

An Efficient Synthesis of Magallanesine Using [1,2]-Meisenheimer Rearrangement and Heck Cyclization

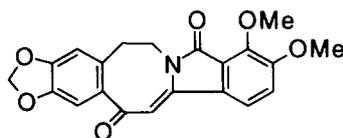
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Abstract: A straightforward total synthesis of magallanesine **1** was accomplished from readily available isoquinolineacetate **14**. This synthesis is emphasized by the following two points; i. the [1,2]-Meisenheimer rearrangement of the azetidine N-oxide **22** for the preparation of azocine ring, ii. the Pd-catalyzed intramolecular Heck reaction of N-benzoylenaminone **38** for the construction of isoindoloazocine skeleton. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

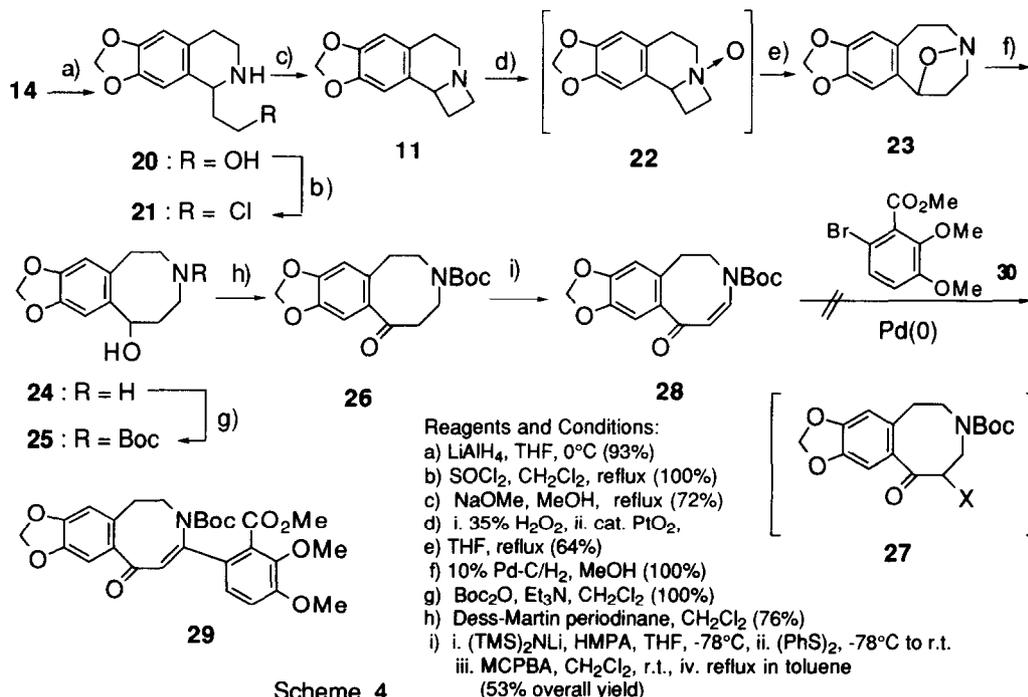
The first example of a new class of alkaloid, magallanesine **1**,^{1,2} isolated from *Berberis darwinii* Hook in 1985 by Shamma and co-workers,³ has attracted our attention due to its unique heterocyclic ring system including azocine ring. As it is rather difficult to prepare the medium membered ring systems by the cyclization of acyclic precursors, the ring-opening strategy has been favored for the synthesis.⁴



1 : Magallanesine (5,6-Dihydro-9,10-dimethoxy-1,3-dioxolo[4,5-*f*]-
isoindolo[2,1-*c*][3]benzazocine-8,14-dione)

During the course of our extensive works on the Meisenheimer rearrangements⁵ of azetopyridindole N-oxides, we found a novel ring expansion of azetidine **2** to indoloazocine **5** via reductive cleavage of the N-O bond of indoloepoxyazocine **4**⁶(Scheme 1). On the basis of the encouraging result of successful synthesis of **5**, our investigation was expanded to a total synthesis of magallanesine **1**.⁷

Next, our attention was focused on the synthesis of aryl enaminone **6** *via* Route B. Reduction of ester **14** with LiAlH_4 gave alcohol **20**, which was treated with thionyl chloride to give chloride **21** in quantitative yield (Scheme 4). Cyclization of **21** to yield azetidione **11** was successively achieved by refluxing with NaOMe ¹¹ in MeOH in 72% yield. Assignment of the structure of **11** was made on the basis of MS [m/z 203 (M^+)], and $^1\text{H-NMR}$ [δ 4.65 (dd, $J = 8.0, 3.0$ Hz, 9b-H)]. Oxidation of **11** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 ⁶ gave only tarry material because of an instability of the corresponding N-oxide under acidic condition. Accordingly, MCPBA oxidation of **11** in the presence of NaHCO_3 followed by refluxing in THF afforded the [1,2]-Meisenheimer rearrangement product **23**, which was assigned as epoxyazocine by means of MS m/z : 219 (M^+), in 41% yield. Use of magnesium monoperoxyphthalate (MMPP),¹² which is known as an useful reagent for oxidation of acid-sensitive substrates, resulted in a lowering of the amount of **23** (12%). Finally, oxidation of **11** with 35% H_2O_2 ¹³ in a mixture of CH_2Cl_2 : MeOH (1 : 1) at room temperature gave the corresponding N-oxide **22**. Refluxing of **22**, without purification, in THF gave the best result to lead **23** in 64% yield. Catalytic hydrogenation of **23** over 10% Pd-C gave hydroxybenzazocine **24** quantitatively, whose amino group was protected by a Boc group. After several attempts, carbamate **25** was successively oxidized with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess-Martin periodinane)¹⁴ to give ketone **26** in 76% yield. Introduction of a double bond was achieved by phenylsulfinylation [(PhS)₂ / (TMS)₂NLi in HMPA and THF] and MCPBA oxidation followed by thermolysis of the resulting sulfoxide **27** [X = S(O)Ph] in toluene to lead to an enaminone **28** in 53% yield. Attempts to prepare **28** by thermolysis of the corresponding selenoxide **27** [X = Se(O)Ph] or dehydrobromination of the bromide **27** (X = Br) gave less satisfactory results.

