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STEREOCONTROLLED ROUTE TO A KEY INTERMEDIATE FOR THE SYNTHESIS OF MAYTANSINE

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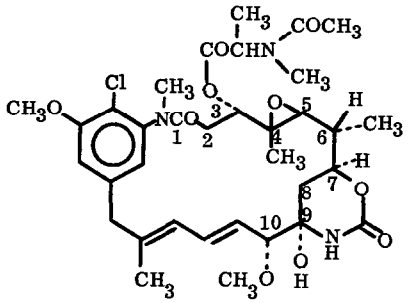
Maytansine (1) is an anti-tumor agent of novel structure and also of possible clinical interest.[1,2] We have undertaken a synthesis of this substance as part of a broader program in the area of biologically active macrocyclic natural products. One attractive approach to the synthesis of maytansine involves the introduction of chirality at carbons 3, 4, 5, 10, and 9 after formation of the macro ring, thereby allowing control of stereochemistry by cyclic conformational effects. The acyclic intermediate 2, which corresponds to carbons 5 to 9 of maytansine, appeared to us to be especially valuable in such a scheme, since carbons 6 and 7 in principle direct the generation of the other stereocenters and also since the elaboration of this intermediate is possible from both ends, in either order. An efficient stereocontrolled synthesis of 2 is reported herein along with methodology for further transformations.[3]



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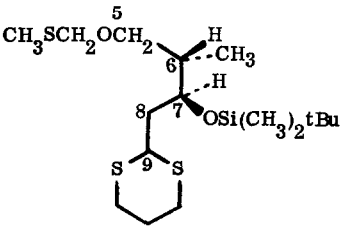
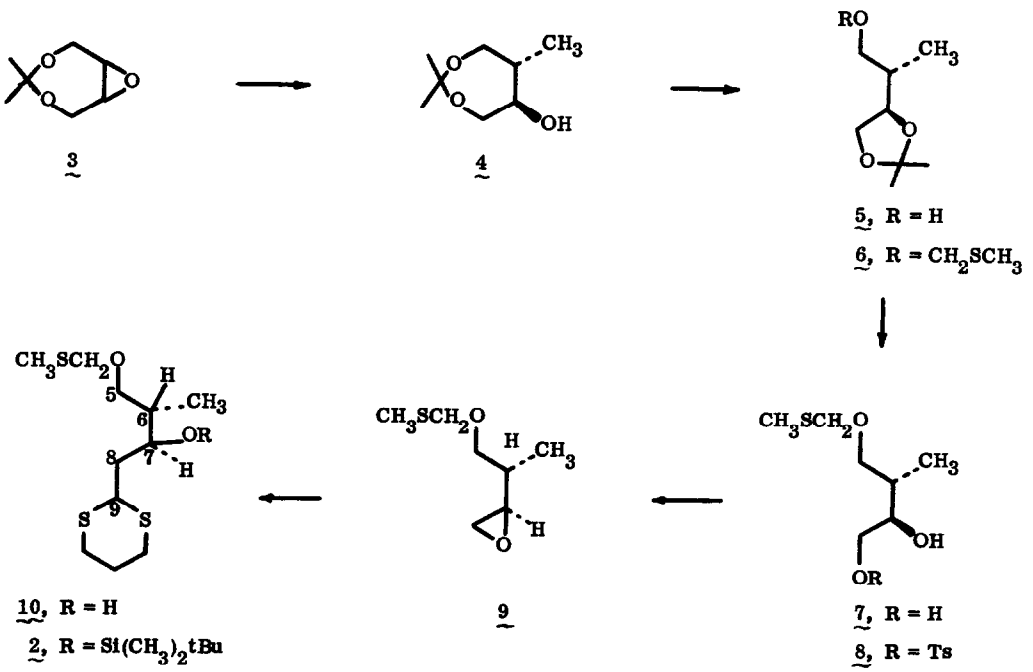
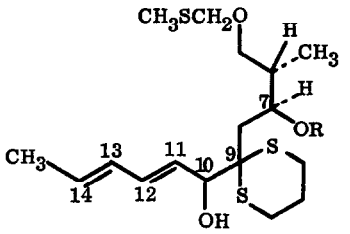


