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New Synthesis of Pyrrolo-1,4-benzodiazepines by Utilizing Palladium-Catalyzed Carbonylation

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A pyrrolo-1,4-benzodiazepine skeleton which constitutes the common part of a series of antibiotics exhibiting antitumor activity was synthesized by insertion of carbon monoxide into *o*-bromoprolylaniline derivatives in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3. In this reaction, hexamethylphosphoramide (HMPA) gave a good result as the solvent and the use of a high pressure of carbon monoxide (5 atom) increased the yield of the desired pyrrolo-1,4-benzodiazepine.

Keywords——1,4-benzodiazepine; pyrrolo-1,4-benzodiazepine; palladium catalyzed carbonylation; palladium acetate; triphenyl phosphine; carbon monoxide

Since the 1,4-benzodiazepine skeleton is very important for verious pharmacological activities, many synthetic methods have already been reported.[2] In particular, the prrolo-1,4-benzodiazepine skeleton constitutes the common part of antibiotics such as anthramycin,[3] neothramycin,[4] tomaymycin,[5] sibiromycin,[6] and SEN-215,[7] which have strong antitumor activities.[8] Their fundamental skeleton has usually been synthesized by reductive cyclization of *o*-nitrobenzoic acid derivatives.[2b] We have already reported the synthesis of benzolactams **2** from *o*-haloaminoalkylbenzenes **1** by the use of palladium-catalyzed carbonylation.[9] In this reaction, five-, six- and seven-membered benzolactams were synthesized in fairly good yields. In general, the secondary amine is preferable to the corresponding primary amine as a starting materials. This method has been further extended to the synthesis of 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-diones **6** by insertion of carbon monoxide into aryl halides **5**, which can be readily prepared from *o*-bromoaniline derivatives **3** and amino acids **4**. Syntheses of diazepam,[10a] *dl*-cyclopeptine,[10b] *dl*-cyclopenin,[10b] *dl*-cyclopenol[10b] and related metabolites have been achieved by us using this method. This reaction seemed fascinating because many 1,4-benzodiazepine derivatives could be prepared from various amino acids.

Now we would like to report the synthesis of pyrrolo-1,4-benzodiazepines from l-proline and *o*-bromoaniline as a further development of this method. Thus, *o*-bromoaniline was condensed with *N*-benzyloxycarbonyl-l-proline (**4a**′) in the presence of ethyl chloroformate and triethylamine *via* the mixed anhydride, followed by treatment with HBr–AcOH to afford the secondary amine **9** in good yield. When **9** was warmed with a catalytic amount of $Pd(OAc)_2$ and PPh_3 in the presence of n-Bu_3N under 1 atm pressure of carbon monoxide at 120 °C for 26 h, the unexpected compounds **10** and **11** were obtained.[11] The former compound **10** was considered to be a product of intramolecular insertion of carbon monoxide between the nitrogen of the secondary amide and the basic nitrogen of proline of **9**, whereas **11** was an intermolecular insertion product of carbon monoxide at the same nitrogens to generate **12**, followed by removal of the proline part from the imide group, as shown in Chart 2. When hexamethylphosphoramide (HMPA) was used as the solvent, only **10** was obtained.

These results suggest that carbon monoxide reacts preferentially with the secondary

