STUDIES ON TOMAYMYCIN. II

TOTAL SYNTHESES OF THE ANTITUMOR ANTIBIOTICS, *E*- AND *Z*-TOMAYMYCINS*

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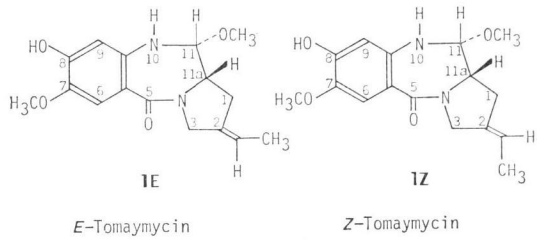
The total syntheses of naturally occurring *E*-tomaymycin (**1E**) and its olefinic geometrical isomer, *Z*-tomaymycin (**1Z**) are described. The *Z*-isomer was found to have the same antibacterial activity as *E*-isomer (**1E**).

Tomaymycin[1] is an antitumor antibiotic possessing the pyrrolo(1,4)benzodiazepine skeleton, such as anthramycin[2], neothramycin[3], and sibiromycin[4]. In a previous paper[5], we reported the structural determination of tomaymycin on the basis of NMR spectra. The structure of naturally occurring *E*-tomaymycin (**1E**) was determined as (11*R*, 11a*S*)-(*E*)-2-ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7,11-dimethoxy-5-oxo-1*H*-pyrrolo(2,1-c)-(1,4)benzodiazepine, although its plane structural formula has been determined by the chemical degradation method.[6]



In this paper we will describe the total syntheses of *E*- (**1E**) and *Z*-tomaymycins (**1Z**) and their antibacterial activity.

Chemistry

We first designed the total synthesis of tomaymycin according to Scheme 1. Condensation of 2-nitro-4-(2-nitrobenzyloxy)-5-methoxybenzoyl chloride (**2**) with L-hydroxyproline (**3**) under SCHOTTEN-BAUMANN's conditions gave *N*-[2-nitro-4-(2-nitrobenzyloxy)-5-methoxybenzoyl]-L-hydroxyproline (**4**) in 96% yield. The treatment of **4** with *N*,*N*'-carbonyldiimidazole and $LiAlH_4$ in tetrahydrofuran (THF) by the method of STAAB[7] gave the corresponding aldehyde (**5**) in 76% yield. Hydrogenation of **5** in the presence of 10% Pd-carbon gave a pyrrolo(1,4)benzodiazepine derivative (**6**) in 89% yield. However, attempted oxidation of **6** by a number of methods did not produce the desired ketone (**7**), because **6** was unstable under acidic or basic conditions.

Therefore, the introduction of the ethylidene group into the pyrrole ring by the WITTIG reaction must be done before cyclization to a pyrrolo(1,4)benzodiazepine derivative. In a previous paper[5] the WITTIG reaction of *N*-*t*-butoxycarbonyl-4-oxo-L-proline diphenylmethyl ester (**8**) according to the modified procedure reported by BETHELL *et al.*[8] gave a mixture of the corresponding 4*E*- and 4*Z*-ethylidene derivatives (**9E**, **9Z**), which were separated by repeated column chromatography on silica gel.

