Total Synthesis of (±)-Deoxypenostatin A

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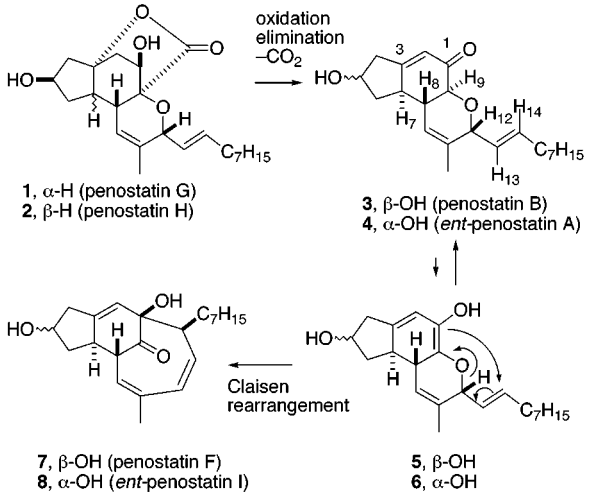
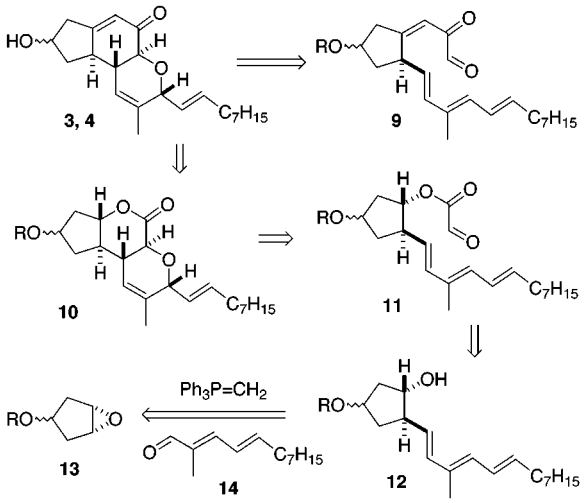
The cytotoxic penostatins A (*ent*-**4**) and B (**3**) were isolated from a *Penicillium* sp. separated from the green alga *Enteromorpha intestinalis* by Numata and co-workers in 1996.[1,2] More recently, the same group has reported the isolation of cytotoxic penostatins F (**7**), G (**1**), H (**2**), and I (*ent*-**8**) from the same source.[3] Penostatin B (**3**) is probably derived from penostatin G (**1**) by oxidation of the cyclohexanol to a cyclohexanone, elimination, and decarboxylation. Penostatins F (**7**) and I (*ent*-**8**) are probably derived from penostatins B (**3**) and A (*ent*-**4**), respectively, by a Claisen rearrangement of the enol tautomers **5** and *ent*-**6**. The novel ring systems and functionality of the penostatins and their cytotoxicity prompted us to undertake their syntheses.



The dihydropyran ring of penostatins A and B (**3**, **4**) could, in principle, be formed by an intramolecular Diels−Alder reaction with an aldehyde as the dienophile. The obvious precursor **9** was rejected because the tetraenonal functionality was expected to be both synthetically inaccessible and too unstable. Lactone **10** was a more attractive precursor since it should be easily convertible to **3** and **4** and might be available by an intramolecular Diels−Alder reaction of trienyl glyoxylate **11**. 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, there are no examples of intramolecular Diels−Alder reactions of glyoxylate esters, possibly because the conditions required to dehydrate the stable glyoxylate hydrate to give the very reactive free aldehyde may be incompatible with a diene. Furthermore, the Diels−Alder reaction of **11** can give four stereoisomers. Despite these concerns, this approach is still attractive, since trienol **12** should be available in a single step by addition of methylenetriphenylphosphorane to epoxide **13**,[7] deprotonation of the resulting betaine to give a γ-oxido ylide, and addition of dienal **14**.[8]



We report here the synthesis of deoxypenostatin A (**25**) that demonstrates the validity of this route. Treatment of the lithium enamide of *N*-propylidenecyclohexanamine[9] with 2(*E*)-decenal afforded dienal **14** containing ≤5% of the 2*Z* isomer.[10] Reaction of methylenetriphenylphosphorane with cyclopentene oxide in THF at 25 °C for 16 h afforded betaine **15**, which was deprotonated to give the γ-oxido ylide, which was treated with **14** to give 51% of **16** as a single stereoisomer.[11] Conversion of **16** to crude partially hydrated glyoxylate **20** was accomplished by the Kornblum procedure as shown.[13]

