SYNTHESIS OF 2-INDOLYL-1,4-BENZODIAZEPIN-5-ONES UTILIZING A MANNICH TYPE CYCLIZATION*,[1]

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Abstract — 2-Indolyl-1,4-benzodiazepin-5-ones (**3**) have been efficiently synthesized from Boc-α-amino acids (**4**), 3-hydroxyanthranilic acid (**8**), and indole; the key step is a Mannich type cyclization accompanied with introduction of indole.

Tilivalline (**1a**), a metabolite isolated from *Klebsiella pneumoniae* var. *oxytoca*,[2] belongs to a group of pyrrolo[2,1-*c*][1,4]benzodiazepines, a characteristic skeleton of anthramycin-type antibiotics. We have already accomplished a completely stereoselective, efficient, and convenient synthesis of tilivalline (**1a**) utilizing a new Mannich type cyclization as a key step.[3] Application of the analogous synthetic methodology culminated in the synthesis of *O*- and 2-substituted tilivallines (**1b-e**) and 11-substituted-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (**2**).[3] Since the anthramycin-type antibiotics are known to exhibit interesting antitumor activity,[4] tilivalline and its analogs will also be expected to have analogous biological activity. To aim at both the extension of the scope of the new Mannich type cyclization and the studies on the structures and biological activities relationship, we now extended the method to the synthesis of 2-indolyl-1,4-benzodiazepin-5-ones (**3**) lacking the C-ring of tilivalline.

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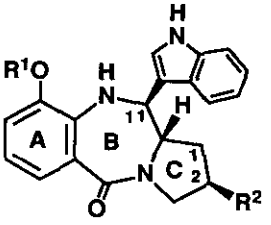
* Dedicated to Professor Emeritus Masatomo Hamana on the occasion of his 75th birthday.



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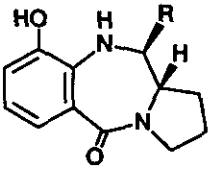

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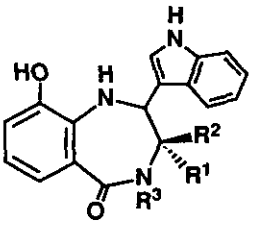

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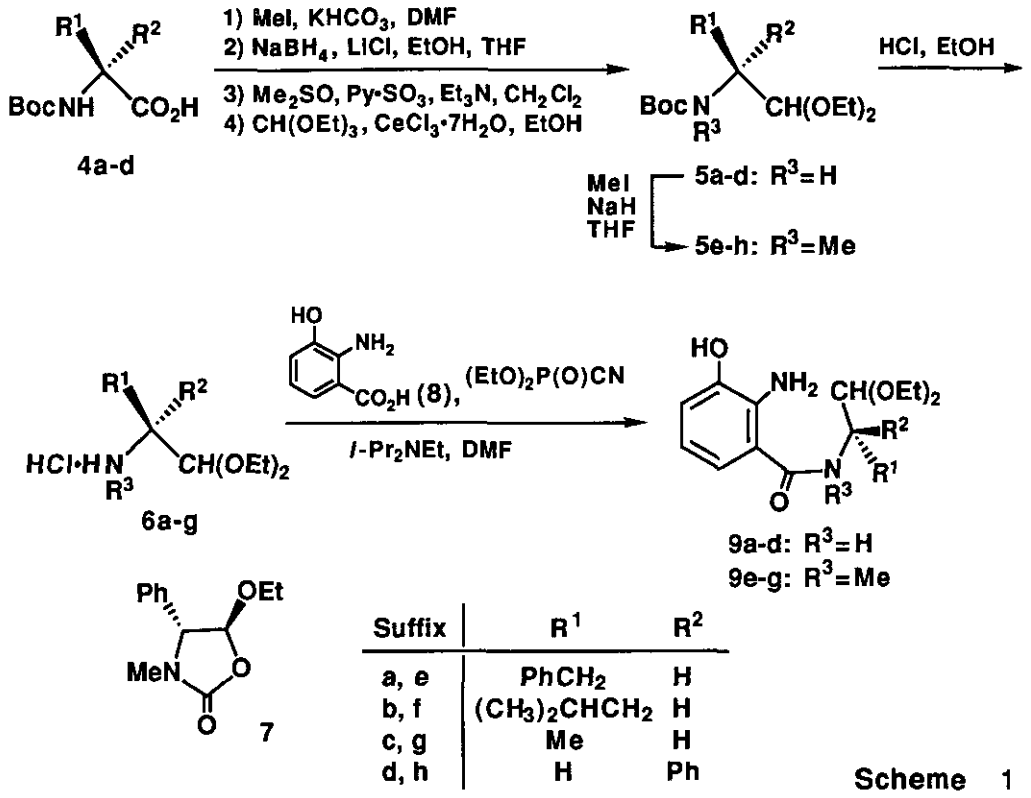
a: $R^1=R^2=H$
b: $R^1=CH_3$, $R^2=H$
c: $R^1=PhCH_2$, $R^2=H$
d: $R^1=H$, $R^2=OH$
e: $R^1=H$, $R^2=PhCH_2O$

The key intermediates for the Mannich type cyclization are the acetal amides (**9**) which were easily prepared starting from the *tert*-butoxycarbonyl (Boc) amino acids (**4a-d**) and 3-hydroxyanthranilic acid (**8**). Conversion of **4** to the acetal (**5a-d**) was carried out according to our method[3,5] by methyl esterification, reduction, oxidation, and then acetalization, shown in Scheme 1. Treatment of **5a-d** with methyl iodide and sodium hydride in tetrahydrofuran afforded the corresponding *N*-methyl acetals (**5e-h**). Interestingly, these *N*-methyl derivatives exist as a mixture of two rotamers. In the case of **5g**, for example, its proton nuclear magnetic resonance (^{1}H-nmr) spectrum at room temperature shows two singlet signals at δ 2.77 and 2.80 which are assignable to the *N*-methyl protons. These signals merge into a singlet signal at δ 2.78 at 50°C, revealing the presence of rotamers. Deprotection of the Boc group of the acetal (**5a-g**) was easily achieved with ethanolic hydrogen chloride to give the corresponding hydrochlorides of the amino acetals (**6a-g**) in nearly quantitative yields. The phenyl-*N*-methyl analog (**5h**), however, did not give the hydrochloride (**6h**) under the analogous acidic conditions. Instead, the oxazolidinone (**7**) was obtained as a sole isolable product. Attempted deprotection of **5h** to **6h** with trifluoroacetic acid or iodotrimethylsilane[6] also furnished **7**. The configuration of **7** was confirmed to be trans by its ^{1}H-nmr, in which the $J_{4,5}$ value of *ca.* 2.5 Hz was consistent with the assigned *trans* configuration.[7] Condensation of **6a-g** with 3-hydroxyanthranilic acid (**8**) was accomplished by use of diethyl phosphorocyanidate (DEPC)[8] in the presence of diisopropylethylamine to give the acetal amides (**9a-g**). The *N*-methylamides (**9e-g**) again exist as the mixture of two rotamers.

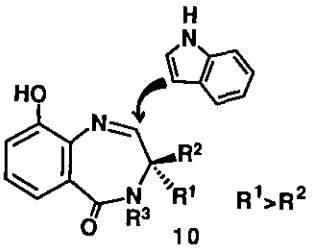


4a-d 6a-g 7

Scheme 1

The final construction of the 2-indolyl-1,4-benzodiazepin-5-ones (**3**) by the Mannich type cyclization has been achieved by the sequential treatment of the acetal amides (**9**) in a one-pot process with (1) chlorotrimethylsilane - sodium iodide - pyridine in acetonitrile, (2) zinc chloride, and (3) indole.[9] In our tilivalline synthesis,[3] this Mannich type cyclization proceeded in a completely stereoselective manner and indole attacked only from the less hindered face of the intermediate imine molecule (**10**), as depicted in Scheme 2. In fact, the one-pot Mannich type reaction of **9e** afforded **11e** (id., *trans*-**3e**) as the major isomer. In addition to **11e**, its C_2-epimer (**12e**) (id., *cis*-**3e**), produced by the attack of indole from the more hindered face, was also produced in 31% yield, shown in Table 1. Thus the stereoselectivity of the indole introduction in this reaction was not complete as compared with the tilivalline synthesis. Similarly, the other acetal amides (**9a-d,f,g**) also underwent the Mannich type reaction with indole giving a mixture of the *trans*-isomers (**11**) (or **12d**) as the major products and the *cis*-isomers (**12**) (or **11d**) as the minor ones. The assignment of the *trans*- and *cis*-configurations was made using the coupling constants between C_2 and C_3

protons on their ^{1}H-nmr spectra by reference to those of tilivalline and its 11-epimer.[2,3] Namely, each C_2 proton of the *trans*-isomers is clearly visible as a doublet peak with a larger coupling constant ($J_{2,3}$=5-9 Hz) while the *cis*-isomers show a singlet or doublet peak with a smaller coupling constant ($J_{2,3}$< 2 Hz) of each C_2 proton.



