A Practical Synthesis of the ABC Ring Model of Ecteinascidins

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Received February 29, 2000; accepted April 24, 2000

A practical synthesis of 1,2,3,4,5,6-hexahydro-1,5-imino-10-hydroxy-9-methoxy-3,8,11-trimethyl-3-benzazocin-4-one (3) as an ABC ring model compound of ecteinascidin 743 and safracins from 3-hydroxy-4-methoxy-5-methylbenzaldehyde (7) is described. The overall yield in 15 steps is 27%.

Key words ecteinascidin; safracin; synthesis; Baeyer–Villiger oxidation; regioselectivity

Ecteinascidin 743 (**1a**) is a novel natural marine product discovered from the Caribbean tunicate *Ecteinascidia turbinata* along with ecteinascidin 729 (**1b**) and related compounds.[1] Among this group, **1a** has exceedingly potent antitumor activity and is now undergoing phase II clinical trials.[2] It is a tetrahydroisoquinoline derivative that is structurally related to microbial safracins.[3] Because of their novel and diverse structure, general approaches to their construction have been explored.[4]

We are very interested in the preparation of the ABC ring model compound (**3**), which has a structure common to **1a** and **2**. We previously reported the preparation of **3** with the idea of introducing the hydroxy group at a later stage[5]; however, the overall yield was low (1.4—1.7%). Recently, we completed an improved synthesis of **3** from **4** in 11 steps *via* the useful intermediates **5** and **6**, which introduces a phenolic hydroxy group, at an early stage.[6] In this paper, we report the full account of our synthesis of **3** along with the practical synthesis from a benzaldehyde derivative **7**, which was easily prepared in seven steps from 2,3-dihydroxytoluene and is used to protect the phenolic hydroxy functionality as an isopropyl group.[7]

A mixture of **7** and 1,4-diacetyl-2,5-piperazinedione (**8**) was treated with potassium *tert*-butoxide in dimethylformamide (DMF) to give 3-arylidene-2,5-piperazinedione (**9**) in 74% yield according to the procedure of Gallina and Liberatori (Chart 1).[8] The geometric structure of **9** was confirmed by the chemical shift of the olefinic proton at δ 7.18. Alkylation of **9** with 4-methoxybenzyl chloride in the presence of sodium hydride in DMF furnished **10** in quantitative yield, and successive treatment with hydrazine hydrate afforded **11** in 94% yield. Methylation of **11** with methyl iodide (1.1 eq) in the presence of sodium hydride in DMF afforded **12** in 79% yield.[9] Deprotection of **12** with trifluoroacetic acid (TFA) and concentrated H_2SO_4 produced the phenol **13** in 85% yield. Reduction of the double bond of **13** with hydrogen over 20% palladium hydroxide on carbon in ethanol occurred cleanly accompanied by debromination to afford **5** in 88% yield.

On the other hand, we studied the conversion of **4**[5] into **5**

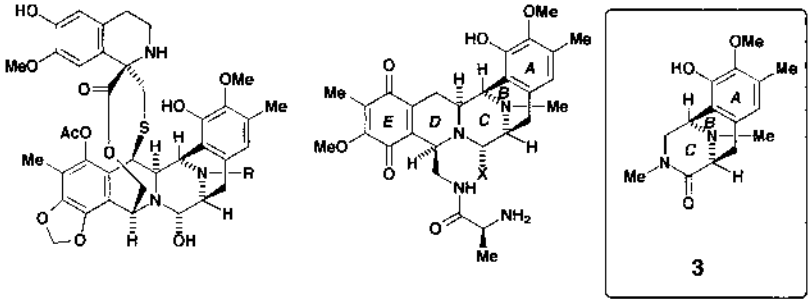

Fig. 1

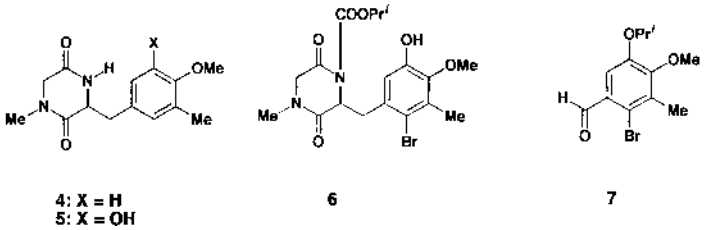

Fig. 2

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Dedicated to the memory of Dr. Kyosuke Tsuda.

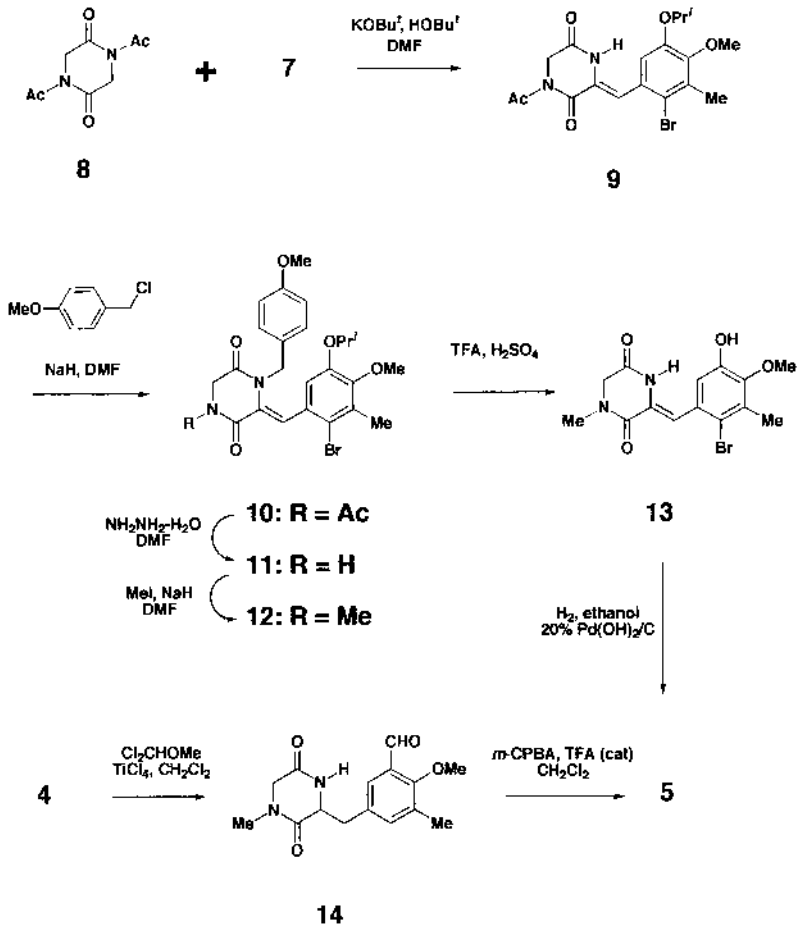

Chart 1

via the benzaldehyde derivative **14**. Titanium tetrachloride and α,α-dichloromethyl methyl ether promoted formylation to afford **14** in 77% yield. Baeyer–Villiger oxidation of **14** with *m*-chloroperbenzoic acid (*m*-CPBA) was performed in the absence of a protic acid to give **5** with a maximum yield of only 38%. Knölker and Fröhner recently demonstrated that some acetophenone derivatives are able to be transformed into the corresponding acetates by acid-catalyzed Baeyer–Villiger oxidation.[10] Numerous efforts for the preparation of **5** employing *m*-CPBA with a variety of protic acids are summarized in Table 1. We found the reaction conditions in entry 5 were best in terms of product yield on a small scale. Unfortunately, the product yield was dramatically decreased (<25—30%) on a large scale. From a practical point of view, the process from **7** to **5** as described above is better in terms of overall yield and reproducibility in a large scale preparation.

We then studied the conversion of **5** to a cyclized compound (Chart 2). Protection of the phenol (**5**) with benzyl bromide and K_2CO_3 in DMF afforded the *O*-benzylated compound (**15**), which was then transformed by introduction of an isopropyloxycarbonyl group using isopropyl chloroformate, triethylamine, and 4-dimethylaminopyridine (DMAP) to give **16** in 89% overall yield. Deprotection of **16** by hydrogenolysis afforded **17** in 93% yield. The chemoselective reduction of **17** with an excess of lithium tri-*tert*-butoxyaluminium hydride in tetrahydrofuran (THF) gave a diastereomeric mixture of the alcohol (**18**), which was treated with

Table 1. Baeyer–Villiger Oxidation of **14** with *m*-CPBA in CH_2Cl_2[a]

Entry	Catalyst[b]	Eq	Time (h)	Temp (°C)	Yield (%)[c]
1	None		18	40	21[d]
2	None		24	25	38[d]
3	TsOH–H_2O	0.2	8	25	30
4	TfOH	0.2	8	25	38
5	TFA	0.2	8	25	75
6	TFA	0.1	8	25	51
7	CSA	0.2	8	25	25

a) The reactions were carried out on a 0.4 mol scale. *b*) TsOH=*p*-toluenesulfonic acid; TfOH=trifluoromethanesulfonic acid; CSA=10-camphorsulfonic acid. *c*) Isolated yield. *d*) Basic workup with 5% $NaHCO_3$.

TFA at 25 °C for 1 h to generate **19a** and **19b** in 22% and 66% yields, respectively. The structure of the cyclized compounds were fully supported by the molecular weight determined by mass spectrometry along with elemental analysis. The regiochemistry of both products, however, was undetermined at this stage because the signals in the ^{1}H-NMR spectra of **19a** and **19b** were not split, which indicated that they were a mixture of two rotational isomers. Conversion of **19a** to the final product (**3**) was accomplished using deprotection with TFA and H_2SO_4 at room temperature followed by reductive methylation in 74% overall yield. Similarly, **19b** was converted to **21** *via* **20b** in 61% overall yield. In the ^{1}H-NMR spectra of **3**, when H-7 (δ 6.48) was irradiated, nuclear Overhauser enhancement (NOE) (10%) of the methyl protons (δ 2.25) was observed, whereas NOE was negligible in the

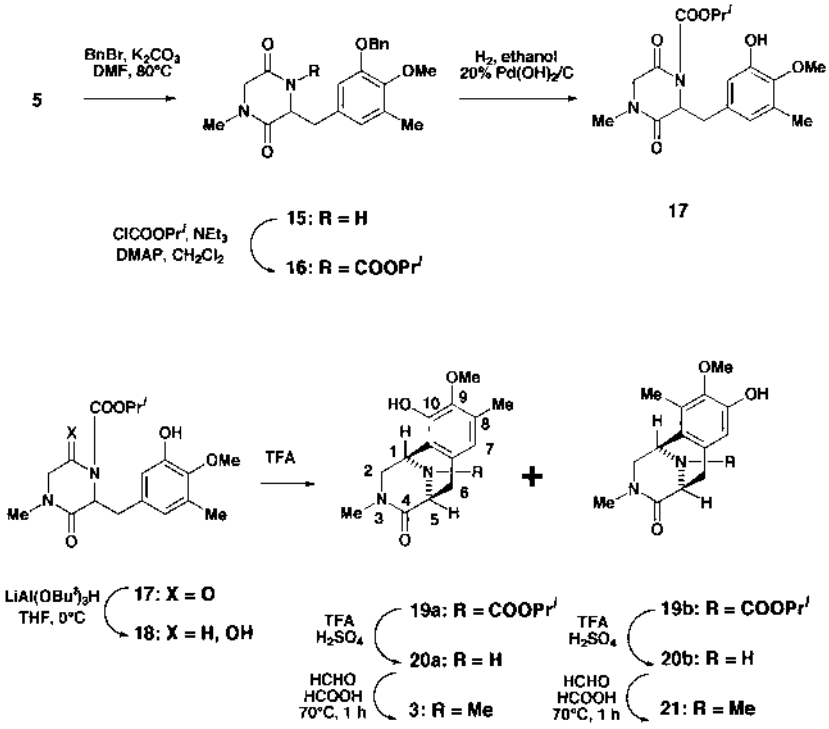

Chart 2

spectra of **21**.