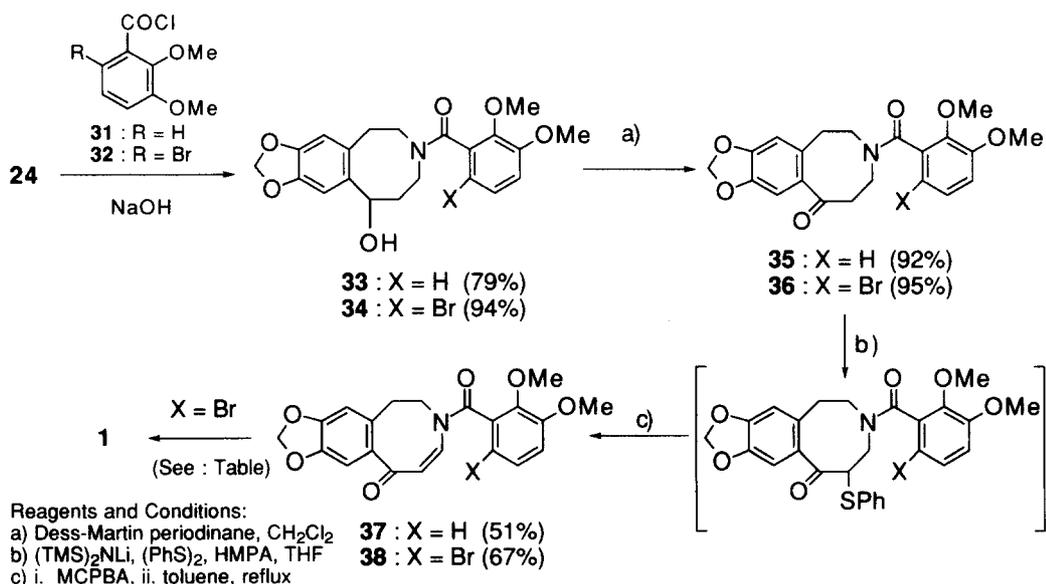


Scheme 4

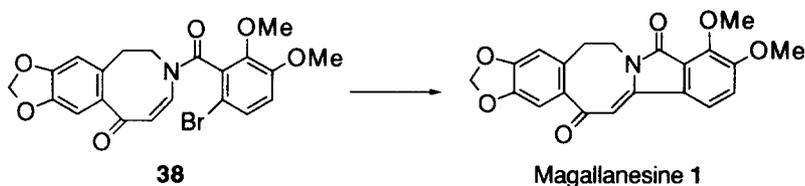
Insertion of an aromatic ring at C-4 of **28** was now required. Today, the intermolecular Heck reactions are reasonably routine.¹⁵ In arylations of β -substituted α,β -unsaturated enones with aryl halides, varying amounts of different products such as products of 1,4-addition and those of vinylic substitution, are frequently obtained.¹⁵ However, application of the Heck arylation to *N*-protected enaminones is rarely known so far. As a result of many considerations, attempted reactions of **28** with bromide **30**¹⁶ in the presence of Pd(OAc)₂ and Ph₃P using triethylamine, TIOAc¹⁷ or ⁿBu₄NCl¹⁸ as additives gave none of the arylated product **29**, with only starting material being recovered. Therefore, Route B also had to be discarded.

Total Synthesis of Magallanesine

Construction of the C-ring of **1** was then investigated by an intramolecular Heck arylation (Route C). A few examples of intramolecular cyclization of *N*-benzoyl enamines^{17,19} or *N*-benzoyl-3-formylindoles²⁰ (special *N*-benzoyl enaminones functionality) under Pd-catalyzed reaction conditions have recently been reported. Schotten-Baumann reaction of **24** with benzoyl chlorides (**31** and **32**) gave amides **33** (79%), **34** (94%), which were converted into *N*-benzoyl enaminones **37** (51%), **38** (67%) via analogous sequences used for the preparation of *N*-protected enaminone **28** (Scheme 5). When we first carried out the cyclization of **37** with a stoichiometric amount of Pd(OAc)₂ under an *ortho*-palladation method,²¹ only a complex mixture was obtained. On the other hand, treatment of the bromide **38** under ordinary Heck reaction conditions [Pd(OAc)₂ (0.1 eq), Ph₃P (0.2 eq), and triethylamine (1.2 eq) as additives (Run 1, Table)] afforded **1** in only 12% yield, with a recovery of **38** (41%). After several attempts (Runs 2~5) by changing additive (Ag₂CO₃²² or TIOAc¹⁷), solvents (MeCN or DMF), and reaction temperature, the best result for ring closure of **38** to magallanesine **1** was accomplished by means of Run 5 in 93% yield. However, the condition developed by Jeffery¹⁸ (Run 6) did not give a better result. The melting point (254-256°C) and spectral data (see Experimental) of synthesized **1** were identical with those reported³ for magallanesine **1**.



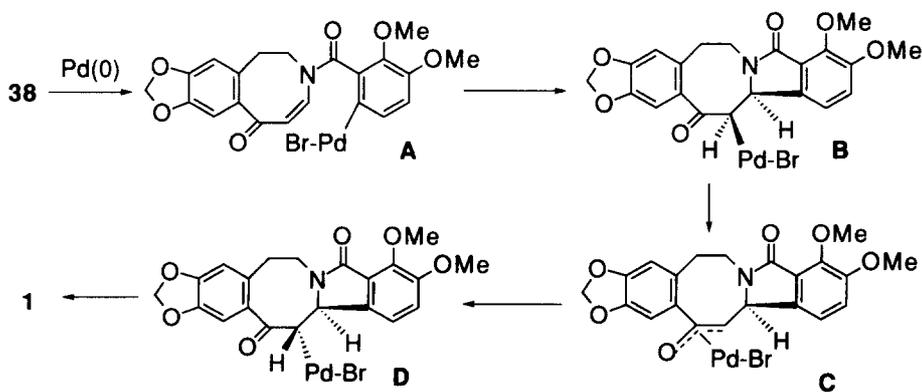
Scheme 5

Table. Palladium-catalyzed Cyclization of **38**

Run	Pd(OAc) ₂ (eq.)	Ph ₃ P (eq.)	Additive (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%) of 1 a) [Recovery of 38]
1	0.1	0.2	Et ₃ N (1.3)	MeCN	80	96	12 [41]
2	0.1	0.2	Ag ₂ CO ₃ (1.2)	MeCN	80	96	21 [62]
3	0.1	0.2	Ag ₂ CO ₃ (1.2)	DMF	130	96	25 [25]
4	0.1	0.2	TIOAc (1.2)	MeCN	80	96	36 [36]
5	0.1	0.2	TIOAc (1.2)	DMF	130	24	93 [0]
6	0.05	-	<i>n</i> Bu ₄ NCl (1.0) NaHCO ₃ (2.5)	DMF	50	24	41 [10]

