SYNTHESIS OF SAFRAMYCINS. IV. SELENIUM OXIDE OXIDATION OF 4-OXO-HEXAHYDRO-1,5-IMINO-3-BENZAZOCIN-7,10-DIONE; PROMISING METHOD TO CONSTRUCT SAFRAMYCINS C AND D FROM SAFRAMYCIN B [1)]

Naoki SAITO, Yoko ŌHIRA, and Akinori KUBO*
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

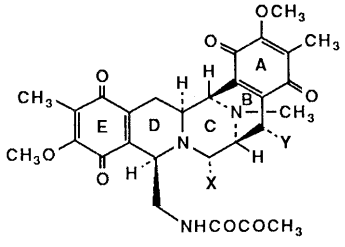
9-Methoxy-3,8,11-trimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocin-7,10-dione (**13**) is oxidized to the corresponding 6-hydroxy compound (**14**) with selenium oxide. This is a good way to make saframycins C (**3**) and D (**4**) from saframycin B (**2**).

KEYWORDS saframycin; preparation; hydroxylation; selenium oxide oxidation; stereoselective synthesis; redox reaction

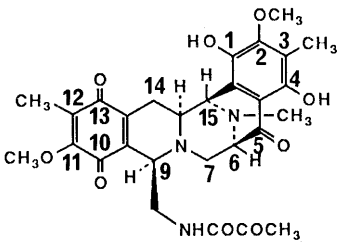
Recently we totally synthesized (±)-saframycin B (**2**),[2)] one of the antitumor antibiotics saframycins A-D (**1-4**)[3)] and renieramycins A-F (**5-10**)[4)] (Chart 1). Here we report the synthesis of saframycins C (**3**) and D (**4**), involving the first successful construction of the unique ABC ring systems of **3** and **4** from the *p*-quinone (**13**) by stereoselectively introducting the hydroxy function at the C-6 position[5)] using selenium oxide.

The partial demethylation of the readily available tricyclic lactam (**11**) [6)] with boron tribromide in dichloromethane at -78°C for 1 h gave the phenol (**12**,[7)] mp 199-201°C) (73% yield). Oxidation of **12** with 10N HNO_3 gave the *p*-quinone (**13**,[7)] mp 150-152°C) (87% yield). The hydroxy function was introduced at the C-6 position by selenium oxide oxidation. Treating **13** with selenium oxide (3 eq) in dioxane under reflux for 4 h afforded the alcohol (**14**,[7)] mp 175.5-178°C) (80% yield).[8)] Oxidation of the phenol (**12**) with selenium oxide in dioxane under reflux for 5 h afforded **14** in 71% yield.[9)] The ^{1}H NMR spectrum of **14** displayed H-6 as a doublet at δ 4.797 (J = 1 Hz), whereas the ^{1}H NMR spectrum of **21** (vide infra) showed the H-6 as a doublet at δ 5.102 (J = 6.8 Hz).[10)] Acetylation of **14** with acetic anhydride in acetic acid at 100°C for 2 h afforded **15** [7)](mp 182-184°C) (91% yield), whose ^{1}H NMR spectrum indicated a low-field shift of the signal of the H-6 proton (δ 5.960, J = 1.7 Hz). Treating **13** with selenium oxide in methanol under reflux for 30 h gave **16**[7)] (mp 158-159°C) (61% yield), ^{1}H NMR ($CDCl_3$): δ 1.985 (3H, s, quinone-CH_3), 2.642 (3H, s, amine-CH_3), 2.949 (1H, d, J = 13.2 Hz, 2-Hα), 3.580 (1H, dd, J = 1.5, 0.5 Hz, 5-H), 3.599 (3H, s, OCH_3), 3.960 (1H, dd, J = 13.2, 5.4 Hz, 2-Hβ), 3.980 (3H, s, OCH_3), 4.046 (1H, dd, J = 5.4, 0.5 Hz, 1-H), 4.261 (1H, d, J = 1.5 Hz, 6-H). Introduction of a hydroxy function (or methoxyl group) at the C-6 position occurred cleanly from the less hindered α-face. This is a promising method to make saframycin C and renieramycin A from saframycin B (Chart 2).

