A β-lactam route to short peptide segments related to Angiotensin-converting enzyme (ACE) inhibitors

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Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday

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Abstract

The stereocontrolled synthesis of the Angiotensin Converting Enzyme (ACE) inhibitor enalapril is reported. The key transformation of the synthesis is a formal carboxylation of imines, which lies in the sequence: imine-ketene [2+2] cycloaddition reaction, ring expansion of the resulting 3-hydroxy β-lactam to a *N*-carboxy α-amino acid anhydride (NCA), and final opening of the NCA with alcohols.

Keywords: B-Lactam, stereocontrolled synthesis, angiotensin converting enzyme inhibitors, enalapril, cycloadditions

Introduction

Angiotensin converting enzyme (ACE) inhibitors are a family of peptides of major significance for controlling hypertension and congestive heart failure.[1] Most of them possess a common structural element, a *N*-substituted ethyl (S)-2-amino-4-phenylbutyrate moiety, as exemplified in the therapeutic agents enalapril, quinapril, trandolapril, and moexipril, Figure 1.[1,2]

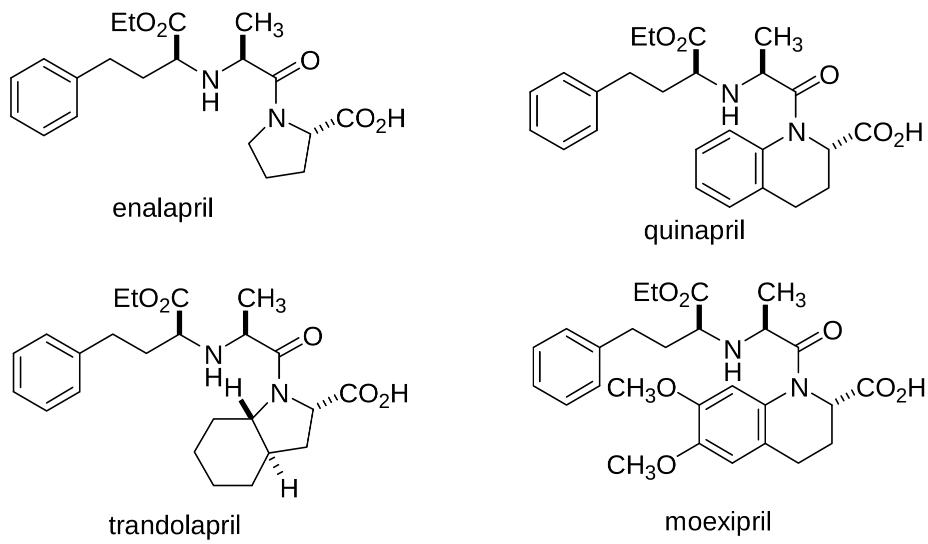


Figure 1. Representative ACE inhibitors characterized by the presence of the N-substituted-(S)-2-amino-ethyl 4-phenyl butyrate moiety.

The syntheses of this moiety have been reported via reductive amination of 2-oxo-4-phenylbutyrate,[3] conjugate addition of amines to ethyl 4-oxo-4-phenylcrotonate followed by reduction,[4] S_N2 displacement of (R)-2-hydroxybutyric acid-derived triflate intermediates by amines[5] and via asymmetric alkylations.[6] An alternative route to the ethyl 2-amino-4-phenylbutyrate moiety would be the coupling of alcohols with the corresponding α-amino acid *N*-carboxy anhydride (NCA).[7] However, the NCA required in this particular case is not directly accessible from DNA-encoded α-amino acids. In this respect, recent reports from this laboratory have documented a concise approach to non proteinogenic NCAs through β-lactam substrates which is illustrated in Figure 2, thus opening the way for new applications.[8] We wish to describe the successful implementation of this methodology to the synthesis of peptides of the ACE family of inhibitors.

