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).<sup>10</sup> The <sup>1</sup>H NMR comparison<sup>8</sup> of 7 and 8 indicated the 7S, 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 10,11bis(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 7S, 7'S, 9R, 9'R, 13S, 13'S, 15S, 15'S, 16S, 16'S, 17S, 17'S, 19R, 19'R, 20S, 20'S, 21S, 21'S, 22S, 22'S, 23S, 23'S, 24S, 24'S, 27S, 27'S, 29R, 29'R, 31S, 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.

## Total Synthesis of $(\pm)$ -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.<sup>3</sup> 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.<sup>4</sup> In this communication we report a straightforward total synthesis of  $(\pm)$ -1 that takes advantage of the dimeric nature of the molecule.



Condensation of the readily available,  $C_2$ -symmetrical N,N'diacetylpiperazinedione (4) and the aldehyde 5<sup>4a</sup> gave arylidenepiperazinedione 6 in 86% yield as the sole product (t-BuOK/t-BuOH, THF, 0 °C).<sup>5</sup> The non- $C_2$ -symmetrical element thus introduced to the piperazinedione system plays the key role in our synthesis of biosynthetically dimeric,<sup>6</sup> yet structurally nonsymmetric saframycin A. Catalytic hydrogenation of olefin 6 furnished 7 with concomitant hydrogenolysis of the benzyl ether (H<sub>2</sub> (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<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux; (2) PhCH2OCOCI, Et3N, DMAP, CH2Cl2, -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 silvl group afforded the desired bicyclic compound 10 in 75% overall yield ((1) NaBH<sub>4</sub>, AcOH, EtOH, -25 °C; (2) HCOOH, 23 °C; (3) n-Bu<sub>4</sub>NF, THF, 23 °C).<sup>4a</sup> 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<sub>2</sub> (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<sub>3</sub>CN, TFA, MeOH, 23 °C, 85%).<sup>7</sup> Cleavage of the hindered lactam 12 was facilitated by employing the protocol developed by Grieco<sup>8</sup> to give the alcohol 13 ((1) t-Boc<sub>2</sub>O, DMAP, DMF, 60 °C, 81%; (2) NaBH<sub>4</sub>, EtOH, 0 °C, 92%). Deprotection of the t-Boc groups followed by the Pictet-Spengler cyclization with t-BocNHCH<sub>2</sub>CHO gave the desired  $\beta$ -isomer 14 in 82% yield with a trace amount of its  $\alpha$ -isomer ((1) TFA, 23 °C; (2) t-BocNHCH<sub>2</sub>CHO, MeOH, 60 °C).<sup>9</sup> Careful oxidation<sup>10</sup> of alcohol 14 and subsequent treatment of the resultant unstable aminal with NaCN furnished amino nitrile 15 in 67% yield ((1) (COCl)<sub>2</sub> (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<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 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

tet-Spengler cyclization was carried out under acidic conditions.

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

<sup>(10) (+)-</sup>MTPA ester 7: FABMS m/z 1924 (M + Na)<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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)<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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)<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  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).

<sup>(1) (</sup>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.

<sup>(2)</sup> 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

<sup>(3)</sup> Arai, T.; Takahashi, K.; Ishiguro, K.; Mikami, Y. Gann (Tokyo) 1980, 71. 790.

<sup>(4) (</sup>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, 54, 560. 5391

<sup>(5)</sup> 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.

<sup>(7)</sup> The present route is much more suited for a larger scale (40 g of 9) preparation than our previous one.<sup>44</sup> (8) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. J. Org. Chem. 1983, 48, 2424. (9) The undesired  $\beta$ -isomer was the predominant product when the Pic-

Scheme I<sup>a</sup>







9



12: X = Me

88%





16: X = COCOMe



<sup>a</sup>The reagents and reaction conditions were the following: (a) *t*-BuOK/*t*-BuOH, THF, 0 °C. (b) H<sub>2</sub> (1000 psi), 10% Pd/C, EtOAc, 80 °C. (c) TBSCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux. (d) PhCH<sub>2</sub>OCOCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, -15 °C. (e) **5**, *t*-BuOK/*t*-BuOH (1 equiv), THF, -78 °C, then DBU, 0 °C. (f) NaBH<sub>4</sub>, AcOH, EtOH, -25 °C. (g) HCOOH, 23 °C. (h) *n*-Bu<sub>4</sub>NF, THF, 23 °C. (i) H<sub>2</sub> (1500 psi), Raney Ni-W2, EtOH, 120 °C. (j) 37% HCHO, NaBH<sub>3</sub>CN, TFA, MeOH, 23 °C. (k) *t*-Boc<sub>2</sub>O, DMAP, DMF, 60 °C. (l) NaBH<sub>4</sub>, EtOH, 0 °C. (o) (COCl)<sub>2</sub> (2.2 equiv), DMSO (4.4 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; Et<sub>3</sub>N (8 equiv) warmed to 23 °C then NaCN, MeOH, 23 °C. (p) MeCOCOCl, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C. (q) DDQ (3 equiv), ace-tone-H<sub>2</sub>O (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".<sup>1,2</sup> Metal-carbon double bonds of Fischer carbene complexes such as (CO)<sub>5</sub>W=  $C(OCH_3)C_6H_5^3$  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 carbon.<sup>4</sup> In contrast, metal-carbon double bonds in Schrock carbene complexes such as Cp<sub>2</sub>ClTa=CHR<sup>5</sup> 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 carbon carbon on the carbonyl carbon of the ketone.<sup>6</sup> We and others7 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 carbon is Roper's (CO)<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub>Ru=CF<sub>2</sub>,

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

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 © 1990 American Chemical Society

 <sup>(</sup>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.

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

 <sup>(3)</sup> 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.