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Total Syntheses of Prothracarcin and Tomaymycin by Use of Palladium Catalyzed Carbonylation

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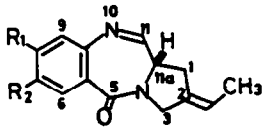
Total syntheses of optically active prothracarcin(1) and pretomaymycin(2), which is readily convertible to tomaymycin(3), were achieved via a palladium catalyzed carbonylation developed by us. The structure of prothracarcin(1) was determined to be (11aS)(E)-2-ethylidene-2,3,5,11a-tetrahydro-5-oxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine by comparison of the ^{13}C-NMR spectra of the synthetically obtained E- and Z-isomers.

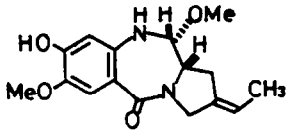
Tomaymycin(3), an antitumor antiviral antibiotic, was isolated from Streptomyces achromogenes var. tomaymycetics by Arima et al.[1] and its chemical structure proposed by Kariyone[2] was established by X-ray analysis.[3] Prothracarcin(1), a novel antibiotic, was isolated from the culture broth of Streptomyces umbrosus subsp. raffinophilus DO-62, and was active against Gram-positive and Gram-negative bacteria and murine tumors.[4] These antibiotics belong to the pyrrolo-1,4-benzodiazepine antibiotics and the structure of prothracarcin(1) has been correlated to pretomayamycin(2) by comparison of their mass and NMR spectra.[4] The total synthesis of tomaymycin(3) was reported by only one group[5] and the synthesis of prothracarcin(1) has not been reported previously.

Scheme 1



Prothracarcin (1)
R_1=R_2=H

Pretomaymycin (2)
R_1=OH, R_2=OMe

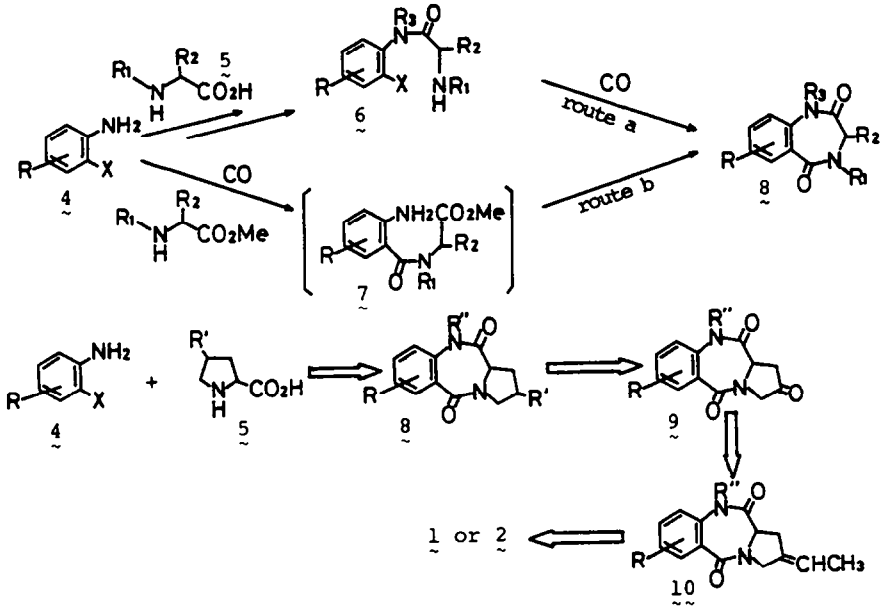


Tomaymycin (3)

During the course of our synthetic studies of 1,4-benzodiazepines using palladium catalyzed carbonylation,[6] we reported two synthetic methods for obtaining this skeleton. One of them involved the insertion of carbon monoxide into an aryl halide 6 which was prepared by condensation of o-haloaniline 4 with amino acid 5(route a).[6] The other one involved the direct one-step synthesis of pyrrolo-[1,4]benzodiazepine skeleton by the reaction of carbon monoxide, o-haloaniline 4 and amino acid methyl ester 5 (route b).[7] We succeeded in the formal total synthesis of anthramycin[6c] through route a and dehydroxy-demethoxy-methyl-neothramycins were synthesized by use of the latter procedure(route b).[7] We now wish to report that the former method was applied with success to the total

syntheses of prothracarcin(1) and pretomaymycin(2), which is readily convertible to tomaymycin(3), in optically active forms. As a result the stereochemistry of prothracarcin(1) has been determined using the synthetically obtained E and Z-isomers. The outstanding problem in the synthesis of these antibiotics included: an efficient formation of the 1,4-benzodiazepine ring system, stereoselective formation of the ethylidene group and chemo-selective reduction of the N-10-C-11 amide group to the imino group. The reaction of carbon monoxide to o-haloaniline derivative(4) as an aromatic- and 4-hydroxy-l-proline as an amino acid-moiety could be expected to afford compound 8. The conversion of the hydroxy group at C-2 of 8 to an ethylidene group and chemo-selective reduction[8] of the amide group to an imino group developed by us[7] was applied to the present synthesis to give the desired prothracarcin(1) and pretomaymycin(2). Pretomaymycin(2) was readily converted to tomaymycin(3) by treatment with MeOH.[5]

Scheme 2

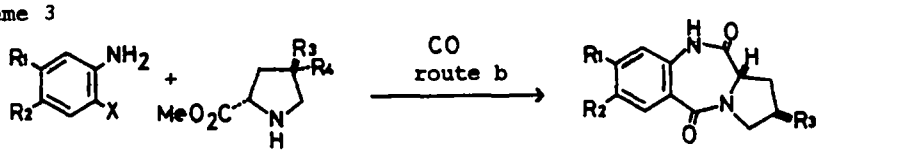


Results

Total Synthesis of Prothracarcin

Initially, the synthesis of the pyrrolo-1,4-benzodiazepine skeleton was attempted by a one pot method(route b). For the amino acid, l-proline methyl ester or 4-hydroxy-l-proline methyl ester was used. A solution of o-bromo-aniline(4a), l-proline methyl ester, tri-n-butylamine and a catalytic amount of $Pd(OAc)_2$(10 mol %)-PPh_3(40 mol %) in hexamethylphosphoramide(HMPA) was heated under carbon monoxide at 5 atmospheres at 110 °C for 2 days to afford compound 8c in 10 % yield. The yield was raised to 79 % when xylene was used instead of HMPA in the presence of K_2CO_3 as base. The use of 2-bromo-4-methoxy-5-tosyloxy-aniline(4b) and l-proline methyl ester 5b gave compound 8e in 41 % yield. However, the insertion of carbon monoxide into a mixture of 4a or 4b and 4-acetoxy-l-proline methyl ester(5c) gave the desired compound 8d or 8f in lower yields(Table 1, Run 3 and 5). Moreover, the use of various 4-hydroxy-l-proline derivatives protected with methoxymethyl, benzyl and trimethylsilyl groups, or of the oxidation product 5d of 4-hydroxy-l-proline methyl ester and its derivatives 5e and 5f did not afford the desired 1,4-benzodiazepines. Although the reason for the decreased yields of the desired compounds when 4-hydroxy-l-proline derivatives were used instead of l-proline as amino acid is not yet clear, we have chosen another route for the synthesis of the pyrrolo-1,4-benzodiazepine skeleton.

Scheme 3



4a; $R_1=R_2=H$, X=Br or I
4b; R_1=OTs, R_2=OMe, X=Br

5b; $R_3=R_4=H$
5c; R_3=OAc, $R_4=H$
5d; $R_3=R_4=$ =O
5e; $R_3=R_4$=OMe
5f; $R_3=R_4=$

8c; $R_1=R_2=R_3=H$
8d; $R_1=R_2=H$, R_3=OAc
8e; R_1=OTs, R_2=OMe, $R_3=H$
8f; R_1=OTs, R_2=OMe, R_3=OAc

Table 1 One pot reaction of pyrrolo-1,4-benzodiazepines

Run	4	R_1	R_2	X	5 R_3	Yield of product 8	
1	4a	H	H	Br	H	10 %	8c
2	4b	H	H	I	H	79	8c
3	4b	H	H	I*	OAc	22	8d
4	4c	TsO	MeO	Br	H	41	8e
5	4c	TsO	MeO	Br	OAc	9	8f

* in the presence of KI

Thus N,O-bis(trifluoroacetyl)-4-hydroxy-l-proline was condensed with o-iodo or o-bromoaniline(4a) followed by treatment with aqueous sodium bicarbonate to give compound 11a, quantitatively. For the methoxymethyl protection of the amide nitrogen and the hydroxy group, because of the low yields when compound 11a was treated with 2 eq. of methoxymethyl chloride(MOMCl) in the presence of NaH, it was sequentially treated with MOMCl and diisopropylethylamine, then MOMCl and NaH. The N-trifluoroacetyl group was cleaved with NH_3-MeOH to afford compound 6a. The insertion of carbon monoxide(5 atm) to compound 6a(X=Br) at 110°C for 48 h in xylene proceeded smoothly to afford pyrrolo-1,4-benzodiazepine derivative 8a in a yield of 49 %. In a similar manner, the o-iodoaniline derivative 6a(X=I) gave 8a in high yield(90 %). The O-methoxymethyl group of compound 8a was cleaved with HCl-MeOH to give compounds 12a and 13a in yields of 65 % and 30 %, respectively. The latter compound 13a was easily converted to 8a by treatment with NaH-MOMCl in 93 % yield. Oxidation of compound 12a with PCC produced the ketone 9a, which was treated with ethyltriphenylphosphonium bromide in the presence of freshly sublimed t-BuOK at room temperature to afford 10a in high yield. The ^{1}H-NMR spectrum of this compound shows two peaks of the ethylidene methyl[δ 1.66(brd. J=6.8) and 1.74(brd, J=6.8)] in a ratio of 9 to 1. HPLC of 10a also shows two peaks in a ratio of 88 to 12. The stereochemistry of these isomers was determined by ^{13}C-NMR(see below). The proportion of the major product increased when the reaction was carried out at 0°C(Table 2). For the chemoselective reduction of the amide group to an imino-group required the presence of the methoxymethyl substituent on the amide nitrogen.[7] Compound 10a was treated with sodium borohydride($NaBH_4$) in EtOH at 0°C followed by treatment with silica gel to produce compound 14a. However, the melting point(m.p. 120-122°C) and ^{13}C-NMR spectrum of compound 14a did not agree with those of the natural product 1(m.p. 85-87°C) kindly supplied by Dr. F. Tomita.[4] These results suggest that prothracarcin(1) is the geometrical isomer of 14a.

