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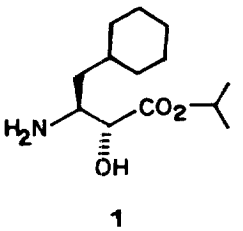
A short and efficient enantioselective synthesis of cyclohexylnorstatine, a key component of a renin inhibitor

T. T. Upadhya and A. Sudalai *
Organic Chemistry Division, National Chemical Laboratory, Pune 411 008, India

Abstract: A catalytic asymmetric synthesis of ethyl (2R,3S)-N-(p-toluenesulfonyl)-3-amino-4-cyclohexyl-2-hydroxybutyrate **7** in 96% ee from cheaply available cyclohexanone is described employing Sharpless asymmetric aminohydroxylation as the key step. © 1997 Elsevier Science Ltd

Renin, an aspartic protease, generates angiotension I from angiotensinogen, and a large number of inhibitory peptides of human renin have been investigated as potential agents of antihypertensive therapy.[1] The isopropyl ester of cyclohexylnorstatine [(2R,3S)-3-amino-4-cyclohexyl-2-hydroxybutyrate **1**] constitutes the C-terminal moiety of the potent renin inhibitor, a tripeptide KRI 1314.[2] It has been found that other bioactive small peptides also contain this α-hydroxy β-amino acid sub-structure.[3]



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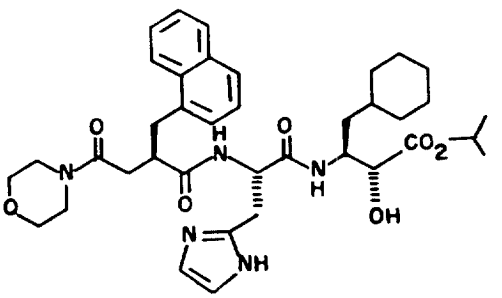


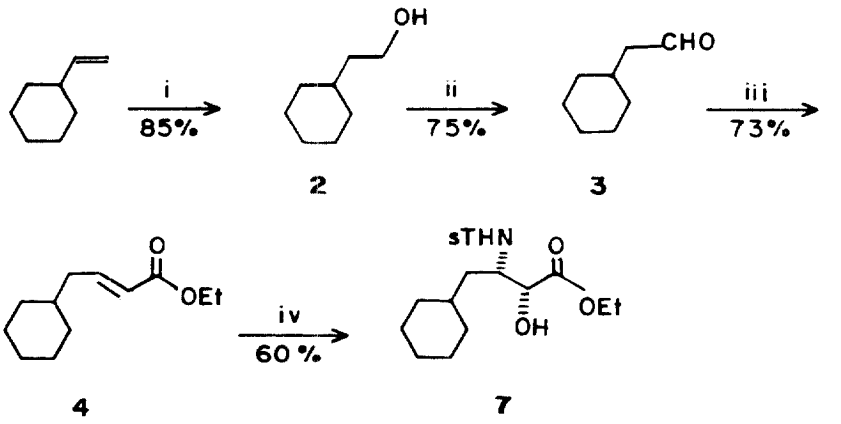
KRI 1314

During the past few years, a number of reports have appeared on the asymmetric synthesis of **1**.[4] However, all these reported procedures to synthesize **1** involve either chiral natural products as starting materials or employ stoichiometric amounts of expensive chiral auxiliaries or chiral promoters. Most recently, a catalytic approach utilizing Sharpless asymmetric epoxidation as the key step has been reported[5] but this involves a large number of steps including one inversion of configuration at the C-2 carbon atom. Hence, there is a need to develop a new, short and efficient catalytic asymmetric synthesis of **1** which could be of high interest for the potential large scale production of the compound.

The OsO_4-catalyzed asymmetric aminohydroxylation of olefins[6] using chloramine-T as the nitrenoid source and water as the hydroxyl source, has become the most powerful method for the preparation of a wide variety of enantiomerically pure aminoalcohols. The asymmetric aminohydroxylation of olefins has now become an effective process because only catalytic amounts of both osmium and chiral ligand are required and the reactions are performed at room temperature with commercially available reagents and are not influenced by water or oxygen. We wish to report here a short and efficient enantioselective synthesis of **1** in a fully protected form by employing Sharpless asymmetric aminohydroxylation as the key step.

