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# NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 92.[1] A STEREOSELECTIVE SYNTHESIS OF TILIVALLINE AND ITS ANALOGS[2]

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***Key Word*** : Tilivalline; Pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one; Mannich type cyclization; Diphenyl phosphorazidate; Diethyl phosphorocyanidate.

***Abstract:*** Tilivalline (**1a**), a metabolite from *Klebsiella pneumoniae* var *oxytoca*, and its derivatives **1** have been efficiently and stereoselectively synthesized from diphenyl phosphorazidate, the 2-oxazoline **2**, the L-proline derivatives **5**, and indole; the key step is a Mannich type intramolecular cyclization accompanied with completely stereoselective introduction of indole. Furthermore, 11-substituted 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (**16**) have been also synthesized from the acetal amide **9a** and various nucleophiles by the use of this new Mannich type cyclization.

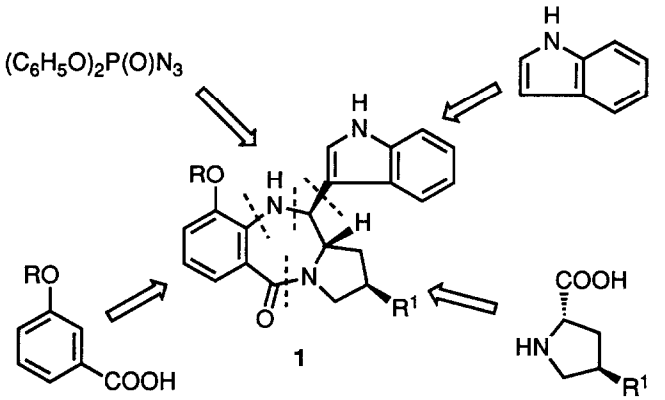
Tilivalline (**1a**) is a pyrrolo[2,1-*c*][1,4]benzodiazepine metabolite isolated from *Klebsiella pneumoniae* var. *oxytoca* by Mohr and Budzikiewicz.[4] The synthesis of **1a** has also been accomplished by the same group though it is neither stereoselective nor efficient. Since the pyrrolo[2,1-*c*][1,4]benzodiazepine skeleton is the fundamental constituent of a series of antitumor anthramycin antibiotics,[5] we have had a keen interest in veiled biological activities of tilivalline (**1a**) and its analogs. We have already accomplished a completely stereoselective, efficient, and convenient synthesis of **1a** utilizing a new Mannich type intramolecular cyclization.[2] This Mannich reaction is also applicable to the synthesis of tilivalline derivatives **1** and 11-substituted 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

analogs (**16**). The details of our synthesis will be disclosed here. Recently, Nagasaka and co-workers reported the third synthesis of tilivalline (**1a**).[6]

## Synthesis of Tilivallines (1)

Our basic scheme for the synthesis of **1** is shown in Scheme I. The key step in this convergent synthesis is construction of the seven-membered diazepine ring accompanied with simultaneous and stereoselective introduction of indole.

**Scheme I**



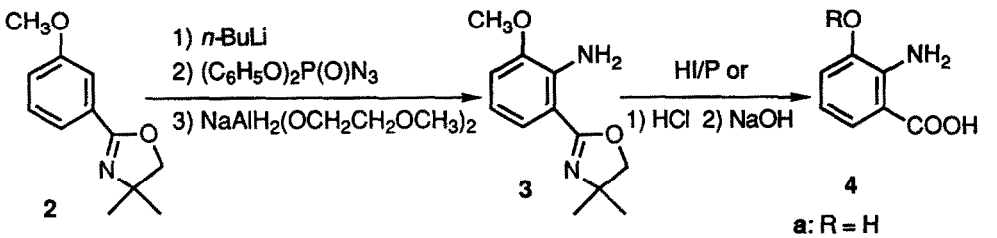

**1**

**a**: R = $R^1$ = H (Tilivalline) **d**: R = H, $R^1$ = OH
**b**: R = $CH_3$, $R^1$ = H **e**: R = H, $R^1$ = $PhCH_2O$
**c**: R = $PhCH_2$, $R^1$ = H

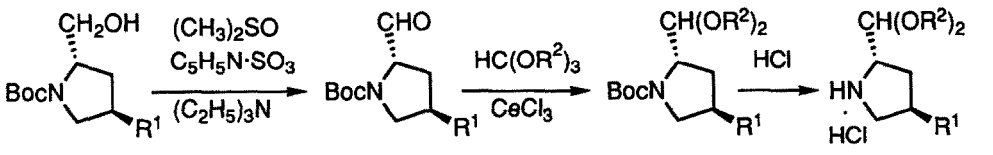
3-Substituted anthranilic acids (**4**), important intermediates, were easily prepared from the 2-oxazoline **2**,[7] as shown in Scheme II. Regioselective amination of **2** was achieved using diphenyl phosphorazidate (DPPA) as a $^+NH_2$ synthon.[8] Thus, sequential treatment of **2** in tetrahydrofuran with *n*-butyllithium, DPPA, and sodium bis(2-methoxyethoxy)aluminum hydride gave the amine **3** in 67% yield. Hydrolysis of **3** with 55% hydriodic acid in the presence of red phosphorus in a sealed tube at 100°C gave 3-hydroxyanthranilic acid (**4a**) in 86% yield. 3-Methoxyanthranilic acid (**4b**) was also obtained in quantitative yield by treatment of **3** with 3*N* hydrochloric acid, followed by 50% aqueous sodium hydroxide in methanol.

The second key intermediates are the amino acetals **8**, which were prepared as their hydrochlorides in three steps from *N*-*tert*-butoxycarbonyl (Boc)-L-prolinols (**5**) as shown in Scheme II. Boc-L-prolinol (**5a**) was prepared in quantitative yield from Boc-L-proline according to our method[9] by treatment with methyl iodide-potassium hydrogen carbonate in dimethylformamide and then sodium

**Scheme II**

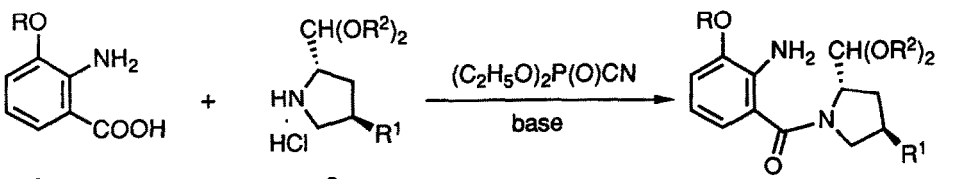



**a**: R = H
**b**: R = $CH_3$
**c**: R = $Ph_2CH_2$




| 5 | 6 | 7 | 8 |
|---|---|---|---|
| **a**: $R^1$ = H | **a**: $R^1$ = H | **a**: $R^1$ = H, $R^2$ = $CH_3$ | **a**: $R^1$ = H, $R^2$ = $CH_3$ |
| **b**: $R^1$ = TBDMSO | **b**: $R^1$ = TBDMSO | **b**: $R^1$ = TBDMSO, $R^2$ = $C_2H_5$ | **b**: $R^1$ = OH, $R^2$ = $C_2H_5$ |
| **c**: $R^1$ = $PhCH_2O$ | **c**: $R^1$ = $PhCH_2O$ | **c**: $R^1$ = $PhCH_2O$, $R^2$ = $C_2H_5$ | **c**: $R^1$ = $PhCH_2O$, $R^2$ = $C_2H_5$ |

