MITOMYCIN ANTIBIOTICS: SYNTHESIS OF 9a-FUNCTIONALIZED MITOSANES

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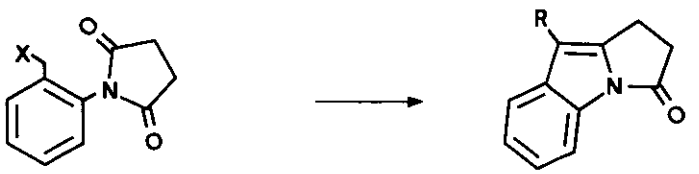
Abstract — Two closely related rapid entries into the mitosane ring system are described which allow for structural modifications. First examples of a hydroxylation and a methoxylation at the 9a-position of mitosanes are reported.

Widespread interest in mitomycins has developed because of their antibacterial and antitumor activity.[1] The biosynthesis[2] as well as the mechanisms of action are under investigation and possibilities of improving the selectivity of the antibiotics against cancer cells have been discussed.[3] In spite of numerous efforts[4] synthetic investigations have only rarely led to results of biochemical and/or pharmaceutical interest. There is a shortage of effective routes to mitosanes which allows for structural modifications. An introduction of a 9a-oxygen-functionality into the pyrrolizidine ring of mitosanes has not been achieved so far.[5]
It seems promising from a strategic point of view, to aim at the mitosane skeleton early in the synthetic sequence since the number of steps of a mitomycin synthesis may be kept small[6] allowing for structural variations at the same time. Following this objection we used intramolecular imide olefination which previously rendered possible a synthesis of pyrrole-3-carboxylates[7] and (±)-isoretronecanol.[8]



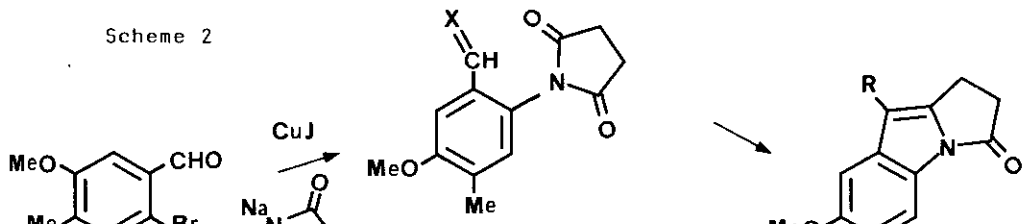
Scheme 1

1a X = Br(70%)
1b X = $PPh_3^+Br^-$ (89%)

2a R = H (85%)
2b R = CHO (97%)
2c R = CH_2OAc (69%)
2d R = CH_2OCONH_2 (66%)

Our approach to the mitosene ring system is depicted in Scheme 1. Starting from o-toluyl succinimide[9] the bromide 1a[10] was obtained with NBS and transformed to the phosphonium salt 1b[11] on a conventional route. The intramolecular Wittig olefination gave optimal yields if a solution of 1b in DMF was slowly added to potassium tert-butoxide in DMF at 120°C.[12] Vilsmeier formylation of 2a[11] gave the aldehyde 2b[11] which was reduced selectively with $LiBH_4$ in THF and acetylated to give 2c.[11] From a reduction of 2b which was followed by an acylation with phenoxycarbonyl chloride and treatment with ammonia[13] the mitosene 2d[11] was obtained.

Scheme 2



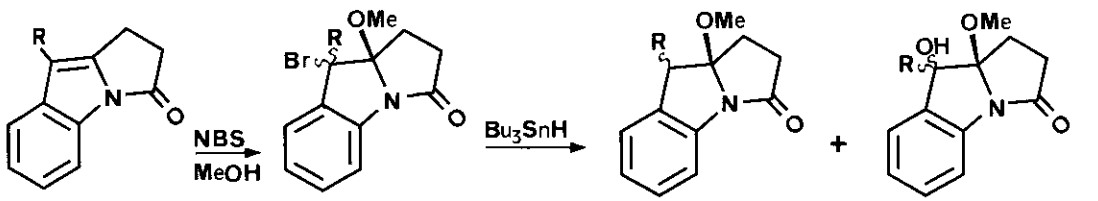
3

4a X = O (71%)
4b X = H,OH (95%)
4c X = H,Br (97%)
4d X = H,$PPh_3^+Br^-$ (89%)

2e R = H (71%)
2f R = CHO (96%)

It may be seen from Scheme 2[11,14] that using this method structural modifications are within easy reach. Since the yield of each single step of the synthetic sequence is acceptable, substantial amounts of the mitosenes are accessible.

