

Synthetic Approaches toward Ecteinascidins. Part 2.¹⁾ Preparation of the ABCDE Ring System of Ecteinascidins Having Characteristic Substituents in Both Benzene Rings

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A synthesis of an advanced ABCDE ring system (24c) having characteristic substituents in both benzene rings of ecteinascidin marine natural products is described based on our model studies.

Key words ecteinascidin; marine natural product; synthesis; pentacyclic framework; protected phenol

Since the crude aqueous extract of the colonial tunicate *Ecteinascidia turbinata* was reported to possess *in vivo* anti-tumor activity in 1969,²⁾ a number of research groups had attempted to isolate the active constituents in the extract and determine their chemical structures. However, the isolation and structure determination of the active compounds was not completed until 1990 by an Illinois University group.^{3–6)} Among the isolated marine natural products, ecteinascidin 743 (**1a**) was ultimately selected for further clinical studies because it was available in the greatest amount from natural sources. In contrast, we have recently succeeded in the discovery of a Thai tunicate, *Ecteinascidia thurstoni* HERDMAN 1891, around Phuket Island, and in the extraction, separation, and isolation of ecteinascidin 770 (**1b**) in its stable form by potassium cyanide pretreatment.⁷⁾ The combination of unique structural features and a high degree of functionalization in **1a** presents a formidable challenge to the synthetic chemist. Corey and co-workers described the first elegant total synthesis including an improved process.^{8–10)} Fukuyama and co-workers recently described an alternative route for the practical synthesis of **1a**.^{11,12)} In addition, the 22 steps transformation of **1a** from cyanosafracin B, which is readily available from microbial safracin B,^{13–16)} was described by Pharma Mar Laboratories.¹⁷⁾ However, one of the most intriguing problems, which is how to maintain a consistent supply of ecteinascidins for drug development: by isolation from marine sources or by total synthesis still remains.

In connection with the development of a short-step synthesis of ecteinascidin 770 (**1b**), we have previously reported the preparation of the tricyclic lactam intermediate (**2**)¹⁾ and the practical synthesis of the ABC ring model compound

3.^{18,19)} Encouraged by the results of our studies, we applied these strategies for total synthesis of **1b**. We describe herein an efficient synthesis of a pentacyclic framework (**24c**) that has characteristic substituents in both benzene rings.

In order to reduce the number of steps, we employed the method of reducing the double bond in **4** storing the bromine (Chart 1).²⁰⁾ After numerous attempts under a variety of conditions,^{21–23)} catalytic hydrogenation of **4a**¹⁸⁾ in the presence of 5% rhodium on carbon (Rh/C) in methanol was achieved. Catalytic hydrogenation of **4a** over 5% Rh/C at 1 atm for 1 h afforded **5a** in quantitative yield. Acetylation of **5a** with acetic anhydride and 4-dimethylaminopyridine (DMAP) in pyridine gave **6a** in 77% yield. On the other hand, the readily available phenol (**7**)¹⁾ was protected with a *p*-toluenesulfonyl group to afford the benzaldehyde derivative (**8**) in 91% yield. Condensation of **8** with **6a** in the presence of potassium *tert*-butoxide gave (*Z*)-arylidene-piperazinedione (**9a**) and its (*E*)-isomer (**10a**) in 78 and 6% yields, respectively. The *Z* stereochemical assignment of **10a** was based on ¹H-NMR spectral evidence. Alkylation of **9a** with benzyl chloride and sodium hydride in dimethylformamide (DMF) gave **11a** in 88% yield. It was difficult to remove the acetyl group in **11a** under hydrazine-hydrate in DMF for generating **12a**, because the tosyl protecting group of **11a** was unstable under these conditions.²⁴⁾ Thus, the following procedure was attempted and optimized. Deacetylation of **11a** with K₂CO₃ in methanol gave the deacetylated compound (**12a**) in 66% yield. The piperazine ring of **12a** was activated by the introduction of a 2-propyloxycarbonyl group to give the imide (**13a**) in 99% yield.

The transformation of **13a** into the tricyclic lactam (**15a**),

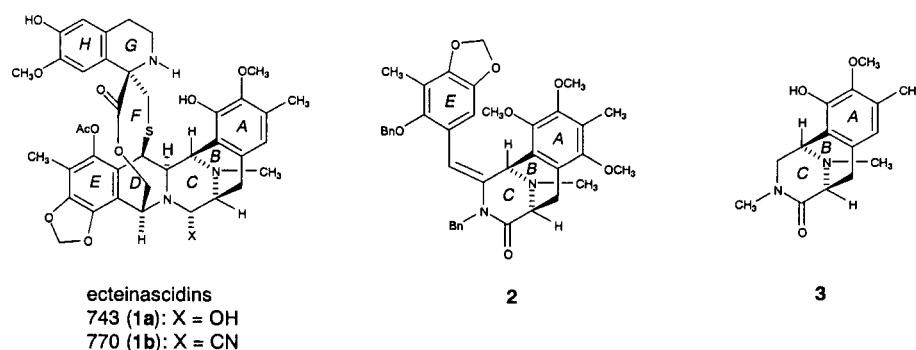
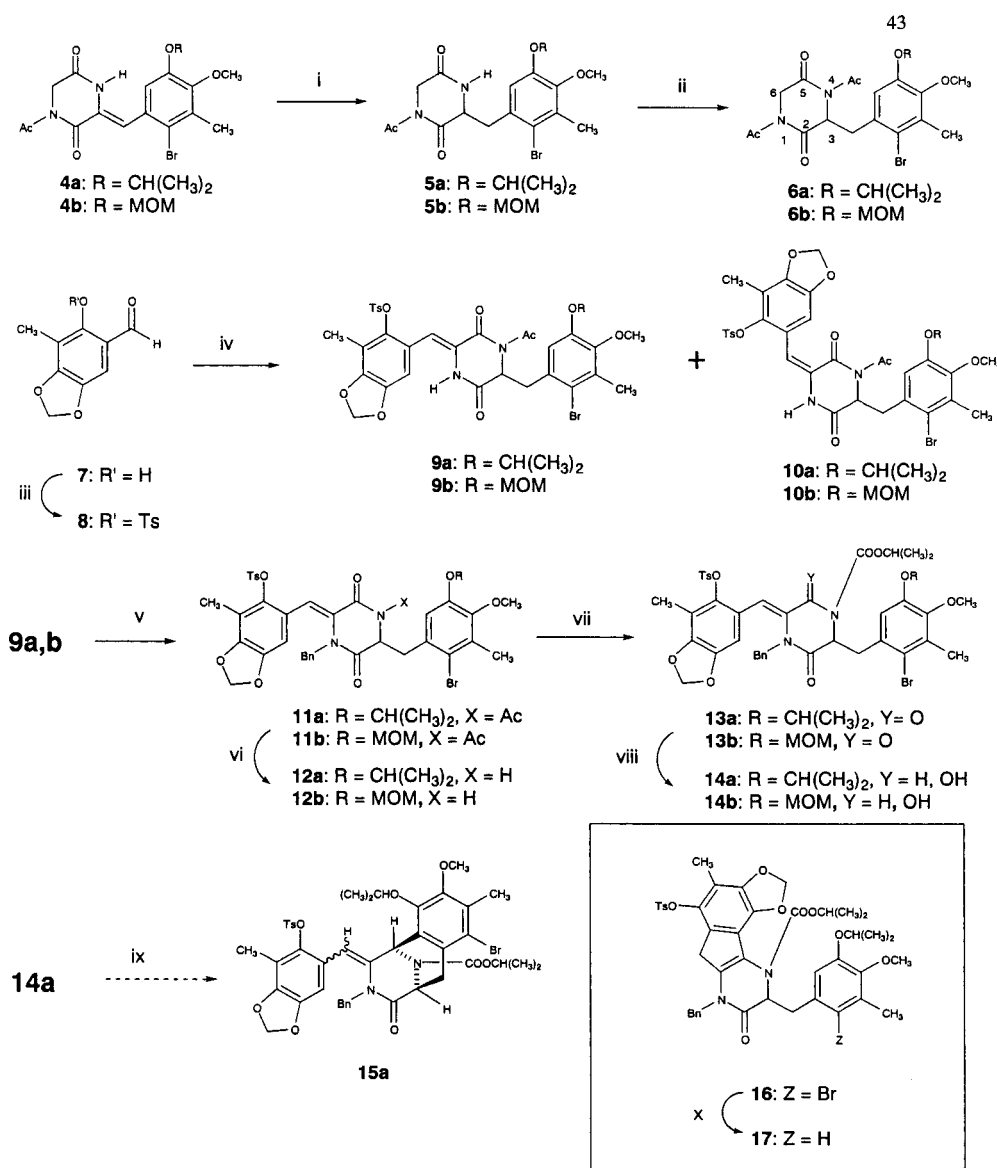


Fig. 1

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Reagent: i) H₂, 5% Rh/C, methanol for **4a** (100%); H₂, 5% Rh/C, 2-propanol for **4b** (100%); ii) Ac₂O, DMAP, pyridine, 25°C; **6a** (77%), **6b** (87%); iii) TsCl, NEt₃, CH₂Cl₂, 25°C (91%); iv) **6a**, *tert*-BuOK, DMF: **9a** (78%) and **10a** (6%); **6b**, *tert*-BuOK, DMF: **9b** (73%) and **10b** (5%); v) BnCl, NaH, DMF; vi) K₂CO₃, MeOH, 25°C; vii) ClCOOCH(CH₃)₂, TEA, DMAP, CH₂Cl₂; **13a** (58%; 3 steps), **13b** (69%; 3 steps); viii) LiAl(*tert*-BuO)₃H, THF, 0°C, ix) TFA, 0°C; **16** (84%; 2 steps); x) H₂, 20% Pd/C, EtOH (75%).

Chart 1

which is the key stage in our synthetic plan, began with the chemoselective reduction of **13a** with lithium tri-*tert*-butoxyaluminumhydride in tetrahydrofuran (THF) to afford a diastereomeric mixture of the alcohol (**14a**). When **14a** was treated with trifluoroacetic acid (TFA) at 0°C for 1 h, no desired compound **15a** could be detected; instead, compound **16** was formed in 84% yield. Assignment of indeno[1,2-*b*]pyrazine-2-one (**16**) was made based on the results of NMR analysis. The ¹H-NMR spectrum of **16** displayed only one singlet at δ 6.46 in the aromatic region along with the characteristic AB type methylene proton peaks (δ 3.29 and 3.50). Hydrogenation of **16** in the presence of palladium on carbon gave the corresponding debrominated compound **17** in 75% yield. The *ortho* coupling (*J* = 1.7 Hz) was observed in the ¹H-NMR spectrum of **17**. The probable mechanistic

pathways for the formation of **16** from **14a** including the isomerization are shown in Chart 2. The results indicated that cyclization of **E-A** to the desired compound **15a** was relatively slow because of the steric hindrance by the isopropyl protecting group at the A ring.

Next, we attempted to increase the reactivity of the A ring such as the phenol (**13c**). The substrate (**13b**) was prepared in six steps from **4b**^{25,26} using the same procedure as used for the preparation of **13a** in 44% overall yield. Reduction and dehydration/cyclization sequence of **13b** afforded the desired compound **15c**, but the maximum yield was only 29%. In order to improve the reactivity of the A ring, the sequence of reactions in Chart 3 was studied. The removal of the MOM group in **13b** gave **13c** in 94% yield, hydride reduction of **13c** followed by cyclization afforded **15c** in 86% yield.