Boc = *tert*-butyloxycarbonyl
TBDMSO = *tert*-butyldimethylsilyloxy



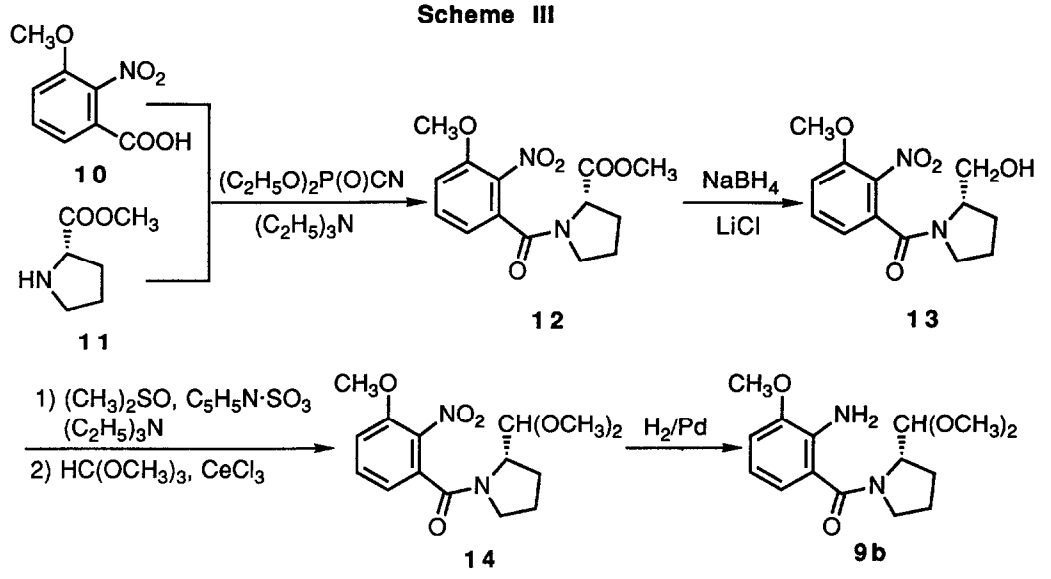

**a**: R = $R^1$ = H, $R^2$ = $CH_3$
**b**: R = $CH_3$, $R^1$ = H, $R^2$ = $CH_3$
**c**: R = $PhCH_2$, $R^1$ = H, $R^2$ = $CH_3$
**d**: R = H, $R^1$ = OH, $R^2$ = $C_2H_5$
**e**: R = H, $R^1$ = $PhCH_2O$, $R^2$ = $C_2H_5$

borohydride-lithium chloride in tetrahydrofuran-ethanol. *Trans*-4-*O*-substituted L-prolinols (**5b**) and (**5c**) were prepared from *trans*-4-hydroxy-L-proline by successive treatment with (1) di-*tert*-butyl dicarbonate, (2) methyl iodide, (3) *tert*-butyldimethylsilyl chloride or benzyl bromide, and (4) sodium borohydride-lithium chloride. Racemization-free oxidation of Boc-L-prolinols (**5**) with sulfur trioxide-pyridine complex and dimethylsulfoxide in the presence of triethylamine[9] gave the aldehydes **6** in good yield. Subsequent treatment of **6a** with trimethyl orthoformate and cerium chloride[10] in methanol easily afforded the dimethyl acetal **7a** in 61% yield. The aldehydes **6b** and **6c** did not smoothly undergo the acetalization with trimethyl orthoformate. However, the use of triethyl orthoformate in ethanol was effective and the desired diethyl acetals **7b** and **7c** were obtained in good yields. Deprotection of the Boc and *tert*-butyldimethylsilyl (TBDMS) groups of **7** was easily achieved with 10% hydrogen chloride in methanol (or ethanol) giving the corresponding hydrochlorides of the amino acetals **8** in nearly quantitative yields. No racemization was found to occur during the conversion of **6a** to **8a** since the *N*-3,5-dinitrobenzoyl derivative of **8a** showed no peak of its antipodal D-isomer on high performance liquid chromatography (HPLC) using a chiral column.

Condensation of **4** and **8** was easily accomplished by use of diethyl phosphorocyanidate(DEPC)[11] in the presence of base to give the acetal amides **9** in 57~85% yields.

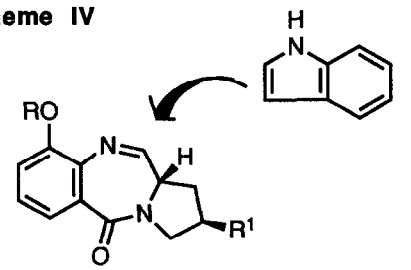
The acetal amide **9b** was also obtained from 3-methoxy-2-nitrobenzoic acid (**10**) and L-proline methyl ester (**11**) by the similar sequence of the reactions as above via **12** - **14**, shown in Scheme III.

**Scheme III**



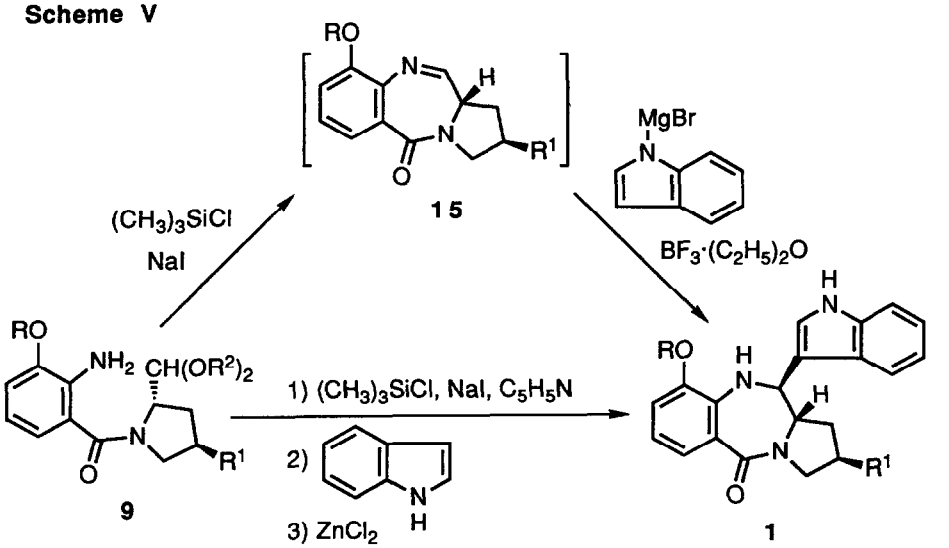
We considered that final construction of the tilivalline skeleton would be attained from **9** by an intramolecular cyclization followed by the nucleophilic attack of indole from the less hindered top face of the imine **15**, as shown in Scheme IV. In fact, cyclization of **9b** was successfully carried out with chlorotrimethylsilane and sodium iodide in acetonitrile to give the crude imine **15b** (R = $CH_3$, $R^1$ = H) as an unstable oil. Subsequent treatment of **15b** with indolyl Grignard reagent in the presence of boron trifluoride etherate in tetrahydrofuran gave *O*-methyltilivalline (**1b**), but the yield was very poor (5%), as shown in Scheme V. However, dramatic improvement of the final construction was achieved by the sequential treatment of **9b** in a one-pot process with (1) chlorotrimethylsilane-sodium iodide-pyridine in acetonitrile, (2) indole, and (3) zinc chloride. This new Mannich type condensation afforded **1b** in 71% yield. The acetal amides **9a** and **9c-e** also easily underwent this simple one-pot Mannich type condensation to furnish tilivalline (**1a**) and its derivatives **1c-e**, respectively. The results are summarized in Table I.

**Scheme IV**




**15**

**Scheme V**




**9** **1**

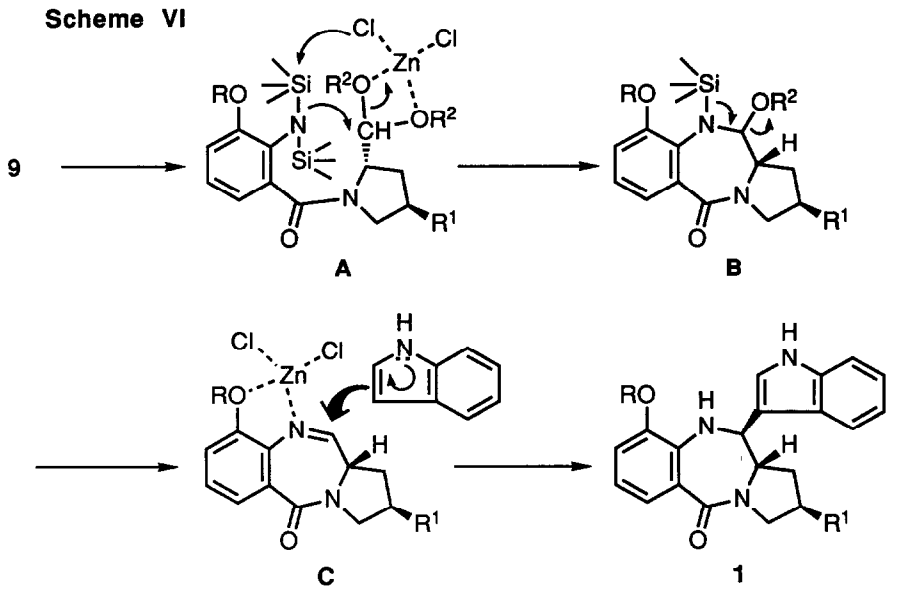
**Table I Synthesis of Tilivallines (1)**

| Compd. No. | R | $R^1$ | Reaction Conditions Temp.(°C) | Time | Yield(%) |
|---|---|---|---|---|---|
| **a** | H | H | r.t.<br>50 | 18 h<br>2 h | 83 |
| **b** | $CH_3$ | H | r.t.<br>55 | overnight<br>3 h | 71 |
| **c** | $PhCH_2$ | H | r.t.<br>45 | 14.5 h<br>3.5 h | 41 |
| **d** | H | OH | r.t. | 22 h | 63 |
| **e** | H | $PhCH_2O$ | r.t. | 12.5 h | 84 |

