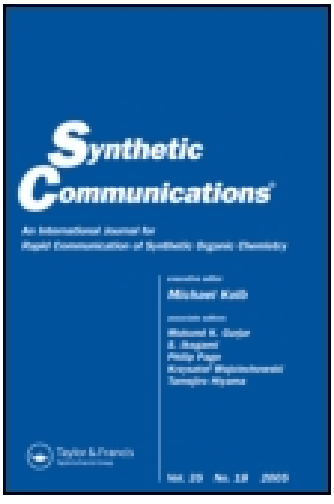

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Expeditious Synthesis of Ramipril: An Angiotensin Converting Enzyme (ACE) Inhibitor

Golla China Malakondaiah,[1,2] V. M. Gurav,[1] Lekkala Amarnath Reddy,[2] Karrothu Srihari Babu,[2] Bolugoddu Vijaya Bhaskar,[2] Padi Pratap Reddy,[2] Apurba Bhattacharya,[2] and Ramasamy Vijaya Anand[2]

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Abstract: We document an efficient and cost-effective synthesis of ramipril **1** utilizing (i) an environmentally benign process for the esterification of *racemic* 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride **2** using boric acid as a catalyst and (ii) a robust resolution process for the synthesis of **3a** by means of inexpensive and recyclable L-(+)-mandelic acid as key steps.

Keywords: Boric acid, esterification, L-(+)-mandelic acid, ramipril, resolution

INTRODUCTION

Ramipril **1**[1] (Fig. 1), a 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid derivative, belongs to a class of angiotensin converting enzyme (ACE) inhibitors,[2] which are used for treating high blood pressure and congestive heart failure and also for preventing kidney failure due to high blood pressure

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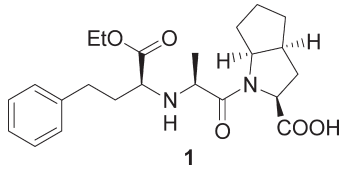

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Figure 1. Molecular framework of ramipril **1**.

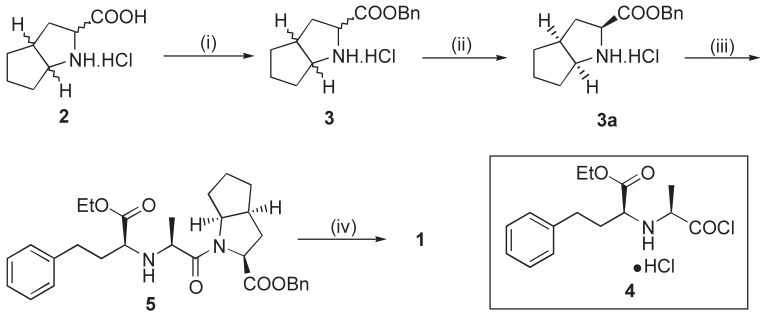
and diabetes. It is a prodrug that gets hydrolyzed in the liver after absorption from the gastrointestinal tract to form the active ACE inhibitor ramiprilate.[3] Ramiprilate lowers the conversion of angiotensin I to angiotensin II (which is responsible for tightening the blood vessels), which results in dilation of peripheral vessels and reduction in vascular resistance. Ramipril is available in the market under the brand name Altace® as capsules for oral administration.

Structurally, ramipril **1** features five chiral centers, all are having the *S* configuration, three of which are on a 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid core and two from the *N*-substituted alanine derivative. These two fragments are connected through an amide tether. Few literature precedents are available for the synthesis of ramipril **1**[4]; unfortunately all of them involve purification techniques such as column chromatography and repeated recrystallization at least in one of the stages, which made them industrially less attractive. Herein, we divulge our efforts to synthesize optically pure ramipril **1** utilizing the following key steps: (a) environmentally benign process for the esterification of **2** using boric acid as a catalyst and (b) resolution of the bicyclic amino ester intermediate **3** with inexpensive and recyclable L(+)-mandelic acid.[5]

RESULTS AND DISCUSSION

Our approach to the synthesis of ramipril **1** starts with readily available *racemic* 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid **2**.[6] While exploring the concept of green chemistry in industrial processes,[7] we discovered that boric acid[8] efficiently catalyzed the esterification of **2** with 2 equivalents of benzyl alcohol in toluene under reflux conditions to provide the ester **3** in 83% yield (Scheme 1). In contrast to this, the hitherto known routes for the synthesis of **3** invole benzylation of **2** with a large excess of benzyl alcohol and thionyl chloride, and the product **3** was precipitated by the addition of 15 volumes of diisopropyl ether with respect to benzyl alcohol, which made the workup process combersome and not ecofriendly. The synthesis of **3** by our method is an environmentally benign process because no effluents are generated and no additional solvents are required to precipitate the product.

