for an additional 17 h at 25 °C, the solution was concentrated. Purification of the residue by flash chromatography (6 × 10 cm, linear gradient of 30%–45% EtOAc/hexane) afforded 1.18 g (88%) of oxazoline **52b** as a colorless oil: $[\alpha]^{23}_{577}$ +70.9° (*c* 0.875, CH_2Cl_2); IR (thin film) 2979, 1745, 1697, 1659, 1456, 1394, 1368, 1286, 1258, 1125, 980, 857, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.72 (dd, 1 H, *J* = 7.8, 10.5 Hz, C_{27}-*H*), 4.48 (dd, 1 H, *J* = 7.9, 8.5 Hz, C_{28}-*H*), 4.39 (dd, 1 H, *J* = 8.7, 10.5 Hz, C_{28}-*H*), 3.78 (s, 3 H, CO_2CH_3), 3.61 (m, 2 H, C_{32}-*H*), 2.55 (m, 1 H, C_{30}-*H*), 1.98 (m, 1 H, C_{31}-*H*), 1.73 (m, 1 H, C_{31}-*H*), 1.50 (s, 18 H, $((CH_3)_3CO)_2$), 1.24 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 171.7, 152.3, 82.1, 69.2, 67.9, 52.5, 44.3, 32.9, 31.3, 28.0, 17.5; TLC R_f = 0.44 (50% EtOAc/hexane). Exact mass: calcd for $C_{19}H_{32}N_2O_7Na$, 423.2107; found, 423.2126 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[4S,2(1R)]-2-[3-(Bis(*tert*-butoxycarbonyl)amino)-1-methylpropyl]-2-oxazole-4-carboxylic Acid Methyl Ester (53b). To a solution of 960 mg (2.40 mmol) of oxazoline **52b** in 20 mL of THF at −78 °C was added 2.81 mL (2.64 mmol) of KHMDS (0.94 M in THF). The resultant brightly yellow-colored solution was stirred at −78 °C for 10 min, and then 506 mg (2.64 mmol) of phenylselenenyl chloride as a solution in 5 mL of THF (1 mL rinse) was added by cannula. The solution was stirred for 15 min and then allowed to warm to 25 °C. The reaction was then quenched by the addition of 100 mL of saturated aqueous $NaHCO_3$ and 120 mL of EtOAc. The layers were separated. The organic layer was washed with 100 mL of saturated aqueous NH_4Cl, dried (Na_2SO_4), filtered, and concentrated. The yellow oil thus obtained was used without further purification.

To a solution of the yellow oil in 20 mL of CH_2Cl_2 at 0 °C was added 388 μL (380 mg, 4.80 mmol) of pyridine. To this solution was then added dropwise over 2 min 735 μL (7.20 mmol) of 30% aqueous H_2O_2. The resultant heterogeneous mixture was stirred vigorously at 0 °C for 1 h. The reaction was quenched by the addition of 40 mL of saturated aqueous $NaHCO_3$ and 20 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with 20 mL of CH_2Cl_2. The combined organic layers were washed with 40 mL of saturated aqueous NH_4Cl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (4 × 12 cm, linear gradient of 15%–25% EtOAc/hexane) provided 542 mg (57% for 2 steps from **52b**) of oxazole **53b** as a colorless oil: $[\alpha]^{23}_{577}$ −8.7° (*c* 0.86, CH_2Cl_2); IR (thin film) 2979, 2936, 1748, 1697, 1584, 1479, 1455, 1439, 1395, 1368, 1281, 1222, 1124, 1000, 857, 801, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16 (s, 1 H, C_{28}-*H*), 3.91 (s, 3 H, CO_2CH_3), 3.67–3.53 (m, 2 H, C_{32}-*H*), 3.07 (m, 1 H, C_{30}-*H*), 2.13 (m, 1 H, C_{31}-*H*), 1.89 (m, 1 H, C_{31}-*H*), 1.48 (s, 18 H, $((CH_3)_3CO)_2$), 1.39 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 161.6, 152.2, 143.6, 132.9, 82.2, 52.0, 44.1, 33.6, 31.5, 27.9, 18.2; TLC R_f = 0.46 (30% EtOAc/hexane). Exact mass: calcd for $C_{19}H_{30}N_2O_7Na$, 421.1951; found, 421.1976 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2R,3R,4R,*N*(3R)]-4-[*N*-[(Phenylmethoxy)carbonyl]-*N*-methylamino]-*N*-[3-[4-(carbomethoxy)-2-oxazolyl]butyl]-2,3-dihydroxy-5-methoxyvaleramide (54a). Into a solution of 222 mg (0.557 mmol) of oxazole **53b** in 5 mL of EtOAc at 0 °C was bubbled HCl gas until saturation was achieved (approximately 30 s). The solution was then stirred at 0 °C for 20 min. Nitrogen gas was then bubbled through the reaction mixture for 5 min, during which time a white precipitate formed. After concentration, the residue was concentrated from 10 mL of CH_2Cl_2 three times to afford a white solid which was used without further purification.

To a suspension of the white solid in 5 mL of CH_2Cl_2 at 25 °C was added 555 μL (1.11 mmol) of trimethylaluminum (2.0 M in toluene) with concomitant gas evolution. The resultant homogeneous solution was stirred for 10 min, and then 271 mg (0.446 mmol) of imide **48** as a solution in 2 mL of CH_2Cl_2 was added by cannula (1 mL CH_2Cl_2 rinse) accompanied by more gas evolution. The resultant heterogeneous solution was stirred at 25 °C for 2 h, at which time was added 836 μL (1.67 mmol) of trimethylaluminum (2.0 M in toluene). After 2 h, the reaction mixture was cooled to 0 °C and quenched by the *dropwise at first* (vigorous gas evolution) addition of 10 mL of 1.0 M $NaHSO_4$ and 5 mL of CH_2Cl_2. The mixture was stirred vigorously at 0 °C for 30 min. The

layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 10 cm, 50% EtOAc/hexane followed by linear gradient of 0–10% MeOH/CH_2Cl_2) afforded 66 mg (84%) of recovered auxiliary, followed by 177 mg (78%) of diol **54a** as a colorless oil: $[\alpha]_{577}$ +6.9° (*c* 0.75, CH_2Cl_2); IR (thin film) 3370 (br), 2940, 1740, 1675 (br), 1583, 1535, 1445, 1404, 1325, 1147, 1111, 1001, 802, 771, 738, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz, 125 °C) δ 8.48 (s, 1 H, C_{28}-*H*), 7.36–7.27 (m, 5 H, Ar*H*), 5.07 (s, 2 H, CH_2Ar), 4.35 (ddd, 1 H, *J* = 6.2, 8.9, 4.6 Hz, C_{36}-*H*), 3.94 (dd, 1 H, *J* = 6.2, 4.7 Hz, C_{35}-*H*), 3.89 (d, 1 H, *J* = 4.6 Hz, C_{34}-*H*), 3.81 (s, 3 H, CO_2CH_3), 3.67 (dd, 1 H, *J* = 8.9, 10.8 Hz, C_{37}-*H*), 3.62 (dd, 1 H, *J* = 4.6, 10.8 Hz, C_{37}-*H*), 3.24 (s, 3 H, OCH_3), 3.19–3.11 (m, 2 H, C_{32}-H_2), 3.07 (m, 1 H, C_{30}-*H*), 2.83 (s, 3 H, NCH_3), 1.96 (m, 1 H, C_{31}-*H*), 1.76 (m, 1 H, C_{31}-*H*), 1.29 (d, 3 H, *J* = 7.1 Hz, C_{30}-CH_3); TLC R_f = 0.12 (50% EtOAc/hexane). Exact mass: calcd for $C_{24}H_{33}N_3O_9Na$, 530.2114; found, 530.2135 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*R*,3*R*,4*R*,*N*(3*R*)]-4-(Dimethylamino)-*N*-[3-(4-carbomethoxy-2-oxazolyl)butyl]-5-methoxy-2,3-bis((triethylsilyl)oxy)valeramide (55). To a solution of 49 mg (0.067 mmol) of urethane **54b** in 0.5 mL of methanol was added 36 mg of 10% Pd on C as a slurry in 1 mL of methanol, followed sequentially by 100 μL (1.33 mmol) of formaldehyde (37% aqueous solution) and 1.9 μL (0.0067 mmol) of acetic acid (20% in methanol). The reaction flask was flushed with nitrogen, and hydrogen gas was then introduced (balloon with needle through septum). The black slurry was stirred under 1 atm of H_2 for 45 min. The reaction mixture was filtered through a small pad of Celite (5 × 10 mL methanol rinse), and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2, filtered through a small plug of cotton, and concentrated to afford 41 mg (100%) of dimethylamine **55** as a colorless oil, which was pure by ^{1}H NMR and TLC: $[\alpha]^{20}_{577}$ +4.3° (*c* 0.70, CH_2Cl_2); IR (thin film) 3435, 2960, 2882, 1756, 1680, 1587, 1518, 1460, 1321, 1236, 1196, 1141, 1110, 1073, 1005, 857, 838, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (s, 1 H, C_{28}-*H*), 6.56 (br t, 1 H, *J* = 5.8 Hz, N*H*), 4.28 (s, 1 H, C_{34}-*H*), 4.05 (d, 1 H, *J* = 10.1 Hz, C_{35}-*H*), 3.91 (s, 3 H, CO_2CH_3), 3.53 (d, 2 H, *J* = 6.2 Hz, C_{37}-H_2), 3.29 (s, 3 H, OCH_3), 3.27 (m, 1 H, C_{32}-*H*), 3.15 (m, 1 H, C_{32}-*H*), 3.11–3.05 (m, 2 H, C_{30}-*H*, C_{36}-*H*), 2.24 (s, 6 H, $N(CH_3)_2$), 2.04 (m, 1 H, C_{31}-*H*), 1.82 (m, 1 H, C_{31}-*H*), 1.39 (d, 3 H, *J* = 7.1 Hz, C_{30}-CH_3), 0.97 (m, 18 H, $SiCH_2CH_3$), 0.67 (m, 12 H, $SiCH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 168.5, 161.7, 143.7, 133.0, 77.3, 73.8, 70.5, 61.5, 58.3, 52.1, 41.7, 36.8, 34.7, 31.6, 18.3, 6.9, 6.8, 4.9, 4.7; TLC R_f = 0.47 (50% EtOAc/hexane). Exact mass: calcd for $C_{29}H_{57}N_3O_7Si_2Na$, 638.3633; found, 638.3651 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*R*,3*R*,4*R*,*N*(3*R*)]-4-(Dimethylamino)-*N*-[3-(4-hydroxymethyl-2-oxazolyl)butyl]-5-methoxy-2,3-bis((triethylsilyl)oxy)valeramide (56a). To a solution of 250 mg (0.406 mmol) of ester **55** in 6 mL of Et_2O at −78 °C was added 1.22 mL (1.22 mmol) of lithium aluminum hydride (1.0 M in Et_2O). After 1.5 h, 15 mL of EtOAc was added, the mixture was warmed to room temperature, and 2.5 mL of H_2O was added. The heterogeneous mixture was stirred vigorously for 5 min, and then anhydrous Na_2SO_4 was introduced until the solution was dry. The mixture was filtered with a total of 150 mL of EtOAc washes. Concentration and flash chromatography (3 × 8 cm, linear gradient of 80% EtOAc/hexane to EtOAc) afforded 180 mg (75%) of alcohol **56a** as a colorless oil: $[\alpha]_D$ +4.8° (*c* 1.12, CH_2Cl_2); IR (thin film) 3400, 2960, 2870, 1660, 1530, 1455, 1070, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1 H, C_{28}-*H*), 6.58 (br s, 1 H, C_{32}-N*H*), 4.55 (s, 2 H, C_{26}-*H*), 4.26 (s, 1 H, C_{34}-*H*), 4.04 (d, 1 H, *J* = 9.7 Hz, C_{35}-*H*), 3.52 (d, 2 H, *J* = 5.8 Hz, C_{37}-*H*), 3.28 (s, 3 H, OCH_3), 3.20 (m, 2 H, C_{30}-*H*, C_{32}-*H*), 3.02 (m, 2 H, C_{32}-*H*, C_{36}-*H*), 2.23 (s, 6 H, C_{36}-N(CH_3)$_2$), 1.96 (m, 1 H, C_{31}-*H*), 1.78 (m, 1 H, C_{31}-*H*), 1.34 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3), 0.96 (m, 18 H, $SiCH_2CH_3$), 0.63 (m, 12 H, $SiCH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 168.0, 139.9, 134.6, 77.4, 73.7, 70.5, 61.5, 58.4, 56.8, 41.7, 36.8, 34.9, 31.5, 18.4, 6.9, 6.8, 4.9, 4.7; TLC R_f = 0.20 (75% EtOAc/hexane). Exact mass: Calcd for $C_{28}H_{57}N_3O_6Si_2$, 588.3864; found, 588.3846 (FAB, *m*-nitrobenzyl alcohol).