The reaction was completely stereoselective and no diastereoisomers of **1** could be detected in their 400 MHz proton nuclear magnetic resonance ($^1$H-NMR) spectra. The spectral data of the synthetic **1a** and **1b** were completely identical with those of natural tilivalline and synthetic *O*-methyltilivalline, respectively.[4] Reductive debenzylation of **1c** was easily carried out under a hydrogen atmosphere over 5% palladium-carbon in ethanol to give **1a** in 80% yield. However, removal of the methyl group from **1b** was unsuccessful under a variety of reaction conditions (e.q., boron tribromide, boron trichloride, lithium *tert*-butyl sulfide-hexamethylphosphoric triamide, or aluminum chloride-ethanethiol). The $^1$H-NMR spectra of tilivalline (**1a**) and its diastereoisomer have been reported to show characteristic differences, viz. a coupling constant for the protons at C-11 and C-11a of 9 Hz and 3 Hz, respectively. From these data, the stereochemistry of the indole group in **1d** and **1e** was determined to be β, since the signals of C(11)-H showed a large coupling constant (J = 8~8.3 Hz) in $^1$H-NMR spectra.

The new Mannich type condensation developed above requires both chlorotrimethylsilane-sodium iodide-pyridine and zinc chloride in addition of indole. Hence, the reaction might proceed as follows. Trimethylsilylation of the amino group in **9** followed by activation with zinc chloride gives **A**, which furnishes **B**, as shown in Scheme VI. Elimination of alkoxytrimethylsilane from **B** affords the imine which will be activated with zinc chloride to give **C**. Nucleophilic attack of indole to **C** from the less hindered top face produces the tilivallines (**1**).

**Scheme VI**

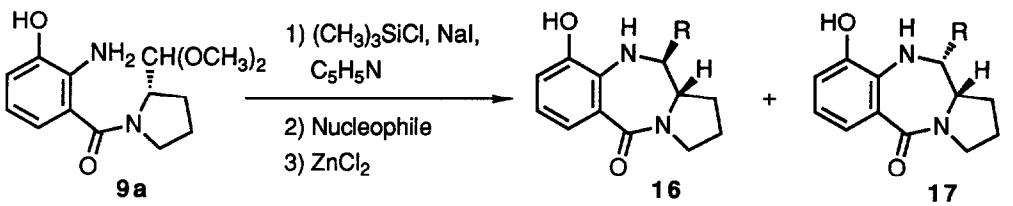



**Synthesis of 11-Substituted 5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (16)**

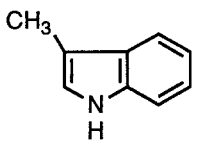
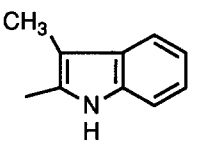
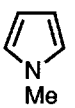
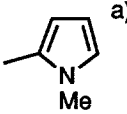
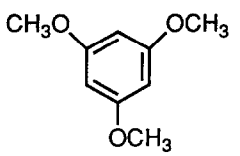
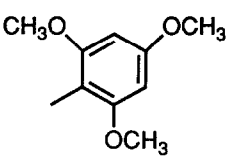
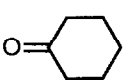
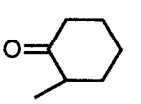
Next we investigated the application of the above new Mannich type condensation to the synthesis of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (**16**) bearing various substituents at the C-11 position. We have found that the reaction of the acetal amide **9a** with various nucleophiles under similar reaction conditions as described above proceeded smoothly to give **16**. The results are summarized in Table II.

3-Methylindole and *N*-methylpyrrole easily reacted with **9a** to give **16a** and **16b** in good yields, respectively. Unfortunately, no condensation products were obtained when other heterocycles such as pyrazole, imidazole, thiophene, and furan were used as nucleophiles. 1,3,5-Trimethoxybenzene, representative of an electron-rich benzene derivative, also underwent the reaction with **9a** giving **16c**. However, benzene derivatives less electron-rich than 1,3,5-trimethoxybenzene, such as pentamethylbenzene and 1,3-dimethoxybenzene, were unreactive to **9a**. Other nucleophiles such as cyclohexanone and acetone could also be used for this condensation affording **16d** and **16e**, though in moderate yields. Again, this condensation was completely stereoselective, and the stereochemistry of the substituent at C-11 in **16a-d** was determined to be β, since the signals for C(11)-H showed a large coupling constant (J = 9~12 Hz) in $^1$H-NMR spectra as described earlier. Although the stereochemistry of the acetonyl group on **16e** could not be determined by $^1$H-NMR spectrum, it might be β in analogy with **16a-d**. Interestingly, the reaction of **9a** with sodium cyanide in the presence of sodium

**Table II Synthesis of 11-Substituted 5*H*-Pyrrolo[2,1-*c*][1,4]benzodiazepin -5-ones (16)**




**9a** **16** **17**

| Compd. No. | Nucleophile | Reaction Conditions Temp.(°C) | Time(h) | R | Yield(%) **16** | **17** |
|---|---|---|---|---|---|---|
| **a** |  | r.t.<br>50 | 15.5<br>5 |  | 67 | 0 |
| **b** |  | r.t.<br>50 | 19<br>6.5 |  a) | 79 | 0 |
| **c** |  | r.t.<br>50 | 15<br>8 |  | 69 | 0 |
| **d** |  | r.t.<br>50 | 14.5<br>22.5 |  | 40 | 0 |
| **e** | $CH_3COCH_3$ | r.t.<br>50 | 6<br>12 | $-CH_2COCH_3$ | 41 | 0 |
| **f** | NaCN | 50 | 21 | —CN | 60 | 40 |
| | $(C_2H_5O)_2P(O)CN$ | 50 | 4 | —CN | 26 | 3 |

a) Mannich reaction with *N*-methylpyrrole have been reported to occur at 2 position of pyrrole ring; S. Raines and C.A. Kovacs, *J. Heterocycl. Chem.*, **7**, 223 (1970).

hydrogen sulfite[12] proceeded quantitatively, but the product was a mixture of **16f** and its isomer **17f** (**16f/17f** = 60:40). The low selectivity of the nitrile introduction in this reaction is presumably due to the less bulky sodium cyanide molecule. In fact, the use of DEPC,[13] a bulkier cyanation reagent than sodium cyanide, showed a remarkable increase in the selectivity with preference for the β-isomer (**16f/17f** = 89/11) with a decrease in yield.

In conclusion, two particularly interesting features of this synthesis of tilivallines (**1**) and its analogs (**16**) are an overall efficiency suitable for large scale production and the complete stereoselectivity of the new Mannich type cyclization of **9**. Furthermore, the above synthesis includes generally useful processes developed by our own group: 1) regioselective amination of arenes using DPPA as a $^{+}NH_2$ synthon,[8] 2) conversion of α-amino acids to α-amino aldehydes without racemization,[9] 3) racemization-free acetal formation from α-amino aldehydes, 4) the amide bond formation using DEPC,[11] and 5) the new Mannich type cyclization.

Biological testing of **1** and **16** is now underway and will be discussed elsewhere.

## Experimental

All melting points are uncorrected. Distillation was carried out by a Kugelrohr apparatus. Infrared (IR) spectra were measured with a JASCO IRA-2 spectrometer. $^1$H-NMR spectra were recorded on a JEOL JNM PMX-60, JNM MH-100, JNM FX-100, or JNM 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. HPLC was carried out with a JASCO Tri Rotar-II high-pressure liquid chromatograph. Silica gel (Merck Art. 7734, BW-820MH, BW-200, or Mallinckrodt CC-7) was used for the column chromatography. Preparative layer chromatography (PLC) was carried out on silica gel plates (Merck Art. 5717 (2 mm thickness), 5744 (0.5 mm thickness), or 5715 (0.25 mm thickness)). Zinc chloride used was dried at 150°C for 2h under reduced pressure before use.