a) Determine by ¹H-NMR

After publication of our short communication,⁷ Comins and co-workers²³ reported intramolecular Heck reactions of *N*-(2-iodobenzoyl)-2,3-dihydro-4-pyridones, which had the almost same functionality as **38**. A reasonable explanation for the formation of **1** from **38** involves the initial formation of *syn*-cyclization product **B**, which has the unfavorable stereochemistry for the *syn* elimination of HPdBr, via σ -complex **A**. Since the PdBr moiety of **B** is located at the enolizable position, the isomerized new σ -complex **D**, which has the favorable stereochemistry for *syn*-elimination of HPdBr, must be formed *via* the enol complex **C**.^{19, 24}



Scheme 6

In conclusion, we have established straightforward synthesis of magallanesine **1** in 24% overall yield from isoquinolineacetate **14** in 10 steps. The key transformation in the synthesis is the [1,2]-Meisenheimer rearrangement of azetidine N-oxide **22** to lead epoxyazocine **23**. In addition, an efficient Pd-catalyzed intramolecular Heck arylation of **38** is also noteworthy for the construction of isoindoloazocine skeleton.

Experimental

General. Melting points (mp) were determined on a Yanagimoto micromelting point apparatus and were uncorrected. The IR spectra were recorded on a Shimadzu IR-435 spectrometer. The ^1H - and ^{13}C -NMR spectra were measured in deuteriochloroform, unless otherwise stated, with a Varian Gemini-200 spectrometer; signals are given in ppm. Low-resolution and high-resolution mass (HR-MS) were recorded on a Hitachi M-4000H instrument. All reactions with air- and moisture-sensitive compounds were carried out under an nitrogen atmosphere. Unless other noted, all extracts were dried over Na_2SO_4 , and the solvent was removed by rotary evaporator under reduced pressure. THF was distilled from sodium-benzophenone. For column chromatography, FL-60D (Fuji Silysia Chemical LTD) was used.

Methyl 6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (14) A solution of **13** (3.79 g, 15.4 mmol) in a mixture of MeOH (50 ml) and AcOH (50 ml) was hydrogenated with 10% Pd-C (400 mg) at an initial pressure of 4 kg/cm^3 for 3 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. The residue was neutralized with saturated NaHCO_3 solution and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The resulting solid was recrystallized from diisopropyl ether to give **14** (3.81 g, 99%), mp 73-76°C. IR (KBr): 3300 (NH), 1730 cm^{-1} (CO). ^1H -NMR: 2.70 (4H, m, $\text{CH}_2\text{COOCH}_3$, 3-H₂), 3.05 (2H, m, 4-H₂), 3.72 (3H, s, COOCH_3), 4.35 (1H, dd, $J = 8.9, 3.8 \text{ Hz}$, 1-H), 5.89 (2H, s, OCH_2O), 6.55 (2H, s, 5-H, 8-H). MS m/z : 249 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.70; H, 6.13; N, 5.61.

Methyl *N*-tert-Butoxycarbonyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (15) A solution of Boc₂O (1.08 g, 4.8 mmol) in THF (5 ml) was added to a solution of **14** (1.0 g, 4 mmol) in THF (5 ml), and the mixture was stirred for 30 min. The solvent was removed, and the residue was purified by column chromatography (CHCl_3) to give **15** (1.40 g, 100%) as an oil. IR (neat): 1740 (COOCH_3), 1690 cm^{-1} (NCOO). ^1H -NMR: 1.45 [9H, s, $\text{C}(\text{CH}_3)_3$], 2.70 (4H, m, $\text{CH}_2\text{COOCH}_3$, 4-H₂), 3.25 (1H, m, 3-Ha), 3.68 (3H, s, COOCH_3), 3.95 (1H, m, 3-Hb), 5.45 (1H, m, 1-H), 5.90 (2H, s, OCH_2O), 6.56 and 6.63 (each 1H, each s, 5-H, 8-H). MS m/z : 349 (M^+). HR-MS m/z : calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_6$ 349.1523, found: 349.1522.

(1,2-*trans*)-Methyl 9,10-Methylenedioxy-4-oxo-2-phenyl-1,6,7,11b-tetrahydro-2H, 4H-[1,3]oxazino[4,3-*a*]isoquinoline-1-carboxylate (17), (1,2-*cis*)-Methyl 9,10-Methylenedioxy-4-oxo-2-phenyl-1,6,7,11b-tetrahydro-2H, 4H-[1,3]oxazino[4,3-*a*]isoquinoline-1-carboxylate (18), and Methyl 2-(6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-phenyl-2-propenoate (19) A solution of **15** (240 mg, 0.69 mmol) in THF (10 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (0.12 ml, 0.83 mmol) and *n*-BuLi (15% hexane solution 0.52 ml, 0.83 mmol)] in THF (2 ml) at -78°C, and the mixture was stirred for 10 min. Then, benzaldehyde (0.14 ml, 1.38 mmol) was added to the solution, and the whole was stirred at this temperature for 20 min. The reaction was quenched with water (1 ml), and the solvent was removed. The residue was extracted with EtOAc, and the extract was washed with brine, dried, and evaporated.

