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SYNTHESIS OF NEOCARZILIN A: AN ABSOLUTE STEREOCHEMISTRY

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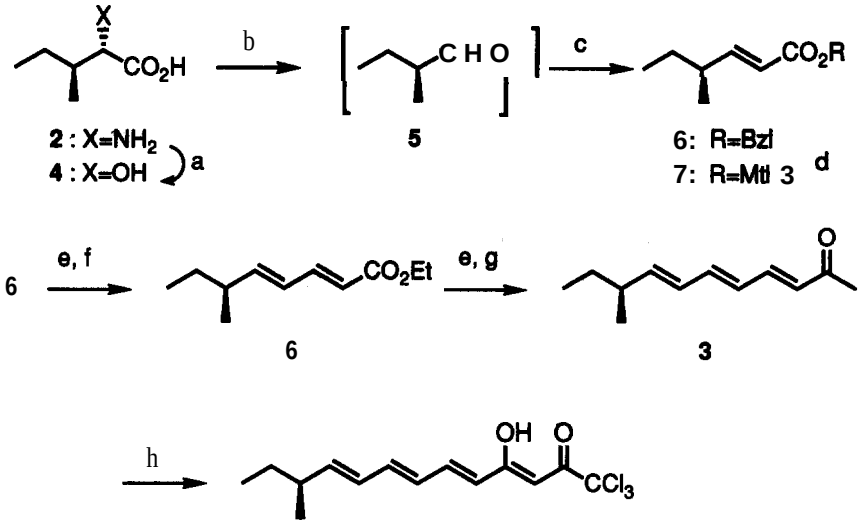
Abstract: Neocarzilin A **(1)** was synthesized from ***L*-isoleucine** for determination of the absolute configuration of an alkyl branch at C-l 1, and for the precise analysis of biological activities.

In the course of our investigation on biologically active substances from natural sources, new polyenone antibiotics, neocarzilin A and B have been isolated from the mycelium of ***Streptomyces carzinostaticus*** var. F41, as described in a previous report.[1] Succeeding the structural elucidation by spectroscopic analysis, we synthesized neocarzilin A **(1)** and found that **1** has ***S*-configuration** at C-l 1. In this communication we would like to report a synthesis of neocarzilin A **(1)** and its biological activities.

The synthesis was started from ***L*-isoleucine** (2) as an optically active ***sec*-butyl** terminal, and directed toward preparation of variously substituted halogen analogs ***via*** the versatile intermediate (3). The hydroxy acid (4) derived from ***L*-isoleucine** was first oxidized with periodate under neutral condition, to avoid racemization. The aldehyde (5) was transformed, without isolation, to the enoate (6) by treatment with a stable ylid. The preservation of the optical purity was determined by ^{1}**H** NMR analysis of the ***L*-menthyl** ester (7). After conventional elongation of the ester **(6),** the trienone (3) was obtained in 25% yield from ***L*-isoleucine.** The trienone (3) was then transformed regioselectively into "kinetic': **enolate**[2] and treated with trichloroacetic anhydride to give the trichloride **(1).** Overall yield from ***L*-isoleucine** (2) was 18%. Acylation with halogenated acid chlorides or acid anhydrides gave variously halogenated **congeners** whose biological activity will be reported elsewhere. The synthesized trichloride **(1), $[\alpha]_D^{29}$ +45.7°** (c 0.09, **$CHCl_3$),** gave identical spectral data including optical rotation with those of natural neocarzilin A. Thus the stereostructure of neocarzilin A was proved to be represented by the formula **1.**

The synthesized compound **(1)** showed weak antimicrobial activity against gram positive bacteria, ***Micrococcus luteus*** and ***Bacillus megaterium,*** and showed essentially the same cytotoxic activity with that of natural product, against K562 chronic myelogenous leukemia cells with **IC_{50}** of 0.06 **μg/ml** which indicated that the activity of neocarzilin A **(1)** is as potent as **neocarzinostatin,**[3] **IC_{50}** 0.09 **μg/ml,** produced by the same actinomycete, S. ***carzinostaticus*** var. F41.4 Acute toxicity of neocarzilin A **(1)** on ICR mice, **LD_{50}** 88.1 **mg/kg,** was lower than that of neocarzinostatin, **LD_{50}** 2 **mg/kg.**



1

a) HNO_2, 89%; b) $(n\text{-}Bu)_4NIO_4$, CH_2Cl_2, A; C) Ph_3PCHCO_2Bzl, 77% from 4; d) 1N NaOH, EtOH; (-)-menthol, DCC, DMAP, CH_2Cl_2, 56% e) $LiAlH_4$-$AlCl_3$ (3:1), Et_2O, -10 °C; MnO_2, hexane; f) Ph_3PCHCO_2Et, CH_2Cl_2, 42% from 6; g) $Ph_3PCHCOCH_3$, CH_2Cl_2, A, 86% from **8**; h) $LiN[Si(CH_3)_3]$, THF, -78 °C; $(CCl_3CO)_2O$, 73%.

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References and Notes

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4. Biological activities of neocarzilin A (1) including cytocidal activity on other tumor cells will be reported elsewhere.

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