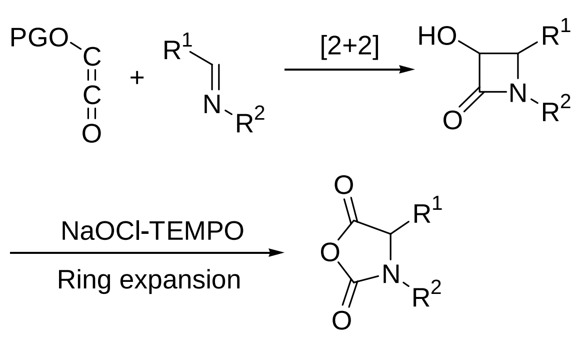
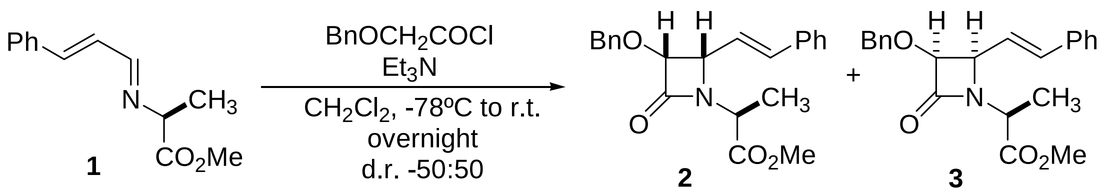


Figure 2. General strategy for the access to nonproteinogenic α-amino acid *N*-carboxy anhydrides (NCAs).

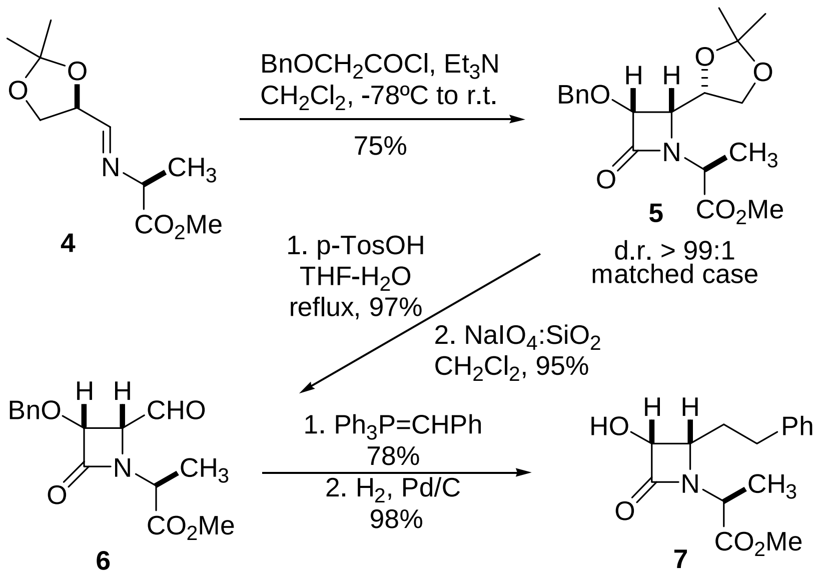
Results and Discussion

The realization of the above strategy must fulfil several requirements. Namely: (1) the appropriate 3-hydroxy β-lactam should be constructed with high chemical and stereochemical efficiency; (2) the oxidative ring expansion of the prepared 3-hydroxy β-lactam should be performed under reaction conditions, compatible with the whole molecule functionality; and (3) the coupling, or ring opening, of the intermediate NCA with the corresponding nucleophile should proceed without isomerization of the sensitive stereocenters. We first took steps towards the preparation of the 3-benzyloxy β-lactam **2**, Scheme 1, which would be a convenient substrate for our planned synthesis. To this end, we performed the reaction of benzyloxyketene, generated from benzyloxyacetyl chloride and triethylamine, with imine **1**, which unfortunately led to a mixture of diastereomeric β-lactams **2** and **3** in nearly equal amounts. This → result, which indicates the poor stereoinducting power of the chiral group attached to the nitrogen atom during the [2+2] cycloaddition process, reinforces other prior observations.[9]



