$(CO)_8(\mu\text{-}(\mu^2\text{-}C{\equiv}CPh))$, as the major product.[13]

A very interesting and novel photochemical reaction pathway for III is seen in the photochemical reaction of $Re_2(CO)_{10}$ with ethylene. Although the major product of this photolysis is IIIe, we observe the formation of IIIb and IIIf[14] in 10–15% yield each. These 1-butenyl compounds are isomers that differ only in the mode of coordination of the 1-butenyl ligand. They apparently result from subsequent photochemical reaction of IIIe. Photolysis of a solution of IIIe under 1 atm of C_2H_4 produces approximately equal amounts of IIIb and IIIf. This reaction, which represents a dimerization of ethylene, is not observed in the thermal reactions of III with C_2H_4. The initial reaction process is probably photodissociation of CO from III, inasmuch as photolysis of IIIb in the presence of 1 equiv of pyridine yields a substituted compound, $(\mu\text{-H})Re_2(CO)_7(\mu\text{-}(\eta^2\text{-}CH{=}CHC_2H_5))py$,[15] as the major product. Photodissociation of CO from IIIe would create a vacant site for coordination of an ethylene molecule, which could then undergo an insertion into the Re–H or Re–CH:CH_2 bond, followed by rearrangement to yield the butenyl products. It is noteworthy that IIIf is not produced to any appreciable extent (<1%) in the photolysis of $Re_2(CO)_{10}$ under a 1-butene atmosphere. Studies of the photochemical reactions of other derivatives of III with ethylene and other small molecules are in progress.

Acknowledgment. This research was sponsored by the National Science Foundation through Research Grant NSF CHE 81-19525. The authors are grateful to Kenneth S. Suslick for a helpful discussion.

Registry No. IIIa, 82638-69-5; IIIb, 82621-39-4; IIIc, 82621-40-7; IIId, 82621-41-8; IIIe, 82621-42-9; IIIf, 82621-43-0; $(\mu\text{-H})Re_2(CO)_8(\pm\text{-}(\eta^2\text{-CPh}))$, 82621-44-1; $Re_2(CO)_{10}$, 14285-68-8; *dieg*-1,2-$Re_2(CO)_8(py)_2$, 67605-95-2; Re, 7440-15-5; propylene, 115-07-1; 1-butene, 106-98-9; 1-hexene, 592-41-6; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; phenyl acetylene, 536-74-3; ethylene, 74-85-1.

(13) $(\mu\text{-H})Re_2(CO)_8(\mu\text{-}(\eta^2\text{-C}{\equiv}CPh))$: IR 2119 (vw), 2094 (w), 2023 (s), 2002 (m), 1982 (ms) cm^{-1} (heptane solution); ^1H NMR (360 MHz, CD_2Cl_2) δ −13.01 (s, 1 H, μ-H), 7.57 (m, 2 H, α-H), 7.44 (m, 3 H, β- and γ-H); *m/e* (M^+) 698 (70 eV EIMS, Re_2 372).

(14) IIIf: ^1H NMR (90 MHz, $CDCl_3$) β −14.42 (s, 1 H, μ-H), 5.76 (d, 1 H, H_1 or H_3), 4.06 (d, 1 H, H_1 or H_3), 2.88 (q, 2 H, CH_2), 1.31 (t, 3 H, CH_3), $^3J_{H_1\text{-}H_3}$ = 2.2 Hz, $^3J_{CH_2\text{-}CH_3}$ = 7.4 Hz.

(15) Two isomers of this product are obtained.

