SYNTHESIS OF HYBRID TILIVALLINES AND THEIR 11-CYANO ANALOGS†

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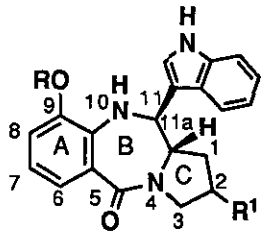
Abstract — Hybrid tilivallines (**4**), derived from tilivalline (**1a**) and anthramycin (**2**) or tomaymycin (**3**), and their 11-cyano analogs (**15**) have been efficiently synthesized from the acetal amides (**7a, b**) : the key step is an intramolecular Mannich type cyclization accompanied with introduction of indole or nitrile function.

Tilivalline (**1a**), a metabolite isolated from *Klebsiella pneumoniae* var. *oxytoca*,[1] is a member of pyrrolo[2,1-*c*][1,4]benzodiazepine family, a characteristic skeleton of anthramycin-type antibiotics.[2] Since anthramycin (**2**) and tomaymycin (**3**) have potent antitumor activity,[2] tilivalline (**1a**) and its derivatives will also be expected to exhibit analogous activity. We have already accomplished a completely stereoselective synthesis of **1a**, its analogs (**1b-e**), and 11-substituted pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones utilizing a novel intramolecular Mannich type cyclization as a key step.[3] More recently, we have found that this Mannich type cyclization is also efficiently applicable to construction of 2-indolyl-1,4-benzodiazepin-5-ones.[4] Our continued interest in both extension of the scope of this synthetic methodology and studies on the structure-activity relationships

† Dedicated to Professor Alan R. Katritzky on the occasion of his 65 th birthday.



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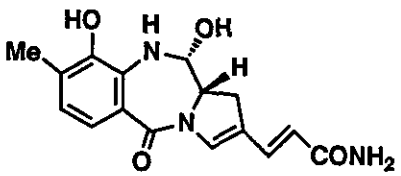
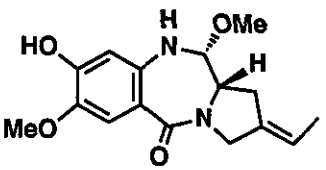
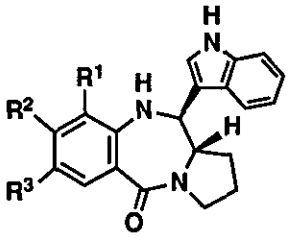


Anthramycin (2)



Tomaymycin (3)

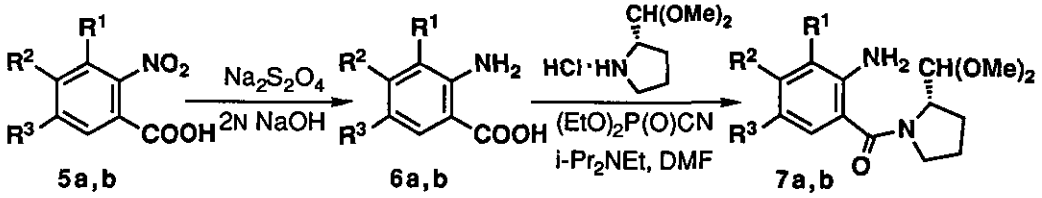
a: R = R^1 = H (Tilivalline)
b: R = Me, R^1 = H
c: R = $PhCH_2$, R^1 = H
d: R = H, R^1 = OH
e: R = H, R^1 = $PhCH_2O$



4 **a**: R^1= OH, R^2= Me, R^3= H
b: R^1= H, R^2= OH, R^3= MeO

led us to investigate the synthesis of hybrid tilivallines (**4**) which bear two substituents on the A ring of tilivalline (**1a**) derived from **1a** and anthramycin (**2**) or tomaymycin (**3**).[5] Furthermore, we studied synthesis of the 11-cyano analogs of **4** which is also expected to have interesting biological activity.[6]

The key intermediates for the Mannich type cyclization are the acetal amides (**7a,b**) which are easily prepared starting from *o*-nitrobenzoic acids (**5a,b**) as shown in Scheme 1. Reduction of **5** with sodium hydrosulfite in 2N aqueous sodium hydroxide solution gave the anthranilic acids (**6a,b**). Condensation of **6** with hydrochloride of L-prolinal dimethyl acetal was accomplished by use of diethyl