The yield of this process was low because of the formation of an unwanted *para*-cyclized product (**19b**). Thus, we attempted to block the *para* position by introducing a bromine (Chart 3). Selective bromination of **5** with bromine in dichloromethane–THF (2 : 1) at 0 °C for 2 h gave the desired *para*-brominated compound **22** in 91% yield along with the regioisomer (**23a**) and the bisbrominated compound (**23b**) in 2.0% and 1.8% yields, respectively. The structure of **22** was supported by the ^{1}H-NMR spectrum, and the NOE was negligible between the aromatic proton at δ 6.76 and the methyl protons at δ 2.37, whereas the NOE (8.3%) was observed in the ^{1}H-NMR spectrum of **23a**. These results indicated that **22** was a *para*-brominated compound and **23a** was an *ortho*-brominated compound. Direct conversion of **22** to **6** was not possible, and produced the *O*-acylated product **24** in 67% yield. Accordingly, the sequence of reactions was studied. Protection of the phenol **22** with benzyl bromide gave **25** in 90% yield. This compound was converted into the imide (**26**) in 95% yield. The subsequent removal of the benzyl group of **26** proved troublesome. The acid-catalyzed removal of the benzyl unit in **26** with TFA at room temperature for 18 h afforded the desired compound (**6**) in only 51% yield because of the migration of the *O*-substituent to the free α-position to give **27a** in 31% yield.[11] The structure of **27a** was supported by the spectral data, and this compound was transformed to **28** in 73% yield. To trap the benzyl carbocation that was produced, treatment of **26** in TFA with an excess of 1,3-dimethoxybenzaldehyde gave **6** in 72% yield, but the migration product **27a** (21%) was also produced. When the transformation was performed with trimethylsilyl iodide (TMSI) in chloroform at 50 °C for 24 h to give **6** in 18% yield, the major product was the catecohol (**27b**) in 28% yield.[12] On the other hand, the direct bromination of the phenol (**17**) with bromine in dichloromethane at 0 °C for 1 h afforded **6** in 89% yield.

With the precursors for construction of the ABC ring model in hand, we then attempted to convert **26** or **6** into the final goal **3** (Chart 4). Attempts under a variety of conditions to cyclize **29** directed from **26** were fruitless; the yield was disappointingly low because of deprotection and migration of the benzyl group. When this dehydration/cyclization reaction was performed with methanesulfonic anhydride (Ms_2O) in dichloromethane, the cyclized compound could not be isolated; instead, the enamine (**30**) was formed in quantitative yield.[13] Numerous efforts to convert **30** to the cyclized compound were unsuccessful, indicating that relatively slow cyclization of **29** or **30** was the reason for the steric hindrance of the benzyl protecting group which was unstable under acidic conditions. Indeed, treatment of **29** under strong acid conditions (TFA, H_2SO_4) generated **31** in 65% overall yield. In contrast, treatment of **32** (which was prepared from **6**) with TFA gave the desired cyclized compound (**33**) in 96% overall yield. Deprotection of **33** with TFA and H_2SO_4 at room temperature for 19 h gave the amine (**31**) in 94% yield. Methylation of **31** with formaldehyde and formic acid at 70 °C for 1 h gave the *N*-methylamine (**34**) in 94% yield. Finally, debromination of **34** with hydrogen over 20% palladium hydroxide on carbon in ethanol achieved our final goal (**3**) in 95% yield.

In summary, we succeeded in a practical synthesis of the ABC ring model of ecteinascidins from **7** in 15 steps. The overall yield of **3** from **7** was 27%. Application of this strategy to the total synthesis of ecteinascidin natural products are under intensive investigation in our laboratories.

Experimental

All melting points were determined with a Yanagimoto micromelting

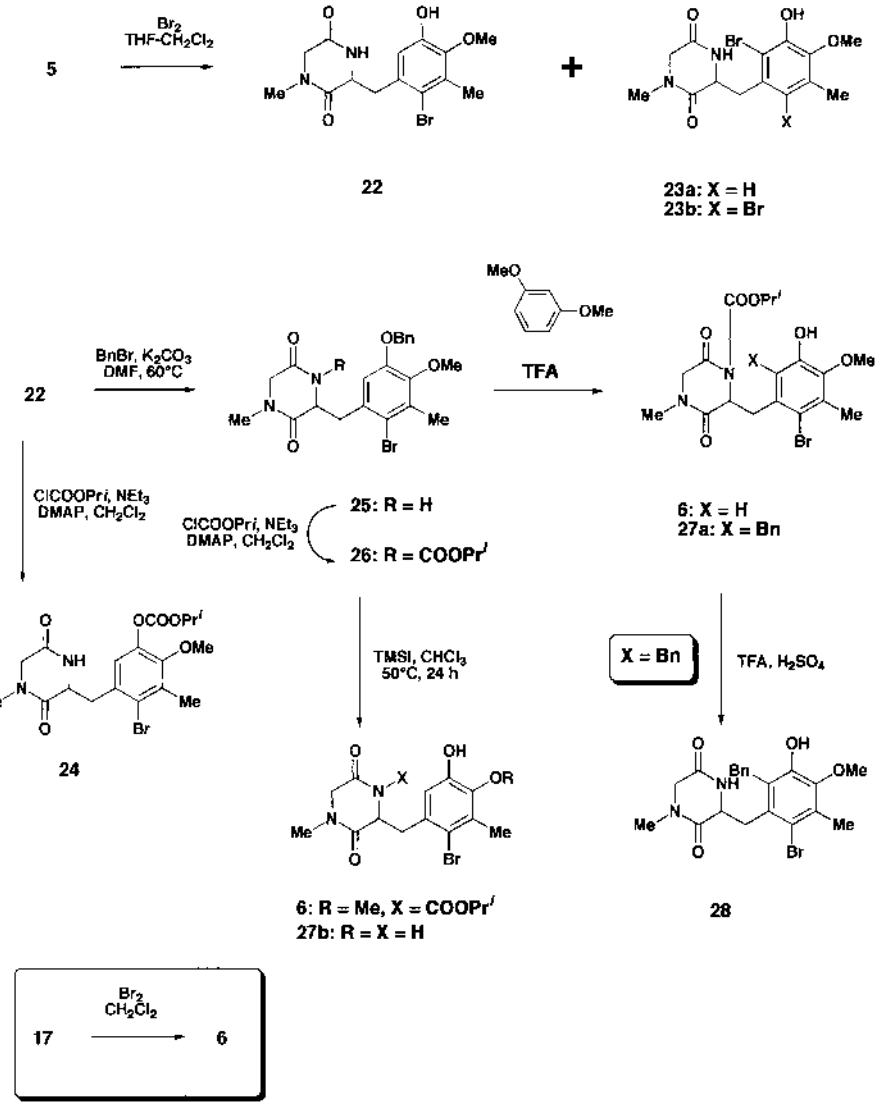

Chart 3

points apparatus and are uncorrected. IR spectra were obtained with a Hitachi 260-10 IR Fourier-transform spectrometer. ^{1}H-NMR were recorded at 270 MHz with a JEOL JNM-EX 270 spectrometer and at 300 MHz with a JEOL JNM-AL300 spectrometer. Peak multiplicities are denoted by s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet) or by a combination of these *e.g.* dd (double doublet), with coupling constants (*J*) given in Hz. ^{13}C-NMR spectra were recorded at 67.5 MHz (multiplicity determined from off-resonance decoupled or distortionless enhancement by polarization transfer (DEPT) spectra). NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to internal $(CH_3)_4Si$ as a standard. Mass spectra were recorded on a JMS-DX 302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained on a Perkin-Elmer Model 240B elemental analyzer. All reactions were conducted under an argon atmosphere. Dry solvents and reagents were obtained using standard procedure. Anhydrous sodium sulfate was used for drying organic solvent extracts. Removal of the solvent was done with a rotary evaporator and, finally, under high vacuum. Column chromatography was performed with E. Merck silica gel (70—230 mesh).

(*Z*)-1-Acetyl-3-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethylene)-2,5-piperazinedione (9) A solution of potassium *tert*-butoxide (5.633 g, 50.2 mmol) in *tert*-butyl alcohol (100.4 ml) was added to a stirred solution of 2-bromo-5-isopropoxy-4-methoxy-3-methylbenzaldehyde **7** (14.427 g, 50.2 mmol) and 1,4-diacetyl-2,5-piperazinedione **8** (9.957 g, 50.2 mmol) in dry DMF (100.4 ml). After being stirred at room temperature for 1 h, the reaction mixture was poured into brine (600 ml) and extracted with ethyl acetate (600 ml×3). The combined extracts were washed with water (600 ml), dried, and concentrated *in vacuo* to give the residue as a pale yellow solid, recrystallization of which from ethyl acetate gave **9** (15.876 g, 74.3%) as pale yellow prisms, mp 145—147 °C. ^{1}H-NMR δ: 1.36 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 2.38 (3H, s, $ArCH_3$), 2.68 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3), 4.50 (1H, sept, J=6.1 Hz, OCH), 4.51 (2H, s, 6-H_2), 6.70 (1H, s, ArH), 7.18 (1H, s, C=CH), 7.64 (1H, br s, NH). IR (KBr) cm^{-1}: 3230, 1710, 1685, 1640. MS *m/z* (%): 426 (M^++2, 10), 424 (M^+, 10), 346 (13), 345 (54), 304 (14), 303 (69), 262 (16), 261 (100), 246 (19), 43 (13). *Anal.* Calcd for $C_{18}H_{21}BrN_2O_5$: C, 50.84; H, 4.98; N, 6.59. Found: C, 50.83, H, 4.98; N, 6.56.