**2-(2-Amino-3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (3).** *n*-Butyllithium (1.56 M in hexane, 0.71 mL, 1.1 mmol) was added dropwise to a solution of 2-(3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (**2**)[7] (205 mg, 1 mmol) in THF (8 mL) at -45°C under argon, and the mixture was stirred at -45°C for 1.5 h. A solution of DPPA (303 mg, 1.1 mmol) in THF (2 mL) was then added at -45°C. After being stirred at -45°C for 1 h, sodium bis(2-methoxyethoxy)aluminum hydride (3.58 M in toluene, 1.23 ml, 4.4 mmol) was added to the mixture at -45°C, and the mixture was stirred at -5°C for 35 min, then at room temperature for 1 h. Ice-water was added at 0°C, and the mixture was extracted with AcOEt-benzene (2:1). The extracts were washed with saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel

column chromatography with $CHCl_3$ to give **3** (147 mg, 67%) as colorless crystals, mp 113-114°C ($EtOH-H_2O$). IR (KBr) 3450, 3300, 1627 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.4 (s, 6H), 3.9 (s, 3H), 4.0 (s, 2H), 5.3-7.4 (m, 5H, 2H disappeared with $D_2O$). Anal. Calcd for $C_{12}H_{16}N_2O_2$ : C, 65.43; H, 7.32; N, 12.72. Found : C, 65.58; H, 7.23; N, 12.63.

**3-Hydroxyanthranilic Acid (4a).** A mixture of **3** (20 mg, 0.091 mmol), red phosphorus (5 mg, 0.16 mmol), and 55% hydriodic acid (0.4 mL) was heated at 100°C for 14 h in a sealed tube and poured into ice-water. The mixture was neutralized with $Na_2CO_3$, salted out by the addition of NaCl, and extracted with AcOEt. The water layer was again salted out by the addition of $NH_4Cl$ and extracted with AcOEt. The combined extracts were dried over $Na_2SO_4$, and concentrated *in vacuo* to give **4a** (12 mg, 86%), mp 233-235°C (decomp.) (Lit.,[14] mp 246-252°C, decomp. 250-252°C).

**3-Methoxyanthranilic Acid (4b).** A mixture of **3** (20 mg, 0.091 mmol) and 3*N* HCl (1 mL) was stirred at 100°C for 20 min, then concentrated *in vacuo*. Methanol (0.6 mL) and 50% aqueous NaOH (0.4 mL) were added to the residue, and the mixture was refluxed for 30 min. After concentration *in vacuo*, the residue was neutralized with 1*N* aqueous HCl, salted out by the addition of NaCl, and extracted with AcOEt. The extracts were washed with saturated aqueous NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to give **4b** (16 mg, quantitative), mp 169°C ($MeOH-H_2O$) (Lit.,[14] mp 169-170°C).

3-Benzyloxyanthranilic acid (**4c**) was prepared from 3-hydroxy-2-nitrobenzoic acid according to the literature.[15]

***N*-Boc-*trans*-4-*tert*-butyldimethylsilyloxy-L-proline Methyl Ester as the Precursor of the Amino Alcohol (5b).** A solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (1.4 g, 5.7 mmol), TBDMSCl (1.72 g, 11.4 mmol), and imidazole (0.93 g, 13.7 mmol) in DMF (6 mL) was stirred at room temperature for 12 h, and diluted with benzene-AcOEt (1:1). The mixture was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with hexane, then hexane-AcOEt (1:1) to give *N*-Boc-*trans*-4-*tert*-butyldimethylsilyloxy-L-proline methyl ester (2.01 g, 98%) as a colorless oil, bp 137-150°C/1.1 mmHg. IR (film) 2920, 1745, 1700, 1250, 830 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 0.05 and 0.07 (2xs, 6H), 0.87 and 0.91 (2xs, 9H), 1.41 (s, 9H), 1.78-2.25 (m, 2H), 3.18-3.62 (m, 2H), 3.69 (s, 3H), 4.10-4.60 (m, 2H). Anal. Calcd for $C_{17}H_{33}NO_5Si$ : C, 56.79; H, 9.25; N, 3.90. Found : C, 56.54; H, 9.24; N, 3.96.

***N*-Boc-*trans*-4-benzyloxy-L-proline Methyl Ester as the Precursor of the Amino Alcohol (5c).** Silver oxide (5.84 g, 25.2 mmol) and then benzyl bromide (3.75 mL, 31.5 mmol) were added to a solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (3.1 g, 12.6 mmol) in DMF (50 mL) at 0°C under argon. The

mixture was stirred at 0°C for 5 min, then at room temperature for 24 h, and diluted with $Et_2O$. After filtration, the filtrate was washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave a pale yellow oil (4.52 g), which was used for the next step without further purification.

A part of the crude oil was purified by silica gel column chromatography with $Et_2O$-benzene (1:3) to give pure *N*-Boc-*trans*-4-benzyloxy-L-proline methyl ester as a colorless oil. IR (film) 1740, 1695 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.53 (s, 9H), 1.82-2.60 (m, 2H), 3.40-3.92 (m, 2H), 3.74 (s, 3H), 4.02-4.68 (m, 2H), 4.51 (s, 2H), 7.32 (s, 5H). Anal. Calcd for $C_{18}N_{25}NO_5$ : C, 64.46; H, 7.51; N, 4.18. Found : C, 64.21; H, 7.46; N, 4.15.

***N*-Boc Amino Alcohols 5.** General Procedure[9] : The *N*-Boc amino acid methyl ester (136 mmol) was dissolved in THF (180 mL) under argon, and anhydrous LiCl (11.6 g, 272 mmol) and then sodium borohydride (10.3 g, 272 mmol) were added. EtOH (360 mL) was added dropwise below 5°C during 30 min, and the mixture was stirred at 0°C for 1 h, then at room temperature for 19.5 h. The mixture was cooled with ice-water, adjusted to pH 4 by the addition of 10% aqueous citric acid (160 mL), and concentrated *in vacuo*. Water was added and the mixture was extracted with $CH_2Cl_2$. The extracts were washed with saturated aqueous NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo* to give **5**.

Compounds **5a** and **5b** were used for the next step without further purification.

**Compound 5a.** Prepared from *N*-Boc-L-proline methyl ester (31.19 g, 136 mmol). Colorless crystals (25.69 g, 94%), mp 58.5-59.8°C ($Et_2O$-hexane), $[\alpha]^{24.5}_D$ -53.9° (*c* = 1.04, MeOH). IR (nujol) 3420, 1660, 1440, 1120 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.55~2.13 (m, 4H), 3.28-3.63 (m, 2H), 3.70 (d, 2H, *J* = 5Hz), 3.87-4.17(m, 1H), 4.73 (br, 1H, disappeared with $D_2O$). Anal. Calcd for $C_{10}H_{19}NO_3$ : C, 59.68; H, 9.51; N, 6.96. Found : C, 59.79; H, 9.64; N, 6.83.

**Compound 5b.** Prepared from *N*-Boc-*trans*-4-*tert*-butyldimethylsilyloxy-L-proline methyl ester (1.8 g, 5 mmol). A colorless oil (1.38 g, 84%), bp 130-140°C/1.2 mmHg. IR (film) 3380, 2930, 1670, 1250, 835 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.43 (s, 9H), 1.63-2.00 (m, 2H), 3.25-4.35 (m, 7H, 1H disappeared with $D_2O$). Anal. Calcd for $C_{16}H_{33}NO_4Si$ : C, 57.97; H, 10.03; N, 4.22. Found : C, 58.07; H, 9.91; N, 4.29.

**Compound 5c.** Prepared from crude *N*-Boc-*trans*-4-benzyloxy-L-proline methyl ester (4.52 g). A colorless oil (2.18 g, 56% from *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester), purified by silica gel column chromatography with AcOEt-hexane (2:3 to 3:2), bp 165-171°C/1 mmHg. IR (film) 3360, 2970, 1690 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.82-2.38 (m, 2H), 3.10-4.30 (m, 7H, 1H disappeared with $D_2O$), 4.45 (s, 2H), 7.25 (s, 5H). Anal. Calcd for $C_{17}H_{25}NO_4$ : C, 66.43; H, 8.20; N, 4.56. Found : C, 66.89; H, 8.32; N, 4.71.