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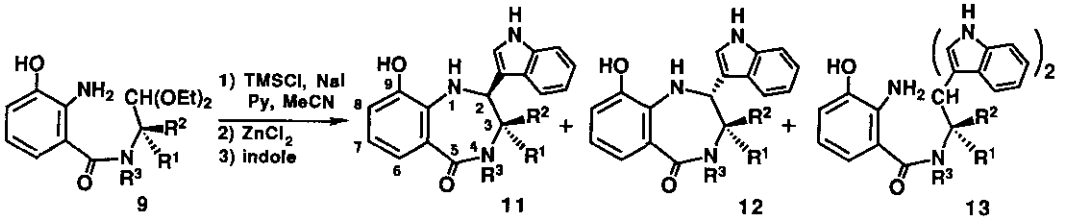
Scheme 2

Table 1. Synthesis of 2-Indolyl-1,4-benzodiazepin-5-ones



9 11 12 13

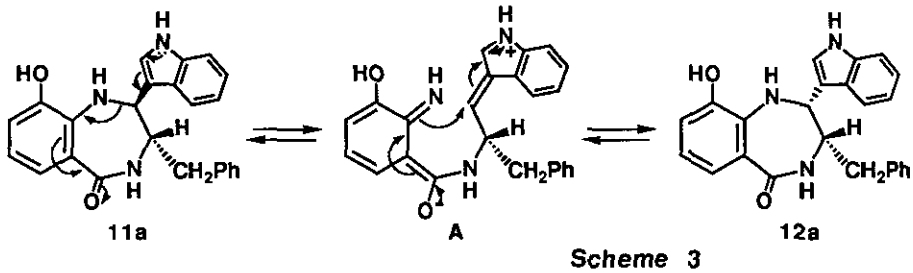
Starting Material	R^1	R^2	R^3	Time(h)[a]	Yield (%) 11	12	13
9a	$PhCH_2$	H	H	6	33	11	29
9b	$(CH_3)_2CHCH_2$	H	H	6	43	18	22
9c	Me	H	H	6[b]	49	12	15
9d	H	Ph	H	19[b,c]	trace	20	10
9e	$PhCH_2$	H	Me	6	67	31	trace
9f	$(CH_3)_2CHCH_2$	H	Me	6	64	26	trace
9g	Me	H	Me	6	64	9	-

a Reactions were carried out at 52-55°C.

b The crude product was treated with tetra-*n*-butylammonium fluoride in THF.

c The starting material was recovered in 14% yield.

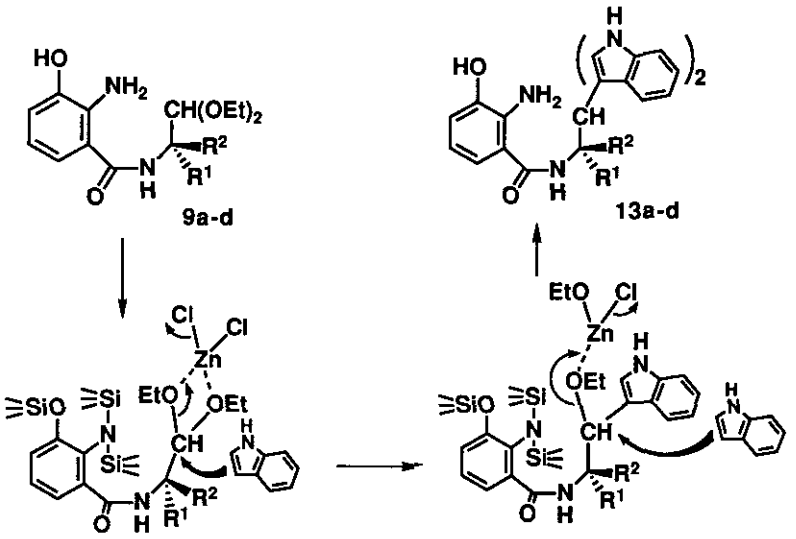
Interestingly, treatment of the *trans*-isomer (**11a**) or the *cis*-isomer (**12a**) with chlorotrimethylsilane - sodium iodide - pyridine in acetonitrile and then zinc chloride under the conditions of the Mannich type reaction was found to cause isomerization at the C_2 chiral center, giving a mixture of **11a** and **12a**. This isomerization probably occurs by the formation of the enolate (A) due to the cleavage of the N_1-C_2 bond and the recyclization to **11a** or **12a**, as shown in Scheme 3. This result prompted us to test whether analogous isomerization would occur in tilivalline itself. Indeed, isomerization did occur by treatment of tilivalline (**1a**) under the similar Mannich type reaction conditions for rather long time. Superior stereoselectivity in the tilivalline synthesis in which no epimer was formed[3] may be explained by kinetically controled process due to the presence of more bulky and rigid pyrrolidine ring which will directs the attack of indole. In contrast, the acetal amides (**9**) have less bulky and rigid branches at the α-position and the both isomers will be formed in preference to the *trans*-isomers. The isomerization might further help this tendency.



Scheme 3

In the Mannich type reaction of the acetal amides (**9a-d**) which have no methyl group at the N_2 position, the bisindolyl adducts (**13**) were produced as the by-products in addition to the Mannich products (**11**) and (**12**). However, it should be noted that **9e-g** having the N_2-methyl function hardly gave the bisindolyl adducts (**13**). Although the mechanism for the formation of **13** remains for further studies, it may be explained as shown in Scheme 4. The acetal portion of **9a-d** is first activated with zinc chloride and successively attacked by two equivalents of indole before the Mannich type cyclization occurs to give the bisindolyl adduct (**13**). The alternative mechanism will be that the Mannich product (**11**) or (**12**) first formed gives the enolate (A) shown in Scheme 3, to which another molecule of indole attacks again. However, this possibility was clearly objected since no bisindolyl adduct (**13**) was formed when

the isomerization was carried out in the presence of indole under the isomerization conditions in Scheme 3.



Scheme 4

In conclusion, the Mannich type cyclization is a new method for the synthesis of 1,4-benzodiazepine derivatives and its further extension in organic synthesis will be expected. Biological testing of **11-13** is now underway and will be reported elsewhere.

EXPERIMENTAL

All melting and boiling points are uncorrected. Distillation was carried out by a Kugelrohr apparatus. Infrared (ir) spectra were measured with a JASCO IRA-2 or SHIMADZU FTIR-8100 spectrophotometer. ^{1}H-Nmr spectra were recorded on a JOEL PMX-60, FX-100, EX-270, or GSX-400 spectrometer with tetramethylsilane as an internal standard. Ms spectra were obtained on a JEOL DX-300 spectrometer. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Silica gel (BW-820MH or BW-200) was used for column chromatography. Analytical thin layer chromatography was carried out on a silica gel plate (Merck Art. 5715). Zinc chloride was dried at 150-160°C for 2 h under reduced pressure before use.

***N*-Boc-D-phenylglycine methyl ester.** A mixture of **4d** (22.7 g, 90.4 mmol), methyl iodide (11.3 ml, 181 mmol), and potassium hydrogen carbonate (18.1 g, 181 mmol) in DMF (350 ml) was

stirred at room temperature for 3 h, and diluted with AcOEt-PhH (1:1) (700 ml). The mixture was washed with water (300 ml), 10% aqueous citric acid (300 ml), water (300 ml×2), and saturated aqueous NaCl (300 ml), and dried over Na_2SO_4. Removal of the solvent gave *N*-Boc-D-phenylglycine methyl ester (22.1 g, 92%) as yellowish white crystals, which was used for the next step without further purification. A part of the crude product was purified by recrystallization to give pure *N*-Boc-D-phenylglycine methyl ester as colorless crystals, mp 102-103.5°C (hexane). $[\alpha]^{21}_D$ -115.0° (*c*=1.09, MeOH). Ir (nujol): 3405, 1738, 1728, 1701, 1505, 1321, 1167 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.47 (s, 9H), 3.74 (s, 3H), 5.2-5.8 (br m, 2H, 1H disappeared with D_2O), 7.44 (s, 5H). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.50; H, 7.35; N, 5.00.

***N*-Boc-D-phenylglycinol.** *N*-Boc-D-phenylglycine methyl ester (21.5 g, 81.0 mmol) was dissolved in THF (100 ml), and anhydrous lithium chloride (6.87 g, 162 mmol) and then sodium borohydride (6.12 g, 162 mmol) were added. Ethanol (200 ml) was added dropwise below 0°C during 1 h, the mixture was stirred below 0°C for 30 min and at room temperature for 5 h. The mixture was cooled with ice-water, gradually added 10% aqueous citric acid (100 ml), and concentrated *in vacuo*. Water (200 ml) was added to the residue, and the mixture was extracted with CH_2Cl_2 (200 ml×4). The organic layer was washed with saturated aqueous NaCl (150 ml×2), and dried over Na_2SO_4. Removal of the solvent gave *N*-Boc-D-phenylglycinol as white crystals (18.3 g, 95%), which was used for the next step without further purification. A part of the crude product was purified by recrystallization to give pure *N*-Boc-D-phenylglycinol as white crystals, mp 127-128°C (benzene). $[\alpha]^{22.5}_D$ -43.1° (*c*=1.01, MeOH). Ir (nujol): 3312, 3245, 1673, 1553, 1455, 1368, 1298, 1179, 762, 702 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.40 (s, 9H), 2.3-2.7 (m, 1H disappeared with D_2O), 3.75 (t changed d with D_2O, 2H, J=6 Hz), 4.5-4.9 (m, 1H), 5.1-5.5 (br, 1H disappeared with D_2O), 7.21 (s, 5H). *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.83; H, 8.17; N, 5.56.