2

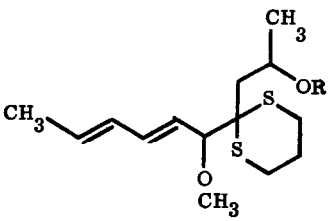
cis-2-Buten-1,4-diol was converted to the corresponding acetonide[4] (92% yield) by reaction with 2,2-dimethoxypropane (1 equiv.) and acetone (1 equiv.) in benzene (2 ml/g of diol) containing 0.05 mole % of sulfuric acid at reflux followed by removal of benzene at atmospheric pressure and distillation of the product. Epoxidation of the acetonide (1.2 equiv. of m-chloroperbenzoic acid in chloroform (10 ml/g of olefin)) at 0° for 1 hr and 25° for 3 hr afforded the oxido ketal 3 (85%), which upon treatment with dimethylcopperlithium (5 equiv.) in ether (30 ml/g of 3) at 25° for 10 hr gave stereospecifically the hydroxy ketal 4 in 92% yield.[5-7] Brief exposure of 4 to 0.1 mole % boron trifluoride etherate in ether (25°, 2 hr) led quantitatively to the isomeric hydroxy ketal 5,[7] the structure of which was confirmed by benzylation, ketal hydrolysis and periodate oxidation to give exclusively and in high yield 2-benzyloxymethylpropionaldehyde. The hydroxyl function of 5 was protected by conversion to the alkoxide (1.1 equiv. of sodium hydride) in dimethoxyethane (DME) and reaction with a mixture of chloromethyl methyl sulfide and dry sodium iodide (1 equiv. of each) in DME at 0° for 1 hr and 25° for 1.5 hr, to form the methylthiomethyl ether 6 in 82% yield. Exposure of 6 to 4:1 acetic acid--water at 45° for 1 hr gave the diol 7 (94%) which was converted via the monotosylate 8 (from 1 equiv. of tosyl chloride in pyridine at 0° for 8 hr) to the epoxide 9 (sodium hydride in tetrahydrofuran at 0°, 1 hr and 25°, 5 hr) in ca. 75% yield. Reaction of 9 in tetrahydrofuran with 1.1 equiv. of 2-lithio-1,3-dithiane[8] at -20° for 8 hr afforded the hydroxy dithiane 10 (93%) which was further transformed into the silyl ether 2 (88%) by reaction with t-butyldimethylsilylchloride-imidazole in dimethylformamide at 27° for 16 hr.[9]



The possible elaboration of 2 by attachment of carbons 10-15 and the aromatic ring to C(9) was tested using sorbaldehyde as a model. Thus, treatment of 2 with n-butyllithium (1 equiv.) and tetramethylethylenediamine (1 equiv.) in tetrahydrofuran led to a lithio derivative which reacted in the desired manner with sorbaldehyde to give the dienol 11 in 77% yield. From 11 the corresponding methyl ether is available by treatment with sodium hydride and methyl iodide.



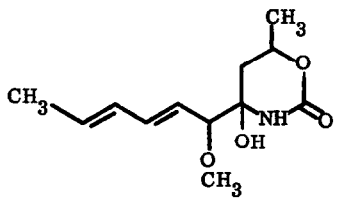
11, R = $Si(CH_3)_2tBu$



12, R = $Si(CH_3)_2tBu$

13, R = H

14, R = $CONH_2$



15

The alternative elaboration of 2 by the addition of a C(1) to C(4) unit to carbon 5 requires the selective cleavage of the methylthiomethyl ether. This is readily accomplished by taking advantage of the unique susceptibility of the methylthiomethyl ether protecting group to fission under neutral conditions in the presence of mercuric ion. Removal of this protecting group to form the corresponding alcohol can be effected using mercuric chloride (2 equiv.), calcium carbonate (3 equiv.) in acetonitrile--water (4:1) at 25° for 1-2 hr, under which conditions both the 1,3-dithiane unit and the silyl ether grouping are unaffected.

The methylthiomethyl ether protecting group promises to be of great value in organic synthesis. Further examples of its application to provide more detail on scope and utility will be presented in a forthcoming paper dealing with this new method for hydroxyl protection.

The facile removal of the t-butyldimethylsilyl group from oxygen by fluoride ion[9] allows selective deprotection of hydroxyl in the presence of a 1,3-dithiane unit as has been demonstrated with the model

system 12 which was smoothly converted to the alcohol 13. Reaction of 13 sequentially with sodium hydride, phosgene, and ammonia led to the urethane 14. As we had hoped, the urethane 14 underwent facile loss of the dithiane unit when treated with mercuric chloride--calcium carbonate in acetonitrile--water (neutral conditions) to afford cleanly the heterocycle 15 which possesses the characteristic structure of the C(8) to C(14) part of maytansine. It is possible that the urethane function participates in this reaction so as to accelerate cleavage of the trimethylene thioketal.

The further steps for the synthesis of maytansine from 2 are now under investigation.[10]

References and Notes

1. 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. Amer. Chem. Soc., 94, 1354 (1972).
2. See also M. C. Wani, H. L. Taylor, and M. E. Wall, Chem. Commun., 390 (1973).
3. For recent studies on non-stereocontrolled synthetic approaches to various model compounds related to segments of the maytansine structure, see (a) A. I. Meyers and C. C. Shaw, Tetrahedron Lett., 717 (1974); (b) A. I. Meyers, C. C. Shaw, D. Horne, L. M. Trefonas, and R. J. Majeste, ibid., 1745 (1975); (c) A. I. Meyers and R. S. Brinkmeyer, ibid., 1749 (1975).
4. G. B. Sterling, D. W. Watson, and C. E. Pawloski, U. S. patent 3,116,298 [Chem. Abstr., 60, 6856g (1964)].
5. For the stereospecific opening of epoxides by the methyl Gilman reagent, see G. H. Posner, Ph. D. dissertation, Harvard University, 1968; and R. W. Herr, D. W. Wieland, and C. R. Johnson, J. Amer. Chem. Soc., 92, 3814 (1970).
6. The structures of this and the other intermediates described herein were confirmed by infrared, proton magnetic resonance (pmr), and mass spectral data.
7. Purity was established rigorously by spectroscopic and chromatographic analysis.
8. E. J. Corey and D. Seebach, Angew. Chem. Intern. Ed. Engl., 4, 1075, 1077 (1965); J. Org. Chem., 40, 231 (1975).
9. E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).
10. This research was assisted financially by a grant from the Cancer Institute of the National Institutes of Health.