Total Synthesis of (±)-Deoxypenostatin A. Approaches to the Syntheses of Penostatins A and B

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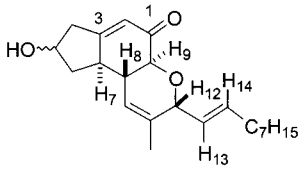
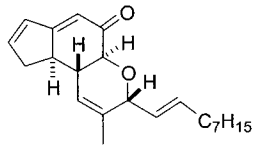
A short synthesis of (±)-deoxypenostatin A (**28**) has been carried out using the convergent coupling of dienal **11**, epoxide **13**, and methylenetriphenylphosphorane (**17**) to prepare trienol **19** in only two steps. The key step is the $Yb(OTf)_3$-catalyzed intramolecular Diels−Alder reaction of hydrated trienyl glyoxylate **23**, which gives lactone **24** stereoselectively. Elaboration of lactone **24** to enone **27** by an intramolecular Horner−Emmons Wittig reaction and epimerization completes the synthesis of **28**. Modest yields of Diels−Alder adducts **45a** and **46a** could be prepared analogously from MEM ether **44c**, but the sensitivity of several of the intermediates precluded the elaboration of **45a** to penostatin A (**1**).

Introduction

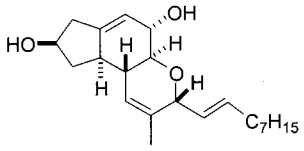
Penostatins A (*ent*-**1**), B (**2**), C (*ent*-**3**), D (**4**), and E (*ent*-**5**) were isolated from a *Penicillium* sp. separated from the green alga *Enteromorpha intestinalis* by Numata and co-workers.[1−3] All the penostatins except for penostatin D exhibited significant cytotoxic activity against P388 cells. Penostatins A and B have the same stereochemistry at C-5 and the opposite stereochemistry at the other four carbons. The novel ring systems and functionality of the penostatins and their cytotoxicity prompted us to undertake their syntheses.



1, α-OH (*ent*-penostatin A)
2, β-OH (penostatin B)



3 (*ent*-penostatin C)



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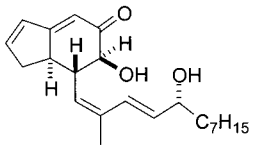

5 (*ent*-penostatin E)

The dihydropyran ring of penostatins A and B (*ent*-**1, 2**) could, in principle, be formed by an intramolecular Diels−Alder reaction with an aldehyde as the dienophile. The obvious precursor **6** was rejected because the tetraenonal functionality was expected to be both synthetically inaccessible and too unstable. Lactone **7** was a more attractive precursor, since it should be easily convertible to **1** and **2** and might be available by an intramolecular Diels−Alder reaction of trienyl glyoxylate **8**. Intramolecular Diels−Alder reactions with aldehydes are known but little studied.[4,5] Intermolecular Diels−Alder reactions of glyoxylate esters have been extensively studied,[5] and intramolecular ene reactions of glyoxylates are known.[6] However, to the best of our knowledge, the only example of an intramolecular Diels−Alder reaction of a glyoxylate ester was reported after this work was completed.[7] Furthermore, the Diels−Alder reaction of **8** can give four stereoisomers. Despite these concerns, this approach is still attractive, since glyoxylate ester **8** should be accessible by the Kornblum procedure[8] from trienol **9**, which should be available in a single step by addition of methylenetriphenylphosphorane to epoxide **10**,[9] deprotonation of the resulting betaine to give a γ-oxido ylide, and addition of dienal **11**.[10]

Results and Discussion

Synthesis of Deoxypenostatin A. We chose to test this scheme by synthesizing deoxypenostatin A (**28**) starting with epoxycyclopentane (**13**) rather than **10**.[11] Dienal **11** was prepared by a Wittig aldol condensation.[12] Addition of propanal to neat cyclohexylamine at -20 °C followed by dehydration gave 76% of imine **12**. Treatment of **12** with LDA afforded the lithium enamide, which was

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(7) Craig, D.; Gordon, R. S. *Tetrahedron Lett.* **1998**, *39*, 8337−8340.

(8) (a) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865−866. (b) Tschaen, D. M.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 2604−2605.

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(10) (a) Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1982**, *104*, 4724−4725. (b) Corey, E. J.; Kang, J.; Kyler, K. *Tetrahedron Lett.* **1985**, *26*, 555−558.

(11) For a preliminary communication see: Snider, B. B.; Liu, T. *J. Org. Chem.* **1999**, *64*, 1088−1089.

(12) Wittig, G.; Hesse, A. In *Organic Syntheses*; Wiley: New York, 1988; *Collect. Vol. 6*, pp 901−904.

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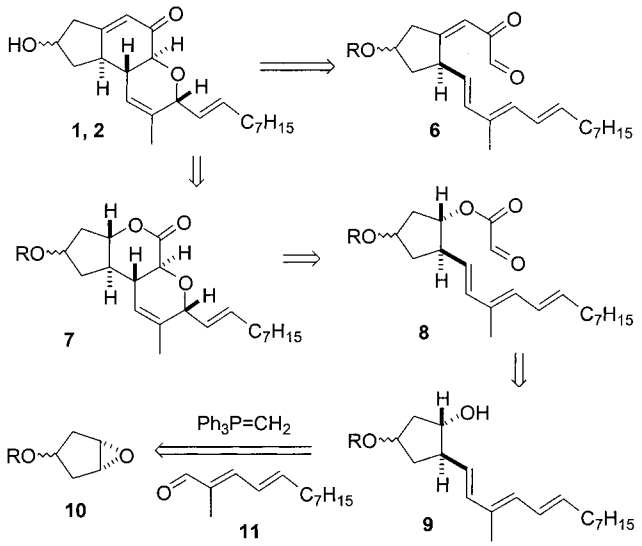
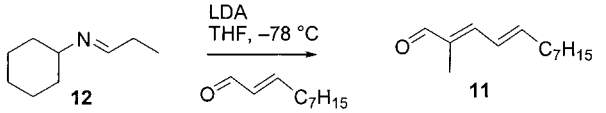
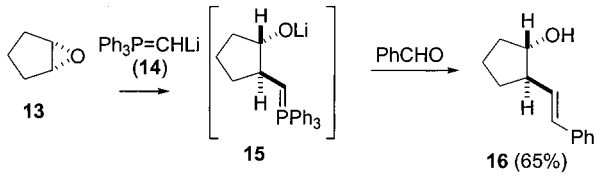


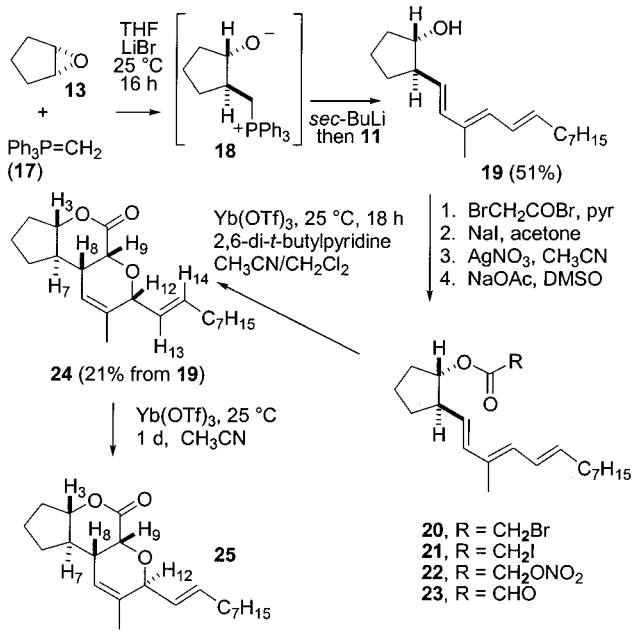
treated with 2-*E*-decenal to afford 81% of dienal **11** containing ≤5% of the 2*Z*-isomer.[13]



In 1982, Corey and Kang reported the preparation and reactivity of α-lithio ylide **14** by treatment of methyltriphenylphosphonium bromide with 2 equiv of *s*-BuLi.[10] Addition of **14** to epoxide **13** generated γ-oxido ylide **15**, which was treated with benzaldehyde to form 65% of the homoallylic alcohol **16**. Despite considerable controversy as to whether the second deprotonation of methyltriphenylphosphonium bromide occurs at the CH_2 group or on the phenyl ring,[14] this route has been widely used to synthesize homoallylic alcohols.[15]



We obtained **19** in <20% yield from **11**, **13**, and **14** prepared either as described above[10a] or from bromomethyltriphenylphosphonium bromide.[10b] Fortunately, a slight variation of the reaction conditions led to 51% of **19**. Treatment of methyltriphenylphosphonium bromide with 1 equiv of *s*-BuLi in THF generated ylide **17** and LiBr, which reacted with epoxycyclopentane (**13**) to give betaine **18**.[16] Treatment of **18** with a second equivalent of *s*-BuLi afforded γ-oxido ylide **15**, which reacted with dienal **11** to give 51% of the required trienol **19** as a single stereoisomer.



Conversion of **19** to crude partially hydrated glyoxylate **23** was accomplished by the Kornblum procedure.[8] Treatment of alcohol **19** with bromoacetyl bromide and pyridine gave the unstable crude bromo ester **20**, which was directly converted to iodo ester **21** with sodium iodide in acetone. Crude **21** was dissolved in the acetonitrile and treated with silver nitrate to afford nitrate ester **22** in 80% yield for this three-step sequence. Treatment of **22** with sodium acetate in DMSO afforded a crude mixture of glyoxylate ester **23** and its hydrate, which decomposed on attempted dehydration. Acid-catalyzed esterification of **19** with glyoxylic acid monohydrate was unsuccessful.[17] Presumably the triene moiety of **23** makes it very sensitive, restricting the methods that can be used to introduce the glyoxylate ester or convert the hydrate to the free aldehyde.