***N*-Boc-D-phenylglycinal.** A solution of sulfur trioxide-pyridine complex (14.3 g, 90 mmol) in DMSO (100 ml) was added in one portion to a mixture of *N*-Boc-D-phenylglycinol (7.11 g, 30 mmol) and triethylamine (12.5 ml, 90 mmol) in CH_2Cl_2 (100 ml) under ice-methanol cooling. The mixture was stirred for 15 min at room temperature, poured into ice-water (300 ml), and extracted with Et_2O (150 ml×4). The organic extracts were washed with 10% aqueous citric acid

(150 ml×2), water (150 ml), saturated aqueous $NaHCO_3$ (150 ml), water (150 ml), and saturated aqueous NaCl (150 ml), and dried over $MgSO_4$, and concentrated *in vacuo* to give *N*-Boc-D-phenylglycinal (6.67 g, 95%) as a brown oil, which was used for the next step without further purification. A part of the crude product was purified by distillation (bp 108-110°C/1.5 mmHg) to give pure *N*-Boc-D-phenylglycinal as white crystals, mp 52-56°C. $[\alpha]^{19.5}_D$ -95.5° (*c*=0.53, CH_2Cl_2). Ir (nujol): 3374, 1740, 1688, 1510, 1291, 1171, 1065, 866, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.42 (s, 9H), 5.19 (d, 1H, J=6 Hz), 5.4-5.9 (br, 1H disappeared with D_2O), 7.22 (s, 5H), 9.35 (s, 1H). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.39; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.31; N, 5.71.

***N*-Boc amino aldehyde diethylacetals (5a-d).** General Procedure: A solution of *N*-Boc amino aldehydes (8.73 mmol), triethyl orthoformate (11.6 ml, 70 mmol), and 0.4M cerium chloride heptahydrate in EtOH (22 ml, 8.73 mmol) were stirred at 50-60°C for 13-63 h. The mixture was poured into 5% aqueous $NaHCO_3$, and extracted with Et_2O. The extracts were washed with 10% aqueous citric acid, water, and saturated aqueous NaCl, and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by column chromatography to give **5a-d.**

***N*-Boc-L-phenylalaninal diethyl acetal (5a).** Prepared from *N*-Boc-L-Phe-al[5b] (4.75 g, 19.1 mmol), triethyl orthoformate (25.4 ml, 153 mmol), and 0.4M cerium chloride heptahydrate in EtOH (48 ml, 19.1 mmol). Orangish white crystals (3.27 g, 53%), purified by silica gel column chromatography with hexane-AcOEt (7:1), mp 45-47°C (hexane-pentane). $[\alpha]^{24.5}_D$ -31.4° (*c*=1.00, MeOH). Ir (nujol): 3370, 1680, 1525, 1175, 1065, 755, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.12 and 1.15 (2×t, 6H, J=7 Hz), 1.29 (s, 9H), 2.65-2.92 (m, 2H), 3.22-3.92 (m, 5H), 4.26 (d, 1H, J=3 Hz), 4.68 (br, 1H disappeared with D_2O), 7.15 (s, 5H). *Anal.* Calcd for $C_{18}H_{29}NO_4$: C, 66.85; H, 9.04; N, 4.33. Found: C, 66.39; H, 9.28; N, 4.06.

***N*-Boc-L-leucinal diethyl acetal (5b).** Prepared from *N*-Boc-L-Leu-al[5a] (1.88 g, 8.73 mmol), triethyl orthoformate (11.6 ml, 70 mmol), and 0.4M cerium chloride heptahydrate in EtOH (22 ml, 8.73 mmol). Yellow crystals (1.66 g, 66%), purified by silica gel column chromatography with hexane-AcOEt (8:1), mp 33-35°C. $[\alpha]^{22}_D$ -33.3° (*c*=0.77, MeOH). Ir (nujol): 3360, 2950, 1700, 1500, 1365, 1245, 1170, 1110, 1055 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.91 and 0.93 (2×d, 6H, J=6.4 Hz), 1.21 (t, 6H, J=7.1 Hz), 1.3-1.8 (m, 3H), 1.44 (s, 9H), 3.5-3.9 (m, 5H), 4.33 (d, 1H, J=2.6 Hz),

4.5-4.7 (m, 1H). *Anal.* Calcd for $C_{15}H_{31}NO_4$: C, 62.25; H, 10.80; N, 4.84. Found: C, 62.18; H, 10.54; N, 4.80.

***N*-Boc-L-alaninal diethyl acetal (5c).** Prepared from *N*-Boc-L-Ala-al[5a] (2.57 g, 14.9 mmol), triethyl orthoformate (19.8 ml, 119 mmol), and 0.4M cerium chloride heptahydrate in EtOH (35 ml, 14.9 mmol). A yellow oil (1.29 g, 35%), purified by silica gel column chromatography with hexane-AcOEt (6:1). A part of yellow oil was purified by distillation to give pure **5c** as a colorless oil, bp 80°C/0.3 mmHg. $[\alpha]^{23.5}_D$ -29.4° (*c*=0.71, MeOH). Ir (film): 3380, 3320, 2960, 1705, 1500, 1375, 1240, 1170, 1060 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.08 (d, 3H, J=7Hz), 1.17 (t, 6H, J=6Hz), 1.42 (s, 9H), 3.2-4.0 (m, 5H), 4.27 (d, 1H, J=4Hz), 4.4-4.9 (br, 1H). *Anal.* Calcd for $C_{12}H_{25}NO_4$: *C, 58.27; H, 10.19; N, 5.66. Found: C, 58.27; H, 10.39; N, 5.63.*

***N*-Boc-D-phenylglycinal diethyl acetal (5d).** Prepared from *N*-Boc-D-phenylglycinal (6.23 g, 26.5 mmol), triethyl orthoformate (35.2 ml, 212 mmol), and 0.4M cerium chloride heptahydrate in EtOH (73 ml, 26.5 mmol). Yellow crystals (2.50 g, 30%), purified by silica gel column chromatography with hexane-AcOEt (6:1), mp 65-66°C (EtOH-H_2O). $[\alpha]^{22.5}_D$ -5.6° (*c*=0.30, CH_2Cl_2). Ir (nujol): 3350, 1684, 1533, 1458, 1173, 1076, 876, 756 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.10 and 1.14 (2×t, 6H, J=7 Hz), 1.36 (s, 9H), 3.1-3.8 (m, 4H), 4.38 (d, 1H, J=3 Hz), 4.64 (dd, 1H, J=7, 3 Hz), 5.40 (br d, 1H disappeared with D_2O, J=7 Hz), 7.14 (s, 5H). *Anal.* Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.71; H, 8.90; N, 4.23.

***N*-Boc-*N*-methyl amino aldehyde diethylacetals (5e-h).** General Procedure: Compounds **5a-d** (6.0 mmol) and then methyl iodide (3.0 ml, 48 mmol) were added to a suspension of sodium hydride (60% oil suspension) (0.72 g, 18 mmol) washed with hexane (3 ml×4) in THF (20 ml). The mixture was stirred at room temperature for 14-20 h, and diluted with AcOEt (150 ml). The mixture was washed with water (60 ml), 5% aqueous $Na_2S_2O_3$ (60 ml), water (60 ml), and saturated aqueous NaCl (60 ml), and dried over Na_2SO_4. Removal of the solvent gave **5e-h**.

***N*-Boc-*N*-methyl-L-phenylalaninal diethyl acetal (5e).** Prepared from **5a** (1.94 g, 6.0 mmol), methyl iodide (3.0 ml, 48 mmol), and sodium hydride (0.72 g, 18 mmol) in THF (20 ml). A brown oil (1.95 g, 96%), which was used for the next step. A part of the brown oil was purified

by distillation to give pure **5e** as a colorless oil, bp 83-90°C/0.07 mmHg. $[\alpha]^{23.5}_{D}$ -49.5° (*c*=0.81, CH_2Cl_2). Ir (film): 2970, 1685, 1360, 1170, 1135, 1060, 695 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.15 (t, 6H, J=7 Hz), 1.25 and 1.35 (2×s, 9H), 2.61 and 2.74 (2×s, 3H), 2.4-3.2 (m, 2H), 3.66 (q, 4H, J=7 Hz), 4.0-4.8 (m, 2H), 6.9-7.4 (m, 5H). *Anal.* Calcd for $C_{19}H_{31}NO_4$: C, 67.63; H, 9.26; N, 4.15. Found: C, 67.41; H, 9.34; N, 3.96.