The resolution of racemic 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester **3** was carried out by means of commercially available and



Scheme 1. Synthesis of ramipril **1**. Conditions: (i) H_3BO_3 (cat.), BnOH, phme, Δ, 83%; (ii) NaOH then L(+)-mandelic acid, EtOAc, 0–5 °C, aq. HCl, 90%, 2 steps (with respect to single isomer); (iii) **4**, Et_3N, CH_2Cl_2, 0–5 °C, 94%; (iv) Pd-C/H_2, EtOH, 0–10 °C, 95%.

inexpensive L(+)-mandelic acid to furnish (*S,S,S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester **3a** in 45% yield (90% with respect to a single isomer).[5] Apart from L(+)-mandelic acid, various other resolving agents such as L-(+)-tartaric acid, (+)-dibenzyl tartaric acid, (+)-di-*p*-toluoyl tartaric acid, (+)-camphorsulfonic acid, (+)-naproxen, and (+)-ibuprofen were screened but gave unsatisfactory results. The L(+)-mandelic acid used for the resolution process was recycled and reused several times without affecting the yield and chiral purity of **3a** (Table 1).

The (*S,S,S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester **3a** thus obtained was coupled with benzyl *N*-(2*S*-carbethoxy-3-phenyl propyl)-*S*-alanine acid chloride **4**, which in turn was prepared by the reaction of PCl_5 with the corresponding acid (commercially available from Aarthi Drugs Pvt. Ltd., Mumbai) in the presence of triethylamine to furnish ramipril benzyl ester **5** in 94% yield. The reaction was very efficient, and no other side products or impurities were detected. We also carried out the condensation reaction between **3a** and **4** in the presence of a catalytic

Table 1. Resolution of **3** using recycled L(+)-mandelic acid

S. no.	Number of cycles	Yield of **3a** (%)[a]	Chiral purity of **3a** (%)[b]
1	1	90	99.85
2	2	90	99.66
3	3	91	99.70

[a]With respect to single isomer.
[b]Determined by HPLC.

amount of boric acid under reflux conditions in toluene, but the desired product **5** was formed only in 20% yield; this might be due to the instability of **4** under thermal conditions. Finally, hydrogenolysis of ramipril benzyl ester **5** provided optically pure ramipril **1** in 95% yield (Scheme 1).[5]

CONCLUSION

A simple, commercially viable process for the synthesis of ramipril **1** was accomplished through esterification of *racemic* 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid **2**, in an environmentally benign manner, using boric acid as a catalyst and a robust resolution process for the synthesis of **3a** by means of inexpensive and recyclable L-(+)-mandelic acid. This process addressed all the manufacturing concerns with respect to environmental safety and quality. Upon practicing the disclosed process, a significant cost reduction in the synthesis of ramipril **1** was realized.

EXPERIMENTAL SECTION

General Methods

^{1}H NMR spectra were recorded on a 400-MHz Varian Gemini FT NMR spectrometer, and ^{13}C NMR spectra were recorded using a 200-MHz Varian Gemini FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The Fourier transform infra red (FT-IR) spectra were recorded using a Perkin-Elmer 16650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on a HP-5989A LC-MS spectrometer. The melting points were determined using the capillary method on a Polmon (model MP-96) melting-point apparatus and are uncorrected. The solvents and reagents were used without further purification.

Preparation of *Racemic* 2-Azabicyclo-[3.3.0]-octane-3-carboxylic Acid Benzyl Ester Hydrochloride (3)

A mixture of *racemic* 2-azabicyclo-[3.3.0]-octane-3-carboxylic acid (10.0 g, 0.065 mol), boric acid (0.30 g, 0.0048 mol), benzyl alcohol (40.6 g, 0.195 mol), and toluene (100 mL) was charged in a Dean-Stark container and refluxed (105–110 °C) for 10 h. During the reaction, water was removed azeotropically. After the reaction was complete (monitored by thin-layer chromatography, TLC), the reaction mass was cooled to room temperature. Boric acid was filtered off, and the filtrate was concentrated under reduced pressure to yield the crude product. Dry HCl was passed through the crude product in DCM (50 mL) to precipitate the title compound **3**[6c] as a white powder. Yield 15 g (83%); mp 180 °C (lit.[6c] mp

185 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 1H), 1.58–1.75 (m, 2H), 1.82–2.01 (m, 3H), 2.32–2.37 (m, 1H), 2.58 (dt, $J = 13.2$, 8.4 Hz, 1H), 2.83–2.88 (m, 1H), 4.31 (td, $J = 8.0$, 3.6 Hz, 1H), 4.43 (t, $J = 8.4$ Hz, 1H), 5.20 (AB q, $J = 12.0$ Hz, 2H), 7.33–7.37 (m, 5H); ^{13}C NMR (50 MHz, DMSO) δ 24.12, 29.59, 31.04, 33.45, 41.35, 60.07, 63.77, 66.95, 128.12, 128.26, 128.42, 135.17, 167.30; FT IR (KBr disc) 1761 cm^{-1}; MS: m/e 246 (M^+).

