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Total Synthesis of an Enantiomeric Pair of FR900482. 1.[1] Synthetic and End-Game Strategies

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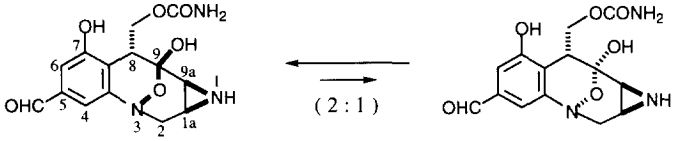
Abstract: *A synthetic strategy for an enantiomeric pair of FR900482 (**1**) was developed, which features a convergent and enantioselective sequence starting from 5-hydroxyisophthalic acid (**16**) and each enantiomer of diethyl tartrate (**17** and ent-**17**). The proposed key intermediate **10** was synthesized from FK973 (**3**), the triacetyl derivative of **1**, and successful reconversion of **10** into **1** was also achieved. These preliminary studies definitely demonstrated that **10** is suitable as a potential advanced key intermediate for **1** and that the crucial final sequence of reactions (**10**→**1**) involving delicate deprotection and oxidation steps can be realized.*

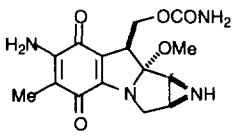
FR900482 (**1**) isolated from the culture broth of *Streptomyces sandaensis* No.6897 at Fujisawa Pharmaceutical Co., Ltd. in Japan in 1987,[2] exhibits exceptionally potent antitumor activity against various types of mammalian solid tumors including LX-1, MX-1, SC-6, and LC-6 carcinomas.[2] This novel antibiotic shows the antitumor activity equal to or superior to that of mitomycin C (MMC) (**2**) and is also found to be effective against MMC- and vincristine-resistant P388 murine leukemia cells.[3] FK973 (**3**), the more stable semisynthetic triacetyl derivative of **1**, has been reported to display *ca.* three times more potent antitumor activity than **2** with a significantly low toxicity.[4] FR66979 (**4**), a dihydro derivative of **1** isolated from the same culture broth, also exhibits antitumor activity but has not been studies in detail as much as **1** and **3**.[5]

The stereostructure of **1** except for its absolute configuration was revealed by extensive spectroscopic analyses and chemical correlation with **3** to have a novel 3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine skeleton; the relative stereochemistry of **3** was established by X-ray diffraction.[6] The absolute configuration of **1** pictured in **Figure 1** was suggested on the basis of the biogenetic studies exploring that the aliphatic portion in

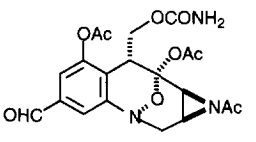
Figure 1. Structures of FR900482 (**1**), Mitomycin C (**2**), FK973 (**3**), and FR66979 (**4**)



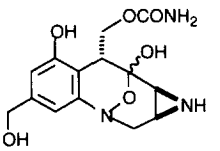
1 : FR900482



2 : Mitomycin C

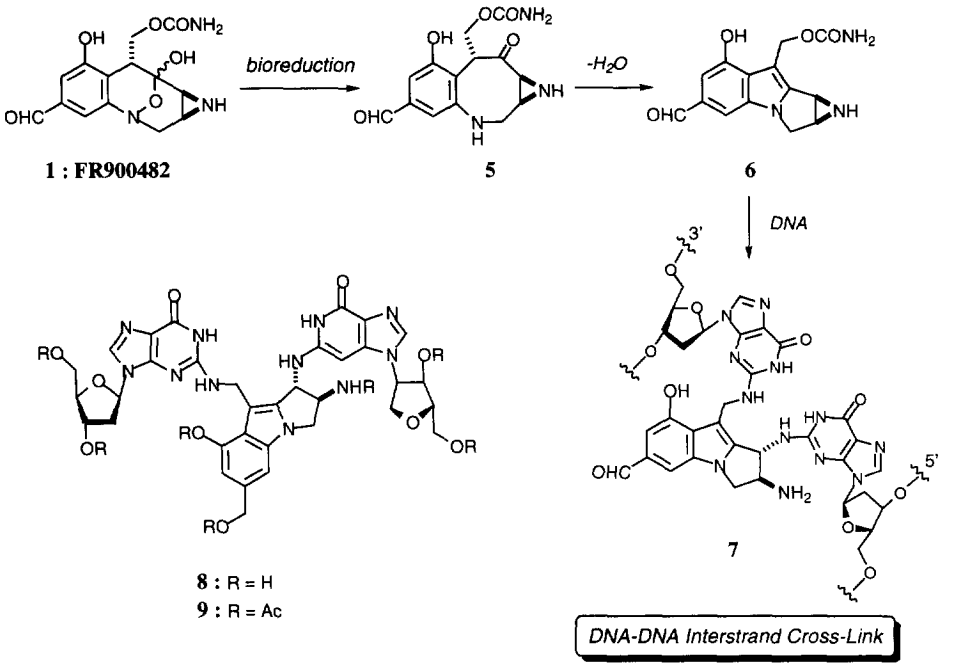


3 : FK973



4 : FR66979

Scheme 1. Proposed Mechanism for the Mode of Action of FR900482 (**1**)



1 is derived from D-glucosamine.[7] This unusual natural product exists as a 2:1 mixture of two tautomers due to its unique hydroxylamine hemiacetal functionality. Similarly to **2**, **1** possesses an aziridine ring and a carbamoyloxymethyl group, but lacks a quinoid nucleus.

