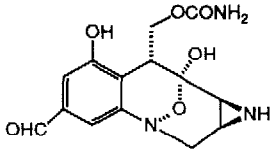
Tetrahedron Letters,Vol.30,No.26,pp 3397-3400,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHETIC STUDIES ON FR900482: PROMISING METHOD TO CONSTRUCT THE BICYCLIC HYDROXYLAMINE HEMI-KETAL RING SYSTEM

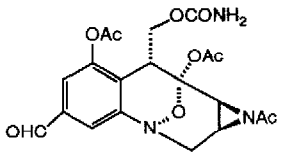
Nobuyoshi Yasuda[*1a] *and Robert M. Williams*[*1b]
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Abstract: *Intramolecular reductive amination is utilized as a key 8-membered ring-forming cyclization reaction to construct the novel bicyclic hydroxylamine hemi-ketal ring system of FR900482.*

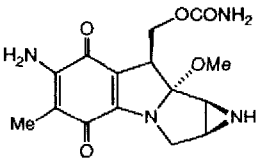
The recently discovered anti-tumor antibiotic FR-900482 (**1**) was obtained from the fermentation harvest of *Streptomyces sandaensis No. 6897* at Fujisawa Pharmaceutical Co. in Japan.[2] The derived triacetate, FK973 (2) has shown very promising activity[3] against various transplanted murine and human tumors. These substances are structurally related to mitomycin C but lack the quinone moiety and contain the novel hydroxylamine hemi-ketal. FK973 has been shown[4] to form DNA-DNA cross-links and DNA-protein cross-links in L1210 cells; unlike the mitomycins and other quinone anti-tumor antibiotics, FK973 does not cause oxidative scission of single-strand DNA. Furthermore, FK973 is *ca* three-fold more potent than mitomycin C and has significantly lower toxicity. Syntheses of these novel structures or approaches to the unique dihydrobenzoxazine ring system have not yet appeared. In this paper, we wish to detail the first successful construction of the unique central bicyclic hydroxylamine hemi-ketal ring system of these medicinally significant substances.



