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Structure Revision and Syntheses of Epohelmins A and B

Barry B. Snider* and Xiaolei Gao

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

snider@brandeis.edu

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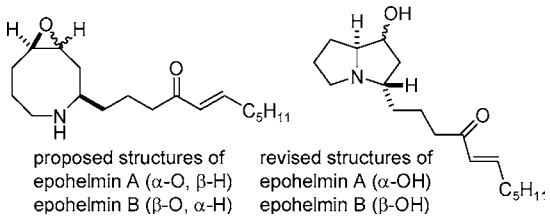
ABSTRACT



Epohelmins A (24) and B (26) have been reassigned as pyrrolizidin-1-ols, rather than the proposed 9-oxa-4-azabicyclo[6.1.0]nonane structures 1 and 2, respectively. Syntheses of epohelmin A (24) (eight steps, 52% overall yield) and epohelmin B (26) (11 steps, 43% overall yield) have been achieved starting from *N*-Cbz-(*S*)-prolinal (9) and ortho ester ketone 17 using a stereoselective aldol reaction and a stereoselective reductive cyclization as the key steps.

Shibuya, Ebizuka, and co-workers recently reported the isolation of the novel lanosterol synthase inhibitors epohelmins A (**1**) and B (**2**) from a fungal strain FKI-0929.[1] The structures were determined by detailed spectroscopic analysis and proposed to be novel 9-oxa-4-azabicyclo[6.1.0]-nonanes (see Figure 1).

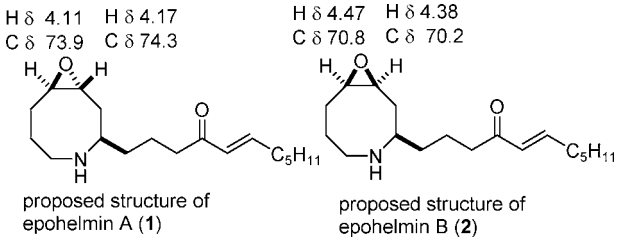
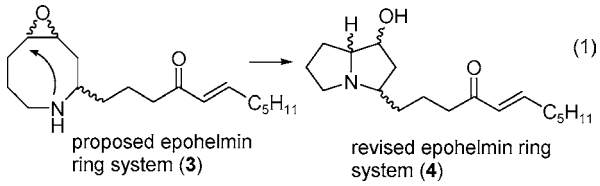


Figure 1. Proposed structures of epohelmins A (**1**) and B (**2**).

There were both chemical and spectroscopic grounds to question these structure assignments. 9-Oxa-4-azabicyclo-[6.1.0]nonanes cyclize readily to give pyrrolizidin-1-ols.[2,3] Such a cyclization of any of the four isomers of **3** would give pyrrolizidin-1-ols **4** (see eq 1). The protons assigned to



(1)

the epoxy groups of epohelmins A and B absorb in the range δ 4−4.5 and the carbons in the range δ 70−74 (see Figure 1). The analogous protons and carbons of *trans*- and *cis*-epoxy cyclooctanes (**5** and **6**) absorb at much higher field than those of the epohelmins with the protons at δ 2.8 and 2.9 and the carbons at δ 59.6 and 55.6, respectively (see Figure 2).[4]

On the other hand, the methine hydrogens and carbons of *trans*- and *cis*-pyrrolizidin-1-ols (**7** and **8**) have similar chemical shifts to the epohelmins as shown.[5] Although

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(2) Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Tetrahedron Lett.* **1978**, 2965−2968.

(3) Subramanian, T.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079−4082.

(4) Poon, T. H. W.; Pringle, K.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 7611−7618.

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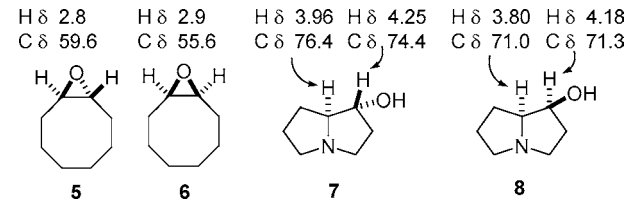


Figure 2. NMR data of epoxycyclooctanes (**5** and **6**) and pyrrolizidin-1-ols (**7** and **8**).