The residual oil was purified by column chromatography (20% EtOAc in benzene) to give methyl 2-(*N*-tert-butoxycarbonyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-yl)-3-hydroxy-3-phenylpropanoate (**16**) as an oil (298 mg, 95%) as a diastereomeric mixture [MS m/z : 455 (M^+)], whose $^1\text{H-NMR}$ spectrum was not sufficiently well resolved to permit assignments of all signals. Then, triethylamine (0.19 ml, 1.38 mmol) and MsCl (0.11 ml, 1.38 mmol) were added successively to a solution of **16** obtained above in CH_2Cl_2 (5 ml) under ice-cooling, and the mixture was stirred for 20 min. The reaction was quenched with water (1 ml), and diluted with CH_2Cl_2 (20 ml). The organic layer was washed with brine, dried, and concentrated. The residual mesylate was, without purification, dissolved in 2.3 *N* HCl in EtOAc (3.4 ml), and the solution was stirred for 5 min. The solvent was removed, and the residue was dissolved in DMSO (1 ml) containing DBU (0.21 ml, 1.38 mmol). The mixture was allowed to stand for 1 h, diluted with water (10 ml), then extracted with EtOAc. The extract was washed brine ($\times 2$), dried, and evaporated. The residue was subjected to column chromatography using 10% EtOAc in benzene for elution to give **17** (29 mg, 11% overall yield from **15**), **18** (20 mg, 8% overall yield from **15**) followed by **19** (19 mg 8% overall yield from **15**).

17: A colorless oil. IR (neat): 1730 (COOCH_3), 1700 cm^{-1} (NCOO). $^1\text{H-NMR}$: 2.70 (1H, dt, $J = 15.6, 3.7$ Hz, 6-Ha), 3.11 (1H, t, $J = 10.4$ Hz, 1-H), 3.00-3.30 (2H, m, 7-H₂), 3.47 (3H, s, COOCH_3), 4.29 (1H, dt, $J = 11.9, 3.7$ Hz, 6-Hb), 5.16 (2H, d, $J = 10.4$ Hz, 2-H), 5.32 (1H, d, $J = 10.4$ Hz, 11b-H), 5.92 (2H, s, OCH_2O), 6.46 and 6.65 (each 1H, each s, 8-H, 11-H), 7.35 (5H, m, ArH). MS m/z : 381 (M^+). HR-MS m/z : calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_6$ 381.1211, found: 381.1217.

18: A colorless oil. IR (neat): 1740 (COOCH_3), 1690 cm^{-1} (NCOO). $^1\text{H-NMR}$: 2.55 (1H, m, 6-Ha), 2.94 (2H, m, 7-H₂), 3.50 (1H, dd, $J = 3.8, 1.7$ Hz, 1-H), 3.58 (3H, s, COOCH_3), 4.54 (1H, d, $J = 3.8$ Hz, 11b-H), 4.68 (1H, m, 6-Hb), 5.80 (1H, br d, $J = 1.7$ Hz, 2-H), 5.90 (2H, s, OCH_2O), 6.36 and 6.59 (each 1H, each s, 8-H, 11-H), 7.41 (5H, m, ArH). MS m/z : 381 (M^+). HR-MS m/z : calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_6$ 381.1211, found: 381.1214.

19: A colorless oil (stereochemistry was not determined unsolved). IR (neat): 1710 cm^{-1} (COOCH_3). $^1\text{H-NMR}$: 2.50-3.50 (4H, m, 3-H₂, 4-H₂), 3.70 (3H, s, COOCH_3), 5.13 (1H, s, 1-H), 5.85 (2H, s, OCH_2O), 6.41 and 6.56 (each 1H, each s, 5-H, 8-H), 7.40 (5H, m, ArH), 7.97 (1H, s, =CH). MS m/z : 337 (M^+). HR-MS m/z : calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$ 337.1312, found: 337.1308.

1-(2-Hydroxyethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (20) A solution of **14** (2.90 g, 11.7 mmol) in THF (17 ml) was added to a suspension of LiAlH_4 (576 mg, 15.2 mmol) in THF (8 ml) under ice-cooling. After being stirred for 10 min at room temperature, the reaction was quenched with water (10 ml). Celite (5 g) was added, and the mixture was vigorously stirred. The Celite was removed by filtration, and the filtrate was diluted with EtOAc (30 ml), and the organic solution was washed with brine, dried, and evaporated. The residue was recrystallized from benzene to give **20** (2.40 g, 93%), mp 95-97°C. IR (KBr): 3300-3100 cm^{-1} (OH, NH). $^1\text{H-NMR}$: 1.70-2.05 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 2.60 (2H, m, 4-H₂), 2.80-3.20 (2H, m, 3-H₂), 3.75 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 3.90 (2H, br s, NH, OH), 4.05 (1H, dd, $J = 9.8, 3.3$ Hz, 1-H), 5.81 (2H, s, OCH_2O), 6.46 (2H, s, 5-H, 8-H). MS m/z : 222 ($M^+ + 1$). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3 \cdot 1/10 \text{H}_2\text{O}$: C, 64.62; H, 6.87; N, 6.28. Found: C, 64.66; H, 6.74; N, 6.27.

1-(Chloroethyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (21) A solution of **20** (1.0 g, 4.5 mmol) and SOCl_2 (0.7 ml, 9.0 mmol) in CH_2Cl_2 (20 ml) was refluxed for 2 h. After removal of the solvent and excess SOCl_2 under reduced pressure, the residue was neutralized with saturated NaHCO_3 solution and

extracted with CH_2Cl_2 . The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography (50% CHCl_3 in hexane) to give **21** (1.07 g, 100%), which was recrystallized from a mixture of 2-propanol and hexane to give crystals, mp 78–80°C. IR (KBr): 3400 cm^{-1} (NH). $^1\text{H-NMR}$: 2.15 (2H, m, $\text{CH}_2\text{CH}_2\text{Cl}$), 2.65 (2H, t, $J = 6.3$ Hz, 4- H_2), 3.04 (2H, m, 3- H_2), 3.75 (2H, m, $\text{CH}_2\text{CH}_2\text{Cl}$), 4.09 (1H, dd, $J = 7.6, 6.0$ Hz, 1-H), 5.90 (2H, s, OCH_2O), 6.54 and 6.59 (each 1H, each s, 5-H, 8-H). MS m/z : 239 (M^+). *Anal.* Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2\text{Cl}$: C, 60.01; H, 5.89; N, 5.84. Found: C, 59.89; H, 5.94; N, 5.80.

