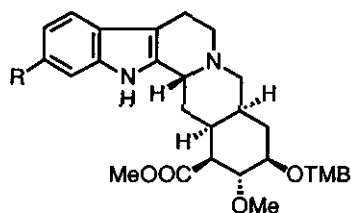


**PHOTOCYCLIZATION OF ENAMIDES. 37.^{1,2} SYNTHESIS OF
DESPYRROLO ANALOGUES OF RESERPINE DEMONSTRATING
A VERSATILE ADDITION-ELIMINATION REACTION STRATEGY
FOR THE PREPARATION OF FUNCTIONALIZED RESERPINE RING
SYSTEM²**

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Abstract--Despyrrolo analogues (25) and (26) of reserpine and were prepared via the routes involving reductive photocyclization of the enamide (4) and addition-elimination reaction of the resulting β -methoxy enones (7) and (8).

Reserpine (1) and its close relative deserpidine (2) have attracted wide interests owing to their roles not only as medicinals in the treatment of hypertension and other disorders but also as synthetic targets in natural product chemistry.³ There are numerous studies^{3,4} aimed at the development and application of new strategies for the preparation of functionalized yohimbanes which have basic pentacyclic skeleton of reserpine and related alkaloids. Szántay's group⁵ has also synthesized despyrrolo derivatives of reserpine of which several compounds are found to show potent antiinflammatory activity in addition to antihypertensive and hypotensive activities. Independently, Clark's group⁶ has also described the synthesis of the related compounds and their structure-affinity relationship at α -adrenoceptors. Considering these situations, we report here a full detail of the synthesis of the despyrrolo analogues of reserpine via the route involving hydrocyanation reaction⁷ of the β -methoxy enone and the Michael addition of methoxide anion to α,β -unsaturated cyano system, thereby established a synthetic route to the parent alkaloid.



1: R=OMe reserpine
2: R=H deserpidine

TMB=3,4,5-trimethoxybenzoyl

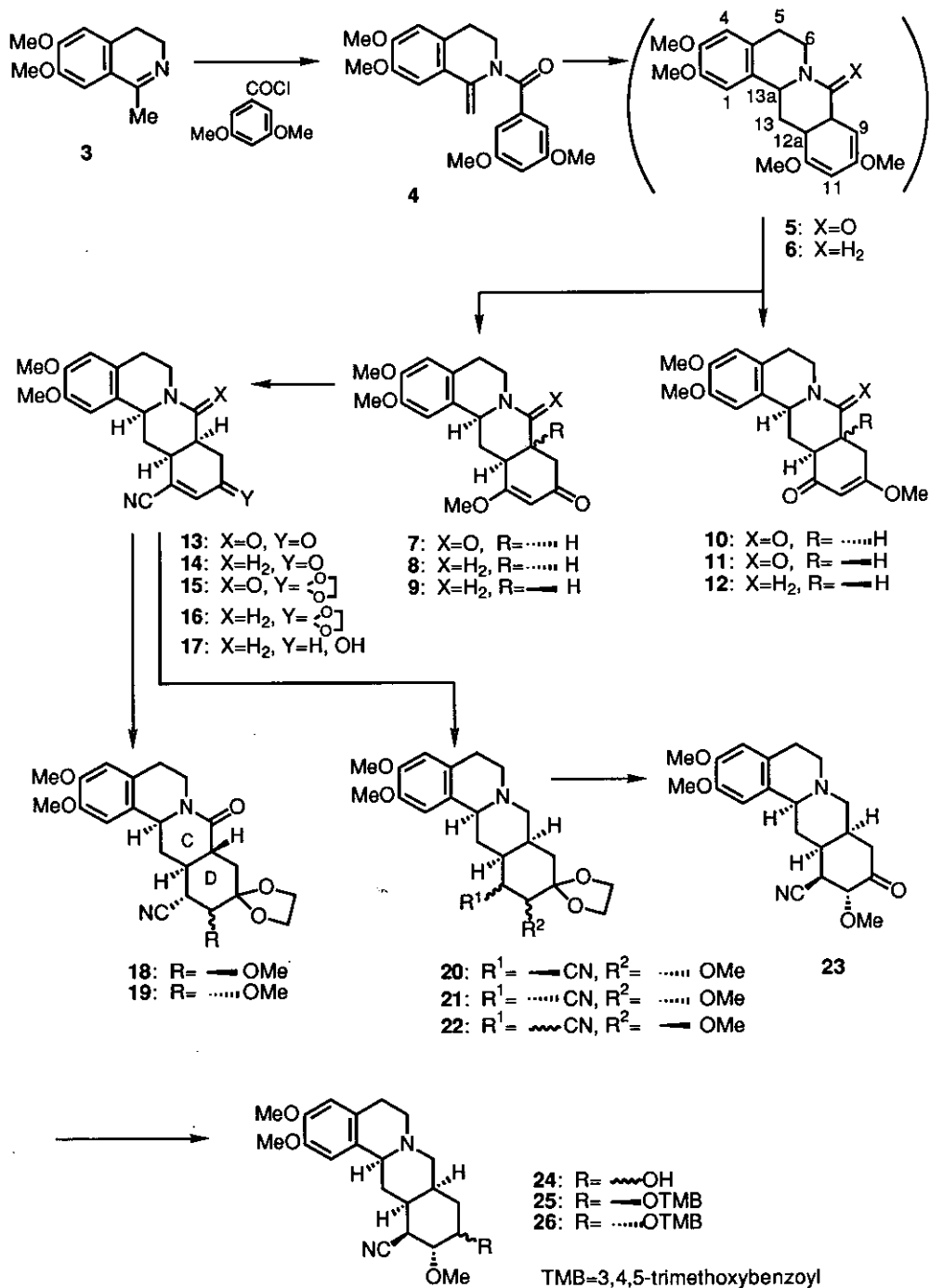
Preparation of Methoxy Enones Acylation of the dihydroisoquinoline (**3**) with 3,5-dimethoxybenzoyl chloride in the presence of triethylamine gave the unstable enamide (**4**) in quantitative yield which was characterized by the proton nuclear magnetic resonance ($^1\text{H-nmr}$) spectrum [δ 5.53 and 4.20 (each 1H, br s, $\text{C}=\text{CH}_2$)] and was then subjected to irradiation⁸ in the presence of sodium borohydride in benzene-methanol (10:1). The irradiation yielded the photocyclized lactam (**5**) as an unstable and inseparable mixture of stereoisomers. This mixture showed two spots very close on thin layer chromatography (tlc) and exhibited $^1\text{H-nmr}$ at δ 4.23-5.23 (4H, complex multiplet) due to two olefinic and 13a- and 6-equatorial protons. We then investigated the indirect characterization of the photocyclized products through the derivatives having more stable functional groups. Hydrolysis of a mixture of the crude products, which was obtained by reductive photocyclization⁸ of the enamide (**4**) in three different solvent systems, by treatment with 10% hydrochloric acid gave three stable enones (**7**), (**10**), and (**11**) in the yields as shown in Table 1 after chromatographic separation. Similar procedures involving reductive photocyclization⁸ of the enamide (**4**) in the presence of lithium borohydride as a reducing agent and the subsequent acid hydrolysis of the photocyclized products gave the amine (**8**) in addition to a small amount of three lactams (**7**), (**10**), and (**11**) as shown in Table 1. This is the first example of reductive photocyclization in the presence of lithium borohydride which has resulted in the double reductions of iminium and lactam carbonyl group.⁹

Table 1. Products Formed from Enamide (**4**)

Reducing Agent	Solvent (Ratio)	Yield (%)			
		7	8	10	11
NaBH_4	C_6H_6 -MeOH (10 : 1)	44	--	--	16
NaBH_4	THF-MeOH (9 : 1)	47	--	1	46
NaBH_4	MeCN-MeOH (10 : 1)	17	--	5	--
LiBH_4	THF-MeOH (10 : 1)	10	45	0.5	10
LiBH_4	THF	22	15	2	10

Reduction of crude mixture of the lactam (**5**) and its isomer, which was obtained by reductive photocyclization of the enamide (**4**) in the presence of sodium borohydride, with either lithium borohydride in THF-methanol (10:1) or lithium aluminum hydride, followed by acid treatment of the crude amines gave the identical mixture of three amino enones (**8**), (**9**), and (**12**).

