Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3769–3776

TETRAHEDRON: *ASYMMETRY*

Stereochemistry in enzyme inhibition: synthesis and evaluation of enantiomerically pure 2-benzyl-3-formylpropanoic acids as inhibitors of carboxypeptidase A

Dong H. Kim * and Suhman Chung

Center for Biofunctional Molecules and Department of Chemistry, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, South Korea

Received 26 July 1999; accepted 13 September 1999

Abstract

Both enantiomers of 2-benzyl-3-formylpropanoic acid were synthesized in five steps starting with hydrocinnamic acid and each enantiomer assayed for inhibitory activity against carboxypeptidase A to find that the (*R*)-form is 674-fold more potent than its enantiomer. The finding that the (*R*)-form which belongs to the L-series is mostly responsible for the inhibitory activity accords with the explanation that the present inhibitor is a transition state analog inhibitor because, as such, its stereochemistry should belong to the same series as that of the substrate, i.e., the L-series. The *gem*-diol form of the inhibitor generated in situ mimics the transition state in the catalytic process.
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1. Introduction

Enzyme inhibitors are compounds that bind enzymes at the active site but fail to undergo the chemical reaction that substrates would. Design of enzyme inhibitors has been the subject of intensive research especially in reference to the discovery of lead compounds as new therapeutic agents.[1] Galardy and Kortylewicz[2] reported that 2-benzyl-3-formylpropanoic acid in the racemic form is a potent competitive inhibitor for CPA,[3] a much studied prototypic zinc-containing protease which catalyzes the cleavage of the C-terminal amide bond of peptide substrate. The enzyme shows specificity for peptides having the C-terminal amino acid residue with a hydrophobic side chain such as Phe. In connection with our ongoing efforts directed to define the stereochemistry associated with inhibition of enzymes,[4] it was thought to be of interest to find which enantiomeric form of the inhibitor is responsible for its CPA inhibitory activity. This paper describes efficient syntheses of both enantiomers of 2-benzyl-3-formylpropanoic acid in an enantiomerically pure form and their evaluation as inhibitors for CPA.

* Corresponding author. Tel: (82) 562-279-2101; fax: (82) 562-279-5877; e-mail: dhkim@vision.postech.ac.kr

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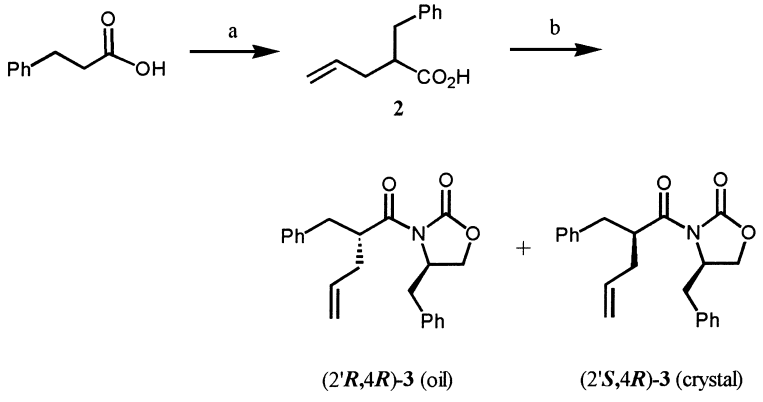
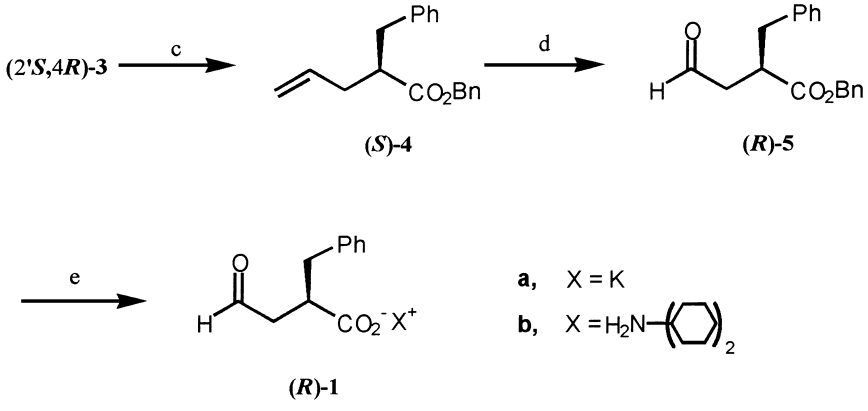
PII: S0957-4166(99)00421-8