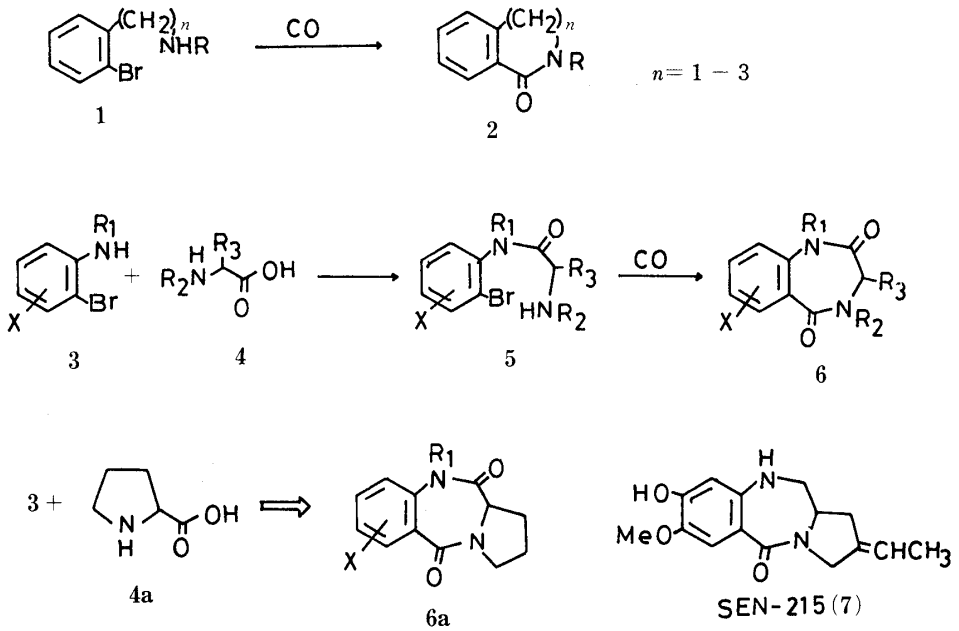


Chart 1

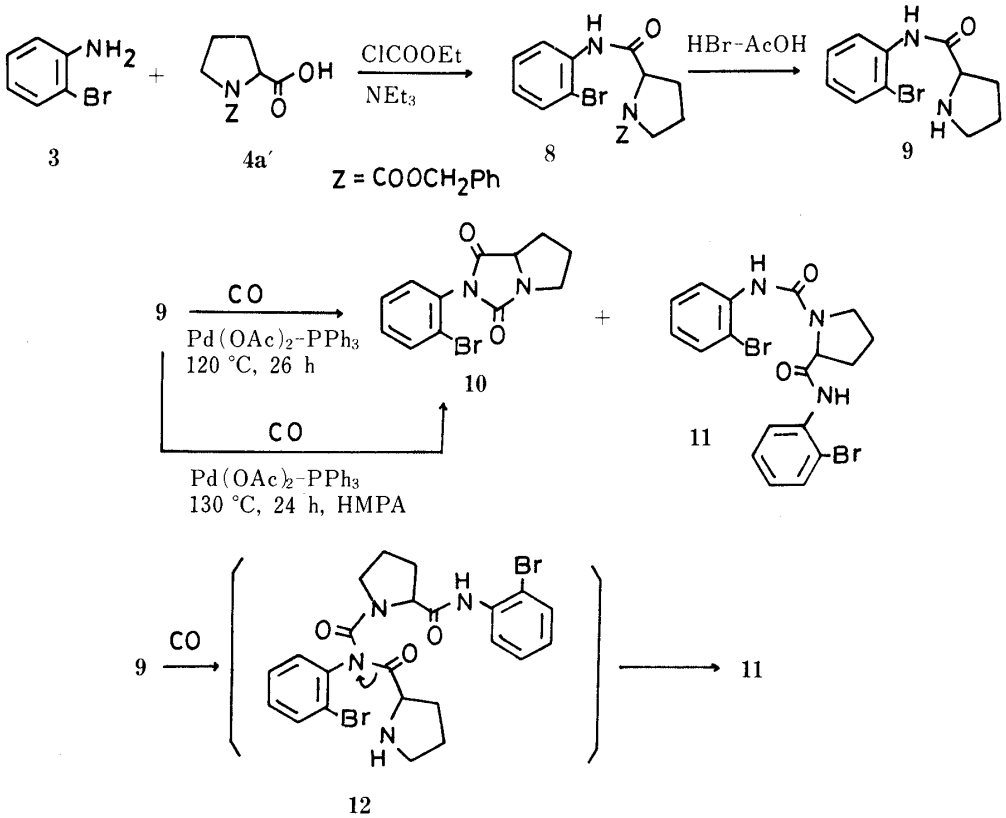


Chart 2

amide to give an imide under these reaction conditions.[12] Therefore, compound **8** was converted to the tertiary amide **8a** by treatment with methyl iodide. Removal of the benzyloxycarbonyl group of **8a** with HBr–AcOH gave **5a**, which was allowed to react with carbon monoxide under the same conditions. However, the expected compound **6a** could not be detected.[11] In order to achieve the total synthesis of SEN-215 (**7**)[7] by use of this method,

the amide should be reduced to the secondary amine. Thus, compound **8** was reduced with $NaBH_4$–AcOH in dioxane[13] to afford **13** in good yield. Acetylation of **13** followed by treatment with HBr–AcOH proceeded smoothly to afford **15a**. The insertion of carbon monoxide into **15a** in the usual manner gave the desired pyrrolo-1,4-benzodiazepine derivative **16a**, but the yield was rather low. The other product **17a** was produced in 14.1% yield by acetyl migration from anilino nitrogen to proline nitrogen, and the quinoxaline derivative **18a**, whose formation mechanism is discussed later, was obtained in 3.4% yield. Benzonitrile was used as a solvent instead of HMPA to afford exclusively the acetyl migration product **17a** in a yield of 42%.