It was reported that **1** inhibits DNA synthesis in preference to RNA and protein synthesis in cultured murine L1210 leukemia cells and forms DNA-DNA interstrand cross-links in the cells.[8] The mode of antitumor action for **1** shown in **Scheme 1** which is similar to that of **2**, has hitherto been proposed.[9] Thus, **1** is activated *in vivo* by bioreduction of the hydroxylamine moiety. Subsequent cyclization of the resulting azocinone **5** occurs spontaneously to generate the mitosene-like compound **6**, which undergoes DNA-DNA interstrand cross-linking. Similar formation of DNA-DNA interstrand cross-link is well precedented for the mitosene derivative *in situ* produced from **2**.[10] This speculation is strongly supported by successful isolation of the interstrand cross-linked product **8** from the reaction mixture of **4** and synthetic DNA duplex.[11] Structural elucidation of this adduct has been achieved for the corresponding heptaacetyl derivative **9** by means of extensive spectroscopic studies.[11]

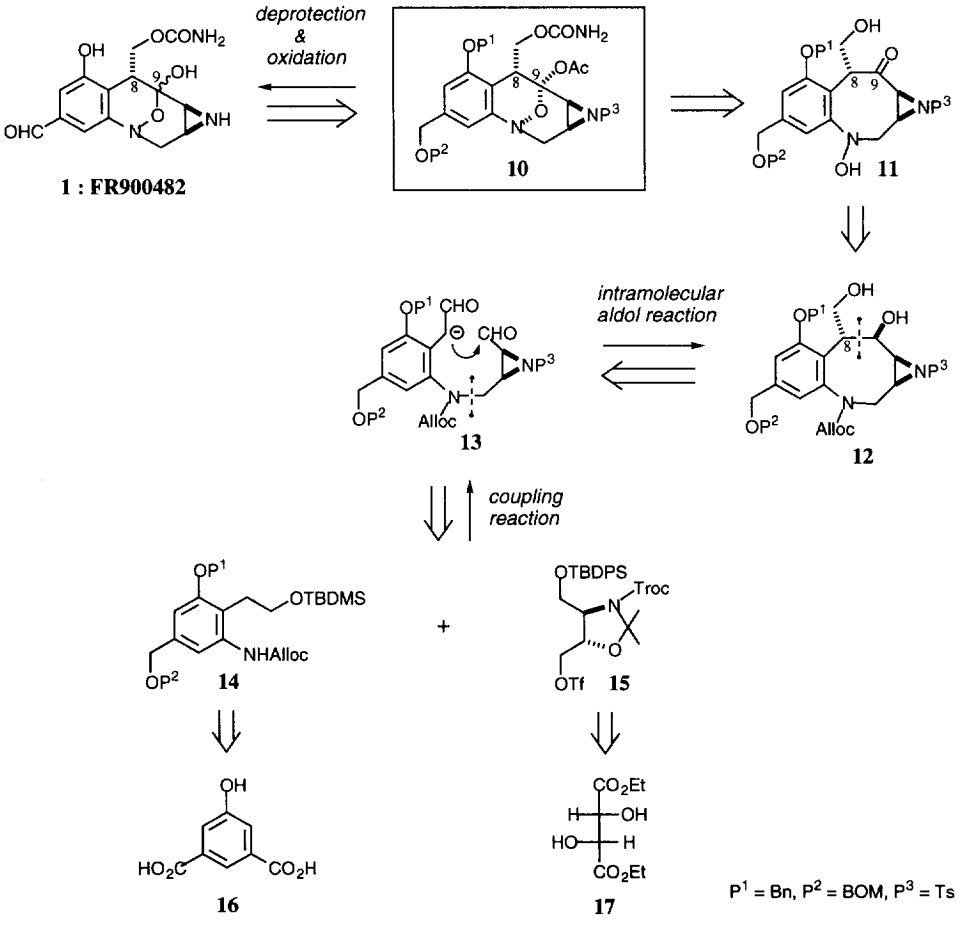
Its remarkable antitumor activity as well as its unique structural features make **1** an exceptionally intriguing and timely target for total synthesis. A number of synthetic approaches toward **1** have been reported to date,[9a,b,12] and the two total syntheses of racemic **1** were accomplished by Fukuyama *et al.*[13] in 1992 and by Schkeryantz and Danishefsky[14] in 1995. We embarked on a project directed at the total synthesis of **1**, its enantiomer *ent*-**1**, and their congeners in enantiomerically pure forms with the aim of exploring the structure-activity relationships. Our earnest endeavors culminated in completing the first total synthesis of natural **1** in 1996.[1] This series of papers concerns with complete details of our enantioselective total synthesis of both

enantiomers of FR900482 (**1** and *ent*-**1**).[15] Successful synthesis of **1** and *ent*-**1** obviously shows efficiency of the explored synthetic scheme. Furthermore, we carried out the *in vitro* cytotoxicity assay of **1**, its synthetic intermediates, and their enantiomers against P388 murine leukemia cells,[15b] disclosing some novel aspects of the structure-activity relationships for **1**.

Synthetic Strategies

The retrosynthetic analysis for FR900482 (**1**) is outlined in **Scheme 2**. The most crucial step in this scheme is envisaged to be the intramolecular aldol reaction of the highly functionalized dialdehyde **13** to construct the eight-membered 1*H*-azirino[2,3-*c*][1]benzazocine system **12** representing the core skeleton of **1** (**13**→**12**). It is worthy to note that this aldol cyclization involves interesting possibility for controlling the stereochemistry at the C-8 position in **1**. When this synthetic strategy was designed, whether the aldol cyclization reaction might afford the desired stereochemistry at the C-8 position was quite ambiguous due to the flexible conformation of the eight-membered transition state. However, since **1** carries the (8*R*)-configuration

Scheme 2. Retrosynthetic Analysis of FR900482 (**1**)



in nature, we expected that the C-8 position can be epimerized to the desired configuration in a later synthetic stage even if the undesired (8*S*)-epimer is obtained as a sole product or as a mixture with the desired (8*R*)-isomer. The cyclization product **12** would be transformed to the advanced key intermediate **10** possessing the requisite carbon framework and functional groups with correct stereochemistries by proper functional group manipulations *via* internal hemiacetalization of the hydroxylamine **11**. The key intermediate **10** may be converted to the target molecule **1** by sequential deprotection and oxidation. The cyclization precursor **13** in turn could be elaborated by coupling of the aromatic segment **14** and the enantiomerically pure aliphatic segment **15** accessible from commercially available 5-hydroxyisophthalic acid (**16**) and (2*R*, 3*R*)-diethyl tartrate (natural diethyl L-tartrate) (**17**), respectively.

