Asymmetric Synthesis of the Benzoquinoid Ansamycin Antitumor Antibiotics: Total Synthesis of (+)-Macbecin

David A. Evans,* Scott J. Miller,[1] and Michael D. Ennis[1]

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received July 24, 1992

A convergent asymmetric synthesis of the antitumor antibiotic macbecin I has been achieved. Six of the seven stereogenic centers within the target structure were controlled using asymmetric aldol methodology, while the final stereogenic center was established through internal asymmetric induction. Fragment coupling was accomplished using a mild, titanium tetrachloride mediated aldol reaction. The C_1–C_5 unsaturated dienic ester was stereoselectively incorporated through a kinetically controlled Horner–Emmons olefination. Macrolactamization and subsequent refunctionalization afforded macbecin I.

The benzoquinoid antibiotics, the macbecins, the herbimycins, and geldanamycin, are representative of an emerging class of ansa-bridged macrocyclic lactams possessing a significant range of antitumor activity.[2] Macbecin I, along with its hydroquinone analog, macbecin II, were isolated in 1980.[2] The structure and absolute stereochemistry of this natural product were subsequently determined by X-ray crystallography.[3] An X-ray structure has also been obtained for herbimycin A (Figure 1),[4] and although this study did not include an absolute configurational assignment, this issue has been resolved through a recently reported asymmetric synthesis.[5] Finally, the stereochemical relationships in geldanamycin have not yet been reported despite the fact that this antibiotic was the first of the benzoquinoid ansamycins to have been isolated.[6]

Recent studies have indicated that the benzoquinoid ansamycins, specifically the herbimycins, have antitumor functions. In addition to reversing the characteristics of oncogene expression,[7] herbimycin A has been shown to have potent antiangiogenic activity.[8] This latter biological activity distinguishes the benzoquinoid ansamycins from their benzenoid[9] and naphthoquinoid[10] ansamycin relatives.

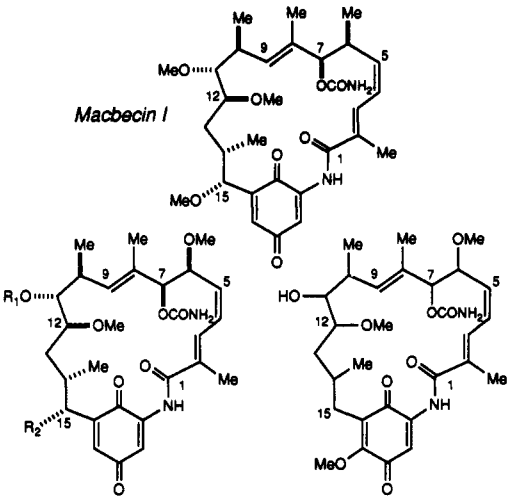


Figure 1. Representative benzoquinoid antibiotics.

Solid-State Structure.[11] The Muroi X-ray structure of macbecin I lacking the C_7 urethane moiety is provided in Figure 2.[3] By inspection, it is evident that nonbonding interactions, particularly in the C_6–C_{10} region, along with ring unsaturation, significantly restrict the number of low-energy conformations of the macrocycle. In particular, the C_8 methyl group is the focal point of both an A(1,3) allylic strain interaction with the C_{10} substituents and a potential gauche pentane interaction with the carbon substituents at C_6. In entertaining a synthesis of macbecin, we were aware of the fact that an unprotected C_7 hydroxyl substituent possessed the capacity to undergo an intramolecular conjugate addition to the dienic amide at C_3. However, the local conformational constraints in this region of the structure serve to orient the C_7 oxygen away from the interior of the macrocycle and the electrophilic C_3 center. It is also significant that the diene electrophilicity is probably further reduced by the constraints of

(1) National Science Foundation Predoctoral Fellow: S.J.M. (1989–1992), M.D.E. (1979–1982).

(2) (a) Yamaki, H.; Iguchi-Ariga, S.; Ariga, H. *J. Antibiot.* **1989**, *42*, 604–610. (b) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiot.* **1980**, *33*, 199–204.

(3) Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123–1130.

(4) Herbimycin A. (a) Omura, S.; Nakagawa, A.; Matsumoto, T.; Furusaki, A. *J. Antibiotics* **1980**, *33*, 781–782. (b) Omura, S.; Iwai, Y.; Takahashi, Y.; Sadakane, N.; Nakagawa, A.; Oiwa, H.; Hasegawa, Y.; Ikai, T. *J. Antibiot.* **1980**, *32*, 261–262. (c) Omura, S.; Sadakane, N.; Nakagawa *Tetrahedron Lett.* **1979**, 4323–4326. Herbimycin B. (d) Iwai, Y.; Nakagawa, A.; Sadakane, N.; Omura, S.; Oiwa, H.; Matsumoto, S.; Takahashi, M.; Ikai, T.; Ochiai, Y. *J. Antibiot.* **1980**, *33*, 1114–1119. Herbimycin C. (e) Shibata, K.; Satsumabayashi, S.; Nakagawa, A.; Omura, S. *J. Antibiot.* **1986**, *39*, 1630–1633.

(5) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T., Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 6015–6018.

(6) (a) DeBoer, C.; Meulman, R.; Wnuk, R. J.; Peterson, J. *J. Antibiot.* **1970**, *23*, 442. (b) Sasaki, K.; Rinehart, K. L., Jr.; Slomp, G. S.; Grostic, M. F.; Olson, E. C. *J. Am. Chem. Soc.* **1970**, *92*, 7591–7593.

(7) Uehara, Y.; Murakami, Y.; Suzukake-Tsuchiya, K.; Moriya, Y.; Sano, H.; Shibata, K.; Omura, S. *J. Antibiot.* **1988**, *41*, 831–834.

(8) (a) Oikawa, T.; Hirotani, K.; Shimamura, M.; Ashino-Fuse, H.; Iwaguchi, T. *J. Antibiot.* **1989**, *42*, 1202–1204. (b) Yamashita, T.; Sakai, M.; Kawai, Y.; Aono, M.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1015–1017.

(9) Tanida, S.; Hasegaw, T.; Hatano, K.; Higashide, E.; Yoneda, M. *J. Antibiot.* **1980**, *33*, 192–198.

(10) Wehrli, W.; Staehelin, M. *Bacteriol. Rev.* **1971**, *35*, 290–309.

(11) The numbering systems appearing in the literature for the macbecin and herbimycin skeletons differ, with neither adhering to the accepted IUPAC rules. The numbering system chosen for the discussion is that corresponding to the numbering system for the seco acid and identical to that used for herbimycin; however, the IUPAC names of macbecin derivatives reported in the Experimental Section are those derived from the 2-azabicyclo[16.3.1]docosane ring system.

0022-3263/93/1958-0471$04.00/0

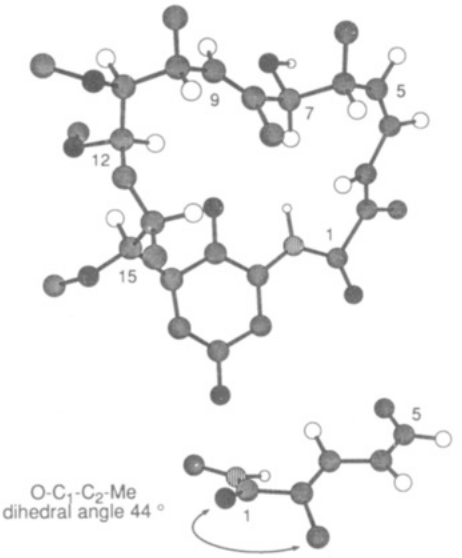


Figure 2. Partial X-ray structure of macbecin I.[3]

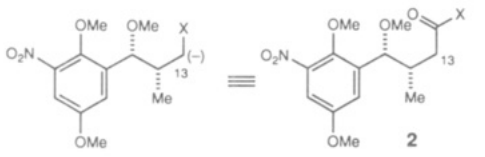
the macrocycle which deconjugates the carbonyl moiety from the C_2–C_3 double bond. This is evident from the illustrated O–C_1–C_2–Me dihedral angle of 44°.

Both the structural complexity and the promising antitumor potential of these molecules have made this family of antitumor agents attractive as targets for total synthesis.[12] In addition to the present study,[13] the asymmetric synthesis by Baker[14] and formal syntheses of macbecin by Martin[15] and Kallmerten[16] have been reported. Recently, the first synthesis of herbimycin A has also been completed by Tatsuta.[5]

Synthesis Plan. The prominent stereochemical motif in both macbecin and the herbimycins are the three pairs of stereochemically related vicinal, stereogenic centers at C_6–C_7, C_{10}–C_{11}, and C_{14}–C_{15}. For the projected macbecin synthesis it was anticipated that all three of the syn methyl–oxygen relationships might be established by the illustrated asymmetric boron aldol addition process (eq 1)[17] while a herbimycin synthesis might employ, in addition to two iterations of this reaction, the related alkoxyacetate variant (eq 2) to provide six of the seven stereogenic centers in the target structures. The disconnection strategy which was followed for the macbecin seco acid is illustrated in Scheme I. The important C_{12}–C_{13} bond construction anticipated for the union of the aromatic and C_5–C_{12} fragments required the use of some type of removable carbanion-stabilizing functional group, X. As an added constraint on the selection of this activating group, it was our desire to carry the aromatic nitrogen substituent through the assemblage of the seco acid as a nitro group, thus eliminating the necessity of protecting this heteroatom at intermediate points in the synthesis. In the following discussion we describe studies culminating in the successful asymmetric synthesis of (+)-macbecin I.[18]

Results and Discussion

C_{13}–C_{21} Aromatic Fragment. The synthesis plan for this macbecin fragment hinged on the identification of a removable carbanion-stabilizing "X" group to be employed for C_{13} activation and coupling. While a number of options were explored (X = –I, –SPh, –SOPh, $-SO_2Ph$, $-PPh_3$, $-POPh_2$), that derivative wherein X was a carboxyl function was ultimately selected. It is noteworthy that, with the exception of the case where X = CO_2R, all other activating groups required that the nitro group be sacrificed (i.e., reduced and protected) at some point during the fragment coupling sequence. Thus, the specific identity of the aromatic synthon was designated as **2**.



The synthesis of **2** began with the construction of the illustrated aromatic aldehyde[19] which was prepared in two high-yielding steps (Scheme II). Sequential nitration and methylation of 2-hydroxy-5-methoxybenzaldehyde proceeded in 71% overall yield to afford 2,5-dimethoxy-3-nitrobenzaldehyde as a yellow crystalline solid. Treatment of this aldehyde with the (*Z*) boron enolate derived from imide **1a**[20] according to the standard conditions[17] then afforded the desired aldol adduct **3** (80%) as a single diastereomer.

Conversion of this aldol adduct to the completed aromatic acid required two necessary operations. In the first of these required transformations, conversion of the C_{15} hydroxyl moiety in **3** into the derived methyl ether **4** was carried out under sufficiently mild conditions (Me_3OBF_4, proton sponge[21]) so that the potential problem of retroaldolization was avoided. With this intermediate in hand, the one-carbon homologation via the Wolff rearrangement[22] was addressed. Imide **4** was first treated with lithium hydrogen peroxide[23] to provide the derived acid **5** (95%) which was transformed into the diazoketone with

(12) (a) Baker, R.; Cummings, W. J.; Hayes, J.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1237–1239. (b) Baker, R.; Castro, J.; Swain, C. *Tetrahedron Lett.* **1988**, *29*, 2247–2250. (c) Baker, R.; Castro, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 190–192. (d) Baker, R.; Castro, J. *J. Chem. Soc., Chem. Commun.* **1989**, *378*–381. (e) Baker, R.; Castro, J. *J. Chem. Soc., Chem. Commun.* **1990**, 47–65. (f) Pearson, A. *Synlett* **1990**, *1*, 9–19. (g) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (h) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496–5498.

(13) (a) Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067–1069. (b) For an earlier approach to the synthesis of macbecin see: Evans, D. A. *Proceedings of The Robert A. Welch Foundation Conferences on Chemical Research. XXXVII. Stereospecificity in Chemistry and Biochemistry*; Houston, TX, 1983; p 13–49.

(14) (a) Baker, R.; Castro, J. *J. Chem. Soc., Chem. Commun.* **1989**, 378–381. (b) Baker, R.; Castro, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65.

(15) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, *57*, 1070–1072.

(16) (a) Coutts, S.; Wittman, M.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301–4304. (b) Coutts, S.; Kallmerten, J. *Ibid.* **1990**, *31*, 4305–4308.

(17) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. For a detailed procedure for carrying out the aldol reactions see: Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83–91.

(18) For early studies on the synthesis see: (a) Evans, D. A.; Ornstein, P. L.; Ennis, M. D. 187th National Meeting of the American Chemical Society, St. Louis, April 8–13, 1984; MEDI-154. (b) Ennis, M. D. Ph.D. Dissertation, California Institute of Technology, 1983.

(19) Rubenstein, L. *J. Chem. Soc.* **1925**, *127*, 1998–2004.

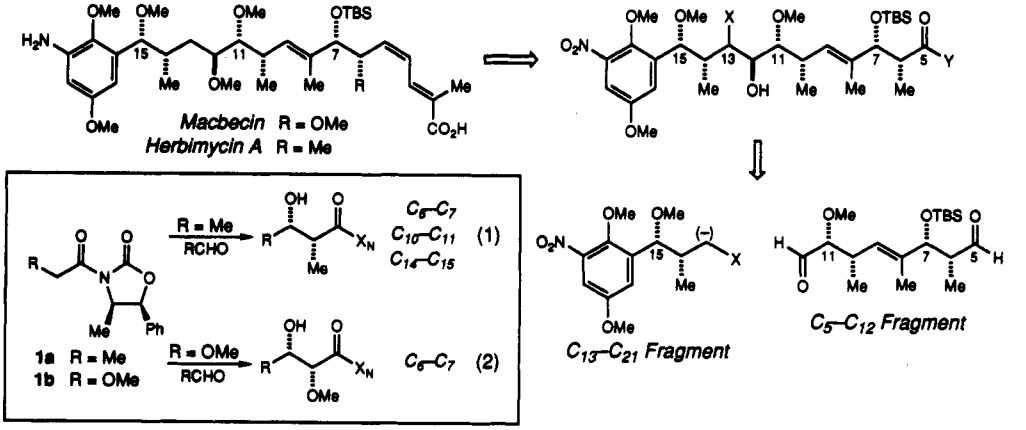
(20) For experimental procedures for the synthesis of **1a** see: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.

(21) Diem, M. J.; Burow, D. F.; Fry, J. L. *J. Org. Chem.* **1977**, *42*, 1801–1802.

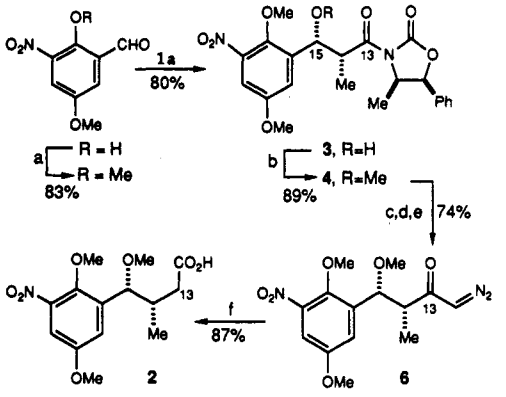
(22) (a) Meier, H.; Zeller, K. P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32–43. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513–3518. (c) Teshima, T.; Matsumoto, T.; Wakamiya, T.; Shiba, T.; Armaki, Y.; Nakajima, T.; Kawai, N. *Tetrahedron Lett.* **1991**, *47*, 3305–3312.

(23) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

Scheme I



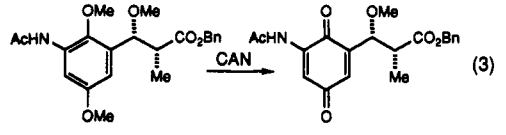
Scheme II[a]



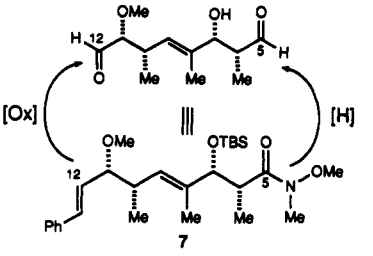
[a] Key: (a) NaH, MeI; (b) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 25 °C; (c) LiOOH, THF/H_2O; (d) $(ClCO)_2$, DMF, CH_2Cl_2; (e) CH_2N_2, Et_2O/CH_2Cl_2, 0 °C; (f) $AgNO_3$, THF/H_2O, 25 °C.

excess diazomethane via the intermediate acid chloride in 74% overall yield. The Wolff rearrangement was found to proceed very cleanly under the influence of silver nitrate in THF/H_2O to afford the aromatic synthon **2** in 87% yield. In contrast, attempts to promote the Wolff rearrangement photochemically resulted in extensive decomposition with only trace amounts of the desired product being isolated.

With the aromatic synthon **2** in hand, its viability as a precursor to the quinoid nucleus was evaluated. Accordingly, the hydroquinone dimethyl ether **5** was transformed into a suitable aromatic amide model system for the completed macrocycle. The oxidation of this hydroquinone derivative with ceric ammonium nitrate[24] was accomplished in good yield (eq 3) to provide a precedent for this transformation.



C_5–C_{12} Fragment. The operational equivalent **7** for the C_5–C_{12} dialdehyde synthon which was selected is illustrated below. Each aldehyde function, incorporated as an olefinic and amidic[25] equivalent, respectively, is accessible through oxidation or reduction of the desired terminus.[26] As with the aromatic synthon, the construction

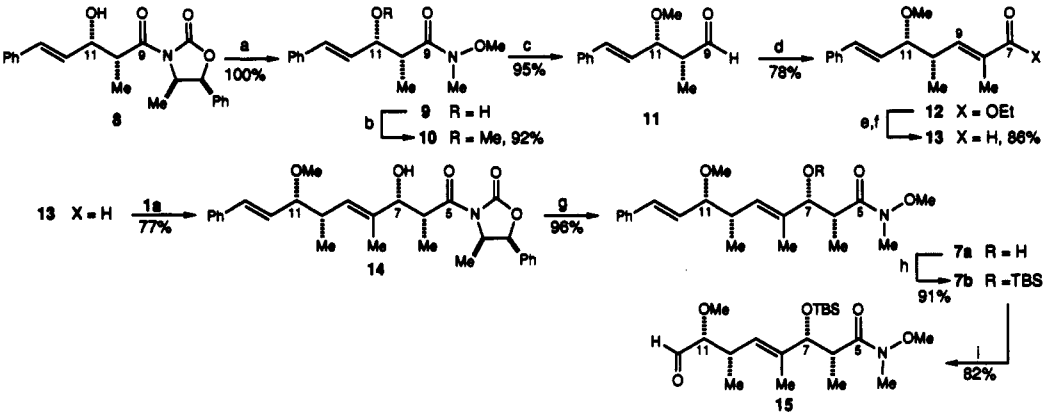


of this fragment centered around the incorporation of the four stereocenters through the successive use of the chiral propionate imide **1a** in the illustrated aldol reactions (Scheme III). Treatment of *trans*-cinnamaldehyde with the boron enolate derived from imide **1a** according to the standard conditions[17] afforded the aldol adduct **8** (70%) in high diastereomeric purity. Subsequent transamination of **8** with the aluminum amide reagent derived from *N,O*-dimethylhydroxylamine[25] provided the *N*-methoxy-*N*-methylamide **9** which was methylated in high yield (MeI, NaH, THF/DMF, 0 °C) to provide the derived C_{11} methyl ether **10** in 94% yield. As expected, DIBAL-H reduction afforded aldehyde **11** which was transformed into the homologated (*E*) trisubstituted olefinic ester **12** with (carbethoxymethylene)triphenylphosphorane[27] in refluxing toluene. Capillary GLC analysis revealed the reaction produced a 94:6 mixture of olefin isomers from which the major (*E*) isomer **12** was isolated by chromatography in 78% yield. The second iteration of the chiral propionate aldol reaction to give **14** and its subsequent transamination to the assembled fragment **7a** proceeded in good yield as did the protection of the C_7 hydroxyl function.

