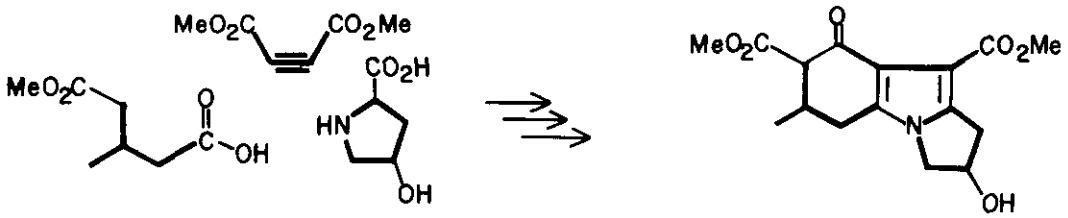
RECENT PROGRESS TOWARD THE SYNTHESIS OF MITOSENES

Julius Rebek, Jr.* and Steven Shaber

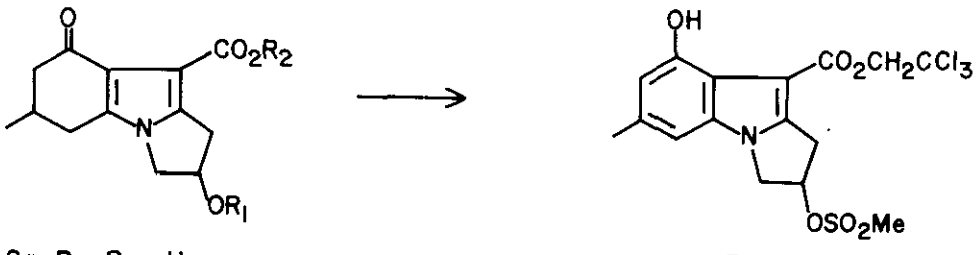
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

ABSTRACT The tricyclic ketone 1 has been converted to the mitosene 7 in nine steps. The methods described appear to offer access to mitosenes derived from natural products.

We have recently[1] described the facile preparation of the tricyclic ketone 1, a promising intermediate for the synthesis of mitosene[2] derivatives. The key steps involve Huisgen pyrrole synthesis using the acetylenic diester and the münchnone derived from the glutaroyl proline derivative, followed by Dieckmann cyclization.[3] Presently the overall yield of 1 is 50%. Here we describe some of the further elaborations on this system.



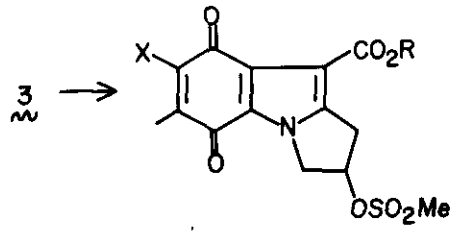
Saponification/decarboxylation afforded 2a from which the mesylate 2b was prepared, thence the trichloroethyl ester 2c ($((CF_3CO)_2O/CCl_3CH_2OH)$). Dehydrogenation (DDQ/EtOAc) gave the phenol 3, mp 181-182°, $[\alpha]_D^{25}$ = +10.7, (c = 1.07 Me_2CO). The latter gave the yellow bromoquinone 4a, mp 191-193°, λ_{max} 287 (log ε = 3.87), 325 (log ε = 3.35) and 418 nm (log ε = 2.95), on brief treatment with excess bromine water (33% from 1).



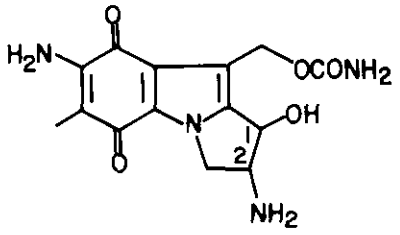
2a $R_1 = R_2 = H$
2b $R_1 = SO_2Me$, $R_2 = H$
2c $R_1 = SO_2Me$, $R_2 = CH_2CCl_3$

3

Nitrogen was introduced as the azide 4b (NaN_3, MeCN/EtOH) and treatment of this substance with Zn/THF/HOAc reduced both the quinone and azide, and exposed the carboxyl function. Reoxidation ($FeCl_3$) gave the exceedingly insoluble, deep blue purple amino quinone acid 4c, λ_{max} 243 (log ε = 4.234), 307 (log ε = 4.063), 350 sh (log ε = 3.677) and 520 nm (log ε = 2.983) in 45% from 4a. Thus the appropriate functionalization of the quinone ring of a mitosene 5, was achieved.

