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REGIOSPECIFIC SYNTHESIS OF THE ACYL PORTION OF HARRINGTONINE

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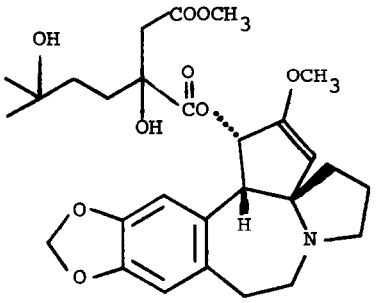
The alkaloid harringtonine was recently assigned[2] structure 1, primarily on the basis of its methoxide-induced cleavage to cephalotaxine(2)[3] and diester 3. Assignment of structure 3 to the diester rests principally on a consideration of its spectral properties.



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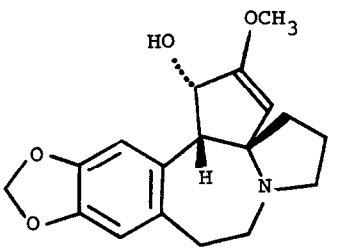

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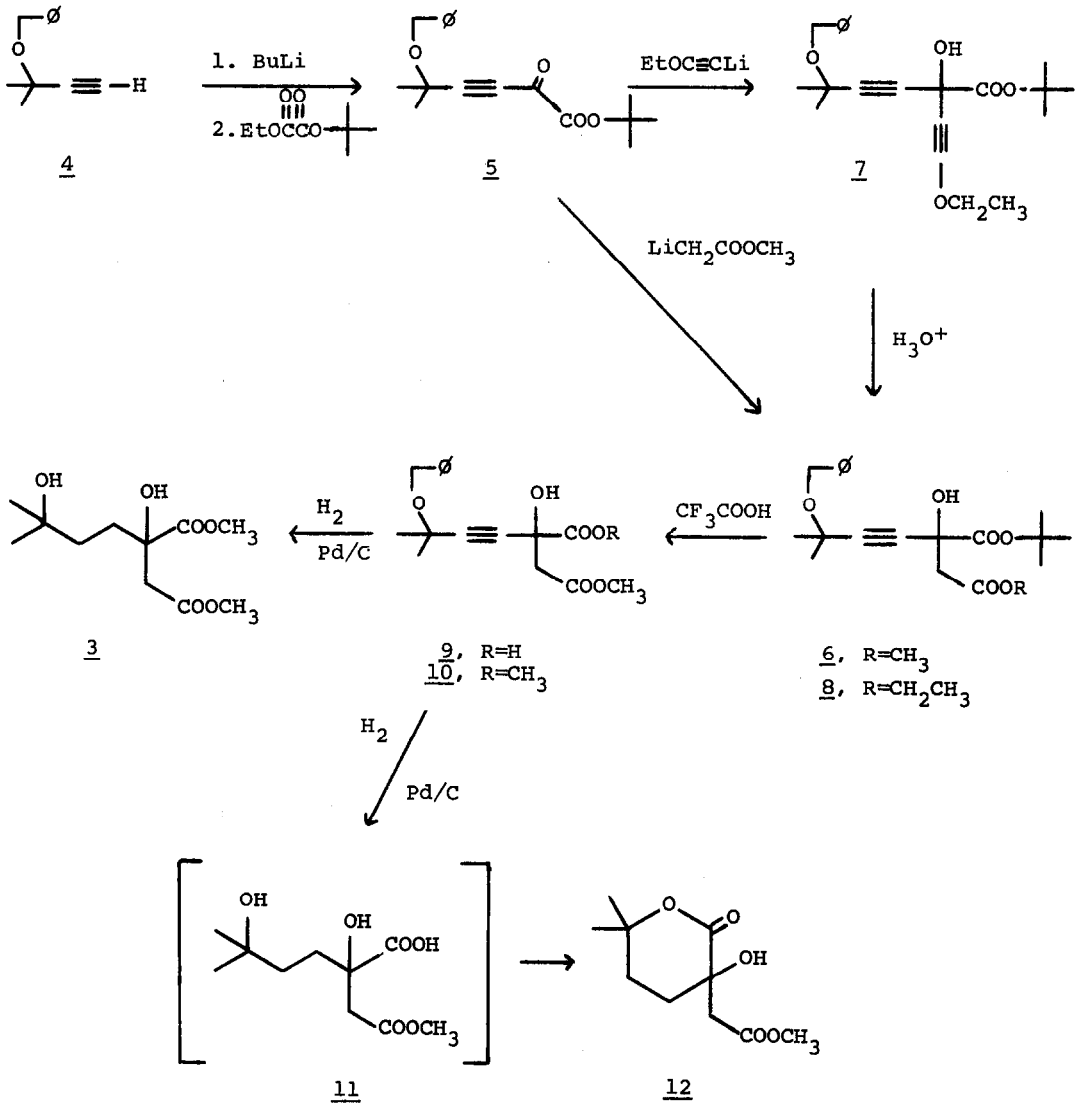
We wish to report a regiospecific synthesis of the acyl portion of harringtonine, which (a) confirms the structure assigned to 3 and (b) provides a number of derivatives of 3, the synthesis and transformations of which may prove useful in developing a partial synthesis of harringtonine(1) from the relatively more abundant cephalotaxine(2).[4] The development of such a synthesis takes on a note of urgency because the demonstration of possible anticancer activity[5] in harringtonine has generated a demand for 1 which is greater than present natural sources can satisfy.[5]

