Tetrahedron Letters No. 33, pp 2835 - 2838, 1977. Pergamon Press. Printed in Great Britain.

ANSA MACROLIDE SYNTHESIS II ‡

A CONVERGENT APPROACH TO MAYTANSINE

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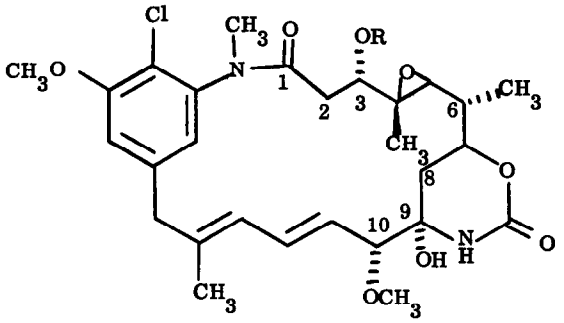
(Received in USA 9 March 1977; received in UK for publication 23 June 1977)

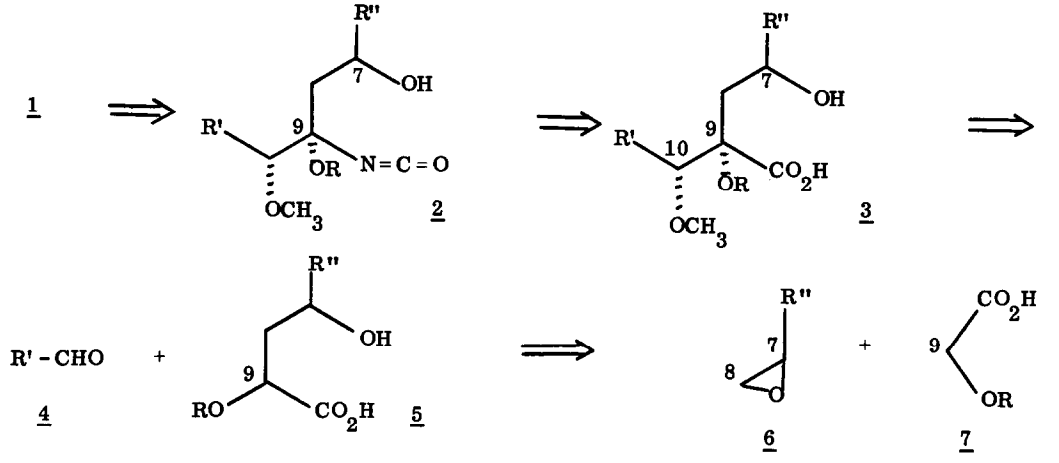
One approach to the total synthesis of clinically interesting maytansinoids[1] 1 relies on closure of the macrocyclic ring at the C1 - N peptide bond. To be preparatively useful any plan of this nature requires the smooth stereospecific assembly of an appropriate acyclic precursor, consequently we have devised a convergent scheme which employs C9 as a connecting point for suitably protected C1-C8 and C10 - C21 fragments. This Letter describes our coupling method, based on the principle of "umpolung", and details the subsequent elaboration of maytansine's carbinolamide functionality in a representative model system 18.[2]



1 R= —CO-CH-CH3 (N; H3C, COCH3)

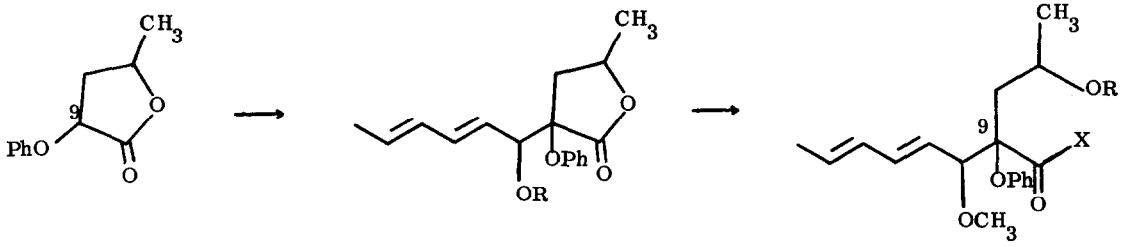
Retrosynthetic analysis suggests that the six-membered carbamate in 1 might be formed by intramolecular interception of a C9 isocyanate with an hydroxyl substituent at C7 of 2. Precedents exist for this type of cyclization during the Curtius rearrangement of γ-hydroxyacid hydrazides.[3, 2c] In the case of maytansine, the appropriate α, γ-dihydroxyacid synthon in 3 can be imagined to arise from the condensation of C9 glycolate fragment 7, a C7-C8 epoxide 6, and a C10 aldehyde 4. With current improvements in the Curtius and Lossen rearrangements,[4] these "umpolung" transformations can be achieved under very mild, near-neutral conditions which are compatible with maytansine's sensitive functionality.