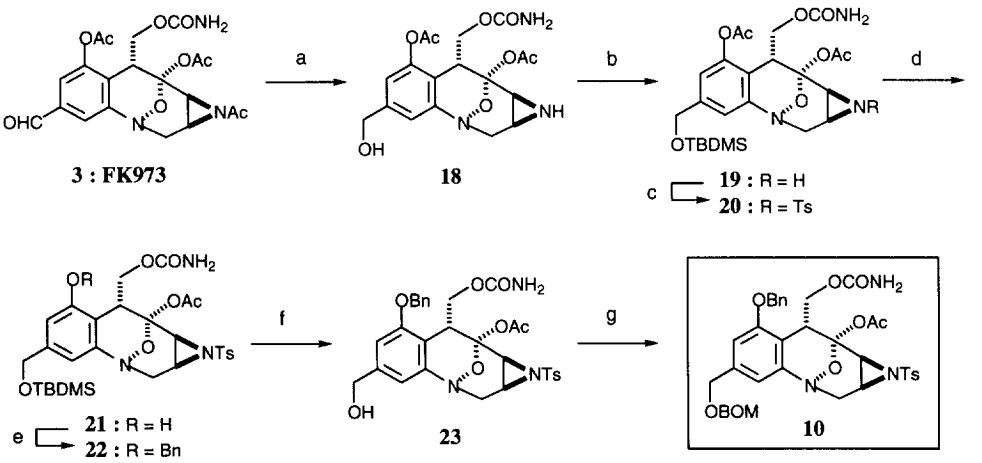
Taking into account the well-known chemical instability of FR900482,[2] benzyl (Bn), benzyloxymethyl (BOM), and *p*-toluenesulfonyl (Ts) groups might be selected for promising protective groups P^1, P^2, and P^3, respectively. This is because these protective groups are expected to be removed under almost neutral conditions under which the delicate core skeleton and functionalities involved in **1** could survive. Prior to execution of the designed synthetic scheme, we decided to examine the feasibility of **10** as an advanced key intermediate for **1**. In the first part of this series of papers, we wish to report full details of the synthesis of the proposed key intermediate **10** starting from FK973 (**3**)[15] (**Scheme 3**) and the successful reconversion of **10** into FR900482 (**1**) (**Scheme 4**), definitely establishing the synthetic and end-game strategies for **1**.

Results and Discussion

1. Synthesis of the Proposed Key Intermediate 10 from FK973 (3)

To explore the feasibility of our planned synthetic strategy, the synthesis of the proposed key intermediate **10** was first investigated starting from FK973 (**3**)[16] provided from Fujisawa Pharmaceutical Co., Ltd. As shown in **Scheme 3**, treatment of **3** with sodium borohydride in a mixture of tetrahydrofuran (THF)-H_2O at 0°C followed by warming to room temperature, effected simultaneous reduction of the formyl group and

Scheme 3. Synthesis of the Proposed Key Intermediate **10** from FK973 (**3**)



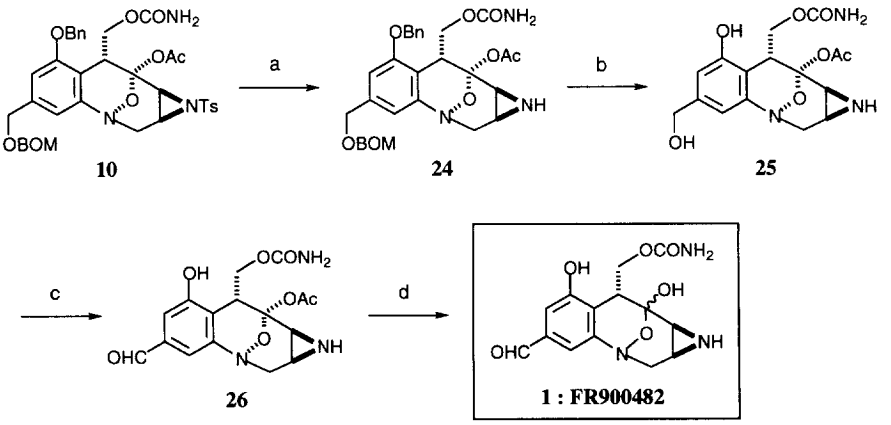
a) $NaBH_4$, THF-H_2O, 0°C→rt, 100% b) TBDMSCl, imidazole, DMF, rt, 91% c) TsCl, Et_3N, MeCN, rt, 91% d) NH_3, THF, rt, 73% e) BnBr, Cs_2CO_3, DMF, rt, 84% f) TBAF, THF, 0°C, 85% g) BOMCl, *i*-Pr_2EtN, CH_2Cl_2-THF, rt, 82%

removal of the acetyl group in the aziridine moiety to provide the alcohol **18** in a quantitative yield. Protection of the hydroxy group in **18** as its *tert*-butyldimethylsilyl (TBDMS) ether followed by tosylation of the aziridine function in the resulting silyl ether **19** afforded the *N*-Ts-aziridine **20** in 83% yield for the two steps. Compound **20** was further converted to the benzyl ether **22** in 61% overall yield by selective cleavage of the aryl acetate with ammonia in THF followed by benzylation of the resulting phenol **21**. Finally, exchange of the silyl protecting group in **22** with a BOM group gave the objective compound **10** in 70% yield for the two steps *via* the benzyl alcohol **23**.