Scheme 4

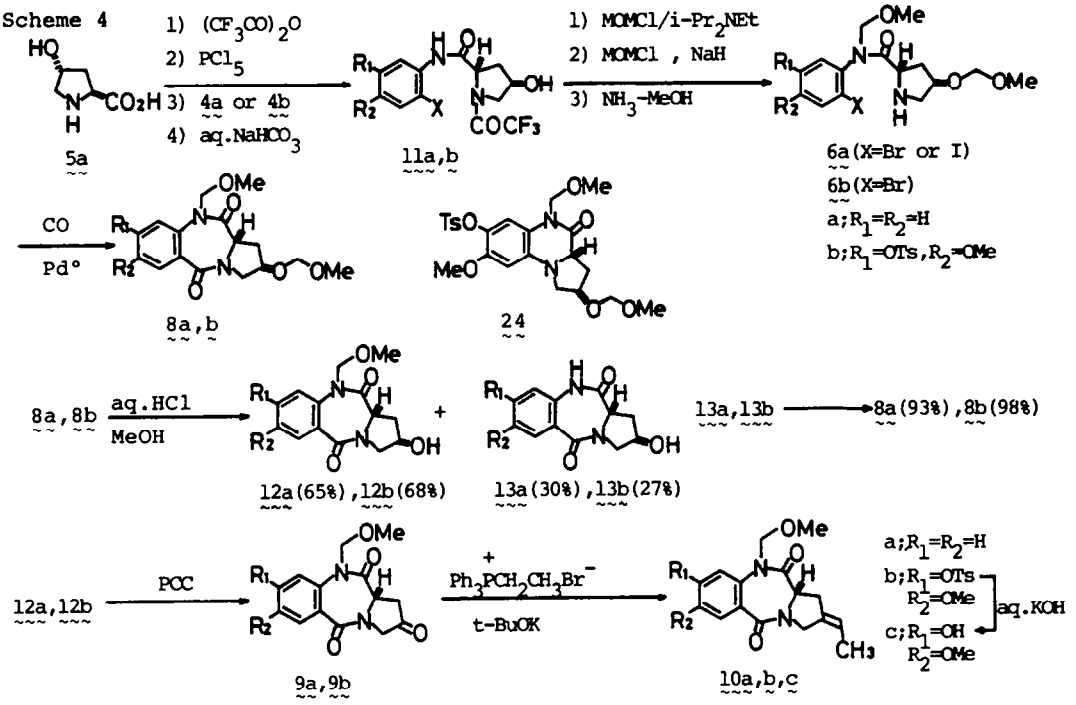


Table 2 Wittig Reaction to Compound 10a

Temp.	Yield of 10a	Ratio of Z to E*
50°C	quant.	83 : 17
room temp.	quant.	88 : 12
0°C	93 %	92 : 8

*determined by HPLC

For inversion of the ethylidene group, epoxidation of compound 10a with MCPBA afforded compounds 15 and 16 in a ratio of 7 to 3. Each isomer was treated with lithium diphenylphosphide and then MeI[9] to give compound 17a, but the corresponding yields were not satisfactory. Therefore, compound 10a was converted to diols 18a and 20a with N-methylmorpholine N-oxide and OsO_4. This was followed by treatment with MsCl in the presence of NEt_3 to give compounds 19a and 21a in a ratio of 4 to 1. The separated isomers when treated with KOH afforded epoxides 22a and 23a in quantitative yield. Since the epoxides were formed by rear side attack of the hydroxy group, these epoxides 22a and 23a were the methyl-inversion products of 15 and 16. Deoxygenation of 22a and 23a with diphosphrous tetraiodide(P_2I_4) in the presence of pyridine[10] afforded compound 17a in high yields which possessed the desired ethylidene group. Compound 17a was reduced with $NaBH_4$ followed by treatment with silica gel to produce compound 18a(m.p. 87-88°C, authentic sample m.p. 85-87°C), which was optically active [$[\alpha]_D^{17}$ +18.3°(c=0.21, ethyl acetate)]. An authentic sample had [$[\alpha]_D^{22}$ +17.1°(c=0.1, ethyl acetate)]. C^{13}-NMR spectra of the synthetic products 14a, 18a and prothracarcin(1) are shown in Table 3. These results establish compound 18a as prothracarcin(1).

Scheme 5

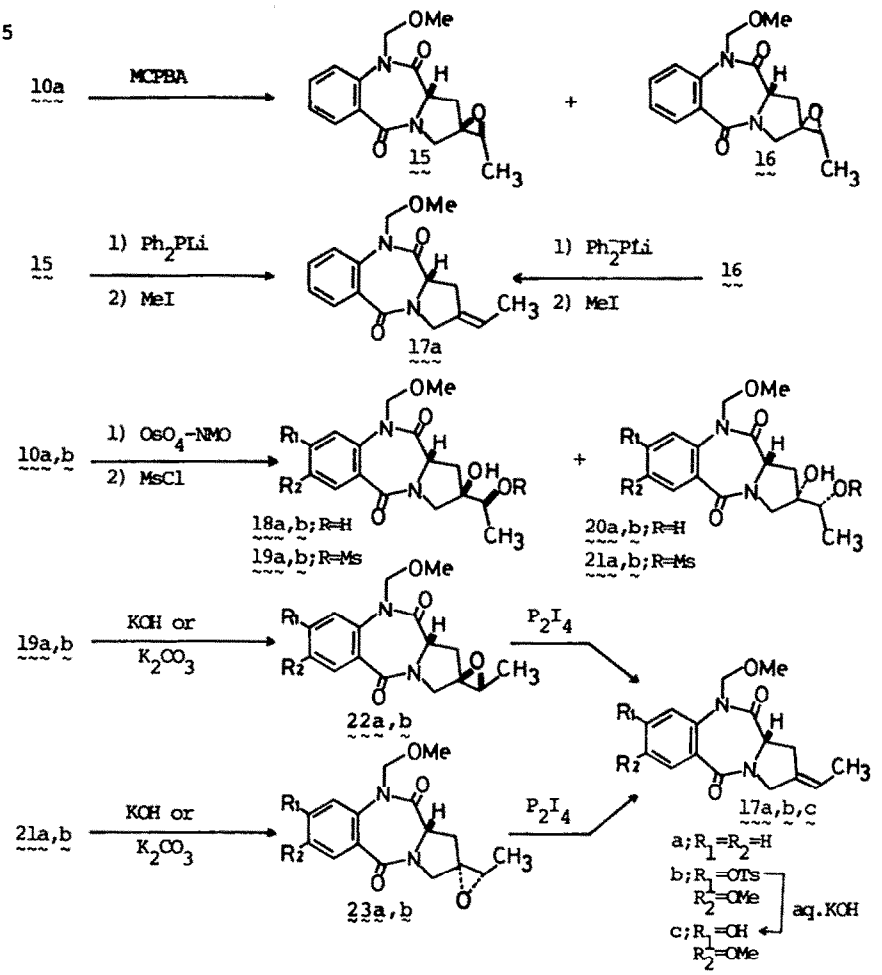
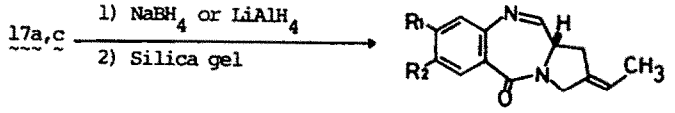


Table 3 ^{13}C-NMR spectra of prothracarcin and their derivatives

	Chemical schift of				
	10a	17a	14a	18a	Prothracarcin
C-1	32.0	28.2	35.3	31.2	31.1
C-2	129.6	129.6	-	-	-
C-3	48.0	51.1	48.3	51.6	51.6
C-11a	57.1	57.6	53.3	53.8	53.7
C-12	118.7	118.4	119.5	119.1	119.1
C-12-CH_3	14.9	14.5	14.8	14.6	14.6
C-11	170.1	170.2	165.0	165.0	164.9

Table 4 ^{13}C-NMR spectra of compounds 10b and 17b

	Chemical shift of	
	10b(Z-isomer)	17b(E-isomer)
C-1	32.0	28.1
C-3	48.2	51.2
C-11a	57.6	57.6
C-12	118.8	118.8
C-12-CH_3	14.8	14.5



Total synthesis of tomaymycin

To achieve the total synthesis of tomaymycin, 2-bromo-4-methoxy-5-tosyloxy-aniline(4b) was used as the aromatic synthon. Protection of compound 11b with MOMCl in the presence of diisopropylethylamine afforded the N,O-dimethoxy-methylated o-haloaniline derivative, whose N-trifluoroacetyl group was cleaved with NH_3-MeOH to furnish the secondary amine 6b. The insertion of carbon monoxide to compound 6b in toluene afforded only a 9 % yield of the desired 8b along with the quinoxaline derivative 24(15 % yield).[6d] Consequently, the reaction was carried out under various conditions(Table 5). The yield was raised to 69 % when the reaction was carried out under 10 atm pressure of carbon monoxide in the presence of $Pd(PPh_3)_4$.

Table 5 Insertion of Carbon Monoxide to Compound 6b

Run	Catalyst (mol %)	Base	CO (atm.)	Reaction Time(h)	Yield of (%) 8b	19
1	$Pd(OAc)_2$* (10)	K_2CO_3	5	48	9	15
2	$Pd(OAc)_2$* (10)	$n\text{-}Bu_3N$	5	48	32	-
3	$Pd(OAc)_2$* (20)	$n\text{-}Bu_3N$	5	48	26	-
4	$Pd(PPh_3)_4$ (10)	$n\text{-}Bu_3N$	5	48	41	7
5	$Pd(PPh_3)_4$ (10)	$n\text{-}Bu_3N$	10	24	69	23

Reaction was carried out in toluene at 110°.
* An equimolar amount of PPh_3 was used.

Deprotection of the methoxymethyl group of compound 8b afforded 12b and 13b, in yields of 68 % and 27 %, respectively. The latter compound was also converted to 8b in high yield. Oxidation with PCC followed by the Wittig reaction at room temperature afforded compound 10b, whose HPLC showed two peaks in a ratio of 95 to 5. The ethylidene group of 10b was smoothly converted to the other form 17b in a similar manner. Hydrolysis of 17b with KOH afforded the phenolic compound 17c. Since the reduction of 17c with $NaBH_4$ at 0°C proceeded very slowly, $LiAlH_4$ was used at -60°C. After reaction, the product was treated with silica gel to afford pretomaymycin(2), whose ^{1}H-NMR and IR specta were identical with those kindly supplied by Dr. T. Kaneko. The synthetic pretomaymycin shows optically activity: $[\alpha]_D^{25}$ +215°(c=0.08, pyridine). An authentic sample had $[\alpha]_D^{24}$ +240°(c=0.08, pyridine)[5] and the interconversion of pretomaymycin(2) to tomaymycin(3) could be observed.[5] Thus, the total synthesis of tomaymycin(3) was achieved in a fairly good overall yield, chemically establishing that the ethylidene group of compound 17b is in the E-form. Thus, compound 14b should be Z-tomaymycin.