***N*-Boc-*N*-methyl-L-leucinal diethyl acetal (5f).** Prepared from **5b** (1.74 g, 6.0 mmol), methyl iodide (3.0 ml, 48 mmol), and sodium hydride (0.72 g, 18 mmol) in THF (20 ml). A yellow oil (1.75 g, 96%), which was used for the next step. A part of the yellow oil was purified by distillation to give pure **5f** as a colorless oil, bp 85°C/0.7 mmHg. $[\alpha]^{23.5}_{D}$ -40.5° (*c*=1.00, CH_2Cl_2). Ir (film): 2960, 1690, 1160, 1125, 1065 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.92 (d, 6H, J=6 Hz), 1.19 and 1.21 (2×t, 6H, J=7 Hz), 1.3-1.7 (m, 3H), 1.47 (s, 9H), 2.74 and 2.76 (2×s, 3H), 3.3-3.8 (m, 4H), 3.9-4.5 (br m, 2H). *Anal.* Calcd for $C_{16}H_{33}NO_4$: C, 63.33; H, 10.96; N, 4.62. Found: C, 63.09; H, 11.38; N, 4.30.

***N*-Boc-*N*-methyl-L-alaninal diethyl acetal (5g).** Prepared from **5c** (1.72 g, 7.0 mmol), methyl iodide (3.5 ml, 56 mmol), and sodium hydride (0.84 g, 21 mmol) in THF (23 ml). A yellow oil (1.72 g, 94%), which was used for the next step. A part of the yellow oil was purified by distillation to give pure **5g** as a colorless oil, bp 80°C/0.1 mmHg. $[\alpha]^{24}_{D}$ -33.7° (*c*=1.07, MeOH). Ir (film): 2980, 1690, 1475, 1440, 1390, 1365, 1335, 1155, 1120, 1065 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 50°C) δ: 1.16 (d, 3H, J=7.3 Hz), 1.18 and 1.20 (2×t, 6H, J=7.1 Hz), 1.46 (s, 9H), 2.79 (s, 3H), 3.5-3.8 (m, 4H), 3.9-4.3 (br, 1H), 4.42 (br d, 1H, J=5.6 Hz). *Anal.* Calcd for $C_{13}H_{27}NO_4$: C, 59.74; H, 10.41; N, 5.36. Found: C, 59.42; H, 10.53; N, 5.00.

***N*-Boc-*N*-methyl-D-phenylglycinal diethyl acetal (5h).** Prepared from **5d** (1.40 g, 4.5 mmol), methyl iodide (2.5 ml, 40 mmol), and sodium hydride (0.60 g, 15 mmol) in THF (16 ml). A yellow oil (1.33 g, 91%), purified by silica gel column chromatography with hexane-AcOEt (8:1). A part of the yellow oil was purified by distillation (bp 90-100°C/0.06 mmHg) to give pure **5h** as white crystals, mp 44-47°C. $[\alpha]^{22.5}_{D}$ -26.9° (*c*=1.13, CH_2Cl_2). Ir (nujol): 1674, 1441, 1391, 1310, 1148, 1073, 750, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 55°C) δ: 1.14 and 1.21 (2×t, 6H, J=7.1 Hz), 1.47 (s, 9H), 2.73 (s, 3H), 3.5-3.8 (m, 4H), 4.99 (d, 1H, J=6.9 Hz), 5.26 (br, 1H), 7.2-7.4 (m, 5H). *Anal.* Calcd for $C_{18}H_{29}NO_4$: C, 66.85; H, 9.04; N, 4.33. Found: C, 66.55; H, 9.26; N, 4.14.

Acetal amides (9). General Procedure: A solution of **5** (6.3 mmol) in 8% HCl in EtOH (14 ml) was stirred at room temperature for 1 h, and concentrated *in vacuo*. Benzene (15 ml) was added to the residue, and evaporated *in vacuo*. This workup using benzene was repeated twice. The residue was dissolved in DMF (43 ml), and 3-hydroxyanthranilic acid (**8**) (0.82 g, 5.4 mmol) was added. A solution of DEPC (0.82 ml, 5.4 mmol) in DMF (11 ml) and then *N,N*-diisopropylethylamine (2.03 ml, 11.7 mmol) were added dropwise to the mixture at 0°C, and the whole was stirred at 0°C for 0.5 h, then at room temperature for 2 h. A solution of DEPC (0.24 ml, 1.6 mmol) in DMF (5 ml) was further added, and the mixture was stirred at room temperature for additional 1.5-2.5 h, and concentrated *in vacuo*. For compounds (**9a,b,d-f**), the residue was dissolved in benzene (150 ml), and washed with water (×4), then saturated aqueous NaCl, and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica gel column chromatography to give **9a,b,d-f**. For compounds (**9c,g**), the residue was dissolved in benzene-AcOEt (1:1) (150 ml), and washed with 10% aqueous citric acid (50 ml) and saturated aqueous NaCl (50 ml×2). The 10% citric acid washing was neutralized with 1N NaOH, salted out by the addition of NaCl, and extracted with benzene-AcOEt (1:1) (30 ml×3). The combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **9c,g.**

***N*-(2-Amino-3-hydroxybenzoyl)-L-phenylalaninal diethyl acetal (9a).** Prepared from **5a** (2.03 g, 6.3 mmol) and **8** (0.82 g, 5.4 mmol). A reddish brown amorphous solid (1.23 g, 63%), purified by silica gel column chromatography with $CHCl_3$-MeOH (50:1). $[\alpha]^{23.5}_D$ -41.2° (*c*=1.13, CH_2Cl_2). Ir (film): 3500-3000, 2970, 1630, 1520, 1370, 1275, 1195, 1120, 1060, 745, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.17 (t, 3H, J=7.0 Hz), 1.24 (t, 3H, J=7.1 Hz), 2.92 (dd, 1H, J=14.0, 7.8 Hz), 3.02 (dd, 1H, J=14.0, 6.7 Hz), 3.5-3.8 (m, 4H), 4.43 (d, 1H, J=2.8 Hz), 4.5-4.8 (m, 1H), 4.8-5.8 (br, 3H disappeared with D_2O), 6.41 (d, 1H disappeared with D_2O, J=8.5 Hz), 6.44 (t, 1H, J=7.8 Hz), 6.75 (d, 1H, J=7.7 Hz), 6.82 (d, 1H, J=7.9 Hz), 7.2-7.3 (m, 5H). *Anal.* Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.11; H, 6.94; N, 8.10.

***N*-(2-Amino-3-hydroxybenzoyl)-L-leucinal diethyl acetal (9b).** Prepared from **5 b** (1.45 g, 5.0 mmol) and **8** (0.65 g, 4.3 mmol). A brown amorphous solid (0.63 g, 46%), purified by silica gel column chromatography with hexane-AcOEt (1:1) then with $CHCl_3$-MeOH (30:1). $[\alpha]^{25.5}_D$ -37.2° (*c*=0.50, CH_2Cl_2). Ir (film): 3700-3000, 2970, 1630, 1525, 1470, 1375, 1280, 1205,

1125, 1065, 820, 750 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.94 and 0.96 (2×t, 6H, J=6.4 Hz), 1.20 and 1.23 (2×t, 6H, J=7.1 Hz), 1.49 (t, 2H, J=7.1 Hz), 1.68 (m, 1H), 3.5-3.8 (m, 4H), 4.3-4.4 (m, 1H), 4.44 (d, 1H, J=2.9 Hz), 5.0-7.0 (br, 3H disappeared with D_2O), 6.20 (d, 1H, J=9.3 Hz), 6.50 (t, 1H, J= 7.9 Hz), 6.79 (dd, 1H, J=7.7, 1.3 Hz), 6.91 (dd, 1H, J=8.1, 1.1 Hz). *Anal.* Calcd for $C_{17}H_{28}N_2O_4 \cdot 1/8CHCl_3$: C, 60.61; H, 8.35; N, 8.26. Found: C, 60.68; H, 8.55; N, 8.32.

***N*-(2-Amino-3-hydroxybenzoyl)-L-alaninal diethyl acetal (9c).** Prepared from **5c** (0.99 g, 4.0 mmol) and **8** (0.52 g, 3.4 mmol). Brown crystals (0.47 g, 49%), purified by silica gel column chromatography with $CHCl_3$-MeOH (50:1) then with hexane-AcOEt (1:1), mp 70-71.5°C (Et_2O-hexane). $[\alpha]^{22.5}_D$ -25.8° (*c*=0.50, CH_2Cl_2). Ir (nujol): 3391, 3295, 3274, 1630, 1538, 1460, 1377, 1069 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.2-1.3 (m, 9H), 2.0-6.0 (br, 3H, disappeared with D_2O), 3.5-3.6 (m, 2H), 3.7-3.8 (m, 2H), 4.33 (ddq, 1H, J=8.6, 3.1, 6.8 Hz), 4.44 (d, 1H, J=3.1 Hz), 6.30 (d, 1H disappeared with D_2O, J=8.8 Hz), 6.52 (t, 1H, J=7.9 Hz), 6.79 (dd, 1H, J=7.7, 1.3 Hz), 6.94 (dd, 1H, J=8.1, 1.1 Hz). *Anal.* Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.23; H, 8.07; N, 9.81.

