Tetrahedron Letters No. 9, pp 717 - 720, 1974. Pergamon Press. Printed in Great Britain.

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF MAYTANSINE. THE PREPARATION AND PROPERTIES OF THE CARBINOLAMIDE MOIETY.

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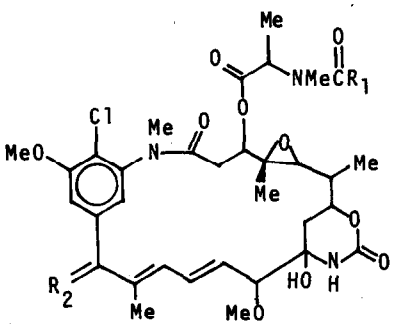
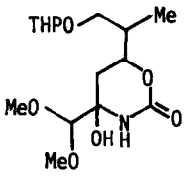
(Received in USA 19 November 1973; received in UK for publication 21 January 1974)

The recent isolation of the antileukemic ansa macrolides maytansine (1),[1] maytanprine (2),[2] maytanbutine (3)[2] from maytenus ovatus and colubrinol (4)[3] has propelled this series of substances into the forefront of chemotherapeutic investigations.[4] The extremely low isolation yields (2×10^{-5} - 2×10^{-4}%) of these materials coupled with the high antileukemic activity[5] makes a viable synthetic route a goal of considerable significance.

We wish to describe an efficient route to the cyclic carbinolamide 5 which possesses the





5

1 R_1=Me, R_2=H_2

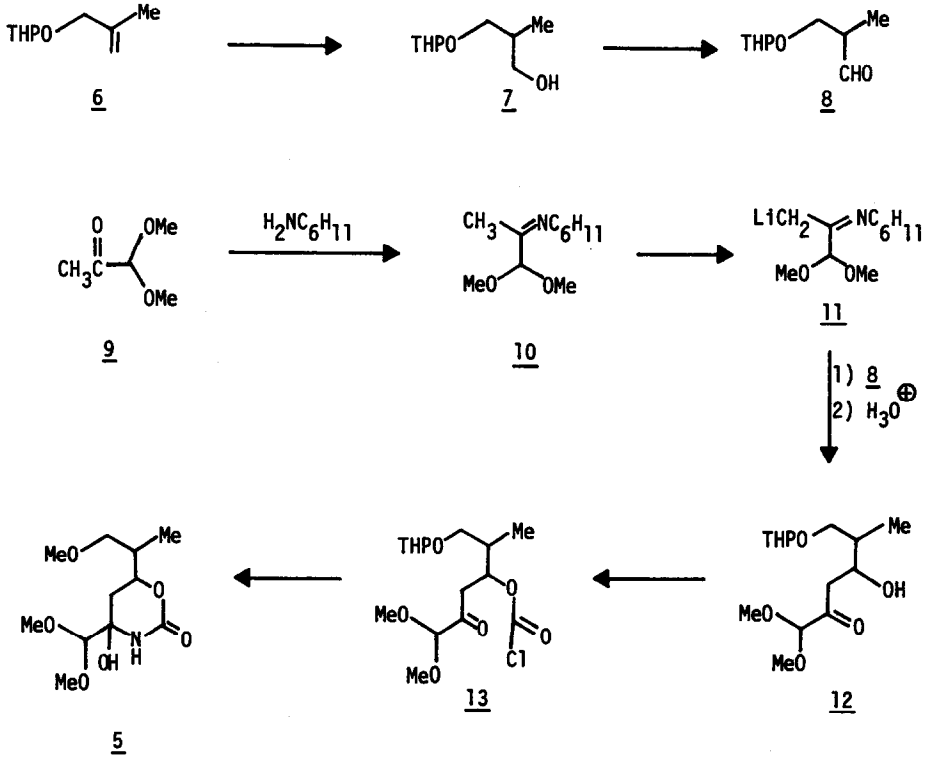
2 R_1=CH_2Me, R_2=H_2

3 R_1=$CHMe_2$, R_2=H_2

4 R_1=$CHMe_2$, R_2=H, OH

requisite functionality for further elaboration.

Treatment of the tetrahydropyranyl ether of methallyl alcohol 6 with diborane followed by oxidation gave the primary alcohol 7 which was further oxidized (DCC, DMSO, TFA, pyridine)[6] to the aldehyde 8 in 79% overall yield. Condensation[7] of the latter with the lithio imine 11, (generated at -78° with lithium diisopropylamide, THF from 10,[8] which in turn was prepared from