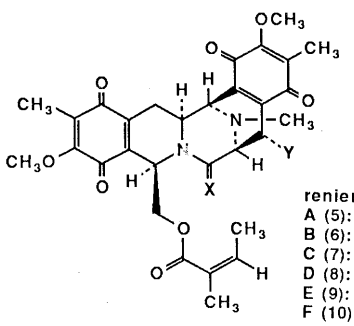
Then we studied the conversion of **14** into the hydroquinone (**18**) (Chart 3). Initial attempts to oxidize **14** by conventional methods using $Cu(OAc)_2$, PCC, PDC, and other oxidants failed. Only the starting material was recovered. However, treatment of **14** with selenium oxide in *p*-xylene under reflux for 3 h afforded the unstable ketone (**17**,[7)] mp 230-235°C (dec.)) (7.3% yield), IR (KBr): 1725, 1660, 1645 cm^{-1}, and **18**[7)] (mp 232.5-234°C) (29.6% yield), IR (KBr): 3300-2500, 1670, 1625 cm^{-1}; UV λmax (log ε) nm: 241 (3.93), 283 (3.95), 374 (3.71); EI-MS (m/z): 306 (M^+); ^{1}H NMR



saframycins
A (1): X = CN, Y = H
B (2): X = Y = H
C (3): X = H, Y = OCH_3



saframycin D (4)



renieramycins
A (5): X = H_2, Y = OH
B (6): X = H_2, Y = OC_2H_5
C (7): X = O, Y = OH
D (8): X = O, Y = OC_2H_5
E (9): X = H, OH, Y = H
F (10): X = H, OH, Y = OCH_3

Chart 1

(400 MHz, $CDCl_3$): 2.198 (3H, s, Ar CH_3), 2.550 (3H, s, amine-CH_3), 2.915 (3H, s, amide-CH_3), 3.299 (1H, dd, J = 12.2, 1.2 Hz, 2-Hα), 3.886 (3H, s, OCH_3), 3.924 (1H, dd, J = 1.2, 0.5 Hz, 5-H), 4.043 (1H, dd, J = 12.2, 5.2 Hz, 2-Hβ), 4.386 (1H, ddd, J = 5.2, 1.2, 1.2 Hz, 1-H), 5.580 (1H, br s, OH), 11.521 (1H, br s, OH). The intramolecular redox reaction of **14** produced **18**.[11] Hydrogenation of **17** with 10% Pd/C in ethyl acetate gave **18** in 98% yield. Its spectra were identical with those of an authentic sample described above. Thus we efficiently synthesized the hydroquinone (**18**), embodying all of the skeletal features of the "right half" of saframycin D (**4**).

