Stereospecific Synthesis of (*R*)- and (*S*)-Baclofen and (*R*)- and (*S*)-PCPGABA [4-Amino-2-(4-chlorophenyl)butyric Acid] *via* (*R*)- and (*S*)-3-(4-Chlorophenyl)pyrrolidines

Shigeyuki YOSHIFUJI* and Mamoru KANAME

Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920–11, Japan.
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(*R*)- and (*S*)-Baclofen and (*R*)- and (*S*)-PCPGABA [4-amino-2-(4-chlorophenyl)butyric acid] were stereospecifically synthesized *via* (*R*)- and (*S*)-3-(4-chlorophenyl)pyrrolidines, starting from *trans*-4-hydroxy-L-proline. The syntheses involve two key operations, namely, 1) a stereoselective hydrogenation of dehydroproline derivatives controlled by the C-2 carboxyl function and 2) an effective ruthenium tetroxide oxidation to prepare chiral 3- and 4-(4-chlorophenyl)pyrrolidin-2-ones, which are dehydrated precursors of the target molecules.

Key words ruthenium tetroxide oxidation; baclofen; 4-amino-2-(4-chlorophenyl)butyric acid; pyrrolidine synthesis; lactam synthesis; decarboxylation

GABA (γ-aminobutyric acid)[1] is an inhibitory neurotransmitter in the mammalian central nervous system, and is also found in the peripheral tissues, including the lung. Recent pharmacological studies[2] using selective ligands for GABA-A and GABA-B receptors suggest that the GABA-B receptor subtype is a potentially important receptor controlling lung and airway functions, and therefore, GABA-B receptor agonists may have wider applicability as general antitussive drugs. Baclofen [4-amino-3-(4-chlorophenyl)butyric acid] and PCPGABA [4-amino-2-(4-chlorophenyl)butyric acid] are typical GABA-B receptor agonists. Racemic baclofen has been widely used as an antispastic agent. Most of the agonistic activity of baclofen to the GABA-B receptor resides in the (−)-form,[3] which was assigned the (*R*)-configuration on the basis of a crystal X-ray analysis.[4] On the other hand, PCPGABA was used always in the racemic form for pharmacological tests on vagal efferent activity.[5] In view of recent interest in the pharmacology of these compounds, it is necessary to examine the individual enantiomers in more detail and to evaluate the relative activities of baclofen and PCPGABA. For this purpose, enantiomeric forms must be synthesized on a practical scale. One method[3] to prepare optically active baclofen relied on optical resolution by the chromatographic separation of diastereoisomeric derivatives of the racemate. Recently, a synthesis of (*R*)- and (*S*)-baclofen using chemoenzymatic resolution[6] and a stereoselective synthesis of (*R*)-baclofen from (*S*)-glutamic acid[7] have been reported. These methods, however, cannot be directly applied for the preparation of optically active PCPGABA which has not yet been synthesized. We sought an easy access to the four enantiomerically pure isomers of baclofen and PCPGABA for pharmacological research.

We considered the possibility that the (*R*)- and (*S*)-forms of baclofen and PCPGABA might be abreast prepared from (*R*)- and (*S*)-3-(4-chlorophenyl)pyrrolidines, respectively, by utilizing an effective oxidation process to afford the corresponding pyrrolidones, the dehydrated precursors of the targets. One approach would be to use ruthenium tetroxide (RuO_4) oxidation, which is a practical method[8] for synthesizing lactams from the corresponding *N*-protected cyclic amines, oxidizing one of the two methylenes adjacent to the nitrogen atom, and has been investigated by us in the field of amino acid chemistry.[9] Therefore, *N*-protected (*R*)- and (*S*)-3-(4-chlorophenyl)-pyrrolidines are key intermediates for the present work and can be prepared from a chiral source without the need for optical resolution of racemic 3-(4-chlorophenyl)pyrrolidine at the final stage. We used *trans*-4-hydroxy-L-proline as a starting material, since it has the desired pyrrolidine ring system, the proper functionality at the C-4 position for introduction of the 4-chlorophenyl group, and a chiral carboxylic function as a possibe stereocontroller at C-4. We wish to report here asymmetric synthesis of (*R*)- and (*S*)-forms of baclofen and PCBGABA *via* (*R*)- and (*S*)-3-(4-chlorophenyl)pyrrolidines, starting from *trans*-4-hydroxy-L-proline.

Initially, we prepared (*R*)-forms of baclofen and PCPGABA as shown in Chart 2. Commercially available *trans*-4-hydroxy-L-proline (**1**) was converted in 92% yield to the *N*-benzoylated methyl ester **2**,[10] which was oxidized by the Swern protocol[11] to afford the 4-ketoproline derivative **3** in 94% yield. Grignard reaction of the ketone **3** with 4-chlorophenylmagnesium bromide in ether in the presence of cerium chloride ($CeCl_3$)[12] at room tempera-

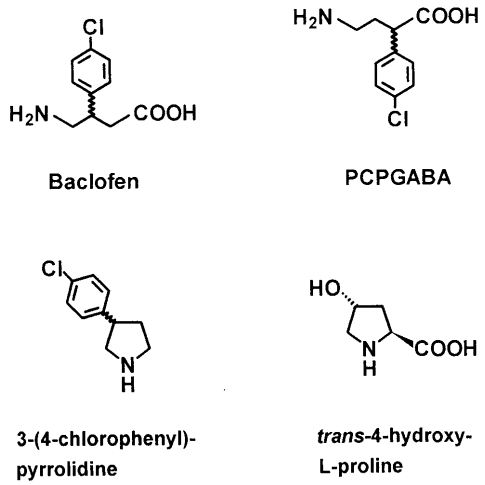

Chart 1

* To whom correspondence should be addressed.