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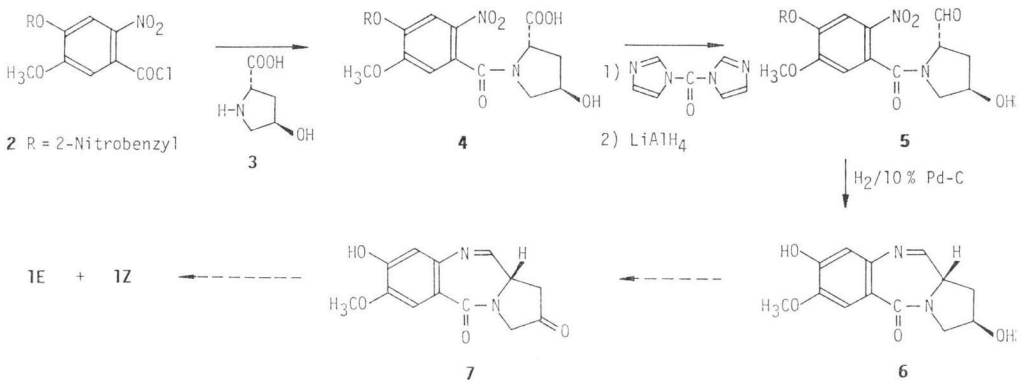
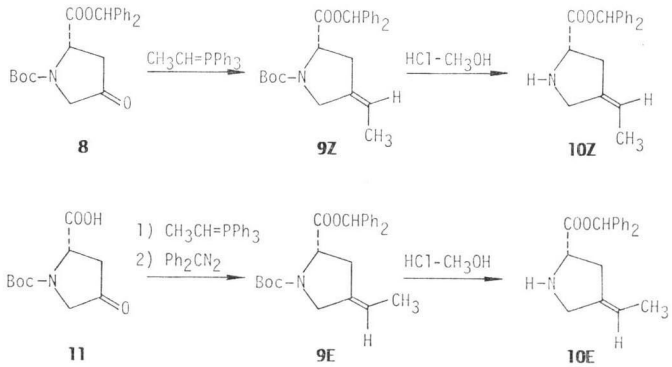
Scheme 1.



Scheme 2.

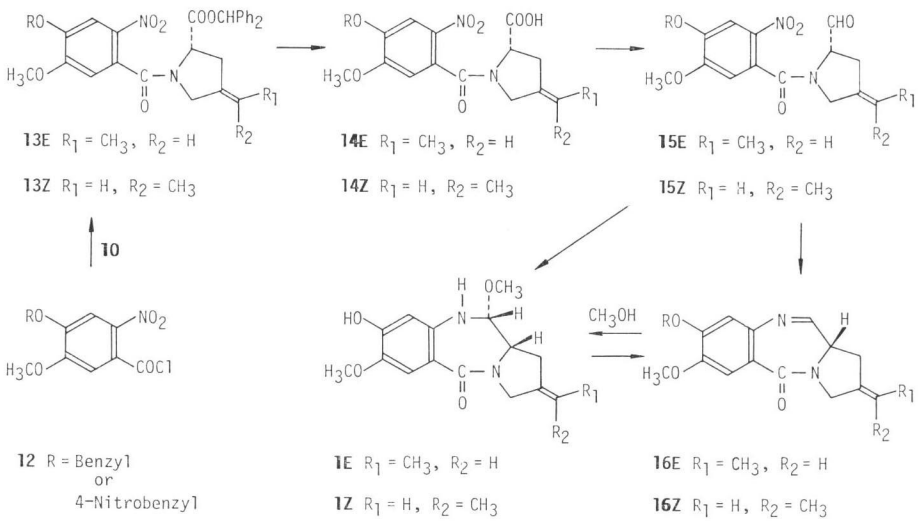


Now, we wish to report a stereoselective synthesis of **9E** and **9Z** as shown in Scheme 2. The NMR spectrum of **8** at room temperature predicted rotational isomerism due to restricted rotation of the two bulky groups (*t*-butoxycarbonyl group, of which three methyl group protons were split at 1.27 ppm and 1.40 ppm (2: 1), and diphenylmethyloxycarbonyl group). The rotational isomerism was not observed in the NMR spectrum of **8** at 90°C. These bulky groups affected the orientation of the intermediate in the WITTIG reaction of the 4-oxo group of **8** with ethylidenetriphenylphosphorane to give mainly the 4*Z*-ethylidene derivative (**9Z**), which was isolated in 49% by fractional crystallization.

On the other hand, the *t*-butoxycarbonyl group of **11** was freely rotatable at room temperature as indicated by a singlet at 1.40 ppm in the ^{1}H NMR spectrum of **11**. The *N*-*t*-butoxycarbonyl group, which is bulkier than the 2-carboxyl group of **11**, affected the orientation of the intermediate in the WITTIG reaction. The WITTIG reaction of **11** with ethylidenetriphenylphosphorane followed by esterification with diphenyldiazomethane gave mainly the 4*E*-ethylidene derivative (**9E**), which was isolated in 58% yield by fractional crystallization. Deprotection of the *t*-butoxycarbonyl group of **9E** with a methanol solution saturated with HCl gas gave the corresponding amine (**10E**) in 90% yield. In a similar manner **9Z** was converted to the corresponding amine (**10Z**) in 72% yield (Scheme 2).