Not surprisingly, Diels–Alder reactions of **23** with strong Lewis acid catalysts or heating were unsuccessful. We were intrigued by the report by Qian and Huang that $Yb(OTf)_3$ catalyzes the Diels–Alder reaction of glyoxylate esters with isoprene, since lanthanide triflates are mild Lewis acids and compatible with water liberated from the hydrate of **23**.[18]

Treatment of crude, partially hydrated **23** with 0.2 equiv of $Yb(OTf)_3$ in 20:1 CH_3CN/CH_2Cl_2 for 2 d afforded a 3:5 mixture of Diels–Alder adducts **24** and **25** in 24% yield from trienol **19**, whose structures were established by NOE experiments. We observed strong NOE cross-peaks in the minor product **24** between H-3 and H-8, H-3 and H-9, H-8 and H-9, and H-9 and H-12. These results established that these four hydrogens are on the same side of the molecule, so the adduct must be **24**. We observed strong NOE cross-peaks in the major product **25** between H-3 and H-8, H-3 and H-9, and H-8 and H-9, but no cross-peaks from either H-8 or H-9 to H-12. This

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(17) Whitesell, J. K.; Lawrence, R. M.; Chen, H. *J. Org. Chem.* **1986**, *51*, 4779–4784.

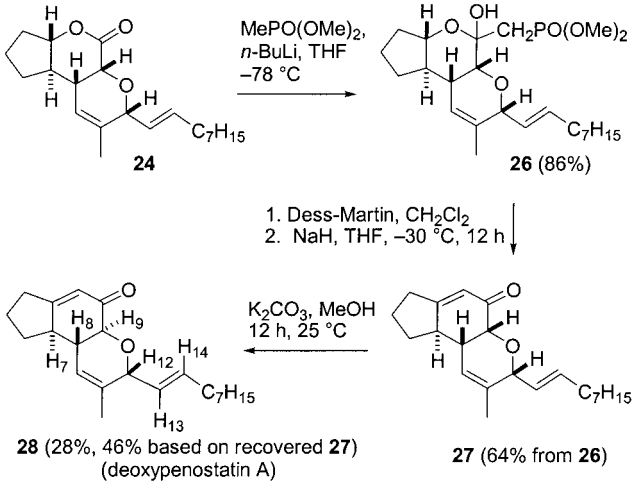
(18) Qian, C.; Huang, T. *Tetrahedron Lett.* **1997**, *38*, 6721–6724.

suggests that the major product **25** differs from the minor product **24** only in the stereochemistry at C-12.

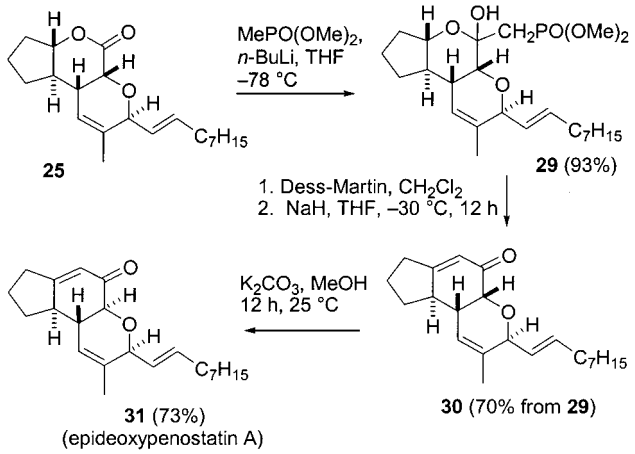
Lactone **25** cannot be a primary adduct, since Diels–Alder addition to an *E*,*E*-diene must give products with H-8 and H-12 cis. It is probably formed by isomerization at the doubly allylic C-12 in **24**. This was established by treatment of **24** with $Yb(OTf)_3$ in CH_3CN for 1 d to afford a 1:1 mixture of **24** and **25**, indicating that the pyran of **24** opens to the pentadienyl cation in the presence of Lewis or Brønsted acids. No isomerization occurs on treatment of **25** with $Yb(OTf)_3$ in CH_3CN for 3 d, suggesting that **25** is more thermodynamically stable than **24**. The recent isolation of penostatin E (*ent*-**5**)[3] suggests that this process is equally facile in nature. Acid-catalyzed ring opening of the pyran of penostatin C (*ent*-**3**) and reaction of the pentadienyl cation with water at the distal position will give *ent*-**5**.

Fortunately, this isomerization can be suppressed by carrying out the Diels–Alder reaction in the presence of 2,6-di-*tert*-butylpyridine. Treatment of a 0.01 M solution of crude **23** in 15:1 CH_3CN/CH_2Cl_2 with 0.2 equiv of $Yb(OTf)_3$ and 0.15 equiv of 2,6-di-*tert*-butylpyridine for 18 h provided **24** as a single stereoisomer in 21% overall yield from alcohol **19**. Diels–Alder adduct **24** is one of two possible endo products and has the same stereochemistry as the penostatins at all centers except C-9, which should be readily epimerizable since it is adjacent to the carbonyl group.

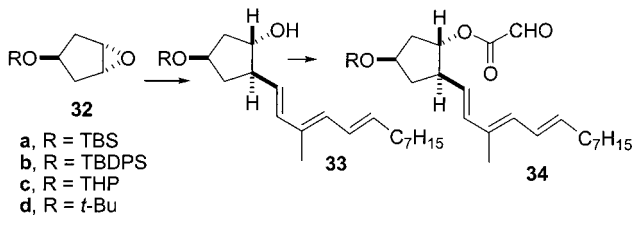
Treatment of lactone **24** with $LiCH_2PO(OMe)_2$ gave 86% of the hydroxy keto phosphonate as hemiacetal **26**. Oxidation of **26** with the Dess–Martin reagent in CH_2Cl_2 provided the unstable diketophosphonate, which was treated with NaH in THF[19] at −30 °C overnight to give cyclohexenone **27** in 52% (64% based on recovered **26**) yield. Although **27** is somewhat unstable to base, isomerization with K_2CO_3 in MeOH for 12 h at 25 °C afforded 28% of deoxypenostatin A (**28**) and 40% of recovered **27**. This is not an equilibrium mixture, since **28** was not isomerized back to **27** under these conditions. Unfortunately, isomerization of **27** for longer periods of time resulted in extensive decomposition, which precluded the determination of the equilibrium ratio under these isomerization conditions. The ^1H and ^{13}C NMR spectral data of **28** are identical to those of penostatins A and B, except for the expected differences in the cyclopentane ring.



An analogous series of reactions converted lactone **25** to *epi*-deoxypenostatin A (**31**). Treatment of **25** with $LiCH_2PO(OMe)_2$ gave 93% of the hydroxy keto phosphonate as hemiacetal **29**. Oxidation of **29** with the Dess–Martin reagent in CH_2Cl_2 provided the unstable diketophosphonate, which was treated with NaH in THF at −30 °C overnight to give cyclohexenone **30** in 70% yield. Isomerization of **30** with K_2CO_3 in MeOH for 12 h at 25 °C afforded 73% of *epi*-deoxypenostatin A (**31**) as the only product.



Approaches to the Syntheses of Penostatins A and B. We have developed a very short, convergent synthesis of deoxypenostatin A (**28**) that features a novel, stereoselective, intramolecular Diels–Alder reaction of hydrated glyoxylate ester **23** catalyzed by $Yb(OTf)_3$. We now turned our attention to the application of this sequence to the synthesis of penostatin B (**2**). *trans*-Epoxide **32a**[9] was converted to trienol **33a** in 42% yield analogously to the preparation of **19**. The Kornblum sequence afforded a 68% yield of the nitrate ester, which was converted to crude partially hydrated glyoxylate **34a** with NaOAc in DMSO. To our surprise, treatment of crude **34a** with 0.35 equiv of $Yb(OTf)_3$ and 0.25 equiv of 2,6-di-*tert*-butylpyridine in 20:1 of CH_3CN and CH_2Cl_2 for more than 2 d afforded polymer but no desired Diels–Alder product. No adduct was obtained with excess $Yb(OTf)_3$ with or without di-*tert*-butylpyridine. Heating **34a** in toluene at 160 °C in a resealable tube led to extensive decomposition. We investigated other Lewis acids that have been used to catalyze Diels–Alder reactions of aldehydes. Unfortunately, treatment of **34a** with $BiCl_3$[20] or scandium(III) perfluorooctanesulfonate[21] with or without di-*tert*-butylpyridine was also unsuccessful.



Since the Diels–Alder reaction was not compatible with the TBDMS ether, we prepared the more hindered

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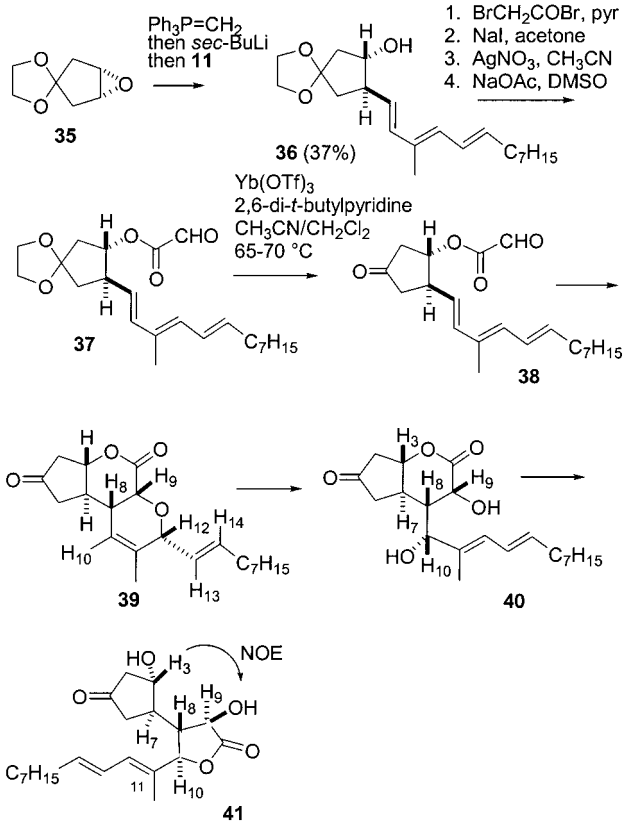
(21) Hanamoto, T.; Sugimoto, Y.; Jin, Y.; Inanaga, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1421–1426.