Preparation of (*S,S,S*)-2-Azabicyclo-[3.3.0]-octane-3-carboxylic Acid Benzyl Ester Hydrochloride (3a)

A suspension of racemic 2-azabicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester hydrochloride (100.0 g, 0.36 mol) in EtOAc (400 mL) was treated with 20% aqueous sodium hydroxide solution (130 mL, 0.65 mol) and stirred for an hour at 0–5 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic layer was then concentrated under reduced pressure to yield the free base (87.0 g, 0.36 mol). A solution of L-(+)-mandelic acid (54.0 g, 0.36 mol) in EtOAc (350 mL) was added to this crude product, and the resulting reaction mixture was stirred for 2 h at 0–5 °C. The reaction mixture was filtered, and the salt was washed with chilled EtOAc (100 mL) and dried at 60–65 °C to provide (*S,S,S*)-2-azabicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester mandelate salt as a white powder (67.0 g, 47.5% [95% with respect to single isomer]); mp 116 °C; $[\alpha]_D^{20} = +14.0$ (c = 1, H_2O); ^{1}H NMR (400 MHz, DMSO) δ 1.36–1.55 (m, 5H), 1.61–1.64 (m, 2H), 2.24–2.31 (m, 1H), 2.55–2.59 (m, 1H), 3.65 (bt, $J = 6.8$ Hz, 1H), 3.81 (dd, $J = 10.0$, 6.8 Hz, 1H), 4.89 (s, 1H), 5.13 (AB q, $J = 12.4$ Hz, 2H), 7.22–7.41 (m, 10H); ^{13}C NMR (50 MHz, DMSO) δ 23.64, 31.92, 32.45, 36.03, 41.86, 60.45, 63.20, 65.92, 72.75, 126.49, 127.02, 127.79, 127.86, 128.07, 128.42, 135.83, 141.45, 171.15, 174.48; IR (KBr disc) 1752, 1646, 1584, 1358 cm^{-1}; MS: m/e 246 (M^+).

A suspension of (*S,S,S*)-2-azabicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester mandelate salt (50.0 g, 0.13 mol) in CH_2Cl_2 (250 mL) was treated with 25% aqueous sodium hydroxide solution (40.0 mL, 0.25 mol) at 0–5 °C and stirred for 30–40 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). Conc. HCl (12 mL) was added to the combined organic layer at 0–5 °C, stirred for an hour, and filtered. The resultant solid was washed with chilled CH_2Cl_2 (50 mL) and dried at 60 °C for 4–5 h under vacuum to provide the title compound **3a** as a white solid. Yield 33.7 g (95%); mp 178–180 °C (lit.[6c] mp 180 °C); $[\alpha]_D^{20} = -40.0$ (c = 1, H_2O) [lit.[6c] $[\alpha]_D^{30} = -38.4$ (c = 1, H_2O)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 1H), 1.58–1.75 (m, 2H), 1.82–2.01 (m, 3H), 2.32–2.37 (m, 1H), 2.58 (dt, $J = 13.2$, 8.4 Hz, 1H), 2.83–2.88 (m, 1H), 4.31 (td, $J = 8.0$, 3.6 Hz, 1H), 4.43 (t, $J = 8.4$ Hz, 1H), 5.20 (AB q,

$J = 12.0$ Hz, 2H), 7.33–7.37 (m, 5H); ^{13}C NMR (50 MHz, DMSO) δ 24.07, 29.60, 31.02, 33.45, 41.37, 60.11, 63.81, 66.99, 128.11, 128.28, 128.43, 135.14, 167.32; FT IR (KBr disc) 1758 cm^{-1}; MS: m/e 246 (M^+).

Preparation of *N*-(2*S*-Carbethoxy-3-phenyl Propyl)-*S*-alanoyl Chloride Hydrochloride (4)

A mixture of *N*-(2*S*-carbethoxy-3-phenyl propyl)-*S*-alanine (27.0 g, 0.091 mol), toluene (240 mL), and chloroform (30 mL) was charged into a clean, dry, round-bottom flask and cooled to 15–20 °C. Dry HCl gas was passed through it for about 15–20 min. The resultant suspension was further cooled to 0–5 °C, and PCl_5 (25 g, 0.12 mol) to this was added. The reaction mixture was stirred for an hour at 0–5 °C and at 25–30 °C for 3 h. It was filtered, and the solid collected was washed with toluene (30 mL) and petroleum ether (75 mL) to afford *N*-(2*S*-carbethoxy-3-phenyl propyl)-*S*-alanoyl chloride hydrochloride **4** as a white solid. Yield 30.6 g (95%); this compound was used as such in the next step.