Discussion

Tables 3 and 4 show the ^{13}C-NMR spectra of E and Z-isomers of prothracarcin and their derivatives. Since the stereochemistry of tomaymycin was already determined to be in the E-form by X-ray analysis[3], the ethylidene group of compound 17b has to be in the the E-configuration. The chemical shift(28.1 ppm) of the methylene group at C-1 of the E-isomer(17b), which is influenced by the steric compression effect of the methyl group in the ethylidene moiety, is 3.9 ppm, at higher field than that of the Z-isomer 10b (32.0 ppm). Moreover, the chemical shift(48.2 ppm) of the methylene group at C-3 of the Z-isomer 10b is 3.00 ppm at higher field than that of the E-isomer 17b (51.2 ppm) due to the same steric compression effect (Table 4). The same results were observed in the prothracarcin series. The chemical shifts(28.2 ppm and 48.0 ppm, respectively) of the methylene group at C-1 of 17a and at C-3 of 10a were 3.8 ppm and 3.1 ppm in higher field than those(32.0 ppm and 51.1 ppm, respectively) of the methylene group at C-1 of 10a and at C-3 of

17a. A similar tendency was shown in the chemical shifts of the methylene group at C-1 and at C-3 of compounds 18a and 14a(Table 3). These results suggest that the ethylidene group of compounds 17a and 18a should be in the E-configuration because the chemical shifts of the methylene groups at C-1 of 17a and 18a and at C-3 of 10a and 14a were also influenced by the steric compression as already indicated. Moreover, chemical shifts(31.2 ppm and 51.6 ppm) of the methylene group at C-1 and at C-3 of compound 18a were identical with those (31.1 ppm at C-1 and 51.6 ppm at C-3) of the methylene group of natural prothracarcin. On the basis of these steric compression effects in the chemical shifts of ^{13}C-NMR spectra, the ethylidene group of prothracarcin(1) has to have the E-configuration. We have already synthesized optically active anthramycin from 4-hydroxy-l-proline by use of palladium catalyzed carbonylation,[7] and now, the total syntheses of prothracarcin(1) and tomaymycin(3) had been achieved in optically active forms from 4-hydroxy-l-proline. These results establish that the asymmetric C-11a of prothracarcin(1) is in the S-configuration.

Acknowledgement: We sincerely thank Dr. F. Tomita, Kyowa Hakko Kogyo Co. Ltd, and Dr. T. Kaneko, Bristol-Myers Company, for kindly supplying ^{1}H- and ^{13}C-NMR spectra of prothracarcin(1) and pretomaymycin(2), respectively.

Experimental

Melting points were measured with a hot stage microscope(Yanagimoto Special No.815) and with a melting point apparatus(Ishii) and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in indicated solvent on a JEOL JNM-FX 90-Q (90 MHz), a JEOL JNM-FX 100 (100 MHz), a JEOL JNM-FX 200 (200 MHz) and a JEOL JNM-GX 270 (270 MHz) spectrometers using Me_4Si as an internal standard. Coupling constants are reported in hertz. A Jasco A-302 diffraction-grating infrared spectrophotometer and JEOL JMS-D 300 mass spectrophotometer were used to determine IR and mass spectra, respectively. Optical rotations were measured using a JASCO DIP-4 Digital Polarimeter and HPLC was performed on a Cica-Merck prepacked column RT-250-4 equipped with a ERMA Optical Works ERC-7520 RI detector. Column chromatography was performed on silica gel.

2-Bromo-4-methoxy-5-tosyloxyaniline(4c)——To a suspension of 2-tosyloxy-4-nitroanisole(2.65 g, 8.20 mmol) in EtOH(300 ml) and c-HCl(3 ml) was added 10 % Pd-C(1.4 g) and the mixture was stirred under hydrogen at room temperature. After the absorption of hydrogen ceased, the reaction mixture was filtered and the filtrate was evaporated to give colorless 3-tosyloxy-4-methoxyaniline hydrochloride(2.7 g, quant.). Bromine(1.5 g,9.26 mmol) was added to a solution of the above solid(2.7 g) in AcOH(80 ml) containing AcONa(770 mg, 9.39 mmol) and a mixture was stirred for 3 h at room temperature. The product which had precipitated was filtered off and the brown solid was treated with ethyl acetate and sat. $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from n-hexane-ethyl acetate to afford 4c(2.486 g, 81 %), m.p. 113-114°C(Found: C,45.24; H, 3.79; N, 3.57; S, 8.56; Br, 21.64. $C_{14}H_{14}BrNO_4S$ requires C, 45.17; H, 3.79; N, 3.76; S, 8.61; Br, 21.47%); ν max(nujol) 3450, 3350, 1625, 1600, 1510 cm^{-1}; δ ($CDCl_3$) 2.42(s, 3 H, CH_3), 3.45(s, 3 H, OCH_3), 3.75(brs, 2 H, NH_2), 6.71(s, 1 H, aromatic), 6.92(s, 1 H, aromatic), 7.31(d, J=9.0 Hz, 2 H, aromatic), 7.80(d, J=9.0 Hz, 2 H, aromatic); m/z 373, 371(M^+).

General Procedure for One Step Syntheses of Pyrrolo-1,4-Benzodiazepines(8).— A solution of o-haloaniline derivative(4)(1 mmol), amino acid methyl ester(5)(1.3 mmol), Pd catalyst(10 mol %) and base(2 mmol) in HMPA, toluene or xylene (2 ml) was heated under carbon monoxide(5 atm) at 110°C for 3 days. After ethyl acetate had been added to the reaction mixture, the organic layer was washed with 10 % HCl solution, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography to afford pyrrolo-1,4-benzodiazepine derivative(8).

(11aS)-2,3,5,10,11,11a-Hexahydro-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine(8c).——The crude product obtained from 4b(328 mg, 1.5 mmol), l-proline methyl ester hydrochloride(513 mg, 3.1 mmol), $Pd(OAc)_2$(34 mg, 0.15 mmol), PPh_3(160 mg, 0.6 mmol) and K_2CO_3(455 mg, 3.3 mmol) in xylene(2 ml) under carbon monoxide(5 atm.) was purified by column chromatography. Elution with CH_2Cl_2-acetone(5:1) gave colorless crystals(256 mg, 79 %), m.p. 223-225°C(from n-hexane-acetone),(Found: C, 66.65; H, 5.59; N, 12.95. $C_{12}H_{12}N_2O_2$ requires C, 66.64; H,

5.52; N, 12.81%); $[\alpha]_D^{20}$ +505°(c 0.1 in MeOH); ν max(nujol) 3200, 1700, 1630 cm^{-1}; δ($CDCl_3$) 1.60-2.40(m, 3 H), 2.42-3.0(m, 1 H), 3.2-4.0(m, 2 H), 4.0-4.2(m, 1 H, C-11a), 6.80-7.62(m, 3 H, aromatic), 7.9-8.18(m, 1 H, aromatic), 8.30-8.45(brs, 1 H, NH); ^{13}C-NMR ($CDCl_3$) 23.5, 26.3, 47.3, 56.7, 121.2, 124.9, 127.0, 131.1, 132.4, 135.6, 165.5, 171.5; m/z 216(M^+).188(M^+-CO), 70.

(2R,11aS)-2-Acetoxy-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]-benzodiazepine(8d).——The crude product obtained from 4b(597 mg, 2.7 mmol), 4-acetoxy-1-proline methyl ester(5c)(663 mg, 3.55 mmol), $Pd(OAc)_2$(61 mg, 0.27 mmol), PPh_3(715 mg, 2.7 mmol) and K_2CO_3(753 mg, 5.4 mmol) in toluene(4 ml) under carbon monoxide(5 atm.) was purified by column chromatography. Elution with n-hexane-ethyl acetate-MeOH(2:1:0.1) gave a colorless powder(166 mg, 22 %),(Found: M^+, 274.0954. $C_{14}H_{14}N_2O_4$ requires M, 274.0954); νmax($CHCl_3$) 1740, 1690, 1635, 1480 cm^{-1}; δ($CDCl_3$) 2.04(s, 3 H, $COCH_3$), 2.14-2.23(m, 1 H, C-1), 3.10(ddd, J=5.4, 6.8 and 14.7Hz, 1 H, C-1), 3.74(dd, J=4.6 and 13.5 Hz, 1 H, C-3), 4.06-4.18(m, 2 H, C-11a and C-3), 5.34-5.51(m, 1 H, C-2), 6.94-8.04(m, 4 H, aromatic), 7.98(brs, 1 H, NH). m/z 274(M^+), 214.

(11aS)-2,3,5,10,11,11a-Hexahydro-7-methoxy-8-tosyloxy-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(8e).——The crude product obtained 4c(1.12 g, 3 mmol), 5b.hydrochloride(744 mg, 4.5 mmol), $Pd(OAc)_2$(68 mg, 0.3 mmol), PPh_3(320 mg, 1.2 mmol), K_2CO_3(450 mg, 3.3 mmol) and KI(598 mg, 3.6 mmol) in HMPA(4 ml) under carbon monoxide(5 atm.) was purified by column chromatography. Elution with CH_2Cl_2-acetone(5:1) gave colorless prisms(567 mg, 41 %), m.p. 261-261.5 °C(Found: C, 57.61; H, 4.74; N, 6.52; S, 7.64. $C_{20}H_{20}N_2O_6S$ requires C,57.68; H, 4.84; N, 6.73; S, 7.70%); νmax(nujol) 1690, 1630 cm^{-1}; δ($CDCl_3$) 1.6-2.2(m, 4 H), 2.44(s, 3 H, CH_3), 2.6-2.9(bs, 1 H), 3.75(s, 3 H, OCH_3), 3.75-3.9(m, 1 H), 3.95-4.18(m, 1 H, C-11a), 7.08(s, 1 H, aromatic), 7.30(d, J=9 Hz, 2 H, aromatic), 7.41(s, 1 H, aromatic), 7.78(d, J=9 Hz, 2 H, aromatic); m/z 416(M^+), 387(M^+-CO-1), 261(M^+-Ts).