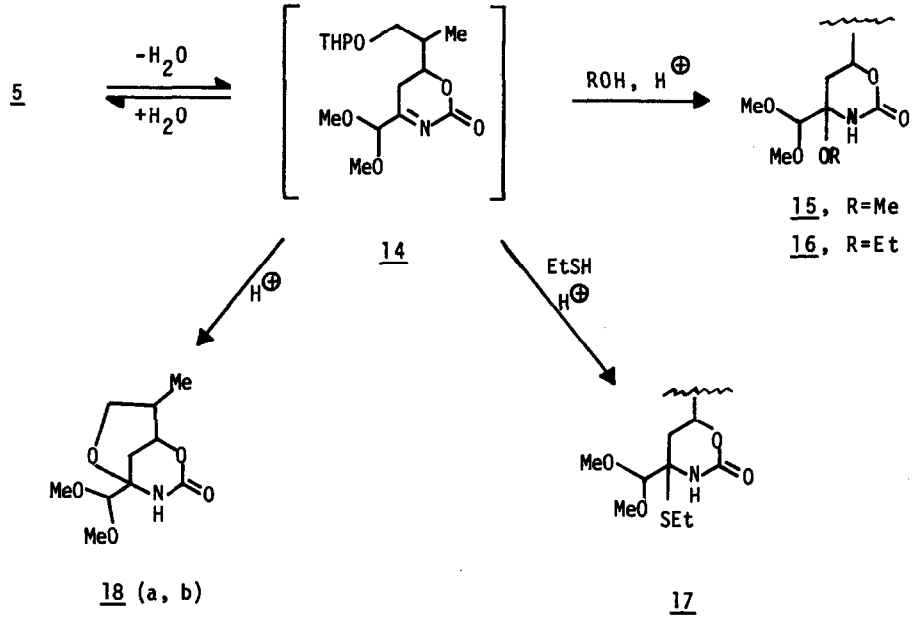
pyruvaldehyde dimethyl acetal 9[8])produced the β-hydroxy ketone, after hydrolysis, in 80% yield [oil from silica gel chromatography, hexane-acetone, 95:5; ir (film) 3480, 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (3, d, J=7 Hz), 2.78 (2, m), 4.51 (1, s), 3.20 (1, exch. with D_2O)]. Addition of 1.0 equiv of phosgene in ether to 12 containing pyridine (r.t. 2 h) gave the chloroformate 13 which

was treated directly with excess ammonia in methanol at -50°. Workup led to the desired carbinolamide 5 (56% based on ketone 12); mp 90-92.5 (ether); ir ($CHCl_3$) 3570 (OH), 3420 (NH), 1710 (C=O); pertinent nmr signals ($CDCl_3$) 1.03 (3, d, J=7 Hz), 1.93 (3, m), 4.23 (1, s), 4.63 (2, m), 6.50 (1, m, exch. with D_2O), 3.9 (1, exch. with D_2O). (Anal. Found: C, 53.74; H, 8.22; N, 4.25). Although 5 possesses 3 chiral centers, tlc examination exhibited a single spot. It was found that the tertiary hydroxyl group is quite labile and readily displaced by nucleophilic reagents. This behavior would be consistent with an acid catalyzed reversible dehydration-hydration, 5 → 14.[9] Thus, treatment of 5 with simple alcohols in the presence of a trace of p-toluenesulfonic acid led to the alkoxy derivative 15 [ir 3420 (NH); nmr ($CDCl_3$) 3.35 (MeO)] and 16 [ir 3420 (NH); nmr ($CDCl_3$) 3.6 (OCH_2-)], while 17 was smoothly formed upon addition of ethanthiol to a solution 5 in dichloromethane [ir 3410 (NH); nmr ($CDCl_3$) 2.8 (q, SCH_2), 1.3 (t, SCH_2CH_3)]. It is noteworthy to mention here that the tertiary hydroxyl function in maytansine[1] also exhibited this facile exchange with alcohols. This result would explain why only a single isomer was detected (nmr, tlc) in the formation of 5. If the hydroxy group is as labile as shown above, epimerization would be expected to lead to the most stable conformer, namely that which possesses an axial hydroxy group. However, the 3°-ring proton and the exocyclic methyl group still reside at diastereomeric centers and at this time it is not possible to ascertain their relative configuration.

It was observed that, upon treatment of 5 with dilute hydrochloric acid in methanol, a rapid conversion to the bicyclic ether 18 occurred. Two isomers 18a (mp 148-149°)[10] and 18b (mp 90-93°)[10] in approximately equal amounts were isolated. The nmr spectrum of both isomers were highly similar except for the chemical shift of the C-methyl doublet (18a, δ 1.15, J=7 Hz) (18b, δ 1.00, J=7 Hz) which indicates their differing environment.

Work is continuing to further elaborate 5 as well as other synthetic units aimed at reaching our final goal.[11]

Acknowledgment - The authors wish to thank the National Institutes of Health (CA14152-02) for continued financial support of this work.



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4. Maytansine is currently undergoing clinical investigation. Personal communication from Dr. R. E. Engle, National Cancer Institute.
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8. Formed by treating 9 with cyclohexyl amine in the presence of sodium sulfate, bp 70-80° (0.7 mm), ir (film) 1670 cm^{-1}, nmr ($CDCl_3$) δ 1.13-1.80 (11, m), 1.83 (3, s), 3.41 (6, s), 4.46 (1, s).
9. This behavior is analogous to the acid-catalyzed exchange of N-hydroxymethyl amides, H. E. Zaugg, A. M. Kotre, and J. E. Fraser, J. Org. Chem., 34, 11 (1969).
10. Elemental analysis found: C, 52.00; H, 7.42; N, 6.13.
11. We thank Professor S. Morris Kupchan for providing us with authentic ir, nmr, and uv spectra of maytansine for comparison purposes.