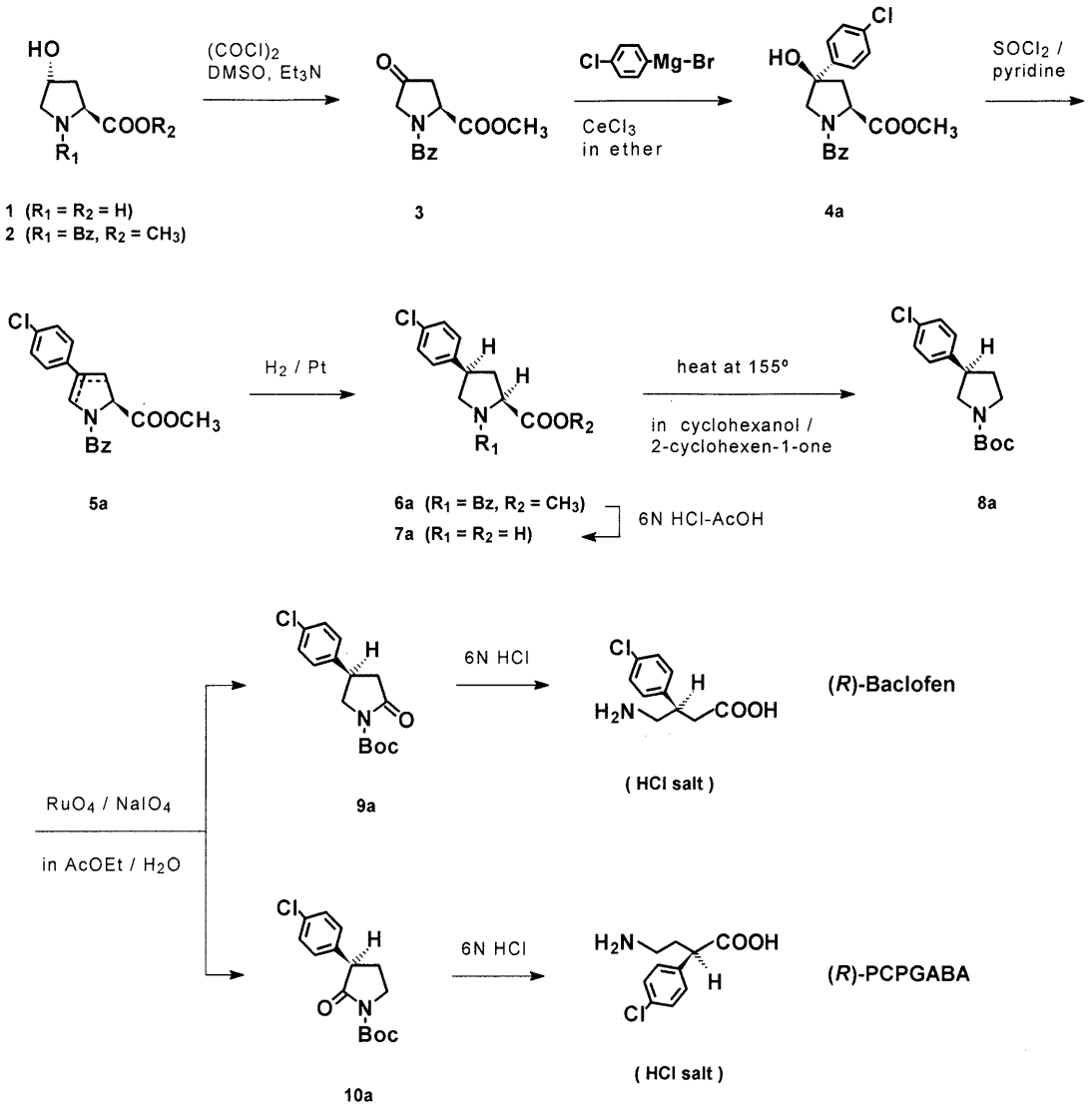

Chart 2

ture proceeded stereoselectively to afford almost a single adduct, **4a** (78% yield), probably having a 2,4-*trans* relationship. Stereochemical assignment at the C-4 position was not required for the next step of olefin construction. The reaction without $CeCl_3$ afforded **4a** in only 45% yield. Since an attempt at direct removal of the hydroxyl function in **4a** using a standard hydrogenolysis method with Pd–C catalyst was unsuccessful, **4a** was treated with a combination of thionyl chloride and pyridine at room temperature to provide a mixture of two isomeric olefins **5a** in 79% yield. Catalytic hydrogenation of the mixture **5a** was accomplished using Pt catalyst at 1 atm to give only one (**6a**) of the possible diastereoisomers in 84% yield after chromatographic purification; its stereochemistry was expected to be (4*R*)-form, due to attack of the hydrogen from the less hindered face. The (4*R*)-configuration was confirmed by the observation of a nuclear Overhauser effect (NOE) between the C_2-H and C_4-H protons in the ^{1}H-NMR spectrum.

