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STEREOSELECTIVE SYNTHESIS AND ABSOLUTE CONFIGURATION OF EPOXYKETONES IN CHLAMYDOCIN AND RELATED CYCLIC TETRAPEPTIDES[1]

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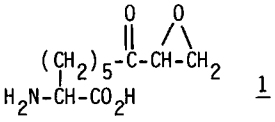
Abstract: The epoxyketone group in the amino acid, 2S-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) has been synthesized by chiral epoxidation of the corresponding allylic alcohol cyclic tetrapeptide precursor to form chlamydocin and epichlamydocin. These compounds have been used as standards to assign by circular dichroism spectroscopy the Aoe epoxyketone configurations in HC-toxin and WF-3161.

The amino acid, 2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) 1, has been found in the biologically active cyclic tetrapeptides chlamydocin (2a), HC-toxin (3), WF-3161 (4), Cyl-2 (5), and Cyl-1 (6).[2] The configuration of the Aoe side-chain epoxide, a group which appears to be essential for the activity of these peptides, has been assigned in only one case by X-ray crystallography.[3] As part of a program designed to determine the structural and conformational features of these cyclic tetrapeptides necessary for biological activity[4], we required an efficient method for synthesizing the epoxy ketone group in a stereoselective manner. We report here the successful application of the Sharpless chiral epoxidation reaction[5] to prepare chlamdocin 2a and the 9R epimer, epichlamydocin 2b. CD studies of these compounds have provided a simple spectroscopic method for assigning the chirality of the Aoe epoxyketone group in other natural products.



1

cyclo (Aib-L-Phe-D-Pro-2S,9S-Aoe) 2a

2S,9R-Aoe 2b

cyclo (D-Pro-L-Ala-D-Ala-L-Aoe) 3

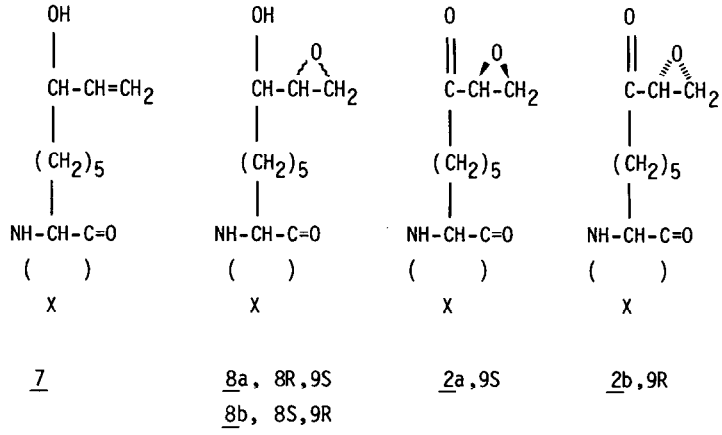
cyclo (D-Phe-L-Leu-L-Pip-L-Aoe) 4

cyclo (D-OMeTyr-L-ILe-L-Pip-L-Aoe) 5

cyclo (D-OMeTyr-L-ILe-L-Pro-L-Aoe) 6

The steroselective synthesis of chlamydocin (9S-epoxide) and epi-chlamydocin (9R-epoxide) is shown in the Scheme. Epoxidation of the 8RS allylic alcohol 7[4e] (0.6 equiv. mole TBHP in the presence of 1.3 equiv. mole of (-)-D-DIPT and 1.1 equiv. mole of $Ti(Oipr)_4$ in CH_2Cl_2)

gave, after column chromatography, the S-epoxide 8a in 27% yield along with 48% recovered starting material. The 9S-expoxy alcohol 8a was oxidized (MCPBA, TMP•HCl) according to the reported procedure.[6,4e] 9S-Epoxyketone (2a) was obtained in 59% yield. When (+)-L-DIPT was employed as the chiral auxillary, the corresponding 9R-epoxide diastereomer 8b was obtained in 24% yield plus 63% starting material. After oxidation, the 9R-epoxyketone 2b (epichlamydocin) was obtained in 79% yield. The C9-Aoe diastereomers 2a and 2b (epichlamydocin) were indistinguishable by 270 MHz NMR or by TLC in several solvent systems.



