SYNTHETIC APPROACHES TOWARD MITOMYCINS : SYNTHESIS OF THE DECARBAMOYLOXYMITOMYCIN DERIVATIVE†

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Abstract-----The benzazocine derivative (**2**) obtained by the criss-cross annulation reaction has been successfully converted to the decarbamoyloxy-mitomycin derivative (**1**) in a highly regio and stereocontrolled manner.

Mitomycins[1] are an important class of antitumour antibiotics among which mitomycin C[2] has been used in the treatment of various neoplastic diseases.[3] Although numerous synthetic studies[4] toward *mitomycins* have been carried out since its structural elucidation,[5] only Kishi,[6] Fukuyama,[7] and Danishefsky,[8] have achieved the total synthesis of mitomycins. In 1990 we reported the synthesis of the decarbamoyloxy-

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†Dedicated to Dr. Arnold Brossi, Scientist Emeritus NIH, Visiting Research Professor, Department of Chemistry, Georgetown University, Washington, D. C., on the occasion of his 70th birthday.

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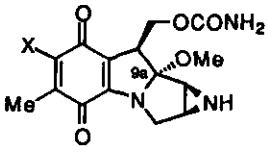
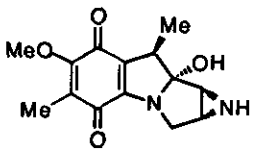
mitomycin derivative (**1**) starting with the benzazocine derivative (**2**),[9] which had been efficiently synthesized in these laboratories with the criss-cross annulation reaction as a key step.[10] Herein we wish to report a detailed account of the synthesis of **1**.



mitomycin A : X = OMe
mitomycin C : X = NH_2



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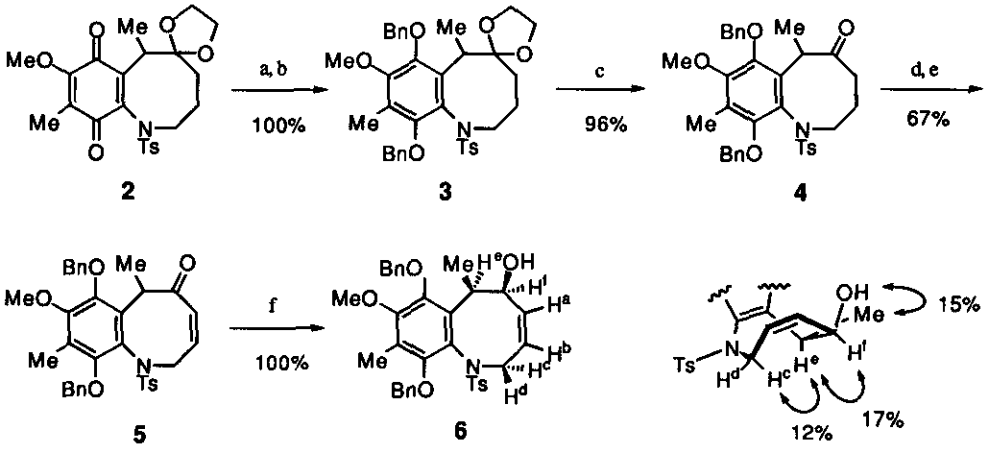
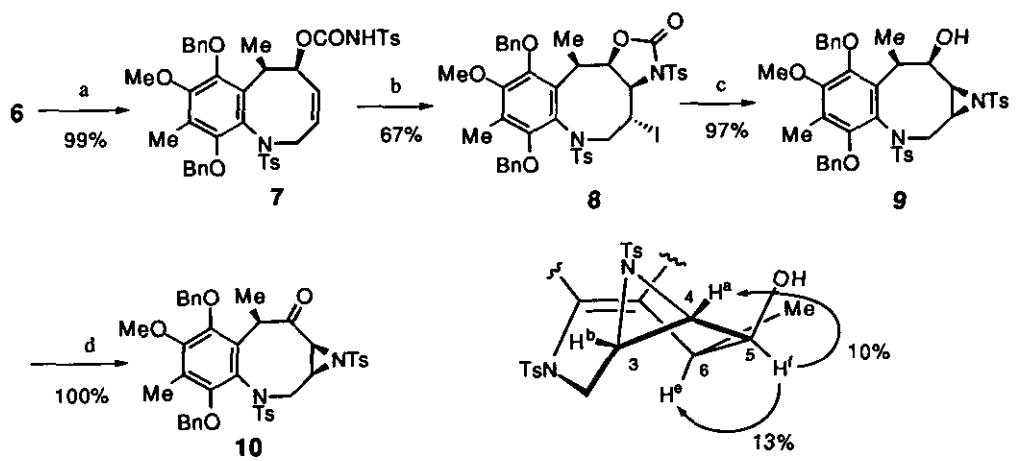
The benzazocine derivative (**2**) was reduced by $Na_2S_2O_4$ and then protected as a benzyl ether to give **3** (100% yield). Cleavage of a ketal group by treatment with conc. HCl afforded the ketone (**4**) (96%). Next, in order to introduce an aziridine group to the eight-membered ring, **4** was converted to the allylic alcohol (**6**). Namely, exposure of **4** to phenylselenenyl chloride under the acidic conditions followed by oxidation with $NaIO_4$ provided the enone (**5**), which was reduced by diisobutylaluminum hydride (DIBAL) to give the allylic alcohol (**6**) in a highly regio- and stereocontrolled manner (67%). The stereochemistry of **6** was unequivocally determined from the ^1H nmr spectrum. The coupling constant between H^e and H^f was 4.4 Hz and J_{af} was 2.0 Hz. Furthermore, nuclear Overhauser enhancements (NOEs) were observed as shown in Scheme 1, suggesting that **6** has the twist-boat conformation. It appears that the enone (**5**) having the twist-boat conformation underwent stereocontrolled reduction from the α-face.