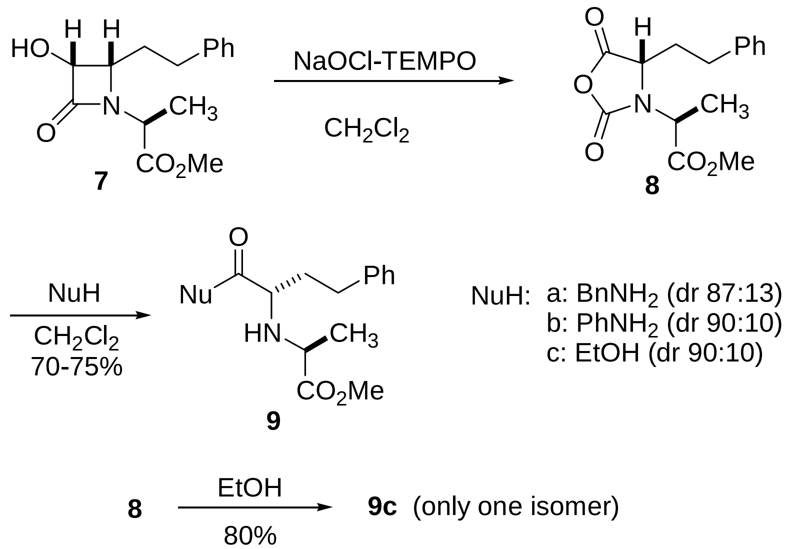
Scheme 1

We then adopted the approach depicted in Scheme 2, where the imine **4** bears chiral groups attached not only to the amine component but also to the aldehyde component. In this respect, it is known that the cycloaddition reaction of hydroxyketene equivalents with chiral α–oxy aldehyde-derived imines, independently developed by Hubschwerlen[10] and Bose,[11] usually proceeds with high diastereoselectivity. In our case, given the assumption that both chiral components of the imine are in a matched relationship,[12] an excellent level of reaction diastereoselection should be achieved. In that way, the resulting β-lactam **5** could be further elaborated into the target intermediate **7** in a concise way. We were pleased to observe that treatment of benzyloxyketene with imine **4** gave the β-lactam **5** in 75% yield and as the only detectable diastereomer. The relative *cis* configuration of the cycloadduct was determined on the basis of the ^{1}H NMR coupling constants corresponding to both hydrogen atoms at C_3 and C_4 positions ($J_{3,4}$≈5 Hz). The absolute configuration was primarily established by the assumption of an uniform reaction mechanism with regard to that in closely related reactions of known stereochemical outcome.[9] Further chemical correlation of **5** with the ACE inhibitor enalapril, *vide infra*, confirmed the configurational assignment. As pointed out, removal of the acetonide protecting group in **5**, followed by oxidative cleavage of the resulting glycol intermediate[13] provided the 4-formyl-azetidin-2-one **6**. Subsequent Wittig reaction of **6**, and exposure of the resulting olefinic intermediate to hydrogen over palladium on charcoal, furnished the β-lactam **7** in good overall yield.



