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# Stereoselective reduction of enantiopure *α*-l-amino-*β*-keto esters using oxazaborolidine catalysts for the synthesis of statine analogues

**Malapati Venkateswara Reddy [1,2], Shyamala Pulipaka [2]* and Arvind Kumar Sharma [1] ***

[1]*Dept of Chemistry solutions, Aragen life sciences Pvt. Ltd. Nacharam, Hyderabad, India*
[2]*Dept of Chemistry, Andhra University, Andhra Pradesh, India*

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**Abstract:** An efficient diastereoselective synthesis of Boc-protected 4-amino 3-hydroxy esters starting from natural amino acids is described. The key synthetic strategy involves diastereoselective reduction of *α*-*L*-amino-*β*-keto esters in the presence of enantiopure **R** and **S**-2-Methyl-CBS-oxazaborolidine catalysts using borane as hydride source. The product diastereoselectivity depends upon the use of (*R)* or (*S)* enantiomer of 2-Methyl-CBS-oxazaborolidine. A reasonable mechanism is included which explains the diastereoselectivity of the reactions with the use of different enantiomers of 2-Methyl-CBS-oxazaborolidine. Furthermore, the resulting diastereomeric mixture of the reduced products can be separated by column chromatography to gain access to the single pure diastereomers.

**Keywords:** L-amino-β-keto esters; statine; (R)-2-Methyl-CBS-oxazaborolidine; (S)-2-Methyl-CBS-oxazaborolidine; borane reduction. 

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## 1. Introduction

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid **(1)**,[1] is a constituent of the naturally occurring small peptide pepstatin which is a strong and general inhibitor of aspartic Proteases, e.g., pepsin, renin, and cathepsin D.[2,3] In addition, several natural peptides containing statines or modified statines, such as didemnins,[4] dolastatins,[5] hapalosin,[6] tamandarins,[7] etc., displayed promising anticancer properties. There are detailed studies in literature indicating the significance of the side chains on statines on the biological activity of the peptides [8,9] Recently, there has been interest in statine-based peptidomimetics as cysteine protease inhibitors against SARS-CoV-2 Mpro, including antiviral activity.[10]

As statines have proven useful for developing new inhibitors of aspartic proteinases, numerous syntheses of **1** and its N-protected ester derivatives have been published (Figure 1).[11,12] The most reliable and stereo selective method was reported by Patrick Jouin, which involves the reaction of amino acids with Meldrum's acid, leading to the formation of cyclic tetramic acid which upon reduction with sodium borohydride followed by hydrolysis, leads to the formation of stereoselective stanines. [12] This approach gives highly stereoselective products, but the number of steps is higher. Other approaches include the asymmetric hydrogenation of *α*-L-amino-*β*-keto esters

* Corresponding author:E-Mail: sharma.arvindkumar@aragen.com

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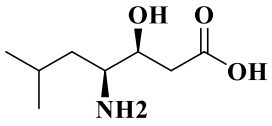
[13] and condensation of an *N*-protected (*S*)-amino aldehyde with a metalated ethyl acetate to form the **3S, 4S** and **3R, 4S** diastereoisomer mixture of Boc-statine ester. [1, 14]




**1**

**Figure 1.** (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid

Asymmetric reduction of *α*-L-amino-*β*-keto esters to get the statines is an important synthetic methodology.[15,16] Recently we have published the synthesis of eznamide derivatives and in the synthesis of key scaffold, we used the asymmetric reduction of *α*-L-amino-*β*-keto esters with CBS catalyst to obtain the desired statine.[17] Herein, in this paper we are reporting the further expansion of this work while studying the effect of different substituents on the stereo selectivity.

## 2. Experimental

### *2.1. Materials and Methods*

All the chemicals were obtained from commercial suppliers and used without further purification. The reactions were conducted in oven-dried glass wares and maintained under the appropriate atmospheric conditions. To monitor the progress of the reactions, thin-layer chromatography (TLC) was employed, specifically, 0.25 mm Merck Silica gel 60 $F_{254}$ plates were used, and visualization was achieved using UV light. Flash column chromatography used 100-200 mesh silica gel as the stationary phase. Elution was carried out using a mixture of hexane and ethyl acetate as the mobile phase. NMR spectra were recorded on a Bruker 400R spectrometer ($^1$H at 400 MHz and $^{13}$C at 100 MHz) using $CDCl_3$ as the solvent with TMS as the internal standard. Liquid chromatography mass spectrometric analysis was carried out in ESI quadrupole time of flight Agilent mass spectrometer.