a) $Na_2S_2O_4$, H_2O, $^nBu_4NHSO_4$, CH_2Cl_2, room temperature; b) BnBr, K_2CO_3, 18-crown-6, THF, reflux, 19 h; c) conc. HCl, THF, 0 °C, 4.5 h; d) PhSeCl, 10% HCl, AcOEt, room temperature, 18 h; e) $NaIO_4$, H_2O, THF, room temperature, 16 h; f) DIBAL, THF, -70 °C, 30 min.

Scheme 1.

Many attempts to introduce an aziridine group using intermolecular reactions such as epoxidation followed by treatment with NaN_3 were unfruitful. Therefore, we undertook the aziridine formation by an intramolecular reaction. The allylic alcohol (**6**) was converted to the allylic carbamate (**7**), which was followed by exposure to I_2 to give the cyclic carbamate (**8**) (67%).[11] Treatment of **8** with K_2CO_3 in MeOH-CH_2Cl_2 provided the aziridine (**9**) in 97% yield. Irradiation of H^f showed an enhancement of H^a (10%) and H^e (13%), thereby confirming the stereochemistry of **9**. Furthermore, the stereochemistry of **9** was unequivocally determined by the X-rary analysis of **11** derived from **9**. Oxidation of **9** with pyridinium chlorochromate (PCC) gave **10** in 100% yield, whose ir spectrum had an absorption at 1700 cm^{-1}, indicating the presence of a transannular effect (see Scheme 2).



a) Ts-N=C=O, THF, room temperature, 5 min; b) I_2, K_2CO_3, THF, room temperature, 4.5 h; c) K_2CO_3, MeOH-CH_2Cl_2 (1:2), 35-40 °C, 3 h; d) PCC, MS 4A, CH_2Cl_2, room temperature, 4 h.

Scheme 2.

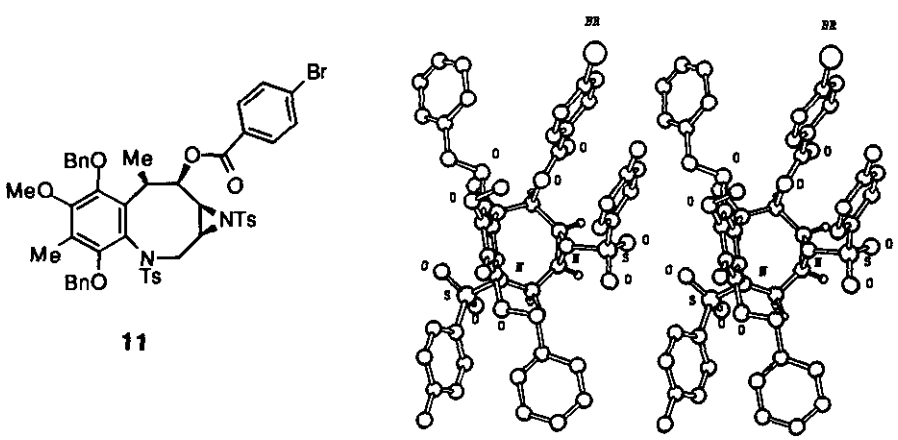
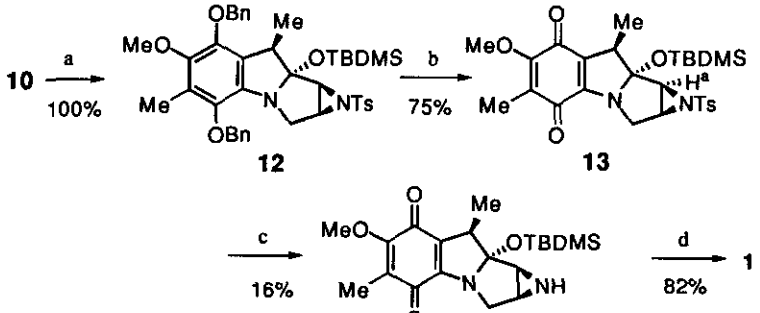


