Stereoselective Synthesis of Tilivalline[1]

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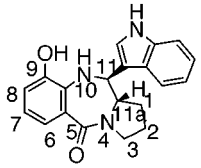
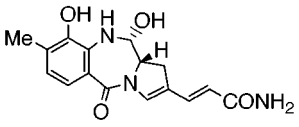
Tilivalline **1**, a metabolite from *Klebsiella pneumoniae* var. ocytoca, was easily synthesized in five steps from (*S*)-proline and 3-(benzyloxy)isatoic anhydride **4g**. This synthesis is based on modified Curtius reactions of 3-substituted phthalic anhydrides **11** to 3-substituted isatoic anhydrides **4**, conversion of lactams **6** to the acyliminium precursors **7** and stereoselective introduction of indole from the less hindered side of **7**.

Introduction

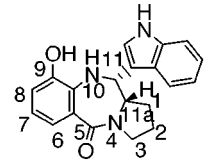
Tilivalline **1**, a metabolite, was isolated by Mohr and Budzikiewicz[2] from *Klebsiella pneumoniae* var. oxytoca. Its pyrrolo[2,1-*c*][1,4]benzodiazepine skeleton is similar to those of anthramycin (**2**) antibiotics.[3] The first synthesis[2] of **1** has been reported in 1982, but was considered unsatisfactory since the formation ratio of **1** to its 11-epimer **3** was 8:92. In 1986, a brilliant stereoselective synthesis of **1** was carried out by Shioiri et al.[4] via a new type of Mannich reaction. Tilivalline **1** and its analogues have since been found to possess strong cytotoxicity toward mouse leukemia L1210[5] and thus are of value.



1
tilivalline



2
anthramycin

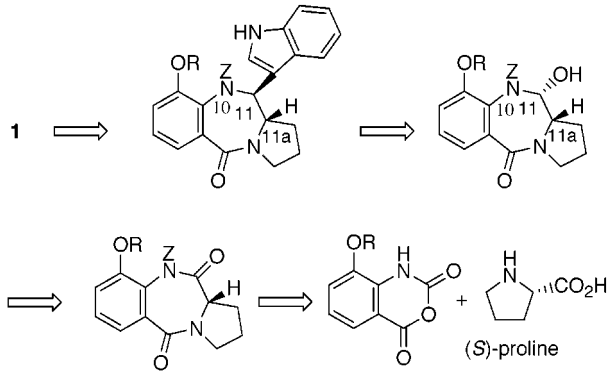


3
(epimer of **1**)

We reported an alternative stereoselective synthesis[1] of **1** in 1989. The results are presented in this paper.

The strategy for **1** is shown in Scheme 1. The reaction of isatoic anhydride (2*H*-3,1- benzoxazine-2,4(1*H*)-dione) with (*S*)-proline gives the pyrrolo[2,1-*c*][1,4]benzoazepin-5,11- dione skeleton,[6] and thus it is necessary to establish how to synthesize 3-substituted isatoic anhydrides as starting materials in this research. The key step in Scheme 1 is the enantioselective introduction of indole at the C-11 position from the less hindered side, because there is a possibility of epimerization[5a] at the C-11 due to cleavage−recyclization of the N(10)−C(11) bond or racemization at the C-11a via acyliminium−enamine equilibration. Activation of lactam carbonyl groups by introducing alkoxycarbonyl groups at N-positions followed by reduction of amide carbonyl groups with sodium borohydride and substitution by various functional groups at α-positions via *N*-acyliminium ions have been examined in detail.[7] A model experiment on the reaction of 2-ethoxy-1-(ethoxycarbonyl)hexahydroazepine with indole was carried out to give the desired 1-(ethoxycarbonyl)-2-(3′-indolyl)hexahydroazepine in 55% yield.[8]

Scheme 1



R=CH_2Ph, Z=CO_2CH_2Ph

Results and Discussion

The approach in the present synthesis is based on use of readily available enantiopure lactams, whose conversion to benzodiazepines possessing indole at the β-side

(1) This work has been presented as a brief communication: Nagasaka, T.; Koseki, Y.; Hamaguchi, F. *Tetrahedron Lett.* **1989**, *30*, 1871.
(2) Mohr, N.; Budzikiewicz, H. *Tetrahedron* **1982**, *38*, 147.
(3) For anthramycin antibiotics, see (a) Hurley, L. H. J. *Antibiot.* **1977**, *30*, 349. (b) Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, 52. (c) Remers, W. A. *The Chemistry of Antitumor Antibiotics* John Wiley & Sons: New York, 1988; Vol. 2, pp 28−92.
(4) Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 6111.
(5) (a) Aoyama, T.; Shioiri, T. *Yakugaku Zasshi* **1995**, *115*, 446. (b) Shioiri, T.; Aoyama, T.; Yamagami, N.; Shimizu, N.; Mori, N.; Kohda, K. *Anti-Cancer Drug Design* **1995**, *10*, 167. (c) Kohda, K.; Yamagami, N.; Kasamatsu, T.; Aoyama, T.; Shioiri, T. *Biochem. Pharmacol.* **1995**, *49*, 1063.
(6) Wright, W. B. Jr.; Brabander, H. J.; Greenblatt, E. N.; Day, I. P.; Hardy, R. A., Jr. *J. Med. Chem.* **1978**, *21*, 1087.
(7) For conversion of lactams to α-substituted cyclic amines, see (a) Nagasaka, T.; Abe, M.; Ozawa, N.; Kosugi, Y.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 985. (b) Nagasaka, T.; Tamano, H.; Maekawa, T.; Hamaguchi, F. *Heterocycles* **1987**, *26*, 617.
(8) Nagasaka, T.; Koseki, Y.; Hayashi, H.; Yasuda, Y.; Hamaguchi, F. *Yakugaku Zasshi* **1989**, *109*, 823.