The effectiveness of intermediate **7** in the synthesis scheme required the selective oxidation of the disubstituted olefin. This transformation was realized in the presence of the trisubstituted olefin[28] with osmium tetraoxide (20 mol %) using *N*-methylmorpholine *N*-oxide (1.1 equiv) as the reoxidant according to the conditions of VanRheenen and Kelly.[29] ^1H NMR spectroscopic analysis of the intermediate diol indicated that no detectable

(24) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629.
(25) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.
(26) A similarly designed synthon was also emloyed in the synthesis of X-206: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2505–2526.
(27) Kishi, Y.; Johnson, M. R. *Tetrahedron Lett.* **1979**, 4347–4750.
(28) For an interesting example see: Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368–4378.
(29) VanRheenen, V.; Kelley, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.

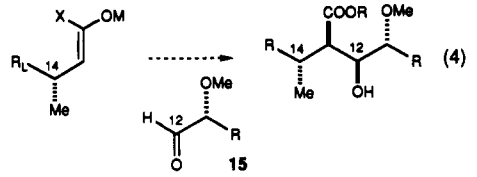
Scheme III[a]



[a] Key: (a) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2; (b) MeI, NaH, THF/DMF, 0 °C; (c) DIBAL-H, CH_2Cl_2; (d) $Ph_3P{=}C(Me)CO_2Me$, toluene, reflux; (e) DIBAL-H, CH_2Cl_2 -78 °C; (f) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, -60 °C; (g) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2; (h) TBSCl, imidazole, DMF, 25 °C; (i) OsO_4, NMO, *t*-BuOH/THF/H_2O; $NaIO_4$, $NaHCO_3$.

oxidation of the trisubstituted olefin had occurred. Cleavage of the diol with sodium periodate afforded the desired aldehyde **15** in 82% yield.

Fragment Coupling. Due to the constraints of the nitro function in the C_{13}–C_{21} aromatic acid moiety, which precluded the use of strong bases for example, a mild aldol union of the two fragments was chosen. In the initial analysis of this reaction, it was concluded that the most desirable coupling would be the (*E*) enolate derived from the aromatic fragment **2** with the aldehyde **15**. In this double stereodifferentiating aldol reaction both enolate and aldehyde face selectivity would be expected to operate in concert to afford the illustrated adduct having the desired hydroxyl stereochemistry at C_{12} (eq 4).[30]

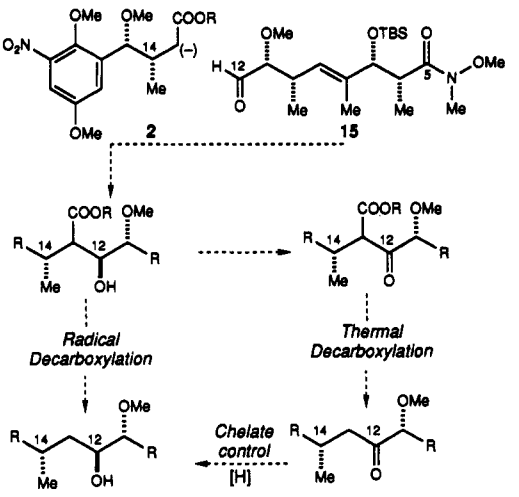


(4)

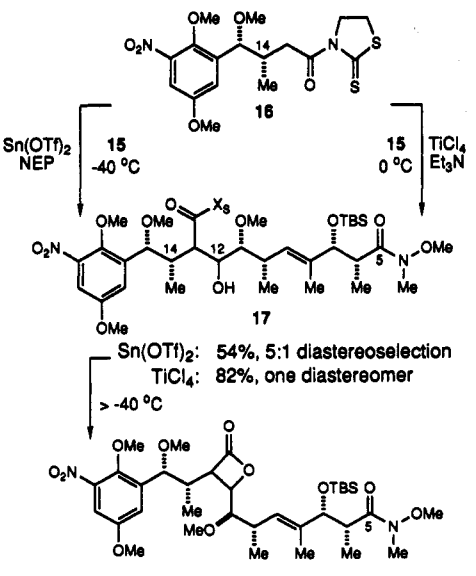
In the event that this option were to be pursued, a subsequent radical-mediated decarboxylation would complete the assemblage process (Scheme IV). In a variant of this strategy which postpones establishing the C_{12} hydroxyl center until the last step, decarboxylation might be achieved through the derived β-keto acid. A final chelate-controlled reduction of the C_{12} ketone would also complete the stereoselective coupling process.

Our initial plan was to form the bis-boryl enediolate derived from **2** (*n*-Bu_2BOTf, Et_3N, 0 °C) based on the precedent established in these laboratories some years ago.[31] However, when these conditions failed to result in appreciable amounts of enolization in the face of apparent labilization of the C_{15} methoxyl moiety, **2** was transformed into its derived 2-mercaptothiazoline[32] derivative **16** with the intention of increasing the acidity of the substrate (Scheme V). When thioimide **16** was transformed into its

Scheme IV



Scheme V



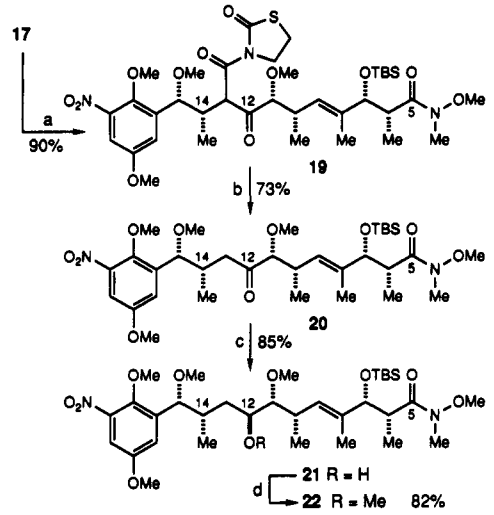
derived boron enolate (*n*-Bu_2BOTf, Et_3N, 0 °C), and subsequently treated with benzaldehyde, a 1:1:1 mixture of starting material, desired aldol adducts, and byproducts where the C_{15}-methoxyl had been lost were obtained. Other Lewis acid/base enolization variants were evaluated with the hope of suppressing the side reaction at C_{15}. Following

(30) This analysis presumes that nonchelate-controlled stereoinduction imparted by the aldehyde coupling partner from the C_{11} methoxyl substituent would be dominant.

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

(32) (a) Hsiao, C. N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206. (b) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903.

Scheme VI[a]



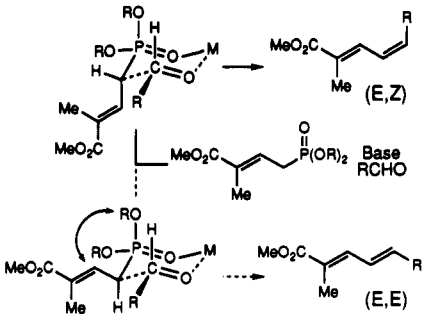
[a] Key: (a) Dess–Martin periodinane, pyridine/CH_2Cl_2, 25 °C; (b) LiOH, THF/H_2O, 25 °C; (c) $Zn(BH_4)_2$, cyclohexene, Et_2O, −78 to +20 °C; (d) Me_3OBF_4, Proton Sponge, CH_2Cl_2, 25 °C.

literature precedent,[33] the Sn(II) triflate/*N*-ethylpiperidine (NEP) reagent pair was found to effectively mediate the coupling process to provide a 54% yield of aldol products, obtained as a mixture of diastereomers. It is interesting to note that at temperatures above −40 °C the Sn(II)-aldolate is unstable and readily undergoes cyclization to the corresponding β-lactone **18**. Even better results were obtained using the titanium tetrachloride/triethylamine enolization procedure recently developed in these laboratories.[34] Enolization of imide **16** (1.05 equiv of $TiCl_4$, 1.10 equiv of Et_3N, CH_2Cl_2, 0 °C, 1 h) followed by addition of aldehyde **15** (0 °C, 3.3 h) afforded 73% of aldol adduct **17** as a single diastereomer, along with 9% of recovered aldehyde and complete recovery of unreacted imide **16**.

It is interesting that the titanium aldol reaction proceeds with complete stereocontrol. Although we have not definitively established the absolute stereochemical relationships at C_{12} and C_{13}, we have confirmed that the reaction exhibits syn aldol diastereoselection from an analysis of the stereochemistry of the derived β-lactone **18** readily obtained from **17** (K_2CO_3, THF, reflux, 88%). The trans stereochemical assignment in **18** is based on the characteristic vicinal coupling constants between the C_{12} and C_{13} protons (3.7 Hz).[35]

After considerable experimentation, it was concluded that decarbonylation of carboxylic acid derivatives derived from hydroxythioimide **17** via radical precursors (e.g., *O*-acyl thiohydroxamates,[36] selenium ester[37]) was not practical due either to intervening β-lactone formation at the decarbonylation reaction temperatures (refluxing benzene) or to competitive reduction of the nitro group. At this point the alternative decarboxylation option was explored (Scheme VI). Aldol adduct **17** was readily

Scheme VII



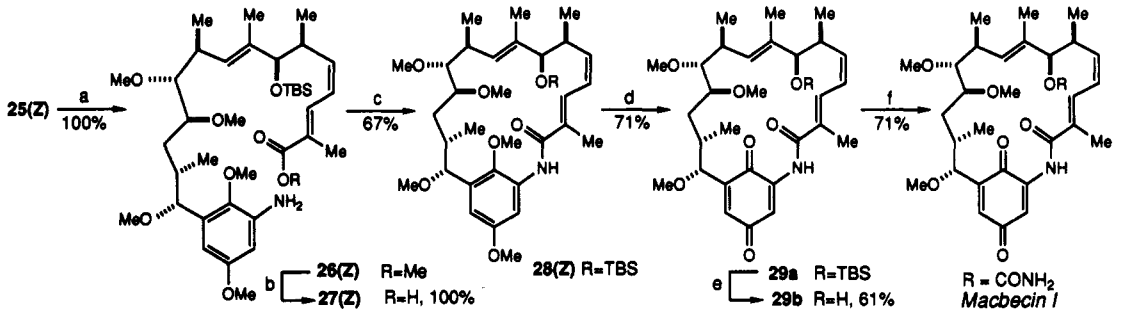
oxidized to the β-keto imide **19** (90%) using the pyridine-buffered version of the Dess–Martin oxidation.[38] It is interesting to note that one of the sulfur atoms in the thiozolidinethione moiety is replaced by oxygen during this transformation, presumably during the Na_2SO_3 work-up. Decarboxylation was then achieved by a simple lithium hydroxide hydrolysis (THF/H_2O, 25 °C) to afford, after acidification, the desired ketone **20** in 73% yield.

The last stereogenic center at C_{12} in the target structure was incorporated through the chelate-controlled reduction of ketone **20**. Treatment of this ketone with $Zn(BH_4)_2$ (Et_2O, −78 °C → −20 °C)[39] afforded what was presumed to be the desired secondary alcohol **21** as a single isomer (>95:5 by ^1H NMR analysis) in 85% yield. Although an unambiguous stereochemical assignment of the newly generated hydroxyl center was not made at this point, it was felt that the high diastereoselectivity of the reaction reflected the anticipated, and well-precedented, high degree of chelate organization in the transition state. At this late stage in the synthesis it was concluded that the most expeditious proof of stereochemistry would be to carry **21** forward to the natural product where a direct comparison could be made. Finally, methylation of the C_{12} alcohol with trimethyloxonium tetrafluoroborate and proton sponge furnished **22** (83%), the completed C_5–C_{21} macbecin subunit lacking only the C_1–C_4 dienic amide appendage.

Stereoselective Dienic Ester Formation. Although ample precedent exists for the stepwise stereoselective synthesis of (2*E*,4*Z*)-2-methylhexadienoates,[14] it was our intention to attempt to incorporate the C_1–C_4 diene ester stereoselectively in a single operation. In closely related transformations it has been demonstrated that the related vinylogous phosphorane[40] and phosphonate[41] reagents undergo selective (*E*,*E*) olefination with aldehydes. Although the control elements of such reactions are still a matter of some debate,[42] this outcome may be rationalized on either kinetic or thermodynamic grounds. In the present instance, the plan was to attempt to rely on kinetic control in the preferential generation of the (*E*,*Z*) transition state using activated,[43] sterically demanding phosphonate enolates.[44] The rationale for anticipating the desired olefination stereoselection is presented in Scheme VII.

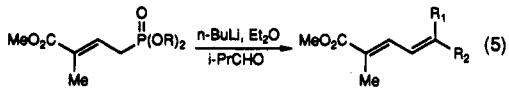
(33) (a) Mukaiyama, T.; Iwasaw, N. *Chem. Lett.* **1986**, 637–640. (b) Kinoshita, M.; Nakata, M. *Tetrahedron Lett.* **1984**, *25*, 1373–1376.
(34) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
(35) (a) Mulzer, J.; Zippel, M. *Tetrahedron Lett.* **1980**, *21*, 751–754. (b) Mulzer, J.; Zippel, M.; Bruntrup, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 465–466. In addition, when **20** was thermally decarboxylated (150 °C, DMF, 6 h) in low yield the *E*(C_{12}–C_{13}) alkene was produced, corroborating the assignment based on the ^1H NMR coupling constant (16.0 Hz).
(36) Barton, D. H. R. *Aldrichim. Acta* **1990**, *23*, 993–1012.
(37) Ireland, R. E.; Norbeck, R. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294.
(38) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4166.
(39) (a) Gensler, W. J.; Johnson, F.; Sloan, A. B. D. *J. Am. Chem. Soc.* **1960**, *82*, 6074–6081. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338–344.
(40) (a) Butchta, E.; Andree, F. *Chem. Ber.* **1960**, *93*, 1349. (b) Roush, W. R.; Brown, B. *Tetrahedron Lett.* **1989**, *30*, 7903–7912.
(41) (a) Pattendon, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984–1997, 1997–2006.
(42) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386–3388.
(43) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
(44) Breuer, E. *Tetrahedron* **1978**, *34*, 997–1002.

Scheme VIII[a]



[a] Key: (a) H_2, quinoline, $Pd(CaCO_3)PbO$, EtOH; (b) LiOH, THF/MeOH/H_2O; (c) BOP-Cl, Hunig's base, $PhCH_3$, 85 °C; (d) CAN, H_2O/CH_3CN; (e) TBAF, THF, 25 °C, 48 h; (f) NaOCN, TFA, CH_2Cl_2.

Given the assumption that the aldehyde addition step can be rendered product-determining, steric congestion at the phosphorus center could destabilize the pseudoequatorial unsaturated ester moiety in the (*E,E*) transition structure in favor of its (*E,Z*) counterpart. The phosphonates illustrated below (eq 5) were prepared from



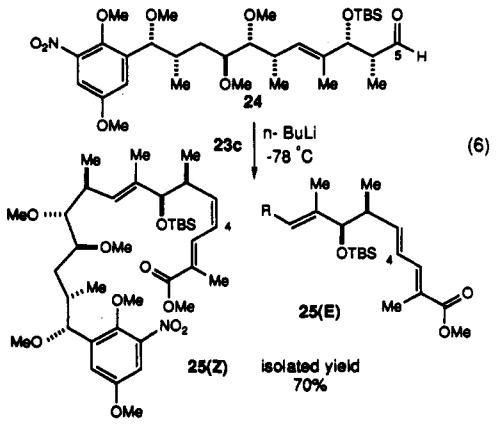
(5)

Phosphonate	(*E,Z*) : (*E,E*)
23a, R = Me	1 : 5
23b, R = $[CH(Me)]_2$	1 : 2
23c, R = CH_2CF_3	3 : 2

(E,Z) R_1 = $CHMe_2$, R_2 = H
(E,E) R_2 = $CHMe_2$, R_1 = H

the parent dimethyl phosphonate **23a** in analogy to the literature procedure.[41] Treatment of phosphonate **23a** with PCl_5 provided the derived dichloride which was esterified with a selection of alcohols to provide the phosphonates of interest. After screening phosphonates **23a–c** under a range of olefination conditions with isobutyraldehyde, it was found that the lithium enolate of phosphonate **23c** (*n*-BuLi, Et_2O, −78 °C, 1–8 equiv) afforded the best ratio (3:2 = *E,Z*:*E,E*) of olefin isomers. The modest trend toward (*Z*) olefin diastereoselection documented by the three cases provides some support for the kinetic model presented above.[45]

With this data in hand, the analogous olefination was carried out with the macbecin fragment **24**. The initial reactions of phosphonate **23c** (1–4 equiv) with aldehyde **24** closely paralleled the reactions with isobutyraldehyde wherein selectivities of ca. 3:2 were observed; however, when the same transformation was conducted with 8 equiv of phosphonate, a surprising 73:27 mixture of diene esters was obtained from which the desired adduct **25(*Z*)** was isolated in 70% yield (eq 6).



(6)

Macbecin I. The completion of the synthesis of (+)-macbecin I is summarized in Scheme VIII. After experiencing limited success with a number of reducing systems ($SnCl_2$; H_2-Pd/C; Al/Hg), catalytic hydrogenation with Lindlar's catalyst[46] afforded the anilinic ester **26(*Z*)** in 94% yield along with 6% of unreacted starting material. Subsequent hydrolysis of the methyl ester (LiOH, THF/MeOH/H_2O) provided the aniline acid **27(*Z*)** (100%) which was cyclized according to the conditions of Baker and Castro using *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[47] in the presence of Hunig's base (0.001 M in toluene, 85 °C) to provide the intact macrocycle **28(*Z*)** (67%). Oxidation of **28(*Z*)** to the derived quinone **29a** using the conditions developed for the model system (eq 3, CAN, MeCN) proceeded in 71% yield. Subsequent desilylation[48] (TBAF, THF, 25 °C, 48 h) afforded decarbamoyl macbecin **29b** in 51% yield along with 10% recovered starting material. Finally, acylation of the C_7 hydroxyl using NaOCN, TFA provided synthetic (+)-macbecin I which agreed in all respects with the data (^1H NMR, ^{13}C NMR, IR, $[\alpha]_D$, MS, TLC R_f in several solvent systems) reported in literature for the natural product.[49] In addition, direct comparison with a sample of the natural product[50] confirmed the assignment.

