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

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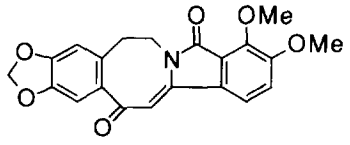
Abstract: A straightforward total synthesis of magallanesine 1 was accomplished from readily available isoquinolineacetate **14**. This synthesis is emphasized by the following two points; i. the [1,2]-Meisenheimer rearrangement of the azetidine N-oxide **22** for the preparation of azocine ring, ii.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

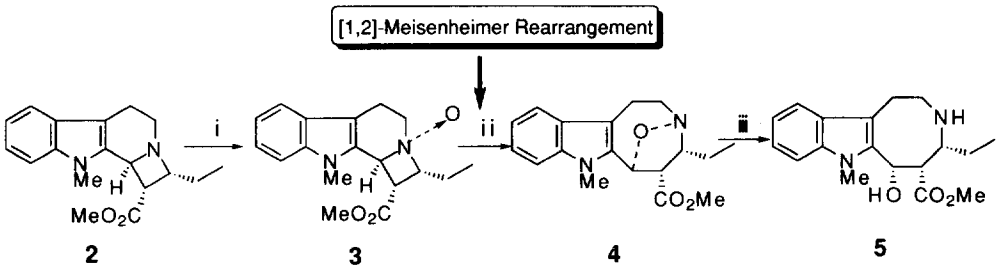
INTRODUCTION

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-*i*]-isoindolo[2,1-*c*][3]benzazocine-8,14-dione)

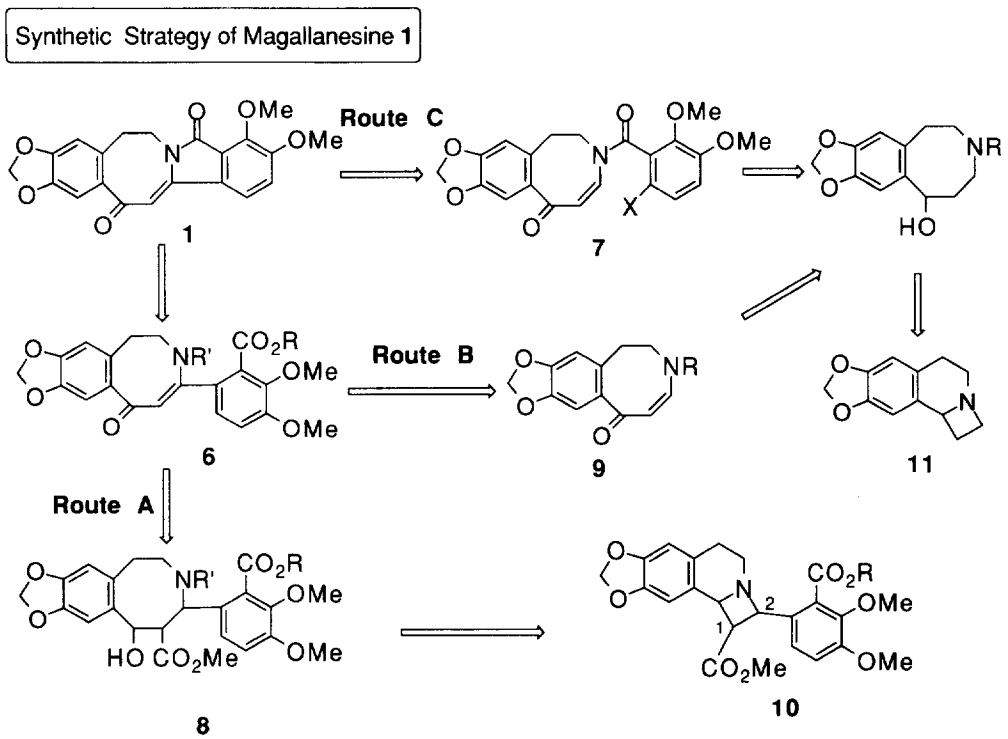
During the course of our extensive works on the Meisenheimer rearrangements [5] of azetopyridoindole N-oxides, we found a novel ring expansion of azetidine **2** to indoloazocine **5** *via* reductive cleavage of the N-O bond of indoloepoxyazocine **4** [6](Scheme 1). On the basis of the encouraging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