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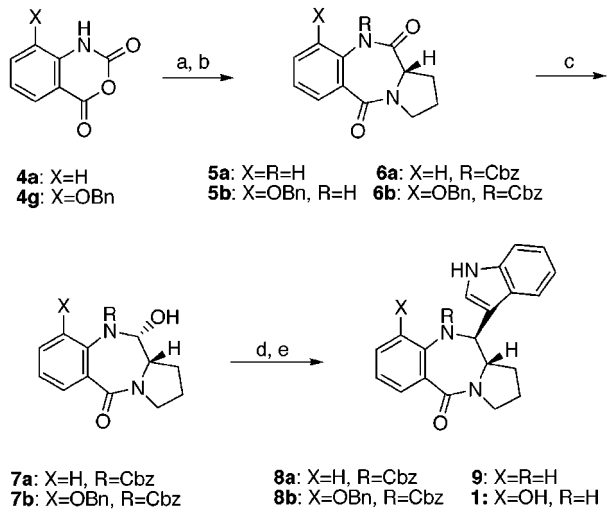
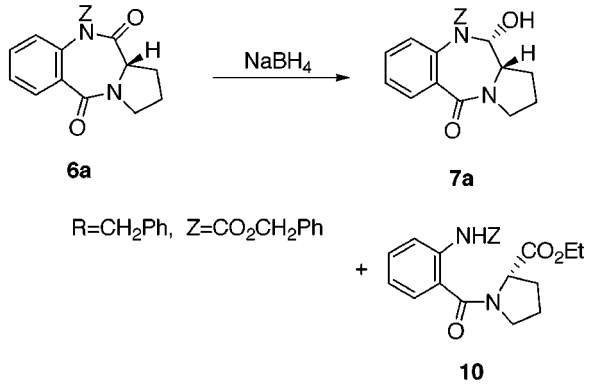
Scheme 2



(a) (*S*)-proline, DMSO, 110°C, 6 h; (b) n-BuLi, 0 °C, or $(TMS)_2NLi$, THF, r.t., 30 min, then CbzCl, r.t., 2 h; (c) $NaBH_4$, EtOH-THF, H^+, 0°C; (d) indole, AcOH, sealed tube, 150°C, 5 h; (e) 5% Pd-C, MeOH-THF (1:1), H_2, 1 atm.

Table 1. Reduction of 6a with Sodium Borohydride



run	$NaBH_4$ (equiv)	temp. (°C)	time[a] (h)	solvent	product (yield, %) 7a	10
1	1.1	−5−0	2	EtOH	50	45
2	1.1	−5−0	2	CH_2Cl_2	no reaction	
3	2.1	rt	2	CH_2Cl_2	62	17
4	1.1	−5−0	2	THF	69	−

[a] A few drops of ethanol solution containing a small amount of hydrogen chloride were added every 10 min during the reactions.

of the 11-position appears promising.[4] Initially, as a model experiment, the synthesis of deoxytilivalline **9** was carried out as shown in Scheme 2.

Treatment of pyrrolobenzodiazepine **5a**, obtained in high yield from isatoic anhydride **4a** and (*S*)-proline by a known method,[6] with benzyl chloroformate in the presence of n-BuLi gave *N*-benzyloxycarbonyl compound **6a** in 62% yield. The controlled reduction[9] of **6a** with sodium borohydride was examined in detail, and some of results are shown in Table 1. Ordinary conditions using ethanol near 0 °C afforded a mixture of alcohol **7a** (50%) and cleavage product **10** (45%) (run 1). Dichloromethane failed to make the reaction at 0 °C (run 2) but, at room temperature, increased the yield (62%) of **7a** along with the undesired byproduct **10** (17%) (run 3). The best results were obtained using tetrahydrofuran (THF) near 0 °C (run 4), in which only alcohol **7a** formed in 69% yield. Generally acidic conditions in ethanol should afford not α-hydroxy- but α-ethoxyamines via acyliminium ion.[9] That the corresponding α-ethoxyamine of **7a** was not detected means that **7a** may form directly by attack of borohydride at the less hindered *β*-side and possibly may have a hydroxy group on the α-side. The condensation of **7a** with indole did not proceed at room temperature or under reflux conditions in various solvents, but heat application at 150 °C in acetic acid in a sealed tube produced **8a** in 50% yield as the sole product. Stereoselectivity for this reaction was reasonable if the nucleophile (indole) be considered to attack on the less hindered side[4] of the acyliminium intermediate[9] formed from alcohol **7a**. The catalytic hydrogenetion of **8a** gave **9** in 93% yield.[10] On the basis of ^{1}H NMR spectra of **1**, **3** (11-epimer of 1),[2] and **9** (Table 2), the protons of C-11 and C-11a of **9** were concluded to have a trans configuration as tilivallin **1**.