Unnatural Macbecin Isomers. In the event that the desired olefination reaction (eq 6) had not been successful, it was our intention to construct the unnatural trans Δ-4 olefinic macbecin analog and then to attempt an isomerization of this macrocycle to the natural product. This plan was based on the assumption that the (*E,Z*) C_1–C_5 diene configuration in the natural product was more stable than the (*E,E*) analog **28(*E*)** and was fortified by molecular mechanics calculations[51] which predicted that the desired (*E,Z*) macrocycle **28(*Z*)** was more stable than the corre-

(45) After the completion of this study, Professor W. R. Roush informed us that a similar study had been carried out in his laboratory: Palkowitz, A. Ph.D. Thesis, Massachusetts Institute of Technology, 1989.

(46) For a related reduction of azides in the presence of olefins see: Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590–591.

(47) (a) Reference 14. (b) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R. *Synthesis* **1980**, 547–551. (c) Van Der Auwera, C.; Anteunis, M. J. O. *Int. J. Peptide Protein Res.* **1987**, *29*, 574–588.

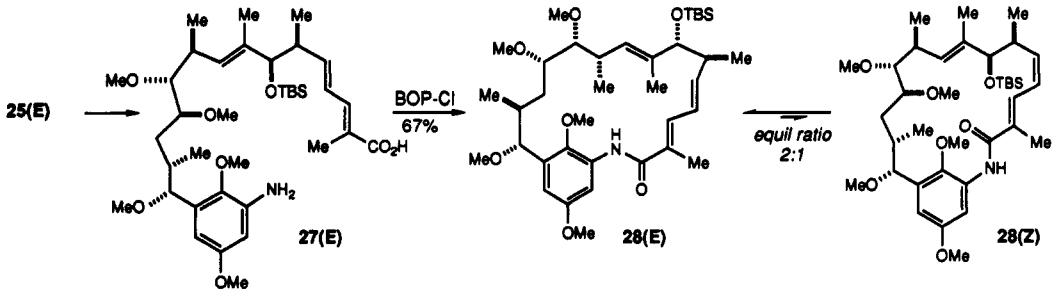
(48) It is of interest to note that both HF/acetonitrile and HF/pyridine provided unsatisfactory results with the former leading to decomposition and the latter to no significant extent of reaction even after several days.

(49) The ^{13}C NMR spectrum reported by Baker and Castro (ref 13b) contains an error. The resonance at 15.26 ppm should be replaced by a resonance at 12.44 ppm (R. Baker, private communication).

(50) We gratefully acknowledge Professor Muroi (Takeda Chemical Industries, Ltd., Osaka, Japan) for providing us with a natural sample of macbecin I for comparison purposes.

(51) Using the MacroModel 3.5X program provided by Professor W. C. Still (Columbia University), 1000 starting conformations for both the (*E,Z*) and (*E,E*) macrocycles were generated in the MONTECARLO mode and subsequently minimized using the MM2 force field.

Scheme IX



sponding isomer 28(*E*). The validity of this postulate was tested in the following set of experiments (Scheme IX). Using chemistry analogous to that employed for the synthesis (Scheme VIII), the anilino acid 27(*E*) was also cyclized to macrocycle 28(*E*) with BOP-Cl in good yield. It is testimony to the utility of this cyclization procedure that these conditions were equally successful in affecting macrocyclization of two substrates with significantly different structural requirements.

When both 28(*E*) and 28(*Z*) were independently submitted to radical-mediated olefin equilibration (*n*-Bu_3SnH, AIBN, PhH, 75 °C;[52] PhSSPh, PhH, 75 °C[53]), the same 2:1 mixture of 28(*E*) to 28(*Z*) was obtained along with a third unidentified reaction constituent of lower mass (Scheme IX). It is thus concluded that this 2:1 mixture represents the equilibrium mixture of macrocyclic lactams. Although the greater stability of the (*E*,*E*) macrocyclic lactam contradicts our prediction, these experiments demonstrate that the undesired Δ-4 olefin isomer can be transformed into the desired macbecin macrocycle 28(*Z*).

Conclusion

The preceding discussion describes our successful efforts to synthesize (+)-macbecin. Chiral imide aldol methodology has been pivotal in the control of absolute stereochemical relationships in this and an earlier synthesis plan[13b] developed in this laboratory. It is of some pedagogical interest that the other syntheses of this structure, reported by Baker[14] and by Martin,[15] have also utilized these auxiliary-based bond constructions to address the issues of absolute stereochemical control.

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AM-250 (250 MHz), AM-300 (300 MHz), AM-400 (400 MHz), or AM-500 (500 MHz) spectrometers. The numbering used in all assignments is based on standard IUPAC rules unless otherwise indicated. Optical rotations were recorded on a JASCO DIP-181 digital polarimeter at 589 nm or other λ and are reported as $[\alpha]_\lambda$ (concentration in g/100 mL of solvent). Combustion analyses were performed by Spang Microanalytical Laboratories (Eagle Harbor, MI). Mass spectra were measured on either a JEOL Model SX-500 or JEOL Model AX-102 high-resolution magnetic sector mass spectrometer. Flash chromatography was performed as previously described[54] on EM silica gel 60 (230–240 mesh). Gas chromatography, HPLC, and TLC were performed as previously described.[55] When specified as "anhydrous," solvents were purified as previously described.[55] Unless otherwise noted, nonaqueous reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere.

(4*R*,5*S*)-3-[(2*R*,3*R*)-3-(2,5-Dimethoxy-3-nitrophenyl)-3-hydroxy-2-methylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (3). To a cooled (−78 °C) solution of 7.0 g (30 mmol) of carboximide 1a in 60 mL of anhydrous CH_2Cl_2 were added successively 8.4 mL (33 mmol) of di-*n*-butylboron triflate and 5.1 mL (36 mmol) of anhydrous Et_3N. The reaction was stirred at −78 °C for 30 min and then warmed to 0 °C and stirred for an additional 1 h. After the mixture was cooled to −78 °C, a solution of 6.34 g (30 mmol) of the 2,5-dimethoxy-3-nitrobenzaldehyde in 30 mL of CH_2Cl_2 was added to the reaction mixture, and the reaction was stirred at −78 °C for 30 min and then warmed to 0 °C. The reaction was stirred for 1 h and then quenched by addition of 60 mL of pH = 7 phosphate buffer. The solution was diluted with 240 mL of MeOH and treated with 90 mL of a 2:1 mixture of MeOH/30% hydrogen peroxide. After being stirred for 1 h at room temperature, the mixture was concentrated and the resulting aqueous residue was extracted three times with 50 mL of CH_2Cl_2. The combined organic phases were then washed with 30 mL of 5% aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated to a pale solid. GLC (SE-54, oven temperature = 250 °C, injector temperature = 275 °C, t_R = 3.91 min) of the silylated (a small portion of the unpurified product was withdrawn and treated with CH_2Cl_2, (dimethylamino)pyridine, and (trimethylsilyl)diethylamine; after 1 h, the mixture was filtered through a plug of silica gel) unpurified aldol adducts showed the reaction to have produced 97% of one compound. Recrystallization from ethyl acetate–hexane afforded 10.6 g (80%) of the pure (>99% by GC) aldol adduct 3 as a crystalline, yellow solid: mp 204–206 °C; $[\alpha]_D$ +35.3° (*c* 2.16, DMSO); IR ($CHCl_3$) 3650–3300, 3040, 1786, 1678, 1532, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.23 (m, 7 H, Ar*H*), 5.67 (d, 1 H, *J* = 7 Hz, –OC*H*Ph), 5.41 (apparent t, 1 H, *J* = 3 Hz, C_3-*H*), 4.80 (apparent quintet, 1 H, *J* = 7 Hz, –NC*H*), 4.06 (dq, 1 H, *J* = 3 Hz, 7 Hz, C_2-*H*), 3.84 (s, 3 H, ArOCH_3), 3.83 (s, 3 H, ArOCH_3), 3.79 (d, 1 H, *J* = 3 Hz, –O*H*), 1.20 (d, 3 H, *J* = 7 Hz, –NCCH_3), 0.90 (d, 3 H, *J* = 7 Hz, C(O)CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 155.1, 143.3, 138.1, 133.0, 128.8, 125.6, 119.5, 109.0, 78.8, 68.2, 62.7, 56.1, 54.8, 42.4, 14.4, 10.8; TLC R_f 0.27 (40% ethyl acetate–hexane). Anal. Calcd for $C_{22}H_{24}O_8N_2$: C, 59.46; H, 5.44. Found: C, 59.53; H, 5.32.

(4*R*,5*S*)-3-[(2*R*,3*R*)-3-(2,5-Dimethoxy-3-nitrophenyl)-3-methoxy-2-methylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (4). To a solution of 745 mg (1.68 mmol) of the starting alcohol 3 in 20 mL of anhydrous CH_2Cl_2 was added 1.79 g (8.40 mmol) of Proton Sponge followed by 1.11 g (8.40 mmol) trimethyloxonium tetraflouroborate to produce a brown heterogeneous mixture. The mixture was stirred for 24 h at room temperature, at which time an additional 719 mg (3.36 mmol) of Proton Sponge and 442 mg (3.36 mmol) of trimethyloxonium tetrafluoroborate were added. After an additional 48 h, the mixture was diluted with 10 mL of CH_2Cl_2. The mixture was

(52) For a review of olefin inversions see: Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557–604.
(53) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123–1125.
(54) W. C. Still, M. Kahn, A. Mitra *J. Org. Chem.* **1978**, *43*, 2923–2925.
(55) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.
(56) The numbering used for the assignments of the ^1H NMR resonances for this compound corresponds to that used in the discussion.
(57) Inhoffen, H. H.; Isler, O.; von der Bey, G.; Raspe, G.; Zeller, P.; Arhens, R. *Liebigs Ann. Chem.* **1953**, *580*, 7.

washed successively with two 50-mL portions of 1 N HCl, 50 mL of H_2O, and 50 mL of brine. The resulting yellow solution was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (4-cm × 12-cm silica gel, solvent gradient: 20% ethyl acetate/hexane to 40% ethyl acetate/hexane) afforded 491 mg (64%) of the desired adduct 4 as a yellow oil in addition to 185 mg (25%) of recovered starting material: $[\alpha]_D$ +105° (*c* 0.50, CH_2Cl_2); IR (thin film) 3110–2750, 1785, 1705, 1640, 1580, 1535, 1485, 1460, 1430, 1370, 1345, 1230, 1195, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (m, 5 H, Ph*H*), 7.26 (d, 1 H, *J* = 3.3 Hz, Ar*H*), 7.24 (d, 1 H, *J* = 3.6 Hz, Ar*H*), 5.32 (d, 1 H, *J* = 7.1 Hz, C′$_5$-*H*), 4.70 (d, 1 H, *J* = 8.5 Hz, C$_3$-*H*), 4.51 (apparent quintet, 1 H, *J* = 6.9 Hz, C′$_4$-*H*), 4.36 (apparent quintet, 1 H, C$_2$-*H*), 3.90 (s, 3 H, ArOC*H*$_3$), 3.84 (s, 3 H, ArOC*H*$_3$), 3.29 (s, 3 H, C$_3$-OC*H*$_3$), 1.38 (d, 3 H, *J* = 6.9 Hz, CHC*H*$_3$), 0.82 (d, 3 H, *J* = 6.7 Hz, CHC*H*$_3$), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 155.4, 152.5, 145.2, 144.1, 137.3, 133.1, 128.7, 128.7, 125.6, 118.4, 110.2, 78.9, 78.4, 63.3, 57.3, 56.1, 55.2, 43.7, 14.3; TLC R_f 0.38 (25% ethyl acetate–hexane); exact mass calcd for $C_{23}H_{26}O_8N_2$ + Na requires *m/z* 481.1587, found *m/z* 481.1590 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,3*R*)-(2,5-Dimethoxy-3-nitrophenyl)-3-methoxy-2-methylpropionic Acid (5). To a stirred solution of 485 mg (1.06 mmol) of carboximide 4 in 5 mL of 4:1 THF/H_2O at 0 °C was added 457 μL (4.24 mmol) of 30% aqueous hydrogen peroxide followed by 38 mg (1.59 mmol) of sodium lithium hydroxide. The resulting solution was stirred for 30 min at which time the reaction was quenched by addition of 7 mL of saturated sodium sulfite solution (caution: gas evolution). The mixture was stirred for 5 min and then concentrated to remove the volatiles. The residue was extracted with three 25-mL portions of CH_2Cl_2 to remove the oxazolidinone. The aqueous layer was acidified to pH = 2 with 6 N HCl and extracted with four 25-mL portions of ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4, filtered, and concentrated to afford 300 mg (95%) of the acid 5 which was pure by ^1H NMR: $[\alpha]_D$ +42.2 °C (*c* 1.15, CH_2Cl_2); IR (thin film) 3400–2550, 1715, 1625, 1580, 1540, 1485, 1465, 1430, 1350, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.17 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 5.05 (d, 1 H, *J* = 3.8 Hz, C$_3$-*H*), 3.87 (s, 3 H, ArOC*H*$_3$), 3.82 (s, 3 H, ArOC*H*$_3$), 3.30 (s, 3 H, C$_3$-OC*H*$_3$), 2.90 (m, 1 H, C$_2$-*H*), 1.02 (d, 3 H, *J* = 7.2 Hz, C$_2$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 155.2, 145.0, 143.7, 136.8, 119.0, 108.9, 77.8, 62.7, 57.9, 56.0, 44.1, 9.5; exact mass calcd for $C_{13}H_{17}O_7N_1$ + Na requires *m/z* 322.0903, found *m/z* 322.0880 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,3*R*)-3-(2,5-Dimethoxy-3-nitrophenyl)-3-methoxy-2-methylpropionyl Chloride. To a solution of 1.80 g (6.02 mmol) of acid 5 in 40 mL of CH_2Cl_2 at rt was added 630 μL (7.22 mmol) of oxalyl chloride followed by 46 μL (0.602 mmol) of DMF (caution: gas evolution). The resulting solution was stirred for 16 h at room temperature. Direct concentration of the mixture in vacuo afforded the acid chloride (pure by ^1H and ^{13}C NMR) as an oily residue which was used directly in the next reaction without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 1 H, *J* = 2.9 Hz, Ar*H*), 7.14 (d, 1 H, *J* = 2.8 Hz, Ar*H*), 5.22 (d, 1 H, *J* = 2.8 Hz, C$_3$-*H*), 3.91 (s, 3 H, ArOC*H*$_3$), 3.83 (s, 3 H, ArOC*H*$_3$), 3.34 (s, 3 H, C$_3$OC*H*$_3$), 3.28 (m, 1 H, C$_2$-*H*), 1.03 (d, 3 H, *J* = 7.0 Hz, C$_2$-C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 155.4, 144.7, 143.7, 135.6, 119.1, 109.1, 77.5, 62.6, 58.2, 56.0, 55.5, 10.1.

(4*R*,3*R*)-1-Diazo-4-(2,5-dimethoxy-3-nitrophenyl)-4-methoxy-3-methyl-2-butanone (6). To a 0 °C solution of ~1.85 g (~6.02 mmol) of the unpurified acid chloride derived from 5 in 50 mL of 2:3 CH_2Cl_2/Et_2O was added ~28 mmol of diazomethane (caution: gas evolution). The cloudy yellow mixture is stirred for 30 min before it was quenched by addition of 50 mL of H_2O. The mixture was extracted with two 50-mL portions of Et_2O, and the combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 15-cm silica gel, solvent gradient: 25% ethyl acetate/hexane to 40% ethyl acetate/hexane) afforded 1.51 g (78% for two steps) of the desired diazoketone 6 as a yellow oil: $[\alpha]_D$ −11.2° (*c* 3.2, CH_2Cl_2); IR (thin film) 3700–3400, 3100, 2980, 2940, 2910, 2840, 2100, 1690, 1635, 1580, 1530, 1470, 1430, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.10 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 5.35 (br s, 1 H, C$_1$-*H*), 4.80 (d, 1 H, *J* = 4.1 Hz, C$_4$-*H*), 3.84 (s, 3 H, ArOC*H*$_3$), 3.80 (s, 3 H, ArOC*H*$_3$), 3.23 (s, 3 H, C$_4$-OC*H*$_3$), 2.73 (br s, 1 H, C$_3$-*H*), 1.05 (d, 3 H, *J* = 7.1 Hz, C$_3$-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 155.1, 145.2, 143.8, 137.3, 119.3, 108.8, 78.2, 62.9, 57.6, 55.9, 54.4, 49.6, 11.1; TLC R_f 0.50 (40% ethyl acetate–hexane); exact mass calcd for $C_{14}H_{17}O_6N_3$ + H requires *m/z* 324.1196, found *m/z* 324.1214 (CI, isobutane).

(4*R*,3*R*)-4-(2,5-Dimethoxy-3-nitrophenyl)-4-methoxy-3-methylbutanoic acid (2). To a solution of 1.45 g (4.49 mmol) of the diazo ketone 6 in 270 mL of 2:1 THF/H_2O was added 801 mg (4.71 mmol) of silver nitrate. The yellow/green solution was stirred for 23 h after which time TLC showed complete consumption of starting material. The reaction mixture was concentrated to remove THF, and the resulting slurry was partitioned between 400 mL of H_2O and 150 mL of CH_2Cl_2. The aqueous layer was extracted with five 120-mL portions of CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to afford 1.23 g (87%) of the desired acid 2 which required no further purification: $[\alpha]_D$ +79.2° (*c* 1.1, CH_2Cl_2); IR (thin film) 3700–2400, 1710, 1620, 1580, 1535, 1480, 1430, 1355, 1310, 1230, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.14 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 4.51 (d, 1 H, *J* = 4.1 Hz, C$_4$-*H*), 3.83 (s, 3 H, ArOC*H*$_3$), 3.82 (s, 3 H, ArOC*H*$_3$), 3.25 (s, 3 H, C$_4$-OC*H*$_3$), 2.50 (dd, *J* = 12.8, 5.5 Hz, 1 H, C$_2$-*H*), 2.31, (m, 2 H, C$_2$-*H* and C$_3$-*H*), 0.88 (d, 3 H, *J* = 6.7 Hz, C$_3$-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 155.2, 145.4, 143.7, 137.8, 118.9, 108.9, 79.8, 62.7, 57.7, 56.0, 38.0, 35.7, 14.2; exact mass calcd for $C_{14}H_{19}O_7N_1$ + H requires *m/z* 336.1060, found *m/z* 336.1080 (FAB, *m*-nitrobenzyl alcohol).