***N*-(2-Amino-3-hydroxybenzoyl)-D-phenylglycinal diethyl acetal (9d).** Prepared from **5d** (0.81 g, 2.6 mmol) and **8** (0.34 g, 2.2 mmol) according to the general procedure. The crude product was purified by silica gel column chromatography with hexane-AcOEt (1:2) to give **9d** (0.42 g, 55%). A part of **9d** was dissolved in CH_2Cl_2, and the solution was concentrated to give a brown amorphous solid. $[\alpha]^{26}_D$ -3.9° (*c*=0.45, CH_2Cl_2). Ir (film): 3494, 3377, 2979, 1634, 1277, 1198, 1117, 1059, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.14 and 1.21 (2×t, 6H, J=7.1 Hz), 3.4-3.8 (m, 4H), 4.0-6.0 (br, 3H disappeared with D_2O), 4.63 (d, 1H, J=3.0 Hz), 5.26 (dd, 1H, J=7.8, 2.8 Hz), 6.49 (t, 1H, J=7.9 Hz), 6.72 (d, 1H, J=7.9 Hz), 7.03 (d, 1H, J=8.3 Hz), 7.08 (d, 1H disappeared with D_2O, J=7.9 Hz), 7.2-7.4 (m, 5H). *Anal.* Calcd for $C_{19}H_{24}N_2O_4 \cdot 0.1CH_2Cl_2$: C, 65.01; H, 6.91; N, 7.94. Found: C, 65.38; H, 7.01; N, 6.96.

***N*-(2-Amino-3-hydroxybenzoyl)-*N*-methyl-L-phenylalaninal diethyl acetal (9e).** Prepared from **5e** (1.69 g, 4.8 mmol) and **8** (0.62 g, 4.1 mmol). A brown amorphous solid (0.83 g, 54%), purified by silica gel column chromatography with hexane-AcOEt (2:3). $[\alpha]^{24}_D$ -40.0° (*c*=0.57, CH_2Cl_2). Ir (film): 3470, 3380, 3200, 2980, 1600, 1475, 1440, 1400, 1280, 1130, 1070, 750, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.2-1.3 (m, 6H), 1.6-2.2 (br), 2.8-3.2 (m, 5H), 3.4-3.8 (m, 4.6H), 4.0-4.1 (br m, 0.4H), 4.48 (d, 0.4H, J=5.0 Hz), 4.76 (br, 0.6H), 4.5-5.3 (br), 6.32 (dd, 1H, J=7.6, 1.3 Hz), 6.40 (t, 1H,

J=7.8 Hz), 6.53 (dd, 1H, J=7.8, 1.6 Hz), 7.0-7.3 (m, 5H). *Anal.* Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.42; H, 7.68; N, 7.33.

***N*-(2-Amino-3-hydroxybenzoyl)-*N*-methyl-L-leucinal diethyl acetal (9f).** Prepared from **5f** (1.52 g, 5.0 mmol) and **8** (0.65 g, 4.3 mmol). Yellowish green crystals (0.60 g, 42%), purified by silica gel column chromatography with hexane-AcOEt (1:1), then with $CHCl_3$-MeOH (40:1), mp 98.5-99.0°C (hexane). $[\alpha]^{23.5}_D$ -35.8° (*c*=0.62, CH_2Cl_2). Ir (nujol): 3490, 3480, 3060, 1595, 1565, 1460, 1400, 1285, 1175, 1130, 1065, 1050 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.61, 0.87, 0.97, and 1.01 (4×d, 6H, J=6.3Hz), 1.2-1.3 (m, 6H), 1.4-1.8 (m, 3H), 2.83 and 2.99 (2×s, 3H), 3.3-3.8 (m, 4H), 3.9-5.0 (br m, 0.3H), 4.44 (d, 0.3H, J=5.3 Hz), 4.53 (d, 0.7H, J=5.9 Hz), 4.8-5.0 (br, 0.7H), 6.5-6.7 (m, 3H). *Anal.* Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.97; H, 8.95; N, 8.06.

***N*-(2-Amino-3-hydroxybenzoyl)-*N*-methyl-L-alaninal diethyl acetal (9g).** prepared from **5g** (150 mg, 0.55 mmol) and **8** (72 mg, 0.47 mmol). Brown crystals (68 mg, 49%), purified by silica gel column chromatography with hexane-AcOEt (1:1), and then $CHCl_3$-MeOH (40:1), mp 77-80°C. $[\alpha]^{25.5}_D$ +45.1° (*c*=1.02, CH_2Cl_2). Ir (nujol): 3370, 3350-3000, 1600, 1570, 1460, 1375, 1080, 750 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.2-1.3 (m, 9H), 2.0-5.0 (br, 3H), 2.88 and 2.98 (2×s, 3H), 3.4-3.7 (m, 4H), 3.94 (br, 0.4H), 4.36 (br, 0.4H), 4.60 (br, 0.6H), 4.83 (br, 0.6H), 6.53 (t, 1H, J=7.7 Hz), 6.67 (d, 2H, J=7.7 Hz). *Anal.* Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 60.44; H, 8.07; N, 9.90.

(4*R*,5*S*)-5-Ethoxy-3-methyl-4-phenyloxazoliolin-2-one (7). Prepared from **5h** (1.19 g, 3.7 mmol) by the same manner from **5** to **6**. A yellow oil (0.40 g, 49%), purified by silica gel column chromatography with hexane-AcOEt (2:3), bp 126-130°C/0.9 mmHg. $[\alpha]^{21.5}_D$ +58.2° (*c*=0.79, CH_2Cl_2). Ir (film): 2980, 2934, 1763, 1458, 1431, 1400, 1233, 1109, 1042, 764, 702 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.30 (t, 3H, J=7.1 Hz), 2.77 (s, 3H), 3.58 (dq, 1H, J=9.5, 7.0 Hz), 3.93 (dq, 1H J=9.4, 7.0 Hz), 4.39 (d, 1H, J=2.6 Hz), 5.18 (d, 1H, J=2.3 Hz), 7.2-7.3 (m, 2H), 7.4-7.5 (m, 3H). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 7.09; N, 6.27.

Mannich Type Intramolecular Cyclization of 9. General Procedure: Chlorotrimethylsilane (0.25 ml, 2.0 mmol) was added dropwise to a suspension of **9** (0.50 mmol), sodium iodide (300 mg, 2.0 mmol), and pyridine (0.20 ml, 2.5 mmol) in acetonitrile (5 ml) at

-15°C under argon, and the mixture was stirred at -15°C for 30 min. Zinc chloride (273 mg, 2.0 mmol) was added to the mixture. After the mixture was stirred at -15°C for 30 min, indole (64 mg, 0.55 mmol) was added and the whole was warmed to room temperature, and stirred at 50-55°C for 6-19 h. Saturated aqueous $NaHCO_3$ (5 ml), then AcOEt (100 ml) were added to the mixture, and insoluble materials were filtered off. The filtrate was separated and the organic layer was washed with saturated aqueous NaCl (50 ml×2) then dried over Na_2SO_4. Concentrated *in vacuo* gave the residue, which was purified by silica gel column chromatography to give **11a,b,e-g**, **12a,b,e-g**, and **13a,b,e,f**. For compounds (**9c,d**), the residue was treated with tetra-*n*-butylammonium fluoride (TBAF) (0.3 mmol) in THF (0.3 ml), and the mixture was concentrated *in vacuo*. AcOEt (60 ml) and water (30 ml) were added to the residue and the mixture was salted out by the addition of NaCl. The organic layer was separated and aqueous layer was extracted with AcOEt. The combined AcOEt layer was dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography to give **11c,d**, **12c,d** and **13c,d**.

Compounds 11a, 12a, and 13a. Prepared from **9a** (179 mg, 0.50 mmol) and indole (64 mg, 0.55 mmol) according to the general procedure. After usual work-up, the mixture was purified by silica gel column chromatography with AcOEt-hexane (2:1), then with $CHCl_3$-MeOH (50:1) to give **11a** (64 mg, 33%), **12a** (22 mg, 11%), and **13a** (73 mg, 29%).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-3-benzyl-9-hydroxy-2-(3'-indolyl)-5*H*-1,4-benzodiazepin-5-one (11a). White powder, mp 170°C (decomp.). $[\alpha]^{23.5}_D$ -23.5° (*c*=0.52, MeOH). Ir (nujol): 3400, 3300-3100, 1630, 1455, 1375, 740, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.63 (dd, 1H, J=13.7, 4.2 Hz), 2.72 (dd, 1H, J=13.8, 9.8 Hz), 4.1-4.2 (m, 1H), 4.94 (d, 1H, J=7.3 Hz), 5.61 (br, 1H, disappeared with D_2O), 6.52 (t, 1H, J=7.9 Hz), 6.83 (d, 1H, J=7.5 Hz), 6.96 (t, 1H, J=7.5 Hz), 7.1-7.2 (m, 8H), 7.36 (d, 1H, J=8.1 Hz), 7.44 (d, 1H, J=7.9 Hz), 7.76 (br, 1H, disappeared with D_2O), 9.65 (br, 1H, disappeared with D_2O), 10.92 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{24}H_{21}N_3O_2$: C, 75.17; H, 5.52; N, 10.96. Found: C, 74.81; H, 5.28; N, 11.01.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-3-benzyl-9-hydroxy-2-(3'-indolyl)-5*H*-1,4-benzodiazepin-5-one (12a). Brown crystals, mp 165°C (decomp.)($CHCl_3$). $[\alpha]^{25}_D$ +5.2° (*c*=0.51, MeOH). Ir (nujol): 3400, 3350-3250, 1600, 1565, 1510, 1450, 1430, 1375, 1265, 1185, 745, 700 cm^{-1}.