[2*R*,3*R*,4*R*,*N*(3*R*)]-4-(Dimethylamino)-*N*-[3-(4-bromomethyl-2-oxazolyl)butyl]-5-methoxy-2,3-bis((triethylsilyl)oxy)valeramide (56b). To a solution of 19 mg (0.032 mmol) of alcohol **56a** and 17.0 mg (0.065 mmol) of triphenylphosphine in 1 mL of acetonitrile were added 3.8 μL (3.5 mg, 0.032 mmol) of 2,6-lutidine and 21.4 mg (0.065 mmol) of carbon tetrabromide. After 30 min, the orange solution was added to 15 mL of $NaHCO_3$, and the resulting mixture was extracted with three 15-mL portions of diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (2 × 7 cm, 75% EtOAc/hexane) afforded 17.5 mg (83%) of bromide **56b** as an oil: $[\alpha]_D$ +3.0° (*c* 0.87, CH_2Cl_2); IR (thin film) 3440, 2960, 2880, 1670, 1520, 1460, 1235, 1100, 1070, 1010, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (s, 1 H, C_{28}-*H*), 6.57 (br s, 1 H, C_{32}-N*H*), 4.34 (s, 2 H, C_{26}-*H*), 4.26 (s, 1 H, C_{34}-*H*), 4.04 (d, 1 H, *J* = 9.7 Hz, C_{35}-*H*), 3.52 (d, 2 H, *J* = 5.7 Hz, C_{37}-*H*), 3.28 (s, 3 H, OCH_3), 3.20 (m, 2 H, C_{30}-*H*, C_{32}-*H*), 3.02 (m, 2 H, C_{32}-*H*, C_{36}-*H*), 2.23 (s, 6 H, C_{36}-N(CH_3)$_2$), 1.96 (m, 1 H, C_{31}-*H*), 1.80 (m, 1 H, C_{31}-*H*), 1.35 (d, 3 H, *J* = 7.0 Hz, C_{30}-CH_3), 0.96 (m, 18 H, $SiCH_2CH_3$), 0.63 (m, 12 H, $SiCH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 168.1, 137.0, 135.8, 73.8, 70.5, 61.5, 58.4, 41.8, 36.8, 34.8, 31.5, 23.0, 18.3, 6.9, 6.8, 4.9, 4.7; TLC R_f = 0.24 (75% EtOAc/hexane).