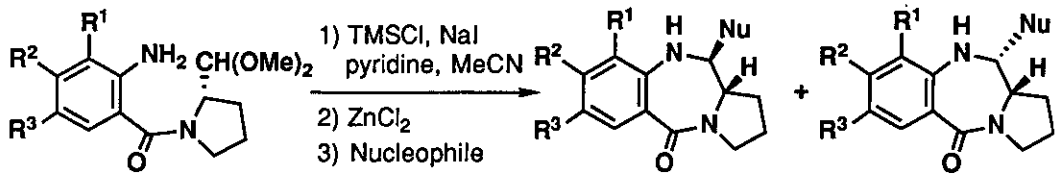


5a,b **6a,b** **7a,b**

a: R^1= $PhCH_2O$, R^2= Me, R^3= H
b: R^1= H, R^2= $PhCH_2O$, R^3= MeO

Scheme 1

Table. Products of the Mannich type cyclization of the acetal amides (**7**)



7a,b

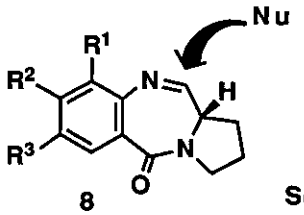
9: Nu = 3'-indolyl
11: Nu = CN

10: Nu = 3'-indolyl
12: Nu = CN

Starting **7**	R^1	R^2	R^3	Product	Nu	Yield (%)
7a	$PhCH_2O$	Me	H	**9a**	3'-indolyl	84
				10a	3'-indolyl	16
7b	H	$PhCH_2O$	MeO	**9b**	3'-indolyl	75
				10b	3'-indolyl	6
7a	$PhCH_2O$	Me	H	**11a**	CN	63
				12a	CN	30
7b	H	$PhCH_2O$	MeO	**11b**	CN	45
				12b	CN	41

phosphorocyanidate (DEPC)[7] in the presence of diisopropylethylamine to give the corresponding acetal amides (**7a,b**) in good yields.

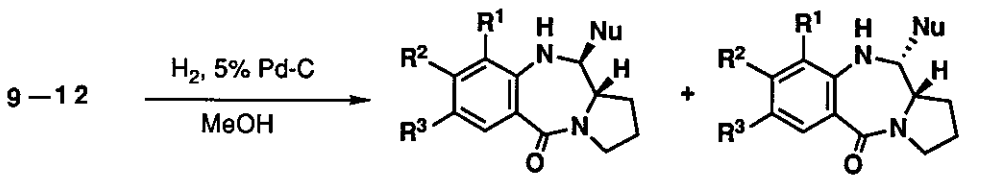
Construction of 11-(3'-indolyl)-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (**9a,b**) by the Mannich type cyclization has been achieved in one-pot process by successive treatment of the acetal amides (**7**) with (1) chlorotrimethylsilane-sodium iodide-pyridine in acetonitrile, (2) zinc chloride, and (3) indole.[3,4] In our tilivalline synthesis,[3] this Mannich type cyclization proceeded in a completely stereoselective manner and the attack of indole occurred only from the less hindered face of the intermediate imine (**8**) as depicted in Scheme 2. In fact, the one-pot Mannich type reaction of **7a** afforded **9a** as the major product, but considerable amounts of its C_{11} epimer (**10a**), resulting from the attack of indole from the more hindered face of **8**, was formed as shown in Table. The acetal amide (**7b**) also gave a mixture of



8 **Scheme 2**

9b and **10b** in preference of the former. Analogously, the acetal amides (**7a,b**) also underwent the Mannich type reaction with sodium cyanide in the presence of sodium hydrogen sulfide,[3] giving a mixture of 11-cyano derivatives (**11a,b**) and their C_{11} epimers (**12a,b**) with low stereoselectivity. Similar selectivity of the nitrile introduction has been observed in the reaction with the acetal amide (**7**) (R^1=OH, R^2=R^3=H). The stereochemistries of 11 positions of **9-12** were determined by comparisons with the coupling constants between C_{11} and C_{11a} protons on their ^{1}H-nmr spectra.[3]

Finally, reductive debenzylation of **9** and **10** was easily carried out under a hydrogen atmosphere over 5% palladium carbon in methanol to furnish the corresponding hybrid tilivallines (**4a,b**) and their C_{11} epimers (**13a,b**) in nearly quantitative yields as shown in Scheme 3. Similarly, **11** and **12** gave the corresponding cyano derivatives (**14, 15**), respectively.