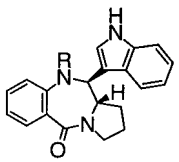
Table 2. ^{1}H NMR Spectra of 1, 3 (*epi*-1), and 9

compd	11-H	11a-H
1	4.92 (d, J = 9 Hz)	4.43 (m)
3	5.30 (d, J = 3 Hz)	4.32 (m)
9	4.74 (d, J = 9 Hz)	4.32 (m)

Tilivalline **1** was synthesized by the above route (Scheme 2), but under refined conditions. Washburne et al.[11] reported the reaction of phthalic anhydride **11a** with trimethylsilyl azide (TMSA) (modified Curtius reaction) to give isatoic anhydride **4a**, via an equilibrium mixture of trimethylsilyl 2-isocyanatobenzoate and *N*-(trimethylsilyl)isatoic anhydride, in total yield of 76%. The reaction of 3-nitrophthalic anhydride **11b** with sodium azide has been reported by Caronna[12] to give 3-nitroisatoic anhydride **4b** exclusively. To obtain starting materials (3-substituted isatoic anhydrides **4**) of **1**, the modified Curtius reaction of various 3-substituted phthalic anhydrides **11** with TMSA was examined, and the results are shown in Table 3. Reactions of 3-amino- and 3-acetaminophthalic anhydrides, **11d** and **11e**, gave 6-amino- and 3-acetaminoisatoic anhydrides, **12d** and **4e**, respectively. Reactions of isatoic anhydrides possessing oxygen functional groups at the 3-position, **11c**, **11f**, and **11g**, gave a mixture of 3- and 6-substituted isatoic anhydrides, **4c** and **12c**, **4f** and **12f**, and **4g** and **12g**. Regioselectivity by attack of azide ion should be explained

(9) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231.

(10) Optimum conditions were not determined in the model experiments for **9**. Compound **13** N-protected by an ethoxycarbonyl group was initially prepared. Removal of the protecting group (CO_2Et) of **13** using HBr−AcOH failed to give **9**, but the crystalline material, mp 188−190 °C, having the same molecular formula of **13** ($C_{23}H_{23}N_3O_3$) was obtained in 57% yield. The structure and formation mechanism of this product will appear in a separate paper.

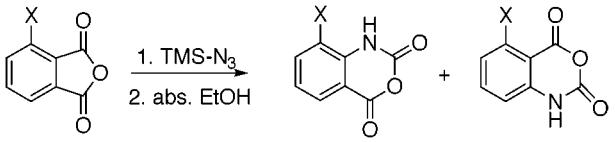


13 : R=CO_2Et

(11) Washburne, S. S.; Peterson, W. R., Jr.; Berman, D. A. *J. Org. Chem.* **1972**, *37*, 1738.

(12) Caronna, G. *Gazz. Chim. Ital.* **1941**, *71*, 470.

Table 3. Reactions of 3-Substituted Phthalic Anhydrides with Trimethylsilyl Azide



11a-g **4a-g** **12a-g**

				product (yield, %)	
run	**11a−g**	X	solvent	**4a−g**	**12a−g**
1	**11a**	H	benzene	**4a** (76)	−
2	**11b**	NO_2	benzene	**4b** (75)	**12b** (0)
3	**11c**	OAc	benzene	**4c** (12)	**12c** (41)
4	**11d**	NH_2	THF	**4d** (0)	**12d** (85)
5	**11e**	NHAc	benzene	**4e** (74)	**12e** (0)
6	**11f**	OMe	benzene	**4f** (55)	**12f** (6)
7	**11g**	OCH_2Ph	benzene	**4g** (68)	**12g** (9)

based on further study, but 3-(benzyloxy)isatoic anhydride **4g**, the most suitable starting material, was predominantly obtained. The structures of 3- and 6-substituted isatoic anhydrides **4** and **12** were determined based on comparison of ^{1}H NMR spectra of **4** with those of **12**. Signals of aromatic protons of **4** appear in lower field than those of **12**. Furthermore, some compounds were converted to those identical to authentic samples. The hydrolysis of **4b** and **4f** afforded 3-substituted anthranilic acids, respectively, whose melting points were identical with authentic samples, respectively. Hydrogenation of **4b** over Pd−C under hydrogen atmosphere gave 3-aminoisatoic anhydride **4d** in 90% yield which is quite different from 6-aminoisatoic anhydride **12d**.

Condensation of **4g** with (*S*)-proline gave diazepine **5b** in 84% yield. Carbamate **6b** could not be obtained at all under the same reaction conditions using n-BuLi as described for the preparation of **6a**. This compound was obtained in 88% yield using lithium hexamethyldisilazide (LHMDS) instead of n-BuLi. The reaction of **5a** with benzyl chloroformate using LHMDS caused no increase in yield, and many byproducts were formed. The controlled reduction[9] of compound **6b** with sodium borohydride in THF provided only alcohol **7b** in 76% yield. In this case, ethanol solvent gave a mixture of the desired product **7b** and a cleavage amide-ester like **10**-analogue in a ratio of 1:1. Alcohol **7b**, via acyliminium ion, condensed with indole to afford **8b** exclusively in 93% yield. The catalytic hydrogenation of **8b** gave tilivalline **1** in 82% yield. This tilivalline **1** was found to have mp 180−185 °C and $[\alpha]_D$ +210° (*c* = 1.01 MeOH), different from mp 168 °C (Mohr and Budzikiewicz)[2] and 242−245 °C (Shioiri)[4] and $[\alpha]_D$ +126.8 (MeOH) (Mohr and Budzikiewicz)[2] and +245° (Shioiri),[4] respectively. However, the purity of the present tilivalline **1** was comfirmed pure (>98% ee) by HPLC using a chiral column.[13] The spectral data (IR, ^{1}H- and ^{13}C NMR, mass, and UV) of tilivalline produced here showed complete agreement with those of an authentic sample provided through the courtesy of Prof. Shioiri.