Structures of the lactams (**7**), (**10**), and (**11**) and the amines (**8**), (**9**), and (**12**) were established from their spectral data (Tables 2 and 3) and chemical correlation reactions as follows. Three lactams (**7**), (**10**), and (**11**) exhibited molecular ion peak at m/z 357 in the mass spectra (ms) and infrared (ir) absorption at around 1600 and 1640 cm^{-1} due to a mono-enol ether moiety of β -diketone, suggesting its cyclohexenone structure.

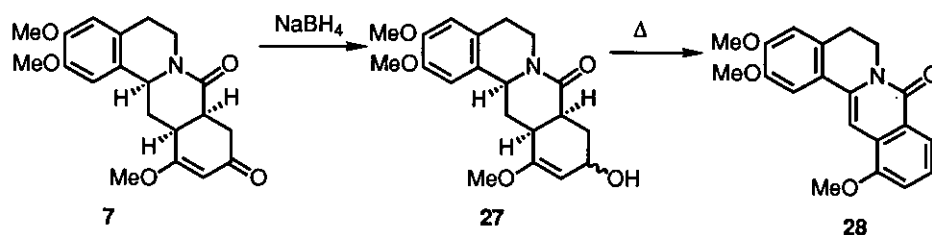


Scheme 1

Table 2. Spectral Data of Lactams (7), (10), and (11)

	7	10	11
¹ H-nmr (δ ppm)			
8a-H	3.19 (dt, J=13, 5 Hz)	3.18 (dt, J=12, 6 Hz)	
9-Hax	2.42 (dd, J=18, 13 Hz)	2.63 (ddd, J=17, 12, 1 Hz)	
9-Heq	2.84 (dd, J=18, 5 Hz)	2.84 (dd, J=17, 6 Hz)	
11-H	5.48 (s)	5.47 (d, J=1 Hz)	5.49 (s)
12a-H	2.94 (ddd, J=13, 5, 3 Hz)		
13-Hax	1.89 (q, J=13 Hz)	1.91 (q, J=12 Hz)	1.52 (br q, J=13 Hz)
13-Heq			3.29 (ddd, J=13, 5, 2 Hz)
13a-H	4.78 (dd, J=13, 5 Hz)	4.74 (dd, J=12, 5 Hz)	4.70 (dd, J=12, 5 Hz)
OMe	3.80 (s)	3.76 (s)	3.78 (s)
Ms m/z (M ⁺)	357	357	357
Ir (cm ⁻¹)	1615, 1640	1605, 1640	1605, 1645

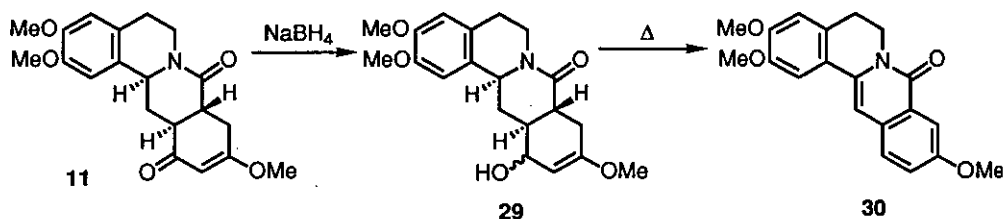
Structure of Lactam (7)—The position of a methoxyl group was established by the chemical conversion involving sodium borohydride reduction and thermal dehydration-oxidation of the resulting allyl alcohol (27) into the known¹⁰ 12-methoxy lactam (28). 8a/12a-*cis*-12a/13a-*syn*-Stereochemistry was deduced from ¹H-nmr signals [δ 3.19 (1H, dt, J= 13, 5 Hz, 8a-H), 2.94 (1H, ddd, J= 13, 5, 3 Hz, 12a-H), and 1.89 (1H, q, J= 13 Hz, 13-Hax)] (Scheme 2).



Scheme 2

Structure of Lactam (10)—The position of a methoxyl group was deduced from a signal at δ 5.47 (d, J= 1 Hz) due to 11-H and the observation of allylic coupling (J= 1Hz) between 11-H and 9-Hax in the ¹H-nmr spectrum. Comparison of ¹H-nmr spectrum with that of 8a/12a-*cis*-12a/13a-*syn*-lactam (7), particularly very close signals due to protons at the 8a-, 13-, and 13a-positions, suggested that the lactams (10) and (7) have the same stereochemistry with respect to the ring juncture (Table 2).

Structure of Lactam (11)—The position of a methoxyl group was deduced from the conversion of the lactam (11) into the known¹⁰ 10-methoxy lactam (30) via the allyl alcohol (29) as in the case of the lactam (7). 12a/13a-*syn*-Stereochemistry was deduced from the ¹H-nmr signal [δ 1.52 (1H, br q, J= 13 Hz, 13-Hax)] and C/D-*trans*-juncture was established by its conversion into the *trans*-amino alcohol (31) by reduction with lithium borohydride as described later (Scheme 3).

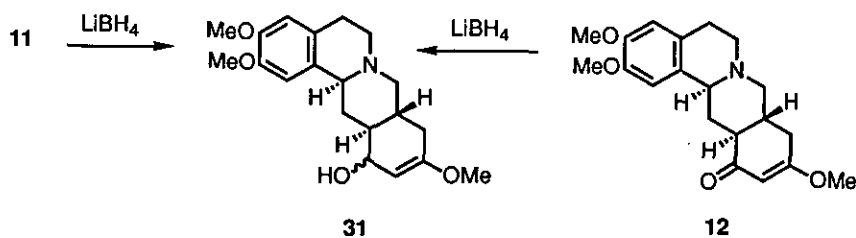


Scheme 3

Structures of Amines (8), (9), and (12)--Three amines (8), (9), and (12) showed the same molecular ion peak at m/z 343 in their ms and ir absorptions at $2700\text{--}2800\text{ cm}^{-1}$ due to Bohlmann bands and around 1600 and 1640 cm^{-1} due to a mono-enol ether moiety of β -diketone. 8a/12a-*cis*-12a/13a-*syn*-Stereochemistry of the amine (8) was established by the conversion of the amine (8) into *cis-syn*-nitrile (16) which was also obtained from the lactam (7) as described later. The position of the methoxyl group in the amine (12) was established by the conversions as follows (Schemes 3 and 4). The amine (12) was reduced with lithium borohydride to give the amino alcohol (31) which was derived from the 10-methoxy lactam (11) as described above. 8a/12a-*trans*-12a/13a-*syn* - Stereochemistry in the amine (12) was deduced from the $^1\text{H-nmr}$ signals at δ 2.11 (br td, $J = 11, 3$ Hz) due to 12a-proton. The position of the methoxyl group and 8a/12a-*trans*-12a/13a-*syn*-stereochemistry in the amine (9) were deduced from $^1\text{H-nmr}$ spectra (Table 3) which showed similar signal patterns due to protons at the 11-, 13-, and 13a-positions to those of *trans-syn* -amine (12) and a signal due to 13-Hax at higher field (δ 1.35) than that (δ 1.57) of *cis*-isomer (8). Of all tetracyclic compounds described in this paper, *C/D-trans*-isomers exhibit $^1\text{H-nmr}$ signals due to 13-Hax at higher field than that of the corresponding *cis*-isomers.