4a,b: Nu = 3'-indolyl **13a,b**: Nu = 3'-indolyl
14a,b: Nu = CN **15a,b**: Nu = CN

Scheme 3

a: R^1= OH, R^2= Me, R^3= H
b: R^1=H, R^2= OH, R^3= MeO

In conclusion, the synthesis of the hybrid tilivallines and their 11-cyano analogs was easily achieved by use of the intramolecular Mannich type cyclization as a key step. Biological test of **13-16** is now underway and will be discussed elsewhere.

EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were measured with a SHIMADZU FTIR-8100 spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL EX-270 or a 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*, purchased from *Fuji Davison Co.*) was used for column chromatography. Zinc chloride was dried at 150-160°C for 2 h under reduced pressure before use.

2-Amino-3-benzyloxy-4-methylbenzoic acid (6a). A solution of sodium hydrosulfite (0.97 g, 5.6 mmol) in H_2O (3.5 ml) was added to a solution of 3-benzyloxy-4-methyl-2-nitrobenzoic acid (**5a**)[8] (201 mg, 0.70 mmol) in 2N aqueous NaOH (3.5 ml). The solution was refluxed for 1.5 h, cooled, and neutralized with 10% aqueous HCl. The aqueous solution was diluted with water (15 ml), salted out by the addition of NaCl, and extracted with Et_2O (60 ml × 1, 30 ml × 3). The combined organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with *$CHCl_3$-MeOH (15:1)* to give **6a** as a brown solid (106 mg, 59%), mp 147-149°C (pale red crystals from Et_2O-hexane). Ir (nujol): 3478, 3364, 3200-2000, 1665, 1456, 1312, 1244, 980, 774, 752 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 2.29 (s, 3H), 4.84 (s, 2H), 3.5-5.5 (br, 2H, disappeared with D_2O), 5.42 (br, 1H, disappeared with D_2O), 6.47 (d, 1H, J=8.2 Hz), 7.3-7.5 (m, 5H), 7.62 (d, 1H, J=8.2 Hz). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.80; H, 5.85; N, 5.66.

2-Amino-4-benzyloxy-5-methoxybenzoic acid (6b). Prepared from 4-benzyloxy-5-methoxy-2-nitrobenzoic acid (**5b**)[9] (212 mg, 0.70 mmol) according to the same procedure as for the preparation of **6a**. A yellow powder (106 mg, 55%) was obtained by purification on a silica gel column with *CH_2Cl_2-EtOH (3:1)*, mp 168-172°C (pale brown crystals from acetone-hexane). Ir (nujol): 3476, 3376, 3300-

2200, 1661, 1593, 1422, 1252, 986 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 3.66 (s, 3H), 5.06 (s, 2H), 6.45 (s, 1H), 7.20 (s, 1H), 7.3-7.5 (m, 5H), 7.8-8.8 (br, 3H, disappeared with D_2O). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.67; H, 5.42; N, 4.91.

***N*-(2-Amino-3-benzyloxy-4-methylbenzoyl)-L-prolinal dimethyl acetal (7a).** A solution of *N*-Boc-L-prolinal dimethyl acetal[3,4] (1.72 g, 7.0 mmol) in 10% HCl-MeOH (20 ml) was stirred at room temperature for 1 h, and concentrated *in vacuo*. Benzene was added to the residue, and evaporated *in vacuo*. This work-up using benzene was repeated twice. The residue was dissolved in DMF (20 ml), and **6a** (1.44 g, 5.6 mmol) was added. DEPC (0.94 ml, 6.2 mmol) and then *N*,*N*-diisopropylethylamine (2.2 ml, 12.6 mmol) were added to the mixture at 0°C, and the whole was stirred at 0°C for 1 h, then at room temperature for 20 h. After concentration *in vacuo*, the residue was diluted with benzene (200 ml). The mixture was washed with 1N aqueous NaOH (60 ml), water (60 ml × 4), and saturated aqueous NaCl (60 ml), and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica gel column chromatography with hexane-AcOEt-benzene (1:1:1), then with hexane-AcOEt-benzene (3:2:3) to give **7a** (1.52 g, 71%) as a yellow viscous oil. $[\alpha]^{25.5}_D$ -168.8° (*c*=1.08, CH_2Cl_2). Ir (film): 3460, 3362, 2934, 1619, 1414, 1223, 1129, 1078, 1067, 752 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.7-2.2 (m, 4H), 2.28 (s, 3H), 2.5-4.5 (br, 2H) 3.5-3.6 (m, 8H), 4.4-4.5 (m, 1H), 4.7-5.0 (m, 3H), 6.52 (d, 1H, J=7.9 Hz), 6.93 (d, 1H, J=7.9 Hz), 7.3-7.5 (m, 5H). *Anal.* Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.75; H, 7.50; N, 7.25.