*General Procedure for the Synthesis of N-Boc-γ-amino β-keto ester*

To a solution of N-Boc amino acid (4.0 mmol) in 25 mL of THF and then 1, 1′-Carbonyldiimidazole (6.0 mmol, 1.5 eq) was added at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 h and then magnesium chloride (4.0 mmol, 1 eq) and ethyl potassium malonate (4.0 mmol, 1 eq) were added respectively. The resulting mixture was stirred for 15 h at 50 °C. After completion of SM, the reaction mixture was diluted with water, the precipitated solids were filtered through Celite pad and washed with ethyl acetate. The combined organic layer was washed with 0.5 N HCl and 5% of aqueous $NaHCO_3$ solution, dried over magnesium sulfate, filtered off and concentrated to get the crude. The crude compound was purified by flash column chromatography.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-6-methyl-3-oxoheptanoate (**2a**)*[14,17]*:* Colorless oil, Yield: 92%, $[\alpha]_D^{25}$ = -48.7 (c = 1, MeOH). $^1$H NMR ($CDCl_3$, 400 MHz): *δ* 12.07 (s, 1H enolic 5.5%), 4.98–4.97 (d, *J* = 6.4 Hz, 1H, NH), 4.37–4.34 (m, 1H, CH), 4.23–4.17 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 3.52 ($CH_2$, AB system), 1.44 (s, 9H, $C(CH_3)_2$, Boc), 1.38–1.36 (d, *J* = 6.5 Hz, 3H, $CH_3$), 1.29–1.28 (t, *J* = 3.6 Hz, 3H, $CH_3$), 0.97 (b, s, 6H, $C(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 202.9, 167.1, 155.5, 80.1, 61.4, 58.2, 46.3, 39.8, 28.3, 24.8, 23.2, 21.5, 14.2; Mass (ESI): $C_{15}H_{27}NO_5$ $[M+H]^+$; calculated *m/z:* 302.19; found: *m/z:*302.23.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-5-cyclohexyl-3-oxopentanoate (2b)*[18]*:* Colorless liquid, Yield: 89%, $[\alpha]_D^{25}$ = -37.24 (c = 1, MeOH). $^1$H NMR ($CDCl_3$, 400 MHz,): *δ* 12.07 (s, 1H enolic 4.5%), 4.97–4.95 (d, *J* = 7.6 Hz, 1H, NH), 4.38–4.37 (m, 1H, CH), 4.22–4.17 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 3.55 ($CH_2$, AB system), 1.86-1.62 (m, 6 H, $CH_2$), 1.44 (s, 9H, $C(CH_3)_2$, Boc), 1.38–1.15 (m, 8H, $CH_2$, $CH_3$), 1.12-1.01 (m, 2 H, $CH_2$); $^{13}$C

NMR (100 MHz, $CDCl_3$): $\delta$ 203.1, 166.9, 155.5, 80.1, 61.4, 57.4, 46.5, 38.3, 34.1, 33.4, 32.2, 28.2,26.3, 26.2, 26.1, 25.9, 14.1; Mass (ESI): $C_{18}H_{31}NO_5$ $[M+H]^+$; calculated: *m/z:* 342.22; found: *m/z:* 342.25.

*Ethyl (4S,5S)-4-((tert-butoxycarbonyl) amino)-5-methyl-3-oxoheptanoate (2c)*[14]*:* Yellowish liquid, Yield: 90%, $[\alpha]_D^{25}$ = -43.89 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.11 (s, 1H, enolic 7%), 5.08–5.06 (d, *J* = 8.8 Hz,1H, NH), 4.35– 4.31 (m, 1H, CH), 4.22–4.17 (q, *J* = 7.2 Hz, 2H, –$OCH_2$), 3.55 ($CH_2$, AB system), 1.97–1.90 (m, 1H, CH), 1.63–1.57 (m, 2H, $CH_2$), 1.41 (s, 9H, $C(CH_3)_3$, Boc-), 1.27–1.23 (t, *J* = 7.2 Hz, 3H, $CH_3$), 0.97– 0.95 (dd, *J* = 3.64 Hz, *J* = 3.24 Hz, 3H, $CH_3$), 0.89–0.85 (t, *J* = 6.9 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 202.3, 166.6, 155.7, 79.9, 64,2, 61.4, 47.2, 36.2, 28.2, 24.1, 15.9, 14.1, 11.3; Mass (ESI): $C_{15}H_{27}NO_5$ $[M+H]^+$; calculated: *m/z:*302.19; found: *m/z:* 302.23.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-5-methyl-3-oxohexanoate (2d)*[14]*:* Colorless liquid, Yield: 92%, $[\alpha]_D^{25}$ = -41.42 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.11 (s, 1H enolic form 6%), 5.1 (s, b, 1H, NH), 4.35–4.32 (m, 1H, CH), 4.22–4.17 (q, *J* = 7.2 Hz, 2H, –$OCH_2$), 3.57–3.50 ($CH_2$, AB system ) 2.28–2.23 (m, 1H, $CH(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$, Boc-), 1.29–1.26 (t, *J* = 7 Hz, 3H, $CH_3$), 1.02–0.82 (m, 6H, $C(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 202.1, 166.7, 155.8, 79.9, 64.3, 61.5, 47.1, 29.5, 28.2, 19.7, 16.6, 14.1; Mass (ESI): $C_{14}H_{25}NO_5$ $[M+H]^+$; calculated: *m/z:* 288.17; found: *m/z:* 288.2.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-3-oxo-5-phenylpentanoate (2e)*[14]*:* Off-white solid, Yield: 88%, mp = 58.8- 61.4 ˚C (reported mp: 61.4 ˚C) [6], $[\alpha]_D^{25}$ = -51.88 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.14 (s, 1H, enolic 3%), 7.32–7.16 (m, 5H, $C_6H_5$), 5.08–5.06 (d, *J* = 7.2 Hz, 1H, NH), 4.59–4.54 (q, *J* = 7.2 Hz, 1H, CH), 4.19–4.14 (q, *J* = 6.8 Hz, 2H, –$OCH_2$), 3.53–3.44 ($CH_2$, AB system), 3.17–2.96 (m, 2H, $CH_2$Ph), 1.38 (s, 9H, $C(CH_3)_3$), 1.28–1.24 (t, *J* = 7.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 201.9, 166.8, 155.1, 136.1, 129.2, 128.6, 126.9, 80.1, 61.4, 60.4, 46.8, 37.3, 28.1, 14.1; Mass (ESI): $C_{18}H_{25}NO_5$ $[M+H]^+$; calculated: *m/z:* 336.17; found: *m/z:*336.16.