SCHEME. X=Aib-L-Phe-D-Pro

The configurations of the epoxyketone group in 2a and 2b were assigned by CD spectroscopy (Figure 1) by comparison with the CD of chlamydocin in which the 9S-epoxide is established.[3] Synthetic 2a shows the negative $n\rightarrow\pi^*$ transition at 288 nm ([θ] = -830) which is 96% of the ellipticity obtained with chlamydocin. The synthetic 9R-epimer 2b gives the positive Cotton effect at 288 nm ([θ] = +810) while synthetic racemic (9RS) chlamydocin shows no ellipticity. The respective configurations of these products are in accord with those predicted by the Sharpless model.[5] The ellipticity suggests that the enantiomeric excess is not less than 96% for the preparation of either diastereomer. Thus, chiral epoxidation of an allylic alcohol in a peptide system[7] can be used to prepare both epoxide diastereomers of chlamydocin from a common precursor and the route provides an alternate method for the stereospecific synthesis of chlamydocin.[8]

The CD spectra of 2a and 2b indicate that a preferred conformation may exist in the epoxyketone moiety, that there is no peptide bond contribution ($n\rightarrow\pi^*$ transition of the carbonyl) at around 288 nm, and the epoxyketone group follows the reverse octant rule which predicts a negative Cotton effect around 270-300 nm[9]. These observations permit us to establish the chiralities of the epoxyketone group in other Aoe-containing peptides from their respective CD spectra. HC-toxin and WF-3161 (Figure 1) show the negative ellipticities at 288 nm ([θ] = -780 and -760 respectively) clearly indicating that both 3 and 4 have the 9S epoxide configuration.

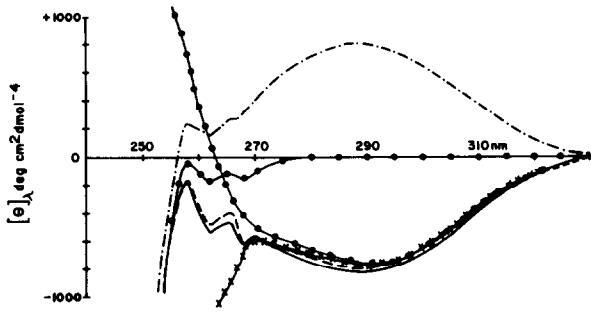


Figure 1. CD spectra of Aoe-containing cyclc tetrapeptides. Natural chlamydocin (2) ———; synthetic chlamydocin ----- (2a);-O-O- (2ab); ·-·-·-· (2b); natural HC-toxin —●—●—● ; natural WF-3161 x-x-x-x-x-x. The peptide concentration was 0.114-2.57 mM in distilled methanol. Circular dichroism [CD] spectra were recorded on a Jasco-40A spectropolarimeter in 0.5 mm-1 cm cells and are reported as mean residue molar ellipticities [deg. cm^2 dmol^{-1}].

Acknowledgments

Natural chlamydocin was donated by Dr. J. Pless of Sandoz. Natural HC-toxin and WF-3161 were obtained from Dr. J.D. Walton at Cornell University and Fujisawa Pharmaceutical Co. of Japan, respectively. This work was supported by grants CA 27985 and CA 34353 from the National Cancer Institute.

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(b) Abbreviations used follow IUPAC-IUB tentative rules as described in J. Biol. Chem. 1972, 247, 977. Additional abbreviations used; Aib, α-aminoisobutyric acid; Pip, pipecolic acid; Aoe, 2-amino-8-oxo-9,10-decanoic acid; TBHP, tert-butyl hydroperoxide; DIPT, diisopropyl tartrate; Ti(Oipr)$_4$, titanium(IV) isopropoxide; MCPBA, m-chloroperbenzoic acid; TMP•HCl, 2,2,6,6-tetramethyl piperidine hydrochloride.

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