(*Z*)-3-(2-Bromo-5-isopropoxy-4-methoxy-3-methylphenylmethylene)-4-(4-methoxyphenylmethyl)-2,5-piperazinedione (11) Sodium hydride (60% oil dispersion, washed with dry hexane three times, 300 mg, 12.5 mmol) was added to a stirred solution of **9** (4.241 g, 10 mmol) in dry DMF (80 ml) under ice-cooling, and stirring was continued at 0 °C for 30 min. 4-Methoxybenzyl chloride (1.96 g, 12.5 mmol) in dry DMF (20 ml) was added during 10 min, and the reaction mixture was stirred at room temperature for 42 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water (100 ml) and extracted with benzene (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to furnish **10** (5.441 g, 100%) as a pale yellow amorphous powder, which was used for the next step without further purification. ^{1}H-NMR δ: 1.36 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 2.40 (3H, s, $ArCH_3$), 2.55 (3H, s, $COCH_3$), 3.75, 3.84 (each 3H, s, OCH_3), 4.47 (1H, sept, J=6.1 Hz, OCH), 4.51 (2H, s, 6-H_2), 4.54 (2H, s, NCH_2), 6.72 (1H, s, ArH), 6.74, 6.87 (each 2H, d, J=8.6 Hz, 2×ArH), 7.35 (1H, s, C=CH). IR ($CHCl_3$) cm^{-1}: 1708, 1630. MS *m/z* (%): 546 (M^++ 2, 5), 544 (M^+, 5), 466 (22), 465 (71), 424 (12), 423 (42), 122 (10), 121 (100). High-resolution MS

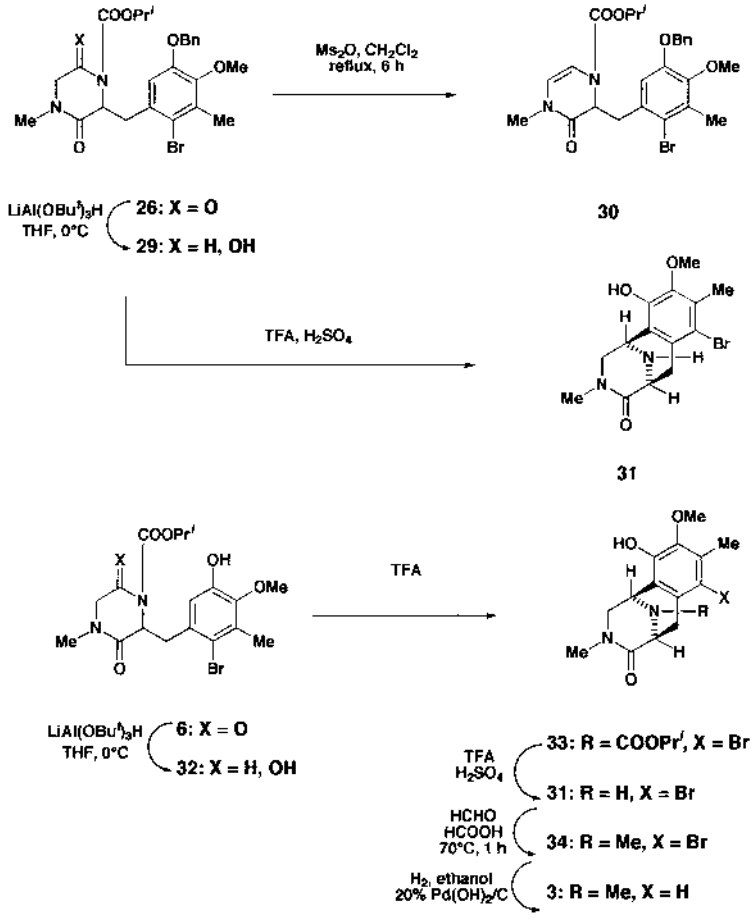

Chart 4

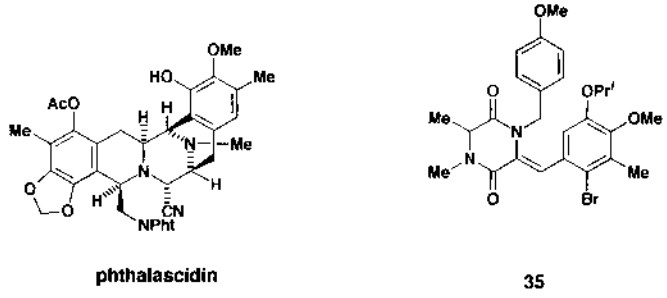

Fig. 3

Calcd for $C_{26}H_{29}BrN_2O_6$: 544.1209. Found: 544.1207.

Hydrazine monohydrate (2.43 ml) was added to a stirred solution of the crude **10** (5.441 g) in dry DMF (100 ml), and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was poured into water (100 ml), and extracted with ethyl acetate (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a residue. Chromatography on a silica gel (120 g) column with dichloromethane–methanol (80 : 1) as the eluent gave **11** (4.720 g, 93.8%) as pale yellow amorphous powder. ^{1}H-NMR δ: 1.35 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 2.39 (3H, s, $ArCH_3$), 3.74, 3.85 (each 3H, s, OCH_3), 4.12 (2H, d, J=2.2 Hz, 6-H_2), 4.44 (1H, sept, J=6.1 Hz, OCH), 4.54 (2H, s, NCH_2), 6.67 (1H, s, ArH), 6.72, 6.87 (each 2H, d, J=8.8 Hz, 2×ArH), 7.18 (1H, s, C=CH), 7.48 (1H, br s, NH). IR ($CHCl_3$) cm^{-1}: 3420, 1692, 1632. MS *m/z* (%): 504 (M^++2, 2), 502 (M^+, 2), 424 (30), 423 (100), 381 (6), 121 (66). High-resolution MS Calcd for $C_{24}H_{27}BrN_2O_5$: 502.1103. Found: 502.1101.

(*Z*)-3-(2-Bromo-5-isopropoxy-4-methoxy-3-methylphenylmethylene)-4-(4-methoxyphenylmethyl)-1-methyl-2,5-piperazinedione (12). Method A Sodium hydride (60% oil dispersion, washed with dry hexane three times, 247.2 mg, 10.3 mmol) was added to a stirred solution of **11** (4.720 g, 9.38 mmol) in dry DMF (94 ml) under ice-cooling, and stirring was continued at 0 °C for 30 min. Methyl iodide (0.642 ml, 10.31 mmol) was added during 30 min, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water (200 ml) and extracted with ether (200 ml×3). The combined extracts were washed with brine (200 ml), dried, and concentrated *in vacuo* to give the residue. Chromatography on a silica gel (120 g) column with hexane–ethyl acetate (1 : 1) as the eluent gave **12** (3.184 g, 78.6%) as a pale yellow amorphous powder. ^{1}H-NMR δ: 1.35 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 2.38 (3H, s, $ArCH_3$), 3.05 (3H, s, NCH_3), 3.74, 3.84 (each 3H, s, OCH_3), 4.10 (2H, s, 6-H_2), 4.43 (1H, sept, J=6.1 Hz, OCH), 4.52 (2H, s, NCH_2), 6.65 (1H, s, ArH), 6.72, 6.87 (each 2H, d, J=8.6 Hz, 2×ArH), 7.22 (1H, s, C=CH). IR ($CHCl_3$) cm^{-1}: 1686, 1630. MS *m/z* (%): 518 (M^++2, 1), 516 (M^+, 1), 438 (31), 437 (100), 121 (42). High-resolution MS Calcd for $C_{25}H_{29}BrN_2O_5$: 516.1260. Found: 516.1253.

Method B The same procedure as described above, but using **11** (617.8 mg, 1.227 mmol) with sodium hydride (44.2 mg, 1.842 mmol) and methyl iodide (0.115 mmol, 1.841 mmol) in dry DMF (15 ml) at room temperature for 20 h, gave the residue (894 mg). Chromatography on a silica gel (30 g) column with hexane–ethyl acetate (3 : 2) as the eluent gave **35** (282.1 mg, 43.4%) as a colorless amorphous powder and further elution with hexane–ethyl acetate (1 : 1) gave **12** (266.8 mg, 42.0%).

(*Z*)-3-(2-Bromo-5-isopropoxy-4-methoxy-3-methylphenylmethylene)-4-(4-methoxyphenylmethyl)-1,6-dimethyl-2,5-piperazinedione (**35**): ^{1}H-NMR δ: 1.34, 1.36 (each 3H, d, J=6.1 Hz, $CH(CH_3)_2$), 1.56 (3H, d, J=7.0 Hz, 6-CH_3), 2.38 (3H, s, $ArCH_3$), 3.03 (3H, s, NCH_3), 3.74, 3.84 (each 3H, s, OCH_3), 3.94 (1H, d, J=14.9 Hz, NCH), 4.04 (1H, q, J=7.0 Hz, 6-H), 4.39 (1H, sept, J=6.1 Hz, OCH), 5.07 (1H, d, J=14.9 Hz, NCH), 6.61 (1H, s, ArH), 6.71, 6.86 (each 2H, d, J=8.6 Hz, 2×ArH), 7.19 (1H, s, C=CH). IR ($CHCl_3$) cm^{-1}: 1682, 1628. MS *m/z* (%): 532 (M^++2, 1), 530 (M^+, 1), 452 (31), 451 (100), 121 (33). High-resolution MS Calcd for $C_{26}H_{31}BrN_2O_5$: 530.1416. Found: 530.1423.

(*Z*)-3-(2-Bromo-5-hydroxy-4-methoxy-3-methylphenylmethylene)-1-methyl-2,5-piperazinedione (13) Concentrated H_2SO_4 (1.0 ml) was added

to a stirred solution of **12** (3.814 g, 7.37 mmol) in TFA (20 ml), and stirring was continued at room temperature for 1 h. The reaction mixture was poured into water (100 ml) and extracted with chloroform–methanol (9 : 1, 100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a solid. Recrystallization of which from methanol gave **13** (2.231 g, 85.2%) as pale yellow prisms, mp 248—250 °C. ^{1}H-NMR δ: 2.37 (3H, s, $ArCH_3$), 2.45 (1H, br s, OH), 3.10 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 4.17 (2H, s, 6-H2), 6.76 (1H, s, ArH), 7.02 (1H, s, C=CH), 8.16 (1H, br s, NH). IR (KBr) cm^{-1}: 3264, 1688, 1638. MS *m/z* (%): 356 (M^++2, 6), 354 (M^+, 6), 276 (18), 275 (100), 260 (60). *Anal.* Calcd for $C_{14}H_{15}BrN_2O_4\cdot 1/8H_2O$: C, 47.04; H, 4.30; N, 7.30. Found: C, 46.91; H, 4.20; N, 7.75.

