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# Practical Synthesis of Abbott Amino-Diol : A Core Unit of the Potent Renin Inhibitor Zankiren

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Abstract: Abbott amino-diol (2S,3R,4S)-2-amino-1-cyclohexyl-6-methyl heptane-3,4-diol 1, a main structural constituent of the orally active renin inhibitor Zankiren has been synthesized using Sharpless asymmetric aminohydroxylation as the key step © 1999 Elsevier Science Ltd. All rights reserved.

### **INTRODUCTION**

Renin, an aspartic protease is the rate-determining enzyme in the cascade leading to the vasopressor substance angiotensin-II, which plays a key role in the regulation of blood pressure.<sup>1</sup> Interruption of the reninangiotensin system by inhibition of angiotensin converting enzyme (ACE) has led to the development of effective antihypertensive agents.<sup>2</sup> Although many potent inhibitors of renin have been reported, poor bioavailalability remained an obstacle to their successful development. It has been reported<sup>3</sup> that inhibitors like Zankiren, Enalkiren etc. contain a core unit which is a peptide hydrolysis transition state mimetic, called the Abbott amino-diol (2S,3R,4S)-2-amino-1-cyclohexyl-6-methyl heptane-3,4-diol (1). The presence of this dihydroxyethylene isostere unit showed an enhancement of oral activity and made the inhibitor the most potent to date.



## **RESULTS AND DISCUSSIONS**

Earlier reports revealed a number of synthetic studies,<sup>4</sup> most of them involve either chiral natural products as starting material or employ a number of steps to complete the synthesis. We wish here to report a short and practical asymmetric synthesis of the Abbott amino-diol 1 in five steps using Sharpless asymmetric aminohydroxylation (SAH) as the prime reaction to yield enantiopure  $\beta$ -amino  $\alpha$ -hydroxy compound 2, the key intermediate as shown in Scheme 1.

Scheme 1



It is difficult to imagine a more efficient means of creating the  $\beta$ -amino  $\alpha$ -hydroxy functionality than by direct addition of the two heteroatom substituents to an olefin, especially if the transformation could also be regio-and/or enantioselective when required. Recently, Sharpless *et al.* have reported a catalytic aminohydroxylation (AA) reaction,<sup>5</sup> where an olefin undergoes enantioselective vicinal addition of a sulfonamido and a hydroxyl group when treated with a chiral alkaloid ligand, catalytic osmium, Chloramine-T as the nitrogen source, and water as the oxygen source. Even though Chloramine-T has been replaced by carbamates<sup>6</sup> and *N*-acetyl bromide<sup>7</sup> by the Sharpless group, we opted to use Chloramine-T as the aminating source in our scheme due to the following advantages. Firstly, Chloramine-T is cheap, commercially available and can be used directly without further purification, whereas preparation of Chloramine-M<sup>8</sup> and *N*-chloro-*N*-sodio carbamates (both independently or in situ) involves the use of t-butyl hypochlorite which is a cumbersome method. Secondly, the recent development of a mild deprotection procedure by us<sup>9</sup> for N-Ts cleavage of aminols with simultaneous acetonation made the NH-Ts aminols more useful intermediates. Thirdly, the products of Chloramine-T based reactions are more crystalline and improvement in ees can be achieved by simple crystallization.

Scheme 2



The  $\alpha,\beta$  unsaturated ester 3 has been prepared from commercially available cyclohexyl ethanol 4 in two steps (Scheme 2). The alcohol 4 is oxidized to the corresponding aldehyde 5 with PCC which on Wittig reaction with carboethoxymethylenetriphenylphosphorane yielded 3. Ester 3 was subjected to SAH using catalytic quinine derived ligand (DHQ)<sub>2</sub>PHAL (5 mol %) and K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (4 mol %) in t-BuOH:H<sub>2</sub>O (1:1) to get (2R, 3S)-*N*-(*p*-toluenesulphonyl)-3-amino-4-cyclohexyl-2-hydroxy butyrate 2 (prepared previously by Sudalai *et al.*<sup>10</sup>), 2.5 g in 65 % yield. The enantiomeric excess was found to be 89 % (after two crystallizations) using chiral HPLC with a chiralcel ASTEC CYCLOBOND I column.