TBDPS ether **32b** in 65% yield[22] by silylation of 3-cyclopentenol[23] and epoxidation.[9] The Wittig sequence afforded 36% of **33b**, which was elaborated to **34b**. Unfortunately, the attempted Diels−Alder reaction of **34b** resulted in polymerization. Since we thought that the silyl ether might be incompatible with the Diels−Alder reaction, we prepared **34c** from THP epoxide **32c**[9] analogously, which also did not undergo the Diels−Alder reaction. Finally we prepared *tert*-butyl ether epoxide **32d** from 3-cyclopentenol by protection[27] and epoxidation in 72% yield.[22] The Wittig sequence afforded 32% of **33d**, which was elaborated to **34d**. Attempted Diels−Alder reaction with $Yb(OTf)_3$ and di-*tert*-butylpyridine in CH_3CN with or without added water,[25] tris(pentafluorophenyl)-borane,[26] $La(OTf)_3$, $Sm(OTf)_3$, or $Sc(OTf)_3$ was unsuccessful. Heating **34d** with $Yb(OTf)_3$ and di-*tert*-butylpyridine in acetonitrile hydrolyzed the ester to give **33d**.

We next prepared ketal protected glyoxylate ester **37** by carrying out the Wittig sequence to give 37% of **36** from epoxy ketal **35**.[27] The Kornblum sequence on **36** gave crude partially hydrated glyoxylate **37**. Treatment of crude **37** with 2 equiv of $Yb(OTf)_3$ and 1 equiv of 2,6-di-*tert*-butylpyridine in 1:10 CH_2Cl_2 and CH_3CN at 70 °C for 6 h afforded **41** in 28% overall yield from alcohol **36**. The initial reaction is hydrolysis of the ketal, since ketone **38** can be isolated after reaction for 0.5 h. The desired Diels−Alder reaction then occurs to give **39**. Unfortunately, the pyran ring is cleaved by acid to form δ-lactone diol **40**, which isomerizes to the more stable γ-lactone **41**.



The structure of **41** was determined by analysis of the ^1H and ^{13}C NMR and IR spectra and $^1H-^1H$ COSY and 1D NOESY experiments. TLC analysis showed that **41** was very polar (R_f = 0.20; hexane:EtOAc 1/9), which suggested that it contained free hydroxyl groups. The TLC spot absorbed at 254 nm, suggesting that it contained a conjugated diene. The presence of a conjugated diene was confirmed by the absorptions for the central hydrogens of the conjugated diene at δ 6.20 and 6.12. The carbonyl groups of **41** absorb at 1775 and 1744 cm^{-1}, as expected for a γ-butyrolactone and a cyclopentanone, respectively. The absorption at 1775 cm^{-1} is not consistent with that expected for the δ-valerolactone of **40**, which should come at 1748 cm^{-1} as in **24**. Furthermore, the absorption for H-9 at δ 4.52 (d, J = 10.4) is not consistent with that expected for the cis coupling between H-8 and H-9 in **40**, which should be 2−5 Hz.

The most characteristic ^1H NMR peak of **41** is that of H-8 at δ 2.41 (ddd, 1, J = 10.4, 10.1, 10.1). The large vicinal coupling constants between H-8 and H-9 and H-8 and H-10 establish that H-8 is trans to both H-9 and H-10 on the lactone ring. Theoretical and experimental studies indicate that one or both coupling constants are smaller in the other three lactone stereoisomers.[28] The NOE between H-8 and the allylic methyl group confirms that H-8 and the conjugated diene side chain are cis on the lactone. Since H-3 and H-7 are trans in the starting material, there are only two possible structures that have the three substituents on the γ-butyrolactone in a trans, trans relationship. The large coupling constant between H-7 and H-8 establishes that H-7 is antiperiplanar to H-8 in the predominant conformation of the product. The structure was assigned as **41** on the basis of the NOE between H-3 and C-9-OH, which should be observed only in **41**.

The formation of **41** was encouraging, since it indicated that the Diels−Alder reaction could occur with an oxygenated cyclopentane. However, we needed to develop milder conditions so that Diels−Alder adduct **39** would not react further. Treatment of **37** with 1.6 equiv of $In(OTf)_3$[29] and 1 equiv of 2,6-di-*tert*-butylpyridine in 1:4 CH_2Cl_2 and CH_3CN at 25 °C for 12 h also gave **41** in 19% yield from **36**. Fortunately, reaction of crude **37** with only 0.6 equiv of $Yb(OTf)_3$ in 1:5 CH_2Cl_2/CH_3CN at 65 °C for 3 h afforded the desired Diels−Alder product **39** in 14% overall yield from alcohol **36**. At longer reaction times, rearrangement occurs to give **41**. The characteristic downfield ^1H NMR absorptions of **39** at δ 5.78 (dt, 1, J = 15.3, 6.7, H-14), 5.59 (br d, 1, J = 6.1, H-10), 5.27 (dd, 1, J = 15.3, 8.5, H-13), 4.45 (br d, 1, J = 8.5, H-12), and 4.40 (d, 1, J = 3.7, H-9) are comparable to those of **24** at δ 5.78 (dt, 1, J = 15.3, 7.2), 5.52 (br d, 1, J = 5.5), 5.31 (dd, 1, J = 15.3, 8.6), 4.51 (br d, 1, J = 8.6), and 4.26 (d, 1, J = 4.6).

The success of this Diels−Alder reaction was quite encouraging. However, the loss of the ketone protecting group complicates the conversion of the lactone to the cyclohexenone, so we decided to examine Diels−Alder reactions of a cyclopentanol protected as the methyl ether, the smallest and most stable hydroxy-protect-

(22) 13−18% of the cis epoxide was also formed.
(23) Hess, H. M.; Brown, H. C. *J. Org. Chem.* **1967**, *32*, 4138−4139.
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(26) Ishihara, K.; Hanaki, N.; Funahashi, M.; Miyata, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721−1730.
(27) Lai, S.; Mendoza, J.; Hubbard, F.; Kalter, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2155−2160.
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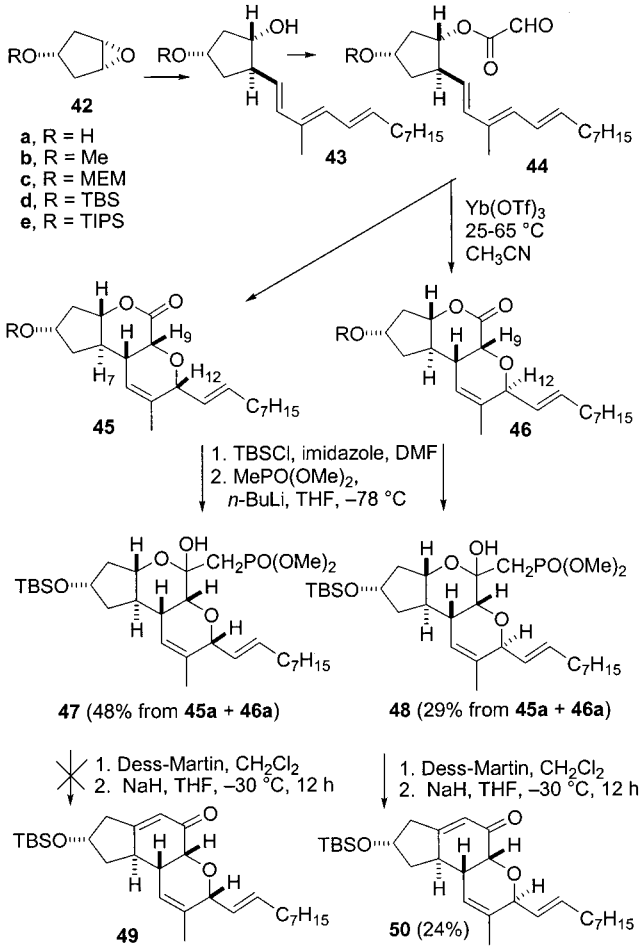
ing group. Epoxidation of 3-methoxycyclopentene with *m*-CPBA gave an inseparable mixture of volatile epoxides. Epoxidation of 3-cyclopentenol with *tert*-butyl hydroperoxide and a catalytic amount of $VO(acac)_2$[9] gave 80% of *cis*-3,4-epoxycyclopentanol (**42a**), which was treated with MeI and sodium hydride to afford 90% of *cis*-4-methoxy-1,2-epoxycyclopentane (**42b**). The Wittig sequence afforded 20% of trienol **43b**, which was converted to partially hydroxylated glyxoylate ester **44b** by the Kornblum sequence.



