Tetrahedron Letters,Vol.30,No.47,pp 6491-6494,1989
Printed in Great Britain

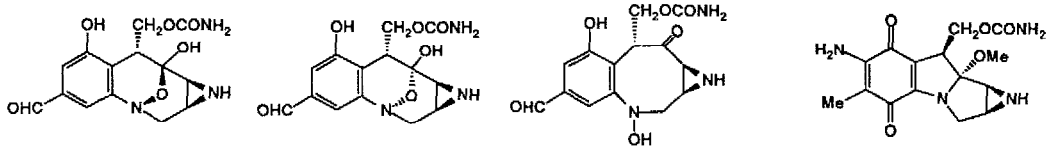
0040-4039/89 $3.00 + .00
Pergamon Press plc

SYNTHETIC APPROACHES TOWARD FR-900482. I. STEREOSELECTIVE SYNTHESIS OF A PENTACYCLIC MODEL COMPOUND.

Tohru Fukuyama* and Shunsuke Goto[1]
Department of Chemistry
Rice University
Houston, Texas 77251

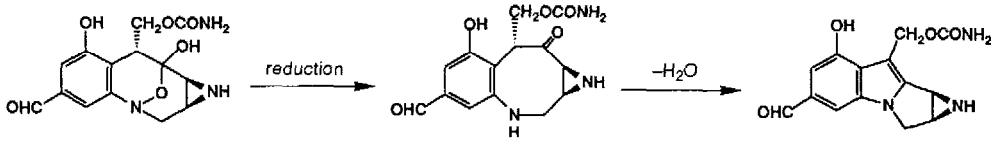
Abstract: An efficient synthesis of a pentacyclic compound **18** possessing all the necessary handles to construct the unique skeleton of antitumor antibiotic FR-900482 **1** is described.

FR-900482 **1** was recently isolated from a culture broth of *Streptomyces sandaensis* and has been shown to exhibit exceptionally potent antitumor activities.[2] Biological testings against experimental tumors have revealed that FR-900482 is at least as active as mitomycin C **2** and is also active against mitomycin C- and vincristine-resistant P388 cells. FR-900482 exists as a 2:1 mixture of tautomers **1a** and **1b** which interconvert presumably through the intermediate keto-hydroxylamine **1c**. Like mitomycin C,[3] FR-900482 is activated in the cells to form interstrand DNA-DNA cross-links.[4] Close resemblance of the structural features of FR-900482 to mitomycin C would suggest the involvement of the aziridinomitosene-like compound **3** in the mode of action (Scheme I). FR-900482 gives a formidable challenge to synthetic chemists because of the presence of a labile hydroxylamine moiety in addition to all the difficulties associated with mitomycin synthesis. We report herein an efficient synthesis of a pentacyclic model compound **18** which possesses all the necessary handles to construct the unique skeleton of FR-900482.



