Tetrahedron Letters No. 21 , pp 1745-1748, 1975. Pergamon Press. Printed in Great Britain.

PROGRESS TOWARD THE TOTAL SYNTHESIS OF MAYTANSINE. A STEREOSELECTIVE SYNTHESIS OF THE C-1 TO C-7 MOIETY (NORTHERN ZONE)

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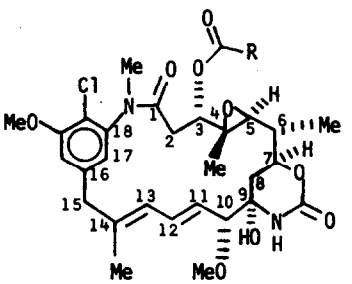
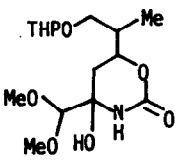
(Received in USA 21 February 1975; received in UK for publication 12 April 1975)

The complex structure of the potent anti-leukemic ansa macrolide, maytansine (1),[1] undoubtedly presents a formidable synthetic challenge. We have recently reported[2] the preparation of the cyclic carbinolamide 2 which represents the so-called "eastern zone" of maytansine. In this communication we wish to describe a stereoselective synthesis of the "northern zone" 9 with all its attending stereochemistry corresponding to the contiguous carbon chain, C-1 to C-7, of maytansine.