Treatment of crude **44b** with 0.6 equiv of $Yb(OTf)_3$ and 0.7 equiv of 2,6-di-*tert*-butylpyridine in 1:4 CH_2Cl_2 and CH_3CN at 25 °C overnight afforded a 1:1 inseparable mixture of Diels–Alder product **45b** and isomer **46b** in 10% yield from **43b**. The most characteristic peaks in the ^1H NMR spectrum are at δ 4.52 (br d, 1, J = 8.4, H-12), and 4.27 (d, 1, J = 4.3, H-9) for **45b**, which are comparable to those at δ 4.51 (br d, 1, J = 8.6), 4.26 (d, 1, J = 4.6) in **24**, and at δ 4.76 (br d, 1, J = 7.3, H-12), and 4.64 (d, 1, J = 8.5, H-9) in **46b**, which are comparable to those at δ 4.75 (br d, 1, J = 8.0), 4.63 (d, 1, J = 8.6) in **25**. The isolation of the Diels–Alder adducts with the methoxy protecting group was encouraging, but the pyran will not withstand the conditions required for deprotection.

cis-4-MEMO-1,2-epoxycyclopentane (**42c**) was prepared in 80% yield by treatment of **42a** with MEMCl and *N*,*N*-diisopropylethylamine. The Wittig sequence afforded 37% of trienol **43c**. The Kornblum sequence afforded partially hydrated glyoxylate **44c**. Treatment of crude **44c** with only 0.6 equiv of $Yb(OTf)_3$ in 1:10 CH_2Cl_2 and CH_3CN at 65 °C for 2.5 h afforded a 3:2 inseparable mixture of Diels–Alder adducts **45a** and **46a** in 16% yield from **43c**. The most characteristic peaks in the ^1H NMR spectrum are at δ 4.52 (br d, 1, J = 7.9, H-12), and 4.27 (d, 1, J = 4.9, H-9) for **45a**, which are comparable to those at δ 4.51 (br d, 1, J = 8.6), and 4.26 (d, 1, J = 4.6) in **24**, and at δ 4.77 (br d, 1, J = 6.7, H-12), and 4.64 (d, 1, J = 7.9, H-9) for **46a**, which are comparable to those at δ 4.75 (br d, 1, J = 8.0), and 4.63 (d, 1, J = 8.6) in **25**. Quenching the reaction after 30 min afforded mainly **44a**, indicating that hydrolysis of the MEM ether precedes the Diels–Alder reaction. Unfortunately the isomerization of **45a** to **46a** could not be prevented by addition of 2,6-di-*tert*-butylpyridine to the reaction mixture, since neither hydrolysis of the MEM ether nor Diels–Alder reaction occur after 5 h at 80 °C.

Treatment of the mixture of **45a** and **46a** with imidazole and TBSCl gave the crude silyl ethers **45d** and **46d**. Unfortunately, **45d** easily isomerized to **46d** on silica gel. Therefore, the crude mixture of **45d** and **46d** was treated with excess $LiCH_2PO(OMe)_2$ to give a chromatographically separable mixture of hydroxy keto phosphonate hemiacetals **47** (48% from **45a** and **46a** mixture) and **48** (29% from **45a** and **46a** mixture).

The structures of **47** and **48** were determined by comparison of the NMR spectra with those of **26** and **29**. The ^1H NMR spectrum of **47** is very similar to that of **26**, except for the expected differences in the cyclopentane ring. The most characteristic peaks in **26** are at δ 5.64 (br s, 1), 4.35 (br d, 1, J = 8.5) and 3.35 (d, 1, J = 1.8), which are comparable to those at δ 5.61 (br s, 1), 4.35 (br d, 1, J = 8.6), and 3.35 (d, 1, J = 2.2) in **26**. The ^1H NMR spectrum of **48** is very similar to that of **29**, except for the expected differences in the cyclopentane ring. The most characteristic peaks in **48** are at δ 4.42 (br d, 1, J = 6.7) and 3.47 (d, 1, J = 2.4), which are comparable to those at δ 4.40 (br d, 1, J = 6.7) and 3.48 (d, 1, J = 2.5) in **29**.

Oxidation of **47** with the Dess–Martin reagent in CH_2Cl_2 provided the unstable diketophosphonate, which was treated with NaH in THF at −30 °C overnight. Unfortunately, the desired enone **49** was not formed. Decomposition occurred at 0 °C. Use of DBU and LiCl as the base also failed.[30]

Oxidation of **48** with the Dess–Martin reagent in CH_2Cl_2 provided the unstable diketophosphonate, which was treated with NaH in THF at −30 °C overnight to give 24% of protected bis-*epi*-penostatin A (**50**). The proton spectrum of **50** is very similar to that of **30**, except for the expected differences in the cyclopentane ring. The most characteristic peaks in **50** are at δ 5.98 (br s, 1), 4.51 (d, 1, J = 6.1), and 3.93 (d, 1, J = 3.7), as compared to δ 5.99 (br s, 1), 4.46 (d, 1, J = 6.7), and 3.90 (d, 1, J = 3.4) in **30**.

These results indicate that the intramolecular glyoxylate Diels–Alder reaction is very sensitive to the oxygen functionality on the cyclopentane ring. The reaction proceeds in modest yield with some scrambling at C_{12} with cyclopentanone **38** and **44b** and **44a**, with methoxy and hydroxy groups cis to the glyoxylate ester. We were not able to determine whether this stereochemical relationship was important, because substrates with methoxy

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and MEM ethers trans to the hydroxy group could not be prepared. However, we prepared **44e** with a hindered TIPS ether, which is known to coordinate poorly to Lewis acids[31] to test whether **44e** with a silyl ether cis to the glyxoylate would undergo the Diels−Alder reaction better than **34a** and **34b** with the silyl ether trans to the glyxoylate.

Treatment of **42a** with TIPSCl and imidazole gave 80% of the required epoxide **42e**. The Wittig sequence gave 41% of triene alcohol **43e**, which was converted to crude partially hydrated glyoxylate ester **44e** by the Kornblum procedure. Treatment of **44e** with $Yb(OTf)_3$ with or without 2,6-di-*tert*-butylpyridine gave no Diels−Alder product, suggesting that the protecting group is more important than the stereochemistry for the success of the intramolecular Diels−Alder reaction.

In conclusion, we have developed an eleven-step, convergent synthesis of deoxypenostatin A (**28**) that features a novel, stereoselective, intramolecular Diels−Alder reaction of a hydrated glyoxylate ester catalyzed by $Yb(OTf)_3$ and a convergent Wittig sequence that formed triene alcohol **19** in only two steps. Diels−Alder adducts **45a** and **46a** could be prepared in modest yield analogously from MEM ether **44d**, but the sensitivity of several of the intermediates precluded the elaboration of **45a** to penostatin A (**1**).

Experimental Section

General. NMR spectra were recorded at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in hertz. IR spectra are reported in cm^{-1}.

2-Methyl-2*E*,4*E*-dodecadienal (11). Cyclohexanamine (10 g, 100 mmol) was added to a dry, 250-mL, round-bottomed flask fitted with a magnetic stir bar. The flask was flushed with N_2 and cooled to −20 °C. Propionaldehyde (7 g, 120 mmol) was added dropwise via a cannula over 10 min. During the initial phase of this addition a large amount of white solid separated, which redissolved as the addition was continued. The resulting cold solution was stirred for 1 h, at which time a large amount of white solid separated and further stirring was impractical. The resulting mixture was allowed to stand for 20 min and 5 g of anhydrous Na_2SO_4 was added. The whole mixture was allowed to melt and warm to 25 °C under N_2 and then was gravity filtered. The residue was washed with ether. The combined filtrates were dried (Na_2SO_4) and concentrated to give 19.6 g of crude imine, which was distilled under reduced pressure to provide 10.5 g (76%) of *N*-propylidenecyclohexanamine (**12**) as a colorless liquid: bp 42−45 °C (3 Torr); ^{1}NMR 7.67 (t, 1, J = 4.9), 2.90 (m, 1), 2.22 (qd, 2, J = 7.3, 4.9), 1.1−1.8 (m, 10), 1.07 (t, 3, J = 7.3).

A solution of diisopropylamine (5.5 g, 54 mmol) in 50 mL of dry THF was treated dropwise with *n*-BuLi (21 mL, 2.5 M, 52.5 mmol) under N_2 at 0 °C. The solution was stirred for 20 min, a solution of 7 g (50 mmol) of **12** in 40 mL of dry THF was added dropwise via a cannula to the cold (0 °C) solution of lithium diisopropylamide, and the resulting solution was stirred for 30 min. This solution was then cooled to −78 °C and a solution of 7.5 g of *trans*-2-decenal (49 mmol) was added over 20 min. The mixture was stirred at −78 °C for 6 h and quenched with saturated aqueous oxalic acid (100 mL) at 0 °C. The mixture was stirred at 0 °C for 6 h and extracted with ether (4 × 100 mL). The combined organic layers were washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated under reduced pressure to give 12.5 g of crude **11**. Flash chromatography on silica gel (97:3 hexane/EtOAc) gave ≤5% of the 2(*Z*)-isomer of **11** followed by 7.82 g (81%) of pure **11**.

Data for the 2(*Z*)-isomer: ^{1}H NMR 10.27 (s, 1), 7.00 (dd, 1, J = 14.1, 11.6), 6.91 (d, 1, J = 11.6), 6.03 (dt, 1, J = 14.1, 7.0), 2.21 (br dt, 2, J = 7.0, 7.3), 1.82 (s, 3), 1.5−1.2 (m, 10), 0.88 (t, 3, J = 6.7). These data correspond closely to those reported for 2-methyl-2*Z*,4*E*-hexadienal.[32]

Data for **11**: ^{1}H NMR 9.41 (s, 1), 6.81 (d, 1, J = 11.6), 6.51 (ddt, 1, J = 15.2, 11.6, 1.5), 6.24 (dt, 1, J = 15.2, 7.3), 2.24 (br dt, 2, J = 7.3, 7.3), 1.83 (s, 3), 1.5−1.2 (m, 10), 0.88 (t, 3, J = 6.7); ^{13}C NMR 195.1, 149.4, 146.0, 135.9, 125.8, 33.5, 31.7, 29.2, 29.1, 28.8, 22.6, 14.1, 9.4; IR (neat) 1683, 1635; HRMS (DCI/NH_3) calcd for $C_{13}H_{23}O$ (MH^+) 195.1748, found 195.1746.