(2R,11aS)-2-Acetoxy-2,3,5,10,11,11a-hexahydro-7-methoxy-8-tosyloxy-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(8f).——The crude product obtained from 4c(746 mg, 2 mmol), 5b(935 mg, 5 mmol), $Pd(OAc)_2$(45 mg, 0.2 mmol), PPh_3(212 mg, 0.8 mmol) and K_2CO_3(287 mg, 2 mmol) in HMPA(4 ml) under carbon monoxide (5 atm.) was purified by column chromatography[CH_2Cl_2-acetone(5:1)] and then preparative thin layer chromatography on silica gel[CH_2Cl_2-acetone(7:1)] to afford a colorless powder of 8f(86 mg, 9 %), νmax(neat) 1740, 1640, 1520, 1440 cm^{-1}; δ($CDCl_3$) 2.05(s, 3 H, CH_3CO), 2.46(s, 3 H, CH_3), 3.60(s, 3 H, OCH_3), 5.20(brs, 1 H, C-2), 7.04(s, 1 H, aromatic), 7.32(d, J=8.0 Hz, 2 H, aromatic)), 7.42(s, 1 H, aromatic), 7.78(d, 2 H, J=8.0 Hz, aromatic), 8.48(brs, 1 H, NH); m/z 474(M^+), 414(M^+-$COCH_3$-CO), 319(M^+-Ts).

2-Iodo-N-(4-hydroxy-1-trifluoroacetyl-l-prolyl)aniline(11a).——To a solution of 4-hydroxy-l-proline(5a)(0.72 g, 5.5 mmol) in CH_2Cl_2(10 ml) was added $(CF_3CO)_2O$(3.7 ml, 11.8 mmol) at 0°C and the mixture was stirred for 1 h. The solvent was evaporated and the residue was dissolved in dry Et_2O(13 mL). To the solution was added PCl_5(1.15 g, 5.5 mmol) at 0°C and the solution was allowed to stir at room temperature for 1.5 h. The solvent was evaporated and the residue was dissolved in benzene(10 ml). A solution of o-iodoaniline(1.1 g, 5.0 mmol) in ethyl acetate(20 ml) was added to reaction mixture at 0°C. Stirring was continued for 1 h at room temperature. The reaction mixture was washed with water and then brine, dried over Na_2SO_4 and evaporated. The crude product was suspended in MeOH(25 ml) and sat.$NaHCO_3$(7 ml) was added. The mixture was stirred for 1 h. The solution was neutralized with 5 % HCl and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and this was washed with water, dried over Na_2SO_4 and evaporated to give colorless crystals of 11a(2.14 g, quant.), (Found: M^+, 427.9819. $C_{13}H_{12}N_2O_3F_3I$ requires M, 427.9846); νmax(nujol) 3500, 3270, 1680, 1665 cm^{-1}; δ(acetone-d_6) 2.40-2.58(m, 2 H), 3.89(s, 2 H), 4.71-4.95(m, 2 H), 6.81-8.10(m, 4 H, aromatic), 8.22(brs, 1 H, NH); m/z 428(M^+), 301, 182.

N-(4-Hydroxy-1-trifluoroacetyl-l-prolyl)-2-bromo-4-methoxy-5-tosyloxy-aniline(11b).——N,O-Bis(trifluoroacetyl)-4-hydroxy-l-proline, which was prepared from 4-hydroxy-l-proline(5a)(1.96 g, 15 mmol) and $(CF_3CO)_2O$(4.5 ml, 32 mmol) in CH_2Cl_2(20 ml), was condensed with 4c(5.5 g, 14.8 mmol) in the presence of PCl_5(3.13 g, 1.5 ml) in ethyl acetate(40 ml) followed by treatment with $NaHCO_3$ as above to afford colorless crystals of 11a(8.3 g, 97 %), (Found: M^+, 582.0097. $C_{21}H_{20}N_2O_7SBrF_3$ requires M, 582.0107); νmax(nujol) 3400, 1690 cm^{-1}; δ($CDCl_3$) 2.10-2.67(m, 2 H), 2.44(s, 3 H, CH_3), 3.57(s, 3 H, OCH_3), 3.80-3.83(m, 2 H), 4.68-4.94(m, 2 H), 7.02(s, 1 H, aromatic), 7.31(d, J=9.4 Hz, 2 H, aromatic)), 7.78(d, J=9.4 Hz, 2 H, aromatic), 8.05(s, 1 H, aromatic), 8.36(brs, 1 H, NH); m/z 582, 580(M^+), 501, 182.

2-Iodo-N-(N-trifluoroacetyl-4-methoxymethoxy-l-prolyl)aniline.—To a solution of 11a(2.14 g, 5 mmol) and diisopropylethylamine(7 ml, 40 mmol) in CH_2Cl_2(25 ml) was added MOMCl(2 ml, 26 mmol) and the solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 5 % HCl and then

water, dried over $MgSO_4$ and evaporated to give a colorless solid, which was recrystallized from n-hexane-acetone to give colorless prisms(2.17 g, 92 %), m.p. 158-159°C(Found: C, 37.99; H, 3.41; N, 5.97; I, 26.89. $C_{15}H_{16}F_3IN_2O_4$ requires C, 38.15; H, 3.41; N, 5.93; I, 26.87 %); νmax(nujol) 3250, 1690, 1670 cm^{-1}; δ ($CDCl_3$) 2.30-2.64(m, 2 H), 3.38(s, 3 H, OCH_3), 3.83-3.94(m, 2 H), 4.50-4.65(m, 1 H), 4.69(s, 2 H, OCH_2),4.78-4.85(m, 1 H), 6.83-6.92(m, 1 H), 7.30-7.38(m, 1 H), 7.79(dd, J=1.5 and 7.8 Hz, 1 H), 8.17(dd, J=1.5 Hz and 8.31 Hz, 1 H), 8.2(brs, 1 H, NH); m/z 472(M^+), 345(M^+-I), 164.

2-Iodo-N-methoxymethyl-N-(N-trifluoroacetyl-4-methoxymethoxy-l-prolyl)aniline.- To a suspension of NaH(60 %, mineral oil suspension, 25 mg, 0.625 mmol) in THF(3 ml) under argon at -30°C was added 2-iodo-N(N-trifluoroacetyl-4-methoxymethoxy-l-prolyl)aniline(284 mg, 0.6 mmol) and the reaction mixture was stirred at the same temperature for 30 min. MOMCl(50 mg, 0.62 ml) was added at -30°C and the mixture was stirred at the same temperature for 90 min. Sat. NH_4Cl was added to the cold reaction mixture and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography eluted with n-hexane-ethyl acetate(3:2) to afford a colorless oil(296 mg, 95 %), which was crystallized from ethyl acetate. m.p. 161-162°C(Found: C, 39.32; H, 3.87; N, 5.69; I, 24.65. $C_{17}H_{20}F_3IN_2O_5$ requires C, 39.55; H, 3.91; N, 5.43; I, 24.58%; ν max(nujol) 3250, 1690, 1670, 1460 cm^{-1}; δ ($CDCl_3$) 2.30(dd, J=3.7 and 8.3 Hz, 2 H), 3.22(s, 3 H, OCH_3), 3.50(s, 3 H, OCH_3), 3.90(s, 2 H), 4.36-4.72(m, 2 H), 4.45(d, J=10.3 Hz, 1 H), 4.59(s, 2 H, OCH_2O), 5.62(d, J=10.3 Hz, 1 H), 7.10-8.0(m, 4 H, aromatic); m/z 516(M^+), 389(M^+-I), 164.

N-Methoxymethyl-N-(4-methoxymethoxy-1-trifluoroacetyl-1-prolyl)-2-bromo-4-methoxy-5-tosyloxyaniline.— To a solution of 11b(12 g, 20.6 mmol) and diisopropylethylamine(26.6 g, 206 mmol) in CH_2Cl_2(50 ml) in an ice-bath was added MOMCl(8.3 g, 103 mmol) in an ice-bath and the reaction mixture was stirred for 5 days. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 5 % HCl, sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography[n-hexane-ethyl acetate(2:1)] to give the desired compound(13.62 g, 99 %), m.p. 116-118°C(colorless needles from n-hexane-ethyl acetate)(Found: C, 44.99; H, 4.13; N, 4.17; S, 4.81; Br,11.82. $C_{25}H_{28}BrF_3N_2O_9S$ requires C, 44.85; H, 4.22; N, 4.18; S, 4.79; Br, 11.94%); $[\alpha]_D^{21}$ -38.5°(c 1.00, in $CHCl_3$); νmax(nujol) 1685 cm^{-1}; δ($CDCl_3$), 2.17(dd, J=3.7, 8.3 Hz, 2 H), 2.45(s, 3 H, CH_3), 3.25-3.50(m, 6 H, $2OCH_3$), 3.79(s, 3 H, OCH_3), 3.87(brs, 2 H), 4.32-4.61(m, 3 H), 4.60(s, 2 H, OCH_2O), 5.46-5.65(m, 1 H, NCH_2O), 7.13-7.85(m, 6 H, aromatic); m/z 670, 668(M^+), 589, 164.

2-Iodo-N-methoxymethyl-N-(4-methoxymethoxy-1-prolyl)aniline(6a).——To a solution of 2-iodo-N-methoxymethyl-N-(N-trifluoroacetyl-4-methoxymethoxy-l-prolyl)-aniline(11g, 21.3 mmol) in MeOH(30 ml) was added 20 % NH_3-MeOH(60 ml) solution and the mixture was allowed to stand overnight. The solvent was evaporated and the residue was purified by column chromatography[ethyl acetate-MeOH(10:1)] to afford 6a as a pale yellow oil(7.83 g, 87 %): ν max(neat) 3300, 1670, 1470 cm^{-1}; δ($CDCl_3$) 1.80-2.04(m, 2 H), 2.43(brs, 1 H, NH), 2.84-3.02(m, 1 H), 3.20 and 3.22(s and s, 3 H, OCH_3), 3.45 and 3.46(s and s, 3 H, OCH_3), 3.60-3.95(m, 1 H), 4.19-4.39(m, 2 H), 4.52(s, 2 H, OCH_2O), 5.58-5.70(m, 1 H), 7.02-7.95(m, 4 H, aromatic); m/z 293(M^+-I), 68.

N-Methoxymethyl-N-(4-methoxymethyl-1-prolyl)-2-bromo-4-methoxy-5-tosyloxy aniline(6b).——A solution of 11b(350 mg, 0.61 mmol) in 20 % NH_3-MeOH(10 ml) solution was stirred for 4 h. After evaporation of the solvent, the residue was purified by column chromatography[ethyl acetate-MeOH(10:1)] to afford 6b as a pale yellow oil(300 mg, quant); ν max(neat) 3300, 1675 cm^{-1}; δ ($CDCl_3$) 1.82-2.16(m, 2 H), 2.46(s, 3 H, CH_3), 3.15-3.70(m, 11H), 4.24-4.48(m, 2 H), 4.56(s, 2 H, OCH_2O), 5.52(d, J=10.3, 1 H, NCH_2O), 7.10-7.36(m, 4 H, aromatic), 7.76(d, J=8.3 Hz, 2 H, aromatic); m/z 492(M^+-HBr), 417, 415, 337.

