

APPROACHES TO THE MITOMYCINS: 4,4a-SECODEIMINOQUINONES

Richard W. Franck and Katsuji Miyano

Department of Chemistry, Fordham University, Bronx, NY 10458

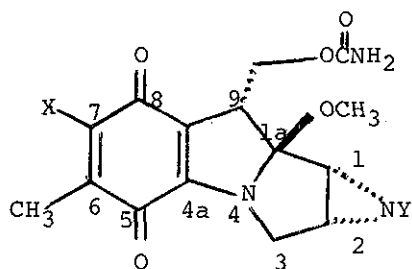
and

John F. Blount

Research Division, Hoffman-La Roche, Nutley, NJ 07110

Frameworks containing all the stereochemical and functional features except the aziridine and the 4,4a C-N bond of both epimeric series of the mitomycins are prepared in a short synthesis.

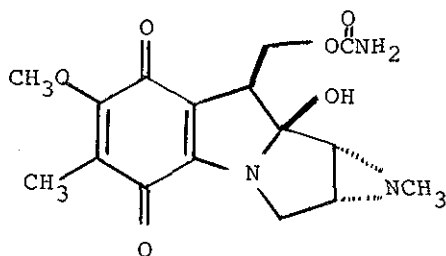
The mitomycin antibiotics have been the object of many synthetic studies. Recently, a Harvard group has reported the total synthesis of mitomycin A (1), mitomycin C (2), and porfiromycin (3).¹ In addition to the Harvard total synthesis, only two other reports describe successful approaches to the introduction of the 1a oxygen function of the antibiotics. As a model for the total synthesis program referred to above, a deimino-mitomycin was prepared using a variation of a transannular at-