N-Deprotection and ester cleavage of **6a** were achieved by hydrolysis in 6 N hydrochloric acid (HCl)–acetic acid (AcOH) at 110 °C and a new analogue of L-proline, (2*S*,4*R*)-4-(4-chlorophenyl)proline (**7a**), was obtained in 83% yield. Decarboxylation of the α-amino acid **7a** to the required chiral pyrrolidine was effected by utilizing Hashimoto's method.[13] Thus, **7a** was heated in cyclohexanol with a catalytic amount of 2-cyclohexen-1-one at 155 °C for 15 h and the resulting product was immediately *N*-protected with a *tert*-butoxycarbonyl (Boc) group to give *N*-Boc-(*R*)-3-(4-chlorophenyl)pyrrolidine **8a** ($[\alpha]_D^{25}$ +18.3° (c=3.0, $CHCl_3$)) in 98% yield (two steps). An efficient transformation of **8a** into the corresponding lactams (**9a** and **10a**) was achieved by RuO_4 oxidation according to our standard procedure[9a] using a catalytic amount of RuO_2·hydrate and an excess of 10% aqueous sodium metaperiodate ($NaIO_4$) in a two-phase system of ethyl acetate (AcOEt)–water. The reaction at room temperature for 3 h gave a mixture of two lactams, which were separated by silica-gel chromatography to provide the (*R*)-4-(4-chlorophenyl)-2-pyrrolidone derivative **9a** (51%) and the (*R*)-3-(4-chlorophenyl)-2-pyrrolidone derivative **10a** (32%) in a ratio of 61 : 39. The location of the lactam carbonyl group of these products was simply determined by comparison of the ^{13}C-NMR chemical shifts (**9a**: 35.87 ppm, **10a**: 49.18 ppm) of the tertiary carbon bearing the chlorophenyl group. Deprotection and hydrolysis of the lactam **9a** in refluxing 6 N HCl for 18 h furnished the required (*R*)-baclofen hydrochloride in