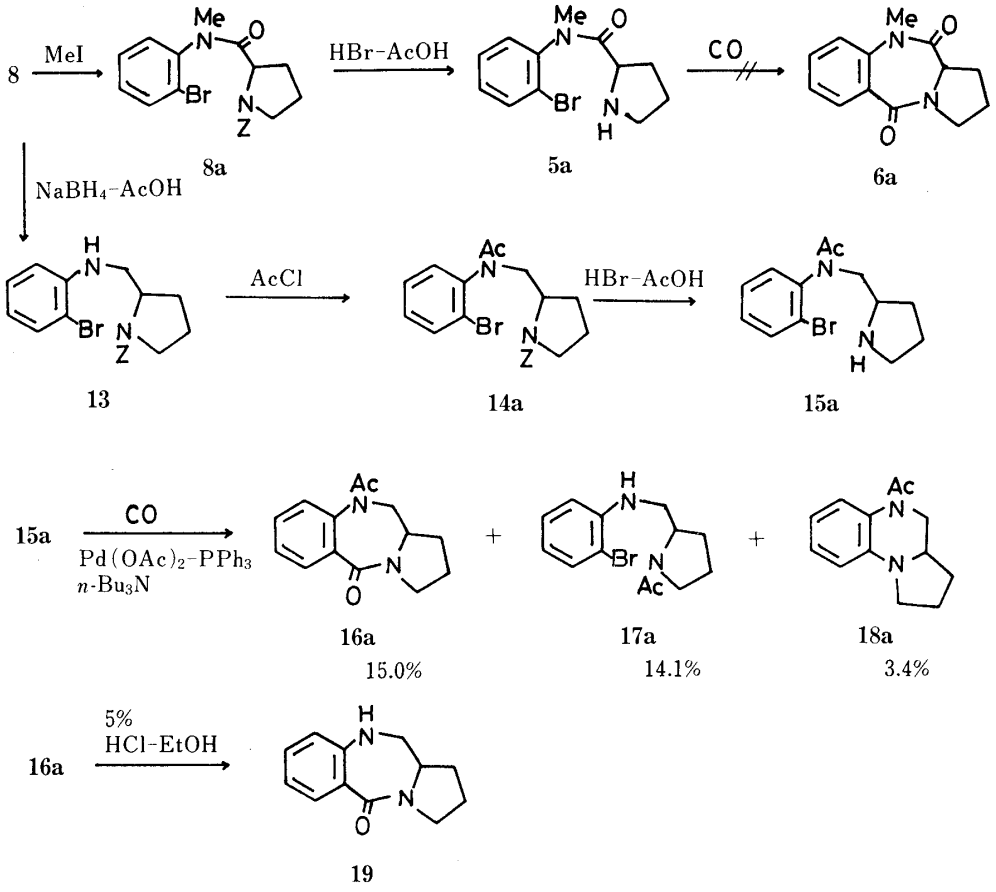


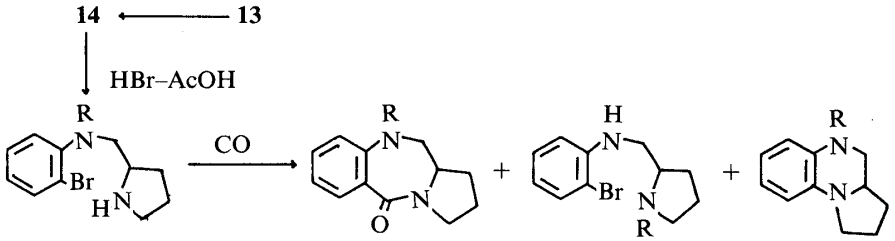
Chart 3

To raise the yield of the desired diazepine derivatives **16**, the substrates **15** with different protecting groups at the anilino nitrogen were allowed to react with carbon monoxide under the conditions described in Table I.

In the case of the N-formyl compound **15b**, the desired diazepine derivative **16b** was not obtained and only formyl migration product **17b** was obtained. Since the benzoyl group is bulkier than the acetyl or formyl group, the formation of the acyl migration product **17c** should be depressed in the carbonylation. As expected, the yield of diazepine derivative **16c** increased to 25.5%, while the yield of the acyl migration product **17c** was 9.3%. As for the catalyst, $Pd(acac)_2$ gave the same results as $Pd(OAc)_2$. The methanesulfonyl amide **15d** gave the diazepine derivative **16d** in an improved yield of 35.0%. Moreover, higher pressure (4—5 atm) of carbon monoxide in the reaction of **15a** and **15b** furnished the desired diazepines, **16a** and **16c**, improved yields of 35 and 54%, respectively.

To elucidate the structure and mechanism of formation of the unusual product **18**,

TABLE I. Palladium-Catalyzed Carbonylation of **15** under Various Conditions



15 **a**: R=Ac
b: R=CHO
c: R=PhCO
d: R=$MeSO_2$

Run	R	Catalyst	Solvent	CO (atm)	Temp. (°C)	Yield (%)		
						16	**17**	**18**
1	Ac	$Pd(OAc)_2$	HMPA	1	110	15.0	14.1	3.4
2	Ac	$Pd(OAc)_2$	PhCN	1	110	—	42.0	—
3	CHO	$Pd(OAc)_2$	HMPA	1	130	—	25.4	—
4	PhCO	$Pd(OAc)_2$	HMPA	1	120	25.5	9.3	5.3
5	PhCO	$Pd(acac)_2$	HMPA	1	120	24.3	8.6	7.3
6	CH_3SO_2	$Pd(acac)_2$	HMPA	1	120	35.0	—	9.0
7	PhCO	$Pd(OAc)_2$	HMPA	4	110	54.0	3.7	3.8
8	Ac	$Pd(OAc)_2$	HMPA	5	110	35.0	—	2.0

TABLE II. Reaction of **15c** under Various Conditions

Run	Catalyst	Atmosphere of	Yield (%)		
			16c	**17c**	**18c**
1	$Pd(acac)_2$	CO	24.3	8.6	7.3
2	$Pd(acac)_2$	Argon		13.1	12.9
3	—	Argon		25.2	4.3

The reaction was carried out at 120 °C.

compound **15c** was warmed in the same manner under an atmosphere of argon without carbon monoxide to afford **17c** and **18c** (Table II). Moreover, when **15c** was heated under an atmosphere of argon without palladium catalyst, only a small amount of **18c** (4.3%) was obtained along with the acyl migration product **17c** (25.2%). Accordingly, though it is not yet clear whether or not palladium catalyst is necessary for the formation of **18**, carbon monoxide was not required at least for the generation of **18**. In accordance with previous reports,[10] these results and the spectral data for **18** suggest that compound **18** is a quinoxaline derivative, which could be generated by replacement of the bromine atom on the aromatic ring with the secondary amino group on the side chain in HMPA. Subsequently, the N-acetyl diazepine derivative **16a** was refluxed with 5% hydrochloric acid in ethanol overnight to afford pyrrolo-1,4-benzodiazepine-2,5-dione (**19**).

