

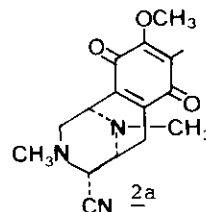
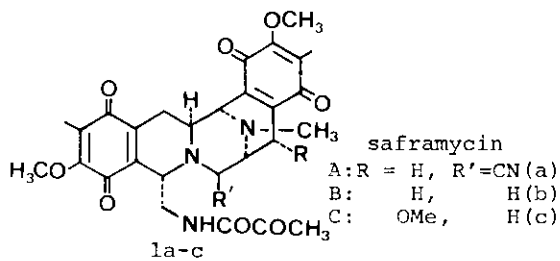
A SYNTHESIS OF 4-CYANO-HEXAHYDRO-1,5-IMINO-3-BENZAZOCINE-7,10-DIONE;
A POTENTIAL INTERMEDIATE TO SAFRAMYCIN SYNTHESIS¹

Hideshi Kurihara, Hiroshi Mishima, and Mamoru Arai
Fermentation Research Laboratories, Sankyo Co., Ltd.
2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140, Japan

Abstract - A simple and efficient synthesis of 4-cyano-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-8-methyl-3-benzazocine-7,10-dione (**2a**) is described starting from the corresponding lactam (**3**). Reduction of the lactam (**3**) with DIBAH followed by oxidation with HNO_3 and neutralization of the resulting quinone in the presence of KCN afforded an α -aminonitrile derivative as the single product; the stereochemistry of the introduced cyano group being determined to be α -axial.

Isoquinolinequinone antibiotics, which include such naturally occurring quinones as cyanocyclines,² naphthyridinomycins,³ saframycins,⁴ mimosamycin,⁵ mimocin,⁶ renieramycins,⁷ and renierone,⁸ constitute a group of structurally intriguing compounds into which there have so far been a number of synthetic studies.⁹

Our interest in the synthesis towards saframycins (**1a-c**), which exhibit a wide-spectrum of antimicrobial activity and are active against several types of tumor in mice, resulted in the development of the efficient synthesis of



hexahydro-1,5-imino-3-benzazocine derivatives¹⁰, embodying all of the skeletal features of the 'right half' of saframycin.¹

Saframycin A (1a) is the most potent antineoplastic agent of all saframycins¹¹ and differs from other saframycin congeners in regard to having a cyano group at C-21 (orientation not known), while the congeners have either a hydroxy group at C-21 or an unsubstituted methylene moiety.

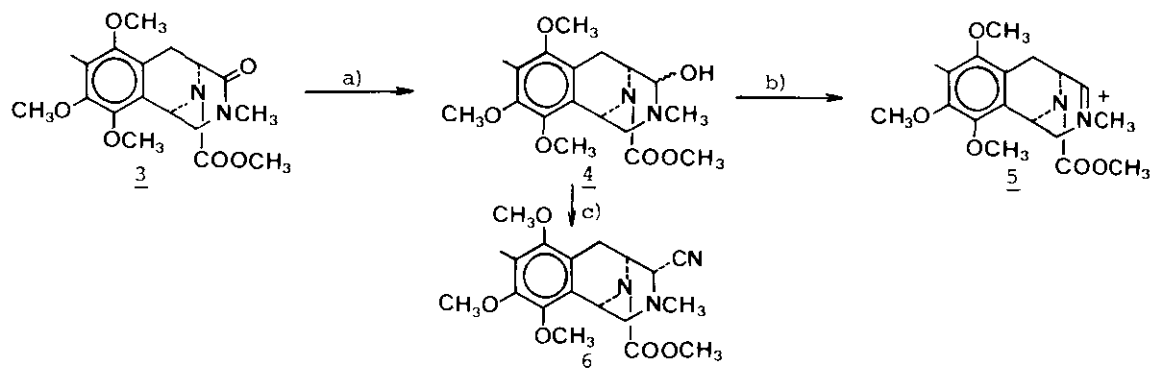
THIS paper reports the stereoselective synthesis of the 'right half' of saframycin A.

The lactam (3), 1,2,3,4,5,6-hexahydro-1,5-methoxyimino-8-methyl-7,9,10-trimethoxy-3-benzazocin-4-one,¹ was chosen as a starting material, because its functionality is obviously suitable for the synthetic manipulation to give the desired 4-cyano-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-8-methyl-3-benzazocine-7,10-dione (2a).