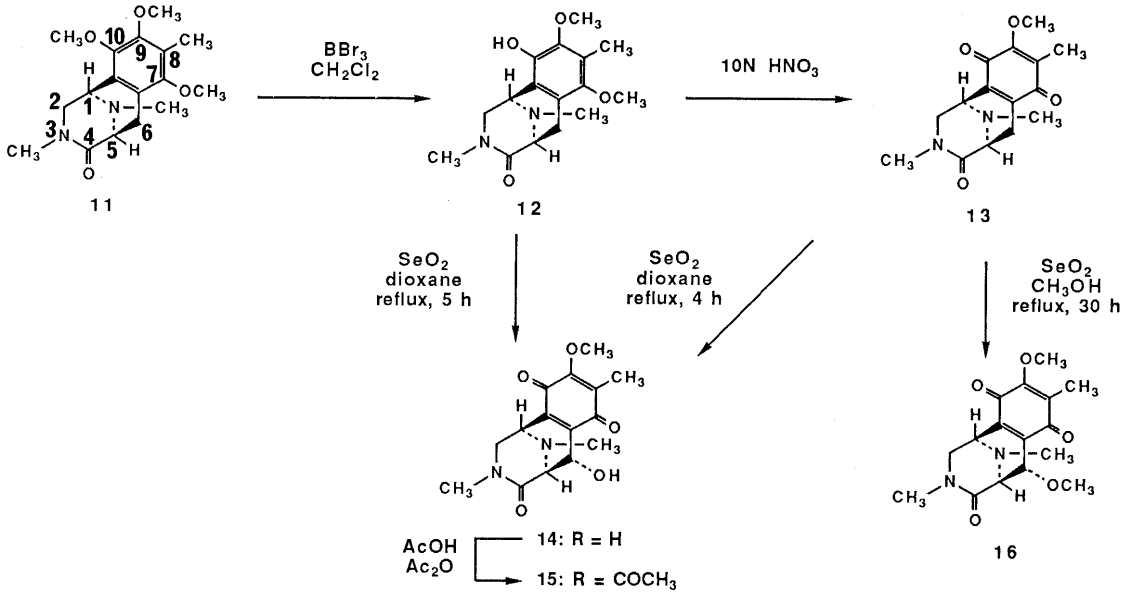


Chart 2

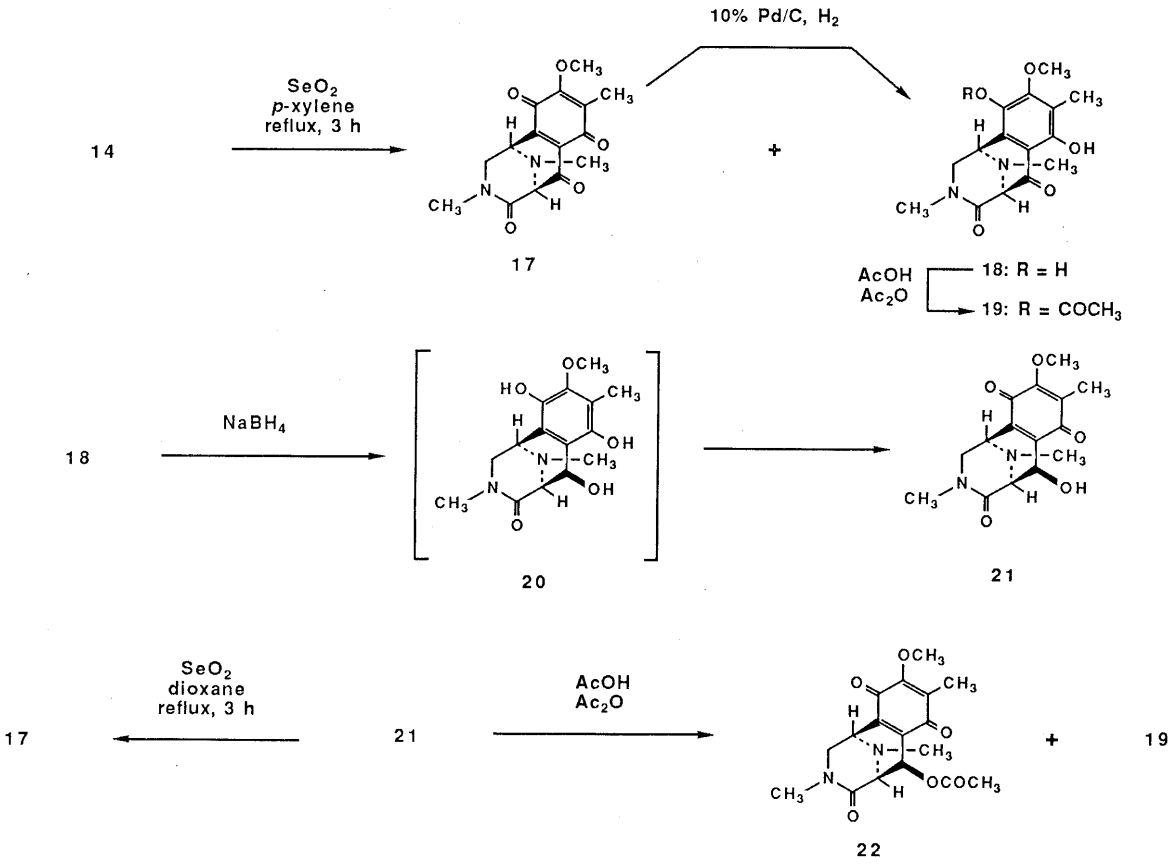


Chart 3

Finally, we synthesized the alcohol (**21**), with the stereochemistry of the C-6 position epimeric to that of saframycins. Reduction of **18** with sodium borohydride in ethanol at room temperature for 1 h accompanied by auto-oxidation (through **20**) gave **21**[7] (mp 157-159°C) (81% yield) as the sole product. The stereochemical course of this reaction could be rationalized as proceeding through a hydride attack from the less hindered α-face. Treatment of **21** with selenium oxide in dioxane under reflux for 3 h afforded **17** (57.4% yield) and **18** (7.5% yield). The oxidation was especially rapid for an axial alcohol (**21**) because steric strain was relieved in going from the reactant to the product. Acetylation of **21** with acetic anhydride in acetic acid at 100°C for 1 h afforded **22**[7] (mp 183-185°C) (5.4% yield), ^{1}H NMR δ 6.070 (1H, d, J = 7.3 Hz, 6-H) and **19**[7] (mp 176-177.5°C) (75.5% yield) which was identical in all respects with **19** prepared from **18** (acetic anhydride, acetic acid, 100°C, 2 h, 76% yield).

Efforts to apply this transformation to the total syntheses of saframycins (**3**, **4**) and renieramycins (**5-10**) are under intensive investigation in our laboratories.

ACKNOWLEDGMENT We are grateful for financial support from the Ministry of Education, Science, and Culture of Japan in the form a Grant-in-Aid (63571010) for Scientific Research.