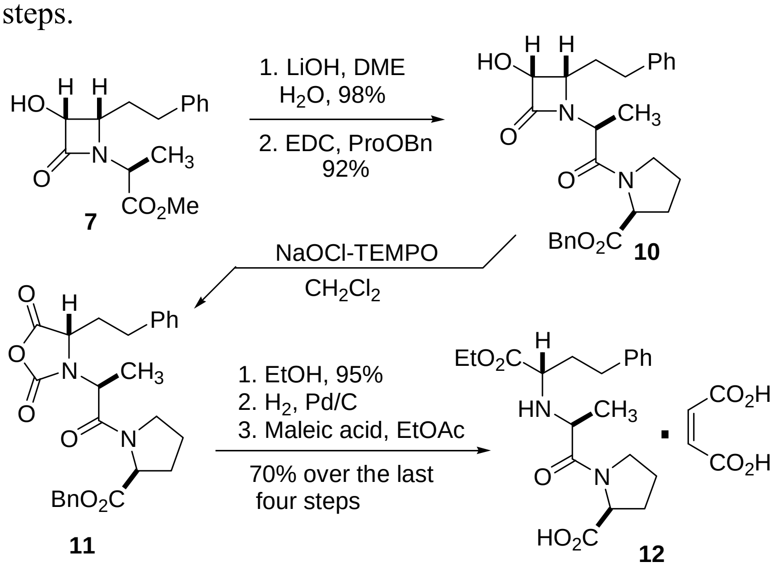
Scheme 2

With this compound in hand, a direct pathway to NCA **8** was available, Scheme 3. This allowed us to examine the optimal conditions for the opening of the NCA precursor of enalapril, *vide infra*, using **8** as a study model. To this end, the β-lactam **7** was transformed into the NCA **8** in 95% yield by treatment with a solution of commercial bleach and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO). Then, the coupling reaction of this NCA with three representative nucleophiles in methylene chloride (mol ratio of **8** to nucleophile 1:2) was carried out, and the isomerization degree for each reaction was determined by ^{13}C NMR. The coupling reactions with benzylamine and aniline gave **9a** and **9b**, along with the corresponding epimers, in ratios of 87:13 and 90:10, respectively. The reaction of **8** with ethanol in methylene chloride as solvent afforded a mixture of **9c** and its epimeric isomer in a 90:10 ratio. These results corroborate previous observations that establish varying degrees of isomerization when phenylethyl substituted NCA's are treated with *N*- and *O*-nucleophiles in solvents such as methylene chloride, diethyl ether, or DMF.[14] In these studies, it was also shown that the opening of such a type of NCA with methanol, using the latter as the reaction solvent, proceeded with no isomerization. In accordance with this previous observation, we were gratified to observe that the treatment of NCA **8** with ethanol, using the latter as the reaction solvent, at room temperature for 14 hours furnished the adduct **9c** as the only detectable diastereomer and in a 80% isolated yield.



Scheme 3

With these results in hand, the synthesis of enalapril was undertaken. As illustrated in Scheme 4, saponification of the ester group in **7**, followed by peptide coupling with (L)-proline benzyl ester under standard peptide coupling conditions, gave the dipeptide **10** in 90% yield over the two steps. Treatment of **10** with a solution of commercial bleach and a catalytic amount of TEMPO furnished, in almost quantitative yield, the NCA **11**. Treatment of **11** with ethanol, followed by hydrogenation and treatment with maleic acid, afforded the salt **12** in 70% yield over the last three steps.



Scheme 4. EDC: *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide.

In conclusion, a concise and stereocontrolled synthesis of the ACE inhibitor enalapril has been achieved. It is also clear that the present methodology can be easily adapted to the synthesis of other structurally related ACE-inhibitors.

Experimental Section

Preparation of the β-lactam (5). A mixture of D-glyceraldehyde dimethyl acetonide (1.30 g , 10 mmol), triethylamine (2.77 ml, 20 mmol), alanine methyl ester (0.82 g, 8 mmol), and $MgSO_4$ (10 g) in methylene chloride (50 ml) was stirred at 0ºC for 3 h. The solution was then filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in dry methylene chloride (50 ml) and cooled to -78 ºC under a nitrogen atmosphere, and to the resulting solution were successively added triethylamine (4.47 ml, 25 mmol) and dropwise a solution of benzyloxyacetyl chloride (2.05 ml, 13 mmol) in dry methylene chloride (20 ml). The resulting mixture was stirred overnight at room temperature and was then washed with water (50 ml), 0.1 N HCl (2 x 50 ml), and a saturated solution of $NaHCO_3$ (50 ml). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude β-lactam **5**, obtained as an oil, was purified by column chromatography (silica gel, ethyl acetate: hexane 1:4 as eluent). Yield 2.18 g (75 %); $[\alpha]_D^{25}$ = +79.3 (*c*=1, CH_2Cl_2); IR (film, ν) 1760.5, 1736.5 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.39-7.26 (m, 5H, aromat), 4.92 (d, 1H, J=11.9 Hz, *H*CH), 4.67 (d, 1H, J=5.3 Hz, *H*CCO), 4.65 (d, 1H, J=11.9 Hz, HC*H*), 4.5 (q, 1H, J=7.3 Hz, *H*CCH_3), 4.32 (ddd, 1H, J=9.1 Hz, J'=3.7 Hz, J''=2.7 Hz, *H*CO), 4.18 (dd, 1H, J=8.7 Hz, J'=3.7 Hz, *H*CH), 3.92 (dd, 1H, J=9.1 Hz, J'=5.3 Hz, *H*CN), 3.74 (s, 3H, OCH_3), 3.62 (dd, 1H, J=8.7 Hz, J'=2.7 Hz, HC*H*), 1.6 (d, 3H, J=7.3 Hz, *H*CCH_3), 1.38 (s, 3H, CH_3CCH_3), 1.31 (s, 3H, CH_3CCH_3); ^{13}C NMR ($CDCl_3$, δ) 171.0, 167.6, 136.8, 128.5, 128.1, 127.6, 109.3, 80.1, 76.3, 73.0, 66.8, 61.3, 52.4, 50.3, 26.7, 25.1, 16.4; Anal. Calcd for: $C_{19}H_{25}O_6N$ (363.41): C, 62.80; H, 6.93; N, 3.85. Found: C, 62.71; H, 6.72; N, 3.83.