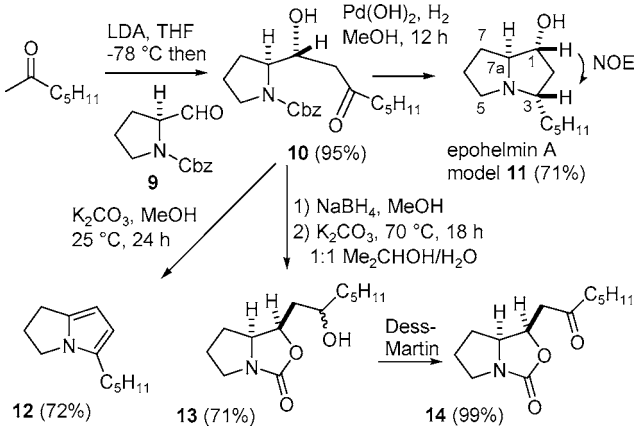
pyrrolizidin-1-ols **4** look quite different than 9-oxa-4-azabicyclo[6.1.0]nonanes **3**, the only difference is the formation of a C−N bond and cleavage of a C−O bond so that the 2D NMR correlations used to assign the structure of epohelmins A and B as **1** and **2** will be equally applicable to the stereoisomers of **4**.

This analysis suggests that epohelmins A and B are two of the four stereoisomers of **4**. If this is the case, the stereochemical analysis of **1** and **2** is based on the wrong skeleton and may not be applicable to the stereochemistry of **4**. We decided that the stereochemistry was best determined by the synthesis of model 3-alkylpyrrolizidin-1-ols such as **11**. Aldol addition of the kinetic enolate of 2-undecanone to *N*-Cbz-phenylalaninal followed by reductive pyrrolidine formation and methylation led to all four isomers of preussin (2-benzyl-1-methyl-5-(nonyl)pyrrolidin-3-ol).[6] This short sequence seemed ideal since at this time we did not know the stereochemistry of the epohelmins.

Treatment of 2-heptanone with LDA in THF at −78 °C provided the kinetic enolate, which was treated with *N*-Cbz-(*S*)-prolinal (**9**)[7] to afford **10** with excellent stereoselectivity in 95% yield (see Scheme 1). Hydrogenolysis (1 atm) of **10** over $Pd(OH)_2$ in MeOH for 12 h liberated the secondary amine, which reacted with the ketone to form an iminium salt or enamine, which was reduced to give pyrrolizidinol **11** in 71% yield. Several minor byproducts were formed that may include diastereomers of **11** other than epohelmin B model **16**. Similar results were obtained with other Pd catalysts. As expected, the ^1H and ^{13}C NMR spectra of **11** vary as a function of pH. The epohelmins were isolated using an eluent containing HOAc, suggesting that the natural products were isolated as acetate salts. We were pleased to find that the ^1H and ^{13}C NMR spectra of a $CDCl_3$ solution of **11** containing 0.85−0.90 equiv of HOAc corresponded precisely with those of the ring portion of epohelmin A.[8]

We had not expected either step in the formation of **11** to be stereoselective. Kitahara obtained mixtures in the addition

Scheme 1. Synthesis of Epohelmin A Model **11**



of lithium enolates to *N*-Cbz-phenylalaninal; the zinc enolate added stereoselectively.[6] Addition of zinc and lithium enolates of ethyl acetate to *N*-Boc-prolinal afforded 2:1 to 4:1 mixtures of isomers favoring the Felkin−Anh product.[9] We decided to prepare oxazolidinone **14** to prove the stereochemistry of aldol product **10**. Treating **10** with K_2CO_3 did not form the expected oxazolidinone but instead resulted in hydrolysis and double dehydration to give pyrrole **12**.[10] Reduction of the ketone with $NaBH_4$ in MeOH followed by treatment with K_2CO_3 in 1:1 2-propanol/water for 18 h at 70 °C provided oxazolidinone **13** in 71% overall yield as a mixture of stereoisomers. Dess−Martin oxidation afforded the desired oxazolidinone ketone **14** in 99% yield. The coupling constant between the methine hydrogens of **14** is 7.3 Hz as in related compounds indicating that the hydrogens are cis; in similar compounds with anti hydrogens the coupling constant is 4.0 Hz.[11] This established that the enolate of 2-heptanone added to **9** with high Felkin−Anh selectivity to give **10**.