Figure 1. X-ray Structure of 11

With the benzazocine derivative (**10**) having an aziridine group in hand, the construction of the mitomycin skeleton with oxygen functionality at C-9a was the next task. First **10** was treated with methyl trifluoromethanesulfonate in CH_2Cl_2, but many products were formed. However, exposure of **10** to trimethylsilyl trifluoromethanesulfonate and triethylamine in CH_2Cl_2 effected the transannular cyclization; unfortunately, the cyclized product was decomposed during the isolation process. Finally, we have found that **10** undergoes transannular cyclization [*t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and triethylamine in CH_2Cl_2] to give **12** (100%) in a highly stereoselective manner. It was found that the presence of benzyl ethers was crucial for the transannular cyclization. Use of a *t*-butyldimethylsilyl ether instead of a benzyl ether (C=O stretching frequency, 1730 cm^{-1}) afforded none of the cyclized product.

Hydrogenolysis of **12** (1 atm H_2, NEt_3, 10% Pd-C/AcOEt) followed by treatment with oxygen afforded the benzoquinone (**13**) (75%). The stereochemistry of **13** was unequivocally determined form the ^1H nmr spectrum (COSY and NOE). Namely, irradiation of the methyl group at C-9 showed an enhancement of H^a. Cleavage of the toluenesulphonyl group was achieved by treatment with Na-naphthalene to give **14** (16%).[12] Finally, the decarbamoyloxymitomycin derivative (**1**) was obtained in 82% yield on treatment with tetrabutylammonium fluoride (TBAF) in THF containing acetic acid.[13]



a) TBDMSOTf, NEt_3, CH_2Cl_2, -78 °C → room temperature; b) 10% Pd-C, H_2, NEt_3, AcOEt, 10 min; then O_2, 10 min; c) Na-naphthalene, THF, -98 °C; then O_2; d) TBAF, AcOH, THF, room temperature, 90 h.

Scheme 3.

In conclusion, we have achieved the synthesis of the decarbamoyloxymiyomycin derivative (**1**) *via* the benzazocine derivative (**2**) as a key intermediate, demonstrating that (**2**) is a reasonable synthetic intermediate for the synthesis of mitomycins and their analogues. This synthesis is the first example of the introduction of an aziridine group onto a benzazocine derivative and the novel *t*-butyldimethylsilyl trifluoromethanesulfonate mediated transannular cyclization.

EXPERIMENTAL

Ir spectra were measured on a JASCO A-300 infrared spectrophotometer. ^{1}H Nmr spectra were recorded with a JEOL JNM-FX-100 or JEOL JNM-GX 270 NMR spectrometer with tetramethylsilane as an internal standard. Low-resolution ms spectra and high resolution ms spectra were obtained from a JEOL JMS-DX 303 mass spectrometer. Optical rotation was measured on a JASCO DIP-370 digital polarimeter. Melting points were determined using an Ishii melting point apparatus and are uncorrected.

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

7, 10-Dibenzyloxy-5, 5-ethylenedioxy-8-methoxy-6, 9-dimethyl-1-*p*-toluenesulfonyl-1, 2, 3, 4, 5, 6-hexahydro-1-benzazocine 3. To a stirred solution of **2**[10] (10.0 g, 22 mmol) in CH_2Cl_2 (800 ml) were successively added H_2O (300 ml), sodium hydrosulfite (18.5 g, 0.11 mol) and tetrabutylammonium hydrogen sulfate (750 mg, 2.2 mmol) at room temperature, and the whole solution was vigorously stirred for 0.5 h at the same temperature. The organic layer was separated, dried over Na_2SO_4, and concentrated to give the hydroquinone. To a stirred solution of the crude hydroquinone in THF (130 ml) were added benzyl bromide (10 ml, 88 mmol), K_2CO_3 (12.0 g, 88 mmol) and 18-crown-6 (600 mg, 2.2 mmol) at room temperature. The reaction mixture was refluxed with stirring for 19 h, quenched with saturated aqueous NH_4Cl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and concentrated to give crude **3**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 2 : 1) to give **3** (14.0 g, 100%) as a white solid : ^{1}H Nmr ($CDCl_3$) δ 1.43 (d, J = 7 Hz, 3H), 1.2 - 2.0 (m, 4H), 2.24 (s, 3H), 2.34 (s, 3H), 2.96 (ddd, J = 15.0, 12.1, 1.8 Hz, 1H), 3.65 (q, J = 7.0 Hz, 1H), 3.81 (s, 3H), 3.5 - 3.9 (m, 4H), 4.21 (dt, J = 15.0, 3.3 Hz, 1H), 4.81 (ABq, J = 11.0 Hz, 2H), 5.17 (ABq, J = 11.0 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.2 - 7.6 (m, 10H); ir ($CHCl_3$) 1335, 1155cm^{-1}; ms (*m/z*), 643 (M^+), 552 (M^+ - Bn), 448 (M^+ - Ts), 397 (M^+ - Ts - Bn), 306 (M^+ - Ts - Bn - Bn), 91 (Bn, bp); Anal. Calcd for $C_{37}H_{41}NO_7S$: C, 69.03; H, 6.42; N, 2.18. Found : C, 68.92; H, 6.55; N, 2.09; mp 173 - 175 °C.