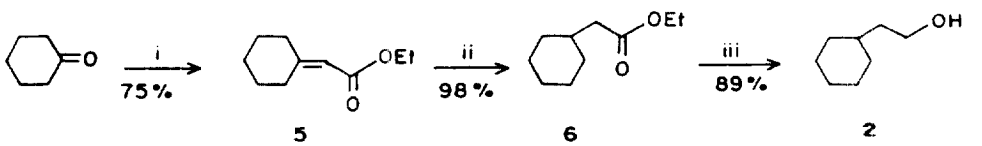
* Corresponding author. Email: otech@ems.ncl.res.in

Our synthetic strategy is presented in Scheme 1. We envisaged the olefinic ester **4** as the key intermediate. The synthesis of **4** has been achieved in three steps. Hydroboration–oxidation of vinylcyclohexane[7] afforded 2-cyclohexylethanol **2** in 85% yield, the oxidation of **2** with PCC in CH_2Cl_2 gave cyclohexylacetaldehyde **3** in 75% yield. Wittig–Horner reaction of aldehyde **3** with triethyl phosphonoacetate produced the *trans* olefinic ester **4** in good yield, which is required for the synthesis of **7**.



Scheme 1. (i) BH_3·DMS, THF; NaOH, 30% H_2O_2; (ii) PCC, CH_2Cl_2; (iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, C_6H_6; (iv) OsO_4, $(DHQ)_2$–PHAL, chloramine-T, t-BuOH: H_2O (1:1), 10 h, RT.

Considering the difficulties involved in the synthesis of vinylcyclohexane,[8] we turned our attention to providing an alternative and cheap method for the preparation of 2-cyclohexylethanol **2**. Accordingly, we synthesised **2** in a three-step sequence starting from readily available cyclohexanone (Scheme 2). Wittig–Horner[9] reaction of cyclohexanone with triethyl phosphonoacetate followed by the selective hydrogenation of C=C using Pd/C–H_2 (50 psi) gave the saturated ester **6**. Surprisingly, our efforts to reduce the ester function in **6** either with LAH, DIBAL or $NaBH_4$–PEG 400[10] failed to yield the required alcohol **2**. However, reduction of the same ester function could be achieved with $NaBH_4$–$AlCl_3$ in diglyme[11] in excellent yield.



Scheme 2. (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, ΦH; (ii) 10% Pd/C, MeOH, H_2 (50 Psi), 5 h; (iii) $NaBH_4$, $AlCl_3$, diglyme.

We have chosen asymmetric aminohydroxylation of α,β-unsaturated ester[6] **4** as a key reaction to accomplish the corresponding N-tosylderivative **7**. It may be noted that the deprotection of the N-tosyl group has now become easier by Fukuyama's procedure.[12] Catalytic asymmetric aminohydroxylation of **4** using OsO_4, $(DHQ)_2$–PHAL, chloramine-T in *t*-butanol–H_2O (1:1) afforded the fully protected cyclohexylnorstatine **7**, as a colourless liquid in 60% yield. The enantiomeric excess of **7** was 96%, as determined by chiral HPLC with a Chiralcel ASTEC CYCLOBOND I column.

In conclusion, an efficient and highly enantioselective synthesis of ethyl (2R,3S)-N-(p-toluenesulfonyl)-3-amino-4-cyclohexyl-2-hydroxybutarate **7** starting from cheaply available cyclohexanone has been achieved by employing Sharpless asymmetric aminohydroxylation as the key step (96% ee).

Experimental section

All solvents were distilled and dried before use. Chromatography was performed over silica gel (60–120 mesh). IR spectra were recorded on a Perkin–Elmer 137 E spectrometer. ^1H and ^{13}C NMR spectra were recorded on Brucker FT90 and 200 MHz instruments using TMS as an internal standard. The mass spectra (MS) were recorded on an automated Finnigan MAT 1020C mass spectrometer using an ionization energy of 70 eV. The optical rotations were carried out on JASCO-181 digital polarimeter at 25°C using sodium D light.

Preparation of 2-cyclohexylethanol 2

Vinylcyclohexane (0.22 g; 0.002 mol) was added dropwise to a solution of $BH_3 \cdot DMS$ (0.002 mol) in dry THF (10 ml) and the mixture was stirred at RT for 3 h and then refluxed for 1.5 h. The reaction flask was cooled at 0°C and NaOH (0.16 g; 0.004 mol) in ethanol (2 ml) was added to the reaction mixture followed by 30% H_2O_2 (0.006 mol) added at such a rate as to maintain the gentle reflux. It was then allowed to stir at RT for 2 h and the product was taken up in ethyl acetate washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography over silica gel (5% ethyl acetate in pet. ether) gave **2** as a colorless oil (0.216 g; 85% yield). IR (neat, cm^{-1}): 3300, 1440, 1050; ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–1.0 (m, 2H), 1.0–1.35 (m, 4H), 1.35–1.5 (m, 2H), 1.5–1.85 (m, 5H), 2.85 (bs, 1H), 3.6 (t, J=5 Hz, 2H).