Carbonylation of compound 6a.— A mixture of 6a(611 mg, 1.46 mmol), $n\text{-}Bu_3N$(590 mg, 3.19 mmol), $Pd(OAc)_2$(32.5 mg, 0.146 mmol), and PPh_3(384 mg, 1.46 mmol) in toluene(3 ml) was heated under 5 atm. of carbon monoxide at 110°C for 48 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with 5 % HCl, 5 % $Na_2S_2O_3$, sat. $NaHCO_3$ and then brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography[CH_2Cl_2-acetone(7:1)] to 8a(417 mg, 90 %) as a gum(417 mg, 90 %), (Found: M^+, 320.1357. $C_{16}H_{20}N_2O_5$ requires M, 320.1372); ν max(neat) 1690, 1640, 1460 cm^{-1}; δ ($CDCl_3$) 2.14(ddd, J=3.9, 8.1 and 13.5 Hz, 1 H, C-1), 2.89-3.16(m, 1 H), 3.37(s, 3 H, OCH_3), 3.47(s, 3 H, OCH_3), 3.76(dd, J=5.1 and 10.1 Hz, 1 H, C-3), 3.98(dd, J=4.2 and 10.1 Hz, 1 H, C-3'), 4.26(dd, J=8.1 and 5.1 Hz, 1 H, C-11a), 4.39-4.59(m, 1 H, C-2), 4.70(s, 2 H, OCH_2), 4.73(d, J=9.9 Hz, 1 H, NCH_2O), 5.47(d, J=9.9 Hz, 1 H, NCH_2O), 7.27-7.97(m, 4 H, aromatic); m/z 320(M^+), 288, 258, 226, 198, 146.

Carbonylation of compound 6b.——A mixture of 6b(6.3 mg, 11 mmol), $Pd(PPh_3)_4$(1.27)

g, 1.1 mmol) and n-Bu_3N(4.47 g, 24.2 mmol) in toluene(20 ml) was heated under carbon monoxide(10 atm) at 110°C for 24 h. After usual work up, the residue was purified by column chromatography[ethyl acetate-CH_2Cl_2(1:1)]. The first fraction was 12(1.219 g, 23 %) and the second fraction was 8b(3.93 g, 69 %). 12: νmax(nujol) 1670, 1530 cm^{-1}; δ ($CDCl_3$) 2.29-2.45(m, 1 H), 2.45(s, 3 H, CH_3), 3.16-3.40(m, 1 H), 3.31(s, 3 H, OCH_3), 3.40(s, 3 H, OCH_3), 3.61(s, 3 H, OCH_3), 3.70-4.00(m, 2 H), 4.28(m, 2 H), 4.69(s, 2 H, OCH_2O), 4.70(d, J=10.5 Hz, 1 H, NCH_2O), 5.55(d, J=10.5 Hz, 1 H, NCH_2O), 6.97(s, 1 H, aromatic), 7.26(s, 1 H, aromatic), 7.31(d, J=8.3 Hz, 2 H, aromatic), 7.77(d, J=8.3 Hz, 2 H, aromatic); m/z 492(M^+), 428, 337, 273. 8b:(Found: M^+,520.1514. $C_{24}H_{28}N_2O_9S$ requires M, 520.1515); $[\alpha]_D^{22}$ +224.0°(c 0.20 in $CHCl_3$); νmax(neat) 1690, 1640 cm^{-1}; δ($CDCl_3$) 2.04-2.39(m, 1 H, C-1), 2.44(s, 3 H, CH_3), 3.02(ddd, J=6.0, 8.1 and 13.0 Hz, C-1), 3.36(s, 3 H, OCH_3), 3.40(s, 3 H, OCH_3), 3.65(s, 3 H, OCH_3), 3.91(m, 1 H, C-3), 4.27(dd, J=6.0 and 9.1 Hz, C-11a), 4.39(m, 2 H, C-3 and C-2), 4.59(d, J=9.6 Hz, 1 H, NCH_2O), 4.66(s, 2 H, OCH_2), 5.39(d, J=9.6 Hz, 1 H, NCH_2O), 7.34(d, J=8.3 Hz, 2 H, aromatic), 7.36(s, 1 H, aromatic), 7.50(s, 1 H, aromatic), 7.79(d, J=8.3 Hz, 2 H, aromatic); m/e 520(M^+), 391, 346, 45.

(2R,11aS)-2-Hydroxy-2,3,5,10,11,11a-hexahydro-10-methoxymethyl-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(12a).——A solution of 8a(70 mg, 0.219 mmol) in MeOH-HCl(10% HCl:MeOH=1:10, 4 ml) was allowed to stand for 12 h at 50°C. Ethyl acetate was added and the organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The residue was purified by preparative thin layer chromatography on silica gel[CH_2Cl_2-acetone(5:1)]. The upper fraction was 12a(39 mg, 65 %) and the lower fraction was 13a(15 mg, 30 %). 12a: m.p. 144-145°C(from acetone),(Found. C, 60.91; H, 5.85; N, 10.19. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.88; N, 10.14%); $[\alpha]_D^{22}$ +430.5° (c 0.3 in $CHCl_3$); δmax($CHCl_3$), 3400, 1690, 1630, 1460 cm^{-1}; δ($CDCl_3$) 2.14(dddd, J=1.5, 3.9, 5.8, 13.7 Hz, 1 H, C-1), 2.86-3.11(m, 1 H, C-1), 3.47(s, 3 H, OCH_3), 3.65(dd, J=4.9 and 12.7, C-3), 3.94(ddd, J=1.5, 5.2 and 12.7 Hz, 1 H, C-3), 4.31(dd, J=5.8 and 8.1 Hz, 1 H, C-11a), 4.72(d, J=9.8, C-2), 4.72(d, J=9.8, NCH_2O), 5.47(d, J=9.8, NCH_2O), 7.24-7.82(m, 4 H, aromatic); m/z 276(M^+), 231, 191, 146. 13a: (powder), νmax($CHCl_3$) 3400, 1690, 1630, 1475 cm^{-1}; δ ($CDCl_3$) 2.10-2.29(m, 1 H, C-1), 2.96(ddd, J=5.4, 6.4 and 13.4 Hz, 1 H, C-1), 3.66(dd, J=4.5 and 12.5, 1 H, C-3), 4.31(dd, J=6.4 and 7.6 Hz, 1 H, C-11), 4.63(m, 1 H, C-2), 6.97-8.03(m, 4 H, aromatic), 8.24(brs, 1 H, NH); m/z 232(M^+), 160, 119, 86.

(2R,11aS)-2,3,5,10,11,11a-Hexahydro-2-hydroxy-7-methoxy-10-methoxymethyl-8-tosyloxy-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(12b).——A solution of 8b(1.8 g, 3.46 mmol) in 10% HCl(3.3 ml) and MeOH(30 ml) was warmed at 50°C for 20 h. After the usual work up, the residue was purified by column chromatography-[CH_2Cl_2-acetone(5:1)]. The first fraction 12b was obtained as a colorless amorphous solid(1.11 g, 67 %) and the second fraction 13b was obtained as a colorless powder(446 mg, 30 %). 12b: (Found: M^+, 476.1246. $C_{22}H_{24}N_2O_8S$ requires M, 476.1253); νmax(neat) 3400, 1690, 1640 cm^{-1};δ($CDCl_3$) 2.11-2.34(m, 1 H, C-1), 2.46(s, 3 H, CH_3), 2.98(dt, J=5.6 and 13.9 Hz, 1 H, C-1), 3.41(s, 3 H, OCH_3), 3.58(d, J=12.2 Hz, 1 H, C-3), 3.63(s, 3 H, OCH_3), 3.90(brd, J=12.2 Hz, 1 H, C-3), 4.30(dd, J=5.6 and 8.5 Hz, 1 H, C-11a), 4.60(d, J=9.7 Hz, 1 H, NCH_2O), 4.66(brs, 1 H, C-2), 5.39(d, J=9.7 Hz, 1 H, NCH_2O), 7.33(d, J=8.0 Hz, aromatic), 7.35(s, 1 H, aromatic), 7.50(s, 1 H, aromatic), 7.79(d, J=8.0 Hz, 2 H, aromatic); m/z 476(M^+), 391, 346, 45. 13b: νmax(nujol) 3450, 3200, 1680, 1620 cm^{-1}; δ ($CDCl_3$) 2.18(m, 1 H, C-1), 2.45(s, 3 H, CH_3), 2.64-2.72(m, 1 H, C-1), 3.28-3.81(m, 2 H, C-3), 3.57(s, 3 H, OCH_3), 4.22(d, J=8.3 Hz, 1 H, C-11a), 4.56(brs, 1 H, C-2), 7.16(s, 1 H, aromatic), 7.29(d, J=8.1 Hz, 2 H, aromatic), 7.37(brs, 1 H, NH), 7.43(brs, 1 H, aromatic), 7.77(d, J=8.1 Hz, 2 H, aromatic); m/z 432(M^+), 277, 155, 86.

Conversion of 13a to 8a.——A mixture of NaH(60%, mineral oil suspension, 12.5 mg, 0.31 mmol) and 13a(30 mg, 0.13 mmol) in DMF(1 ml) was stirred under argon at 0°C for 30 min. To the solution was added MOMCl(25 l, 0.33 mmol) and the reaction mixture was stirred at 0°C for 30 min. Sat. NH_4Cl was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography [ethyl acetate-CH_2Cl_2(1:1)] to give 8a(39 mg, 93 %).

Conversion of 13b to 8b.——The crude product from 13b(245 mg, 0.567 mmol), NaH(60 % mineral oil suspension, 57 mg, 1.42 mmol) and MOMCl(137 mg, 1.7 mmol) in THF-DMF(10:1, 4.4 ml) was purified by column chromatography using acetone-CH_2Cl_2(1:8) to afford 8b(290 mg, 98 %).