2. Results and discussion

Scheme 1 outlines the synthetic route for the preparation of (*R*)-2-benzyl-3-formylpropanoic acid. 2-Allyl-3-phenylpropanoic acid obtained by allylation of hydrocinnamic acid was tethered to (*R*)-4-benzyl-2-oxazolidinone, an Evans chiral auxiliary, to give **3** as a diastereoisomeric mixture (Scheme 1). The mixture was readily separated by column chromatography to give a crystalline product and an oil in the ratio of 1:1. The crystalline product, the stereochemistry of which was assigned to be (2′*S*,4*R*) (see Scheme 1), was converted into the benzyl ester of 2-allyl-3-phenylpropanoic acid, (*S*)-**4**, by treatment with BnOLi. Ozonolysis of (*S*)-**4** followed by treatment with thiourea according to the method reported by Gupta et al.[5] transformed the olefinic moiety to a formyl group, giving (*R*)-**5**. Hydrogenolysis of the methanolic solution of (*R*)-**5** in the presence of Pd/C removed the benzyl group to give (*R*)-**1** as a hydroxylactone. Treatment of the latter with aqueous KOH afforded the target compound of *R*-configuration as a potassium salt (*R*)-**1a** (Scheme 2). Treatment of the hydroxylactone with dicyclohexylamine afforded a crystalline salt (*R*)-**1b**.



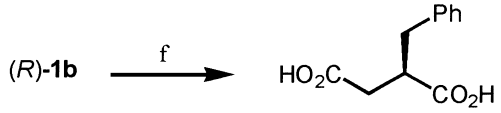
Scheme 1. Reagents, conditions, and yields: (a) LDA (2.1 equiv.), allyl bromide (1.1 equiv.), 0°C, THF (84%); (b) i. $(COCl)_2$, CH_2Cl_2; ii. *n*-BuLi (1.0 equiv.), (*R*)-(+)-4-benzyl-2-oxazolidinone, −78°C, THF (86%)



Scheme 2. Reagents, conditions, and yields: (c) *n*-BuLi (1.5 equiv.), BnOH, 0°C, THF (84%); (d) i. O_3, MeOH; ii. thiourea (60%); (e) i. H_2, Pd/C, MeOH; ii. for **a**, aq. KOH (1.0 equiv.) (92%), for **b**, dicyclohexylamine, Et_2O (96%)

The assigned stereochemistry was ascertained by oxidizing (*R*)-**1b** to give known (*R*)-2-benzylsuccinic acid (Scheme 3). Thus, the $[\alpha]_D$ value of 2-benzylsuccinic acid obtained from oxidizing (*R*)-**1b** by the method of Kraus and Taschner[6] was +26.5 which is in good agreement with the literature value[7] of +27.2

for (*R*)-2-benzylsuccinic acid. In a similar sequence of reactions, we obtained (*S*)-**1** from (2′*R*,4*R*)-**3** as an oil after chromatographic separation of the diastereoisomeric mixture of **3**.