Preparation of 4-formyl-β-lactam (6). To a solution of β-lactam 5 (3.63 g, 10 mmol) in THF (90 ml) and water (20 ml) p-toluensulfonic acid (0.57 g, 3 mmol) was added, and the mixture was heated under reflux overnight. The THF was then evaporated and the residue was partitioned between ethyl acetate (80 mL) and a saturated solution of sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (2 x 25 ml) and the organic layers combined. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The diol product was obtained as a white solid, which was washed with hexane. Yield 2.83 g (97%); M.p. 89-91 ºC; $[\alpha]_D^{25}$ = +79.3 (*c*=1, CH_2Cl_2); IR (KBr, ν) 1748.5, 1731.9 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.4-7.3 (m, 5H, aromat), 4.96 (d, 1H, J=11.7 Hz, *H*CH), 4.69 (d, 1H, J=11.7 Hz, HC*H*), 4.42 (c, 1H, J=7.4 Hz, *H*CCH_3), 4.02 (m, 2H, *H*CN + *H*COH), 3.77 (s, 3H, OCH_3), 3.78-3.55 (m, 2H, H_2COH), 1.6 (d, 3H, J=7.4 Hz, HCCH_3); ^{13}C NMR ($CDCl_3$, δ) 171.8, 167.5, 136.5, 128.5, 128.2, 128.0, 80.2, 73.1, 70.7, 63.9, 60.1, 52.7, 51.3, 16.6; Anal. Calcd for $C_{16}H_{21}O_6N$ (323.34): C, 59.43; H, 6.54; N, 4.33. Found: C, 59.61; H, 6.37; N, 4.38. To a solution of the above obtained diol (3.23 g, 10 mmol) in dry methylene chloride (50 ml) $NaIO_4$ supported over silicagel (for details, see reference 13) was added. The resulting suspension was then stirred for 1h at room temperature. The solid was filtered and the solvent was removed under reduced pressure to give the title compound as an oil. Yield 2.76 g (95%); $[\alpha]^{25}_D$ = + 73.5 (*c* = 1, CH_2Cl_2); IR (KBr, ν) 1765, 1750, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 9.64 (d, 1H, J=3.4 Hz, *H*CO), 7.45-7.30 (m, 5H, aromat), 5.00 (d, 1H, J=5.4 Hz, *H*C), 4.76 (d, 1H, J=11.5 Hz, *H*CH), 4.65 (d, 1H, J=11.5 Hz, HC*H*), 4.64 (c, 1H, J=7.4 Hz, *H*CCH_3), 4.60 (dd, 1H, J=3.4 Hz, J'=5.4 Hz, *H*CN), 3.73 (s, 3H, OCH_3), 1.46 (d, 3H, J=7.4 Hz, HCCH_3); ^{13}C NMR ($CDCl_3$, δ) 199.0, 170.9, 166.6, 135.8, 128.6, 128.4, 128.2, 83.1, 73.4, 64.1, 52.7, 49.5, 16.5; Anal. Calcd for $C_{15}H_{17}O_5N$ (291.30): C, 61.85; H, 5.88; N, 4.80. Found: C, 61.96; H, 5.70; N, 4.71.

