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SYNTHETIC STUDIES TOWARD MITOMYCINS. III.[1] TOTAL SYNTHESES OF MITOMYCINS A AND C.

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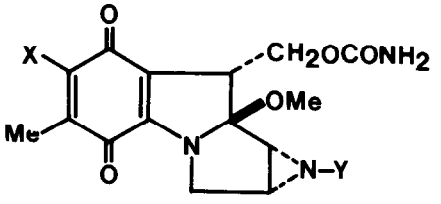
The mitomycins (1a-e) are a class of antibiotics with activity against Gram-positive and Gram-negative bacteria and also against several kinds of tumors.[2] Since their structures were first elucidated in 1962,[2] numerous synthetic approaches to the mitomycins have been reported.[3] We have recently reported the first total synthesis of porfiromycin (1d), one of the naturally occurring mitomycins.[1] In this communication, we wish to describe the first total syntheses of mitomcyins A (1a) and C (1c) by a synthetic route similar to the one we have used for the synthesis of porfiromycin (1d).



1a : mitomycin A ; X=OCH_3, Y=H

1b : mitomycin B ; see reference 4.

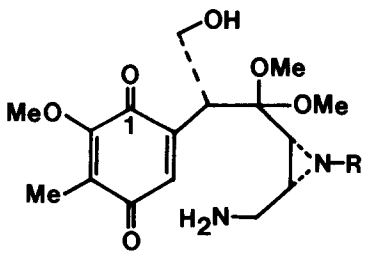
1c : mitomycin C ; X=NH_2, Y=H

1d : porfiromycin ; X=NH_2, Y=CH_3

1e : mitiromycin ; see reference 5.

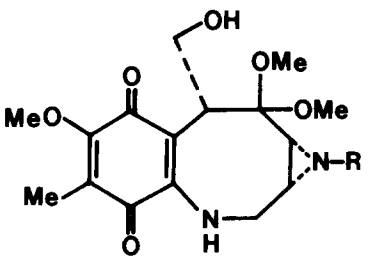
One of the key steps of our porfiromycin synthesis was the intramolecular Michael reaction of 2 to construct the eight-membered quinone 3. On attempting the Micahel reaction on the aziridine 4, we observed the formation of two products in about a 5:1 ratio. The minor product was the desired eight-membered quinone 5, while the major product was most likely formed by an interaction of the aziridine nitrogen with the C.1 carbonyl group.[6] Thus, protection of the aziridine nitrogen is required in order to apply this cyclization reaction to the total syntheses of mitomycins A (1a) and C (1c). The 3-acetoxypropyl group was chosen since conventional protecting groups such as acetyl, benzoyl, ethoxycarbonyl, methoxymethyl etc. proved unsuccessful for the present purposes.