7, 10-Dibenzyloxy-8-methoxy-6, 9-dimethyl-5-oxo-1-*p*-toluenesulfonyl-1, 2, 3, 4, 5, 6-hexahydro-1-benzazocine 4. To a stirred solution of **3** (3.00 g, 4.67 mmol) in THF (80 ml) was added 37% hydrochloric acid (2.5 ml) at 0 °C. The mixture was stirred at room temperature for 4.5 h, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and concentrated to give crude **4**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 3 : 1) to afford **4** (2.68 g, 96 %) as a white solid : ^{1}H Nmr ($CDCl_3$) δ 1.52 (d, J = 7.0 Hz, 3H), 1.5 - 1.7 (m, 1H), 1.8 - 2.0 (m, 1H), 2.1 - 2.5 (m, 2H), 2.26 (s, 3H), 2.35 (s, 3H), 3.02 (ddd, J = 14.7, 11.0, 2.2 Hz, 1H),

3.83 (s, 3H), 4.32 (ddd, J = 14.7, 4.8, 2.9 Hz, 1H), 4.33 (q, J = 7.0 Hz, 1H), 4.77 (ABq, J = 10.3 Hz, 2H), 4.85 (ABq, J = 11.0 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.2 - 7.6 (m, 10H), 7.77 (d, J = 8.4 Hz, 2H); ir ($CHCl_3$) 1700 cm^{-1} ; ms (m/z), 508 (M^+ - Bn), 444 (M^+ - Ts), 91(Bn, bp) ; Anal. Calcd for $C_{35}H_{37}NO_6S$: C, 70.09 ; H, 6.22 ; N, 2.34. Found : C, 69.91; H, 6.25; N, 2.25; mp 143 - 145 °C.

7, 10-Dibenzyloxy-8-methoxy-6, 9-dimethyl-5-oxo-1-*p*-toluenesulfonyl-1, 2, 5, 6-tetrahydro-1-benzazocine 5. To a solution of **4** (3.05 g, 5.1 mmol) in ethyl acetate (80 ml) were added 10 % hydrochloric acid (1.5 ml) and phenylselenenyl chloride (1.46 g, 7.4 mmol) at room temperature. The mixture was stirred for 21 h at the same temperature, and concentrated to give the residue, which was purified by silica gel column chromatography (hexane→ hexane-ethyl acetate, 5 : 1) to afford the phenylselenenyl-ketone (3.60 g, 94%) as a white solid. To a solution of the phenylselenenyl-ketone (3.53 g, 4. 68 mmol) in THF (35 ml) were added H_2O (13 ml) and sodium metaperiodate (2.00 g, 9.35 mmol) at room temperature. The mixture was stirred for 22 h at the same temperature, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give crude **5**. Purification by silica gel column chromatography (hexane-ethyl acetate, 4 : 1) gave **5** (1.97 g, 71%) as a white solid together with the phenylselenenyl-ketone (680 mg, 24% recovery) : ^1H Nmr ($CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.83 (s, 3H), 4.10 (q, J = 7.0 Hz, 1H), 4.15 (dd, J = 16.5, 6.2 Hz, 1H), 4.55 (ddd, J = 16.5, 4.0, 2.2 Hz, 1H), 4.72 (ABq, J = 10.3 Hz, 2H), 4.90 (ABq, J = 11.4 Hz, 2H), 5.68 (ddd, J = 13.2, 6.2, 4.0 Hz, 1H), 5.84 (dd, J = 13.2, 2.2 Hz, 1H), 7.2 - 7.5 (m, 10H), 7.52 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H); ir ($CHCl_3$) 1730, 1675, 1600, 1460, 1370, 1340, 1260, 1160, 1100 cm^{-1}; ms(m/z), 597 (M^+), 506 (M^+ - Bn), 442 (M^+ - Ts), 91 (Bn, bp); Anal. CalCd for $C_{35}H_{35}NO_6S$: C, 70.33; H, 5.90; N, 2.34. Found : C, 69.74; H, 5.89; N, 2.12; mp 143 - 144 °C.