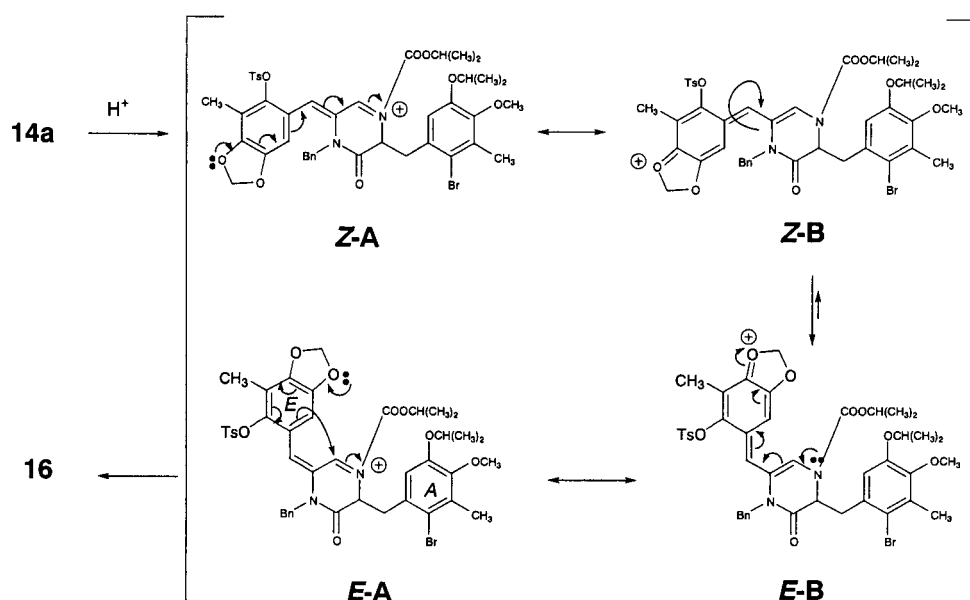


Chart 2

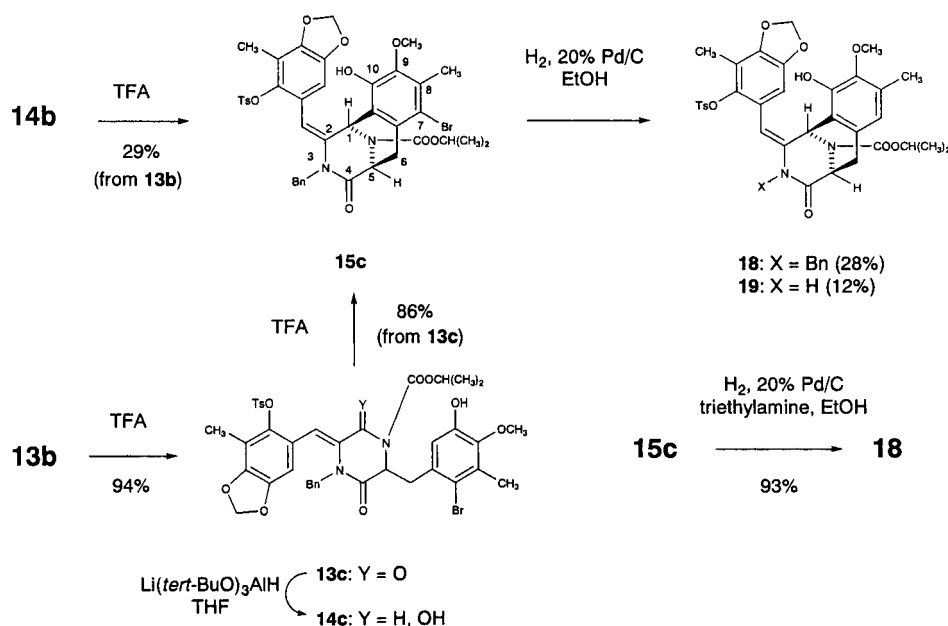
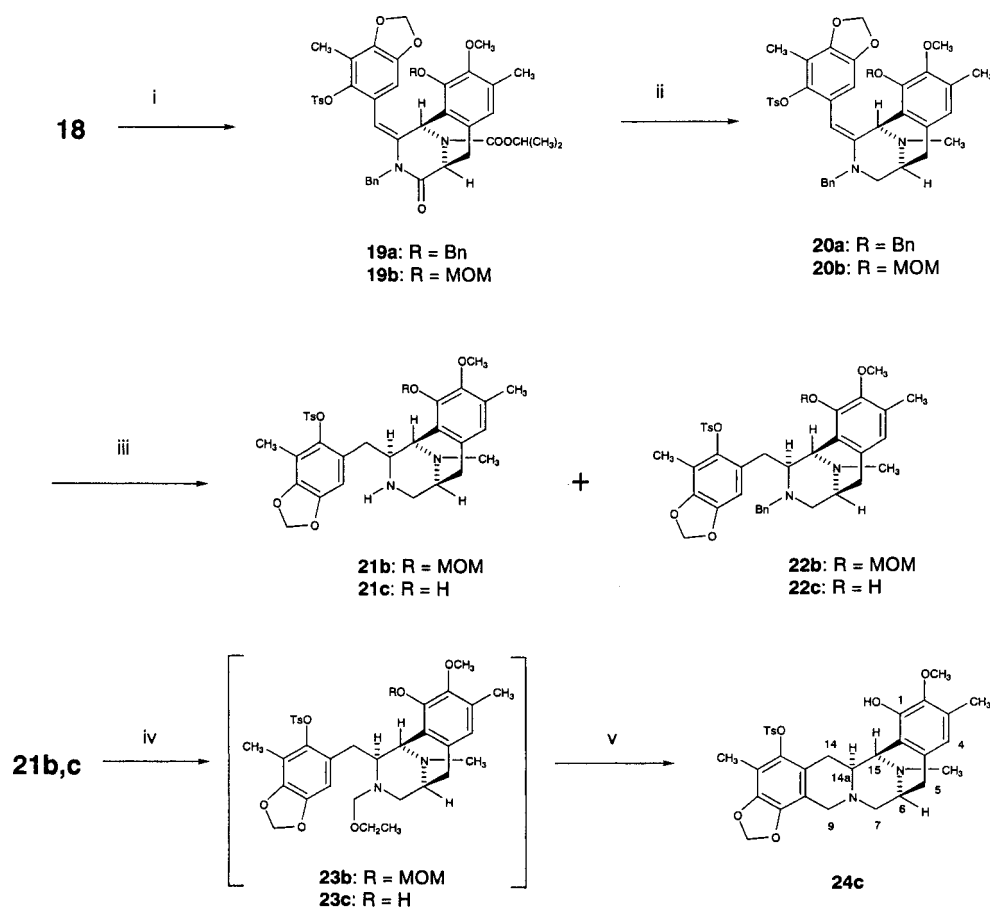


Chart 3

The *E* stereochemical assignment of **15c** was based on 1H -NMR spectral evidence. The δ value observed for the methine proton (δ 6.58) at the C-1 position of **15c** indicated that this proton was positioned in the deshielding zone of the aromatic ring of the side chain at the C-2 position and the carbonyl group of *N*-COOR. Thus, we were able to obtain the desired compound **15c** in high yield.

Having established the construction of the B ring, we then studied the conversion of **15c** into the secondary amine (**21**). Numerous efforts to remove the *N*-blocking group of **15c** under acidic and basic conditions were unsuccessful, causing decomposition of the starting material. Debromination of **15c** also proved to be troublesome. The debromination of **15c** with hydrogen over 20% Pd/C in ethanol afforded the desired

compound **18** in only 28% yield along with the debenzylated product (**19**) in 12% yield. We thought this by-product (**19**) might have been produced by the evolution of hydrogen bromide. In contrast, the debromination of **15c** with hydrogen over 20% Pd/C in the presence of triethylamine gave **18** in 93% yield. Protection of the phenol in **18** with a benzyl group gave **19a** in 95% yield, and hydride reduction of **19a** with aluminium hydride afforded **20a** in 90% yield (Chart 4). Reduction of the double bond of **20a** through the action of hydrogen (4 atm) on 20% Pd/C in ethanol at 80 °C for 40 h occurred from the less hindered α -face to afford **21c** in 47% yield accompanied with **22c** in 28% yield. The other route of this transformation was carried out using the MOM protecting group. Methoxymethylation of **18** gave **19b** in 85% yield,



Reagents: i) BnCl, NaH, DMF: **19a** (95%); MOMBr, NaH, THF: **19b** (85%); ii) AlH_3 , THF, 0°C : **20a** (90%), **20b** (97%); iii) for **20a**: H_2 (4 atm), 20% Pd/C, EtOH, 80°C : **21a** (47%) and **22c** (28%); for **20b**: Method A: H_2 (4 atm), 20% Pd/C, EtOH, 80°C : **21b** (3%) and **22b** (76%); Method B: H_2 (4 atm), 20% Pd(OH) $_2$ /C, EtOH, 80°C : **21b** (66%); iv) paraformaldehyde, K_2CO_3 , EtOH; v) TFA; **24c** (15% from **21c**; 70% from **21b**).

Chart 4

and then hydride reduction of **19b** under the same conditions afforded **20b** in 97% yield. While the conversion **20b** into the amine **21b** was carried out under the same conditions, the debenzoylation was relatively slow to generate **22b** in 76% yield, and the yield of the desired product (**21b**) is only 3%. This problem was solved by using 20% Pd(OH) $_2$ on carbon as a catalyst to give **21b** in 66% yield.

The final stage of the investigation involved the construction of the pentacyclic framework using our modified Pictet–Spengler reaction.²⁷⁾ Reaction of **21c** with a large excess of paraformaldehyde in the presence of K_2CO_3 in ethanol at room temperature for 72 h gave the *O,N*-acetal (**23c**), which was subsequently treated with TFA at room temperature for 24 h to provide the pentacyclic compound **24c** in 15% yield. A large amount of **21c** was recovered because **21c** was relatively highly polar and its solubility in organic solvents was low. In contrast, **21b** was converted into **24c** via **23b** in 70% yield. The stereochemistry of **24c** was readily identified on the basis of the chemical shifts of H-14 β (δ 2.42) and H-14a (δ 2.67) along with their coupling between H-14 β and H-14a (J =12.0 Hz), as noted previously for related systems.²⁸⁾

In summary, we succeeded in the preparation of the

ABCDE ring model of ecteinascidins. The application of this strategy to the total synthesis of natural products is under intensive investigation in our laboratories.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 260-10 IR Fourier-transform spectrometer. ^1H -NMR spectra were recorded at 270 MHz on a JEOL JNM-EX 270 spectrometer, at 300 MHz on a JEOL JNM-AL300 spectrometer, and a 500 MHz on a JEOL JNM-LA-500 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 $(\text{CH}_3)_4\text{Si}$ as the internal standard. Mass spectra were recorded on a JMS-DX 302 and JMS-700 instruments with a direct inlet system operating at 70 eV. Elemental analyses were conducted on Perkin-Elmer Model 240B and YANACO MT-6 CHN CORDER elemental analyzers. All reactions were conducted under argon atmosphere. Dry solvents and reagents were obtained using standard procedures. 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).

1-Acetyl-3-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-2,5-piperazinedione (5a) A solution of **4a**¹⁸⁾ (1.701 g, 4.0 mmol) in

methanol (80 ml) was hydrogenated over 5% Rh/C (800 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with methanol (500 ml). The combined filtrates were evaporated *in vacuo* to give a solid, the recrystallization of which from acetone/hexane gave **5a** (1.708 g, 100%) as colorless prisms, mp 90–92 °C. ¹H-NMR δ: 1.34, 1.36 (each 3H, d, *J*=6.1 Hz, CH(CH₃)₂), 2.36 (3H, s, ArCH₃), 2.61 (3H, s, COCH₃), 3.04 (1H, dd, *J*=14.0, 9.4 Hz, 3-CH), 3.57 (1H, dd, *J*=14.0, 4.4 Hz, 3-CH), 3.80 (3H, s, OCH₃), 4.23, 4.35 (each 1H, d, *J*=18.0 Hz, 6-H), 4.45 (1H, ddd, *J*=9.4, 4.4, 2.2 Hz, 3-H), 4.50 (1H, sept, *J*=6.1 Hz, OCH), 5.92 (1H, brs, NH), 6.66 (1H, s, ArH). IR (KBr) cm⁻¹: 3250, 1730, 1720, 1710. MS *m/z* (%): 428 (M⁺+2, 9), 426 (M⁺, 9), 274 (11), 273 (79), 271 (83), 232 (11), 231 (98), 230 (11), 229 (100), 43 (27). *Anal.* Calcd for C₁₈H₂₃BrN₂O₅: C, 50.60; H, 5.43; N, 6.56. Found: C, 50.40; H, 5.47; N, 6.37.

1,4-Diacetyl-3-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-2,5-piperazinedione (6a) A solution of **5a** (1.708 g, 4.0 mmol) and DMAP (97.6 mg, 0.8 mmol) in pyridine (24 ml) was cooled with ice water, and acetic anhydride (4.8 ml, 50.5 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, and then the residue was taken up in water (160 ml) and extracted with ethyl acetate (160 ml×3). The combined extracts were washed with brine (100 ml) and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **6a** (1.439 g, 76.6%) as colorless needles, mp 139.5–140 °C. ¹H-NMR δ: 1.31, 1.34 (each 3H, d, *J*=6.1 Hz, CH(CH₃)₂), 2.32 (3H, s, ArCH₃), 2.55 (6H, s, 2×COCH₃), 3.29 (1H, dd, *J*=14.1, 5.5 Hz, 3-CH), 3.33 (1H, d, *J*=18.7 Hz, 6-H), 3.53 (1H, dd, *J*=14.1, 6.8 Hz, 3-CH), 3.78 (3H, s, OCH₃), 4.44 (1H, sept, *J*=6.1 Hz, OCH), 4.83 (1H, d, *J*=18.7 Hz, 6-H), 5.47 (1H, dd, *J*=6.8, 5.5 Hz, 3-H), 6.63 (1H, s, ArH). IR (KBr) cm⁻¹: 1730, 1725, 1700. MS *m/z* (%): 470 (M⁺+2, 14), 468 (M⁺, 15), 274 (11), 273 (52), 271 (56), 232 (10), 231 (97), 230 (10), 229 (100), 43 (61). *Anal.* Calcd for C₂₁H₂₅BrN₂O₆: C, 51.18; H, 5.37; N, 5.97. Found: C, 51.16; H, 5.32; N, 5.75.

1,4-Diacetyl-3-(2-bromo-4-methoxy-5-methoxymethoxy-3-methylphenylmethyl)-2,5-piperazinedione (6b) A solution of **4b** (4.26 g, 10.0 mmol) in 2-propanol (75 ml) was hydrogenated over 5% Rh/C (750 mg) at 1 atm for 19 h. The catalyst was removed by filtration and washed with methanol (500 ml). The combined filtrates were evaporated *in vacuo* to give **5b** as a colorless amorphous powder that was used in the subsequent step without further purification. ¹H-NMR δ: 2.38 (3H, s, ArCH₃), 2.62 (3H, s, COCH₃), 3.11 (1H, dd, *J*=14.1, 8.8 Hz, 3-CH), 3.49 (3H, s, OCH₃), 3.58 (1H, dd, *J*=14.1, 4.6 Hz, 3-CH), 3.81 (3H, s, OCH₃), 4.12, 4.32 (each 1H, d, *J*=18.0 Hz, 6-H), 4.44 (1H, ddd, *J*=8.8, 4.6, 2.2 Hz, 3-H), 5.16, 5.20 (each 1H, d, *J*=6.9 Hz, OCHO), 5.95 (1H, brs, NH), 6.91 (1H, s, ArH). IR (CHCl₃) cm⁻¹: 3420, 1730, 1700. MS *m/z* (%): 430 (M⁺+2, 5), 428 (M⁺, 5), 275 (76), 273 (77), 45 (100), 43 (17). High-resolution MS Calcd for C₁₇H₂₁⁷⁹BrN₂O₆: 428.0583. Found: 428.0580.

A solution of **5b** (4.29 g, 10.0 mmol) and DMAP (244.0 mg, 2.0 mmol) in pyridine (60 ml) was cooled with ice water, and acetic anhydride (12.0 ml, 127.2 mmol) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, and then the residue was taken up in water (400 ml) and extracted with ethyl acetate (400 ml×3). The combined extracts were washed with brine (300 ml), and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **6b** (4.106 g, 87.4%) as colorless needles, mp 118–119.5 °C. ¹H-NMR δ: 2.36 (3H, s, ArCH₃), 2.56, 2.58 (each 3H, s, COCH₃), 3.03 (1H, d, *J*=18.9 Hz, 6-H), 3.35 (1H, dd, *J*=14.1, 4.8 Hz, 3-CH), 3.44 (3H, s, OCH₃), 3.57 (1H, dd, *J*=14.1, 6.2 Hz, 3-CH), 3.79 (3H, s, OCH₃), 4.73 (1H, d, *J*=18.9 Hz, 6-H), 5.07, 5.19 (each 1H, d, *J*=6.8 Hz, OCHO), 5.49 (1H, dd, *J*=6.2, 4.8 Hz, 3-H), 6.83 (1H, s, ArH). IR (KBr) cm⁻¹: 1715, 1700, 1670. MS *m/z* (%): 472 (M⁺+2, 8), 470 (M⁺, 8), 275 (64), 273 (66), 45 (100), 43 (44). *Anal.* Calcd for C₁₉H₂₃BrN₂O₇: C, 48.42; H, 4.92; N, 5.94. Found: C, 48.20; H, 4.85; N, 5.76.

3-Methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxybenzaldehyde (8) *p*-Toluenesulfonyl chloride (2.00 g, 10.5 mmol) was added to a stirred solution of **7**¹⁾ (1.26 g, 7.0 mmol) and triethylamine (1.46 ml, 10.5 mmol) in dichloromethane (14 ml) at 0 °C for 10 min, and the mixture was stirred at the room temperature for 2 h. The reaction mixture was diluted with brine (40 ml) and extracted with dichloromethane (80 ml×3). The combined extracts were washed with water (50 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/hexane gave **8** (2.135 g, 91.2%) as colorless needles, mp 127–128 °C. ¹H-NMR δ: 2.13 (3H, s, 3-CH₃), 2.49 (3H, s, Ar-CH₃), 6.09 (2H, s, OCH₂O), 7.15 (1H, s, 6-H), 7.39, 7.77 (each 2H, d, *J*=8.3 Hz, ArH×4), 9.52 (1H, s, CHO). IR (KBr) cm⁻¹: 1680. MS *m/z* (%): 334 (M⁺, 38), 180 (12), 179 (100), 155 (11), 121 (12), 91 (17). *Anal.* Calcd for C₁₆H₁₄O₆S: C, 57.48; H,

4.22. Found: C, 57.30; H, 4.25.

Condensation of Acetate (6a) and Aldehyde (8) A solution of potassium *tert*-butoxide (112.5 mg, 1.0 mmol) in *tert*-butyl alcohol (2 ml) was added to a stirred solution of **6a** (467.3 mg, 1.0 mmol) and **8** (334.4 mg, 1.0 mmol) in DMF (4 ml) at 0 °C over 20 min. After stirring for 4 h at room temperature, the reaction mixture was poured into brine (100 ml) and extracted with ethyl acetate (100 ml×3). The combined extracts were washed with water (100 ml), dried, and concentrated *in vacuo* to give a solid. Chromatography on a silica gel (100 g) column with hexane–ethyl acetate (5:2) as the eluent gave **9a** (579.8 mg, 78.0%) and **10a** (46.9 mg, 6.3%).

