[Chem. Pharm. Bull. 34(7)2852—2858(1986)]

Design and Synthesis of *N*-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine (CV-3317), a New, Potent Angiotensin Converting Enzyme Inhibitor[1)]

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(Received December 9, 1985)

A new angiotensin converting enzyme (ACE) inhibitor, *N*-[*N*-[(*S*)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine (**9a**), was found as a result of extensive studies on the structural requisites for the C-terminal amino acid moiety in ACE inhibitors. The synthesis and the determination of the absolute configuration of **9a** are described.

Keywords——angiotensin converting enzyme (ACE); enzyme inhibitor; ACE inhibitor; CV-3317; indanylglycine; antihypertensive; prodrug; drug design

Since the discovery of captopril (**1**) by Ondetti *et al.*,[2)] angiotensin converting enzyme (ACE) inhibitors have occupied an important position in hypertension therapy. Captopril was discovered as a result of extensive modifications of a snake venom polypeptide. Most of the active compounds found during subsequent investigations involve proline as the C-terminal amino acid.[3,4)] To determine whether this proline is essential for the activity, we undertook to replace the proline moiety of **1** with a variety of unnatural amino acids, and found that the derivatives of 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**2**) exhibit potent ACE inhibitory activities.[5)] Investigation of the structure–activity relations among more than eighty derivatives of **2** revealed that introducing a hydrophobic bulky group (R_3) at the 7-position and 1-methyl substitution ($R_5 = CH_3$) with *R*-configuration tends to enhance the activity. Based on these results, we postulated the existence of a hydrophobic pocket in the area of the substituents at the 1, 7 and 8 positions (R_5, R_3, R_4) and envisaged a tetracyclic structure (**3**) as an active compound. Furthermore, to afford some conformational flexibility to the highly rigid structure of **3**, bicyclic compounds **4**, **5** and **6**, each comprising a pair of rings from **3**, were designed and some fifty derivatives of types **5** and **6** were prepared.[6)]

In accord with our assumption, almost all of these compounds were found to exhibit potent ACE inhibitory activities. Among them, compounds **7** and **8** having a 2-indanyl substituent were selected as the best in these series. 2-Indanyl derivatives not only were superior in activity but also were convenient as regards synthesis, because no asymmetric center is involved in the bicyclic moiety. In view of the possible side effects of captopril that, reportedly, might be due to the mercapto group,[7)] we proceeded to modify **7** and **8** further by introducing a non-sulfur-containing substituent in place of the 3-acylthio-2-methylpropanoyl group. From among a variety of derivatives, *N*-[*N*-[(*S*)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine hydrochloride (**9a**: CV-3317), having the same *N*-acyl substituent as that of enalapril (**19**),[8)] has emerged as a new potential ACE inhibitor. CV-3317 is currently undergoing clinical studies.

It is noteworthy in this connection that a number of new ACE inhibitors having the skeleton **4** have recently been discovered. Among them are *N*-acyl derivatives of 2-indolinecarboxylic acid,[9–11)] octahydro-1*H*-indole-2-carboxylic acid,[12,13)] and 2-aza-