***N*-Boc Amino Aldehydes 6.** General Procedure[9] : A solution of sulfur trioxide-pyridine complex (47.7 g, 300 mmol) in DMSO (300 mL) was added in one portion to a solution of **5** (100 mmol) and triethylamine (41.8 mL, 300 mmol) in $CH_2Cl_2$ (300 mL) at -10°C. The mixture was stirred vigorously at 10-20°C for 10 min, poured into ice-water, and extracted with $Et_2O$. The extracts were washed with 10% citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave **6**, which was used for the next step without further purification.

**Compound 6a.** Prepared from **5a** (20.1 g, 100 mmol). A yellow oil (18.9 g, 95%). IR (film) 2980, 1730, 1690, 1390 $cm^{-1}$.

**Compound 6b.** Prepared from **5b** (5 g, 15 mmol). Colorless crystals (4.46 g, 90%), mp 47-54°C. IR (nujol) 1710, 1670, 1415, 1250, 830 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.46 (s, 9H), 1.84-2.19 (m, 2H), 4.07-4.52 (m, 2H), 9.33-9.57 (m, 1H).

**Compound 6c.** Prepared from **5c** (21.5 g, 70 mmol). A pale yellow oil (17.75 g, 84%). IR (film) 2970, 1730, 1690, 1390, 1365 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.73-2.37 (m, 2H), 3.27-3.77 (m, 2H), 3.97-4.45 (m, 2H), 4.48 (s, 2H), 7.25 (s, 5H), 9.27-9.60 (broad s, 1H).

***N*-Boc Amino Aldehyde Dialkylacetals 7.** General Procedure[10] : A solution of **6** (94.8 mmol), trialkyl orthoformate (667 mmol) and 0.4M cerium chloride in alcohol (237 mL, 94.7 mmol) was stirred at 40-45°C for 67 h (for **6a**) or at 55°C for 21 h (for **6b** and **6c**). The mixture was poured into 5% aqueous $NaHCO_3$, and extracted with $Et_2O$. The extracts were washed with 10% 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.

**Compound 7a.** Prepared from **6a** (18.89 g, 94.8 mmol), trimethyl orthoformate (73 mL, 667 mmol), and 0.4M cerium chloride in MeOH (237 mL, 94.7 mmol). A colorless oil (14.19 g, 61%), purified by silica gel column chromatography with hexane-AcOEt (5:1), bp 74-76°C/0.5 mmHg. IR (film) 2960, 1690, 1400, 1170 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.72-2.25 (m, 4H), 3.30 (s, 6H), 3.23-3.43 (m, 2H), 3.75-4.03 (m, 1H), 4.60 (d, 1H, $J$ = 4Hz).

**Compound 7b.** Prepared from **6b** (4.46 g, 13.5 mmol), triethyl orthoformate (18 mL, 108 mmol), and 0.4M cerium chloride in EtOH (34 mL, 13.5 mmol). A colorless oil (2.65 g, 49%), purified by silica gel column chromatography with hexane-AcOEt (6:1), bp 104-120°C/0.38 mmHg, $[\alpha]^{22}_D$ -45.8° ($c$ = 1.08, MeOH). IR (film) 2920, 1690, 1390, 1250, 830 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.15 and 1.18 (2xt, 6H, $J$ = 6,5Hz), 1.48 (s, 9H), 1.70-2.51 (m, 2H), 3.15-4.07 (m, 7H), 4.23-4.78 (m, 2H). Anal. Calcd for $C_{20}H_{41}NO_5Si$ : C, 59.51; H, 10.24; N, 3.47. Found : C, 59.42; H, 10.32; N, 3.48.

**Compound 7c.** Prepared from **6c** (17.95 g, 58.8 mmol), triethyl orthoformate (78 mL, 470 mmol), and 0.4M cerium chloride in EtOH (147 mL, 58.8

mmol). Colorless crystals (14.42 g, 65%), purified by silica gel column chromatography with hexane-AcOEt (6:1), mp 58-60°C (pentane), $[\alpha]^{22}_D$ -43.8° (*c* = 1.02, MeOH). IR (nujol) 1690, 1400, 1365, 1170, 1110 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.13 and 1.18 (2xt, 6H, *J* = 7Hz), 1.45 (s, 9H), 1.97-2.55 (m, 2H), 3.13-4.33 (m, 9H), 4.43 (s, 2H), 7.22 (s, 5H). Anal. Calcd for $C_{21}H_{33}NO_5$ : C, 66.46; H, 8.77; N, 3.69. Found : C, 65.98; H, 8.42; N, 3.67.

**Determination of Optical Purity of 8a. (1) Preparation of Optically Active *N*-3,5-Dinitrobenzoyl Derivative of 8a.** Compound **7a** (160 mg, 0.65 mmol) was dissolved in 10% HCl in MeOH (3 mL) and the mixture was stirred at room temperature for 1 h. MeOH was concentrated *in vacuo*, and the residue was dissolved in THF (6 mL). Triethylamine (0.2 mL, 1.43 mmol) and 3,5-dinitrobenzoyl chloride (180 mg, 0.78 mmol) was added, and the mixture was stirred at room temperature for 7 h. After concentration of the solvent *in vacuo*, the residue was dissolved in AcOEt, washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with AcOEt-hexane (1:2) to give *N*-3,5-dinitrobenzoyl derivative of **8a** (158 mg, 72%) as pale yellow crystals.

**(2) Preparation of Racemic *N*-3,5-Dinitrobenzoyl Derivative of 8a.** The optically active aldehyde **6a** was racemized by treatment with silica gel (BW-820 MH) at 40°C in AcOEt. Acetalization of the racemic **6a**, thus obtained, with trimethyl orthoformate as described for **7a** gave racemic **7a**, which was converted to *N*-3,5-dinitrobenzoyl derivative as described above.

**(3) HPLC Analysis.** Each 3,5-dinitrobenzoyl derivative (2.5 mg) was dissolved in 1,2-dichloroethane (0.5 mL), and 0.4 μL of them was subjected to HPLC using chiral Sumipax OA-1000 (i.d. 4.6x250 mm, purchased from Sumitomo Chemicals Co. Ltd.) (flow rate, 1.5 mL/min; eluate, hexane : 1,2-dichloroethane : EtOH = 100:6:1; detection UV 254 nm). The racemic 3,5-dinitrobenzoyl derivative showed two peaks at R.T. = 19.02 min (D-form) and 20.52 min (L-form), while optically active one showed a single peak at R.T. = 20.52 min, and no peak of D-isomer was detected.

**The Acetal Amides 9.** General Procedure : Method A. A solution of **7** (22.8 mmol) in 10% HCl in MeOH (45 mL) (or EtOH for **7b** and **7c**) was stirred at room temperature for 1 h, and concentrated *in vacuo*. The residue was dissolved in DMF (150 mL), and the anthranilic acid **4** (19 mmol) was added. A solution of DEPC (3.1 g, 19 mmol) in DMF (38 mL) and then *N*,*N*-diisopropylethylamine (7.43 mL, 41.8 mmol) were added dropwise to the mixture at 0°C, and the whole was stirred at 0°C for 1 h, then at room temperature for 2 h. A solution of DEPC (0.93 g, 5.7 mmol) in DMF (19 mL) was further added, and the mixture was stirred at room temperature for additional 1.5 h, and concentrated *in vacuo*. Benzene was added, and the mixture was washed with water. The washings were salted out by the addition of

NaCl, and extracted with benzene-AcOEt (1:1). The combined extracts were dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography to give **9**.

Method B. A solution of **7** (1.32 mmol) in 10% HCl in MeOH (2 ml) was stirred at room temperature for 1 h and concentrated *in vacuo*. The residue was dissolved in THF (9 mL), and triethylamine (0.37 mL, 2.64 mmol) and then the anthranilic acid **4** (1.1 mmol) were added. To the mixture was added a solution of DEPC (215 mg, 1.32 mmol) in THF (1 mL) at 0°C, and the whole was stirred at 0°C for 1 h, then at room temperature for 40 min. After concentration *in vacuo*, the residue was dissolved in AcOEt-benzene (2:1), washed with saturated aqueous $NaHCO_3$, 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 **9**.