***trans*-2-(3-Methyl-1*E*,3*E*,5*E*-tridecatrienyl)cyclopentanol (19).** *s*-BuLi (1.3 M, 13 mL, 16.9 mmol) was added dropwise over 20 min to a solution of methyltriphenylphosphonium bromide (5 g, 14 mmol) in 50 mL of anhydrous ether at −78 °C under N_2. The solution was stirred for 20 min at −78 °C, 1.5 h at −40 °C, and 3 h at 25 °C. The resulting orange-red suspension was cooled to 0 °C, and a solution of cyclopentene oxide (**13**) (1.34 g, 16 mmol) in 15 mL of dry THF was added. Stirring for 16 h at 25 °C furnished a brown suspension which was cooled to −78 °C and treated with *s*-BuLi (1.3 M, 13 mL, 16.9 mmol) dropwise over 20 min. After stirring for 20 min at −78 °C, 1 h at −40 °C, and 3 h at 25 °C, the resulting brown solution was cooled to −78 °C and treated with a solution of dienal **11** (2.3 g, 12 mmol) in 30 mL of THF. After stirring for 6 h at 25 °C, the reaction mixture was quenched by the addition of water (50 mL). The solution was extracted with ether (3 × 80 mL), which was dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica gel (95:5 hexane/EtOAc) gave 0.72 g (32%) of 3-methyl-1,3*E*,5*E*-tridecatriene followed by 1.69 g (51%) of pure **19** as a colorless liquid.

Data for 3-methyl-1,3*E*,5*E*-tridecatriene: ^{1}H NMR 6.39 (dd, 1, J = 10.5, 17.5), 6.36 (ddt, 1, J = 10.9, 14.9, 1.3), 6.04 (d, 1, J = 10.9), 5.76 (dt, 1, J = 14.9, 7.1), 5.14 (d, 1, J = 17.5), 5.00 (d, 1, J = 10.5), 2.15 (dt, 2, J = 7.1, 8.5), 1.85 (s, 3), 1.5−1.1 (m, 10), 0.88 (t, 3, J = 6.8).

Data for **19**: ^{1}H NMR 6.34 (ddt, 1, J = 15.0, 11.0, 1.8), 6.17 (d, 1, J = 15.9), 5.98 (d, 1, J = 11.0), 5.71 (dt, 1, J = 15.0, 6.7), 5.54 (dd, 1, J = 15.9, 8.3), 3.86 (dddd, 1, J = 7.0, 7.0, 7.0, 3.4), 2.38 (dddd, 1, J = 8.3, 8.4, 8.4, 7.0), 2.12 (br dt, 2, J = 6.7, 7.3), 2.05−1.90, (m, 2), 1.82 (s, 3), 1.80−1.70 (m, 1), 1.7−1.5 (m, 2), 1.63 (d, 1, J = 3.4, OH), 1.5−1.35 (m, 3), 1.2−1.35 (m, 8), 0.88 (t, 3, J = 6.8); ^{13}C NMR 135.7, 135.6, 132.4, 130.2 (2), 126.6, 78.9, 52.4, 33.4, 33.2, 31.8, 30.3, 29.5, 29.2 (2), 22.6, 21.2, 14.1, 12.7; IR (neat) 3344, 965; HRMS (DEI) calcd for $C_{19}H_{32}O$ (M^+) 276.2453, found 276.2448.

A similar reaction using crude **11** which contained 3−5% of the 2(*Z*)-isomer gave 3−5% of *trans*-2-(3-Methyl-1*E*,3*Z*,5*E*-tridecatrienyl)cyclopentanol, which eluted faster than **11**: ^{1}H NMR 6.70 (d, 1, J = 16), 6.48 (dd, 1, J = 15, 11), 5.88 (d, 1, J = 11), 5.64 (dt, 1, J = 15, 7), 5.57 (dd, 1, J = 16, 9), 3.9−3.8 (m, 1), 2.45−2.35 (m, 1), 2.2−2.0 (m, 2), 2.0−1.8 (m, 2), 1.8 (s, 3), 1.8−1.2 (m, 15), 0.9 (t, 3, J = 6.8). These data correspond to those expected for a triene with a central *Z*-trisubstituted double bond.[33]

***trans*-2-(3-Methyl-1*E*,3*E*,5*E*-tridecatrienyl)cyclopentyl Bromoacetate (20).** A solution of 1.05 g (3.8 mmol) of **19** and 0.8 mL of pyridine in 15 mL of CH_2Cl_2 was cooled to 0 °C. Bromoacetyl bromide (0.83 g, 4.2 mmol) was added to the solution dropwise with a syringe. The mixture was stirred for an additional 15 min and was poured into 15 mL of ice water, which was extracted with CH_2Cl_2. The organic layers were washed with 1 N HCl and water, dried (Na_2SO_4), and concentrated to give 1.58 g of crude **20**, which decomposed on chromatography: ^{1}H NMR 6.34 (ddt, 1, J = 15.0, 11.0, 1.3), 6.12 (d, 1, J = 15.6), 5.98 (d, 1, J = 11.0), 5.71 (dt, 1, J = 15.0, 7.1), 5.54 (dd, 1, J = 7.7, 15.6), 4.94 (ddd, 1, J = 7.1, 5.2, 5.2),

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3.80 (s, 2), 2.66 (dddd, 1, J = 7.1, 7.3, 7.3, 7.7), 2.10 (br dt, 2, J = 7.1, 7.1), 2.08−1.88 (m, 2), 1.80 (s, 3), 1.75−1.59 (m, 3), 1.52−1.40 (m, 1), 1.40−1.30 (m, 2), 1.30−1.18 (m, 8), 0.85 (t, 3, J = 6.6); ^{13}C NMR 167.1, 135.8, 135.5, 132.4, 130.4, 128.6, 126.6, 83.0, 82.9, 48.6, 33.1, 31.8, 31.1, 30.4, 29.4, 29.1 (2), 26.2, 22.6, 14.1, 12.6.

***trans*-2-(3-Methyl-1*E*,3*E*,5*E*-tridecatrienyl)cyclopentyl Nitrooxyacetate (22).** A solution of NaI (0.6 g) and crude **20** (1.30 g of the above 1.58 g) in 10 mL of acetone was stirred at 25 °C for 6 h. The resulting precipitate was filtered off and the solid was washed with CH_2Cl_2. The filtrate was concentrated to give a brown residue that was dissolved in CH_2Cl_2. The solution was washed with 10% $NaHSO_3$ and water, dried (Na_2SO_4), and concentrated in vacuo to yield 1.5 g of crude iodoacetate **21** as a yellow liquid, which was dissolved in 15 mL of acetonitrile. Silver nitrate (0.8 g, 4.5 mmol) was added and the mixture was stirred in the dark overnight at 25 °C. The solution was filtered through Celite, which was washed with ether. The combined organic filtrates were washed with water, dried (Na_2SO_4), and concentrated to afford 1.25 g of crude **22**. Flash chromatography on silica gel (97:3 hexane/EtOAc) gave 0.91 g of **22** (90% pure as determined by analysis of the ^{1}H NMR spectrum), which was used for the next step: ^{1}H NMR 6.33 (dd, 1, J = 15.0, 11.0), 6.11 (d, 1, J = 15.6), 5.99 (d, 1, J = 11.0), 5.73 (dt, 1, J = 15.0, 7.0), 5.52 (dd, 1, J = 15.6, 7.7), 5.01 (ddd, 1, J = 5.0, 6.0, 6.0), 4.88 (s, 2), 2.68 (dddd, 1, J = 5.0, 7.7, 7.0, 7.0), 2.16−2.02 (m, 3), 2.0−1.9 (m, 1), 1.81 (s, 3), 1.80−1.62 (m, 3), 1.54−1.46 (m, 1), 1.44−1.32 (m, 2), 1.32−1.20 (m, 8), 0.88 (t, 3, J = 6.6); ^{13}C NMR 165.6, 135.9, 135.7, 132.3, 130.6, 128.2, 126.6, 83.0, 67.3, 48.7, 33.1, 31.8, 31.2, 30.3, 29.4, 29.2 (2), 22.6, 22.2, 14.1, 12.6; IR (neat) 1755, 1655.

***trans*-2-(3-Methyl-1*E*,3*E*,5*E*-tridecatrienyl)cyclopentyl Oxoacetate (23).** To a solution of 0.43 g of the above 90% pure **22** in 8 mL of DMSO was added 110 mg of sodium acetate. The solution was stirred vigorously at 25 °C for 25 min and poured into 40 mL of ice-cold brine, which was extracted with ether (6 × 50 mL). The organic layers were washed with saturated sodium bicarbonate solution and water, dried (Na_2SO_4), and concentrated to give 0.42 g of crude **23** which was used immediately in the next step.

(3α[*E*],4a*β*,6a*β*,9aα,9b*β*)-4a,6,6a,7,8,9,9a,9b-octahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*]pyrano[3,4-*n*]pyran-5(3*H*)-one (24). A solution of crude **23** (0.42 g) in 20 mL of CH_2Cl_2 was added dropwise to a solution of $Yb(OTf)_3$ (150 mg, 0.25 mmol) and 2,6-di-*tert*-butylpyridine (36 mg, 0.19 mmol) in 300 mL of CH_3CN. The mixture was stirred at 25 °C overnight and concentrated. The residue was taken up in ether and filtered through a short silica gel column. The eluent was concentrated to give 0.55 g of crude **24**. Flash chromatography on silica gel (93:7 hexane/EtOAc) gave 106 mg (21% from **19**) of **24**: ^{1}H NMR 5.78 (dt, 1, J = 15.3, 7.2), 5.52 (br d, 1, J = 5.5), 5.31 (dd, 1, J = 8.6, 15.3), 4.51 (br d, 1, J = 8.6), 4.26 (d, 1, J = 4.6), 4.03 (ddd, 1, J = 11.1, 8.6, 8.6), 2.20−1.62 (m, 9), 1.59 (s, 3), 1.44−1.32 (m, 2), 1.32−1.18 (m, 9), 0.87 (t, 3, J = 6.7); ^{13}C NMR 170.0, 137.0, 136.5, 127.8, 119.6, 84.5, 80.2, 71.5, 43.9, 38.9, 32.3, 31.8, 29.2, 29.1, 28.9, 28.6, 23.7, 22.6, 19.5, 19.3, 14.1; IR (neat) 1748. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.74, H, 9.41. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.51; H-9, δ 4.26; H-3, δ 4.03; H-7, δ 1.90−2.1; H-8, δ 2.15.