1 X = OCH₃, Y = H

2 X = NH₂, Y = H

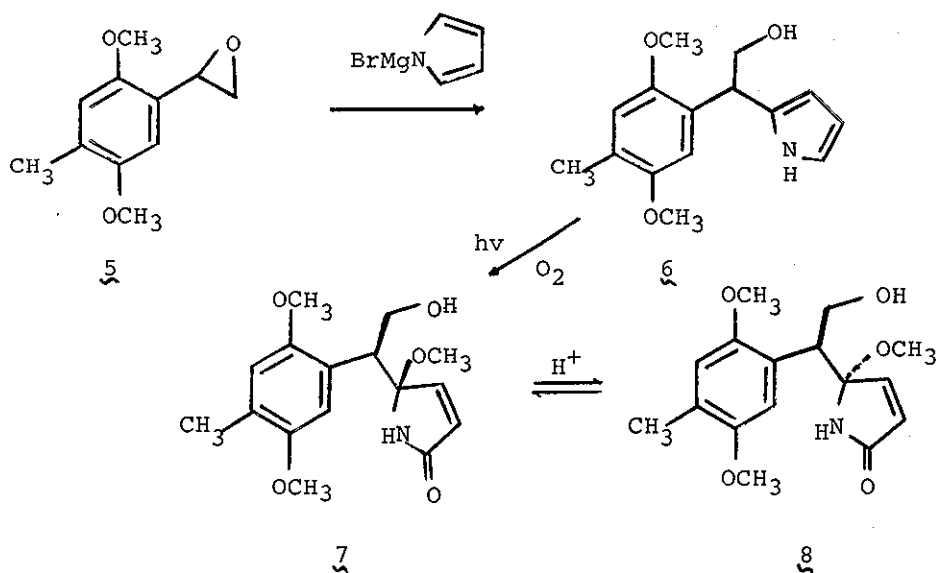
3 X = NH₂, Y = CH₃



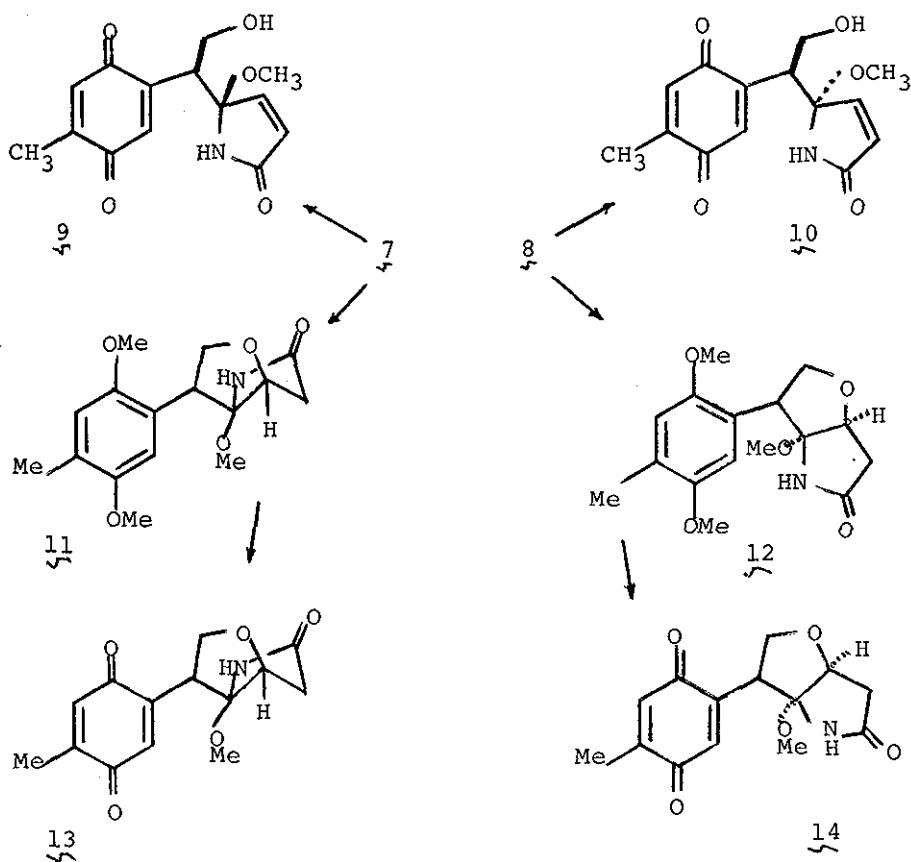
4 Mitomycin B

tack which established the N4,C1a bond;² whereas the Tohoku group used a photo-oxidation of a pyrrolo(1,2a)indole to prepare a la-hydroxy compound.³ In this report, we wish to describe our synthesis of la-methoxy compounds in both stereochemical families of the mitomycins. Our scheme begins with styrene oxide 5, available in four steps and 43% yield from toluhydroquinone dimethyl ether, which is reacted with pyrrole magnesium bromide to yield adduct 6 which has the entire mitomycin framework. The unpurified pyrrole 6 is photo-oxidized in methanol with Rose Bengal as a sensitizer, and after chromatography on silica gel (CHCl₃-2% CH₃OH), there is obtained methoxy lactam 7, mp 151-152 (m/e 307.1458) in 15 % yield. The stereochemistry of the photo-oxidation product was established as corresponding to the B series by X-ray crystallography. Crystals of 7 are monoclinic, space group P2₁/c, with a = 7.601(4), b = 19.737(15), c = 10.837(8) Å, β = 107.51(3)° and d_{calc} = 1.316 g cm⁻³ for z = 4. The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu K radiation, θ-2θ scans, pulse height discrimination). A total of 2089 independent reflections were recorded for θ < 57°, of which 1867 were considered to be observed. The structure was solved by a multiple solution procedure⁴ and was refined by full-matrix least squares. In the final refinement anisotropic temperature factors were used for the heavier atoms and isotropic factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculation but their parameters were not refined. The final discrepancy indices are R = 0.60 and

$wR = 0.076$ for the 1867 observed reflections. The final differences map has no features greater than $0.2 \text{ e } \text{Å}^{-3}$ in magnitude. Lactam **7** could be isomerized to a chromatographically separable mixture (silica gel, $\text{CHCl}_3\text{-CH}_3\text{OH}$) of itself (50%) and its epimer **8** (50%) by treatment with 0.1% $\text{H}_2\text{SO}_4\text{-CH}_3\text{OH}$. Lactam **8**, mp 118-119, with the relative stereochemistry of the A,C series, was characterized by its mass spectrum (m/e 307.1409) and nmr spectrum which were very similar to those of **7**. The major differences in the nmr's of **7** and **8** were the β -vinyl H, δ 6.90 and 6.64 respectively and one aromatic H, δ 6.89 and 6.76 respectively, which suggest differing relationships between the lactam and aromatic rings in the epimers. It is interesting to note that lactam **8** could not be found in the crude photo-oxidation product. We have no rationale for the specificity of this step.