Then this N-tosylated aminol was subjected to acetonation conditions using 2,2-dimethoxy propane and PPTS (cat.) to get product 6 with concomitant loss of the tosyl group along with 6a (Scheme 3).



Compound 6 was reduced to aldehyde 7 using DIBAL-H at -78 °C which on Grignard reaction with preformed isobutylmagnesium bromide in THF gave a diastereometric mixture of alcohol 8 and 8a in 80:20 ratio. This reasonable diastereofacial selectivity towards the formation of *anti* isomer may be explained using Felkin-Anh model.<sup>11</sup> The mixture was separated by column chromatography using pet ether:ethyl acetate (4:1) mixture as eluent. Finally, amino-diol 1 was obtained by the deprotection of 8 with methanolic 6N HCl (Scheme 4).



In conclusion, a short, practical and enantioselective synthesis of (2S,3R,4S)-2-amino-1-cyclohexyl-6methyl heptane-3,4-diol (1) has been achieved employing Sharpless asymmetric aminohydroxylation as the key step. The flexibility in the approach allows the synthesis of various analogs of related enzyme inhibitors.

#### EXPERIMENTAL SECTION

IR spectra were recorded on Perkin-Elmer infrared 683 spectrophotometer with NaCl optics. <sup>1</sup>H NMR spectra were recorded on a Varian Gemini-200 MHz machine. The samples were made in CDCl<sub>3</sub> using tetramethylsilane as the internal standard and are given in the  $\delta$  scale. Splitting patterns are designated as "s, d, t, q, m, dt, dd and bs" indicating "singlet, doublet, triplet, quartet, multiplet, double triplet, double doublet and broad singlet," respectively. Mass measurements were carried out on CEC-21-110B double focussing mass spectrometer operating at 70 ev and are given in the mass units (m/z). TLC was performed on 0.25 mm E.Merck precoated silica gel plates (60 F-254). All the products were purified by column chromatography on

silica gel (100-200 mesh). Optical rotations were recorded on Jasco DIP 360 digital polarimeter. Cyclohexylethanol, Chloramine-T trihydrate, (DHQ)<sub>2</sub>PHAL, K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, 2,2-dimethoxy propane were purchased from Aldrich and used directly.

2-Cyclohexyl acetaldehyde (5) : To a solution of 2-cyclohexyl ethanol 4 (10 g, 78.12 mmol) in dry  $CH_2Cl_2(100 \text{ mL})$  at 0 °C was added pyridinium chlorochromate (26.8 g, 117.1 mmol) and stirred at room temperature for 6 h. After the reaction was complete (monitered by TLC), ether (100 mL) was added and the supernatant solution was filtered through a short silicagel pad. The insoluble residue was washed with ether (3x50 mL) and the combined organic extracts were concentrated to give 7.8 g of 5 in 80 % yield as a light yellow oil. IR (neat): 3300, 1441, 1050 cm<sup>-1</sup>;<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta 0.75 - 2.0$  (11H, m), 2.2 - 2.35 (2H, m), 9.75 (1H, t, J=2 Hz, CHO).

#### Ethyl (2E)-4-cyclohexyl-2-butenoate (3):

To a stirred solution of aldehyde 5 (7.5 g, 59.5 mmol) in dry benzene (50 mL) at room temperature under nitrogen atmosphere was added carboethoxymethylene triphenylphosphorane (20.7 g, 59.5 mmol) portion wise and stirred overnight at the same temperature. Then the solvent was removed in *vacuo*, and the crude mixture was column chromatographed (pet ether: ethyl acetate 98:2 ratio) to give 9.56 g of ester 3 in 82 % yield as a colourless liquid. IR (neat) : 1720, 1450, 1050 <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.85 - 1.1 (2H, m), 1.15 - 1.45 (3H, m), 1.30 (3H, t, J = 6.6 Hz), 1.60 - 1.82 (6H, m), 2.05 - 2.20 (2H, t, J = 6.6 Hz), 4.18 (2H, q, J = 6.6 Hz), 5.75 (1H, d, J = 15.5 Hz), 6.95 (1H, dt, J = 15.5 Hz). MS: m/z 196 (M<sup>+</sup>) Anal. Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>: C, 73.43 H, 10.27; Found : C, 73.44 H, 10.18.