The stereochemistry at C_3 of epohelmin A model **11** was established by the NOE between H_1 and H_3. We had not expected the reductive cyclization to be stereoselective because reductive cyclization of related pyrrolidine ketones lacking the hydroxyl group gave 1:1 mixtures of 3-alkylpyrrolizidines.[12] Presumably, the hydroxyl group blocks the bottom face so that hydrogenation occurs preferentially from the top face to give **11**.

We now turned our attention to the preparation of an epohelmin B model. As suggested by Ebizuka and Shibuya, we suspected that epohelmins A and B differed in the alcohol, not alkyl, stereochemistry. Changing the stereochemistry at the alkyl group should change the ^{13}C NMR

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(6) (a) Okue, M.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2001**, *57*, 4107−4110. (b) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093−1096.

(7) (a) Langley, D. R.; Thurston, D. E. *J. Org. Chem.* **1987**, *52*, 91−97. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861−2863. (c) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *Bioorg. Med. Chem.* **2003**, *11*, 4103−4112.

(8) We thank Prof. M. Shibuya for a complete set of 1D and 2D NMR spectra of epohelmins A and B.

(9) (a) Andrés, J. M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* **2001**, *57*, 8521−8530. (b) Hanson, G. J.; Baran, J. S.; Lindberg, T. *Tetrahedron Lett.* **1986**, *27*, 3577−3580.

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(11) (a) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654−655. (b) Kiyooka, S.-i.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org. Chem.* **1989**, *54*, 5409−5411. (c) St-Denis, Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078−3085.

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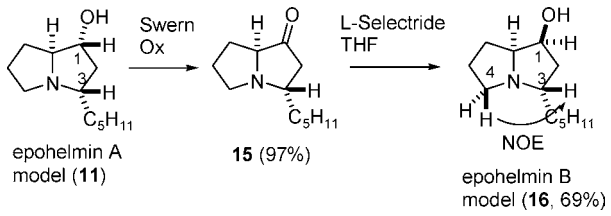
Scheme 2. Conversion of Epohelmin A Model **11** to Epohelmin B Model **16**