(*Z*)-1-Acetyl-6-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]piperazine-2,5-dione (**9a**): mp 171.5–173 °C (from ethyl acetate/ether). ¹H-NMR δ: 1.28, 1.29 (each 3H, d, *J*=6.1 Hz, CH(CH₃)₂), 2.17, 2.23, 2.39 (each 3H, s, ArCH₃), 2.60 (3H, s, COCH₃), 3.28 (1H, dd, *J*=14.1, 4.2 Hz, 6-CH), 3.50 (1H, dd, *J*=14.1, 5.7 Hz, 6-CH), 3.55 (3H, s, OCH₃), 4.40 (1H, sept, *J*=6.1 Hz, OCH), 5.40 (1H, dd, *J*=5.7, 4.2 Hz, 6-H), 6.06, 6.07 (each 1H, d, *J*=1.3 Hz, OCHO), 6.42 (1H, s, C=CH), 6.42, 6.54 (each 1H, s, ArH), 7.28 (2H, d, *J*=8.3 Hz, ArH×2), 7.49 (1H, brs, NH), 7.49 (2H, d, *J*=8.3 Hz, ArH×2). ¹³C-NMR δ: 10.7 (q), 17.0 (q), 21.7 (q), 22.0 (q), 22.1 (q), 27.1 (q), 38.4 (t), 57.0 (d), 60.2 (q), 71.5 (d), 102.3 (t), 104.9 (d), 115.0 (d), 116.6 (s), 116.7 (d), 119.7 (s), 125.0 (s), 128.5 (d×2), 129.6 (s), 129.9 (d×2), 132.9 (s), 133.3 (s), 141.5 (s), 145.8 (s), 148.1 (s), 148.9 (s), 149.8 (s), 159.2 (s), 165.9 (s), 172.0 (s). IR (KBr) cm⁻¹: 3180, 2975, 1700, 1675, 1625. MS *m/z* (%): 744 (M⁺+2, 12), 742 (M⁺, 11), 589 (15), 587 (12), 547 (16), 545 (15), 505 (20), 503 (21), 273 (56), 271 (55), 231 (67), 229 (70), 219 (36), 218 (21), 217 (23), 192 (31), 191 (30), 190 (40), 172 (15), 155 (14), 139 (30), 123 (22), 92 (19), 91 (68), 77 (15), 65 (24), 43 (100). *Anal.* Calcd for C₃₄H₃₅BrN₂O₁₀S: C, 54.92; H, 4.74; N, 3.77. Found: C, 54.64; H, 4.71; N, 3.77.

(*E*)-1-Acetyl-6-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]piperazine-2,5-dione (**10a**): mp 204.5–206 °C (from ethyl acetate–ether). ¹H-NMR δ: 1.28, 1.31 (each 3H, d, *J*=6.2 Hz, CH(CH₃)₂), 1.98, 2.31, 2.41 (each 3H, s, ArCH₃), 2.54 (3H, s, COCH₃), 3.20 (1H, dd, *J*=14.1, 4.4 Hz, 6-CH), 3.53 (3H, s, OCH₃), 3.65 (1H, dd, *J*=14.1, 5.3 Hz, 6-CH), 4.42 (1H, sept, *J*=6.2 Hz, OCH), 5.43 (1H, dd, *J*=5.3, 4.4 Hz, 6-H), 5.76 (1H, s, C=CH), 6.00, 6.02 (each 1H, d, *J*=1.3 Hz, OCHO), 6.24, 6.63 (each 1H, s, ArH), 7.30 (2H, d, *J*=8.4 Hz, ArH×2), 7.34 (1H, brs, NH), 7.74 (2H, d, *J*=8.4 Hz, ArH×2). IR (KBr) cm⁻¹: 3200, 2930, 1690, 1680, 1650. MS *m/z* (%): 744 (M⁺+2, 6), 742 (M⁺, 6), 590 (16), 586 (16), 547 (11), 546 (20), 545 (12), 544 (18), 278 (14), 275 (21), 273 (25), 271 (33), 257 (21), 246 (35), 231 (35), 229 (36), 220 (14), 219 (345), 218 (17), 217 (56), 193 (19), 192 (20), 191 (25), 190 (37), 172 (25), 156 (13), 155 (17), 151 (21), 139 (39), 123 (38), 108 (16), 107 (17), 92 (25), 91 (90), 89 (12), 79 (19), 77 (24), 65 (35), 63 (14), 45 (31), 43 (100). *Anal.* Calcd for C₃₄H₃₅BrN₂O₁₀S: C, 54.92; H, 4.74; N, 3.77. Found: C, 54.96; H, 4.75; N, 3.67.

Condensation of Acetate (6b) and Aldehyde (8) A solution of potassium *tert*-butoxide (225.0 mg, 2.0 mmol) in *tert*-butyl alcohol (4 ml) was added to a stirred solution of **6b** (942.6 mg, 2.0 mmol) and **8** (668.7 mg, 2.0 mmol) in DMF (8 ml) at 0 °C for 20 min. After stirring for 2 h at room temperature, the reaction mixture was poured into brine (200 ml) and extracted with ethyl acetate (200 ml×3). The combined extracts were washed with water (200 ml), dried, and concentrated *in vacuo* to give a solid. Chromatography on a silica gel (100 g) column with hexane–ethyl acetate (2:1) as the eluent gave **9b** (1.086 g, 72.9%) and **10b** (80.2 mg, 5.4%).

(*Z*)-1-Acetyl-6-(2-bromo-4-methoxy-5-methoxymethoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]piperazine-2,5-dione (**9b**): mp 187–188.5 °C (from ethyl acetate). ¹H-NMR δ: 2.17, 2.23, 2.38 (each 3H, s, ArCH₃), 2.62 (3H, s, COCH₃), 3.36 (1H, dd, *J*=14.3, 5.7 Hz, 6-CH), 3.45 (1H, dd, *J*=14.3, 4.0 Hz, 6-CH), 3.46 (3H, s, CH₂OCH₃), 3.56 (3H, s, ArOCH₃), 5.06, 5.09 (each 1H, d, *J*=6.7 Hz, OCHOCH₃), 5.40 (1H, dd, *J*=5.7, 4.0 Hz, 6-H), 6.06, 6.08 (each 1H, d, *J*=1.3 Hz, OCHO), 6.39 (1H, s, C=CH), 6.42, 6.73 (each 1H, s, ArH), 7.26 (2H, d, *J*=8.3 Hz, ArH×2), 7.29 (1H, brs, NH), 7.70 (2H, d, *J*=8.3 Hz, ArH×2). IR (KBr) cm⁻¹: 3230, 1720, 1705, 1640. MS *m/z* (%): 746 (M⁺+2, 1), 744 (M⁺, 1), 204 (10), 190 (10), 139 (22), 92 (26), 91 (42), 65 (20), 45 (100), 43 (20), 39 (11). *Anal.* Calcd for C₃₃H₃₃BrN₂O₁₁S·1/2H₂O: C, 52.52; H, 4.54; N, 3.71. Found: C, 52.63; H, 4.41; N, 3.69.

(*E*)-1-Acetyl-6-(2-bromo-4-methoxy-5-methoxymethoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]piperazine-2,5-dione (**10b**): mp 191–193 °C (from ethyl

acetate/ether). $^1\text{H-NMR}$ δ : 2.01, 2.31, 2.39 (each 3H, s, ArCH_3), 2.55 (3H, s, COCH_3), 3.21 (1H, dd, $J=14.1$, 4.0 Hz, 6-CH), 3.48 (3H, s, CH_2OCH_3), 3.55 (3H, s, ArOCH_3), 3.68 (1H, dd, $J=14.1$, 5.1 Hz, 6-CH), 4.97, 5.18 (each 1H, d, $J=6.7$ Hz, OCH_2OCH_3), 5.42 (1H, dd, $J=5.1$, 4.0 Hz, 6-H), 5.72 (1H, s, C=CH), 5.99, 6.02 (each 1H, d, $J=1.3$ Hz, OCHO), 6.14, 6.85 (each 1H, s, ArH), 7.30 (2H, d, $J=8.3$ Hz, $\text{ArH}\times 2$), 7.64 (1H, br s, NH), 7.74 (2H, d, $J=8.3$ Hz, $\text{ArH}\times 2$). IR (KBr) cm^{-1} : 3230, 3100, 2950, 1710, 1690, 1680. MS m/z (%): 746 ($\text{M}^+ + 2$, 6), 744 (M^+ , 6), 517 (15), 515 (15), 275 (22), 273 (21), 257 (17), 231 (22), 230 (16), 229 (21), 219 (28), 217 (16), 204 (30), 192 (12), 191 (24), 190 (36), 92 (13), 91 (30), 65 (12), 45 (100), 43 (31). Anal. Calcd for $\text{C}_{33}\text{H}_{33}\text{BrN}_2\text{O}_{11}\text{S}$: C, 53.16; H, 4.46; N, 3.76. Found: C, 53.13; H, 4.59; N, 3.60.

(Z)-1-Acetyl-6-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]-4-phenylmethylpiperazine-2,5-dione (11a) Sodium hydride (60% oil dispersion, washed with dry hexane three times, 2.9 mg, 0.12 mmol) was added to a stirred solution of **9a** (74.4 mg, 0.10 mmol) in DMF (1 ml) under ice cooling, and stirring was continued at 0 °C for 30 min. Benzyl chloride (13.8 μl , 0.12 mmol) was added over 20 min, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and then the residue was diluted with water (10 ml) and extracted with ethyl acetate (10 ml $\times$ 3). The combined extracts were washed with brine (10 ml), dried, and concentrated *in vacuo* to furnish a solid, the recrystallization of which from ethyl acetate/ether gave **11a** (73.2 mg, 87.9%) as pale yellow prisms, mp 150.5–152 °C. $^1\text{H-NMR}$ δ : 1.32, 1.33 (each 3H, d, $J=6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.13, 2.24, 2.44 (each 3H, s, ArCH_3), 2.47 (3H, s, COCH_3), 3.28 (1H, dd, $J=14.0$, 6.6 Hz, 6-CH), 3.33 (1H, dd, $J=14.0$, 6.6 Hz, 6-CH), 3.60 (3H, s, OCH_3), 4.24 (1H, d, $J=14.6$ Hz, NCHAr), 4.46 (1H, sept, $J=6.1$ Hz, OCH), 5.10 (1H, d, $J=14.6$ Hz, NCHAr), 5.49 (1H, t, $J=6.6$ Hz, 6-H), 6.08, 6.09 (each 1H, d, $J=1.2$ Hz, OCHO), 6.60, 6.76 (each 1H, s, ArH), 7.10 (1H, s, C=CH), 7.10–7.14 (2H, m, $\text{ArH}\times 2$), 7.19–7.22 (3H, m, $\text{ArH}\times 3$), 7.29, 7.83 (each 2H, d, $J=8.4$ Hz, $\text{ArH}\times 2$). IR (KBr) cm^{-1} : 1760, 1725, 1710. FAB-MS (Magic Bullet) m/z : 833 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{41}\text{H}_{41}\text{BrN}_2\text{O}_{10}\text{S}$: C, 59.06; H, 4.96; N, 3.36. Found: C, 58.86; H, 5.06; N, 3.14.

(Z)-6-(2-Bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]-4-phenylmethylpiperazine-2,5-dione (12a) A suspended solution of **11a** (367.0 mg, 0.44 mmol) and anhydrous K_2CO_3 (138.2 mg, 1.0 mmol) in methanol (40 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (50 ml $\times$ 3). The combined extracts were washed with brine (50 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **12a** (230.4 mg, 66.2%) as colorless prisms, mp 172–174 °C. $^1\text{H-NMR}$ δ : 1.32, 1.36 (each 3H, d, $J=6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.10, 2.36, 2.43 (each 3H, s, ArCH_3), 3.06 (1H, dd, $J=14.0$, 9.7 Hz, 6-CH), 3.57 (1H, dd, $J=14.0$, 4.2 Hz, 6-CH), 3.76 (3H, s, OCH_3), 4.42 (1H, ddd, $J=9.7$, 4.2, 2.2 Hz, 6-H), 4.51 (1H, sept, $J=6.1$ Hz, OCH), 4.58, 4.71 (each 1H, d, $J=14.9$ Hz, NCHAr), 5.59 (1H, d, $J=2.2$ Hz, NH), 6.06 (2H, s, OCH_2O), 6.62, 6.70 (each 1H, s, ArH), 6.96 (1H, s, C=CH), 7.05–7.08 (2H, m, $\text{ArH}\times 2$), 7.17–7.24 (3H, m, $\text{ArH}\times 3$), 7.30, 7.82 (each 2H, d, $J=8.3$ Hz, $\text{ArH}\times 2$). IR (KBr) cm^{-1} : 3220, 1700, 1690. FAB-MS (Magic Bullet) m/z : 791 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{39}\text{H}_{39}\text{BrN}_2\text{O}_9\text{S}$: C, 58.50; H, 5.04; N, 3.50. Found: C, 58.48; H, 4.76; N, 3.43.

(Z)-1-Isopropylloxycarbonyl-6-(2-bromo-5-isopropoxy-4-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]-4-phenylmethylpiperazine-2,5-dione (13a) A solution of **12a** (1.583 g, 2.0 mmol), triethylamine (558.0 μl , 4.0 mmol), and 4-DMAP (489.0 mg, 4.0 mmol) in dichloromethane (40 ml) was cooled with ice water, after which isopropyl chloroformate (910.0 μl , 8.0 mmol) was added dropwise over 10 min, and the mixture was stirred at room temperature for 2 h. The organic layer was washed with 1 N HCl (20 ml), and then water (20 ml), dried, and concentrated *in vacuo* to give a residue (2.336 g). Chromatography on a silica gel (150 g) column with hexane–ethyl acetate (4 : 1) as the eluent gave a solid, the recrystallization of which from ethyl acetate/ether afforded **13a** (1.736 g, 98.9%) as colorless prisms, mp 186–188 °C. $^1\text{H-NMR}$ δ : 1.07, 1.21 (each 3H, d, $J=6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.31, 1.32 (each 3H, d, $J=5.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.21, 2.29, 2.45 (each 3H, s, ArCH_3), 3.19 (1H, dd, $J=13.8$, 8.8 Hz, 6-CH), 3.41 (1H, dd, $J=13.8$, 5.3 Hz, 6-CH), 3.67 (3H, s, OCH_3), 4.26 (1H, d, $J=14.7$ Hz, NCHAr), 4.46 (1H, sept, $J=5.9$ Hz, OCH), 4.88 (1H, sept, $J=6.2$ Hz, OCH), 5.02 (1H, d, $J=14.7$ Hz, NCHAr), 5.24 (1H, dd, $J=8.8$, 5.3 Hz, 6-H), 6.07, 6.08 (each 1H, d, $J=1.3$ Hz, OCHO), 6.56, 6.71 (each 1H, s, ArH), 7.13–7.23 (5H, m, $\text{ArH}\times 5$), 7.19 (1H, s, C=CH), 7.32, 7.89 (each 2H, d, $J=8.5$ Hz, $\text{ArH}\times 2$).