3-[(3*S*,4*R*)-4-(2,5-Dimethoxy-3-nitrophenyl)-4-methoxy-3-methylbutyryl]-2-thiazolidinethione (16). To a solution 1.36 g (4.36 mmol) of the acid 2 in 105 mL of anhydrous CH_2Cl_2 is added 571 mg (4.79 mmol) of thiodone, 1.04 g (5.45 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 80 mg (0.654 mmol) of DMAP. The yellow solution was stirred for 24 h before being transferred into 200 mL of saturated sodium bisulfate solution. The layers were separated, and the aqueous layer was extracted with three 150-mL portions of CH_2Cl_2. The combined organic layers were washed successively with 150 mL of saturated $NaHCO_3$ solution and 150 mL of brine, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (6-cm × 14-cm silica gel, solvent gradient: 25% ethyl acetate/hexane to 35% ethyl acetate/hexane) afforded 1.52 g (84%) of the desired product 16 as a yellow oil: $[\alpha]_D$ +47.7° (*c* 2.8, CH_2Cl_2); IR (thin film) 3120–2860, 2830, 1700, 1620, 1575, 1530, 1480, 1425, 1355 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.28 (d, 1 H, *J* = 3.1 Hz, Ar*H*), 7.18 (d, 1 H, *J* = 3.1 Hz, Ar*H*), 4.55 (m, 3 H, –C′-*H*$_2$–, and C$_4$-*H*), 3.85 (s, 3 H, ArOC*H*$_3$), 3.84 (s, 3 H, ArOC*H*$_3$), 3.36 (dd, 1 H, *J* = 5.8, 16.8 Hz, C$_2$-*H*), 3.26 (s, 3 H, C$_4$-OC*H*$_3$), 3.32–3.22 (m, 3 H, –C′-*H*$_2$–, and C$_2$-*H*) 2.48 (m, 1 H, C$_2$-*H*), 0.90 (d, 3 H, *J* = 6.8 Hz, C$_3$-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) d 201.5, 173.6, 155.1, 145.4, 143.6, 137.8, 118.8, 109.1, 79.8, 62.8, 57.6, 56.1, 56.0, 41.7, 35.6, 28.2, 14.5; TLC R_f 0.52 (40% ethyl acetate–hexane); exact mass calcd for $C_{17}H_{22}O_6N_2S_2$ + Na requires *m/z* 437.0817; found *m/z* 437.0841 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(4*R*,5*S*)-3-[(2*R*,3*R*,4*E*)-3-Hydroxy-2-methyl-5-phenyl-4-pentenoyl]-4-methyl-5-phenyl-2-oxazolidinone (8). To a cooled (−78 °C) solution of 21.8 g (93.0 mmol) of 1a in 200 mL of anhydrous CH_2Cl_2 were added 15.6 mL (112 mmol) of anhydrous Et_3N and 26.1 mL (103 mmol) of di-*n*-butylboron triflate succesively. The solution was stirred at −78 °C for 30 min and 0 °C for 15 min before the solution was recooled to −78 °C and 11.8 mL (93.0 mmol) of *trans*-cinnamaldehyde was added. The solution was stirred at −78 °C for 35 min and at 0 °C for 45 min before being quenched by the addition of 200 mL of a 1:1 mixture of pH 7 phosphate buffer/MeOH. Subsequently 250 mL of a 2:3 mixture of 30% aqueous hydrogen peroxide/MeOH was added over 60 min. The resulting mixture was then concentrated and extracted with two 200-mL portions of ethyl acetate. The combined organic phases were washed successively with 200-mL portions of saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. Analysis of the ^1H NMR spectrum of the unpurified mixture showed the product to be >95% one diastereomer. The product was purified by recrystallization from ethyl acetate–hexane to afford 23.6 g (70%)

of the desired aldol adduct 8 as a white solid: $[\alpha]_D$ −9.3° (c 0.16, $CHCl_3$); IR ($CHCl_3$) 3600–3400, 3050, 1790, 1700, 1500, 1460, 1370, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.27 (m, 10 H, ArH), 6.73 (d, 1 H, J = 15.9 Hz, C_5-H), 6.28 (dd, 1 H, J = 15.9, 5.9 Hz, C_4-H), 5.63 (d, 1 H, J = 7.3 Hz, OCHPh), 4.81 (dq, 1 H, J = 6.9, 6.6 Hz, NCH), 4.72 (m, 1 H, C_3-H), 4.05 (m, 1 H, C_2-H), 3.02 (d, 1 H, J = 3 Hz, −OH), 1.33 (d, 3 H, J = 7.0 Hz, NC(H)CH_3), 0.94 (d, 3 H, J = 6.6 Hz, C_2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 152.7, 136.5, 133.0, 131.3, 128.8, 128.7, 128.5, 127.7, 126.5, 125.6, 125.5, 78.9, 72.9, 54.8, 43.0, 14.3, 11.2; TLC R_f 0.20 (30% ethyl acetate–hexane). Anal. Calcd for $C_{22}H_{23}O_4N$: C, 72.35; H, 6.30. Found: C, 72.08; H, 6.24.

(2*R*,3*R*,4*E*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-5-phenyl-4-pentenamide (9). To a cooled (−10 °C) suspension of 18.9 g (195 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 500 mL of anhydrous CH_2Cl_2 was added 96.9 mL (195 mmol) of 2.0 M trimethylaluminum in toluene (caution: much gas was evolved). After the addition was complete, the cooling bath was removed and the solution was stirred for 30 min at room temperature. The solution was then recooled to −20 °C and a solution of 23.6 g (64.7 mmol) of the aldol adduct 8 in 500 mL of anhydrous CH_2Cl_2 was added. The cloudy reaction mixture was stirred for 2 h at −10 °C. The reaction mixture was then quenched by the addition of 500 mL of 1.0 N aqueous tartaric acid. After the mixture was stirred vigorously for 1 h the layers were separated and extracted two times with 300 mL of CH_2Cl_2. The combined organic phases were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by chromatography (8-cm × 10-cm of silica gel, 40% ethyl acetate–hexane) afforded 17.8 g (>100%) of the desired amide 9 as a clear oil which contained a small amount (<5%) of recovered oxazolidinone. A small portion of the product was purified further by chromatography for the purposes of analysis. The data for amide 9: $[\alpha]_D$ −32.9° (c 0.68, $CHCl_3$); IR (thin film) 3400, 2960, 1650, 1460, 1425, 1390, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.19 (m, 5 H, ArH), 6.68 (dd, 1 H, J = 16.0, 1.3 Hz, C_5-H), 6.18 (dd, 1 H, J = 16.0, 5.4 Hz, C_4-H), 4.62 (m, 1 H, C_3-H), 3.95 (br s, 1 H, −OH), 3.72 (s, 3 H, NOCH_3), 3.21 (s, 3 H, NCH_3), 3.04 (m, 1 H, C_2-H), 1.20 (d, 3 H, J = 7.1 Hz, C_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 136.8, 130.6, 129.4, 128.3, 127.3, 126.2, 72.5, 61.3, 39.9, 31.9, 11.0; TLC R_f 0.33 (50% ethyl acetate–hexane). Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.49; H, 7.63. Found: C, 67.61; H, 7.69.

(2*R*,3*R*,4*E*)-3,*N*-Dimethoxy-*N*,2-dimethyl-5-phenyl-4-pentenamide (10). To a solution of 4.00 g (16.1 mmol) of the alcohol 9 in 80 mL of anhydrous THF was added 30 mL of anhydrous DMF and 10.2 mL (161 mmol) of iodomethane. The mixture was cooled to 0 °C, and 1.61 g (40.3 mmol) of sodium hydride (60% dispersion in mineral oil) was added under a positive flow of nitrogen. The mixture was stirred for 1 h before 20 mL of pH 7 phosphate buffer was added to quench the reaction. The resulting mixture was partitioned between 70 mL of CH_2Cl_2 and 150 mL of brine. The aqueous layer was extracted with three 100-mL portions of CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 14-cm silica gel, 50% ethyl acetate–hexane) afforded 3.9 g (92%) of the desired amide 10 as a clear oil: $[\alpha]_D$ +21.1° (c 2.88, $CHCl_3$); IR ($CHCl_3$) 3150–2900, 2400, 1660, 1550–1390, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5 H, ArH), 6.56 (d, 1 H, J = 15.9 Hz, C_5-H), 6.14 (dd, 1 H, J = 15.9, 8.0 Hz, C_4-H), 3.91 (apparent t, 1 H, J = 8.1 Hz, C_3-H), 3.66 (s, 3 H, NOCH_3), 3.34 (s, 3 H, C_3-CH_3), 3.22 (m, 1 H, C_2-H), 3.11 (s, 3 H, NCH_3) 1.26 (d, 3 H, J = 6.8 Hz, C_2-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 136.6, 133.3, 128.5, 128.1, 127.6, 126.6, 84.3, 61.5, 56.8, 41.0, 32.1, 14.4; TLC R_f 0.38 (50% ethyl acetate–hexane). Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.45; H, 7.97. Found: C, 68.37; H, 8.08.

(2*R*,3*R*,4*E*)-3-Methoxy-2-methyl-5-phenyl-4-pentenal (11). To a cooled (−78 °C) solution of 1.9 g (7.2 mmol) of the starting amide 10 in 50 mL of anhydrous CH_2Cl_2 was added 9.6 mL of (14.4 mmol) of DIBAL (1.5 M in toluene). The solution was stirred for 1 h before 5 mL of acetone was added to quench the reaction. The mixture was then warmed to rt, and 12 mL of saturated aqueous 1 N tartaric acid solution was added. The solution was stirred for 20 min and was then extracted three times with 40-mL portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (4 cm × 12 cm silica gel, 20% ethyl acetate–hexane) afforded 1.25 g (85%) of the desired aldehyde 11 as a clear oil: $[\alpha]_D$ −15.8° (c 4.50, $CHCl_3$); IR ($CHCl_3$) 3100–2800, 2750, 2400, 1725, 1630, 1600, 1500, 1450, 1400, 1200 cm^{-1}; ^1H NMR (2.50 MHz, $CDCl_3$) δ 9.80 (d, 1 H, J = 1 Hz, −CHO), 7.43–7.24 (m, 5 H, ArH), 6.63 (d, 1 H, J = 15.9 Hz, C_5-H), 6.09 (dd, 1 H, J = 15.9, 7.9 Hz, C_4-H), 4.13 (dd, 1 H, J = 7.9, 4.7 Hz, C_3-H), 3.39 (s, 3 H, C_3-OCH_3), 2.70–2.57 (m, 1 H, C_2-H), 1.15 (d, 3 H, J = 7.0 Hz, C_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 136.0, 134.0, 128.6, 128.1, 126.6, 126.4, 82.1, 56.8, 51.3, 8.8; TLC R_f 0.52 (30% ethyl acetate–hexane); exact mass calcd for $C_{13}H_{16}O_2$ + Na requires m/z 227.1048, found m/z 227.1050 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Ethyl (2*E*,4*S*,5*R*,6*E*)-5-Methoxy-2,4-dimethyl-7-phenyl-2,6-heptadienoate (12). To a three-neck 100-mL flask fixed with a reflux condenser charged with 4.2 g (9.8 mmol) of (carbethoxyethylidene)triphenylphosphorane was added 1.0 g (4.9 mmol) of the aldehyde 11 in 50 mL of anhydrous toluene. The mixture was stirred at refluxing temperature for 9 h and was then cooled to room temperature. The reaction mixture was concentrated to provide a 94:6 mixture of trans–cis olefin isomers (GC analysis-DB-1, oven temperature = 180 °C, injector temperature = 250 °C, t_R = 3.77 min for the major adduct). Purification of the residue by chromatography (5-cm × 12-cm silica gel, 10% ethyl acetate–hexane) afforded 1.1 g (78%) of the trans product 12 as a clear oil: $[\alpha]_D$ +20.3° (c 2.00, $CHCl_3$); IR ($CHCl_3$) 3150–2750, 2400, 1720, 1650, 1550–1400, 1380, 1300–1200 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5 H, ArH), 6.67 (dd, 1 H, J = 10.2, 1.3 Hz, C_3-H), 6.55 (d, 1 H, J = 15.9 Hz, C_7-H), 6.04 (dd, 1 H, J = 15.9, 8.0 Hz, C_6-H), 4.16 (q, 2 H, J = 7.1 Hz, OCH_2CH_3), 3.61 (apparent t, 1 H, J = 7.1 Hz, C_5-H), 3.32 (s, 3 H, −OCH_3), 2.86–2.71 (m, 1 H, C_4-H), 1.85 (d, 3 H, J = 1.3 Hz, C_2-CH_3), 1.27 (t, 3 H, J = 7.1 Hz, −OCH_2CH_3), 1.08 (d, 3 H, J = 6.8 Hz, C_4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 143.2, 136.5, 133.4, 128.6, 127.9, 127.7, 165.5, 126.4, 85.9, 60.4, 56.8, 38.7, 15.8, 14.2, 12.7; TLC R_f 0.32 (10% ethyl acetate–hexane). Anal. Calcd for $C_{18}H_{24}O_3$: C, 75.02; H, 8.33. Found: C, 75.11; H, 8.39.

(2*E*,4*S*,5*R*,6*E*)-5-Methoxy-2,4-dimethyl-7-phenyl-2,6-heptadien-1-ol. To a cooled (−78 °C) solution of 1.5 g (5.2 mmol) of the starting ester 12 in 40 mL of anhydrous CH_2Cl_2 was added 13.8 mL (20.8 mmol) of DIBAL (1.5 M in toluene). The solution was stirred for 1 h before 10 mL of acetone was added to quench the reaction. The solution was then warmed to rt, and 15 mL of a 1 N aqueous solution of tartaric acid was added. The cloudy mixture was stirred for 30 min, and 20 mL of a concentrated aqueous tartaric acid solution was added. This solution was stirred for 30 min until a biphasic solution appeared. The aqueous phase was extracted three times with 40-mL portions of CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (4-cm × 12-cm silica gel, 30% ethyl acetate–hexane) afforded 1.15 g (90%) of the desired alcohol as a colorless oil: $[\alpha]_D$ +69.1° (c 1.30, $CHCl_3$); IR ($CHCl_3$) 3610, 3550–3200, 3150–2800, 2400, 1500, 1450, 1380, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5 H, ArH), 6.49 (d, 1 H, J = 15.9 Hz, C_7-H), 6.05 (dd, 1 H, J = 15.9, 8.0 Hz, C_6-H), 5.31 (dd, 1 H, J = 10, 1.3 Hz, C_3-H), 3.97 (d, 2 H, J = 5.5 Hz, CH_2OH), 3.51 (dd, 1 H, J = 7.5, 6.6 Hz, C_5-H), 3.31 (s, 3 H, OCH_3), 2.72–2.64 (m, 1 H, C_4-H), 1.66 (d, 3 H, J = 1.3 Hz, C_2-CH_3), 1.23 (t, 1 H, J = 6.3 Hz, −OH), 1.03 (d, 3 H, J = 6.8 Hz, C_4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.2, 132.8, 128.6, 128.5, 127.9, 127.6, 126.4, 86.7, 68.9, 56.8, 37.5, 16.8, 14.1; TLC R_f 0.28 (40% ethyl acetate–hexane). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.06; H, 8.94. Found: C, 78.09; H, 8.93.

(2*E*,4*S*,5*R*,6*E*)-5-Methoxy-2,4-dimethyl-7-phenyl-2,6-heptadienal (13). To a cooled (−60 °C) mixture of 30 mL of anhydrous CH_2Cl_2 and 1.0 mL (14.6 mmol) of anhydrous DMSO was added 0.85 mL (9.70 mmol) of oxalyl chloride. The mixture was stirred for 10 min, and 1.0 g (4.05 mmol) of the starting alcohol was added in 20 mL (followed by a 20-mL rinse) of anhydrous CH_2Cl_2. The mixture was stirred for 20 min, and then 3.37 mL (24.3 mmol) of anhydrous Et_3N was added. The mixture was then stirred for 2 h and 15 min before it was poured into 30 mL of a 1 N aqueous solution of sodium bisulfate to quench the reaction. The aqueous phase was extracted three times with 50-mL portions of CH_2Cl_2, and the combined organic