[2*Z*,4*E*,6*E*,8*E*,10*S*,11*S*,12*R*,13*R*,15*R*,15(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-[bis(*p*-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]-dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (59a). To a solution of 212 mg (0.199 mmol) of alcohol **43a** in 4 mL of pyridine was added 35 μL (55 mg, 0.398 mmol) of phosphorus trichloride. After 10 min, during which time the solution turned red-brown, 130 μL (144 mg, 1.04 mmol) of *p*-methoxybenzyl alcohol was added. After 20 min, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and to this solution was added 406 μL (3.98 mmol) of 30% aqueous H_2O_2. The biphasic mixture was stirred vigorously for 20 min and then quenched by the addition of 75 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with 3 × 60 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (5 × 10 cm, linear gradient of 20%–35% EtOAc/hexane) afforded 231 mg (84%) of phosphate **59a** as a colorless oil: $[\alpha]^{21}_{577}$ +102.5° (*c* 1.30, CH_2Cl_2); IR (thin film) 2955, 2929, 2858, 2209, 1614, 1589, 1516, 1472, 1464, 1380, 1360, 1253, 1176, 1110, 1069, 1032, 1004, 963, 836, 775, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, 2 H, Ar*H*), 7.02 (d, 2 H, Ar*H*), 7.02 (dd, 1 H, *J* = 11.2, 14.8 Hz, C_5-*H*), 6.83 (d, 1 H, *J* = 15.2 Hz, C_4-*H*), 6.80 (d, 2 H, Ar*H*), 6.77 (d, 2 H, Ar*H*), 6.36 (d, 1 H, *J* = 11.2 Hz, C_6-*H*), 6.07 (d, 1 H, *J* = 9.1 Hz, C_9-*H*), 5.06 (s, 1 H, C_2-*H*), 5.03 (dd, 1 H, *J* = 9.3, 11.8 Hz, $POCH_2$Ar), 4.91 (dd, 1 H, *J* = 11.9, 14.0 Hz, $POCH_2$Ar), 4.76 (dd, 1 H, *J* = 5.2, 11.3 Hz, $POCH_2$Ar), 4.67 (dd, 1 H, *J* = 5.9, 11.3 Hz, $POCH_2$Ar), 4.53 (dd, 1 H, *J* = 4.7, 8.4 Hz, C_{17}-*H*), 4.48 (m, 1 H, C_{23}-*H*), 4.38 (m, 1 H, C_{13}-*H*), 4.04 (m, 1 H, C_{16}-*H*), 3.82 (m, 1 H, C_{21}-*H*), 3.78 (s, 6 H, 2 ArOCH_3), 3.65 (s, 3 H, C_{15}-OCH_3), 3.67–3.57 (m, 2 H, C_{25}-H_2), 3.53 (m, 1 H, C_{15}-*H*), 3.47 (dd, 1 H, *J* = 2.0, 7.9 Hz, C_{11}-*H*), 2.74 (m, 1 H, C_{10}-*H*), 2.07 (d, 3 H, *J* = 1.1 Hz, C_3-CH_3), 2.01 (s, 3 H, C_7-CH_3), 1.87 (s, 3 H, C_8-CH_3), 1.85–1.79 (m, 2 H, C_{12}-*H*, C_{14}-*H*), 1.74–1.65 (m, 2 H, C_{20}-*H*, C_{24}-*H*), 1.54–1.45 (m, 3 H, C_{20}-*H*, C_{22}-*H*, C_{24}-*H*), 1.24 (m, 1 H, C_{14}-*H*), 1.13 (s, 3 H, C_{18}-CH_3), 1.02 (d, 3 H, *J* = 7.0 Hz, C_{10}-CH_3), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 3 H, C_{18}-CH_3), 0.88–0.80 (m, 33 H, 3 $SiC(CH_3)_3$, C_{12}-CH_3, C_{22}-CH_3), 0.18 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), −0.02 (s, 6 H, 2 $SiCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 159.5, 156.6, 144.3, 134.7, 133.9, 133.2, 130.4, 129.4, 128.6, 128.5, 128.4, 124.1, 117.4, 114.0, 113.8, 113.6, 106.9, 94.6, 86.7 (d, J_{CP} = 7.7 Hz), 85.6 (d, J_{CP} = 5.2 Hz), 78.1, 77.6, 71.2, 69.3 (d, J_{CP} = 5.1 Hz), 68.5 (d, J_{CP} = 6.0 Hz), 68.3, 64.5, 60.6, 60.5, 55.2, 50.8, 44.9, 37.6 (d, J_{CP} = 6.1 Hz), 36.0, 33.1, 30.9, 26.4, 26.2, 26.0, 25.9, 23.0, 19.4, 18.6, 18.5, 18.3, 18.1, 17.6, 14.5, 14.1, 10.8, 10.3, −3.4, −3.6, −3.8, −3.9, −4.7, −4.9, −5.2, −5.2; TLC R_f = 0.43 (30% EtOAc/hexane). Exact mass: calcd for $C_{74}H_{128}NO_{13}PSi_4Na$, 1404.8098; found, 1404.8054 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*Z*,4*E*,6*E*,8*E*,10*S*,11*S*,12*R*,13*R*,15*R*,15(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-(2-hydroxyethyl)-3-[bis(*p*-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (59b). To a solution of 228 mg (0.165 mmol) of phosphate **59a** in 3 mL of THF in a Nalgene tube was added 2.5 mL of freshly prepared, buffered pyridinium hydrofluoride (stock solution prepared from 2.0 g of ALdrich pyridinium hydrofluoride, 4 mL of pyridine, and 16 mL of THF). After 6 h, another 0.5-mL portion of the stock solution was added. After 8 h total, the reaction mixture was poured into 75 mL of saturated aqueous $NaHCO_3$ and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (3 × 8 cm, linear gradient 35–50% EtOAc/hexane) afforded 23 mg (10%) of recovered phosphate **59a** followed by 160 mg (76%) of alcohol **59b** as a colorless oil: $[\alpha]^{20}_{577}$ +107.5° (*c* 1.03, CH_2Cl_2); IR (thin film) 3423, 2929, 2856, 2208, 1613, 1515, 1463, 1379, 1251, 1176, 1030, 962, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, 2 H, Ar*H*), 7.14 (d, 2 H, Ar*H*), 7.01 (dd, 1 H, *J* = 11.2, 15.0 Hz, C_5-*H*), 6.83 (d, 1 H, *J* = 15.0 Hz, C_4-*H*), 6.80 (d, 2 H, Ar*H*), 6.77 (d, 2 H, Ar*H*), 6.36 (d, 1 H, *J* = 11.2 Hz, C_6-*H*), 6.08 (d, 1 H, *J* = 9.1 Hz, C_9-*H*), 5.15–5.07 (m, 2 H, $POCH_2$Ar), 5.06 (s, 1 H, C_2-*H*), 4.84 (dd, 1 H, *J* = 7.8, 11.4 Hz, $POCH_2$Ar), 4.73 (dd, 1 H, *J* = 6.6, 11.4 Hz, $POCH_2$Ar), 4.59–4.56 (m, 2 H, C_{23}-*H*, C_{17}-*H*), 4.42 (m, 1 H, C_{13}-*H*), 4.10 (m, 1 H, C_{16}-*H*), 3.85 (m, 1 H, C_{25}-*H*), 3.82 (m, 1 H, C_{21}-*H*), 3.78 (s, 3 H, ArOCH_3), 3.77