Reduction of the lactam (3), which was readily available from a phenylalanine derivative in three steps,¹⁰ with one equivalent of DIBAH at -78°C in toluene afforded a somewhat unstable and inseparable mixture of α -hydroxyamine (4) almost quantitatively as per the Sanders' protocol.¹²

The IR spectrum of 4 exhibited an absorption band at 3350 cm^{-1} due to a hydroxy group and did not show any of the characteristics for an aldehyde group around 1735 cm^{-1} . The NMR spectrum of the mixture of α -hydroxyamine (4) in CDCl_3 showed the common absorption peaks at δ 2.15(s, CH_3), 2.27(s, CH_3), 3.65(s, CH_3), 3.66(s, CH_3), 3.78(s, CH_3), and 3.84(s, CH_3) ppm, but its NMR spectrum in TFA was noteworthy; in a relatively lower field, a proton resonating at δ 8.73 ppm (br s) was coupled with a proton assigned as a C-5 bridge-head proton (δ 5.85, br s) and N-methyl protons resonating at δ 2.27 ppm in CDCl_3 were shifted to δ 3.71 ppm as a relatively broad singlet. These resonances, which are reasonably assigned as a methin (at C-4) and an N-methyl attached to an iminium moiety, establish the preferential formation of 5 in acidic medium. Based on the expectation that such a type of ion remains intact by HNO_3 oxidation, HNO_3 was the favored choice for oxidation of a compound having α -hydroxyamine moiety to get a quinone having an iminium moiety.

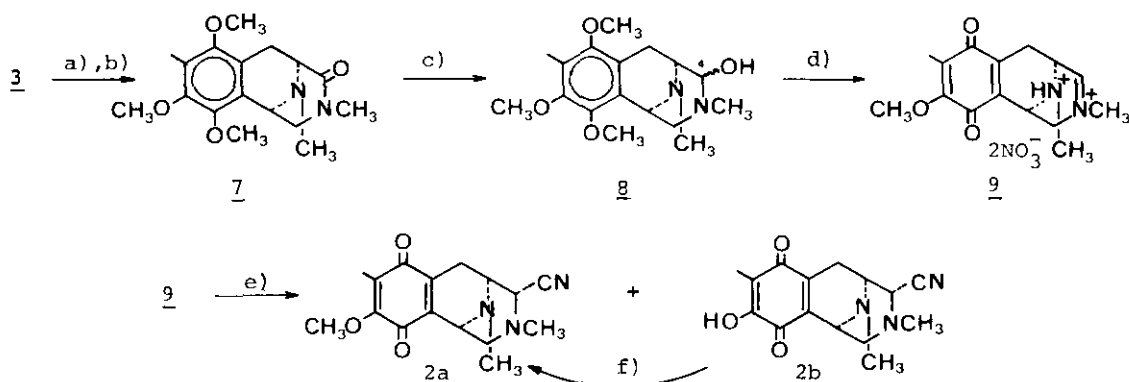
When the epimeric mixture of α -hydroxyamine (4) was treated directly with one equivalent of HCN in DMF for a few minutes at room temperature, aminonitrile (6)¹³ was obtained as a single product in 93% yield. This transformation of tertiary lactam thereby provides a convenient method for the preparation of α -aminonitrile.¹²



a) DIBAH/tolu., -78°C, b) TFA, r.t., c) HCN, pH 5 /DMF

Thus, synthesis of the quinone (2a) - the 'right half' of saframycin A - from compound 3 was performed as shown in Scheme I.