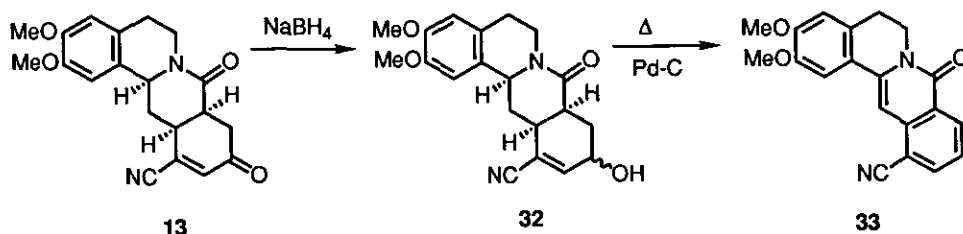
Table 3. Spectral Data of Amines (8), (9), and (12)

	8	9	12
$^1\text{H-nmr}$ (δ ppm)			
9-Hax	3.00 (dd, $J=18, 15$ Hz)		
9-Heq	2.28 (dd, $J=18, 4.5$ Hz)		
11-H	5.38 (s)	5.40 (d, $J=1$ Hz)	5.42 (s)
12a-H			2.11 (br td, $J=11, 3$ Hz)
13-Hax	1.57 (q, $J=12$ Hz)	1.35 (br q, $J=12$ Hz)	1.37 (dt, $J=13.5, 11$ Hz)
13-Heq	2.45 (ddd, $J=12, 4.5, 2.5$ Hz)	2.72 (dt, $J=13, 3$ Hz)	2.86 (dt, $J=13.5, 3$ Hz)
13a-H	3.13 (br d, $J=12$ Hz)	3.27 (br d, $J=11$ Hz)	3.21 (br d, $J=11$ Hz)
OMe	3.76 (s)	3.77 (s)	3.72 (s)
Ms m/z (M^+)	343	343	343
Ir (cm^{-1})	2800-2700 1600, 1640	2800-2700 1600, 1650	2800-2700 1610, 1650



Scheme 4

Preparation of Despyrrolo Analogues of Reserpine Two 12-methoxy enones (**7**) and (**8**), described in the preceding section, have been proved to be potential intermediates for the preparation of despyrroloreserpine derivatives (**25**) and (**26**) as follows (Scheme 1). We first investigated the introduction of C_1 -unit by applying addition-elimination reaction to these enones (**7**) and (**8**) which would be potential Michael acceptors due to the inherent enone moieties. Agosta's group¹¹ had already reported a facile preparation of 3-cyanocyclohexenone from 3-methoxycyclohexenone by the addition-elimination type of the conjugate hydrocyanation with dialkylaluminum cyanide.⁷ Treatment of either the lactam (**7**) or the amine (**8**) with diethylaluminum cyanide in benzene-methylene dichloride (30:1) at 60 °C furnished the desired β -cyano enone (**13**) or (**14**) in 61 or 68% yield. Similarly, treatment of the lactam (**7**) with more safe and readily available cyanotrimethylsilane-triethylaluminum, which is known¹² as an efficient reagent for 1,4-addition of cyano group, gave the identical nitrile (**13**) in 61% yield, while the amine (**8**) was recovered completely under the same reaction conditions. Application of the most classical hydrocyanation reaction⁷ using potassium cyanide-ammonium chloride to two enones (**7**) and (**8**) was unsuccessful and the starting materials were completely recovered. The position of the nitrile group in the lactam (**13**) was firmly established by its conversion into the known¹³ 12-cyano lactam (**33**) *via* the allyl alcohol (**32**) (Scheme 5).



Scheme 5

The structure of the amine (**14**) was deduced from the spectral data and unambiguously established from its conversions into the final products (**25**) and (**26**) as described later. Thus, we have readily prepared two unsaturated nitriles (**13**) and (**14**) which are expected to have high potentiality for the following Michael addition reaction of methanol into the 11-position compared with the corresponding unsaturated ester. In the synthesis of deserpidine, Szántay¹⁴ had already investigated the Michael addition of methanol into the unsaturated ester which, however, gave only 10% yield of the desired adduct even after prolonged reaction (72 h). Since attempted direct Michael addition reaction of the nitrile (**13**) with sodium methoxide was unsuccessful, we then investigated the same reaction of the protected nitrile (**15**), which was readily prepared by treatment of the enone (**13**) with ethylene glycol in the presence of *p*-toluenesulfonic acid. Treatment of the nitrile (**15**) with sodium methoxide in absolute methanol at 60 °C gave a mixture of two adducts (**18**) and (**19**) in 58 and 29% yields, respectively, upon chromatographic separation. Both adducts (**18**) and (**19**) exhibited the same molecular ion peak at *m/z* 428 in the ms spectra. The ¹H-nmr spectra of both adducts (**18**) and (**19**) suggested that the undesired epimerization reaction occurred at the 8a-position α to a lactam carbonyl group during the course of the addition reaction. The ¹H-nmr spectrum of the adduct (**18**), particularly signal patterns [δ 3.73 (3H, s, 11-OMe), 3.44 (1H, d, *J* = 12 Hz, 11-H), and 2.68 (1H, t, *J* = 12 Hz, 12-H),] established that both 11-methoxyl and 12-cyano groups are in the equatorial orientations and *C/D-trans*-juncture was deduced from the signal patterns [δ 2.28 (1H, br dt, *J* = 12, 4 Hz, 8a-H) and 2.02 (1H, dq, *J* = 12, 2 Hz, 12a-H)]. Similarly, the structure of another adduct (**19**) was deduced from its ¹H-nmr spectrum, thus suggesting as having *C/D-trans*-juncture and 11-axial methoxyl and 12-equatorial cyano groups.

Next, we investigated the Michael addition of methanol to the amino nitrile (**16**) which was readily prepared either by protection of the enone (**14**) with ethylene glycol or reduction of the lactam (**15**) with lithium borohydride. The Michael addition of sodium methoxide to the nitrile (**16**) proceeded only slowly to give the adducts (**20-22**) in 20, 6, and 6% yields, respectively, with 42% recovery of the starting nitrile (**16**). Though we attempted optimization of the reaction to improve the yield of the desired adduct (**20**) by changing the concentration of sodium methoxide or by employing 15-Crown-5 as a complexing agent, all efforts were unsuccessful. Furthermore, attempted Michael addition reaction to the allyl alcohol (**17**), prepared by sodium borohydride reduction of the enone (**14**), has resulted in the appearance of many spots on tlc and no isolable product was obtained.

All the adducts (**20-22**) exhibited the same molecular ion peak at *m/z* 414 in the ms suggesting that they are desired addition products. Their stereostructures were established from their ¹H-nmr spectra (Table 4) and from their isomerization reactions as follows.

Table 4. Spectral Data of Adducts (20), (21), and (22)

	20	21	22
¹ H-nmr (δ ppm)			
8a-H	2.05 (br d, J=14 Hz)	2.06 (br d, J=14 Hz)	2.00 (br d, J=14 Hz)
9-Hax	2.32 (t, J=14 Hz)		2.55 (t, J=14 Hz)
9-Heq		1.60 (br d, J=14 Hz)	1.33 (br d, J=14 Hz)
11-H	3.38 (d, J=12 Hz)	3.36 (d, J=6 Hz)	3.28 (dd, J=3, 2 Hz)
12-H	3.10 (dd, J=12, 5 Hz)	3.21 (br d, J=6 Hz)	3.13 (t, J=3 Hz)
13-Hax	1.63 (br q, J=12 Hz)		
13a-H	3.08 (br d, J=12 Hz)		
OMe	3.61 (s)	3.51 (s)	3.53 (s)

First, C/D-*cis*-stereochemistry of all adducts (20-22) was deduced from the signals at δ 2.00-2.06 (br d, J= 14 Hz) due to 8a-proton. The J value (J= 12 Hz) between the 11- and 12-protons suggested that both 11-methoxyl and 12-cyano groups are in the equatorial orientations in the adduct (20). Though signal patterns due to 11- and 12-protons in the adduct (21) gave no affirmative information on the configuration of methoxyl and cyano groups, we deduced that 21 is an epimer with respect of the configuration at the 12-position of the adduct (20) from the fact that the adduct (21) was readily isomerized into the former adduct (20) by treatment with sodium hydride. Though the axial orientation of 11-methoxyl group in the third adduct (22) was deduced from the observation of a W-shaped long-range coupling between 9- and 11-protons in the ¹H-nmr, the configuration of the cyano group remained to be determined. The conversion of the main adduct (20) into the final product (25) was accomplished by three reaction processes. Deprotection of the acetal group by treatment with 4N-hydrochloric acid, reduction of the resulting ketone (23) with sodium borohydride, and acylation of a mixture of two epimeric alcohols (24) with 3,4,5-trimethoxybenzoyl chloride in the presence of triethylamine and 4-dimethylaminopyridine gave a mixture of two products (25) and (26) which were readily separated by preparative tlc. Their stereostructures were firmly established from their spectral data, particularly, comparison of the ¹H-nmr signals due to 10-proton appeared at δ 5.04 (ddd, J= 12.5, 9, 6 Hz) in 25 and at δ 5.73 (br s) in 26. Thus, the stereochemistry of the substituents on the D ring has been proved identical with that of natural reserpine¹⁵ from the fact that the signal patterns due to 10-, 11-, and 12-protons in the product (25) are close to those of natural reserpine. Two products (25) and (26) have been tested for their pharmacological activity.