#### (2R, 3S)-N-(p-Toluenesulphonyl)-3-amino-4-cyclohexyl-2-hydroxybutyrate (2) :

To a 100 mL single neck round bottomed flask fitted with a magnetic bar and nitrogen inlet, was added  $(DHQ)_2PHAL (0.39 \text{ g}, 0.51 \text{ mmol})$ , t-BuOH (30 mL), and water (30 mL). The flask was immersed in a room temperature water bath. To the resulting solution was added, in order, 6.9 g of Chloramine-T trihydrate (Ca. 4/5 of the total added which is 8.63 g, 30.6 mmol), olefin 3 (1 g, 5.1 mmol, half of the total amount of the olefin, which is 2 g, 10.2 mmol) and  $K_2OSO_2(OH)_4$  (0.15 g, 0.40 mmol). As the reaction mixture was stirred, the colour changed from yellow to green in 15 min and back to yellow after 1 h. The flask was then immersed in an ice bath (0 °C) for 20 min. To this cold, stirred suspension, the remainder of the Chloramine-T, trihydrate (1.73 g) and olefin (1 g) was added. The ice bath was replaced by room temperature water bath and stirred for 12 h. Over the course of reaction the colour changed from green to yellow. After addition of sodium sulfite (5 g in 20 mL water), the two phases were separated and the aq. phase was extracted with ethyl acetate (3x25 mL). The combined organic extracts were wasthen purified by column chromatography (30 % pet ether in ethyl acetate) to give 2 (2.54 g, 65% as a white solid), which was recrystallised from pet ether : ether (8:2) mixture. mp: 112° - 116°C;  $[\alpha]_D^{25}$ : -15.7 (c 1.1 in CHCl<sub>4</sub>); Lit<sup>10</sup> = -17 (c 1 in CHCl<sub>4</sub>); IR (neat) :

 $3500 - 3300, 1735, 1450, 815, {}^{1}H NMR (CDCl_3): \delta 0.95-1.95 (16H, m), 2.45 (3H, s), 3.05 (1H, bs), 3.90-4.0 (2H, m), 4.30 (2H, q, J=6.8 Hz), 4.85-5.05 (1H, bs), 7.25 (2H, m), 7.62 - 7.80 (2H, m); MS: m/z 384 (M<sup>+</sup>+1); HRMS: Calcd. for C<sub>10</sub>H<sub>29</sub>NO<sub>5</sub>S : 384.1845; Found : 384.1846.$ 

(2R,3S)-2,3-(N,Q Isoproylidene)-3-amino-4-cyclohexyl-2-hydroxybutyrate (6) : Compound 2 (2.25 g, 5.8 mmol) was taken in dry toluene(10 mL) and to it under nitrogen atmosphere, 2,2-dimethoxy propane (14.3 mL, 117.4 mmol) was added followed by PPTS (catalytic, 65 mg) and stirred at 70 °C for 6 h. Then solvent was evaporated, mixture was chromatographed [pet ether:ethyl acetate(4:1)] to get 1.20 g of 6 in 76% yield as a liquid.  $[\alpha]_D^{25}$ : -14.1 (c 0.95 in CHCl<sub>3</sub>). IR (neat) : 1734, 1450 <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.85-1.85 (22H, m), 1.30 (2H, t, J=8.3 Hz), 1.42 (6H, s), 4.0 (1H, d, J=8.3 Hz), 4.10-4.30 (3H, m); MS : m/z 269; (M<sup>+</sup>); HRMS: Calcd. for C<sub>15</sub>H<sub>27</sub>NO<sub>3</sub> : 269.1542; Found : 269.1541.