Reagents and Conditions:
i. MCPBA, ii. THF / r.t., iii. Pd-C / H_2

Scheme 1

First, we mention briefly the important items of the retrosynthetic format for the synthesis of **1**, outlined in Scheme 2. Isoindoline skeleton being the right part of **1** might be constructed *via* three routes, that is, a) amide cyclization of aryl enaminone **6**, which may be obtained from azetidine**10** bearing a substituted phenyl group at C-2 (Route A) or from an intermolecular arylation of benzazocinone **9** (Route B), and b) intramolecular Heck cyclization of N-benzoyl enaminone **7**, which may be prepared from unsubstituted azetidine **11** *via* Route C.

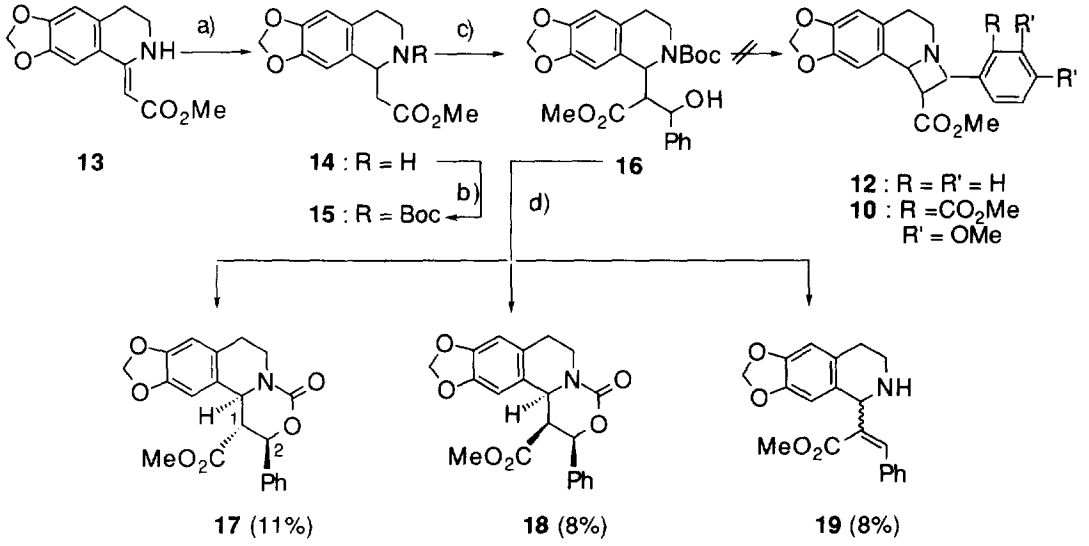


Scheme 2

RESULTS AND DISCUSSION

Synthetic Study of 3-Arylbenzazocine 6

For the construction of aryl enaminone **6**, we first examined on the adaptability of the Meisenheimer rearrangement of azetidine **10** (Route A). Thus, as a model experiment, we tried to synthesize 2-phenylazetidine **12** according to our methodology[8] (Scheme 3). Catalytic hydrogenation of enaminoester **13**, obtained from piperonal,[9] gave a saturated ester **14**, whose amino function was then protected by *tert*-butoxycarbonyl (Boc) group to yield a carbamate **15**. Aldol condensation of **15** with benzaldehyde in the presence of lithium diisopropylamide (LDA) gave alcohols **16** in 95% yield as a diastereomeric mixture. According to the method developed by us, successive treatments {i. methanesulfonyl chloride in the presence of triethylamine, ii. deprotection with dry hydrogen chloride in EtOAc, iii. 1.8-diazabicyclo[5,4,0]undec-7-ene (DBU)} of **15** provided none of the expected azetidine **12**, but only undesired three products (**17**-**19**). Two (**17** and **18**) of them were readily confirmed as benzpyrido-3,5-oxazin-4-ones with the stereochemistries shown in Scheme 3, based on comparisons of their IR and ^{1}H-NMR [$J_{1,2}$ = 10.4 Hz in **17** and $J_{1,2}$ = 1.7 Hz in **18**] spectra with those of the corresponding indolopyrido-3,5-oxazin-4-ones.[8] The third one **19** was unsaturated ester, which was presumably obtained from the oxazinones **17** and/or **18** with base-induced decarboxylation[10] or from the mesylate of **16**. In consequence of these unfavored results, the approach (Route A) was placed aside.