These results suggest that pyrrolo-1,4-benzodiazepine derivatives can be easily synthesized by utilizing palladium-catalyzed carbonylation of compound derived from *o*-bromoaniline and L-proline, especially at high pressure of carbon monoxide, and should open up a new synthetic pathway to antibiotics having antitumor activities, such as anthramycin, neothramycin and others.

Experimental

Melting points were measured with a hot-stage microscope (Yanaco MP-J2) and with a Yamato MP-1 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in the indicated solvent on JEOL JNM-FX100 (100 MHz) and Hitachi R-20B (60 MHz) spectrometers with Me_4Si as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are reported in hertz. A JASCO IRA-2 diffraction grating infrared spectrophotometer and Hitachi RMU-7M double focusing mass spectrometer were used to determine infrared (IR) and mass spectra (MS), respectively. For carbonylation, a balloon filled with carbon monoxide was connected to the top of the reaction vassel at 1 atm pressure of carbon monoxide, or a stainless steel tube was used at 4—5 atm pressure of carbon monoxide.

2-Bromo-*N*-[*N*-(benzyloxycarbonyl)prolyl]aniline (8)——Ethyl chloroformate (543 mg, 5 mmol) in THF (2 ml) was added to a solution of 1-benzyloxycarbonylproline (1.246 g, 5 mmol) and triethylamine (520 mg, 5 mmol) in anhydrous THF (10 ml) over 15 min at −20 °C. The mixture was stirred at the same temperature for 5 min, then *o*-bromoaniline (650 mg, 5 mmol) in THF (10 ml) was added to the solution and the whole was stirred at the same temperature for 1 h then at room temperature overnight. The solvent was removed under reduced pressure and water was added to the residue. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with 10% HCl solution, 5% $NaHCO_3$ solution and sat. NaCl solution, then dried over Na_2SO_4 and evaporated. The residual oil was purified by column chromatography on silica gel with benzene–hexane (3 : 1) to give **8** as colorless crystals (314 g, 65.2%), mp 85.0—85.5 °C (from *n*-hexane–ether). IR ν_{max} (Nujol): 3300, 3150 (NH), 1700 (C=O), 1590, 1520 cm^{-1}. NMR ($CDCl_3$) δ: 1.8—2.5 (m, 4H), 3.59 (br t, 2H, NCH_2), 4.52 (m, 1H, NCH), 5.20 (s, 2H, $PhCH_2O$), 6.8—7.6 (m, 3H, aromatic), 8.32 (dd, 1H, aromatic), 8.6 (br s, 1H, NH). MS *m/e*: 404, 402 (M^+), 270, 268 ($M^+ - PhCH_2COO$). *Anal.* Calcd for $C_{19}H_{19}BrN_2O_3$: C, 56.59; H, 4.75; N, 6.95; Br, 19.82. Found, C, 56.66; H, 4.78; N, 7.00; Br, 19.84.

***N*-Benzyloxycarbonyl-2-[(2-bromophenyl)aminomethyl]pyrrolidine (13)**——AcOH (1.5 g, 25 mmol) in dioxane (5 ml) was added to a suspension of **8** (1 g, 2.48 mmol) and $NaBH_4$ (946 mg, 25 mmol) in dioxane (5 ml), and the mixture was stirred at room temperature for 10 min in a water bath then refluxed for 2 h. Ethyl acetate was added to the reaction mixture and water was added carefully. The aqueous layer was acidified with conc. HCl solution and washed with ether. The acidic fraction was made basic with K_2CO_3 and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over K_2CO_3 and evaporated. The residue was purified by column chromatography on alumina with benzene to afford **13** as a colorless oil (589 mg, 76.5%). IR ν_{max} (neat): 3350, 3400 (NH), 1695 (C=O), 1600 cm^{-1}. NMR ($CDCl_3$) δ: 1.7—2.0 (m, 4H), 3.0—3.7 (m, 5H), 4.15 (br s, 1H, NH), 5.20 (s, 2H, $PhCH_2O$), 6.35—7.5 (9H, aromatic). MS *m/e*: 390, 388 (M^+), 391, 389 ($M^+ + 1$), 204, 186, 184. High resolution MS, calcd. for $C_{19}H_{21}BrN_2O_2$ *m/e* 390.0767, 388.0888, found *m/e* 390.0772, 388.0806.

***N*-Benzyloxycarbonyl-2-[*N*-acetyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (14a)**——A solution of acetyl chloride (370 mg, 4.71 mmol) in ether (2 ml) was added to a solution of **13** (917 mg, 2.363 mmol) and K_2CO_3 (662 mg, 4.76 mmol) in acetone (20 ml) and the mixture was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on alumina with *n*-hexane–benzene–ether (2 : 2 : 1) to give **14** as colorless oil (931 mg, 91.5 mmol). IR ν_{max} (neat): 1700 (C=O), 1670 (C=O), 1585 cm^{-1}. NMR ($CDCl_3$) δ: 1.80 (br s, 3H, $COCH_3$), 1.85—2.15 (m, 4H), 3.1—4.5 (m, 5H), 4.8—5.1 (s, 2H, $PhCH_2O$), 7.0—7.8 (9H, aromatic). MS *m/e*: 433, 431 ($M^+ + 1$), 430 (M^+), 297, 295 ($M^+ - COOCH_2Ph$), 230, 228, 217, 204, 160, 91; high resolution MS, calcd. for $C_{21}H_{23}BrN_2O_3$ *m/e*: 432.0871, 430.0891, found *m/e*: 432.0851, 430.0878.