Each of the 4*E*- and 4*Z*-ethylidene-L-proline diphenylmethyl esters (**10E**, **10Z**) was condensed with the acid chloride (**12**) in a similar manner as shown in Scheme 1 to give respectively the *N*-(2-nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-L-proline diphenylmethyl esters (**13E**, **13Z**), which were

Scheme 3.



treated with trifluoroacetic acid (TFA) in anisole to give respectively the corresponding acids (**14E**, **14Z**) in good yields. Each of **14E** and **14Z** was converted to the corresponding aldehydes (**15E**, **15Z**) in a moderate yield by the treatment with STAAB's reagent. *E*- And *Z*-tomaymycins (**1E**, **1Z**) were prepared respectively from **15E** and **15Z** by hydrogenation catalyzed with 5% Pd-$BaSO_4$ in methanol. Demethanolated tomaymycins (**16E**, **16Z**) were also prepared respectively from **15E** and **15Z** by similar hydrogenation in THF. Each of **16E** and **16Z** was dissolved in methanol and stored in a refrigerator for three days to give **1E** and **1Z** respectively. Reversely, each of **1E** and **1Z** was converted to **16E** and **16Z** respectively by repeated refluxing in chloroform and evaporation *in vacuo* (Scheme 3).

Biological Activity

Table 1 shows *in vitro* antimicrobial activity of **1E** and **1Z**, measured by a paper disc method. Paper

Table 1. Antibacterial activity of naturally occurring *E*-tomaymycin (**1E**) and its *Z*-isomer (**1Z**).

	Concentration (μg/ml)	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*	*P. aeruginosa*
	1,320	19	25	11	22	—
	660	17	21	+	20	—
	330	15	17	—	18	—
1Z	165	12	13	—	16	—
	83	10	11	—	14	
	42	—	+	—	11	
	21	—	—	—	+	
	1,360	20	25	11	22	—
	680	18	21	+	20	—
	340	16	17	—	18	—
1E	170	13	13	—	16	—
	85	10	11	—	14	
	42	+	+	—	12	
	21	—	—	—	+	

(diameter of inhibition zones: mm)

discs (10 mm diameter) were saturated with solutions of **1E** and **1Z** and placed on the surface of the seeded agar plates. After incubation inhibiting growth of the test organism was measured by the diameter of inhibition zones. The product **1Z** exhibits the same antimicrobial activity as that of naturally occurring **1E**.

Experimental

Melting points were taken with an Arther H. Tomas melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrophotometer. NMR spectra were measured at 100 MHz on a JEOL-MH 100 NMR spectrometer and at 60 MHz on a JNM-PMX 60 NMR spectrometer using Me_4Si as an internal standard. Mass spectra were measured on a Hitachi M-80 and JEOL JMS-D300 mass spectrometer. Elemental analyses were measured on a Yanaco CHN corder MT-3.

N-[2-Nitro-4-(2-nitrobenzyloxy)-5-methoxybenzoyl]-L-hydroxyproline (**4**)

A solution of **2** (9 g) in THF (30 ml) was added dropwise to an ice-cooled solution of **3** (3.86 g) and triethylamine (TEA) (5.95 g) in H_2O (40 ml) with stirring. The mixture was stirred at room temperature for 10 minutes and evaporated *in vacuo*. The concentrated aqueous solution was adjusted to pH 1.5 with conc. HCl. The resulting precipitate was filtered, washed with water, dried over P_2O_5, and recrystallized from EtOH to give **4** (10.9 g, 96.5%), mp 219~220°C: IR (Nujol) 1720, 1635 cm^{-1}: NMR (DMSO-d_6) δ 2.0~2.4 (2H, m), 3.08 (1H, d, J=8 Hz), 3.55 (1H, dd, J=11 Hz, 5 Hz), 3.97 (3H, s), 4.2~4.5 (1H, m), 4.47 (1H, t, J=8Hz), 4.9~5.3 (1H, br. s), 5.62 (2H, s), 6.95 (1H, s), 7.5~8.0 (3H, m), 8.18 (1H, d, J=8 Hz).

