A PROMISING CYCLIZATION OF THE 3-ARYLIDENE-6-ARYLMETHYL-2,5-PIPERAZINEDIONE TO CONSTRUCT TRICYCLIC LACTAM AS AN INTERMEDIATE TO SAFRAMYCIN SYNTHESIS

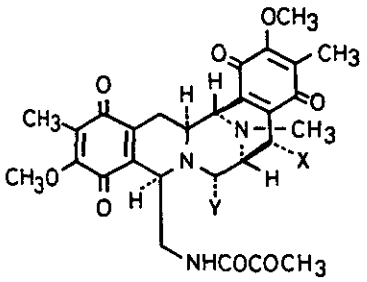
Akinori Kubo,* Naoki Saito, and Madoka Nakamura
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan
Koreharu Ogata and Shin-ichiro Sakai
Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Chiba 260, Japan

Abstract —— Regioselective reduction of the 3-arylidene-6-arylmethyl-2,5-piperazinedione (7b) at the C-2 position, followed by effective intramolecular cyclization to afford the tricyclic lactam (10b) is described. The structure of 16 as an intermediate to saframycin synthesis is confirmed by an X-ray crystallographic analysis.

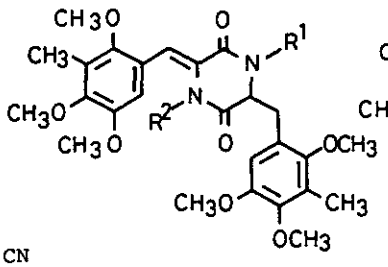
Recent years several naturally occurring isoquinolinequinones[1] have been isolated from *Actinomycetes* and marine sponge. Saframycins[1,2] are antitumor antibiotics produced by *Streptomyces lavendulae*. They constitute a class of the dimeric isoquinolinequinone antibiotic group, which includes safracins[3] and renieramycins.[4] A few synthetic studies[5] toward them have been appeared because of their unique structral features and because of their biological interests. An elegant total synthesis of saframycin B (2) has been reported by Fukuyama and Sachleben.[6] In this paper, we report an efficient synthesis of a key tricyclic lactam (16) as an intermediate toward a total synthesis of 1 and 2.

Benzylation of 4[7] (BnBr, NaH, DMF, room temperature, 1 h) furnished 5, and successive treatment with hydrazine hydrate (DMF, room temperature, 24 h) to afford 6 [mp 170-172°C] in 94% overall yield. The amide 6 was converted into the imide 7a-e[8] in 89-94% yield according to the procedure of Grieco.[9]

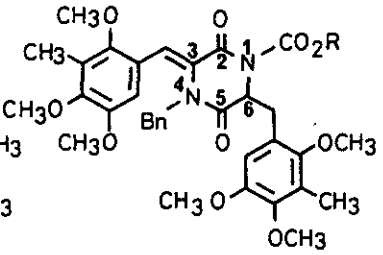
The regioselective reduction of 7 at the C-2 position to the corresponding allylic