***N*-(2-Amino-4-benzyloxy-5-methoxybenzoyl)-L-prolinal dimethyl acetal (7b).** Reaction was carried out with *N*-Boc-L-prolinal dimethyl acetal (88 mg, 0.36 mmol) and **6b** (98 mg, 0.36 mmol) according to the same procedure as for the preparation of **7a**. After being stirred at room temperature for 3 h, the mixture was concentrated *in vacuo*. The residue was diluted with benzene (30 ml), and the mixture was washed with water (10 ml × 4), saturated aqueous NaCl (10 ml), and

dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica gel column chromatography with AcOEt-hexane (3:1) to give a mixture of **7b** and DEPC (110 mg). ^{1}H-Nmr analysis of the mixture showed that the ratio of **7b**/DEPC was 2/1. The mixture was recrystallized from Et_2O to give pure **7b** as white crystals, mp 95.0-95.5°C (benzene-hexane). $[\alpha]^{26}_D$ -119.0° (*c*=0.62, CH_2Cl_2). Ir (nujol): 3436, 3351, 1626, 1597, 1464, 1406, 1271, 1059 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.7-2.2 (m, 4H), 3.5-3.6 (m, 8H), 3.81 (s, 3H), 4.4-4.5 (br, 1H), 4.7-4.8 (br, 1H), 4.0-5.2 (br, 2H), 5.12 (s, 2H), 6.34 (s, 1H), 6.81 (s, 1H), 7.3-7.4 (m, 5H). *Anal.* Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.25; H, 7.23; N, 7.00.

11-(3'-Indolyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (9a and 10a). Chlorotrimethylsilane (0.2 ml, 1.6 mmol) was added dropwise to a suspension of **7a** (54 mg, 0.4 mmol), sodium iodide (240 mg, 1.6 mmol), and pyridine (0.16 ml, 2 mmol) in acetonitrile (4 ml) at -15°C under argon, and the mixture was stirred at -15°C for 30 min. Zinc chloride (218 mg, 1.6 mmol) was added to the mixture. After the mixture was stirred at -15°C for 30 min, indole (52 mg, 0.44 mmol) was added and the whole was warmed to room temperature, and stirred at 53-55°C for 4 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. After concentration *in vacuo*, the residue was purified by silica gel column chromatography with AcOEt-hexane (2:1) to give **9a** (147 mg, 84%) and **10a** (28 mg, 16%).

(11*S*,11a*S*)-1,2,3,10,11,11a,-Hexahydro-9-benzyloxy-11-(3'-indolyl)-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (9a). Pale brown crystals, mp 165°C (decomp.) (acetone). $[\alpha]^{26}_D$ +110.3° (*c*=0.83, MeOH). Ir (nujol): 3420, 3246, 1615, 1592, 1516, 1433, 1208, 750 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.6-1.9 (m, 4H), 2.30 (s, 3H), 3.7-3.8 (m, 1H), 3.9-4.0 (m, 1H), 4.4-4.6 (m, 3H), 4.71 (d, 1H, J=7.6 Hz), 5.3 (br, 1H, disappeared with D_2O), 6.65 (d, 1H, J=7.6 Hz), 6.80-6.83 (m, 2H), 7.0-7.3 (m, 6H), 7.42 (d, 1H, J=6.9 Hz), 7.61 (d, 1H, J=6.9 Hz), 7.76 (d, 1H, J=7.6