Glyoxylate **20** polymerized readily and could not be converted to the free aldehyde. Fortunately, treatment of crude hydrated **20** with $Yb(OTf)_3$ in CH_3CN[14] at 25 °C for 2 d afforded a 3:5 mixture of Diels−Alder adducts **21** and **22** in 24% yield from **16**, whose structures were established by NOE experiments. The major product **22** cannot be a primary adduct, since Diels−Alder addition to an *E*,*E*-diene must give products with H_8 and H_{12} cis. We established that

(1) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enomoto, S.; Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto, K. *Tetrahedron Lett.* **1996**, *37*, 655−658.

(2) Penostatins F and I have the opposite configuration at all centers except for the cyclopentanol.[3] This relationship is probably the same for penostatins A and B since their optical rotations are similar in magnitude and opposite in sign.[1]

(3) Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449−456.

(4) Ciganek, E. In *Organic Reactions*; Wiley: New York, 1984; Vol. 32, Chapter 1.

(5) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.2.

(6) (a) Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111−5114. (b) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790−7792.

(7) Both isomers of **13**, R = TBDMS, are readily available: Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402−1408.

(8) (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. (c) Schlosser, M.; Tuong, H. B.; Respondek, J.; Schaub, B. *Chimia* **1983**, *37*, 10−11.

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

(10) Meyers, A. I.; Brinkmeyer, R. S. *Tetrahedron Lett.* **1975**, 1749−1752.

(11) This sequence proceeds in lower yield with $Ph_3P{=}CHLi$,[8,12] which reacts with the epoxide to give the γ-oxido ylide directly.

(12) (a) Schaub, B.; Jenny, T.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 4097−4100. (b) Schaub, B.; Schlosser, M. *Tetrahedron Lett.* **1985**, *26*, 1623−1626. (c) Cristau, H. J. *Chem. Rev.* **1994**, *94*, 1299−1313.

(13) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865−866.

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

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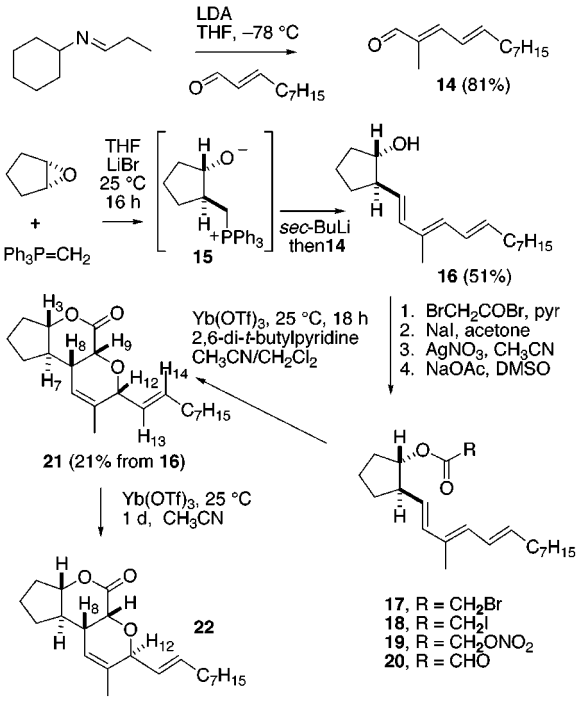