phases were washed with 20-mL portions of saturated $NaHCO_3$ and brine solutions, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (3-cm × 10-cm silica gel, 20% ethyl acetate–hexane) afforded 944 mg (95%) of the desired aldehyde **13** as a clear oil: $[\alpha]_D$ +51.8° (*c* 1.00, $CHCl_3$); IR (thin film) 3320, 3090–2710, 1690, 1645, 1605, 1580, 1495, 1450, 1370, 1225 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.38 (s, 1 H, –C*H*O), 7.40–7.23 (m, 5 H, Ar*H*), 6.56 (d, 1 H, *J* = 15.9 Hz, C_7-*H*), 6.41 (dd, 1 H, *J* = 9.9, 1.3 Hz, C_3-*H*), 6.04 (dd, 1 H, *J* = 15.9, 7.9 Hz, C_6-*H*), 3.67 (dd, 1 H, *J* = 7.9, 6.0 Hz, C_5-*H*), 3.33 (s, 3 H, –OCH_3), 3.03–2.94 (m, 1 H, C_4-*H*), 1.76 (d, 3 H, *J* = 1.3 Hz, C_2-CH_3), 1.13 (d, 3 H, *J* = 6.8 Hz, C_4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 155.5, 139.1, 136.1, 133.8, 128.7, 128.0, 127.1, 126.6, 85.5, 56.8, 38.8, 15.5, 9.5; TLC R_f 0.39 (30% ethyl acetate–hexane); exact mass calcd for $C_{16}H_{20}O_2$ + Na requires *m/z* 267.1361, found *m/z* 267.1371 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(4*R*,5*S*)-3-[(2*R*,3*R*,4*E*,6*S*,7*R*,8*E*)-3-Hydroxy-7-methoxy-2,4,6-trimethyl-9-phenyl-4,8-nonadienoyl]-4-methyl-5-phenyl-2-oxazolidinone (14). To a cooled (–78 °C) solution of 3.50 g (15.02 mmol) of **1a** in 13 mL of anhydrous CH_2Cl_2 were added 2.12 mL (15.12 mmol) of anhydrous Et_3N and 3.80 mL (15.02 mmol) of di-*n*-butylboron triflate. The solution was stirred at –78 °C for 30 min and 0 °C for 15 min before the solution was recooled to –78 °C, and 0.94 g (3.85 mmol) of the aldehyde **13** in 10 mL of anhydrous CH_2Cl_2 was added. The solution was stirred at –78 °C for 100 min and was then quenched by addition of 10 mL of a 1:4 mixture of pH 7 phosphate buffer/MeOH. To this was added 5 mL of 30% aqueous hydrogen peroxide solution, and the resulting solution was stirred for 15 min. The resultant solution was concentrated and extracted with two 30-mL portions of CH_2Cl_2. The combined organic phases were washed with 50-mL portions of saturated aqueous $NaHCO_3$ and brine solutions, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (4-cm × 15-cm silica gel, 25% ethyl acetate–hexane) afforded 1.41 g (77%) of the desired product **14** as a white foam: $[\alpha]_D$ +29° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3610–3300, 3100–2750, 1790, 1700, 1600, 1500, 1450, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.21 (m, 10 H, Ar*H*), 6.48 (d, 1 H, *J* = 15.9 Hz, C_9-*H*), 6.0 (dd, 1 H, *J* = 15.9, 8.1 Hz, C_8-*H*), 5.64 (d, 1 H, *J* = 7.3 Hz, OC*H*Ph), 5.43 (dd, 1 H, *J* = 9.9, 1.0 Hz, C_5-*H*), 4.75 (quintet, 1 H, *J* = 6.7 Hz, NC*H*CH_3), 4.38 (br m, 1 H, C_3-*H*), 3.96 (dq, 1 H, *J* = 7.0, 3.2 Hz, C_2-*H*), 3.47 (apparent t, 1 H, *J* = 7.7 Hz, C_7-*H*), 3.30 (s, 3 H, OCH_3), 2.71–2.64 (m, 1 H, C_6-*H*), 2.64 (d, 1 H, *J* = 3.1 Hz, –O*H*), 1.65 (d, 3 H, *J* = 1.0 Hz, C_4-CH_3), 1.05 (d, 3 H, *J* = 6.7 Hz, C_2-CH_3), 0.94 (d, 3 H, *J* = 7.0 Hz, C_6-CH_3), 0.87 (d, 3 H, *J* = 6.6 Hz, NC(H)CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 153.0, 136.8, 134.2, 133.2, 132.8, 128.8, 128.7, 128.6, 128.5, 128.4, 127.6, 126.5, 125.6, 86.8, 78.8, 75.6, 58.8, 54.9, 40.7, 37.5, 17.0, 14.3, 13.6, 10.6; TLC R_f 0.26 (30% ethyl acetate–hexane); exact mass calcd for $C_{29}H_{35}O_5N_1$ + Na requires *m/z* 500.2413, found *m/z* 500.2425 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,3*R*,4*E*,6*S*,7*R*,8*E*)-*N*,7-Dimethoxy-3-hydroxy-9-phenyl-*N*,2,4,6-tetramethyl-4,8-nonadienamide (7a). To a cooled (–10 °C) suspension of 0.80 g (8.18 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 10 mL of anhydrous CH_2Cl_2 was added 4.10 mL (8.18 mmol) of 2.0 M trimethylaluminum in toluene (caution: much gas was evolved). After the addition was complete, the cooling bath was removed and the solution was stirred for 30 min at room temperature. The solution was then recooled to –10 °C, and a solution of 1.30 g (2.73 mmol) of the aldol adduct **14** in 20 mL of anhydrous CH_2Cl_2 was added. The cloudy reaction mixture was stirred for 18 h at –20 °C before the reaction was quenched by addition of 15 mL of 1.0 N aqueous tartaric acid. After the mixture was stirred vigorously for 30 min the layers were separated and extracted three times with 50 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (4.0-cm × 10-cm of silica gel, 50% ethyl acetate–hexane) afforded 0.95 g (96%) of the desired amide **7a** as a yellow oil: $[\alpha]_D$ +55.8° (*c* 1.00, $CHCl_3$); IR (thin film) 3600–3250, 3100–2850, 2820, 1650, 1450, 1390, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5 H, Ar*H*), 6.49 (d, 1 H, *J* = 15.8 Hz, C_9-*H*), 6.00 (dd, 1 H, *J* = 15.9, 8.2 Hz, C_8-*H*), 5.46 (br d, 1 H, *J* = 10.0 Hz, C_5-*H*), 4.23 (br s, 1 H, C_3-*H*), 3.98 (br s, 1 H, –O*H*), 3.63 (s, 3 H, NOCH_3), 3.48 (apparent t, 1 H, *J* = 7.9 Hz, C_7-*H*), 3.32 (s, 3 H, C_7-OCH_3), 3.16 (s, 3 H, NCH_3), 2.93 (m, 1 H, C_2-*H*), 2.65 (m, 1 H, C_6-*H*), 1.58 (d, 3 H, *J* = 1.1 Hz, C_4-CH_3), 1.09 (d, 3 H, *J* = 6.7 Hz, C_6-CH_3), 0.90 (d, 3 H, *J* = 7.1 Hz, C_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 136.7, 132.9, 132.4, 129.4, 128.9, 127.7, 126.6, 126.4, 87.2, 74.9, 61.5, 56.7, 37.9, 36.3, 31.9, 17.3, 14.3, 9.9; TLC R_f 0.25 (50% ethyl acetate–hexane). Anal. Calcd for $C_{21}H_{31}O_4N$: C, 69.82; H, 8.58. Found: C, 69.65; H, 8.34.

(2*R*,3*R*,4*E*,6*S*,7*R*,8*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-*N*,7-Dimethoxy-9-phenyl-*N*,2,4,6-tetramethyl-4,8-nonadienamide (7b). To a solution of 0.84 g (2.30 mmol) of the alcohol **7a** in 20 mL of anhydrous DMF was added 1.26 g (18.40 mmol) of imidazole and 1.39 g (9.20 mmol) of *tert*-butyldimethylsilyl chloride. The reaction was stirred for 18 h before being quenched by the addition of 50 mL of saturated aqueous sodium carbonate solution. The aqueous layer was extracted three times with 50 mL of CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Initial purification of the residue by chromatography (4-cm × 12-cm silica gel, 20% ethyl acetate–hexane) afforded a mixture of the desired product **7b** and *tert*-butyldimethylsilanol (TBSOH). The mixture was then dissolved in 40 mL of a 1:1 mixture of ethyl acetate–hexane. Repeated washings (5×) with saturated $NaHCO_3$ solution afforded 1.0 g (91%) of the pure product **7b** (no TBSOH observed by NMR) as a faint yellow oil: $[\alpha]_D$ +42.8° (*c* 1.00, $CHCl_3$); IR (thin film) 3100–2750, 2250, 1660, 1500, 1465, 1390, 1250, 1190 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43–7.15 (m, 5 H, Ar*H*), 6.47 (d, 1 H, *J* = 16.0 Hz, C_9-*H*), 6.03 (dd, 1 H, *J* = 16.0, 7.6 Hz, C_8-*H*), 5.26 (d, 1 H, *J* = 9.8 Hz, C_5-*H*), 4.18 (d, 1 H, *J* = 8.8 Hz, C_3-*H*), 3.56 (s, 3 H, C_7-OCH_3), 3.44 (apparent t, 1 H, *J* = 7.3 Hz, C_7-*H*), 3.26 (s, 3 H, NOCH_3), 3.09 (m, 1 H, C_2-*H*), 2.94 (s, 3 H, NCH_3), 2.61 (m, 1 H, C_6-*H*), 1.60 (d, 3 H, *J* = 1.1 Hz, C_4-CH_3), 1.14 (d, 3 H, *J* = 6.8 Hz, C_2-CH_3), 0.95 (d, 3 H, *J* = 6.8 Hz, C_6-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.30 (s, 3 H, SiCH_3), –0.04 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 br, 135.7, 132.5, 129.8, 128.5, 128.4, 127.5, 126.6, 86.8, 79.9, 61.3, 56.6, 40.2, 37.6, 31.9, 25.8, 25.7, 16.6, 14.6, 14.1, 11.7, –4.5, –5.0; TLC R_f 0.62 (20% ethyl acetate–hexane). Anal. Calcd for $C_{27}H_{45}O_4NSi$: C, 68.22; H, 9.47. Found: C, 68.03; H, 9.67.

(2*R*,3*R*,4*E*,6*S*,7*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-7-formyl-*N*,7-dimethoxy-*N*,2,4,6-tetramethyl-4-heptenamide (15). To a solution of 1.04 g (2.20 mmol) of the starting material **7b** in 70 mL of a 10:3:1 mixture of 2-methyl-2-propanol/THF/H_2O was added 283 mg (2.42 mmol) of *N*-methylmorpholine *N*-oxide and 2.93 mL (0.44 mmol) of osmium tetraoxide solution (0.15 M in H_2O). The solution gradually turned an amber color. After being stirred, at rt for 3 h, the solution was diluted eith 30 mL of H_2O, and 2.21 g (26.4 mmol) of $NaHCO_3$ and 1.41 g (6.60 mmol) of $NaIO_4$ were added successively. The heterogeneous mixture was stirred vigorously for 45 min, filtered through a plug of glass wool with copious ethyl acetate, and concentrated. The aqueous residue was poured into 150 mL of saturated Na_2SO_3 solution. The mixture was extracted with three 200-mL portions of 1:1 ethyl acetate/hexane, washed with 100 mL of $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (3-cm × 12-cm silica gel, 40% ethyl acetate–hexane) afforded 724 mg (82%) of the pure aldehyde **15** as a clear oil: $[\alpha]_D$ +5.52° (*c* 2.52, $CHCl_3$); IR (thin film) 3050–2800, 1735, 1710, 1650, 1460, 1390, 1360, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, 1 H, *J* = 1.6 Hz, –C*H*O), 5.32 (d, 1 H, *J* = 10.1 Hz, C_5-*H*), 4.16 (d, 1 H, *J* = 9.1 Hz, C_3-*H*), 3.64 (s, 3 H, NOCH_3), 3.39 (s, 3 H, C_7-OCH_3), 3.32 (dd, 1 H, *J* = 7.4, 1.6 Hz, C_7-*H*), 3.13 (s, 3 H, NCH_3), 3.10 (m partially obscured by NCH_3, 1 H, C_2-*H*), 2.68 (m, 1 H, C_6-*H*), 1.58 (d, 3 H, *J* = 1.3 Hz, C_4-CH_3), 1.17 (d, 3 H, *J* = 6.8 Hz, C_2-CH_3), 1.02 (d, 3 H, *J* = 6.7 Hz, C_6-CH_3), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.06 (s, 3 H, SiCH_3), –0.02 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 175.2, 136.9, 127.8, 89.0, 79.9, 61.4, 58.7, 39.9, 34.6, 31.6, 25.7, 18.1, 16.3, 14.9, 11.3, –4.6, –5.1; TLC R_f 0.31 (40% ethyl acetate–hexane). Anal. Calcd for $C_{20}H_{39}O_5N_1Si_1$: C, 59.86; H, 9.72. Found: C, 60.01; H, 9.90.

(2*R*,3*R*,4*E*,6*S*,7*R*,10*S*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-11-(2,5-dimethoxy-3-nitrophenyl)-8-hydroxy-*N*,7,11-trimethoxy-*N*,2,4,6,10-pentamethyl-9-[(2-thioxo-3-thiazolidinyl)carbonyl]-4-undecenamide (17). To a cooled (0 °C) solution of 1.46 g (3.53 mmol) of imide **16** in 50 mL of anhydrous CH_2Cl_2 was added 406 μL (3.70 mmol) of titanium tetrachloride to produce a yellow-orange heterogeneous solution. Within 60 s,

540 μL (3.88 mmol) of anhydrous triethylamine was added to produce a deep brown solution which was stirred for 1 h. A solution of 1.27 g (3.17 mmol) of aldehyde **15** in 25 mL of CH_2Cl_2 was then transferred to the reaction mixture via cannula, and the resulting mixture was stirred at 0 °C for 3.3 h. The reaction was quenched by transferring the reaction mixture via cannula to a rapidly stirred 0 °C mixture of 250 mL of saturated aqueous sodium bicarbonate solution and 125 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with one 200-mL portion of CH_2Cl_2. The combined organic extracts were washed with one 150-mL portion of brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 12-cm silica gel, solvent gradient: 35% ethyl acetate–hexane to 50% ethyl acetate–hexane) afforded 440 mg (30%) recovered thioimide **16**, 114 mg (9%) of recovered aldehyde **15**, and 1.88 g (73% based on aldehyde) of one aldol diastereomer **17**: $[\alpha]_D$ + 10.0° (c 0.45, CH_2Cl_2); IR (thin film) 3510–3400, 3020–2800, 1705, 1660, 1535, 1460, 1425, 1360, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 1 H, J = 3.2 Hz, Ar*H*), 7.09 (d, 1 H, J = 3.2 Hz, Ar*H*), 5.16, (d, 1 H, J = 9.7 Hz, C_5-*H*), 4.76 (m, 1 H, C′-*H*), 4.63–4.56 (m, 2 H, C′-*H* and C_{11}-*H*), 4.13 (d, 1 H, J = 8.4 Hz, C_3-*H*), 4.04 (d, 1 H, J = 10.3 Hz, –O*H*), 3.81 (s, 6 H, 2 × –OCH_3), 3.80 (obscured dd, 1 H, C_9-*H*), 3.75 (ddd, 1 H, C_8-*H*), 3.57 (s, 3 H, –OCH_3), 3.35 (s, 3 H, –OCH_3), 3.27 (m, 2 H, C′-H_2), 3.13 (s, 3 H, –OCH_3), 3.07 (m, 1 H, C_2-*H*), 3.06 (s, 3 H, –OCH_3), 2.98 (dd, 1 H, J = 2.8 Hz, 9.1 Hz, C_7-*H*), 2.75 (m, 1 H, C_6-*H*), 2.43 (m, 1 H, C_{10}-H), 1.56 (s, 3 H, C_4-CH_3), 1.10 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.91 (d, 3 H, J = 6.6 Hz, C_6-CH_3), 0.85 (s, 9 H, C(CH_3)$_3$), 0.83 (obscured d, 3 H, C_{14}-CH_3), 0.01 (s, 3 H, SiCH_3), –0.03 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) d 200.4, 177.9, 175.4, 154.7, 145.3, 143.6, 137.7, 135.8, 131.0, 119.2, 108.2, 90.1, 79.4, 78.4, 75.1, 62.6, 61.4, 61.2, 57.0, 56.3, 55.9, 45.3, 40.6, 40.0, 34.2, 31.8, 27.8, 25.8, 18.1, 16.1, 14.3, 12.0, 11.3, –4.6, –5.1; TLC R_f 0.20 (40% ethyl acetate–hexane); exact mass calcd for $C_{37}H_{61}O_{11}N_3S_2Si_1$ + Na m/z 838.3414, found m/z 838.3448 (FAB, *m*-nitrobenzyl alcohol, added NaI).