1a **1b** **1c** **2**

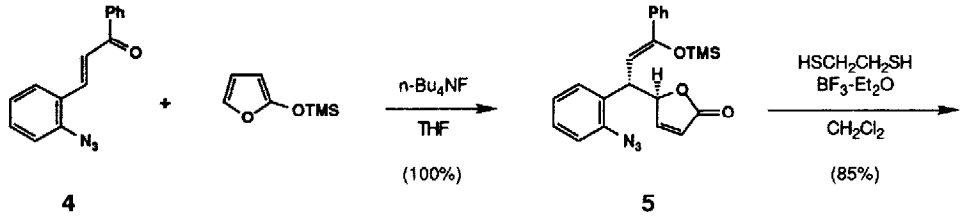
Scheme I



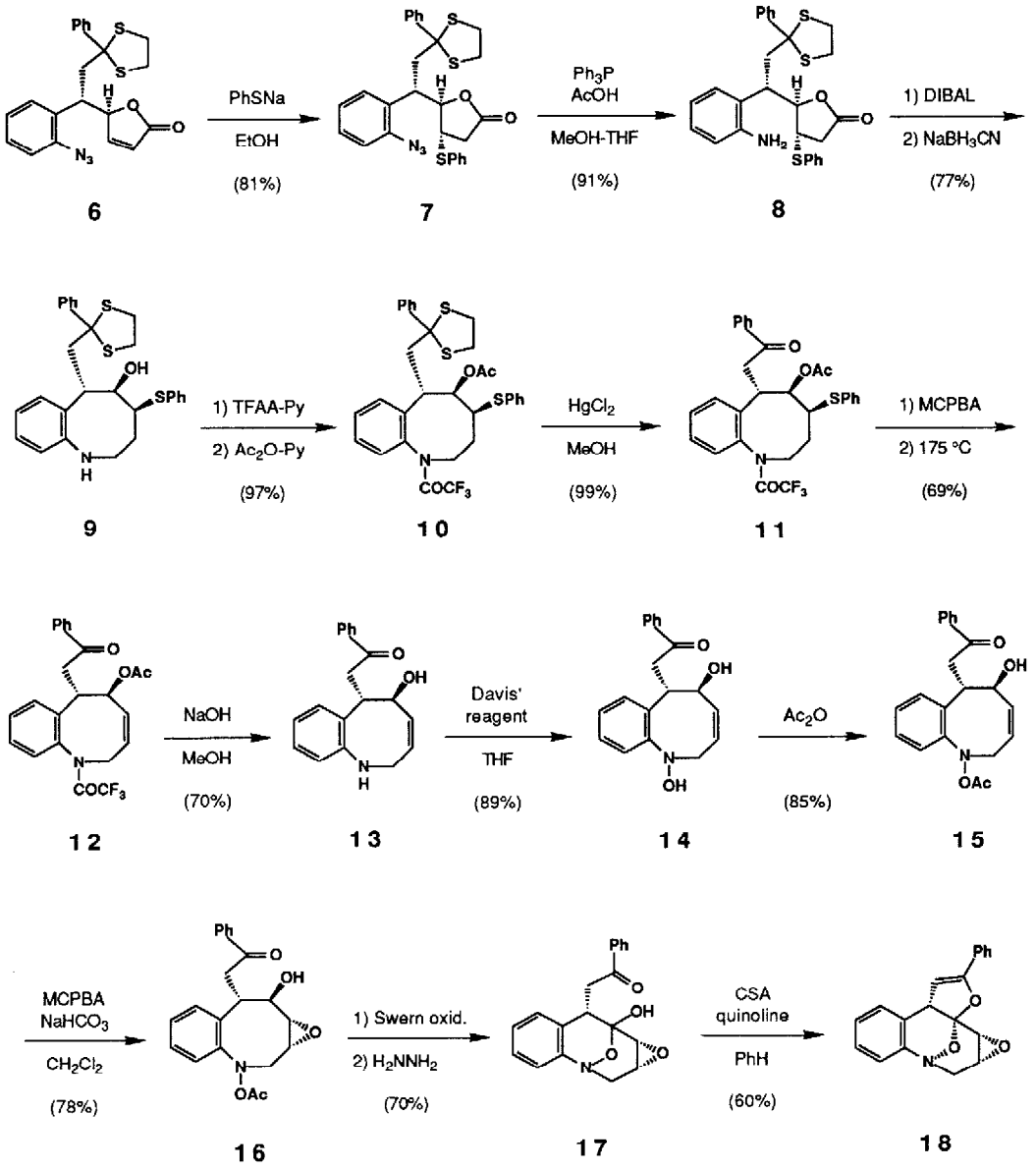
1 **3**

Addition of 2-trimethylsiloxyfuran to the readily available chalcone **4**[5] gave the desired adduct **5** as the sole product in a quantitative yield (0.1 equiv n-Bu_4NF, THF, -78 °C)[6] (Scheme II). After the labile silyl enol ether **5** was converted to the thioketal **6** ($HSCH_2CH_2SH$, BF_3-Et_2O, CH_2Cl_2, 85%), protection of the highly reactive butenolide was performed by adding thiophenol to give the sulfide **7** (PhSNa, EtOH, 81%). With the butenolide being protected, the azide **7** could be reduced cleanly to give the amine **8** in 91% yield (Ph_3P, AcOH, MeOH, THF, 23 °C).[7] Partial reduction of the lactone **8** followed by intramolecular reductive amination gave the 8-membered amine **9** in 77% yield ((1) DIBAL, CH_2Cl_2, -78 °C; (2) $NaBH_3CN$, TFA, MeOH, CH_2Cl_2). The amino and hydroxy groups of **9** were protected as trifluoroacetamide and acetate **10**, respectively, in 97% yield ((1) TFAA, Py, CH_2Cl_2; (2) Ac_2O, Py). Subsequent deprotection of the thioketal **10** furnished the ketone **11** in 99% yield ($HgCl_2$, MeOH, reflux). The sulfide **11** was then converted to the olefin **12** in 69% yield through thermolysis of the corresponding sulfoxide ((1) MCPBA, CH_2Cl_2; (2) toluene, 175 °C). Alkaline hydrolysis of **12** gave the aminoalcohol **13** in 70% yield (NaOH, H_2O, MeOH, reflux). After numerous attempts to oxidize the amine **13** to the corresponding hydroxylamine **14**, we found the Davis' reagent[8] to be quite satisfactory for this purpose (2-(phenylsulfonyl)-3-phenyloxaziridine, THF, 23 °C, 89%).[9] The unstable hydroxylamine **14** was immediately protected as the acetate **15** in 85% yield (Ac_2O, 23 °C). Facile oxidation of the allyl alcohol **15** with MCPBA in the presence of $NaHCO_3$ at 23 °C furnished the desired epoxide **16** as the sole product in 78% yield. Since epoxidation of the allyl acetate derived from **15** gave the epoxide with the same configuration as **16**, it is quite likely that MCPBA attacked the olefin from the sterically less hindered, α-face of the molecule.