*Ethyl (S)-4-((tert-butoxy carbonyl) amino)-5,5-dimethyl-3-oxohexanoate (2f):* Pale-yellow solid, Yield: 81%, mp = 41.5 - 43.24 ˚C, $[\alpha]_D^{25}$ = -31.4 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.18 (s, 1H enolic form 11%), 5.14–5.12 (d, *J* = 9.2 Hz, 1H, NH), 4.22–4.16 (m, 2H, –$OCH_2$, 1H-CH), 3.61–3.54 ($CH_2$, AB system), 1.44 (s, 9H, $C(CH_3)_3$, Boc-), 1.29–1.26 (t, *J* = 7 Hz, 3H, $CH_3$), 1.01 (s, 9H, $C(CH_3)_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 203.2, 166.6, 155.5, 91.4, 80.0, 61.4, 49.9, 34.8, 28.3, 26.8, 14.2; Mass (ESI): $C_{15}H_{27}NO_5$ $[M+H]^{+;}$ calculated: 301.19; found: 302.23.

E*thyl (S)-4-((tert-butoxycarbonyl) amino)-4-cyclopropyl-3-oxobutanoate (2g):* Pale yellow oil, Yield: 89%, $[\alpha]_D^{25}$ = -32.7 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.31–5.23 (d, *J* = 30.4 Hz, 1H, NH), 4.23–4.18 (q, *J* = 7.2 Hz, 2H, –$OCH_2$), 3.83–3.79 (t, *J* = 7.2 Hz, 1H, CH), 3.63 (s, 2H, $CH_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.28–1.24 (t, *J* = 7.2 Hz, 3H, $CH_3$) 0.96–0.94 (m, 1H, CH), 0.72–0.69 (m, 1H, CH), 0.56–0.47 (m, 3H, CH, $CH_3$) ; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 200.9, 166.7, 155.4, 80.0, 63.0, 61.5, 60.4, 46.6, 28.2, 14.2, 13.1, 4.3, 2.8; Mass (ESI): $C_{14}H_{23}NO_5$ $[M+H]^+$; calculated: *m/z:* 286.16; found: *m/z:* 286.19.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-3-oxo-6-phenylhexanoate (2h):* Gummy liquid, Yield: 87%, $[\alpha]_D^{25}$ = -46.3 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.12 (s, 1H, enolic 5%), 7.3–7.16 (m, 5H, $C_6H_5$), 5.17–5.16 (d, *J* = 5.6 Hz, 1H, NH), 4.40–4.35 (q, *J* = 7.6 Hz, 1H, CH), 4.22–4.15 (q, *J* = 7.2 Hz, 2H, –$OCH_2$), 3.57–3.46 ($CH_2$, AB system), 2.26-2.2 (m, 1H, CH), 1.89-1.78 (m, 1H), 1.45 (s, 9H, $C(CH_3)_3$), 1.29–1.27 (t, *J* = 7.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 202.1, 166.9, 155.4, 140.9, 128.5, 128.4, 126.9, 80.2, 61.5, 59.4, 46.2, 34.7, 32.1, 28.3, 14.1; Mass (ESI): $C_{19}H_{27}NO_5$ $[M+H]^+$; calculated: *m/z:*350.19; found: *m/z:* 350.18.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-5-(1H-indol-3-yl)-3-oxopentanoate (2i)*[22]*:* Pale-yellow solid, Yield: 74%, mp = 78.2 - 81.1 ˚C, $[\alpha]_D^{25}$ = -5.15 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.23 (s, 1H, enolic

5%), 8.29 (bd, 1H, Ar-NH), 7.61-7.59 (d, *J* = 7.6 Hz, 1H, CH), 7.36–7.33 (m, 1H, CH), 7.21–7.18 (t, *J* = 7.2 Hz, 1H, CH), 7.16–7.12 (t, *J* = 5.2 Hz, 1H, CH), 6.66 (s, 1H, CH), 5.17–5.16 (d, *J* = 5.6 Hz, 1H, NH), 4.70–4.65 (q, *J* = 6.4 Hz, 1H, CH), 4.22–4.15 (q, *J* = 7.2 Hz, 2H, –$OCH_2$), 3.5–3.39 ($CH_2$, AB system), 3.3-3.18 (m, 2H, $CH_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.26–1.22 (t, *J* = 7.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 202.7, 167.1, 155.4, 136.2, 127.4, 123.1, 122.3, 119.7, 118.7, 111.3, 109.9, 80.2, 61.6, 59.9, 46.9, 28.3, 26.9, 14.1; Mass (ESI): $C_{20}H_{26}N_2O_5$ $[M+H]^+$; calculated: *m/z:* 375.18; found: *m/z:* 375.21.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-3-oxohexanoate (2j)*[23]*:* Pale- yellowish liquid, Yield: 82%, $[\alpha]_D^{25}$ = -35.4 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): *δ* 12.09 (s, 1H enolic 4.5%), 5.19–5.17 (d, *J* = 6.8 Hz, 1H, NH), 4.33–4.32 (m, 1H, CH), 4.22–4.17 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 3.59-3.49 ($CH_2$, AB system ), 1.97-1.92 (m, 1H, CH), 1.65-1.58 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.29–1.28 (t, *J* = 3.6 Hz, 3H, $CH_3$), 0.95-0.91 (m, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 202.1, 166.7, 155.4, 79.9, 62.3, 60.6, 58.1, 46.2, 28.2, 24.1, 14.1, 9.3; Mass (ESI): $C_{13}H_{23}NO_5$ $[M+H]^+$; calculated: *m/z:* 274.16; found: *m/z:* 274.18.

*Ethyl (S)-4-((tert-butoxycarbonyl) amino)-3-oxoheptanoate (2k):* Yellowish liquid, Yield: 85%, $[\alpha]_D^{25}$ = -41.1 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): *δ* 12.09 (s, 1H enolic 4.5%), 5.11–5.09 (d, *J* = 7.2 Hz, 1H, NH), 4.37-4.32 (dd, *J* = 7.6 Hz, *J* = 12.4 Hz, 1H, CH), 4.22–4.17 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 3.59-3.49 ($CH_2$, AB system), 1.89-1.76 (m, 1H, CH), 1.57-1.51 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.39-1.32 (m, 2 H, $CH_2$), 1.29–1.28 (t, *J* = 3.6 Hz, 3H, $CH_3$), 0.95–0.92 (t, *J* = 7.2 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 202.3, 166.8, 155.4, 79.9, 61.4, 59.4, 46.2, 32.9, 28.3, 18.8, 14.1, 13.6; Mass (ESI): $C_{14}H_{25}NO_5$ $[M+H]^+$; calculated: *m/z:*288.17; found: *m/z:* 288.2.