Preparation of 2-cyclohexylacetaldehyde 3

To a mixture containing pyridinium chlorochromate (PCC) (2.58 g; 0.012 mol) and dichloromethane (25 ml) at RT was added in one lot cyclohexylethanol (1.1 g; 0.0086 mol) in dichloromethane (10 ml). After the reaction was complete (5 h), 25 ml of dry ether was added and the supernatant solution was decanted from the black gum. The insoluble residue was washed with anhyd. ether (3×10 ml). The combined organic extract was then passed through a column containing Celite and concentration *in vacuo* gave **3**, which was further purified by column chromatography (1% ethyl acetate in pet. ether) to yield colorless liquid **3** (0.81 g; 75% yield). IR (neat, cm^{-1}): 2700, 1690, 1435, 1290, ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–2.0 (m, 11H), 2.2–2.35 (m, 2H), 9.75 (t, J=2 Hz, 1H).

Preparation of olefinic ester 4

A mixture of ethyl bromoacetate (10 g; 0.06 mol) and triethyl phosphite (11.62 g; 0.07 mol) was heated on an oil bath at 160°C for 3 h, with the generation of ethyl bromide. The crude oil was distilled to give triethyl phosphonoacetate (13 g, 97% yield). IR (neat, cm^{-1}: 1730, 1450, 1400, 1380, 1280, 1110, 1050, 970, 800; ^1H NMR (200 MHz, $CDCl_3$): δ 1.15–1.25 (m, 9H), 2.8 (d, J=21 Hz, 2H), 4.05–4.15 (m, 6H); MS: m/z (% rel. intensity): 224 (M^+, 13), 197 (100), 181 (15), 179 (90), 169 (37), 152 (51), 151 (70), 137 (14), 125 (19), 123 (86), 109 (35), 107 (20), 97 (15), 88 (18), 81 (20), 65 (13).

To a mixture containing NaH (0.15 g; 0.0064 mol) and 10 ml of dry benzene, triethyl phosphonoacetate (1.5 g; 0.0067 mol) was added dropwise over a 15 min. period. During the addition period, the temperature was maintained at 30°C (vigorous evolution of H_2 was observed). The mixture was stirred for 45 min. at RT followed by the addition of cyclohexylacetaldehyde (0.8 g; 0.0064 mol) over a 20 min. period maintaining the temperature at 25°C. The reaction mixture was then heated at 65°C for 30 min., cooled to RT, extracted with ethylacetate (3×10 ml), washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give **4**. Column chromatography of this (2% ethyl acetate in pet. ether) provided pure **4** (0.91 g; 73% yield). IR (neat, cm^{-1}): 1720, 1650, 1450, 1380, 1315, 1270, 1175, 1140, 1050, 995; ^1H NMR (200 MHz, $CDCl_3$): δ 0.85–1.1 (m, 2H), 1.15–1.45 (m, 3H), 1.25 (t, J=4 Hz, 3H), 1.55–1.9 (m, 6H), 1.95–2.25 (m, 2H), 4.2 (q, J=4 Hz, 2H), 5.75 (d, J=13 Hz, 1H), 6.95 (dt, J=13.75, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.98, 25.86, 26.0, 32.8, 32.94, 37.1, 39.9, 41.6, 59.8, 122.0, 147.8, 177.96; MS: m/z (% rel. intensity) 197 (M+1, 8) 196 (M^+, 16), 170 (4), 151 (22), 150 (52), 114 (100), 113 (33), 96 (8), 83 (22), 81 (18), 67 (12), 55 (15). Anal: $C_{12}H_{20}O_2$ requires C, 73.47; H, 10.2. Found C, 73.32; H, 10.23.