Reagents and Conditions:

a) 10% Pd-C / H_2, MeOH-AcOH (1:1), 4 kg/cm^2 (99%)

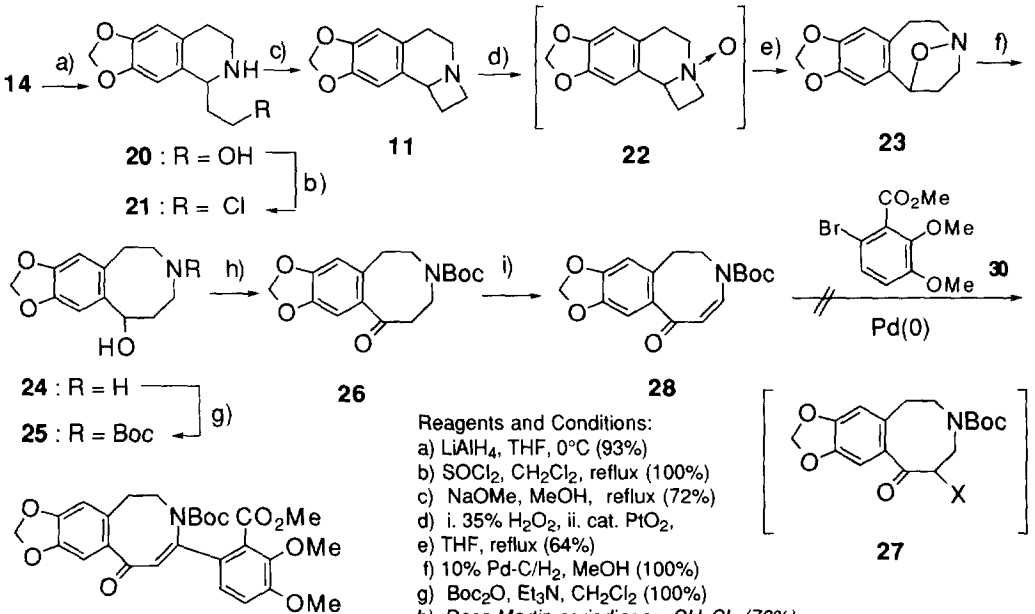
b) Boc_2O, THF (100%)

c) PhCHO, LDA, THF, -78°C (95%)

d) i. MsCl, Et_3N, CH_2Cl_2, ii. 2.3 N HCl in EtOAc, iii. DBU, DMSO

Scheme 3

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 azetidine **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}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 lowing 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.



