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A ROUTE TO FUNCTIONALIZED MITOSANES

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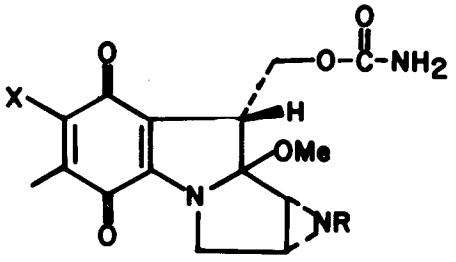
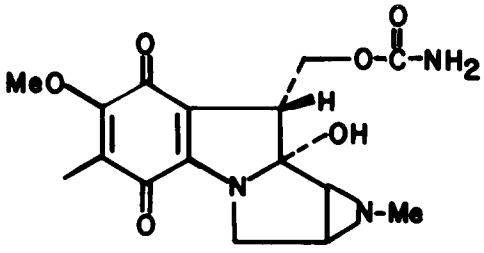
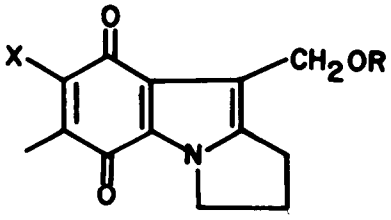
The objective of the synthesis of the naturally occurring mitomycins has attracted considerable attention.[1,2] Most of the progress has been recorded in the synthesis of the mitosenes, themselves biologically active degradation products of the mitomycins.[1] One approach to the mitomycins would involve the preparation of a suitably functionalized mitosane which might possess the requisite implements for the introduction of a 1,2-aziridino linkage and for the introduction and maintenance of the all critical C_{1a} oxygen function.[2] Below we wish to report a synthesis of lactamhydrazide 15, a heavily functionalized mitosane from which one might hope to introduce additional groupings required for the objective. Our route involves the elaboration of a C_9 hydroxymethyl group with concurrent closure of the A and B rings. The key steps involve a Claisen rearrangement for the introduction of carbons 10, 9, 1a and 1, and intramolecular opening of an activated cyclopropane[3a,b] for construction of the functionalized system.



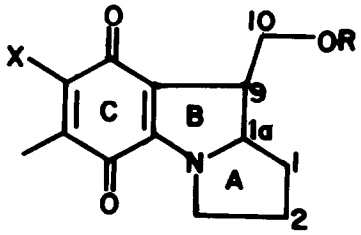
Mitomycin A X = OMe; R = H
Mitomycin C X = NH_2; R = H
Mitomycin D X = NH_2; R = Me



Mitomycin B[4]



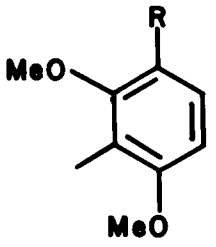
A Mitosene



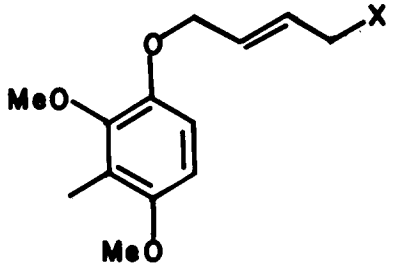
A Mitosane

Friedel Crafts acyclation ($AcCl/SnCl_4/CS_2$) of commercially available 1 gives 2 in 92% yield. Baeyer-Villager oxidation of 2 with 50% hydrogen peroxide in methanol was followed by alkaline hydrolysis to give 3[5], mp 35-36°. The phenoxide salt was alkylated with trans-1,4-dichloro-2-butene and the resultant 4 was transformed (NaOAc, AcOH; overall 53%) into acetate 5.[6] Claisen rearrangement occurred at 225° in diethylaniline to afford an 85% yield of 6[6] which was methylated to give 7.[6]

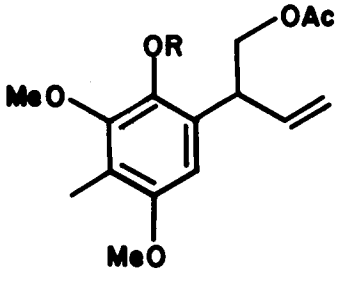
Nitration of 7[7] (70% HNO_3, CS_2) was followed by hydrolysis of the acetate to give 8 (49%).[6] Reduction of 8[6] (zinc dust, aq. HCl) afforded 9[6], which was transformed into phthaloyl derivative 10[6], mp 144-145°, by the action of phthalic anhydride (Et_3N-toluene). Acylation with carbomethoxyacetyl chloride-pyridine gave 11 which was converted (tosyl azide, Et_3N, CH_3CN) into the mixed diazomalonate 12, mp 153-155°.[6]