**Compound 9a.** Prepared from **7a** (5.6 g, 22.8 mmol) and **4a** (2.91 g, 19 mmol) by method A. A reddish brown amorphous solid (3.73 g, 70%), purified by silica gel column chromatography with $CHCl_3$-benzene-MeOH (15:3:1), mp 99.5-100°C ($Et_2O$), $[\alpha]^{24}_D$ -191.8° (*c* = 1.00, MeOH). IR (nujol) 3450, 3350, 3060, 1620, 1590 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.40-2.40 (m, 4H), 3.46 (s, 3H), 3.50 (s, 3H), 3.04-3.74 (m, 2H), 4.24-5.44 (m, 5H, 3H disappeared with $D_2O$), 6.24-6.48 (m, 3H). Anal. Calcd for $C_{14}H_{20}N_2O_4$ : C, 59.99; H, 7.19; N, 9.99. Found : C, 59.67; H, 6.85; N, 10.15.

**Compound 9b.** Prepared from **7a** (325 mg, 1.32 mmol) and **4b** (184 mg, 1.1 mmol) by method B. A colorless oil (272 mg, 84%), purified by silica gel column chromatography with AcOEt-hexane (1:2 to 1:1). $[\alpha]^{24}_D$ -173° (*c* = 1.2, MeOH). IR (film) 3460, 3360, 2970, 1615 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.5-2.6 (m, 4H), 3.2-3.8 (m, 2H), 3.48 (s, 3H), 3.53 (s, 3H), 3.9 (s, 3H), 4.2-5.2 (m, 2H), 4.8 (s, 2H), 6.5-7.1 (m, 3H). MS *m/z* : 294 ($M^+$).

**Compound 9c.** Prepared from **7a** (148 mg, 0.6 mmol) and **4c** (122 mg, 0.5 mmol) by method B. A yellow oil (142 mg, 77%), purified by silica gel column chromatography with AcOEt-hexane (1:1). IR (film) 3450, 3350, 2800, 1615 $cm^{-1}$.

**Compound 9d.** Prepared from **7b** (1.33 g, 3.3 mmol) and **4a** (480 mg, 2.92 mmol) by method A. A pale brown amorphous solid (538 mg, 57%), purified by silica gel column chromatography with $CHCl_3$-MeOH (12:1). IR (nujol) 3350, 1630, 1605, 1225, 1070 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.22 (t, 6H, *J* = 7 Hz), 1.72-2.60 (m, 2H), 3.00-4.28 (m, 12H, 3H disappeared with $D_2O$), 6.30-6.92 (m, 3H), 7.27 (d, 1H, *J* = 6 Hz, disappeared with $D_2O$).

**Compound 9e.** Prepared from **7c** (364 mg, 0.96 mmol) and **4a** (123 mg, 0.8 mmol) by method A. Pale brown crystals (247 mg, 75%), purified by silica gel column chromatography with $CHCl_3$-MeOH (30:1), mp 134-136°C ($Et_2O$), $[\alpha]^{26.5}_D$ -123.3° (*c* = 1.00, MeOH). IR (nujol) 3450, 3380, 3230, 1610, 1590 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.18 (t, 6H, *J* = 7Hz), 1.94-2.56 (m, 2H), 3.32-3.96 (m, 6H), 4.00-4.20 (m, 2H), 4.00 (br s, 3H, disappeared with $D_2O$), 4.40 (s, 2H), 4.96-5.16 (m, 1H), 6.34-6.8

(m, 3H), 7.25 (s, 5H). Anal. Calcd for $C_{23}H_{30}N_2O_5$ : C, 66.65; H, 7.30; N, 6.76. Found : C, 66.83; H, 7.30; N, 6.77.

***N*-(3-Methoxy-2-nitrobenzoyl)-L-proline Methyl Ester (12).** To a mixture of 3-methoxy-2-nitrobenzoic acid (**10**) (15.9 g, 80.6 mmol) and L-proline methyl ester (**11**) (12.5 g, 97 mmol) in DMF (160 mL) was added DEPC (18.4 g, 113 mmol) in DMF (20 mL) followed by triethylamine (11.4 g, 113 mmol) in DMF (20 mL). The mixture was stirred at 0°C for 0.5 h, and then at room temperature for 2 days. After dilution with AcOEt-benzene (2:1, 750 mL), the mixture was successively washed with 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave crystals, which were recrystallized from AcOEt-hexane to give **12** (18.4 g, 74%) as pale yellow crystals, mp 100-101°C. IR (KBr) 2950, 1725, 1640 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.83-2.50 (m, 4H), 3.37-3.75 (m, 2H), 3.80 (s, 3H), 3.97 (s, 3H), 4.23-4.85 (m, 1H), 6.97-7.97 (m, 3H). Anal. Calcd for $C_{14}H_{16}N_2O_6$ : C, 54.54; H, 5.23; N, 9.09. Found : C, 54.82; H, 5.39; N, 9.12.

***N*-(3-Methoxy-2-nitrobenzoyl)-L-prolinol (13).** Prepared from **12** (2.06 g, 6.7 mmol) as in the general procedure for the preparation of *N*-Boc amino alcohols **5**. The crude product was purified by silica gel column chromatography with AcOEt-benzene (10:1) to give **13** (1.67 g, 89%) as a yellow viscous oil. IR (film) 3350, 2930, 1620, 1525 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.65-2.42 (br m, 4H), 3.25-3.58 (m, 2H), 3.58-3.93 (m, 2H), 3.97 (s, 3H), 4.08-4.63 (m, 2H), 6.92-7.77 (m, 3H).

***N*-(3-Methoxy-2-nitrobenzoyl)-L-prolinal Dimethyl Acetal (14).** DMSO oxidation of **13** (13.25 g, 47 mmol) was carried out as in the general procedure for the preparation of *N*-Boc amino aldehydes **6** to give *N*-(3-methoxy-2-nitrobenzoyl)-L-prolinal (9.9 g, 77%). The aldehyde (9.9 g) was converted to its dimethyl acetal **14** (9.18 g, 79%) as in the general procedure for the preparation of *N*-Boc amino aldehyde dialkylacetals **7**. A pale brown oil, $[\alpha]^{24}_D$ -206° (*c* = 0.5, MeOH). IR (film) 2920, 2820, 1630 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ 1.93-2.45 (br m, 4H), 3.08-3.83 (m, 2H), 3.58 (s, 3H), 3.62 (s, 3H), 4.07 (s, 3H), 4.28-4.67 (br m, 1H), 4.91 (d, 1H, *J* = 3 Hz), 6.73-7.65 (m, 3H).

***N*-(3-Methoxy-2-aminobenzoyl)-L-prolinal Dimethyl Acetal (9b).** The nitro acetal **14** (1.05 g, 3.1 mmol) was hydrogenated over palladium black (200 mg) in ethanol (20 mL) at room temperature for 18 h under stirring and hydrogen atmosphere. Filtration followed by concentration of the filtrate afforded **9b** (939 mg, 98.5%), which was identical with the sample prepared by coupling of **7a** and **4b**, described earlier.

**Tilivallines 1.** General Procedure : Chlorotrimethylsilane (1.07 mL, 8.4 mmol) was added dropwise to a suspension of **9** (2.1 mmol), sodium iodide (1.26 g, 8.4 mmol), and pyridine (0.85 mL, 10.5 mmol) in acetonitrile (21 mL) at -15°C under argon, and the mixture was stirred at -15°C for 30 min. Indole (0.49 g, 4.2 mmol) was added to the mixture. After being stirred at room temperature for 30

min, zinc chloride (1.15 g, 8.4 mmol) was added and the whole was stirred at room temperature for 12.5~22 h, then at 45-55°C for 2~3.5 h. Saturated aqueous $NaHCO_3$, then AcOEt were added to the mixture, and the insoluble materials were filtered off. The filtrate was washed with saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave the residue, which was purified by column chromatography to give **1**.

The reaction temperature and times are shown in Table 1.