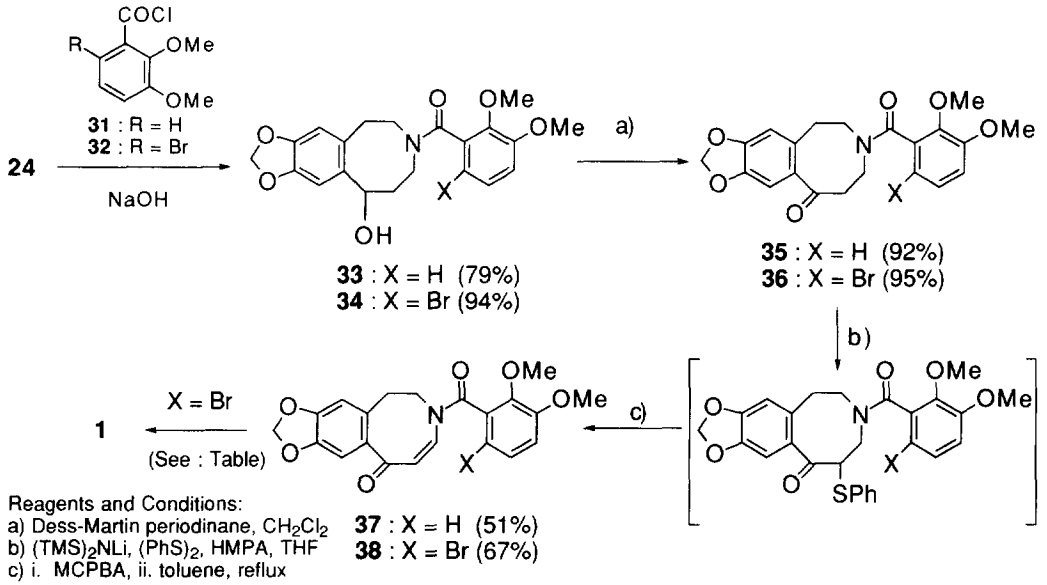
Reagents and Conditions:
a) $LiAlH_4$, THF, 0°C (93%)
b) $SOCl_2$, CH_2Cl_2, reflux (100%)
c) NaOMe, MeOH, reflux (72%)
d) i. 35% H_2O_2, ii. cat. PtO_2,
e) THF, reflux (64%)
f) 10% Pd-C/H_2, MeOH (100%)
g) Boc_2O, Et_3N, CH_2Cl_2 (100%)
h) Dess-Martin periodinane, CH_2Cl_2 (76%)
i) i. $(TMS)_2NLi$, HMPA, THF, -78°C, ii. $(PhS)_2$, -78°C to r.t.
iii. MCPBA, CH_2Cl_2, r.t., iv. reflux in toluene
(53% overall yield)

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 results of many considerations, attempted reactions of **28** with bromide **30**[16] in the presence of $Pd(OAc)_2$ and Ph_3P using triethylamine, TlOAc[17] or $^nBu_4NCl$[18] as additives gave none of the arylated product **29**, with only starting material being recovered. Therefore, Route B also had to be discarded.

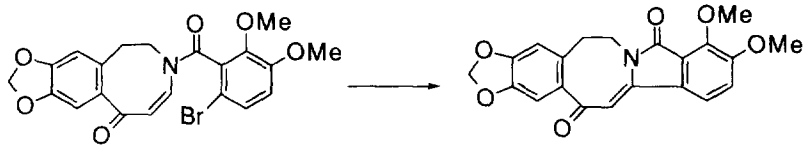
Total Synthesis of Magallanesine

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-formylindoles[20] (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), Ph_3P (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 (Ag_2CO_3[22] or TlOAc[17]), 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 Jeffery[18] (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 reported[3] for magallanesine **1**.



