

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

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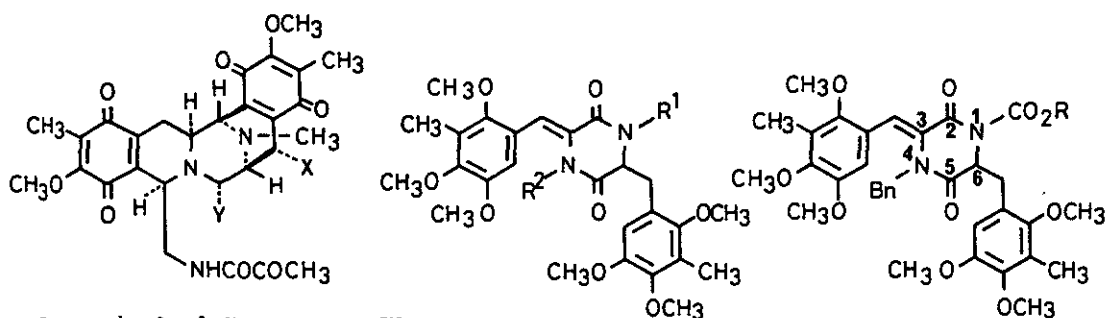
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Abstract — Regioselective reduction of the 3-arylidene-6-aryl-methyl-2,5-piperazinedione (7b) at the C-2 position, followed by effective intramolecular cyclization to afford the tricycllic lactam (10b) is described. The structure of 16 as an intermediate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

Recent years several naturally occurring isoquinolinequinones¹ have been isolated from *Actinomyces* 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 safracins³ and renieramycins.⁴ A few synthetic studies⁵ toward them have been appeared because of their unique structural 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 tricycllic lactam (16) as an intermediate toward a total synthesis of 1 and 2.

Benzylation of 4⁷ (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-e⁸ 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 = OCH₃, Y = H

