of **1** was determined as follows. Treatment of **3** with (+)- and (-)-MTPA chloride at room temperature furnished 7,7'-bis-MTPA esters (**7**, **8** respectively).[10] The ^1H NMR comparison[8] of **7** and **8** indicated the 7*S*, 7'*S* configurations in **3**. Furthermore, catalytic hydrogenation over Pd-C in alkaline solution of diacetonide methyl ester **10**, which was obtained by NaOMe-MeOH treatment followed by acetonidation of **1**, furnished a 2,3;4,5-tetrahydro derivative **11**. **11** was acetylated and then oxidized with osmium tetroxide to give a 10,11-diol, which was converted to 10,11-bis(*p*-bromobenzoate) **12**.[11] The CD spectrum of **12** showed a negative CD maximum ($\Delta\epsilon$ -41.5) at 253 nm, which was consistent with the result obtained above by the MTPA-NMR analysis of **3**. Consequently, the absolute stereostructure of swinholide A has been confirmed to be 7*S*, 7'*S*, 9*R*, 9'*R*, 13*S*, 13'*S*, 15*S*, 15'*S*, 16*S*, 16'*S*, 17*S*, 17'*S*, 19*R*, 19'*R*, 20*S*, 20'*S*, 21*S*, 21'*S*, 22*S*, 22'*S*, 23*S*, 23'*S*, 24*S*, 24'*S*, 27*S*, 27'*S*, 29*R*, 29'*R*, 31*S*, 31'*S* shown as **1**.

It should be noted that the configurations of each asymmetric carbon in swinholide A (**1**) are identical with those of scytophycin C (**2**). By electron microscopic analysis, we have recently found much symbiotic blue-green alga inhabiting our marine sponge *Theonella swinhoei*. We are currently engaged in the cultivation study of this symbiotic alga in order to find a genuine producer of **1**.

Acknowledgment. This work was supported in part by a grant from the Ministry of Education, Science, and Culture of Japan (Grant-in Aid for Cancer Research).

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles (10 pages). Ordering information is given on any current masthead page.

(10) (+)-MTPA ester **7**: FABMS *m/z* 1924 (M + Na)$^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (2 H, d, 3,3'-H), 5.84 (2 H, dd, 5,5'-H), 5.53 (2 H, d, 10,10'-H), 4.13 (2 H, br d, 9,9'-H). (-)-MTPA ester **8**: FABMS *m/z* 1924 (M + Na)$^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (2 H, d, 3,3'-H), 5.67 (2 H, dd, 5,5'-H), 5.61 (2 H, d, 10,10'-H), 4.26 (2 H, br d, 9,9'-H).

(11) FABMS *m/z* 1275 (M + Na)$^+$. ^1H NMR (500 MHz, CD_3OD) δ 5.56 (1 H, ddd, J = 9.8, 5.8, 2.4 Hz, 11-H), 5.39 (1 H, br d, J = 2.4 Hz, 10-H), 4.16 (1 H, br dd, J = 9.5, 4.8 Hz, 9-H).

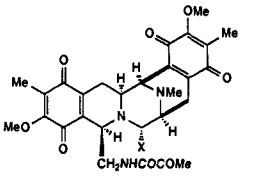
Total Synthesis of (±)-Saframycin A

Tohru Fukuyama,* Lihu Yang, Karen L. Ajeck, and Richard A. Sachleben

Department of Chemistry, Rice University Houston, Texas 77251

Received December 6, 1989

Saframycin A (**1**) was isolated as a satellite antibiotic from a culture broth of *Streptomyces lavendulae* No. 314.[1,2] Among a variety of saframycins isolated, saframycin A and its precursor saframycin S (**2**) have been shown to exhibit the strongest antitumor activities.[3] The hitherto unknown dimeric bisquinone structure of saframycins has stimulated curiosity of a number of synthetic chemists, and total synthesis of the simplest, biologically less active saframycin B (**3**) has been reported by two groups to date.[4] In this communication we report a straightforward total synthesis of (±)-**1** that takes advantage of the dimeric nature of the molecule.