2. Reconversion of the Proposed Key Intermediate 10 to FR900482 (1)

With the proposed key intermediate **10** in hand, we next attempted the reconversion of **10** into FR900482 (**1**) as shown in **Scheme 4**. The crucial removal of the *N*-Ts protecting group in **10** turned out to be effected by employing sodium naphthalenide[17,18] in 1,2-dimethoxyethane (DME) at -70°C, leading to the aziridine **24** in 81% yield. Both the Bn and BOM protecting groups in **24** were simultaneously deleted by catalytic hydrogenolysis over palladium-carbon in ethyl acetate to give the benzyl alcohol **25** in 87% yield. Oxidation of the benzylic hydroxyl group in **25** to the corresponding formyl group was best achieved by employing Swern oxidation at -78°C, providing the aldehyde **26** in 86% yield.[19] Finally, deprotection of the acetyl group in **26** was carried out by careful treatment with ammonia in methanol, producing **1**, mp 174°C (dec) [lit.,[2b] mp 175°C (dec)], $[\alpha]_D^{23}$ +7.8° (*c* 1.08, H_2O) [lit.,[2b] $[\alpha]_D^{23}$ +8.0° (*c* 1.00, H_2O)], in 79% yield. The spectroscopic properties (IR, ^{1}H-NMR, MS) were identical with those of an authentic natural sample of **1** which was kindly provided by Fujisawa Pharmaceutical Co., Ltd.

Scheme 4. Reconversion of the Proposed Key Intermediate **10** to FR900482 (**1**)



a) sodium naphthalenide, DME, -70°C, 81% b) H_2 (1 atm), 10%Pd-C, EtOAc, rt, 87% c) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 86% d) NH_3, MeOH, rt, 79%

Conclusion

We have succeeded in synthesizing the advanced key intermediate **10** starting with FK973 (**3**) and in developing an efficient synthetic pathway to (+)-FR900482 (**1**) from **10**. These preliminary studies definitely demonstrated that the proposed key intermediate **10** is suitable as a potential advanced key intermediate in our

designed scheme for the total synthesis of **1**, and that the crucial final sequence of reactions (**10**→**1**, **Scheme 2**) can be realized. The successful first enantioselective total synthesis of both natural (+)- and unnatural (–)-FR900482 (**1** and *ent*-**1**) was accomplished employing these synthetic and end-game strategies. This is the subject of the two following papers.[15]

Experimental

General. All melting points were determined with a Yamato MP-21 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. ^{1}H-NMR spectra were measured with a Bruker AC-200 (200 MHz) and a Brucker AM-400 (400 MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25) and benzene (δ=7.20) as internal standards. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HRMS) spectra were obtained on a Hitachi M-80A spectrometer. Routine monitoring of reactions was carried out using Merck 60 F254 silica gel, glass-supported TLC plates. Flash column chromatography was performed with indicated solvents on Wakogel C-300. Solvents and commercial reagents were dried and purified before use. Tetrahydrofuran and 1,2-dimethoxymethane were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-7,9-Diacetoxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-methanol (18)

Sodium borohydride (76.5 mg, 2.0 mmol) in water (3 ml) was added dropwise to a stirred solution of FK973 (**3**)[16] (300 mg, 0.67 mmol) in tetrahydrofuran (30 ml) at 0°C. After 20 min, the mixture was allowed to warm up to room temperature and then stirring was continued for 1 h. The reaction was quenched with saturated aqueous ammonium chloride (2 ml), and the resulting mixture was diluted with ethyl acetate (200 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate-methanol, 20:1) to give **18** (273 mg, 100%) as a white solid. Recrystallization from chloroform-methanol afforded an analytical sample of **18** as colorless leaves, mp 129-131°C and $[\alpha]_D^{20}$ +108° (c 0.91, $CHCl_3$). IR (KBr): 3475, 3400, 1750, 1625, 1595, 1440, 1415, 1380, 1340, 1240, 1210, 1165, 1110, 1080, 1040, 980, 925, 880, 850, 805, 760 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.48-0.68 (1H, br s, $W_{1/2}$=53 Hz, NH), 2.22 (3H, s, C9-OAc), 2.37 (3H, s, C7-OAc), 2.30-2.45 (1H, m, C1a-H), 3.09 (1H, br d, J=5.9 Hz, C9a-H), 3.62 (1H, d, J=14.4 Hz, C2-*H*2), 3.82 (1H, t, J=5.5 Hz, C8-H), 3.96 (1H, dd, J=14.4, 2.2 Hz, C2-*H*2), 4.32 (2H, d, J=5.5 Hz, C*H*2OCONH2), 4.57 (2H, br s, $W_{1/2}$=17 Hz, $CONH_2$), 4.65 (2H, s, C*H*2OH), 6.67 (1H, s, C4-H), 6.81 (1H, s, C6-H). EIMS m/z: 407 (M^+), 365 [(M-Ac+H)$^+$], 348 [(M-CONH2+H)$^+$], 287 [(M-AcOH-OCONH2)$^+$]. HRMS calcd for $C_{18}H_{21}N_3O_8$ (M^+): 407.1329. Found: 407.1324.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-7,9-Diacetoxy-5-*tert*-butyldimethylsiloxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (19)