EXPERIMENTAL SECTION

$^1\text{H-Nmr}$ spectra were measured with JEOL PMX-60 and Varian XL-200 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), ms spectra with Hitachi M-80 instruments, and ir spectra for solutions in chloroform on a Hitachi 215 spectrophotometer. Mps were determined with Kofler-type hot-stage apparatus. The extracts from the reaction mixtures were dried over anhydrous sodium sulfate. Photochemical reactions were carried out by irradiation with a high-pressure (100 or 300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100 or PIH-300); during irradiation the solutions were kept at $0-5^\circ\text{C}$ whilst being stirred and treated with bubbling nitrogen. Ether refers to diethyl ether. All other reactions were carried out in a nitrogen stream. Thin layer chromatography (tlc) was performed on pre-coated silica gel 60F-254 plates (0.25 mm thick, Merck) and preparative tlc (p-tlc) on pre-coated silica gel 60F-254 plates (0.5 mm thick, Merck), and spots were detected by ultraviolet irradiation of the plates at 254 and 300 nm or exposure to iodine vapor. Medium-pressure column chromatography (MCC) was undertaken on a Yamazen 530-10V using a Lobar grosse B column (310-25, Lichroprep Si60, Merck). Short column chromatography (SCC) was undertaken on a short glass filter using silica gel 60F-254 (Merck) under reduced pressure.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(3,5-dimethoxybenzoyl)-1-methyleneisoquinoline (4). A solution of 3,5-dimethoxybenzoyl chloride (1.14 g, 5.7 mmol) in benzene (30 ml) was added to a solution of the imine (3) (1.2 g, 5.85 mmol) and triethylamine (0.6 g, 6 mmol) in benzene (50 ml) with stirring at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide (4) (2 g, 99 %) as a pale yellow amorphous after trituration by ether. Ir: 1630 (NCO) cm^{-1} . $^1\text{H-Nmr}$ (60 MHz) δ : 5.25, 4.53 (each 1H, br s, $\text{C}=\text{CH}_2$), 3.85 (6H, s, OMex2), 3.68 (6H, s, OMex2).

Reductive Photocyclization of Enamide (4) in the Presence of Sodium Borohydride.

Sodium borohydride (570 mg, 15 mmol) and methanol (30 ml) were added successively to a stirred solution of the enamide (4) (553 mg, 1.5 mmol) in the solvent as shown in Table 1 at room temperature. When the added sodium borohydride had dissolved, the resulting solution was cooled at $0-5^\circ\text{C}$ and irradiated for 30 min.

(1) Irradiation in Benzene:Methanol=10:1. After being diluted with benzene, the reaction mixture was washed, dried, and evaporated to give a residue which was dissolved in a mixture of THF (40 ml) and 10% HCl (1.7 ml) at 0°C . After being stirred at 0°C for 1 h, the reaction mixture was diluted with water, made alkaline by adding saturated aqueous sodium bicarbonate, and then extracted

with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by SCC (hexane:methylene dichloride=1:1) to afford (8 α ,12 α ,13 α)-(±)-5,8a,9,12a,13,13a-hexahydro-2,3,12-trimethoxy-6*H*-dibenzo[*a,g*]quinolizine-8,10-dione (**7**) (280 mg, 44%) as colorless crystals, and (8 α ,12 α ,13 α)-(±)-5,8a,9,12a,13,13a-hexahydro-2,3,10-trimethoxy-6*H*-dibenzo[*a,g*]quinolizine-8,12-dione (**11**) (101 mg, 16%) as colorless crystals.

7: mp 184-187 °C (from ether-methanol). Ir: 1640, 1615 (MeOC=C-CO)cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.72, 6.68 (each 1H, s, 1-, 4-H), 5.48 (1H, s, 11-H), 4.95-4.85 (1H, m, 6-Heq), 4.78 (1H, dd, J= 13, 5 Hz, 13a-H), 3.92, 3.90 (each 3H, s, OMex₂), 3.80 (3H, s, OMe), 3.19 (1H, dt, J= 13, 5 Hz, 8a-H), 2.94 (1H, ddd, J= 13, 5, 3 Hz, 12a-H), 2.84 (1H, dd, J= 18, 5 Hz, 9-Heq), 2.78-2.66 (1H, m, 13-Heq), 2.42 (1H, dd, J= 18, 13 Hz, 9-Hax), 1.89 (1H, q, J= 13 Hz, 13-Hax). *Anal.* Calcd for C₂₀H₂₃NO₅: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.97; H, 6.54; N, 4.03.

11: mp 222-224 °C (from methanol). Ir: 1645, 1605 (MeOC=C-CO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.82, 6.66 (each 1H, s, 1-, 4-H), 5.49 (1H, s, 11-H), 5.00-4.80 (1H, m, 6-Heq), 4.70 (1H, dd, J= 12, 5 Hz, 3-H), 3.92, 3.88 (each 3H, s, OMex₂), 3.78 (3H, s, OMe), 3.29 (1H, ddd, J= 13, 5, 2 Hz, 13-Heq), 1.52 (1H, br q, J= 13 Hz, 13-Hax). *Anal.* Calcd for C₂₀H₂₃NO₅ 1/4H₂O: C, 66.38; H, 6.58; N, 3.87. Found: C, 66.25; H, 6.76; N, 3.75.

(2) Irradiation in THF:Methanol=9:1. The reaction mixture was then evaporated at room temperature under reduced pressure. Water was added to the residue and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was treated with 10% HCl as described in (1). Purification of the crude product with SCC (hexane:methylene dichloride=1:1) gave three lactams (**7**) (299 mg, 47%), (**11**) (290 mg, 46%) and (8 α ,12 α ,13 α)-(±)-5,8a,9,12a,13,13a-hexahydro-2,3,10-trimethoxy-6*H*-dibenzo[*a,g*]quinolizine-8,12-dione (**10**) (6 mg, 1%), of which the former two lactams (**7**) and (**11**) were identical respectively with the samples obtained in (1), upon comparisons of their R_f values and ir and nmr spectra.

10: colorless crystals. mp 184-185 °C (from hexane-benzene). Ir: 1640, 1605 (MeOC=C-CO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.72, 6.66 (each 1H, s, 1-, 4-H), 5.47 (1H, d, J= 1 Hz, 11-H), 4.92-4.81 (1H, m, 6-Heq), 4.74 (1H, dd, J= 12, 5 Hz, 13a-H), 3.90, 3.88 (each 3H, s, OMex₂), 3.76 (3H, s, OMe), 3.18 (1H, dd, J= 12, 6 Hz, 8a-H), 2.84 (1H, dd, J= 17, 6 Hz, 9-Heq), 2.63 (1H, ddd, J= 17, 12, 1 Hz, 9-Hax), 1.91 (1H, q, J= 12 Hz, 13-Hax). High-resolution ms *m/z*: Calcd for C₂₀H₂₃NO₅ (M⁺) 357.1572. Found: 357.1567.

(3) Irradiation in Acetonitrile:Methanol=10:1. The same work-up as described in (2) and purification of the crude product by MCC (ethyl acetate) gave two lactams (**7**) (102 mg, 17%) and (**10**) (30 mg, 5%), which were identical respectively with the samples obtained in (2), upon comparisons of their R_f values and ir and nmr spectra.

Reductive Photocyclization of Enamide (4) in the Presence of Lithium Borohydride.