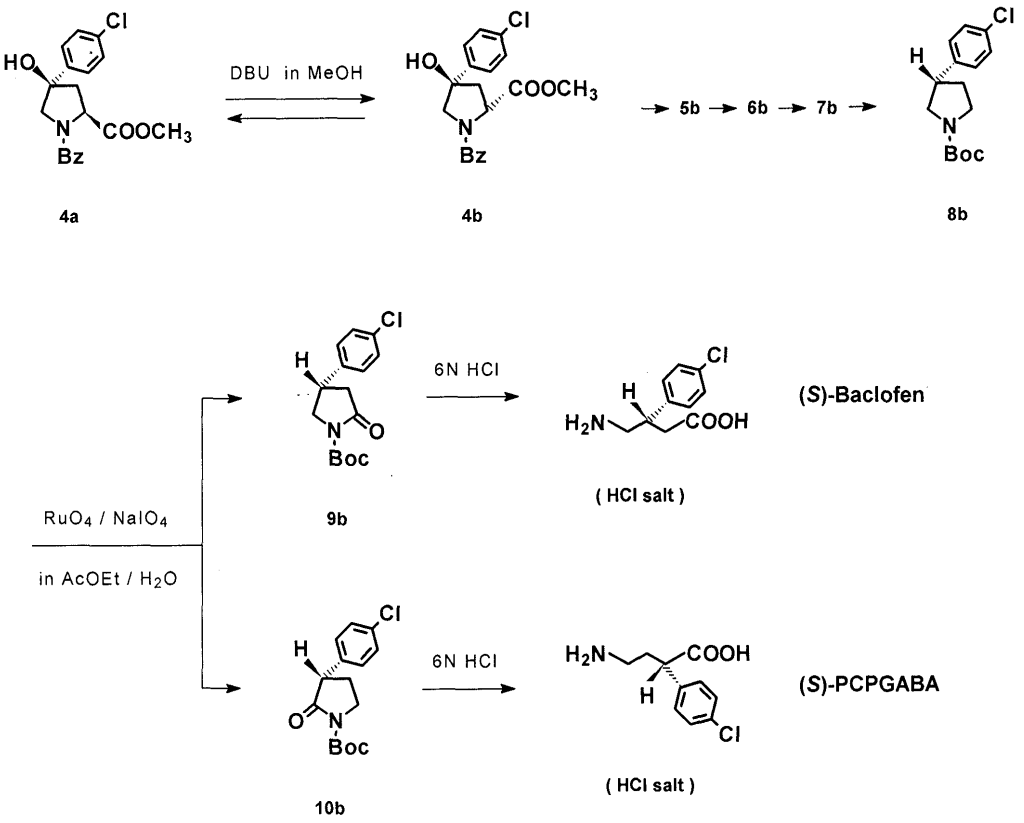

Chart 3

nearly quantitative yield. Our synthetic (*R*)-baclofen hydrochloride ($[\alpha]_D^{25}$ $-1.3°$ ($c=0.2$, H_2O)) was identical (melting point, spectral data, optical rotation) with authentic (*R*)-baclofen hydrochloride[3,6,7] (lit.[6] $[\alpha]_D^{25}$ $-1.5°$ ($c=0.2$, H_2O)). Since the rotation value of (*R*)-baclofen hydrochloride is small, the *N*-Boc derivative of (*R*)-baclofen was also synthesized from the lactam **9a** by selective hydrolysis of the lactam ring with 1 N lithium hydroxide (LiOH)[14] in tetrahydrofuran (THF) at room temperature for 1.5 h. The *N*-Boc-(*R*)-baclofen obtained in 87% yield showed an optical rotation of $[\alpha]_D^{21}$ $+13.2°$ ($c=0.2$, methanol) (lit.[7] $[\alpha]_D^{20}$ $+14°$ ($c=0.2$, methanol)). On the other hand, the regioisomeric lactam **10a** was treated in refluxing 6 N HCl to afford the desired novel (*R*)-PCPGABA hydrochloride ($[\alpha]_D^{26}$ $-39.3°$ ($c=1.0$, H_2O)) in 99% yield; its structure was determined on the basis of analytical and spectral properties. Thus, efficient preparation of the (*R*)-forms of baclofen and PCPGABA was achieved.

Next, our efforts were directed to the synthesis of the (*S*)-forms of baclofen and PCPGABA from the same chiral source, *trans*-4-hydroxy-L-proline (**1**). For this purpose, epimerization at the C-2 position of the Grignard adduct **4a** in the (*R*)-series was required. Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing methanol for 3 d, (2*S*)-form **4a** underwent epimerization to give an equilibrated mixture of two diastereoisomers (**4a** and **b**, Chart 3), from which the pure (2*R*)-form **4b** was isolated in 54% yield by chromatography on silica gel. The yield of **4b** was raised to 74% when **4a** recovered from the mixture was repeatedly subjected to the same epimerization. From the epimer **4b**, the key compound, *N*-Boc-(*S*)-3-(4-chlorophenyl)pyrrolidine (**8b**), was synthesized through the same sequence (**4b**→**5b**→**6b**→**7b**→**8b**) as used in the (*R*)-series and exhibited spectral properties in accordance with those of the (3*R*)-form **8a**, except for the sign of the optical rotation ($[\alpha]_D^{25}$ $-18.0°$ ($c=1.0$, $CHCl_3$)). RuO_4 oxidation of **8b** afforded a mixture of the (*S*)-4-(4-chlorophenyl)-2-pyrrolidone derivative **9b** (48%) and the (*S*)-3-(4-chlorophenyl)-2-pyrrolidone derivative **10b** (34%) in a ratio of 59:41. These lactams were hydrolyzed in refluxing 6 N HCl for 18 h to provide (*S*)-baclofen hydrochloride [97% yield, $[\alpha]_D^{25}$ $+2.0°$ ($c=0.2$, H_2O), (lit.[6] $[\alpha]_D^{25}$ $+1.5°$ ($c=0.2$, H_2O))] and a novel (*S*)-PCPGABA hydrochloride [98% yield, $[\alpha]_D^{22}$ $+39.1°$ ($c=1.0$, H_2O)], respectively.

In summary, we have developed a new synthetic method for (*R*)- and (*S*)-baclofen and PCPGABA from *trans*-4-hydroxy-L-proline. The route described above is potentially applicable to the preparation of any of the baclofen-type compounds and optically active 3-substituted pyrrolidines.

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. MS were obtained on a JEOL JMS-DX300 spectrometer. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL PMX-60-SI or JNM-EX90A or JNM-GSX-400 spectrometer using tetramethylsilane as an internal standard. ^{13}C-NMR spectra were measured on a JEOL JNM-GSX-400 spectrometer. The following abbreviations are used: m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet, and br s = broad singlet. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck). Flash chromatography was performed on silica gel (Silica gel 60, 230—400 mesh, Nacalai Tesque).

Methyl (2*S*,4*R*)-1-Benzoyl-4-hydroxy-2-pyrrolidinecarboxylate (2)

Compound **2** was prepared from commercial *trans*-4-hydroxy-L-proline (**1**) by esterification (quantitative yield) with thionyl chloride–methanol, followed by acylation (92% yield) with benzoyl chloride under basic conditions (aqueous Na_2CO_3, 0 °C, 4 h). Colorless needles, mp 144—145 °C (benzene) (lit.[10] 145—146 °C), $[\alpha]_D^{24}$ −148.5° (c=1.16, EtOH) (lit.[10] $[\alpha]_D^{26}$ −139.2° (c=1.15, EtOH)). MS m/z: 249 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3472, 1742, 1612. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.61 (2H, m), 3.17—3.90 (6H, m), 4.40 (1H, m), 4.81 (1H, t), 7.27—7.70 (5H, m).

