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Short Communications

Absolute Configuration of 2,3-Dihydroxy-2-isopentylbutanedioic Acid, a Component of the Alkaloid Isoharringtonine

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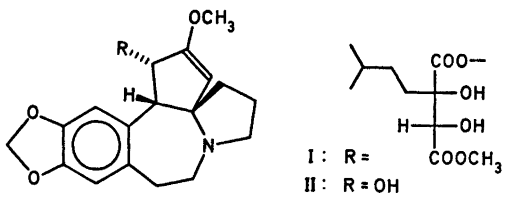
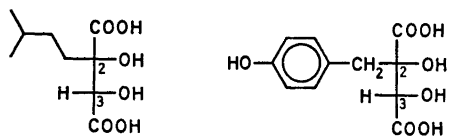
Isoharringtonine (I) is one of the alkaloids isolated from *Cephalotaxus harringtonia* which show antileukemia activity.[1] The alkaloid I is an ester of an amino alcohol, cephalotaxine (II) with a monomethyl ester of an optically active



diacid, 2,3-dihydroxy-2-isopentylbutanedioic acid (III). The absolute configuration of cephalotaxine has been determined in an X-ray investigation.[2] The relative configuration of the natural diacid III has been shown to be *erythro*,[3] but its absolute configuration has not been determined.

We here report that the absolute configuration of III is 2*R*, 3*S*, as found by comparison between the CD spectra of molybdate com-



III IV

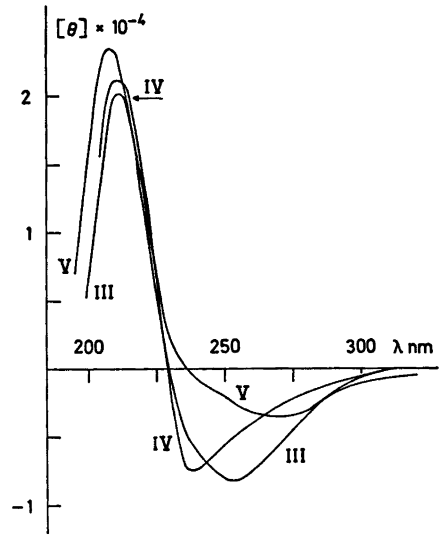


Fig. 1. CD spectra of molybdate complexes of the acid from isoharringtonine (III), piscidic acid (IV), and the hexahydro derivative of piscidic acid (V). The solutions had pH 2.9, 2.9, and 3.1, respectively.

plexes[4] of III and piscidic acid (IV). Acid IV is of natural origin and has a known absolute configuration (2*R*, 3*S*).[5] (In this paper[5] the reversed numbering is used.) The similarity between the CD spectra of the molybdate complexes (Fig. 1), taken together with the known *erythro* configuration[3] of III gave its absolute stereochemistry as 2*R*, 3*S*, thereby completing the knowledge about the configuration of isoharringtonine.

Other alkyltartaric acids of natural origin than the two ones mentioned above are known. The methyl homologue has been detected in wine,[6] and the isobutyl homologue has been found as a component of a glucoside from *Orchis militaris*.[7] Fukiic acid, the 3,4-dihydroxyphenyl analogue of piscidic acid, is also of natural origin.[8]

Experimental. The dimethyl esters of III and IV were hydrolysed with 4 M hydrochloric acid (reflux, 4 days), and excess hydrochloric acid was evaporated under diminished pressure. The crude acids so obtained were used directly in

preparation of CD solutions, which were 3.0 mM with respect to hydroxy acid and 2.7 mM with respect to sodium molybdate. Hydrochloric acid and sodium hydroxide solution were added until pH 2.9 – 3.1 was reached. Measurements of the CD spectra were carried out in a 0.5 mm cell using a Cary 60 spectropolarimeter (a Jasco J-40 instrument was used for the measurement on the hexahydro derivative of IV) five days after the solutions had been prepared.

The hexahydro derivative of IV was prepared by hydrogenation (1 atm, 23 °C, 24 h) of the dimethyl ester of IV (3.5 mg) in methanol (3 ml) using 5 % rhodium on alumina as catalyst (16 mg) followed by hydrolysis. The starting material was contaminated by approximately 5 % of an unknown compound, and after hydrogenation one further compound, probably dimethyl (cyclohexylmethyl)tartrate (GLC-MS), contaminated the desired hydrogenation product to the extent of about 5 %. Hydrolysis of the ester and preparation of the molybdate complex were performed as described above.

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Strained Heterocyclic Compounds. 7. Preparation of α-Phthalimido-β-lactams from α-Halo-β-lactams

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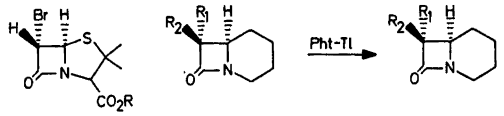
For some time we have been trying to develop a general synthesis of penicillins. In particular we are interested in synthesizing penicillin analogues containing a modified nucleus. In one approach carbene insertion has been used to produce halo-β-lactams of the types *1* and *2*.[1]



1

2a R_1=Br, R_2=H
2b R_1=H, R_2=Br
2c R_1=Cl, R_2=H

3a R_1=H, R_2=Pht
3b R_1=Pht, R_2=H
(Pht=Phthalimido)

As expected, these cyclizations yield predominantly the more stable *trans*-halo-β-lactams, *e.g. 1*, *2a*, and *2c*. Nucleophilic displacement of the halogen with an amine function should therefore yield amino-β-lactams with the *cis*-configuration characteristic for the penicillins and cephalosporins. Simple amines were found to destroy the β-lactams *2a* – *2c*, which were used as model compounds. Likewise, the use of metal amides were of no success.[2] Nor was it possible to use sodium azide which has been used for an unfused halo-β-lactam.[3] Therefore, we turned our attention to phthalimide salts. Potassium phthalimide reacted with the halo-β-lactams *2a* and *2c* to give a very low yield of phthalimido-β-lactam *3a*. The major part of the starting material was decomposed. On the other hand mercury(II) and silver(I) phthalimides were completely unreactive towards α-bromo-β-lactams. (In fact, silver phthalimide reacts reluctantly even with dilute HCl.)

In the search for compounds of intermediate reactivity we have now found that thallium(I) phthalimide reacts fairly readily in dimethyl sulfoxide at 150 °C with the bromo-β-lactams *2a* and *2b* to give phthalimido-β-lactams. The *trans*-compound *2a* gave the *cis*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]octane *3a* (55 % yield, 90 % stereoselectivity as determined by NMR and TLC), while the *cis*-compound *2b* gave *trans*-7-phthalimido-8-oxo-1-azabicyclo[4.2.0]-octane *3b* (24 % yield) with nearly complete stereospecificity. Since the halo-β-lactams isomerize slowly at 150 °C, the 10 % *trans*-phthalimido-β-lactam obtained from *trans*-bromo-β-