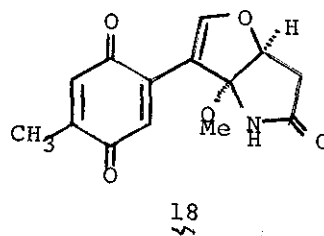
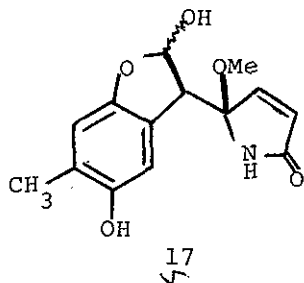
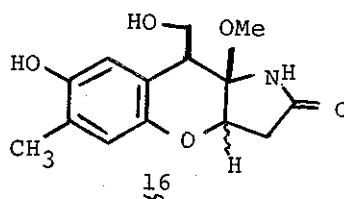
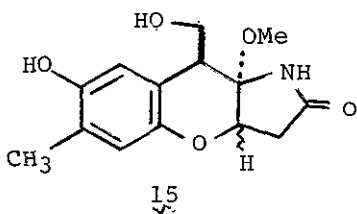


Both 7 and 8 were easily converted to quinones 9 (m/e 277.0940) and 10 (m/e 277.0926) by the use of argentic oxide in essentially quantitative yield.⁵ The nmr spectra for these quinones were nearly identical and showed characteristic splitting of the vinyl methyl signals. Both lactams 7 and 8 could be cyclized to tetrahydrofuryllactams 11 and 12 (m/e 307.1401) using NaOMe-MeOH in 90% yield. The major difference between these epimers was the angular methoxyl resonances, δ 3.06 and 3.28 respectively. Again, argentic oxide smoothly and quantitatively converted 11 and 12 to quinones 13 and 14 (m/e 277.0912). In



their nmr spectra, the angular methoxyls differed, δ 3.11 and 3.31 respectively, and the quinone H ortho to the functional side chain in 13 was split into a doublet, $J = 2$ Hz, by the benzylic methine H. This observation suggests a fixed relationship between the quinone and tetrahydrofuryllactam rings.

Extensive studies were undertaken to form the 4-4a bond by intramolecular nucleophilic addition of the lactam N to the quinone with all four candidates, 9, 10, 13 and 14. Such a conjugate addition of an amide to a cyclohexenone has been observed.⁶ In our case, the reaction required belongs to the 5-endo-trig class according to Baldwin's classification scheme.⁷ Due to orbital approach and overlap constraints, the desired reaction is dis-favored. Thus, products obtained in our studies include 15 (from 9, DABCO, CH₃OH, air), 16 (from 10, DABCO, CH₃OH, air), 17 (from 9, hv) and 18 (from 13 or 14, DABCO, CH₃OH, air). Further studies to close the crucial 4,4a bond are required.



Acknowledgement- We wish to acknowledge grants RR-798 and RR-317 from the Biotechnology Resources Branch of N.I.H. for support of the Southern New England High Field NMR Facility and the support for high-resolution mass spectra determined by Dr. Catherine Costello, Department of Chemistry, M.I.T. We also acknowledge Biomedical Sciences Grant RR-07150 and N.C.I. grant CA-11421 for support of the research at Fordham.

References

1. (a) T. Fukuyama, F. Nakatsubo, A.J. Cocuzza and Y. Kishi, *Tetrahedron Letters*, 4295 (1977).
- (b) F. Nakatsubo, T. Fukuyama, A.J. Cocuzza and Y. Kishi, *J. Amer. Chem. Soc.*, 99, 8115 (1977).
- (c) Recent publications on mitomycin syntheses which do not deal with the angular oxygen problem include: S. Danishefsky and R. Doehner, *Tetrahedron Letters*, 3031 (1977); J. Rebeck, Jr. and J.-C.E. Gehret, *Tetrahedron Letters*, 3027 (1977); M. Akiba, Y. Kosugi, M. Okuyama and T. Takada, *J. Org. Chem.*, 43, 181 (1978).
2. F. Nakatsubo, A.J. Cocuzza, D.E. Kealey and Y. Kishi, *J. Am. Chem. Soc.*, 99, 4835 (1977).
3. T. Kametani, T. Ohsawa, K. Takahashi, M. Ihara and K. Fukumoto, *Heterocycles*, 4, 1637 (1976).
4. G. Germain, P. Main and M.M. Woolfson, *Acta Cryst.* A27, 368 (1971).
5. C.D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 94, 227 (1972).
6. T.A. Bryson and C.A. Wilson, *Synthetic Commun.*, 6, 521 (1976).
7. J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R.C. Thomas, *J.C.S. Chem. Commun.*, 736 (1977).

Received, 6th April, 1978