3-[(1*S*,2*R*)-2-(2,5-Dimethoxy-3-nitrophenyl)-2-methoxy-1-methylethanyl]-4-[(1*R*,2*S*,3*E*,5*R*,6*R*)-5-(*tert*-butyldimethylsiloxy)-*N*,1-dimethoxy-*N*,2,4,6-tetramethylhept-3-en-7-amido]-oxetan-2-one (18).[56] To a solution of 40 mg (0.049 mmol) of aldol adduct **17** in 4 mL of anhydrous THF was added 20 mg (0.15 mmol) of solid K_2CO_3. The reaction was heated to reflux and stirred for 2 h. The reaction mixture was then cooled to rt and concentrated. Purification of the residue by preparative TLC (0.5 mm silica gel, 40% ethyl acetate–hexane) afforded 30 mg (88%) of the desired β-lactone **18** as a yellow oil: $[\alpha]_D$ +20.5° (c 1.45, CH_2Cl_2); IR (CH_2Cl_2) 3700–3020, 3010–2800, 1820, 1660, 1535, 1450, 1365, 1305, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.25 (d, 1 H, J = 3.2 Hz, Ar*H*), 7.16 (d, 1 H, J = 3.2 Hz, Ar*H*), 5.23 (d, 1 H, J = 9.3 Hz, C_9-*H*), 5.03 (d, 1 H, J = 2.0 Hz, C_{15}-*H*), 4.27 (apparent t, 1 H, J = 3.1 Hz, C_{12}-*H*), 4.16 (d, 1 H, J = 9.2 Hz, C_7-*H*), 3.85 (s, 3 H, –OCH_3), 3.84 (s, 3 H, –OCH_3), 3.79 (dd, 1 H, J = 3.7, 11.5 Hz, C_{13}-*H*), 3.53 (s, 3 H, –OCH_3), 3.47 (s, 3 H, –OCH_3), 3.38 (s, 3 H, –OCH_3), 3.24 (dd, 1 H, J = 2.6, 8.8 Hz, C_{11}-*H*), 2.97 (m, 1 H, C_6-*H*), 2.90 (s, 3 H, NCH_3), 2.33 (m, 1 H, C_{10}-*H*), 2.25 (m, 1 H, C_{14}-*H*), 1.50 (d, 3 H, J = 1.1 Hz, C_8-CH_3), 1.13 (d, 3 H, J = 6.9 Hz, C_6-CH_3), 1.03 (d, 3 H, J = 6.7 Hz, C_{10}-CH_3), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.61 (d, 3 H, J = 6.9 Hz, C_{14}-CH_3), 0.04 (s, 3 H, SiCH_3), –0.06 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 170.6, 154.9, 144.4, 143.8, 137.6, 136.2, 129.4, 118.5, 107.7, 84.2, 79.6, 77.1, 62.5, 61.8, 60.8, 57.7, 55.8, 53.8, 39.8, 37.4, 34.3, 31.4, 25.6, 17.9, 16.0, 14.9, 11.2, 11.0, –4.7, –5.2, TLC R_f 0.66 (40% ethyl acetate–hexane); exact mass calcd for $C_{34}H_{56}O_{11}N_2Si_1$ + Na requires m/z 719.3534, found m/z 719.3527 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*E*,6*S*,7*R*,10*S*,11*R*)-3-(*tert*-Butyldimethylsiloxy)-11-(2,5-dimethoxy-3-nitrophenyl)-*N*,7,11-trimethoxy-*N*,2,4,6,10-pentamethyl-8-oxo-9-[(2-oxo-3-thiazolidinyl)carbonyl]-4-undecenamide (19). To a solution of 1.88 g (2.31 mmol) of aldol adduct **17** in 80 mL of CH_2Cl_2 was added 9.30 mL (115 mmol) of pyridine followed by 2.94 g (6.92 mmol) of the Dess–Martin periodinane.[38] The cloudy yellow reaction mixture was stirred for 30 min before being diluted with 150 mL of Et_2O. The reaction mixture was then transferred into a separatory funnel containing 250 mL of saturated $NaHCO_3$ solution and carefully treated with 25 mL of saturated sodium bisulfite solution (caution: gas evolution). The layers were separated, and the aqueous layer was extracted with an additional three 100-mL portions of Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 12-cm silica gel, solvent gradient: 50% ethyl acetate–hexane to 70% ethyl acetate–hexane) afforded 1.49 g (81%) of the desired β-keto imide **19** as a yellow oil: $[\alpha]_D$ +104° (c 1.00, CH_2Cl_2); IR (thin film) 3700–3200, 3090–2880, 1725, 1675, 1580, 1540, 1450, 1350, 1260, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 1 H, J = 3.2 Hz, Ar*H*), 7.14 (d, 1 H, J = 3.2 Hz, Ar*H*), 5.34, (d, 1 H, J = 10.2 Hz, C_5-*H*), 5.29 (d, 1 H, J = 5.9 Hz, C_{11}-*H*), 4.61 (d, 1 H, J = 2.5 Hz, C_9-*H*), 4.34 (m, 1 H, C′-*H*), 4.21 (m, 2 H, C′-*H*), 4.14 (d, 1 H, J = 8.9 Hz, C_3-*H*), 3.91 (s, 3 H, –OCH_3), 3.83 (s, 3 H, –OCH_3), 3.65 (s, 3 H, –OCH_3), 3.33 (m, 2 H, C′-H_2), 3.29 (s, 3 H, –OCH_3), 3.27 (m, 1 H, C_7-*H*), 3.12 (s, 3 H, –OCH_3), 3.12–3.07 (obscured m, 1 H, C_2-*H*), 3.07 (s, 3 H, –NCH_3), 2.92 (m, 1 H, C_6-*H*), 2.67 (m, 1 H, C_{10}-*H*), 1.63 (d, 3 H, J = 1.3 Hz, C_4-CH_3), 1.16 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.88 (obscured d, 3 H, C_{10}-CH_3), 0.88 (s, 9 H, C(CH_3)$_3$), 0.83 (d, 3 H, J = 6.8 Hz, C_6-CH_3), 0.04 (s, 3 H, SiCH_3), –0.04 (s, 3 H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 175.6, 171.4, 168.1, 154.8, 145.5, 143.8, 137.5, 135.6, 129.7, 119.3, 108.6, 89.5, 80.1, 77.7, 62.8, 61.5, 60.3, 57.5, 57.0, 55.9, 47.6, 40.0, 38.3, 35.7, 31.8, 25.8, 24.4, 18.1, 14.9, 14.0, 12.1, 11.2, –4.6, –5.0; TLC R_f 0.25 (60% ethyl acetate–hexane); exact mass calcd for $C_{37}H_{59}O_{12}N_3S_1Si_1$ + Na requires m/z 820.3486, found m/z 820.3470 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*E*,6*S*,7*R*,10*S*,11*R*)-3-[(*tert*-Butyldimethylsilyl)-oxy]-11-(2,5-dimethoxy-3-nitrophenyl)-8-oxo-*N*,7,11-trimethoxy-*N*,2,4,6,10-pentamethyl-4-undecenamide (20). To a cooled (0 °C) solution of 1.49 g (1.83 mmol) of the β-keto imide **19** in 80 mL of THF and 20 mL of H_2O was added 2.19 g (91.6 mmol) of sodium lithium hydroxide. The reaction mixture was stirred at 0 °C for 5 min and then at rt for 3 h before being quenched by addition of 250 mL of pH = 4.5 NaH_2PO_4 solution. The mixture was extracted with three 150-mL portions of CH_2Cl_2. The aqueous layer was then carefully acidified to pH = 2 with 1 N HCl solution and extracted with 150 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 12-cm silica gel, 35% ethyl acetate–hexane) afforded 870 mg (70%) of the desired ketone **20** as a yellow oil: $[\alpha]_D$ +55° (c 0.86, CH_2Cl_2); IR (thin film) 3000–2800, 1720, 1670, 1540, 1470, 1435, 1360, 1255, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 1 H, J = 3.2 Hz, Ar*H*), 7.15 (d, 1 H, J = 3.2 Hz, Ar*H*), 5.34 (d, 1 H, J = 9.7 Hz, C_5-*H*), 4.53 (d, 1 H, J = 4.1 Hz, C_{11}-*H*), 4.15 (d, 1 H, J = 8.5 Hz, C_3-*H*), 3.90 (s, 3 H, –OCH_3), 3.84 (s, 3 H, –OCH_3), 3.66 (s, 3 H, –OCH_3), 3.35 (s, 3 H, –OCH_3), 3.29 (d, 1 H, J = 4.3 Hz, C_7-*H*), 3.24 (s, 3 H –OCH_3), 3.12 (s, 3 H, –NCH_3), 3.12 (obscured m, 1 H, C_2-*H*), 2.79 (m, 1 H, C_6-*H*), 2.72, (m, 1 H, C_9-*H*), 2.45–2.39 (m, 2 H, C_9-*H* and C_{10}-*H*), 1.62 (d, 3 H, J = 1.1 Hz, C_4-CH_3), 1.16 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.90 (obscured d, 3 H, C_6-CH_3), 0.89 (s, 9 H, C(CH_3)$_3$), 0.83 (d, 3 H, J = 6.5 Hz, C_{10}-CH_3), 0.05 (s, 3 H, SiCH_3), –0.03 (s, 3 H, SiCH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 175.5, 155.1, 145.5, 143.8, 138.2, 135.8, 129.1, 118.8, 108.7, 90.5, 79.9, 79.6, 62.8, 61.4, 59.4, 57.5, 55.9, 42.6, 40.3, 34.9, 33.7, 31.9, 25.8, 19.8, 18.1, 14.6, 14.5, 11.6, –4.6, –5.1; TLC R_f 0.82 (60% ethyl acetate–hexane); exact mass calcd for $C_{33}H_{56}O_{10}N_2Si_1$ + Na requires m/z 691.3602, found m/z 691.3619 (FAB, *m*-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*E*,6*S*,7*R*,8*S*,10*S*,11*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-11-(2,5-dimethoxy-3-nitrophenyl)-8-hydroxy-*N*,7,11-trimethoxy-*N*,2,4,6,10-pentamethyl-4-undecenamide (21). To a cooled (–78 °C) solution of 860 mg (1.28 mmol) of the starting ketone **20** and 521 μL (5.15 mmol) of cyclohexene in 60 mL of CH_2Cl_2 was added 10.3 mL (1.54 mmol) of $Zn(BH_4)_2$ (0.15 mmol in Et_2O). The solution was stirred for 30 min at –78 °C, 1 h at –45 °C, and 1 h at –15 °C before 10 mL of saturated ammonium chloride solution was added to quench the reaction. The mixture was transferred into 120 mL of saturated NH_4Cl solution and 125 mL CH_2Cl_2 and extracted with two 100-mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 12-cm silica gel, solvent gradient: 50% ethyl acetate–hexane to 60% ethyl acetate hexane) afforded 850 mg (98%) of the desired alcohol **21** as a yellow oil: $[\alpha]_D$ +19.8°

(c 1.75, CH_2Cl_2); IR (thin film) 3650–3200, 3020–2820, 1650, 1540, 1475, 1430, 1370, 1260, 1240, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1 H, J = 3.2 Hz, ArH), 7.19 (d, 1 H, J = 3.2 Hz, ArH), 5.31 (d, 1 H, J = 10.0 Hz, C_5-H), 4.49 (d, 1 H, J = 4.8 Hz, C_{11}-H), 4.15 (d, 1 H, J = 9.0 Hz, C_3-H), 3.85 (s, 3 H, $-OCH_3$), 3.84 (s, 3 H, $-OCH_3$), 3.64 (s, 3 H, $-OCH_3$), 3.50 (m, 1 H, C_8-H), 3.44 (s, 3 H, $-OCH_3$), 3.26 (s, 3 H, $-OCH_3$), 3.08 (s, 3 H, $-NCH_3$), 3.08 (obscured m, 1 H, C_2-H), 2.77 (dd, 1 H, J = 5.1, 7.5 Hz, C_7-H), 2.48 (m, 1 H, C_6-H), 2.37 (d, 1 H, J = 5.0 Hz, -OH), 2.04 (m, 1 H, C_{10}-H), 1.56 (d, 3 H, J = 0.9 Hz, C_4-CH_3), 1.49 (m, 2 H, C_9-H_2), 1.18 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.99 (d, 3 H, J = 6.7 Hz, C_6-CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.84 (d, 3 H, J = 6.0 Hz, C_{10}-CH_3), 0.06 (s, 3 H, $SiCH_3$), -0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 155.1, 145.5, 143.7, 138.7, 134.6, 131.6, 118.8, 108.6, 89.4, 81.8, 80.3, 71.2, 62.7, 61.4, 61.0, 57.5, 55.9, 40.2, 35.8, 35.6, 35.5, 31.9, 25.8, 18.2, 16.3, 15.0, 13.9, 11.2, -4.5, -5.0; TLC R_f 0.45 (50% ethyl acetate–hexane); exact mass calcd for $C_{33}H_{58}O_{10}N_2Si_1$ + Na requires m/z 693.3759, found m/z 693.3754 (FAB, m-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*E*,6*S*,8*S*,10*S*,11*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-11-(2,5-dimethoxy-3-nitrophenyl)-*N*,7,8,11-tetramethoxy-*N*,2,4,6,10-pentamethyl-4-undecenamide (22). To a solution of 840 mg (1.25 mmol) of the starting alcohol 21 in 72 mL of anhydrous CH_2Cl_2 was added 1.61 g (7.52 mmol) of Proton Sponge followed by 988 mg (7.52 mmol) trimethyloxonium tetrafluoroborate to produce a brown heterogeneous mixture. The mixture was stirred for 3 h at ambident temperature, at which time the mixture was diluted with 150 mL of CH_2Cl_2. The mixture was washed successively with 200 mL of 1 N sodium bisulfate solution and 200 mL of brine. The resulting yellow solution was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (5-cm × 12-cm silica gel, 35% ethyl acetate/hexane) afforded 730 mg (86%) of the desired adduct 22 as a yellow oil: $[\alpha]_D$ +42.4° (c 1.25, CH_2Cl_2); IR (thin film) 3010–2800, 1665, 1540, 1460, 1360, 1310, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1 H, J = 3.2 Hz, ArH), 7.16 (d, 1 H, J = 3.2 Hz, ArH), 5.25 (d, 1 H, J = 9.7 Hz, C_5-H), 4.47 (d, 1 H, J = 4.3 Hz, C_{11}-H), 4.19 (d, 1 H, J = 8.8 Hz, C_3-H), 3.84 (s, 3 H, $-OCH_3$), 3.83 (s, 3 H, $-OCH_3$), 3.61 (s, 3 H, $-OCH_3$), 3.45 (s, 3 H, $-OCH_3$), 3.33 (s, 3 H, $-OCH_3$), 3.24 (s, 3 H, $-OCH_3$), 3.12 (m, 1 H, C_8-H), 3.07 (m, 1 H, C_7-H), 3.04 (s, 3 H, NCH_3), 3.04 (m, 1 H, C_2-H), 2.41 (m, 1 H, C_6-H), 1.98 (m, 1 H, C_{10}-H), 1.68 (m, 1 H, one of C_9-H), 1.55 (d, 3 H, J = 1.1 Hz, C_4-CH_3), 1.37 (m, 1 H, one of C_9-H), 1.17 (d, 3 H, J = 6.8 Hz, C_2-CH_3), 0.98 (d, 3 H, J = 6.7 Hz, C_6-CH_3), 0.89 (s, 9 H, $C(CH_3)_3$), 0.77 (d, 3 H, J = 6.8 Hz, C_{10}-CH_3), 0.05 (s, 3 H, $SiCH3$), -0.01 (s, 3 H, $SiCH3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 155.0, 145.5, 143.7, 139.1, 134.5, 131.8, 118.9, 108.5, 84.6, 81.9, 80.8, 79.9, 62.7, 61.3, 60.8, 57.6, 57.0, 55.9, 40.1, 35.2, 34.6, 33.5, 32.0, 25.9, 18.2, 16.5, 14.8, 13.8, 11.4, -4.3, -5.0; TLC R_f 0.48 (40% ethyl acetate–hexane); exact mass calcd for $C_{34}H_{60}O_{10}N_2Si_1$ + Na requires m/z 707.3914, found m/z 707.3914 (FAB, m-nitrobenzyl alcohol, added NaI).

(2*R*,3*R*,4*E*,6*S*,7*R*,8*S*,10*S*,11*R*)-[(*tert*-Butyldimethylsilyl)oxy]-11-(2,5-dimethoxy-3-nitrophenyl)-8-hydroxy-*N*,7,8,11-tetramethoxy-*N*,2,4,6,10-pentamethyl-4-undecenal (24). To a cooled (-78 °C) solution of 191 mg (0.279 mmol) of the starting amide 22 in 10 mL of anhydrous THF was added 1.96 mL (1.96 mmol) of DIBAL (1.0 M in toluene). The solution was stirred for 45 min before 20 mL of acetone was added to quench the reaction. The mixture was then gradually warmed to -20 °C over several min, and 100 mL of saturated aqueous tartaric acid solution was added. The solution was extracted with two 75-mL portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (1.5-cm t 10-cm silica gel, 25% ethyl acetate–hexane) afforded 165 mg (95%) of the desired aldehyde 24 as a yellow oil: $[\alpha]_D$ +37.2° (c 3.30, CH_2Cl_2); IR (thin film) 3600–3250, 3050–2800, 1730, 1535, 1460, 1355, 1310, 1250, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, 1 H, J = 1.9 Hz, RCHO), 7.26 (d, 1 H, J = 3.2 Hz, ArH), 7.15 (d, 1 H, J = 3.2 Hz, ArH), 5.22 (d, 1 H, J = 10.2 Hz, C_5-H), 4.45 (d, 1 H, J = 4.0 Hz, C_{11}-H), 4.24 (d, 1 H, J = 6.4 Hz, C_3-H), 3.83 (s, 3 H, $-OCH_3$), 3.82 (s, 3 H, $-OCH_3$), 3.46 (s, 3 H, $-OCH_3$), 3.30 (s, 3 H, $-OCH_3$), 3.22 (s, 3 H, $-OCH_3$), 3.12–3.10 (m, 2 H, C_7-H and C_8-H), 2.53 (m, 1 H, C_2-H), 2.45 (m, 1 H, C_6-H), 1.97 (m, 1 H, C_{10}-H), 1.71 (m, 1 H, one of C_9-H), 1.56 (d, 3 H, J = 1.1 Hz, C_4-CH_3), 1.36 (m, 1 H, one of C_9-H), 1.02 (apparent t, 6 H, C_2-CH_3 and C_6-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.73 (d, 3 H, J = 6.9 Hz, C_{10}-CH_3), 0.02 (s, 3 H, $SiCH_3$), -0.01 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 155.0, 145.5, 143.6, 139.0, 134.8, 130.6, 118.8, 108.5, 84.4, 81.8, 80.9, 77.8, 62.7, 60.8, 57.5, 56.9, 55.9, 51.1, 35.1, 34.8, 33.3, 25.7, 17.9, 17.0, 13.1, 12.4, 9.4, -4.4, -5.1; TLC R_f 0.50 (25% ethyl acetate–hexane); exact mass calcd for $C_{32}H_{55}O_9N_1Si_1$ + Na requires m/z 648.3544, found m/z 648.3528 (FAB, m-nitrobenzyl alcohol, added NaI).

Dimethyl 3-(Methoxycarbonyl)-3-methylprop-2-enylphosphonate (23a). A mixture of 2.05 g (10.6 mmol) of methyl (2*E*)-4-bromo-2-methyl-2-butenoate[57] and 1.97 g (15.9 mmol) of trimethyl phosphite was heated at 110 °C for 60 min. Distillation through a 5-cm Vigreux column (125 °C, 0.1 mm) afforded 1.73 g (73%) of the desired phosphonate 23a as a colorless oil: IR (CH_2Cl_2) 2965, 1718, 1655, 1442, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (m, 1 H, C_2-H), 3.74 (d, 6 H, J = 11 Hz, $POCH_3$), 3.73 (s, 3 H, $-OCH_3$), 2.77 (dd, 2 H, J = 23, 8.3 Hz, C_1-H), 1.87 (br d, 3 H, J = 4.4 Hz, C_3-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (CO_2CH_3), 140.8 (d, J = 10 Hz, C_3), 129.5 (d, J = 11 Hz, C_2), 52.3 (d, J = 7 Hz, $POCH_3$), 51.4 ($-OCH_3$), 26.0 (d, J = 139 Hz, C_1), 12.0 (d, J = 3 Hz, C_3-CH_3); exact mass calcd for $C_8H_{15}O_5P_1$ + Na requires m/z 245.0555, found m/z 245.0572 (FAB, m-nitrobenzyl alcohol, added NaI).

Bis(2,2,2-trifluoroethyl) 3-(Methoxycarbonyl)-3-methylprop-2-enylphosphonate (23c). The neat phosphonate 23a (4.93 g, 22.2 mmol) was treated with 13.9 g (66.6 mmol) of phosphorus pentachloride (PCl_5) to produce a solid mass. Within 60 s the solid mass had become a free-flowing slurry which was stirred at rt for 2 h and then 75 °C for 6 h. The mixture was then cooled to room temperature, and the byproduct $POCl_3$ and residual PCl_5 were removed in vacuo ($POCl_3$, 0.1 mm, rt; PCl_5, 0.1 mm, 75 °C). The unpurified dichloride was then dissolved in 30 mL of anhydrous benzene, and the resulting solution was cooled to 0 °C. In a separate flask, a solution of 19.3 mL (111 mmol) of Hunig's base in 30 mL of anhydrous benzene was treated with 8.10 mL (111 mmol) of 2,2,2-trifluoroethanol. This mixture was the transferred via cannula to the 0 °C solution of the dichloride. The resulting deep orange solution was stirred at 0 °C for 30 min and then rt for 13 h before being concentrated and filtered through a plug of silica gel (5-cm × 12-cm silical gel, 60% ethyl acetate–hexane) to remove base-line material. The filtrate was concentrated, and the residue purified by chromatography (5-cm × 12-cm silica gel, solvent gradient: 25% ethyl acetate–hexane to 50% ethyl acetate–hexane) to afford 3.04 g (38%) of the desired phosphonate 23c as an orange oil which solidified in a -12 °C freezer: IR (CH_2Cl_2) 2965, 1720, 1435, 1300, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (br q, 1 H, J = 7.0 Hz, C_2-H), 4.41 (m, 4 H, $-CH_2CF_3$), 3.78 (s, 3 H, $-OCH_3$), 2.92 (dd, 2 H, J = 8.2, 24.3 Hz, C_1-H), 1.91 (br d, 3 H, J = 5.0 Hz, C_3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (CO_2CH_3), 142.7 (d, J_{CP} = 11 Hz, C_3), 127.1 (d, J_{CP} = 12 Hz, C_2), 125.4 (dq, J_{CF} = 277 Hz, J_{CP} = 13 Hz, $-CF_3$), 62.1 (dq, J_{CF} = 38 Hz, J_{CP} = 6 Hz, $-CH_2CF_3$), 52.0 ($-OCH_3$), 26.7 (d, J_{CP} = 142 Hz, C_1), 12.5 (C_3-CH_3); TLC R_f 0.70 (60% ethyl acetate–hexane); exact mass calcd for $C_{10}H_{13}O_5F_6P_1$ + Na requires m/z 381.0302, found m/z 381.0318 (FAB, m-nitrobenzyl alcohol, added NaI).