(11aS)-2,3,4,5,10,11a-Hexahydro-10-methoxymethyl-2,5,11-trioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(9a).——To 12a(560 mg, 2.03 mmol) in CH_2Cl_2(25 ml) containing molecular sieve 3A(2.5 g) was added PCC(1.2 g, 5.57 mmol) and the mixture was stirred at room temperature for 2 h. Ether(25 ml) was added and the reaction mixture was chromatographed on a silica gel column to afford colorless crystals of 9a(556 mg, quant.), m.p. 180-181°C(from ethyl acetate)(Found: C, 61.36; H, 5.02; N, 10.30. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.15; N, 10.21 %); νmax($CHCl_3$) 1765, 1690, 1640, 1460 cm^{-1};δ($CDCl_3$) 2.80(ddd, J=1.2, 10.0 and 19.3 Hz, 1 H, C-1),

3.48(s, 3 H, OCH_3), 3.80(dd, J=19.3 and 3.2, 1 H, C-1), 3.91(d, J=20.3, 1 H, C-3), 4.26(d, J=20.3 Hz, 1 H, C-3), 4.66(dd, 1 H, J=10.0 and 3.2 Hz, 1 H, C-11a), 4.77(d, J=10.0 Hz, 1 H, NCH_2O), 5.50(d, J=10.0 Hz, 1 H, NCH_2O), 7.27-7.96(m, 4 H, aromatic); m/z 274(M^+), 259, 242, 191, 146.

(11aS)-2,3,5,10,11,11a-Hexahydro-7-methoxy-10methoxymethyl-8-tosyloxy-2,5,11-trioxo-1H-pyrrolo-[2,1-c]-[1,4]benzodiazepine(9b).——The crude product obtained from 12b(10 mg, 0.021 mmol), PCC(10 mg, 0.046 mmol) and molecular sieve 3A(20 mg) in CH_2Cl_2(1 ml) in a manner similar to that described above was purified by column chromatography using ethyl acetate to afford 9b(10 mg, quant.): (Found: M^+, 474.1098. $C_{22}H_{22}N_2O_8S$ requires M, 474.1097); νmax(neat) 1775, 1695, 1640 cm^{-1}; δ($CDCl_3$) 2.47(s, 3 H, CH_3), 2.82(dd, J=9.9 and 19.0 Hz, C-1), 3.42(s, 3 H, OCH_3), 3.51-3.79(m, 1 H, C-1), 3.66(s, 3 H, OCH_3), 3.93(d, J=19.7 Hz, 1 H, C-3), 4.24(d, J=19.7 Hz, 1 H, C-3), 4.59-4.70(m, 2 H, C-11a and NCH_2O), 5.43(d, J=9.8 Hz, 1 H, NCH_2O), 7.34(s, 1 H, aromatic), 7.35(d, J=7.8 Hz, 2 H, aromatic), 7.54(s, 1 H, aromatic), 7.79(d, J=7.8 Hz, 2 H, aromatic); m/z 474(M^+), 346, 177, 45.

(11aS)(Z)-2-Ethylidene-2,3,5,10,11a-hezahydro-10-methoxymethyl-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepiune(10a).——A suspension of dry $Ph_3PCH_2CH_3Br$(700 mg, 1.88 mmol) and freshly sublimed t-BuOK(190 mg, 1.70 mmol) in dry THF(2 ml) was stirred under argon for 20 min. A solution of 9a(50 mg, 0.18 mmol) in THF(1.5 ml) was added at 0°C and the mixture was stirred at room temperature for 1 h. Sat. NH_4Cl was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatograpy using n-hexane-ethyl acetate(1:1) to give 10a as a colorless oil(53 mg, quant.),(Found: M^+, 286.1292. $C_{16}H_{18}N_2O_3$ requires M, 286.1316); νmax(neat) 1690, 1640, 1460 cm^{-1}; δ($CDCl_3$) 1.66(brd, J=6.8 Hz, 3 H, CH_3), 2.70-2.88(m, 1 H, C-1), 3.33-3.42(m, 1 H, C-1), 3.48(s, 3 H, OCH_3), 4.22-4.27(m, 3 H, C-3 and C-11a), 4.77(d, J=9.7 Hz, 1 H, NCH_2O), 5.46(d, J=9.7 Hz, 1 H, NCH_2O), 5.57-5.63(m, 1 H, CH=), 7.31-7.94(m, 4 H, aromatic); m/z 286(M^+), 254, 226, 146;

(11aS)(Z)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-7-methoxy-10-methoxymethyl-8-tosyloxy-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]-benzodiazepine(10b).——The crude product obtained from dry $Ph_3PCH_2CH_3Br$(820 mg, 2.2 mmol), freshly sublimed t-BuOK(224 mg, 2 mmol) and 9b(95 mg, 0.2 mmol) in THF in a manner similar to that described above was purified by column chromatography using ethyl acetate-CH_2Cl_2(2:3) to afford 10b(86 mg, 88 %) as a colorless amorphous powder,(Found: M^+, 486.1479. $C_{24}H_{26}N_2O_7S$ requires M, 486.1460); νmax(neat) 1690, 1640 cm^{-1}; δ($CDCl_3$) 1.65(d, J=6.6 Hz, 3 H, CH_3), 2.46(s, 3 H, CH_3), 2.73-2.83(m, 1 H, C-1), 3.34-3.42(m, 1 H, C-1), 3.40(s, 3 H, OCH_3), 3.65(s, 3 H, OCH_3), 4.21-4.25(m, 3 H), 4.58(d, J=9.9 Hz, 1 H, NCH_2O), 5.38(d, J=9.9 Hz, 1 H, NCH_2O), 5.55-5.58(m, 1 H, =CH), 7.33(d, J=8.4 Hz, 2 H, aromatic), 7.35(s, 1 H, aromatic), 7.49(s, 1 H, aromatic), 7.78(d, J=8.4 Hz, 2 H, aromatic); m/z 486(M^+), 426, 332, 155, 91, 45.

Epoxidation of 14a with MCPBA.——To a solution of 10a(53 mg, 0.185 mmol) was added MCPBA(40 mg, 0.23 mmol) and $NaHCO_3$(28 mg, 0.33 mmol) and a mixture was stirred overnight. The solvent was evaporated and the residue was purified by column chromatography [n-hexane-ethyl acetate(2:3)]. The first fraction 15 was obtained as a colorless amorphous powder(39 mg, 70 %) and the second fraction 16 was obtained as a colorless amorphous powder(17 mg, 30 %). 15: νmax($CHCl_3$) 1680, 1630 cm^{-1}; δ($CDCl_3$) 1.36(d, J=5.6 Hz, 3 H, CH_3), 2.25(dd, J=9.0 and 14.2, 1 H, C-1), 3.04(dd, J=3.7 and 14.2 Hz, 1 H, C-1), 3.36(q, J=5.6 Hz, 1 H, OCH), 3.50(s, 3 H, OCH_3), 3.80(s, 2 H, C-3), 4.41(dd, J=3.7 and 9.0 Hz, 1 H, C-11a), 4.72(d, J=9.8 Hz, 1 H, NCH_2O), 5.51(d, J=9.8 Hz, 1 H, NCH_2O), 7.28-7.95(m, 4 H, aromatic); m/z 302(M^+), 146. 16: ν max($CHCl_3$) 1680, 1630 cm^{-1}; δ ($CDCl_3$) 1.36(d, J=5.4 Hz, 3 H, CH_3), 2.51(dd, J=2.2 Hz and 14.2 Hz, 1 H, C-1), 2.80(dd, J=2.2 and 14.2 Hz, 1 H, C-1), 3.28(q, J=5.4, 1 H, OCH), 3.52(s, 3 H, OCH_3), 3.64(d, J=12.6 Hz, 1 H, C-3), 4.04(d, J=12.6 Hz, 1 H, C-3H), 4.34(dd, J=2.2 and 9.0 Hz, 1 H, C-11a), 4.75(d, J=10 Hz, 1 H, NCH_2O), 5.55(d, J=10.0 Hz, 1 H, NCH_2O), 7.33-7.96(m, 4 H, aromatic); m/z 302(M^+), 146.

(11aS)(E)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-10-methoxymethyl-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine(17a).——From 15: To a suspension of Li(80 mg) in THF(25 ml) was added $ClPPh_2$(0.5 mL, 2.8 mmol) slowly under argon in an water-bath and the mixture was stirred for 2 h. To the $LiPPh_2$ solution(100 l, 0.093 mmol) was added a solution of 15(15 mg, 0.05 mmol) in THF(1 ml). After stirring for 1 h, freshly distilled MeI(15 l, 0.245 mmol) was added slowly to the reaction mixture and the solution was stirred at 0°C for 30 min. Water was added to the mixture and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporate. The residue was purified by column chromatography[n-hexane-ethyl acetate(1:1)] to give 17a as a colorless oil(5 mg, 35 %),(Found: M^+, 286.1328. $C_{16}H_{18}N_2O_3$ requires M, 286.1318); ν max(neat) 1690, 1640 cm^{-1}; δ($CDCl_3$) 1.74(brd, J=6.8 Hz, 3 H, CH_3), 2.56-2.69(m, 1 H, C-1), 3.43-3.49(m, 1 H, C-1), 3.48(s, 3 H, OCH_3), 4.13-4.34(m, 3 H, C-3-CH_2 and C-11a), 4.70(dd, J=9.8 Hz, NCH_2O), 5.47(d, J=9.8 Hz, 1 H, NCH_2O), 5.52-5.56(m, 1 H, =CH), 7.28-7.95(m, 4 H, aromatic); m/z 286(M^+), 254, 226, 146. From 16: To the $LiPPh_2$

solution (100 l, 0.093 mmol) was added a solution of 16(15 mg, 0.05 mmol) in THF(1 ml) and the mixture was stirred for 1 h and then MeI(15 l, 0.24 mmol) was added to the reaction mixture. After similar work-up, the desired compound 17a(3.6 mg, 25 %) was obtained.

Oxidation of 10a with OsO_4.—A solution of 13a(30 mg, 0.105 mmol) in acetone-CH_2Cl_2(8:3)(2 ml) was added to the solution of N-methylmorpholine-N-oxide monohydrate(36 mg, 0.3 mmol) and OsO_4(0.1 ml of 1 % t-BuOH solution) in H_2O-acetone-t-BuOH(5:2:1)(3 ml) and the mixture was stirred at room temperature for 6 h. A mixture of $Na_2SO_3.7H_2O$(12.5 mg) and magnesium silicate(150 mg) was added to the reaction mixture and this was stirred for 30 min. Undissolved material was filtered off and the filtrate was acidfied with dil.H_2SO_4. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative thin layer chromatography on silica gel[ethyl acetate-MeOH(10:1)]. The upper fraction 20a(6 mg, 18 %) and the lower fraction 18a(24 mg, 72 %) were obtained. 18a: ν max(neat) 3450, 1700-1635, 1470 cm^{-1}; δ($CDCl_3$) 1.30(d, J=6.6 Hz, 3 H, CH_3), 2.21(dd, J=5.6 and 11.7 Hz, 1 H, C-1), 3.01(dd, J=7.6 and 11.7 Hz, 1 H, C-1), 3.37(d, J=12.9 Hz, 1 H), 3.47(s, 3 H, CH_3), 3.90-4.37(m, 3 H), 4.73(d, J=9.6 Hz, 1 H, NCH_2O), 5.46(d, J=9.6 Hz, 1 H, NCH_2O), 7.34-7.94(m, 4 H, aromatic); m/z 320(M^+), 276, 244, 191, 146. 21a: ν max(neat) 3450, 1700-1635 1470 cm^{-1}; δ($CDCl_3$) 1.29(d, J=6.1 Hz, 3 H, CH_3), 2.30(dd, J=8.5 and 14.2 Hz, C-1), 2.81(d, J=14.2 Hz, C-1), 3.49(s, 3 H, OCH_3), 3.50-4.39(m, 4 H), 4.78(d, J=9.8 Hz, 1 H, NCH_2O), 5.52(d, J=9.8 Hz, 1 H, NCH_2O), 7.32-7.98(m, 4 H, aromatic); m/z 320 (M^+), 276, 244, 191, 146.