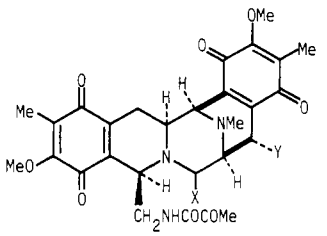
Stereocontrolled Total Synthesis of (±)-Saframycin B

Tohru Fukuyama* and Richard A. Sachleben

Department of Chemistry, Rice University
Houston, Texas 77251

Received May 7, 1982

Saframycin B (**2**) was isolated as a satellite antibiotic from



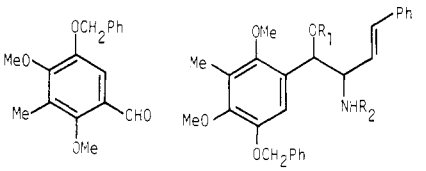
1 X = CN, Y = H

2 X = Y = H

3 X = H, Y = OMe

cultures of *Streptomyces lavendulae*, which is known to produce streptothricins.[1] Saframycin B and its congeners A (**1**), C(**3**), D, and E have been shown to be active against Gram-positive bacteria. Saframycins also exhibit antitumor activities, with saframycin A being particularly active.[1,2] The structure of saframycin B was elucidated by comparison of spectroscopic data with saframycin C, whose structure had been determined by X-ray crystallographic analysis.[3] Saframycin B represents a hitherto unknown class of compounds with bisquinone attached to a piperazine ring.[4] In this communication we report the first total synthesis of (±)-saframycin B.

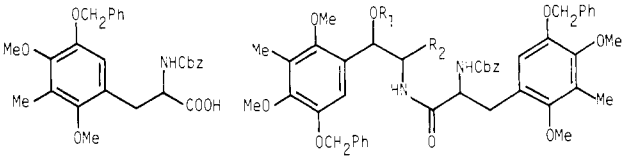
The highly substituted benzaldehyde **4** was prepared from



4

5 R_1 = COPh, R_2 = CHO

6 R_1 = R_2 = H

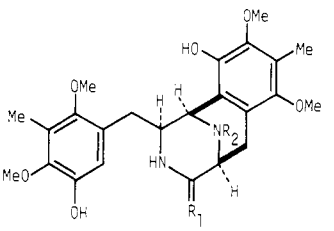


7

8 R_1 = H, R_2 = CH=CHPh

9 R_1 = COMe, R_2 = CH=CHPh

10 R_1 = COMe, R_2 = CHO



16 R_1 = O, R_2 = H

17 R_1 = O, R_2 = Me

18 R_1 = H_2, R_2 = Me

readily available 2,4-dimethoxy-3-methylbenzaldehyde[5] in seven steps [(1) 37% HCHO–H_2O, HCl, reflux; (2) NaOAc, AcOH, reflux; (3) *m*-CPBA, $CHCl_3$, reflux;[5] (4) Et_3N, MeOH, room temperature; (5) $PhCH_2Br$, K_2CO_3, DMF, 80 °C; (6) 3 N NaOH, MeOH, room temperature; (7) PCC, CH_2Cl_2, room temperature] in 76% overall yield. Addition of the carbanion of cinnamyl isocyanide, generated by 1.1 equiv of *n*-butyllithium at −78 °C, to the aldehyde **4** followed by esterification (PhCOCl, THF, −78 °C to room temperature) and hydration of the isocyanide (3 N HCl, THF, room temperature) gave a diastereomeric mixture (1:1) of the formamide **5** in 92% overall yield.[6] Upon basic hydrolysis

(1) Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015.