Saframycin

1: A X = CN
2: S X = OH
3: B X = H

Condensation of the readily available, C_2-symmetrical *N,N'*-diacetylpiperazinedione (**4**) and the aldehyde **5**[4a] gave arylidenepiperazinedione **6** in 86% yield as the sole product (*t*-BuOK/*t*-BuOH, THF, 0 °C).[5] The non-C_2-symmetrical element thus introduced to the piperazinedione system plays the key role in our synthesis of biosynthetically dimeric,[6] yet structurally nonsymmetric saframycin A. Catalytic hydrogenation of olefin **6** furnished **7** with concomitant hydrogenolysis of the benzyl ether (H_2 (1000 psi), 10% Pd/C, EtOAc, 80 °C, 100%). After renewed protection of the phenol as *t*-butyldimethylsilyl ether, the piperazinedione ring was activated by introduction of a carbobenzyloxy group to give compound **8** ((1) TBSCl, Et_3N, CH_2Cl_2, reflux; (2) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2, -15 °C; 84%). Condensation of **8** with the aldehyde **5** proceeded smoothly to give exclusively arylidenepiperazinedione **9** in 88% yield (*t*-BuOK/*t*-BuOH (1 equiv), THF, -78 °C, then DBU, 0 °C). Selective reduction of the activated ring carbonyl group, facile acylimminium ion mediated cyclization, and subsequent deprotection of the phenolic silyl group afforded the desired bicyclic compound **10** in 75% overall yield ((1) $NaBH_4$, AcOH, EtOH, -25 °C; (2) HCOOH, 23 °C; (3) *n*-Bu_4NF, THF, 23 °C).[4a] Catalytic hydrogenation of the exocyclic double bond of the bicyclo[3.3.1] system **10** occurred from the less hindered exo side to give diphenol amine **11** in 99% yield (H_2 (1500 psi), Raney Ni-W2, EtOH, 120 °C). Reductive methylation of **11** gave **12** which was our key intermediate for saframycin B synthesis (37% HCHO, $NaBH_3CN$, TFA, MeOH, 23 °C, 85%).[7] Cleavage of the hindered lactam **12** was facilitated by employing the protocol developed by Grieco[8] to give the alcohol **13** ((1) *t*-Boc_2O, DMAP, DMF, 60 °C, 81%; (2) $NaBH_4$, EtOH, 0 °C, 92%). Deprotection of the *t*-Boc groups followed by the Pictet-Spengler cyclization with *t*-$BocNHCH_2CHO$ gave the desired β-isomer **14** in 82% yield with a trace amount of its α-isomer ((1) TFA, 23 °C; (2) *t*-$BocNHCH_2CHO$, MeOH, 60 °C).[9] Careful oxidation[10] of alcohol **14** and subsequent treatment of the resultant unstable aminal with NaCN furnished amino nitrile **15** in 67% yield ((1) $(COCl)_2$ (2.2 equiv), DMSO (4.4 equiv), CH_2Cl_2, -78 °C; Et_3N (8 equiv) warmed to 23 °C; (2) NaCN, MeOH, 23 °C). Pyruvamide **16** was easily obtained from **15** in 86% yield ((1) TFA, 23 °C; (2) MeCOCOCl, $NaHCO_3$, CH_2Cl_2, 23 °C). Finally, phenols **15** were carefully oxidized with DDQ to give (±)-saframycin A (**1**) in 60% yield (DDQ (3 equiv), acetone-H_2O (10:1), 0 °C). The

(1) (a) Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015. (b) Arai, T.; Takahashi, K.; Nakahara, S.; Kubo, A. *Experientia* **1980**, *36*, 1025.

(2) For a review of saframycins and related alkaloids, see: (a) Arai, T.; Kubo, A. *The Alkaloids Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, Chapter 3. (b) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1988; Vol. 2, Chapter 3.

(3) Arai, T.; Takahashi, K.; Ishiguro, K.; Mikami, Y. *Gann (Tokyo)* **1980**, *71*, 790.

(4) (a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (b) Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295. For recent synthetic approaches to **1**, see: Saito, N.; Yamauchi, R.; Nishioka, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391.

(5) Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667.

(6) Mikami, Y.; Takahashi, K.; Yazawa, K.; Arai, T.; Namikoshi, M.; Iwasaki, S.; Okuda, S. *J. Biol. Chem.* **1985**, *260*, 344.