*General Procedure for the Synthesis of N-Boc Anti (3S,4S) β-Hydroxy-amino ester*

(*R*)-(+)-2-Methyl-CBS-oxazaborolidine (1 M in Toluene, Aldrich, 0.2 eq) was charged in dry RBF, added drop wise $BH_3$-THF (1 M in THF, 1.2 eq) or $BH_3$-DMS (2 M in THF, 1.2 eq) at 0 °C. The reaction mixture was stirred in 30 min at 0 °C, in this time clear solution was observed. After 30 min, *N*-Boc-γ-amino *β*-keto ester (1 eq) in dry DCM (15 mL) was added drop wise by using syringe pump over a period of 1 h at 0 °C. The reaction mixture was stirred for 3 h at room temperature. After 3 h, reaction mixture was quenched with ethanol and stirred room temperature. After 1 h, reaction mixture was partitioned between ethyl acetate and water. Organic layer was dried over sodium sulphate and concentrated with vacuum to get the crude. The crude compound was purified by flash column chromatography over silica gel eluted with ethyl acetate / hexane to afford the N-Boc Anti (3S,4S) *β*-Hydroxy-γ-amino ester. Purification of compound 3i was unsuccessful using silica gel chromatography; therefore, it was purified using a C18 reversed-phase column eluting with acetonitrile/water.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-6-methylheptanoate (3a)*[1,17]*:* Colorless oil, Yield: 81%, $[\alpha]_D^{25}$ = -36.8 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): *δ* 4.74–4.71 (d, *J* = 10 Hz, 1H, NH), 4.19–4.14 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 4.03-4.01 (d, *J* = 8 Hz, 1H, -CH-OH), 3.64-3.58 (m, 1H, CH), 3.32-3.17 (d, *J* = 2 Hz, 1H, OH), 2.58-2.51 (m, 2H, -$CH_2$CO), 1.69-1.64 (m, 1H, CH), 1.56-1.50 (m, 1H, CH), 1.36-1.32 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc) ,1.30-1.25 (t, J = 7.2 Hz, 3H, -$CH_3$), 0.94-0.92 (m, 6H, -$(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): *δ* 173.5, 156.1, 79.2, 69.8, 60.8, 52.1, 41.7, 38.7, 28.3, 24.7, 23.1, 22.2, 14.1; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$; calculated: *m/z:* 304.2; found: *m/z:* 304.24.

Reaction yielding 3a was performed on 1 g scale and obtained product 3a in 77% yield. Diastereomeric ratio obtained was 96:4.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-5-cyclohexyl-3-hydroxypentanoate (3b)*[18]*:* Colorless oil, Yield: 76%, $[\alpha]_D^{25}$ = -31.1 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): *δ* 4.71–4.68 (d, *J* = 10 Hz, 1H, NH), 4.19–4.14 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 4.01-3.99 (m, 1H, -CH-OH), 3.67-3.61 (m, 1H, CH), 3.28-3.27 (d, *J* = 2.8 Hz, 1H, OH), 2.58-2.46 (m, 2H, -$CH_2$CO), 1.84-1.65 (m, 6H, $CH_2$), 1.52-1.46 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.41-1.34 (m, 1H, CH), ,1.29-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 1.22-1.11 (m, 4H, -$(CH_2)_2$), 1.02-0.82 (m,

1H, $CH_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 173.5, 156.1, 79.2, 69.6, 60.8, 51.3, 40.3, 38.7, 34.2, 33.7, 32.9, 28.4, 26.5, 26.3, 26.2, 14.1; Mass (ESI): $C_{18}H_{33}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 344.24; found: *m/z:* 344.24.