24 and (3α[*E*],4aα,6aα,9a*β*,9bα)-4a,6,6a,7,8,9,9a,9b-octahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*]pyrano[3,4-*n*]pyran-5(3*H*)-one (25). A solution of crude **23** (0.27 g) in 15 mL of CH_2Cl_2 was added dropwise to a solution of $Yb(OTf)_3$ (90 mg, 0.14 mmol) and 200 mL of CH_3CN. The mixture was stirred at 25 °C for 2 d. Workup as described above gave 0.28 g of a crude 2:3 mixture of **24** and **25**. Flash chromatography on silica gel (93:7 hexane/EtOAc) gave 45 mg (15% from **19**) of **25** followed by 28 mg (9% from **19**) of **24**. Data for **25**: ^{1}H NMR 5.82 (dt, 1, J = 15.3, 6.7), 5.41 (q, 1, J = 1.3), 5.35 (ddt, 1, J = 8.0, 15.3, 1.2), 4.75 (br d, 1, J = 8.0), 4.63 (d, 1, J = 8.6), 4.19 (ddd, 1, J = 11.0, 8.6, 8.6), 2.61 (br dd, 1, J = 10.3, 8.5), 2.14−2.0 (m, 3), 1.94−1.72 (m, 2), 1.69−1.58 (m, 1), 1.57 (s, 3), 1.58−1.56 (m, 1), 1.42−1.32 (m, 2), 1.32−1.31 (m, 1), 1.3−1.2 (m, 9), 0.86 (t, 3, J = 7.3); ^{13}C NMR 172.2, 137.1, 134.3, 127.4, 120.5, 80.3, 74.8, 68.7, 47.7, 35.7, 32.3, 31.8, 29.3, 29.1, 29.0, 28.6, 25.6, 22.6, 20.4, 19.8, 14.1; IR (neat) 1757; HRMS (DEI) calcd for $C_{21}H_{32}O_3$ (M^+) 332.2351, found 332.2358. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.75; H-9, δ 4.63; H-3, δ 4.19; H-7, δ 1.6; H-8, δ 2.61.

Hydroxyketophosphonate 26. A solution of 35 mg (0.28 mmol) of dimethyl methylphosphonate in 4 mL of THF at −78 °C was treated dropwise with 120 mL (0.3 mmol) of 2.5 M *n*-butyllithium in hexane. The resulting solution was stirred for 1 h at −78 °C and then treated dropwise with the solution of 45 mg (0.14 mmol) of **24** in 1 mL of THF. The resulting solution was stirred at −78 °C for 1 h and quenched with 0.5 mL of saturated NH_4Cl solution and 2 mL of water. The mixture was extracted with ether (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 76 mg of crude **26**. Flash chromatography on silica gel (85:15 hexane/EtOAc) gave 53 mg (86%) of pure **26**: ^{1}H NMR 5.68 (dt, 1, J = 15.3, 6.8), 5.63 (br d, 1, J = 6.4), 5.61 (br s, 1), 5.32 (dd, 1, J = 15.3, 8.6), 4.35 (br d, 1, J = 8.6), 3.88 (ddd, 1, J = 7.0, 10.7, 10.7), 3.79 (br d, 3, J_{H-P} = 11.0), 3.70 (br d, 3, J_{H-P} = 11.0), 3.35 (d, 1, J = 2.2), 2.71 (dd, 1, J_{H-P} = 17.4, J_{H-H} = 15.3), 2.22−2.14 (m, 1), 2.07 (dd, 1, J_{H-P} = 17.4, J_{H-H} = 15.3), 2.06−2.0 (m, 2), 1.86−1.74 (m, 2), 1.68−1.54 (m, 2), 1.52 (s, 3), 1.51−1.46 (m, 1), 1.42−1.34 (m, 2), 1.32−1.22 (m, 9), 1.22−1.1 (m, 1), 0.87 (t, 3, J = 6.8); ^{13}C NMR 135.3, 134.7, 129.4, 123.6, 97.7 (d, 1, J_{C-P} = 7.6), 81.2, 75.5, 74.0 (d, 1, J_{C-P} = 12.2), 53.7 (d, 1, J_{C-P} = 5.3), 51.5 (d, 1, J_{C-P} = 6.9), 44.7, 37.1 (d, 1, J_{C-P} = 1.6), 33.4 (d, 1, J_{C-P} = 137), 32.2, 31.8, 29.2, 29.1, 29.1, 27.6, 24.1, 22.6, 19.3, 19.2, 14.1; IR (neat) 3345, 1454.

Hydroxyketophosphonate 29 (34 mg, 93%) was prepared analogously from 27 mg of **25**: ^{1}H NMR 5.68 (s, 1), 5.65 (br d, 1, J = 5.5), 5.61 (dt, 1, J = 15.3, 6.7), 5.49 (dd, 1, J = 15.6, 6.7), 4.40 (br d, 1, J = 6.7), 3.92 (ddd, 1, J = 10.8, 10.8, 7.0), 3.77 (d, 3, J_{H-P} = 10.8), 3.68 (d, 3, J_{H-P} = 12.0), 3.48 (d, 1, J = 2.5), 2.71 (dd, 1, J_{H-P} = 17.9, J_{H-H} = 15.6), 2.22−2.12 (m, 1), 2.05 (dt, 2, J = 6.7, 7.3), 1.97 (dd, 1, J_{H-P} = 17.1, J_{H-H} = 15.6), 1.84−1.76 (m, 2), 1.72−1.68 (m, 2), 1.56 (s, 3), 1.54−1.42 (m, 2), 1.38−1.30 (m, 2), 1.30−1.20 (m, 8), 1.18−1.08 (m, 1), 0.86 (t, 3, J = 7.0); ^{13}C NMR 135.8, 133.6, 126.9, 124.0, 98.0 (d, 1, J_{C-P} = 10.4), 77.7, 75.1, 68.0 (d, 1, J_{C-P} = 13.0), 53.8 (d, 1, J_{C-P} = 5.3), 51.3 (d, 1, J_{C-P} = 6.9), 44.3, 36.9, 33.6 (d, 1, J_{C-P} = 137), 32.3, 31.8, 29.1 (2), 29.1, 27.6, 24.0, 22.7, 19.9, 19.3, 14.1; IR (neat) 3348, 1451.

(3a[*E*],4a*β*,9aα,9b*β*)-4a,7,8,9,9a,9b-Hexahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*][1]benzopyran-5(3*H*)-one (27). Dess−Martin reagent (50 mg, 0.12 mmol) was added to a solution of **26** (35 mg, 0.08 mmol) in 0.8 mL of dry CH_2Cl_2. The mixture was stirred for 1 h at 25 °C. An additional 30 mg of Dess−Martin reagent was added and the reaction was stirred for another 1 h. Saturated $Na_2S_2O_3$ solution (0.5 mL) was added dropwise and the mixture turned clear after 5 min. Saturated $NaHCO_3$ solution (0.5 mL) was added dropwise, and the solution was extracted with ether (3 × 5 mL). The organic layers were dried (Na_2SO_4) and concentrated to give 33 mg of crude diketophosphonate, which decomposed on chromatography.

The crude diketophosphonate was dissolved in 4 mL of dry THF. The resulting solution was added dropwise to a suspension of NaH (4.5 mg, 60% dispersion in mineral oil, 0.11 mmol) in 4 mL of dry THF at −78 °C under N_2. The mixture was stirred at −30 °C for overnight and quenched with 3 mL of water. The mixture was extracted with ether (4 × 5 mL), which was dried (Na_2SO_4) and concentrated to give 28 mg of crude **27**. Flash chromatography on silica gel (95:5 hexane/EtOAc) gave 13.6 mg (52%, 64% based on recovered **26**) of pure **27** followed by 6.5 mg (19%) of unreacted **26**: ^{1}H NMR 5.98 (d, 1, J = 1.9), 5.79 (dt, 1, J = 15.3, 6.7), 5.75 (br d, 1, J = 5.8), 5.29 (dd, 1, J = 15.3, 8.9), 4.56 (br d, 1, J = 8.9), 3.81 (d, 1, J = 3.1), 2.68 (br dd, 1, J = 19.4, 9.5), 2.64 (m, 1), 2.50 (br ddd, 1, J = 19.4, 9.0, 9.5), 2.22 (ddd, 1, J = 11.6, 6.9, 6.9), 2.16−2.08 (m, 1), 2.08−1.99 (m, 2), 1.99−1.90 (m, 1), 1.76−1.64 (m, 1), 1.60 (s, 3), 1.42−1.30 (m, 2), 1.30−1.20 (m, 9), 0.87 (t, 3, J =

6.8); ^{13}C NMR 195.2, 176.0, 137.1, 136.4, 127.9, 122.2, 121.2, 81.5, 75.1, 46.0, 41.4, 32.3, 32.0, 31.8, 30.7, 29.2, 29.1, 28.9, 23.8, 22.6, 19.4, 14.1; IR (neat) 1673; HRMS (GC/MS, EI 20 eV) calcd for $C_{22}H_{32}O_2$ (M^+) 328.2402, found 328.2410. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.56; H-9, δ 3.81; H-7, δ 2.64; H-8, δ 2.12. NOESY experiments showed cross-peaks between H-9 and H-12, and H-8 and H-9.