Hz), 8.36 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60. Found: C, 76.93; H, 6.25; N, 9.65.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-benzyloxy-11-(3'-indolyl)-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (10a). A brown amorphous solid, mp 95°C (decomp.). $[\alpha]^{26}_D$ +254.8° (*c*=0.59, MeOH). Ir (nujol): 3412, 3243, 1615, 1509, 1456, 1377, 1211, 743 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.8-1.0 (m, 1H), 1.4-1.5 (m, 1H), 1.8-1.9 (m, 1H), 2.0-2.2 (m, 1H), 2.34 (s, 3H), 3.1-3.3 (m, 1H), 3.6-3.7 (m, 1H), 4.1-4.2 (m, 1H), 4.60 (s, 1H), 4.76 (d, 1H, J=11.5 Hz), 4.86 (d, 1H, J=11.2 Hz), 6.69 (d, 1H, J=8.3 Hz), 7.1-7.4 (m, 10H), 7.55 (d, 1H, J=7.6 Hz), 7.67 (d, 1H, J=7.6 Hz), 8.48 (br s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{28}H_{27}N_3O_2 \cdot 5/4CH_3COCH_3$: C, 74.75; H, 6.82; N, 8.24. Found: C, 74.83; H, 6.31; N, 8.67.

Compounds 9b and 10b. Prepared from **7b** (200 mg, 0.50 mmol) and indole (64 mg, 0.55 mmol) according to the same procedure as for the preparation of **9a**, except the reaction was carried out at room temperature for 21 h. After usual work-up, the mixture was purified by silica gel column chromatography with AcOEt-hexane (2:1), then with $CHCl_3$-MeOH (100:1) to give **9b** (170 mg, 75%) and **10b** (14 mg, 6%).

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-benzyloxy-11-(3'-indolyl)-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (9b). A pale brown amorphous solid. $[\alpha]^{23.5}_D$ +135.7° (*c*=0.50, MeOH). Ir (nujol): 3480-3120, 3376, 1622, 1595, 1507, 1456, 1250, 742 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.6-2.0 (m, 4H), 3.6-3.9 (m, 2H), 3.88 (s, 3H), 4.2-4.3 (m, 1H), 4.66 (d, 1H, J=9.2 Hz), 5.04 (s, 2H), 6.06 (s, 1H), 7.01 (d changed s with D_2O, 1H, J=2.3 Hz), 7.07 (dt, 1H, J=0.8, 7.5 Hz), 7.2-7.6 (m, 10 H), 8.41 (br s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{28}H_{27}N_3O_3 \cdot 0.5CHCl_3$: C, 66.70; H, 5.40; N, 8.19. Found: C, 66.44; H, 5.49; N, 8.22.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-benzyloxy-11-(3'-indolyl)-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (10b). A colorless powder, mp 135°C (decomp.). Ir (nujol): 3500-3100, 1624, 1597, 1509, 1456, 1377,

1223, 1100, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.8-0.9 (m, 1H), 1.4-1.5 (m, 1H), 1.8-1.9 (m, 1H), 2.0-2.1 (m, 1H), 3.2-3.3 (m, 1H), 3.6-3.7 (m, 1H), 3.90 (s, 3H), 4.28-4.32 (m, 1H), 5.08 (d, 1H, J=3.3 Hz) 5.09 (s, 2H), 6.17 (s, 1H), 7.1-7.4 (m, 10H), 7.52 (s, 1H), 7.65 (d, 1H, J=8.2 Hz), 8.33 (br s, 1H).

11-Cyano-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (11a and 12a). Chlorotrimethylsilane (0.25 ml, 2.0 mmol) was added dropwise to a suspension of **7a** (192 mg, 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 (272 mg, 2.0 mmol) was added to the mixture. After being stirred at -15°C for 30 min, sodium hydrogen sulfite (57 mg, 0.55 mmol), then sodium cyanide (27 mg, 0.55 mmol) was added and the whole was warmed to room temperature, and stirred at 55°C for 21 h. After usual work-up, the crude product was purified by silica gel column chromatography with AcOEt-hexane (3:2) to give **11a** (109 mg, 63%) and **12a** (52 mg, 30%).