*Ethyl (3S, 4S, 5S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-methylheptanoate (3c)*[1]*:* Light yellowish liquid, Yield: 61%, $[\alpha]_D^{25}$ = -36.1 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.86-4.84 (d, *J* = 10 Hz, 1H, NH), 4.28-4.26 (dd, *J* = 1.6 Hz, *J* = 10 Hz, 1H, - CH-OH), 4.19-4.15 (t, *J* = 7.2, 2H,-$OCH_2$), 3.31-3.28 (d , *J* = 2.6 Hz 1H, OH), 3.24-3.20 (t, *J* = 8.6 Hz, 1H, -$CH_2$), 2.58-2.41 (m, 2H, -$CH_2$), 1.68-1.52 (m, 2H, -$CH_2$), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.29-1.26 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 1.18-1.10 (m, 1H, -CH), 0.97-0.96 (d, *J* = 5.3 Hz, 3H, -$CH_3$), 0.91-0.88 (t, *J* = 5.5 Hz, 3H, -$CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 173.7, 156.2, 79.1, 66.9, 60.8, 58.1, 39.1, 36.6, 28.4, 25.6, 15.7, 14.1, 11.1; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 304.2; found: *m/z:* 304.2.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-methylhexanoate (3d)*[1]: Yellowish liquid, Yield: 56%, $[\alpha]_D^{25}$ = -35.4 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.86-4.83 (d, *J* = 10 Hz, 1H, NH), 4.26-4.24 (d, *J* = 8.2 Hz, 1H,-CH-OH), 4.19-4.14 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 3.29-3.28 (d, *J* = 10 Hz, 1H, -OH), 3.17-3.12 (t, *J* = 9.2 Hz, 1H, -CH-), 2.59-2.42 (m, 2H, -$CH_2CO$), 1.90-1.83 (m, 1H, -CH-), 1.44 (s, 9H, $C(CH_3)_3$, Boc) ,1.30-1.26 (t, *J* = 7.2 Hz, 3H, - $CH_3$), 0.99-0.95 (m, 6H, -$(CH_3)_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) : $\delta$ 173.7, 156.3, 79.1, 67.1, 60.8, 59.6, 39.4, 30.4, 28.4, 19.7, 19.5, 14.1: Mass (ESI): $C_{14}H_{27}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 290.19; found: *m/z:* 290.13.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-phenylpentanoate (3e)*[1]*:* Off-white solid, Yield: 62%, mp = 67.2- 69.1 °C, $[\alpha]_D^{25}$ = -36.2 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.3-7.2 (m, 5H, -Ph), 4.96-4.94 (d, *J* = 9.6 Hz, 1H, NH), 4.15-4.1 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 3.99-3.96 (d, J = 9.2 Hz, 1H,-CH-OH), 3.73-3.71 ( m, 1H, -CH-), 3.5 (b, 1H, -OH), 2.92-2.9 (d, *J* = 7.6 Hz, 2H, -$CH_2$-Ph), 2.61-2.55 (m, 1H, -CH-CO), 2.39-2.34 (m, 1H, -CH-CO), 1.4 (s, 9H, $C(CH_3)_3$, Boc) ,1.27-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) : $\delta$ 173.5, 155.8, 138.1, 129.4, 128.4, 126.3, 79.4, 66.9, 60.8, 55.3, 38.5, 28.3, 14.1; Mass (ESI): $C_{18}H_{27}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 337.19; found: *m/z:* 338.17.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5,5-dimethylhexanoate (3f):* Colorless gummy, Yield: 63%, $[\alpha]_D^{25}$ = -27.7 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.11-5.08 (d, *J* = 10.4 Hz, 1H, NH), 4.39-4.36 (d, *J* = 10.4 Hz, 1H,-CH-OH), 4.19-4.15 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 3.21(b, 1H, -OH), 3.18 (b, 1H, -CH-), 2.62-2.37 (m, 2H, -$CH_2CO$), 1.45 (s, 9H, $C(CH_3)_3$, Boc) ,1.29-1.25 (t, *J* = 8.8 Hz, 3H, - $CH_3$), 0.99(s, 9H, -$(CH_3)_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) : $\delta$ 173.7, 156.4, 79.0, 66.2, 60.8, 39.8, 35.2, 28.4, 27.2, 14.1; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 304.2; found: *m/z:* 304.16.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-4-cyclopropyl-3-hydroxybutanoate (3g):* Yellowish liquid, Yield: 52%, $[\alpha]_D^{25}$ = -24.7 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.94-4.92 (d, *J* = 5.6 Hz, 1H, NH), 4.21-4.14 (m, 3H,-CH-OH, -$OCH_2$), 3.33-3.28 (m, 1H,-CH-), 2.85-2.83 (d, *J* = 8.4 Hz, 1H, -OH), 2.53-2.46 (m, 2H, -$CH_2CO$), 1.44 (s, 9H, $C(CH_3)_3$, Boc) ,1.28-1.25 (t, *J* = 7.2 Hz, 3H, - $CH_3$), 1.15–1.05 (m, 1H, CH), 0.55–0.52 (m, 3H, CH, $CH_3$), 0.29–0.25 (m, 1H, CH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 173.1, 156.1, 79.3, 70.4, 60.8, 58.8, 38.9, 28.3, 14.1, 11.1, 5.1, 3.6, 1.7; Mass (ESI): $C_{14}H_{25}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 288.17; found: *m/z:* 288.17.

*Ethyl (3S, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-6-phenylhexanoate (3h):* Off- white solid, Yield: 71%, mp = 83.4- 86.1 °C, $[\alpha]_D^{25}$ = -42.5 (c = 1, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.27-7.18 (m, 5H, -Ph), 4.82-4.79 (d, *J* = 9.6 Hz, 1H, NH), 4.18-4.15 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 4.08-4.06 (m, 1H,-CH-OH), 3.58-3.55 (m, 1H, -CH-), 3.31-3.3(d, *J* = 2.4 Hz, 1H, -OH), 2.71-2.48 (m, 4H, -$CH_2$-Ph, -$CH_2$-), 1.93-1.85 (m, 2H, -$CH_2CO$), 1.45 (s, 9H, $C(CH_3)_3$, Boc) ,1.28-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) : $\delta$ 173.4, 156.1, 141.7, 128.3, 125.8, 79.3, 69.3, 60.8, 53.6, 38.6, 34.6, 32.4, 28.3, 14.1; Mass (ESI): $C_{19}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 352.20; found: *m/z:* 352.20.

*Ethyl (3S,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-(1H-indol-3-yl) pentanoate (3i):* Pale-yellow solid, Yield: 53%, mp = 77.2- 78.7 °C, $[\alpha]_D^{25}$ = -2.2 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.19 (br, s, 1H, Ar-NH), 7.64-7.62 (d, *J* = 8 Hz, 1H, CH), 7.35–7.33 (d, *J* = 8 Hz, 1H, CH), 7.2–7.16 (t, *J* = 6.8 Hz, 1H, CH), 7.13–7.1 (t, *J* = 7.2 Hz, 1H, CH), 7.05 (br, s, 1H, CH), 4.64 (d, *J* = 5.6 Hz, 1H, NH), 4.18–4.13 (q, *J* = 6.8 Hz, 1H, CH), 3.97 (m, 1H,-CH-OH), 3.71 (m, 1H, -CH-), 3.07(bd, 1H, -OH), 2.61-2.48 (m, 2H, -$CH_2$CO), 1.37 (s, 9H, C($CH_3$)$_3$, Boc) ,1.27-1.23 (t, *J* = 7.2 Hz, 3H, -CH*3*); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.1, 155.9, 136.2, 127.9, 122.8, 122.1, 119.4, 118.8, 111.3, 111.1, 79.5, 70.1, 60.8, 54.5, 38.1, 28.2, 25.5, 14.1; Mass (ESI): $C_{20}H_{28}N_2O_5$ $[M+H]^+$ ; calculated: *m/z:* 377.20; found: *m/z:* 377.14.