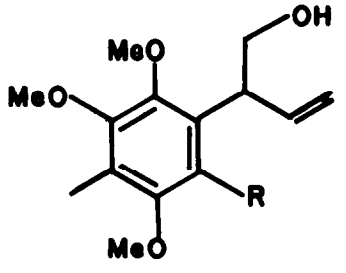
1 R = H
2 R = Ac
3 R = OH



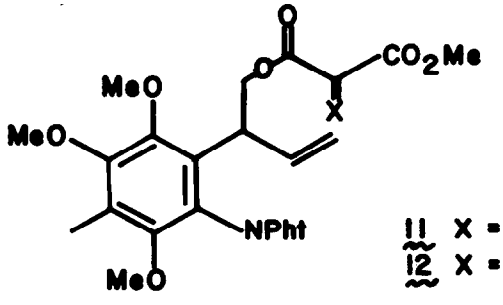
4 X = Cl
5 X = OAc



5 → 6 R = H
7 R = Me



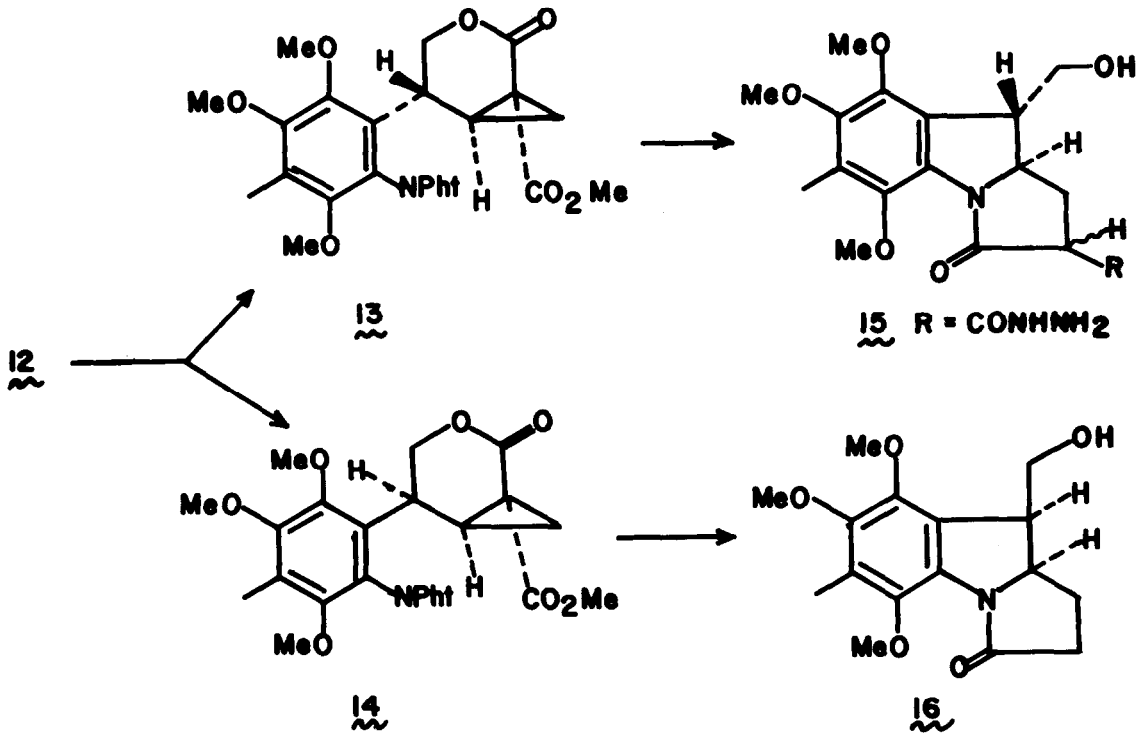
8 R = NO_2
9 R = NH_2
10 R = phthalimido



11 X = H_2
12 X = N_2

Compound 12 was heated in toluene under reflux in the presence of copper bronze to give ca. a 5:1[8] ratio of 13:14[6], which could be separated by fractional crystallization from ether. The minor cyclopropane, 14, mp 239-240° was treated with excess hydrazine in hot methanol. Thermolysis of the resultant amine hydrazide, at 135°,[3b,10] gave a lactam hydrazide which on acidic hydrolysis and decarboxylation afforded mitosane precursor 16,[6,11] mp 158-161°. The yield of 16 from 14 was 33%.