(1) Irradiation in THF:Methanol=10:1. Lithium borohydride (589 mg, 37 mmol) and methanol (30 ml) were added successively to a stirred solution of the enamide (4) (553 mg, 1.5 mmol) in THF (300 ml) at 0-5°C. When the added lithium borohydride had dissolved, the resulting solution was irradiated at 0-5°C for 30 min. Same work-up as described in reductive photocyclization in the presence of sodium borohydride and hydrolysis of the crude product by stirring in a mixture of 10% HCl (1.7 ml) and THF (40 ml) at 0°C for 1 h gave a mixture of the photocyclized products which was purified by MCC (hexane:ethyl acetate=1:2) to afford (8 α ,12 α ,13 α)-(±)-5,8a,9,12a,13,13a-hexahydro-2,3,12-trimethoxy-6H-dibenzo[a,g]quinolizin-10(8H)-one (8) (230 mg, 45%), *cis-syn*-12-methoxy lactam (7) (64 mg, 10%), *trans-syn*-10-methoxy lactam (11) (64 mg, 10%), and *cis-syn*-10-methoxy lactams (10) (3 mg, 0.5 %), respectively. Three lactams (7), (10), and (11) were identical respectively with the samples obtained by the reductive photocyclization of the enamide (4) in the presence of sodium borohydride upon comparisons of their R_f values and ir and nmr spectra.

8: colorless crystals. mp 137-140 °C(from hexane-benzene). Ir: 2800-2700 (Bohlmann bands), 1640, 1600 (MeOC=C-CO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.70, 6.62 (each 1H, s, 1-, 4-H), 5.38 (1H, s, 11-H), 3.88, 3.86 (each 3H, s, OMex2), 3.76 (3H, s, OMe), 3.13 (1H, br d, J= 12 Hz, 13a-H), 3.00 (1H, dd, J= 18, 15 Hz, 9-Hax), 2.45 (1H, ddd, J= 12, 4.5, 2.5 Hz, 13-Heq), 2.28 (1H, dd, J= 18, 4.5 Hz, 9-Heq), 1.57 (1H, q, J= 12 Hz, 13-Hax). Anal. Calcd for C₂₀H₂₅NO₄: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.03; H, 7.35; N, 3.97.

(2) Irradiation in THF. The same reaction condition except using THF as a solvent and purification of the crude product as described in (1) afforded *cis-syn*-12-methoxy amine (8) (77 mg, 15%), *cis-syn*-12-methoxy lactam (7) (141 mg, 22%), *cis-syn*-10-methoxy lactam (10) (13 mg, 2%), and *trans-syn*-10-methoxy lactam (11) (64 mg, 10%). All products (7), (8), (10), and (11) were identical respectively with the samples obtained in (1) upon comparisons of their R_f values and ir and nmr spectra.

Reduction of Photocyclized Lactam (5) with Lithium Borohydride. Lithium borohydride (589 mg, 37 mmol) and methanol (27 ml) were slowly and successively added to a THF solution (270 ml) of the residue, which was obtained by reductive photocyclization of the enamide (4) (553 mg, 1.5 mmol) in benzene (300 ml), under ice-cooling. After the mixture was stirred at room temperature for 30 min, the solvent was evaporated. The residue was extracted with methylene dichloride. The extract was washed, dried, and evaporated. Hydrolysis of the residue by stirring in a mixture of 10% HCl (1.7 ml) and THF (40 ml) followed by purification by MCC (hexane:ethyl acetate=1:2) afforded *cis-syn*-12-methoxy amine (8) (228 mg, 45%), *cis-syn*-12-methoxy lactam (7) (63 mg, 10%), *cis-syn*-10-methoxy lactam (10) (5 mg, 1%), and *trans-syn*-10-methoxy lactam (11) (64 mg, 10%). Products (7), (10), and

(11) were identical respectively with the samples obtained by reductive photocyclization of the enamide (4) in the presence of sodium borohydride. The product (8) was also identical with the sample obtained by reductive photocyclization of the enamide (4) in the presence of lithium borohydride.

Reduction of Photocyclized Lactam (5) with Lithium Aluminum Hydride. Under the usual manner, reduction of the crude product, prepared by reductive photocyclization of the enamide (4) (553 mg, 1.5 mmol) in benzene (300 ml) in the presence of sodium borohydride, with lithium aluminum hydride (1 g, 26 mmol) in ether (30 ml) gave the crude amine. Hydrolysis of the crude product in a mixture of 10% HCl (1.7 ml) and THF (40 ml) followed by purification by MCC (hexane:ethyl acetate=1:2) gave *cis-syn*-12-methoxy amine (8) (130 mg, 20%), (8 α , 12 $\alpha\beta$, 13 $\alpha\beta$)-(±)-5,8 α ,9,12 α ,13,13 α -hexahydro-2,3,10-trimethoxy-6*H*-dibenzo[*a,g*]quinolizin-12(8*H*)-one (12) (67 mg, 10%) and (8 α , 12 $\alpha\beta$, 13 $\alpha\beta$)-(±)-5,8 α ,9,12 α ,13,13 α -hexahydro-2,3,12-trimethoxy-6*H*-dibenzo[*a,g*]quinolizin-10(8*H*)-one (9) (118 mg, 18%). Ir and nmr spectra of 8 were superimposable to those of the sample obtained by reductive photocyclization of 4 in the presence of lithium borohydride and the subsequent hydrolysis of the photocyclized product.

12: colorless crystals. mp 162-164°C (from hexane-benzene). Ir: 2800-2700 (Bohlmann bands), 1650, 1610 (MeOC=C-CO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.84, 6.61 (each 1H, s, 1-, 4-H), 5.42 (1H, s, 11-H), 3.90, 3.86 (each 3H, s, OMex₂), 3.72 (3H, s, OMe), 3.21 (1H, br d, J= 11 Hz, 13 α -H), 2.86 (1H, dt, J= 13.5, 3 Hz, 13-Heq), 2.11 (1H, br td, J= 11, 3 Hz, 12 α -H), 1.37 (1H, dt, J= 13.5, 11 Hz, 13-Hax). *Anal.* Calcd for C₂₀H₂₅NO₄: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.14; H, 7.48; N, 3.94.

9: colorless crystals. mp 158-160°C (from hexane-benzene). Ir: 2800-2700 (Bohlmann bands), 1650, 1600 (MeOC=C-CO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.78, 6.63 (each 1H, s, 1-, 4-H), 5.40 (1H, d, J= 1 Hz, 11-H), 3.95, 3.87 (each 3H, s, OMex₂), 3.77 (3H, s, OMe), 3.27 (1H, br d, J= 11 Hz, 13 α -H), 2.72 (1H, dt, J= 13, 3 Hz, 13-Heq), 1.35 (1H, br q, J= 12 Hz, 13-Hax). *Anal.* Calcd for C₂₀H₂₅NO₄: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.79; H, 7.39; N, 4.00.

Conversion of *cis-syn*-12-Methoxy Lactam (7) into 5,6-Dihydro-2,3,12-trimethoxy-8*H*-dibenzo[*a,g*]quinolizin-8-one (28). According to the usual manner, reduction of *cis-syn*-12-methoxy lactam (7) (40 mg, 0.1 mmol) with sodium borohydride (38 mg, 1 mmol) in methanol (10 ml) gave the allyl alcohol (27) which was successively heated at 200 °C under neat condition to give the aromatized lactam (28) (20 mg, 53%) after purification by p-tlc (methylene dichloride:methanol= 98:2). The lactam (28) is identical with the authentic sample¹⁰ upon comparisons of their spectral data. **27:** ¹H-Nmr (60 MHz) δ : 6.63, 6.57 (each 1H, s, 1-, 4-H), 4.97-4.30 (3H, m, 6-Heq, 11-, 13 α -H), 3.83 (6H, s, OMex₂), 3.57 (3H, s, OMe).

Conversion of *trans-syn*-10-Methoxy Lactam (11) into 5,6-Dihydro-2,3,10-trimethoxy-8*H*-dibenzo[*a,g*]quinolizin-8-one (30). According to the reduction procedure described for 7, treatment of the lactam (11) (40 mg, 0.1 mmol) with sodium borohydride (38 mg, 1 mmol) gave (8 α ,12 α ,13 α)-(\pm)-5,6,8 α ,9,12,12 α ,13,13 α -octahydro-12-hydroxy-2,3,10-trimethoxy-8*H*-dibenzo[*a,g*]quinolizin-8-one (29) which, without purification, was heated at 200 °C under neat condition to give the aromatized lactam (30) (15 mg, 49%). The lactam (30) is identical with the authentic sample¹⁰ upon comparisons of their spectral data.