(s, 3 H, ArOCH_3), 3.75 (m, 1 H, C_{25}-H), 3.67 (s, 3 H, C_{15}-OCH_3), 3.63 (m, 1 H, C_{15}-H), 3.50 (dd, 1 H, J = 1.9, 8.1 Hz, C_{11}-H), 3.02 (br m, 1 H, C_{25}-OH), 2.76 (m, 1 H, C_{10}-H), 2.06 (d, 3 H, J = 0.8 Hz, C_3-CH_3), 2.01 (s, 3 H, C_7-CH_3), 1.88 (s, 3 H, C_8-CH_3), 1.94–1.83 (m, 3 H, C_{12}-H, C_{14}-H, C_{24}-H), 1.68 (dd, 1 H, J = 3.8, 14.3 Hz, C_{20}-H), 1.48 (m, 1 H, C_{20}-H), 1.44–1.38 (m, 2 H, C_{22}-H, C_{24}-H), 1.29 (m, 1 H, C_{14}-H), 1.08 (s, 3 H, C_{18}-CH_3), 1.03 (d, 3 H, J = 7.0 Hz, C_{10}-CH_3), 0.95 (s, 9 H, SiC(CH_3)$_3$), 0.91 (s, 3 H, C_{18}-CH_3), 0.89 (s, 9 H, SiC(CH_3)$_3$), 0.87 (d, 3 H, J = 7.1 Hz, C_{12}-CH_3), 0.85 (d, 3 H, J = 7.2 Hz, C_{22}-CH_3), 0.78 (s, 9 H, SiC(CH_3)$_3$), 0.19 (s, 3 H, SiCH_3), 0.09 (s, 3 H, SiCH_3), 0.06 (s, 6 H, 2 SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.02 (s, 3 H, SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 159.5, 156.6, 144.2, 134.8, 133.9, 132.9, 130.3, 129.7, 128.7, 128.6, 128.5, 128.4, 124.1, 117.4, 114.0, 113.7, 113.6, 107.2, 94.7, 87.1 (d, J_{CP} = 6.8 Hz), 85.7 (d, J_{CP} = 5.1 Hz), 78.2, 77.3, 71.1, 69.3 (d, J_{CP} = 5.4 Hz), 68.9 (d, J_{CP} = 4.8 Hz), 68.6, 68.3, 65.0, 62.3, 60.3, 55.3, 55.2, 50.9, 44.9, 39.0, 37.6, 35.2, 32.8, 31.0, 26.5, 26.2, 25.9, 23.4, 19.4, 18.6, 18.5, 18.3, 17.7, 14.5, 14.1, 10.8, 10.7, -3.2, -3.6, -3.9, -4.1, -4.7, -5.0; TLC R_f = 0.73 (50% EtOAc/hexane). Exact mass: calcd for $C_{68}H_{114}NO_{13}PSi_3Na$, 1290.7233; found 1290.7275 (FAB, *m*-nitrobenzyl alcohol, added NaI).

[2*Z*,4*E*,6*E*,8*E*,10*S*,11*S*,12*R*,13*R*,15*R*,15(2*S*,3*S*,5*S*,7*R*,8*R*,9*S*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-(2-oxoethyl)-3-[bis(*p*-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (60). The oxidation of 159 mg (0.125 mmol) of alcohol **59b** was performed using the exact procedure used in the conversion of **40b** to **41** (121 μL, 1.50 mmol of pyridine; 265 mg, 0.625 mmol of Dess–Martin periodinane;[37] 1 h). Flash chromatograpy (3 × 8 cm, 25% EtOAc/hexane) gave 137 mg (87%) of aldehyde **60** as a white foam: $[\alpha]^{21}_{577}$ +109.6° (*c* 0.700, CH_2Cl_2); IR (thin film) 2955, 2928, 2855, 2208, 1728, 1613, 1587, 1515, 1463, 1379, 1252, 1176, 1111, 1068, 1031, 1002, 963, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.83 (t, 1 H, J = 2.4 Hz, C_{25}-H), 7.30 (d, 2 H, ArH), 7.07 (d, 2 H, ArH), 7.01 (dd, 1 H, J = 11.2, 15.0 Hz, C_5-H), 6.85–6.80 (m, 3 H, C_4-H, ArH), 6.77 (d, 2 H, ArH), 6.36 (d, 1 H, J = 11.1 Hz, C_6-H), 6.06 (d, 1 H, J = 9.1 Hz, C_9-H), 5.09–5.04 (m, 2 H, C_2-H, POCH_2Ar), 4.98 (m, 1 H, C_{23}-H), 4.90 (apparent t, 1 H, J = 12.0 Hz, POCH_2Ar), 4.73 (dd, 1 H, J = 7.1, 11.3 Hz, POCH_2Ar), 4.64 (dd, 1 H, J = 5.9, 11.3 Hz, POCH_2Ar), 4.52 (dd, 1 H, J = 4.4, 8.7 Hz, C_{17}-H), 4.39 (m, 1 H, C_{13}-H), 4.08 (m, 1 H, C_{16}-H), 3.87 (m, 1 H, C_{21}-H), 3.78 (s, 6 H, 2 ArOCH_3), 3.64 (s 3 H, C_{15}-OCH_3), 3.53–3.46 (m, 2 H, C_{11}-H, C_{15}-H), 2.74 (m, 1 H, C_{10}-H), 2.44 (m, 1 H, C_{24}-H), 2.15 (m, 1 H, C_{24}-H), 2.07 (d, 3 H, J = 0.9 Hz, C_3–CH_3), 2.00 (s, 3 H, C_7–CH_3), 1.87 (s, 3 H, C_8-CH_3), 1.85–1.79 (m, 2 H, C_{12}-H, C_{14}-H), 1.70 (dd, 1 H, J = 3.6, 14.2 Hz, C_{20}-H), 1.51–1.48 (m, 2 H, C_{20}-H, C_{22}-H), 1.25 (m, 1 H, C_{14}-H), 1.10 (s, 3 H, C_{18}-CH_3), 1.02 (d, 3 H, J = 7.0 Hz, C_{10}-CH_3), 0.94 (s, 9 H, SiC(CH_3)$_3$), 0.91 (s, 3 H, C_{18}-CH_3), 0.89 (s, 9 H, SiC(CH_3)$_3$), 0.83 (d, 6 H, C_{12}-CH_3, C_{22}-CH_3), 0.80 (s, 9 H, SiC(CH_3)$_3$), 0.18 (s, 3 H, SiCH_3), 0.08 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3), 0.05 (s, 3 H, SiCH_3), 0.03 (s, 6 H, 2 SiCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.6, 159.7, 159.6, 156.6, 144.2, 134.8, 133.9, 133.0, 130.1, 129.5, 128.6, 124.2, 119.5, 117.4, 113.8, 113.7, 107.2, 94.7, 87.1 (d, J_{CP} = 7.0 Hz), 85.4 (d, J_{CP} = 5.6 Hz), 78.2, 77.4, 71.1, 69.2, 68.6, 68.4, 63.0, 60.2, 55.2, 50.8, 46.3, 44.8, 38.2, 37.6, 32.8, 30.6, 26.5, 26.2, 26.0, 22.9, 19.4, 18.6, 18.5, 18.3, 17.6, 14.5, 14.1, 10.8, 10.5, -3.3, -3.6, -4.0, -4.7, -5.0; TLC R_f = 0.32 (30% EtOAc/hexane). Exact mass: calcd for $C_{68}H_{112}NO_{13}PSi_3Na$, 1288.7076; found, 1288.7102 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*R*)-*N*-[(3*R*)-3-[4-[(1*E*)-3-[(2*S*,3*S*,5*S*,7*R*,8*S*,9*S*)-2-[(1*R*,3*R*,4*R*,5*S*,6*S*,7*E*,9*E*,11*E*,13*Z*)-3,5-Bis(*tert*-butyldimethylsiloxy)-14-cyano-1-methoxy-4,6,8,9,13-pentamethyl-7,9,11,13-tetradecatetraenyl]-9-(*tert*-butyldimethylsiloxy)-3-[bis(*p*-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-7-yl]propenyl]-2-oxazolyl]butyl]-4-(dimethylamino)-5-methoxy-2,3-bis(triethylsiloxy)valeramide (61). To a solution of 60 mg (0.092 mmol) of bromide **56b** in 1.2 mL of DMF was added 115 μL (93 mg, 0.461 mmol) of tributylphosphine. After 30 min, the solution of **56c** thus obtained was cooled to 0 °C and used immediately in the Wittig reaction. During the formation of **56c**, a solution of lithium diisopropylamide in THF was prepared as follows: To a solution of 13 μL (9.3 mg, 0.092 mmol) of diisopropylamine in 0.7 mL of THF at -78 °C was added 60 μL (0.092 mmol, 1.53 M in hexane) of *n*-butyllithium. The solution was stirred for 10 min at -78 °C and was then warmed to 0 °C just prior to addition to the phosphonium salt/aldehyde mixture.

