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PREPARATION OF A BENZENOID INTERMEDIATE FOR USE IN THE SYNTHESIS OF MAYTANSINE[1]

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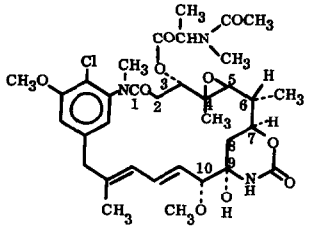
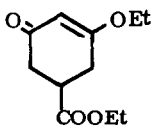
This note reports a straightforward synthetic route developed some time ago for the preparation of a synthetic intermediate corresponding to the benzenoid part of maytansine (1)[2,3].

The enone ester 2, readily available from gallic acid (Birch reduction[4] followed by work-up with aqueous acid and reaction with acidic ethanol (90% overall), was treated with N-methylbenzylamine at 85° for 18 hr to give the enamino ketone 3 (85%) which upon reaction with 1 equiv of t-butylhypochlorite in chloroform at -50° furnished the 2-chloro derivative 4 (80% yield).[5] Aromatization of 4 to give the benzoic ester 5 (MP 110-111°, 80%) was accomplished by reaction successively with 1.2 equiv of lithium diethylamide in THF at -78° and 1.2 equiv of benzeneselenyl bromide (prepared in situ in THF from diphenyldiselenide and Br_2) (-78° for 1 hr, 25° for 15 hr) followed by isolation and column chromatography on silica gel. The phenolic methyl ether 6, obtained in 95% yield by treatment of 5 with methyl iodide and potassium carbonate in acetone, underwent hydrogenolysis quantitatively (Pd-C in ethanol) to give the desired amino ester 7. The further elaboration of 7 (obtained in quantity by the above route) to the dienal 8 has been accomplished and will be reported separately along with the coupling of 8 with an appropriate dithiane component that has been described previously.[3b,6,7]



1



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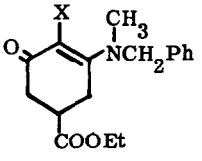
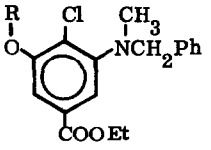
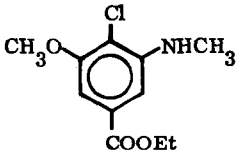


3, X=H
4, X=Cl



5, R=H
6, R=CH_3



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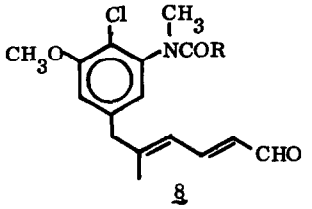

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References and Notes

1. Dedicated to the memory of the late S. Morris Kupchan.
2. For structure and background data on maytansine see, S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, J. Am. Chem. Soc., 94, 1354 (1972).
3. For previous papers on synthetic studies in the maytansine area see, (a) A. I. Meyers, C. C. Shaw, D. Horne, L. M. Trefonas, and R. J. Majeste, Tetrahedron Lett., 1745 (1975); A. I. Meyers and R. S. Brinkmeyer, ibid., 1749 (1975); (b) E. J. Corey and M. G. Bock, ibid., 2643 (1975); (c) W. J. Elliott and J. Fried, J. Org. Chem., 41, 2469 (1976).
4. M. E. Kuehne and B. F. Lambert, J. Am. Chem. Soc., 81, 4278 (1959).
5. Satisfactory spectral and analytical data were obtained for all reaction products.
6. This work was assisted financially by a grant from the Cancer Institute of NIH. H. F. W. and A. P. K. were holders of Swiss National Science Foundation and NIH Fellowships, respectively, for 1974-1975.
7. Other preparative routes to similar synthetic intermediates have recently been disclosed by the groups of Ganem and Meyers (Tetrahedron Lett., in press).