REFERENCES AND NOTES

1) This paper is dedicated to Professor Shin-ichiro Sakai (Chiba University) on the occasion of his 60th birthday.
2) A. Kubo, N. Saito, H. Yamato, K. Masubuchi, and M. Nakamura, *J. Org. Chem.*, **53**, 4295 (1988). For an alternative total synthesis of (±)-**2**: see T. Fukuyama and R. Sachleben, *J. Am. Chem. Soc.*, **104**, 4975 (1982).
3) T. Arai, K. Takahashi, A. Kubo, S. Nakahara, S. Sato, K. Aiba, and C. Tamura, *Tetrahedron Lett.*, 2355 (1979); T. Arai, K. Takahashi, A. Kubo, and S. Nakahara, *Experientia*, **36**, 1025 (1980); A. Kubo, N. Saito, Y. Kitahara, K. Takahashi, Y. Yazawa, and T. Arai, *Chem. Pharm. Bull.*, **35**, 440 (1987).
4) Renieramycins A-D were first isolated from the sponge *Reniera* sp. and the relative stereochemistry differed only at the point of attachment of the side chain at the C-9 position; J. M. Frincke and D. J. Faulkner, *J. Am. Chem. Soc.*, **104**, 265 (1982). Recently, He and Faulkner reported the isolation of a new series of renieramycins E and F, and determined that the stereochemistry of all renieramycins is the same as that of saframycins; H. He and D. J. Faulkner, *J. Org. Chem.*, **54**, 5822 (1989).
5) For simplicify, the proper IUPAC names and numbering systems for all tricyclic lactam intermediates are used in this paper.
6) H. Kurihara and H. Mishima, *Tetrahedron Lett.*, **23**, 3639 (1982); H. Kurihara, H. Mishima, and M. Arai, *Heterocycles*, **24**, 1549 (1986). A. Kubo, N. Saito, H. Yamato, R. Yamauchi, K. Hiruma, and S. Inoue, *Chem. Pharm. Bull.*, 36, 2607 (1988).
7) All structural assignments were confirmed by proton magnetic resonance, infrared, ultraviolet, and mass spectra. The molecular composition of the compound given with the chemical formula was determined by elemental analysis.
8) In the chemistry of tetrasubstituted *p*-benzoquinones, duroquinone and 2,3-dimethyl-1,4-naphthoquinone are known to react with a variety of nucleophiles such as enolates or amines to give side-chain oxidation products.[12] In terms of natural product synthesis, this internal redox strategy has been used to convert nanaomycin A to nanaomycin D.[13]
9) A preliminary experiment for the introduction of a hydroxy function at the C-6 position of the phenol (**12**) was carried out using lead tetraacetate oxidation: see H. Hara, H. Shinoki, O. Hoshino, and B. Umezawa, *Heterocycles*, **20**, 2149 (1983); Treatment of **12** with lead tetraacetate in dichloromethane gave the *p*-quinone (**13**) (51% yield) and the *p*-quinol acetal (**23**,[7] mp 166-168°C) (43% yield) which was identical in all respects with **23** prepared by DDQ oxidation in methanol [14] from **13** (87% yield). Homolytic bromination of **12** with bromine in carbon tetrachloride followed by solvolysis also failed. On the other hand, exposure of **23** to molecular oxygen in a dimethyl sulfoxide-*tert*-butyl alcohol (4:1) solution containing potassium *tert*-butoxide (1.5 eq)[15] gave the phenol (**24**[7], mp 203-205°C) (13% yield) (Chart 4). Acetylation of **24** with acetic anhydride in pyridine afforded **25**[7] (mp 208-209°C) (68% yield) whose ^{1}H NMR spectrum indicated a low-field shift of the singlet of H-6 proton (**24**: δ 4.82; **25**: δ 6.05). Presented at 20th Congress of Heterocyclic Chemistry, Gifu, Abstr. p 185, Oct. (1989).
10) The ^{1}H NMR spectrum of **13** showed the 6-Hβ signal at δ 2.747 (1H, dd, J = 20.5, 1.7 Hz) and 6-Hα signal at δ 2.760 (1H, dd, J = 20.5, 6.1 Hz).
11) Photochemical intramolecular redox reaction of the 1,4-benzoquinone: see K. A. Abdulla, A. L. Abdul-Rahman, R. Al-Hamdany, and Z. Y. Al-Saigh, *J. Prakt. Chem.*, **324**, 498 (1982).
12) K. T. Findly, "The Chemistry of the Quinonoid Compounds", Vol. 2, ed. by S. Patai, John Wiley and Sons, Inc., New York, 1974; p 877.
13) S. Ōmura, H. Tanaka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 320 (1976); T. Li and R. H. Ellison, *J. Am. Chem. Soc.*, **100**, 6264 (1978). Recently, this redox strategy has been used in the total synthesis of pleurotin; D. J. Hart, H. Huang, R. Krishnamurthy, and T. Schwartz, *J. Am. Chem. Soc.*, **111**, 7507 (1989).
14) K. A. Parker and S. Kang, *J. Org. Chem.*, **45**, 1218 (1980); S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, *J. Am. Chem. Soc.*, **107**, 3891 (1985).
15) J. Gutzwiller and M. R. Uskokovic, *J. Am. Chem. Soc.*, **100**, 576 (1978).

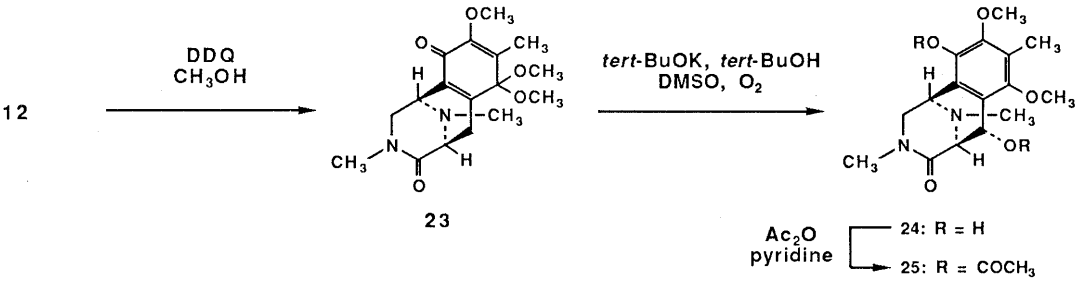


Chart 4

(Received January 11, 1990)