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STEREOSELECTIVE SYNTHESIS OF HC TOXIN AND ITS (9R) EPOXIDE EPIMER

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Abstract : HC Toxin and its (9R) epoxide epimer have been synthesized *via* the Sharpless epoxidation of the allylic alcohol precursor 2. The epoxyketone configuration has been assigned by circular dichroism spectroscopy.

Several biologically active fungal cyclotetrapeptides such as : Cyl-2, Chlamydo cin, WF-3161, HC Toxin and (Gly) HC Toxin contain a common aminoacid residue : 2-amino-8-oxo-9,10-epoxy decanoic acid (Aoe).[1] In almost all of these peptides the 2C-carbon atom has been shown to have the S-configuration. The S-configuration of the epoxide carbon atom has been assigned for Chlamydocin by X-ray crystallography.[2] CD studies of natural or synthetic Chlamydocin[3,4,5] have shown negative ellipticities at 288 nm while synthetic epi-Chlamydocin exhibited the opposite ellipticity.[3]

Very recently, Rich et al.[6] have described a spectroscopic method based on circular dichroism studies for assigning the chirality of the epoxyketone group for the other natural cyclotetrapeptides. Since HC Toxin shows the same negative ellipticity as Chlamydocin, it is assumed to have the same (9S) epoxide configuration ($(\theta)_{288nm}$= -780 deg. cm^2 $dmol^{-1}$).

Using the strategy previously used by us for Aoe derivative stereoselective synthesis[7] and by Rich et al.[3 6] for Chlamydocin synthesis, we have successfully applied the Sharpless chiral epoxidation[8] to prepare HC toxin 4a and its (9R) epimer 4b. In the first step, cyclopeptide[9a] 1 bearing a terminal olefinic bond was converted to the 8 (R,S) allylic alcohol[9b] 2 by a TBHP oxidation catalysed by SeO_2 (scheme).

Then 2 was subjected to epoxidation in CH_2Cl_2 with 1.2 mole equiv. (-)-D-DIPT, 1 mole equiv. Ti $(Oipr)_4$ and 2 mole equiv.TBHP in the presence of 4Å molecular sieve with stirring at -20°. The reaction was monitored by TLC (SiO_2, Hexane-Acetone-1:1) and stopped before reaching 40% conversion (5 days) by addition of an ether-acetone (9:1) solution containing 0.33 mole equiv. of citric acid. The titanium citrate salt was removed by filtration over

celite and the filtrate, after Column chromatography (SiO_2 Hexane-Acetone (1:1)), gave the epoxy alcohol 3a in 20% yield along with 38% allylic alcohol partially enriched with the (8S) epimer. The (9S) epoxyalcohol 3a was further oxidized in CH_2Cl_2 with 3 mole equiv. MCBA and 0.05 mole equiv. TMP, HCl and give, after 12 hours at 20°, HC Toxin 4a isolated in 60% yield after two successive column chromatographies (SiO_2, hexane-Acetone (1:1) and CH_3OH-$CHCl_3$ 6%). The recovered allylic alcohol was subjected to Sharpless epoxidation using (+)-L-DIPT under the same experimental conditions. It gave 3b which was further oxidized to epi HC toxin 4b.[10]

C(NH(S)CHRCO-DPro-LAla-DAla)

Scheme

According to Rich al.[6], CD spectroscopic analysis in distilled methanol gives opposite ellipticities at 288 nm for 4a and 4b.

These products are currently undergoing biological studies to determine the effect of the epoxyketone group configuration.

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References :

1 - Abbreviations used : Aoe, 2-amino-8-oxo-9,10-epoxydecanoic acide ; DIPT, Diisopropyl tartrate ; Ti (Oipr)$_4$, Titanium IV isopropoxide ; TBHP, Tert-Butyl hydroperoxide; MCBA, m-Chloroperbenzoic acid ; TMP, HCl, 2,2,6,6 tetramethyl piperidine hydrochloride.

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b) To be published
10 - HC toxin 4a and epi HC toxin 4b have been identified by TLC analysis, ^{1}H NMR and MS spectroscopies.They gave the same results as those published for natural HC toxin.Only CD spectroscopy gave opposite spectra between 4a and 4b within the 260-350 nm region.

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