Preparation of Ramipril Benzyl Ester (5)

A solution of **4** (28.7 g, 0.086 mol) in CH_2Cl_2 (500 mL) was added in a drop wise manner to a mixture of (*S,S,S*)-2-azabicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester hydrochloride **3a** (18.2 g, 0.065 mol) and Et_3N (22.5 g, 0.222 mol) in CH_2Cl_2 (300 mL) at 0–5 °C, and the resulting solution was stirred for 3 h. After the reaction was complete (vide TLC), water (500 mL) was added to the reaction mixture, and the organic layer was separated out. It was washed with saturated aqueous sodium carbonate solution (275 mL) followed by brine solution. The organic layer was dried over anhydrous Na_2SO_4. Removal of solvent under vacuum at 30–35 °C afforded the ramipril benzyl ester **5**[9] as a viscous paste. Yield 32.1 g (94%); $[\alpha]_D^{24} = -13.5$ (c = 1 in 0.1 N methanolic HCl);^{1}H NMR (400 MHz, $CDCl_3$) (2:1 rotamers) δ 1.23 (d, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.50–1.63 (m, 1H), 1.71–1.81 (m, 3H), 1.86–2.07 (m, 3H), 2.11–2.22 (m, 1H), 2.29–2.40 (m, 2H), 2.63–2.79 (m, 3H), 3.19 (t, $J = 6.8$ Hz, 1H), 3.32–3.34 (m, 0.5H), 3.64 (q, $J = 6.8$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 4.08–4.31 (m, 1H), 4.43–4.47 (m, 0.5H), 4.68 (dd, $J = 8.8$, 6.4 Hz, 1H), 5.10 (d, $J = 12.4$ Hz, 1H), 5.19 (d, $J = 12.4$ Hz, 1H), 7.15–7.19 (m, 3H), 7.22–7.28 (m, 2H), 7.32–7.35 (m, 5H); FT IR (neat) 1739, 1645 cm^{-1}; MS: m/e 529 (M^++ Na).

Preparation of Ramipril (1)

A mixture of ramipril benzyl ester **5** (32.0 g, 0.063 mol), ethanol (200 mL), water (20 mL), and wet palladium carbon (6.5 g [10% Pd]) was charged in

an autoclave and maintained at 2.5–3.0 kg/cm^2 of hydrogen pressure at 0–10 °C. The reaction was monitored by high performance liquid chromatography (HPLC). After the reaction was complete, the reaction mixture was filtered through a pad of Celite® followed by washing with acetone (50 mL). The filtrate was concentrated at 15–20 °C under vacuum to afford the crude ramipril **1**. It was dissolved in a mixture of diisopropyl ether (65 mL) and diethyl ether (33 mL), cooled to 0–5 °C, and maintained for 45–60 min. The separated solid was filtered and washed with a mixture of di-isopropyl ether and diethyl ether (33 mL: 17 mL) to provide pure ramipril **1**[4h] as a white solid. Yield 25.0 g (95%); mp 110 °C (lit.[4h] mp 108 °C); $[\alpha]_D^{20} = +38.0$ (c = 1 in 0.1 N methanolic HCl) [lit.[10] $[\alpha]_D^{24} = +33.2$ (c = 1 in 0.1 N ethanolic HCl)]; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, $J = 7.2$ Hz, 3H), 1.39 (d, $J = 6.8$ Hz, 3H), 1.58–1.66 (m, 3H), 1.74–1.88 (m, 4H), 2.23–2.33 (m, 1H), 2.37–2.44 (m, 1H), 2.52–2.79 (m, 4H), 3.98–4.04 (m, 2H), 4.10–4.26 (m, 3H), 4.31 (dd, $J = 8.0$, 5.6 Hz, 1H), 7.17–7.21 (m, 3H), 7.27–7.31 (m, 2H); FT IR (KBr disc) 3445, 1744, 1653 cm^{-1}; MS: m/e 417 (M^+).

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11. Chiral cell *OJ* 205 × 4.6 mm or equivalent, flow rate 0.5 mL/min with a UV detector at 215 nm, 20 μL, run time 40 min. Mobile phase: a mixture of 94 volumes of *n*-hexane, 6 volumes of ethanol, 2.2 mL of diethyeamine and 0.2 mL of trifluoroacetic acid.