29: ¹H-Nmr (60 MHz) δ : 6.63, 6.50 (each 1H, s, 1-, 4-H), 4.87-4.34 (3H, m, 6-Heq, 11-, 13a-H), 3.77 (6H, s, OMex2), 3.47 (3H, s, OMe).

(8 α ,12 α ,13 α)-(\pm)-5,8,8 α ,9,12,12 α ,13,13 α -Octahydro-2,3,10-trimethoxy-6*H*-dibenzo[*a,g*]quinolizin-12-ol (31). A solution of the 10-methoxy lactam (11) (10 mg, 0.03 mmol) or 10-methoxy amine (12) (11 mg, 0.03 mmol) and lithium borohydride (11.3 mg, 0.3 mmol) in THF-methanol (15:1)(1.6 ml) was stirred at 0 °C for 1 h. Water was added to the reaction mixture which was then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p-tlc(methylene dichloride:methanol=96:4) to afford the allyl alcohol (31) (5-9 mg, 52-81%) as colorless crystals, mp 169-171°C (from ether). Ir: 3400 (OH) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.80, 6.61 (each 1H, s, 1-, 4-H), 4.74 (1H, br s, OH), 4.68 (1H, br s, 11-H), 4.09 (1H, br d, J= 6 Hz, 12-H), 3.87, 3.84 (each 3H, s, OMex2), 3.56 (3H, s, OMe), 3.15 (1H, br d, J= 10 Hz, 13a-H). *Anal.* Calcd for C₂₀H₂₇NO₄ 1/4H₂O: C, 68.65; H, 7.92; N, 4.00. Found: C, 68.60; H, 7.89; N, 4.03.

(8 α ,12 α ,13 α)-(\pm)-5,8,8 α ,9,10,12 α ,13,13 α -Octahydro-2,3-dimethoxy-8,10-dioxo-6*H*-dibenzo[*a,g*]quinolizine-12-carbonitrile (13).

(1) With Diethylaluminum Cyanide Diethylaluminum cyanide (1.3 M solution in benzene) (5 ml, 6.5 mmol) was added every 40 min to a solution of *cis-syn*-12-methoxy lactam (7) (300 mg, 0.85 mmol) in benzene-methylene dichloride (30:1)(20 ml) with stirring. After being refluxed for 3.5 h, 0.05% sodium hydroxide was added to the reaction mixture which was extracted with methylene dichloride. The extract was washed with 5% aqueous sodium bicarbonate, water, dried, and evaporated to give a residue which was purified by SCC (hexane:ethyl acetate=2:1) to afford the starting material (7) (36.5 mg, 12%) and the nitrile (13) (182 mg, 61%) as yellow crystals, mp 123-127 °C (from ether-methanol-methylene dichloride).

13: Ir: 2225 (CN), 1690 (C=C-CO), 1625 (NCO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.73, 6.69 (each 1H, s, 1-, 4-H), 6.62 (1H, s, 11-H), 4.94-4.74 (1H, m, 6-Heq), 4.84 (1H, dd, J= 12, 5 Hz, 13a-H), 3.92, 3.90 (each 3H, s, OMex2), 3.27 (1H, dt, J= 13, 5 Hz, 8 α -H), 2.98 (1H, dd, J= 17, 5 Hz, 9-Heq), 2.54 (1H, dd,

$J = 17, 13$ Hz, 9-Hax), 1.89 (1H, br q, $J = 12$ Hz, 13-Hax). *Anal.* Calcd for $C_{20}H_{20}N_2O_4 \cdot 2/3H_2O$: C, 65.92; H, 5.90; N, 7.69. Found: C, 65.75; H, 5.86; N, 7.86.

(2) With Cyanotrimethylsilane-Triethylaluminum. Cyanotrimethylsilane (0.32 ml, 2.3 mmol) and triethylaluminum (1.0 M solution in hexane) (2.3 ml, 2.3 mmol) were successively added to a solution of *cis-syn*-12-methoxy lactam (7) (400 mg, 1.12 mmol) in THF (100 ml). After being refluxed for 1.5 h, 10% aqueous ammonium chloride was added to the reaction mixture which was extracted with methylene dichloride. The extract was washed with saturated aqueous sodium bicarbonate, water, dried, and evaporated to give a residue which was purified with SCC (hexane:methylene dichloride=1:1) to afford the nitrile (13) (240 mg, 61%). The product (13) was identical with the sample obtained in (1) upon comparisons of their R_f values and ir and nmr spectra..

Conversion of Nitrile (13) into 5,8-Dihydro-2,3-dimethoxy-8-oxo-6H-dibenzo[a,g]-quinolizine-12-carbonitrile (33). According to the reduction procedure described for 7, treatment of the nitrile (13) (20 mg, 0.06 mmol) with sodium borohydride (9 mg, 0.24 mmol) gave (8 α ,12 α ,13 α)-(±)-5,8,8a,9,10,12a,13,13a-octahydro-10-hydroxy-2,3-dimethoxy-8-oxo-6H-dibenzo[a,g]quinolizine-12-carbonitrile (32) which, without purification, was heated at 200°C in the presence of 10% palladium on carbon (10 mg) for 40 min to give the aromatized lactam (33) (8 mg, 43%). The nitrile (33) was identical with the authentic sample¹³ upon comparisons of their spectral data.

33: Ir: 3380 (OH), 2225 (CN), 1625 (NCO) cm^{-1} . 1H -Nmr (200 MHz) δ : 6.72 (2H, br s, 11-, 1- or 4-H), 6.68 (1H, s, 1- or 4-H), 4.74 (1H, dd, $J = 11, 3.5$ Hz, 13a-H), 4.48 (1H, br q, $J = 7$ Hz, 10-H), 3.92, 3.90 (each 3H, s, OMex2), 3.19 (1H, br d, $J = 6.5$ Hz, OH), 2.48 (1H, br dd, $J = 13, 5$ Hz, 9-Heq), 1.74 (1H, t, $J = 13$ Hz, 9-Hax), 1.72 (1H, br q, $J = 11$ Hz, 13-Hax).

(8 α ,12 α ,13 α)-(±)-5,8,8a,9,10,12a,13,13a-Octahydro-2,3-dimethoxy-10-oxo-6H-dibenzo[a,g]quinolizine-12-carbonitrile (14). According to the procedure described in the preparation of 13, treatment of the amine (8) (277 mg, 0.8 mmol) with triethylaluminum cyanide (1.3 M solution in benzene) (5 ml, 6.5 mmol) followed by purification of the crude product with SCC (hexane:ethyl acetate=3:2) gave the starting material (8) (47 mg, 17%) and the nitrile (14) (185 mg, 68%) as colorless glass. Ir: 2800-2700 (Bohlmann band), 2230 (CN), 1675 (C=C-CO) cm^{-1} . 1H -Nmr (200 MHz) δ : 6.70, 6.63 (each 1H, s, 1-, 4-H), 6.54 (1H, s, 11-H), 3.90, 3.87 (each 3H, s, OMex2), 3.22 (1H, br d, $J = 12$ Hz, 13a-H), 3.11 (1H, dd, $J = 18, 15$ Hz, 9-Hax), 2.45 (1H, dd, $J = 18, 4.5$, 9-Heq), 1.55 (1H, br q, $J = 12$ Hz, 13-Hax). High-resolution ms m/z : Calcd $C_{20}H_{22}N_2O_3$ (M^+) 338.1628. Found: 338.1612.

