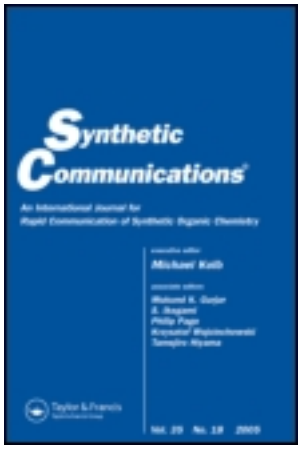

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ASYMMETRIC SYNTHESIS OF (*S,S,S*)-2-AZA-BICYCLO-[3.3.0]-OCTANE-3-CARBOXYLIC ACID BENZYL ESTER: FORMAL SYNTHESIS OF RAMIPRIL

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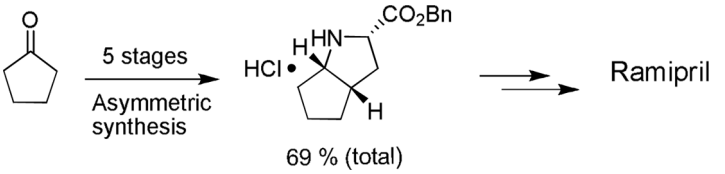
GRAPHICAL ABSTRACT



Abstract *An asymmetric synthesis of (*S,S,S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester* ***2*** *as an intermediate of angiotensin converting enzyme (ACE) inhibitor, ramipril* ***1****, is described.*

Keywords (*S*)-1-Amino-2-methoxy methylpyrrolidine (SAMP); angiotensin converting enzyme (ACE) inhibitor; asymmetric synthesis; chiral auxiliary; enantiomerically pure ramipril

INTRODUCTION

Stereoselective reactions, employing chiral auxiliaries or chiral catalysts, have become one major interest in academia and industry. This is repeatedly evident in synthetic organic chemistry, because the biologically active molecule, as one of the enantiomers, often shows the desired activity whereas the other one is either ineffective or undesired in terms of toxicity. We adopted a novel approach for an asymmetric synthesis of **2**, which was used in the formal synthesis of enantiomerically pure ramipril **1** (Fig. 1).[1]

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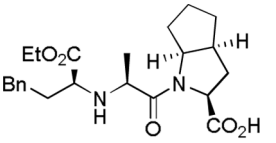
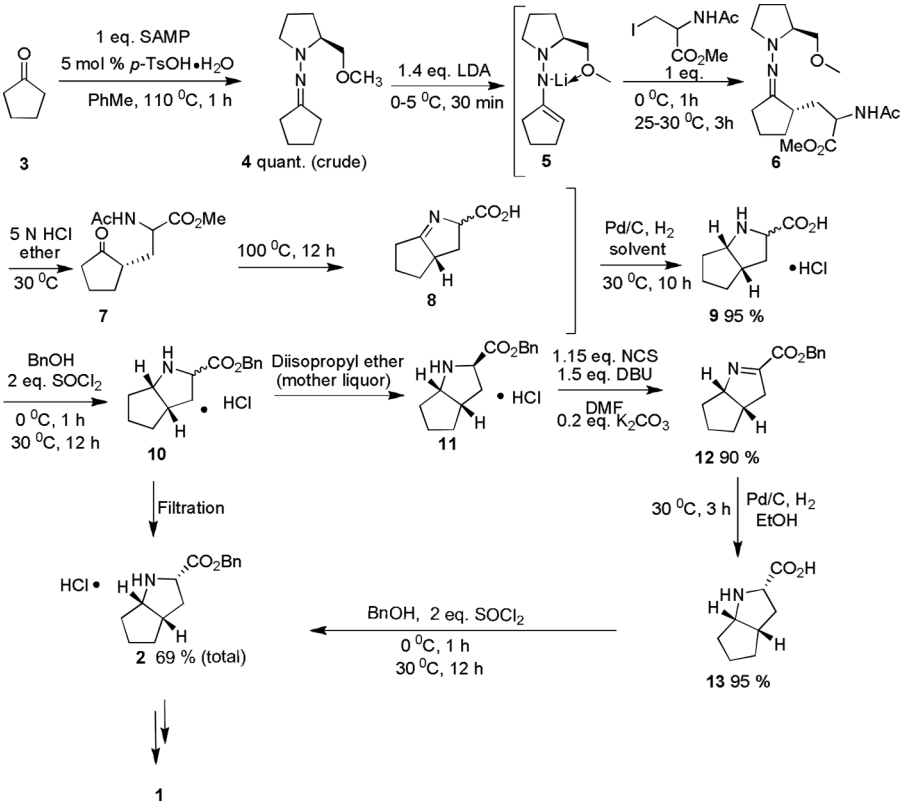


Ramipril **1**

Figure 1. Structure of ramipril **1**.

A plethora of synthetic routes for the preparation of the precursor of **2**, racemic 2-azabicyclo-[3.3.0]-octane-3-carboxylic acid, have been used: anodic oxidation of *N*-acyl cyclopentapyrroles and subsequent cyanation and hydrolysis,[2] 1,3-dipolar cycloaddition of azomethines strategy,[3] strategy starting from serine,[4] resolution-based methods,[4b,5–7] conjugate addition–based protocol,[8,9] ethyl bromo pyruvate–based synthesis,[10] and menthol-based strategy.[7b] The intramolecular approaches have also been developed to synthesize intermediate **2**.[11] Additionally, the preparation of *racemic* benzyl ester was accomplished via Gilbert Stork condensation.[12]



Scheme 1. Synthesis of advanced intermediate **2** and formal synthesis of ramipril **1**.