Scheme 5

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

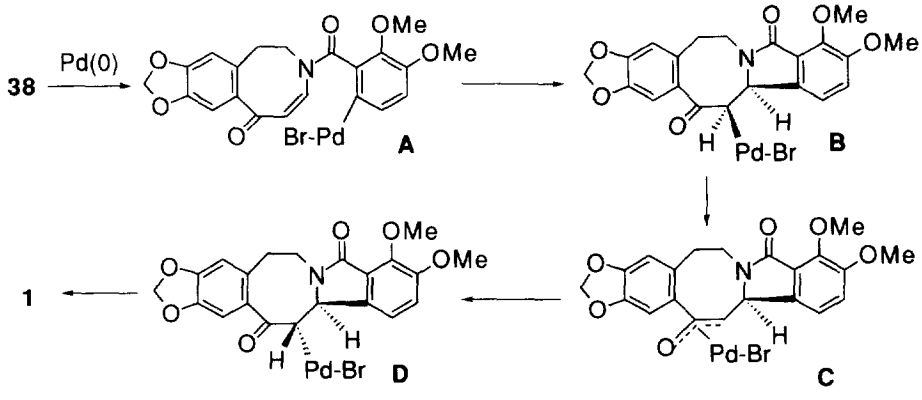


38 Magallanesine **1**

Run	$Pd(OAc)_2$ (eq.)	Ph_3P (eq.)	Additive (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%) of **1** [a] [Recovery of **38**]
1	0.1	0.2	Et_3N (1.3)	MeCN	80	96	12 [41]
2	0.1	0.2	Ag_2CO_3 (1.2)	MeCN	80	96	21 [62]
3	0.1	0.2	Ag_2CO_3 (1.2)	DMF	130	96	25 [25]
4	0.1	0.2	TlOAc (1.2)	MeCN	80	96	36 [36]
5	0.1	0.2	TlOAc (1.2)	DMF	130	24	93 [0]
6	0.05	-	^{n}BuNCl (1.0) $NaHCO_3$ (2.5)	DMF	50	24	41 [10]

a) Determine by ^{1}H-NMR

After publication of our short communication,[7] Comins and co-workers[23] 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 spectometer. The ^{1}H- 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-tetrahydroisquinoline-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). ^{1}H-NMR: 2.70 (4H, m, C<u>H</u>$_2$COOCH$_3$, 3-H$_2$), 3.05 (2H, m, 4-H$_2$), 3.72 (3H, s, COOCH$_3$), 4.35 (1H, dd, J = 8.9, 3.8 Hz, 1-H), 5.89 (2H, s, OCH$_2$O), 6.55 (2H, s, 5-H, 8-H). MS *m/z*: 249 (M$^+$). *Anal.* Calcd for $C_{13}H_{15}NO_4$: 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 Boc_2O (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). ^{1}H-NMR: 1.45 [9H, s, C(CH$_3$)$_3$], 2.70 (4H, m, C<u>H</u>$_2$COOCH$_3$, 4-H$_2$), 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$_2$O), 6.56 and 6.63 (each 1H, each s, 5-H, 8-H). MS *m/z*: 349 (M$^+$). HR-MS *m/z*: calcd for $C_{18}H_{23}NO_6$ 349.1523, found: 349.1522.

(1,2-*trans*)-Methyl 9,10-Methylenedioxy-4-oxo-2-phenyl-1,6,7,11b-tetrahydro-2*H*, 4*H*-[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-2*H*, 4*H*-[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}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 (x 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}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-H_2), 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 $C_{21}H_{19}NO_6$ 381.1211, found: 381.1217.

18: A colorless oil. IR (neat): 1740 ($COOCH_3$), 1690 cm^{-1} (NCOO). ^{1}H-NMR: 2.55 (1H, m, 6-Ha), 2.94 (2H, m, 7-H_2), 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 $C_{21}H_{19}NO_6$ 381.1211, found: 381.1214.

19: A colorless oil (stereochemistry was not determined unsolved). IR (neat): 1710 cm^{-1} ($COOCH_3$). ^{1}H-NMR: 2.50-3.50 (4H, m, 3-H_2, 4-H_2), 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 $C_{20}H_{19}NO_4$ 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}H-NMR: 1.70-2.05 (2H, m, CH_2CH_2OH), 2.60 (2H, m, 4-H_2), 2.80-3.20 (2H, m, 3-H_2), 3.75 (2H, m, CH_2CH_2OH), 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 $C_{12}H_{15}NO_3 \cdot 1/10\ H_2O$: 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-tertahydroisoquinoline (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}H-NMR: 2.15 (2H, m, C<u>H</u>$_2$CH$_2$Cl), 2.65 (2H, t, J = 6.3 Hz, 4-H$_2$), 3.04 (2H, m, 3-H$_2$), 3.75 (2H, m, CH$_2$C<u>H</u>$_2$Cl), 4.09 (1H, dd, J = 7.6, 6.0 Hz, 1-H), 5.90 (2H, s, OCH$_2$O), 6.54 and 6.59 (each 1H, each s, 5-H, 8-H). MS *m/z*: 239 (M^+). *Anal.* Calcd for $C_{12}H_{14}NO_2Cl$: 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-2*H*-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 evaporaion of the solvent, the residue was extracted 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}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$_2$O), 6.49 and 6.62 (each 1H, each s, 6-H, 9-H). ^{13}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 $C_{12}H_{13}NO_2$ 203.0945, found: 203.0942.