(8 α ,12 α ,13 α)-(±)-5,8a,9,12a,13,13a-Hexahydro-2,3-dimethoxy-8-oxospiro[6H-dibenzo[*a,g*]quinolizine-10(8H),2'-[1,3]dioxolane]-12-carbonitrile (15). A solution of the nitrile (13) (109 mg, 0.3 mmol), *p*-toluenesulfonic acid (153 mg, 0.9 mmol), ethylene glycol (3.1 g) in benzene (164 ml) was refluxed with a Dean-Stark apparatus for 40 min. The reaction mixture was washed with saturated aqueous sodium bicarbonate, water, dried, and evaporated to give a residue which was purified with SCC (hexane:methylene dichloride=1:1) to afford the acetal (15) (111 mg, 91%) as colorless crystals. mp 107-108°C (from hexane-benzene) Ir: 2220 (CN), 1625 (NCO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.72, 6.66 (each 1H, s, 1-, 4-H), 6.45 (1H, br s, 11-H), 4.92-4.82 (1H, m, 6-Heq), 4.74 (1H, dd, J= 12, 4 Hz, 13a-H), 4.15-3.97 (4H, m, OCH₂CH₂O), 3.92, 3.89 (each 3H, s, OMex₂), 3.09 (1H, dt, J= 13, 4 Hz, 8a-H), 2.33 (1H, br ddd, J= 13, 4, 2 Hz, 9-Heq), 1.76 (1H, t, J= 13 Hz, 9-Hax), 1.69 (1H, br q, J= 12 Hz, 13-Hax). Anal. Calcd for C₂₂H₂₄N₂O₅ C₆H₆: C, 70.87; H, 6.37; N, 5.90. Found: C, 70.74; H, 6.47; N, 5.74.

Michael Reaction of Nitrile (15). A solution of the nitrile (15) (11 mg, 0.03 mmol) in methanol (3 ml) was added to a methanolic solution of sodium methoxide, prepared from sodium (210 mg, 9 mmol) and methanol (3 ml). The resulting solution was stirred at 60 °C for 2 h. Water was added to the reaction mixture which was then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified by p-tlc (ethyl acetate:methanol=99:1) to afford the starting material (15) (1 mg, 10%). (8 α ,11 α ,12 β ,12a β , 13a β)-(±)-5,8a,9,11,12,12a,13,13a-octahydro-2,3,11-trimethoxy-8-oxospiro[6H-dibenzo[*a,g*]quinolizine-10(8H),2'-[1,3]dioxolane]-12-carbonitrile (18) (7.4 mg, 58%), and (8 α ,11 β ,12 β ,12a β ,13a β)-(±)-5,8a,9,11,12,12a,13,13a-octahydro-2,3,11-trimethoxy-8-oxospiro[6H-dibenzo[*a,g*]quinolizine-10(8H),2'-[1,3]dioxolane]-12-carbonitrile (19) (3.7 mg, 29%).

18: pale-yellow glass. Ir: 2240 (CN), 1625 (NCO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.73, 6.66 (each 1H, s, 1-, 4-H), 4.94-4.81 (1H, m, 6-Heq), 4.74 (1H, dd, J= 12, 6 Hz, 13a-H), 4.23-3.98 (4H, m, OCH₂CH₂O), 3.92, 3.90 (each 3H, s, OMex₂), 3.73 (3H, s, OMe), 3.44 (1H, d, J= 12 Hz, 11-H), 2.90 (1H, ddd, J= 12, 6, 2 Hz, 13-Heq), 2.68 (1H, t, J= 12 Hz, 12-H), 2.50 (1H, dd, J= 13, 4 Hz, 9-Heq), 2.28 (1H, br td, J= 12, 4 Hz, 8a-H), 2.02 (1H, qd, J= 12, 2 Hz, 12a-H), 1.61 (1H, q, J= 12 Hz, 13-Hax), 1.54 (1H, t, J= 13 Hz, 9-Hax). High-resolution ms m/z: Calcd C₂₃H₂₈N₂O₆ (M⁺) 428.1945. Found: 428.1933.

19: pale-yellow glass. Ir: 2240 (CN), 1625 (NCO) cm⁻¹. ¹H-Nmr (200 MHz) δ : 6.72, 6.64 (each 1H, s, 1-, 4-H), 4.89-4.80 (1H, m, 6-Heq), 4.72 (1H, dd, J= 12, 5 Hz, 13a-H), 4.18-3.92 (4H, m, OCH₂CH₂O), 3.90, 3.88 (each 3H, s, OMex₂), 3.69 (3H, s, OMe), 3.38 (1H, dd, J= 3, 1 Hz, 11-H), 2.73 (1H, dd, J= 12, 3 Hz, 12-H), 2.15 (1H, br td, J= 12, 4 Hz, 8a-H), 1.88 (1H, t, J= 13 Hz, 9-Hax), 1.51 (1H, br q, J= 12 Hz, 13-Hax). High-resolution ms m/z: Calcd C₂₃H₂₈N₂O₆ (M⁺) 428.1946. Found: 428.1958.

(8 α , 12 α , 13 α)-(±)-5,8a,9,12a,13,13a-Hexahydro-2,3-dimethoxySpiro[6*H*-dibenzo[*a,g*]quinolizine-10(8*H*),2'-[1,3]dioxolane]-12-carbonitrile (16).

(1) From Amine (14). According to the procedure described in 15, treatment of the amine (14) (40 mg, 0.1 mmol) with ethylene glycol (2.2 g) in the presence of *p*-toluenesulfonic acid (68 mg, 0.4 mmol) followed by purification of the crude product with p-tlc (hexane:ethyl acetate=1:1) gave the acetal (16) (42 mg, 93%) as yellow glass.

16: Ir: 2800-2700 (Bohlmann bands), 2230 (CN) cm^{-1} . $^1\text{H-Nmr}$ (200 MHz) δ : 6.71, 6.61 (each 1H, s, 1-, 4-H), 6.35 (1H, d, $J = 1$ Hz, 11-H), 4.12-3.91 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.89, 3.87 (each 3H, s, OMex2), 3.10 (1H, br d, $J = 12$ Hz, 13a-H), 2.20 (1H, br d, $J = 13$ Hz, 8a-H), 1.71 (1H, dt, $J = 13, 1$ Hz, 9-Heq), 1.46 (1H, br q, $J = 12$ Hz, 13-Hax). High-resolution ms m/z : Calcd $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$ (M^+) 382.1891. Found: 382.1922.

(2) From Lactam (15). According to the procedure given for 31, treatment of the lactam (15) (70 mg, 0.2 mmol) with lithium borohydride (116 mg, 5.3 mmol) followed by the purification of the crude product with SCC (hexane:methylene dichloride=1:1) gave the amine (16) (58 mg, 86%) which was identical with the sample prepared in (1) upon comparison of their spectral data.

Michael Reaction of Amine (16). According to the procedure given for 18 and 19, treatment of the nitrile (16) (142 mg, 0.4 mmol) with sodium methoxide, prepared from sodium (1.25 g, 54 mmol) and methanol (25 ml), followed by the purification of the crude product with MCC (methylene dichloride) gave (8 α , 11 α , 12 β , 12 α , 13 α)-(±)-5,8a,9,11,12,12a,13,13a-octahydro-2,3,11-trimethoxySpiro[6*H*-dibenzo[*a,g*]quinolizine-10(8*H*),2'-[1,3]dioxolane]-12-carbonitrile (20) (30 mg, 20%), (8 α , 11 α , 12 α , 12 α , 13 α)-(±)-5,8a,9,11,12,12a,13,13a-octahydro-2,3,11-trimethoxySpiro[6*H*-dibenzo[*a,g*]quinolizine-10(8*H*),2'-[1,3]dioxolane]-12-carbonitrile (21) (9 mg, 6%), and (8 α , 11 β , 12 α , 13 α)-(±)-5,8a,9,11,12,12a,13, 13a-octahydro-2,3,11-trimethoxySpiro[6*H*-dibenzo[*a,g*]quinolizine-10(8*H*),2'-[1,3]dioxolane] -12-carbonitrile (22) (9 mg, 6%).

20: pale-yellow glass. Ir: 2800-2700 (Bohlmann bands), 2250 (CN) cm^{-1} . $^1\text{H-Nmr}$ (200 MHz) δ : 6.77, 6.61 (each 1H, s, 1-, 4-H), 4.20-3.94 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.89, 3.86 (each 3H, s, OMex2), 3.61 (3H, s, OMe), 3.38 (1H, d, $J = 12$ Hz, 11-H), 3.10 (1H, dd, $J = 12, 5$ Hz, 12-H), 3.08 (1H, br d, $J = 12$ Hz, 13a-H), 2.32 (1H, t, $J = 14$ Hz, 9-Hax), 2.05 (1H, br d, $J = 14$ Hz, 8a-H), 1.63 (1H, br q, $J = 12$ Hz, 13-Hax). High-resolution ms m/z : Calcd $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5$ (M^+) 414.2152. Found: 414.2144.