(5*S, 6*R**)-7, 10-Dibenzyloxy-5-hydroxy-8-methoxy-6, 9-dimethyl-1-*p*-toluenesulfonyl-1, 2, 5, 6-tetrahydro-1-benzazocine 6.** To a stirred solution of **5** (1.09 g, 1.83 mmol) in THF (20 ml) was added diisobutylaluminum hydride (1*M* solution in hexane, 3.7 ml, 3.7 mmol) at - 70 °C. The whole reaction mixture was stirred for 0.5 h at the same reaction temperature, quenched with 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was successively washed with 10% hydrochloric acid, satd. aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give crude **6**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 3 : 1) to give **6** (1.09 g, 100%) as a white solid : ^1H Nmr ($CDCl_3$) δ 1.38 (d, J = 7.3 Hz, 3H), 2.11 (s, 3H), 2.41 (s, 3H), 3.15 (dq, J = 4.4, 7.3 Hz, 1H), 3.49 (br d, J = 8.1 Hz, 1H), 3.74 (s, 3H), 4.03 (ABXqd, J = 11.7, 7.3, 8.4 Hz, 2H), 4.40 (br s, 1H), 4.73 (ABq, J = 11.0 Hz, 2H), 5.17 (ABq, J = 11.0 Hz, 2H), 5.29 (dddd, J = 11.7, 8.4, 7.3, 2.5 Hz, 1H), 5.71 (dd, J = 2.0,

11.7 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.3 - 7.5 (m, 10H), 7.74 (d, J = 8.4 Hz, 2H); ir ($CHCl_3$) 3500, 1600, 1460, 1420, 1370, 1350, 1160, 1100 cm^{-1}; ms (*m/z*), 599 (M^+), 508 (M^+ - Bn), 480 (M^+ - H_2O), 444(M^+ - Ts), 400 (M^+ - Bn - Bn - OH), 353 (M^+ -Ts - Bn), 336 (M^+ - Ts - Bn - OH), 245 (M^+ - Ts - Bn - Bn - OH), 244 (M^+ - Ts - Bn - Bn - OH + 1), 91(Bn, bp); Anal. Calcd for $C_{35}H_{37}NO_6S$: C, 70.09; H, 6.22; N, 2.34. Found : C, 69.56; H, 6.27; N, 2.17; mp 175 - 177 °C.

(5*S, 6*R**)-7, 10-Dibenzyloxy-8-methoxy-6, 9-dimethyl-1-*p*-toluenesulfonyl-5-(*N*-*p*-toluenesulfonyl)-carbamoyloxy-1, 2, 5, 6-tetrahydro-1-benzazocine 7.** To a stirred solution of **6** (0.98 g, 1.63 mmol) in THF (20 ml) was added *p*-toluenesulfonyl isocyanate (7.38*M* solution in THF, 0.26 ml, 1.92 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 5 *min*, and diluted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford crude **7**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 1 : 1) to give **7** (1.28 g, 99%) as a white solid : ^1H Nmr ($CDCl_3$) δ 1.20 (d, J = 7.3 Hz, 3H), 2.17 (s, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 3.15 (dq, J = 4.8, 7.3 Hz, 1H), 3.83 (s, 3H), 3.99 (d, J = 6.2 Hz, 2H), 4.69 (ABq, J = 11.0 Hz, 2H), 5.03 (ABq, J = 11.7 Hz, 2H), 5.2 - 5.5 (m, 2H), 5.6 - 5,7 (m, 1H), 6.70 (br s, 1H), 7.1 - 7.9 (m, 18H); ir ($CHCl_3$) 3220, 1750, 1600, 1500, 1460, 1420, 1350, 1160 cm^{-1}; ms (*m/z*), 427 (M^+ - Ts - OCONHTs), 336 (M^+ - Ts - Bn - OCONHTs), 245 (M^+ - Ts - Bn - Bn - OCONHTs), 244 (M^+ - Ts - Bn - Bn - OCONHTs - 1), 91 (Bn, bp); Anal. Cadcd for $C_{43}H_{44}N_2O_9S_2$: C, 64.81; H, 5.56; N, 3.52. Found : C, 64.88; H, 5.61; N, 3.58; mp 105 - 107 °C.