(*R*) - 6

Scheme 3. Reagents, conditions, and yields: (f) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O (72%)

Each enantiomer of **1** thus synthesized was assayed as the potassium salt for its CPA inhibitory activity according to the method reported by Galardy and Kortylewicz[2] to find that the inhibitory activity resides mostly with (*R*)-**1** having the K_i value of 0.38±0.03 μM for the potassium salt (Fig. 1). The K_i value of (*S*)-**1a** was shown to be 256±19 μM. Racemic **1** was reported to have the K_i value of 0.48±0.1 μM.[2]

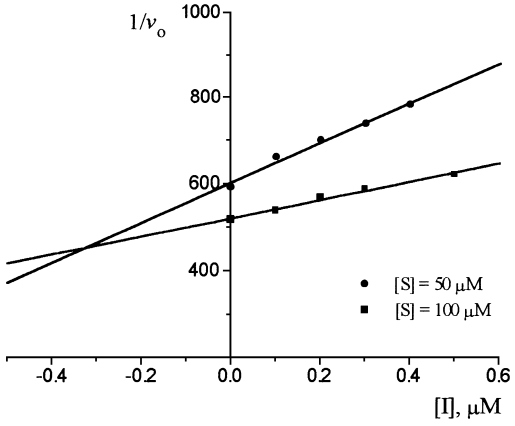


Figure 1. The Dixon plot for the inhibition of CPA with potassium (*R*)-2-benzyl-3-formylpropanoate (*R*)-**1a** (substrate, Cl-CPL; Tris buffer of pH 7.5; 25°C)

When the inhibitors were assayed as dicyclohexylamine salts, the inhibitory potencies were considerably reduced as can be seen from Table 1, which is probably due to lowered solubility of these organic salts in the assay medium.

Previously, Galardy and Kortylewicz proposed that the high binding affinity of 2-benzyl-3-formylpropanoic acid is due to the facile tendency of its formyl moiety, in an aqueous solution, to form a *gem*-diol that mimics the tetrahedral transition state generated in the CPA-catalyzed proteolytic process (Fig. 2).[2] In the CPA-catalyzed peptide cleavage, the active site water molecule that is activated dually by the active site zinc ion and the carboxylate of Glu-270 attacks the carbonyl carbon of the scissile peptide bond to form a tetrahedral transition state (Fig. 2a).[8] Transition state analogs in the enzymic reaction have been known to bind the active site with high affinity.[9] The present observation that (*R*)-**1**, which belongs to the L-series, is mostly responsible for the observed inhibitory activity of **1** accords with the proposition, since the stereochemistry of the substrate is retained at the transition state.

3. Conclusion

Although the role of the chirality of the inhibitor in enzyme inhibitions is of utmost importance especially in the design of therapeutically useful inhibitors, the factors controlling and determining the

Table 1
Inhibition of CPA-catalyzed hydrolysis of *O*-(*trans*-*p*-chlorocinnamoyl)-L-β-phenyllactate

Inhibitor	K_i (μM)
(*R,S*)-2-Benzyl-3-formylpropanoic acid (potassium salt)	0.48±0.1[a]
(*R*)-2-Benzyl-3-formylpropanoic acid (potassium salt) ((*R*)-**1a**)	0.38±0.03
(*R*)-2-Benzyl-3-formylpropanoic acid (dicyclohexylamine salt) ((*R*)-**1b**)	15±2
(*S*)-2-Benzyl-3-formylpropanoic acid (potassium salt) ((*S*)-**1a**)	256±19
(*S*)-2-Benzyl-3-formylpropanoic acid (dicyclohexylamine salt) ((*S*)-**1b**)	283±26