Oxidation of 10b with OsO_4.—The crude product obtained from 10b(50 mg, 0.1 mmol) in acetone-CH_2Cl_2(8:3, 11 ml), N-methylmorpholine-N-oxide monohydrate(40 mg, 0.3 mmol) and OsO_4(0.1 ml of 1 % t-BuOH solution) in t-BuOH-H_2O-acetone(1:5:2, 1 ml) was purified by column chromatography using ethyl acetate-MeOH(10:1) to afford a mixture of diol 18b and 20b(53 mg, quant), νmax(neat) 3400, 1685, 1630 cm^{-1}; δ($CDCl_3$) 1.28(d, J=6.3 Hz, 3 H, CH_3), 2.1(brs, 2 H, OH), 2.19(m, 1 H, C-1), 2.46(s, 3 H, CH_3), 2.95(dd, J=7.8 and 14.2 Hz, 1 H, C-1), 3.41(s, 3 H, OCH_3), 3.63(s, 3 H, OCH_3), 3.57-4.43(m, 4 H), 4.62(d, J=9.5 Hz, 1 H, NCH_2O), 5.39(d, J=9.5 Hz, 1 H, NCH_2O), 7.33(d, J=8.8 Hz, 2 H, aromatic), 7.36(s, 1 H, aromatic), 7.51(s, 1 H, aromatic), 7.78(d, J=8.8 Hz, 2 H, aromatic); m/z 520(M^+), 444, 391, 155, 91, 45.

Mesylation of 18a.—A solution of 18a(17 mg, 0.053 mmol), Et_3N(10 l, 0.072 mmol) and MsCl(45 l, 0.058 mmol) in CH_2Cl_2(1 ml) was stirred at 0°C for 5 min. 5 % HCl was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using ethyl acetate to afford 19a(21 mg, quant.), νmax(neat) 3400, 1690, 1630, 1175 cm^{-1}; δ ($CDCl_3$) 1.56(d, J=6.3 Hz, 3 H, CH_3), 2.21(ddd, J=2.5, 8.0 and 13.9 Hz, 1 H, C-1), 3.05(dd, J=8.3 and 13.9 Hz, C-1), 3.12(s, 3 H, OMs), 3.41(d, J=13.7 Hz, 1 H, C-3), 3.48(s, 3 H, OCH_3), 4.13(dd, J=2.5 and 13.7 Hz, 1 H, C-3), 4.40(t, J=8.0 Hz, 1 H, C-11a), 4.74(d, J=9.8 Hz, 1 H, NCH_2O), 4.98(q, J=6.3 Hz, 1 H, CHOMs), 5.48(d, J=9.8 Hz, NCH_2O, 1 H), 7.32-7.90(m, 4 H, aromatic); m/z 398(M^+), 302, 146.

Mesylation of 20a.—The crude product obtained from 20a(5 mg, 0.0156 mmol), Et_3N(3 l, 0.0215 mmol) and MsCl(1.3 l, 0.0168 mmol) in a similar manner described above was purified by column chromatography using ethyl acetate to afford 21a(6.5 mg, quant.), ν max(neat) 3400, 1690, 1630, 1175 cm^{-1}; δ ($CDCl_3$) 1.56(d, J=6.3 Hz, J=6.6 Hz, CH_3), 2.37(dd, J=8.7 and 14.2 Hz, 1 H, C-1), 2.80(d, J=14.2 Hz, 1 H, C-1), 3.10(s, 3 H, Ms), 3.49(s, 3 H, OCH_3), 3.59(d, J=12.9 Hz, 1 H, C-3), 3.86(d, J=12.9 Hz, 1 H, C-3), 4.35(d, J=8.7 Hz, 1 H, C-11a), 4.78(d, J=9.8 Hz, 1 H, NCH_2O), 4.84(q, J=6.6 Hz, 1 H, , CHOMs), 5.52(d, J=9.8, 1 H, NCH_2O), 7.29-7.98(m, 4 H, aromatic); m/z 398(M^+), 302, 146.

Mesylation of 18b and 20b.—The crude product which was prepared from a mixture of 18b and 21b(260 mg, 0.5 mmol), MsCl(57 mg, 0.5 mmol) and NEt_3(90 l, 0.065 mmol) at -30°C in a similar manner described above, was purified by chromatography using ethyl acetate to afford a mixture of 19b and 21b(300 mg, quant.), νmax(neat) 3350, 1690, 1630 cm^{-1}; δ ($CDCl_3$) 1.55(d, J=6.6 Hz, 3 H, CH_3), 2.18(ddd, J=1.5, 8.1 and 14.2 Hz, 1 H, C-1), 2.46(s, 3 H, CH_3), 3.01(dd, J=8.6 and 14.2 Hz, C-1), 3.11(s, 3 H, CH_3), 3.37(d, J=12.5 Hz, 1 H, C-3), 3.41(s, 3 H, OCH_3), 3.63(s, 3 H, CH_3), 3.98-4.46(m, 2 H, C-3 and C-11a), 4.63(d, J=9.8 Hz, 1 H, NCH_2O), 4.96(q, J=6.6 Hz, 1 H, CHOMs), 5.40(d, J=9.8 Hz, 1 H, NCH_2O), 7.34(d, J=8.5 Hz, 2 H, aromatic), 7.35(s, 1 H, aromatic), 7.52(s, 1 H, aromatic), 7.79(d, J=8.5 Hz, 2 H, aromatic); m/z 502(M^+-MsOH), 391, 346, 155, 91, 45.

Epoxidation of 19a.—A solution of 19a(20 mg, 0.05 mmol) in MeOH(2 ml) containing KOH(6 mg) was stirred at 0°C for 2 min. Ethyl acetate was added to the reaction mixture and the organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography[ethyl acetate-CH_2Cl_2(1:1)] to afford 22a(15 mg, quant.), (Found: M^+, 302.1260. $C_{16}H_{18}N_2O_4$

requires M, 302.1266); νmax($CHCl_3$) 1680, 1630 cm^{-1}; δ ($CDCl_3$), 1.47(d, J=5.4, CH_3), 2.19(dd, J=9.0 and 14.4 Hz, 1 H, C-1), 2.30(dd, J=3.6 and 14.4, 1 H, C-1), 3.25(q, J=5.4, 1 H, C-12), 3.48(s, 3 H, OCH_3), 3.80(s, 2 H, C-3), 4.42(dd, J=3.6 and 9.0 Hz, 1 H, C-11a), 4.70(d, J=9.8 Hz, 1 H, NCH_2O), 5.48(d, J=9.8 Hz, 1 H, NCH_2O), 7.28-7.95(m, 4 H, aromatic); m/z 302(M^+), 146.

Epoxydation of 21a.——Same treatment of 21a(5 mg) with KOH in MeOH afforded 23a(6.5 mg, quant), (Found: M^+, 302.1278. $C_{16}H_{18}N_2O_4$ requires M, 302.1267); ν max($CHCl_3$) 1680, 1630 cm^{-1}; δ ($CDCl_3$) 1.42(d, J=5.2 Hz, 3 H, CH_3), 2.48(dd, J=9.0 and 14.2 Hz, 1 H, C-1), 2.81(dd, J=2.4 and 14.2, 1 H, C-1), 3.26(q, J=5.2 Hz, 1 H, C-12), 3.52(s, 3 H, OCH_3), 3.76(d, J=13.7 Hz, 1 H, C-3), 4.02(d, J=13.7 Hz, 1 H, C-3), 4.34(dd, J=2.4 and 9.0 Hz, 1 H, C-11a), 4.75(d, J=10.0 Hz, 1 H, NCH_2O), 5.55(d, J=10 Hz, 1 H, NCH_2O), 7.33-7.95(m, 4 H, aromatic); m/z 302(M^+), 146.

Epoxydation of 19b and 21b.——The crude product obtained from a mixture of 19b and 21b(300 mg, 0.5 mmol) and K_2CO_3(50 mg) in MeOH(10 ml) was purified by chromatography using ethyl acetate-CH_2Cl_2(1:1) to afford a mixture of 22b and 23b(242 mg, 96 %). The crude mixture(22b and 23b, 49 mg) was separated by preparative thin layer chromatography on silica gel [ethyl acetate-CH_2Cl_2(1:1)]. The upper band 22b(45 mg) and the lower band 23b(2 mg) were obtained. 22b: (Found: M^+, 502.1393. $C_{24}H_{26}N_2O_8S$ requires M, 502.1409); ν max(neat) 1690, 1640 cm^{-1}; (CDCl$_3$) 1.46(d, J=5.4 Hz, 3 H, CH_3), 2.19(dd, J=9.0 and 14.4 Hz, 1 H, C-1), 2.46(s, 3 H, CH_3), 3.04(dd, J=3.7 and 14.4 Hz, 1 H, C-1), 3.25(q, J=5.4 Hz, 1 H, C-12), 3.42(s, 3 H, OCH_3), 3.63(s, 3 H, OCH_3), 3.77(s, 2 H, C-3), 4.41(dd, J=3.7 and 9.0 Hz, 1 H, C-11a), 4.60(d, J=9.8 Hz, 1 H, NCH_2), 5.41(d, J=9.8 Hz, 1 H, NCH_2O), 7.33(s, 1 H, aromatic), 7.34(d, J=8.3 Hz, 2 H, aromatic), 7.54(s, 1 H, aromatic), 7.78(d, J=8.3 Hz, 2 H, aromatic); m/z 502(M^+), 391, 346, 155, 91, 45. 23b: (Found:M^+, 502.1393. $C_{24}H_{26}N_2O_8S$ requires M, 502.1410); ν max(neat) 1690, 1640 cm^{-1}; δ ($CDCl_3$) 1.40(d, J=5.6 Hz, 3 H, CH_3), 2.35(dd, J=9.0 and 12.7 Hz, 1 H, C-1), 2.46(s, 3 H, CH_3), 2.84(dd, J=2.3 and 12.7 Hz, 1 H, C-1), 3.22(q, J=5.6 Hz, 1 H, C-12), 3.43(s, 3 H, OCH_3), 3.56(d, J=14.2 Hz, 1 H, C-3), 3.67(s, 3 H, OCH_3), 4.01(d, J=14.2 Hz, 1 H, C-3), 4.34(dd, J=2.3 and 9.0 Hz, 1 H, C-11a), 4.58(d, J=10.0 Hz, 1 H, NCH_2O), 5.47(d, J=10.0 Hz, 1 H, NCH_2O), 7.34(d, J=8.2 Hz, 2 H, aromatic), 7.35(s, 1 H, aromatic), 7.52(s, 1 H, aromatic), 7.79(d, J=8.2 Hz, 2 H, aromatic); m/z 502(M^+), 391, 346, 155, 91, 45.

