

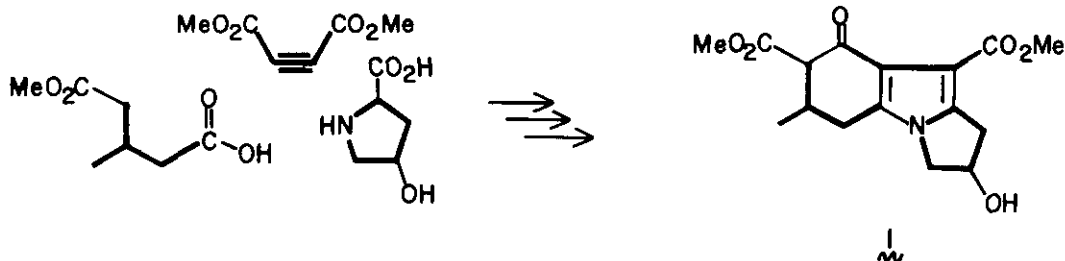
RECENT PROGRESS TOWARD THE SYNTHESIS OF MITOSENES

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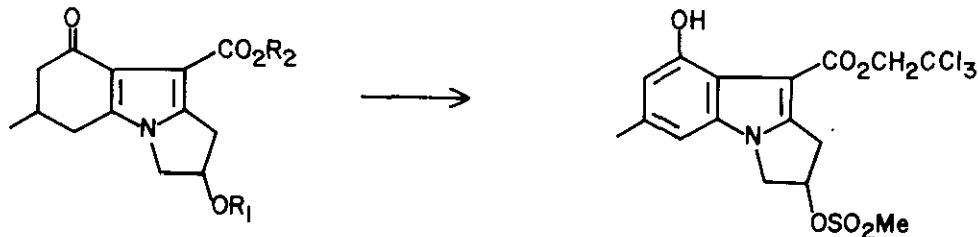
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ABSTRACT The tricyclic ketone **1** has been converted to the mitosene **7** in nine steps. The methods described appear to offer access to mitosenes derived from natural products.

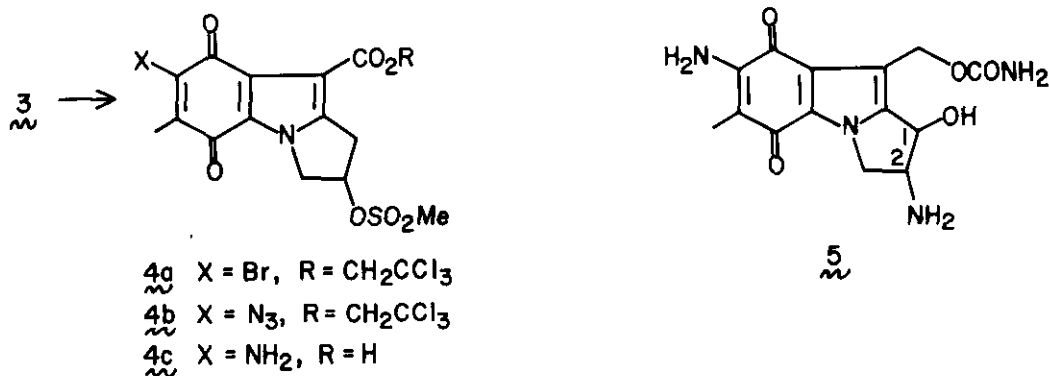
We have recently¹ described the facile preparation of the tricyclic ketone **1**, a promising intermediate for the synthesis of mitosene² derivatives. The key steps involve Huisgen pyrrole synthesis using the acetylenic diester and the malachonone derived from the glutaroyl proline derivative, followed by Dieckmann cyclization.³ Presently the overall yield of **1** is 50%. Here we describe some of the further elaborations on this system.



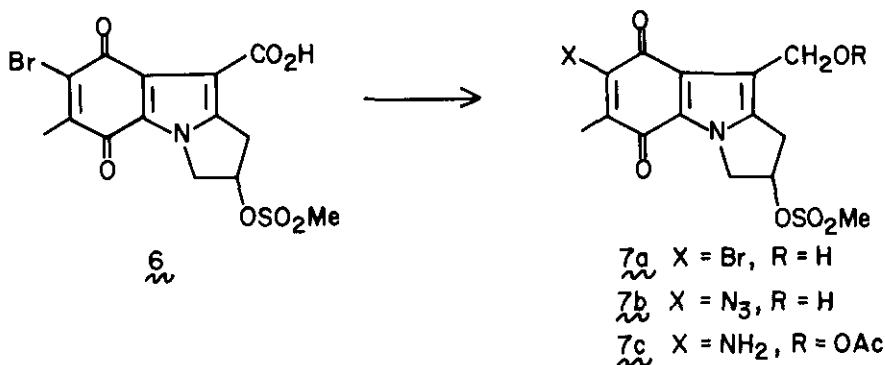
Saponification/decarboxylation afforded **2a** from which the mesylate **2b** was prepared, thence the trichloroethyl ester **2c** ((CF₃CO)₂O/CCl₃CH₂OH). Dehydrogenation (DDQ/EtOAc) gave the phenol **3**, mp 181-182°, [α]_D²⁵ = +10.7, (c = 1.07 Me₂CO). The latter gave the yellow bromoquinone **4a**, 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** R₁ = R₂ = H**2b** R₁ = SO₂Me, R₂ = H**2c** R₁ = SO₂Me, R₂ = CH₂CCl₃

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 ($\log \epsilon = 4.234$), 307 ($\log \epsilon = 4.063$), 350 sh ($\log \epsilon = 3.677$) and 520 nm ($\log \epsilon = 2.983$) in 45% from 4a. Thus the appropriate functionalization of the quinone ring of a mitosene 5, was achieved.



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).



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 ($\text{Ac}_2\text{O/py}$) 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

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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.
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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. Post 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.

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