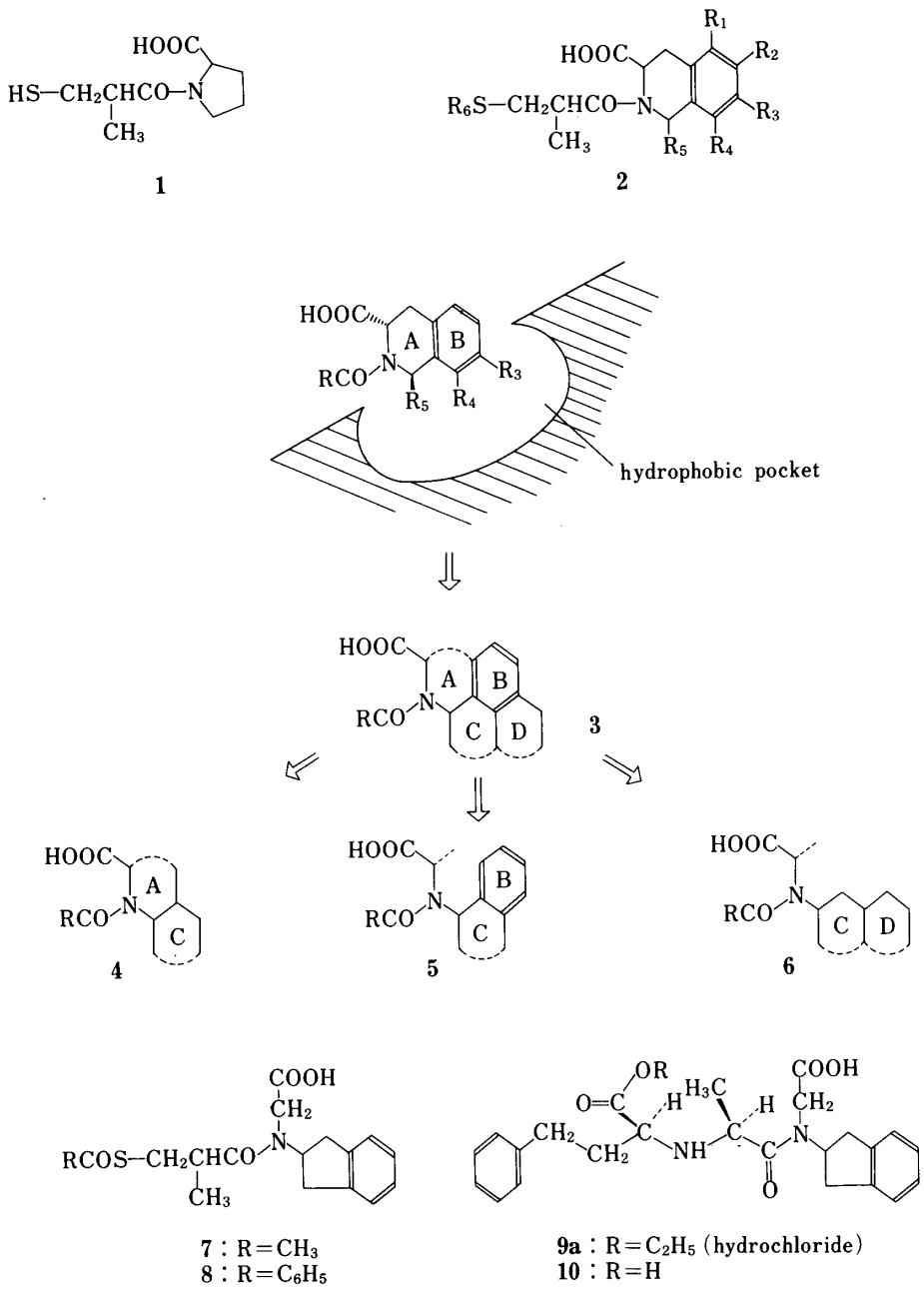


Chart 1

bicyclo[3.3.0]octane-3-carboxylic acid.[14] Therefore, it seems probable that skeletons **4**, **5**, and **6**, which are derived from a comprehensive structure **3**, can fit the hydrophobic pocket of the enzyme. A more quantitative conformational analysis of these structures using a molecular modeling system with computer graphics[15] is in progress.

Synthesis of **9a** was achieved according to the scheme shown in Chart 2. Thus, *N*-(2-indanyl)glycine *tert*-butyl ester (**11**), prepared by the reductive condensation of 2-indanone with glycine *tert*-butyl ester, was coupled with *N*-benzyloxycarbonyl-L-alanine by the mixed-anhydride method using ethyl chloroformate to give *N*-[*N*-benzyloxycarbonyl-L-alanyl]-*N*-(2-indanyl)glycine *tert*-butyl ester (**12**). The catalytic hydrogenation of **12** over palladium–charcoal yielded the free base of L-alanyl-*N*-(2-indanyl)glycine *tert*-butyl ester (**13**), which proved to be very susceptible to cyclization to a dioxopiperazine derivative (**14**); consequently, the hydrogenation was conducted in the presence of oxalic acid to afford **13** as the crystalline

oxalate in 68% yield. Reductive condensation of **13** with an excess of ethyl 2-oxo-4-phenylbutyrate by catalytic hydrogenation over Raney nickel gave **15a**, the *tert*-butyl ester of **9a**, as a mixture with its diastereomer (**15b**). Separation of each isomer by column chromatography revealed that considerable asymmetric induction had occurred during the hydrogenation process, affording **15a** (61%, $[\alpha]_D^{22} -12.6°$) and **15b** (7.8%, $[\alpha]_D^{22} -16.4°$) in a ratio of eight to one.[16] Treatment of each isomer with hydrogen bromide in acetic acid followed by conversion of the product to the hydrochloride gave **9a** and its diastereomer (**9b**).