Anal. Calcd. for $C_{20}H_{19}N_3O_{10}$: C 52.06, H 4.15, N 9.11.
Found: C 51.95, H 3.95, N 9.08.

(2*S*, 4*R*)-*N*-[2-Nitro-4-(2-nitrobenzyloxy)-5-methoxybenzoyl]-4-hydroxy-2-pyrrolidinecarbaldehyde (**5**)

A mixture of **4** (6.17 g) and *N*,*N*'-carbonyldiimidazole (4.35 g) in dry THF (100 ml) was stirred at 40°C for one hour. To the resulting solution was added $LiAlH_4$ (2×0.5 g) at −10°C with stirring under a nitrogen atmosphere. The mixture was stirred at the same temperature for 10 minutes and then water (10 ml) was added. The resulting precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in EtOAc. The solution was washed with 5% aqueous $NaHCO_3$ and water, dried over $MgSO_4$, treated with charcoal, and evaporated to dryness *in vacuo* to give **5** (4.5 g, 75%). An analytical sample was recrystallized from THF, mp 190~192°C (dec.): IR (Nujol) 1740, 1620 cm^{-1}: NMR (DMSO-d_6) δ 1.9~2.3 (2H, m), 2.98 (1H, dd, J=10 Hz, 3.4 Hz), 3.56 (1H, dd, J=10 Hz, 4 Hz), 4.0 (3H, s), 4.1~4.5 (2H, m), 5.63 (2H, s), 7.14 (1H, s), 7.5~8.0 (3H, m), 9.65 (1H, d, J=3.4 Hz).

Anal. Calcd. for $C_{20}H_{19}N_3O_9$: C 53.93, H 4.30, N 9.44.
Found: C 53.29, H 4.44, N 9.46.

(2*R*,11a*S*)-2,3,5,11a-Tetrahydro-2,8-dihydroxy-7-methoxy-5-oxo-1*H*-pyrrolo(2,1-c)(1,4)benzodiazepine (**6**)

A solution of **5** (2.54 g) in THF (200 ml) was shaken at room temperature for 3 hours in the presence of 10% Pd-carbon (3.2 g) and hydrogen at one atmosphere. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was triturated with ether to give **6** (1.33 g, 90%), mp 155°C (dec.): IR (Nujol) 3320, 1595, 1455, 1430 cm^{-1}: NMR (DMSO-d_6) δ 1.6~2.2 (2H, m), 2.8~4.0 (3H, m), 3.62 (3H, s), 4.0~4.5 (1H, m), 6.13 (1H, s), 7.28 (1H, d, J=4 Hz), 7.37 (1H, s).

(*E*)-*N*-*t*-Butoxycarbonyl-4-ethylidene-L-proline Diphenylmethyl Ester (**9E**)

To a suspension of potassium *t*-butoxide (7.0 g) in dry THF (120 ml) were added **11**[5] (5.7 g) and ethyltriphenylphosphonium bromide (13.9 g) under a nitrogen atmosphere. The mixture was refluxed for one hour with stirring and evaporated *in vacuo*. To the residue were added EtOAc and water. The water layer was separated and adjusted to pH 2.0 with 10% HCl, and the acidified solution was extracted with EtOAc. The extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in EtOAc (50 ml) and treated with a solution of diphenyldiazomethane[5] in EtOAc (one mole/

liter) at room temperature overnight. After evaporation, the residue was purified by column chromatography on silica gel. The eluates of *n*-hexane - isopropylether (iPE) (7: 3) were evaporated and the residue was recrystallized from *n*-hexane - iPE (1: 1) to give **9E** (5.9 g, 58%), mp 95~96°C: IR (Nujol) 1755, 1695 cm^{-1}: NMR (90°C, DMSO-d_6) δ 1.36 (9H, s), 1.4~1.7 (3H, m), 2.4~2.7 (1H, m), 2.7~3.2 (1H, m), 4.06 (2H, s), 4.1~4.7 (1H, m), 5.3~5.7 (1H, m), 6.96 (1H, s), 7.48 (10H, s): Mass *m/z* 407 (M^+).