7,8-Methylenedioxy-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinoline (11) A 28% MeOH solution of NaOMe (2.6 ml, 12.6 mmol) was added to a solution of **21** (2.0 g, 8.4 mmol) in MeOH (30 ml), and the mixture was refluxed for 1.5 h. After evaporation of the solvent, the residue was extracted with CH_2Cl_2 and the extract was washed with brine, dried and evaporated. The residue was purified by column chromatography (50% MeOH in CHCl_3) to give **11** (1.23 g, 72%) as an oil. $^1\text{H-NMR}$: 1.80 (1H, m, 1-Ha), 2.42 (1H, br d, $J = 16.0$ Hz, 4-Ha), 2.60–3.10 (4H, m, 1-Hb, 2-Ha, 4-Hb, 5-Ha), 3.40 (2H, m, 2-Hb, 5-Hb), 4.65 (1H, dd, $J = 8.0, 3.0$ Hz, 9b-H), 5.90 (2H, s, OCH_2O), 6.49 and 6.62 (each 1H, each s, 6-H, 9-H). $^{13}\text{C-NMR}$: 23.6, 28.3, 45.3, 47.6, 60.0, 101.1, 106.6, 109.0, 128.1, 132.1, 132.5, 146.4, 147.0. MS m/z : 203 (M^+). HR-MS m/z : calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2$ 203.0945, found: 203.0942.

8,9-Methylenedioxy-1,2,5,6-tetrahydro-4H-3,6-epoxy-3-benzazocine (23) To a solution of **11** (1.10 g, 5.4 mmol) in a mixture of CHCl_3 (10 ml) and MeOH (10 ml) was added 35% H_2O_2 (2 ml) at room temperature. After being stirred for 15 h, PtO_2 (10 mg) was added to the reaction mixture. The whole was stirred for additional 4.5 h, then filtered through a Celite pad. The filtrate was condensed *in vacuo* to give a residue, which was dissolved in CHCl_3 . The CHCl_3 solution was dried (MgSO_4), and evaporated to give crude *N*-oxide (**22**) as an oil [$^1\text{H-NMR}$: 2.01 (1H, quint, $J = 9.0$ Hz, 1-Ha), 2.60–2.80 (2H, m, 1-Hb, 4-Ha), 3.30–3.60 (3H, m, 4-Hb, 5- H_2), 4.08 (1H, dt, $J = 9.0, 3.0$ Hz, 2-Ha), 4.34 (1H, q, $J = 9.0$ Hz, 2-Hb), 5.14 (1H, t, $J = 9.0$ Hz, 9b-H), 5.90 (2H, s, OCH_2O), 6.42 and 6.63 (each 1H, each s, 6-H, 9-H). MS m/z : 219 (M^+). HR-MS m/z : calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$ 219.0894, found: 219.0902]. A solution of **22** obtained above in THF (15 ml) was refluxed for 1 h, then concentrated *in vacuo*. The residual oil was purified by column chromatography (CHCl_3) to give **23** (754 mg, 64%) as an oil. $^1\text{H-NMR}$: 2.40 (1H, m, 5-Ha), 2.54 (1H, m, 1-Ha), 2.74 (1H, m, 5-Hb), 3.02 (1H, m, 2-Ha), 3.24 (1H, m, 1-Hb), 3.35 (2H, m, 4- H_2), 3.52 (1H, m, 2-Hb), 4.99 (1H, dd, $J = 10.0, 3.5$ Hz, 6-H), 5.90 (2H, s, OCH_2O), 6.63 and 6.65 (each 1H, each s, 7-H, 10-H). $^{13}\text{C-NMR}$: 39.4, 37.8, 53.4, 56.7, 84.4, 101.5, 109.3, 111.6, 133.5, 138.3, 146.2, 146.9. MS m/z : 219 (M^+). HR-MS m/z : calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$ 219.0895, found: 219.0889.

6-Hydroxy-8,9-methylenedioxy-1,2,3,4,5,6-hexahydro-3-benzazocine (24) A solution of **23** (110 mg, 0.5 mmol) in MeOH (20 ml) was hydrogenated with 10% Pd-C (50 mg) under atmospheric pressure for 15 h. The catalyst was removed by filtration through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was recrystallized from MeOH to give **24** (112 mg, 100%) as crystals, mp 187–189°C. IR (KBr): 3400–3125 cm^{-1} (OH, NH). $^1\text{H-NMR}$ (CD_3OD): 1.70 and 2.35 (each 1H, each m, 5- H_2), 2.67 (1H, m, 4-Ha), 3.05 (3H, m, 1- H_2 , 2-Ha), 3.22 (1H, m, 4-Hb), 3.40 (1H, m, 2-Hb), 5.12 (1H, dd, $J = 10.5, 4.2$ Hz, 6-H), 5.95 (2H, d, $J = 5.0$ Hz, OCH_2O), 6.75 and 7.05 (each 1H, each s, 7-H, 10-H). $^{13}\text{C-NMR}$: 31.8, 40.3, 46.5, 53.3, 70.5, 104.1, 108.0, 112.1, 130.9, 138.9, 150.2, 150.6. MS m/z : 221 (M^+). *Anal.* Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3 \cdot 1/10 \text{H}_2\text{O}$: C, 64.62; H, 6.87; N, 6.28. Found: C, 64.49; H, 6.74; N, 6.26.

***N*-tert-Butoxycarbonyl-6-hydroxy-8,9-methylenedioxy-1,2,3,4,5,6-hexahydro-3-benzazocine (25)** A solution of Boc₂O (261 mg, 1.2 mmol) in CH₂Cl₂ (4 ml) was added to a solution of **24** (221 mg, 1 mmol) and triethylamine (0.14 ml, 1 mmol) in CH₂Cl₂ (3 ml). After being stirred for 10 min, the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (50% EtOAc in hexane) to give **25** (346 mg, 100%), which was recrystallized from a mixture of EtOH and hexane to give crystals, mp 126–128°C. The ¹H-NMR spectrum clearly showed that **25** exists as a mixture of *cis* and *trans* (ca. 2:1)²⁵ of rotational isomers. IR (KBr): 3375 (OH), 1660 cm⁻¹ (NCOO). ¹H-NMR: 1.38 [9/3H, s, C(CH₃)₃], 1.45 [18/3H, s, C(CH₃)₃], 1.60 (4/3H, m, 5-H₂), 2.20–3.00 (14/3H, m, 1-H₂, 2-H₂, 4-Ha, 5-H₂), 3.51 (1H, m, 4-Hb), 3.92 (1/3H, m, 2-Ha), 4.21 (2/3H, m, 2-Hb), 4.92 (1H, m, 6-H), 5.89 (2/3H, s, OCH₂O), 5.92 (4/3H, s, OCH₂O), 6.55 (1/3H, s, 10H), 6.57 (2/3H, s, 10-H), 7.10 (1H, s, 7-H). MS *m/e*: 321 (M⁺). Anal. Calcd for C₁₇H₂₃NO₅: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.62; H, 7.24; N, 4.33.