tert-Butyldimethylsilyl chloride (371 mg, 2.5 mmol) was added to a stirred solution of **18** (250 mg, 0.61 mmol) in dry *N*,*N*-dimethylformamide (20 ml) containing imidazole (250 mg, 3.7 mmol) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:2) to give **19** (292 mg, 91%) as a white solid. Recrystallization from ethyl acetate-hexane afforded an analytical sample of **19** as colorless needles, mp 208-209°C and $[\alpha]_D^{20}$ +85.3° (c 1.11, $CHCl_3$). IR (KBr): 3500, 3400, 3340, 2970, 2900, 2870, 1760, 1630, 1600, 1590, 1460, 1440, 1400, 1380, 1340, 1260, 1240, 1200, 1160, 1110, 1080, 1020, 980, 930, 880, 840, 780 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.07 (3H, s, Si-Me), 0.08 (3H, s, Si-Me), 0.55 (1H, br t, J=8.4 Hz, NH), 0.92 (9H, s, Si-*tert*-Bu), 2.22 (3H, s, C9-OAc), 2.36 (3H, s, C7-OAc), 2.31-2.38 (1H, m, C1a-H), 3.09 (1H, br t, J=7.9 Hz, C9a-H), 3.59 (1H, d, J=14.4 Hz, C2-*H*2), 3.81 (1H, t, J=5.6 Hz, C8-H), 3.96 (1H, d, J=14.4, 2.2 Hz, C2-*H*2), 4.32 (2H, d, J=5.5 Hz, C*H*2OCONH2), 4.56 (2H, br s, $W_{1/2}$=16 Hz, $CONH_2$), 4.67 (2H, s, C*H*2OTBDMS), 6.63 (1H, s, C4-H), 6.75 (1H, s, C6-H). EIMS m/z: 521 (M^+), 506 [(M-Me)$^+$], 479 [(M-Ac+H)$^+$], 462 [(M-OAc)$^+$]. HRMS calcd for $C_{24}H_{35}N_3O_8Si$ (M^+): 521.2195. Found: 521.2171. *Anal.* Calcd for $C_{24}H_{35}N_3O_8Si$: C, 55.26; H, 6.76; N, 8.06%. Found: C, 55.44; H, 6.83; N, 8.04%.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-7,9-Diacetoxy-5-*tert*-butyldimethylsiloxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (20)

p-Toluenesulfonyl chloride (91.2 mg, 4.8 mmol) was added to a stirred solution of **19** (250 mg, 0.48 mmol) in dry acetonitrile (30 ml) containing triethylamine (2.00 ml, 14 mmol) at room temperature. After 5 h, the mixture was diluted with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **20** (295 mg, 91%) as a colorless amorphous powder. $[\alpha]_D^{20}$ +73.9° (c 1.13, $CHCl_3$). IR (neat): 3500, 3400, 2970, 2950,

2900, 2870, 1775, 1760, 1740, 1630, 1605, 1470, 1440, 1410, 1380, 1200, 1170, 1110, 1050, 1020, 1000, 900, 930, 840, 820, 780, 690, 580, 560 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.10 (3H, s, Si-Me), 0.11 (3H, s, Si-Me), 0.95 (9H, s, Si-*tert*-Bu), 2.21 (3H, s, C9-OAc), 2.27 (3H, s, C7-OAc), 2.42 (3H, s, Ts-*Me*), 3.10 (1H, dd, J=7.4, 1.9 Hz, C1a-H), 3.42 (1H, dd, J=7.5, 3.6 Hz, C8-H), 3.48 (1H, d, J=14.9 Hz, C2-*H*2), 3.77 (1H, d, J=7.4 Hz, C9a-H), 3.98 (1H, dd, J=14.4, 1.9 Hz, C2-*H*2), 4.19 (1H, dd, J=11.6, 3.6 Hz, C*H*2OCONH2), 4.35 (1H, dd, J=11.6, 7.5 Hz, C*H*2OCONH2), 4.54 (2H, br s, W1/2=20 Hz, CONH2), 4.67 (2H, s, C*H*2OTBDMS), 6.51 (1H, d, J=1.0 Hz, C4-H), 6.75 (1H, d, J=1.0 Hz, C6-H), 7.22 (2H, d, J=8.1 Hz, Ts-*H* x 2), 7.40 (2H, d, J=8.1 Hz, Ts-*H* x 2). EIMS m/z: 675 (M^+), 633 [(M-Ac+H)$^+$], 618 [(M-*tert*-Bu)$^+$]. HRMS calcd for $C_{31}H_{41}N_3O_{10}SSi$ (M^+): 675.2283. Found: 675.2273.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-5-*tert*-butyldimethylsiloxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-7-ol (21)

Gaseous ammonia was induced to a stirred solution of **20** (200 mg, 0.30 mmol) in tetrahydrofuran (30 ml) for 5 min at 0°C, and stirring was continued for 24 h at room temperature. Concentration of the mixture *in vacuo* gave a residue, which was purified by column chromatography (chloroform-methanol, 20:1) to give **21** (137 mg, 73%) as a colorless amorphous powder. $[\alpha]_D^{20}$ +75.5° (c 1.13, $CHCl_3$). IR (neat): 3500, 3380, 2970, 2950, 2900, 2870, 1760, 1715, 1630, 1600, 1500, 1470, 1440, 1420, 1360, 1335, 1260, 1235, 1165, 1110, 990, 900, 840, 780 cm^{-1}. ^{1}H-NMR (400 MHz, C_6D_6): δ 0.09 (6H, s, Si(Me)2), 1.01 (9H, s, Si-*tert*-Bu), 1.56 (3H, s, C9-OAc), 2.11 (3H, s, Ts-*Me*), 2.80 (1H, dd, J=7.2, 2.0 Hz, C2-*H*2), 3.30 (1H, d, J=14.9 Hz, C9a-H), 3.33 (1H, t, J=5.1 Hz, C8-H), 3.52 (1H, dd, J=14.9, 2.0 Hz, C1a-H), 3.58 (2H, br s, W1/2=8 Hz, CONH2), 3.84 (1H, d, J=7.2 Hz, C2-*H*2), 3.91 (2H, d, J=5.1 Hz, C*H*2OCONH2), 4.57 (2H, s, C*H*2OTBDMS), 6.36 (1H, d, J=1.2 Hz, C4-H), 6.94 (1H, d, J=1.2 Hz, C6-H), 7.05 (2H, d, J=8.1 Hz, Ts-*H* x 2), 7.73 (2H, d, J=8.1 Hz, Ts-*H* x 2), 8.53 (1H, s, C7-OH). EIMS m/z: 633 (M^+), 590 [(M-CONH2+H)$^+$], 576 [(M-*tert*-Bu)$^+$], 534 [(M-*tert*-Bu-Ac+H)$^+$], 533 [(M-*tert*-Bu-CONH2+H)$^+$], 473 [(M-*tert*-Bu-Ac+H-CONH2+H-H2O)$^+$]. HRMS calcd for $C_{29}H_{39}N_3O_9SSi$ (M^+): 633.2178. Found: 633.2167.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-5-*tert*-butyldimethylsiloxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (22)