**Tilivalline (1a).** Prepared from **9a** (131 mg, 0.47 mmol). A yellow amorphous solid (130 mg, 83%), purified by silica gel column chromatography with $CHCl_3$-benzene-MeOH (15:3:1). A solution of the synthetic **1a** in MeOH was concentrated and the residue was solidified with $Et_2O$ to give a colorless amorphous solid, mp 169-171°C, $[\alpha]^{25}_D$ +197° (*c* = 0.98, MeOH) (lit.,[4] mp 168°C, $[\alpha]^{25}_D$ +126.8° (MeOH)), which was recrystallized from aqueous MeOH to give yellow prisms, mp 242-245°C. $[\alpha]^{27}_D$ +243° (*c* = 0.57, MeOH). IR (KBr) 3380, 3200, 2900, 1610 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.4-2.1 (m, 4H), 3.6-4.2 (m, 2H), 4.2-4.6 (m, 1H), 4.9 (d, 1H, *J* = 9 Hz), 6.7-8.4 (m, 10H), 12.2 (s, 1H). MS *m/z* : 333 ($M^+$), 264, 247, 216, 130, 117, 90, 89. HRMS calcd for $C_{20}H_{19}N_3O_2$ 333.1477, found 333.1481. UV (MeOH) λmax (nm) : 220, 240, 257, 281, 289, 334.

The spectral data (IR, $^1$H-NMR, MS, and UV) of synthetic **1a** were identical with those of natural tilivalline.[4]

***O*-Methyltilivalline (1b).** Prepared from **9b** (294 mg, 1 mmol). An amorphous solid (246 mg, 71%), purified by silica gel column chromatography with AcOEt-hexane (3:1 to 5:1), mp 135°C (moistend) (AcOEt-hexane) (Lit.[4] mp 130°C), $[\alpha]^{19}_D$ +241° (*c* = 0.56, MeOH). IR (nujol) 3380, 3200, 1610 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.58-2.03 (m, 4H), 3.59-4.57 (m, 3H), 3.72 (s, 3H), 4.83 (d, 1H, *J* = 9 Hz), 5.4 (br s, 1H), 6.67-7.97 (m, 8H), 9.5 (br s, 1H). MS *m/z* : 347 ($M^+$), 278, 230, 215, 130, 117. HRMS calcd for $C_{21}H_{21}N_3O_2$ 347.1634, found 347.1631.

The spectral data (IR, $^1$H-NMR, and MS) of synthetic **1b** were identical with those of *O*-methyltilivalline.[4]

***O*-Benzyltilivalline (1c).** Prepared from **9c** (142 mg, 0.38 mmol). Pale yellow prisms (66 mg, 41%), purified by PLC (AcOEt : hexane = 5:1), mp 125-126°C, $[\alpha]^{20}_D$ +132.5° (*c* = 0.52, MeOH). IR (KBr) 3350, 2850, 1615 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 1.5-2.2 (m, 4H), 3.7-4.2 (m, 2H), 4.2-4.7 (m, 1H), 4.8 (d, 1H, *J*=10 Hz), 4.9 (s, 2H), 5.3 (br s, 1H), 6.8-7.9 (m, 13H), 9.6 (s, 1H). HRMS calcd for $C_{27}H_{25}N_3O_2$ 423.1947, found 423.1946.

**2-β-Hydroxytilivalline (1d).** Prepared from **9d** (680 mg, 2.1 mmol). A colorless amorphous solid (461 mg, 63%), purified by silica gel column chromatography with AcOEt to AcOEt-MeOH (10:1), mp 181-190°C (decomp.), $[\alpha]^{22.5}_D$ +213.7° (*c* = 0.51, DMSO). IR (nujol) 3200, 1610, 1560, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-$d_6$) δ 1.59-1.66 (m, 1H), 1.69-1.78 (m, 1H), 3.60-3.66 (m, 1H), 3.95 (d, 1H, *J* = 12.6 Hz), 4.23 (br, 1H), 4.46-4.54 (m, 1H), 4.66 (d, 1H, *J* = 8.3 Hz),

4.75 (br s, 1H, disappeared with $D_2O$), 5.28 (br s, 1H, disappeared with $D_2O$), 6.56 (t, 1H, $J$ = 7.8 Hz), 6.83 (dd, 1H, $J$ = 1.5, 7.5 Hz), 6.95-6.99 (m, 1H), 7.09-7.13 (m, 1H), 7.26 (s, 1H), 7.36-7.42 (m, 2H), 7.49 (d, 1H, $J$ = 7.9 Hz), 9.39 (s, 1H, disappeared with $D_2O$), 10.82 (s, 1H, disappeared with $D_2O$). Anal. Calcd for $C_{20}H_{19}N_3O_3 \cdot 3/5CH_3CO_2C_2H_5$ : C, 66.88; H, 5.96; N, 10.44. Found : C, 66.61; H, 5.57; N, 10.63.

**2-β-Benzyloxytilivalline (1e).** Prepared from **9e** (95 mg, 0.23 mmol). A pale yellow amorphous solid (85 mg, 84%), purified by silica gel column chromatography with $CHCl_3$-MeOH (30:1), $[\alpha]^{22.5}_D$ +220.6° ($c$ = 0.51, DMSO). IR (nujol) 3400, 3200, 1615, 1590, 1550 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-$d_6$) δ 1.62-1.96 (m, 2H), 3.12-3.86 (m, 2H), 3.90-4.56 (m, 2H), 4.39 (s, 2H), 4.70 (d, 1H, $J$ = 8 Hz), 5.18 (s, 1H, disappeared with $D_2O$), 6.36-7.72 (m, 8H), 7.24 (s, 5H), 8.17 (s, 1H, disappeared with $D_2O$), 9.62 (s, 1H, disappeared with $D_2O$). Anal. Calcd for $C_{27}H_{25}N_3O_3 \cdot H_2O$ : C, 70.88; H, 5.95; N, 9.18. Found : C, 70.42; H, 5.57; H, 8.95.

**Catalytic Debenzylation of 1c.** Hydrogen gas was bubled into a mixture of 5% Pd-C (17 mg) in EtOH (3 mL) at room temperature for 1 h. A solution of **1c** (19 mg, 0.045 mmol) in EtOH (1 mL) was added to the above mixture, and hydrogen gas was again bubled at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **1a** (12mg, 80%), whose spectral data were identical with the authentic sample prepared as above.

**Preparation of 1b by Grignard Reaction.** Chlorotrimethylsilane (0.089 mL, 0.7 mmol) was added dropwise to a suspension of **9b** (138 mg, 0.47 mmol) and sodium iodide (105 mg, 0.7 mmol) in acetonitrile (5 mL) at -18°C under argon, and the mixture was stirred at -18°C for 20 min. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with AcOEt. The extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* to give the residue, which was used for the next step without further purification.

The MS spectrum of the residue showed the molecular ion peak at $m/z$ 230 corresponding to the imine **15b**.

To a solution of the above residue in THF (10 mL) was added $BF_3 \cdot Et_2O$ (0.056 mL, 0.47 mmol) at 0°C and the mixture was stirred at 0°C for 1 h. A solution of the indolyl Grignard reagent, prepared from indole (110 mg, 0.94 mmol) and ethylmagnesium bromide (3M in THF, 0.31 mL, 0.93 mmol) in THF (2 mL), was added at once at -71°C, and the mixture was stirred at -71°C for 1 h, then at room temperature for 1 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with AcOEt. The extracts were washed with saturated aqueous NaCl, and dried over $Na_2SO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with AcOEt-hexane (5:1), then by PLC (AcOEt-hexane = 5:1) to give **1b** (9 mg, 5%).

The spectral data of the compound were identical with those of the authentic sample prepared as above.

**11-Substituted 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (16).** Compounds **16a~e** were prepared from **9a** according to the general procedure for the preparation of **1**.

The reaction temperature and times are shown in Table 2.

**Compound 16a.** Prepared from **9a** (140 mg, 0.5 mmol) and 3-methylindole (131 mg, 1 mmol). Colorless crystals (116 mg, 67%), purified by silica gel column chromatography with AcOEt-hexane (3:1), mp 248-251°C (deomp.) (MeOH), $[\alpha]^{22.5}_{D}$ +67° (*c* = 0.50, DMSO). IR (nujol) 3400, 3350, 3250, 1620, 1590 $cm^{-1}$. $^1$H-NMR (CDCl3 + DMSO-*d*6) δ 1.38-1.44 (m, 1H), 1.69-1.91 (m, 3H), 2.27 (s, 3H), 3.57-3.62 (m, 1H), 3.66-3.73 (m, 1H), 4.22-4.28 (m, 1H), 4.78 (d, 1H, *J* = 9 Hz), 4.99 (s, 1H, disappeared with D2O), 6.57 (t, 1H, *J* = 8 Hz), 6.83 (d, 1H, *J* = 8.1 Hz), 6.99 (t, 1H, *J* = 8 Hz), 7.08 (t, 1H, *J* = 7.7 Hz), 7.22 (d, 1H, *J* = 8.1 Hz), 7.29 (d, 1H, *J* = 8.1 Hz), 7.48 (d, 1H, *J* = 8.1 Hz), 9.86 (s, 1H, disappeared with D2O), 10.91 (s, 1H, disappeared with D2O). HRMS calcd for $C_{21}H_{21}N_3O_2$ 347.1619, found 347.1635.