3-(3-Hydroxy-4-methoxy-5-methylphenylmethyl)-1-methyl-2,5-piperazinedione (5) A solution of **13** (1.471 g, 4.14 mmol) in ethanol (140 ml) was hydrogenated over 20% $Pd(OH)_2$/C (700 mg) at 1 atm for 5 h. The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were evaporated to give a soild, recrystallization of which from acetone gave **5** (1.020 g, 88.4%) as colorless needles, mp 201—203 °C. ^{1}H-NMR δ: 2.24 (3H, s, $ArCH_3$), 2.88 (3H, s, NCH_3), 2.96 (1H, dd, J=13.8, 6.5 Hz, ArCH), 3.00 (1H, br s, OH), 3.04 (1H, dd, J=13.8, 4.1 Hz, ArCH), 3.19, 3.64 (each 1H, d, J=17.6 Hz, 6-H), 3.78 (3H, s, OCH_3), 4.23 (1H, m, 3-H), 6.50, 6.63 (each 1H, d, J=2.0 Hz, ArH), 6.96 (1H, br s, NH). ^{13}C-NMR δ: 15.8 (q), 33.7 (q), 40.2 (t), 51.2 (t), 56.3 (d), 60.6 (q), 114.7 (d), 123.5 (d), 131.3 (s), 131.5 (s), 145.1 (s), 149.2 (s), 165.5 (s), 165.7 (s). IR (KBr) cm^{-1}: 3184, 3120, 1690, 1646. MS *m/z* (%): 278 (M^+, 17), 152 (12), 151 (100). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.22; H, 6.50; N, 9.93.

3-(3-Formyl-4-methoxy-5-methylphenylmethyl)-1-methyl-2,5-piperazinedione (14) A stirred solution of **4** (471.6 mg, 1.8 mmol) and α,α-dichloromethyl methyl ether (1.06 ml, 11.7 mmol) in dry dichloromethane (9 ml) was cooled in ice-water, and $TiCl_4$ (0.594 ml, 5.4 mmol) was added dropwise to it over 1 h. The resulting solution was stirred at 0 °C for 2 h. The reaction mixture was diluted with water (30 ml) and the phane were separated. The aqueous layer was extracted with dichloromethane (30 ml×2). The combined extracts were washed with water (50 ml), dried, and concentrated *in vacuo* to give a soild, recrystallization of which from ethyl acetate gave **14** (400.4 mg, 76.7%) as pale yellow prisms, mp 148—150 °C. ^{1}H-NMR δ: 2.31 (3H, s, $ArCH_3$), 2.90 (3H, s, NCH_3), 3.15 (2H, d, J=5.3 Hz, $ArCH_2$), 3.26, 3.70 (each 1H, d, J=17.5 Hz, 6-H), 3.87 (3H, s, OCH_3), 4.31 (1H, t like, 3-H), 7.30 (1H, d, J=2.0 Hz, ArH), 7.34 (1H, br s, NH), 7.52 (1H, d, J=2.0 Hz, ArH), 10.31 (1H, s, CHO). ^{13}C-NMR δ: 15.4 (q), 33.6 (q), 39.5 (t), 51.1 (t), 56.1 (d), 63.2 (q), 127.6 (d), 129.1 (s), 131.5 (s), 132.8 (s), 138.9 (d), 161.0 (s), 165.2 (s), 165.7 (s), 189.8 (s). IR (KBr) cm^{-1}: 3280, 1680, 1665, 1655, 1640, 1605. MS *m/z* (%): 290 (M^+, 25), 163 (100). *Anal.* Calcd for $C_{15}H_{18}N_2O_4\cdot 1/10H_2O$: C, 61.68; H, 6.28; N, 9.59. Found: C, 61.58; H, 6.29; N, 9.65.

Baeyer–Villiger Oxidation of 14 A solution of **14** (116.0 mg, 0.4 mmol) and TFA (0.0062 ml, 0.08 mmol) in dry dichloromethane (10 ml) was cooled with ice-water, and *m*-CPBA acid (80%, 259 mg, 1.2 mmol) was added over 10 min, the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with 5% $NaHCO_3$ solution (30 ml), and extracted with chloroform (30 ml×3). The combined extracts were washed with water (30 ml), dried, and concentrated *in vacuo* to give a residue (225.6 mg). Chromatography on a silica gel (10 g) column with chloroform–methanol (50 : 1) afforded **5** (83.3 mg, 75.0%) as colorless needles, mp 199—201 °C, which were identical in all respects with an authentic sample described above.

3-(3-Benzyloxy-4-methoxy-5-methylphenylmethyl)-1-methyl-2,5-piperazinedione (15) A suspended solution of **5** (1.113 g, 4.0 mmol) and anhydrous K_2CO_3 (1.106 g, 8.0 mmol) in dry DMF (80 ml) was cooled with ice-water, and benzyl bromide (0.952 ml, 8.0 mmol) was added over 5 min. The reaction mixture was heated at 80 °C for 24 h. The reaction mixture was diluted with water (100 ml), and extracted with chloroform (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a residue (2.509 g). Chromatography on a silica gel (10 g) column with chloroform–methanol (100 : 1) afforded a solid, recrystallization of which from ethyl acetate–ether gave **15** (1.334 g, 91.2%) as colorless prisms, mp 140—141 °C. ^{1}H-NMR δ: 2.23 (3H, s, $ArCH_3$), 2.83 (3H, s, NCH_3), 2.97 (1H, dd, J=13.8, 6.4 Hz, ArCH), 3.05 (1H, dd, J=13.8, 4.4 Hz, ArCH), 3.16, 3.61 (each 1H, d, J=17.5 Hz, 6-H), 3.82 (3H, s, OCH_3), 4.20 (1H, m, 3-H), 5.04 (2H, s, OCH_2), 6.61, 6.64 (each 1H, d, J=2.0 Hz, ArH), 6.76 (1H, br s, NH), 7.27—7.45 (5H, m, 5×ArH). ^{13}C-NMR δ: 16.1 (q), 33.8 (q), 40.8 (t), 51.4 (t), 56.7 (d), 60.5 (q), 71.0 (t), 113.5 (d), 124.8 (d), 127.5 (d×2), 128.2 (d), 128.8 (d×2), 130.5 (s), 132.7 (s), 137.1 (s), 147.5 (s), 152.2 (s), 165.7 (s), 166.0 (s). IR (KBr) cm^{-1}: 3590, 3450, 1680, 1670, 1660. MS *m/z* (%): 368 (M^+, 51), 242 (18), 241 (100), 228 (12), 181 (18), 151 (20), 91 (79). High-resolution MS Calcd for $C_{21}H_{24}N_2O_4$: 368.1736. Found: 368.1731. *Anal.* Calcd for $C_{21}H_{24}N_2O_4\cdot 1/2H_2O$: C, 66.83; H, 6.68; N, 7.42. Found: C, 67.07; H, 6.49; N, 7.41.

3-(3-Benzyloxy-4-methoxy-5-methylphenylmethyl)-4-isopropyloxycarbonyl-1-methyl-2,5-piperazinedione (16) A solution of **15** (921.1 mg, 2.5 mmol), triethylamine (0.697 ml, 5.0 mmol), and (DMAP) (610.9 mg, 5.0 mmol) in dichloromethane (50 ml) was cooled with ice-water, and isopropyl chloroformate (1.14 ml, 10.0 mmol) was added dropwise over 10 min. The solution was stirred at room temperature for 43 h. The organic layer was washed with 1 N HCl (50 ml), and then water (50 ml), dried, and concentrated *in vacuo* to give a residue (1.695 g). Chromatography on a silica gel (40 g) column with dichloromethane–methanol (100 : 1) as the eluent gave **16** (1.114 g, 98.0%) as a colorless amophous powder. ^{1}H-NMR δ: 1.35, 1.38 (each 3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 2.22 (3H, s, $ArCH_3$), 2.46 (1H, d, J=18.2 Hz, 6-H), 2.72 (3H, s, NCH_3), 3.11 (1H, dd, J=13.9, 4.3 Hz, ArCH), 3.23 (1H, dd, J=13.9, 4.0 Hz, ArCH), 3.45 (1H, d, J=18.2 Hz, 6-H), 3.82 (3H, s, OCH_3), 5.01 (3H, m, 3-H, OCH_2), 5.14 (1H, sept, J=6.3 Hz, OCH), 6.54, 6.55 (each 1H, br s, ArH), 7.34—7.47 (5H, m, 5×ArH). IR ($CHCl_3$) cm^{-1}: 1780, 1730, 1670. MS *m/z* (%): 454 (M^+, 55), 277 (13), 242 (22), 241 (100), 209 (13), 181 (18), 151 (14), 91 (51). High-resolution MS Calcd for $C_{25}H_{30}N_2O_6$: 454.2104. Found: 454.2102.

3-(3-Hydroxy-4-methoxy-5-methylphenylmethyl)-4-isopropyloxy-carbonyl-1-methyl-2,5-piperazinedione (17) A solution of **16** (1.114 g, 2.45 mmol) in ethanol (40 ml) was hydrogenated over 20% $Pd(OH)_2$/C (500 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were evaporated to give a solid, recrystallization of which from acetone gave **17** (833.3 mg, 93.3%) as colorless prisms, mp 123—124 °C. ^{1}H-NMR δ: 1.35, 1.37 (each 3H, d, J=6.2 Hz, $CH(C\underline{H}_3)_2$), 2.23 (3H, s, $ArCH_3$), 2.56 (1H, d, J=18.2 Hz, 6-H), 2.80 (3H, s, NCH_3), 3.08 (1H, dd, J=14.0, 4.6 Hz, ArCH), 3.21 (1H, dd, J=14.0, 4.0 Hz, ArCH), 3.49 (1H, d, J=18.2 Hz, 6-H), 3.78 (3H, s, OCH_3), 4.98 (1H, dd, J=4.6, 4.0 Hz, 3-H), 5.13 (1H, sept, J=6.2 Hz, OCH), 6.17 (1H, br s, OH), 6.43, 6.55 (each 1H, d, J=2.0 Hz, ArH). ^{13}C-NMR δ: 15.7 (q), 21.6 (q), 21.7 (q), 32.9 (q), 38.8 (t), 52.2 (t), 60.0 (d), 60.8 (q), 72.3 (d), 114.9 (d), 124.3 (d), 130.9 (s), 131.4 (s), 145.4 (s), 149.2 (s), 151.1 (s), 164.4 (s), 166.0 (s). IR (KBr) cm^{-1}: 3352, 1730, 1664. MS *m/z* (%): 364 (M^+, 20), 278 (12), 153 (13), 152 (100). *Anal.* Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.31; H, 6.64; N, 7.56.

Attempted Cyclization of 17 *via* 18 A stirred solution of **17** (36.4 mg, 0.1 mmol) in dry THF (4 ml) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminium hydride (178.0 mg, 0.7 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water (1 ml) and then filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of the alcohols **18** (37 mg) obtained was used for the next step without further purification. A solution of **18** in TFA (1 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 ml), and extracted with chloroform (20 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (20 ml), dried, and concentrated *in vacuo* to give the residue (36.7 mg). Column chromatography on a silica gel (12 g) gave **19a** (7.8 mg, 22.4%) as a solid and **19b** (23.0 mg, 66.1%) as a solid.