*Ethyl (3S,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxyhexanoate (3j)*[23]*:* Colorless liquid, Yield: 66%, $[\alpha]_D^{25}$ = -26.5 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.77–4.74 (d, *J* = 9.2 Hz, 1H, NH), 4.19–4.14 (q, *J* = 6.8 Hz, 2H, $OCH_2$), 4.07-4.06 (d, *J* = 1.6 Hz, 1H, -CH-OH), 3.42-3.4 (m, 1H, CH), 3.27-3.26 (d, *J* = 2.4 Hz, 1H, OH), 2.59-2.44 (m, 2H, -$CH_2$CO), 1.63-1.56 (m, 2H, $CH_2$), 1.44 (s, 9H, C($CH_3$)$_3$, Boc) ,1.29-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 0.97-0.93 (t, *J* = 7.6 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.4, 156.2, 79.1, 68.7, 60.8, 55.4, 38.7, 28.3, 25.6, 14.1, 10.6; Mass (ESI): $C_{13}H_{25}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 275.17; found: *m/z:* 276.15.

*Ethyl (3S,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxyheptanoate (3k):* Yellowish liquid, Yield: 74%, $[\alpha]_D^{25}$ = -32.2 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.79–4.76 (d, *J* = 9.6 Hz, 1H, NH), 4.19–4.14 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 4.07-4.04 (m, 1H, -CH-OH), 3.54-3.48 (m, 1H, CH), 3.33-3.29 (d, *J* = 2.8 Hz, 1H, OH), 2.58-2.44 (m, 2H, -$CH_2$CO), 1.74-1.51 (m, 2H, $CH_2$), 1.44 (s, 9H, C($CH_3$)$_3$, Boc), 1.41-137 (m, 1H, $CH_2$), 1.29-1.25 (t, *J* = 7.2 Hz, 3H, -CH3), 0.94-0.91 (t, *J* = 7.6 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.4, 156.1, 79.1, 69.2, 60.7, 53.7, 38.7, 34.8, 28.3, 19.3, 14.1, 13.9; Mass (ESI): $C_{14}H_{27}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 289.19; found: *m/z:* 290.18.

*General Procedure for the Synthesis of N-Boc Syn (3R, 4S) β-Hydroxy-γ-amino ester*

(*S*)-(-)-2-Methyl-CBS-oxazaborolidine (1M in Toluene, Aldrich, 0.2 eq) was charged in dry RBF, added drop wise $BH_3$-THF (1M in THF, 1.2 eq) at 0 °C. The reaction mixture was stirred in 30 min at 0 °C, in this time clear solution was observed. After 30 min, N-Boc γ-amino *β*-keto ester (1 eq) in dry DCM (15 mL) was added drop wise by using syringe pump over a period of 1 h at 0 °C. The reaction mixture was stirred for 3 h at room temperature. After 3 h, reaction mixture was quenched with ethanol and stirred room temperature. After 1 h, reaction mixture was partitioned between ethyl acetate and water. Organic layer was dried over magnesium sulphate, filtered off and concentrated. The crude compound was purified by flash column chromatography over silica gel eluted with ethyl acetate / hexane to afford the N-Boc *Syn* (3*R*,4*S*) *β*-Hydroxy-γ-amino ester. Purification of compound 4i was unsuccessful using silica gel chromatography; therefore, it was purified using a C18 reversed-phase column eluting with acetonitrile/water.

*Ethyl (3R, 4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-6-methylheptanoate (4a)*[1,17]*:* Colorless oil, Yield: 86%, $[\alpha]_D^{25}$ = -27.5 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.59-4.57 (d, *J* = 8 Hz, 1H, NH), 4.20-4.14 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 4.01-4.00 (m,1H, OCH), 3.67 (bd, 1H, -CH), 3.44-3.43 (d, *J* = 3.6 Hz, 1H, -OH), 2.51-2.42 (m, 2H, -$CH_2$CO-), 1.73-1.64 (m, 1H, CH), 1.44 (s, 9H, C($CH_3$)$_2$, Boc), 1.34-1.31 (m, 2H, $CH_2$) 1.29-1.27 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 0.94-0.90 (m, 6H, -($CH_3$)$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.8, 156.1, 79.5, 71.4, 60.8, 52.7, 38.8, 38.1, 28.3, 24.7, 23.6, 21.5, 14.1; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 304.20; found: *m/z:* 304.24.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-5-cyclohexyl-3-hydroxypentanoate (4b)*[18]*:* Off-white solid, Yield: 83%, mp = 52.5- 53.9 °C, $[\alpha]_D^{25}$ = -23.7 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.57–4.55 (d, *J* = 8.4 Hz, 1H, NH), 4.19–4.14 (q, *J* = 6.8 Hz, 2H, $OCH_2$), 4.01-3.99 (m, 1H, -CH-OH), 3.70 (m, 1H, CH), 3.44-3.43 (d, *J* = 3.6 Hz, 1H, OH), 2.47-2.41 (m, 2H, -$CH_2$CO), 1.86-1.83 (m, 1H, CH), 1.69-1.61 (m, 5H, $CH_2$), 1.44 (s, 9H, C($CH_3$)$_3$, Boc), 1.29-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 1.22-1.12 (m, 3H, -($CH_2$)$_2$), 1.02-1.01 (m, 1H, CH), 0.88-0.77 (m, 1H, CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.8, 156.2, 79.5, 71.4, 60.8, 52.1, 38.1, 37.5,

34.1, 32.3, 28.3, 26.5, 26.3, 26.1, 14.1; Mass (ESI): $C_{18}H_{33}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 344.24; found: *m/z:* 344.26.