[a]Galardy, R.E.; Kortylewicz, Z.P. *Biochemistry*, **1984**, *23*, 2083

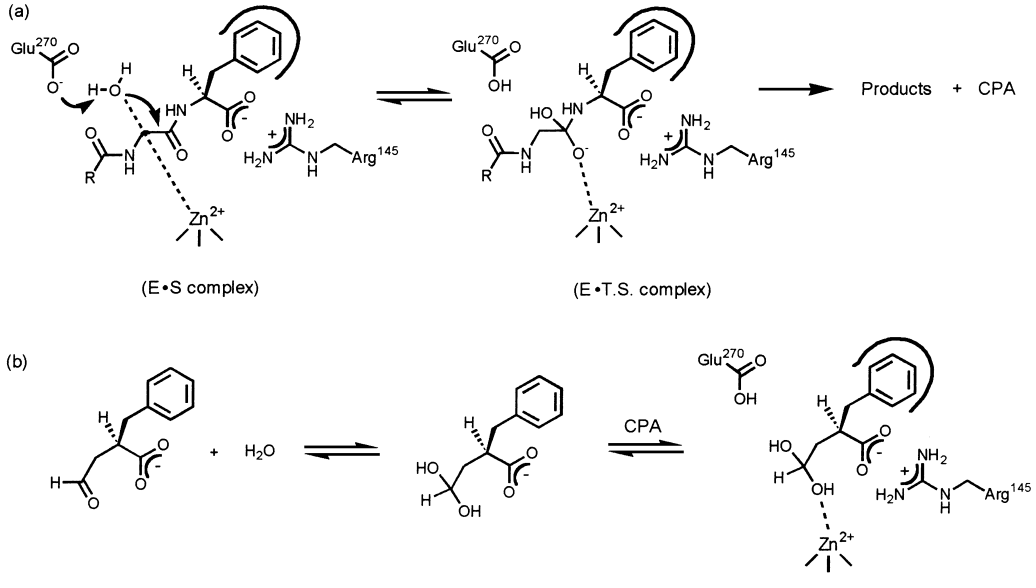


Figure 2. (a) Schematic representation that shows the general-base pathway of CPA-catalyzed hydrolysis of peptide substrate. A tetrahedral transition state that is generated by the attack of the activated water molecule at the active site on the scissile carbonyl carbon of the substrate collapses to products; (b) 2-benzyl-3,3-dihydroxypropanoic acid that is generated from 2-benzyl-3-formylpropanoic acid in aqueous solution resembles structurally the tetrahedral transition state in the enzymic reaction and binds the active site of CPA with high affinity

inhibitor stereospecificity are still poorly understood. We hope that the present observation will be of value for designing transition state analog inhibitors of pharmacologically important zinc-containing proteases such as angiotensin converting enzyme and matrix metalloproteases. Inhibitors of these enzymes are valuable as potential therapeutic agents.

4. Experimental

Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Bruker Equinox 55 FT-IR spectrometer. Flash chromatography was performed on silica gel (230–400 mesh) and thin layer chromatography (TLC) was carried out on silica coated glass sheets (Merck silica gel 60 F-254). Optical rotations were measured on a Rudolph Research Autopol III digital polarimeter. Elemental analyses were performed at the Center of Biofunctional Molecules, Pohang University of Science and Technology, Pohang, Korea.

*4.1. 2-Allyl-3-phenylpropanoic acid **2***

To an ice-chilled solution of diisopropylamine (9.2 mL, 70.2 mmol) in dry THF (50 mL) was slowly added *n*-butyllithium (28.1 mL of 2.5 M solution in *n*-hexane, 70.2 mmol) under a nitrogen atmosphere. After the mixture was stirred for 30 min, hydrocinnamic acid (5.0 g, 33.3 mmol) in dry THF (30 mL) was added dropwise over a period of 20 min. The resulting yellowish solution was stirred for 40 min, and then allyl bromide (3.2 mL, 37.0 mmol) was added dropwise. The reaction mixture was stirred for 3 h to give a colorless solution. The pH of the solution was adjusted to 2.5 with 3N HCl solution. The organic layer was separated and extracted with saturated sodium bicarbonate solution. The aqueous layer was acidified with 3N HCl solution to pH 2, saturated with sodium chloride, and extracted with ethyl acetate (50 mL×3). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with a solution of ethyl acetate and *n*-hexane (1:3) to give **2** (5.3 g, 84%) as a colorless oil. IR (neat) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.29–2.46 (m, 2H), 2.75–2.85 (m, 2H), 2.97–3.05 (m, 1H), 5.08–5.15 (m, 2H), 5.74–5.88 (m, 1H), 7.19–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 36.0, 37.7, 47.4, 117.9, 126.9, 128.9, 129.3, 135.1, 139.2, 181.2.