Anal. Calcd. for $C_{25}H_{29}NO_4$: C 73.68, H 7.17, N 3.44.
Found: C 73.32, H 7.09, N 3.39.

(*Z*)-*N*-*t*-Butoxycarbonyl-4-ethylidene-L-proline Diphenylmethyl Ester (**9Z**)

To a suspension of potassium *t*-butoxide (20.4 g) in dry THF (720 ml) were added **8**[5] (51.4 g) and ethyltriphenylphosphonium bromide (67.6 g) under a nitrogen atmosphere. The mixture was refluxed for 45 minutes with stirring and evaporated *in vacuo*. The residue was dissolved in EtOAc. The solution was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel with benzene to give an oily **9Z** (34.8 g, 66%) which was recrystallized from *n*-hexane to give pure **9Z** (7.68 g, 15%), mp 74~75°C: IR (Nujol) 1740, 1690 cm^{-1}: NMR (90°C, DMSO-d_6) δ 1.35 (9H, s), 1.5~1.7 (3H, m), 2.3~2.7 (1H, m), 4.06 (2H, s), 4.58 (1H, dd, J=10 Hz, 3 Hz), 5.2~5.6 (1H, m), 6.96 (1H, s), 7.48 (10H, s); Mass *m/z* 407 (M^+).

Anal. Calcd. for $C_{25}H_{29}NO_4$: C 73.68, H 7.17, N 3.44.
Found: C 73.29, H 7.08, N 3.32.

(*E*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-L-proline Diphenylmethyl Ester (**13E**)

To a solution of **10E**[5] (0.62 g) in dry THF (20 ml) were added TEA (0.3 g) and a solution of 2-nitro-4-benzyloxy-5-methoxybenzoyl chloride (0.64 g) in dry THF (10 ml) at 20~25°C with stirring. The solution was stirred at the same temperature for 10 minutes and the EtOAc (100 ml) and H_2O (50 ml) were added. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from Et_2O - iPE to give **13E** (1.0 g, 85%), mp 183~184°C: IR (Nujol) 1740, 1635 cm^{-1}: NMR (DMSO-d_6) δ 1.2~1.8 (3H, m), 2.5~3.1 (2H, m), 3.73 (3H, s), 3.7~4.6 (2H, m), 4.7~5.0 (1H, m), 5.16 (2H, s), 5.1~5.6 (1H, m), 6.59, 6.66 (1H, two s peak), 6.77 (1H, s), 7.1~7.6 (15H, m), 7.70, 7.76 (1H, two s peak): Mass *m/z* 592 (M^+).

Anal. Calcd. for $C_{35}H_{32}N_2O_7$: C 70.93, H 5.44, N 4.73.
Found: C 71.10, H 5.61, N 4.77.

(*Z*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-L-proline Diphenylmethyl Ester (**13Z**)

13Z was prepared from **10Z**[5] in 86% yield by the method described above, mp 171~172°C: IR (Nujol) 1740, 1635 cm^{-1}: NMR (DMSO-d_6) δ 1.2~1.8 (3H, m), 2.70 (2H, br. s), 3.80 (3H, s), 3.93 (2H, br. s), 4.1~4.6 (1H, m), 5.23 (2H, s), 5.3~5.6 (1H, m), 6.83 (1H, s), 7.25 (1H, s), 7.33 (10H, s), 7.40 (5H, s), 7.77, 7.83 (1H, two s peak): Mass *m/z* 592 (M^+).

Anal. Calcd. for $C_{35}H_{32}N_2O_7$: C 70.93, H 5.44, N 4.73.
Found: C 71.26, H 5.46, N 4.74.

(*E*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-L-proline (**14E**)

To a solution of **13E** (9.54 g) in CH_2Cl_2 (30 ml) were added anisole (6.9 g) and TFA (14.6 g) under ice-cooling. The solution was stirred at 15~20°C for one hour and poured into EtOAc (200 ml). The organic layer was washed with water and extracted with 5% aqueous K_2CO_3. The separated aqueous layer was adjusted to pH 2.0 with 10% HCl and extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give **14E** (5.96 g, 87%), mp 165~166°C: IR (Nujol) 3150, 1740, 1600 cm^{-1}: NMR (DMSO-d_6) δ 1.2~1.8 (3H, m), 2.5~3.1 (2H, m), 3.5~4.4 (2H, m), 3.87, 3.95 (3H, two s peak), 4.4~4.8 (1H, m), 5.0~5.6 (1H, m), 5.23 (2H, s), 6.97, 7.03 (1H, two s peak), 7.43 (5H, s), 7.80, 7.83 (1H, two s peak): Mass *m/z* 426 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_7$: C 61.97, H 5.20, N 6.57.
Found: C 62.00, H 5.32, N 6.49.