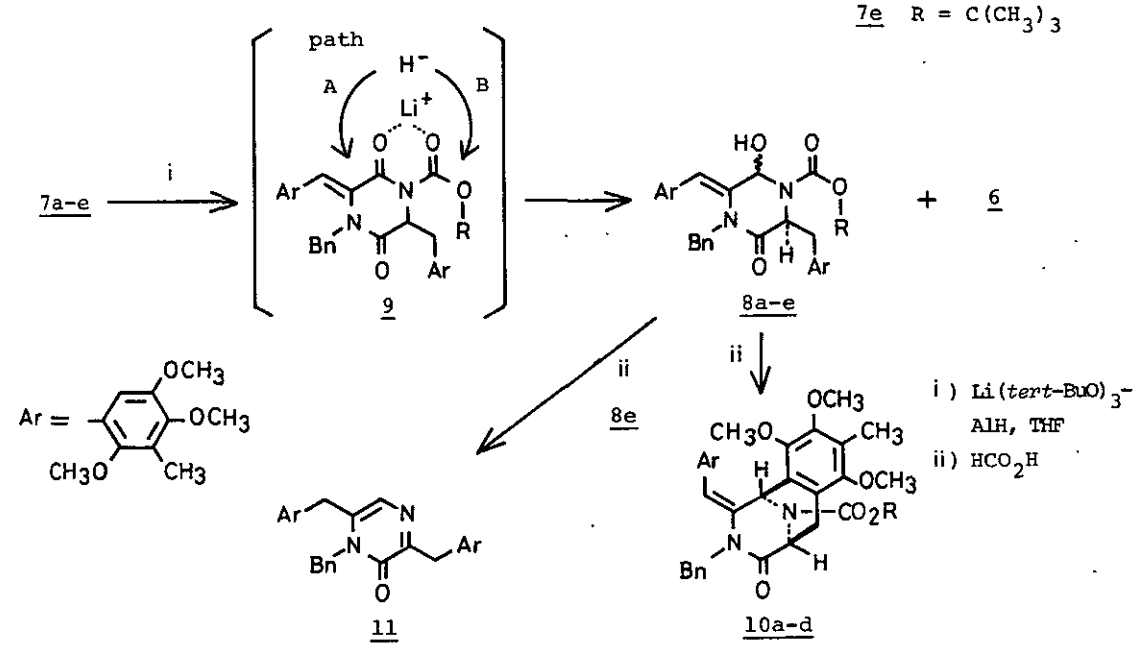
Saframycin A: 1 X = H, Y = CN
B: 2 X = Y = H
C: 3 X = OCH_3, Y = H



4 R^1 = $COCH_3$, R^2 = H
5 R^1 = $COCH_3$, R^2 = Bn
6 R^1 = H, R^2 = Bn



7a R = CH_3
7b R = $CH(CH_3)_2$
7c R = $CH_2CH(CH_3)_2$
7d R = Bn
7e R = $C(CH_3)_3$



alcohol 8, that was a crucial step for the total synthesis of saframycins, was achieved as followed. After several attempts,[10] we found that lithium tri-*tert*-butoxyaluminohydride was most effective for the 1,2-reduction of the imide 7. Thus, 7a-e were reduced with an excess lithium tri-*tert*-butoxyaluminohydride (THF, 0°C, 1 h) to afford a diastereomeric mixture of the unstable alcohols 8a-e along with 6. It was our hope that the bulky carbamate 7b (or 7e) would exert a steric influence on the course of the reduction/hydrolysis reactions, thus forcing the reduction of the amide carbonyl (path A in 9) to occur regioselectively. (Table I) Whereas cyclization of 8a-d was effected by treatment with formic acid (60°C, 1 h)

to afford the desired 1,5-imino-3-benzazocine derivatives 10a-d (Table II) in 58-64% yield, cyclization of 8e [mp 155-159°C] under the same conditions gave the pyrazinone 11[11] in 53% yield.

Table I.

Starting Material		Yield[a] (%)		Yield[b] (%)	
	mp (°C)	8	6	10	mp (°C)
7a	153.5-155	21	40	64 (16)	156.5-158
7b	137 -138.5	69	7	60 (52)	176.5-178
7c	127.5-129	45	36	60 (31)	146.5-148
7d	127.5-128	29	57	58 (17)	amorphous powder
7e	123 -124.5	69	7	———	