***N*-Benzyloxycarbonyl-2-[*N*-formyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (14b)**——A solution of **13** (836 mg, 2.15 mmol) in formic acid (10 ml) and acetic acid (2 ml) was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on alumina with *n*-hexane–benzene–ether (2 : 2 : 1) to give **14b** as a colorless oil (463 mg, 51.8%). IR ν_{max} (neat): 1690 (C=O), 1580 cm^{-1}. NMR ($CDCl_3$) δ: 1.9—2.1 (m, 4H), 3.25—3.7 (m, 3H), 3.8—4.1 (m, 2H), 5.06 (s, 2H, $PhCH_2O$), 7.1—7.4 (3H, aromatic), 7.5—7.8 (1H, aromatic), 8.19 (br s, 1H, NCHO), MS *m/e*: 419, 417 ($M^+ + 1$), 418, 416 (M^+), 285, 283 ($M^+ - PhCH_2COO$), 217, 204, 186, 184, 160, 105, 91. High resolution MS, calcd. for $C_{20}H_{21}BrN_2O_3$ *m/e* 418.0716, 416.0737, found *m/e* 418.0706, 416.0740.

***N*-Benzyloxycarbonyl-2-[*N*-benzoyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (14c)**——A solution of **13** (321 mg, 0.83 mmol) and benzoyl chloride (232 mg, 1.66 mmol) in benzene (10 ml) was refluxed for 3 h, then allowed to cool. Benzene was added to the reaction mixture and the organic layer was washed with sat. $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on alumina with *n*-hexane–ether (4 : 1) to give **14c** as a colorless viscous oil (337.5 mg, 83.0%). IR ν_{max} (neat): 1690 (C=O), 1650 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.0—2.5 (m, 4H), 3.5—3.8 (m, 2H), 3.9—4.9 (m, 3H), 5.0 and 5.1 (ss, 2H, $PhCH_2O$). MS *m/e*: 495, 493 ($M^+ + 1$), 494, 492 (M^+), 359, 357 ($M^+ - PhCH_2COO$), 291, 289, 290, 288, 277, 275, 218, 204, 160, 105, 91. High resolution MS, calcd. for $C_{20}H_{25}BrN_2O_3$ *m/e* 494.1030, 492.1048, found *m/e* 494.1053, 492.1023.

***N*-Benzyloxycarbonyl-2-[*N*-methanesulfonyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (14d)**——A solution of **13** (688 mg, 1.77 mmol), methanesulfonic anhydride (587 mg, 3.37 mmol) and *n*-Bu_3N (360 mg, 1.95 mmol) in toluene (10 ml) was refluxed for 3 h then allowed to cool. Ethyl acetate was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on alumina with *n*-hexane–ethyl acetate (1 : 1) to give colorless crystals of **14d** (572 mg, 88.0%), mp 131.5—132.5 °C (from ether). IR ν_{max} (Nujol): 1700 (C=O), 1580, 1420, 1340 cm^{-1}. NMR ($CDCl_3$) δ: 1.6—2.4 (m, 4H), 2.96 and 3.09 (s and s, 3H, SO_2CH_3), 3.2—3.5 (m, 2H), 3.5—4.0 (m, 3H), 5.01 (s, 2H, $PhCH_2O$). MS *m/e*: 390, 388 ($M^+ - SO_2CH_3$), 264, 262. *Anal.* Calcd for $C_{20}H_{23}BrN_2O_4S$: C, 51.38; H, 4.96; N, 6.00. Found: C, 51.38; H, 4.84; N, 6.00.

General Procedure for the Removal of the Benzyloxycarbonyl Group of 14——A solution of **14** in 25% HBr–AcOH solution was stirred at room temperature for 1 h. Ether and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was made basic with K_2CO_3 and extracted with ethyl acetate. The organic layer was dried over K_2CO_3 and evaporated to give the desired **15**.

2-[*N*-Acetyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (15a)——A pale yellow oil (**15a**; 601 mg, 94%) was obtained from **14a** (931 mg, 2.17 mmol) in 25% HBr–AcOH solution (6 ml). IR ν_{max} (neat): 3400, 3300 (NH), 1660 (C=O), 1580 cm^{-1}. NMR ($CDCl_3$) δ: 1.4—2.0 (m, 4H), 1.81 (s, 3H, $COCH_3$), 2.42 (s, 1H, NH), 2.7, 3.5 (m, 4H), 3.9—4.5 (m, 1H), 7.2—7.9 (4H, aromatic). MS *m/e*: 299, 297 ($M^+ + 1$), 298, 296 (M^+), 280, 278, 199, 149, 105, 70. High resolution MS, calcd. for $C_{13}H_{17}BrN_2O$ *m/e* 298.0505, 296.0526, found *m/e* 298.0515, 296.0541.

2-[*N*-Formyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (15b)——A colorless oil (**15b**; 197.6 mg, 83.9%) was obtained from **14b** (348 mg, 0.84 mmol) in 25% HBr–AcOH solution (1.5 ml). IR ν_{max} (neat): 3350 (NH), 1680 (C=O), 1580 cm^{-1}. NMR ($CDCl_3$) δ: 1.8—2.0 (m, 4H), 2.24 (s, 1H, NH), 7.2—7.55 (m, 1H, aromatic), 7.75 (m, 1H, aromatic), 8.19 and 8.39 (ss, 1H, NCHO). MS *m/e*: 284, 282 (M^+), 255, 253 ($M^+ - CHO$). High resolution MS calcd. for *m/e* $C_{12}H_{15}BrN_2O$ *m/e* 284.0348, 282.0367, found *m/e* 284.0346, 282.0359.