*4.2. (2′*R*,4*R*)- and (2′*S*,4*R*)-*N*-(2′-Allyl-3′-phenylpropanoyl)-4-benzyl-1,3-oxazolidin-2-one (2′*R*,4*R*)-**3** and (2′*S*,4*R*)-**3***

To an ice-chilled solution of **2** (5.2 g, 27 mmol) in dry CH_2Cl_2 was added dropwise oxalyl chloride (2.4 mL, 27 mmol). The reaction mixture was refluxed for 2 h, and then concentrated in vacuo to give acyl chloride as a colorless oil. A solution of (*R*)-(+)-4-benzyl-2-oxazolidinone (4.8 g, 27 mmol) in dry THF, stirred at −78°C under a nitrogen atmosphere, was treated dropwise with *n*-butyllithium (11 mL of 2.5 M solution in *n*-hexane, 27 mmol). After the mixture was stirred for 30 min, the above acyl chloride dissolved in dry THF was added dropwise. The resulting mixture was stirred at −78°C for 30 min, then quenched with saturated ammonium chloride solution and partitioned between ether and water. The combined ether extracts were washed with 5% sodium bicarbonate solution and brine, then dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting diastereomeric mixture (1:1) was separated by column chromatography, eluting with ethyl acetate and *n*-hexane (1:30) to give (2′*S*,4*R*)-**3** (4.1 g, 43%) as a pale yellow oil and (2′*R*,4*R*)-**3** (4.1 g, 43%) as a white crystalline solid.

Compound (2′*R*,4*R*)-**3**: $[\alpha]_D$=−114.5 (*c* 0.7, $CHCl_3$); IR (neat) 3062, 1779, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.36 (m, 1H), 2.54–2.58 (m, 1H), 2.60–2.68 (dd, 1H), 2.80–2.99 (m, 2H), 3.20–3.26 (dd, 1H), 3.82 (t, 1H), 3.99–4.03 (dd, 1H), 4.33 (m, 1H), 4.45 (m, 1H), 5.06–5.16 (m, 2H), 5.82–5.87 (m,

1H), 7.18–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 36.7, 38.4, 38.7, 44.4, 55.9, 66.3, 117.8, 126.8, 127.7, 128.8, 129.3, 129.5, 129.8, 135.5, 135.8, 139.3, 153.4, 175.7.

Compound (2′*S*,4*R*)-**3**: mp 86–88°C; $[\alpha]_D$=−30.7 (*c* 0.5, $CHCl_3$); IR (neat) 3027, 1777, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30 (m, 1H), 2.40–2.49 (m, 2H), 2.79–2.86 (dd, 1H), 2.97–3.10 (m, 2H), 4.03–4.13 (m, 2H), 4.33 (m, 1H), 4.64 (m, 1H), 5.01–5.10 (m, 2H), 5.75–5.81 (m, 1H), 6.99–7.29 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 36.7, 38.0, 38.5, 44.7, 55.5, 66.2, 117.7, 126.9, 127.6, 128.8, 129.3, 129.8, 135.6, 139.3, 153.5, 175.7. Anal. calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.87; H, 6.52; N, 3.61.

*4.3. Benzyl (*S*)-2-allyl-3-phenylpropanoate (*S*)-**4***

To an ice-chilled solution of benzyl alcohol (2.1 g, 19.4 mmol) in dry THF (50 mL) was slowly added *n*-butyllithium (5.7 mL of 2.5 M solution in *n*-hexane, 14.3 mmol) under a nitrogen atmosphere. After the mixture was stirred for 1 h, a solution of (2′*S*,4*R*)-**3** (3.3 g, 9.4 mmol) in dry THF (20 mL) was added dropwise over a period of 30 min. The resulting mixture was stirred at −78°C for 30 min, then quenched with saturated ammonium chloride solution and partitioned between ether and water. The combined ether extracts were washed with 5% sodium bicarbonate solution and brine, then dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with a solution of ethyl acetate and *n*-hexane (1:10) to give (*S*)-**4** (2.2 g, 84%) as a colorless oil. $[\alpha]_D$=+25.8 (*c* 0.5, $CHCl_3$); IR (neat) 3029, 1731, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.32–2.46 (m, 2H), 2.80–2.91 (m, 2H), 2.94–3.03 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 36.5, 38.2, 47.7, 66.5, 117.5, 126.7, 128.4, 128.6, 128.8, 129.3, 135.5, 136.4, 139.5, 175.0.