Methyl (2*S*)-1-Benzoyl-4-oxo-2-pyrrolidinecarboxylate (3) A solution of dimethyl sulfoxide (42 ml, 0.59 mol) in CH_2Cl_2 (130 ml) was added to a stirred solution of oxalyl chloride (25 ml, 0.29 mol) in CH_2Cl_2 (625 ml) at −50 to −60 °C. A solution of **2** (62.3 g, 0.25 mol) in CH_2Cl_2 (250 ml) was added dropwise to the above solution over a period of 4 h and the mixture was stirred for an additional 2 h. Triethylamine (166 ml, 1.25 mol) was added dropwise with stirring for 4 h, and the whole was allowed to warm to room temperature. Water (800 ml) was added to the reaction solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (500 ml × 2). The extracts were combined with the original CH_2Cl_2 solution and washed successively with 10% HCl, saturated aqueous $NaHCO_3$, and water. The solution was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to leave an oil, which was purified by column chromatography (AcOEt–hexane, 1 : 2, v/v) to give **3** (58.1 g, 94%) as a colorless oil, $[\alpha]_D^{25}$ +26.1° (c=1.02, $CHCl_3$). MS m/z: 247 (M^+). IR ν_{max}^{neat} cm^{-1}: 1764, 1746, 1648. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (1H, dd, J=3.7, 19.0 Hz), 3.00 (1H, dd, J=9.6, 19.0 Hz), 3.69 (3H, s), 3.97 (2H, br s), 5.17 (1H, dd, J=3.7, 9.6 Hz), 7.46 (5H, br s). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.80; H, 5.21; N, 5.49.

Methyl (2*S*,4*R*)-1-Benzoyl-4-(4-chlorophenyl)-4-hydroxy-2-pyrrolidinecarboxylate (4a) Initially, $CeCl_3$·heptahydrate (9.32 g, 25 mmol) was dried by heating at 140 °C *in vacuo*, and dry ether (200 ml) was added under an argon atmosphere. A solution of the ketone **3** (6.18 g, 25 mmol) in dry ether (175 ml) was added to the $CeCl_3$ solution at 0 °C, and then 4-chlorophenylmagnesium bromide (1.0 M in ether) (25 ml, 25 mmol) was added dropwise with stirring at −50 °C. The reaction mixture was allowed to stand with stirring at room temperature for 3 h. After the reaction was completed, 10% aqueous ammonium chloride (250 ml) was added dropwise to the reaction mixture under ice-cooling. The precipitate was collected by filtration with Hyflo Super-cel (Johns–Manville) and well washed with ether (200 ml). The filtrate was transferred to a separatory funnel and the ether layer was separated. The aqueous layer was extracted with ether (300 ml × 2). The combined ether solution was washed successively with 1 N NaOH, 2% HCl, and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (AcOEt–hexane, 1 : 2, v/v) to give **4a** (7.02 g, 78%). Colorless needles, mp 171—171.5 °C (benzene–hexane), $[\alpha]_D^{26}$ −36.0° (c=1.0, $CHCl_3$). MS m/z: 359 (M^+), 361 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 3288, 1740, 1602. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (1H, dd, J=3.6, 14.1 Hz), 2.72 (1H, dd, J=9.7, 14.1 Hz), 3.63—4.14 (2H, m), 3.87 (3H, s), 4.85 (1H, dd, J=3.6, 9.7 Hz), 4.15—4.93 (1H, br s), 7.14—7.71 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 42.37 (t), 53.11 (q), 58.84 (t), 63.58 (d), 79.78 (s), 126.71 (d), 127.19 (d), 128.44 (d), 128.64 (d), 130.53 (d), 133.75 (s), 135.24 (s), 139.30 (s), 169.94 (s). *Anal.* Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.68; H, 5.03; N, 3.77.

Formation of Two Isomeric Olefins (5a) A solution of **4a** (5.58 g, 15.5 mmol) in pyridine (50 ml) was stirred under cooling at −40 °C. Thionyl chloride (1.35 ml, 18.6 mmol) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 1 h. The mixture was concentrated under reduced pressure. The residue was mixed with $CHCl_3$ (160 ml) and 5% HCl (80 ml), and after vigorous shaking, two layers were separated. The aqueous layer was extracted with $CHCl_3$ (160 ml × 2). The combined $CHCl_3$ solution was washed with saturated aqueous $NaHCO_3$ (80 ml) and brine (80 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was separated by column chromatography (AcOEt–hexane, 1 : 1, v/v) to give a *ca.* 1 : 1 mixture of two isomeric olefins **5a** (4.19 g, 79%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.25 and 5.63 (total *ca.* 0.5H, each m, C_3-H in 3,4-dehydro compound, rotamer), 6.05 and 6.21 (total *ca.* 0.5H, each br s, C_5-H in 4,5-dehydro compound, rotamer).

Methyl (2*S*,4*R*)-1-Benzoyl-4-(4-chlorophenyl)-2-pyrrolidinecarboxylate (6a) The mixture of olefins **5a** (2.49 g, 7.9 mmol) was hydrogenated in methanol (50 ml) using PtO_2 (249 mg) for 18 h under 1 atm of H_2. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (AcOEt–hexane, 1 : 2, v/v) to give **6a** (2.10 g, 84%) as a white solid. Recrystallization of the solid from methanol furnished an analytical sample of **6a**. Colorless needles, mp 124—125.5 °C (methanol), $[\alpha]_D^{21}$ −22.2° (c=1.0, $CHCl_3$). MS m/z: 343 (M^+), 345 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 1742, 1634. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.19 (1H, m, C_3-*trans*H), 2.71—2.77 (1H, m, C_3-*cis*H), 3.30—3.39 (1H, m, C_4-H), 3.62—3.91 (2H, m, C_5-H_2), 3.80 (3H, s, $COOCH_3$), 4.80 (1H, dd, J=7.7, 10.3 Hz, C_2-H), 7.14—7.62 (9H, m, aromatic protons). NOE experiment: when the C_2-H was irradiated, strong difference NOE was seen at the C_3-*cis*H, together with weak difference NOE at the C_4-H. While, irradiation of the C_3-*cis*H gave strong difference NOE at the C_4-H and C_2-H. ^{13}C-NMR ($CDCl_3$) δ: 36.25 (t), 43.96 (d), 52.41 (q), 56.41 (t), 59.34 (d), 127.57 (d), 128.31 (d), 128.51 (d), 128.89 (d), 130.59 (d), 133.14 (s), 135.50 (s), 137.04 (s), 169.37 (s), 172.39 (s). *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.43; H, 5.34; N, 4.10.