Isopropyl 1,2,3,4,5,6-Hexahydro-1,5-imino-10-hydroxy-9-methoxy-3,8-dimethyl-4-oxo-3-benzazocine-11-carboxylic Acid (**19a**): mp 237—239 °C (from acetone). ^{1}H-NMR δ (at 50 °C): 1.25 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 2.24 (3H, s, $ArCH_3$), 2.84 (3H, s, NCH_3), 2.99 (1H, dd, J=16.5, 1.0 Hz, 6-Hβ), 3.10 (1H, dd, J=16.5, 5.9 Hz, 6-Hα), 3.29 (1H, dd, J=11.9, 1.0 Hz, 2-Hβ), 3.77 (3H, s, OCH_3), 3.84 (1H, dd, J=11.9, 4.6 Hz, 2-Hα), 4.92 (1H, br s, 5-H), 4.96 (1H, sept, J=6.3 Hz, OCH), 5.61 (1H, br s, 1-H), 5.97 (1H, br s, OH), 6.48 (1H, s, ArH). ^{13}C-NMR δ (at 55 °C): 15.7 (q), 22.1 (q), 22.1 (q), 31.4 (t), 34.3 (q), 44.9 (d), 53.0 (d), 54.2 (t), 60.8 (q), 69.4 (d), 119.3 (s), 122.3 (d), 129.4 (s), 129.8 (s), 143.7 (s), 144.9 (s), 153.5 (s), 168.4 (s). IR (KBr) cm^{-1}: 3220, 1715, 1640. MS *m/z* (%): 348 (M^+, 88), 277 (21), 276 (40), 262 (48), 261 (43), 235 (38), 234 (62), 191 (18), 190 (100), 175 (21), 158 (11), 43 (20). *Anal.* Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.98; H, 6.99; N, 7.93.

Isopropyl 1,2,3,4,5,6-Hexahydro-1,5-imino-8-hydroxy-9-methoxy-3,10-dimethyl-4-oxo-3-benzazocine-11-carboxylic Acid (**19b**): mp 206—207 °C (from ethyl acetate). ^{1}H-NMR δ (at 50 °C): 1.25 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 2.25 (3H, s, $ArCH_3$), 2.86 (3H, s, NCH_3), 3.04 (2H, AB d, J=16.2, 1.0 Hz, 6-H_2), 3.14 (1H, d, J=11.5 Hz, 2-Hβ), 3.76 (3H, s, OCH_3), 3.89 (1H, dd, J=11.5, 4.6 Hz, 2-Hα), 4.90 (1H, br s, 5-H), 4.94 (1H, sept, J=6.3 Hz, OCH), 5.44 (1H, br s, 1-H), 5.82 (1H, br s, OH), 6.55 (1H, s,

ArH). ^{13}C-NMR δ (at 55 °C): 11.6 (q), 22.1 (q), 22.1 (q), 32.2 (t), 34.3 (q), 46.2 (d), 52.6 (d), 54.7 (t), 60.8 (q), 69.6 (d), 113.7 (d), 125.7 (s), 127.3 (s), 129.6 (s), 144.7 (s), 148.5 (s), 153.6 (s), 168.5 (s). IR (KBr) cm^{-1}: 3280, 1710, 1685, 1670, 1645. MS *m/z* (%): 348 (M^+, 64), 277 (27), 276 (73), 235 (43), 234 (100), 191 (12), 190 (76), 175 (21), 43 (22). *Anal.* Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.84; H, 7.00; N, 7.90.

1,2,3,4,5,6-Hexahydro-1,5-imino-10-hydroxy-9-methoxy-3,8,11-trimethyl-3-benzazocin-4-one (3) from 19a *via* 20a Concentrated H_2SO_4 (0.05 ml) was added to a stirred solution of **19a** (5.9 mg, 0.024 mmol) in TFA (1 ml), and stirring was continued at room temperature for 15 h. The reaction mixture was poured into water (10 ml), made alkaline with concentrated NH_4OH, and extracted with chloroform–methanol (9 : 1). The combined extracts were washed with brine (10 ml), dried, and concentrated *in vacuo* to give **20a** (4.8 mg, 100%) as a solid, which was used for the next step without further purification. ^{1}H-NMR δ: 2.25 (3H, s, $ArCH_3$), 2.86 (3H, s, NCH_3), 2.90—3.10 (2H, br, NH, OH), 2.99 (2H, d, J=5.9 Hz, 6-H$_2$), 3.30 (1H, dd, J=11.9, 1.0 Hz, 2-Hβ), 3.78 (3H, s, OCH_3), 3.82 (1H, dd, J=11.9, 4.6 Hz, 2-Hα), 3.95 (1H, d, J=5.9 Hz, 5-H), 4.52 (1H, d, J=4.9 Hz, 1-H), 6.49 (1H, s, ArH). ^{13}C-NMR δ ($CDCl_3$+CD_3OD): 15.6 (q), 31.9 (t), 34.2 (q), 44.7 (d), 52.8 (d), 55.1 (t), 60.5 (q), 120.5 (s), 121.8 (d), 128.4 (s), 129.8 (s), 143.4 (s), 145.0 (s), 170.5 (s). IR (KBr) cm^{-1}: 3280, 1650. MS *m/z* (%): 262 (M^+, 26), 191 (19), 190 (100), 175 (16). High-resolution MS Calcd for $C_{14}H_{18}N_2O_3$: 262.1317. Found: 262.1320.

Formaldehyde (37% solution in water, 0.29 ml, 0.365 mmol) was added to a stirred solution of **20a** (4.8 mg, 0.0183 mmol) in formic acid (0.34 ml) at 60 °C. After having been stirred at 70 °C for 2 h, the reaction mixture was poured into water (10 ml), and extracted with chloroform (10 ml×3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (5.6 mg). Chromatography on a silica gel (8 g) column with dichloromethane–methanol (25 : 1) gave **3** (3.9 mg, 74.0%) as colorless prisms, mp 216—217.5 °C, which were identical in all respects with an authentic sample described earlier.[5)]

1,2,3,4,5,6-Hexahydro-1,5-imino-8-hydroxy-9-methoxy-3,10,11-trimethyl-3-benzazocin-4-one (21) from 19b *via* 20b The same procedure as described above but using **19b** (27.8 mg, 0.08 mmol) in concentrated H_2SO_4 (0.05 ml) and TFA (1 ml), gave **20b** (21.0 mg, 100%) as a solid, which was used for the next step without further purification. ^{1}H-NMR δ: 2.21 (3H, s, $ArCH_3$), 2.20—2.40 (2H, br, NH, OH), 2.88 (3H, s, NCH_3), 2.97 (1H, d, J=16.5 Hz, 6-Hβ), 3.08 (1H, dd, J=16.5, 6.6 Hz, 6-Hα), 3.14 (1H, dd, J=11.5, 0.5 Hz, 2-Hβ), 3.76 (3H, s, OCH_3), 3.87 (1H, dd, J=11.5, 4.9 Hz, 2-Hα), 3.94 (1H, d, J=5.0 Hz, 5-H), 4.34 (1H, d, J=4.9 Hz, 1-H), 6.52 (1H, s, ArH). ^{13}C-NMR δ ($CDCl_3$+CD_3OD): 11.2 (q), 32.5 (t), 34.3 (q), 46.5 (d), 52.4 (d), 55.1 (t), 60.5 (q), 113.8 (d), 125.1 (s), 127.5 (s), 128.9 (s), 144.6 (s), 148.6 (s), 169.8 (s). IR ($CHCl_3$) cm^{-1}: 3290, 1645, 1605. MS *m/z* (%): 262 (M^+, 17), 191 (16), 190 (100), 175 (13). High-resolution MS Calcd for $C_{14}H_{18}N_2O_3$: 262.1317. Found: 262.1313.

Formaldehyde (37% solution in water, 0.29 ml, 0.365 mmol) was added to a stirred solution of **20b** (21.0 mg, 0.08 mmol) in formic acid (1.16 ml) at 60 °C. After having been stirred at 70 °C for 2 h, the reaction mixture was poured into water (10 ml), and extracted with chloroform (10 ml×3). The combined extracts were washed with 5% $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (35.0 mg). Chromatography on a silica gel (10 g) column with dichloromethane–methanol (25 : 1) gave **21** (13.4 mg, 60.7%) as colorless prisms, mp 223—225 °C (from ethyl acetate). ^{1}H-NMR δ: 2.20 (3H, s, $ArCH_3$), 2.49 (3H, s, NCH_3), 2.81 (1H, d, J=17.1 Hz, 6-Hβ), 2.86 (3H, s, NCH_3), 3.02 (1H, dd, J=14.0, 3.0 Hz, 2-Hβ), 3.17 (1H, dd, J=17.1, 7.0 Hz, 6-Hα), 3.60 (1H, d, J=7.0 Hz, 5-H), 3.77 (3H, s, OCH_3), 3.95 (1H, dd, J=14.0, 4.9 Hz, 2-Hα), 3.96 (1H, br s, 1-H), 6.55 (1H, s, ArH). ^{13}C-NMR δ: 11.4 (q), 28.1 (t), 34.1 (q), 40.3 (q), 52.9 (t), 52.9 (d), 59.0 (d), 60.7 (q), 113.3 (d), 124.9 (s), 127.7 (s), 129.0 (s), 144.6 (s), 148.2 (s), 170.5 (s). IR (KBr) cm^{-1}: 3400—3050, 1650, 1620. MS *m/z* (%): 276 (M^+, 15), 205 (17), 204 (100), 189 (12). High-resolution MS Calcd for $C_{15}H_{20}N_2O_3$: 276.1474. Found: 276.1471. *Anal.* Calcd for $C_{15}H_{20}N_2O_3 \cdot 1/5H_2O$: C, 64.36; H, 7.35; N, 10.01. Found: C, 64.34; H, 7.33; N, 9.76.