*Ethyl (3R, 4S, 5S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-methylheptanoate (4c)*[1]*:* Light yellowish liquid, Yield: 79%, $[\alpha]_D^{25}$ = -32.15 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.43-4.41 (d, *J* = 10 Hz, 1H, NH), 4.20-4.15 (t, *J* = 7.2 Hz, 2H,-$OCH_2$), 4.02-3.99 (t, *J* = 7.8 Hz, 1H,-CH-OH), 3.59-3.54 (m, 1H, -CH), 3.30-3.31 (d , J = 2.8 Hz, 1H, OH), 2.59-2.43 (m, 2H, -$CH_2$ ), 1.81-1.79 (m, 1H, -CH), 1.60-1.55 (m, 1H, -CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.29-1.26 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 1.04-0.91 (m, 7H, -$(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) : $\delta$ 173.4, 156.4, 79.5, 69.1, 60.7, 58.9, 38.2, 34.6, 28.3, 23.3, 16.2, 14.1, 11.7; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 304.20; found: *m/z:* 304.24.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-methylhexanoate (4d)*[1]*:* Colorless liquid, Yield: 77%, $[\alpha]_D^{25}$ = -26.1 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.45-4.43 (d, *J* = 9.6 Hz, 1H, NH), 4.20-4.15 (q, *J* = 7.1 Hz, 2H, -$OCH_2$), 3.94-3.92 (m, 1H,-CH-OH), 3.55-3.50 (m, 1H, -CH), 3.33-3.32 (d, J = 4.8 Hz, 1H, -OH), 2.62-2.43 (m, 2H, -$CH_2CO$), 2.16-2.11 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$, Boc), 1.30-1.26 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 0.95-0.87 (m, 6H, -$(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) : $\delta$ 173.2, 156.3, 79.5, 69.2, 60.8, 58.7, 38.3, 28.3, 27.5, 20.1, 16.2, 14.1; Mass (ESI): $C_{14}H_{27}NO_5$ $[M+H]^+$; calculated: *m/z:* 290.19; found: *m/z:* 290.18.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-phenylpentanoate (4e)*[1]*:* Off-white solid, Yield: 78%, mp = 61.9- 63.2 °C, $[\alpha]_D^{25}$ = -14.1 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.31-7.19 (m, 5H, -Ph), 4.57-4.55 (d, *J* = 8 Hz, 1H, NH), 4.19-4.14 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 4.00-3.99 (d, *J* = 6.5 Hz, 1H,-CH-OH), 3.90-3.84 (m, 1H, -CH-), 3.61 (b, 1H, -OH), 3.01-2.82 (m, 2H, -$CH_2$-Ph), 2.61-2.47 (m, 2H, -$CH_2CO$), 1.36 (s, 9H, $C(CH_3)_3$, Boc) ,1.30-1.26 (t, *J* = 7.2 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.9, 155.7, 137.6, 129.4, 128.4, 126.3, 79.5, 70.1, 60.8, 55.1, 38.1, 35.8, 28.2, 14.1; Mass (ESI): $C_{18}H_{27}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 338.19; found: *m/z:* 338.17.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5,5-dimethylhexanoate (4f):* Pale-yellow solid, Yield: 72%, mp = 49.2- 51.1 °C, $[\alpha]_D^{25}$ = -17.2 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.51-4.48 (d, *J* = 10.4 Hz, 1H, NH), 4.18-4.14 (m, 3H, -CH-OH, -$OCH_2$), 3.53-3.47 (m, 1H, -CH-), 3.39-3.38 (d, *J* = 6.8 Hz, 1H, -OH), 2.53-2.47 (m, 2H, -$CH_2CO$), 1.44 (s, 9H, $C(CH_3)_3$, Boc) ,1.29-1.25 (t, *J* = 7.2 Hz, 3H, - $CH_3$), 1.01(s, 9H, -$(CH_3)_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.9, 156.6, 79.7, 69.5, 63.1, 60.7, 39.5, 34.1, 28.3, 27.2, 14.1; Mass (ESI): $C_{15}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 3043.20; found: *m/z:* 304.20.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-4-cyclopropyl-3-hydroxybutanoate (4g):* Colorless oil, Yield: 66%, $[\alpha]_D^{25}$ = -15.1 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.06-4.97 (d, *J* = 5.2 Hz, 1H, NH), 4.22-4.14 (m, 3H,-CH-OH, -$OCH_2$), 3.57-3.51 (m, 1H,-CH-), 2.93-2.91 (d, *J* = 8.4 Hz, 1H, -OH), 2.53-2.46 (m, 2H, -$CH_2CO$), 1.44 (s, 9H, $C(CH_3)_3$, Boc) ,1.28-1.25 (t, *J* = 7.2 Hz, 3H, - $CH_3$), 1.09–0.95 (m, 1H, CH), 0.65–0.31 (m, 4H, $CH_2$, $CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) : $\delta$ 172.7, 156.1, 79.6, 70.9, 60.8, 59.3, 38.3, 28.3, 14.1, 11.1, 5.1, 3.1, 1.7; Mass (ESI): $C_{14}H_{25}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 288.17; found: *m/z:* 288.12.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-6-phenylhexanoate (4h):* Off-white solid, Yield: 80%, mp = 74.5- 76.1 °C, $[\alpha]_D^{25}$= -21.8 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.29-7.17 (m, 5H, -Ph), 4.72-4.7 (d, *J* = 8.4 Hz, 1H, NH), 4.18-4.13 (q, *J* = 7.2 Hz, 2H, -$OCH_2$), 4.02 (m, 1H,-CH-OH), 3.62 (m, 1H, -CH-), 3.37(bd, 1H, -OH), 2.79-2.4 (m, 4H, -$CH_2$-Ph, -$CH_2$-), 1.92-1.67 (m, 2H, -$CH_2CO$), 1.45 (s, 9H, $C(CH_3)_3$, Boc) ,1.25-1.23 (t, *J* = 7.2 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.8, 156.1, 141.6, 128.4, 125.9, 79.6, 70.9, 60.8, 54.2, 38.1, 32.3, 31.6, 28.4, 14.1; Mass (ESI): $C_{19}H_{29}NO_5$ $[M+H]^+$ ; calculated: *m/z:* 352.20; found: *m/z:* 352.20.