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-benzyloxy-11-cyano-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (11a). Pale yellow crystals, mp 60°C (decomp.). $[\alpha]^{25.5}_D$ +136.7° (*c*=1.08, MeOH). Ir (nujol): 3262, 2226, 1620, 1603, 1455, 1375, 1225, 743 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.0-2.1 (m, 3H), 2.3-2.4 (m, 1H), 2.40 (s, 3H), 3.7-3.8 (m, 2H), 4.0-4.1 (m, 1H), 4.28 (d, 1H, J=10.6 Hz), 4.87 (d, 1H, J=11.2 Hz), 5.06 (d, 1H, J=11.2 Hz), 6.91 (d, 1H, J=7.9 Hz), 7.4-7.6 (m, 6H). *Anal.* Calcd for $C_{21}H_{21}N_3O_2 \cdot 0.8CHCl_3$: C, 59.12; H, 4.96; N, 9.49. Found: C, 59.02; H, 5.00; N, 9.17.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-benzyloxy-11-cyano-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (12a). A pale yellow amorphous solid. $[\alpha]^{24}_D$ +262.8° (*c*=0.58, MeOH). Ir (nujol): 3393, 2934, 2240, 1619, 1509, 1244, 1210, 752 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.8-2.4 (m, 4H), 2.37 (s, 3H), 3.7-3.8 (m, 2H), 3.95-4.02 (m, 2H), 4.79 (d, 1H, J=11.5 Hz), 4.88 (d, 1H, J=11.5 Hz), 5.17 (br, 1H, disappeared with D_2O), 6.76 (d, 1H, J=8.3 Hz), 7.4-7.5 (m, 5H), 7.72 (d, 1H, J=8.3 Hz). *Anal.* Calcd for $C_{21}H_{21}N_3O_2 \cdot 0.1CHCl_3$: C, 70.52; H, 5.92; N, 11.69. Found: C, 70.90; H,

5.99; N, 11.83.

Compounds 11b and 12b. Prepared from **7b** (100 mg, 0.25 mmol), sodium hydrogen sulfite (29 mg, 0.28 mmol), and sodium cyanide (14 mg, 0.28 mmol) according to the same procedure as for the preparation of **11a**. After usual work-up, the crude product was purified by silica gel column chromatography with AcOEt-hexane (4:1), then with AcOEt-hexane (2:1) to give **11b** (41 mg, 45%) and **12b** (37 mg, 41%).

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-benzyloxy-11-cyano-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (11b). Colorless crystals, mp 194-196°C (decomp.) (AcOEt-hexane). $[\alpha]^{22.5}_D$ +104.3°C (*c*=0.31, MeOH). Ir (nujol): 3262, 2226, 1622, 1433, 1374, 1267, 1221, 1198, 994 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 2.0-2.3 (m, 4H), 3.6-3.8 (m, 3H, 1H disappeared with D_2O), 3.89 (s, 3H), 3.9-4.0 (m, 1H), 4.15 (d, 1H, J=10.6 Hz), 5.13 (d, 1H, J=12.2 Hz), 5.20 (d, 1H, J=12.2 Hz), 6.47 (s, 1H), 7.3-7.4 (m, 6H). *Anal.* Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.57; H, 5.79; N, 11.66.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-benzyloxy-11-cyano-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (12b). Colorless crystals, mp 165°C (decomp.) (acetone). $[\alpha]^{23.5}_D$ +185.4° (*c*=0.50, acetone). Ir (nujol): 3301, 2238, 1634, 1595, 1510, 1435, 1248, 1026, 747 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.8-2.4 (m, 4H), 3.6-3.9 (m, 1H), 3.87 (s, 3H), 3.9-4.1 (m, 2H), 4.34 (d, 1H, disappeared with D_2O, J=5.9 Hz), 4.58 (dd, 1H, J=6.1, 1.8 Hz), 5.10 (d, 1H, J=12.5 Hz), 5.14 (d, 1H, J=12.5 Hz), 6.10 (s, 1H), 7.3-7.4 (m, 5H), 7.57 (s, 1H). *Anal.* Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.58; H, 5.91; N, 11.54.