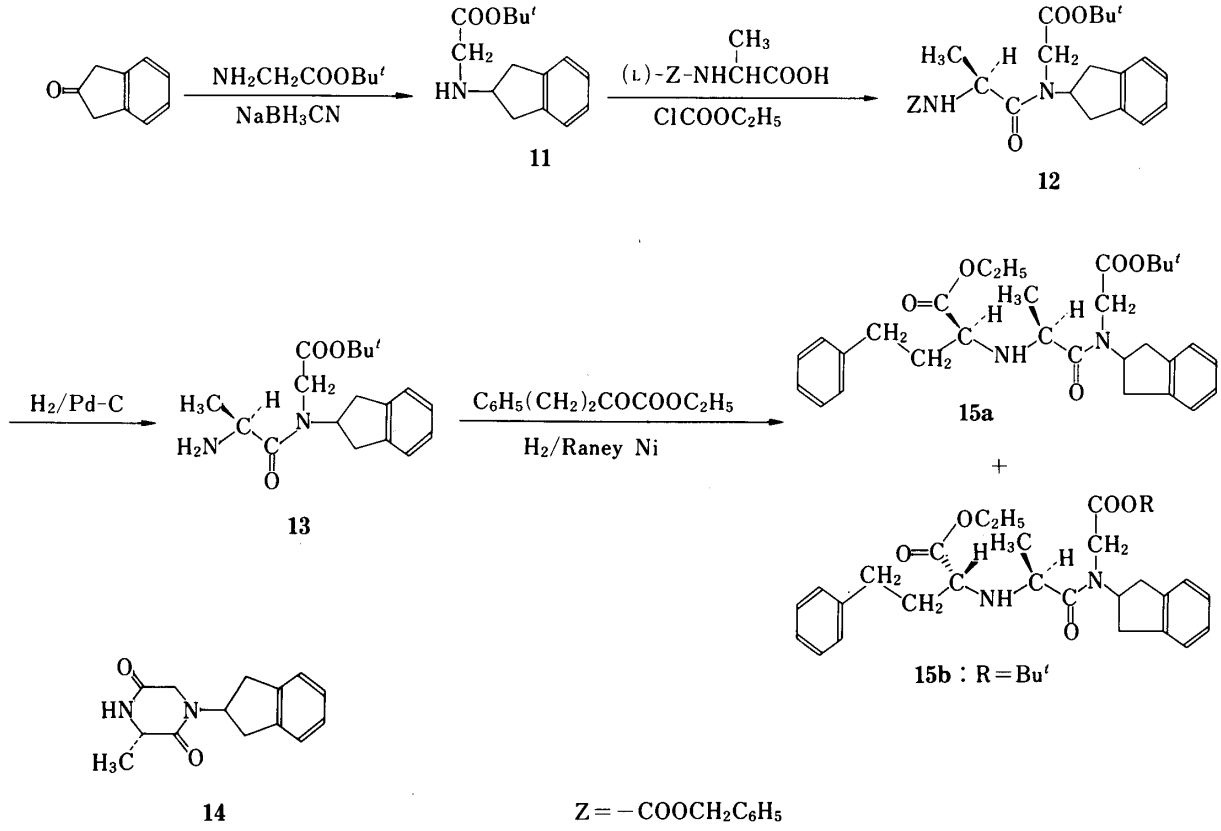
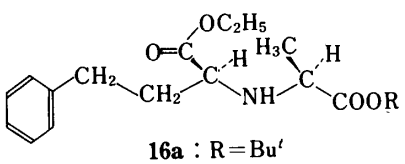