Benzyl bromide (0.225 ml, 1.9 mmol) was added to a stirred solution of **21** (120 mg, 0.19 mmol) in dry *N*,*N*-dimethylformamide (30 ml) containing cesium carbonate (124 mg, 0.38 mmol) at room temperature. After 30 min, the mixture was diluted with ethyl acetate (200 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **22** (115 mg, 84%) as a white solid. Recrystallization from ether-hexane afforded an analytical sample of **22** as colorless needles, mp 185-186°C and $[\alpha]_D^{20}$ +68.0° (c 1.02, $CHCl_3$). IR (KBr): 3440, 3350, 3300, 2960, 2945, 2870, 1750, 1730, 1620, 1600, 1500, 1470, 1440, 1420, 1370, 1360, 1340, 1280, 1260, 1240, 1170, 1130, 1090, 1040, 990, 970, 900, 860, 840, 820, 780, 740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.11 (3H, s, Si-Me), 0.12 (3H, s, Si-Me), 0.97 (9H, s, Si-*tert*-Bu), 2.13 (3H, s, Ts-*Me*), 2.19 (3H, s, C9-OAc), 3.15 (1H, dd, J=7.4, 1.9 Hz, C1a-H), 3.36 (1H, dd, J=7.0, 1.6 Hz, C8-H), 3.57 (1H, d, J=14.9 Hz, C2-*H*2), 3.78 (1H, d, J=7.4 Hz, C9a-H), 3.99 (1H, d, J=7.2 Hz, C2-*H*2), 4.26 (1H, dd, J=11.3, 1.6 Hz, C*H*2OCONH2), 4.51 (1H, dd, J=11.3, 7.0 Hz, C*H*2OCONH2), 4.51 (2H, br s, W1/2=14 Hz, CONH2), 4.68 (2H, s, C*H*2OTBDMS), 5.02 (1H, d, J=12.1 Hz, OC*H*2Ph), 5.08 (1H, d, J=12.1 Hz, OC*H*2Ph), 6.30 (1H, d, J=0.8 Hz, C4-H), 6.66 (1H, d, J=1.2 Hz, C6-H), 7.07 (2H, d, J=8.4 Hz, Ts-*H* x 2), 7.31 (2H, d, J=8.4 Hz, Ts-*H* x 2), 7.26-7.38 (5H, m, Bn). EIMS m/z: 723 (M^+), 681 [(M-Ac+H)$^+$], 664 [(M-OAc)$^+$], 620 [(M-OAc-CONH2)$^+$]. HRMS calcd for $C_{36}H_{45}N_3O_9SSi$ (M^+): 723.2648. Found: 723.2640.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-methanol (23)

Tetrabutylammonium fluoride in tetrahydrofuran (1.0 M solution, 0.20 ml, 0.20 mmol) was added dropwise to a stirred solution of **22** (95.0 mg, 0.13 mmol) in tetrahydrofuran (25 ml) at 0°C. After 30 min, the mixture was diluted with ethyl acetate (180 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:3) to give **23** (68.0 mg, 85%) as a white solid. Recrystallization from dichloromethane-hexane afforded an analytical sample of **23** as colorless needles, mp 211-213°C and $[\alpha]_D^{20}$ +85.4° (c 0.34, MeOH). IR (KBr): 3440, 1755, 1730, 1700, 1620, 1600, 1500, 1440, 1420, 1360, 1330, 1270, 1240, 1160, 1125, 1090, 1040, 990, 980, 880, 840, 820 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.71 (1H, t, J=5.9 Hz, OH), 2.11 (3H, s, Ts-*Me*), 2.19 (3H, s, C9-OAc), 3.16 (1H, dd, J=7.4, 2.0 Hz, C1a-H), 3.33 (1H, dd, J=6.8, 1.6 Hz, C8-H), 3.61 (1H, d, J=14.8 Hz, C2-*H*2), 3.76 (1H, d, J=7.4 Hz, C9a-H), 4.00 (1H, dd, J=14.8, 2.0 Hz, C2-*H*2), 4.25 (1H, dd, J=11.3, 1.6 Hz, C*H*2OCONH2), 4.51 (1H, dd, J=11.3, 6.8 Hz, C*H*2OCONH2), 4.51 (2H, br s, W1/2=22 Hz, CONH2), 4.65 (2H, d, J=5.9 Hz, C*H*2OTBDMS), 5.05 (1H, d, J=11.9 Hz, OC*H*2Ph), 5.10 (1H, d, J=11.9 Hz, OC*H*2Ph), 6.36 (1H, s, C4-H), 6.69 (1H, s, C6-H), 7.08 (2H, d, J=8.2 Hz, Ts-*H* x 2), 7.34 (2H, d, J=8.2 Hz, Ts-*H* x 2), 7.26-7.38 (5H, m, Bn). EIMS m/z: 609 (M^+), 567 [(M-Ac+H)$^+$], 566 [(M-CONH2+H)$^+$], 506 [(M-OAc-CONH2)$^+$]. HRMS calcd for $C_{30}H_{31}N_3O_9S$ (M^+): 609.1782. Found: 609.1762.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (10)