(2*S*,4*R*)-4-(4-Chlorophenyl)-2-pyrrolidinecarboxylic Acid (7a) A solution of **6a** (3.42 g, 10 mmol) in a mixture of 6 N HCl (75 ml) and AcOH (75 ml) was heated at 110 °C (oil bath) for 12 h, and then concentrated under reduced pressure. The residue was diluted with 6 N HCl (800 ml), and washed with ether (100 ml × 2). The aqueous solution was concentrated under reduced pressure to give (2*S*,4*R*)-4-(4-chlorophenyl)-2-pyrrolidinecarboxylic acid hydrochloride (2.22 g, 85%), which was dissolved in H_2O (300 ml). The solution was adjusted to pH 4 with K_2CO_3 under cooling and allowed to stand overnight in a refrigerator (5 °C) to give crystals. The crystals were collected, washed with H_2O (50 ml), and dried to give **7a** (1.86 g, 83%). Colorless needles, mp 260—261 °C (H_2O). $[\alpha]_D^{20}$ −32.3° (c=0.78, AcOH). MS m/z: 225 (M^+), 227 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 3512, 1620. ^{1}H-NMR (CD_3COOD) δ: 2.17—2.26 (1H, m), 2.82—2.88 (1H, m), 3.44 (1H, dd, J=11.2, 11.4 Hz), 3.60—3.70 (1H, m), 3.88 (1H, dd, J=7.4, 11.2 Hz), 4.59 (1H, dd, J=7.7, 10.1 Hz), 7.29 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz). ^{13}C-NMR (CD_3COOD) δ: 37.55 (t), 44.73 (d), 52.76 (t), 63.10 (d), 130.25 (d), 130.33 (d), 134.55 (s), 138.07 (s), 174.79 (s). *Anal.* Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.44; H, 5.24; N, 6.42.

(3*R*)-1-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)pyrrolidine (8a) A mixture of **7a** (2.26 g, 10 mmol), cyclohexanol (10 ml) and 2-cyclohexen-1-one (0.1 ml) was heated in an oil bath (155 °C) for 15 h. The homogenized reaction solution was cooled to room temperature, diluted with hexane (20 ml), and extracted with 6 N HCl (30 ml × 3). The acidic solutions were combined and concentrated under reduced pressure to give (3*R*)-3-(4-chlorophenyl)pyrrolidine hydrochloride (2.32 g) as a hard brown oil, which was dissolved in water (5 ml). A solution of triethylamine (2.23 g, 22 mmol) in 1,4-dioxane (2.5 ml) and a solution of Boc_2O (2.62 g, 12 mmol) in 1,4-dioxane (2.5 ml) were added dropwise to the stirred solution of the hydrochloride. The reaction solution was stirred at room temperature for 48 h, then concentrated under reduced pressure. The residue was diluted with water (100 ml) and extracted with AcOEt (200 ml × 2). The combined AcOEt extract was washed successively with 5% HCl (80 ml), saturated aqueous $NaHCO_3$ (80 ml), and brine (80 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography (AcOEt–hexane, 1 : 5, v/v) to give **8a** (2.77 g, 98% for two steps). Colorless prisms, mp 58—60.5 °C (hexane), $[\alpha]_D^{25}$ +18.3° (c=3.0, $CHCl_3$). MS m/z: 281 (M^+), 283 (M^++2). IR ν_{max}^{neat} cm^{-1}: 1692. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.88—1.98 (1H, m), 2.18—2.30 (1H, m), 3.21—3.83 (5H, m), 7.16 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 28.54 (q), 32.44 and 33.33 (each t, rotamer), 42.74 and 43.67 (each d), 45.54 and 45.83 (each t), 51.75 and 52.44 (each t), 79.30 (s), 128.40 (d), 128.70 (d), 132.47 (s), 140.00 (s), 154.45 (s). *Anal.* Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.91; H, 7.22; N, 4.93.