Chart 2

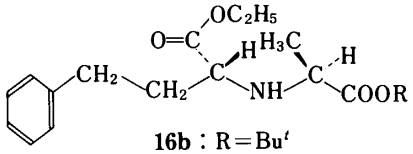
Although the predominant isomer was presumed to be **9a**, judging from the significantly higher ACE inhibitory activity, its absolute configuration was confirmed by chemical correlation to enalapril, whose configuration had been established.[8,17] L-Alanine *tert*-butyl ester was subjected to reductive condensation with ethyl 2-oxo-4-phenylbutyrate to give *N*-(1-ethoxycarbonyl-4-phenylpropyl)-L-alanine *tert*-butyl ester as a mixture of two diastereomers (**16a** and **16b**), each of which was separated by column chromatography. Removal of the *tert*-butyl group in **16a** and **16b** by treatment with hydrogen chloride in ethyl acetate afforded the corresponding isomers of *N*-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanine hydrochloride, **17a** and **17b**, in quantitative yield. Compound **17a**, with higher optical rotation, was coupled with L-proline *tert*-butyl ester using diethyl phosphorocyanidate (DEPC)[18] as a condensing agent to give *N*-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline *tert*-butyl ester (**18**) in 67% yield. Removal of the *tert*-butyl group in **18** followed by treatment with maleic acid yielded *N*-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate (**19**), $[\alpha]_D^{22} -42.6°$ (methanol), which was identical with enalapril.[8] Since the absolute configuration at the three asymmetric centers in enalapril has been established as *S*,*S*,*S* by the X-ray crystallography of its carboxy derivative (**20**), the configuration at the 1-position in the 1-ethoxycarbonyl-3-phenylpropyl moiety in **17a** was proved to be *S*.

On the other hand, condensation of **17a** with *N*-(2-indanyl)glycine *tert*-butyl ester (**11**) in the presence of DEPC to give **15a** followed by treatment with hydrogen bromide in acetic acid yielded **9a**. Both **15a** and **9a** obtained by this method were identical with the samples prepared by the above process. Therefore, the absolute configuration at the 1-ethoxycarbonyl-3-phenylpropyl moiety in **9a** was determined as *S*. Compound **9a** was further led to its diacid derivative (**10**) by alkaline hydrolysis.

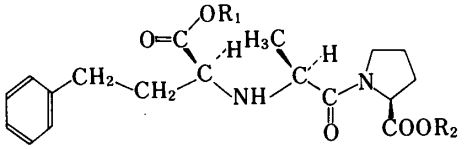
In the *in vitro* ACE inhibitory assay using rabbit lung ACE, **9a**, **10** and captopril showed IC_{50} values of 1.2×10^{-7}, 4.0×10^{-8} and 5.8×10^{-7} M, respectively, indicating that the former two compounds were 4.8 and 14.5 times, respectively, more active than captopril. In the *in vivo* test for the inhibition of pressor response to angiotensin I in rats, ID_{50} values for orally administered **9a** and captopril were 1.9 and 5.4 μmol/kg, respectively. Compound **10** had little effect in this test even at an oral dose of 13.8 μmol/kg, although it showed significant activity upon intravenous administration of 0.138 μmol/kg. These results together with the results of a metabolic study[19] of **9a** revealed that **10** is the physiologically active species of **9a**, analogously to the case of enalapril.[8] Details of the ACE inhibitory activity of CV-3317 (**9a**) and its antihypertensive activities in animals will be described in separate papers.[20]



16a : R=Bu^t
17a : R=H



16b : R=Bu^t
17b : R=H



18 : $R_1=C_2H_5$, $R_2=Bu^t$
19 : $R_1=C_2H_5$, $R_2=H$ (maleate)
20 : $R_1=R_2=H$

Chart 3

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus (a hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 260-10 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Varian T-60, EM-360 or EM-390 instruments in the indicated solvent. Chemical shifts are reported as δ-values relative to tetramethylsilane (TMS) as the standard. Mass spectra (MS) were obtained on a JEOL JMS-01SC mass spectrometer. Secondary ion mass spectra (SIMS) were measured with a Hitachi M-80A mass spectrometer. The $[\alpha]_D$ values were determined with a JASCO DIP-181 4-4822 instrument in the indicated solvent.

Reactions were run at room temperature unless otherwise noted, and traced by thin-layer chromatography using Merck F-254 silica gel plates. Chromatographic separation employed Merck silica gel 60 using the indicated eluents.