Preparation of the 3-hydroxy β-lactam (7). To a suspension of benzyltriphenylphosphonium chloride (0.46 g, 1.2 mmol) in dry THF (10 ml) at 0ºC , sodium bistrimethylsilyl amide (1M in THF, 1.1 ml) was added and the mixture was stirred for 30 min. The mixture was then cooled a –78ºC and a solution of β-lactam **6** (0.29 g, 1 mmol) in dry THF (5 ml) was added. After stirring the resulting mixture for one additional hour at the same temperature, the reaction was quenched with a saturated solution of sodium chloride. The aqueous phase was separated and extracted with diethyl ether (2 x 20 ml). The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give the title compound which was purified by column chromatography (silica gel, ethyl acetate:hexane 1:2 as eluent). Yield 0.28 g (78%); ^{1}H NMR ($CDCl_3$, δ) 7.4-7.2 (m, 10H, aromat.), 6.8 (d, 1H, J=11.5 Hz, *H*CH), 5.89 (dd, 1H, J=11.5 Hz, J'=9.8 Hz, *H*CCH), 5.00 (dd, 1H, J=9.8 Hz, J'=4.9 Hz, HCC*H*), 4.87 (d, 1H, J=4.9 Hz, *H*CCO), 4.76 (d, 1H, J=11.7 Hz, *H*CH), 4.72 (d, 1H, J=11.7 Hz, HC*H*), 4.57 (c, 1H, J=7.5 Hz, *H*CCH_3), 3.64 (s, 3H, OCH_3), 1.43 (d, 3H, J=7.5 Hz, HCCH_3). To a solution of the above product in methanol (5 ml) Pd over charcoal (10% w/w) was added and the mixture was kept for 14 h under H_2 (1 atm). The solid was then filtered through a pad of celite and the solvent was removed under reduced pressure. Yield 0.21 g (98%); M.p. 81-83ºC; $[\alpha]^{25}_D$ = + 63.9 (*c*=1, CH_2Cl_2); IR (KBr, ν) 3426, 1746, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 7.3-7.15 (m, 5H, aromat.), 4.95 (d, 1H, J=4.8 Hz, *H*CCO), 4.43 (c, 1H, J=7.5 Hz, *H*CCH_3), 3.98 (m, 1H, *H*CCN), 3.70 (s, 3H, OCH_3), 2.82 (m, 1H, H_2CCH_2), 2.63 (m, 1H, H_2CCH_2), 2.11 (m, 2H, H_2CCH_2), 1.47 (d, 3H, J=7.5 Hz, HCCH_3); ^{13}C NMR ($CDCl_3$, δ) 170.8, 169.6, 141.3, 128.3, 128.2, 126, 75.7, 59.2, 52.1, 49.6, 31.8, 30.9, 16.6; Anal. Calcd for $C_{15}H_{19}O_4N$ (277.32): C, 64.96; H, 6.90; N, 5.05. Found: C, 64.79; H, 6.72, N, 5.18.

Preparation of dipeptide (10). To a solution of 3-hydroxy-β-lactam 7 (0.27 g, 1 mmol) in a mixture of dimethoxyethane (5 ml) and water (3.5 ml) at 0ºC, lithium hydroxide (0.08 g, 2 mmol) was added. After stirring the reaction mixture for 1 h, it was quenched with 6N HCl. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product thus obtained was dissolved in dry methylene chloride (10 ml) and L-proline benzyl ester (0.20 g, 1 mmol) and 1-hydroxy-benzotriazole (0.13 g, 1 mmol) were successively added. The mixture was cooled to 0ºC, EDC (0.29 g, 1.5 mmol) added, and the mixture was stirred overnight. The solution was then washed with an aqueous solution of potassium acid sulfate (0.1M, 10 ml) and water (2 x 10 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give dipeptide 10 as an oil. Yield 0.40 g (92%); $[\alpha]^{25}_D$ = –35.6 (c=1, CH_2Cl_2); IR (KBr, ν) 3409, 1953, 1743, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 7.40-7.20 (m, 10H, aromat.), 5.25 (d, 1H, J=12.3 Hz, *H*CH), 5.08 (d, 1H, J=12.3 Hz, HC*H*), 4.90 (d, 1H, *H*CCO), 4.70 (q, 1H, J=7.2 Hz, *H*CCH_3), 4.53 (dd, 1H, J=4.08 Hz, J'= 3.98 Hz, *H*CCOO), 4.18 (m, 1H, *H*CCH_2), 3.61 (m, 2H, CH_2), 2.80 (m, 1H, *H*CH), 2.62 (m, 1H, HC*H*), 2.29-1.91 (m, 6H, 3CH_2), 1.38 (d, 3H, J=7.2 Hz, HCCH_3); ^{13}C NMR ($CDCl_3$, δ) 172, 169.5, 169.3, 142.1, 136.0, 129.0, 128.9, 128.8, 128.7, 128.6, 126.5, 76.3, 67.4, 60.7, 59.3, 48.5, 47.4, 32.4, 31.7, 29.3, 25.3, 16.9. Anal. Calcd for $C_{26}H_{30}O_5N_2$ (450.53): C, 69.31; H, 6.71; N, 6.22. Found: C, 69.17; H, 6.87; N, 6.36.