(3α[*E*],4aα,9a*β*,9bα)-4a,7,8,9,9a,9b-Hexahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*][1]benzopyran-5(3*H*)-one (30). (9.5 mg, 70%) was prepared analogously from 18 mg of **29**: ^{1}H NMR 5.99 (br s, 1), 5.72−5.65 (m, 2), 5.60 (dd, 1, J = 15.6, 6.4), 4.46 (d, 1, J = 6.7), 3.90 (d, 1, J = 3.4), 2.66 (dd, 1, J = 8.3, 19.0), 2.62−2.51 (m, 1), 2.51−2.41 (m, 1), 2.21 (dt, 1, J = 11.9, 6.7), 2.1−2.0 (m, 2), 1.92 (dt, 1, J = 13.1, 7.4), 1.66 (s, 3), 1.76−1.62 (m, 1), 1.42−1.32 (m, 2), 1.32−1.20 (m, 10), 0.86 (t, 3, J = 6.8); ^{13}C NMR 195.5, 175.6, 136.1, 135.5, 126.1, 122.3, 121.2, 78.1, 69.2, 45.2, 41.1, 32.5, 32.0, 31.8, 30.7, 29.2, 29.1 (2), 23.8, 22.6, 20.2, 14.1; IR (neat) 1673, 1641. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.46; H-9, δ 3.90; H-7, δ 2.40; H-8, δ 2.10; H-13, δ 5.60; and H-14 δ 5.71−5.65. NOESY experiments showed cross-peaks between H-9 and H-8, H-12 and H-7, and H-9 and both H-13 and H-14.

(3α[*E*],4aα,9aα,9b*β*)-4a,7,8,9,9a,9b-Hexahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*][1]benzopyran-5(3*H*)-one (Deoxypenostatin A) (28). K_2CO_3 (4 mg, 0.03 mmol) was added to a solution of **27** (8 mg, 0.024 mmol) in 0.3 mL of dry MeOH under N_2. The mixture was stirred for 12 h, giving a 3:2 mixture of **27** and **28** as indicated by TLC analysis. Longer reaction time led to decomposition. Concentration followed by flash chromatography on silica gel (93:7 hexane/EtOAc) gave 3.2 mg (40%) of recovered **27**, which can be recycled, followed by 2.2 mg (28%, 46% based on recovered **27**) of **28**: ^{1}H NMR 5.94 (q, 1, J = 1.8), 5.67 (dt, 1, J = 15.3, 6.7), 5.57 (br s, 1), 5.56 (dd, 1, J = 15.3, 6.1), 4.59 (br d, 1, J = 6.1), 4.02 (d, 1, J = 11.0), 2.7−2.6 (m, 1), 2.54−2.44 (m, 1), 2.44−2.30 (m, 1), 2.29−2.21 (m, 1), 2.05 (q, 2, J = 7.9), 2.02−1.92 (m, 1), 1.8−1.66 (m, 1), 1.66 (br s, 3), 1.42−1.32 (m, 2), 1.32−1.2 (m, 10), 0.87 (t, 3, J = 6.4); ^{13}C NMR 196.4, 172.5, 136.2, 136.1, 126.1, 122.1, 121.7, 73.8, 48.1, 44.8, 32.4, 31.8, 31.5, 30.1, 29.1, 29.1, 29.0, 23.8, 22.6, 20.0, 14.1 (one C obscured by $CDCl_3$); IR (neat); 1693, 1633. The chemical shifts of the methine protons: H-12, δ 4.59; H-9, δ 4.02; H-7, δ 2.40; H-14, δ 5.67; and H-13, 5.56. NOESY experiments showed cross-peaks between H-9 and H-7, and H-9 and both H-13 and H-14.

(3α[*E*],4a*β*,9a*β*,9bα)-4a,7,8,9,9a,9b-Hexahydro-2-methyl-3-(1-nonenyl)cyclopenta[*f*][1]benzopyran-5(3*H*)-one (31). Similar treatment of **30** (7.6 mg, 0.23 mmol) with 4 mg of K_2CO_3 in MeOH (0.5 mL) for 3 h provided 5.5 mg (73%) of **31** as the only product: ^{1}H NMR 5.95 (q, 1, J = 1.8), 5.79 (dt, 1, J = 15.3, 6.7), 5.55 (q, 1, J = 1.8), 5.33 (ddt, 1, J = 15.3, 9.2, 1.2), 4.53 (br d, 1, J = 9.2), 3.89 (d, 1, J = 11.0), 2.65 (dd, 1, J = 18.6, 10.1), 2.56−2.3 (m, 2), 2.26 (dt, 1, J = 12.2, 6.4), 2.1−2.0 (m, 2), 2.0−1.92 (m, 1), 1.8−1.58 (m, 1), 1.60 (s, 3), 1.42−1.32 (m, 2), 1.32−1.2 (m, 10), 0.87 (t, 3, J = 6.8); ^{13}C NMR 195.4, 172.6, 136.8 (2), 128.0, 121.7, 121.6, 81.0, 78.9, 47.9, 44.3, 32.3, 31.8, 31.6, 30.1, 29.2, 29.1, 28.9, 23.7, 22.6, 19.4, 14.1; IR (neat) 1685. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.53; H-9, δ 3.89; H-7, δ 2.35; H-8, δ 2.45. NOESY experiments showed cross-peaks between H-12 and H-9, and H-7 and H-9.

Lactone 41. A solution of crude **37** (20 mg) in 1 mL of CH_2Cl_2 was added dropwise to a solution of $Yb(OTf)_3$ (30 mg, 0.048 mmol) and 2,6-di-*tert*-butylpyridine (8 mg, 0.04 mmol) in 10 mL of CH_3CN. The mixture was stirred overnight. An additional 30 mg of $Yb(OTf)_3$ was added, and the reaction mixture was stirred at 42 °C for 16 h. The reaction temperature was then elevated to 70 °C for 6 h. Water (2 mL) was added to the mixture and the organic layer was extracted with ether (3 × 6 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 23.6 mg of crude product. Flash chromatography on silica gel (80:20 hexane/EtOAc, then 50:50 hexane/EtOAc) gave 7.6 mg of partially pure hydrolyzed product (the glyoxylate ester and the ketal protecting group were gone) and 6.8 mg of **41** (41% from nitrooxyacetate): ^{1}H NMR 6.20 (dd, 1, J = 14.7, 11.0), 6.12 (d, 1, J = 11.0), 5.82 (dt, 1, J = 14.7, 6.7), 4.52 (br d, 1, J = 10.4, H-9), 4.50 (d, 1, J = 10.1, H-10), 4.31 (dddd, 1, J = 7.3, 10.4, 8.5, 3.7, H-3), 3.83 (br d, 1, J = 3.7, C-3-OH), 3.53 (br s, 1, C-9-OH), 2.71 (dd, 1, J = 18.3, 7.3, H-4), 2.54 (dd, 1, J = 6.7, 18.9, H-6), 2.41 (ddd, 1, J = 10.4, 10.1, 10.1, H-8), 2.31 (ddd, 1, J = 10.4, 18.3, 1.2, H-4), 2.2−2.14 (m, 1, H-7), 2.13 (br dt, 2, J = 7.3, 7.8), 1.76 (dd, 1, J = 12.2, 18.9, H-6), 1.73 (s, 3), 1.44−1.32 (m, 2), 1.32−1.20 (m, 8), 0.89 (t, 3, J = 6.7); ^{13}C NMR 212.0, 175.2, 139.9, 134.2, 127.3, 124.8, 87.0, 73.4, 72.5, 50.7, 46.9, 45.8, 43.3, 33.0, 31.8, 29.2, 29.1, 29.0, 22.6, 14.1, 11.2; IR (neat) 3262, 1775, 1744; HRMS (DEI) calcd for $C_{21}H_{32}O_5$ (M^+) 364.2250, found 364.2266. The chemical shifts of the methine protons were assigned by COSY experiments. NOESY experiments showed cross-peaks between H-7 and H-4, H-7 and C-3-OH, H-4 and H-12 (CH_3 group).

(3α[*E*],4a*β*,6a*β*,9aα,9b*β*)-4a,6,6a,7,8,9,9a,9b-octahydro-2-methyl-3-(1-nonenyl)-8-oxocyclopenta[*f*]pyrano[3,4-*n*]-pyran-5(3*H*)-one (39). A solution of crude **37** (13 mg from 14 mg of nitrooxyacetate) in 1.2 mL of CH_2Cl_2 was added dropwise to a solution of $Yb(OTf)_3$ (10 mg, 0.6 equiv) in 6 mL of CH_3CN. The mixture was heated to 65 °C and stirred for 3 h. TLC analysis showed that the desired DA product **39** was present and was isomerizing to **41**. The reaction mixture was cooled to room temperature and filtered through a short silica gel column. The filtrate was concentrated to give 23 mg of crude product containing some $Yb(OTf)_3$. Flash chromatography on silica gel (80:20 hexane/EtOAc, then 50:50 hexane/EtOAc) gave 2.2 mg (∼ 20% from nitrooxyacetate) of 90% pure **39** as determined by analysis of the NMR spectrum: ^{1}H NMR 5.78 (dt, 1, J = 15.3, 6.7), 5.59 (br d, 1, J = 6.1), 5.27 (dd, 1, J = 15.3, 8.5), 4.45 (br d, 1, J = 8.5), 4.40 (d, 1, J = 3.7), 4.26−4.15 (m, 1), 3.0−2.92 (m, 1), 2.62 (dd, 1, J = 7.3, 18.3), 2.57 (br dt, 1, J = 19.5, 7.2), 2.20−2.00 (m, 4), 1.88−1.80 (m, 1), 1.62 (s, 3), 1.44−1.32 (m, 2), 1.32−1.20 (m, 8), 0.88 (t, 3, J = 6.7); HRMS (DEI) calcd for $C_{21}H_{30}O_4$ (M^+) 346.2144, found 346.2152.