***N*-(2-Indanyl)glycine *tert*-Butyl Ester (11)**——$NaBH_3CN$ (23 g) was added portionwise to a stirred mixture of 2-indanone (40 g), glycine *tert*-butyl ester·H_3PO_3[21] (78 g), water (150 ml) and MeOH (300 ml) during 15 min at water-bath temperature. The resulting mixture was stirred for 4 h, diluted with 20% H_3PO_4 (400 ml) and water (200 ml), and extracted with Et_2O (800 ml). The aqueous layer was made alkaline (pH 10) with 20% NaOH and extracted with $CHCl_3$ (500 ml). The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give an oily residue, which was

crystallized from EtOH–water to afford **11** (47 g, 63%) as colorless prisms, mp 54—55 °C. *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.30; H, 8.42; N, 5.81.

***N*-(L-Alanyl)-*N*-(2-indanyl)glycine *tert*-Butyl Ester (13)**——ClCOOEt (8.5 g) was added dropwise to a stirred mixture of *N*-benzyloxycarbonyl-L-alanine (21.8 g), Et_3N (12.8 ml) and tetrahydrofuran (THF 200 ml) at −15 °C. After the addition was complete, stirring was continued for a further 15 min, and then a solution of **11** (22 g) in $CHCl_3$ (100 ml) was added dropwise at below −10 °C. When the addition was complete, stirring was continued for a further 1 h at room temperature, and the mixture was poured into water (500 ml). The organic layer was separated and concentrated *in vacuo*. The residue was dissolved in AcOEt (300 ml). The solution was washed with 1 N NaOH (50 ml × 2), water (50 ml), 20% H_3PO_4 (50 ml × 2) and water (50 ml) successively, dried ($MgSO_4$) and evaporated *in vacuo* to give *N*-(*N*-benzyloxycarbonyl-L-alanyl)-*N*-(2-indanyl)glycine *tert*-butyl ester **12** (35 g, 87%) as a colorless oil. A mixture of **12** (35 g), $(COOH)_2$ (7 g) and MeOH (300 ml) was subjected to catalytic reduction over 10% Pd–C (50% wet, 8.5 g) under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* and Et_2O (500 ml) was added to the residue. The resulting colorless crystals were collected by filtration to give **13**·oxalate (21.8 g, 68%), mp 138—141 °C. $[\alpha]_D^{22}$ +20.4° (*c* = 1, MeOH). *Anal.* Calcd for $C_{18}H_{26}N_2O_3 \cdot C_2H_2O_4 \cdot 1/2H_2O$: C, 57.54; H, 7.00; N, 6.71. Found: C, 57.72; H, 7.07; N, 6.70.

(*S*)-1-(2-Indanyl)-3-methyl-2,5-piperazinedione (14)——A solution of **12** (42 g) in MeOH (350 ml) was hydrogenated using 10% Pd–C (50% wet, 9 g) as a catalyst under atmospheric pressure. Work-up was carried out as in the case of **13**. Compound **14** (8.7 g, 38%) was crystallized from a solution of the products in EtOH. mp 149—150 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.65; H, 6.72; N, 11.33.

***N*-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine *tert*-Butyl Ester (15a) and *N*-[*N*-[(*R*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine *tert*-Butyl Ester (15b)**——Method A: A mixture of **13**·oxalate (21 g), AcONa (4.1 g), AcOH (10 ml), ethyl 2-oxo-4-phenylbutyrate (25 g), molecular sieves 3A (25 g) and EtOH (200 ml) was subjected to catalytic hydrogenation over Raney nickel (30 g) as the catalyst under atmospheric pressure. After absorption of hydrogen had ceased, the supernatant layer was separated and the catalyst was rinsed with EtOH. The EtOH solutions were combined and evaporated *in vacuo*. The residue was dissolved in AcOEt (500 ml). The solution was washed with aq. $NaHCO_3$ and water successively, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow liquid, which was chromatographed on silica gel using acetone–benzene (1 : 9) as an eluent. Evaporation of the first fraction afforded **15b** (2 g, 7.8%) as a colorless viscous oil. $[\alpha]_D^{22}$ −16.4° (*c* = 1, MeOH). MS *m/z*: 508 (M^+). IR ν_{max}^{neat} cm^{-1}: 3300 (NH); 1730, 1640 (C=O). *Anal.* Calcd for $C_{30}H_{40}N_2O_5$: C, 70.84; H, 7.93; N, 5.51. Found: C, 70.58; H, 8.02; N, 5.45.