(11aS)(E)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-10-methoxymethyl-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(17a).——From 22a: To a solution of 22a(14 mg, 0.046 mmol) in CH_2Cl_2-pyridine(3.5:1, 2 ml) was added P_2I_4(26 mg, 0.046 mmol) and the mixture was warmed at 30°C for 16h. Ethyl acetate was added and the organic layer was washed with 5 % HCl, 1 % $Na_2S_2O_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography[ethyl acetate-CH_2Cl_2(1:1)] to give a colorless oil of 17a(13 mg, 98 %). From 23a: Compound 17a(4 mg, quant) was obtained from 23a(4 mg, 0.013 mmol) and P_2I_4(8 mg, 0.014 mmol) in a similar manner.

(11aS)(E)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-7-methoxy-10-methoxymethyl-8-tosyloxy-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(17b).——The crude product obtained a mixture of 22b and 23b(36 mg, 0.072 mmol) and P_2I_4(41 mg, 0.072 mmol) in CH_2Cl_2-pyridine(6:1) was purified by column chromatography using ethyl acetate-CH_2Cl_2(1:1) to afford 17b(31.5 mg, 90 %),(Found: M^+, 486.1454. $C_{24}H_{26}N_2O_7S$ requires M, 486.1459); νmax(neat) 1690, 1640 cm^{-1}; δ($CDCl_3$) 1.74(d, J=6.6 Hz, 3 H, CH_3), 2.46(s, 3 H, CH_3), 2.59-2.68(m, 1 H, C-1); 3.41(s, 3 H, OCH_3), 3.42-3.50(m, 1 H, C-1), 3.64(s, 3 H, OCH_3), 4.18-4.34(m, 3 H, C-3, C-11a), 4.58(d, J=9.9 Hz, 1 H, NCH_2O), 5.39(d, J=9.9 Hz, 1 H, NCH_2O), 5.53-5.56(m, 1 H, =CH), 7.34(d, J=8.0 Hz, 2 H, aromatic), 7.34(s, 1 H, aromatic), 7.50(s, 1 H, aromatic), 7.77(d, J=8.0 Hz, 2 H, aromatic); m/z 486(M^+), 426, 332, 155, 91, 45.

(11aS)(Z)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7-methoxy-10-methoxy methyl-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(10c).——A solution of 10b(85 mg, 0.175 mmol) in MeOH(5 ml) and 10 % KOH(1.5 ml) was stirred at room temperature for 4 h. The mixture was neutralized with 5 % HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using ethyl acetate to afford 10c(57 mg, 98 %), (Found: M^+, 332.1367. $C_{17}H_{20}N_2O_5$ requires M, 332.1372); ν max(neat) 3200, 1680, 1620 cm^{-1}; δ ($CDCl_3$) 1.67(brd, J=6.9 Hz, 3 H, CH_3), 2.60-2.92(m, 1 H, C-1), 3.28-3.42(m, 1 H, C-1), 3.41(s, 3 H, OCH_3), 3.92(s, 3 H, OCH_3), 4.18-4.30(m, 3 H, C-3 and C-11a), 4.66(d, J=10.0 Hz, 1 H, NCH_2O), 5.40(d, J=10.0 Hz, 1 H, NCH_2O), 5.40-5.60(m, 1 H, =CH), 6.16(brs, 1 H, OH), 7.20(s, 1 H, aromatic), 7.34(s, 1 H, aromatic); m/z 332(M^+), 272, 192, 178.

(11aS)(E)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7-methoxy-10-methoxy methyl-5,11-dioxo-1H-pyrrolo-[2,1-c][1,4]benzodiazepine(17c).——The crude product obtained from 17b(14 mg, 0.029 mmol) in MeOH(0.7 ml) and 10 % KOH(0.2 ml) was purified by column chromatography using ethyl acetate to afford 17c(10 mg, quant.), (Found: M^+, 332.1369. $C_{17}H_{20}N_2O_5$ requires M, 332.1371); νmax(neat) 3200,

1680, 1620 cm^{-1}; δ ($CDCl_3$) 1.77(brd, J=6.9 Hz, 3 H, CH_3), 2.44-2.75(m, 1 H, C-1), 3.40-3.56(m, 1 H, C-1), 3.41(s, 3 H, OCH_3), 3.96(s, 3 H, OCH_3), 3.94-4.36(m, 3 H, C-3 and C-11a), 4.68(d, J=10.0 Hz, 1 H, NCH_2O), 5.43(d, J=10.0 Hz, 1 H, NCH_2O), 5.42-5.60(m, 1 H, =CH), 6.01(brs, 1 H, OH), 7.21(s, 1 H, aromatic), 7.33(s, 1 H, aromatic); m/z 332(M^+), 272, 192, 178.

(E)-Prothracarcin(18a).——To a solution of 17a(44 mg, 0.16 mmol) in EtOH(2 ml) was added $NaBH_4$(57 mg, 1.5 mmol) and the mixture was stirred at 0°C for 3 h. Benzene was added to the reaction mixture and the organic layer was washed with water dried over Na_2SO_4 and evaporated. To the residue dissolved in benzene was added silica gel(230-400 mesh, Merck Art. 9385, 200 mg) and the mixture was strried at room temperature for 30 min. Solvent was evaporated and the residual solid was placed on a column of silica-gel. Elution with n-hexane-acetone(1:1) gave 18a as a pale yellow powder(31 mg, 89 %), m.p. 87-88°C(triturated with ether, lit[4] m.p. 85-87°C),(Found: M^+, 226.1107. $C_{14}H_{14}N_2O$ requires M, 226.1107); $[\alpha]_D^{17}$ +18.3°(c 0.21 in ethyl acetate); ν max($CHCl_3$) 1620, 1440 cm^{-1}; δ ($CDCl_3$) 1.75(dt, J=1.5, 6.8 Hz, 3 H, CH_3), 2.97(brd, J=5.8 Hz, 2 H, C-1), 3.91(dd, J=5.8, 10.7 Hz, 1 H, C-11a), 4.20-4.39(m, 2 H, C-3), 5.53-5.64(m, 1 H, =CH), 7.33-7.63(m, 3 H), 7.77(d, J=4.4 Hz, 1 H, C-11), 8.01-8.06(m, 1 H, C-6); m/z 226(M^+).

(Z)-Prothracarcin(14a).——(Z)-Prothracarcin(8 mg, 84 %) was obtained from 10a(10 mg, 0.036 mmol) and $NaBH_4$(13 mg, 0.34 mmol) in a similar manner as described above. m.p. 120-122°C (triturated from ether),(Found: M^+, 226.1114. $C_{14}H_{14}N_2O$ requires M, 226.1106), $[\alpha]_D^{18}$ +16.9°(c 0.148 in ethyl acetate); ν max($CHCl_3$) 1620, 1440 cm^{-1}; δ ($CDCl_3$) 1.70(brd, J=6.8 Hz, 3 H, CH_3), 2.85-3.20(m, 2 H, C-1), 3.86-3.95(m, 1 H, C-11a), 4.20-4.35(m, 2 H, C-3), 5.60-5.90(m, 1 H, =CH), 7.30-7.72(m, 3 H, aromatic), 7.78(d, J=4.9 Hz, 1 H, C-11), 8.02-8.07(m, 1 H, C-6); m/z 226(M^+).

(Z)-Pretomaymycin(14c).——To a solution of 10c(18 mg, 0.054 mmol) in THF(0.5 ml) was added $LiAlH_4$(3 mg, 0.079 mmol) under argon and a mixture was stirred at -60°C for 30 min. $Na_2SO_4.10H_2O$ was added to the reaction mixture and the mixture was stirred for several hours. CH_2Cl_2 was added and the organic layer was washed with brine dried over Na_2SO_4 and evaporated. The residue was dissolved in MeOH(4 ml) and silica gel(30 mg) was added to the mixture. After stirring for 5 min, undissolved material was filtered off and the filtrate was concentrated. The residue was purified by column chromatography using ethyl acetate to afford a pale yellow powder of (Z)-pretomaymycin(14c, 11 mg, 75 %), ν max(nujol) 3300, 1630, 1600 cm^{-1}; δ($CDCl_3$) 1.70(brd, J=6.6 Hz, 3 H, CH_3), 2.79-3.06(m, 2 H), 3.74-4.18(m, 3 H), 3.98(s, 3 H, OCH_3), 5.42-5.69(brs, 1 H, =CH), 6.09(brs, 1 H, OH), 6.89(s, 1 H, aromatic), 7.52(s, 1 H, aromatic), 7.67(d, J=4.4 Hz, C-11); m/z 272(M^+).

(E)-Pretomaymycin(2).——The crude product obtained from 18c(20 mg, 0.060 mmol) and $LiAlH_4$(3 mg, 0.079 mmol) in THF(0.5 ml) followed by treatment with silica gel in AcOEt(4 ml) was purified by column chromatography using ethyl acetate to afford (E)-pretomaymycin(2) as pale yellow powder(15 mg, 92 %),(Found: M^+, 272.1178. $C_{15}H_{16}N_2O_3$ requires M, 272.1161); $[\alpha]_D^{25}$ +215°(c 0.08 in pyridine); νmax(nujol) 3300, 1630, 1600 cm^{-1}; δ ($CDCl_3$) 1.75(dt, J=1.5, 6.6 Hz, 3 H, CH_3), 2.96(brd, J=5.9 Hz, 2 H, C-1), 3.85-3.92(m, 1 H, C-11a), 3.97(s, 3 H, OCH_3), 4.26(s, 2 H, C-3), 5.60(m, 1 H, =CH), 6.06(brs, 1 H, OH), 6.89(s, 1 H, aromatic), 7.51(s, 1 H, aromatic), 7.66(d, J=4.6 Hz, C-11); m/z 272(M^+).

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