Benzyl chloromethyl ether (0.140 ml, 1.0 mmol) was added to a stirred solution of **23** (61 mg, 0.10 mmol) in dry tetrahydrofuran-dichloromethane (10:1) (6 ml) containing *N,N*-diisopropylethylamine (0.278 ml, 1.6 mmol) at room temperature under argon. After 15 h, the mixture was diluted with ethyl acetate (150 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **10** (59.8 mg, 82%) as a white solid. Recrystallization from ethyl acetate-hexane afforded an analytical sample of **10** as colorless needles, mp 130-132°C and $[\alpha]_D^{20}$ +68.1° (c 0.76, $CHCl_3$). IR (neat): 3500, 3400, 3220, 3070, 3050, 2940, 1730, 1620, 1600, 1500, 1460, 1440, 1410, 1380, 1330, 1280, 1220, 1170, 1130, 1100, 1050, 1000, 900, 820, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.10 (3H, s, Ts-*Me*), 2.19 (3H, s, C9-OAc), 3.15 (1H, dd, J=7.4, 2.0 Hz, C1a-H), 3.35 (1H, dd, J=6.9, 1.6 Hz, C8-H), 3.58 (1H, d, J=14.8 Hz, C2-*H*2), 3.77 (1H, d, J=7.4 Hz, C9a-H), 3.98 (1H, dd, J=14.9, 2.0 Hz, C2-*H*2), 4.25 (1H, dd, J=11.3, 1.6 Hz, C*H*2OCONH2), 4.51 (1H, dd, J=11.3, 6.9 Hz, C*H*2OCONH2), 4.51 (2H, br s, W1/2=16 Hz, CONH2), 4.59 (2H, s, C*H*2OBOM), 4.67 (2H, s, PhC*H*2OCH2O), 4.83 (2H, s, PhCH2OC*H*2O), 5.02 (1H, d, J=11.9 Hz, OC*H*2Ph), 5.08 (1H, d, J=11.9 Hz, OC*H*2Ph), 6.35 (1H, d, J=0.8 Hz, C4-H), 6.64 (1H, d, J=0.8 Hz, C6-H), 7.06 (2H, d, J=8.0 Hz, Ts-*H* x 2), 7.26-7.38 (12H, m, Bn, BOM and Ts-*H* x 2). EIMS m/z: 729 (M^+), 687 [(M-Ac+H)$^+$], 686 [(M-CONH2+H)$^+$], 626 [(M-OAc-CONH2)$^+$]. HRMS calcd for $C_{38}H_{39}N_3O_{10}S$ (M^+): 729.2358. Found: 729.2364.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (24)

Sodium naphthalenide in 1,2-dimethoxyethane (0.2 M solution, 1.30 ml, 0.26 mmol) was added dropwise to a stirred solution of **10** (62.5 mg, 86 μmol) in dry 1,2-dimethoxyethane (30 ml) at -70°C. After 15 min, saturated aqueous sodium hydrogen carbonate (10 ml) was added, and the mixture was extracted with ethyl acetate (3 x 60 ml). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **24** (39.9 mg, 81%) as a white powder. $[\alpha]_D^{20}$ +89.3° (c 0.62, $CHCl_3$). IR (KBr): 3400, 2940, 1730, 1620, 1590, 1500, 1460, 1440, 1400, 1380, 1340, 1280, 1240, 1160, 1120, 1080, 1040, 990, 840, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.49 (1H, br s, W1/2=26 Hz, NH), 2.20 (3H, s, C9-OAc), 2.32 (1H, br d, J=6.0 Hz, C1a-H), 3.13 (1H, br s, W1/2=26 Hz, C9a-H), 3.60 (1H, d, J=14.1 Hz, C2-*H*2), 3.86 (1H, dd, J=7.0, 1.6 Hz, C8-H), 3.94 (1H, d, J=14.1 Hz, C2-*H*2), 4.36 (1H, dd, J=11.2, 1.6 Hz, C*H*2OCONH2), 4.52 (1H, dd, J=11.2, 7.0 Hz, C*H*2OCONH2), 4.54 (2H, br s, W1/2=22 Hz, CONH2), 4.58 (2H, s, C*H*2OBOM), 4.63 (2H, s, PhC*H*2OCH2O), 4.82 (2H, s, PhCH2OC*H*2O), 5.09 (2H, s, OC*H*2Ph), 6.41 (1H, s, C4-H), 6.64 (1H, s, C6-H), 7.29-7.44 (10H, m, Bn and BOM). EIMS m/z: 575 (M^+), 516 [(M-OAc)$^+$], 455 [(M-OAc-OCONH2-H)$^+$]. HRMS calcd for $C_{31}H_{33}N_3O_8S$ (M^+): 575.2669. Found: 575.2291.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-7-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-methanol (25)

A mixture of **24** (35.8 mg, 62 μmol) and 10% palladium on carbon (28 mg) in ethyl acetate (7 ml) was stirred for 5 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (chloroform-methanol, 10:1) to give **25** (19.8 mg, 87%) as a white solid. Recrystallization from ethyl acetate-hexane afforded an analytical sample of **25** as colorless needles, mp 130-132°C and $[\alpha]_D^{20}$ +81.3° (c 0.13, MeOH). IR (KBr): 3450, 2950, 1710, 1630, 1600, 1460, 1440, 1420, 1380, 1350, 1240, 1175, 1110, 1080, 1040, 980, 920, 790 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.57 (1H, br t, J=8.4 Hz, NH), 2.24 (3H, s, C9-OAc), 2.30 (1H, br t, J=8.4 Hz, C1a-H), 3.13 (1H, br t, J=8.4 Hz, C9a-H), 3.53 (1H, br s, W1/2=160 Hz, OH), 3.65 (1H, d, J=14.5 Hz, C2-*H*2), 3.95 (1H, d, J=14.5 Hz, C2-*H*2), 4.12 (1H, dd, J=6.3, 3.7 Hz, C8-H), 4.22 (1H, d, J=3.7 Hz, C*H*2OCONH2), 4.23 (1H, d, J=3.7 Hz, C*H*2OCONH2), 4.59 (2H, s, C*H*2OH), 4.77 (2H, br s, W1/2=10.8 Hz, CONH2), 6.34 (1H, s, C4-H), 6.70 (1H, s, C6-H), 8.65 (1H, s, C7-OH). EIMS m/z: 365 (M^+), 323 [(M-Ac+H)$^+$], 322 [(M-CONH2+H)$^+$], 306 [(M-OAc)$^+$]. HRMS calcd for $C_{16}H_{19}N_3O_7$ (M^+): 365.1224. Found: 365.1226.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-7-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxaldehyde (26)