***N*-tert-Butoxycarbonyl-8,9-methylenedioxy-6-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (26)** A solution of **25** (2.40 g, 7.5 mmol) in CH₂Cl₂ (10 ml) was added to a solution of Dess-Martin periodinane (4.80 g, 12.4 mmol) in CH₂Cl₂ (20 ml) at room temperature. After being stirred for 30 min, 1.4 M aqueous NaOH solution (50 ml) was added to the reaction mixture, and the whole was stirred vigorously for 5 min. The organic phase was separated, and washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (CHCl₃) to give **26** (1.80 g, 76%) as an oil. The ¹H-NMR spectrum clearly showed that **26** exists as a mixture of *cis* and *trans* (ca. 3:2) of rotational isomers. IR (neat): 1680 (CO), 1655 cm⁻¹ (NCOO). ¹H-NMR: 1.20 [18/5H, s, C(CH₃)₃], 1.31 [27/5H, s, C(CH₃)₃], 3.00 and 3.63 (each 4H, each m, 1-H₂, 2-H₂, 4-H₂, 5-H₂), 5.97 (2H, s, OCH₂O), 6.64 (2/5H, s, 10-H), 6.68 (3/5H, s, 10-H), 7.06 (2/5H, s, 7-H), 7.16 (3/5H, s, 7-H). MS *m/z*: 319 (M⁺). HR-MS *m/z*: calcd for C₁₇H₂₁NO₅ 319.1419, found: 319.1433.

***N*-tert-Butoxycarbonyl-8,9-methylenedioxy-6-oxo-1,2,3,6-tetrahydro-3-benzazocine (28)** A solution of **26** (114 mg, 0.36 mmol) and HMPA (0.31 ml, 1.79 mmol) in THF (3 ml) was added to a solution of (TMS)₂NLi (1 M hexane solution, 0.71 ml, 0.71 mmol) in THF (1 ml) at -78°C. After being stirred for 20 min, a solution of (PhS)₂ (155 mg, 0.71 mmol) in THF (3 ml) was added to the reaction mixture, and stirring was continued for 1 h at room temperature. The reaction was quenched with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give the sulfide (**27**, X = SPh). A solution of **27** thus obtained in CH₂Cl₂ (6 ml) was treated with NaHCO₃ (30 mg, 0.36 mmol) and 80% MCPBA (78 mg, 0.36 mmol) at room temperature. After stirring was continued for 10 min, the mixture was quenched with water (10 ml), and extracted with CH₂Cl₂. The extract was washed with brine, dried, and evaporated. The residual oil (sulfoxide of **27**), without purification, was dissolved in toluene (5 ml), and the solution was refluxed for 1 h. The solvent was evaporated *in vacuo*, and the residue was purified by column chromatography (5% EtOAc in hexane) to give **28** (60 mg, 53%) as an oil. IR (neat): 1710 (CO), 1630 cm⁻¹ (NCOO). ¹H-NMR: 1.42 [9H, s, C(CH₃)₃], 3.05 (2H, t, *J* = 5.0 Hz, 1-H₂), 3.78 (2H, t, *J* = 5.0 Hz, 2-H₂), 5.85 (1H, d, *J* = 10.0 Hz, 5-H), 5.99 (2H, s, OCH₂O), 6.65 (1H, s, 10-H), 6.79 (1H, br d *J* = 10.0 Hz, 4-H), 7.07 (1H, s, 7-H). MS *m/z*: 317 (M⁺). HR-MS *m/z*: calcd for C₁₇H₁₉NO₅ 317.1262, found: 317.1262.

***N*-(2,3-Dimethoxybenzoyl)-6-hydroxy-8,9-methylenedioxy-1,2,3,4,5,6-hexahydro-3-benzazocine (33)** A mixture of 2,3-dimethoxybenzoic acid (182 mg, 1 mmol) and SOCl₂ (0.1 ml, 1.5 mmol) in benzene (5 ml) was refluxed for 5 h. After removal of the solvent and excess SOCl₂ by evaporation *in vacuo*, the resulting 2,3-

dimethoxybenzoyl chloride (**31**) was dissolved in dimethoxyethane (3 ml). The solution was added to a solution of **24** (180 mg, 0.81 mmol) in dimethoxyethane (2 ml) containing a 10% aqueous NaOH solution (0.31 ml), and the whole was stirred for 10 min, then diluted with CH₂Cl₂ (50 ml). The solution was washed with brine, dried, and evaporated. The residue was purified by column chromatography (5% MeOH in CHCl₃) to give **33** (248 mg, 79%), which was recrystallized from EtOH to give crystals, mp 174-176°C. The ¹H-NMR spectrum clearly showed that **33** exists as a mixture of *cis* and *trans* (ca. 2:1) of rotational isomers. IR (KBr): 3300 (OH), 1630 cm⁻¹ (NCO). ¹H-NMR: 1.64 (4/3H, m, 5-H₂), 2.22 (1H, br s, OH), 2.30-3.30 (14/3H, m, 2-Ha, 4-H₂, 5-H₂), 3.62 (1H, m, 4-H₂), 3.82 (1H, s, 3'-OCH₃), 3.88 (1H, s, 2'-OCH₃), 3.91 (4H, s, 2'-OCH₃, 3'-OCH₃), 3.95 (1/3H, m, 2-Hb), 4.15 (2/3H, m, 2-Hb), 5.04 (1/3H, dd, *J* = 10.0, 4.4 Hz, 6-H), 5.22 (2/3H, dd, *J* = 10.0, 4.4 Hz, 6-H), 5.95 (2H, s, OCH₂O), 6.43 (2/3H, s, 10-H), 6.47 (1/3H, s, 10-H), 6.64 (1/3H, s, 7-H), 7.16 (2/3H, s, 7-H), 6.50-7.10 (3H, m, 4'-H, 5'-H, 6'-H). MS *m/z*: 385 (M⁺). *Anal.* Calcd for C₁₂H₂₃NO₆: C, 65.44; H, 6.02, N, 3.63. Found; C, 65.53; H, 6.20; N, 3.58.