Catalytic Debenzylation of 9-12. General Procedure: A suspension of **9** (0.24 mmol) and 5% Pd-C (51 mg) in MeOH (15 ml) was stirred under hydrogen atmosphere at room temperature for 0.5-2 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **13**.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-hydroxy-11-(3'-indolyl)-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (4a). Prepared from **9a** (103 mg, 0.24 mmol) and 5% Pd-C (51 mg) in MeOH (15 ml). A brown powder (79 mg, 95%) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (50:1), mp 170°C (decomp.) (white crystals from acetone-hexane). $[\alpha]^{24.5}_D$ +211.0° (*c*=0.51, MeOH). Ir (nujol): 3405, 3327, 3260, 1703, 1615, 1584, 1456, 1445, 1208, 743 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 1.7-2.0 (m, 4H), 2.22 (s, 3H), 3.7-3.9 (m, 2H), 4.2-4.3 (m, 1H), 4.77 (d, 1H, J=9.2 Hz), 5.3-6.0 (br, 1H, disappeared with D_2O), 6.63 (d, 1H, J=8.2 Hz) 7.01 (t, 1H, J=7.6 Hz), 7.14 (t, 1H, J=7.6 Hz), 7.20 (d, 1H, J=2.0 Hz), 7.4-7.5 (m, 3H), 7.97 (br, 1H, disappeared with D_2O), 10.49 (s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{21}H_{21}N_3O_2 \cdot 1.2CH_3COCH_3$: C, 70.84; H, 6.81; N, 10.07. Found: C, 70.64; H, 6.89; N, 10.41.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-hydroxy-11-(3'-indolyl)-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (13a). Prepared from **10a** (16 mg, 0.037 mmol) and 5% Pd-C (10 mg) in MeOH (3 ml). A brown powder (13 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (40:1). Ir (nujol): 3500-3100, 3372, 1595, 1456, 1377, 1208, 743 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.8-0.9 (m, 1H), 1.4-2.1 (m, 3H), 2.23 (s, 3H), 3.1-3.2 (m, 1H), 3.5-3.7 (m, 1H), 4.17-4.19 (m, 1H), 5.10 (s, 1H), 6.79 (d, 1H, J=6.4 Hz), 7.1-7.4 (m, 5H), 7.56 (d, 1H, J=6.1 Hz), 8.6-9.0 (br, 1H, disappeared with D_2O). Hrms calcd for $C_{21}H_{21}N_3O_2$ 347.1635, found 347.1734.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-hydroxy-11-(3'-indolyl)-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (4b). Prepared from **9b** (57 mg, 0.125 mmol) and 5% Pd-C (25 mg) in MeOH (8 ml). A colorless powder (45 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (40:1), mp 145°C (decomp.). $[\alpha]^{24.5}_D$ +118.2° (*c*=0.57, MeOH). Ir (nujol): 3500-3100, 1626, 1592, 1456, 1266, 745 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 1.6-