$^{13}\text{C-NMR}$ δ : 10.5 (q), 16.8 (q), 21.3 (q), 21.6 (q), 21.7 (q), 22.0 (q), 22.1 (q), 39.4 (t), 50.1 (t), 59.1 (d), 60.1 (q), 71.3 (d), 71.6 (d), 102.3 (t), 115.2 (d), 116.0 (s), 116.1 (d), 118.7 (s), 120.6 (d), 121.1 (s), 127.6 (d), 127.9 (d $\times$ 2), 128.4 (d $\times$ 4), 129.8 (s), 130.0 (s), 130.2 (d $\times$ 2), 132.7 (s), 133.1 (s), 136.2 (s), 142.1 (s), 145.6 (s), 145.8 (s), 148.4 (s), 148.5 (s), 149.8 (s), 150.7 (s), 161.5 (s), 166.6 (s). IR (KBr) cm^{-1} : 3000, 1785, 1740, 1710. FAB-MS (Magic Bullet) m/z : 877 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{43}\text{H}_{43}\text{BrN}_2\text{O}_{11}\text{S}$: C, 58.84; H, 5.17; N, 3.19. Found: C, 58.84; H, 5.29; N, 3.07.

(Z)-1-Isopropylloxycarbonyl-6-(2-bromo-4-methoxy-5-methoxy-methoxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]-4-phenylmethylpiperazine-2,5-dione (13b) This compound was prepared by the three-step reaction as described above from **9b** (4.464 g, 6.0 mmol) in 69.2% overall yield. Analytical samples including all of the intermediates were obtained by recrystallization from ethyl acetate/ether.

11b: mp 159.5–161 °C. $^1\text{H-NMR}$ δ : 2.11, 2.22, 2.44 (each 3H, s, ArCH_3), 2.51 (3H, s, COCH_3), 3.29 (1H, dd, $J=14.1$, 6.2 Hz, 6-CH), 3.43 (1H, dd, $J=14.1$, 6.1 Hz, 6-CH), 3.46 (3H, s, CH_2OCH_3), 3.54 (3H, s, ArOCH_3), 4.23, 5.12 (each 1H, d, $J=14.5$ Hz, NCHAr), 5.13 (2H, s, OCH_2OCH_3), 5.48 (1H, dd, $J=6.2$, 6.1 Hz, 6-H), 6.08 (2H, s, OCH_2O), 6.71, 6.77 (each 1H, s, ArH), 7.00 (1H, s, C=CH), 7.10–7.19 (2H, m, $\text{ArH}\times 2$), 7.22–7.24 (3H, m, $\text{ArH}\times 3$), 7.27, 7.81 (each 2H, d, $J=8.4$ Hz, $\text{ArH}\times 2$). IR (KBr) cm^{-1} : 1735, 1725, 1710. FAB-MS (Magic Bullet) m/z : 835 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{40}\text{H}_{39}\text{BrN}_2\text{O}_{11}\text{S}$: C, 56.87; H, 4.77; N, 3.32. Found: C, 57.16; H, 5.10; N, 3.09.

12b: mp 161–163 °C. $^1\text{H-NMR}$ δ : 2.10, 2.36, 2.41 (each 3H, s, ArCH_3), 3.09 (1H, dd, $J=14.1$, 9.7 Hz, 6-CH), 3.48 (3H, s, CH_2OCH_3), 3.55 (1H, dd, $J=14.1$, 4.2 Hz, 6-CH), 3.75 (3H, s, ArOCH_3), 4.41 (1H, ddd, $J=9.7$, 4.2, 2.0 Hz, 6-H), 4.56, 4.71 (each 1H, d, $J=14.9$ Hz, NCHAr), 5.16, 5.19 (each 1H, d, $J=6.6$ Hz, OCH_2OCH_3), 5.62 (1H, d, $J=2.0$ Hz, NH), 6.05 (2H, s, OCH_2O), 6.60 (1H, s, C=CH), 6.93 (2H, s, $\text{ArH}\times 2$), 7.06–7.09 (2H, m, $\text{ArH}\times 2$), 7.17–7.24 (3H, m, $\text{ArH}\times 3$), 7.28, 7.81 (each 2H, d, $J=8.4$ Hz, $\text{ArH}\times 2$). $^{13}\text{C-NMR}$ δ : 10.5 (q), 16.9 (q), 21.6 (q), 39.2 (t), 49.5 (t), 55.0 (d), 56.3 (q), 60.5 (q), 95.1 (t), 102.2 (t), 105.8 (d), 115.5 (s), 116.9 (d), 117.7 (d), 120.0 (s), 121.7 (s), 127.3 (d), 127.6 (d $\times$ 2), 128.3 (d $\times$ 2), 128.4 (d $\times$ 2), 129.9 (d $\times$ 2), 130.4 (s), 130.8 (s), 133.1 (s), 136.6 (s), 141.7 (s), 145.4 (s), 145.5 (s), 147.9 (s), 148.1 (s), 149.3 (s), 164.0 (s), 167.0 (s). IR (KBr) cm^{-1} : 3200, 1700, 1625. FAB-MS (Magic Bullet) m/z : 793 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{BrN}_2\text{O}_{10}\text{S}$: C, 57.18; H, 4.74; N, 3.51. Found: C, 56.91; H, 4.78; N, 3.42.

13b: mp 125–127 °C. $^1\text{H-NMR}$ δ : 1.10, 1.23 (each 3H, d, $J=6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.21, 2.29, 2.44 (each 3H, s, ArCH_3), 3.27 (1H, dd, $J=14.0$, 8.1 Hz, 6-CH), 3.40 (1H, dd, $J=14.0$, 5.7 Hz, 6-CH), 3.45 (3H, s, CH_2OCH_3), 3.65 (3H, s, ArOCH_3), 4.26 (1H, d, $J=14.7$ Hz, NCHAr), 4.91 (1H, sept, $J=6.2$ Hz, OCH), 5.01 (1H, d, $J=14.7$ Hz, NCHAr), 5.13, 5.16 (each 1H, d, $J=6.6$ Hz, OCH_2OCH_3), 5.20 (1H, dd, $J=8.1$, 5.7 Hz, 6-H), 6.07, 6.08 (each 1H, d, $J=1.3$ Hz, OCHO), 6.71, 6.79 (each 1H, s, ArH), 7.13 (1H, s, C=CH), 7.13–7.25 (5H, m, $\text{ArH}\times 5$), 7.30, 7.88 (each 2H, d, $J=8.2$ Hz, $\text{ArH}\times 2$). IR (KBr) cm^{-1} : 1730, 1720, 1690. FAB-MS (Magic Bullet) m/z : 879 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{42}\text{H}_{43}\text{BrN}_2\text{O}_{12}\text{S}$: C, 57.34; H, 4.93; N, 3.18. Found: C, 57.43; H, 5.25; N, 2.90.

Attempted Conversion of 13a into 15a A stirred solution of **13a** (43.8 mg, 0.05 mmol) in dry THF (4 ml) was cooled with ice water, and lithium tri-*tert*-butoxyaluminumhydride (50.9 mg, 0.8 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 (0.5 ml) and then filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of alcohols **14a** (45.0 mg) obtained was used in the subsequent step without further purification. A solution of **14a** in TFA (1 ml) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (10 ml $\times$ 3). The combined extracts were washed with 5% NaHCO_3 (20 ml), dried, and concentrated *in vacuo* to give the residue (50 mg). Chromatography on a silica gel (10 g) column with hexane–ethyl acetate (4 : 1) as the eluent afforded **16** (36.0 mg, 83.5%) as a colorless amorphous powder.

6,7,8,9-Tetrahydro-9-[(2-bromo-5-isopropoxy-4-methoxy-3-methylphenyl)methyl]-4-methyl-5-(4-methylbenzenesulfoxy)-4-methyl-8-oxo-7-phenylmethyl-10H-1,3-dioxolo-[6,7]indeno[1,2-b]pyrazine-10-carboxylic acid 1-methylethyl ester (16): $^1\text{H-NMR}$ δ (at 55 °C): 1.03 (3H, d, $J=5.9$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.16 (3H, d, $J=6.3$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.21 (3H, d, $J=5.9$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.25 (3H, d, $J=6.3$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.88, 2.30, 2.45 (each 3H, s, ArCH_3), 2.83 (1H, dd, $J=18.8$, 10.3 Hz, 9-CHAr), 3.27 (1H, dd, $J=18.8$, 5.3 Hz, 9-CHAr), 3.29, 3.50 (each 1H, d, $J=22.4$ Hz, 6-H), 3.72 (3H, s, OCH_3), 4.23 (1H, sept, $J=5.9$ Hz, OCH), 4.83 (1H, sept, $J=6.3$ Hz,

OCH), 4.83 (2H, s, NCH₂Ar), 5.42 (1H, dd, $J=10.3, 5.3$ Hz, 9-H), 5.89 (2H, s, OCH₂O), 6.46 (1H, s, ArH), 7.23–7.31 (5H, m, ArH $\times$ 5), 7.35, 7.82 (each 2H, d, $J=8.5$ Hz, ArH $\times$ 2). ¹³C-NMR δ (at 55 °C): 9.7 (q), 16.8 (q), 21.5 (q), 21.6 (q), 21.8 (q), 21.9 (q), 22.4 (q), 32.0 (t), 37.1 (t), 46.9 (t), 58.0 (d), 60.2 (q), 70.2 (d), 71.6 (d), 101.6 (t), 109.9 (s), 117.5 (s), 118.0 (s), 119.2 (d), 120.2 (s), 124.6 (s), 127.3 (d $\times$ 2), 127.8 (d), 128.3 (d $\times$ 2), 128.9 (d $\times$ 2), 129.9 (d $\times$ 2), 130.9 (s), 131.7 (s), 132.5 (s), 134.1 (s), 136.6 (s), 137.2 (s), 138.4 (s), 145.4 (s), 147.2 (s), 148.7 (s), 149.5 (s), 153.7 (s), 166.3 (s). IR (CHCl₃) cm^{-1} : 1720, 1710, 1680. MS m/z (%): 862 (M^+ +2, 12), 860 (M^+ , 10), 706 (13), 503 (15), 349 (22), 339 (10), 193 (47), 192 (20), 151 (49), 139 (18), 123 (17), 92 (30), 91 (100), 77 (10), 65 (21), 43 (49), 41 (16), 39 (19). High-resolution MS Calcd for C₄₃H₄₅⁷⁹BrN₂O₁₀S: 860.1978. Found: 860.1980.

6,7,8,9-Tetrahydro-9-[(5-isopropoxy-4-methoxy-3-methylphenyl)-methyl]-4-methyl-5-(4-methylbenzenesulfoxy)-4-methyl-8-oxo-7-phenylmethyl-10H-1,3-dioxolo[6,7]indeno[1,2-b]pyrazine-10-carboxylic Acid 1-Methylethyl Ester (17) A solution of **16** (49.0 mg, 0.057 mmol) in ethanol (10 ml) was hydrogenated over 20% Pd/C (49.0 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethanol (20 ml). The combined filtrates were evaporated to give a residue. Chromatography on a silica gel column with hexane–ethyl acetate (6 : 1) as the eluent gave **17** (33.4 mg, 75.1%) as a colorless amorphous powder. ¹H-NMR δ (at 55 °C): 1.08 (3H, d, $J=5.9$ Hz, OCH(CH₃)₂), 1.17 (3H, d, $J=6.3$ Hz, OCH(CH₃)₂), 1.27 (3H, d, $J=5.9$ Hz, OCH(CH₃)₂), 1.28 (3H, d, $J=6.3$ Hz, OCH(CH₃)₂), 1.88, 2.03, 2.44 (each 3H, s, ArCH₃), 2.76 (1H, dd, $J=13.6, 8.6$ Hz, 9-CHAr), 2.89 (1H, dd, $J=13.6, 4.3$ Hz, 9-CHAr), 3.05, 3.42 (each 1H, d, $J=22.0$ Hz, 6-H), 3.68 (3H, s, OCH₃), 4.35 (1H, sept, $J=5.9$ Hz, OCH), 4.73, 4.83 (each 1H, d, $J=15.2$ Hz, NCHAr), 4.85 (1H, sept, $J=5.9$ Hz, OCH), 5.16 (1H, dd, $J=10.3, 5.3$ Hz, 9-H), 5.94, 5.95 (each 1H, brs, OCHO), 6.45, 6.51 (each 1H, d, $J=1.7$ Hz, ArH), 7.21–7.32 (5H, m, ArH $\times$ 5), 7.33, 7.80 (each 2H, d, $J=8.5$ Hz, ArH $\times$ 2). ¹³C-NMR δ (at 55 °C): 9.6 (q), 15.6 (q), 21.5 (q), 21.6 (q), 21.9 (q), 22.2 (q), 22.3 (q), 31.8 (t), 36.7 (t), 46.8 (t), 59.7 (q), 60.0 (d), 70.3 (d), 71.1 (d), 101.5 (t), 109.9 (s), 115.6 (d), 117.7 (s), 120.5 (s), 124.4 (d), 124.7 (s), 124.5 (s), 127.3 (d $\times$ 2), 127.8 (d), 128.3 (d $\times$ 2), 128.9 (d $\times$ 2), 129.9 (d $\times$ 2), 131.2 (s), 131.3 (s), 131.7 (s), 134.0 (s), 136.5 (s), 137.2 (s), 138.5 (s), 145.4 (s), 147.1 (s), 147.8 (s), 150.4 (s), 166.9 (s). MS m/z (%): 782 (M^+ , 21), 628 (13), 503 (15), 349 (22), 339 (25), 193 (47), 192 (20), 151 (49), 139 (18), 123 (19), 106 (16), 91 (100), 77 (12), 65 (25), 43 (40). High-resolution MS Calcd for C₄₄H₄₆N₂O₁₀S: 782.2813. Found: 782.2811.

(Z)-1-Isopropoxy-4-methyl-6-(2-bromo-4-methoxy-5-hydroxy-3-methylphenylmethyl)-3-[3-methyl-2-(4-methylbenzenesulfoxy)-4,5-methylenedioxyphenylidene]-4-phenylmethylpiperazine-2,5-dione (13c) A solution of **13b** (176.0 mg, 0.2 mmol) in TFA (4 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (10 ml $\times$ 3). The combined extracts were washed with 5% NaHCO₃ (20 ml), dried, and concentrated *in vacuo* to give a solid, recrystallization of which from ethyl acetate/ether gave **13c** (156.9 mg, 93.9%) as colorless needles, mp 188–190 °C. ¹H-NMR δ : 1.11, 1.24 (each 3H, d, $J=6.2$ Hz, CH(CH₃)₂), 2.24, 2.30, 2.44 (each 3H, s, ArCH₃), 3.18 (1H, dd, $J=14.0, 8.4$ Hz, 6-CH), 3.44 (1H, dd, $J=14.0, 5.3$ Hz, 6-CH), 3.61 (3H, s, ArOCH₃), 4.25 (1H, d, $J=14.7$ Hz, NCHAr), 4.92 (1H, sept, $J=6.2$ Hz, OCH), 5.01 (1H, d, $J=14.7$ Hz, NCHAr), 5.24 (1H, dd, $J=8.4, 5.3$ Hz, 6-H), 5.46 (1H, brs, OH), 6.07, 6.08 (each 1H, d, $J=1.3$ Hz, OCHO), 6.66, 6.70 (each 1H, s, ArH), 7.11 (1H, s, C=CH), 7.13–7.23 (5H, m, ArH $\times$ 5), 7.31, 7.88 (each 2H, d, $J=8.2$ Hz, ArH $\times$ 2). IR (KBr) cm^{-1} : 3275, 1770, 1690, 1675. FAB-MS (Magic Bullet) m/z : 835 (M^+ +1). Anal. Calcd for C₄₀H₃₉BrN₂O₁₁S: C, 57.49; H, 4.70; N, 3.35. Found: C, 57.35; H, 4.77; N, 3.23.