Our strategy has now been realized in the synthetic direction by the successful consecutive alkylation of 7 (R = C_6H_5) with representative structures 4 and 6.



Our choice of phenoxyacetic acid as a nucleophilic C9 reagent was guided by three considerations: (1) C9 must possess sufficient reactivity to undergo S_N2 opening of a monosubstituted oxirane, (2) there must be a favorable equilibrium in the aldol condensation of 5 with 4 to form a quaternary carbon at C9, and (3) the O-protecting group at C9 must be readily removable at the end of the synthesis.

Base-catalyzed addition of various O-protected glycolic acid esters[5] to propylene oxide resulted in extensive ester self-condensation. However the dianion of 7 (R = C_6H_5), prepared using two equiv of lithium diisopropylamide ("LDA", THF, -20°), condensed readily with 6 (R'' = CH_3), and after NH_4Cl workup (pH 5) the stereoisomeric γ-lactones 8 were isolated (1:1 ratio) in 70% yield. While these could be separated by prep tlc (cis isomer, mp 69.5-71°; trans isomer, mp 55.5-56°)[6,7], it was more convenient to employ the mixture of 8 for the next alkylation. Generation of the lactone enolate (LDA, THF, 1 hr) and addition of freshly distilled sorbaldehyde 9 (1.0 equiv) was carried out at -78°; after 30 min, addition of NH_4Cl enabled the isolation of aldol product 10. Warming the reaction mixture to 0° before protonation led only to 9 and unalkylated lactone. Since C10 of maytansine bears a methoxyl group, it was most convenient to O-alkylate the alkoxide anion in situ (5 equiv CH_3I, 5 equiv HMPA). Using this one-pot reaction, dienic lactone 11 could be produced in 75% yield from 8.[2b] The pmr spectrum of 11 showed three OCH_3 singlets, confirming the presence of a diastereomeric mixture. Modified experimental conditions to achieve kinetic stereoselection in this condensation are currently being explored.[8]



8

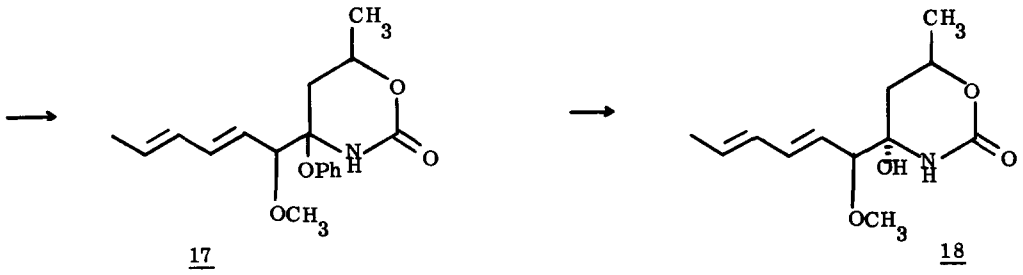
10 R = H

11 R = CH_3

12 X = $NHNH_2$, R = H

13 $X = N_3$, R = TMS

14 X = NHOH, R = H



17 18

Exposure of 11 to excess 95% hydrazine hydrate in ethanol or THF furnished the hydroxyhydrazide 12 in excellent yield. If immediately treated with N_2O_4 (1 equiv., -78°, CH_2Cl_2, 1hr) and then with chlorotrimethylsilane/triethylamine (1:1 ratio, 10 equiv.), 12 was smoothly oxidized to the silyloxyazide 13.[2c] Curtius rearrangement (benzene, NaOAc, reflux) transformed 13 into the corresponding silyloxyisocyanate 15. This substance was relatively stable in the presence of acid or base but was efficiently desilylated using tetra-n-butylammonium fluoride (1 equiv., THF, 20 min). Spontaneous cyclization of the intermediate hydroxyisocyanate 16 produced cyclic carbamate 17.[6] In accordance with the chemistry of 1[1], the phenoxy substituent in 17 was readily exchanged by acid-catalyzed elimination-hydration, yielding 18. This mechanism thus would establish correct C9 functionality and stereochemistry late in the actual synthesis.

We have also observed that γ-lactones 8 and 11 furnished the corresponding hydroxy hydroxamic acids when stirred with excess hydroxylamine in THF. Lossen rearrangement of derivatives such as 14 is also under investigation as we attempt to apply this convergent coupling strategy to the total synthesis of maytansine.

Acknowledgement: We wish to thank the National Institutes of Health (Grant #CA-19686 from the National Cancer Institute) and Eli Lilly & Company for generous financial support.

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6. The structures of these and other intermediates were confirmed by ir, pmr, and mass spectral data. Detailed information will be provided upon request.

7. The identity of these isomers was established using pmr shift reagents.

8. For recent progress in this area see W. A. Kleschick, C. T. Buse, C. H. Heathcock, J. Amer. Chem. Soc., 99, 247 (1977)