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

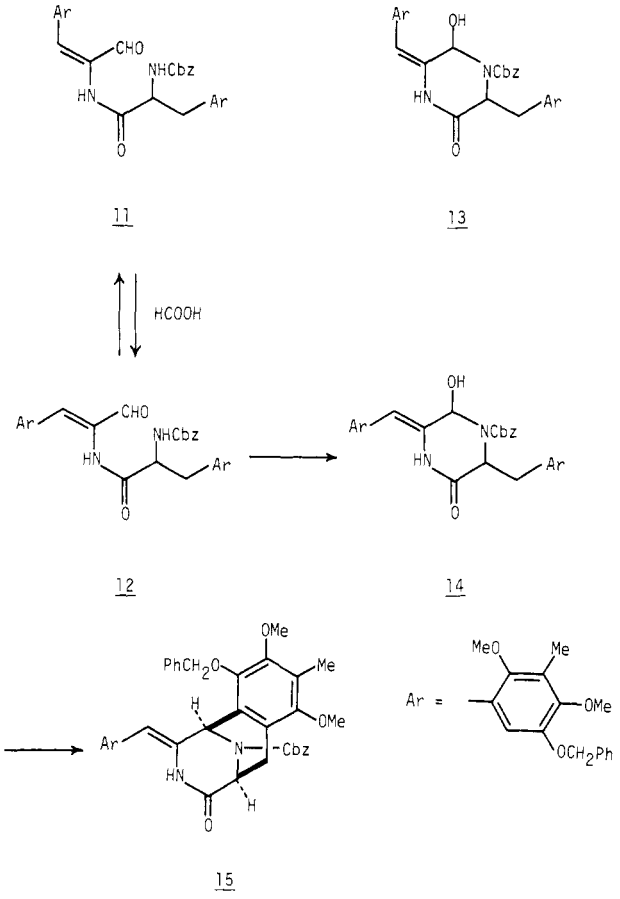
(3) Arai, T.; Takahashi, K.; Kubo, A.; Nakahara, S.; Sato, S.; Aiba, K.; Tamura, C. *Tetrahedron Lett.* **1979**, 2355.

(4) Renieramycins, structurally similar to saframycins, have been recently isolated from a marine sponge: Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265.

(5) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

0002-7863/82/1504-4957$01.25/0

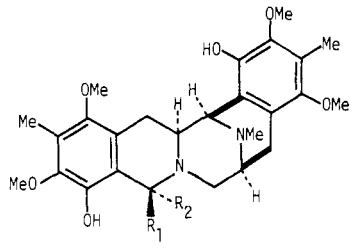
Scheme I



(3 N NaOH, MeOH, room temperature) **5** yielded the amino alcohol **6** (83%). The *N*-carbobenzoxy amino acid **7** was prepared from the aldehyde **4** in six steps [(1) $CNCH_2CO_2Et$, KH, THF, 0 °C;[6] (2) H_2, Raney Ni–W2, EtOH, 80 °C, 1200 psi; (3) $PhCH_2Br$, K_2CO_3, DMF, 80 °C; (4) HCl, EtOH, 60 °C; (5) $PhCH_2OCOCl$, $PhNMe_2$, CH_2Cl_2, room temperature; (6) 3 N NaOH, MeOH, room temperature, acidic workup] in 84% overall yield.

Condensation of the amine **6** and the acid **7** was carried out by means of DCC (CH_2Cl_2, room temperature) to give the amide **8** (83%), which was then converted to the acetate **9** (Ac_2O, Py, 60 °C, 98%). The crucial double cyclization to form a benzobicyclo[3.3.1] system was performed in a three-step sequence. Careful ozonolysis of **9** (50% MeOH–CH_2Cl_2, −78 °C) followed by treatment with dimethyl sulfide produced a diastereomeric mixture of the unstable aldehydes **10**. Upon treatment with 1.5 equiv of DBU (CH_2Cl_2, 0 °C) **10** yielded a mixture of cis- and trans-α,β-unsaturated aldehydes, **11** and **12** (1:1). When heated in formic acid (60 °C, 20 min), the mixture, **11** and **12**, was exclusively converted to the desired bicyclic compound **15**[7] in 74% overall yield from **9**.[8,9] This highly selective cyclization can be explained in terms of the rapid isomerization of **11** to **12** through protonation–deprotonation of the enamide and the unfavorable cyclization of **11** to **13** presumably due to steric compression of the bulky aromatic ring[10] (Scheme I).