Compound **15a** (16.5 g, 61%) was obtained from the second fraction. $[\alpha]_D^{22}$ −12.6° (*c* = 1, MeOH). MS *m/z*: 508 (M^+). IR ν_{max}^{neat} cm^{-1}: 3300 (NH); 1730, 1640 (C=O). *Anal.* Calcd for $C_{30}H_{40}N_2O_5$: C, 70.84; H, 7.93; N, 5.51. Found: C, 70.58; H, 7.83; N, 5.48.

Method B: A solution of DEPC (0.2 g) in dimethylformamide (DMF 5 ml) was added dropwise to a stirred mixture of **17a**·HCl (0.2 g), **11** (0.22 g) and DMF (10 ml). When the addition was complete, a solution of Et_3N (0.15 g) in DMF (1 ml) was added to the mixture. After being stirred for 1 h, the mixture was diluted with water (100 ml) and extracted with AcOEt (300 ml). The extract was washed with 10% H_3PO_4 (50 ml × 2), 1 N NaOH (20 ml) and water successively, dried ($MgSO_4$) and evaporated *in vacuo* to give an oily residue, which was purified by silica gel column chromatography (hexane–AcOEt = 2 : 1—1 : 1) to yield **15a** (0.22 g, 68%) as a colorless oil. $[\alpha]_D^{22}$ −12.5° (*c* = 0.9, MeOH).

Compound **17b**·HCl (3.3 g) was condensed with **11** (2 g) in a manner similar to that described above for the (*S*),(*S*)-isomer **15a** to give **15b** (3 g, 73%) as a colorless oil.

***N*-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine (9a)**——A 25% HBr–AcOH solution (20 ml) was added to a solution of **15a** (5 g), prepared by Method A, in AcOH (5 ml). The resulting mixture was stirred for 10 min and diluted with Et_2O (300 ml) to deposit colorless crystals of the hydrobromide which were collected by filtration to give **9a**·HBr (5 g, 95%), mp 180—183 °C. $[\alpha]_D^{20}$ +15.6° (*c* = 1.4, MeOH).

The above hydrobromide of **9a** (16.2 g) was added to a stirred mixture of AcOEt (500 ml), $NaHCO_3$ (33 g) and water (500 ml). After acidification (pH 4) with 1 N HCl, the AcOEt layer was separated, washed with water and dried ($MgSO_4$). Then 7 N HCl–AcOEt (20 ml) was added to the solution, and the mixture was concentrated *in vacuo*. The residue was diluted with Et_2O (250 ml) and petroleum ether (250 ml) to deposit the hydrochloride of **9a** (11 g, 74%) as colorless crystals, which were recrystallized from acetone–1 N HCl to give colorless plates, mp 166—170 °C (dec.). $[\alpha]_D^{22}$ +18.5° (*c* = 1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1705, 1640 (C=O). *Anal.* Calcd for $C_{26}H_{32}N_2O_5 \cdot HCl$: C, 63.86; H, 6.86; N, 5.73. Found: C, 63.95; H, 6.47: N, 5.84. MS *m/z*: 434 ($M^+ - H_2O$). SIMS *m/z*: 453 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, *J* = 7 Hz), 1.50 (3H, d, *J* = 6 Hz), 2.10—3.20 (4H, m, CH_2), 2.60—2.90 (2H, m, CH_2), 3.00—3.20 (4H, m, CH_2), 3.90 (2H, s, CH_2), 4.10—4.40 (3H, m, CH_2 and CH), 4.80—5.15 (2H, m), 7.20 (4H, s), 7.30 (5H, s).

The same procedure using 0.2 g of **15a** prepared by method B afforded 0.1 g (52%) of **9a**·HCl, $[\alpha]_D^{22}$ +18.5° (*c* = 1, MeOH), which was identical with the sample obtained above.