21: pale-yellow glass. $^1\text{H-Nmr}$ (200 MHz) δ : 6.68, 6.63 (each 1H, s, 1-, 4-H), 4.16-3.94 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.90, 3.86 (each 3H, s, OMex2), 3.51 (3H, s, OMe), 3.36 (1H, d, $J = 6$ Hz, 11-H), 3.21 (1H, br d, $J = 6$ Hz, 12-H), 2.06 (1H, br d, $J = 14$ Hz, 8a-H), 1.59 (1H, br d, $J = 14$ Hz, 9-Heq). High-resolution ms m/z : Calcd $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5$ (M^+) 414.2152. Found: 414.2171.

22: $^1\text{H-Nmr}$ (200 MHz) δ : 6.79, 6.60 (each 1H, s, 1-, 4-H), 4.10-3.92 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.89, 3.86 (each 3H, s, OMex_2), 3.53 (3H, s, OMe), 3.28 (1H, dd, $J = 3, 2$ Hz, 11-H), 3.13 (1H, t, $J = 3$ Hz, 12-H), 2.55 (1H, t, $J = 14$ Hz, 9-Hax), 2.00 (1H, br d, $J = 14$ Hz, 8a-H), 1.33 (1H, br d, $J = 14$ Hz, 9-Heq). High-resolution ms m/z : Calcd $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5$ (M^+) 414.2152. Found: 414.2123.

Isomerization of α -Nitrile (21) to β -Isomer (20). A suspension of α -nitrile (**21**) (3 mg, 0.007 mmol) and sodium hydride (60% suspension in oil) (10 mg, 0.25 mmol) in THF-ether (1:1) (5 ml) was refluxed for 1 h. Usual work-up gave β -nitrile (**20**) (1.5 mg, 50%) which was identical with the sample (**20**) obtained by Michael reaction of **16**.

(8 α ,12 α ,13 α) - (\pm)-5,8,8a,9,10,12a,13,13a-Octahydro-10-hydroxy-2,3-dimethoxy-6H-dibenzo[*a,g*]quinolizine-12-carbonitrile (17). According to the usual manner, reduction of α , β -unsaturated ketone (**14**) (18 mg, 0.05 mmol) with sodium borohydride (30 mg, 0.8 mmol) in methanol (10 ml) and purification of the crude product with p-tlc (ethyl acetate:methanol=95:5) gave the alcohol (**17**) (13 mg, 73%) as pale-yellow glass. Ir: 3400 (OH), 2800-2700 (Bohlmann bands), 2240 (CN) cm^{-1} . $^1\text{H-Nmr}$ (200 MHz) δ : 6.72, 6.62 (each 1H, s, 1-, 4-H), 6.56 (1H, t, $J = 1$ Hz, 11-H), 4.46 (1H, br t, $J = 8$ Hz, 10-H), 3.90, 3.87 (each 3H, s, OMex_2), 3.12 (1H, br d, $J = 12$ Hz, 13a-H), 1.51 (1H, br q, $J = 12$ Hz, 13-Hax). High-resolution ms m/z : Calcd $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ (M^+) 340.1785. Found: 340.1774.

(8 α ,11 α ,12 β ,12 α ,13 α) - (\pm)-5,8,8a,9,10,11,12,12a,13,13a-Decahydro-2,3,11-trimethoxy-10-oxo-6H-dibenzo[*a,g*]quinolizine-12-carbonitrile (23). A solution of the acetal (**20**) (19 mg, 0.05 mmol) in 4M HCl (45 ml) was heated at 100°C with stirring for 2.5 h. After being cooled, the reaction mixture was made alkaline by adding saturated aqueous sodium bicarbonate and then extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue which was purified with p-tlc (acetonitrile:methylene dichloride=3:7) to afford **23** (10 mg, 60%) as yellow glass. Ir: 2800-2700 (Bohlmann bands), 2245 (CN), 1730 (CO) cm^{-1} . $^1\text{H-Nmr}$ (200 MHz) δ : 6.78, 6.62 (each 1H, s, 1-, 4-H), 3.89 (6H, s, OMex_2), 3.86 (1H, d, $J = 12$ Hz, 11-H), 3.56 (3H, s, OMe), 3.22 (1H, br t, $J = 14.5$ Hz, 9-Hax), 3.04 (1H, dd, $J = 12, 5$ Hz, 12-H), 2.36 (1H, dd, $J = 14.5, 4.5$ Hz, 9-Heq), 2.18 (1H, brd, $J = 14.5$ Hz, 8a-H), 1.79 (1H, br q, $J = 12$ Hz, 13-Hax). High-resolution ms m/z : Calcd $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4$ (M^+) 370.1891. Found: 370.1894.

Conversion of Ketone (23) to Despyrrolo Analogues (25 and 26) of Reserpine.

A solution of the ketone (23) (7 mg, 0.02 mmol) and sodium borohydride (19 mg, 0.5 mmol) in methanol (5 ml) was stirred at 0°C for 1 h. Water was added to the reaction mixture which was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the alcohol (24) which, without purification, was acylated with 3,4,5-trimethoxybenzoyl chloride (11 mg, 0.05 mmol) in the presence of dimethylaminopyridine (DMAP) (2 mg, 0.02 mmol) and triethylamine (4 mg, 0.04 mmol) in methylene dichloride (2 ml) by stirring at room temperature for 20 h. The reaction mixture was directly subjected to SCC (hexane:methylene dichloride=1:1) to remove DMAP and then purified by p-tlc (methylene dichloride:methanol=98.2:1.8) to give (8 α ,10 β ,11 α ,12 β ,12 α ,13 α)-(±)-5,8,8a,9,10,11,12,12a,13,13a-decahydro-2,3,11-trimethoxy-10-(3,4,5-trimethoxybenzoyloxy)-6H-dibenzo[a,g]quinolizine-12-carbonitrile (25) (3.6 mg, 37%) and (8 α ,10 α ,11 α ,12 β ,12 α ,13 α)-(±)-5,8,8a,9,10,11,12,12a,13,13a-decahydro-2,3,11-trimethoxy-10-(3,4,5-trimethoxybenzoyloxy)-6H-dibenzo[a,g]quinolizine-12-carbonitrile (26) (3.1 mg, 29%).

24: pale-yellow glass. ¹H-Nmr (60 MHz) δ : 6.65, 6.50 (each 1H, s, 1-, 4-H), 4.23-4.10 (1H, m, 10-H), 3.80, 3.78 (each 3H, s, OMex₂), 3.63 (1.5 H, s, OMex_{0.5}), 3.43 (1.5 H, s, OMex_{0.5}).

25: pale-yellow glass. ¹H-Nmr (200 MHz) δ : 6.82, 6.64 (each 1H, s, 1-, 4-H), 5.04 (1H, ddd, J= 12.5, 9, 6 Hz, 10-H), 3.92 (12H, s, OMex₄), 3.88 (3H, s, OMe), 3.64 (1H, dd, J= 11, 9 Hz, 11-H), 3.60 (3H, s, OMe), 3.16 (1H, br d, J= 12 Hz, 13a-H), 2.92 (1H, dd, J= 11, 5 Hz, 12-H), 1.71 (1H, br q, J= 12 Hz, 13-Hax). High-resolution ms m/z: Calcd C₃₁H₃₈N₂O₈ (M⁺) 566.2625. Found: 566.2620.

26: pale-yellow glass. ¹H-Nmr (200 MHz) δ : 6.80, 6.63 (each 1H, s, 1-, 4-H), 5.73 (1H, br s, 10-H), 3.96 (6H, s, OMex₂), 3.94, 3.91, 3.88 (each 3H, s, OMex₃), 3.51 (1H, dd, J= 11, 3 Hz, 11-H), 3.46 (3H, s, OMe), 3.30 (1H, dd, J= 11, 5 Hz, 12-H), 3.13 (1H, br d, J= 12 Hz, 13a-H), 2.13 (1H, br d, J= 13 Hz, 8a-H), 1.90 (1H, dt, J=15, 3.5 Hz, 9-Heq), 1.62 (1H, br q, J= 12 Hz, 13-Hax). High-resolution ms m/z: Calcd C₃₁H₃₈N₂O₈ (M⁺) 566.2625. Found: 566.2634.

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