*4.4. Benzyl (*R*)-2-allyl-3-phenylpropanoate (*R*)-**4***

This compound was synthesized from (2′*R*,4*R*)-**3** in a manner analogous to that used for its enantiomer. $[\alpha]_D$=−24.2 (*c* 0.6, $CHCl_3$).

*4.5. Benzyl (*R*)-2-benzyl-3-formylpropanoate (*R*)-**5***

Ozonized oxygen was bubbled through a solution of (*S*)-**4** (0.5 g, 1.8 mmol) in anhydrous MeOH (10 mL) at −10°C for 30 min. Nitrogen was then bubbled through the solution to displace any remaining ozone and the solution was added to a solution of thiourea (70 mg, 0.9 mmol) in anhydrous MeOH at 0°C under stirring. Thiourea *S*-dioxide started depositing as white crystals within 15 min. After stirring for another 40 min, the reaction mixture was filtered and evaporated under reduced pressure. The residue was diluted with ether and washed with 5% sodium bicarbonate and water. The resulting solution was evaporated under reduced pressure and purified by flash column chromatography to give (*R*)-**5** as a colorless oil (0.3 g, 60%). $[\alpha]_D$=+16.1 (*c* 0.6, $CHCl_3$); IR (neat) 3030, 1778, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52–2.60 (dd, 1H), 2.77–2.93 (m, 2H), 3.06–3.13 (dd, 1H), 3.25–3.31 (m, 1H), 5.13 (s, 2H), 7.13–7.39 (m, 5H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 38.0, 41.3, 44.8, 67.1, 127.2, 128.7, 129.0, 129.1, 129.4, 136.1, 138.4, 174.4, 200.3.

*4.6. Benzyl (*S*)-2-benzyl-3-formylpropanoate (*S*)-**5***

This compound was synthesized from (*R*)-**4** in a manner analogous to that used for its enantiomer. $[\alpha]_D$=−15.3 (*c* 0.5, $CHCl_3$).

4.7. Potassium (R)-2-benzyl-3-formylpropanoate (R)-**1a**

To a solution of (*R*)-**5** (200 mg, 0.7 mmol) in anhydrous methanol (3 mL) was added a catalytic amount of 10% Pd/C and the resulting suspension was stirred under hydrogen gas for 1 h. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give hydroxylactone. To 130 mg of hydroxylactone was added 0.68 mL of 1N KOH solution, and this mixture was stirred at ambient temperature until the organic layer had disappeared. Lyophilization gave (*R*)-**1a** (150 mg, 92%) as a white solid: mp 155–158°C; $[\alpha]_D$=−8.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6): δ 1.87–1.94 (dd, 1H), 2.08–2.22 (m, 1H), 2.46–2.65 (m, 2H), 3.05–3.11 (dd, 1H), 7.08–7.26 (m, 5H), 9.49 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 39.4, 47.4, 50.2, 126.3, 128.9, 129.8, 142.8, 196.5.

4.8. Potassium (S)-2-benzyl-3-formylpropanoate (S)-**1a**

This compound was synthesized from (*S*)-**5** in a manner analogous to that used for its enantiomer. $[\alpha]_D$=+7.5 (*c* 0.5, $CHCl_3$).