(3a*R, 4*R**, 11*R**, 11a*R**)-7, 10-Dibenzyloxy-4-iodo-9-methoxy-8, 11-dimethyl-2-oxo-3, 6-bis(*p*-toluenesulfonyl)-2, 3, 3a, 4, 5, 6, 11, 11a-octahydrooxazolo[4, 5-*d*][1]benzazocine 8.** To a stirred solution of **7** (50 mg, 0.06 mmol) in THF (2.5 ml) were successively added K_2CO_3 (43 mg, 0.31 *mmol*) and I_2 (35 *mg*, 0.14 *mmol*) at room temperature. The reaction mixture was stirred for 4.5 h at the same temperature, and diluted with ethyl acetate. The organic layer was successively washed with 5% aqueous sodium thiosulfate and brine, dried over Na_2SO_4, and concentrated to give crude **8**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 3 : 1) to afford **8** (39 mg, 67%) as a white solid : ^1H Nmr ($CDCl_3$) δ 1.49 (d, J = 7.3 Hz, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 2.39 (s, 3H), 3.71 (s, 3H), 4.2 - 5.4 (m, 10H), 7.1 - 7.8 (m, 18H); ir ($CHCl_3$) 1790, 1600, 1500, 1460, 1420, 1380, 1360, 1270, 1160, 1100 cm^{-1}; FDms (*m/z*) 922 (M^+, bp); Anal. Calcd for $C_{43}H_{43}N_2O_9IS_2$: C, 55.96; H, 4.70; N, 3.04. Found : C, 55.99; H, 4.66; N, 2.91; mp 200 - 202 °C.

(1a*S, 8*R**, 9*R**, 9a*S**)-4, 7-Dibenzyloxy-9-hydroxy-6-methoxy-5, 8-dimethyl-1, 3-bis(*p*-toluenesulfonyl)-1a, 2, 3, 8, 9, 9a-hexahydro-1*H*-azirino[2, 3-*c*][1]benzazocine 9.** To a solution of **8** (955 mg,

1.04 mmol) in CH_2Cl_2 (4.7 ml) and MeOH (2.5 ml) was added K_2CO_3 (720 mg, 5.21 mmol) at room temperature. The reaction mixture was then stirred for 28 h at the same temperature, and diluted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give crude **9**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 6 : 1) to afford **9** (772 mg, 97%) as a colorless oil : ^{1}H Nmr ($CDCl_3$) δ 1.53 (d, J = 7.3 Hz, 3H), 2.19 (s, 3H), 2.32 (s, 3H), 2.37 (s, 3H), 2.55 (d, J = 4.8 Hz, 1H), 3.1 - 3.2 (m, 2H), 3.45 (dd, J = 16.5, 4.8 Hz, 1H), 3.70 (dq, J = 3.3, 7.3 Hz, 1H), 3.78(s, 3H), 4.12 (br s, 1H), 4.32 (dd, J = 16.5, 3.7 Hz, 1H), 4.51 (ABq, J = 11.4 Hz, 2H), 5.04 (ABq, J = 11.0 Hz, 2H), 7.0 - 7.7 (m, 18H); ir ($CDCl_3$) 3550, 1600, 1500, 1460, 1420, 1375, 1340, 1260, 1160, 1090 cm^{-1}; ms (*m* /z) 768 (M^+), 677 (M^+ - Bn), 613 (M^+ - Ts), 586 (M^+ - Bn - Bn +1), 569 (M^+ - Bn - Bn - OH), 522 (M^+ - Ts - Bn), 521 (M^+ - Ts - Bn - 1), 505 (M^+ - Ts - Bn - OH), 91 (Bn, bp); HRms (M^+) calcd for $C_{42}H_{44}N_2O_8S_2$ 768.2540, found 442.2388.

(1a*S, 8*R**, 9a*S**)-4, 7-Dibenzyloxy-6-methoxy-5, 8-dimethyl-9-oxo-1, 3-bis(*p*-toluenesulfonyl)-1a, 2, 3, 8, 9, 9a-hexahydro-1*H*-azirino[2, 3-*c*][1]benzazocine 10.** A mixture of **9** (50 mg, 0.065 mmol), molecular sieves, 4A (126 mg) and PCC (42 mg, 0.19 mmol) in CH_2Cl_2 (0.5 ml) was stirred at room temperature for 35 h, filtered through silica gel, and washed with ethyl acetate. The organic layer was cancentrated to give the oily residue, which was purified by silica gel column chromatography (hexane-ethyl acetate, 3 : 1) to afford **10** (50 mg, 100%) as a colorless oil : ^{1}H Nmr ($CDCl_3$) δ 1.58 (d, J = 7.3 Hz, 3H), 2.10 (s, 3H), 2.37 (s, 3H), 2.39 (s, 3H), 3.35 (ddd, J = 7.7, 3.3, 2.0 Hz, 1H), 3.51 (dd, J = 15.4, 2.0 Hz, 1H), 3.60 (d, J = 7.7 Hz, 1H), 3.93 (s, 3H), 4.13 (q, J = 7.3 Hz, 1H), 4.22 (ABq, J = 12.1 Hz, 2H), 4.20 (dd, J = 15.4, 3.3 Hz, 1H), 4.88 (ABq, J = 11.0 Hz, 2H), 6.7 - 6.8 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.2 - 7.5 (m, 8H); ms (*m* /z) 675 (M^+ - Bn), 611 (M^+ - Ts), 584 (M^+ - Bn - Bn), 91 (Bn, bp); HRms (M^+ - Bn) calcd for $C_{35}H_{35}N_2O_8S_2$ 675.1836, found 675.1816.