RuO_4 Oxidation of 8a [Preparation of (4*R*)-1-*tert*-Butoxycarbonyl-4-(4-chlorophenyl)-2-pyrrolidone (9a) and (3*R*)-1-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)-2-pyrrolidone (10a)] A solution of **8a** (2.25 g, 8 mmol) in AcOEt (27 ml) was added to a mixture of RuO_2·hydrate (67 mg) and 10% aqueous $NaIO_4$ (80 ml). The mixture was vigorously stirred at room temperature for 3 h in a sealed flask. The two layers were separated and the aqueous layer was extracted with AcOEt (40 ml × 2). The combined organic solution was treated with isopropyl alcohol (2 ml) for 2 h in order to decompose the oxidant (RuO_4), and then the black RuO_2 was filtered off. The filtrate was washed with H_2O (40 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a brown oil, which was separated by column chromatography (AcOEt–hexane, 1 : 5,

v/v) to give **10a** (0.75 g, 32% from the first fractions) and **9a** (1.20 g, 51% from the second fractions).

9a: Colorless plates, mp 103—103.5 °C (isopropyl ether–hexane) (lit.[7] mp 103 °C), $[\alpha]_D^{25}$ +4.4° (c=0.2, $CHCl_3$) (lit.[7] $[\alpha]_D^{20}$ +4.5° (c=0.2, $CHCl_3$)). MS m/z: 295 (M^+), 297 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 1788. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s), 2.67 (1H, m), 2.90 (1H, m), 3.52 (1H, m), 3.66 (1H, dd, J=8.3, 10.8 Hz), 4.15 (1H, dd, J=8.1, 10.8 Hz), 7.18 (2H, d, J=8.5 Hz), 7.33 (2H, d, J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 28.04 (q), 35.87 (d), 40.22 (t), 52.94 (t), 83.24 (s), 128.13 (d), 129.16 (d), 133.29 (s), 139.10 (s), 149.83 (s), 172.57 (s). *Anal.* Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.95; H, 6.24; N, 5.06.

10a: Colorless needles, mp 116—117 °C (isopropyl ether), $[\alpha]_D^{25}$ +4.3° (c=1.0, $CHCl_3$). MS m/z: 295 (M^+), 297 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 1776. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s), 2.09—2.19 (1H, m), 2.42—2.50 (1H, m), 3.68—3.76 (2H, m), 3.88—3.93 (1H, m), 7.21 (2H, d, J=8.6 Hz), 7.32 (2H, d, J=8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.56 (t), 28.04 (q), 44.32 (t), 49.18 (d), 83.20 (s), 128.87 (d), 129.46 (d),133.33 (s), 136.00 (s), 150.33 (s), 173.25 (s). *Anal.* Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.96; H, 6.19; N, 5.00.

(*R*)-Baclofen Hydrochloride A mixture of **9a** (1.48 g, 5 mmol) and 6 N HCl (50 ml) was heated under reflux for 18 h. The reaction mixture was washed with ether (50 ml × 2) and evaporated *in vacuo* to give (*R*)-baclofen hydrochloride (1.26 g, quantitative) as a white solid. Recrystallization of the solid from ethanol–ether afforded an analytical sample. Colorless powder, mp 215 °C (EtOH–ether) (lit.[6] mp 215 °C), $[\alpha]_D^{25}$ −1.3° (c=0.2, H_2O) (lit.[6] $[\alpha]_D^{25}$ −1.5° (c=0.2, H_2O)). MS m/z: 213 (M^+−HCl), 215 (M^++2−HCl). IR ν_{max}^{KBr} cm^{-1}: 3084, 1724. ^{1}H-NMR (D_2O) δ: 2.64—2.75 (2H, m), 3.10—3.40 (3H, m), 7.22 (2H, d, J=9.1 Hz), 7.35 (2H, d, J=9.1 Hz). ^{13}C-NMR (D_2O) δ: 38.90 (t), 40.13 (d), 44.42 (t), 130.08 (d), 130.26 (d), 134.14 (s), 137.81 (s), 175.91 (s). *Anal.* Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; N, 5.60. Found: C, 47.99; H, 5.02; N, 5.64.

***N*-*tert*-Butoxycarbonyl-(*R*)-baclofen** The lactam **9a** (414 mg, 1.4 mmol) was treated with 1 N LiOH (4.2 ml) for 1.5 h at room temperature,[14] and the crude product was purified by recrystallization from $CHCl_3$–hexane to give *N*-Boc-(*R*)-baclofen (381 mg, 87%). Colorless needles, mp 135—138 °C ($CHCl_3$–hexane). (lit.[7] mp 135—138 °C), $[\alpha]_D^{21}$ +13.2° (c=0.2, methanol) (lit.[7] $[\alpha]_D^{20}$ +14° (c=0.2, methanol)). MS m/z: 313 (M^+). *Anal.* Calcd for $C_{15}H_{20}ClNO_4$: C, 57.42; H, 6.42; N, 4.46. Found: C, 57.06; H, 6.28; N, 4.71. Spectral data (IR and ^{1}H- and ^{13}C-NMR) were in accord with the reported data.[7]

(*R*)-PCPGABA Hydrochloride A mixture of **10a** (148 mg, 0.5 mmol) and 6 N HCl (5 ml) was heated under reflux for 18 h. The reaction mixture was washed with Et_2O (10 ml × 2) and evaporated *in vacuo* to give (*R*)-PCPGABA hydrochloride (124 mg, 99%) as a white solid. Recrystallization of the solid from ethanol–ether afforded an analytical sample. Colorless powder, mp 168—170.5 °C (EtOH–ether), $[\alpha]_D^{26}$ −39.3° (c=1.0, H_2O). MS m/z: 213 (M^+−HCl), 215 (M^++2−HCl). IR ν_{max}^{KBr} cm^{-1}: 3128, 1702. ^{1}H-NMR (D_2O) δ: 1.80—3.05 (4H, m), 3.70 (1H, dd, J=6.9, 8.1 Hz), 7.19 (2H, d, J=9.0 Hz), 7.32 (2H, d, J=9.0 Hz). ^{13}C-NMR (D_2O) δ: 30.12 (t), 37.88 (t), 48.20 (d), 129.53 (d), 129.89 (d), 133.62 (s), 136.45 (s), 176.97 (s). *Anal.* Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; N, 5.60. Found: C, 47.81; H, 5.05; N, 5.78.

