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A SYNTHETIC APPROACH TO THE MITOSENES

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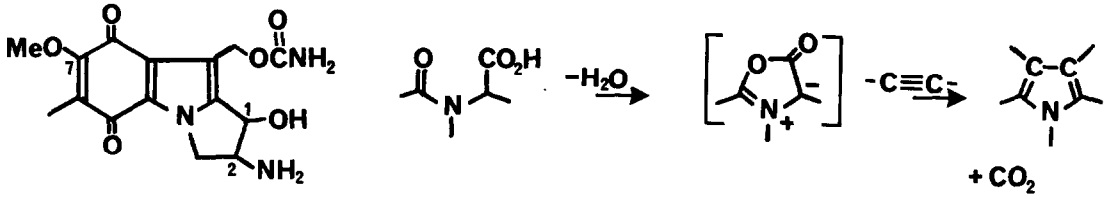
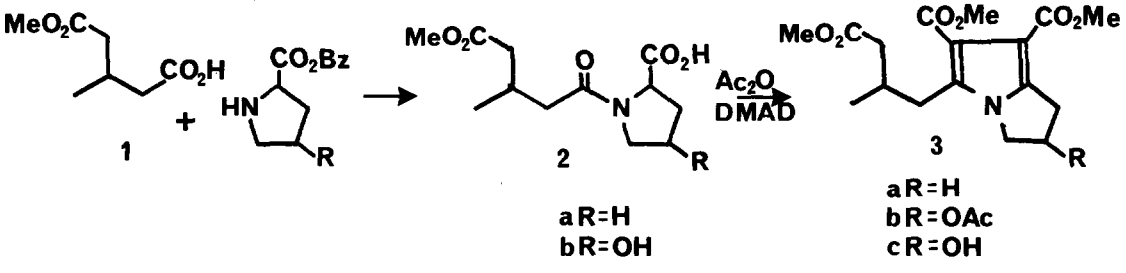
Mitosenes, the chemical degradation products of the mitomycins,[1] are synthetically accessible through a number of approaches which build the pyrrolizidine system onto an existing 6-membered ring.[2] We offer here an alternative, rapid assembly of the ring system, from which access to optically active mitosenes appears feasible. Our approach is based on Huisgen's[3,4] pyrrole synthesis formalized below; applied to the case at hand, a münchnone is generated from

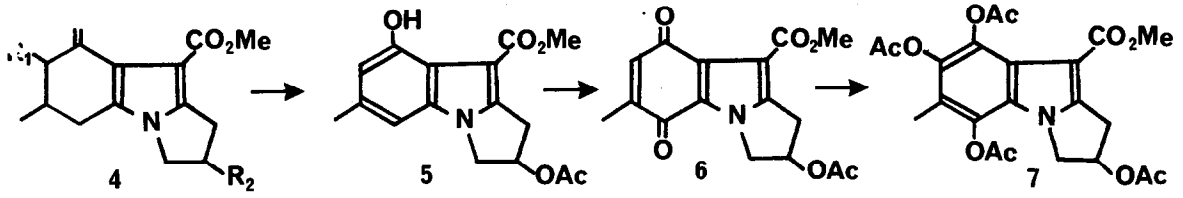


an N-glutaroyl proline such as 2, and condensed in situ with dimethyl acetylenedicarboxylate, DMAD. This affords an appropriately functionalized pyrrolizidine from which the 6-membered ring may be constructed by Dieckmann cyclization. Accordingly, coupling proline benzyl ester to the glutarate derivative 1 (DCC, mixed anhydride or acid chloride procedures) gave, after hydrogenolysis (Pd/C), the acid 2a, (DCHA salt mp 140°). Crystalline pyrrole 3a, mp 99°, was obtained in 80-85% overall yields (from proline) by treatment of the acid 2a in Ac_2O containing DMAD at 135° for 2 hrs, then evaporation of the volatiles. A parallel series of reactions, using L-hydroxy proline as starting material, gave 3b (70% overall) as a mixture of diastereomers from which one isomer was obtained in crystalline form (mp 91°).[5]



Cyclization of 3a (KH/THF) gave 80% yields of 4a, but only modest (35%) yields of crystalline 4b (mp 210°d.) were obtained from 3c through KOt-Bu/THF treatment. Since the other products were identified as mixtures of tricyclic acids and esters, the partially purified Dieckmann products were carefully saponified then re-esterfied (CH_2N_2) and acetylated to give 4c, mp 205°, (50% overall from 3b).

Oxidation of 4c (DDQ) gave optically active phenol 5, mp 159°, $[\alpha]_D^{25}$= +32.2 (c=1,$CHCl_3$), from which the yellow quinone 6, mp 169°, $[\alpha]_D^{25}$ = +19.5 (c=1, $CHCl_3$), could be obtained by Fremy's salt oxidation (95% from 4c). Thiele acetylation gave high yields of the amorphous 7; exploitation of this approach to the synthesis of mitosenes is underway.



a R_1= CO_2Me; R_2= H
b R_1= " ; R_2= OH
c R_1= H ; R_2= OAc

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References and Notes

1. Nomenclature for these substances is that proposed by J. S. Webb, et al, J. Amer. Chem. Soc., 84, 3185 (1962). The structure shown, derived from mitomycin A, is 1-hydroxy-2-amino-7-methoxy mitosene.
2. For approaches to the mitosene/mitomycin structures see 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); W. G. Taylor, G. Leadbetter, D. L. Fost and W. A. Remers, J. Med. Chem., 20, 138 (1977); T. Kametani, K. Takahashi, Y. Kigawa, M. Ihara and K. Fukumoto, J. Chem. Soc., Perkin I, 28 (1977); J. W. Lown and T. Itoh, Can. J. Chem., 53, 960 (1975); T. Takada, Y. Kosugi and M. Akiba, Tetrahedron Lett., 3283 (1974); T. Hirata, Y. Yamada and M. Matsui, ibid, 4107 (1969); and references cited therein.
3. R. Huisgen, H. Gotthard, H. O. Bayer and F. C. Schafer, Chem. Ber., 103, 2611 (1970).
4. See also F. M. Hershenson, J. Org. Chem, 40, 1260 (1975).
5. Removal of the acetyl group (MeOH/Et_3N) from the oily isomer gave crystalline 3c mp 85°; however, mixtures of both diastereomers of 3c were used in subsequent reactions.
6. All new compounds showed the expected spectroscopic features.