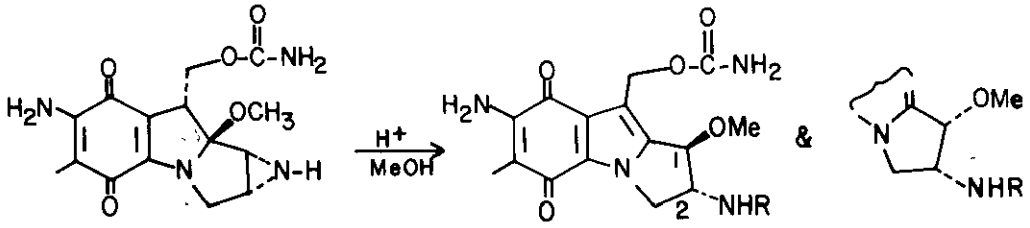
THE TOTAL SYNTHESIS OF A MITOSENE

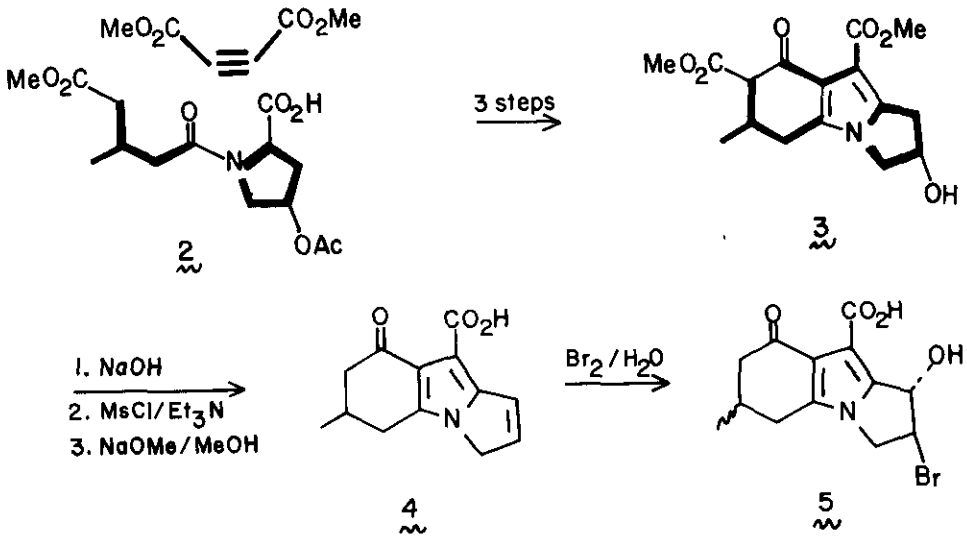
J. Rebek, Jr.* and S. H. Shaber
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

ABSTRACT - The conversion of L-hydroxyproline to a mitosene (degradation product of a mitomycin) is described. The synthesis involves 19 steps and the key stereochemical feature arises from an unusual *cis* opening of an epoxide. The synthetic product, 1-methoxy-2,7-diamino-mitosene is shown to be identical with the *trans* isomer obtained from acid-catalyzed methanolysis of mitomycin C.

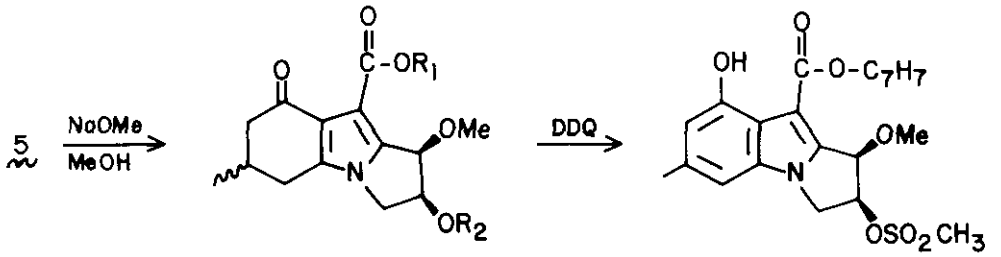
Mitosenes comprise a family of substances obtained from the chemical degradation of the mitomycin natural products.[1] The fragile structural elements of the mitomycins are absent in the mitosenes, yet some of the biological activity remains. Accordingly, the mitosenes, rather than the mitomycins, have been the objects of most synthetic schemes, yet of the dozen or so published approaches[2], none has yielded a mitosene obtainable from a natural product. Only Kishi's[3] total synthesis of the mitomycins can be said to have increased the availability of the simpler mitosenes. Our own efforts have now produced mitosenes 1, and while it is unlikely that our methods can be adapted to the synthesis of the parent mitomycin, the prompt access described below may compensate for the modesty of the goal.