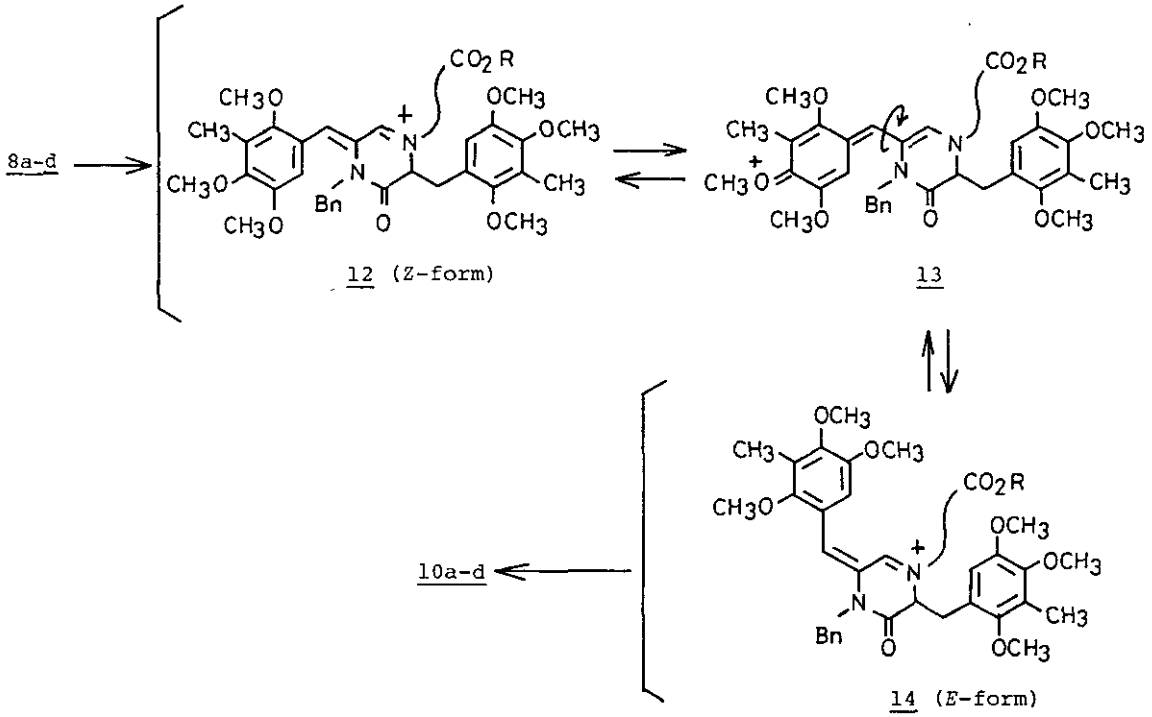
a, Yields are based on the chromatographycally pure material.

b, Yields in parentheses were obtained by reduction and cyclization sequence of 7 (without isolation of 8 and 6).

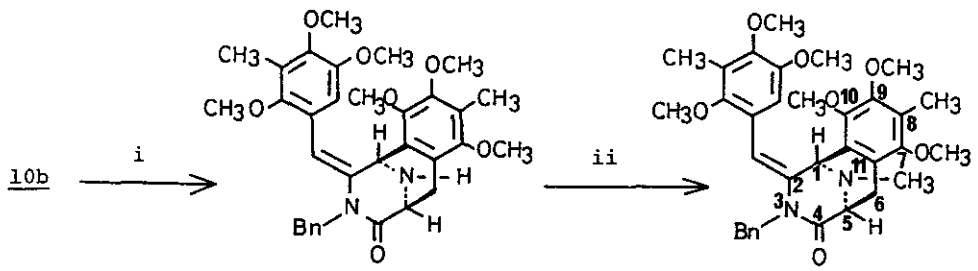
Consequently, the reduction of 7b gave 8b and 6, this mixture was treated with formic acid gave 10b in 52% yield. The stereochemical assignments for structures of 10a-d were based on the structural studies on the tricyclic lactam 16 (*vide infra*). It was apparent that this cyclization was accompanied by isomerization of the double bond in 12 (Z-form) due to the steric compression between the two aromatic rings.