Scheme 3



2a R = H
2c R = CH_2OAc

5a R = H (88%)
5b R = CH_2OAc

6a R = H (90%)
6b R = CH_2OAc (72%)

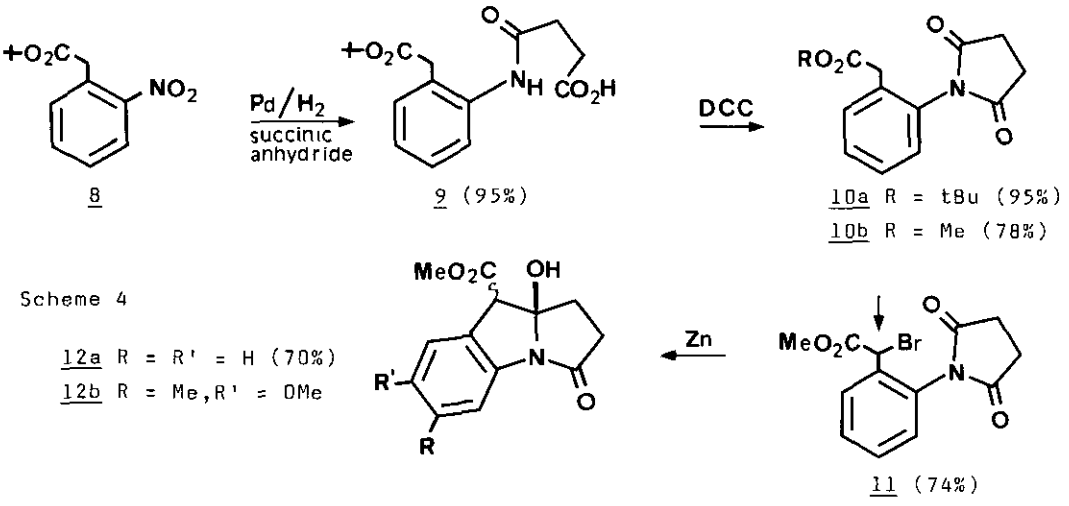
7a R = H (6%)
7b R = CH_2OAc (3%)

Attempts to an introduction of a 9a-methoxy group into mitosenes are based on two considerations: (1) It is well known that the quinone part stabilizes the 9a-methoxy group of mitomycins.[4a] This may be caused by a push-pull interaction between one of the carbonyl groups of the quinone and the lone pair electrons of the bridgehead nitrogen atom thus impeding an elimination of the angular methoxy group. The same stabilizing effect should be exerted - probably even stronger - by an amide carbonyl group. (2) It can

be shown by simple PMO-arguments that N-acylation of indoles, raising the electronegativity of the heteroatom, shifts the chemical properties towards those of benzofuranes. Experimental evidence is in agreement with this expectation.[15] As a consequence an electrophilic attack of bromine to 1,2-dihydro-5,6-benzopyrrolizines 2 should result in an addition to the indole double bond if a nucleophile, e.g. methanol, is present. Acylimmonium salts are intermediates of these reactions which are important intermediates in the synthesis of heterocyclic natural products.[16]

Using both principles we have been able to introduce a 9a-methoxy group into mitosenes 2 (Scheme 3). The bromine atom in position of 5a/b[11] can be removed easily using n-Bu_3SnH. Interestingly only one of the two possible isomers of 5b is formed. Minor amounts of 9-hydroxy derivatives 7[11] were obtained simultaneously. 6b[11] is the first example of a mitosane containing suitable substituents in the 9a- and 10-position which was obtained using the benzopyrrolizine route.

Intramolecular Reformatzki reaction provides a second route to the mitomycin skeleton which allows for an introduction of a 9a-oxygen functionality simultaneously as shown in Scheme 4:



8 — 9 (95%) — 10a R = tBu (95%); 10b R = Me (78%)

Scheme 4

12a R = R' = H (70%)
12b R = Me, R' = OMe

11 (74%)

A suitably substituted benzopyrrolizidine 12b[11] was obtained on a slightly modified way in similar yields.[17]

Using additional functionalizations, which have been reported by other groups[4], mitomycins containing the natural substitution pattern should be within reach now. We are trying to obtain compounds of this type and to achieve a stereochemical control of the reactions needed.

ACKNOWLEDGEMENT

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