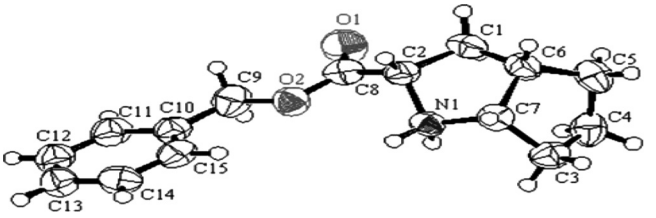


Figure 2. X-ray structure of HCl salt of **2**.

To the best of our knowledge, there is not much research devoted to the asymmetric synthesis of (*S,S,S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester **2**. Herein, we report our efforts to develop a novel and efficient transformation to access intermediate **2** by utilizing (*S*)-1-amino-2-methoxy methylpyrrolidine (SAMP) as chiral auxiliary.

Enders et al. discovered[13] SAMP as a chiral auxiliary to access the corresponding isomer as a major species for carbocyclic compounds.

RESULTS AND DISCUSSION

We utilized the SAMP chemistry to synthesize the key starting material **2** of ramipril **1**, as shown in Scheme 1. Intermediate **2** was prepared by using SAMP, a little excess of cyclopentanone **3**, and a catalytic amount of *p*-TsOH · H_2O (5 mol%). The by-product, water, was removed azeotropically with toluene to afford chiral imine **4**. The corresponding lithium salt of chiral enamine **5** was obtained by the reaction of **4** and lithium diisopropylamide (LDA).

In the subsequent steps, the key intermediate **6** was prepared by addition of substituted iodide (obtained from *N*-acetyl-serine methyl ester) to freshly prepared **5**. In situ–generated intermediate **6** was treated with 5 N HCl to effect hydrolysis to obtain **7**, and eventually SAMP was recovered. Intermediate **7** benzyl alcohol and thionyl chloride afforded HCl salt of **2** in 69% overall yield. The stereochemistry and structure of HCl salt of **2** were confirmed by x-ray crystallography as shown in Fig. 2. This is a new and innovative approach that offers a viable asymmetric transformation relatively better than the hitherto known synthesis for intermediate **2**.[14] This intermediate was utilized to synthesize ramipril **1**.[7a]

CONCLUSION

We developed asymmetric synthesis of HCl salt of (*S,S,S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid benzyl ester **2** in moderate yields and high purity using the recoverable chiral auxiliary SAMP. The absolute configuration at chiral centers present in **2** was also supported by x-ray crystallography (Fig. 2). The SAMP was recovered and used in the next cycle of preparation of **2** with good yield and purity.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were recorded on a 400-MHz Varian Gemini Fourier transform (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 d ppm relative to tetramethylsilane (TMS). The FT FT-IR spectra were recorded using a Perkin-Elmer 16650 FT-IR spectrometer. Mass spectra (70 eV) were recorded on a HP-5989A liquid chromatography–mass spectrometry (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.

Synthesis of (S,S,S)-2-Aza-bicyclo-[3.3.0]-octane-3-carboxylic Acid Benzyl Ester (2)

A mixture of (*S,S,R/S*)-2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid (**9**) (21.3 g, 0.11 mol) and benzyl alcohol (100 mL) was charged into a flask under nitrogen atmosphere and cooled to 0–5 °C, and then thionyl chloride (40 g, 0.34 mol) was slowly added for 1 h. After stirring for 12 h at 25 °C, the reaction mass was saturated with diisopropyl ether (300 mL) to precipitate compound **2** (12.5 g, 80% with respect to single isomer) and filtered. The remaining mother liquor was evaporated under reduced pressure to get **11** as a oily crude; then the pH adjusted to 7.5–8.0 by using aqueous NaOH solution at 10–15 °C and extracted with ethyl acetate (3 × 200 mL) followed by evaporation to furnish a free base of **11** (oily yellow color crude). N-Chlorosuccimide (NCS; 9.8 g, 0.07 mol) in portions was added to a mixture of crude **11**, free base (15.7 g, 0.06 mol), dimethylformamide (DMF; 30 ml), and K_2CO_3 (1.8 g, 0.013 mol) at 0 °C. After the mixture was stirred for 0.5 h, 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU; 14.6 g, 0.1 mol) was added (exothermic). After stirring for 3 h at 25 °C, water (60 mL) was added. Subsequently, reaction mass was extracted with ether (4 × 100 mL) and evaporated under reduced pressure to furnish compound **12** with 90% yield (13.9 g). A mixture of compound **12**, ethanol (25 mL), and 5% wet Pd/C (type 39 K) (1.0 g) were added, and the total reaction mass was transferred into an autoclave and maintained at 2.5–3.0 kg/cm^2 of hydrogen pressure at 25–30 °C for 3 h. The reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, it was filtered through a pad of celite, followed by washing with ethanol (10 mL). The filtrate was concentrated completely at 40–50 °C under vacuum to afford **13** with 95% yield (8.4 g). Compound **13** (8.4 g, 0.03 mol) and benzyl alcohol (20 mL) was charged into a flask under a nitrogen atmosphere and cooled to 0–5 °C. Afterward, thionyl chloride (6.7 g, 0.089 mol) was slowly added for 1 h. After stirring for an additional 12 h at 25 °C, the reaction mass was saturated with diisopropyl ether (60 mL) to precipitate compound **2** in 64% yield (10.7 g based on available isomer) [overall yield 69% (23.2 g)]; mp 178–180 °C (lit.[4b] mp 180 °C); $[\alpha]_D^{20} = -40.0$ (c = 1, H_2O) (lit.[4b] $[\alpha]_D^{30} = -38.4$ (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 (ABq, $J = 12.0$ Hz, 2H),

7.33–7.37 (m, 5H); ^{13}C NMR (100 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^+).

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