To the solution of phosphonium salt **56c** in DMF at 0 °C from above was added 80 mg (0.063 mmol) of aldehyde **60** in 0.6 mL of DMF (0.3 mL rinse) by cannula. The LDA solution was then added by cannula (0.3-mL THF rinse), resulting in a yellow color. The solution was stirred at 0 °C for 30 min and was then quenched by the addition of 30 mL of aqueous saturated $NaHCO_3$. The mixture was extracted with 3 × 25 mL of EtOAc, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 8 cm, 30% EtOAc/hexane) afforded 16 mg (20%) of recovered aldehyde **60**, followed by 75 mg (65%) of olefin **61** as an oil: $[\alpha]^{21}_{577}$ +105.4° (*c* 1.40, CH_2Cl_2); IR (thin film) 3436, 2956, 2930, 2880, 2856, 2208, 1676, 1613, 1588, 1516, 1463, 1379, 1304, 1253, 1176, 1097, 1068, 1032, 1004, 963, 883, 836, 775, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (s, 1 H, C_{28}-H), 7.27 (d, 2 H, ArH), 7.01 (m, 3 H, C_5-H, 2 ArH), 6.83 (d, 1 H, J = 15.0 Hz, C_4-H), 6.79 (m, 4 H, ArH), 6.55 (br t, 1 H, J = 5.9 Hz, N-H), 6.36 (d, 1 H, J = 11.1 Hz, C_6-H), 6.16 (m, 2 H, C_{25}-H, C_{26}-H), 6.07 (d, 1 H, J = 9.0 Hz, C_9-H), 5.06 (s, 1 H, C_2-H), 5.01 (dd, 1 H, J = 9.3, 11.8 Hz, one of ArCH_2OP), 4.91 (dd, 1 H, J = 11.9, 14.0 Hz, one of ArCH_2OP), 4.78 (dd, 1 H, J = 5.1, 11.3 Hz, one of ArCH_2OP), 4.66 (dd, 1 H, J = 5.6, 11.2 Hz, one of ArCH_2OP), 4.57 (m, 1 H, C_{23}-H), 4.54 (dd, 1 H, J = 4.9, 8.3 Hz, C_{17}-H), 4.37 (m, 1 H, C_{13}-H), 4.26 (s, 1 H, C_{34}-H), 4.09 (m, 1 H, C_{16}-H), 4.05 (d, 1 H, J = 10.0 Hz, C_{35}-H), 3.84 (m, 1 H, C_{21}-H), 3.78 (s, 3 H, ArOCH_3), 3.77 (s, 3 H, ArOCH_3), 3.66 (s, 3 H, C_{15}OCH_3), 3.59 (m, 1 H, C_{15}-H), 3.53 (m, 2 H, C_{37}-H_2), 3.47 (dd, 1 H, J = 2.0, 8.1 Hz, C_{11}-H), 3.28 (s, 3 H, C_{37}OCH_3), 3.26–3.13 (m, 2 H, C_{32}-H_2), 3.07 (m, 1 H, C_{36}-H), 2.98 (m, 1 H, C_{30}-H), 2.73 (m, 1 H, C_{10}-H), 2.37 (m, 1 H, C_{24}-H), 2.23 (s, 6 H, N(CH_3)$_2$), 2.21 (m, 1 H, C_{24}-H), 2.07 (d, 3 H, J = 1.1 Hz, C_3-CH_3), 2.01 (s, 3 H, C_7-CH_3), 1.95 (m, 1 H, C_{31}-H), 1.87 (s, 3 H, C_8-CH_3), 1.85–1.77 (m, 2 H, C_{12}-H, C_{14}-H), 1.75 (m, 1 H, C_{31}-H), 1.70 (m, 1 H, C_{20}-H), 1.59 (m, 1 H, C_{22}-H), 1.48 (m, 1 H, C_{20}-H), 1.32 (d, 3 H, J = 7.0 Hz, C_{30}-CH_3), 1.26 (m, 1 H, C_{14}-H), 1.16 (s, 3 H, C_{18}-CH_3), 1.02 (d, 3 H, J = 7.0 Hz, C_{10}-CH_3), 0.98–0.92 (m, 27 H, 2 Si(CH_2CH_3)$_3$, SiC(CH_3)$_3$), 0.90 (s, 3 H, C_{18}-CH_3), 0.85 (s, 9 H, SiC(CH_3)$_3$), 0.84 (s, 9 H, SiC(CH_3)$_3$), 0.82–0.79 (m, 6 H, C_{12}-CH_3, C_{22}-CH_3), 0.69–0.59 (m, 12 H, 2 Si(CH_2CH$_3$)$_3$), 0.19 (s, 3 H, SiCH_3), 0.08 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3), 0.04 (s, 3 H, SiCH$_3$), 0.03 (s, 3 H, SiCH_3), -0.02 (s 3 H, SiCH$_3$): ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 167.3, 159.8, 159.5, 156.6, 144.2, 138.8, 134.7, 133.9, 133.4, 133.0, 130.4, 130.3, 129.4, 128.5, 128.2, 127.6, 124.1, 120.5, 117.4, 113.8, 113.6, 107.2, 94.6, 86.4 (d, J_{CP} = 7.7 Hz), 85.4 (d, J_{CP} = 3.4 Hz), 77.9 (d, J_{CP} = 4.4 Hz), 77.5, 73.8, 71.2, 70.5, 