8,9-Methylenedioxy-1,2,5,6-tetrahydro-4*H*-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 evaporate to give crude *N*-oxide (**22**) as an oil [^{1}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$_2$O), 6.42 and 6.63 (each 1H, each s, 6-H, 9-H). MS *m/z*: 219 (M^+). HR-MS *m/z*: calcd for $C_{12}H_{13}NO_3$ 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}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$_2$O), 6.63 and 6.65 (each 1H, each s, 7-H, 10-H). ^{13}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 $C_{12}H_{13}NO_3$ 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 concentraded *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}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$_2$O), 6.75 and 7.05 (each 1H, each s, 7-H, 10-H). ^{13}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 $C_{12}H_{15}NO_3 \cdot 1/10\ H_2O$: 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-methyllenedioxy-1,2,3,4,5,6-hexahydro-3-benzazocine (25)** A solution of Boc_2O (261 mg, 1,2 mmol) in CH_2Cl_2 (4 ml) was added to a solution of **24** (221 mg, 1 mmol) and triethylamine (0.14 ml, 1 mmol) in CH_2Cl_2 (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 ^{1}H-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). ^{1}H-NMR: 1.38 [9/3H, s, $C(CH_3)_3$], 1.45 [18/3H, s, $C(CH_3)_3$], 1.60 (4/3H, m, 5-H_2), 2.20-3.00 (14/3H, m, 1-H_2, 2-H_2, 4-Ha, 5-H_2), 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, OCH_2O), 5.92 (4/3H, s, OCH_2O), 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 $C_{17}H_{23}NO_5$: 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 CH_2Cl_2 (10 ml) was added to a solution of Dess-Martin periodinane (4.80 g, 12.4 mmol) in CH_2Cl_2 (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 ($CHCl_3$) to give **26** (1.80 g, 76%) as an oil. The ^{1}H-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). ^{1}H-NMR: 1.20 [18/5H, s, $C(CH_3)_3$], 1.31 [27/5H, s, $C(CH_3)_3$], 3.00 and 3.63 (each 4H, each m, 1-H_2, 2-H_2, 4-H_2, 5-H_2), 5.97 (2H, s, OCH_2O), 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 $C_{17}H_{21}NO_5$ 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 CH_2Cl_2 (6 ml) was treated with $NaHCO_3$ (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 CH_2Cl_2. 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). ^{1}H-NMR: 1.42 [9H, s, $C(CH_3)_3$], 3.05 (2H, t, J = 5.0 Hz, 1-H_2), 3.78 (2H, t, J = 5.0 Hz, 2-H_2), 5.85 (1H, d, J = 10.0 Hz, 5-H), 5.99 (2H, s, OCH_2O), 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 $C_{17}H_{19}NO_5$ 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 $SOCl_2$ (0.1 ml, 1.5 mmol) in benzene (5 ml) was refluxed for 5 h. After removal of the solvent and excess $SOCl_2$ 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 CH_2Cl_2 (50 ml). The solution was washed with brine, dried, and evaporated. The residue was purified by column chromatography (5% MeOH in $CHCl_3$) to give **33** (248 mg, 79%), which was recyrstallized from EtOH to give crystals, mp 174-176°C. The ^{1}H-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). ^{1}H-NMR: 1.64 (4/3H, m, 5-H_2), 2.22 (1H, br s, OH), 2.30-3.30 (14/3H, m, 2-Ha, 4-H_2, 5-H_2), 3.62 (1H, m, 4-H_2), 3.82 (1H, s, 3'-OCH_3), 3.88 (1H, s, 2'-OCH_3), 3.91 (4H, s, 2'-OCH_3, 3'-OCH_3), 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, OCH_2O), 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 $C_{12}H_{23}NO_6$: 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 acid[16] (52 mg, 0.2 mmol), and this was purified by column chromatography ($CHCl_3$) to give **34** (78 mg, 94%), which was recrystallized from EtOH to give crystals, mp 120-122°C. The ^{1}H-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). ^{1}H-NMR: 1.50 (8/5H, m, 5-H_2), 2.20-3.10 (22/5H, m, 1-H_2, 2-Ha, 4-H_2, 5-H_2), 3.58 (1H, m, 4-H_2), 3.76 (3/5H, s, 3'-OCH_3), 3.85 (3H, s, 2'-OCH_3, 3'-OCH_3), 3.88 (1/5H, m, 2-Hb), 3.90 (12/5H, s, 2'-OCH_3), 4.08 (4/5H, m, 2-Hb), 5.20 (1H, dd, J = 9.6, 4.1 Hz, 6-H), 5.90 (2H, s, OCH_2O), 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 $C_{21}H_{22}NO_6Br$•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 ($CHCl_3$) to give **35** (3.16 g, 92%), which was recrystallized from EtOH to give crystals, mp 131-133°C. The ^{1}H-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). ^{1}H-NMR: 2.62 (1H, m, 5-Ha, 1-Ha), 2.90-3.60 (6H, m, 1-Hb, 2-H_2, 4-H_2, 5-Hb), 3.74 (6/5H, s, 3'-OCH_3), 3.78 (9/5H, s, 3'-OCH_3), 3.85 (3H, s, 2'-OCH_3), 4.29 (3/5H, m, 4-H), 4.53 (2/5H, m, 4-H), 5.98 (4/5H, s, OCH_2O), 6.01 (6/5H, s, OCH_2O), 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 $C_{21}H_{21}NO_6$: 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