(7) The present route is much more suited for a larger scale (40 g of **9**) preparation than our previous one.[4a]

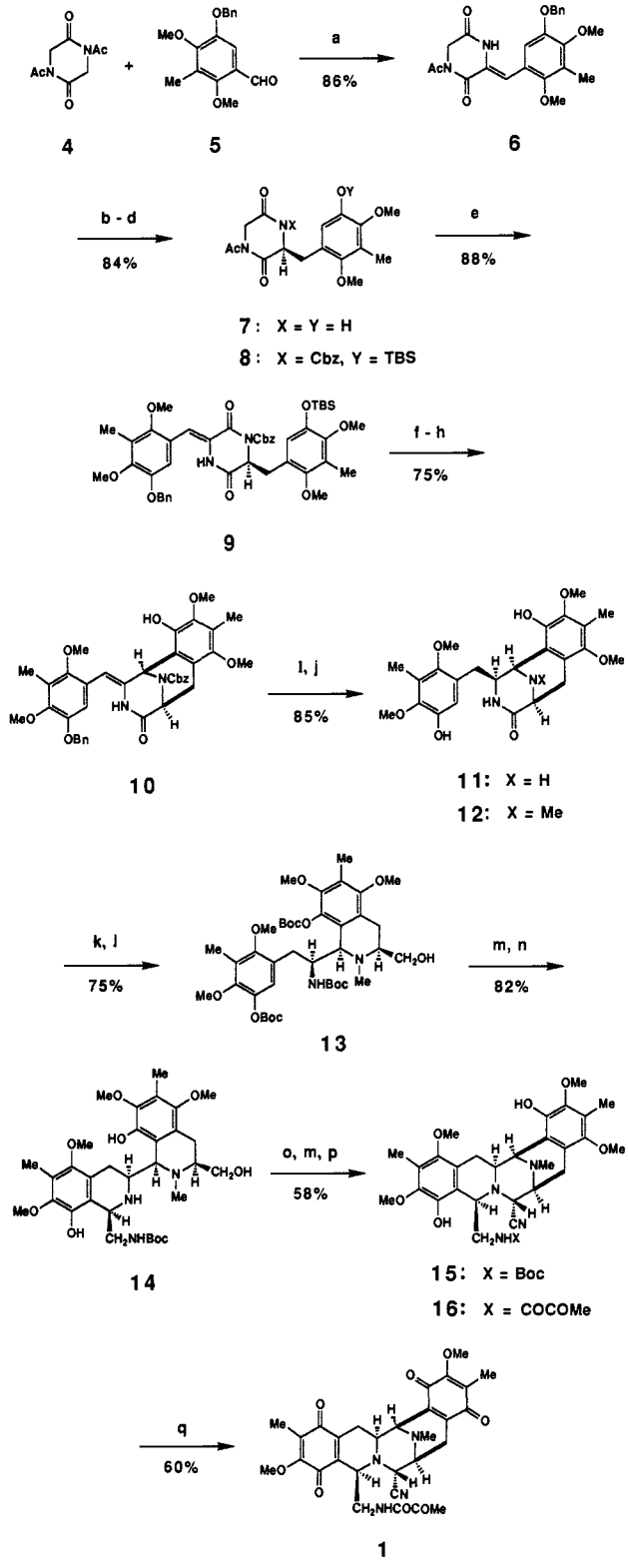
(8) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(9) The undesired β-isomer was the predominant product when the Pictet-Spengler cyclization was carried out under acidic conditions.

(10) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

0002-7863/90/1512-3712$02.50/0

Scheme I[a]