(E)-7-Bromo-1,2,3,4,5,6-hexahydro-10-hydroxy-9-methoxy-8-methyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxo-5-yl]methylene]-4-oxo-3-phenylmethyl-1,5-imino-3-benzazocine-11-carboxylic Acid 1-Methylethyl Ester (15c) from 13b A stirred solution of **13b** (44.0 mg, 0.05 mmol) in dry THF (4 ml) was cooled with ice water, and lithium tri-*tert*-butoxyaluminumhydride (50.9 mg, 0.2 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 (0.5 ml) and then filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of alcohols **14b** (47.0 mg) obtained was used in the subsequent steps without further purification. A solution of **14b** in TFA (1 ml) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (10 ml $\times$ 3). The combined extracts were washed with 5% NaHCO₃ (20 ml), dried, and concentrated *in vacuo* to give a residue (50 mg). Chromatography on a silica gel (10 g) column with hexane–ethyl acetate (4 : 1) as the eluent afforded **15c** (11.9 mg, 29.0%) as

colorless prisms, mp 123.5–125.5 °C (from ethyl acetate/ether).

From 13c A stirred solution of **13c** (83.6 mg, 0.1 mmol) in dry THF (8 ml) was cooled with ice water, and lithium tri-*tert*-butoxyaluminumhydride (101.7 mg, 0.4 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 (0.5 ml) and then filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The unstable diastereomeric mixture of alcohols **14c** (101.0 mg) obtained was used in the subsequent steps without further purification. A solution of **14b** in TFA (2 ml) was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (10 ml) and extracted with chloroform (20 ml $\times$ 3). The combined extracts were washed with 5% NaHCO₃ (20 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **15c** (70.2 mg, 85.6%) as colorless prisms, mp 123.5–125.5 °C (from ethyl acetate/ether). ¹H-NMR δ (at 55 °C): 1.29 (6H, d, $J=6.3$ Hz, CH(CH₃)₂), 2.14, 2.33, 2.43 (each 3H, s, ArCH₃), 3.05 (1H, dd, $J=17.2, 5.6$ Hz, 6-H α), 3.30 (1H, dd, $J=17.2, 1.3$ Hz, 6-H β), 3.65 (3H, s, OCH₃), 4.11 (1H, d, $J=15.8$ Hz, NCHAr), 5.04 (1H, sept, $J=6.3$ Hz, OCH), 5.05 (1H, d, $J=15.8$ Hz, NCHAr), 5.21 (1H, dd, $J=5.6, 1.3$ Hz, 5-H), 5.53 (1H, brs, OH), 5.88 (1H, s, 2a-H), 5.96, 5.99 (each 1H, d, $J=1.3$ Hz, OCHO), 6.58 (1H, brs, 1-H), 6.95 (2H, d, $J=7.6$ Hz, ArH $\times$ 2), 7.08–7.17 (3H, m, ArH $\times$ 3), 7.13 (1H, s, ArH), 7.23, 7.72 (each 2H, d, $J=8.3$ Hz, ArH $\times$ 2). ¹³C-NMR δ (at 55 °C): 10.8 (q), 16.7 (q), 21.6 (q), 22.1 (q), 22.1 (q), 34.1 (t, C-6), 45.1 (d, C-1), 46.2 (t, NCH₂Ar), 53.5 (d, C-5), 61.1 (q, OCH₃), 70.2 (d, OCH), 101.7 (t, OCH₂O), 101.7 (d), 107.1 (d), 114.7 (s), 117.9 (s), 120.6 (s), 124.2 (s), 126.5 (d $\times$ 2), 126.9 (d), 127.8 (d $\times$ 2), 128.4 (d $\times$ 2), 128.9 (s), 129.7 (d $\times$ 2), 131.3 (s), 134.8 (s), 136.8 (s), 142.1 (s), 144.8 (s), 145.2 (s), 145.3 (s), 145.5 (s), 145.9 (s), 153.0 (s, NCOO), 168.0 (s, C-4). IR (KBr) cm^{-1} : 3530, 1695, 1680, 1645, 1635. MS m/z (%): 820 (M^+ +2, 4), 818 (M^+ , 4), 666 (10), 664 (18), 663 (21), 579 (25), 577 (25), 282 (11), 281 (16), 270 (21), 268 (23), 191 (41), 189 (13), 139 (14), 92 (27), 91 (100), 65 (22), 43 (29), 41 (10), 39 (12). FAB-MS (Magic Bullet) m/z 819 (M^+ +1). High-resolution MS Calcd for C₄₀H₃₉⁷⁹BrN₂O₁₀S: 818.1514. Found: 818.1509. Anal. Calcd for C₄₀H₃₉BrN₂O₁₀S $\cdot$ 1/2H₂O: C, 57.97; H, 4.87; N, 3.38. Found: C, 58.21; H, 5.26; N, 2.95.

Hydrogenolysis of 15c. Method A A solution of **15c** (70.2 mg, 0.086 mmol) in ethanol (10 ml) was hydrogenated over 20% Pd/C (70.2 mg) at 1 atm for 2 h. The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were concentrated *in vacuo* to give a residue (71.9 mg). Chromatography on a silica gel (6 g) column using hexane–ethyl acetate (5 : 1 to 3 : 1) as the eluent gave **18** (18.0 mg, 28.4%) and **19** (6.6 mg, 11.8%).

(E)-1,2,3,4,5,6-Hexahydro-10-hydroxy-9-methoxy-8-methyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxo-5-yl]methylene]-4-oxo-3-phenylmethyl-1,5-imino-3-benzazocine-11-carboxylic Acid 1-Methylethyl Ester (18) Colorless amorphous powder. ¹H-NMR δ (at 55 °C): 1.28 (6H, d, $J=6.3$ Hz, CH(CH₃)₂), 2.19, 2.33, 2.41 (each 3H, s, ArCH₃), 3.07 (1H, d, $J=14.9$ Hz, 6-H β), 3.15 (1H, dd, $J=14.9, 5.0$ Hz, 6-H α), 3.66 (3H, s, OCH₃), 4.05, 4.75 (each 1H, brd, NCHAr), 5.03 (1H, sept, $J=6.3$ Hz, OCH), 5.12 (1H, brd, 5-H), 5.47 (1H, brs, OH), 5.77 (1H, s, 2a-H), 5.97, 6.00 (each 1H, d, $J=1.3$ Hz, OCHO), 6.50 (2H, s, 1-H, 7-H), 6.83–6.86 (2H, m, ArH $\times$ 2), 7.10–7.12 (4H, m, ArH $\times$ 4), 7.15, 7.69 (each 2H, d, $J=8.3$ Hz, ArH $\times$ 2). ¹³C-NMR δ (at 55 °C): 10.9 (q), 15.7 (q), 21.6 (q), 22.1 (q), 22.1 (q), 31.9 (t, C-6), 45.7 (t, NCH₂Ar), 46.0 (d, C-1), 53.7 (d, C-5), 60.6 (q, OCH₃), 70.0 (d, OCH), 101.7 (t, OCH₂O), 107.7 (d), 114.7 (s), 118.5 (s), 122.4 (d), 124.0 (s), 126.5 (s), 126.8 (d $\times$ 2), 126.9 (d), 127.9 (d $\times$ 2), 128.4 (d $\times$ 2), 128.7 (s), 129.7 (d $\times$ 2), 129.8 (d), 130.3 (s), 135.0 (s), 136.6 (s), 142.3 (s), 144.2 (s), 145.1 (s), 145.3 (s), 145.9 (s), 146.1 (s), 153.2 (s, NCOO), 168.4 (s, C-4). IR (CHCl₃) cm^{-1} : 3550, 1700, 1690. MS m/z (%): 740 (M^+ , 18), 587 (12), 586 (43), 585 (80), 584 (36), 500 (21), 499 (65), 409 (12), 282 (12), 281 (17), 234 (24), 191 (30), 190 (100), 175 (24), 91 (91), 65 (41), 43 (45), 41 (12). High-resolution MS Calcd for C₄₀H₄₀N₂O₁₀S: 740.2405. Found: 740.2404.

(E)-1,2,3,4,5,6-Hexahydro-10-hydroxy-9-methoxy-8-methyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxo-5-yl]methylene]-4-oxo-1,5-imino-3-benzazocine-11-carboxylic acid 1-methylethyl ester (19) Colorless prisms, mp 225–226.5 °C. ¹H-NMR δ (at 55 °C): 1.30 (6H, d, $J=6.3$ Hz, CH(CH₃)₂), 2.27, 2.30, 2.33 (each 3H, s, ArCH₃), 3.02 (1H, d, $J=16.5$ Hz, 6-H β), 3.16 (1H, dd, $J=16.5, 6.0$ Hz, 6-H α), 3.73 (3H, s, OCH₃), 5.03 (1H, sept, $J=6.3$ Hz, OCH), 5.03 (1H, brd, 5-H), 5.10 (1H, brs, OH), 5.57 (1H, s, 2a-H), 6.01, 6.04 (each 1H, s, OCHO), 6.30 (1H, s, ArH), 6.55 (2H, s, 1-H, 7-H), 6.87, 7.53 (each 2H, d, $J=8.3$ Hz, ArH $\times$ 2). ¹³C-NMR δ (at 55 °C): 10.8 (q), 15.8 (q), 21.5 (q), 22.1 (q), 22.1 (q), 31.4 (t, C-6), 44.6 (d, C-1), 52.5 (d, C-5), 60.7 (q, OCH₃), 70.4 (d, OCH), 101.7 (t,

OCH₃O), 105.1 (d), 114.7 (s), 118.2 (s), 122.3 (d), 127.7 (d×2), 128.2 (s), 129.4 (d×2), 130.6 (s), 134.2 (s), 135.1 (s), 143.0 (s), 144.4 (s), 145.3 (s), 145.4 (s), 145.9 (s), 146.3 (s), 153.2 (s, NCOO), 168.5 (s, C-4). IR (KBr) cm⁻¹: 3510, 1710, 1680, 1660. MS *m/z* (%): 650 (M⁺, 19), 497 (12), 496 (50), 495 (100), 494 (49), 410 (21), 409 (77), 277 (16), 235 (18), 234 (22), 192 (14), 191 (38), 190 (88), 175 (24), 158 (10), 91 (15), 43 (18). High-resolution MS Calcd for C₃₃H₃₄N₂O₁₀S: 650.1939. Found: 650.1934.

Method B A solution of **15c** (818.0 mg, 1.0 mmol) and triethylamine (0.167 ml, 1.2 mmol) in ethanol (30 ml) was hydrogenated over 20% Pd/C (818 mg) at 1 atm for 30 min. The catalyst was removed by filtration and washed with ethanol (400 ml). The combined filtrates were concentrated *in vacuo* to give a solid (786.8 mg). Chromatography on a silica gel (25 g) column using hexane–ethyl acetate (4:1) as the eluent gave **18** (690.1 mg, 93.3%) as a colorless amorphous powder, which was identical in all respects with the authentic sample described above.

(E)-10-Benzoyloxy-1,2,3,4,5,6-hexahydro-9-methoxy-8-methyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-4-oxo-3-phenylmethyl-1,5-imino-3-benzazocine-11-carboxylic Acid 1-Methylethyl Ester (19a) Sodium hydride (60% oil dispersion, washed with dry hexane three times, 7.8 mg, 0.325 mmol) was added to a stirred solution of **18** (199.8 mg, 0.27 mmol) in DMF (5.4 ml) under ice-cooling, and stirring was continued at 0 °C for 30 min. Benzyl chloride (38.5 μl, 0.325 mmol) was added over 10 min, and the reaction mixture was stirred at room temperature for 21 h. The reaction mixture was concentrated *in vacuo*, and then the residue was diluted with water (50 ml) and extracted with chloroform (50 ml×3). The combined extracts were washed with brine (50 ml), dried, and concentrated *in vacuo* to give a residue, the recrystallization of which from ethyl acetate/ether afforded **19a** (212.3 mg, 94.7%) as colorless prisms, mp 200–202 °C. ¹H-NMR δ (at 55 °C): 1.29 (6H, d, *J*=5.8 Hz, CH(CH₃)₂), 2.01, 2.20, 2.43 (each 3H, s, ArCH₃), 3.06 (2H, brs, 6-H₂), 3.51 (3H, s, OCH₃), 4.15 (1H, d, *J*=12.5 Hz, OCHAr), 4.41 (1H, d, *J*=15.8 Hz, NCHAr), 4.59 (1H, d, *J*=12.5 Hz, OCHAr), 4.74 (1H, d, *J*=15.8 Hz, NCHAr), 5.01 (1H, sept, *J*=5.8 Hz, OCH), 5.07 (1H, brd, 5-H), 5.73, 5.80 (each 1H, d, *J*=1.3 Hz, OCHO), 5.94 (1H, s, 2a-H), 6.52 (1H, brs, 1-H), 6.69, 6.74 (each 1H, s, ArH), 6.74 (2H, m, ArH×2), 6.95–7.13 (8H, m, ArH×8), 7.19, 7.52 (each 2H, d, *J*=7.9 Hz, ArH×2). ¹³C-NMR δ (at 55 °C): 10.7 (q), 15.6 (q), 21.6 (q), 22.2 (q), 22.2 (q), 32.3 (t, C-6), 45.0 (t, NCH₂Ar), 46.6 (d, C-1), 53.5 (d, C-5), 60.3 (q, OCH₃), 69.9 (d, OCH), 74.0 (t, OCH₂Ar), 101.5 (t, OCH₂O), 107.6 (d), 115.2 (s), 123.1 (s), 125.1 (s), 126.0 (d), 126.6 (d), 126.8 (d), 126.9 (d×2), 127.1 (d×4), 128.1 (d×2), 128.2 (d×4), 129.7 (d×2), 132.4 (s), 134.8 (s), 136.5 (s), 136.6 (s), 137.7 (s), 142.0 (s), 145.1 (s), 145.3 (s), 145.9 (s), 149.3 (s), 149.5 (s), 153.0 (s, NCOO), 168.2 (s, C-4). IR (KBr) cm⁻¹: 1705, 1690, 1660. MS *m/z* (%): 830 (M⁺, 18), 677 (15), 676 (52), 675 (93), 590 (13), 589 (35), 585 (11), 584 (12), 499 (13), 281 (16), 280 (13), 191 (13), 190 (54), 189 (12), 92 (15), 91 (100), 65 (12), 43 (22). Anal. Calcd for C₄₇H₄₆N₂O₁₀S: C, 67.94; H, 5.58; N, 3.37. Found: C, 67.63; H, 5.72; N, 3.11.