2.0 (m, 4H), 3.7-3.8 (m, 1H), 3.8-3.9 (m, 1H), 3.89 (s, 3H), 4.2-4.3 (m, 1H), 4.70 (d, 1H, J=9.5 Hz), 6.14 (s, 1H), 7.07 (ddd, 1H, J=7.9, 7.1, 0.9 Hz), 7.08-7.14 (br, 1H, disappeared with D_2O), 7.15 (d changed s with D_2O, 1H, J=2.6 Hz), 7.20 (ddd, 1H, J=8.1, 7.1, 1.0 Hz), 7.42 (d, 1H, J=8.3 Hz), 7.46 (s, 1H), 7.52 (d, 1H, J=7.9 Hz), 9.5 (br s, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{21}H_{21}N_3O_3 \cdot 1.2CH_3COCH_3$: C, 68.22; H, 6.56; N, 9.70. Found: C, 67.82; H, 6.35; N, 10.01.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-8-hydroxy-11-(3'-indolyl)-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (13b). Prepared from **10b** (16 mg, 0.035 mmol) and 5% Pd-C (11 mg) in MeOH (2 ml). A brown amorphous solid (14 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (30:1), mp 190°C (decomp.). Ir (nujol): 3500-3000, 3358, 1626, 1590, 1561, 1499, 1456, 1262, 1011, 752 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 0.87-0.92 (m, 1H), 1.46-1.50 (m, 1H), 1.8-1.9 (m, 1H), 2.0-2.1 (m, 1H), 3.27-3.33 (m, 1H), 3.6-3.7 (m, 1H), 3.90 (s, 3H), 4.27-4.31 (m, 1H), 5.11 (d, 1H, J=3.3 Hz), 6.45 (br s, 1H), 7.07 (dt, 1H, J=1.1, 8.0 Hz), 7.17 (dt, 1H, J=1.1, 8.0 Hz), 7.28-7.32 (br changed s with D_2O, 1H), 7.41 (d, 1H, J=8.2 Hz), 7.42 (s, 1H), 7.65 (d, 1H, J=7.9 Hz), 9.46 (br, 1H, disappeared with D_2O). Hrms calcd for $C_{21}H_{21}N_3O_3$ 363.1584, found 363.1560.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-11-cyano-9-hydroxy-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (14a). Prepared from **11a** (16 mg, 0.037 mmol) and 5% Pd-C (16 mg) in MeOH (3 ml). A white powder (11 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (40:1), mp 225°C (decomp.) (white crystals from MeOH). $[\alpha]^{24}_D$ +284.2° (*c*=0.29, DMSO). Ir (nujol): 3400-3000, 3376, 2230, 1622, 1611, 1566, 1437, 1202, 885, 768 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-d_6) δ: 2.0-2.1 (m, 3H), 2.2-2.3 (m, 1H), 2.28 (s, 3H), 3.6-3.7 (m, 1H), 3.68-3.74 (m, 1H), 3.88 (t, 1H, J=8.8 Hz), 4.32 (d, 1H, J=10.8 Hz), 6.84 (d, 1H, J=7.9 Hz), 7.09 (d, 1H, J=7.9 Hz), 8.0-9.0 (br, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.07; H, 5.75; N, 16.25.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-11-cyano-9-hydroxy-8-methyl-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (15a). Prepared from **12a** (65 mg, 0.19 *mmol*) and 5% Pd-C (28 mg) in MeOH (10 ml). A colorless amorphous solid (47 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (40:1), mp 195°C (decomp.) (white crystals from acetone). $[\alpha]^{24}_D$ +411.4° (*c*=0.30, MeOH). Ir (nujol): 3400-3000, 3366, 2238, 1597, 1559, 1449, 1354, 1248, 1213, 770 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 1.9-2.0 (m, 1H), 2.0-2.1 (m, 1H), 2.2-2.3 (m, 1H), 2.26 (s 3H), 2.4-2.5 (m, 1H), 3.7-3.8 (m, 1H), 3.95-4.00 (m, 1H), 4.04 (t, 1H, J=7.2 Hz), 4.77 (s, 1H), 6.65 (d, 1H, J=8.4 Hz), 7.48 (d, 1H, J=8.3 Hz). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.47; H, 5.90; N, 16.50.

(11*R*,11a*S*)-1,2,3,10,11,11a-Hexahydro-11-cyano-8-hydroxy-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (14b). Prepared from **11b** (40 mg, 0.11 mmol) and 5% Pd-C (20 mg) in MeOH (9 ml). A white powder (32 mg, quant.) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (50:1), mp 215°C (decomp.) (white crystals from acetone-hexane). $[\alpha]^{25}_D$ +61.7° (*c*=0.46, MeOH). Ir (nujol): 3349, 3191, 2228, 1626, 1590, 1458, 1269, 1125, 1019 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 2.0-2.3 (m, 4H), 3.6-3.8 (m, 2H), 3.9-4.0 (m, 1H), 3.89 (s, 3H), 4.18 (d, 1H, J=11.0 Hz), 4.24 (s, 1H, disappeared with D_2O), 6.58 (s, 1H), 7.24 (s, 1H), 7.5-7.8 (br, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C,61.41; H, 5.34; N, 14.99.

(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-11-cyano-8-hydroxy-7-methoxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (15b). Prepared from **12b** (40 mg, 0.11 mmol) and 5% Pd-C (28 mg) in MeOH (24 ml). White crystals (28 mg, 93%) was obtained by purification on a silica gel column with $CHCl_3$-MeOH (30:1), mp 215°C (decomp.) (acetone-hexane). $[\alpha]^{25}_D$ +322.5° (*c*=0.24, acetone). Ir (nujol): 3400-3000, 3372, 2244, 1636, 1613, 1586, 1503, 1455, 1439, 1279, 1181, 1021 cm^{-1}. ^{1}H-Nmr ($CDCl_3$+DMSO-*d6*) δ: 1.87-1.91 (m, 1H), 2.0-2.1 (m, 1H), 2.1-2.2 (m, 1H), 2.38-2.41 (m, 1H), 3.7-4.0 (m, 3H), 3.85 (s, 3H), 4.65 (s, 1H), 5.4-6.0 (br, 1H,

disappeared with D_2O), 6.27 (s, 1H), 7.52 (s, 1H), 7.6-8.3 (br, 1H, disappeared with D_2O). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.56; H, 5.39; N, 15.62.

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