(*Z*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-L-proline (**14Z**)

14Z was prepared from **13Z** in 85% yield by the method described above, mp 163~164°C (from EtOAc): IR (Nujol) 3150, 1740, 1600 cm^{-1}: NMR (DMSO-d_6) δ 1.2~1.8 (3H, m), 2.5~3.1 (2H, m), 3.80, 3.85 (3H, two s peak), 3.9~4.3 (2H, m), 4.4~4.8 (1H, m), 5.15 (2H, s), 5.1~5.6 (1H, m), 6.83,

6.86 (1H, two s peak), 7.34 (5H, s), 7.73 (1H, s): Mass *m/z* 426 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_7$: C 61.97, H 5.20, N 6.57.
Found: C 61.51, H 5.03, N 6.42.

(2*S*)(*E*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-2-pyrrolidinecarbaldehyde (**15E**)

A solution of **14E** (5.7 g) and *N*,*N*′-carbonyldiimidazole (3.23 g) in dry THF (60 ml) was stirred at 45~50°C for 2 hours. The reaction mixture was cooled at −10°C and added to a suspension of $LiAlH_4$ (0.4 g) in dry THF (60 ml) at −50~−15°C. The mixture was stirred at −15°C for 30 minutes and poured into a mixture of EtOAc and H_2O. The mixture was adjusted to pH 10 with 5% aqueous K_2CO_3 and filtered. The filtrate was extracted with EtOAc. The extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel and eluted with a solution of iPE - EtOAc (2: 8) to give **15E** (1.81 g, 34%), mp 127~128°C (from EtOAc): IR (Nujol) 1730, 1635 cm^{-1}: NMR (DMSO-d_6) δ 1.4~1.8 (3H, m), 2.4~2.9 (2H, m), 3.8~4.4 (2H, m), 3.86, 3.95 (3H, two s peak), 4.4~4.8 (1H, m), 5.1~5.7 (1H, m), 5.23 (2H, s), 7.0~7.3 (1H, m), 7.45 (5H, s), 7.80 (1H, d, *J*=3Hz), 9.60 (1H, d, *J*=3Hz): Mass *m/z* 410 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_6$: C 64.38, H 5.40, N 6.83.
Found: C 63.66, H 5.35, N 6.78.

(2*S*)(*Z*)-*N*-(2-Nitro-4-benzyloxy-5-methoxybenzoyl)-4-ethylidene-2-pyrrolidinecarbaldehyde (**15Z**)

15Z was prepared from **14Z** in 67% yield by the method described above, mp 157~158°C (from EtOAc): IR (Nujol) 1735, 1640 cm^{-1}: NMR (DMSO-d_6) δ 1.3~1.8 (3H, m), 2.6~2.9 (2H, m), 3.7~4.3 (2H, m), 3.85, 3.93 (3H, two s peak), 4.4~4.8 (1H, m), 5.1~5.6 (1H, m), 5.20 (2H, s), 6.9~7.2 (1H, m), 7.40 (5H, s), 7.80 (1H, s), 9.56 (1H, d, *J*=3Hz): Mass *m/z* 410 (M^+).

Anal. Calcd. for $C_{22}H_{22}N_2O_6$: C 64.38, H 5.40, N 6.83.
Found: C 63.57, H 5.36, N 6.71.