Dibenzylamine aziridine 6[1] was converted to 3-acetoxypropylaziridine 7[7] [oil; nmr ($CDCl_3$) δ 1.90 ppm (3H, s), 2.18 (3H, s), 3.02 (3H, s), 3.17 (3H, s), 3.75 (3H, s)] in 3 steps (1. CH_2=CHCHO/CH_2Cl_2/RT, 2. BH_3/THF-CH_2Cl_2/-78°C⟶RT, 3. Ac_2O-Py/RT) in 78% overall yield. Hydrogenolysis (H_2/Pd-C/AcOH/RT) of 7, followed by treatment with oxygen (O_2/CH_3OH/RT), yielded the eight-membered quinone 8[7] [oil; ms M^+ found 438.1984, $C_{21}H_{30}N_2O_8$ requires 438.2002; nmr ($CDCl_3$) δ 1.86 ppm (3H, s), 2.02 (3H, s), 3.15 (3H, s), 3.36 (3H, s), 4.03 (3H, s); uv (CH_3OH) λ_{max} 219 nm (log ε 4.32), 305 (4.12), 505 (3.11)] in 42% yield. Careful treatment of 8 with tetrafluoroboric acid in methylene chloride at room temperature afforded exclusively decarbamoyl-N_1-(3-acetoxypropyl)mitomycin A (9)[7] [77% yield; ms M^+ found 406.1716, $C_{20}H_{26}N_2O_7$ requires 406.1740; nmr ($CDCl_3$) δ 1.85 ppm (3H, s), 1.99 (3H, s), 3.15 (3H, s), 4.05 (3H, s); uv (CH_3OH) λ_{max} 218 nm (log ε 4.27), 320 (3.98), 530 (2.99)], which was converted to N_1-(3-acetoxypropyl)mitomycin A (10)[7] [85% yield; ms M^+ found 449.1805, $C_{21}H_{27}N_3O_8$ requires 449.1798; nmr ($CDCl_3$) δ 1.84 ppm (3H, s), 2.00 (3H, s), 3.15 (3H, s), 4.05 (3H, s); uv (CH_3OH) λ_{max} 217 nm (log ε 4.21), 320 (3.98), 530 (3.08)]. The stereospecific cyclization reaction of the eight-membered quinone 3 to the mitosane 11 has been discussed in our earlier communication.[1] The protecting group of the aziridine moiety of 10 was removed in 3 steps [1. $NaOCH_3$/CH_3OH-CH_2Cl_2/RT, 2. DMSO-DCC/TFA-Py/RT, 3. $HClO_4$/$C_6H_5N(CH_3)_2$/CH_2Cl_2/RT] to give d,l-mitomycin A



2 : R=CH_3

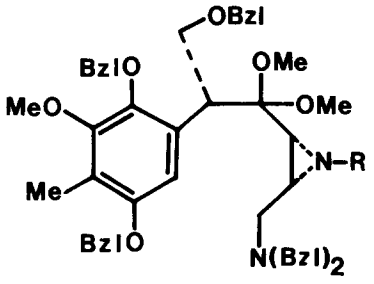
4 : R=H



3 : R=CH_3

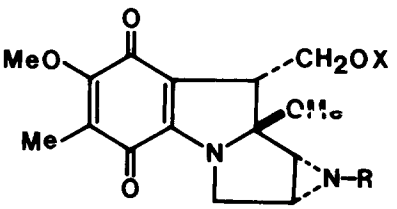
5 : R=H

8 : R=$(CH_2)_3OAc$



6 : R=H

7 : R=$(CH_2)_3OAc$



9 : R=$(CH_2)_3OAc$, X=H

10 : R=$(CH_2)_3OAc$, X=$CONH_2$

11 : R=CH_3, X=H

(1a)[7] (mp 163-165°C dec.) in 35% yield. The synthetic substance was identical with natural mitomycin A[8] in all respects (nmr, uv, ms, ir, and tlc). The transformation of mitomycin A (1a) to mitomycin C (1c) and porfiromycin (1d) has been previously reported.[9]

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References and Footnotes

1. Part II of this series, F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, submitted to J. Am. Chem. Soc.
2. See, for example, The Merck Index 9th Edition, ed. M. Windholz, Merck & Co., Rahway, N. J., 1976, p 807 ff and references cited therein.
3. See the references cited in the Part I of this series [F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, J. Am. Chem. Soc., 99, 4835 (1977)].
4. The structure of mitomycin B including its absolute configuration was recently confirmed by X-ray crystallography; R. Yahashi and I. Matsubara, J. Antibiot., 29, 104 (1976).
5. G. O. Morton, G. E. Van Lear, and W. Fulmor, J. Am. Chem. Soc., 92, 2588 (1970).
6. Elucidation of the complete structure of this product is in progress.
7. Satisfactory spectroscopic data were obtained for this substance.
8. We are indebted to Dr. J. S. Webb, Lederle Laboratories, and Dr. K. Nakano, Kyowa Hakko Kogyo Co., for a sample of mitomycin A.
9. 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. Pidachs, and J. E. Lancaster, J. Am. Chem. Soc., 84, 3185 (1962).