3-(2-Bromo-5-hydroxy-4-methoxy-3-methylphenylmethyl)-1-methyl-2,5-piperazinedione (22) A carbon tetrachlorode solution of bromine (1.0 M, 1.3 ml, 1.3 mmol) was added to a stirred solution of **5** (278.0 mg, 1.0 mmol) in dry THF–dichloromethane (2 : 1, 10 ml) at 0 °C for 10 min, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with water (100 ml), and extracted with chloroform (50 ml×3). The combined extracts were washed with water (50 ml), dried, and concentrated *in vacuo* to give a solid (363 mg). Chromatography on a silica gel (50 g) column with dichloromethane–methanol (100 : 3) gave a soild (352 mg), recrystallization of which from methanol gave **22** (324 mg, 91%) as colorless needles, mp 232—234 °C. ^{1}H-NMR δ: 2.37 (3H, s, $ArCH_3$), 3.00 (3H, s, NCH_3), 3.01 (1H, dd, J=14.0, 9.1 Hz, ArCH), 3.61 (1H, dd, J=14.0, 4.0 Hz, ArCH), 3.75 (1H, d, J=17.7 Hz, 6-H), 3.78 (3H, s, OCH_3), 3.88 (1H, d, J=17.7 Hz, ArCH), 4.34 (1H, dd, J=9.1, 4.0 Hz, 3-H), 5.87 (2H, br s, NH, OH), 6.76 (1H, s, ArH). ^{13}C-NMR δ ($CDCl_3$+CD_3OD): 16.8 (q), 33.8 (q), 40.2 (t), 51.0 (t), 55.5 (d), 60.4 (q), 116.0 (d), 117.3 (s), 130.5 (s), 133.0 (s), 146.0 (s), 148.9 (s), 165.5 (s), 166.0 (s). IR (KBr) cm^{-1}: 3280, 1685, 1655. MS *m/z* (%): no M^+, 277 (100), 231 (52), 229 (54). *Anal.* Calcd for $C_{14}H_{17}BrN_2O_4$: C, 47.07; H, 4.80; N, 7.84. Found: C, 46.83; H, 4.81; N, 7.79.

Further elution with dichloromethane–methanol (50 : 3) gave the residue (20 mg), which showed two major spots on TLC (*Rf* 0.35 and 0.45, 4 : 5 acetone–chloroform). This material was subjected to chromatography on preparative layer silica gel plates (Merck 5715, solvent, 1 : 2 acetone–chloroform) to afford **23a** (7.0 mg, 2.0%) and **23b** (8.0 mg, 1.8%).

3-(2-Bromo-3-hydroxy-4-methoxy-5-methylphenylmethyl)-1-methyl-2,5-piperazinedione (**23a**): Recrystallization from methanol gave colorless prisms, mp 113—115.5 °C. ^{1}H-NMR δ: 2.25 (3H, s, $ArCH_3$), 2.98 (1H, dd, J=14.0, 9.2 Hz, ArCH), 2.99 (3H, s, NCH_3), 3.54 (1H, dd, J=14.0, 3.6 Hz, ArCH), 3.70 (1H, d, J=17.7 Hz, 6-H), 3.81 (3H, s, OCH_3), 3.85 (1H, d, J=17.7 Hz, ArCH), 4.32 (1H, dd, J=9.2, 3.6 Hz, 3-H), 6.16 (1H, br s, OH), 6.34 (1H, br s, NH), 6.63 (1H, s, ArH). ^{13}C-NMR δ: 15.7 (q), 33.9 (q), 39.7 (t), 51.6 (t), 55.2 (d), 60.6 (q), 109.7 (s), 124.2 (d), 130.6 (s), 130.8 (s), 145.4 (s), 147.0 (s), 165.1 (s), 165.4 (s). IR (KBr) cm^{-1}: 3600—2800, 1705, 1660. MS *m/z* (%): 358 (M^++2, 4), 356 (M^+, 4), 278 (15), 277 (85), 231 (98), 229 (100). *Anal.* Calcd for $C_{14}H_{17}BrN_2O_4 \cdot 1/2H_2O$: C, 45.92; H, 4.95; N, 7.65. Found: C, 46.12; H, 4.82; N, 7.54.

3-(2,6-Dibromo-3-hydroxy-4-methoxy-5-methylphenylmethyl)-1-methyl-2,5-piperazinedione (**23b**): Recrystallization from methanol gave colorless prisms, mp 222—224 °C. ^{1}H-NMR δ: 2.32 (3H, s, $ArCH_3$), 3.04 (3H, s, NCH_3), 3.50 (1H, dd, J=13.9, 10.2 Hz, ArCH), 3.72 (1H, dd, J=13.9, 5.0 Hz, ArCH), 3.77 (3H, s, OCH_3), 3.94, 4.14 (each 1H, d, J=17.5 Hz, ArCH), 4.46 (1H, ddd, J=10.2, 5.0, 3.0 Hz, 3-H), 6.18 (1H, br s, NH), 6.80 (1H, br s, OH). ^{13}C-NMR δ: 17.3 (q), 34.1 (q), 41.2 (t), 51.6 (t), 53.9 (d), 61.0 (q), 110.7 (s), 118.5 (s), 130.5 (s), 132.1 (s), 145.4 (s), 146.5 (s), 165.2 (s), 165.7 (s). IR (KBr) cm^{-1}: 3280, 1685, 1655. MS *m/z* (%): no M^+, 358 (17), 357 (98), 356 (20), 355 (100), 311 (49), 309 (97), 307 (52). *Anal.* Calcd for $C_{14}H_{16}Br_2N_2O_4$: C, 38.56; H, 3.70; N, 6.42. Found: C, 38.52; H, 3.78; N, 6.37.

Attempted Direct Conversion of 22 to 6 A solution of **22** (35.8 mg, 0.1 mmol), triethylamine (0.028 ml, 0.2 mmol), and DMAP (24.5 mg, 0.2 mmol) in dry dichloromethane (2 ml) was cooled with ice-water, and isopropyl chloroformate (0.0455 ml, 0.4 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (20 ml), the organic layer was washed with 1 N HCl (10 ml), and then water (20 ml), dried, and concentrated *in vacuo* to give the residue. Chromatography on a silica gel (5 g) column with dichloromethane–methanol (80 : 1) as the eluent gave **24** (29.4 mg, 66.7%) as a solid, recrystallization of which from acetone afforded colorless needles, mp 146—147.5 °C. Further elution with dichloromethane–methanol (30 : 1) as the eluent gave the starting material (8.1 mg, 22.6% recovery). This reaction was done using NaH as base in DMF to give **24** and **22** in 74.1% and 5.6% yields, respectively.

Compound **24**: ^{1}H-NMR δ: 1.38 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 2.39 (3H, s, $ArCH_3$), 2.95 (3H, s, NCH_3), 3.15 (1H, dd, J=13.9, 6.9 Hz, ArCH), 3.56 (1H, d, J=17.5 Hz, 6-H), 3.60 (1H, dd, J=13.9, 4.6 Hz, ArCH), 3.73 (1H, d, J=17.7 Hz, 6-H), 3.78 (3H, s, OCH_3), 4.34 (1H, m, 3-H), 4.96 (1H, sept, J=6.3 Hz, OCH), 6.36 (1H, br s, NH), 6.93 (1H, s, ArH). IR (KBr) cm^{-1}: 3400—3050, 1785, 1715, 1695. MS *m/z* (%): 444 (M^++2, 2), 442 (M^+, 2), 364 (11), 363 (50), 319 (10), 278 (18), 277 (100), 231 (49), 229 (50), 43 (19). *Anal.* Calcd for $C_{18}H_{23}BrN_2O_6$: C, 48.77; H, 5.23; N, 6.32. Found: C, 48.72; H, 5.24; N, 6.32.

3-(5-Benzyloxy-2-bromo-4-methoxy-3-methylphenylmethyl)-1-methyl-2,5-piperazinedione (25) A suspension of **22** (1.074 g, 3.0 mmol) and anhydrous K_2CO_3 (0.622 g, 4.5 mmol) in dry DMF (60 ml) was cooled with ice-water, and benzyl bromide (0.428 ml, 3.6 mmol) was added over 5 min. This mixture was heated at 60 °C for 3 h. The reaction mixture was diluted with water (100 ml), and extracted with chloroform (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a residue, recrystallization of which from ethyl acetate–ether afforded **25** (1.207 g, 89.8%) as colorless prisms, mp 150.5—151 °C. ^{1}H-NMR δ: 2.38 (3H, s, $ArCH_3$), 2.96 (3H, s, NCH_3), 3.06 (1H, dd, J=14.2, 8.6 Hz, ArCH), 3.57 (1H, dd, J=14.2, 4.0 Hz, ArCH), 3.68 (1H, d, J=17.8 Hz, 6-H), 3.82 (3H, s, OCH_3), 3.84 (1H, d, J=17.8 Hz, ArCH), 4.30

(1H, m, 3-H), 5.04, 5.09 (each 1H, d, J=11.9 Hz, OCHAr), 5.87 (1H, br s, NH), 6.73 (1H, s, ArH), 7.31—7.45 (5H, m, 5×ArH). IR (KBr) cm^{-1}: 3350—2850, 1680. MS *m/z* (%): 448 (M^++2, 7), 446 (M^+, 7), 368 (28), 367 (97), 321 (39), 319 (28), 277 (11), 276 (13), 275 (8), 91 (100). *Anal.* Calcd for $C_{21}H_{23}BrN_2O_4$: C, 56.39; H, 5.18; N, 6.26. Found: C, 56.19; H, 5.23; N, 6.14.

3-(5-Benzyloxy-2-bromo-4-methoxy-3-methylphenylmethyl)-4-isopropyloxycarbonyl-1-methyl-2,5-piperazinedione (26) A solution of **25** (626.3 mg, 1.40 mmol), triethylamine (0.488 ml, 3.50 mmol), and DMAP (428.0 mg, 3.50 mmol) in dry dichloromethane (30 ml) was cooled with ice-water, and isopropyl chloroformate (0.795 ml, 7.00 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with dichloromethane (30 ml), the organic layer was washed with 1 N HCl (30 ml), and then water (30 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from acetone afforded **26** (706.3 mg, 94.6%) as colorless prisms, mp 146—147.5 °C. ^{1}H-NMR δ: 1.27, 1.32 (each 3H, d, J=6.3 Hz, OCH(C$\underline{H}_3$)$_2$), 2.35 (3H, s, $ArCH_3$), 2.84 (3H, s, NCH_3), 3.13 (1H, d, J=18.2 Hz, 6-H), 3.28, 3.60 (each 1H, dd, J=14.2, 5.3 Hz, ArCH), 3.65 (1H, d, J=18.2 Hz, 6-H), 3.81 (3H, s, OCH_3), 5.03 (2H, s, OCH_2Ar), 5.05 (1H, sept, J=6.3 Hz, OCH), 5.10 (1H, t, J=5.3 Hz, 3-H), 6.68 (1H, s, ArH), 7.33—7.46 (5H, m, 5×ArH). ^{13}C-NMR δ: 17.7 (q), 22.2 (q), 22.4 (q), 33.9 (q), 39.4 (t), 53.2 (t), 60.3 (d), 61.4 (q), 71.6 (t), 72.8 (d), 114.9 (d), 120.5 (s), 128.0 (d×2), 128.8 (d), 129.2 (s), 129.3 (d×2), 131.0 (s), 134.8 (s), 137.1 (s), 148.6 (s), 151.7 (s), 164.6 (s), 166.5 (s). IR (KBr) cm^{-1}: 1790, 1690, 1665. MS *m/z* (%): 534 (M^++2, 26), 532 (M^+, 26), 454 (32), 453 (100), 367 (31), 321 (37), 319 (38), 276 (11), 275 (17), 240 (17), 91 (89), 43 (14). *Anal.* Calcd for $C_{25}H_{29}BrN_2O_6$: C, 56.29; H, 5.48; N, 5.25. Found: C, 56.14; H, 5.49; N, 5.20.