69.3 (d, J_{CP} = 6.7 Hz), 68.4, 65.9, 61.6, 60.2, 58.3, 55.2, 51.0, 44.9, 41.7, 37.5, 36.8, 35.9, 35.4, 34.9, 32.9, 31.6, 30.8, 26.4, 26.2, 25.9, 22.8, 19.4, 18.6, 18.4, 18.3, 18.3, 18.2, 17.6, 14.5, 14.0, 10.7, 9.7, 6.9, 6.8, 5.0, 4.7, -3.4, -3.7, -3.7, -4.1, -5.0; TLC R_f = 0.22 (30% EtOAc/hexane). Exact mass: calcd for $C_{96}H_{168}N_4O_{17}PSi_5$, 1821.1010; found, 1821.0914 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(+)-Calyculin A (1). To a solution of 72 mg (0.040 mmol) of **61** in a Nalgene tube was added 3 mL of freshly prepared HF solution (stock solution prepared from 500 μL of 48% aqueous HF, 8.6 mL of MeCN, and 900 μL of H_2O). Two additional 1-mL portions of the stock solution were added after 40 and 72 h. After a total reaction time of 92 h, the solution was poured into 30 mL of 1 M HCl and extracted with 3 × 30 mL of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (3 × 7 cm, linear gradient of 0%–10% MeOH/CH_2Cl_2) afforded 28 mg (70%) of synthetic calyculin A as a glass: $[\alpha]_D$ +60° (*c* 0.10, EtOH);[57] IR (CCl_4), 3531, 3315, 3165, 2969, 2933, 2212, 1647, 1591, 1536, 1468, 1447, 1379, 1114, 1065, 1012, 960 cm^{-1};[62] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 12.15 (br s, 1 H, OH), 11.81 (br s, 1 H, OH), 8.22 (br d, 1 H, J = 8.7 Hz, amide NH), 7.71 (br d, 1 H, J = 10.6 Hz, OH), 7.32 (s, 1 H, C_{28}-H), 6.98 (dd, 1 H, J = 11.2, 15.0 Hz, C_5-H), 6.94 (m, 1 H, C_{25}-H), 6.83 (d 1 H, J = 14.9 Hz, C_4-H), 6.55 (s, 1 H, OH), 6.35 (d, 1 H, J = 11.1 Hz, C_6-H), 6.22 (d, 1 H, J = 9.5 Hz, C_9-H), 6.15 (d, 1 H, J = 9.9 Hz, OH), 6.11 (dd, 1 H, J = 1.4, 16.2 Hz, C_{26}-H), 6.06 (s, 1 H, OH), 5.06 (s, 1 H, C_2-H), 4.49 (d, 1 H, J = 10.1 Hz, C_{34}-H), 4.33 (m, 1 H, C_{23}-H), 4.08 (dd, 1 H, J = 3.7, 10.4 Hz, C_{17}-H), 4.05 (m, 2 H, C_{32}-H, C_{36}-H), 4.00 (m, 1 H, C_{16}-H), 3.95 (dd, 1 H, J = 8.9, 12.6 Hz, C_{37}-H), 3.85 (m, 1 H, C_{21}-H), 3.76 (apparent t, 1 H, J = 9.7 Hz, C_{15}-H), 3.70 (dd, 1 H, J = 2.1, 12.6 Hz, C_{37}-H), 3.60 (m, 1 H, C_{35}-H), 3.58 (dd, 1 H, J = 1.8, 9.6 Hz, C_{11}-H), 3.51 (s, 3 H, C_{15}-OCH_3), 3.45 (m, 1 H, C_{13}-H), 3.41 (s, 3 H, C_{37}-OCH_3), 3.21 (m, 1 H, C_{30}-H), 3.03 (m, 1 H, C_{32}-H), 2.88 (s, 3 H, N-CH_3), 2.80 (s, 3 H, N-CH_3), 2.77 (m, 1 H, C_{10}-H), 2.47 (m, 1 H, C_{24}-H), 2.04 (s, 6 H, C_3-CH_3, C_7-CH_3), 1.96 (m, 1 H, C_{24}-H), 1.92 (m, 1 H, C_{31}-H), 1.87 (s, 3 H, C_8-CH_3), 1.84–1.76 (m, 3 H, C_{14}-H, C_{20}-H, C_{31}-H), 1.71 (m, 1 H, C_{22}-H), 1.61–1.54 (m, 2 H, C_{14}-H, C_{20}-H), 1.46 (m, 1 H, C_{12}-H), 1.32 (d, 3 H, J = 6.8 Hz, C_{30}-CH_3), 1.24 (s, 3 H, C_{18}-CH_3), 1.05 (d, 3 H, J = 6.9 Hz, C_{10}-CH_3), 0.91 (s, 3 H, C_{18}-CH_3), 0.88 (d, 3 H, J = 7.1 Hz, C_{22}-CH_3), 0.60 (d, 3 H, J = 6.7 Hz, C_{12}-CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.3, 170.0, 156.3, 144.7, 137.4, 134.8, 133.9, 133.8, 132.8, 132.6, 128.3, 123.8, 117.3, 116.2, 108.8, 94.7, 84.9 (d, J_{CP} = 5.2 Hz), 82.1 (d, J_{CP} = 5.7 Hz), 80.9, 77.4, 75.0, 73.5, 71.5, 69.0, 67.2, 65.8, 63.8,