Hydrolysis of 3 with sodium methoxide in methanol followed by Eschweiler-Clarke methylation afforded methylamine (7),¹³ in 50 % overall yield and reduction of 7 using the method of Sanders by the action of DIBAH at -78°C afforded, almost quantitatively, 4-hydroxy-1,5-methylimino-3-benzazocine (8)¹³ as an epimeric mixture. Upon treatment with 12N-HNO₃¹⁴ below 20°C, hydroxyamine (8) was oxidized with evolution of N₂O₄ to afford a quinone bearing an iminium ion as an HNO₃ salt (9)¹³ in up to 80 % yield. When the quinone HNO₃ salt (9) was treated with aqueous NaHCO₃ in the presence of one equivalent of KCN, α -aminonitriles (2a and 2b) were formed in 39 and 42 % yield, respectively. The proposed structures of these quinones agreed with analytical and spectral properties.¹³ Methylation of 2b with CH₂N₂ yielded, quantitatively, a methoxy derivative identical with 2a.



a) NaOMe/MeOH, refl., b) HCHO/HCOOH, 100°C, c) DIBALH/tolu., -78°C, d) 12N-HNO₃, <20°C, e) KCN, NaHCO₃/H₂O, f) CH₂N₂/CH₂Cl₂-Et₂O.

Scheme I

Inspection of the NMR data allowed assignment of the stereochemistry of a cyano group as shown in Figure I. From the facts that, in the 400MHz NMR spectrum of 2a, H-4 appeared at δ 3.63 ppm as a double doublet ($J=2.5, 0.5\text{Hz}$) and a W-character type long range coupling between this proton and the equatorial proton at C-2 (δ 2.47 ppm, ddd, $J=11.5, 1.9, 0.5\text{ Hz}$) was ascertained by using a double resonance technique, the orientation of the cyano group at C-4 was determined as α -axial.

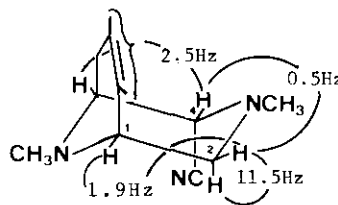
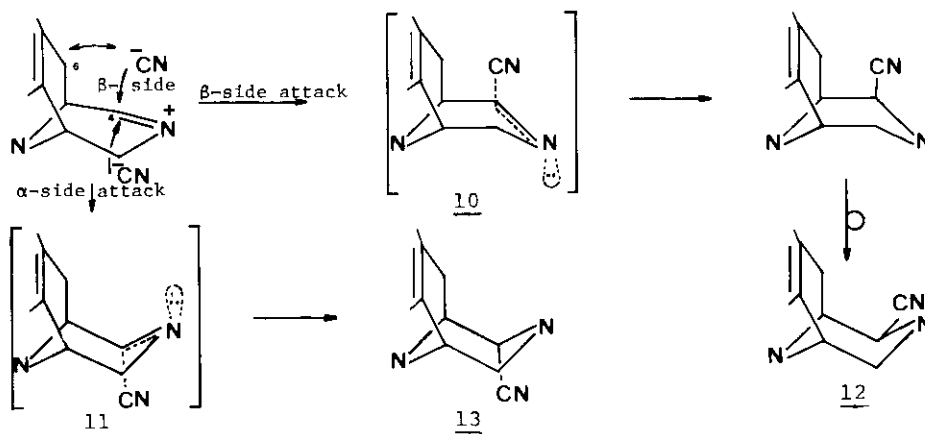


Figure I

Orientation of the cyano group in 6 is also α -axial because, in the NMR spectrum of 6, H-4 appeared at δ 3.73 ppm and its splitting pattern (br d, $J=2.6\text{ Hz}$) was just like the pattern of H-4 in 2a. Contrary to expectations,¹⁵ such an α -aminonitrile group as in 6 or 2a was found to be stable under aqueous acidic conditions: for instance, treatment of 6 with 3N-HCl aqueous solution for 1 h at room temperature resulted in recovery of 6 exclusively. Together with this finding, by considering the facts that the α -aminonitrile was produced not only as a single epimer but also as an α -axial isomer in both cases of the conversion of alcohol (4 or 8) into the corresponding nitrile (6 or 2) via the iminium ion (5 or 9), respectively, may prove the proceeding of the reaction in a kinetically controlled fashion. As

shown in Scheme II, a cyano anion is able to attack the iminium ion either from the β -side or from the α -side of the molecule and to form 10 or 11 as transition states. But, approach from the α -side may be favorable, because the β -side of the iminium ion is sterically more hindered by the C-6 methylene moiety. Moreover, between these two transition states, in which the formation of a carbon-carbon bond (C_4-CN) and the development of a lone pair on the nitrogen atom are anti-coplanar to each other, 10 is kinetically disfavored because of the inevitable formation of a boat-like transition state. Therefore, it seems certain that the reaction proceeds through 11 and an α -axial type product such as 13 is formed stereoselectively.¹⁶