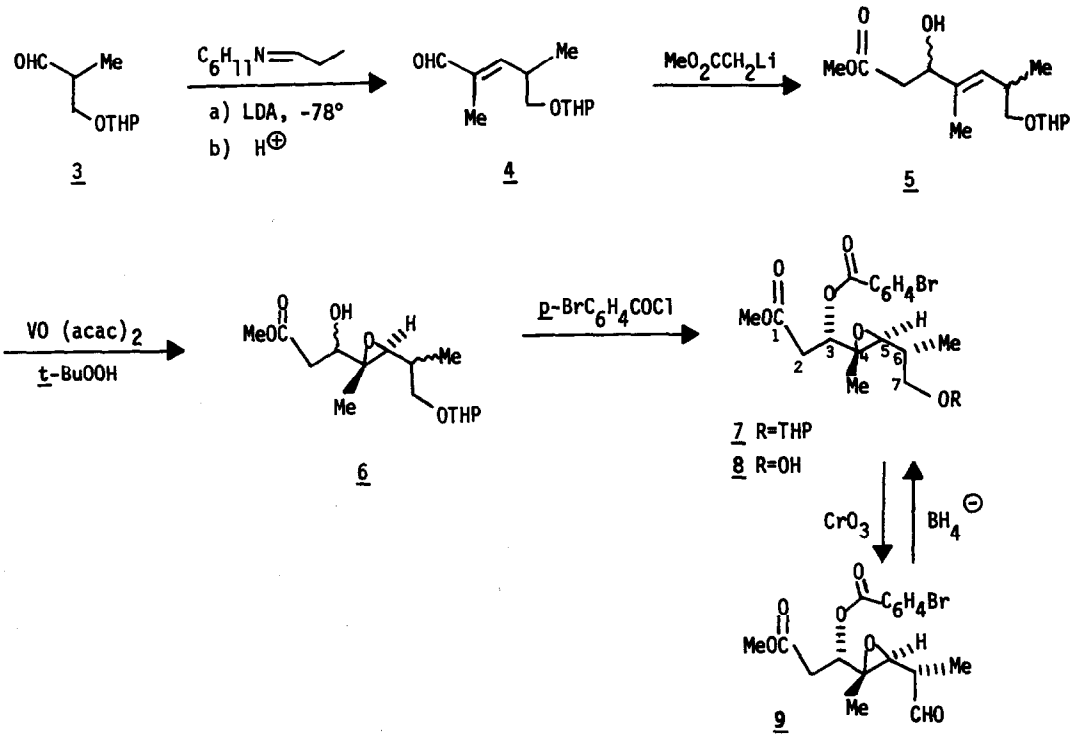


1, R = N-acetylalanine



2

Treatment of the aldehyde 3[2] with the cyclohexylimine of propionaldehyde (lithium diisopropylamide, -78°, THF)[3] followed by dehydration (oxalic acid -H_2O-THF, 25°, 18h) afforded the unsaturated aldehyde 4 [70%, ir (film) 1690 cm^{-1}; nmr ($CDCl_3$) δ 9.77 (s, 1), 6.40 (d, 1)]. Further elaboration of 4 was accomplished by condensation using lithio methylacetate[4] (-78°, -THF) and this furnished the β-hydroxy ester 5 as a mixture of diastereomers [74%, ir (film) 3450, 1745 cm^{-1}; nmr ($CDCl_3$) δ 5.33 (br.d, 1), 4.3-4.6 (m, 2), 3.73 (s, 3), 2.53 (br.d, 2), 1.70 (br.s, 3), 1.03 (br.d, 3)]. This mixture was transformed into the epoxide 6 (56%) using t-butyl



hydroperoxide in the presence of vanadium acetylacetonate[5] (-5°, toluene, 15 h). The oily mixture of epoxides was treated with p-bromobenzoyl chloride (ether-pyridine) and provided the p-bromobenzoate 7 which was hydrolyzed directly (1% HCl-MeOH, 25°, 20 min) to the alcohol 8 (55% from 6) as a component in a mixture of four diastereomers. The mixture was discernible from the 100 MHz nmr spectrum which exhibited four overlapping methyl doublets for the C-methyl group at C-6 and four overlapping methyl singlets for the methyl group at C-4. The isomeric mixture was subjected to preparative layer chromatography (silica gel, Merck-Darmstadt PF_{254}) and eluted three times using 17% acetone in hexane. The major product 8, which accounted for 42% of the total epoxide mixture, was isolated [mp 88-89°, nmr (100 MHz, $CDCl_3$) δ 7.88 (ABq, 4), 5.40 (t, J=6 Hz, 1), 3.76 (s, 3), 3.00 (d, J=10 Hz, 1), 2.92 (d, J=7 Hz, 2), 1.34 (s, 3), 1.04 (d, J=7 Hz, 3)] and its stereochemistry confirmed by single crystal x-ray analysis (Fig. 1).

Compound 8 forms very small, transparent needles with the b-axis coincident with the needle axis. The compound crystallizes in the monoclinic system ($P2_1/c$) with four molecules in a unit cell of dimensions: a = 18.20 ± .01 Å; b = 5.795 ± .003 Å; c = 18.509 ± .006 Å; and β = 110.56

