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SYNTHESIS OF THE DIACID SIDECHAIN OF DEOXYHARRINGTONINE

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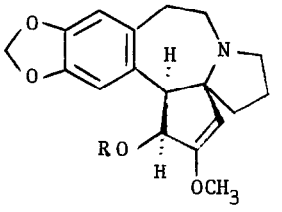
The Cephalotaxus alkaloids are an unusual group of compounds produced by several species of plumyews. Cephalotaxine, the most abundant alkaloid of this group, was shown by X-ray and chemical studies[1-3] to have structure 1 and this has been confirmed by two independent total syntheses.[4] The harringtonines are naturally occuring esters of cephalotaxine with several acyclic dicarboxylic acids which have shown significant inhibitory activity against experimental lymphoid leukemia in mice. Interestingly, neither cephalotaxine nor the diacid sidechains show activity alone. We wish to describ

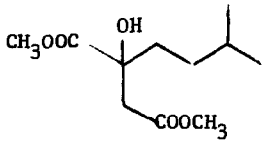


1 R = H

2 R = OC(OH)CH(CH3)2CH2COOCH3

a short synthetic approach to the diacid sidechain of deoxyharringtonine (2)[2c,e] which hopefully can be applied to syntheses of other harringtonine diacids and diacid analogs.

Transesterification of deoxyharringtonine with sodium methoxide produces the dimethyl ester 3,[2c,e] which we have synthesized into two steps.



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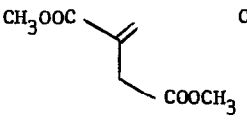

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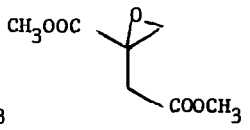

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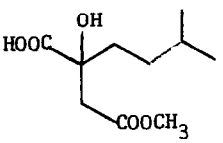
Epoxidation of commercially available dimethyl itaconate (4) with pertrifluoroacetic acid - Na_2HPO_4 buffer in refluxing chloroform for one hour gave the epoxide 5 in 78% yield: ir (film) 1740 cm^{-1}; nmr ($CDCl_3$) δ 2.8-3.3 (4H,m,2 overlapping AB quartets), 3.72 (3H,s), 3.78 (3H,s). Treatment of 5 with the organo-copper reagent prepared in ether from isobutyl lithium (2 eq.) and cuprous iodide (1 eq.) at -40° produced the ester 3 (60%).[6] This compound was identical with natural material derived from deoxyharringtonine.[7]

In order to prepare the monoacid 6 necessary for synthesis of deoxyharringtonine, a similar route was followed. Benzylmethylitaconate (7)[8] could be converted to epoxide 8 with pertrifluoroacetic acid as described for the dimethyl compound. More conveniently, this epoxidation was effected in 96% yield using m-chloroperbenzoic acid in refluxing



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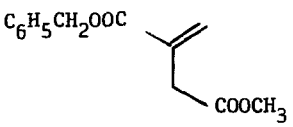

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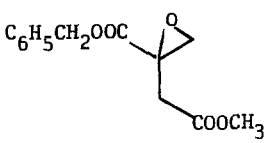

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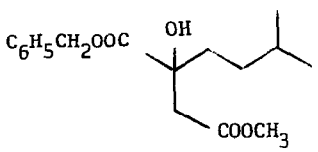

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1,2-dichloroethane containing a trace of 2,6-di-t-butyl-4-methyphenol[9]: nmr ($CDCl_3$) δ 2.5-3.3 (4H,m,2 overlapping AB quartets), 3.58 (3H,s), 5.16 (2H,s), 7.30 (5H,s). Treatment of 8 with the isobutyl copper reagent described above gave 9 in 60% yield: ir (film) 3500 cm^{-1}, 1740 cm^{-1}; nmr ($CDCl_3$) δ 0.82 (6H,d,J=6 Hz), 1.0-1.8

(5H,m), 2.82 (2H,q,J=16 Hz) 3.64 (3H,s), 5.25 (2H,s), 7.40 (5H,s). Benzyl ester 9 was converted to the acid 6 by hydrogenolysis using Adams catalyst in methanol containing hydrochloric acid (79%); mp 88-89° [2c]; ir ($CHCl_3$) 3500 (br), 1740 cm^{-1}; nmr ($CDCl_3$) δ 0.86 (6H,d,J=6 Hz), 1.1-2.0 (5H,m), 2.85 (2H,q,J=16 Hz), 7.6 (2H,br s, OH).

Monoacid 6 was resolved into its enantiomers with ephedrine. (+) Ephedrine afforded the (-) acid: $[\alpha]_D$ - 16° (c 0.41 $CHCl_3$); (-) ephedrine gave the (+) acid: $[\alpha]_D$ + 19° (c 0.134 $CHCl_3$).[10] We have been unable so far to esterify 6 with cephalotaxine to produce deoxyharringtonine (2).[11,12]

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7. We are indebted to Mr.R.G. Powell, USDA, for comparison of our samples.

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10 The $[\alpha]_D$ for the deoxyharringtonine transesterification product 3 has not been reported [2c,e] due to scarcity of material.

11. Esterification of 6 with cephalotaxine is not a trivial problem, evidence by several unsuccessful attempts (Ref. 2c and K.L. Mikolajczak, R.G. Powell and C.R. Smith, Jr., Abstracts, 166th National Meeting, ACS, Chicago, Ill., August 1973)

12. Compounds 3 and 6 have been previously synthesized (Ref.2c) by a somewhat longer route. This earlier method does not allow ready selectivity between the two carboxyl groups and the preparation of half acid 6 gives a mixture of products.