(13) Column (Chiralcel OJ, Daicel Chem. Ind. Ltd.), 25 × 0.46 (i.d) cm stainless tube packed with cellulose esters coated on silica gel; flow rate, 0.5 mL/min at 20 °C; solvent, ^{i}PrOH-*n*-hexane (1:1); detector, a UV-detector at 254 nm; rt, 26.4 min. A trace of (−)-enantiomer (<1%) of tilivalline **1**, probably due to the impurity of the starting (*S*)-proline, was detected; rt, 30.9 min. These chromatograms were carefully checked by (±)- and (+)-tilivallines, prepared from (±)- and (*S*)-(−)-prolines, respectively.

Experimental Section

All melting points were determined on a hot stage apparatus without correction. Optical rotaion was measured at 589 nm. ^{1}H (90 and 400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ with TMS or $CDCl_3$, respectively, as the internal reference. Elemental analyses were performed by Central Analytical Laboratory, Tokyo University of Pharmacy and Life Sciences.

Phthalic anhydride **11a** and 3-nitrophthalic anhydride **11b** were obtained from commercial sources (Tokyo Kasei). 3-Acetoxyphthalic anhydride **11c** was prepared by the method of Cava et al.[14] from 2-acetoxyfuran derived from furan by the method of Clauson and Elming.[15] 3-Amino- and 3-acetaminophthalic anhydrides **11d** and **11e** were prepared by catalytic hydrogenation (5% Pd−C) of **11b** in EtOAc and acetic anhydride, respectively. 3-Methoxyphthalic anhydride **11f** was prepared from 2-methoxyfuran by the method of Rao et al.[16] 3-(Benzyloxy)phthalic anhydride **11g** was prepared by the method of Menard et al.[17] from 3-hydroxyphthalic acid, which was derived from 3-nitrophthalic acid by the method of Gisvold.[18] Compound **5a** was prepared by the method of Wright.[6]

(+)-(11a*S*)-1,2,3,10,11,11a-Hexahydro-10-(benzyloxycarbonyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (6a). To a solution of **5a** (7.5 g, 0.034 mol) in absolute THF (300 mL) was added dropwise at 0 °C a 1.6 M solution of n-BuLi in hexane (21.2 mL) under argon. A 30% solution of benzyl chloroformate in toluene (21 mL) was added at 0 °C to this mixture, which was then stirred for 2 h at this temperature. Saturated NH_4Cl solution was added to terminate the reaction, and the mixture was extracted with $CHCl_3$. The combined extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a solid, which was chromatographed by elution with hexane−acetone (6:1) to afford 7.3 g (60%) of a colorless amorphous solid. Recrystallization from benzene−petroleum ether gave colorless powder, mp 109−119 °C. IR (KBr) 1780, 1735, 1615 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.11 (m, 3H), 2.68 (m, 1H), 3.67 (m, 2H), 4.05 (m, 1H), 5.23 (ABq, J_{AB} = 12 Hz, 2H), 7.08−7.58 (m, 8H), 7.93 (m, 1H); MS *m*/*z* 350 (M^+), 215 ($M^+ - COOCH_2Ph$). $[\alpha]^{25}_D$ +84.3 (*c* 1.05, MeOH); HRMS (FAB) calcd for $C_{20}H_{18}N_2O_4$ 350.1265, found 350.1284.

(+)-(11a*S*)-1,2,3,10,11,11a-Hexahydro-10-(benzyloxycarbonyl)-11-hydroxy- 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (7a). To a solution of **6a** (600 mg, 1.7 mmol) in absolute THF (80 mL) under ice-cooling was added $NaBH_4$ (71 mg, 1.8 mmol). The reaction mixture was stirred for 2 h at 0 °C while adding a few drops of the HCl−EtOH solution, prepared by diluting saturated HCl−EtOH solution with 10 times volume of EtOH, at intervals of 10 min[19] followed by acidfication with the same diluted HCl−EtOH solution so that pH was 3−4 at the end of the reaction. Finally, the system was neutralized with alkali solution of 0.5 N KOH−EtOH. The reaction mixture was evaporated under reduced pressure to give a white mass, which was extracted with $CHCl_3$. The $CHCl_3$ extract was filtered and evaporated under reduced pressure to afford an oil. Chromatography of this oil by elution with hexane−acetone (6:1) afforded 413 mg (69%) of a white amorphous solid. IR (KBr) 3400, 1720, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (m, 2H), 2.12 (m, 2H), 3.45 (m, 1H), 3.56 (m, 1H), 3.73 (m, 1H), 4.96 (ABq, J_{AB} = 12.5 Hz, 2H),

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(16) Rao, A. V. R.; Chanda, B. M.; Wadekar, A. V. *Indian J. Chem.* **1981**, *20B*, 248.
(17) Menard, M.; Erichomovitch, L.; Brooy, M. L. *Canadian J. Chem.* **1963**, *41*, 1722.
(18) Gisvold, O. *J. Am. Pharm. Assoc.* **1942**, *31*, 202 [*Chem Abstr.* **1942**, *36*, 54708].
(19) The general method[9] needs the addition of a catalytic amount of ethanol solution containing hydrogen chloride at regular intervals. Reduction of **6a** and **6b** with sodium borohydride in ethanol and tetrahydrofuran, however, could be also accomplished without addition of acid.