Summary of Crystal Data, Intensity Collection and Least-squares Processing of the Benzoate (11).

Formula : $C_{49}H_{47}N_2O_9S_2Br$	Diffractometer : Rigaku AFC-5R
Formula Weight : 887.96	Radiation : CuKα (λ = 1.54178A) Graphite monochromated
Crystal System : Monoclinic	2θ Max./deg : 120.0
Space Group : $P2_1/c$	Scan Tipe : ω-2θ
a/Å : 20.869 (2)	Crystal Dimensions/mm^3 : 0.1 x 0.2 x 0.3
b/Å : 9.787 (1)	Total No of Reflections Mesured : 7813
c/Å : 23.131 (3)	No. Observations (|Fobs|)>2.667σ (|Fobs|) : 5869

β/Deg. : 103.66 (2)	Final R : 0.080
V/Å^3 : 4590.8	Final Rw : 0.082
Z value : 4	Analysis : Direct Method (SHELXS-86)
D calcd/g cm^{-3} : 1.285	Refinement : Block-diagonal matrix Leastsquare's method
μ (CuKα)/cm^{-1} : 2.536	Weighting Scheme : Unit Weight

(1a*S*, 8*R***, 8a*R***, 8b*S***)-4, 7-Dibenzyloxy-8a-*tert*-butyldimethylsilyloxy-6-methoxy-5, 8-dimethyl-1-*p*-toluenesulfonyl-1, 1a, 2, 8, 8a, 8b-hexahydroazirino[2', 3' : 3, 4]pyrrolo[1, 2-*a*]indole 12.** To a stirred solution of **10** (65 mg, 0.085 mmol) and triethylamine (0.06 ml, 0.42 mmol) in CH_2Cl_2 (1.4 ml) was gradually added *tert* - butyldimethylsilyl trifluoromethanesulfonate (0.04 ml, 0.17 mmol). The reaction mixture was stirred at room temperature for 10 min, again cooled to - 78 °C, quenched with satd. aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extract was successively washed with satd. aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give the oily residue, which was purified by silica gel column chromatography (hexane-ethyl acetate, 5 : 1) to afford **12** (6 mg, 100%) as a colorless oil : ^{1}H Nmr ($CDCl_3$) δ 0.04 (s, 3H), 0.15 (s, 3H), 1.00 (s, 9H), 1.69 (d, *J* = 7.3 Hz, 3H), 1.77 (s, 3H), 2.24 (s, 3H), 3.2 - 3.4 (m, 2H), 3.39 (q, *J* = 7.3 Hz, 1H), 3.84 (d, *J* = 4.8 Hz, 1H), 4.18 (d, *J* = 12.8 Hz, 1H), 4.90 (ABq, *J* = 11.0 Hz, 2H), 4.92 (ABq, *J* = 11.4 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 2H), 7.1 - 7.3 (m, 10H), 7.63 (d, *J* = 8.4 Hz, 2H); ms (*m* /*z*), 726 (M^+), 711 (M^+ - Me), 669 (M^+ - ^{t}Bn), 635(M^+ - Bn), 611 (M^+ - ^{t}BuMe$_2$Si), 91 (Bn, bp); HRms (M^+) calcd for $C_{41}H_{50}N_2O_6SSi$ 726.3159, found 726.3199.