Debenzylation of 26. Method A A solution of **26** (32.0 mg, 0.06 mmol) in TFA (1 ml) was stirred at room temperature for 18 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo*. The residue (38.4 mg), which showed two major spots on TLC (*Rf* 0.3 and 0.1, 1 : 1 hexane–ethyl acetate), was subjected to chromatography on preparative layer silica gel plate (Merck 5715, solvent 1 : 1 hexane–ethyl acetate) afforded **6** (13.4 mg, 51.6%) and **27a** (9.8 mg, 30.6%).

Method B A solution of **26** (53.3 mg, 0.1 mmol) and 1,3-dimethoxybenzene (0.262 ml, 2.0 mmol) in TFA (2 ml) was stirred at room temperature for 18 h. After usual work up described as above gave **6** (31.9 mg, 72.0%) and **27a** (10.9 mg, 20.5%).

Method C A solution of **26** (53.3 mg, 0.1 mmol) in chloroform (2 ml) was cooled with ice-water, and TMSI (0.021 ml, 0.15 mmol) was added dropwise over 10 min. The reaction mixture was heated at 50 °C for 24 h. The reaction mixture was diluted with methanol (5 ml) and brine (10 ml), and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated *in vacuo* to give the residue (40.3 mg). Chromatography on a silica gel (8 g) column with dichloromethane–methanol (50 : 1) gave **6** (7.8 mg, 17.6%). Further elution with dichloromethane–methanol (25 : 1) gave **27b** (9.9 mg, 27.7%).

3-(2-Bromo-5-hydroxy-4-methoxy-3-methylphenylmethyl)-4-iso-propyloxycarbonyl-1-methyl-2,5-piperazinedione (**6**): Recrystallization from ethyl acetate–ether gave colorless prisms, mp 156—158 °C. ^{1}H-NMR δ: 1.29, 1.33 (each 3H, d, J=6.2 Hz, OCH(C$\underline{H}_3$)$_2$), 2.34 (3H, s, $ArCH_3$), 2.90 (3H, s, NCH_3), 3.12 (1H, d, J=18.2 Hz, 6-H), 3.22 (1H, dd, J=14.0, 5.3 Hz, ArH), 3.63 (1H, dd, J=14.2, 5.5 Hz, ArCH), 3.67 (1H, d, J=18.2 Hz, 6-H), 3.78 (3H, s, OCH_3), 5.04 (1H, sept, J=6.2 Hz, OCH), 5.10 (1H, dd, J=5.5, 5.3 Hz, 3-H), 6.54 (1H, br s, OH), 6.74 (1H, s, ArH). ^{13}C-NMR δ: 17.2 (q), 21.6 (q), 21.7 (q), 33.3 (q), 38.5 (t), 52.5 (t), 59.7 (d), 61.1 (q), 72.2 (d), 115.6 (d), 118.6 (s), 131.3 (s), 132.5 (s), 145.8 (s), 148.3 (s), 150.9 (s), 163.8 (s), 166.0 (s). IR (KBr) cm^{-1}: 3600—3050, 1734, 1720, 1662. MS *m/z* (%): 444 (M^++2, 3), 442 (M^+, 3), 364 (21), 363 (100), 278 (10), 277 (55), 231 (60), 229 (63), 43 (12). *Anal.* Calcd for $C_{18}H_{23}BrN_2O_6$: C, 48.77; H, 5.23; N, 6.32. Found: C, 48.74; H, 5.16; N, 6.25.

3-(2-Bromo-5-hydroxy-4-methoxy-3-methyl-6-phenylmethyl-phenylmethyl)-4-isopropyloxycarbonyl-1-methyl-2,5-piperazinedione (**27a**): Recrystallization from methanol gave colorless prisms, mp 255.5—257 °C. ^{1}H-NMR δ ($CDCl_3$+CD_3OD, 55 °C): 1.17, 1.24 (each 3H, d, J=6.3 Hz, OCH(C$\underline{H}_3$)$_2$), 2.36 (3H, s, $ArCH_3$), 2.93 (3H, s, NCH_3), 3.34 (2H, d, J=7.6 Hz, $ArCH_2$), 3.76 (3H, s, OCH_3), 3.86, 4.13 (each 1H, d, J=17.8 Hz, 6-H), 4.21 (2H, s, OCH_2), 4.94 (1H, sept, J=6.3 Hz, OCH), 5.11 (1H, t, J=7.6 Hz, 3-H), 7.10—7.42 (5H, m, 5×ArH). ^{13}C-NMR δ ($CDCl_3$+CD_3OD, 55 °C): 17.3 (q), 21.3 (q), 21.5 (q), 32.0 (t), 33.5 (q), 35.9 (t), 58.2 (t), 59.0 (d), 61.0 (q), 72.2 (d), 119.5 (s), 126.0 (d), 128.2 (d×2), 128.4 (d×2), 129.9 (s), 130.4 (s), 134.2 (s), 139.8 (s), 145.5 (s), 147.0 (s), 151.2 (s), 164.7 (s), 165.7 (s). IR (KBr) cm^{-1}: 3160, 1780, 1700, 1670. MS *m/z* (%): 534 (M^++2, 3), 532 (M^+, 3), 454 (31), 453 (100), 368 (11), 367 (42), 240 (42), 209 (11), 208 (14), 91 (14). *Anal.* Calcd for $C_{25}H_{29}BrN_2O_6$: C, 56.29; H, 5.48; N, 5.25. Found: C, 56.24; H, 5.53; N, 5.15.

3-(2-Bromo-4,5-dihydroxy-3-methylphenylmethyl)-1-methyl-2,5-piperazinedione (**27b**): Recrystallization from methanol gave colorless prisms, mp 206—208 °C. ^{1}H-NMR δ ($CDCl_3$+CD_3OD): 2.31 (3H, s, $ArCH_3$), 2.92 (3H, s, NCH_3), 3.06 (1H, dd, J=13.9, 6.9 Hz, ArCH), 3.37 (1H, d, J=17.2 Hz, ArCH), 3.64—3.78 (2H, m, 6-H, ArCH), 4.25 (1H, t like, 3-H), 6.52 (1H, s, ArH). IR (KBr) cm^{-1}: 3340, 1700, 1655. MS *m/z* (%): 344 (M^++2, 1), 342 (M^+, 1), 264 (8), 263 (100), 217 (35), 215 (35), 128 (85). *Anal.* Calcd for $C_{13}H_{15}BrN_2O_4$: C, 45.50; H, 4.41; N, 8.16. Found: C, 45.29; H, 4.39; N, 8.06.

3-(2-Bromo-5-hydroxy-4-methoxy-3-methyl-6-phenylmethyl-phenylmethyl)-1-methyl-2,5-piperazinedione (28) Concentrated H_2SO_4 (0.025 ml) was added to a stirred solution of **27a** (9.8 mg, 0.0184 mmol) in TFA (0.5 ml). The resulting solution was stirred at room temperature for 60 h. The reaction mixture was poured into water (10 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml×3). The combined extracts were washed with brine (10 ml), dried, and concentrated *in vacuo* to give a residue, recrystallization of which from ethyl acetate–ether gave **28** (6.0 mg, 73.0%) as colorless prisms, mp 193—195 °C. ^{1}H-NMR δ: 2.38 (3H, s, $ArCH_3$), 2.99 (3H, s, NCH_3), 3.23 (1H, dd, J=14.2, 10.9 Hz, ArCH), 3.56 (1H, dd, J=14.2, 4.6 Hz, ArCH), 3.79 (3H, s, OCH_3), 3.86, 3.98 (each 1H, d, J=17.8 Hz, 6-H), 4.07, 4.22 (each 1H, d, J=15.8 Hz, ArCHAr′), 4.22 (1H, m, 3-H), 5.72, 6.05 (each 1 H, br s, D_2O exchangeable, NH and OH), 7.08—7.24 (5H, m, 5×ArH). ^{13}C-NMR δ: 17.4 (q), 32.4 (t), 33.9 (q), 37.1 (t), 51.5 (t), 54.4 (d), 61.2 (q), 119.2 (s), 125.7 (s), 126.2 (d), 127.9 (d×2), 128.6 (d×2), 130.6 (s), 130.8 (s), 139.5 (s), 145.2 (s), 147.1 (s), 165.2 (s), 165.4 (s). IR (KBr) cm^{-1}: 3450—3150, 1700, 1670. MS *m/z* (%): 448 (M^++ 2, 3), 446 (M^+, 3), 368 (27), 367 (100), 240 (29), 225 (12), 209 (12), 208 (14), 91 (11). *Anal.* Calcd for $C_{21}H_{23}BrN_2O_4$: C, 56.39; H, 5.18; N, 6.26. Found: C, 56.52; H, 5.37; N, 6.06.

3-(2-Bromo-5-hydroxy-4-methoxy-3-methylphenylmethyl)-4-isopropyloxycarbonyl-1-methyl-2,5-piperazinedione (6) from 17 A carbon tetrachloride solution of bromine (1.0 M, 2.2 ml, 2.2 mmol) was added to a stirred solution of **17** (728.8 mg, 2.0 mmol) in dry dichloromethane (20 ml) at 0 °C for 10 min, and the mixture was stirred at the same temparature for 1 h. The reaction mixture was diluted with water (40 ml), and extracted with chloroform (40 ml×3). The combined extracts were washed with water (40 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate–ether afforded **6** (790.7 mg, 89.2%) as colorless prisms, mp 156—158 °C, which were identical in all respects with an authentic sample described above.