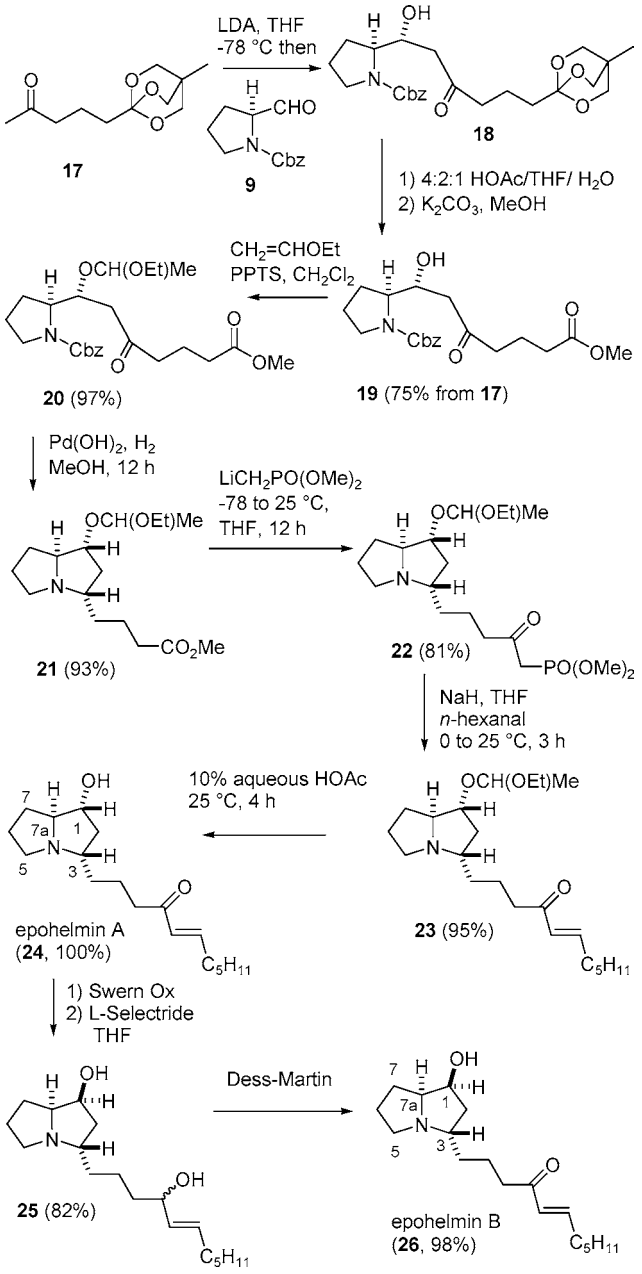


spectrum of the lower portion of the molecule,[13] whereas changing the stereochemistry at the alcohol should change the ^{13}C NMR spectrum of the top portion of the molecule as is observed. Inversion of *trans*-pyrrolizidin-1-ol stereochemistry has been addressed by Chamberlin, who found that this was best accomplished by oxidation to the ketone and reduction with L-Selectride.[14] Swern oxidation of **11** afforded the unstable ketone **15** in 97% yield. Reduction with L-Selectride in THF provided epohelmin B model **16** in 69% yield. The ^1H and ^{13}C NMR spectra of the acetate salt of **16** corresponded precisely with those of the ring portion of epohelmin B. The stereochemistry of the pentyl side chain was confirmed by the NOE between H_3 and H_4, which established that H_3 is on the concave face and the pentyl group is on the convex face. Reduction of **15** with $NaBH_4$ in MeOH gave a 25:1 mixture of **11** and **16** analogous to that observed by Chamberlin in related systems.[14] Although reduction of pyrrolizidin-1-ones with $NaBH(OMe)_3$ in benzene has been reported to give *cis*-pyrrolizidin-1-ols,[15] no reaction occurred with **15** under these conditions.

We now turned our attention to adapting this synthesis to accommodate an enone in the side chain. Ortho ester ketone **17** was prepared from 4-acetylbutyric acid by the literature procedure.[16] Conversion of **17** to the kinetic enolate with LDA and addition of prolinal **9** afforded aldol product **18** (see Scheme 3). Hydrolysis of the ortho ester in 4:2:1 AcOH/THF/H_2O and transesterification with K_2CO_3 in MeOH afforded methyl ester **19** in 75% overall yield from **17**.[17] Protection of the hydroxyl group facilitated purification, the preparation of the keto phosphonate, and the Wittig reaction. Treatment of **19** with excess ethyl vinyl ether and catalytic PPTS in CH_2Cl_2 provided 97% of **20**. Hydrogenolysis and reductive cyclization with H_2 (1 atm) over $Pd(OH)_2$ in MeOH for 12 h afforded 93% of the crude protected pyrrolizidine methyl ester **21**.

Addition of crude **21** to a large excess of $LiCH_2PO(OMe)_2$ in THF at −78 °C and stirring for 12 h with warming to 25 °C gave keto phosphonate **22** in 81% yield after chromatography. Treatment of **22** with NaH in THF followed by addition of hexanal and stirring for 3 h afforded enone **23** in 95% yield. Deprotection by stirring in 10% aqueous HOAc for 4 h at 25 °C gave epohelmin A (**24**) quantitatively. The ^1H and ^{13}C NMR spectra of **24** that is 85−90% protonated with HOAc are identical to those reported for epohelmin A, thereby unambiguously establishing the revised structure of epohelmin A. The optical rotation of **24** that is 85−90% protonated with HOAc, $[\alpha]^{22}_D$ +22, is identical to that of the natural product, indicating that the absolute configuration is as shown since **9** is prepared from (*S*)-proline.