(62) There is some discrepancy between these IR signals and those reported by Fusetani for natural calyculin A.[5] However, the IR spectrum of a natural sample kindly provided by Professor N. Fusetani is completely superimposable with the spectrum of our synthetic material.

60.9, 59.0, 50.2, 44.4, 42.3, 38.5, 37.8, 37.5, 36.1, 36.0, 34.5, 33.7, 29.7, 28.6, 22.5, 19.3, 18.0, 17.6, 17.5, 14.1, 13.8, 12.8, 10.9; TLC R_f = 0.25 (5% MeOH/CH_2Cl_2). Exact mass: calcd for $C_{50}H_{81}N_4O_{15}PNa$, 1031.5333; found, 1031.5358 (FAB, *m*-nitrobenzyl alcohol, added NaI).

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Supplementary Material Available: Full experimental details and complete analytical data for **6** → **7**, **9** → **10**, **11** → **12**, **15** → **16**, **22** → **23a**, **29a** → **29b**, **29b** → **30**, **31** → **32**, **40a** → **40b**, **49a** → **49b**, and **54a** → **54b** and the stereochemical proof of **48** (4 pages). Ordering information is given on any current masthead page.

Insertion of Transition Metals into the Phosphorus-Phosphorus Bond of 1,2-Dihydro-1,2-diphosphetes: Toward the Phosphorus Analogues of Metal Dithiolene Complexes

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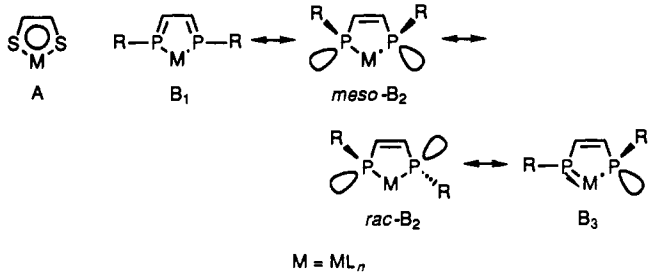
Abstract: The Insertion of NiL_2 (L = phosphine) into the P-P bond of 1,2,3,4-tetraphenyl-1,2-dihydro-1,2-diphosphete has been achieved via two methods. In the first, the P-P bond is initially cleaved with lithium and the derivatized dianion allowed to react with $[NiCl_2L_2]$. This yields primarily a nickeladiphospholene with a distorted square-planar geometry at the metal in which the chelating ligand acts as a (1 + 1) electron donor, and the metal is formally in the +2 oxidation state. The second route involves the direct insertion of a $[NiL_2]$ fragment into the P-P bond at low temperature. In this case the results suggest the formation of a 1,4-diphosphadiene complex of nickel(0) in which the ligand acts as a (2 + 2) electron donor and the geometry at the metal is tetrahedral. Although both forms can be isolated for some coligands, only one form is observed in several cases and isomerization between the two forms has been observed in the other cases. The second route has also been transposed to platinum. The crystal structures of the $Ni(Ph_2PCH_2CH_2PPh_2)$ and $Pt(PPh_3)_2$ complexes have been studied and a distortion from planarity observed in each case as shown by interplane LML/PMP angles of 38° and 57°, respectively. The phosphorus atoms are closer to planarity and the ring C=C bond lengths longer in the platinum complex than in the nickel. The platinum complex can be seen as lying halfway between a 1,4-diphospholene platinum(II) and a 1,4-diphosphadiene platinum(0) complex. This work suggests that with an adequate choice of coligand and substitution pattern it would be possible to achieve an electronic delocalization similar to that observed in metal-dithiolenes.

The metal dithiolene structure (A) is characterized by the indeterminate nature of the metal oxidation state. This kind of metallacycle finds numerous applications as redox catalysts, dyes, organic conductors, etc.[1] We thought it would be interesting to prepare the analogous metalladiphospholenes (B).



To the best of our knowledge no such potentially delocalized metallacycle has been structurally characterized in the literature although two iridadiphospholenes have been identified in solution by NMR spectroscopy.[2] There is an obvious correlation between the oxidation state of the metal and the structure of the ring in a metalladiphospholene. The mesomeric formula (B_1), where the metal is in the 0 oxidation state, corresponds to (2 + 2) electron donation from the chelating ligand, with planar phosphorus atoms, two P=C double bonds, and a C-C single bond. Conversely, the mesomeric formula (B_2), where the metal is in the +2 oxidation state, corresponds to (1 + 1) electron donation from the chelating ligand, with pyramidal phosphorus atoms, two intracyclic P-C single bonds, and a C=C double bond. The presence of two chiral phosphorus atoms in this latter case implies two possible diastereoisomers (meso and racemic). Finally the mesomeric formula (B_3), with the metal still in the +2 oxidation state, corresponds to (3 + 1) electron donation from the chelating ligand, with one pyramidal and one planar phosphorus atom, one single and one double M-P bond, but two P-C single bonds and a C=C double bond as in (B_2).

Situations corresponding to *meso*-B_2, *rac*-B_2, and B_3 have been identified by Lappert and co-workers[3] in the study of benzo analogues with zirconium, tin, or boron as the metal. A priori, benzo annellation has an adverse effect on the electronic delo-

(1) For recent reviews on metal dithiolenes see: Mueller-Westerhoff, U. T.; Vance, B. Dithiolenes and Related Species. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 2, pp 595-631. Mueller-Westerhoff, U. T.; Vance, B.; Yoon, D. I. *Tetrahedron* **1991**, *47*, 909.

(2) Phillips, I. G.; Ball, R. G.; Cavell, R. G. *Inorg. Chem.* **1988**, *27*, 2269.

(3) Bohra, R.; Hitchcock, P. B.; Lappert, M. F.; Leung, W.-P. *Chem. Soc., Chem. Commun.* **1989**, 728.

0002-7863/92/1514-9453$03.00/0