($CHCl_3$) to give **36** (2.43 g, 95%), which was recrystallized from benzene to give crystals, mp 164-167°C. The ^{1}H-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). ^{1}H-NMR: 2.81 (6/4H, m, 1-H_2), 2.95 (2/4H, m, 5-H_2), 3.11 (6/4H, m, 5-H_2), 3.18 (2/4H, m, 1-H_2), 3.41 (6/4H, m, 2-H_2), 3.55 (2/4H, m, 2-H_2), 3.69 (3/4H, s, 3'-OCH_3), 3.79 (9/4H, s, 3'-OCH_3), 3.80 (2/4H, m, 4-H_2), 3.85 (3H, s, 2'-OCH_3), 3.89 (6/4H, m, 4-H_2), 5.99 (2H, s, OCH_2O), 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 $C_{21}H_{20}NO_6Br \cdot 1/3H_2O$: 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). ^{1}H-NMR: 3.08 (2H, br m, 1-H_2), 3.70 (3H, s, 3'-OCH_3), 3.86 (3H, s, 2'-OCH_3), 4.05 (2H, br m, 2-H_2), 5.97 (1H, br m, 5-H), 6.02 (2H, s, OCH_2O), 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 $C_{21}H_{19}NO_6$: 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 ^{1}H-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). ^{1}H-NMR: 2.90 (2/4H, m, 2-H_2), 3.09 (6/4H, t, J = 6.5 Hz, 2-H_2), 3.54 (2/4H, dd, J = 6.5, 4.7 Hz,. 1-H_2), 3.65 (9/4H, s, 3'-OCH_3), 3.71 (3/4H, s, 3'-OCH_3), 3.81 (9/4H, s, 2'-OCH_3), 3.85 (3/4H, s, 2'-OCH_3), 4.05 (6/4H, m, 1-H2), 5.90 (2/4H, s, OCH_2O), 5.95 (6/4H, s, OCH_2O), 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 $C_{21}H_{18}NO_6Br$: 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), TlOAc (34 mg, 0.13 mmol), PPh_3 (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). ^{1}H-NMR: 3.27 (2H, m, 5-H_2), 3.95 (3H, s, 10-OCH_3), 4.11 (2H, m, 6-H_2), 4.11 (3H, s, 9-OCH_3), 6.02 (2H, s, OCH_2O), 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}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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REFERENCES AND NOTES

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