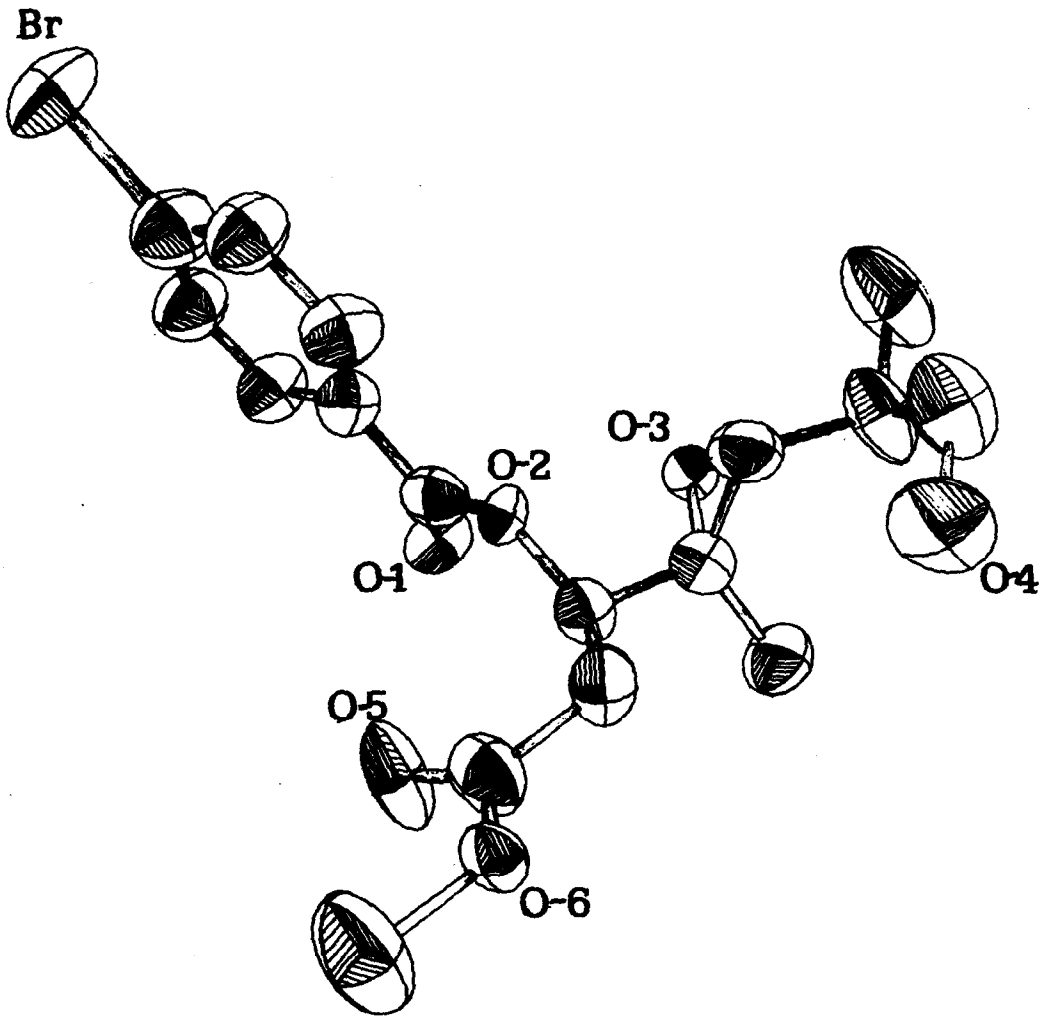


Fig. 1 X-ray Structure of 8.

± .04°. The structure was solved by heavy atom methods utilizing the phases resulting from the position of the bromine atom, which, in turn, was obtained from the solution of the three-dimensional Patterson map. At this stage of refinement (termination of isotropic refinement, hydrogens not included) the usual reliability index has a value of R=0.10 g. The epoxide ring has C-O distances averaging 1.46 ± .02 Å and a C-C distance of 1.44 Å with angles of 60 ± 1°.

The structure determination proves that this compound (Fig. 1) contains all of the salient geometry desired as an intermediate in the synthesis of the natural maytansine. The centrosymmetric space-group confirms the fact that 8 is a racemic mixture.[6]

Since further elaboration necessary to incorporate the "eastern zone" 2 requires an aldehyde 9,[7] it was important to ascertain the stereochemical integrity of C-6 during the transformation of 8 to 9. Oxidation of 8 (CrO_3-pyridine, 25°, 10 min) gave a single aldehyde 9 [80%, nmr ($CDCl_3$) δ 9.83 (d, 1), 1.15 (d, 3), which was then reduced($NaBH_4$, MeOH, 0°)] back to the carbinol 8 without any epimerization of the C-6 methyl group. Thus, it now appears that this stereoselective synthesis of 9 will provide an ample supply of the "northern zone" to continue our journey to maytansine.

Acknowledgement The authors (CSU group) wish to thank the National Institutes of Health for continued financial support. The New Orleans group acknowledges financial support from the Cancer Association of Greater New Orleans.

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6. A more detailed discussion of the x-ray results will appear upon completion of the refinement. Note that the x-ray projection shown in Fig. 1 is the mirror image of the structure drawn in 8.
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