Preparation of ethyl cyclohexylideneacetate 5

To a mixture containing NaH (1.08 g; 0.045 mol) in 50 ml of dry benzene, triethyl phosphonoacetate (10 g; 0.045 mol) was added dropwise over a 50 min. period. During the addition period, the temperature was maintained at 30°C (vigorous evolution of H_2 was observed). The mixture was stirred for 1 h at RT followed by the addition of cyclohexanone (4.41 g; 0.045 mol) over a 40 min. period, maintaining the temperature at 25°C. The reaction mixture was then heated at 65°C for 30 min., cooled to RT, extracted with ethyl acetate (3×25 ml), washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give **5**. Purification by column chromatography (2% ethyl acetate in pet. ether) gave **5** as colorless liquid (5.6 g; 75% yield). IR (neat, cm^{-1}): 1710, 1650, 1450, 1380, 1310, 1275, 1250, 1210, 1160, 1040, 855; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–0.9 (m, 2H), 1.05–1.4 (m, 2H), 1.2–1.25 (t, J=4 Hz, 3H), 1.6–1.7 (m, 2H), 2.1–2.2 (m, 2H), 2.75–2.85 (m, 2H), 4.1 (q, J=5 Hz, 2H), 5.5 (s, 1H); MS: m/z (% rel. intensity): 169 (M+1, 15), 168 (M^+, 100), 140 (53), 139 (37), 123 (61), 122 (53), 121 (45), 112 (25), 111 (28), 95 (47), 94 (38), 80 (53), 79 (58), 67 (48), 55 (55).

Preparation of ethyl cyclohexylacetate 6

Ethyl cyclohexylideneacetate **5** (5 g; 0.03 mol) was hydrogenated at RT with H_2 (50 psi) using 10% Pd/C (0.5 g) as a catalyst in methanol (30 ml) for 5 h. Filtration of the reaction mixture followed by evaporation of methanol gave **6** in pure form (4.95 g; 98% yield). IR (neat, cm^{-1}): 1740, 1450, 1375, 1350, 1295, 1240, 1170, 1120, 1040; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–1.05 (m, 2H), 1.15–1.3 (m, 6H), 1.55–1.8 (m, 6H), 2.15 (d, J=5 Hz, 2H), 4.1 (q, J=4 Hz, 2H); MS: m/z (% rel. intensity): 170 (M^+, 16), 149 (3), 136 (3), 125 (8), 97 (10), 89 (35), 88 (100), 81 (12), 70 (39), 67 (14), 61(16).

Preparation of 2-cyclohexylethanol 2

To a solution of $NaBH_4$ (0.82 g; 0.024 mol) in 50 ml of diglyme with stirring was added ethyl cyclohexylacetate (4 g; 0.023 mol) followed by a solution of anhyd. $AlCl_3$ (1.33 g; 0.01 mol) in 10 ml of diglyme. The rate of addition of $AlCl_3$ was adjusted so that the temperature inside the flask did not rise above 50°C. The reaction mixture was stirred at RT for 1 h followed by heating on a oil bath for 2 h. After cooling to RT, the reaction mixture was poured onto crushed ice (ca 50 g) and 10 ml of conc. HCl. It was then extracted with ethyl acetate (3×50 ml), washed with $NaHCO_3$ and brine, dried over anhyd. Na_2SO_4 and concentrated to give crude compound which, after column chromatography purification (5% ethyl acetate in pet. ether) gave pure **2** (2.67 g; 89% yield) (for characterization of **2**, *vide infra* under experimental).

Preparation of ethyl-(2R,3S)-N-(p-toluenesulfonyl)-3-amino-4-cyclohexyl-2-hydroxy-butyrate 7

To a stirred solution of $(DHQ)_2$–PHAL (0.047 g; 0.06 mmol) in 5 ml of t-butanol and 5 ml water were added in order, olefin (0.223 g; 1.2 mmol), chloramine-T trihydrate (1 g, 3.6 mmol) and OsO_4 (0.012 g; 0.048 mmol). The reaction flask was immersed in a water bath and the slurry stirred for 10 h. Over the course of the reaction the color changed from green to yellow. After addition of sodium sulfite (0.5 g in 5 ml of water), the two phases were separated and the aqueous phase was extracted with ethyl acetate (3×10 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was then purified by column chromatography (30% ethyl acetate in pet. ether) to give **7** (0.24 g; 60% yield). $[\alpha]_D=-17$ (c=1, $CHCl_3$) IR (neat, cm^{-1}): 3500–3300, 1734, 1449, 1330, 1160, 1020, 813; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–1.8 (m, 16H), 2.45 (s, 3H), 3.1 (bs, 1H), 3.45 (bs, 1H), 3.95–4.3 (m, 3H), 5.1 (d, J=8 Hz, 1H), 7.3 (d, J=5 Hz, 2H), 7.75 (d, J=5 Hz, 2H). Anal: $C_{19}H_{29}NO_5S$ requires C, 59.53; H, 7.57; N, 3.655; S, 8.355. Found C, 59.54; H, 7.6; N, 3.6; S, 8.4. Conditions for chiral HPLC analysis: Chiralcel ASTEC CYCLOBOND I column, 30% MeOH/water, 1 ml/min. (2S,3R) 9.43 min. (minor), (2R,3S) 12.48 min. (major).

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