4 R¹ = COCH₃, R² = H

5 R¹ = COCH₃, R² = Bn

6 R¹ = H, R² = Bn

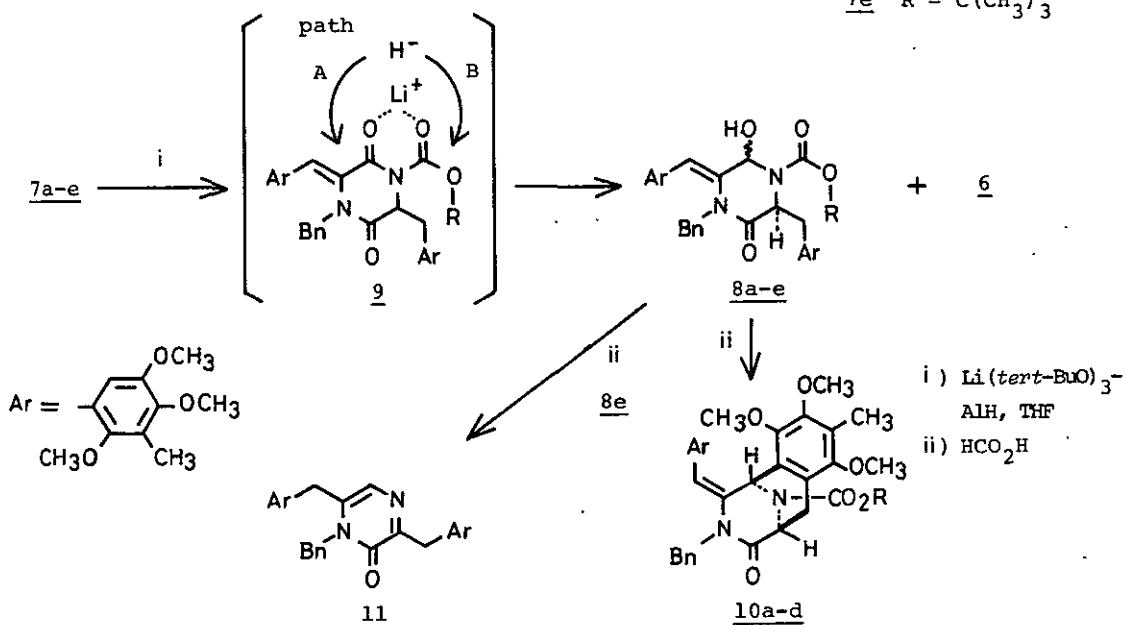
7a R = CH₃

7b R = CH(CH₃)₂

7c R = CH₂CH(CH₃)₂

7d R = Bn

7e R = C(CH₃)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*-butoxyaluminumhydride was most effective for the 1,2-reduction of the imide 7. Thus, 7a-e were reduced with an excess lithium tri-*tert*-butoxyaluminumhydride (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 11¹¹ in 53% yield.

Table I.

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

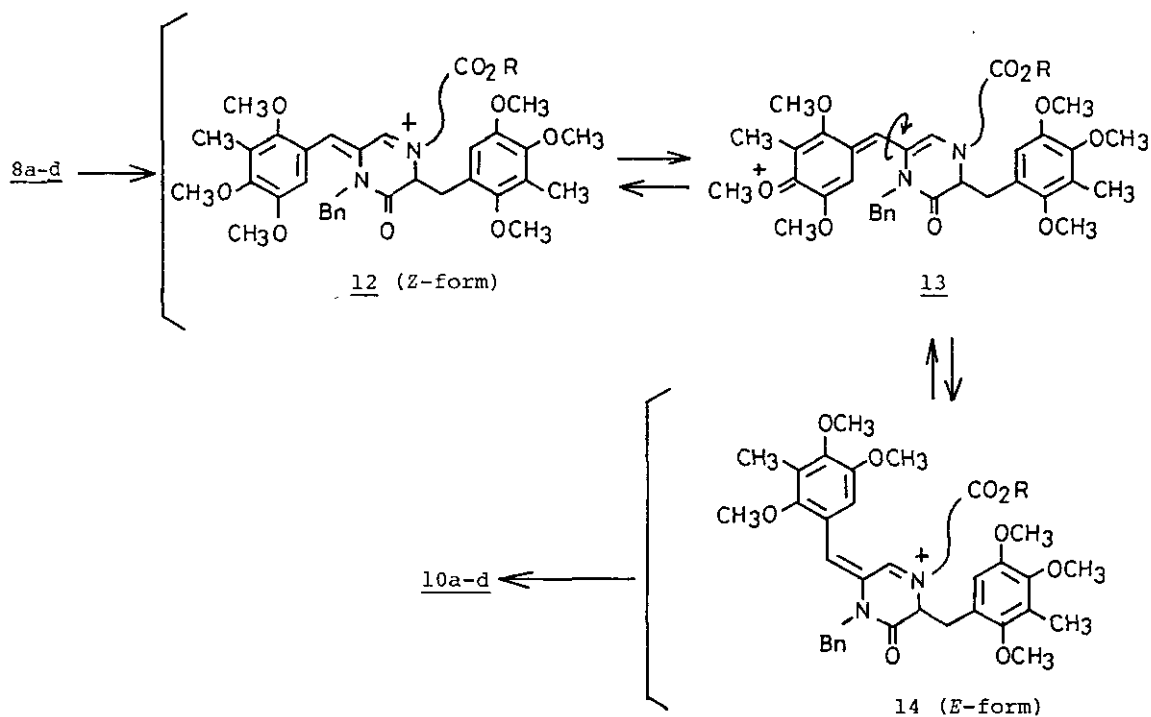
a, Yields are based on the chromatographically pure material.