The tricyclic ketone 3 was prepared from the L-hydroxyproline derivative 2 by way of Huisgen pyrrole synthesis[4] then Dieckmann cyclization as previously described.[5] Saponification, mesylation then methoxide-induced elimination gave the racemic olefin 4, mp 223-225°, from which the *trans* bromohydrin 5 was obtained as a mixture of diastereomers.[6]



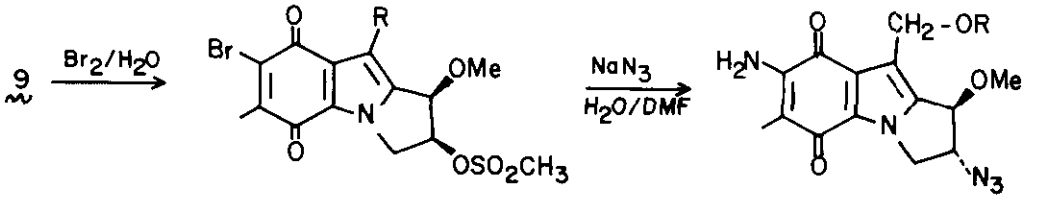
The regiochemistry of the bromohydrin was determined to be as shown[7]; the intermediate 1,2-bromonium ion is therefore opened exclusively at C_1. Treatment of 5 with a number of nucleophiles under basic conditions gave products with regiochemistry consistent with the intermediacy of an elusive 1,2-epoxide which, like the bromonium ion, was attacked only at C_1. The *regiochemistry* here has its parallel in the hydrolysis of the parent mitomycins - only 2-amino mitosenes are isolated from the opening of the aziridine ring. Moreover, this latter reaction has frequently been observed to result in *cis* opening of aziridine in preference to *trans* opening.[9] Whatever the cause[10], this phenomenon has its happy counterpart in the *stereochemistry* of products from 5. In dilute methanolic methoxide 5 gave a 5:1 mixture of isomers in which the *cis* ether 6 was the major component.



6 $R_1 = R_2 = H$
7 $R_1 = H$, $R_2 = SO_2CH_3$
8 $R_1 = C_7H_7$, $R_2 = SO_2CH_3$

9

Mesylation of 6 as before gave 7 and, since the free carboxylic acid could not be dehydrogenated directly, 7 was protected as its benzyl ester (C_7H_7Br/K_2CO_3-18-crown-6, Me_2CO reflux, 16 h) 8 before treatment with DDQ. The product phenol 9, mp 171-172° reacted rapidly with excess bromine water to yield the yellow bromoquinone 10, mp 169-171°.



10 $R = CO_2C_7H_7$
11 $R = CO_2H$
12 $R = COCl$
13 $R = CH_2-OH$

14 $R = H$
15 $R = CO_2C_6H_5$
16 $R = CONH_2$

While the requisite oxidation state of the 6-membered ring was achieved in a single operation from the phenol, subsequent reductions in other parts of the molecule were attended by reduction of the quinone as well. Fortunately, the quinones were easily regenerated through oxidative workup. Thus removal of the ester through cautious hydrogenolysis[11] followed by $FeCl_3$ treatment gave the acid 11, mp 179-180° (dec.). The acid chloride was prepared ($SOCl_2$) and, without isolation, was reduced by careful treatment with $NaBH_4$ (THF, 0°-25°, 3 h). Quenching with phosphate buffer and addition of Fremy's salt then produced the orange alcohol 13, mp 185-187° (dec.).

Transformation of this bromoquinone mesylate 13 into the amino quinone 14, mp 210-212° (N_2 evolves), was accomplished in a single operation by heating with excess NaN_3 in aqueous DMF. Initially the halide is displaced (30° h, ½ h) then reduction of the orange azidoquinone to the purple amino quinone with azide occurs (60°, 2 h), followed slowly by displacement of the mesylate (90°,16 h). These conditions were developed with model compounds; for the case at hand the intermediates described were characterized by spectroscopic means upon interruption of the reaction at the appropriate time and temperature.

Conversion of the alcohol 14 to the carbamate 16 followed the well-trodden path *via* the carbonate 15, mp 155-157°. The final reduction of the azide to the mitosene was accomplished selectively in pyridine with $(C_6H_5)_3P$ and aqueous ammonia.[12] Material obtained in this way was identical with the *trans* isomer 1a obtained from treatment of mitomycin C with acidic methanol.[9] Further confirmation[13] of the identity was obtained through acetylation to 1b. The synthesis was accomplished in 19 steps with an average yield of 80%/step (1% overall).

Acknowledgements - We are grateful to the National Institutes of Health for financial support and the Bristol Laboratories for a sample of mitomycin C.

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Received, 6th April, 1981