(E)-10-Benzoyloxy-1,2,3,4,5,6-hexahydro-9-methoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-3-phenylmethyl-1,5-imino-3-benzazocine (20a) A stirred solution of the lactam **19a** (41.5 mg, 0.05 mmol) in dry THF (2 ml) was cooled with ice water. A THF solution of aluminium hydride (0.5 mol, 0.6 ml, 0.3 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 3 h. After quenching by the addition of methanol (0.5 ml), the reaction mixture was concentrated *in vacuo* to give a residue. Chromatography on a silica gel (5 g) column with benzene–ethyl acetate (5:1) as the eluent gave **20a** (33.5 mg, 90.1%) as a colorless amorphous powder. ¹H-NMR δ: 2.00 (3H, s, NCH₃), 2.01 (3H, s, SO₂C₆H₄CH₃), 2.29, 2.31 (each 3H, s, ArCH₃), 2.39 (1H, d, *J*=16.5 Hz, 6-Hβ), 2.63, 2.73 (each 1H, d, *J*=9.9 Hz, 4-H), 2.92–3.00 (2H, m, 6-Hα, 5-H), 3.04, 3.17 (each 1H, d, *J*=13.9 Hz, NCHAr), 3.68 (3H, s, OCH₃), 4.57 (1H, d, *J*=11.9 Hz, OCHAr), 4.81 (1H, s, 1-H), 4.94 (1H, d, *J*=11.9 Hz, OCHAr), 5.20 (1H, s, 2a-H), 5.89, 5.94 (each 1H, d, *J*=1.3 Hz, OCHO), 6.70, 6.75 (each 1H, s, ArH), 6.88–6.95 (6H, m, ArH×6), 7.17–7.22 (6H, m, ArH×8), 7.69 (2H, d, *J*=8.3 Hz, ArH×2). ¹³C-NMR δ: 11.1 (q), 15.8 (q), 21.3 (q), 27.2 (t, C-6), 40.1 (q, NCH₃), 53.1 (d, C-5), 53.5 (d, C-1), 54.4 (t, NCH₂Ar), 56.9 (t, C-4), 59.8 (q, OCH₃), 73.4 (t, OCH₂Ar), 101.3 (t, OCH₂O), 101.3 (d), 108.1 (d), 115.1 (s), 124.2 (d), 126.8 (d), 127.4 (d), 127.6 (s), 127.9 (d×2), 128.1 (d×2), 128.2 (d×4), 128.4 (d×2), 128.6 (d×2), 129.3 (d×2), 130.0 (s), 130.3 (s), 135.0 (s), 137.3 (s), 138.7 (s), 142.5 (s), 144.5 (s), 144.7 (s), 145.0 (s), 148.2 (s), 148.5 (s). IR (CHCl₃) cm⁻¹: 1635, 1620, 1590. MS *m/z* (%): 744 (M⁺, 1), 590 (20), 589 (53), 588 (32), 497 (12), 296 (14), 295 (19), 294 (50), 204 (25), 203 (26), 156 (23), 139 (12), 107 (11), 92 (45), 91 (100), 65 (35), 63 (19), 39 (14). High-resolution MS Calcd for C₄₄H₄₄N₂O₇S: 744.2869. Found:

744.2873.

Hydrogenolysis of 20a A solution of **20a** (76.7 mg, 0.103 mmol) in ethanol (10 ml) was shaken at 80 °C for 40 h under 4 atm of hydrogen in the presence of 20% Pd/C (40 mg). The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were concentrated *in vacuo* to give a residue (77.3 mg). Chromatography on a silica gel (6 g) column using dichloromethane–methanol (75:1 to 60:1) as the eluent gave **21c** (27.4 mg, 47.0%) and **22c** (18.6 mg, 27.5%).

1α,2α,5α-1,2,3,4,5,6-Hexahydro-10-hydroxy-9-methoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-1,5-imino-3-benzazocine (21c): mp 198–200 °C (colorless needles from acetone/ether). ¹H-NMR δ: 1.90 (3H, s, ArCH₃), 2.16 (1H, dd, *J*=15.3, 11.3 Hz, 2a-Hβ), 2.31 (3H, s, 8-CH₃), 2.35 (3H, s, NCH₃), 2.46 (3H, s, SO₂C₆H₄CH₃), 2.54 (1H, d, *J*=16.8 Hz, 6-Hβ), 2.86 (1H, d, *J*=12.8 Hz, 4-Hβ), 3.03 (1H, brs, 5-H), 3.05 (1H, dd, *J*=16.8, 7.6 Hz, 6-Hα), 3.11 (1H, dd, *J*=15.3, 2.7 Hz, 2a-Hα), 3.22 (1H, dd, *J*=12.8, 2.0 Hz, 4-Hα), 3.48 (1H, brd, *J*=9.2 Hz, 2-H), 3.80 (3H, s, OCH₃), 4.08 (1H, brs, 1-H), 5.90, 5.91 (each 1H, d, *J*=1.2 Hz, OCHO), 6.55, 6.63 (each 1H, s, ArH), 7.33, 7.75 (each 2H, d, *J*=7.9 Hz, ArH×2). ¹³C-NMR δ: 10.6 (q), 15.8 (q), 21.7 (q), 26.4 (t, C-6), 34.0 (t, C-2a), 41.6 (q, NCH₃), 52.3 (d, C-5), 53.4 (t, C-4), 57.3 (d, C-1), 60.0 (d, C-2), 60.8 (q, OCH₃), 101.4 (t, OCH₂O), 107.0 (d), 114.5 (s), 116.3 (s), 121.2 (d), 127.1 (s), 128.1 (d×2), 128.9 (s), 129.8 (d×2), 131.5 (s), 134.1 (s), 141.2 (s), 143.2 (s), 145.0 (s), 145.2 (s), 145.3 (s), 146.9 (s). IR (KBr) cm⁻¹: 3300, 1605, 1585. MS *m/z* (%): 566 (M⁺, 3), 411 (8), 248 (12), 247 (70), 219 (14), 207 (88), 205 (25), 204 (100), 190 (12), 189 (12), 91 (12). Anal. Calcd for C₃₀H₃₄N₂O₇S·1/4H₂O: C, 62.59; H, 6.13; N, 4.87. Found: C, 62.90; H, 6.13; N, 4.42.

1α,2α,5α-1,2,3,4,5,6-Hexahydro-10-hydroxy-9-methoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-3-phenylmethyl-1,5-imino-3-benzazocine (22c): Colorless amorphous powder. ¹H-NMR δ: 1.96 (3H, s, ArCH₃), 2.25 (3H, s, NCH₃), 2.31 (1H, d, *J*=16.5 Hz, 6-Hβ), 2.35 (3H, s, 8-CH₃), 2.38 (3H, s, SO₂C₆H₄CH₃), 2.50 (1H, dd, *J*=11.2, 2.0 Hz, 4-Hβ), 2.52 (1H, dd, *J*=15.8, 6.6 Hz, 2a-Hβ), 2.54 (1H, d, *J*=13.2 Hz, NCHAr), 2.58 (1H, brd, *J*=11.2 Hz, 4-Hα), 2.87 (1H, dd, *J*=16.5, 7.3 Hz, 6-Hα), 2.89 (1H, brs, 5-H), 3.13 (1H, m, 2-H), 3.24 (1H, dd, *J*=16.5, 3.3 Hz, 2a-Hα), 3.63 (1H, d, *J*=13.2 Hz, NCHAr), 3.78 (3H, s, OCH₃), 4.21 (1H, brs, 1-H), 5.94, 5.95 (each 1H, s, OCHO), 6.52, 6.90 (each 1H, s, ArH), 6.90–6.92 (2H, m, ArH×2), 7.11–7.13 (3H, m, ArH×3), 7.17, 7.62 (each 2H, d, *J*=8.3 Hz, ArH×2). ¹³C-NMR δ: 10.7 (q), 15.8 (q), 21.6 (q), 26.9 (t, C-6), 31.1 (t, C-2a), 41.0 (q, NCH₃), 52.9 (d, C-5), 57.0 (t, NCH₂Ar), 58.2 (d, C-1), 59.8 (t, C-4), 60.6 (q, OCH₃), 66.3 (d, C-2), 101.4 (t, OCH₂O), 106.0 (d), 114.5 (s), 118.0 (s), 120.7 (d), 126.3 (d), 127.8 (d×2), 128.1 (d×2), 128.2 (s), 128.6 (d×2), 129.5 (s), 129.7 (d×2), 132.9 (s), 133.9 (s), 140.0 (s), 140.3 (s), 142.7 (s), 144.6 (s), 144.9 (s), 145.2 (s), 146.5 (s). IR (CHCl₃) cm⁻¹: 3550, 2950, 1480. MS *m/z* (%): 656 (M⁺, 0.1), 338 (25), 337 (100), 206 (20), 205 (20), 204 (44), 189 (11), 91 (21). High-resolution MS Calcd for C₃₇H₄₀N₂O₇S: 656.2556. Found: 656.2560.

(E)-1,2,3,4,5,6-Hexahydro-9-methoxy-10-methoxymethoxy-8-methyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-4-oxo-3-phenylmethyl-1,5-imino-3-benzazocine-11-carboxylic Acid 1-Methylethyl Ester (19b) Sodium hydride (60% oil dispersion, washed with dry hexane three times, 18.0 mg, 0.75 mmol) was added to a stirred solution of **18** (370.0 mg, 0.5 mmol) in THF (10 ml) under ice cooling, and stirring was continued at 0 °C for 30 min. Bromomethyl methyl ether (61.2 μl, 0.75 mmol) was added over 10 min, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (100 ml) and then extracted with chloroform (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a residue, the recrystallization of which from ethyl acetate/ether afforded **19b** (334.1 mg, 85.2%) as colorless prisms, mp 199.5–201 °C. ¹H-NMR δ (at 55 °C): 1.19, 1.36 (each 3H, br, CH(CH₃)₂), 2.20 (6H, s, ArCH₃×2), 2.42 (3H, s, ArCH₃), 3.09 (3H, s, CH₂OCH₃), 3.12 (2H, brs, 6-H₂), 3.51 (3H, s, OCH₃), 4.16 (1H, d, *J*=5.6 Hz, OCHOCH₃), 4.58 (2H, br, NCH₂Ar), 4.91 (1H, d, *J*=5.6 Hz, OCHOCH₃), 5.00 (1H, sept, *J*=6.3 Hz, OCH), 5.04 (1H, brd, 5-H), 5.82 (1H, s, 2a-H), 5.98 (2H, s, OCH₂O), 6.36 (1H, brs, 1-H), 6.68 (1H, s, ArH), 6.74 (2H, m, ArH×2), 6.83 (1H, s, ArH), 7.02–7.12 (3H, m, ArH×3), 7.17, 7.69 (each 2H, d, *J*=8.2 Hz, ArH×2). ¹³C-NMR δ (at 55 °C): 10.8 (q), 15.6 (q), 21.6 (q), 22.1 (q), 22.1 (q), 32.0 (t, C-6), 45.0 (t, NCH₂Ar), 46.7 (d, C-1), 53.3 (d, C-5), 57.3 (q, OCH₃), 59.8 (q, OCH₃), 70.0 (d, OCH), 97.3 (t, OCH₂OCH₃), 101.7 (t, OCH₂O), 106.6 (d), 107.9 (d), 115.2 (s), 124.0 (s), 125.0 (s), 126.1 (d), 126.5 (d×2), 126.7 (d), 128.1 (d×2), 128.3 (d×2), 128.5 (s), 128.7 (s), 129.5 (d×2), 132.3 (s), 134.8 (s), 136.4 (s), 137.2 (s), 141.9 (s), 145.1 (s), 146.0 (s), 146.3 (s), 148.9 (s), 153.0 (s, NCOO), 168.2 (s, C-4). IR (KBr)

cm^{-1} : 1700, 1680, 1650. MS m/z (%): 784 (M^+ , 24), 631 (15), 630 (55), 629 (100), 544 (23), 543 (66), 499 (12), 234 (30), 190 (34), 91 (23). *Anal.* Calcd for $\text{C}_{42}\text{H}_{44}\text{N}_2\text{O}_{11}\text{S}$: C, 64.30; H, 5.65; N, 3.57. Found: C, 64.12; H, 5.69; N, 3.33.

(E)-1,2,3,4,5,6-Hexahydro-9-methoxy-10-methoxymethoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-3-phenylmethyl-1,5-imino-3-benzazocine (20b) A stirred solution of the lactam **19b** (297.9 mg, 0.38 mmol) in dry THF (15 ml) was cooled with ice water. A THF solution of aluminium hydride (0.5 mol, 6.1 ml, 3.05 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 3 h. After quenching by the addition of methanol (2.0 ml), the reaction mixture was concentrated *in vacuo* to give a residue. Chromatography on a silica gel (12 g) column with benzene–ethyl acetate (5 : 1) as the eluent gave **20b** (257.4 mg, 97.1%) as a colorless amorphous powder. $^1\text{H-NMR}$ δ : 1.99 (3H, s, $\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$), 2.18, 2.22 (each 3H, s, ArCH_3), 2.35 (3H, s, NCH_3), 2.39 (1H, d, $J=16.2$ Hz, 6-H β), 2.59, 2.78 (each 1H, d, $J=10.6$ Hz, 4-H), 2.92–3.02 (2H, m, 6-H α , NCH), 3.02 (1H, s, 5-H), 3.26 (each 1H, d, $J=13.5$ Hz, NCHAr), 3.52 (3H, s, OCH_3), 4.34, 4.37 (each 1H, d, $J=5.7$ Hz, OCH_2OCH_3), 4.88 (1H, s, 1-H), 5.10 (1H, s, 2a-H), 5.92 (2H, s, OCH_2O), 6.63, 6.71 (each 1H, s, ArH), 6.81–6.87 (2H, m, ArH $\times 2$), 6.89 (2H, d, $J=8.6$ Hz, ArH $\times 2$), 7.13–7.18 (3H, m, ArH $\times 3$), 7.60 (2H, d, $J=8.6$ Hz, ArH $\times 2$). $^{13}\text{C-NMR}$ δ : 11.1 (q), 15.8 (q), 21.3 (q), 27.7 (t, C-6), 40.6 (q, NCH_3), 53.0 (d, C-5), 53.5 (d, C-1), 54.4 (t, NCH_2Ar), 56.3 (t, C-4), 57.3 (q, OCH_3), 59.7 (q, OCH_3), 97.9 (t, OCH_2OCH_3), 101.0 (d), 101.4 (t, OCH_2O), 108.6 (d), 115.0 (s), 124.5 (d), 125.8 (s), 126.8 (d), 127.6 (s), 128.0 (d $\times 2$), 128.1 (d $\times 2$), 128.2 (d $\times 2$), 128.7 (s), 129.3 (d $\times 2$), 129.8 (s), 129.9 (s), 134.9 (s), 138.6 (s), 142.4 (s), 144.7 (s), 145.1 (s), 145.5 (s), 146.9 (s), 147.9 (s). IR (CHCl_3) cm^{-1} : 1630, 1610, 1480. MS m/z (%): 698 (M^+ , 1), 545 (11), 544 (39), 543 (55), 542 (72), 481 (10), 453 (17), 451 (11), 424 (13), 295 (17), 251 (15), 250 (100), 249 (23), 248 (95), 204 (34), 203 (11), 91 (13). High-resolution MS Calcd for $\text{C}_{39}\text{H}_{42}\text{N}_2\text{O}_8\text{S}$: 698.2662. Found: 698.2662.