Table II. ^{1}H-nmr and ^{13}C-nmr spectra of the tricyclic lactams

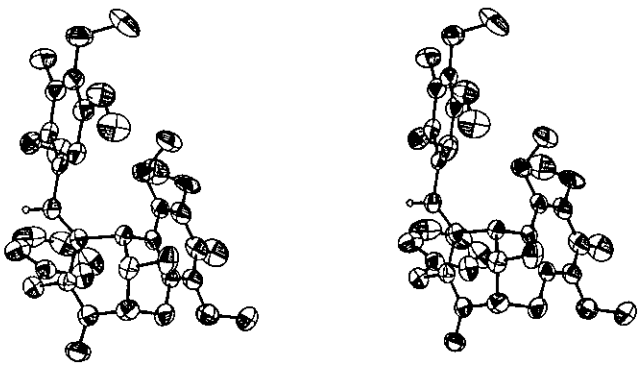
Compounds	^{1}H-nmr ($CDCl_3$) δ ppm				^{13}C-nmr ($CDCl_3$) δ ppm				
	H-1	H-5	C=CH	Ar-H	C-1	C-2	C-5	C-6	C=CH
10a	6.77	5.23	6.10	7.56	45.8	121.6	53.6	28.3	107.6
10b	6.77	5.20	6.06	7.48	45.8	121.7	53.5	28.2	107.6
10c	6.78	5.26	6.10	7.54	46.0	121.7	53.6	28.3	107.7
10d	6.79	5.28	6.10	7.52	46.1	121.6	53.6	28.4	107.8
15	5.53	4.28	5.93	6.71	———				
16	5.41	3.86	6.18	6.89	52.6	122.0	60.6	28.3	109.1



Next we turned our attention to the selective deprotection from the amine nitrogen at the N-11 position in 10b.[12] This was effective by acid-catalyzed conditions (conc. H_2SO_4, CF_3CO_2H, room temperature, 24 h)[13] to give the secondary amine 15 in quantitative yield. Reductive methylation of 15 (37% HCHO-H_2O, HCO_2H, 70°C, 1 h) gave the desired tricyclic lactam 16 [mp 162-163.5°C] in 96% yield. The structure of 16 was confirmed by an X-ray crystallographic analysis.[14] By comparison of ^{1}H-nmr and ^{13}C-nmr spectra of 10a-d, 15, and 16, (Table II) stereochemistries of these tricyclic lactam derivatives were concluded to be identical with each other.



i) H_2SO_4, CF_3CO_2H, ii) 37% HCHO-H_2O, HCO_2H, 60°C.



ORTEP STRUCTURE OF THE COMPOUND 16

Transformation of 16 to the basic ring system of saframycins is currentry under way in our laboratories.

ACKNOWLEDGMENT

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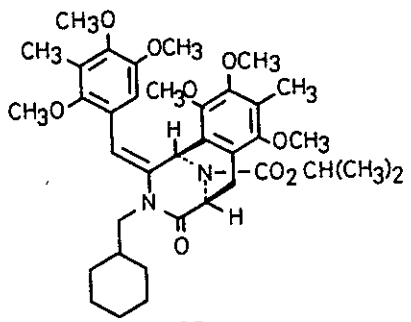
10) Reduction of 7b with $NaBH_3CN$ or $CeCl_3$-$NaBH_4$ gave 6 in quantitative yield. In addition, reduction of 7b with DIBAH or 9-BBN was failed, only starting material was recovered.

11) 11: ms m/z (%) 574(M^+, 100), 543(30), 452(30), 394(21), 91(40); ^{1}H-nmr ($CDCl_3$) δ ppm 2.16(3H, s), 2.21(3H, s), 3.48(3H, s), 3.70(3H, s), 3.77(6H, s), 3.79(6H, s), 3.81(2H, s), 4.18(2H, s), 5.26(2H, s), 6.34(1H, s), 6.72(1H, s), 6.99(1H, s), 7.08-7.32(5H, m).

12) Debenzylation of 10b (PtO_2, H_2, EtOH, 25°C, 24 h) gave the cyclohexylmethyl derivative 17 [mp 177.5-179°C; 87%]. All the other removal conditions were unsuccessful.



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13) M. I. Jones, C. Froussions, and D. A. Evans, J. Chem. Soc., Chem. Commun., 1976, 472.

14) The crystal of 16 belonged to the triclinic space group $P\bar{1}$ with a = 12.911 (3) Å, b = 12.396 (3) Å, c = 10.506 (3) Å, corresponding to a calculated crystal density of 1.26 g/cm^3. The structure was solved by the MULTAN 80 and refined by block-diagonal-matrix least squares method to an R factor of 0.015.

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