Scheme II

Determination of the orientation of the cyano group in saframycin A (1a), which was not clarified till 2a was synthesized, became possible by comparison of the NMR of 1a with that of 2a, the results of which have been reported separately.¹⁷

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- 13) Physicochemical data of compounds synthesized are as follows: 6 (amorph.); $\nu(\text{CHCl}_3)$: 2300(w), 1695, 1443 cm^{-1} ; $\delta(\text{CDCl}_3)$: 2.18 (3H,s), 2.27(3H,s), 2.57 (1H,br d,J=11.7), 2.70(1H,br d,J=18.0), 2.77(1H,dd,J=11.7, 3.5), 3.18(1H,br dd,J=18.0, 7.8), 3.73(1H,d,J=2.6), 3.67, 3.78, 3.83 and 3.90(each 3H,s), 4.85 (1H,br d,J=7.8), 5.43(1H,br s) ppm; m/z : 375(M^+ ,10), 293(25), 292(100), 278

(9), 257(9), 242(14). Anal. ($C_{19}H_{25}N_3O_5$): C, 60.57(60.79); H, 6.80(6.71); N, 11.06(11.19). 7 (mp 115–116°C); ν (KBr): 1650, 1010, 955 cm^{-1} ; δ ($CDCl_3$): 2.19, 2.50 and 2.86(each 3H,s), 3.07(1H,dd,J=16.0, 4.6), 3.60(1H,br m), 3.69, 3.82 and 3.90(each 3H,s), 4.02(1H,d,J=4.5), 4.12(1H,br d,J=4.5) ppm; m/z: 320(M^+ , 29), 249(21), 248(100), 218(20). Anal. ($C_{17}H_{24}N_2O_4$): C, 63.72(63.73); H, 7.58(7.55); N, 8.71(8.74). 8 (amorph.); ν (KBr): 3120, 1600(w), 1066, 1027, 755 cm^{-1} ; δ ($CDCl_3$): 2.19, 2.27 and 2.27(each 3H,s), 3.71, 3.83 and 3.83(each 3H,s), 4.16(1H,br s) ppm; m/z: 322(M^+ , 13), 250(100), 248(58), 218(17). Anal. ($C_{17}H_{26}N_2O_4$): C, 63.50(63.33); H, 8.18(8.13); N, 8.62(8.69). 9 (hygroscopic); only NMR spectrum could be measured, δ (CF_3COOH): 2.06(3H,s), 3.29 and 3.94 (each 3H,br s, Me), 4.14(3H,s), 5.40(1H,br m), 9.04(1H,br s) ppm. 2a (mp 122–124°C (dec.)); ν (KBr): 2220(w), 1650, 1639, 1620, 1233 cm^{-1} ; δ ($CDCl_3$, 400MHz): 1.96(3H,s), 2.21(1H,d,J=20.5), 2.29 and 2.32(each 3H,s), 2.46(1H,ddd,J=11.5, 1.9, 0.5), 2.73(1H,dd,J=20.5, 7.5), 2.79(1H,dd, J=11.5, 3.5), 3.32(1H,ddd,J=7.5, 2.5, 1.5), 3.63(1H,dd,J=2.5, 0.5), 3.81(1H,ddd,J=3.5, 1.9, 1.5), 4.02(3H,s) ppm; λ (EtOH): 270nm(ϵ =13,200); m/z: 301(M^+ , 18), 219(100), 218(87), 204(47). Anal. ($C_{16}H_{19}N_3O_3$): C, 63.56(63.77); H, 6.47(6.36); N, 13.80(13.94). 2b (mp 180–182°C(dec.)); ν (KBr): 2230(w), 1657, 1640, 1626, 1235, 754 cm^{-1} ; δ (DMF- D_7): 1.86, 2.27 and 2.31(each 3H,s), 3.42(1H,m,J=6.3), 3.76(1H,br s), 4.12(1H,d,J=2.5) ppm; m/z: 287(M^+ , 7), 205(100), 204(36), 177(10). Anal. ($C_{15}H_{17}N_3O_3$): C, 62.48(62.70); H, 5.96(5.96); N, 14.46(14.62).

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