^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.59 (dd, 1H, J=14.0, 10.2 Hz), 2.92 (dd, 1H, J=14.0, 3.4 Hz), 3.9-4.0 (br m, 1H), 5.16 (s, 1H), 5.58 (s, 1H, disappeared with D_2O), 6.56 (t, 1H, J=7.9 Hz), 6.88 (dd changed d of J=7.6 Hz with D_2O, 1H, J=7.6, 1.4 Hz), 7.02 (t, 1H, J=7.1 Hz), 7.1-7.2 (m, 6H), 7.31 (d, 1H, J=7.9 Hz), 7.38 (d changed s with D_2O, 1H, J=2.0 Hz), 7.44 (d, 1H, J=8.1 Hz), 7.66 (d, 1H, J=7.9 Hz), 7.88 (d, 1H disappeared with D_2O, J=6.6 Hz), 9.77 (s, 1H, disappeared with D_2O), 11.09 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{24}H_{21}N_3O_2 \cdot 0.6CHCl_3$: C, 64.93; H, 4.78; N, 9.23. Found: C, 64.79; H, 4.67; N, 9.31.

(*S*)-*N*-(2-Amino-3-hydroxybenzoyl)-1-benzyl-2,2-bis(3'-indolyl)ethylamine (13a). White crystals, mp 169-174°C (CH_2Cl_2). $[\alpha]^{25}_D$ -56.1° (*c*=0.51, MeOH). Ir (nujol): 3390, 1615, 1570, 1515, 1450, 1340, 1275, 1265, 740, 700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.85 (dd, 1H, J=13.7, 10.3 Hz), 2.94 (dd, 1H, J=13.9, 3.3 Hz), 4.89 (d, 1H, J=8.6 Hz), 5.22 (br m, 1H), 5.3-5.9 (br, 2H, disappeared with D_2O), 6.24 (t, 1H, J=7.8 Hz), 6.60 (dd, 1H, J=8.0, 1.2 Hz), 6.65 (dd, 1H, J=7.6, 1.2 Hz), 6.8-7.4 (m, 13H), 7.59 (d, 1H, J=7.7 Hz), 7.64 (d, 1H, J=8.1 Hz), 7.68 (d, 1H disappeared with D_2O, J=9.3 Hz), 9.16 (s, 1H, disappeared with D_2O), 10.58 (s, 1H, disappeared with D_2O), 10.71 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{32}H_{28}N_4O_2 \cdot 0.8CH_2Cl_2$: C, 69.29; H, 5.25; N, 9.85. Found: C, 69.04; H, 5.10; N, 9.98.

Compounds 11b, 12b, and 13b. Prepared from **9b** (164 mg, 0.50 mmol) and indole (64 mg, 0.55 mmol) according to the general procedure. After usual work-up, the mixture was purified by silica gel column chromatography with AcOEt-hexane (2:1) then with $CHCl_3$-MeOH (20:1) to give **11b** (75 mg, 43%), **12b** (31 mg, 18%), and **13b** (52 mg, 22%).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-isobutyl-5*H*-1,4-benzodiazepin-5-one (11b). Brown amorphous solid, mp 135°C (decomp.). $[\alpha]^{24}_D$ -5.9° (*c*=0.44, MeOH). Ir (nujol): 3500-3000, 1615, 1450, 1220, 1185, 1090, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.70 (d, 3H, J=6.4 Hz), 0.80 (d, 3H, J=6.8 Hz), 1.1-1.2 (m, 1H), 1.4-1.5 (m, 1H), 1.7-1.8 (m, 1H), 3.9-4.0 (m, 1H), 4.5-5.2 (br, 1H, disappeared with D_2O), 4.80 (d, 1H, J=8.1 Hz), 6.24 (d, 1H disappeared with D_2O, J=5.2 Hz), 6.70 (t, 1H, J=7.9 Hz), 6.90 (dd, 1H, J=7.7, 1.5 Hz), 6.96 (d changed s with D_2O, 1H, J=1.4 Hz), 7.06 (dt, 1H, J=1.1, 7.5 Hz), 7.17 (dt, 1H, J=1.1, 7.3 Hz), 7.36 (d, 1H, J=8.2 Hz), 7.44 (dd, 1H, J=8.1, 1.5 Hz), 7.47 (d, 1H, J=8.1 Hz), 8.23-8.32 (br, 1H, disappeared with D_2O), 8.73 (s, 1H,

disappeared with D_2O). *Anal.* Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.35CHCl_3$: C, 65.28; H, 6.10; N, 10.67. Found: C, 65.55; H, 6.02; N, 10.74.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-isobutyl-5*H*-1,4-benzodiazepin-5-one (12b). Brown amorphous solid, mp 140°C (decomp.). $[\alpha]^{23}_D$ +91.9° (*c*=0.20, MeOH). Ir (nujol): 3380, 3300-3000, 1610, 1505, 1450, 1370, 1215, 1185, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.77 and 0.78 (2×s, 6H, J=6.4 Hz), 1.1-1.2 (m, 1H), 1.3-1.4 (m, 1H), 1.6-1.8 (m, 1H), 3.9-3.95 (m, 1H), 5.06 (d, 1H, J=2.2 Hz), 5.0-5.6 (br, 1H, disappeared with D_2O), 5.93 (d, 1H disappeared with D_2O, J=6.2 Hz), 6.69 (t, 1H, J=7.8 Hz), 6.95 (dd, 1H, J=7.7, 1.5 Hz), 7.03 (d changed s with D_2O, J=2.6 Hz), 7.09 (dt, 1H, J=1.1, 7.1 Hz), 7.18 (dt, 1H, J=1.1, 7.4 Hz), 7.38 (d, 1H, J=8.2 Hz), 7.45 (dd, 1H, J=8.1, 1.5 Hz), 7.61 (d, 1H, J=8.1 Hz), 8.96 (br s, 1H, disappeared with D_2O), 9.00 (s, 1H disappeared with D_2O). *Anal.* Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.3CHCl_3$: C, 66.54; H, 6.28; N, 10.45. Found: C, 66.41; H, 6.10; N, 10.91.

(*S*)-*N*-(2-Amino-3-hydroxybenzoyl)-2,2-bis(3'-indolyl)-1-isobutylethylamine (13b). Brown amorphous solid, mp 100°C (decomp.). $[\alpha]^{25}_D$- 47.9° (*c*=1.00, MeOH). Ir (nujol): 3500-3000, 1630, 1510, 1455, 1375, 1275, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.85 (d, 3H, J=6.6 Hz), 0.98 (d, 3H, J=6.4 Hz), 1.4-1.5 (m, 1H), 1.55-1.6 (m, 1H), 1.7-1.8 (m, 1H), 4.0-6.0 (br, 2H, disappeared with D_2O), 4.80 (d, 1H, J=4.6 Hz), 5.15-5.2 (m, 1H), 6.26 (d, 1H disappeared with D_2O, J=9.9 Hz), 6.31 (t, 1H, J=7.9 Hz), 6.52 (dd, 1H, J=8.2, 1.2 Hz), 6.77 (dd, 1H, J=7.7, 1.3 Hz), 6.86 (dt, 1H, J=0.8, 7.6 Hz), 7.0-7.1 (m, 4H), 7.3-7.4 (m, 4H), 7.62 (d, 1H, J=8.1 Hz), 8.84 (br, 1H, disappeared with D_2O), 9.29 (s, 1H, disappeared with D_2O), 9.40 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{29}H_{30}N_4O_3 \cdot 1/3CHCl_3$: C, 69.58; H, 6.04; N, 11.06. Found: C, 69.90; H, 6.16; N, 10.66.