Hydrogenolysis of 20b. Method A A solution of **20b** (103.6 mg, 0.148 mmol) in ethanol (15 ml) was shaken at 80 °C for 24 h under 4 atm of hydrogen in the presence of 20% Pd/C (60 mg). The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were concentrated *in vacuo* to give a residue (77.3 mg). Chromatography on a silica gel (6 g) column using dichloromethane–methanol (50 : 1 to 10 : 1) as the eluent gave **21b** (2.9 mg, 3.2%) and **22b** (78.6 mg, 75.9%).

Method B A solution of **20b** (257.4 mg, 0.37 mmol) in ethanol (35 ml) was shaken at 80 °C for 48 h under 4 atm of hydrogen in the presence of 20% Pd(OH) $_2$ /C (257 mg). The catalyst was removed by filtration and washed with ethanol (200 ml). The combined filtrates were concentrated *in vacuo* to give a residue, the recrystallization of which from ethyl acetate/ether afforded **21b** (147.3 mg, 65.5%) as colorless needles, mp 74.5–76 °C.

1 α ,2 α ,5 α -1,2,3,4,5,6-Hexahydro-9-methoxy-10-methoxymethoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-1,5-imino-3-benzazocine (21b): mp 198–200 °C (colorless needles from acetone/ether). $^1\text{H-NMR}$ δ : 1.80 (3H, s, ArCH_3), 2.15 (1H, dd, $J=14.9$, 10.9 Hz, 2a-H β), 2.28 (3H, s, 8- CH_3), 2.30 (3H, s, NCH_3), 2.46 (3H, s, $\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$), 2.48 (1H, d, $J=17.5$ Hz, 6-H β), 2.85 (1H, dd, $J=12.2$, 1.7 Hz, 4-H β), 2.91 (1H, br d, $J=7.6$ Hz, 5-H), 2.96 (1H, dd, $J=17.5$, 7.6 Hz, 6-H α), 3.09 (1H, dd, $J=12.2$, 2.6 Hz, 4-H α), 3.20 (1H, dd, $J=14.9$, 3.3 Hz, 2a-H α), 3.38 (1H, ddd, $J=10.9$, 3.3, 2.3 Hz, 2-H), 3.57, 3.78 (3H, s, OCH_3), 4.13 (1H, d, $J=2.3$ Hz, 1-H), 5.12, 5.15 (each 1H, d, $J=5.9$ Hz, OCH_2OCH_3), 5.90, 5.91 (each 1H, d, $J=1.3$ Hz, OCHO), 6.64, 6.78 (each 1H, s, ArH), 7.32, 7.71 (each 2H, d, $J=7.9$ Hz, ArH $\times 2$). $^{13}\text{C-NMR}$ δ : 10.5 (q), 15.8 (q), 21.7 (q), 26.3 (t, C-6), 34.3 (t, C-2a), 41.7 (q, NCH_3), 52.1 (d, C-5), 54.1 (t, C-4), 57.6 (d, C-1), 57.8 (q, OCH_3), 60.1 (q, OCH_3), 60.8 (d, C-2), 99.0 (t, OCH_2OCH_3), 101.4 (t, OCH_2O), 107.5 (d), 114.3 (s), 124.3 (s), 125.3 (d), 127.1 (s), 128.1 (d $\times 2$), 129.8 (d $\times 2$), 129.8 (s), 130.4 (s), 131.5 (s), 134.1 (s), 141.1 (s), 145.0 (s), 145.0 (s), 148.0 (s), 148.5 (s). IR (KBr) cm^{-1} : 2960, 1610. MS m/z (%): 610 (M^+ , 9), 455 (14), 292 (18), 291 (100), 251 (11), 250 (73), 249 (20), 248 (80), 218 (16), 205 (13), 204 (44). *Anal.* Calcd for $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_8\text{S} \cdot 1/4\text{H}_2\text{O}$: C, 61.13; H, 6.41; N, 4.46. Found: C, 61.20; H, 6.20; N, 4.16.

1 α ,2 α ,5 α -1,2,3,4,5,6-Hexahydro-9-methoxy-10-methoxymethoxy-8,11-dimethyl-2-[[7-methyl-6-(4-methylbenzenesulfoxy)-1,3-benzodioxio-5-yl]methylene]-3-phenylmethyl-1,5-imino-3-benzazocine (22b): mp 72.5–75 °C (from ethyl acetate/ether). $^1\text{H-NMR}$ δ : 1.97 (3H, s, ArCH_3), 2.25 (3H, s, NCH_3), 2.31 (3H, s, 8- CH_3), 2.36 (3H, s, $\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$), 2.36 (2H, br, 6-H β , 4-H β), 2.52 (1H, d, $J=13.2$ Hz, NCHAr), 2.54 (1H, dd, $J=16.2$, 2.3 Hz, 2a-H β), 2.57 (1H, d, $J=11.5$ Hz, 4-H α), 2.84 (1H, dd, $J=16.3$, 7.6 Hz, 6-H α), 2.87 (1H, m, 5-H), 3.08 (1H, dd, $J=12.2$, 2.6 Hz, 2a-H α),

3.09 (1H, m, 2-H), 3.44 (3H, s, OCH_2OCH_3), 3.63 (1H, d, $J=13.2$ Hz, NCHAr), 3.78 (3H, s, OCH_3), 4.23 (1H, br s, 1-H), 4.95, 5.05 (each 1H, d, $J=6.0$ Hz, OCH_2OCH_3), 5.93, 5.96 (each 1H, d, $J=1.3$ Hz, OCHO), 6.75, 6.88 (each 1H, s, ArH), 6.88–6.92 (2H, m, ArH $\times 2$), 7.12–7.15 (3H, m, ArH $\times 3$), 7.17, 7.58 (each 2H, d, $J=8.3$ Hz, ArH $\times 2$) (*the signal overlapped with the methyl signal). $^{13}\text{C-NMR}$ δ : 10.7 (q), 15.9 (q), 21.6 (q), 27.0 (t, C-6), 30.9 (t, C-2a), 41.0 (q, NCH_3), 52.9 (d, C-5), 56.9 (t, NCH_2Ar), 57.5 (q, OCH_3), 58.1 (d, C-1), 60.0 (q, OCH_3), 60.1 (t, C-4), 66.5 (d, C-2), 99.0 (t, OCH_2OCH_3), 101.4 (t, OCH_2O), 106.0 (d), 114.5 (s), 124.8 (d), 124.8 (s), 125.0 (s), 126.4 (d), 127.9 (d $\times 2$), 128.2 (d $\times 2$), 128.7 (d $\times 2$), 129.5 (s), 129.7 (d $\times 2$), 130.1 (s), 132.2 (s), 133.9 (s), 140.1 (s), 140.2 (s), 144.7 (s), 145.2 (s), 148.0 (s), 148.5 (s). IR (KBr) cm^{-1} : 2960, 1740, 1610. MS m/z (%): 700 (M^+ , 0.1), 382 (25), 381 (100). *Anal.* Calcd for $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_8\text{S} \cdot 3/2\text{H}_2\text{O}$: C, 65.16; H, 6.45; N, 3.90. Found: C, 64.85; H, 6.30; N, 3.48.

(6 α ,14 α ,15 α)-6,7,9,14,14a,15-Hexahydro-1-hydroxy-2-methoxy-3,12,16-trimethyl-13-(4-methylbenzenesulfoxy)-10,11-methylenedioxy-6,15-imino-5H-isoquino[3,2-b][3]benzazocine (24c). From 21c A mixture of **21c** (12.7 mg, 0.022 mmol) and anhydrous K_2CO_3 (60.8 mg, 0.44 mmol) in ethanol (2 ml) was stirred for 10 min at room temperature. Paraformaldehyde (6.6 mg, 0.22 mmol) was added all at once, and the mixture was stirred for 72 h. The inorganic materials were removed by filtration and washed with ethanol (100 ml). The combined filtrates were concentrated *in vacuo* to give a crude product of the *O,N*-acetal (**23c**: 16.6 mg), that was used in the subsequent step without further purification. The residue was stirred with TFA (1 ml) at room temperature for 24 h. The mixture was diluted with water (20 ml) and extracted with chloroform (20 ml $\times 3$). The combined extracts were washed with 5% NaHCO_3 solution (20 ml), dried, and concentrated *in vacuo* to give a residue (10.5 mg), that was subjected to chromatography on a silica gel (10 g) column with dichloromethane–methanol (60 : 1) as the eluent to give **24c** (1.9 mg, 14.9%) as a solid. Further elution with dichloromethane–methanol (20 : 1) gave the original **21c** (4.5 mg, 35.4%) as a solid.

From 21b A mixture of **21b** (18.7 mg, 0.03 mmol) and anhydrous K_2CO_3 (82.9 mg, 0.6 mmol) in ethanol (4 ml) was stirred for 10 min at room temperature. Paraformaldehyde (9.0 mg, 0.3 mmol) was added all at once, and the mixture was stirred for 72 h. The inorganic materials were removed by filtration and washed with ethanol (100 ml). The combined filtrates were concentrated *in vacuo* to give a crude product of the *O,N*-acetal (**23b**: 36.4 mg) that was used in the subsequent step without further purification. The residue was stirred with TFA (1 ml) at room temperature for 24 h. The mixture was diluted with water (20 ml) and extracted with chloroform (20 ml $\times 3$). The combined extracts were washed with 5% NaHCO_3 solution (20 ml), dried, and concentrated *in vacuo* to give a residue (20.4 mg) that was subjected to chromatography on a silica gel (6 g) column with dichloromethane–methanol (60 : 1) as the eluent to afford a solid, the recrystallization of which from acetone gave **24c** (12.1 mg, 69.8%) as colorless prisms, mp 221–223 °C. $^1\text{H-NMR}$ δ : 1.73 (3H, s, 12- CH_3), 2.22 (3H, s, 3- CH_3), 2.33 (3H, s, NCH_3), 2.42 (1H, dd, $J=17.1$, 12.0 Hz, 14-H β), 2.48 (3H, s, $\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$), 2.65 (1H, d, $J=17.6$ Hz, 5-H β), 2.67 (1H, m, 14a-H), 2.72 (1H, br, 7-H β), 2.94 (1H, dd, $J=17.1$, 3.1 Hz, 14-H α), 3.06 (1H, dd, $J=17.6$, 7.8 Hz, 5-H α), 3.11 (1H, d, $J=15.6$ Hz, 9-H), 3.16 (1H, br d, 6-H), 3.73 (3H, s, OCH_3), 3.88 (1H, d, $J=15.6$ Hz, 9-H), 4.07 (1H, br s, 15-H), 5.84, 5.89 (each 1H, d, $J=1.2$ Hz, OCHO), 6.46 (1H, s, 4-H), 7.7, 7.83 (each 2H, d, $J=8.1$ Hz, ArH $\times 2$). $^{13}\text{C-NMR}$ δ : 10.2 (q, 12- CH_3), 15.9 (q, 3- CH_3), 21.8 (q, $\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$), 26.8 (t, C-5), 28.0 (t, C-14), 41.5 (q, NCH_3), 52.3 (t, C-9), 52.8 (d, C-6), 56.4 (d, C-15), 60.8 (q, OCH_3), 61.1 (d, C-14a), 63.3 (t, C-7), 101.4 (t, OCH_2O), 112.2 (s), 113.8 (s), 121.3 (d), 121.8 (s), 122.8 (s), 128.0 (d $\times 2$), 128.7 (s), 129.6 (d $\times 2$), 130.9 (s), 134.3 (s), 140.3 (s), 140.6 (s), 142.8 (s), 143.6 (s), 144.8 (s), 146.7 (s). IR (KBr) cm^{-1} : 3480, 2940, 1460, 1375, 1185, 1115. MS m/z (%): 578 (M^+ , 3), 423 (20), 220 (18), 219 (25), 218 (18), 206 (22), 205 (21), 204 (100), 203 (13), 189 (17), 173 (10), 91 (17). *Anal.* Calcd for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_7\text{S} \cdot 1/2\text{H}_2\text{O}$: C, 63.36; H, 6.00; N, 4.77. Found: C, 63.77; H, 6.04; N, 4.46.

Hydrogenation of 4a over 10% Pd/C Followed by Acetylation A solution of **4a** (297.7 mg, 0.7 mmol) in ethanol (12 ml) was hydrogenated over 10% Pd/C (150 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethanol (100 ml). The combined filtrates were evaporated *in vacuo* to give a solid (256 mg) that was used in the subsequent step without further purification. A solution of the crude product in acetic anhydride (12 ml) was heated at 100 °C for 3 h. The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (30 ml $\times 3$). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from benzene gave **27** (212.2 mg,

77.6%) as colorless needles, mp 93–94.5 °C. $^1\text{H-NMR}$ δ : 1.29, 1.33 (each 3H, d, $J=6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.17 (3H, s, ArCH_3), 2.55, 2.59 (each 3H, s, COCH_3), 3.08 (1H, dd, $J=14.1, 5.3$ Hz, 3-CH), 3.21 (1H, dd, $J=14.1, 4.2$ Hz, 3-CH), 3.36 (1H, d, $J=18.9$ Hz, 6-H), 3.78 (3H, s, OCH_3), 4.41 (1H, sept, $J=6.1$ Hz, $\text{OCH}(\text{CH}_3)_2$), 4.54 (1H, d, $J=18.9$ Hz, 6-H), 5.41 (1H, dd, $J=5.3, 4.2$ Hz, 3-H), 6.42 (each 1H, s, ArH). IR (KBr) cm^{-1} : 1722, 1684. MS m/z (%): 390 (M^+ , 15), 151 (100), 43 (12). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.55; H, 6.90; N, 7.10.

Hydrogenation of 4c Followed by Acetylation. Using 10% Pd/C A solution of **4c** (236.7 mg, 0.5 mmol) in ethanol (10 ml) was hydrogenated over 10% Pd/C (100 mg) at 1 atm for 2 h. The catalyst was removed by filtration and washed with ethanol (500 ml). The combined filtrates were evaporated *in vacuo* to give a solid (212 mg) that was used in the subsequent step without further purification. A solution of the crude product in acetic anhydride (5 ml) was heated at 100 °C for 2 h. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (20 ml $\times$ 3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **28** (160.0 mg, 82.0%) as colorless needles, mp 111.5–112.5 °C. $^1\text{H-NMR}$ δ : 2.23 (3H, s, ArCH_3), 2.30, 2.56, 2.59 (each 3H, s, COCH_3), 2.79 (1H, d, $J=19.1$ Hz, 6-H), 3.17 (1H, dd, $J=14.1, 5.5$ Hz, 3-CH), 3.19 (1H, dd, $J=14.1, 4.6$ Hz, 3-CH), 3.75 (3H, s, OCH_3), 4.65 (1H, d, $J=19.1$ Hz, 6-H), 5.40 (1H, dd, $J=5.5, 4.6$ Hz, 3-H), 6.64, 6.73 (each 1H, s, ArH). IR (KBr) cm^{-1} : 1770, 1720, 1710, 1700. MS m/z (%): 390 (M^+ , 10), 348 (28), 193 (33), 152 (10), 151 (100), 43 (12). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_7 \cdot 1/4\text{H}_2\text{O}$: C, 57.79; H, 5.74; N, 7.09. Found: C, 57.65; H, 5.63; N, 6.87.