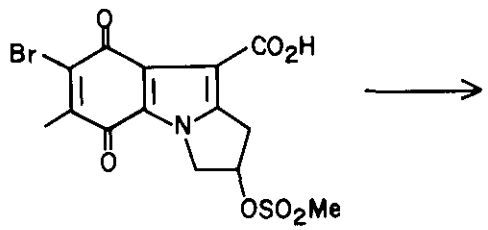


4a X = Br, R = CH_2CCl_3
4b X = N_3, R = CH_2CCl_3
4c X = NH_2, R = H

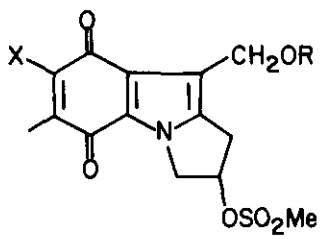


5

In an alternate sequence 4a was treated with Zn/HOAc followed by reoxidation ($FeCl_3$) to give the acid 6, mp 167-169° decomp. The acid chloride was prepared ($SOCl_2$) and without isolation was reduced ($NaBH_4$/THF -20°, then Fremy's Salt) to the alcohol 7a, mp 136-138° decomp. (68% from 4a).



6



7a X = Br, R = H
7b X = N_3, R = H
7c X = NH_2, R = OAc

Nitrogen was introduced as before 7b, and treatment with $NaBH_4$/THF at 35°C reduced both the azide and quinone. Reoxidation with $FeCl_3$ followed by acetylation (Ac_2O/py) gave 7c, a highly functionalized mitosene, mp indeterminate (30% from 6).[5]

Currently we are exploring methods by which functionalization of C_1 can be attained in a manner compatible with the methods described here. We will report on this research in the near *future*.

REFERENCES

1. J. Rebek, Jr. and J. -C. E. Gehret, Tetrahedron Letters, 1977, 3027.

2. For recent total syntheses of the mitomycins, see: F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, J. Am. Chem. Soc., 1977, 99, 4835; F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, Ibid., 1977, 99, 8115; T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, and Y. Kishi, Tetrahedron Letters, 1977, 4295.
For a review of the synthesis of pyrrolo[1,2-a]indoles, see: T. Kametani, and K. Takahashi, Heterocycles, 1978, 9, 293-351.
Other recent synthetic work in the mitosene field includes the following: T. Kametani, K. Takahashi, Y. Kigawa, M. Ihara and K. Fukumoto, J. Chem. Soc. Perkin I, 1977, 28; W. G. Taylor, G. Leadbetter, D. L. Fost and W. A. Remers, J. Med. Chem., 1977, 1, 138; K. Parker, and M. Sworin, Tetrahedron Letters, 1978, 2251; T. Ohnuma, J. Sekine and Y. Ban, ibid., 1979, 2533; R. Coates and C. Hutchins, J. Org. Chem., 1979, 44, 4742; T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, Heterocycles, 1979, 933; T. Kametani, K. Takahashi, M. Ihara, K. Fukumoto, J. Chem. Soc. Perkin I, 1979, 847; H. Rapoport and S. Falling, J. Org. Chem., 1980, 1260.

3. F. M. Hershenson, J. Heterocyclic Chem., 1979, 1093.

4. For structure elucidation and nomenclature, see: J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks and J. E. Lancaster, J. Am. Chem. Soc., 1962, 84, 3185 - 3187. The mitosene 5 is 2,7-Diamino-1-hydroxy-mitosene and is derived from Mitomycin C.

5. All new compounds gave satisfactory spectral data and high resolution mass spectral or combustion analysis.

Received, 17th April, 1980