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SYNTHESIS OF DEOXYHARRINGTONINE

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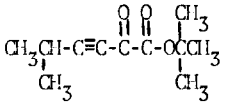
Among the alkaloids which have been isolated from Cephalotaxus harringtonia plant material are cephalotaxine (3a) and a number of its esters.[2,3] Some of these esters, which are derived from relatively complex dicarboxylic acid moieties such as in 3c, have been found to exhibit significant antitumor activity[4] in the P388 system (cephalotaxine itself is inactive). Two of the esters have been approved for the preclinical phase of pharmacological evaluation at the National Cancer Institute. Since continued biological testing of the



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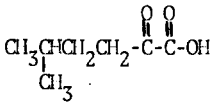

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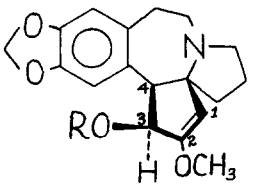

3a: R = -H

3b: R = $-C(=O)-C(=O)-CH_2CH_2CH(CH_3)_2$

3c: R = $-C(=O)-C(OH)(CH_2COOCH_3)-CH_2CH_2CH(CH_3)_2$

3d: R = enantiomeric form of R in 3c

active esters requires quantities which cannot be supplied by natural sources, we have been investigating[3,5] the partial synthesis of these esters from natural 3a which is available in considerably larger quantities.[6] We now describe the first successful conversion of cephalotaxine to one of its active naturally occurring esters, deoxyharringtonine (3c).[3]

Our earlier work[3,5] demonstrated that direct esterification of cephalotaxine with a fully elaborated acid moiety is not likely to succeed because of formidable steric problems; this difficulty is circumvented by the approach described here. In addition to 3c, ester 3d, a diastereomer of 3c, was obtained as a byproduct. Parts of this sequence were applied earlier to the synthesis of the racemic form of the dicarboxylic acid moiety of harringtonine,[9] a related ester alkaloid.

A cold solution (<10°C) of 13.0 g of ethyl t-butyl oxalate[10] in 15 ml of anhydrous[11] THF and 5 ml of hexane was treated dropwise with 0.4 equivalents of the lithium acetylide of 3-methyl-1-butyne[12] in THF and stirred for 20 min. The reaction was quenched with pH 7.0 buffer and the mixture was extracted with ether. After removal of ethyl t-butyl oxalate by vacuum distillation, 1 comprised 52% of the residue and was isolated by chromatography on a silica column. The acetylenic α-keto ester 1 gave: ir (1%, $CHCl_3$) 2210 cm^{-1} (conjugated -C≡C-), 1730 cm^{-1} (ester -C=O), and 1670 cm^{-1} (α,β-unsaturated -C=O); nmr ($CDCl_3$, 100 MHz) δ 1.26 (d, J = 7 Hz, 6H, isopropyl), 1.53 (s, 9H, CH_3- of t-butyl group), and 2.78 (septet, J = 7 Hz, 1H, methine proton). Hydrogenation of 0.430 g of 1 (Pd/C, hexane, ambient conditions) yielded the saturated α-keto ester (no 2210 or 1670 cm^{-1} ir bands), which was treated with trifluoroacetic acid for 45 min at 0°C to give a 94% yield of 2. Treatment of α-keto acid 2 (0.310 g) with excess oxalyl chloride in ethyl ether solution afforded the corresponding acid chloride, which was dissolved in 3 ml of CH_2Cl_2 and added to 0.500 g of natural 3a and 1.0 ml of pyridine in 3 ml of CH_2Cl_2. The crude product (0.568 g), estimated by tlc analysis to be 60-80% 3b was used in the subsequent step without purification. Crude 3b gave: ir (1%, $CHCl_3$) 1725 cm^{-1} with a strong shoulder at 1730 cm^{-1} (ester -C=O, plus α-keto group), 1645 cm^{-1} (vinyl of cephalotaxine), and 935 cm^{-1} ($-OCH_2O-$); nmr ($CDCl_3$, 100 MHz) δ 0.81 (d, J= 6 Hz, 6H, isopropyl), 3.68 (s, 3H, $-OCH_3$), 3.81 (d, J = 10 Hz, 1H, C-4 proton), 5.08 (s, 1H, vinyl), 5.82 (s, 2H, $-OCH_2O-$), 5.86 (d, J = 10 Hz, 1H, C-3 proton),