1, *FR-900482*



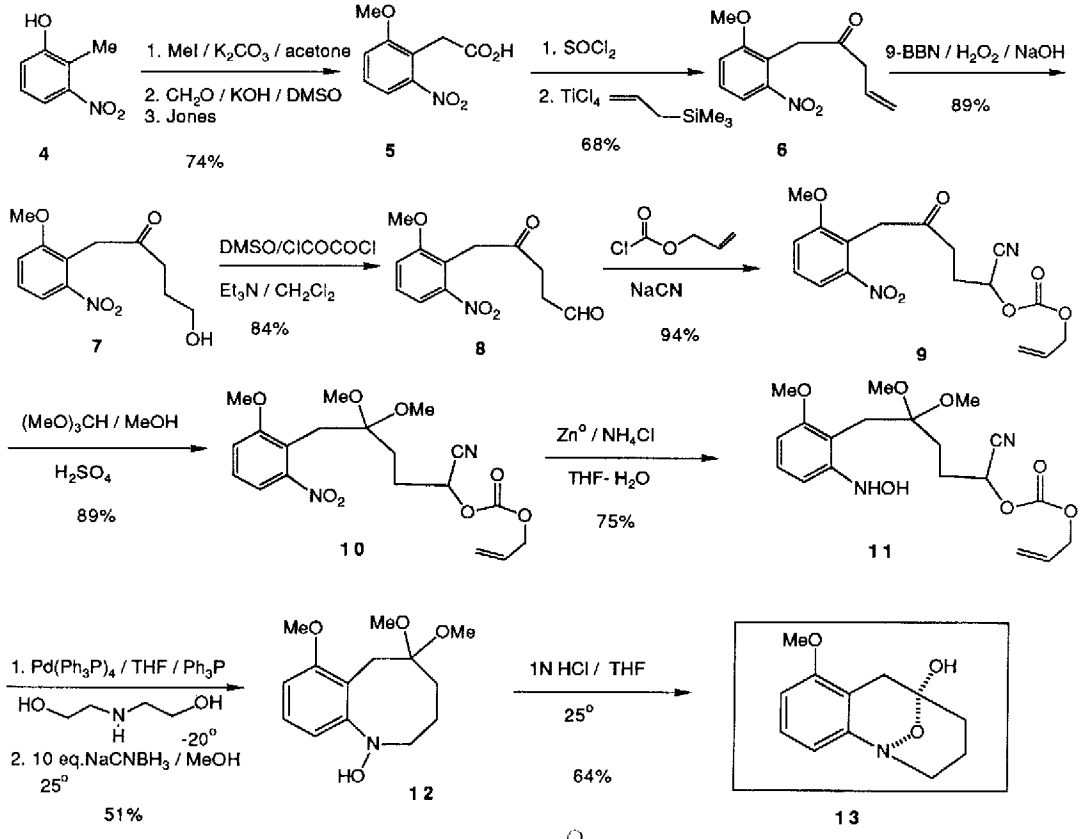
2, *FK973*



3, *MITOMYCIN C*

The model system, detailed in Scheme 1, is the result of numerous attempts in our laboratories to functionalize the delicate aryl hydroxylamine moiety. 2-Methyl-3-nitroanisole (**4**) is converted into the acid **5** (mp 158-159°C; 71% overall)[5] which is subsequently allylated to the β,γ-unsaturated ketone **6** (oil). Hydroboration/oxidation proceeds cleanly furnishing **7** (mp 35-

SCHEME 1



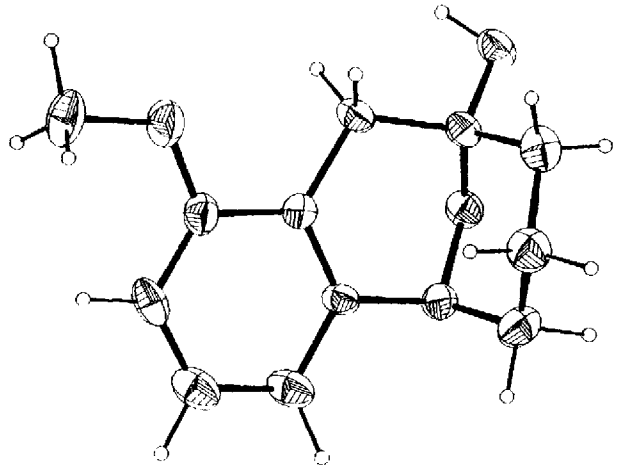


Figure 1. X-Ray stereostructure (thermal ellipsoid plot) for compound **13**. Hydrogen atoms have been rendered as spheres of fixed, arbitrary radius for clarity.

36°C). Swern oxidation to the key keto-aldehyde **8** (mp 69°C) provided a substrate from which numerous attempts to effect construction of the hydroxylamine hemi-ketal were made. After extensive investigation, it was found that the cyanohydrin derived from **8** could be trapped as the corresponding allyl carbonate **9** (oil). Protection of the ketone and zinc reduction of the nitro group afforded the labile [6] hydroxylamine derivative **11** (oil). The allyl carbonate was chosen to allow selective unmasking of the aldehyde for the subsequent intramolecular reductive amination in the presence of the ketal under neutral, mild conditions. Treatment of **11** with *tetra*-kis-triphenyl phosphine palladium (0) (1 mol %) in THF containing 0.04 eq of Ph_3P and 1.7 eq. of diethanolamine at -20°C for 45 min furnished the corresponding stable cyanohydrin species in 88% yield (oil, isolated by PTLC silica gel). Direct reductive amination of the cyanohydrin with sodium cyanoborohydride (10 eq. in MeOH at 25°C for 24h) furnished the crystalline eight-membered ring product[7] (**12**; mp 167-168°C) in 51% overall yield from **11**. Treatment of **12** with 1N HCl in THF (1:2, v:v) at room temperature for 30 min followed by quenching with saturated aqueous $NaHCO_3$, extractive work-up and PTLC silica gel, afforded the crystalline bicyclic hydroxylamine hemi-ketal[8] **13** in 64% yield.[9] The structure of this substance was rigorously secured through single-crystal X-ray analysis (Figure 1).

These investigations demonstrate a viable method to construct the novel bicyclic hydroxylamine hemi-ketal ring system of FR900482. Efforts to apply this strategy to the total synthesis of **1** and several analogs for biological evaluation are under intensive investigation in these laboratories.

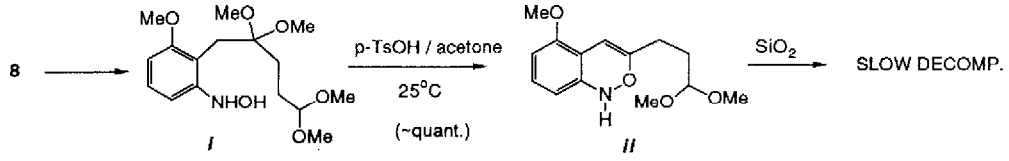
Acknowledgement. We are indebted to Fujisawa Pharmaceutical Co., Ltd., Japan for providing financial assistance (to N.Y.) and assisting in the collection of spectroscopic data and the X-ray analysis. We also thank Fujisawa for the generous gift of a natural sample of FR900482 which was instrumental in determining the chemical stability of the central ring system. R.M.W. also wishes to acknowledge funds from NIH for a Research Career Development Award (1984-89), the Alfred P. Sloan Foundation (1986-90) and Eli Lilly (1986-88) for additional Fellowship support.