2-[*N*-Benzoyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (15c)——A colorless oil (**15c**; 318 mg, 97.3%) was obtained from **14c** (449 mg, 0.86 mmol) in 25% HBr–AcOH solution (3 ml), mp 90.5—91.5 °C (from ether). IR ν_{max} (Nujol): 3350 (NH), 1640 (C=O), 1580 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—2.0 (m, 4H), 2.15 (s, 1H, NH), 2.7—3.2 (m, 2H), 3.2—4.7 (m, 2H), 3.8—4.6 (m, 1H). MS *m/e* 361, 359 ($M^+ + 1$), 360, 358 (M^+), 291, 289 (M^+ – pyrrolidine), 290, 288, 210, 105, 91, 70. High resolution MS, calcd. for $C_{18}H_{19}BrN_2O$ *m/e* 360.0660, 358.0680, found *m/e* 360.0658, 358.0674.

2-[*N*-Methanesulfonyl-*N*-(2-bromophenyl)aminomethyl]pyrrolidine (15d)——A pale yellow oil (**15d**; 132 mg, 91%) was obtained from **14d** (197 mg, 0.377 mmol) in 25% HBr–AcOH solution (3 ml) and CH_2Cl_2 (3 ml). IR ν_{max} (neat): 3350 (NH), 1580, 1340, 1160 cm^{-1}. NMR ($CDCl_3$) δ: 1.5—1.9 (m, 4H), 2.45 (2, 1H, NH), 3.10 (s, 3H, SO_2CH_3), 7.1—7.8 (m, 4H, aromatic). MS *m/e*: 305, 303 (M^+), 255, 253 ($M^+ - SO_2CH_3$), 186, 185, 184, 183, 182, 70. High resolution MS calcd. for $C_{12}H_{18}N_2O_2S$ *m/e* 335.0252, 333.0271, found *m/e* 335.0242, 333.0250.

General Procedure for the Carbonylation of 15——A mixture of **15**, $Pd(OAc)_2$ (2—10 mol%), PPh_3 (4—100 mol%), and *n*-Bu_3N (eq. molar) in HMPA was heated under 1—5 atm pressure of carbon monoxide at 100—130 °C, then allowed to cool. Ethyl acetate was added to the reaction mixture. The organic layer was washed with 10% HCl solution and sat. NaCl solution, dried over $MgSO_4$ and concentrated. The residue was purified by preparative thin layer chromatography (TLC) to give **16**, **17** and **18**.

Carbonylation of 15a——Method a: A crude product (prepared from **15a** (96 mg, 0.32 mmol), $Pd(OAc)_2$ (2 mg), PPh_3 (30 mg), *n*-Bu_3N (115 mg, 0.62 mmol) in HMPA (0.5 ml) under 1 atm pressure of carbon monoxide at 110 °C for 17 h) was purified by preparative TLC on alumina with benzene–ether (4 : 1). The first fraction gave **18a** as a viscous oil (2.2 mg, 3.4%). IR ν_{max} ($CHCl_3$): 1640 (C=O), 1600 cm^{-1}. NMR ($CDCl_3$) δ: 2.27 (s, 3H, $COCH_3$) 3.2—3.5 (m, 1H), 3.5—3.7 (m, 1H), 4.1 (br d, 1H), 6.5—7.2 (m, 4H, aromatic). MS *m/e*: 216 (M^+), 201, ($M^+ - CH_3$), 173 ($M^+ - COCH_3$). High resolution MS, calcd. for $C_{13}H_{16}N_2O$, *m/e* 216.1262, found *m/e* 216.1272. The second fraction gave **17a** as a viscous oil (13.8 mg, 14.1%). IR ν_{max} ($CHCl_3$): 3400 (NH), 1625 (C=O), 1595 cm^{-1}. NMR ($CDCl_3$) δ: 2.08 (s, 3H, $COCH_3$), 4.26 (br s, 1H), 5.10 (br s, 1H), 6.5—7.5 (m, 4H, aromatic). MS *m/e*: 298, 296 (M^+). The third fraction gave **16a** as a viscous oil (11.7 mg, 15.0%). IR ν_{max} ($CHCl_3$): 1650, 1630 cm^{-1}. NMR ($CDCl_3$) δ: 1.82 (s, 3H, $COCH_3$), 3.2—3.8 (m, 4H), 4.51 (t, 1H), 6.66 (m, 1H, aromatic), 7.05—7.4 (m, 2H, aromatic), 7.77 (dd, 1H, aromatic). MS *m/e*: 244 (M^+), 201, ($M^+ - COCH_3$). High resolution MS, calcd. for $C_{14}H_{16}N_2O_2$ *m/e* 244.1213, found *m/e* 244.1224.

Method b: A crude product (prepared from **15a** (290 mg, 0.98 mmol), $Pd(OAc)_2$ (22 mg, 0.098 mmol), PPh_3 (257 mg, 0.98 mmol), *n*-Bu_3N (272 mg, 1.47 mmol) in HMPA (2 ml) under 5 atm pressure of carbon monoxide at 100 °C for 20 h) was purified by column chromatography on silica gel with *n*-hexane–acetone (2 : 1) to give **16a** (84 mg, 35%) and **18a** (4 mg, 2%).