and 6.56 and 6.58 (2s, 1H each, aromatic protons). High-resolution mass spectral analysis of 3b gave M^+ = 441.215; $C_{25}H_{31}NO_6$ requires 441.215.

Successful conversion of 3b to deoxyharringtonine was achieved by reaction with $LiCH_2COOCH_3$ as described for the synthesis of the harringtonine dicarboxylic acid.[9] Preparation of $LiCH_2COOCH_3$ from 2 equivalents of lithium isopropylcyclohexylamide[13] and 1.9 equivalents of CH_3COOCH_3 at -78°C in the presence of 1.0 equivalents of 3b (0.473 g) gave a product which was isolated by pouring the reaction mixture into pH 7.0 buffer and extracting with $CHCl_3$; yield, 0.458 g or 82% of theory. This crude product, however, contained a large proportion of unesterified cephalotaxine, presumably from breakdown of 3b. Instability has been consistently observed in α-keto esters of cephalotaxine.[5]

This reaction of 3b with $LiCH_2COOCH_3$ generated a new asymmetric center and the product contained a mixture of diastereomers 3c and 3d. Preliminary concentration of 3c and 3d was achieved by preparative tlc of the crude product on commercial 2-mm silica gel plates with 20% MeOH in benzene. The resulting concentrate was further fractionated into essentially pure 3c (natural isomer, more mobile) and 3d on analytical (0.25 mm) silica gel plates (commercial precoated) subjected to double development in 20% MeOH in benzene; yield of deoxyharringtonine (3c), 6% and of 3d, 9% based on the α-keto ester of cephalotaxine. Trace amounts of acetylcephalotaxine, an apparent byproduct, were detected in both 3c and 3d by nmr and high-resolution mass spectral analysis.

The 100 MHz nmr and the ir spectra of our synthetic 3c matched those of natural deoxyharringtonine perfectly.[3] High-resolution mass spectral analysis of synthetic 3c gave: M^+ 515.251; $C_{28}H_{37}NO_8$ requires 515.252. The ir spectrum of 3d was indistinguishable from that of 3c and its high-resolution mass spectrum gave: M^+ 515.249; $C_{28}H_{37}NO_8$ requires 515.252. Nmr spectra of these diastereomers differed markedly, however. The pair of doublets due to $-CH_2COOCH_3$ were observed at δ 1.86 and 2.26 for 3c and at δ 2.46 and 2.66 for 3d. In the spectrum of 3c the two $-OCH_3$ groups appeared as two distinct singlets at δ 3.53 and 3.64 while in the spectrum of 3d they gave overlapping singlets at δ 3.60 and 3.62. The doublet

due to the C-3 proton in 3c (δ 5.97) was shifted in the spectrum of 3d to δ 5.86. Finally, aromatic protons in 3c give two singlets, δ 6.50 and 6.59, and the corresponding protons of 3d are equivalent and appear as a singlet at δ 6.56.[14]

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References and Footnotes

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6. Cephalotaxine is by far the most abundant of the Cephalotaxus alkaloids and usually exceeds 50% of the total alkaloids. In addition, two total syntheses of racemic cephalotaxine have been reported (see references 7 and 8).

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11. Anhydrous reagents were prepared by storing them over a commercial 3A-type molecular sieve.

12. Prepared from 3-methyl-1-butyne and n-butyllithium.

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14. The fact that these two para aromatic protons may or may not appear magnetically equivalent has precedents among other cephalotaxine derivatives we have examined,[2a,5] and seems to depend on subtle influences of substituent groups.