Scheme 3. Preparation of Epohelmins A (**24**) and B (**26**)



Epohelmin B (**26**) was prepared from **24** by Swern oxidation to give the unstable dione followed by reduction with L-Selectride in THF to give diol **25** in 82% yield as a

(13) For the assigned spectra of *cis*- and *trans*-3-methylpyrrolizidine, see: Skvortsov, I. M.; Antipova, I. V. *J. Org. Chem. USSR* **1979**, *15*, 777−783; *Zh. Org. Khim.* **1979**, *15*, 868−875.

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(16) (a) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574. (b) Oku, A.; Numata, M. *J. Org. Chem.* **2000**, *65*, 1899−1906. (c) Mohapatra, S.; Capdevila, J. H.; Murphy, R. C.; Hevko, J. M.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 4109−4110.

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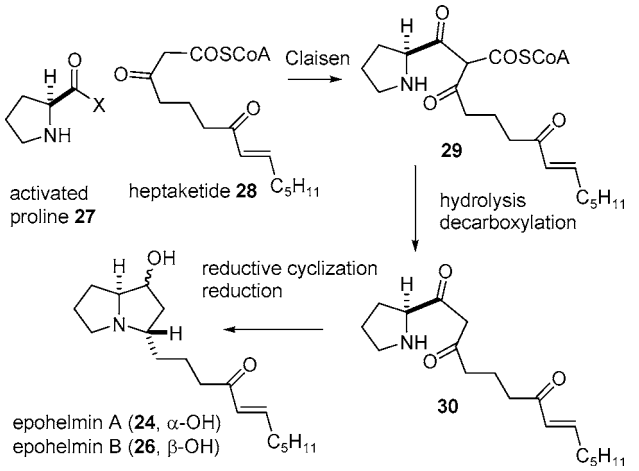
mixture of diastereomers at the side chain alcohol. Oxidation of **25** with MnO_2 proceeded slowly and in modest yield. We had previously observed that the Dess−Martin periodinane was not effective for the oxidation of model **11** or epohelmin A (**24**). As expected from this observation, selective oxidation of diol **25** with Dess−Martin periodinane afforded epohelmin B (**26**) in 98% yield. The ^1H and ^{13}C NMR spectra of the HOAc salt of **26** are identical to those reported for epohelmin B, thereby unambiguously establishing the revised structure of epohelmin B. The optical rotation of the acetate salt of **26**, $[\alpha]^{22}_D$ +29, is similar to that of the natural product, $[\alpha]^{22}_D$ +25, indicating that the absolute configuration is as shown.

A plausible biosynthesis of epohelmins A (**24**) and B (**26**) proceeds through the Claisen condensation of heptaketide **28** with activated proline **27** to give adduct **29**. Hydrolysis and decarboxylation will give trione **30**. Reductive cyclization and reduction of the ring ketone will lead to epohelmins A and B. If this is the biosynthetic pathway, the very efficient key reductive cyclization step leading to **11** and **21** is biomimetic.

In conclusion, we have reassigned the proposed 9-oxa-4-azabicyclo[6.1.0]nonane structures of epohelmins A (**1**) and B (**2**) as pyrrolizidin-1-ols **24** and **26**, respectively. We have developed syntheses from *N*-Cbz-(*S*)-prolinal (**9**) and ortho ester ketone **17** that provide epohelmin A (**24**) in eight steps and 52% overall yield and epohelmin B (**26**) in 11 steps and 43% overall yield using a stereoselective aldol reaction and a stereoselective reductive cyclization as the key steps.

Scheme 4. Possible Biosynthesis of Epohelmins A and B



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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. Comparison of NMR data of epohelmin A and **11**. NOE studies of **11** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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