N-(6-Bromo-2,3-dimethoxybenzoyl)-6-hydroxy-8,9-methylenedioxy-1,2,3,4,5,6-hexahydro-3-benzazocine (34) The same procedure as described for the preparation of **33** provided a crude product from **24** (40 mg, 0.18 mmol) and 6-bromo-2,3-dimethoxybenzoic acid¹⁶ (52 mg, 0.2 mmol), and this was purified by column chromatography (CHCl₃) to give **34** (78 mg, 94%), which was recrystallized from EtOH to give crystals, mp 120-122°C. The ¹H-NMR spectrum clearly showed that **34** exists as a mixture of *cis* and *trans* (ca. 4:1) of rotational isomers. IR (KBr): 3375 (OH), 1630 cm⁻¹ (NCO). ¹H-NMR: 1.50 (8/5H, m, 5-H₂), 2.20-3.10 (22/5H, m, 1-H₂, 2-Ha, 4-H₂, 5-H₂), 3.58 (1H, m, 4-H₂), 3.76 (3/5H, s, 3'-OCH₃), 3.85 (3H, s, 2'-OCH₃, 3'-OCH₃), 3.88 (1/5H, m, 2-Hb), 3.90 (12/5H, s, 2'-OCH₃), 4.08 (4/5H, m, 2-Hb), 5.20 (1H, dd, *J* = 9.6, 4.1 Hz, 6-H), 5.90 (2H, s, OCH₂O), 6.45 (4/5H, s, 10-H), 6.60 (1/5H, s, 10-H), 6.80 (1H, d, *J* = 8.4 Hz, 5'-H), 7.04 (1/5H, s, 7-H), 7.11 (4/5H, s, 7-H), 7.23 (4/5H, d, *J* = 8.4 Hz, 4'-H), 7.25 (1/5H, d, *J* = 8.4 Hz, 4'-H). MS *m/z*: 463 (M⁺). *Anal.* Calcd for C₂₁H₂₂NO₆Br•3/2 EtOH: C, 54.04; H, 5.86; N, 2.63. Found: C, 53.79; H, 5.77; N, 2.61.

N-(2,3-Dimethoxybenzoyl)-8,9-methylenedioxy-6-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (35) The same procedure as described for the preparation of **26** provided a crude product from **33** (3.50 g, 9.0 mmol) and Dess-Martin periodinane (3.70 g, 13.5 mmol), and this was purified by column chromatography (CHCl₃) to give **35** (3.16 g, 92%), which was recrystallized from EtOH to give crystals, mp 131-133°C. The ¹H-NMR spectrum clearly showed that **35** exists as a mixture of *cis* and *trans* (ca. 3:2) of rotational isomers. IR (KBr): 1700 (CO), 1620 cm⁻¹(NCO). ¹H-NMR: 2.62 (1H, m, 5-Ha, 1-Ha), 2.90-3.60 (6H, m, 1-Hb, 2-H₂, 4-H₂, 5-Hb), 3.74 (6/5H, s, 3'-OCH₃), 3.78 (9/5H, s, 3'-OCH₃), 3.85 (3H, s, 2'-OCH₃), 4.29 (3/5H, m, 4-H), 4.53 (2/5H, m, 4-H), 5.98 (4/5H, s, OCH₂O), 6.01 (6/5H, s, OCH₂O), 6.10 (3/5H, dd, *J* = 6.8, 2.2 Hz, 4'-H), 6.35 (2/5H, dd, *J* = 7.4, 1.5 Hz, 4'-H), 6.41 (3/5H, s, 10-H), 6.75 (2/5H, s, 10-H), 6.86 (3/5H, dd, *J* = 8.0, 2.2 Hz, 6'-H), 6.88 (2/5H, dd, *J* = 7.4, 1.5 Hz, 6'-H), 6.93 (3/5H, dd, *J* = 8.0, 6.8 Hz, 5'-H), 6.96 (3/5H, s, 7-H), 7.20 (2/5H, t, *J* = 7.4 Hz, 5'-H), 7.34 (2/5H, s, 7-H). MS *m/z*: 383 (M⁺). *Anal.* Calcd for C₂₁H₂₁NO₆: C, 65.78; H, 5.52; N, 3.65. Found; C, 65.74; H, 5.56; N, 3.72.

N-(6-Bromo-2,3-dimethoxybenzoyl)-8,9-methylenedioxy-6-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (36) The same procedure as described for the preparation of **26** provided a crude product from **34** (2.57 g, 5.55 mmol) and Dess-Martin periodinane (5.53 g, 8.33 mmol), and this was purified by column chromatography

(CHCl₃) to give **36** (2.43 g, 95%), which was recrystallized from benzene to give crystals, mp 164–167°C. The ¹H-NMR spectrum clearly showed that **36** exists as a mixture of *cis* and *trans* (ca. 3:1) of rotational isomers. IR (KBr): 1705 (CO), 1620 cm⁻¹ (NCO). ¹H-NMR: 2.81 (6/4H, m, 1-H₂), 2.95 (2/4H, m, 5-H₂), 3.11 (6/4H, m, 5-H₂), 3.18 (2/4H, m, 1-H₂), 3.41 (6/4H, m, 2-H₂), 3.55 (2/4H, m, 2-H₂), 3.69 (3/4H, s, 3'-OCH₃), 3.79 (9/4H, s, 3'-OCH₃), 3.80 (2/4H, m, 4-H₂), 3.85 (3H, s, 2'-OCH₃), 3.89 (6/4H, m, 4-H₂), 5.99 (2H, s, OCH₂O), 6.48 (3/4H, s, 10-H), 6.73 (1/4H, s, 10-H), 6.77 (3/4H, s, 7-H), 6.78 (1/4H, d, *J* = 8.4 Hz, 4'-H), 6.79 (3/4H, d, *J* = 8.4 Hz, 4'-H), 7.10 (1/4H, s, 7-H), 7.21 (3/4H, d, *J* = 8.4 Hz, 5'-H), 7.22 (1/4H, d, *J* = 8.4 Hz, 5'-H). MS *m/z*: 461 (M⁺). Anal. Calcd for C₂₁H₂₀NO₆Br•1/3H₂O: C, 53.86; H, 4.45; N, 2.99. Found: C, 53.93; H, 4.30; N, 2.94.