5.65 (d, J = 8.8 Hz, 1H), 7.15−7.51 (m, 9H), 7.77 (dd, J = 1.8, 7.4 Hz, 1H); MS m/z 352 (M^+), 217 ($M^+ - COOCH_2Ph$).

(+)-(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-10-(benzyloxycarbonyl)-11-(3′-indolyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (8a). A mixture of **7a** (160 mg, 0.45 mmol), indole (69 mg, 0.58 mmol), and acetic acid (6 mL) was heated for 5 h at 150−160 °C in a sealed tube. The reaction mixture was evaporated under reduced pressure, and the residue was chromatographed by elution with CH_2Cl_2−MeOH (40:1) to give crystals which were recrystallized from acetone to colorless prisms. Yield 50%, mp 223−225 °C. IR (KBr) 3460, 1690, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (m, 1H), 1.98 (m, 2H), 2.15 (m, 1H), 3.65 (m, 1H), 3.84 (m, 1H), 4.11 (m, 1H), 5.02 (ABq, J_{AB} = 12.7 Hz, 2H), 5.78 (d, J = 11.5 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 2.5 Hz, 1H), 7.05 (m, 3H), 7.20 (m, 4H), 7.36 (m, 2H), 7.45 (m, 2H), 7.86 (dd, J = 1.7, 7.6 Hz, 1H) 8.40 (br, 1H); MS m/z 451 (M^+). $[\alpha]^{25}_D$ +107° (c 0.4, $CHCl_3$). Anal. Calcd for $C_{28}H_{25}N_3O_3$: C, 74.78; H, 5.58; N, 9.31. Found: C, 74.64; H, 5.61; N, 9.26. Any product such as the epimer of **8a** was not detected.

9-Deoxytilivalline: (+)-(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-11-(3′-indolyl)- 5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (9). Catalytic hydrogenation (H_2 2 atm, 5% Pd−C 50 mg) of **8a** (75 mg, 0.17 mmol) in a solution of THF−MeOH (1:1) (5 mL) was carried out for 1 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give an oil which was chromatographed by elution with $CHCl_3$−MeOH (30:1) to give a crude powder which, by recrystallization from CH_2Cl_2−hexane afforded 49 mg (93%) of yellow powder: mp 219−224 °C. IR (KBr) 3500, 1610, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 1H), 1.80 (m, 2H), 1.94 (m, 1H), 3.77 (m, 1H), 3.91 (m, 1H), 4.32 (m, 1H), 4.74 (d, J = 9.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.14 (br, 1H), 7.21 (m, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.99 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 30.7, 47.9, 59.9, 62.5, 111.8, 117.1, 119.1, 119.5, 120.0, 121.5, 121.6, 122.6, 122.7, 125.2, 131.6, 132.3, 136.8, 145.0, 167.9; MS m/z 317 (M^+). $[\alpha]^{25}_D$ +58.7 (c 1.01, $CHCl_3$). HRMS (FAB) calcd for $C_{20}H_{19}N_3O$ 317.1527, found 317.1513.

3-Nitroisatoic Anhydride (4b). A mixture of 3-nitrophthalic anhydride (**11b**, 350 mg, 1.8 mmol), TMS-N_3 (2.7 mmol, 0.35 mL) and absolute C_6H_6 (5 mL) was refluxed for 3 h and concentrated under reduced pressure to a viscous oil containing a small amount of benzene which was further heated for 16 h at 100 °C (bath temperature) and evaporated completely under reduced pressure. Absolute EtOH (3 mL) was added to the residue and immediately evaporated under reduced pressure to give crude crystals, which were then recrystallized from C_6H_6 to give 280 mg (75%) of yellow prisms: mp 169−170 °C. IR (KBr) 1800, 1730, 1620, 1480 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 7.45 (dd, J = 7.9, 8.3 Hz, 1H), 8.48 (dd, J = 1.5, 7.9 Hz, 1H), 8.64 (dd, J = 1.5, 8.3 Hz, 1H), 10.6 (br, 1H); MS m/z 208 (M^+), 164 ($M^+ - CO_2$). Anal. Calcd for $C_8H_4N_2O_5$: C,46.16; H, 1.94; N, 13.46. Found: C, 46.30; H, 1.98; N, 13.21.