Carbonylation of 15b——A crude product (prepared from **15b** (197 mg, 0.696 mmol), $Pd(OAc)_2$ (3 mg) PPh_3 (60 mg) and *n*-Bu_3N (260 mg, 1.39 mmol) in HMPA (0.5 ml) under 1 atm pressure of carbon monoxide at 130 °C for 44 h) was purified by preparative TLC on alumina with ether–benzene (1 : 9) to afford **17b** (70.7 mg, 25.4%). IR ν_{max} (neat): 3400 (NH), 1655 (C=O), 1590 cm^{-1}. NMR ($CDCl_3$) δ: 1.7—2.4 (m, 4H), 3.0—3.7 (m, 3H), 4.6 (bs, 1H), 5.2 (br s, 1H), 6.5—7.6 (m, 4H, aromatic), 8.27 and 8.33 (s and s, 1H, NCHO). MS *m/e*: 284, 282 (M^+), 239, 237, 186,

184, 91. High resolution MS, calcd. for *m/e* $C_{12}H_{15}BrN_2O$ *m/e* 284.0348, 282.0269, found *m/e* 284.0353, 282.0385.

Carbonylation of 15c——Method a: A crude product (prepared from **15c** (100 mg, 0.258 mmol), $Pd(OAc)_2$ (2 mg), PPh_3 (30 mg) and *n*-Bu_3N (80 mg, 0.432 mmol) in HMPA (1 ml) under 1 atm pressure of carbon monoxide at 120 °C for 42 h) was purified by preparative TLC on alumina with *n*-hexane–ether–EtOH (4 : 1 : 0.2). The first fraction gave **18c** as a viscous oil (9.3 mg, 9.3%). IR ν_{max} (neat): 1640 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 2.0—2.4 (m, 4H), 2.50 (t, 1H, J=10 Hz), 3.16 (m, 1H), 3.5—4.0 (m, 2H), 5.03 (dd, J=12, 4 Hz), 6.2—7.2 (9H, aromatic). MS *m/e*: 278 (M^+), 263, 173 (M^+ −PhCO), 158, 145, 105, 77. High resolution MS, calcd. for $C_{18}H_{18}N_2O$ *m/e* 278.1420, found *m/e* 278.1421. The second fraction gave **17c** (3.9 mg, 5.3%). IR ν_{max} (neat): 3400 (NH), 1610 (C=O) cm^{-1}. NMR ($CDCl_3$) δ: 1.8—2.5 (m, 4H), 2.5—2.9 (m, 4H), 4.7 (br s, 1H), 5.2 (br s, 1H, NH), 7.2—7.6 (3H, aromatic), 6.95 (br t, 1H, aromatic), 7.4 (5H, aromatic). MS *m/e*: 360, 358 (M^+). The third fraction gave **16c** as colorless crystals (21.7 mg, 24.5%), mp 225.5—226.5 °C (from *n*-hexane–ethyl acetate). IR ν_{max} (Nujol): 1635 (C=O), 1600 cm^{-1}. NMR ($CDCl_3$) δ: 2.0—2.25 (m, 4H), 3.5—4.0 (m, 4H), 4.38 (t, 1H, J=12 Hz), 6.67 (dd, 1H, aromatic), 7.2 (5H, aromatic), 7.78 (dd, 1H, J=2, 7 Hz, aromatic). MS *m/e*: 306 (M^+), 291 ($M^+ - CH_3$), 236 (M^+ −pyrrolidine), 224, 201 (M^+ −PhCO). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.62; H, 5.80; N, 9.03. Found: C, 74.48; H, 5.93; N, 9.14.

Method b: A crude product (prepared from **15c** (540 mg, 1.5 mmol), $Pd(OAc)_2$ (33 mg, 0.15 mmol), PPh_3 (393 mg, 1.5 mmol) and *n*-Bu_3N (555 mg, 3 mmol) in HMPA (2 ml) under 4 atm pressure of carbon monoxide at 110 °C for 40 h) was purified in the same manner as above to afford **16c** (240 mg, 54%), **17c** (16 mg, 3.8%) and **18c** (20 mg, 3.7%).

Carbonylation of 15d——A crude product (prepared from **15d** (291 mg, 0.877 mmol), Pd $(acac)_2$ (5 mg), PPh_3 (19 mg) and *n*-Bu_3N (246 mg, 1.33 mmol) in HMPA (3 ml) under 1 atm pressure of carbon monoxide at 120 °C for 24 h) was purified by preparative TLC on alumina with *n*-hexane–ether–EtOH (4 : 1 : 0.2). The first fraction gave **18d** as colorless prisms (19.8 mg, 9.0%), mp 132.0—133.0 °C (from *n*-hexane). IR ν_{max} (Nujol): 1600, 1340, 1150 cm^{-1}. NMR ($CDCl_3$) δ: 2.82 (s, 3H, SO_2CH_3), 3.22 (m, 1H), 3.4—3.7 (m, 2H), 4.47 (dd, 1H, J=13, 4 Hz), 6.7 (2H, aromatic), 7.1 (1H, aromatic), 7.52 (dd, 1H, aromatic). MS *m/e*: 152 (M^+), 73 ($M^+ - SO_2CH_3$). *Anal.* Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.32; H, 6.29; N, 11.16. Found, C, 57.12; H, 6.39; N, 11.10. The second fraction gave **16d** as colorless needles (85.9 mg, 35.0%), mp 170.5—171.0 °C (from *n*-hexane–ethyl acetate). IR ν_{max} (Nujol): 1640 (C=O), 1600, 1590, 1340, 1155 cm^{-1}. NMR ($CDCl_3$) δ: 2.82 (s, 3H, SO_2CH_3), 3.22 (m, 1H), 3.4—3.7 (m, 2H), 4.47 (dd, 1H, J=13, 4 Hz), 7.5 (3H, aromatic), 7.75 (m, 1H, aromatic). *Anal.* Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found, C, 55.72; H, 5.67; N, 10.09.