Preparation of enalapril maleate (12). To a solution of 3–hydroxy-β-lactam 10 (0.45 g, 1 mmol) in methylene chloride (10 mL) at 0ºC potassium bromide (5 mg, 0.05 mmol), TEMPO (0.1 mg, 0.0025 mmol) and a mixture of a solution of sodium hypochlorite (10 ml, 4% Cl_2, from Aldrich) and phosphate buffer (30 ml, pH= 7) were added. The mixture was stirred for 1 min and the organic layer was then separated. The aqueous phase was extracted with methylene chloride (2 x 10 ml) and the combined organic phase was successively washed with a 2N solution of HCl, a solution of KI (obtained by addition of 0.24 g of KI to 50 ml of 2N HCl), sodium thiosulfate (30 ml, sol. 30 %), and water (30 ml). The organic layer was dried over $MgSO_4$ and the solvent was eliminated under reduced pressure to give the NCA 11. Selected data: IR (KBr, ν) 1844, 1768, 1745 , 1652 cm^{-1}. To the crude product 11 ethanol (5ml) was added, and the solution was stirred for 14 h at room temperature. The residue obtained by evaporation of the solvent was dissolved in methanol, and Pd over charcoal (10% w/w) was added, and the suspension was stirred under hydrogen atmosphere for 14 h. The solid was filtered through celite and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and maleic acid was added to the resulting solution. The mixture was stirred for 3 h at room temperature. The suspension was filtered and the solid was washed with ethyl acetate. Yield 0.35 g (70%); M.p. 146-147ºC; $[\alpha]^{25}_D$= –42.1 (c=1, MeOH) (Lit[3a] M.p. 143-144.5ºC; $[\alpha]^{25}_D$ = –42.2); IR (KBr, ν) 3214, 1751, 1728, 1647 cm^{-1}; ^{1}H NMR (CD_3OD, δ) 7.30-7.19 (m, 5H, aromat.), 6.25 (s, 2H, HCCH), 4.50 (m, 1H, HCCOOH), 4.30-4.20 (m, 3H, $HCCH_3$), 4.08 (minor), 3.94 (minor), 3.86 (t, 1H, J= 3.5 Hz, HCNH) (major), 3.57 (m, 2H, HCN), 2.82 (m, 2H), 2.33-1.99 (m, 6H, $3CH_2$), 1.70 (minor), 1.55 (d, 3H, J= 4.4 Hz, $HCCH_3$) (major), 1.53 (minor), 1.32 (t, 3H, J= 7.1 Hz, CH_2CH_3); ^{13}C NMR (CD_3OD, δ) 176.6, 176.5, 172.3, 172.2, 171.6, 171.2, 170.6, 142.9, 142.8, 137.6, 131.3, 131.2, 129.2, 65.6, 65.5, 62.4, 61.8, 61.6, 58.3, 57.8, 49.7, 35.2, 35.1, 33.7, 33.6, 31.7, 27.6, 24.8, 18.0, 17.5, 16.1, 16.0.

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