Conversion of 26 to 30 *via* 29 A stirred solution of **26** (53.3 mg, 0.1 mmol) in dry THF (5 ml) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminium hydride (152.6 mg, 0.6 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water (1 ml) and then filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of the alcohols **29** (71 mg) obtained was used for the next step without further purification. Methanesulfonic anhydride (20.9 mg, 0.12 mmol) was added to a stirred solution of the crude **29** in dry dichloromethane (4 ml) at 0 °C dropwise for 10 min, the reaction mixture was heated reflux for 6 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ether gave **30** (51.7 mg, 100%) as colorless needles, mp 125—126.5 °C. ^{1}H-NMR δ (71 : 29 a pair of rotamers was existed): major rotamer 0.79, 1.10 (each 3H, d, J=6.3 Hz, OCH(C$\underline{H}_3$)$_2$), 2.36 (3H, s, $ArCH_3$), 2.84 (1H, dd, J=13.9, 10.2 Hz, ArCH), 3.11 (3H, s, NCH_3), 3.18 (1H, dd, J=13.9, 4.0 Hz, ArCH), 3.79 (3H, s, OCH_3), 4.63 (1H, sept, J=6.2 Hz, OCH), 5.05 (2H, s, OCH_2Ar), 5.10 (1H, ddd, J=10.2, 4.0, 1.7 Hz, 3-H), 5.63 (1H, d, J=5.9 Hz, 6-H), 6.28 (1H, dd, J=5.9, 1.7 Hz, 5-H), 6.56 (1H, s, ArH), 7.31—7.47 (5H, m, 5×ArH). Minor rotamer 1.13, 1.22 (each 3H, d, J=6.3 Hz, OCH(C$\underline{H}_3$)$_2$), 2.35 (3H, s, $ArCH_3$), 2.97 (1H, dd, J=13.5, 8.3 Hz, ArCH), 3.06 (3H, s, NCH_3), 3.28 (1H, dd, J=13.5, 5.3 Hz, ArCH), 3.78 (3H, s, OCH_3), 4.83 (1H, sept, J=6.2 Hz, OCH), 5.05 (2H, s, OCH_2Ar), 5.11 (1H, m, 3-H), 5.37 (1H, d, J=5.9 Hz, 6-H), 6.12 (1H, dd, J=5.9, 1.3 Hz, 5-H), 6.71 (1H, s, ArH), 7.31—7.47 (5H, m, 5×ArH). IR (KBr) cm^{-1}: 1705, 1670. MS *m/z* (%): 516 (M^++2, 2), 514 (M^+, 2), 321 (11), 319 (11), 197 (67), 155 (10), 153 (11), 111 (100), 91 (25), 43 (28). *Anal.* Calcd for $C_{25}H_{27}BrN_2O_5 \cdot 1/5H_2O$: C,

57.86; H, 5.32; N, 5.40. Found: C, 57.82; H, 5.61; N, 5.36.

Attempted Cyclization of 26 to 31 *via* 29 The same procedure for the reduction of **26** (53.3 mg, 0.1 mmol) as descrived above afforded **29** (87.3 mg). Concentrated H_2SO_4 (0.1 ml) was added to a solution of **29** in TFA (2 ml), and the resulting solution was stirred at room temperature for 21 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (20 ml), dried, and concentrated *in vacuo* to give a soild (58.9 mg). Recrystallization of which from acetone–methanol afforded **31** (22.0 mg, 64.5%) as colorless prisms, mp 268—270 °C. ^{1}H-NMR δ ($CDCl_3$+CD_3OD): 2.35 (3H, s, $ArCH_3$), 2.87 (3H, s, NCH_3), 2.88 (1H, dd, J=17.8, 6.9 Hz, 6-Hα), 3.06 (1H, dd, J=17.8, 1.7 Hz, 6-Hβ), 3.34 (1H, dd, J=12.2, 1.0 Hz, 2-Hβ), 3.74 (3H, s, OCH_3), 3.83 (1H, dd, J=12.2, 5.0 Hz, 2-Hα), 3.99 (1H, dd, J=6.9, 1.7 Hz, 5-H), 4.55 (1H, dd, J=5.0, 1.0 Hz, 1-H). ^{13}C-NMR δ ($CDCl_3$+CD_3OD): 16.4 (q), 34.1 (q), 34.3 (t), 44.8 (d), 53.1 (d), 55.1 (t), 60.9 (q), 117.4 (s), 122.9 (s), 129.3 (s), 130.5 (s), 144.1 (s), 144.5 (s), 170.5 (s). IR (KBr) cm^{-1}: 3330, 3250, 1640, 1615. MS *m/z* (%): 342 (M^++2, 22), 340 (M^+, 24), 271 (19), 270 (97), 269 (25), 268 (100), 255 (12), 253 (11). *Anal.* Calcd for $C_{14}H_{17}BrN_2O_3$: C, 49.28; H, 5.02; N, 8.21. Found: C, 49.44; H, 5.10; N, 8.12.

Isopropyl 1,2,3,4,5,6-Hexahydro-1,5-imino-7-bromo-10-hydroxy-9-methoxy-3,8-dimethyl-4-oxo-3-benzazocine-11-carboxylic Acid (33) A stirred solution of **6** (541.6 mg, 1.25 mmol) in dry THF (50 ml) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminium hydride (2.225 g, 8.75 mmol) was added to it over 5 min. After continued stirring at the same temperature for 1 h, the reaction mixture was quenched by the addition of water (1 ml) and filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of the alcohols **32** (1.249 g) obtained was used for the next step without further purification. A stirred solution of the crude **32** in TFA (10 ml) was stirred at room temperature for 13 h. The reaction mixture was diluted with water (60 ml) and extracted with chloroform (80 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (80 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from acetone gave **33** (520.0 mg, 97.4%) as colorless prisms, mp 265—266 °C. ^{1}H-NMR δ (at 50 °C): 1.25 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 2.35 (3H, s, $ArCH_3$), 2.85 (3H, s, NCH_3), 2.96 (1H, dd, J=17.5, 5.9 Hz, 6-Hα), 3.17 (1H, dd, J=17.5, 1.7 Hz, 6-Hβ), 3.31 (1H, d, J=11.9 Hz, 2-Hβ), 3.77 (3H, s, OCH_3), 3.85 (1H, dd, J=11.9, 4.6 Hz, 2-Hα), 4.90—4.98 (2H, m, OCH and 5-H), 5.62 (1H, br s, 1-H), 5.83 (1H, br s, OH). ^{13}C-NMR δ (at 55 °C): 16.7 (q), 22.1 (q), 22.1 (q), 33.8 (t), 34.2 (q), 44.8 (d), 53.0 (d), 54.0 (t), 61.2 (q), 69.7 (d), 121.2 (s), 129.8 (s), 130.8 (s), 138.8 (s), 144.2 (s), 144.3 (s), 153.4 (s), 168.1 (s). IR (KBr) cm^{-1}: 3500—3050, 1720, 1650, 1610. MS *m/z* (%): 428 (M^++2, 78), 426 (M^+, 79), 386 (11), 385 (12), 384 (12), 357 (19), 356 (40), 355 (20), 354 (37), 342 (39), 341 (36), 340 (41), 339 (30), 315 (36), 314 (45), 313 (38), 312 (45), 271 (19), 270 (98), 269 (24), 268 (100). *Anal.* Calcd for $C_{18}H_{23}BrN_2O_5$: C, 50.60; H, 5.43; N, 6.56. Found: C, 50.52; H, 5.42; N, 6.44.

1,2,3,4,5,6-Hexahydro-1,5-imino-7-bromo-10-hydroxy-9-methoxy-3,8-dimethyl-3-benzazocin-4-one (31) Concentrated H_2SO_4 (1.5 ml) was added to a stirred solution of **33** (427.0 mg, 0.1 mmol) in TFA (30 ml), and the resulting solution was stirred at room temperature for 19 h. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (100 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (100 ml), dried, and concentrated *in vacuo* to give a solid (58.9 mg), recrystallization of which from acetone–methanol afforded **31** (319.0 mg, 93.5%) as colorless prisms, mp 269—270 °C, which were identical in all respects with an authentic sample described above.

1,2,3,4,5,6-Hexahydro-1,5-imino-7-bromo-10-hydroxy-9-methoxy-3,8,11-trimethyl-3-benzazocin-4-one (34) Formaldehyde (37% solution in water, 10.0 ml, 125.0 mmol) was added to a stirred solution of **31** (214.0 mg, 0.627 mmol) in formic acid (11.6 ml, 308.0 mmol) at 60 °C. After having been stirred at 70 °C for 1 h, the reaction mixture was poured into water (100 ml), and extracted with chloroform (100 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (100 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from methanol gave **34** (209.0 mg, 94.0%) as colorless prisms, mp 265.5—267 °C.^{1}H-NMR δ: 2.36 (3H, s, $ArCH_3$), 2.48, 2.86 (each 3H, s, NCH_3), 2.92 (1H, d, J=18.1 Hz, 6-Hβ), 3.01 (1H, dd, J=18.1, 5.6 Hz, 6-Hα), 3.21 (1H, d, J=11.9 Hz, 2-Hβ), 3.73 (1H, d, J=5.6 Hz, 5-H), 3.76 (3H, s, OCH_3), 3.94 (1H, dd, J=11.9, 4.6 Hz, 2-Hα), 4.24 (1H, d, J=4.6 Hz, 1-H), 6.06 (1H, br s, OH). ^{13}C-NMR δ: 16.7 (q), 29.5 (t), 33.9 (q), 39.7 (q), 51.0 (d), 52.5 (t), 59.4 (d), 61.3 (q), 117.8 (s), 120.6 (s), 129.2 (s), 130.4 (s), 144.0 (s), 144.8 (s), 169.6 (s). IR (KBr) cm^{-1}: 3500—3050, 1655, 1620. MS *m/z* (%): 356 (M^++2, 23), 354 (M^+, 23), 285 (18), 284 (98), 283 (21), 282 (100), 269 (13), 267 (12). *Anal.* Calcd for $C_{15}H_{19}BrN_2O_3$: C, 50.72; H, 5.39; N, 7.89. Found: C, 50.65; H, 5.47; N,7.77.

1,2,3,4,5,6-Hexahydro-1,5-imino-10-hydroxy-9-methoxy-3,8,11-trimethyl-3-benzazocin-4-one (3) A solution of **34** (355.0 mg, 1 mmol) in ethanol (20 ml) was hydrogenated over 20% $Pd(OH)_2$/C (200 mg) at 1 atm for 6 h. The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were evaporated to give a solid, recrystallization of which from ethyl acetate afforded **3** (262.2 mg, 95.0%) as colorless prisms, mp 216—217.5 °C. ^{1}H-NMR δ: 2.25 (3H, s, $ArCH_3$), 2.48 (3H, s, NCH_3), 2.80 (1H, d, J=17.3 Hz, 6-Hβ), 2.87 (3H, s, NCH_3), 3.13 (1H, dd, J=17.3, 6.6 Hz, 6-Hα), 3.18 (1H, d, J=11.9 Hz, 2-Hβ), 3.62 (1H, d, J=6.6 Hz, 5-H), 3.78 (3H, s, OCH_3), 3.90 (1H, dd, J=11.9, 4.9 Hz, 2-Hα), 4.18 (1H, d, J=4.6 Hz, 1-H), 5.96 (1H, br s, OH), 6.48 (1H, s, ArH). ^{13}C-NMR δ: 15.8 (q), 27.3 (t), 34.0 (q), 39.9 (q), 50.9 (d), 52.6 (t), 59.2 (d), 60.8 (q), 118.8 (s), 122.2 (d), 128.7 (s), 129.5 (s), 143.4 (s), 145.5 (s), 169.8 (s). IR (KBr) cm^{-1}: 3500—3050, 1730, 1625, 1605. MS *m/z* (%): 276 (M^+, 24), 205 (19), 204 (100), 189 (15). *Anal.* Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.03; H, 7.28; N, 9.96.

Acknowledgments This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. We would like to thank Ms. T. Kozeki and Ms. A. Ohmae in the Analytical Center of this university for measurement of mass spectral data and micro analytical data.

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