Addition of a tetrahydrofuran solution of the lithium acetylide derived from 4[6] to excess t-butyl ethyl oxalate[7] gives keto ester 5[8] (2,4-DNP,[8,9] mp 133-4°) in good yield. Initial efforts to convert 5 to 6 using either CH_3COOCH_3/NaH or $BrCH_2COOCH_3$/Zn proved unsuccessful but reaction of 5 with the lithium derivative[10] of (commercially available)[11] ethoxyacetylene was found to proceed smoothly to



give 7[8] which could be hydrolyzed selectively[12] and in good yield to ethyl ester 8[8]. Expectations of success notwithstanding, efforts to adapt this sequence to the synthesis of the corresponding methyl ester 6 were suspended when a more direct route to 6 emerged. Thus it was found that generation in tetrahydrofuran at -78° of $LiCH_2COOCH_3$ (from 2 equivalents lithium cyclohexylisopropylamide[13] and 1.5-2 equiv. methyl acetate) in the presence of 5 gives a ~3:2 mixture of 6[8,9] and unreacted 5 which is separable by preparative tlc (benzene on silica gel). Trifluoroacetolysis of 6 at 0° affords in 60% yield the difficultly crystalline half acid 9[8,9] (mp 89-90°) which is converted to dimethyl ester 10[8,9]

by diazomethane. Catalytic hydrogenation (10% Pd/C, EtOAc) of 10 proceeds with concomitant reduction and debenzylation to give (±)-3,[8,9] whose spectra are identical with those of naturally derived, optically active material.

Catalytic hydrogenation (5% Pd/C, isopropanol) of half acid 9 is attended not only by saturation and debenzylation but also by spontaneous lactonization of the resulting hydroxy acid (11) to give 12[8,9] (mp 83.5-34.5°).

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Footnotes and References

1. (a) Postdoctoral research associate 1972-73; (b) NSF Trainee 1970-73.

2. R.G. Powell, D. Weisleder, C.R. Smith, Jr., and W.K. Rohwedder, Tetrahedron Letters, 815 (1970); K.L. Mikolajczak, R.G. Powell and C.R. Smith, Jr., Tetrahedron, 28, 1995 (1972).

3. R.G. Powell, D. Weisleder, C.R. Smith, Jr., and I.A. Wolff, Tetrahedron Letters, 4081 (1969); D.J. Abraham, R.D. Rosenstein and E.L. McGandy, ibid., 4085 (1969).

4. Two total syntheses of (±)-cephalotaxine have recently been reported: J. Auerbach and S.M. Weinreb, J. Amer. Chem. Soc., 94, 7172 (1972); M.F. Semmelhack, B.P. Chong and L.D. Jones, ibid., 94, 8629 (1972). See also L.J. Dolby, S.J. Nelson and D. Senkovich, J. Org. Chem., 37, 3691 (1972).

5. Harringtonine is presently in the preclinical phase of pharmacological evaluation at the National Cancer Institute (R.G. Powell, personal communication). See also R.G. Powell, D. Weisleder and C.R. Smith, Jr., J. Pharm. Sci., 61, 1227 (1972); R.E. Perdue, Jr., L.A. Spetzman and R.G. Powell, Amer. Hort. Mag., 19 (1970).

6. T.A. Favorskaya and O.V. Sergievskaya, Zh. Obshch. Khim., 28, 3233 (1958); Chem. Abstr., 53, 12267a (1959).

7. L.A. Carpino, J. Amer. Chem. Soc., 82, 2725 (1960).

8. This compound gave infrared and nuclear magnetic resonance spectra which support the assigned structure.

9. A satisfactory elemental analysis was obtained for this compound.

10. Prepared by reacting a tetrahydrofuran solution of ethoxyacetylene with butyl lithium at -5° and allowing the reaction to come to room temperature. See J.F. Arens, Advances in Organic Chemistry, 2, 117 (1960).

11. Available as a neat liquid from Farchan Research Laboratories, Willoughby, Ohio.

12. To .449 g ester in 12 ml THF was added 0.75 ml of 10% H_2SO_4 and the resulting solution was stirred overnight at 5°: G.E. Arth, G.I. Poos, R.M. Lukes, F.M. Robinson, W.F. Johns, M. Feurer and L.H. Sarett, J. Amer. Chem. Soc., 76, 1715 (1954).

13. M.W. Rathke and A. Lindert, ibid., 93, 2318 (1971).