6-Acetoxyisatoic Anhydride (12c) and 3-Acetoxyisatoic Anhydride (4c). Colorless prisms (107 mg, 41%) of **12c** were obtained from a mixture of 3-acetoxyphthalic anhydride (**11c**, 240 mg, 1.17 mmol), TMS-N_3 (0.23 mL, 1.75 mmol), and C_6H_6 (5.5 mL), under the same conditions as for **4b**, followed by recrystallization from EtOAc: mp 242−247 °C. IR (KBr) 3250, 1760, 1700, 1620, 1600 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 2.35 (s, 3H), 6.83 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 8.1 Hz, 1H), 11.72 (br, 1H); MS m/z 221 (M^+), 179 ($M^+ - COCH_3$), 135 ($M^+ - CO_2 - COCH_3$). Anal. Calcd for $C_{10}H_7NO_5$ C, 54.30; H, 3.19; N, 6.33. Found C, 54.39; H, 3.46; N, 6.53. The filtrate left from the recrystallization of **12c** was evaporated under reduced pressure, and the residue was chromatographed by elution with CH_2Cl_2−acetone (10:1) to give colorless prisms (30 mg, 12%) of **4c**: mp 222−224 °C. IR (KBr) 1800, 1780, 1740, 1630 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 2.35 (s, 3H), 7.21 (t, J = 7.5 Hz, 1H), 7.44 (dd, J = 1.5, 7.5 Hz, 1H), 7.85 (dd, J = 1.5, 7.5 Hz, 1H); MS m/z 221 (M^+), 179 ($M^+ - COCH_3$), 135 ($M^+ - CO_2 - COCH_3$). Anal. Calcd for $C_{10}H_7NO_5$: C, 54.30; H, 3.19; N, 6.33. Found: C, 54.34; H, 3.21; N, 6.12.

6-Aminoisatoic Anhydride (12d). Yellow prisms (147 mg, 85%) of **12d** were obtained using 3-aminophthalic anhydride (**11d**, 190 mg, 1.17 mmol), TMS-N_3 (0.32 mL, 2.4 mmol) and absolute THF (3 mL), under the conditions for **4b**, followed by recrystallization from isopropyl alcohol: mp 267−270 °C. IR (KBr) 3480, 3330. 1760, 1700, 1610, 1600 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 6.18 (d, J = 7.2 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 6.99 (br, 2H), 7.23 (t, J = 7.2 Hz, 1H), 11.20 (br, 1H); MS m/z 178 (M^+), 134 ($M^+ - CO_2$), 107 ($M^+ -$ COOCO). Anal. Calcd for $C_8H_6O_3N_2$: C, 53.93; H, 3.40; N, 15.73. Found: C, 53.85; H, 3.38; N, 15.67.

3-Acetaminoisatoic Anhydride (4e). Using 3-acetaminophthalic anhydride (**11e**, 200 mg, 0.98 mmol), TMS-N_3 (0.26 mL, 1.96 mmol), and absolute C_6H_6 (4.5 mL), colorless prisms (160 mg, 74%) of **4e** were prepared under the conditions as for **4b**, followed by recrystallization from EtOAC: mp 252−253 °C. IR (KBr) 3150, 1770, 1740, 1700, 1610, 1600 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 2.20 (s, 3H), 6.83 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 10.40 (br, 1H), 11.38 (br, 1H); MS m/z 220 (M^+), 177 ($M^+ - CH_3CO$), 176 ($M^+ - CO_2$), 134 ($M^+ - CO_2 - CH_3CO$). Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.62; H, 3.66; N, 12.74.

3-Methoxyisatoic Anhydride (4f) and 6-Methoxyisatoic Anhydride (12f). Reaction of 3-methoxyphthalic anhydride (**11f**, 250 mg, 1.4 mmol) with TMS-N_3 (0.19 mL, 2.8 mmol) in absolute C_6H_6 (4.5 mL), under the conditions as for **4b**, gave crude crystals which were chromatographed by elution with CH_2Cl_2−hexane−acetone, (30:1:1) followed by recrystallization from EtOAc to give colorless prisms (116 mg, 43%) of **4f** from the first fractions and colorless prisms (15 mg, 6%) of **12f** from the second fractions; **4f**: mp 255−260 °C. IR (KBr) 1800, 1700, 1620, 1610 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 3.95 (s, 3H), 7.17 (t, J = 8.1 Hz, 1H), 7.39 (dd, J = 1.8, 8.1 Hz, 1H), 7.48 (dd, J = 1.8, 8.1 Hz, 1H); MS m/z 193 (M^+), 149 ($M^+ - CO_2$), 121 ($M^+ -$ COOCO). Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.90; H, 3.65; N, 7.31. **12f**: mp 258−261 °C. IR (KBr) 3250, 1780, 1730, 1620 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 3.88 (s, 3H), 6.70 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 7.59 (t, J = 8.1 Hz, 1H); MS m/z 193 (M^+), 149 ($M^+ - CO_2$), 121 ($M^+ -$ COOCO).

3-(Benzyloxy)isatoic Anhydride (4g) and 6-(Benzyloxy)isatoic Anhydride (12g). Colorless prisms (269 mg, 68%) of 4g were prepared under the conditions as for **4b**, followed by recrystallization from EtOAc, using 3-(benzyloxy)-phthalic anhydride (**11g**, 370 mg, 1.46 mmol), TMS-N_3 (0.39 mL, 2.92 mmol), and absolute C_6H_6 (6 mL). The filtrate left from the recrystallization of **4g** was evaporated to a solid which was chromatographed by elution with CH_2Cl_2−acetone (20:1), followed by recrystallization from EtOAc to give colorless prisms (34 mg, 9%) of **12g**. **4g**: mp 204−206 °C. IR (KBr) 3200, 1800, 1730, 1620, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 2H), 7.18 (t, J = 8.0, 1H), 7.25 (dd, J = 1.5, 8.0 Hz, 1H), 7.40−7.46 (m, 5H), 7.67 (dd, J = 1.5, 8.0 Hz, 1H), 8.15 (br, 1H); MS m/z 269 (M^+), 196 ($M^+ -$ COOCO), 92. Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.75; H, 4.10; N, 5.19. **12 g**: mp 224−229 °C. IR (KBr) 1790, 1720, 1620, 1600 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 5.26 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 7.37 (m, 4H), 7.51 (dd, J = 8.2, 8.4 Hz, 1H), 7.54 (m, 1H), 11.31 (br, 1H); MS m/z 269 (M^+), 92. Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.93; H, 4.19; N, 5.17.