Compounds 11c, 12c, and 13c. Prepared from **9c** (141 mg, 0.50 mmol) and indole (64 mg, 0.55 mmol) according to the general procedure. After TBAF treatment, the mixture was purified by silica gel column chromatography with AcOEt-hexane (2:1) then with $CHCl_3$-MeOH (45:1) to give **11c** (75 mg, 49%), **12c**, (18 mg, 12%), and **13c** (32 mg, 15%).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-methyl-5*H*-1,4-benzodiazepin-5-one (11c). Brown amorphous solid, mp 130°C (decomp.). $[\alpha]^{22}_D$ +115.1° (*c*=0.49, MeOH). Ir (nujol): 3410, 1628, 1456, 1233, 1192, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 1.04 (d, 3H,

J=6.8 Hz), 4.0-4.1 (m, 1H), 4.75 (d, 1H, J=8.6 Hz), 5.2-5.4 (br, 1H, disappeared with D_2O), 6.64 (t, 1H, J=7.8 Hz), 6.72 (d, 1H disappeared with D_2O, J=4.2 Hz), 6.89 (dd, 1H, J=7.6, 1.6 Hz), 6.99 (dt, 1H, J=0.9, 7.5 Hz), 7.13 (dt, 1H, J=1.0, 7.6 Hz), 7.18 (d changed s with D_2O, 1H, J=2.6 Hz), 7.38 (dd, 1H, J=8.1, 1.5 Hz), 7.40 (d, 1H, J=8.1 Hz), 7.45 (d, 1H, J=8.1 Hz), 9.10 (s, 1H, disappeared with D_2O), 10.20 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{18}H_{17}N_3O_2 \cdot 0.3CHCl_3$: C, 64.05; H, 5.08; N, 12.24. Found: C, 64.27; H, 5.10; H, 12.19.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-methyl-5*H*-1,4-benzodiazepin-5-one (12c). Brown amorphous solid, mp 130°C (decomp.). $[\alpha]^{22}_D$ +174.0° (*c*=0.11, MeOH). Ir (nujol): 3406, 1624, 1458, 1377, 1229, 1184, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 1.03 (d, 3H, J=6.9 Hz), 3.9-4.0 (m, 1H), 4.99 (d, 1H, J=2.0 Hz), 5.1-5.4 (br, 1H), 6.15 (d, 1H, J=5.9 Hz), 6.59 (t, 1H, J=7.8 Hz), 6.86 (dd, 1H, J=7.6, 1.3 Hz), 7.0-7.1 (m, 3H), 7.3-7.4 (m, 2H), 7.55 (d, 1H, J=7.6 Hz), 9.04 (br s, 1H), 9.52 (br s, 1H). *Anal.* Calcd for $C_{18}H_{17}N_3O_2 \cdot 0.3CHCl_3$: C, 64.05; H, 5.08; N, 12.24. Found: C, 64.58; H, 4.89; N, 11.90. Ms *m/z*: 307 (M^+).

(*S*)-*N*-(2-Amino-3-hydroxybenzoyl)-2,2-bis(3'-indolyl)-1-methylethylamine (13c). Brown amorphous solid, mp 105°C (decomp.). $[\alpha]^{22}_D$ -97.1° (*c*=0.28, MeOH). Ir (nujol): 3410, 1630, 1522, 1458, 1377, 1281, 1098, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 1.31 (d, 3H, J=6.6 Hz), 2.0-5.5 (br, 2H disappeared with D_2O), 4.75 (d, 1H, J=5.3 Hz), 5.1-5.2 (m, 1H), 6.32 (t, 1H, J=7.9 Hz), 6.37 (d, 1H disappeared with D_2O, J=8.8 Hz), 6.51 (d, 1H, J=8.1 Hz), 6.77 (d, 1H, J=7.7 Hz), 6.90 (dt, 1H, J=0.9, 7.5 Hz), 7.0-7.1 (m, 4H), 7.21 (br s, 1H), 7.3-7.4 (m, 3H), 7.61 (d, 1H, J=7.9 Hz), 8.2-9.0 (br, 1H disappeared with D_2O), 8.77 (s, 1H, disappeared with D_2O), 8.87 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{26}H_{24}N_4O_2 \cdot 0.5CHCl_3$: C, 65.14; H, 5.10; N, 11.57. Found: C, 65.26; H, 5.20; N, 11.39.

Compounds 11d, 12d, and 13d. Prepared from **9d** (173 mg, 0.50 mmol) and indole (64 mg, 0.55 mmol) according to the general procedure. After TBAF treatment, the mixture was purified by silica gel column chromatography with $CHCl_3$-MeOH (100:1) to give **11d** (trace),[10] **12d** (37 mg, 20%), and **13d** (24 mg, 10%).

(2*R*,3*R*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-phenyl-5*H*-1,4-benzodiazepin-5-one (12d). Brown amorphous solid, mp 145°C (decomp.). $[\alpha]^{22}_D$ +29.2° (*c*=0.21,

MeOH). Ir (nujol): 3500-3100, 3395, 1619, 1458, 1183, 1094, 693 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 5.07 (dd, 1H, J=8.6, 4.3 Hz), 5.17 (d, 1H, J=8.6 Hz), 5.3-5.7 (br, 1H, disappeared with D_2O), 6.6-6.7 (m, 2H, 1H disappeared with D_2O), 6.86 (d, 1H, J=2.6 Hz), 6.92 (dd, 1H, J=7.6, 1.3 Hz), 6.94 (dt, 1H, J=1.0, 7.4 Hz), 7.0-7.1 (m, 6H), 7.26 (d, 1H, J=7.9 Hz), 7.44 (d, 1H, J=7.9 Hz), 7.52 (dd, 1H, J=8.1, 1.5 Hz), 9.18 (br, 1H, disappeared with D_2O), 9.86 (br, 1H, disappeared with D_2O). *Anal*. Calcd for $C_{23}H_{29}N_3O_2 \cdot 0.2CHCl_3$: C, 70.85; H, 4.92; N, 10.68. Found: C, 71.18; H, 4.97; N, 10.59.

(*R*)-*N*-(2-Amino-3-hydroxybenzoyl)-2,2-bis(3'-indolyl)-1-phenylethylamine (13d). Pale red crystals, mp 155°C (decomp.)(CH_2Cl_2). $[\alpha]^{25}_D$ -0.60° (*c*=0.20, MeOH). Ir (nujol): 3401, 3058, 1638, 1518, 1456, 1204, 743 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.8-4.0 (br, 2H), 5.07 (d, 1H, J=4.3 Hz), 6.11 (dd, 1H, J=7.9, 4.6 Hz), 6.35 (t, 1H, J=7.9 Hz), 6.65 (d, 1H, J=7.9 Hz), 6.8-7.4 (m, 17H), 8.84 (br s, 1H, disappeared with D_2O), 8.96 (br s, 1H, disappeared with D_2O), 7.0-10.0 (br, 1H, disappeared with D_2O). *Anal*. Calcd for $C_{31}H_{26}N_4O_2 \cdot CHCl_3$: C, 67.25; H, 4.94; N, 9.80. Found: C, 67.35; H, 4.80; N, 9.76.

Compounds 11e, 12e, and 13e. Prepared from **9e** (93 mg, 0.25 mmol) and indole (32 mg, 0.28 mmol) according to the general procedure. After usual work-up, the mixture was purified by silica gel column chromatography with $CHCl_3$-MeOH (50:1) then with AcOEt-hexane-C_6H_6 (3:2:2) to give **11e** (67 mg, 67%), **12e** (31 mg, 31%), and **13e** (trace).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-3-benzyl-9-hydroxy-2-(3'-indolyl)-4-methyl-5*H*-1,4-benzodiazepin-5-one (11e). Brown amorphous solid, mp 135°C (decomp.). $[\alpha]^{25}_D$ -256.6° (*c*=0.50, MeOH). Ir (nujol): 3410, 3210, 1610, 1560, 1450, 1230, 1185, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.45 (s, 3H), 2.92 (dd, 1H, J=13.7, 6.6 Hz), 2.99 (dd, 1H, J=13.7, 9.2 Hz), 4.2-4.3 (m, 1H), 5.16 (d, 1H, J=5.0 Hz), 5.6-6.1 (br, 1H, disappeared with D_2O), 6.6-6.7 (m, 1H), 6.94 (d, 1H, 7.0 Hz), 6.98 (d, 1H, J=2.2 Hz), 7.04 (dt, 1H, J=1.0, 7.5 Hz), 7.12 (dt, 1H, J=1.0, 7.5 Hz), 7.2-7.4 (m, 8H), 7.55 (dd, 1H; J=8.2, 1.3 Hz), 9.24 (br s, 1H, disappeared with D_2O), 9.83 (br s, 1H, disappeared with D_2O). *Anal*. Calcd for $C_{25}H_{23}N_3O_2 \cdot 1/3CHCl_3$: C, 69.59; H, 5.38; N, 9.61. Found: C, 69.64; H, 5.24; N, 9.71.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-3-benzyl-9-hydroxy-2-(3'-indolyl)-4-methyl-5*H*-1,4-benzodiazepin-5-one (12e). Brown amorphous solid, mp 175°C (decomp.). $[\alpha]^{25}_D$ -390.9° (*c*=0.43, MeOH). Ir (nujol): 3430, 3400-3150, 1610, 1545, 1450, 1225, 745 cm^{-1}. ^{1}H-Nmr

($CDCl_3$+DMSO-d_6) δ: 2.73 (s, 3H), 2.7-2.8 (m, 1H), 3.00 (dd, 1H, J=14.0, 3.6 Hz), 3.8-4.0 (br, 1H), 5.19 (s, 1H), 5.6-5.8 (br, 1H, disappeared with D_2O), 6.63 (t, 1H, J=7.8 Hz), 6.85-6.9 (m, 3H), 7.1-7.2 (m, 4H), 7.23 (t, 1H, J=7.4 Hz), 7.45 (d, 1H, J=2.2 Hz), 7.50 (d, 1H, J=8.2 Hz), 7.66 (d, 1H, J=7.9 Hz), 9.29 (br, 1H, disappeared with D_2O), 10.47 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.26; H, 5.74; N, 10.45.