[10] Swern oxidation[11] of the alcohol **16** followed by hydrazinolysis gave a tautomeric mixture of the hemiketals **17** in 70% yield ((1) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N; (2) H_2NNH_2, MeOH, CH_2Cl_2, 0 °C). In order to manipulate the side chain, **17** was subjected to dehydrative cyclization to give the enol ether **18**[12] as the only isomer in 60% yield (CSA, quinoline, benzene, reflux). Although we do not have a firm evidence yet, we tentatively assigned a thermodynamically more favorable structure to **18**. Conversion of the epoxide to aziridine as well as manipulation of the side chain will be published in due course. Total synthesis of FR-900482 itself based on these model studies is currently under way in our laboratories.

Scheme II



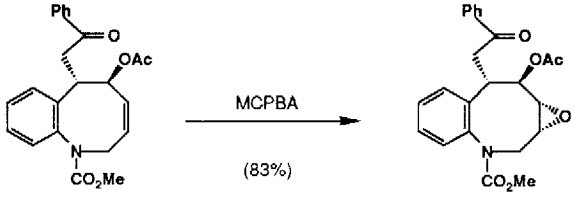
4 5



Acknowledgment: This work was supported in part by a grant from the National Institutes of Health. Financial assistance (to S.G.) from Fujisawa Pharmaceutical Co., Ltd., Japan is gratefully acknowledged. We thank Ms. Lianhong Xu for invaluable assistance.

References and Notes

1. On leave from Fujisawa Pharmaceutical Co., Ltd., Japan (1988-1989).
2. (a) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (b) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *ibid.* **1987**, *40*, 594. (c) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *ibid.* **1987**, *40*, 600. (d) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108.
3. Tomasz, M.; Lipman, R.; McGuinness, B. F.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 5892.
4. Masuda, K.; Nakamura, T.; Shimomura, K.; Shibata, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 1497.
5. Prepared from commercially available 2-aminobenzyl alcohol in 70% overall yield in a three-step sequence ((1) HNO_2; NaN_3. (2) PCC. (3) PhCOMe, NaOH).
6. (a) Fukuyama, T.; Yang, L.-H. *Tetrahedron Lett.* **1986**, *27*, 6299. (b) Fukuyama, T.; Yang, L.-H. *J. Am. Chem. Soc.* **1987**, *109*, 7881.
7. The reported procedure was slightly modified: Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.
8. Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240, and references cited therein.
9. An independent work was published while we were exploring the scope of this reaction: Zajac, W. W., Jr.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856.
10. Oxidation of the olefin **i** with MCPBA gave exclusively the epoxide **ii** whose structure was confirmed by an X-ray analysis.



i ii

11. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
12. ^1H NMR of **18** (300 MHz, $CDCl_3$): δ 3.46 (1H, d, J=4.5), 3.49-3.55 (2H, m), 4.23 (1H, d, J=15.4), 4.43 (1H, d, J=2.2), 5.72 (1H, d, J=2.2), 6.89 (1H, dd, J=1.3, 8.0), 7.15 (1H, dt, J=1.3, 7.5), 7.24 (1H, dt, J=1.3, 7.5), 7.32-7.39 (4H, m), 7.65 (2H, dd, J=1.7, 7.8).

(Received in USA 9 June 1989)