[a] The reagents and reaction conditions were the following: (a) *t*-BuOK/*t*-BuOH, THF, 0 °C. (b) H_2 (1000 psi), 10% Pd/C, EtOAc, 80 °C. (c) TBSCl, Et_3N, CH_2Cl_2, reflux. (d) $PhCH_2OCOCl$, Et_3N, DMAP, CH_2Cl_2, −15 °C. (e) **5**, *t*-BuOK/*t*-BuOH (1 equiv), THF, −78 °C, then DBU, 0 °C. (f) $NaBH_4$, AcOH, EtOH, −25 °C. (g) HCOOH, 23 °C. (h) *n*-Bu_4NF, THF, 23 °C. (i) H_2 (1500 psi), Raney Ni-W2, EtOH, 120 °C. (j) 37% HCHO, $NaBH_3CN$, TFA, MeOH, 23 °C. (k) *t*-Boc_2O, DMAP, DMF, 60 °C. (l) $NaBH_4$, EtOH, 0 °C. (m) TFA, 23 °C. (n) *t*-$BocNHCH_2CHO$, MeOH, 60 °C. (o) $(COCl)_2$ (2.2 equiv), DMSO (4.4 equiv), CH_2Cl_2, −78 °C; Et_3N (8 equiv) warmed to 23 °C then NaCN, MeOH, 23 °C. (p) MeCOCOCl, $NaHCO_3$, CH_2Cl_2, 23 °C. (q) DDQ (3 equiv), acetone–H_2O (10:1), 0 °C.

synthetic saframycin A was identical with an authentic sample in both TLC and spectroscopic properties.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA28119). We thank Prof. T. Arai of Chiba University for providing a sample of natural saframycin A.

Supplementary Material Available: NMR spectra and a listing of high-resolution mass spectroscopic data of key intermediates (13 pages). Ordering information is given on any current masthead page.

Amphiphilic Carbene Complexes: Both Electrophiles and Nucleophiles Attack the Carbene Carbon of $C_5H_5(CO)_2Re{=}CHR$

Charles P. Casey,* Paul C. Vosejpka, and Fredric R. Askham

Department of Chemistry, University of Wisconsin Madison, Wisconsin 53706

Received November 21, 1989

Metal carbene complexes have been discussed in terms of a dichotomy between electrophilic "Fischer carbene complexes" and nucleophilic "Schrock carbene complexes".[1,2] Metal–carbon double bonds of Fischer carbene complexes such as $(CO)_5W{=}C(OCH_3)C_6H_5$[3] typically have an electron-rich late transition metal in a low oxidation state bonded to an electron-poor carbene carbon (often but not necessarily stabilized by an electron-donor heteroatom). Many of the reactions of Fischer carbene complexes such as replacement of a methoxy group by an amine group are initiated by attack of a nucleophile at the carbene carbon.[4] In contrast, metal–carbon double bonds in Schrock carbene complexes such as $Cp_2ClTa{=}CHR$[5] typically have an electron-poor early transition metal in a high oxidation state bonded to an electron-rich carbene carbon. The reactions of Schrock carbene complexes with substrates such as ketones are initiated by nucleophilic attack of the carbene carbon on the carbonyl carbon of the ketone.[6] We and others[7] have considered it possible to synthesize metal carbene complexes of intermediate reactivity. To our knowledge, the only metal carbene complex that has been shown to have amphiphilic reactivity at the carbene carbon is Roper's $(CO)_2(Ph_3P)_2Ru{=}CF_2$,

(1) (a) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1. (b) Schrock, R. R. *Acc. Chem. Res.* **1979**, *12*, 98. (c) Schrock, R. R. *Science* **1983**, *219*, 13. (d) Gallop, M. A.; Roper, W. R. *Adv. Organomet. Chem.* **1986**, *25*, 121. (e) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (f) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (g) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (h) Dötz, K. H.; Popall, M.; Müller, G. *J. Organomet. Chem.* **1987**, *334*, 57. (i) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1988; Vol. 1.

(2) To emphasize the distinctive character of his complexes (and to conform to IUPAC nomenclature), Schrock refers to his compounds as metal alkylidene complexes.

(3) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 380.

(4) Werner, H.; Fischer, E. O.; Heckl, B.; Kreiter, C. G. *J. Organomet. Chem.* **1971**, *28*, 367.

(5) Schrock R. R.; Messerle, L. W.; Wood, C. D.; Guggenberger, L. J. *J. Am. Chem. Soc.* **1978**, *100*, 3792.

(6) (a) Schrock, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 5399. (b) Hartner, F. W.; Schwartz, J.; Clift, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 640. (c) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (d) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733. (e) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316.

(7) (a) Fenske, R. F. In *Organometallic Compounds: Synthesis, Structure, and Theory*; Shapiro, B. L., Ed.; Texas A & M University Press: College Station, TX, 1983; p 305. (b) Hofmann, P. In *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983; p 113.

0002-7863/90/1512-3713$02.50/0