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

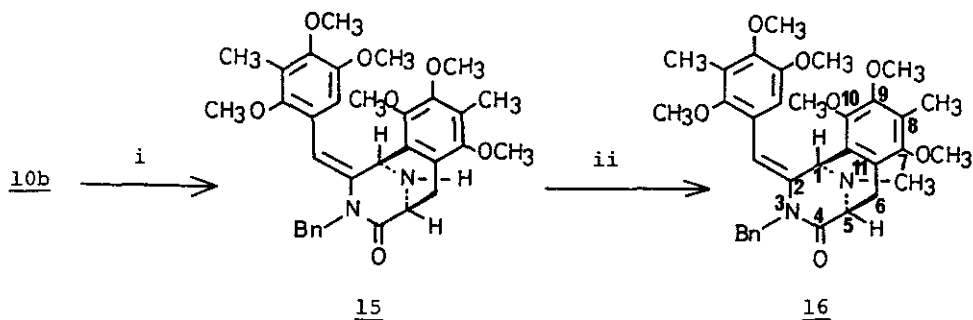
Consequently, the reduction of 7b gave 8b and 6, this mixture was treated with formic acid gave 10b in 52% yield. The stereochemical assignments for structures of 10a-d were based on the structural studies on the tricyclic lactam 16 (*vide infra*). It was apparent that this cyclization was accompanied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

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

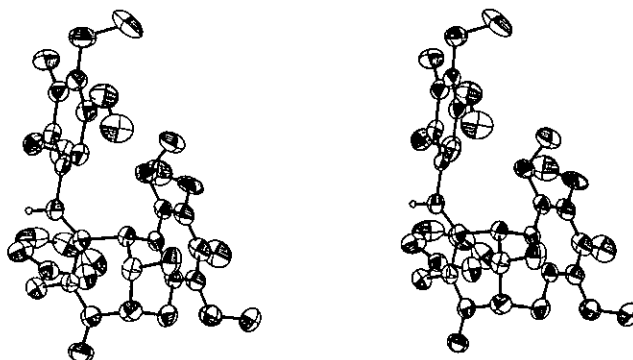
Compounds	¹ H-nmr (CDCl ₃) δ ppm				¹³ C-nmr (CDCl ₃) δ ppm				
	H-1	H-5	C=CH	Ar-H	C-1	C-2	C-5	C-6	C=CH
<u>10a</u>	6.77	5.23	6.10	7.56	45.8	121.6	53.6	28.3	107.6
<u>10b</u>	6.77	5.20	6.06	7.48	45.8	121.7	53.5	28.2	107.6
<u>10c</u>	6.78	5.26	6.10	7.54	46.0	121.7	53.6	28.3	107.7
<u>10d</u>	6.79	5.28	6.10	7.52	46.1	121.6	53.6	28.4	107.8
<u>15</u>	5.53	4.28	5.93	6.71	—				
<u>16</u>	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 , $\text{CF}_3\text{CO}_2\text{H}$, room temperature, 24 h)¹³ to give the secondary amine 15 in quantitative yield. Reductive methylation of 15 (37% $\text{HCHO}-\text{H}_2\text{O}$, HCO_2H , 70°C , 1 h) gave the desired tricyclic lactam 16 [mp $162-163.5^\circ\text{C}$] in 96% yield. The structure of 16 was confirmed by an X-ray crystallographic analysis.¹⁴ By comparison of ^1H -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 , $\text{CF}_3\text{CO}_2\text{H}$, ii) 37% $\text{HCHO}-\text{H}_2\text{O}$, HCO_2H , 60°C .

ORTEP STRUCTURE OF THE COMPOUND 16

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

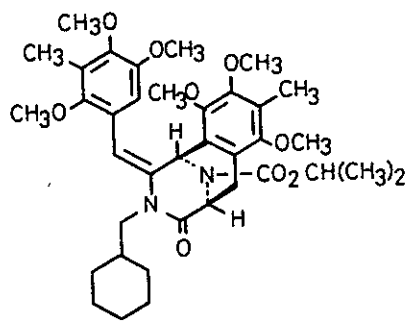
ACKNOWLEDGMENT

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- 8) Satisfactory spectroscopic data were obtained for all the new compounds in this paper.
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- 10) Reduction of 7b with NaBH_3CN or $\text{CeCl}_3\text{-NaBH}_4$ gave 6 in quantitative yield. In addition, reduction of 7b with DIBALH 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); $^1\text{H-nmr}$ (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 $177.5\text{-}179^\circ\text{C}$; 87%]. All the other removal conditions were unsuccessful.
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- 14) The crystal of 16 belonged to the triclinic space group $\text{P}\bar{1}$ 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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