3-Aminoisatoic Anhydride (4d). The catalytic hydrogenation (H_2 2 atm, 5% Pd−C 89 mg) of 3-nitroisatoic anhydride (**4b**, 150 mg, 7.21 mmol) in THF (15 mL) was carried out for 1 h, followed by removal of the catalyst by filtration, evaporation of the filtrate, and recrystallization of the residue from THF to give a colorless powder (116 mg, 90%) of **4d**: mp over 280 °C. IR (KBr) 3200, 1700, 1610 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 6.93 (t, J = 8.1 Hz, 1H), 7.09 (dd, J =

1.5, 8.1 Hz, 1H), 7.45 (dd, J = 1.5, 8.1 Hz, 1H), 9.84 (br, 1H), 10.75 (br, 1H); MS m/z 178 (M^+), 106 ($M^+ - CO_2$).

Hydrolysis of Isatoic Anhydrides: 3-Nitroanthranilic Acid. A solution of **4b** (150 mg, 0.72 mmol) in concd HCl (3 mL) was refluxed for 1 h, followed by evaporation and recrystallization of the residue from C_6H_6 to give yellow prisms (90 mg, 69%) of mp 203−204 °C. IR (KBr) 3460, 3340, 3100−2800, 1680, 1250 cm^{-1}; ^1H NMR (90 MHz, d_6-DMSO + $CDCl_3$) δ 6.68 (t, J = 7.8 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H); MS m/z 164 (M^+).

3-Nitroanthranilic acid: mp 202−203 °C (lit.[20]).

6-Nitroanthranilic acid: mp 184 °C (lit.[20]).

3-Methoxyanthranilic Acid. Colorless prisms (10 mg, 34%) of mp 173−174 °C were prepared from **4f** (34 mg, 0.18 mmol) under the conditions above. IR (KBr) 3500, 3390, 3100−2600, 1670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.83 (s, 1H), 6.55 (t, J = 8.1 Hz, 1H), 6.83 (dd, J = 1.5, 8.1 Hz, 1H), 7.49 (dd, J = 1.5, 8.1 Hz, 1H). Mp and spectra (IR and ^1H NMR) agreed with the data for 3-methoxyanthranilic acid.[21]

(+)-(11a*S*)-1,2,3,10,11,11a-Hexahydro-9-(benzyloxy)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (5b). A solution of **4g** (2.64 g, 9.8 mmol) and (*S*)-proline (1.35 g, 11.7 mmol) in absolute DMSO (7 mL) was heated at 100 °C for 5 h. After the reaction mixture was cooled, ice−water was added, and the crystals that formed were separated by filtration, washed with brine and dried. Recrystallization from C_6H_6 afforded colorless prisms (2.65 g, 84%); mp 178−182 °C. IR (KBr) 2970, 2850, 1690, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (m, 3H), 2.75 (m, 1H), 3.60 (m, 1H), 3.79 (m, 1H), 4.02 (m, 1H), 5.12 (s, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.38 (m, 5H), 7.58 (d, J = 8.0 Hz, 1H), 7.97 (br, 1H); MS m/z 322 (M^+), 231 ($M^+ - CH_2Ph$), 91. $[\alpha]^{25}_D$ +350° (c 1.00, $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 71.08; H, 5.57; N, 8.53.

(11a*S*)-1,2,3,10,11,11a-Tetrahydro-9-(benzyloxy)-10-(benzyloxycarbonyl)-5*H*- pyrrolo[2,1-*c*][1,4]benzodiazepin-5,-11-dione (6b). A solution of LHMDS (lithium hexamethyldisilazide, 3 mL, 3.1 mmol) in hexane was added dropwise at room temperature to **5b** (1 g, 3.1 mmol) in absolute THF (60 mL). After the reaction mixture was stirred at the same temperature for 50 min, a solution of 30% benzyl chloroformate (2.64 g, 4.65 mmol) in toluene was added, and stirring was continued for 2 h. The reaction was terminated by adding saturated NH_4Cl solution and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an oil which was chromatographed by elution with hexane−CH_2Cl_2−acetone (15:15:1) to give yellow amorphous (1.25 g, 88%). Recrystallization from ether gave 1.13 g (80%) of a colorless amorphous solid. IR (KBr) 1790, 1730, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.11 (m, 1H), 2.67 (m, 1H), 3.51 (m, 1H), 3.79 (m, 1H), 3.92 (d, J = 7.5 Hz, 1H), 4.95 (ABq, J_{AB} = 4.0 Hz, 2H), 4.97 (ABq, J_{AB} = 12.0 Hz, 2H), 7.09−7.49 (m, 12H), 7.50 (d, J = 7.7 Hz); MS m/z 456 (M^+), 365 ($M^+ - CH_2Ph$), 321 ($M^+ - COOCH_2Ph$).