**Compound 16b.** Prepared from **9a** (140 mg, 0.5 mmol) and *N*-methylpyrrole (81 mg, 1 mmol). Colorless crystals (117 mg, 79%), purified by silica gel column chromatography with AcOEt-hexane (3:1), mp 145-147°C (MeOH-benzene), $[\alpha]^{22.5}_{D}$ +117.8° (*c* = 0.5, DMSO). IR (nujol) 3380, 3180, 1620, 1590, 1490 $cm^{-1}$. $^1$H-NMR (CDCl3) δ 1.71-1.76 (m, 1H), 1.83-1.97 (m, 3H), 3.61 (s, 3H), 3.70-3.87 (m, 3H), 4.29 (d, 1H, *J* = 9.7 Hz), 4.45 (s, 1H, disappeared with D2O), 6.00 (t, 1H, *J* = 2.2 Hz), 6.51-6.54 (m, 2H), 6.70 (br, 1H, disappeared with D2O), 6.79 (t, 1H, *J* = 7.9 Hz), 6.88 (dd, 1H, *J* = 2.2, 7.9 Hz), 7.40 (dd, 1H, *J* = 2.2, 7.9 Hz). HRMS calcd for $C_{17}H_{19}N_3O_2$ 297.1477, found 297.1479.

**Compound 16c.** Prepared from **9a** (140 mg, 0.5 mmol) and 1,3,5-trimethoxybenzene (168 mg, 1 mmol). Colorless crystals (132 mg, 69%), purified by silica gel column chromatography with AcOEt-hexane (3:1), mp 229-234°C (decomp.) (MeOH), $[\alpha]^{22.5}_{D}$ +43.7° (*c* = 0.50, DMSO). IR (nujol) 3370, 3100, 1620, 1590, 1370 $cm^{-1}$. $^1$H-NMR (CDCl3 + DMSO-*d*6) δ 1.39-2.00 (m, 4H), 3.60 (s, 3H), 3.82 (s, 6H), 3.40-3.98 (m, 2H), 4.26-4.56 (m, 1H), 4.82 (br s, 1H, disappeared with D2O), 5.12 (d, 1H, *J* = 9 Hz), 6.14 (s, 2H), 6.57 (t, 1H, *J* = 7 Hz), 6.86 (dd, 1H, *J* = 2, 7 Hz), 7.38 (dd, 1H, *J* = 2, 7 Hz), 8.76 (s, 1H, disappeared with D2O). Anal. Calcd for $C_{21}H_{24}N_2O_5$ : C, 65.61; H, 6.29; N, 7.29. Found : C, 65.55; H, 6.24; N, 7.31.

**Compound 16d.** Prepared from **9a** (140 mg, 0.5 mmol) and cyclohexanone (98 mg, 1 mmol). Colorless crystals (63 mg, 40%), purified by silica gel column chromatography with CHCl3-benzene-MeOH (15:3:1), mp 188-191.5°C (decomp.) (CHCl3), $[\alpha]^{18.5}_{D}$ +6.9° (*c* = 0.11, DMSO). IR (nujol) 3350, 3050, 1700, 1610, 1550 $cm^{-1}$. $^1$H-NMR (CDCl3 + DMSO-*d*6) δ 1.57-2.59 (m, 13H), 3.59 (ddd, 1H, *J* = 6, 7.5, 11.5 Hz), 3.81 (ddd, 1H, *J* = 4, 7.5, 11.5 Hz), 3.93 (dt, 1H, *J* = 7, 11.5 Hz), 4.13 (d, 1H, *J* = 12 Hz), 4.73 (br s, 1H, disappeared with D2O), 6.67 (t, 1H, *J* = 7.5 Hz), 6.86 (dd, 1H, *J* = 1.3, 7.5 Hz), 7.22 (dd, 1H, *J* = 1.3, 7.5 Hz), 8.79 (s, 1H, disappeared with D2O). HRMS calcd for $C_{18}H_{22}N_2O_3$ 314.1632, found 314.1646.

**Compound 16e.** Prepared from **9a** (140 mg, 0.5 mmol) and acetone (58 mg, 1 mmol). Colorless crystals (56 mg, 41%), purified by silica gel column chromatography with $CHCl_3$-benzene-MeOH (12:2:1), mp 171-172°C (MeOH-$H_2O$), $[\alpha]^{24}_D$ +230.6° (*c* = 0.13, DMSO). IR (nujol) 3340, 3080, 1715, 1610, 1595 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-*d*6) δ 1.62-2.42 (m, 4H), 2.21 (s, 3H), 2.57 (d, 2H, *J* = 8 Hz), 3.34-4.16 (m, 4H, 1H disappeared with $D_2O$), 4.52-4.76 (m, 1H), 6.64-7.34 (m, 3H), 9.10 (s, 1H, disappeared with $D_2O$). HRMS calcd for $C_{15}H_{18}N_2O_3$ 274.1381, found 274.1321.

**11-Cyano-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-ones (16f and 17f). 1) Reaction of 9a with Sodium Cyanide.** Chlorotrimethylsilane (0.38 mL, 3 mmol) was added dropwise to a suspension of **9a** (140 mg, 0.5 mmol), sodium iodide (450 mg, 3 mmol), and pyridine (0.283 mL, 3.5 mmol) in acetonitrile (5 mL) at -20°C under argon, and the mixture was stirred at -20°C for 30 min. Sodium hydrogen sulfite (104 mg, 1 mmol) and then sodium cyanide (49 mg, 1 mmol) was added. After being stirred at room temperature for 30 min, zinc chloride (237 mg, 2 mmol) was added to the mixture and the whole was stirred at 50°C for 21 h. After usual work-up, the crude product was purified by silica gel column chromatography with AcOEt-hexane (2:1 to 4:1), then PLC (AcOEt : hexane = 2:1) to give **16f** (73 mg, 60%) and **17f** (49 mg, 40%).

**16f** : mp 208-210°C (decomp.) (MeOH-AcOEt). $[\alpha]^{22.5}_D$ +332.9 (*c* = 0.50, DMSO). IR (nujol) 3350, 3100, 1620, 1570, 1430 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-*d*6) δ 1.96-2.10 (m, 3H), 2.21-2.92 (m, 1H), 3.54-3.69 (m, 2H), 3.87-3.92 (m, 1H), 4.38 (d, 1H, *J* = 11 Hz), 4.80-5.60 (br, 1H, disappeared with $D_2O$), 6.86 (t, 1H, *J* = 7.8 Hz), 6.97 (d, 1H, *J* = 7.8 Hz), 7.06 (d, 1H, *J* = 7.8 Hz), 9.74 (s, 1H, disappeared with $D_2O$). MS *m/z* : 216 ($M^+$-HCN).

**17f** : mp 198-200.5°C (decomp.) (MeOH-AcOEt). $[\alpha]^{22.5}_D$ +555.3° (*c* = 0.50, DMSO). IR (nujol) 3350, 3100, 1610, 1590, 1560 $cm^{-1}$. $^1$H-NMR ($CDCl_3$ + DMSO-*d*6) δ 1.81-1.91 (m, 1H), 1.92-2.09 (m, 2H), 2.39-2.46 (m, 1H), 3.56-3.64 (m, 1H), 3.82-3.89 (m, 1H), 3.97-4.05 (m, 1H), 4.99 (s, 1H), 6.40 (br s, 1H, disappeared with $D_2O$), 6.57 (t, 1H, *J* = 8 Hz), 6.85 (d, 1H, *J* = 8 Hz), 7.38 (d, 1H, *J* = 8 Hz), 9.80 (br s, 1H, disappeared with $D_2O$). MS *m/z* : 216 ($M^+$-HCN).

**2) Reaction of 9a with DEPC.** Reaction was carried out in 0.5 mmole scale as described for the general procedure for the preparation of **1** except that DEPC (0.152 mL, 1 mmol) was used instead of indole. After usual work-up, the crude product was purified by silica gel column chromatography with AcOEt-hexane (2:1) to give **16f** (31 mg, 26%) and **17f** (4 mg, 3%).

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