Catalytic hydrogenation of **15** (H_2, Raney Ni-W2, EtOH, 100 °C, 1000 psi) occurred from the less hindered side to give **16** as the sole product which, upon reductive alkylation (H_2, 37% HCHO–H_2O, Raney Ni-W2, EtOH, room temperature, 1000 psi), yielded the *N*-methylamine **17** (75% from **15**). Reduction of the lactam **17** to the amine **18** (AlH_3, THF, room temperature) followed by phenolic cyclization[11] ($CbzNHCH_2CHO$, CH_3CN, 70 °C, 45 min) gave the desired cyclized compound **19** and the



19 $R_1 = CH_2NHCbz$, $R_2 = H$

20 $R_1 = H$, $R_2 = CH_2NHCbz$

21 $R_1 = CH_2NHCOCOMe$, $R_2 = H$

epimer **20**, 6:1, respectively,[12] in 75% yield. Deprotection of the carbobenzoxy group of **19** (H_2, 10% Pd–C, AcOH, room temperature, 1 atm) and subsequent acylation with pyruvyl chloride ($PhNMe_2$, CH_2Cl_2, room temperature) provided the pyruvamide **21** in 72% yield. Finally, oxidation of the phenol **21** using ceric ammonium nitrate[13] (THF–H_2O (3:1), 0 °C) gave (±)-saframycin B (**2**) in 37% yield. The synthetic saframycin B (mp 175–180 °C dec) was identical with natural saframycin B in TLC behavior and spectral (^1H NMR, ^{13}C NMR, MS, and UV) properties.

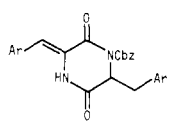
Acknowledgment. This work was supported by Grant CA-28119, awarded by the National Cancer Institute (USPHS). We thank Professor T. Arai for a sample of natural saframycin B.

Registry No. 2, 82660-65-9; **4**, 82622-02-4; (R*,R*)-**5**, 82622-03-5; (R*,S*)-**5**, 82622-04-6; R*,R*)-**6**, 82622-05-7; R*,S*)-**6**, 82622-06-8; **7**, 82622-07-9; **8**, 82638-77-5; **9**, 82638-78-6; **10**, 82622-08-0; **11**, 82622-09-1; **12**, 82622-11-5; **16**, 82622-12-6; **17**, 82622-13-7; **18**, 82622-14-8; **19**, 82638-79-7; **20**, 82660-66-0; **21**, 82638-80-0; 2,4-dimethoxy-3-methylbenzaldehyde, 7149-92-0; cinnamyl isocyanide, 74530-92-0; pyruvyl chloride, 5704-66-5.

Supplementary Material Available: Listing of spectral data for key intermediates in this work (1 page). Ordering information is given on any current masthead page.

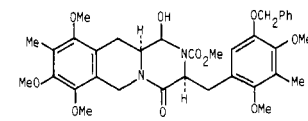
(6) For a review of chemistry of α-metalated isocyanides, see: (a) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339. (b) Hoppe, D. A. *Ibid.* **1974**, *13*, 789.

(7) Stereochemical assignments are based on the independent synthesis of **15** from i, prepared by the method of Gallina and Liberatori, in a two-step sequence [(1) $LiAl(O\text{-}t\text{-}Bu)_3H$, THF, room temperature; (2) HCOOH, 60 °C]: Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667.



i

(8) Atempted cyclization of ii under the same conditions was unsuccessful. On the other hand, the corresponding trans compound cyclized immediately.



ii

(9) Similar type of reactions has been used for construction of the basic skeleton of pavinan alkaloids: Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601 and references cited therein.

(10) Purification of **12** by silica gel TLC caused partial cyclization to form **14**, whereas **11** was isolated without being contaminated by **13**.

(11) Kametani, T. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. III, pp 47–49.

(12) The ratio varied from 11:1 (CH_3CN, room temperature, 3 days) to 4:3 (*t*-AmOH, 100 °C, 30 min).

(13) (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745. (b) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *Ibid.* **1976**, *41*, 3627.