Dimethyl sulfoxide (32 μl, 0.46 mmol) in dry dichloromethane (0.2 ml) was added dropwise to a stirred solution of oxalyl chloride (20 μl, 0.23 mmol) in dry dichloromethane (0.8 ml) at -78°C under argon. After 10 min, a solution of **25** (18.5 mg, 51 μmol) in dry dichloromethane-dimethyl sulfoxide (4:1) (0.5 ml) was added slowly, and stirring was continued for 15 min at -78°C. After addition of triethylamine (92 μl, 0.66 mmol), the mixture was gradually warmed up to -20°C and further stirred for 20 min. The reaction was quenched with water (0.5 ml), and the resulting mixture was diluted with ethyl acetate (100 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (chloroform-methanol, 10:1) to give **26** (15.8 mg, 86%) as a white solid. Recrystallization from ethyl acetate-hexane afforded an analytical sample of **26** as colorless needles, mp 230°C (dec) and $[\alpha]_D^{20}$ +129° (c 0.40, acetone). IR (KBr): 3460, 2970, 2945, 2870, 1740, 1720, 1710, 1710, 1680, 1660, 1630, 1620, 1600, 1465, 1440, 1425, 1380, 1350, 1280, 1240, 1170, 1150, 1120, 1080, 1000 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.56 (1H, br t, J=10.2 Hz, NH), 2.25 (3H, s, C9-OAc), 2.28-2.38 (1H, m, C1a-H), 3.13 (1H, dd, J=10.2, 6.7 Hz, C9a-H), 3.69 (1H, d, J=14.4 Hz, C2-*H*2), 3.75 (1H, t, J=6.7 Hz, C8-H), 3.99 (1H, d, J=14.4 Hz, C2-*H*2), 4.20-4.27 (2H, m, C*H*2OCONH2), 4.81 (2H, br s, W1/2=6.0 Hz, CONH2), 6.81 (1H, d, J=1.4 Hz, C4-

H), 7.13 (1H, s, C6-H), 9.05 (1H, br s, $W_{1/2}$=13.8 Hz, C7-OH), 9.86 (1H, s, C5-CHO). EIMS m/z: 363 (M^+), 321 [(M-Ac+H)$^+$], 320 [(M-$CONH_2$+H)$^+$], 304 [(M-OAc)$^+$]. HRMS calcd for $C_{16}H_{17}N_3O_7$ (M^+): 363.1067. Found: 363.1076.

Mixture of (1a*S*,3*R*,8*R*,9*R*,9a*S*)- and (1a*S*,3*S*,8*R*,9*S*,9a*S*)-8-carbamoyloxymethyl-7,9-dihydroxy-1,1a,2,8,9,9a-hexahydro-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxaldehyde (FR900482) (1)

Gaseous ammonia was induced to a stirred solution of **26** (14.3 mg, 39 μmol) in methanol (8 ml) for 5 min at 0°C, and the mixture was allowed to warm up to room temperature. After 3 h, saturated aqueous ammonium chloride (0.5 ml) was added, and the resulting mixture was concentrated *in vacuo* at 0°C. The residue was purified by column chromatography (chloroform-methanol, 10:1) to give **1** (10.1 mg, 79%) as a white solid. Recrystallization from ethyl acetate-hexane afforded an analytical sample of **1** as colorless needles. mp 174 °C (dec) [lit.,[2b] mp 175°C (dec)] and $[\alpha]_D^{23}$ +7.8° (c 1.08, H_2O) [lit.,[2b] $[\alpha]_D^{23}$ +8.0° (c 1.00, H_2O)]. IR (KBr): 3600-3000, 1690, 1580, 1430, 1410, 1390, 1340, 1270, 1140, 1110, 1080, 980, 850, 810, 780, 730, 650 cm^{-1}. ^{1}H-NMR (400 MHz, D_2O): δ 2.38 (0.3H, dd, J=6.7, 2.0 Hz, C1a-H), 2.51-2.60 (0.7H, m, C1a-H), 2.60 (0.7H, d, J=6.7 Hz, C9a-H), 2.77 (0.3H, d, J=6.7 Hz, C9a-H), 3.30 (0.3H, dd, J=5.5, 1.8 Hz, C8-H), 3.40 (0.7H, d, J=5.5 Hz, C8-H), 3.50 (0.3H, d, J=14.7 Hz, C2-*H*2), 3.62-3.68 (1.4H, m, C2-*H*2), 3.73 (0.3H, dd, J=14.7 Hz, C2-*H*2), 4.32 (0.3H, dd, J=14.7, 2.0 Hz, C*H*2OCONH2), 4.53 (0.7H, dd, J=11.4. 1.0 Hz, C*H*2OCONH2), 4.55 (0.3H, dd, J=11.4. 5.5 Hz, C*H*2OCONH2), 5.03 (0.7H, dd, J=11.4. 5.5 Hz, C*H*2OCONH2), 6.84 (0.3H, d, J=1.2 Hz, C4-H), 6.94 (0.7H, d, J=1.2 Hz, C4-H), 6.96 (0.7H, d, J=1.2 Hz, C6-H), 7.00 (0.3H, d, J=1.2 Hz, C6-H), 9.63 (0.3H, s, C5-CHO), 9.65 (0.7H, s, C5-CHO). Based on the intensity of these signals, the ratio of the two tautomers could be calculated as *ca.* 2:1. EIMS m/z: 321 (M^+), 278 [(M-$CONH_2$+H)$^+$], 260 [(M-$CONH_2$+H-H_2O)$^+$], 242 [(M-$CONH_2$+H-2H_2O)$^+$], 213 [(M-$CONH_2$+H-H_2O-CHO)$^+$]. These spectra were identical with those of an authentic sample of (+)-FR900482 (**1**) kindly provided by Dr. H. Tanaka, Fujisawa Pharmaceutical Co., Ltd.

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