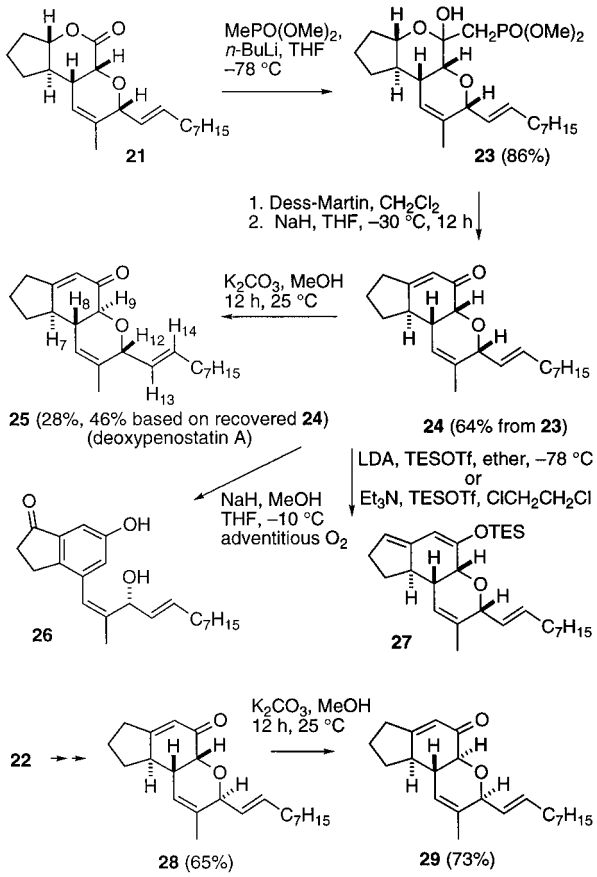

treatment of the minor product **21** with $Yb(OTf)_3$ in CH_3CN for 1 d afforded a 1:1 mixture of **21** and **22**, indicating that the pyran of **21** opens to the pentadienyl cation in the presence of Lewis or Brønsted acids. This isomerization can be suppressed by carrying out the Diels–Alder reaction in the presence of 2,6-di-*tert*-butylpyridine. Treatment of a 0.01 M solution of crude **20** in CH_3CN with 0.2 equiv of $Yb(OTf)_3$ and 0.15 equiv of 2,6-di-*tert*-butylpyridine for 18 h provided **21** as a single stereoisomer in 21% overall yield from alcohol **16**. Diels–Alder adduct **21** 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 **21** with $LiCH_2PO(OMe)_2$ gave 86% of the hydroxy keto phosphonate as hemiacetal **23**. Oxidation of **23** with the Dess–Martin reagent in CH_2Cl_2 provided the unstable diketophosphonate, which was treated with NaH in THF[15] at −30 °C overnight to give cyclohexenone **24** in 52% (64% based on recovered **23**) yield. Although **24** is somewhat unstable to base, isomerization with K_2CO_3 in MeOH for 12 h at 25 °C afforded 28% of deoxypenostatin A (**25**) and 40% of recovered **24**. This is not an equilibrium mixture, since **25** was not isomerized back to **24** under these conditions. Unfortunately, isomerization of **24** for longer periods of time resulted in extensive decomposition, which precluded the determination of the equilibrium ratio with these isomerization conditions. The ^1H and ^{13}C NMR spectral data of **25** are identical to those of penostatins A and B, except for the expected differences in the cyclopentane ring. Lactone **22** was converted to cyclohexenone **28** by the same sequence in 65% overall yield. Isomerization of **28** afforded 73% of **29** as the only product.

We briefly investigated the possibility of converting **24** to deoxypenostatin F (I) by a Claisen rearrangement. Koreeda has shown that anion-accelerated Claisen rearrangements of the enolates of α-allyloxyketones proceed under very mild conditions.[16] The more available enone **24** was used since **24** and **25** will give the same enolate. Treatment of **24** with NaOMe in THF at −10 °C provided 70% of keto phenol **26**, whose formation is probably initiated by reaction of the dienolate precursor to **27** with adventitious oxygen at the γ-position. Elimination of water from the γ-hydroperoxy enone will give an enedione[17] that will undergo base-catalyzed opening of the pyran ring to generate phenol **26**. No reaction occurred on similar treatment of **24** at −20 °C with rigorous exclusion of oxygen. Formation of the triethylsilyl enol ether from **24** with either TESOTf and Et_3N or LDA followed by TESOTf afforded primarily conjugated dienyl silyl ether **27** rather than the required cross-conjugated silyl enol ether analogous to **5**.

In conclusion, we have developed a short, convergent synthesis of deoxypenostatin A (**25**) that features a novel, stereoselective, intramolecular Diels–Alder reaction of a hydrated glyoxylate ester catalyzed by $Yb(OTf)_3$. We are now applying this sequence to the syntheses of penostatins A and B and are continuing to explore the Claisen rearrangement as a route to penostatins F and I.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectral data.

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(15) Aristoff, P. A. *J. Org. Chem.* **1985**, *50*, 1765–1766.

(16) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572–5573.

(17) (a) Malhotra, S. K.; Hostynek, J. J.; Lundin, A. F. *J. Am. Chem. Soc.* **1968**, *90*, 6565–6566. (b) Holland, H. L.; Daum, U.; Riemland, E. *Tetrahedron Lett.* **1981**, *22*, 5127–5128.