2-[3-(Methoxycarbonyl)-3-methylprop-2-enyl]-4,5-dimethyl-2-oxo-1,3,2-dioxaphosholane (23b). The title compound was prepared using a procedure exactly analogous to that described for the trifluoroethyl-derived phosphonate 23c: IR (CH_2Cl_2) 3450, 3000–2800, 1705, 1650, 1430, 1380, 1350, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (br q, 1 H, J = 6.7 Hz, C_2-H), 4.26 (m, 1 H, $-OCHCH_3$), 3.97 (m, 1 H, $-OCHCH_3$), 3.72 (s, 3 H, $-OCH_3$), 2.93 (dd, 2 H, J = 8.3, 23.6 Hz, C_1-H), 1.86 (br d, 3 H, J = 5.1 Hz, C_3-CH_3), 1.37 (d, 3 H, J = 6.2 Hz, $OCHCH_3$), 1.27 (d, 3 H, J = 6.1 Hz, $OCHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5 (CO_2CH_3), 141.4 (br s, C_3), 129.6 (d, J_{CP} = 12 Hz, C_2), 83.2 (s, $OCHCH_3$), 80.5 (s, $OCHCH_3$), 52.0 ($-OCH_3$), 27.7 (d, J_{CP} = 128 Hz, C_1), 17.8 (d, J_{CP} = 6 Hz, $OCHCH_3$), 17.8 (d, J_{CP} = 9 Hz, $OCHCH_3$), 12.5 (C_3-CH_3); TLC R_f 0.70 (60% ethyl acetate–hexane); exact mass calcd for $C_{10}H_{17}O_5P_1$ + Na requires m/z 271.0711, found m/z 271.0723 (FAB, m-nitrobenzyl alcohol, added NaI).

Methyl (2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-7-(*tert*-Butyldimethylsiloxy)-15-(2,5-dimethoxy-3-nitrophenyl)-11,12,-15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoate (25(*Z*)) and Methyl (2*E*,4*E*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,-14*S*,15*R*)-7-(*tert*-Butyldimethylsiloxy)-15-(2,5-dimethoxy-3-nitrophenyl)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoate (25(*E*)). To a cooled (−78 °C) solution of 706 mg (1.97 mmol) of phosphonate **23c** in 10 mL of anhydrous Et_2O was added 1.20 mL (1.97 mmol) of *n*-BuLi (1.64 M in hexane) to produce a peach solution. The solution was stirred at −78 °C for 15 min and then −20 °C for 15 min before being recooled to −78 °C. A cooled (−78 °C) solution of 154 mg (0.246 (mmol) of aldehyde **24** in 3 mL of anhydrous Et_2O was then transferred to the reaction mixture via cannula, and the resulting mixture was stirred for 4 h at −78 to −60 °C. The reaction mixture was then quenched with 50 mL of saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The ^1H NMR (500-MHz) spectrum of the residue showed the reaction to have proceeded with ~3:1 selectivity (*E*,*Z*:*E*,*E*). Purification of the residue by chromatography (2X: 5-cm × 12-cm, 5% ethyl acetate, CH_2Cl_2) afforded 83 mg of a mixture of the undesired ester (**25(*E*)** and some recovered phosphonate **23c**, in addition to 139 mg (78%) of the desired *E*,*Z* unsaturated ester **25(*Z*)**, contaminated with ~5% of recovered aldehyde **24**. The data for the unsaturated ester **25(*Z*)** follow: $[\alpha]_D$ +53.2° (*c* 0.70, CH_2Cl_2); IR (thin film) 3000–2800, 1795, 1735, 1700, 1600, 1530, 1450, 1350, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1 H, *J* = 12.8 Hz, C_3-*H*), 7.26 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.13 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 6.11 (apparent t, 1 H, *J* = 11.7 Hz, C_4-*H*), 5.51 (apparent t, 1 H, *J* = 10.6 Hz, C_5-*H*), 5.10 (d, 1 H, *J* = 9.6 Hz, C_9-*H*), 4.45 (d, 1 H, *J* = 4.1 Hz, C_{15}-*H*), 3.83 (s, 3 H, $-OCH_3$), 3.82 (s, 3 H, $-OCH_3$), 3.74 (s, 3 H, $-OCH_3$), 3.70 (d, 1 H, *J* = 5.0 Hz, C_7-H), 3.44 (s, 3 H, $-OCH_3$), 3.30 (s, 3 H, $-OCH_3$), 3.21 (s, 3 H, $-OCH_3$), 3.13 (br d, 1 H, *J* = 10.5 Hz, C_{12}-*H*), 3.07 (dd, 1 H, *J* = 8.5, 2.2 Hz, C_{11}-*H*), 2.88 (m, 1 H, C_6-*H*), 2.41 (m, 1 H, C_{10}-*H*), 1.91 (m, 1 H, C_{14}-*H*), 1.77 (d, 3 H, *J* = 1.0 Hz, C_2-CH_3), 1.67 (m, 1 H, one of C_{13}-*H*), 1.49 (d, 3 H, *J* = 1.1 Hz, C_8-CH_3), 1.36 (m, 1 H, one of C_{13}-*H*), 1.00 (apparent t, 6 H, *J* = 7.5 Hz, C_6-CH_3 and C_{10}-CH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.67 (d, 3 H, *J* = 6.8 Hz, C_{14}-CH_3), 0.04 (s, 3 H, $SiCH_3$), −0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 155.0, 141.9, 139.0, 136.5, 132.7, 130.6, 127.3, 123.0, 118.9, 118.8, 108.6, 84.6, 83.0, 81.8, 81.2, 62.7, 60.7, 57.6, 56.8, 55.9, 51.8, 37.5, 35.3, 34.5, 33.4, 25.8, 25.7, 18.2, 17.9, 16.7, 13.5, 12.3, 11.7, −4.3, −5.0; TLC R_f 0.50 (5% ethyl acetate–CH_2Cl_2); exact mass calcd for $C_{38}H_{63}O_{10}N_1Si_1$ + Na requires *m*/*z* 744.4119; found *m*/*z* 744.4098 (FAB, *m*-nitrobenzyl alcohol, NaI added).

The data for the unsaturated ester **25(*E*)** follow: $[\alpha]_D$ +57.6° (*c* 0.90, CH_2Cl_2); IR (thin film) 2970–2800, 1710, 1640, 1535, 1470, 1460, 1350, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.14 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 7.05 (d, 1 H, *J* = 11.2 Hz, C_3-*H*), 6.25 (dd, 1 H, *J* = 14.4, 11.3 Hz, C_4-*H*), 5.91 (dd, 1 H, *J* = 15.1, 7.9 Hz, C_5-*H*), 5.11 (d, 1 H, *J* = 9.6 Hz, C_9-*H*), 4.42 (d, 1 H, *J* = 4.1 Hz, C_{15}-*H*), 3.82 (s, 6 H, 2 × $-OCH_3$), 3.72 (d, 1 H, *J* = 7.0 Hz, C_7-*H*), 3.69 (s, 3 H, $-OCH_3$), 3.43 (s, 3 H, $-OCH_3$), 3.27 (s, 3 H, $-OCH_3$), 3.21 (s, 3 H, $-OCH_3$), 3.09 (m, 2 H, C_{12}-*H* and C_{11}-*H*), 2.45 (m, 2 H, C_6-*H* and C_{10}-*H*), 1.93 (m, 1 H, C_{14}-*H*), 1.83 (d, 3 H, *J* = 1.0 Hz, C_2-CH_3), 1.67 (m, 1 H, one of C_{13}-*H*), 1.52 (d, 3 H, *J* = 0.9 Hz, C_8-CH_3), 1.38 (m, 1 H, one of C_{13}-*H*), 1.01 (d, 3 H, *J* = 6.7 Hz, C_6-CH_3) 0.99 (d, 3 H, *J* = 6.4 Hz, C_{10}-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.71 (d, 3 H, *J* = 6.8 Hz, C_{14}-CH_3), 0.01 (s, 3 H, $SiCH_3$), −0.05 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 155.0, 145.6, 145.3, 143.7, 139.0, 138.7, 135.9, 130.6, 125.2, 124.9, 118.9, 108.6, 84.7, 82.3, 81.9, 81.0, 62.7, 60.7, 57.5, 56.9, 55.9, 51.6, 42.1, 35.2, 34.6, 33.7, 25.8, 18.2, 16.8, 16.1, 13.5, 12.5, 12.2, −4.4, −4.9; TLC R_f 0.30 (5% ethyl acetate–CH_2Cl_2); exact mass calcd for $C_{38}H_{63}O_{10}N_1Si_1$ + Na requires *m*/*z* 744.4119, found *m*/*z* 744.4148 (FAB, *m*-nitrobenzyl alcohol, added NaI).

Methyl (2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-15-(3-Amino-2,5-dimethoxyphenyl)-7-(*tert*-butyldimethylsiloxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoate (26(*Z*)). To a solution of 82.5 mg (0.114 mmol) of the nitro ester **25(*Z*)** and 80 μL of quinoline in 20 mL of absolute EtOH was added 165 mg of Lindlar's catalyst (Pd($CaCO_3$)PbO). The resulting black mixture was stirred under an atmosphere of H_2 for 7 h, after which time the system was purged with N_2 and an additional 112 mg of Lindlar's catalyst was added. After an additional 3.5 h under H_2 atmosphere, the system was purged with N_2, and the mixture was filtered through Celite with copiuos EtOH and concentrated. Purification of the residue by rapid flash chromatography (1.5 cm × 12 cm silica gel, solvent gradient: 25% ethyl acetate–hexane to 50% ethyl acetate–hexane) afforded 5 mg (6%) of recovered starting material and 74 mg (94%) of the desired aniline ester **26(*Z*)**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1 H, *J* = 11.9 Hz, C_3-*H*), 6.26 (d, 1 H, *J* = 3.0 Hz, Ar*H*), 6.21 (d, 1 H, *J* = 3.0 Hz, Ar*H*), 6.12 (apparent t, 1 H, *J* = 11.6 Hz, C_4-*H*), 5.52 (apparent t, 1 H, *J* = 10.7 Hz, C_5-*H*), 5.12 (d, 1 H, *J* = 9.6 Hz, C_9-*H*), 4.32 (d, 1 H, *J* = 4.6 Hz, C_{15}-*H*), 3.80 (m, 2 H, $ArNH_2$), 3.74 (s, 3 H, $-OCH_3$), 3.72 (obscured d, 1 H, C_7-*H*), 3.72 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-OCH_3$), 3.43 (s, 3 H, $-OCH_3$), 3.29 (s, 3 H, $-OCH_3$), 3.22 (s, 3 H, $-OCH_3$), 3.15 (br d, 1 H, *J* = 9.0 Hz, C_{12}-*H*), 3.04 (dd, 1 H, *J* = 8.0, 2.5 Hz, C_{11}-*H*), 2.90 (m, 1 H, C_6-*H*), 2.43 (m, 1 H, C_{10}-*H*), 1.94 (m, 1 H, C_{14}-*H*), 1.82 (d, 3 H, *J* = 0.9 Hz, C_2-CH_3), 1.67 (m, 1 H, one of C_{13}-*H*), 1.49 (d, 3 H, *J* = 1.0 Hz, C_8-CH_3), 1.33 (m, 1 H, one of C_{13}-*H*), 1.01 (d, 3 H, *J* = 6.7 Hz, C_6-CH_3), 0.98 (d, 3 H, *J* = 6.7 Hz, C_{10}-CH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.75 (d, 3 H, *J* = 6.8 Hz, C_{14}-CH_3), 0.04 (s, 3 H, $SiCH_3$), −0.03 (s, 3 H, $SiCH_3$); TLC R_f 0.08 (25% ethyl acetate–hexane).

(2*E*,4*Z*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-15-(3-Amino-2,5-dimethoxyphenyl)-7-(*tert*-butyldimethylsiloxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoic Acid (27(*Z*)). To a solution of 74 mg (0.107 mmol) of aniline ester **26(*Z*)** in 20 mL of 2:2:1 MeOH/THF/H_2O was added 51 mg (2.14 mmol) of solid LiOH. The reaction mixture was stirred at ambient temperature for 32 h. The mixture was then concentrated to remove the MeOH and THF, and the dissolved in 50 mL of pH = 4.5 $NaHPO_4$ solution. The mixture was extracted with five 50-mL portions of CH_2Cl_2, with the aqueous layer being saturated with solid NaCl between each extraction. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 72 mg (99%) of the desired aniline acid **27(*Z*)** as a pale yellow glass: ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1 H, *J* = 11.9 Hz, C_3-*H*), 6.29 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 6.23 (d, 1 H, *J* = 3.2 Hz, Ar*H*), 6.16 (apparent t, 1 H, *J* = 11.6 Hz, C_4-*H*), 5.60 (apparent t, 1 H, *J* = 10.7 Hz, C_5-*H*), 5.13 (d, 1 H, *J* = 9.4 Hz, C_9-*H*), 4.34 (d, 1 H, *J* = 4.7 Hz, C_{15}-*H*), 3.75 (d, 1 H, *J* = 4.4 Hz, C_7-*H*), 3.72 (s, 3 H, $-OCH_3$), 3.71 (s, 3 H, $-OCH_3$), 3.44 (s, 3 H, $-OCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.23 (s, 3 H, $-OCH_3$), 3.18 (br d, 1 H, *J* = 9.8 Hz, C_{12}-*H*), 3.06 (dd, 1 H, *J* = 7.9, 2.2 Hz, C_{11}-*H*), 2.91 (m, 1 H, C_6-*H*), 2.43 (m, 1 H, C_{10}-*H*), 1.90 (m, 1 H, C_{14}-*H*), 1.84 (s, 3 H, C_2-CH_3), 1.68 (m, 1 H, one of C_{13}-*H*), 1.50 (s, 3 H, C_8-CH_3), 1.32 (m, 1 H, one of C_{13}-*H*), 1.02 (d, 3 H, *J* = 6.6 Hz, C_6-CH_3), 0.99 (d, 3 H, *J* = 6.6 Hz, C_{10}-CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.78 (d, 3 H, *J* = 6.7 Hz, C_{14}-CH_3), 0.04 (s, 3 H, $SiCH_3$), −0.02 (s, 3 H, $SiCH_3$).

(4*E*,6*Z*,8*S*,9*R*,10*E*,12*S*,13*R*,14*S*,16*S*,17*R*)-9-(*tert*-Butyldimethylsiloxy)-13,14,17,20,22-pentamethoxy-4,8,10,12,16-pentamethyl-2-azabicyclo[16.3.1]docosa-1(22),4,6,10,18,20-hexaen-3-one (28(*Z*)). To a heated solution (85 °C) of 72 mg (0.106 mmol) of the starting amino acid **27(*Z*)** and 371 μL (2.13 mmol) of Hunig's base in 120 mL of anhydrous $PhCH_3$ was added 217 mg (0.852 mmol) of BOP-Cl. The solution was stirred at this temperature for 12 h before it was cooled to room temperature and poured into 50 mL of pH = 4.5 NaH_2PO_4 solution. The layers were separated, and the aqueous layer was extracted with three 50-mL portion of Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (1.5-cm × 12-cm, Et_2O) afforded 46 mg (66% for two steps) of the desired macrocycle **28(*Z*)** as a clear glass: $[\alpha]_D$ +52.4° (*c* 0.70, CH_2Cl_2); IR (CH_2Cl_2) 3030, 2995, 2310, 1715, 1655, 1435, 1360, 1230, 1175, 1055 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.30 (br s, 1 H, N*H*), 6.63 (br s, 1 H, Ar*H*), 6.42 (d, 1 H, *J* = 2.9 Hz, Ar*H*), 5.92 (br d, 1 H, *J* = 10.9 Hz, C_5-*H*), 5.77 (apparent t, 1 H, *J* = 11.0 Hz, C_6-*H*), 5.09 (apparent t, 1 H, *J* = 10.8 Hz, C_7-*H*), 4.87 (d, 1 H, *J* = 10.0 Hz, C_{11}-*H*), 4.30 (d, 1 H, *J* = 5.0 Hz, C_{17}-*H*), 3.68 (s, 3 H, $-OCH_3$), 3.52 (d, 1 H, *J* = 9.7 Hz, C_9-*H*), 3.43 (s, 3 H, $-OCH_3$), 3.39 (s, 3 H, $-OCH_3$), 3.21 (s, 3 H, $-OCH_3$), 3.16 (s, 3 H, $-OCH_3$), 3.10 (d, 1 H, *J* = 9.4 Hz, C_{13}-*H*),