***N*-(2,3-Dimethoxybenzoyl)-8,9-methylenedioxy-6-oxo-1,2,3,6-tetrahydro-3-benzazocine (37)** The same procedure as described for the preparation of **28** provided a crude product from **35** (150 mg, 0.93 mmol), (TMS)₂NLi (1 M hexane solution, 0.78 ml, 0.78 mmol), (PhS)₂ (170 mg, 0.78 mmol), and 80% MCPBA (84 mg, 0.39 mmol), and this was purified by column chromatography (20% EtOAc in benzene) to give **37** (76 mg, 51%), which was recrystallized from EtOH to give crystals, mp 172–174°C. IR (KBr): 1660 (CO), 1610 cm⁻¹ (NCO). ¹H-NMR: 3.08 (2H, br m, 1-H₂), 3.70 (3H, s, 3'-OCH₃), 3.86 (3H, s, 2'-OCH₃), 4.05 (2H, br m, 2-H₂), 5.97 (1H, br m, 5-H), 6.02 (2H, s, OCH₂O), 6.49 (2H, br m, 4-H, 5'-H), 6.71 (1H, br s, 10-H), 6.97 (2H, m, 4'-H, 6'-H), 7.15 (1H, s, 7-H). MS *m/z*: 381 (M⁺). Anal. Calcd for C₂₁H₁₉NO₆: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.26; H, 5.05; N, 3.60.

***N*-(6-Bromo-2,3-dimethoxybenzoyl)-8,9-methylenedioxy-6-oxo-1,2,3,6-tetrahydro-3-benzazocine (38)** The same procedure as described for the preparation of **28** provided a crude product from **36** (200 mg, 0.43 mmol), (TMS)₂NLi (1 M hexane solution, 0.87 ml, 0.87 mmol), (PhS)₂ (190 mg, 0.87 mmol), and 80% MCPBA (93 mg, 0.43 mmol), and this was purified by column chromatography (20% EtOAc in hexane) to give **38** (131 mg, 67%), which was recrystallized from a mixture of EtOH and benzene to give crystals, mp 182–186°C. The ¹H-NMR spectrum clearly showed that **38** exists as a mixture of *cis* and *trans* (ca. 3:1) of rotational isomers. IR (KBr): 1665 (CO), 1620 cm⁻¹ (NCO). ¹H-NMR: 2.90 (2/4H, m, 2-H₂), 3.09 (6/4H, t, *J* = 6.5 Hz, 2-H₂), 3.54 (2/4H, dd, *J* = 6.5, 4.7 Hz, 1-H₂), 3.65 (9/4H, s, 3'-OCH₃), 3.71 (3/4H, s, 3'-OCH₃), 3.81 (9/4H, s, 2'-OCH₃), 3.85 (3/4H, s, 2'-OCH₃), 4.05 (6/4H, m, 1-H₂), 5.90 (2/4H, s, OCH₂O), 5.95 (6/4H, s, OCH₂O), 6.01 (3/4H, d, *J* = 9.3 Hz, 5-H), 6.33 (1/4H, d, *J* = 9.3 Hz, 5-H), 6.39 (3/4H, d, *J* = 9.3 Hz, 4-H), 6.48 (1/4H, s, 10-H), 6.71 (3/4H, s, 10-H), 6.78 (3/4H, d, *J* = 8.8 Hz, 4'-H), 6.81 (1/4H, d, *J* = 8.8 Hz, 4'-H), 7.10 (1/4H, d, *J* = 9.3 Hz, 4-H), 7.14 (1/4H, s, 7-H), 7.16 (3/4H, s, 7-H), 7.17 (3/4H, d, *J* = 8.8 Hz, 5'-H), 7.19 (1/4H, d, *J* = 8.8 Hz, 5'-H). MS *m/z*: 459 (M⁺). Anal. Calcd for C₂₁H₁₈NO₆Br: C, 54.80; H, 3.94; N, 3.04. Found: C, 54.82; H, 4.00; N, 3.02.

5,6-Dihydro-9,10-dimethoxy-1,3-dioxolo[4,5-*i*]isoindolo[2,1-*c*][3]benzazocine-8,14-dione (1) (Magallanesine) A mixture of **38** (50 mg, 0.11 mmol), TiOAc (34 mg, 0.13 mmol), PPh₃ (5.2 mg, 0.02 mmol), and Pd(OAc)₂ (3.0 mg, 0.01 mmol) in DMF (3 ml) was stirred at 130°C for 24 h, then diluted with benzene (50 ml). The mixture was washed with water and brine, dried, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc in hexane) to give **1** (39 mg, 93%), which was recrystallized from MeOH to give crystals, mp 254–256°C. IR (KBr): 1719 cm⁻¹ (CO, NCO). ¹H-NMR: 3.27 (2H, m, 5-H₂), 3.95 (3H, s, 10-OCH₃), 4.11 (2H, m, 6-H₂), 4.11 (3H, s, 9-OCH₃), 6.02 (2H, s, OCH₂O), 6.30 (1H, s, 14-H), 6.66

(1H, s, 4-H), 7.14 (1H, d, $J = 8.4$ Hz, 11-H), 7.25 (1H, s, 1-H), 7.44 (1H, d, $J = 8.4$ Hz, 12-H). $^{13}\text{C-NMR}$: 33.3, 43.9, 56.6, 62.5, 101.8, 104.5, 109.2, 110.4, 116.1, 116.3, 119.7, 130.9, 132.7, 134.7, 139.0, 147.1, 147.4, 150.5, 154.7, 165.9, 192.3.

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