(2R,3S)-2,3-(N,O-Isoproylidene)-3-amino-4-cyclohexyl-2-hydroxybutyraldehyde (7): To ester 6 (1.2 g, 4.46 mmol) in dry  $CH_2Cl_2$  (15 mL) at -78 °C under  $N_2$  atm. DIBAL-H (6.6 mL, 1M, 6.6 mmol) was added and the mixture was stirred at -78 °C for 2 h. Then excess DIBAL-H was quenched by the addition of methanol (5 mL) at -78 °C, brought to room temperature and the reaction mixture was poured into sodium potassium tartrate solution (10 g in 30 mL water), stirred vigorously until the layers separated. The aqueous layer was extracted with  $CH_2Cl_2$  (2x25mL), and the combined organic extracts were washed with brine (1x25 mL), dried over  $Na_2SO_4$ , and evaporated in *vacuo* to give aldehyde 7 (0.81 g, 81%) as a colourless viscous oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta 1.05-1.85$  (19H, m), 1.48 (6H, s), 3.81 (1H, dd, J = 2.7, 4.1 Hz), 4.05-4.19 (1H, m), 9.68 (1H, d, J=2.7 Hz).

# (2S,3R,4S)-2,3(N,O-Isopropylidene)-2-amino-1-cyclohexyl-6-methyl-heptane-3,4-diol (8):

Aldehyde 7 (0.80 g, 3.55 mmol) in THF (10 mL) was added at 0 °C under nitrogen atmosphere to the preformed isobutylmagnesium bromide (1.67 g, 10.04 mmol) generated from isobutyl bromide (1.13 mL, 10.04 mmol) and Mg (0.24 g, 10.04 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 6 h, quenched with saturated NH<sub>4</sub>Cl solution. The aqueous layer was extracted with ether (2x10mL), and the combined organic extracts were washed with brine (15mL), dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated in *vacuo* and column chromatographed to get a mixture of 8 and 8a (0.72 g, 72 %). The crude mixture was once again chromatographed using finer than 200 mesh silica gel to get 8 (0.57 g) and 8a (0.14 g) in 4:1 diastereomeric ratio as a liquid. Data for 8 :  $[\alpha]_D^{25}$  : -30.8 (c 0.5 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.85-0.90 (6H, d, J=2.5Hz), 1.12-1.85 (22H, m), 1.35 (6H, s), 2.5-2.60 (1H, bs), 3.10 (1H, m), 3.65 (1H, d, J=7.5Hz), 4.10 (1H, m); IR (neat): 3250, 2950, 2850, 1400, 1050 and 840 cm<sup>-1</sup>; MS: m/z 283 (M<sup>+</sup>); HRMS: Calcd. for C<sub>17</sub>H<sub>33</sub>NO<sub>2</sub> : 283.1759; Found : 283.1758.

(2S,3R,4S)-2-Amino-1-cyclohexyl-6-methyl-heptane-3,4-diol (1): To compound 8 (0.54 g, 1.90 mmol) in methanol (15 mL) was added 6 N HCl (2 mL) and stirred at room temperature for 6 h. Then the reaction mixture was neutralised by the addition of solid NaHCO<sub>3</sub> and the residue was filtered and washed thoroughly with ethyl acetate (4x5 mL), combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to get amino diol 1 (0.24 g, 52 %) as white solid. mp : 106 °C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.90-1.0 (6H, d, J=4.4 Hz), 1.15-1.95 (16H, m), 2.55-2.8 (4H, bs), 3.40 (1H, m), 3.51-3.65 (1H, m), 3.70-3.89 (1H, m);  $[\alpha]_D^{25}$ : +26.9 (c 1.5 in EtOH), Lit<sup>[4b]</sup>  $[\alpha]_D^{25}$  =+28.9 (c 2, EtOH); IR (CDCl<sub>3</sub>): 3589, 2947, 2835, 1600, 1572, 1460 and 1445 cm<sup>1</sup>; MS: m/z 244(M<sup>+</sup>+1); HRMS: Calcd.for C<sub>14</sub>H<sub>29</sub>NO<sub>2</sub> : 244.1212; Found : 244.1206.

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