2.84 (m, 1 H, C_{14}-*H*), 2.44 (m, 1 H, C_8-*H*), 2.10 (m, 1 H, C_{12}-*H*), 2.03 (m, 1 H, C_{16}-*H*), 1.78 (s, 3 H, C_4-CH_3), 1.40 (m, 1 H, one of C_{15}-*H*), 0.97 (s, 3 H, C_{10}-CH_3), 0.90 (d, 3 H, J = 6.4 Hz, C_{12}-CH_3), 0.84 (obscured d, 3 H, C_8-CH_3), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.64 (d, 3 H, J = 6.6 Hz, C_{16}-CH_3), 0.55 (m, 1 H, one of C_{15}-*H*), 0.00 (s, 3 H, $SiCH_3$), −0.07 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, D_6-DMSO) δ 173.5, 155.3, 146.2, 136.6, 135.3, 133.9, 133.2, 132.7, 128.7, 123.9, 123.0, 109.3, 108.7, 83.4, 82.4, 81.6, 80.3, 60.6, 59.7, 56.5, 56.1, 54.9, 36.1, 34.9, 34.6, 25.7, 20.5, 18.7, 17.8, 17.7, 15.1, 13.2, 10.2, −4.5, −5.1; TLC R_f 0.49 (Et_2O); exact mass calcd for $C_{37}H_{61}O_7N_1Si_1$ + Na requires m/z 682.4115, found m/z 682.4097 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(4*E*,6*Z*,8*S*,9*R*,10*E*,12*S*,13*R*,14*S*,16*S*,17*R*)-9-(*tert*-Butyldimethylsiloxy)-13,14,17-trimethoxy-4,8,10,12,16-pentamethyl-2-azabicyclo[16.3.1]docosa-4,6,10,18,21-pentaene-3,20,22-trione (29a). To a cooled (−10 °C) solution of 46 mg (69.8 μmol) of macrocycle **28** in 46 mL of 10:1 CH_3CN/H_2O was added 349 μL (0.349 mmol) of 1 N aqueous ceric ammonium nitrate (CAN) solution. The solution was stirred at −10 °C for 10 min before 175 mL (0.175 mmol) of additional CAN solution was added. The resulting yellow-orange solution was stirred for 15 min before it was poured into 100 mL of H_2O. The mixture was extracted with five 50-mL portions of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by chromatography (1.5-cm × 12-cm silica gel, Et_2O) afforded 31 mg (71%) of the desired quinone **29a** as a brilliant yellow oil: $[\alpha]_D$ +180° (*c* 0.62, CH_2Cl_2); IR (CH_2Cl_2) 3380, 3000–2840, 1733, 1647, 1610, 1500, 1400, 1250, 1170, 1120, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1 H, N*H*), 7.34 (d, 1 H, J = 2.5 Hz, Qu*H*), 7.11 (d, 1 H, J = 11.6 Hz, C_5-*H*), 6.63 (apparant t, 1 H, J = 1.7 Hz, Qu*H*), 6.30 (apparant t, 1 H, J = 11.8 Hz, C_6-*H*), 5.85 (apparent t, 1 H, J = 7.8 Hz, C_7-*H*), 5.48 (d, 1 H, J = 10.0 Hz, C_{11}-*H*), 4.47 (br s, 2 H, C_9-*H* and C_{17}-*H*), 3.56 (s, 3 H, $-OCH_3$), 3.49 (m, 1 H, C_{14}-*H*), 3.37 (s, 3 H, $-OCH_3$), 3.32 (s, 3 H, $-OCH_3$), 3.29 (m, 1 H, C_{13}-*H*), 2.93 (m, 1 H, C_8-*H*), 2.53 (m, 1 H, C_{12}-*H*), 2.01 (s, 3 H, C_4-CH_3), 1.71, (m, 2 H, C_{15}-*H*), 1.57 (m, 1 H, C_{14}-*H*), 1.45 (s, 3 H, C_8-CH_3), 1.07 (d, 3 H, J = 6.6 Hz, C_{10}-CH_3), 0.96 (s, 9 H, $SiC(CH_3)_3$), 0.96 (obscured d, 3 H, C_8-CH_3), 0.79 (d, 3 H, J = 7.0 Hz, C_{16}-CH_3), 0.09 (s, 3 H, $SiCH_3$), 0.0 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 184.3, 168.8, 145.7, 144.8, 138.3, 135.6, 132.7, 132.5, 129.4, 128.9, 122.6, 112.9, 102.6, 83.3, 82.4, 79.4, 63.6, 60.3, 58.3, 56.0, 36.7, 34.6, 34.1, 26.1, 18.3, 15.6, 15.0, 13.4, 12.8, 12.3, −3.9, −4.5; TLC R_f 0.95 (Et_2O); exact mass calcd for $C_{35}H_{55}O_7N_1Si_1$ + Na requires m/z 652.3646, found m/z 652.3632; exact mass[58] calcd for $C_{35}H_{55}O_7N_1Si_1$ + 2 H + Na requires m/z 654.3802, found m/z 654.3799 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(4*E*,6*Z*,8*S*,9*R*,10*E*,12*S*,13*R*,14*S*,16*S*,17*R*)-9-hydroxy-13,14,17-trimethoxy-4,8,10,12,16-pentamethyl-2-azabicyclo[16.3.1]docosa-4,6,10,18,21-pentaene-3,20,22-trione (29b). To a yellow solution of 10 mg (0.0159 mmol) of ether **29a** in 3 mL of anhydrous THF was added 160 μL (0.159 mmol) of tetrabutylammonium fluoride (1 M in THF). The resulting deep blue solution was stirred for 42 h before it was diluted with 25 mL of Et_2O. The mixture was washed with 25-mL portions of saturated NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by preparative TLC (0.5-mm plate, 40% ethyl acetate–hexane) afforded 1.0 mg (10%) of recovered **33** and 4.0 mg (51%) of the desired alcohol **29b** as a yellow glass: $[\alpha]_D$ +208° (*c* 0.20, CH_2Cl_2); IR (CH_2Cl_2) 3385, 2970, 2930, 2870, 2830, 1700, 1650, 1610, 1505, 1375, 1200, 1050, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (br s, 1 H, N*H*), 7.32 (d, 1 H, J = 2.4 Hz, Qu*H*), 7.13 (d, 1 H, J = 11.6 Hz, C_5-*H*), 6.63 (apparent t, 1 H, J = 1.7 Hz, Qu*H*), 6.38 (apparant t, 1 H, J = 11.9 Hz, C_6-*H*), 5.86 (br t, 1 H, J = 7.2 Hz, C_7-*H*), 5.51 (d, 1 H, J = 9.3 Hz, C_{11}-*H*), 4.61 (br s, 1 H, C_9-*H*) 4.55 (s, 1 H, C_{17}-*H*), 3.53 (s, 3 H, $-OCH_3$), 3.52 (s, 1 H, C_{14}-*H*), 3.35 (s, 3 H, $-OCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.26 (d, 1 H, J = 9.4 Hz, C_{13}-*H*), 3.03 (m, 1 H, C_8-*H*), 2.48 (m, 1 H, C_{12}-*H*), 2.00 (s, 3 H, C_4-CH_3), 1.68 (m, 3 H, C_{16}-*H* and C_{15}-*H*), 1.47 (s, 3 H, C_{10}-CH_3), 1.09 (d, 3 H, J = 6.4 Hz, C_{12}-CH_3), 0.97 (d, 3 H, J = 7.0 Hz, C_8-CH_3), 0.78 (d, 3 H, J = 7.0 Hz, C_{16}-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 184.4, 168.8, 144.9, 143.7, 138.1, 134.9, 133.1, 132.5, 129.3, 127.9, 123.5, 112.9, 83.7, 83.3, 78.0, 76.8 (obscured), 60.6, 58.4, 55.5, 38.1, 35.0, 34.0, 29.7, 17.7, 15.1, 13.1, 12.3, 11.9; TLC R_f 0.30 (Et_2O); exact mass[58] calcd for $C_{29}H_{41}O_7N_1$ + 2 H + Na requires m/z 540.2937, found m/z 540.2952 (FAB, *m*-nitrobenzyl alcohol, NaI added); field desorption MS requires m/z 515, found m/z 515.

Macbecin I. To a 0 °C solution of 4.0 mg (7.8 μmol) of quinone **29b** in 2 mL of anhydrous CH_2Cl_2 was added 12.6 mg (194 μmol) of sodium cyanate and 15.0 μL (194 μmol) of trfluoroacetic acid. The mixture was stirred at 0 °C for 5 min and at ambident temperature for 3 h before the solution was diluted with 15 mL of CH_2Cl_2 and the reaction quenched by addition of 10 mL of 5% $NaHCO_3$ solution. The product was extracted with three 20-mL portions of CH_2Cl_2 and dried over Na_2SO_4. Purification by preparative TLC (0.5 mm, Et_2O) afforded 1.2 mg (30%) of recovered **29b** and 1.8 mg (41%) of synthetic **macbecin I**: $[\alpha]_D$ +348° (*c* 0.11, $CHCl_3$). (lit. Muroi $[\alpha]_D$ +351° (*c* 0.10, $CHCl_3$), Baker $[\alpha]_D$ +377° (*c* 0.10, $CHCl_3$)); IR ($CHCl_3$) 3540, 3420, 3360, 2980, 2930, 1740, 1695, 1665, 1650, 1610, 1585, 1505, 1460, 1375, 1325, 1240, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, 1 H, N*H*), 7.33 (d, 1 H, J = 2.5 Hz, Qu*H*), 7.12 (d, 1 H, J = 11.7 Hz, C_3-*H*), 6.60 (dd, 1 H, J = 2.5, 1.5 Hz, Qu*H*), 6.33 (dt, 1 H, J = 12.1, 1.8 Hz, C_4-*H*), 5.80 (br s, 1 H, C_7-*H*), 5.66 (dd, 1 H, J = 10.7, 6.8 Hz, C_5-*H*), 5.25 (br s, 1 H, C_9-*H*), 4.69 (br s, 2 H, NH_2) 4.57 (br s, 1 H, C_{15}-*H*), 3.54 (br s, 1 H, C_{12}-*H*), 3.52 (s, 3 H, $-OCH_3$), 3.32 (s, 3 H, $-OCH_3$), 3.29 (s, 3 H, $-OCH_3$), 3.25 (m, 1 H, C_{11}-*H*), 3.08 (m, 1 H, C_6-*H*), 2.48 (m, 1 H, C_{10}-*H*), 1.98 (s, 3 H, C_2-CH_3), 1.68 (m, 2 H, C_{13}-*H*), 1.49 (m, 1 H, C_{14}-*H*), 1.48 (s, 3 H, C_8-CH_3), 1.08 (d, 3 H, J = 6.5 Hz, C_{10}-CH_3), 1.02 (d, 3 H, J = 7.0 Hz, C_6-CH_3), 0.79 (d, 3 H, J = 7.0 Hz, C_{14}-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 184.0, 169.2, 155.8, 144.8, 141.2, 138.2, 133.2, 132.2, 131.6, 129.0, 127.3, 124.2, 112.9, 83.6, 83.0, 79.2, 77.1, 60.3, 58.3, 55.6, 34.7, 33.9, 33.5, 17.3, 15.1, 13.4, 13.2, 12.5; TLC R_f 0.25 (Et_2O); exact mass calcd for $C_{30}H_{42}O_8N_2$ + Na requires m/z 581.2839, found m/z 581.2842; exact mass[58] calcd for $C_{30}H_{42}N_2O_8$ + 2 H + Na requires m/z 583.2995, found m/z 583.2980 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Methyl (2*E*,4*E*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-(3-Amino-2,5-dimethoxyphenyl)-7-(*tert*-butyldimethylsiloxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoate (26(*E*)). The reduction was performed in direct analogy to the method used to produce **26**(*Z*) to afford **26**(*E*) in essentially quantitative yield. The product was immediately used in the next reaction without further purification: ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, 1 H, J = 11.3 Hz, C_3-*H*), 6.27 (d, 1 H, J = 3.1 Hz, Ar*H*), 6.23 (dd, 1 H, J = 15.5, 11.0 Hz, C_4-*H*), 6.21 (d, 1 H, J = 3.0 Hz, Ar*H*), 5.91 (dd, 1 H, J = 15.1, 7.9 Hz, C_5-*H*), 5.12 (d, 1 H, J = 9.4 Hz, C_9-*H*), 4.30 (d, 1 H, J = 4.6 Hz, C_{15}-*H*), 3.75 (m, 2 H, $ArNH_2$), 3.71 (obscured d, 1 H, C_7-*H*), 3.71 (s, 3 H, $-OCH_3$), 3.70 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-OCH_3$), 3.42 (s, 3 H, $-OCH_3$), 3.27 (s, 3 H, $-OCH_3$), 3.22 (s, 3 H, $-OCH_3$), 3.13 (dd, 1 H, J = 7.7, 2.3 Hz, C_{12}-*H*), 3.03 (dd, 1 H, J = 7.9, 2.6, 2.5 Hz, C_{11}-*H*), 2.45 (m, 2 H, C_6-*H* and C_{10}-*H*), 1.94 (m, 1 H, C_{14}-*H*), 1.84 (d, 3 H, J = 0.9 Hz, C_2-CH_3), 1.68 (m, 1 H, one of C_{13}-*H*), 1.52 (d, 3 H, J = 0.7 Hz, C_8-CH_3), 1.38 (m, 1 H, one of C_{13}-*H*), 1.01 (d, 3 H, J = 6.7 Hz, C_6-CH_3), 0.98 (d, 3 H, J = 6.6 Hz, C_{10}-CH_3), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.78 (d, 3 H, J = 6.8 Hz, C_{14}-CH_3), 0.04 (s, 3 H, $SiCH_3$), −0.03 (s, 3 H, $SiCH_3$); TLC R_f 0.10 (25% ethyl acetate–hexane).

(2*E*,4*E*,6*S*,7*R*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-15-(3-Amino-2,5-dimethoxyphenyl)-7-(*tert*-butyldimethylsiloxy)-11,12,15-trimethoxy-2,6,8,10,14-pentamethyl-2,4,8-pentadecatrienoic Acid (27(*E*)). The ester was hydrolyzed in direct analogy to the method used to produce **27**(*Z*) to afford **27**(*E*) in essentially quantitative yield. The product was immediately used in the next reaction without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, 1 H, J = 10.8 Hz, C_3-*H*), 6.32 (d, 1 H, J = 2.8 Hz, Ar*H*), 6.27 (s, 1 H, Ar*H*), 6.22 (dd, 1 H, J = 10.7, 10.7 Hz, C_4-*H*), 5.88 (dd, 1 H, J = 15.1, 7.7 Hz, C_5-*H*), 5.14 (d, 1 H, J = 10.0 Hz, C_9-*H*), 4.25 (d, 1 H, J = 5.9 Hz, C_{15}-*H*), 3.72 (s, 3 H, $-OCH_3$), 3.70 (d, 1 H, J = 4.4 Hz, C_7-*H*), 3.69 (s, 3 H, $-OCH_3$), 3.36 (s, 3 H, $-OCH_3$), 3.26 (s, 3 H, $-OCH_3$), 3.22 (s, 3 H, $-OCH_3$), 3.17 (m, 2 H, C_{12}-*H* and C_{11}-*H*), 2.52 (m, 1 H, C_6-*H*), 2.48 (m, 1

(58) Mass spectra of molecules containing the quinone moiety frequently show ions corresponding to the desired molecular species, in addition to that corresponding to the reduced hydroquinone system. For details on the mass spectrometry of quinone-containing natural products, see: Ishihara, Y.; Shirahata, K.; Sano, H. *J. Antibiot.* **1989**, *42*, 49–53 and references therein.

H, C_{10}-*H*), 1.93 (m, 1 H, C_{14}-*H*), 1.83 (s, 3 H, C_2-CH_3), 1.60 (m, 1 H, one of C_{13}-*H*), 1.52 (s, 3 H, C_8-CH_3), 1.35 (m, 1 H, one of C_{13}-*H*), 1.05 (d, 3 H, J = 6.6 Hz, C_6-CH_3), 0.95 (d, 3 H, J = 6.6 Hz, C_{10}-CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.89 (d obscured, 3 H, C_{14}-CH_3), 0.01 (s, 3 H, $SiCH_3$), −0.04 (s, 3 H, $SiCH_3$).

(4*E*,6*E*,8*S*,9*R*,10*E*,12*S*,13*R*,14*S*,16*S*,17*R*)-9-(*tert*-Butyldimethylsiloxy)-13,14,17,20,22-pentamethoxy-4,8,10,12,16-pentamethyl-2-azabicyclo[16.3.1]docosa-1(22),4,6,10,18,20-hexaen-3-one (28(*E*)). The macrocyclization was performed in direct analogy to the method used to prepare **28(*Z*)** to yield **28(*E*)** in 67% yield: $[\alpha]_D$ +129° (c 0.45, CH_2Cl_2); IR (CH_2Cl_2) 3030, 2950, 1710, 1655, 1600, 1435, 1280 cm^{-1}; ^1H NMR (400 MHz, CD_3CN, 327 K) δ 7.23 (br s, 1 H, N*H*), 6.72 (d, 1 H, J = 2.9 Hz, Ar*H*), 6.67 (d, 1 H, J = 2.9 Hz, Ar*H*), 6.17 (br d, 1 H, J = 10.6 Hz, C_5-*H*), 6.01 (dd, 1 H, J = 15.4, 10.8 Hz, C_6-*H*), 5.79 (dd, 1 H, J = 15.2, 6.1 Hz, C_7-*H*), 5.10 (d, 1 H, J = 10.3 Hz, C_{11}-*H*), 4.52 (d, 1 H, J = 3.9 Hz, C_{17}-*H*), 3.83 (d, 1 H, J = 6.9 Hz, C_9-*H*), 3.75 (s, 3 H, $-OCH_3$), 3.59 (s, 3 H, $-OCH_3$), 3.45 (s, 3 H, $-OCH_3$), 3.32 (s, 3 H, $-OCH_3$), 3.28 (s, 3 H, $-OCH_3$), 3.20 (m, 1 H, C_{13}-*H*), 3.06 (m, 1 H, C_{14}-*H*), 2.44 (m, 2 H, C_8-*H* and C_{12}-*H*), 1.89 (m, 1 H, C_{16}-*H*), 1.66 (d, 3 H, J = 0.8 Hz, C_4-CH_3), 1.33 (s, 3 H, C_{10}-CH_3), 1.10 (m, 1 H, one of C_{15}-*H*), 0.99 (apparent t, 6 H, J = 6.6 Hz, C_{12}-CH_3 and C_8-CH_3), 0.90 (s, 10 H, one of C_{15}-*H* and $SiC(CH_3)_3$), 0.62 (d, 3 H, J = 6.7 Hz, C_{16}-CH_3), 0.06 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$); TLC R_f 0.30 (Et_2O); exact mass calcd for $C_{37}H_{61}O_7N_1Si_1$ + Na requires m/z 682.4115, found m/z 682.4100 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Macrocycle Equilibration Studies. (i) To a solution of 14 mg (21 μmol) of macrocycle **28(*E*)** and 100 μL (0.371 mmol) of tributyltin hydride in 20 mL of anhydrous benzene at 80 °C was added 10 mg (0.061 mmol) of AIBN. An additional 100 μL (0.371 mmol) of tributyltin hydride and 10 mg (0.061 mmol) AIBN were added to the reaction mixture in two portions at 30-min intervals. After 90 min total reaction time thin-layer chromatography analysis (ET_2O as eluant) indicated an approximate 2:1 mixture of **28(*E*)**:**28(*Z*)** (identified by cospotting authentic **28(*E*)** and **28(*Z*)** against the reaction mixture) with a third minor decomposition product appearing as well. The reaction mixture was cooled to rt and concentrated. Preparative TLC (0.5 mm, Et_2O) afforded 3.0 mg (22%) of the desired macrocycle **28(*Z*)**, 5.3 mg (38%) of macrocycle **28(*E*)**, and trace amounts of an unidentifiable decomposition product. The products were identified by spectroscopic comparison to authentic samples.

(ii) To a solution of 1.0 mg (1.5 μmol) of macrocycle **28(*Z*)** and 10 μL (0.0371 mmol) of tributyltin hydride in 1 mL of anhydrous benzene at 80 °C was added 1.5 mg (9.1 μmol) of AIBN. After 90 min, thin-layer chromatography analysis as described above, indicated a reaction mixture qualitatively identical to that produced above in case i. Isolation of the products by preparative TLC (0.5 mm, Et_2O) and comparison of the corresponding 500-MHz ^1H NMR spectra with those measured with authentic samples confirmed their identities.

(iii) To a solution of 1.5 mg (2.3 μmol) of macrocycle **28(*E*)** in 2 mL of anhydrous THF at refluxing temperature was added 1.5 mg (6.9 μmol) of diphenyl disulfide. After 24 h, thin-layer chromatography analysis as described above indicated a reaction mixture qualitatively identical to that produced above in case i. Isolation of the products by preparative TLC (0.5 mm, Et_2O) and comparison of the corresponding 500-MHz ^1H NMR spectra with those measured with authentic samples confirmed their identities.

Acknowledgment. Support for this research was provided by the National Science Foundation and the National Institutes of Health. The NIH BRS Shared Instrument Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities. Dr. Andrew Tyler of the Harvard University Mass Spectrometry facility is acknowledged for expert assistance in mass spectral analysis.

Supplementary Material Available: ^1H or ^{13}C NMR spectra for those compounds which have been submitted to high-resolution mass spectral analysis in lieu of combustion analysis (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.