***N*-[*N*-[(*R*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine (9b)**——Compound **15b** (3 g) was treated with HBr–AcOH in a manner similar to that described for **9a** to give **9b**·HBr (1.8 g, 57%) as colorless plates,

mp 154—157 °C (AcOEt). $[\alpha]_D^{25}$ −23.0° (c=0.8, MeOH). *Anal.* Calcd for $C_{26}H_{32}N_2O_5 \cdot HBr$: C, 58.54; H, 6.23; N, 5.25. Found: C, 58.36; H, 6.22; N, 5.36. IR ν_{max}^{Nujol} cm^{-1}: 1755, 1735, 1625 (C=O). This hydrobromide (1 g) was converted to **9b**·hydrochloride (0.7 g, 76%) in a manner similar to that described for the preparation of **9a**·HCl. $[\alpha]_D^{23.5}$ −24.7° (c=0.6, MeOH). mp 150—152 °C (AcOEt–Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1620 (C=O). SIMS m/z: 453 (MH^+). *Anal.* Calcd for $C_{26}H_{32}N_2O_5 \cdot HCl$: C, 63.86; H, 6.80; N, 5.73. Found: C, 63.69; H, 6.78; N, 5.60.

***N*-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]-*N*-(indan-2-yl)glycine (10)**——A 2 N NaOH solution (5 ml) was added to a solution of **9a**·HCl (1.2 g) in MeOH (30 ml), and the resulting mixture was stirred overnight. After removal of the MeOH *in vacuo*, the mixture was diluted with water (30 ml), acidified (pH 5—6) with HCl, and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was crystallized from MeOH (5 ml) to give **10** (0.6 g, 58%) as colorless crystals. mp 140—142 °C. $[\alpha]_D^{22}$ +26° (c=0.6, 1% HCl). *Anal.* Calcd for $C_{24}H_{28}N_2O_5 \cdot H_2O$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.96; H, 6.82; N, 6.20.

***N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine *tert*-Butyl Ester (16a) and *N*-[(*R*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine *tert*-Butyl Ester (16b)**——i) A mixture of L-AlaOBu^t·oxalate (10 g), AcONa (7 g), AcOH (10 g), molecular sieves 3A (20 g), ethyl 2-oxo-4-phenylbutyrate (13 g) and EtOH (200 ml) was catalytically hydrogenated over Raney nickel (wet, 10 g) in a manner similar to that described in method A for the preparation of **15a** and **15b**. The products were purified by silica gel column chromatography using hexane–AcOEt (50 : 1—20 : 1) as an eluent. Evaporation of the first fraction afforded **16b** (3.8 g, 29%) as a colorless oil. *Anal.* Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.32; H, 8.56; H, 4.09. IR ν_{max}^{neat} cm^{-1}: 3310 (NH); 1720 (C=O). $[\alpha]_D^{24}$ −22.5° (c=1, MeOH). MS m/z: 335 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, d, J=7 Hz), 1.25 (3H, t, J=7 Hz), 1.4 (9H, s), 1.8—2.3 (3H), 2.5—2.9 (2H), 2.9—3.4 (2H), 4.1 (2H, q, J=7 Hz), 7.1 (5H, s).

Evaporation of the second fraction gave **16a** (3.8 g, 29%) as a colorless oil. *Anal.* Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.21; H, 8.80; N, 4.04. IR ν_{max}^{neat} cm^{-1}: 3320 (NH), 1720 (C=O). $[\alpha]_D^{24}$ −17.9° (c=1, MeOH). MS m/z: 335 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7 Hz), 1.3 (3H, d, J=7 Hz), 1.4 (9H, s), 1.65—2.15 (3H), 2.5—2.9 (2H), 3.0—3.45 (2H), 4.15 (2H, q, J=7 Hz), 7.1 (5H, s).

ii) A mixture of L-AlaOBu^t·oxalate (20 g), AcONa (13 g), AcOH (10 g), ethyl 2-oxo-4-phenylbutyrate (33 g) and EtOH (150 ml) was stirred for 30 min, and then a solution of $NaBH_3CN$ (10 g) in EtOH (100 ml) was added dropwise to the mixture over 5 h. After being stirred overnight, the mixture was diluted with saturated aqueous NH_4Cl solution (500 ml) and extracted with AcOEt (200 ml × 3). The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give an oily residue, which was dissolved in Et_2O (100 ml) containing oxalic acid (8 g). The resulting solution was diluted with petroleum ether (500 ml) and the supernatant layer was removed by decantation. The precipitate was neutralized with $NaHCO_3$ (excess) and extracted with AcOEt. The extract was dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the residue by silica gel column chromatography in the same manner as described in i) gave **16a** (8 g, 31%) and **16b** (4.3 g, 16%).