References and Footnotes

1. a)Address: Fujisawa Pharmaceutical Co., Ltd. 2-1-6 Kashima, Yodogawa-Ku, Osaka 532, Japan; b) address correspondence to this author at Colorado State University.
2. a) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y., *J. Am. Chem. Soc.* (1987) **109**, 4108; b) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H., *J. Antibiotics* (1987) **40**, 589; c) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H., *ibid* (1987) **40**, 594.
3. Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H., *J. Antibiotics*, (1987) **40**, 600; b) Hirai, O.; Shimomura, K.; Mizota, T.; Matsumoto, S.; Mori, J.; Kikuchi, H., *ibid.* (1987) **40**, 607; c) Shimomura, K.; Manda, T.;

Mukumoto, S.; Masuda, K.; Nakamura, T.; Mizota, T.; Matsumoto, S.; Nishigaki, F.; Oku, T.; Mori, J.; Shibayama, F., *Cancer Res.* (1988) **48**, 1116.

4. a) Masuda, K.; Nakamura, T.; Shimomura ; Shibata, T.; Terano, H.; Kohsaka, M., *J. Antibiotics* (1988) **41**, 1497; b) Masuda, K., Nakamura, T.; Mizota, T.; Mori, J.; Shimomura, K., *Cancer Res.* (1988) **48**, 5172.
5. All new compounds exhibited satisfactory ^{1}H NMR, IR, mass spectra and combustion analytical data consistent with the assigned structures.
6. We found for example, that the bis-dimethoxy ketal *i* obtained from **8** when induced to cyclize, formed the *unwelcome* elimination product *ii*.



7. Data for **12**: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.40 (2H, m); 1.78 (2H, m); 3.15 (2H, s); 3.20 (2H, m); 3.22 (6H, s); 3.83 (3H, s); 5.37 (1H, s, D_2O exch.); 6.73 (1H, dd, J=2Hz, 7Hz); 7.26 (2H, m). ^{13}C NMR (67 MHz, $CDCl_3$) δ : 19.76; 29.22; 32.79; 48.30; 56.06; 63.76; 103.98; 108.31; 113.02; 121.05; 127.74; 153.02; 157.90. IR (Nujol) 3391, 1589, 1289, 1270, 1208, 1197, 1126, 1103, 1090, 1071, 1037, 1031, 976, 952, 807,781, 754, 723 cm^{-1}. mp 167-168°C (recryst. MeOH). Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24 ; found C, 62.99; H, 7.92; N, 5.07 . FAB-MS, m/e=268 (M^++1); 236 (M^+-31).
8. The transannular cyclization is adapted from the original concept deployed by Kishi in the total synthesis of the mitomycins, see: a) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A.J.; Kishi, Y., *J. Am. Chem. Soc.* (1977) **99**, 8115; b) Nakatsubo, F.; Cocuzza, A.J.; Keeley,D.E. Kishi, Y, *J. Am. Chem. Soc.* (1977) **99**, 4825; c)Fukuyama,T.;Nakatsubo,F; Cocuzza, A.J.; Kishi, Y., *Tetrahedron Lett.* (1977)**99**, 4295, d) Kishi, Y., *J. Nat. Prod.* (1979) **42**, 549.
9. Data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$)δ: 1.48 (1H, m); 1.72 (1H, dq J=4.4Hz, 13.1Hz); 1.86 (1H, ddt, J=2.0Hz, 5.0Hz, 13.1Hz); 2.12 (1H, m); 2.85 (1H, dd, J=1.5Hz,J=17.7Hz); 2.97 (1H, s, D_2O exch.); 2.99 (1H,d, J=17.7Hz); 3.19 (1H, m); 3.60 (1H, ddd, J=3.0Hz, 12.5Hz, J=13.8Hz); 3.83 (3H, s); 6.54 (1H,d,J=8.1Hz); 6.58 (1H, d, J=8.1Hz); 7.12 (1H,t, J=8.1Hz). ^{13}C NMR (67MHz, $CDCl_3$) δ: 17.20; 34.05; 36.79; 55.11; 55.36; 93.66; 105.48; 112.94; 116.57; 126.77; 146.10; 156.55. IR (Nujol) 1593, 1360, 1330, 1259, 1231, 1164, 1132, 1101, 1081, 1051, 978 cm^{-1}. mp 166-167°C (recryst. CH_2Cl_2 / hexane). X-ray analysis (Figure 1).FAB-MS, m/e=222(M^++1).

(Received in USA 11 April 1989)