(1a*S*, 8*R***, 8a*R***, 8b*S***)-8a-*tert*-Butyldimethylsilyloxy-6-methoxy-5, 8-dimethyl-4, 7-dioxo-1-*p*-toluenesulfonyl-1, 1a, 2, 4, 7, 8, 8a, 8b-octahydroazirino[2', 3' : 3, 4]pyrrolo[1, 2-*a*]indole 13.** A mixture of **12** (9 mg, 0.012 mmol), triethylamine (0.01 ml, 0.07 mmol) and 10% Pd on C (12 mg) in ethyl acetate (0.2 ml) was stirred at room temperature for 10 min under hydrogen, further stirred at the same temperature for 10 min under oxygen, filtered through celite, and washed with ethyl acetate. The organic layer was concentrated to give crude **13**, which was purified by silica gel column chromatography (hexane-ethyl acetate, 5 : 1) to afforded **13** (5 mg, 75%) as a purple solid : ^{1}H Nmr ($CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.14 (d, *J* = 7.3 Hz, 3H), 1.85 (s, 3H), 2.44 (s, 3H), 3.07 (q, *J* = 7.3 Hz, 1H), 3.4 - 3.6 (m, 3H), 4.06 (s, 3H), 4.06 (dd, *J* = 13.6, 11.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H); ir ($CHCl_3$) 1660, 1640, 1580, 1460, 1330, 1300, 1160, 1120, 1100 cm^{-1}; ms (*m* /*z*), 544 (M^+), 529 (M^+ - Me), 487 (M^+ - ^{t}Bu), 389 (M^+ - Ts), 332 (M^+ - Ts - ^{t}Bu), 317 (M^+ - Ts - ^{t}Bu - Me), 75 (Me$_2$SiOH, bp); Anal. Calcd for $C_{27}H_{36}N_2O_6SSi$: C, 59.53; H, 6.66; N, 5.14. Found : C, 59.57; H, 6.67; N, 4.81; mp 121 -123 °C.

(1a*S*, 8*R***, 8a*R***, 8b*S***)-8a-*tert*-Butyldimethylsilyloxy-6-methoxy-5, 8-dimethyl-4, 7-dioxo-1, 1a, 2, 4, 7, 8, 8a, 8b-octahydroazirino[2', 3' : 3, 4]pyrrolo[1, 2-*a*]indole 14.** To a solution of **13** (53 mg, 0.1 mmol) in THF (3 ml) was added Na naphthalene (0.122 *M* solution in THF, 8 ml, 0.98 mmol) at -98 °C. The mixture was stirred for 10 min at -98 °C, further stirred at the same temperature for 0.5 h under oxygen, quenched with satd. aqueous NH_4Cl, and extrated with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated to give the oily residue, which was purified by silica gel column chromatography (chloroform-acetone, 10 : 1) to afford **13** (6 mg, 16%) as a purple oil : ^{1}H Nmr ($CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.96 (s, 9H), 1.76 (d, *J* = 7.3 Hz, 3H), 1.84 (s, 3H), 1.5 - 1.8 (m, 1H), 2.1 - 2.3 (m, 2H), 3.28 (dd, *J* = 12.8, 2.2 Hz, 1H), 3.39 (q, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 4.09 (d, *J* = 12.8 Hz, 1H); ir (neat) 2950, 1660, 1640, 1580, 1460, 1440, 1370, 1310, 1290, 1230, 11100 cm^{-1}; ms (*m /z*), 390 (M^+), 375 (M^+ - Me), 333 (M^+ - ^{t}Bu), 75 (Me_2SiOH, bp); HRms (M^+) calcd for $C_{20}H_{30}N_2O_4Si$ 390.1975, found 390.1953.

(1a*S*, 8*R***, 8a*R***, 8b*S***)-8a-Hydroxy-6-methoxy-5, 8-dimethyl-4, 7-dioxo-1, 1a, 2, 4, 7, 8, 8a, 8b-octahydroazirino[2', 3' : 3, 4]pyrrolo[1, 2-*a*]indole 1.** To a solution of **14** (5.5 mg, 0.014 mmol) in THF (0.25 ml) were added acetic acid (0.016 ml, 0.28 mmol) and tetrabutylammonium fluoride (0.195 ml, 0.21 mmol) at room temperature. The mixture was stirred at the same temperature for 1.5 h, and concentrated to give the residue, which was purified by silica gel column chromatography (chloroform-acetone, 1 : 1) to afford **1** (3.2 mg, 82%) as a purple oil : ^{1}H Nmr ($CDCl_3$) δ 0.0 - 2.2 (m, 2H), 1.66 (d, *J* = 7.3 Hz, 3H), 1.80 (dd, *J* = 4.4, 1.8 Hz, 1H), 1.87 (s, 3H), 2.04 (d, *J* = 4.4 Hz, 1H), 3.00 (q, *J* = 7.3 Hz, 1H), 3.21 (dd, *J* = 12.5, 1.8 Hz, 1H), 3.83 (s, 3H), 4.07 (d, *J* = 12.5 Hz, 1H); ir (neat) 3300, 2950, 1660, 1640, 1580, 1460, 1450, 1380, 1300, 1240, 1220 cm^{-1}; ms (*m /z*) 276 (M^+), 258 ($M^+ - H_2O$), 243 (M^+ - Me), 57 (bp); HRms (M^+) calcd for $C_{14}H_{16}N_2O_4$ 276.1115, found 276.1110 .

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Received, 25th February, 1994