Using PtO_2 A solution of **4c** (236.7 mg, 0.5 mmol) in ethanol (10 ml) was hydrogenated over PtO_2 (100 mg) at 1 atm for 1 h. The catalyst was removed by filtration and washed with ethanol (500 ml). The combined filtrates were evaporated *in vacuo* to give a residue (275 mg) that was used in the subsequent step without further purification. A solution of the crude product in acetic anhydride (5 ml) was heated at 100 °C for 13 h. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (20 ml $\times$ 3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a residue. Chromatography on a silica gel (25 g) column with hexane–ethyl acetate (3 : 1) as the eluent gave a solid, the recrystallization of which from ethyl acetate/ether gave **28** (45.3 mg, 19.4%) as colorless needles, mp 136–138 °C. $^1\text{H-NMR}$ δ : 2.31 (3H, s, ArCH_3), 2.36, 2.55, 2.56 (each 3H, s, COCH_3), 3.27 (1H, dd, $J=14.0, 5.7$ Hz, 3-CH), 3.37 (1H, d, $J=18.9$ Hz, 6-H), 3.58 (1H, dd, $J=14.0, 6.8$ Hz, 3-CH), 3.75 (3H, s, OCH_3), 4.90 (1H, d, $J=18.9$ Hz, 6-H), 5.49 (1H, dd, $J=6.8, 5.7$ Hz, 3-H), 6.84 (1H, s, ArH). IR (KBr) cm^{-1} : 1770, 1720, 1710, 1700. MS m/z (%): 470 ($\text{M}^+ + 2$, 3), 468 (M^+ , 3), 428 (28), 426 (28), 273 (22), 271 (22), 232 (10), 231 (98), 230 (11), 229 (100), 43 (68). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{BrN}_2\text{O}_7$: C, 48.63; H, 4.51; N, 5.97. Found: C, 49.03; H, 4.53; N, 5.72.

Preparation of 4b A suspended solution of **25**²⁶ (4.901 g, 20.0 mmol) and anhydrous K_2CO_3 (5.528 g, 40 mmol) in dry DMF (200 ml) was cooled with ice water, and chloromethyl methyl ether (3.04 ml, 40 mmol) was added dropwise over 10 min. Then, it was stirred for 1 h at room temperature. The reaction mixture was diluted with water (200 ml) and extracted with ether (200 ml $\times$ 3). The combined extracts were washed with brine (200 ml), dried, concentrated *in vacuo* to give a solid (5.804 g, 100%) that was used in the subsequent step without further purification. 2-Bromo-3-methoxy-5-methoxymethoxy-4-methylbenzaldehyde (**26b**), mp 41–43 °C. $^1\text{H-NMR}$ δ : 2.41 (3H, s, ArCH_3), 3.51, 3.85 (each 3H, s, OCH_3), 5.25 (2H, s, OCH_2OCH_3), 7.58 (1H, s, 6-H), 10.34 (1H, s, CHO). IR (KBr) cm^{-1} : 1700. MS m/z (%): 290 ($\text{M}^+ + 2$, 7), 288 (M^+ , 7), 246 (7), 244 (7), 42 (100). High-resolution MS Calcd for $\text{C}_{11}\text{H}_{13}^{79}\text{BrO}_4$: 287.9997. Found: 287.9995.

A solution of potassium *tert*-butoxide (2.25 g, 20 mmol) in *tert*-butyl alcohol (40 ml) was added to a stirred solution of the crude **26b** and 1,4-diacylpiperazine-2,5-dione (**27**: 3.964 g, 20 mmol) in DMF (40 ml) over 30 min. After stirring for 1 h at room temperature, the reaction mixture was poured into brine (600 ml) and extracted with ethyl acetate (400 ml $\times$ 3). The combined extracts were washed with water (400 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **4b** (6.749 g, 79.0%) as colorless needles, mp 108.5–110.0 °C. $^1\text{H-NMR}$ δ : 2.40 (3H, s, ArCH_3), 2.67 (3H, s, COCH_3), 3.51 (3H, s, OCH_2OCH_3), 3.86 (3H, s, ArOCH_3), 4.50 (2H, s, 6-H), 5.21 (2H, s, OCH_2OCH_3), 7.00 (1H, s, ArH), 7.17 (1H, s, 3a-H), 7.73 (1H, br s, NH). IR (KBr) cm^{-1} : 3580, 3250, 1730, 1720, 1710. MS m/z (%): 428 ($\text{M}^+ + 2$, 6), 426 (M^+ , 7), 347 (38), 305 (51), 45 (100), 43 (10). Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{BrN}_2\text{O}_6 \cdot 1/5\text{H}_2\text{O}$: C, 47.30; H, 4.73; N, 6.49. Found: C, 47.27; H, 4.50; N, 6.21.

Preparation of 4c A suspended solution of **25**²⁶ (245.1 mg, 1.0 mmol) and anhydrous K_2CO_3 (276.4 mg, 2 mmol) in dry DMF (10 ml) was cooled with ice water, and benzyl bromide (238 μl , 2 mmol) was added dropwise over 10 min. Then, it was stirred for 2 h at room temperature. The reaction mixture was diluted with water (10 ml) and extracted with ether (10 ml $\times$ 3). The combined extracts were washed with brine (10 ml), dried, concentrated *in vacuo* to give a solid (330.0 mg, 98.4%) that was used in the subsequent step without further purification.

5-Benzyloxy-2-bromo-4-methoxy-3-methylbenzaldehyde (**26c**), mp 82–83 °C. $^1\text{H-NMR}$ δ : 2.41 (3H, s, ArCH_3), 3.91 (each 3H, s, OCH_3), 5.14 (2H, s, OCH_2Ar), 7.10–7.24 (5H, m, $\text{ArH}\times 5$), 7.46 (1H, s, 6-H), 10.34 (1H, s, CHO). IR (KBr) cm^{-1} : 1690. MS m/z (%): 336 ($\text{M}^+ + 2$, 6), 334 (M^+ , 6), 92 (12), 91 (100), 65 (11). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{BrO}_3$: C, 57.33; H, 4.51. Found: C, 57.39; H, 4.46.

A solution of potassium *tert*-butoxide (112.5 mg, 1.0 mmol) in *tert*-butyl alcohol (2 ml) was added to a stirred solution of the crude **26c** and **27** (198.2 mg, 1.0 mmol) in DMF (2 ml) over 30 min. After stirring for 3 h at room temperature, the reaction mixture was poured into brine (40 ml) and extracted with ethyl acetate (40 ml $\times$ 3). The combined extracts were washed with water (40 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ethyl acetate/ether gave **4c** (394.0 mg, 83.3%) as colorless needles, mp 149.5–151 °C. $^1\text{H-NMR}$ δ : 2.39 (3H, s, ArCH_3), 2.67 (3H, s, COCH_3), 3.88 (3H, s, ArOCH_3), 4.48 (2H, s, 6-H₂), 5.10 (2H, s, OCH_2Ar), 6.74 (1H, s, ArH), 7.15 (1H, s, 3a-H), 7.32–7.41 (5H, m, $\text{ArH}\times 5$), 7.60 (1H, br s, NH). IR (KBr) cm^{-1} : 3210, 1730, 1700, 1650. MS m/z (%): 474 ($\text{M}^+ + 2$, 3), 472 (M^+ , 3), 393 (33), 351 (21), 92 (13), 91 (100). Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{BrN}_2\text{O}_5$: C, 55.83; H, 4.47; N, 5.92. Found: C, 55.82; H, 4.43; N, 5.75.

Attempted Deacetylation of 12b. Method A A mixture of **12b** (416.9 mg, 0.5 mmol) with hydrazine-hydrate (0.5 ml) in DMF (5 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (30 ml $\times$ 3). The combined extracts were washed with brine (30 ml), dried, and concentrated *in vacuo* to give a residue (404 mg). Chromatography on a silica gel (25 g) column with hexane–ethyl acetate (2 : 1) as the eluent gave **30** (75.7 mg, 23.8%) as a colorless amorphous powder. $^1\text{H-NMR}$ δ : 1.19, 1.29 (each 3H, d, $J=6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.24, 2.32 (each 3H, s, ArCH_3), 3.45 (1H, dd, $J=13.6, 7.0$ Hz, 6-CH), 3.54 (1H, dd, $J=13.6, 5.0$ Hz, 6-CH), 3.74 (3H, s, OCH_3), 4.38 (1H, sept, $J=6.1$ Hz, OCH), 4.90 (1H, d, $J=15.9$ Hz, NCHAr), 5.02 (1H, dd, $J=7.0, 5.0$ Hz, 6-H), 5.15 (1H, d, $J=15.9$ Hz, NCHAr), 5.94, 5.95 (each 1H, d, $J=1.3$ Hz, OCHO), 6.10 (1H, br s, NH), 6.80 (1H, s, C=CH), 7.07–7.10 (2H, d, $J=8.3$ Hz, $\text{ArH}\times 2$), 7.16–7.33 (4H, m, $\text{ArH}\times 4$). IR (CHCl_3) cm^{-1} : 3450–3200, 1700, 1685. FAB-MS (Magic Bullet) m/z 637 ($\text{M}^+ + 1$). High-resolution MS Calcd for $\text{C}_{32}\text{H}_{33}^{79}\text{BrN}_2\text{O}_7$: 636.1471. Found: 636.1475.

Method B A mixture of **12b** (416.9 mg, 0.5 mmol) with 2 N KOH (0.5 ml) in DMF (5 ml) was stirred at room temperature for 20 h. The reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (30 ml $\times$ 3). The combined extracts were washed with brine (30 ml), dried, and concentrated *in vacuo* to give a residue (301 mg). Chromatography on a silica gel (20 g) column with hexane–ethyl acetate (5 : 1) as the eluent gave a solid, the recrystallization of which from ethyl acetate/ether afforded **31** (66.2 mg, 21.4%) as pale red needles, mp 242–244.5 °C. $^1\text{H-NMR}$ δ : 1.50 (6H, d, $J=6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.24, 2.39 (each 3H, s, ArCH_3), 3.85 (3H, s, OCH_3), 4.66 (1H, sept, $J=6.1$ Hz, OCH), 4.90 (1H, d, $J=15.9$ Hz, NCHAr), 5.24 (2H, s, NCH_2Ar), 5.97 (2H, s, OCH_2O), 6.34, 6.44 (each 1H, s, $\text{ArH}\times 2$), 7.26–7.38 (5H, m, $\text{ArH}\times 5$), 7.75, 8.35 (each 1H, s, CH=C). IR (KBr) cm^{-1} : 1675, 1605. MS m/z (%): 618 ($\text{M}^+ + 2$, 16), 616 (M^+ , 16), 539 (54), 537 (34), 481 (12), 447 (28), 446 (100), 389 (31), 361 (13), 91 (34), 43 (21). FAB-MS (Magic Bullet) m/z 617 ($\text{M}^+ + 1$). High-resolution MS Calcd for $\text{C}_{32}\text{H}_{29}^{79}\text{BrN}_2\text{O}_6$: 616.1204. Found: 616.1209.

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- 20) Catalytic hydrogenation of **4a** over 10% palladium on carbon (Pd/C) followed by acetylation gave the debrominated compound (**27**) in 82% overall yield (see: Experimental Section).
- 21) We also attempted transforming **4c**²⁵ into the acetate using the se-

quence of reactions including hydrogenation with debromination, selective bromination, and acetylation to generate **28**. When treating **4c** with hydrogen over 10% Pd/C in ethanol followed by acetylation with acetic anhydride gave **29** in 82% overall yield. By contrast, hydrogenation of **4c** with hydrogen over 10% Pd/C in ethanol gave **5c**, which was unstable and easily converted into a high polar insoluble material during purification.

- 22) Another approach based on the selective hydrogenation of **4c** over PtO₂ as catalyst²³ followed by acetylation afforded the desired compound **28** with a maximum yield of only 19%.
- 23) Marvel C. S., Allen R. E., Overberger C. C., *J. Am. Chem. Soc.*, **68**, 1088—1901 (1946).
- 24) Treatment of **11a** with hydrazine-hydrate in DMF at room temperature for 1 d gave phenol (**30**) in 24% yield. Furthermore, treatment of **11a** with 2 N KOH and methanol at room temperature for 21 h gave **31** in 21% yield. The ¹H-NMR spectrum of **31** showed a peak at δ 8.35, which was assigned to the *exo* olefinic proton, thus indicating that **31** has a *Z*-configuration.

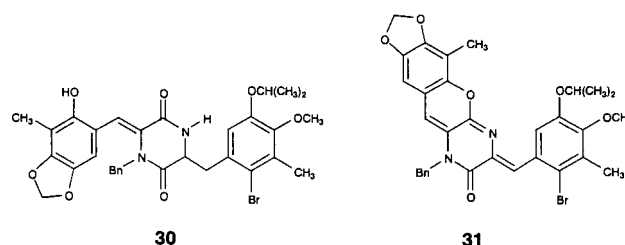


Fig. 2

- 25) Compounds **4b** and **4c** were prepared from **25**,²⁶ which was easily prepared in seven steps from commercially available 2,3-dihydroxy-toluene, in 79% and 82% overall yields, respectively.

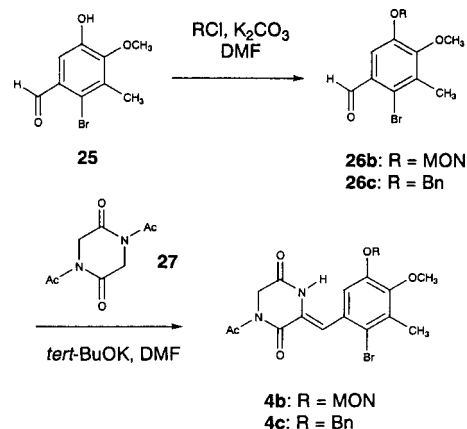


Chart 6

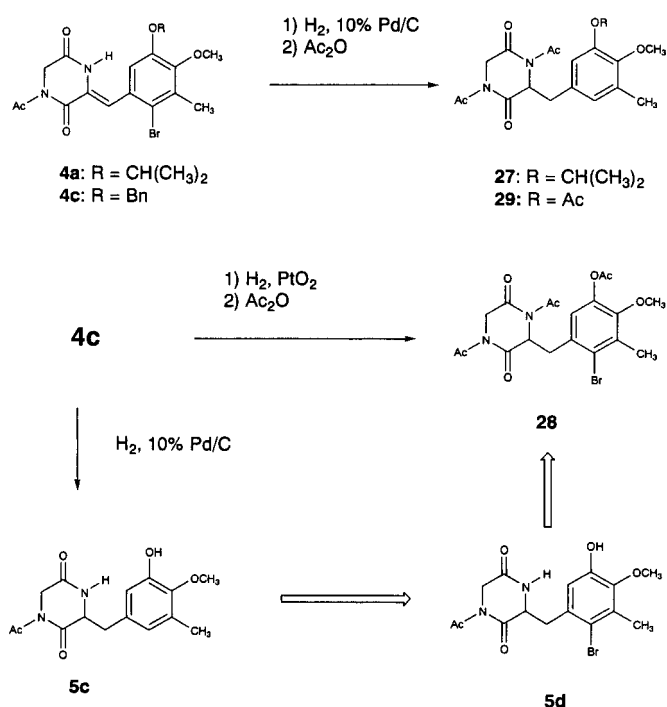


Chart 5

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