(3α[*E*],4a*β*,6a*β*,8α,9aα,9b*β*)-4a,6,6a,7,8,9,9a,9b-octahydro-8-hydroxy-2-methyl-3-(1-nonenyl)cyclopenta[*f*]pyrano-[3,4-*n*]pyran-5(3*H*)-one (45a) and (3α[*E*],4aα,6aα,8*β*,9a*β*,9bα)-4a,6,6a,7,8,9,9a,9b-octahydro-8-hydroxy-2-methyl-3-(1-nonenyl)cyclopenta[*f*]pyrano[3,4-*n*]pyran-5(3*H*)-one (46a). A solution of crude **44c** (400 mg) in 10 mL of CH_2Cl_2 was added dropwise to a solution of $Yb(OTf)_3$ (320 mg, 0.6 equiv) in 100 mL of CH_3CN. The reaction mixture was heated to 65 °C and stirred for 2.5 h. To avoid epimerization at the doubly allylic position, the reaction mixture was treated with 100 μL of 2,6-di-*tert*-butylpyridine, cooled to room temperature, and filtered through a short silica gel column. The filtrate was concentrated to give 484 mg of crude product containing some $Yb(OTf)_3$. Flash chromatography on silica gel (90:10 then 70:30 hexane/EtOAc) afforded 71 mg (23% from nitrooxyacetate) of a 3:2 inseparable mixture of **45a** and **46a**: HRMS (DCI/NH_3) calcd for $C_{21}H_{33}O_4$ (MH^+) 349.2378, found 349.2370.

Hydroxyketophosphonates 47 and 48. A solution of 71 mg (0.2 mmol) of the mixture of **45a** and **46a** in 0.6 mL of DMF was treated with 46 mg (0.8 mmol) of imidazole and 52 mg (0.34 mmol) of TBSCl. The mixture was stirred at room temperature for 40 min, and hexane (40 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give 97 mg of crude silyl ethers that were dissolved in 5 mL of dry THF.

A solution of 68 mg (0.54 mmol) of dimethyl methylphosphonate in 10 mL of THF at −78 °C was treated dropwise with 210 μL (0.53 mmol) of 2.5 M *n*-butyllithium in hexane. The resulting solution was stirred for 1 h at −78 °C and then treated dropwise with the silyl ether solution. The resulting solution was stirred at −78 °C for 1 h and quenched with 4 mL of water. The mixture was extracted with ether (3 × 8 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 125 mg of crude product. Flash chromatography on silica gel (85:15 hexane/EtOAc) gave 57

mg (48%) of pure **47** followed by 34 mg (29%) of pure **48** as colorless liquids.

Data for **47**: ^{1}H NMR 5.69 (dt, 1, J = 15.3, 6.7), 5.64 (br s, 1), 5.58 (br d, 1, J = 5.5), 5.35 (dd, 1, J = 15.3, 8.5), 4.35 (br d, 1, J = 8.5), 4.28 (ddd, 1, J = 6.7, 6.7, 6.1), 3.82−3.70 (m, 1), 3.79 (br d, 3, J_{H-P} = 10.8), 3.74 (br d, 3, J_{H-P} = 10.8), 3.35 (d, 1, J = 1.8), 2.72 (dd, 1, J_{H-P} = 17.7, J_{H-H} = 15.9), 2.24 (ddd, 1, J = 7.0, 7.0, 11.9), 2.16−1.92 (m, 5), 1.72 (dd, 1, J = 13.4, 7.3), 1.59 (dd, 1, J = 11.6, 5.5), 1.53 (s, 3), 1.45 (dd, 1, J = 13.2, 7.6), 1.42−1.34 (m, 2), 1.34−1.2 (m, 8), 0.92−0.84 (m, 3), 0.87 (s, 9), 0.02 (d, 6, J = 3.1); ^{13}C NMR 135.3, 134.9, 129.3, 123.2, 97.7 (d, 1, J_{C-P} = 7.6), 81.3, 74.0 (d, 1, J_{C-P} = 12.2), 73.7, 69.5, 53.7 (d, 1, J_{C-P} = 5.3), 51.5 (d, 1, J_{C-P} = 6.9), 42.3, 40.1, 36.8, 36.1, 33.4 (d, 1, J_{C-P} = 136.6), 32.2, 31.8, 29.2, 29.1, 29.1, 25.9 (3), 22.6, 19.3, 18.1, 14.1, −4.7, −4.8; IR (neat) 3330, 1594, 1039.

Data for **48**: ^{1}H NMR 5.69 (s, 1), 5.63−5.55 (m, 2), 5.48 (dd, 1, J = 15.9, 6.7), 4.42 (br d, 1, J = 6.7), 4.27 (ddd, 1, J = 6.7, 6.7, 6.1), 3.85−3.78 (m, 1), 3.79 (d, 3, J_{H-P} = 11.2), 3.70 (d, 3, J_{H-P} = 11.6), 3.47 (d, 1, J = 2.4), 2.71 (dd, 1, J_{H-P} = 17.7, J_{H-H} = 15.9), 2.25 (ddd, 1, J = 7.0, 7.0, 12.2), 2.12−2.0 (m, 1), 2.05 (dt, 2, J = 7.3, 6.7), 1.94 (dd, 1, J_{H-P} = 17.1, J_{H-H} = 15.9), 1.98−1.84 (m, 1), 1.73 (dd, 1, J = 7.0, 12.8), 1.58 (s, 3), 1.54 (dd, 1, J = 5.5, 11.6), 1.45 (dd, 1, J = 7.3, 12.8), 1.40−1.30 (m, 2), 1.30−1.20 (m, 8), 0.92−0.84 (m, 3), 0.87 (s, 9), 0.01 (d, 6, J = 4.3); ^{13}C NMR 135.7, 133.8, 126.9, 123.6, 97.9 (d, 1, J_{C-P} = 8.4), 77.6, 73.4, 69.4, 68.0 (d, 1, J_{C-P} = 13.0), 53.8 (d, 1, J_{C-P} = 5.3), 51.3 (d, 1, J_{C-P} = 6.9), 41.8, 40.1, 36.6, 33.1, 34.5 (d, 1, J_{C-P} = 136.8), 32.3, 31.8, 29.1 (2), 29.0, 25.8 (3), 22.6, 20.0, 18.1, 14.1, −4.7, −4.9; IR (neat) 3342, 1592, 1039.

(3α[*E*],4aα,8*β*,9a*β*,9bα)-4a,7,8,9,9a,9b-Hexahydro-2-methyl-8-((dimethylethyl)dimethylsilyloxy)-3-(1-nonenyl)cyclopenta[*f*][1]benzopyran-5(3*H*)-one (50). Dess−Martin reagent (35 mg, 0.08 mmol) was added to a solution of **48** (21 mg, 0.04 mmol) in 0.5 mL of dry CH_2Cl_2. The mixture was stirred for 2.5 h at 25 °C. Saturated $Na_2S_2O_3$ solution (0.6 mL) was added dropwise and the mixture turned clear after 5 min. Saturated $NaHCO_3$ solution (0.5 mL) was added dropwise and the solution was extracted with ether (3 × 5 mL). The organic layers were dried (Na_2SO_4) and concentrated to give 24 mg of crude diketophosphonate.

The crude diketophosphonate was dissolved in 3 mL of dry THF. The resulting solution was added dropwise to a suspension of NaH (5.4 mg, 60% dispersion in mineral oil, 0.1 mmol) in 5 mL of dry THF at −78 °C under N_2. The mixture was stirred at −30 °C overnight and quenched with 3 mL of water. The mixture was extracted with ether (4 × 5 mL), which was dried (Na_2SO_4) and concentrated to give 20 mg of crude **50**. Flash chromatography on silica gel (95:5 hexane/EtOAc) gave 4 mg (24% from **48**) of pure **50**: ^{1}H NMR 5.98 (br, s, 1), 5.76−5.68 (m, 2), 5.62 (dd, 1, J = 15.6, 6.1), 4.51 (d, 1, J = 6.1, H-12), 4.46 (dd, 1, J = 4.9, 4.9, H-5), 3.93 (d, 1, J = 3.7, H-9), 3.06−3.00 (m, 1, H-7), 2.76 (dt, 1, J = 19.5, 2.4), 2.60 (d, 1, J = 19.5), 2.22−2.0 (m, 3), 1.67 (s, 3), 1.48 (dd, 1, J = 4.9, 12.2), 1.76−1.62 (m, 1), 1.42−1.32 (m, 2), 1.32−1.20 (m, 8), 0.9−0.82 (m, 3), 0.87 (s, 9), 0.06 (d, 6, J = 3.1); ^{13}C NMR 195.4, 173.9, 136.2, 135.7, 126.1, 122.0, 121.7, 78.0, 71.3, 69.1, 42.8, 41.8, 41.2, 40.1, 32.5, 31.8, 29.2, 29.1 (2), 25.8 (3), 22.6, 20.2, 18.1, 14.1, −4.8, −4.8; IR (neat) 1673, 1594; HRMS (DEI) calcd for $C_{28}H_{46}O_3Si$ (M^+) 458.3216, found 458.3210. The chemical shifts of the methine protons were assigned by COSY experiments: H-12, δ 4.51; H-5, δ 4.46; H-9, δ 3.93; H-7, δ 3.04; H-8, δ 2.05.

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Supporting Information Available: Experimental details for preparation of **37** and **44c** and ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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