4.9. (R)-2-Benzyl-3-formylpropanoic acid, dicyclohexylamine salt (R)-**1b**

To a soluton of the above hydroxylactone (100 mg, 0.5 mmol) in ether was added dicyclohexylamine (0.2 mL). The resulting salt was filtered and recrystallized from CH_2Cl_2–hexane to give (*R*)-**1b** (190 mg, 96% for two steps) as white crystals: mp 129–130°C; $[\alpha]_D$=−11.3 (*c* 0.4, $CHCl_3$); IR (neat) 3500, 2939, 1715, 1561 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.18–1.36 (m, 10H), 1.62–1.97 (m, 10H), 2.29–2.31 (dd, 1H), 2.45–2.58 (ddd, 1H), 2.66–2.74 (dd, 1H), 2.85 (m, 2H), 3.00 (m, 1H), 3.17–3.24 (dd, 1H), 7.15–7.29 (m, 5H), 9.16 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.3, 25.7, 30.2, 39.0, 44.8, 44.9, 52.9, 126.5, 128.7, 129.5, 140.7, 179.1. Anal. calcd for $C_{22}H_{23}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.77; H, 9.29; N, 3.69.

4.10. (S)-2-Benzyl-3-formylpropanoic acid, dicyclohexylamine salt (S)-**1b**

This compound was obtained from (*S*)-**5** in a manner analogous to that for its enantiomer. $[\alpha]_D$=+12.4 (*c* 0.5, $CHCl_3$).

4.11. (R)-2-Benzylsuccinic acid (R)-**6**

To a solution of (*R*)-**1b** (50 mg, 0.13 mmol) and 2-methyl-2-butene (60 μL, 0.57 mmol) in *t*-BuOH (2 mL) was added dropwise a solution containing sodium chlorite (73 mg, 0.80 mmol) and sodium dihydrogen phosphate monohydrate (74 mg, 0.54 mmol) in water (3 mL). The resulting pale yellow solution was stirred at room temperature for 30 min, concentrated in vacuo, and diluted with water (5 mL). The aqueous solution was acidified to pH 2 with 3N HCl and extracted with three 5 mL portions of ethyl acetate. The ethyl acetate layers were combined, dried with $MgSO_4$, concentrated under reduced pressure, and the residue was recrystallized from ether–hexane to give (*R*)-**6** (20 mg, 72%) as a white crystalline solid: mp 165–166°C [lit.: mp 161–163°C]; $[\alpha]_D$=+26.5 (*c* 0.7, ethyl acetate) [lit.: $[\alpha]_D$=+27.2 (*c* 2.9, ethyl acetate)]; ^{1}H NMR (DMSO-d_6): δ 2.18–2.25 (dd, 1H), 2.35–2.44 (dd, 1H), 2.70–2.75 (q, 1H), 2.84–2.91 (m, 2H), 7.15–7.29 (m, 5H).

4.12. General remarks for kinetic experiment

All solutions were prepared by dissolving in doubly distilled and deionized water. Stock assay solutions were filtered before use. Carboxypeptidase A was purchased from Sigma Chemical Co. (Allan form, twice crystallized from bovine pancrease, aqueous suspension in toluene) and used without further purification. CPA stock solutions were prepared by dissolving the enzyme in 0.05 M Tris/0.5 M NaCl, pH 7.5 buffer solution. In the kinetic study, *O*-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate (Cl-CPL) purchased from Sigma Chemical Co. was used as substrate and the decrease in the absorbance at 320 nm was followed using a Perkin–Elmer HP 8453 UV/vis spectrometer at 25°C.

4.13. Determination of K_i

Initial velocities were calculated from the linear initial slopes of the change in absorbance where the amount of substrate consumed was less than 10%. The K_i values were then estimated from the semireciprocal plot of the initial velocity versus the concentration of the inhibitors according to the method of Dixon. Two concentrations of the substrate of Cl-CPL were used. Typically, enzyme stock solution was added to various concentrations of inhibitors in 0.05 M Tris/0.5 M NaCl, pH 7.5 buffer (1 mL cuvette), and the initial rates were measured immediately.

Acknowledgements

The authors wish to express their appreciation to the Korea Science and Engineering Foundation for the financial support of this work.

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