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# RELATIVE CONFIGURATION OF THE DIACID SIDECHAIN OF ISOHARRINGTONINE

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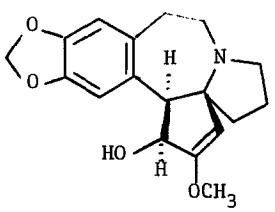
There has been considerable interest in the Cephalotaxus alkaloids recently due both to the unusual structure of the parent alkaloid cephalotaxine (1) and to the promising antileukemia activity of the harringtonines, which are esters of cephalotaxine with several acyclic dicarboxylic acids.[1-4] Isoharringtonine (2) is



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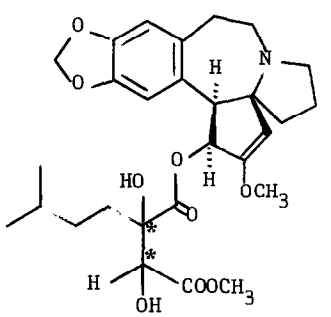

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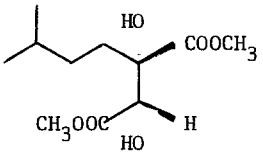
unique in that it is the only one of the four known harringtonines possessing two assymetric centers (*) in its diacid sidechain. Mild transesterification of isoharringtonine (2) with sodium methoxide in methanol[2b,e] produces cephalotaxine (1) and a single dimethyl ester which may have either the threo configuration 3 or the

erythro configuration 4. Structural studies to date have left unanswered the question of the relative stereochemistry in this side-chain. We have stereospecifically

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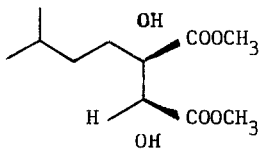


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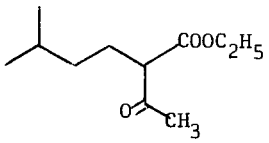
synthesized both 3 and 4 and wish to report that the diester from isoharringtonine has the erythro configuration shown in 4.

Treatment of ethyl isoamylacetoacetate 5 with two equivalents of bromine in refluxing ether, followed by stirring with ethanolic potassium hydroxide gave the alkyl fumaric acid 6, m.p. 203-204° (35% overall yield).[5] The dimethyl ester 7 is produced upon refluxing 6 in methanol containing sulfuric acid. The best support for the fumarate structure for 7 is the characteristic downfield absorbtion of its vinyl

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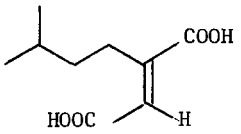


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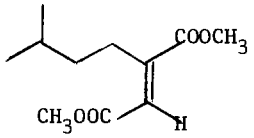


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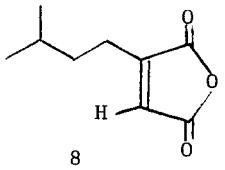


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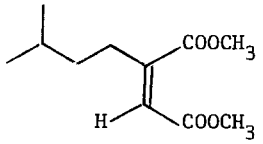


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proton at 6.80 δ in the nmr (vs 6.68 δ for that of dimethyl mesaconate[6]). Hydroxylation of 7 with osmium tetroxide/hydrogen peroxide in t-butanol at 50° for 48 hrs produced a single diol 3 (65%):[7] m.p. 55-56°; ir ($CHCl_3$) 3500, 1740 $cm^{-1}$; nmr ($CDCl_3$) δ 0.88 (6H,d,J = 6 Hz), 1.0-2.0 (5H,m), 3.52 (1H, d,J = 8 Hz, OH), 3.70 (1H,s,OH), 3.80 (6H s), 4.32 (1H, d, J = 8 Hz, collapses to a singlet on $D_2O$ shaking). It is well established that hydroxylation with this combination of reagents gives the cis stereochemistry of the resulting diol. Thus diethyl fumarate and diethyl maleate yield dl and meso tartaric acid esters respectively.[8]

Dehydration of diacid 6 with phosphorous pentoxide affords anhydride 8: ir (film) 1830, 1775 $cm^{-1}$. Conversion of 8 to diester 9 was effected by heating with methanol/sulfuric acid. Diester 9 has its vinyl proton upfield relative to that of 7 at 5.85 δ in the nmr (vs 5.77 δ for that of dimethyl citraconate[6]). Hydroxylation of 9 with osmium tetroxide/hydrogen peroxide in t-butanol at 50° for 48 hrs again produced a single diol, 4 (40%):[7] m.p. 70-72°; ir ($CHCl_3$) 3500, 1740 $cm^{-1}$; nmr ($CDCl_3$) δ 0.88 (6H,d J = 6 Hz), 1.0-2.1 (5H, m), 3.25 (1H,d,J = 8 Hz,OH), 3.42 (1H,s,OH), 3.76 (3H,s), 3.82 (3H,s), 4.41 (1H,d, J = 8 Hz, collapses to a singlet on $D_2O$ shaking).

Comparison of the nmr spectra of 3 and 4 with that of the transesterification product of isoharringtonine[2b,e,9] clearly shows the natural isomer to be identical, except for optical activity, to the erythro isomer 4.

Still unknown however are the absolute configurations of both cephalotaxine (1) and the diacid portion of isoharringtonine. We are currently investigating this proble

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9. Kindly supplied by Mr. R.G. Powell, USDA, Peoria, Illinois.