(*S*)-*N*-(2-Amino-3-hydroxybenzoyl)-*N*-methyl-1-benzyl-2,2-bis(3'-indolyl)ethylamine (13e). Brown amorphous solid. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.64 (s, 3H), 2.6-3.0 (m, 1H), 3.07 (dd, 1H, J=14.6, 3.8 Hz), 4.83 (br, 1H), 5.76 (d, 1H, J=5 Hz), 6.26 (t, 2H, J=7.9 Hz), 6.57 (dd, 1H, J=7.9, 1.3 Hz), 6.97 (t, 1H, J=7.0 Hz), 7.04 (t, 1H, J=7.6 Hz), 7.10-7.36 (m, 10H), 7.60 (s, 1H), 7.65 (d, 1H, J=6.6 Hz), 8.00 (d, 1H, J=4.8 Hz), 8.54 (br, 1H, disappeared with D_2O), 9.66 (s, 1H, disappeared with D_2O), 9.68 (s, 1H, disappeared with D_2O).

Compounds 11f, 12f, and 13f. Prepared from **9f** (85 mg, 0.25 mmol) and indole (32 mg, 0.28 mmol) according to the general procedure. After usual work-up, the mixture was purified by silica gel column chromatography with AcOEt-hexane-C_6H_6 (2:1:1) to give **11f** (58 mg, 64%), **12f** (24 mg, 26%), and **13f** (trace).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-isobutyl-4-methyl-5*H*-1,4-benzodiazepin-5-one (11f). Colorless crystals, mp 125-130°C (decomp.)(C_6H_6). $[\alpha]^{24}_D$ -144.2° (*c*=0.96, MeOH). Ir (nujol): 3420, 3180, 1610, 1560, 1465, 1375, 1225, 1180, 740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.88 and 0.90 (2×d, 6H, J=6.4 Hz), 1.4-1.5 (m, 1H), 1.6-1.7 (m, 2H), 2.74 (s, 3H), 4.1-4.2 (m, 1H), 5.10 (d, 1H, J=5.7 Hz), 5.6-5.7 (br, 1H, disappeared with D_2O), 6.57 (t, 1H, J=7.9 Hz), 6.85 (dd, 1H, J=7.6, 1.6 Hz), 6.88 (d, 1H, J=2.2 Hz), 7.08 (dt, 1H, J=1.1, 7.1 Hz), 7.16 (dt, 1H, J=1.1, 7.6 Hz), 7.38 (d, 1H, J=8.3 Hz), 7.46 (dd, 1H, J=8.2, 1.3 Hz), 7.49 (d, 1H, J=7.9 Hz), 8.83 (s, 1H, disappeared with D_2O), 9.27 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{22}H_{25}N_3O_2 \cdot C_6H_6$: C, 76.16; H, 7.08; N, 9.52. Found: C, 75.73; H, 6.92; N, 9.31.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3-isobutyl-4-methyl-5*H*-1,4-benzodiazepin-5-one (12f). A part of **12f** was dissolved in CH_2Cl_2-MeOH (50:1), and the solution was concentrated to give a brown amorphous solid, mp 135°C (decomp.). Ir (nujol): 3430, 3310, 1610, 1550, 1460, 1375, 1225, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.71 (d, 3H, J=5.5

Hz), 0.76 (d, 3H, J=6.2 Hz), 1.2-1.8 (m, 3H), 3.0-3.2 (br, 3H), 3.8-4.0 (br, 1H), 5.09 (s, 1H), 5.1-5.7 (br, 1H, disappeared with D_2O), 6.62 (m, 1H), 6.89 (d, 1H, J=7.2 Hz), 7.1-7.2 (m, 2H), 7.32 (s, 1H), 7.44 (d, 1H, J=8.2 Hz), 7.4-7.6 (m, 1H), 7.65 (d, 1H, J=8.2 Hz), 9.00 (br, 1H, disappeared with D_2O), 9.85 (br s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{22}H_{25}N_3O_2 \cdot 0.2CH_2Cl_2$: C, 70.09; H, 6.73; N, 11.04. Found: C, 70.53; H, 6.82; N, 10.61.

(*S*)-*N*-(2-Amino-3-hydroxybenzoyl)-*N*-methyl-2,2-bis(3'-indolyl)-1-isobutylethylamine (13f). Brown amorphous solid. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.83 (d, 3H, J=6.6 Hz), 0.98 (d, 3H, J=6.4 Hz), 1.35-1.4 (m, 1H), 1.5-1.6 (m, 1H), 1.65-1.7 (m, 1H), 2.68 (s, 3H), 3.52 (br, 2H, disappeared with D_2O), 4.67 (d, 1H, J=11.4 Hz), 5.92 (br m, 1H), 6.08 (d, 1H, J=7.5 Hz), 6.37 (t, 1H, J=7.8 Hz), 6.65 (dd, 1H, J=7.9, 1.3 Hz), 6.99 (dt, 1H, J=1.1, 7.5 Hz), 7.0-7.1 (m, 3H), 7.22 (d changed s with D_2O, 1H, J=2.4 Hz), 7.28 (d, 1H, J=7.9 Hz), 7.33 (d, 1H, J=7.3 Hz), 7.54 (d changed s with D_2O, 1H, J=2.4 Hz), 7.66 (d, 1H, J=7.9 Hz), 7.88 (d, 1H, J=7.0 Hz), 8.48 (br s, 1H, disappeared with D_2O), 9.18 (s, 1H, disappeared with D_2O), 9.27 (s, 1H, disappeared with D_2O).

Compounds 11g and 12g. Prepared from **9g** (89 mg, 0.30 mmol) and indole (40 mg, 0.34 mmol) according to the general procedure. After usual work-up, the mixture was purified by silica gel column chromatography with AcOEt-hexane-C_6H_6 (4:2:1) to give **11g** (62 mg, 64%) and **12g** (9 mg, 9%).

(2*S*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3,4-dimethyl-5*H*-1,4-benzodiazepin-5-one (11g). Brown amorphous solid, mp 140°C (decomp.). $[\alpha]^{25}_D$ -45.6° (c=0.53, MeOH). Ir (nujol): 3400, 3350-3000, 1610, 1560, 1450, 1240, 1075 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 1.20 (d, 3H, J=7.0 Hz), 2.90 (s, 3H), 4.26 (quint, 1H, J=7.1 Hz), 4.97 (d, 1H, J=7.2 Hz), 5.1-5.5 (br, 1H, disappeared with D_2O), 6.61 (t, 1H, J=7.9 Hz), 6.80 (d changed s with D_2O, 1H, J=2.4 Hz), 6.86 (dd, 1H, J=7.7, 1.5 Hz), 7.04 (dt, 1H, J=1.0, 7.5 Hz), 7.13 (dt, 1H, J=1.1, 7.6 Hz), 7.32 (d, 1H, J=8.2 Hz), 7.42 (dd, 1H, J=8.2, 1.5 Hz), 7.44 (d, 1H, J=8.4 Hz), 8.77 (br, 1H, disappeared with D_2O), 9.15 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{19}H_{19}N_3O_2 \cdot 0.5CHCl_3$: C, 61.46; H, 5.16; N, 11.03. Found: C, 61.03; H, 5.16; N, 10.73.

(2*R*,3*S*)-1,2,3,4-Tetrahydro-9-hydroxy-2-(3'-indolyl)-3,4-dimethyl-5*H*-1,4-benzodiazepin-5-one (12g). Brown amorphous solid. Ir (nujol): 3450-3000, 1610, 1560, 1450, 1260,

1220, 1080, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 1.19 (d, 3H, J=7.1 Hz), 3.03 (s, 3H), 4.0-4.05 (m, 1H), 5.06 (d, 1H, J=1.5 Hz), 5.2-5.4 (br, 1H, disappeared with D_2O), 6.63 (t, 1H, J=7.9 Hz), 6.89 (dd, 1H, J=7.5, 1.5 Hz), 7.10 (dt, 1H, J=0.8, 7.5 Hz), 7.19 (dt, 1H, J=0.8, 7.5 Hz), 7.33 (d changed s with D_2O), 7.44 (d, 1H, J=8.1 Hz), 7.51 (d, 1H, J=7.5 Hz), 7.64 (d, 1H, J=7.7 Hz), 9.05 (s, 1H, disappeared with D_2O), 9.96 (s, 1H, disappeared with D_2O). Ms *m/z* : 321 (M^+).

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9. The addition order of zinc chloride and indole in this Mannich type reaction is reverse to that in the tilivalline synthesis[3] since preliminary experiments revealed that this order gave better results.
10. Although the compound (**11d**) could not be isolated, ^{1}H-nmr spectrum of the mixture of **11d** and **12d** clearly showed a doublet signal (δ 5.20, J=2.2 Hz) assignable to C_2-H of **11d**.

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