(+)-(11a*S*)-1,2,3,10,11,11a-Hexahydro-9-(benzyloxy)-10-(benzyloxycarbonyl)- 11-hydroxy-5*H*-pyrrolo[2,1-*c*][1,4]-benzoazepin-5-one (7b). To a solution of **6b** (1.43 g, 3.13 mmol) in absolute THF (200 mL) was added at 0 °C $NaBH_4$ (130 mg, 3.51 mmol). Stirring was continued at 0 °C for 2 h while adding a few drops of diluted HCl−EtOH solution at intervals of 10 min.[19] The reaction mixture was evaporated under reduced pressure to give a white mass which was extracted with $CHCl_3$. The extract was evaporated under reduced pressure to the residue which was chromatographed by elution with CH_2Cl_2−hexane−acetone (6:6:1) to give colorless prisms (1.09 g, 76%) of **7b**, recrystallized from EtOAc; mp 193−196 °C. IR (KBr) 3240, 1720, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (m, 4H), 3.47 (m, 1H), 3.55 (m, 1H), 3,75 (m, 1H), 4.90 (ABq, J_{AB} = 11.96 Hz, 2H), 4.99 (ABq, J_{AB} = 12.6 Hz, 2H), 5.63 (dd, J = 3.4, 9.6 Hz, 1H), 7.00−7.38 (m, 13H); MS m/z 458 (M^+). $[\alpha]^{25}_D$ +129° (c 0.99, $CHCl_3$). Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.68; H, 5.77; N, 5.91.

(+)-(11*S*,11a*S*)-1,2,3,10,11,11a-Hexahydro-9-(benzyloxy)-10-carbobenzyloxy- 11-(3′-indolyl)-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one (8b). A mixture of **7b** (200 mg, 0.43 mmol), indole (102 mg, 0.87 mmol), and glacial AcOH (7 mL) was heated at 150 °C for 5 h in a sealed tube. The solvent was evaporated under reduced pressure to give a solid which was purified by chromatography with CH_2Cl_2−hexane−acetone (5:5:1) elution to give 228 mg (94%) of colorless prisms, recrystallized from EtOH, mp 260−265 °C. IR (KBr) 3200, 1700, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 1H), 1.97 (m, 2H), 2.14 (m, 1H), 3.67 (m, 1H), 3.87 (m, 1H), 4.30 (m, 1H), 4.35 (ABq, J_{AB} = 11.8 Hz, 2H), 4.90 (ABq, J_{AB} = 12.8 Hz, 2H), 5.68 (d, J = 8.0 Hz, 1H), 6.91−7.28 (m, 16H), 7.40 (d, J = 7.9 Hz, 1H), 7.44 (dd, J = 1.1, 7.7 Hz, 1H), 8.14 (br, 1H); MS m/z 557 (M^+), 466 ($M^+ - CH_2Ph$), 422 ($M^+ - COOCH_2$-Ph), 353 ($M^+ -$ indole $- CH_2Ph$). $[\alpha]^{25}_D$ +267 (c 1.37, $CHCl_3$). Anal. Calcd for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54. Found: C, 75.56; H, 5.63; N, 7.59.

Tilivalline (1). Catalytic hydrogenation (H_2 1 atm, 5% Pd−C 110 mg) of **8b** (180 mg, 0.32 mmol) in THF−MeOH (1:1) (10 mL) was carried out for 10 h, followed by filtration, evaporation under reduced pressure, and chromatography of the residue by elution with $CHCl_3$−MeOH (40:1 to 20:1) to give a solid which was recrystallized from acetonitrile to afford a yellow amorphous mass (88 mg, 82%) of **1**; mp 180−185 °C. IR (THF) 3500, 3350, 1620, 760 cm^{-1}; ^1H NMR (400 MHz, d_5-pyridine) δ 1.61 (m, 1H), 1.71 (m, 2H), 1.79 (m, 1H), 3.84 (m, 1H), 4.08 (m, 1H), 4.50 (m, 1H), 4.99 (d, J = 8.8 Hz, 1H), 5.92 (br, 1H), 6.90 (t, J = 7.7 Hz, 1H), 7.22 (m, 2H), 7.31 (t, J = 7.7 Hz, 1H), 7.57 (m, 2H), 7.86 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 11.97 (br, 1H), 12.19 (br, 1H); ^{13}C NMR (100 MHz, d_5-pyridine) δ 22.8, 31.2, 48.4, 60.8, 62.1, 112.4, 116.0, 117.1, 117.6, 119.9, 120.0, 121.1, 122.3, 123.2, 124.2, 126.3, 136.7, 138.0, 146.8, 167.8; MS m/z 333 (M^+). $[\alpha]^{25}_D$ +210° (c 1.01, MeOH). HRMS (FAB) calcd for $C_{20}H_{19}N_3O_2$: 333.1476, found 333.1479.

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Supporting Information Available: Copies of ^1H NMR spectra for compounds **1**, **4d**, **6a**, **6b**, **7a**, **9**, ^{13}C NMR spectra for compounds **1**, **9**, and mass spectra of **1** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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