Reaction of 15c in the Presence of $Pd(acac)_2$–PPh_3 under Argon without Carbon Monoxide——A mixture of **15c** (79.5 mg, 0.221 mmol), $Pd(acac)_2$ (1.3 mg), PPh_3 (12 mg) and *n*-Bu_3N (62 mg) in HMPA (0.5 ml) was warmed under argon at 120 °C for 10 h. Ethyl acetate was added, then the organic layer was washed with 10% HCl solution, dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC on alumina with benzene–*n*-hexane–ether (4 : 4 : 1) to afford **18c** (8.1 mg, 12.9%) and **17c** (9.7 mg, 13.1%).

Reaction of 15c in the Presence of *n*-Bu_3N without Pd–Catalyst——A mixture of **15c** (50 mg, 0.129 mmol) and *n*-Bu_3N (40 mg, 0.216 mmol) in HMPA (0.5 ml) was warmed under argon at 120 °C for 17 h. Ethyl acetate was added to the reaction mixture. The organic layer was washed with 10% HCl solution, dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC on alumina with benzene–*n*-hexane–ether (2 : 2 : 1) to give **18c** (1.6 mg, 4.3%) and **17c** (12.6 mg, 25.2%).

1,2,3,10,11,11a-Hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (19)[14]——A solution of **16a** (38 mg) in aqueous 20% EtOH–HCl solution (4 ml) was refluxed overnight. The solvent was removed under reduced pressure, and the residue was dissolved in water. The aqueous layer was washed with ethyl acetate, made basic with K_2CO_3 and extracted with ethyl acetate. The organic layer was dried over K_2CO_3 and evaporated to give **19** as colorless crystals (19 mg, 76%). mp 184.5—186.5 °C (from *n*-hexane–ethyl acetate). IR ν_{max} (Nujol): 3300 (NH), 1608 (C=O), 1595, 1575 cm^{-1}. NMR ($CDCl_3$) δ: 1.6—2.5 (m, 4H), 3.2—4.5 (m, 6H), 6.5—7.0 (2H; aromatic), 7.1—7.25 (1H, aromatic), 8.02 (dd, 1H, aromatic). MS *m/e*, 202 (M^+). High resolution MS, calcd. for $C_{12}H_{14}N_2O$ *m/e* 202.1105, found *m/e* 202.1097.

References and Notes

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2) *a)* A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 1998 (1964); *idem, ibid.*, **31**, 4268 (1966); J. Iacobelli, M. Uskokovic, and W. Wenner, *J. Heterocycl. Chem.*, **2**, 323 (1965); *b)* M. Artico, G. De Martino, R. Giuliano, S. Massa, and G. C. Porretta, *J. Chem. Soc., Chem. Commun.*, **1969**, 671; R. V. Stevens, R. M. Cory, and S. Rossen, *ibid.*, **1975**, 742; M. Miyamoto, H. Naganawa, K. Maeda, M. Ohno, and H. Umezawa, *J. Antibiot.*, **30**, 340 (1979).
3) M. D. Tendler and S. Korman, *Nature* (London), **199**, 501 (1963).
4) M. Miyamoto, S. Kondo, H. Naganawa, K. Maeda, M. Ohno, and H. Umezawa, *J. Antibiot.*, **30**, 349 (1977).

5) K. Arima, M. Kohsaka, G. Murata, H. Imanaka, and H. Sasaki, *J. Antibiot.*, **24**, 437 (1972).
6) A. S. Masentev, V. V. Kuljaeva, and L. M. Rubasheva, *J. Antibiot.*, **27**, 866 (1974).
7) S. Matsumura, Y. Ezure, M. Ozaki, H. Watanabe, and O. Tanabe, Japan Kokai, 56693 (1978) [*Chem. Abstr.*, **89**, 161536 (1978)].
8) L. H. Hurley, *J. Antibiot.*, **30**, 349 (1977).
9) M. Mori, K. Chiba, and Y. Ban, *J. Org. Chem.*, **43**, 1684 (1978).
10) *a*) M. Mori, M. Ishikura, T. Ikeda, and Y. Ban, *Heterocycles*, **16**, 1491 (1981); *b*) M. Ishikura, M. Mori, T. Ikeda, M. Terashima, and Y. Ban, *J. Org. Chem.*, **47**, 2456 (1982); *c*) M. Ishikura, M. Mori, M. Terashima, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, **1982**, 741.
11) M. Mori, K. Chiba, G.-E. Purvaneckas, T. Ikeda, and Y. Ban, 70th meeting of Hokkaido Branch, the Pharmaceutical Society of Japan, Sapporo, 1978.
12) We have developed a synthetic method for cyclic imides from *o*-bromo-*N*-acylaminoalkylbenzenes by utilizing this palladium-catalyzed carbonylation; M. Mori, K. Chiba, N. Ohta, and Y. Ban, *Heterocycles*, **13**, 329 (1980).
13) N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, **1976**, 2875.
14) J. W. Lown and A. V. Joshua, *Biochem. Pharmacol.*, **28**, 2017 (1979).