Methyl (2*R*,4*R*)-1-Benzoyl-4-(4-chlorophenyl)-4-hydroxy-2-pyrrolidinecarboxylate (4b) A mixture of **4a** (360 mg, 1.0 mmol), methanol (10 ml) and DBU (0.15 ml) was refluxed for 3 d, then evaporated, and the resulting residue was diluted with $CHCl_3$ (50 ml), and washed successively with 5% HCl (10 ml) and brine (10 ml). The organic solution was dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to give the residue, which was separated by flash chromatography (AcOEt–hexane, 1:4, v/v) to provide the starting **4a** (157 mg, 44%) and an epimer **4b** (193 mg, 54%). The recovered **4a** was treated in the same way to give additional **4b** (74 mg, 20%) (total yield of **4b** was 74%). Colorless powder, mp 187—188 °C (benzene), $[\alpha]_D^{26}$ +16.6° (c=1.0, $CHCl_3$). MS m/z: 359 (M^+), 361 (M^++2). IR ν_{max}^{KBr} cm^{-1}: 3460, 1762, 1628. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (1H, dd, J=9.9, 11.4 Hz), 2.62 (1H, dd, J=7.7, 11.4 Hz), 2.69 (1H, s), 3.74 (1H, d, J=11.2 Hz), 3.81 (3H, s), 3.98 (1H, d, J=11.2 Hz), 5.02 (1H, dd, J=7.7, 9.9 Hz), 7.31—7.56 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 42.67 (t), 52.47 (q), 58.81 (d), 62.85 (t), 79.59 (s), 126.78 (d), 127.54 (d), 128.28 (d), 128.57 (d), 130.60 (d), 133.71 (s), 135.08 (s), 139.69 (s), 170.38 (s), 172.70 (s). *Anal.* Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.17; H, 5.07; N, 3.99.

Syntheses of (*S*)-Series Compounds (*S*)-Forms of baclofen and PCPGABA and their intermediates (**5b**—**10b**) were synthesized by the same procedures as used for the (*R*)-series of compounds described above. Spectral data (MS, IR, ^{1}H- and ^{13}C-NMR) of these compounds were identical with those of the (*R*)-series. Other data are reported below.

Methyl (2*R*,4*S*)-1-Benzoyl-4-(4-chlorophenyl)-2-pyrrolidinecarboxylate (6b) Yield 94% (from **4b**). Colorless needles, mp 124—125 °C (methanol), $[\alpha]_D^{26}$ +26.3° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.67; H, 5.43; N, 4.31.

(2*R*,4*S*)-4-(4-Chlorophenyl)-2-pyrrolidinecarboxylic Acid (7b) Yield 76%. Colorless needles, mp 260—261 °C (H_2O), $[\alpha]_D^{26}$ +26.0° (c=0.73, AcOH). *Anal.* Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.40; H, 5.24; N, 6.16.

(3*S*)-1-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)pyrrolidine (8b) Yield 81% (2 steps). Colorless prisms, mp 58—59 °C (hexane), $[\alpha]_D^{25}$ −18.0° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 64.03; H, 7.30; N, 5.07.

RuO_4 Oxidation of 8b [Preparation of (4*S*)-1-*tert*-Butoxycarbonyl-4-(4-chlorophenyl)-2-pyrrolidone (9b) and (3*S*)-1-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)-2-pyrrolidone (10b)] RuO_4 oxidation of **8b** gave **9b** (48%) and **10b** (34%) in a ratio of 59:41.

9b: Colorless needles, mp 101.5—102.5 °C (isopropyl ether–hexane), $[\alpha]_D^{25}$ −5.3° (c=0.2, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 61.19; H, 6.12; N, 4.72.

10b: Colorless needles, mp 116—117 °C (isopropyl ether), $[\alpha]_D^{25}$ −3.6° (c=0.36, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.83; H, 6.19; N, 4.68.

(*S*)-Baclofen Hydrochloride Yield 97%. Colorless powder, mp 215 °C (EtOH–ether) (lit.[6] mp 215 °C), $[\alpha]_D^{25}$ +2.0° (c=0.2, H_2O) (lit.[6] $[\alpha]_D^{25}$ +1.5° (c=0.2, H_2O)). *Anal.* Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; N, 5.60. Found: C, 47.96; H, 5.28; N, 5.83.

(*S*)-PCPGABA Hydrochloride Yield 98%. Colorless powder, mp 168—170 °C (EtOH–ether), $[\alpha]_D^{22}$ +39.1° (c=1.0, H_2O). *Anal.* Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; N, 5.60. Found: C, 47.96; H, 5.27; N, 5.58.

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