The major cyclopropane 13[6], mp 234-237° was unravelled in a similar way. The sequence was interrupted after thermolysis, thereby affording a 50% yield of the epimeric lactam hydrazides 15[6,12], mp 120-132°.



The susceptibility of 15 to the introduction of functionality which is useful for a total synthesis of the mitomycins is a subject which is receiving continuing attention in the laboratory.

* This work was supported by CA-12107-13.

1. For recent successes in the mitosene area see: G. J. Siuta, R. W. Franck and R. J. Kempton, J. Org. Chem., 39, 3739 (1974); J. W. Lown and T. Itoh, Can. J. Chem., 53, 960 (1975); D. R. Crump, R. W. Franck, R. Gruska, A. A. Ozorio, M. Pagnotta, G. Suita and J. G. White, J. Org. Chem., 42, 105 (1977).

2. The major problem of any mitomycin synthesis, i.e. the construction of a 1a oxygenated mitosane was recently solved in a brilliant fashion by F. Nakatsubo, A. J. Cocuzza, D. E. Keeley and Y. Kishi, J. Amer. Chem. Soc., In Press. We thank Professor Yoshito Kishi for allowing us to cite this major contribution to the area.

3. (a) S. Danishefsky and J. Dynak, J. Org. Chem., 39, 1979 (1974); (b) S. Danishefsky and R. Doehner, Tetrahedron Letters, Preceding Communication.

4. For a recent modification of the stereochemical assignment of mitomycin B see: R. Yahashi and I. Matsubara, J. Antibiotics, 29, 104 (1976) and references therein.

5. R. Boyer, P. Demerseman, A. Laval-Jeantet, J. F. Rossignol and A. Cheutin, Bull. Soc., Chim. France, 1026 (1968).

6. The structure of this compound is in accord with its infrared, nmr and mass spectra.

7. The nitration reaction was severely complicated by quinone formation. In our hands, the ratio of nitration:oxidative demethylation could be improved by working on small (ca. 500 mg) scales. The yield of nitro compound 7 is ca. 60% under these conditions. The quinone may be recycled by reduction and methylation.

8. The major product of internal cyclopropanation is the one where the bulky pentasubstituted aryl group emerges on the convex face of the cup-like bicyclo system. This principle was recently used in a total synthesis of dl-hastanecine and dl-dihydroxyheliotridane see: S. Danishefsky, R. McKee and R. K. Singh, J. Amer. Chem. Soc., In Press.

9. Where we work with cyclopropanes activated as bicyclic lactones,[8] in contrast to those activated through diesters,[3a,b] opening of the lactone is competitive with de-phthaloylation. Accordingly, we use excess hydrazine and the final pyrrolizidine emerges as a lactam hydrazide[8] as opposed to a lactam ester.[3a,b] Since intramolecular as opposed to intermolecular cyclopropanation occurs with high stereoselectivity,[8] and since the lactam hydrazide contains potentially useful functionality, we have thusfar chosen this course.

10. It will be recalled[3a] that the activated cyclopropanes bearing aliphatic W-propylamino side chains suffer essentially instantaneous ring mutation. Where the 2,3-carbons of the side chain are constrained in a benzo setting, the ring mutation is quite slow and requires thermolysis.

11. Oxidative de-methylation of 1,2,4-trimethoxyphenyl groups gives the required 2-methoxy-1,4-p-benzoquinone (R. Doehner-unpublished results).

12. Epimeric mixture 15 has been converted by hydrolysis and decarboxylation to the 9 α-hydroxymethyl epimer, i.e. that of the 1a-desoxymitomycin B stereochemistry. The relative configurations of C_9 and C_{1a} are rigorously defined via their cyclopropane precursors; 16 (9α-hydroxymethyl epimer), mp 178-179°.