***N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine (17a)**——A solution of **16a** (2.5 g) in HCl–AcOEt (3.6 N, 40 ml) was allowed to stand for 4 h. After evaporation of solvent, the residue was crystallized from Et_2O (100 ml) to give **17a**·HCl (2.2 g, 93%) as colorless needles, mp 136—142 °C. *Anal.* Calcd for $C_{15}H_{21}NO_4 \cdot HCl$: C, 57.05; H, 7.02; N, 4.44. Found: C, 56.93; H, 7.04; N, 4.43. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O). $[\alpha]_D^{22}$ +32.4° (c=0.9, MeOH). MS m/z: 279 (M^+). ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.4 (3H, t, J=7 Hz), 1.6 (3H, d, J=7 Hz), 2.4 (2H, t, J=7 Hz), 2.6—3.1 (2H), 4.1—4.5 (4H), 7.4 (5H, s).

***N*-[(*R*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine (17b)**——Deprotection of **16b** (2.5 g) was carried out by the same procedure as used for the preparation of **17a** to yield **17b**·HCl (2.3 g, 98%) as colorless needles, mp 173—177 °C. *Anal.* Calcd for $C_{15}H_{21}NO_4 \cdot HCl$: C, 57.05; H, 7.02; N, 4.44. Found: C, 57.10; H, 6.70; N, 4.43. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1720 (C=O). ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 1.4 (3H, t, J=7 Hz), 1.6 (3H, d, J=7 Hz), 2.2—2.5 (2H), 2.6—3.0 (2H), 4.1—4.5 (4H), 7.4 (5H, s). $[\alpha]_D^{23}$ −28.6° (c=0.9, MeOH). MS m/z: 279 (M^+).

***N*-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline *tert*-Butyl Ester (18)**——L-ProOBu^t (0.25 g) was condensed with **17a**·HCl (0.3 g) using DEPC (0.3 g) in a manner similar to that described for the preparation of **15** in method B. Chromatographic purification on silica gel using hexane–acetone (4 : 1) as an eluent gave **18** (0.31 g, 67%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1730, 1640 (C=O). MS m/z: 432 (M^+). $[\alpha]_D^{22}$ −81.9° (c=1.25, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.3 (3H, d, J=7 Hz), 1.5 (9H, s), 1.7—4.6 (14H, m), 4.15 (2H, q, J=7 Hz), 7.15 (5H, s).

***N*-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-L-proline (19)**——A solution of **18** (0.25 g) in HCl–AcOEt (3.6 N, 10 ml) was allowed to stand overnight. After evaporation of the solvent, the residue was neutralized with saturated aqueous $NaHCO_3$ solution (30 ml) and extracted with Et_2O (50 ml). The ether layer was extracted with saturated aqueous $NaHCO_3$ solution (20 ml × 2). The combined aqueous solution was acidified (pH 4) with 1 N HCl, saturated with NH_4Cl and extracted with $CHCl_3$ (30 ml × 2). The extract was washed with water (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in AcOEt (50 ml) containing a solution of maleic acid (0.1 g) in EtOH (2 ml). The resulting mixture was concentrated to a volume of 10 ml to deposit the maleic acid salt of **9** (enalapril) as colorless crystals, 0.15 g (53%), mp 150—152 °C. $[\alpha]_D^{22}$ −42.6° (c=1, MeOH) [lit.[8] $[\alpha]_D^{25}$ −42° (MeOH)]. *Anal.* Calcd for $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$: C, 58.52; H, 6.55; N, 5.69. Found: C, 58.60; H, 6.72; N, 5.56. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1720, 1640 (C=O).

References and Notes

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16) In view of the fact that the reductive coupling of L-AlaOBu^t with ethyl 2-oxo-4-phenylbutyrate over Raney nickel to give **16a** and **16b** proceeded without selectivity (see Experimental), the indanylglycine moiety of **13** seems to be responsible for this high diastereoselectivity, although details of the transition-state structure are not clear.
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