(11*R*,11a*S*)(*E*)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7,11-dimethoxy-5-oxo-1*H*-pyrrolo-(2,1-c)(1,4)benzodiazepine (**1E**)

A solution of **15E** (47 mg) in MeOH (30 ml) was shaken at room temperature for 3 hours in the presence of 5% Pd-$BaSO_4$ (40 mg) and hydrogen at one atmosphere. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was triturated with iPE to give **1E** (19 mg, 55%). Analytical sample was recrystallized from MeOH, mp 143°C (dec.): IR (Nujol) 3350, 1640, 1600 cm^{-1}: NMR (DMSO-d_6) δ 1.59 (3H, d, *J*=7Hz), 2.55 (1H, d, *J*=18 Hz), 2.96 (1H, dd, *J*=18 Hz, 9 Hz), 3.20 (3H, s), 3.66 (3H, s), 3.88 (1H, dd, *J*=9Hz, 5Hz), 4.12 (2H, s), 4.49 (1H, d, *J*=6 Hz), 5.2~5.6 (1H, m), 6.23 (1H, s), 7.08 (1H, d, *J*=6 Hz), 7.20 (1H, s), 9.32 (1H, s): Mass *m/z* 304 (M^+).

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C 63.14, H 6.62, N 9.21.
Found: C 62.97, H 6.68, N 9.03.

(11*R*,11a*S*)(*Z*)-2-Ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7,11-dimethoxy-5-oxo-1*H*-pyrrolo-(2,1-c)(1,4)benzodiazepine (**1Z**)

1Z was prepared from **15Z** in 45% yield by the method described above, mp 145~146°C (dec.): IR (Nujol) 3350, 1640, 1600 cm^{-1}: NMR (DMSO-d_6) δ 1.61 (3H, d, *J*=7Hz), 2.56 (1H, d, *J*=18 Hz), 2.96 (1H, d, *J*=18 Hz), 3.21 (3H, s), 3.68 (3H, s), 4.12 (2H, s), 4.50 (1H, d, *J*=6Hz), 5.2~5.6 (1H, m), 6.23 (1H, s), 7.10 (1H, d, *J*=6 Hz), 7.20 (1H, s), 9.35 (1H, s): Mass *m/z* 304 (M^+).

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C 63.14, H 6.62, N 9.21.
Found: C 62.72, H 6.95, N 9.35.

(11a*S*)(*E*)-2-Ethylidene-2,3,5,11a-tetrahydro-8-hydroxy-7-methoxy-5-oxo-1*H*-pyrrolo(2,1-c)(1,4)-benzodiazepine (**16E**)

A solution of **15E** in dry THF was hydrogenated in the similar method described above to give **16E** in 70% yield as a yellow powder: IR (Nujol) 3200, 1590, 1450 cm^{-1}: NMR (DMSO-d_6) δ 1.3~1.7 (3H, m), 2.5~2.8 (2H, m), 3.2~3.6 (2H, m), 3.85 (3H, s), 4.10 (1H, br. s), 5.2~5.5 (1H, m), 6.70 (1H, s), 7.40 (1H, s), 7.70 (1H, d, *J*=4 Hz): Mass *m/z* 272 (M^+).

(11a*S*)(*Z*)-2-Ethylidene-2,3,5,11a-tetrahydro-8-hydroxy-7-methoxy-5-oxo-1*H*-pyrrolo(2,1-c)(1,4)-benzodiazepine (**16Z**)

16Z was prepared from **15Z** in 60% yield in the similar method described above: IR (Nujol) 3200,

1590, 1450 cm^{-1}: NMR ($CDCl_3$) δ 1.72 (3H, d, J=8 Hz), 2.7~3.0 (2H, m), 3.6~4.1 (2H, m), 3.88 (3H, s), 4.22 (1H, m), 5.3~5.6 (1H, m), 6.85 (1H, s), 7.45 (1H, s), 7.60 (1H, d, J=4Hz): Mass m/z 272 (M^+).

Conversion of **16E** to **1E**

A solution of **16E** in MeOH was stored in a refrigerator for 3 days to give **1E** quantitatively.

Conversion of **16Z** to **1Z**

16Z was also converted to **1Z** in the similar manner described above.

Conversion of **1E** to **16E**

A solution of **1E** in $CHCl_3$ was refluxed for 10 minutes and evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ and the solution was treated in the similar manner. This operation was repeated several times to give **16E** quantitatively.

Conversion of **1Z** to **16Z**

1Z was converted to **16Z** in the similar manner described above.

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