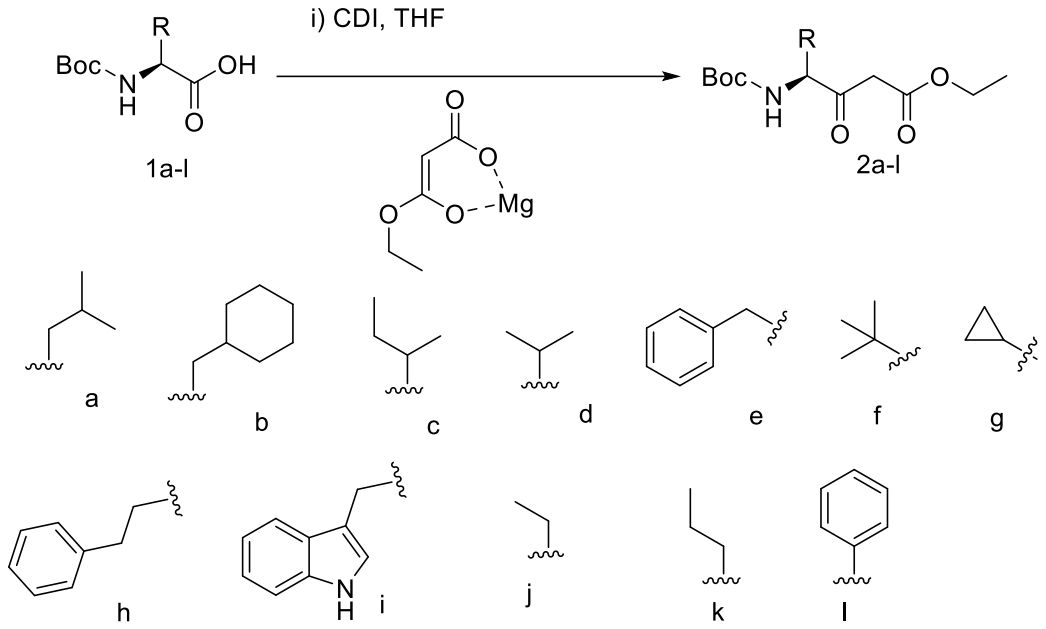
*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxy-5-(1H-indol-3-yl) pentanoate (4i):* Off-white solid, Yield: 67%, mp= 66.4- 67.9 °C, $[\alpha]_D^{25}$= 4.2 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.15 (br, s, 1H, Ar-NH), 7.74-7.72 (d, *J* = 7.6 Hz, 1H, CH), 7.34–7.33 (d, *J* = 8 Hz, 1H, CH), 7.19–7.16 (t, *J* = 6.8 Hz, 1H, CH), 7.13–7.1 (t, *J* = 7.2 Hz, 1H, CH), 7.05 (br, s, 1H, CH), 5.07-5.05 (d, *J* = 9.6 Hz, 1H, NH), 4.16–4.13 (q, *J* = 6.8 Hz, 1H, CH), 3.88-3.82 (m, 1H,-CH-OH), 3.49 (m, 1H, -CH-), 3.07(d, *J* = 7.6 Hz, 1H, -OH), 2.61-2.31 (m, 2H, -$CH_2$CO), 1.37 (s, 9H, C($CH_3$)$_3$, Boc) ,1.27-1.23 (t, *J* = 7.2 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.5, 156.1, 136.2, 127.6, 122.7, 121.9, 119.4, 118.8, 112.2, 111.1, 79.3, 67.1, 60.7, 54.4, 38.6, 28.3, 28.1, 14.1; Mass (ESI): $C_{20}H_{28}N_2O_5$ $[M+H]^+$; calculated: *m/z:* 377.20 found: *m/z:* 377.18.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxyhexanoate (4j)*[23]*:* Off-white solid, Yield: 77%, mp = 51.2- 53.5 °C, $[\alpha]_D^{25}$ = -12.9 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.64–4.62 (d, *J* = 8.4 Hz, 1H, NH), 4.19–4.14 (q, *J* = 7.2 Hz, 2H, $OCH_2$), 4.01-4.00 (d, *J* = 4 Hz, 1H, -CH-OH), 3.51-3.5 (m, 1H, CH), 3.46-3.45 (d, *J* = 3.6 Hz, 1H, OH), 2.54-2.42 (m, 2H, -CH2CO), 1.70-1.64 (m, 1H, CH), 1.44 (s, 9H, C($CH_3$)$_3$, Boc), 1.41-137 (m, 1H, CH), 1.29-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 0.98-0.95 (t, *J* = 7.6 Hz, 3H, -CH3); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.8, 156.2, 79.4, 70.8, 60.7, 56.1, 38.1, 28.3, 22.8, 14.1, 10.4; Mass (ESI): $C_{13}H_{25}NO_5$ $[M+H]^+$; calculated: *m/z:* 276.17; found: *m/z:* 276.15.

*Ethyl (3R,4S)-4-((tert-butoxycarbonyl) amino)-3-hydroxyheptanoate (4k):* Off-white solid, Yield: 80%, mp = 58.9- 61.1 °C, $[\alpha]_D^{25}$ = -17.8 (c = 1, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.58–4.56 (d, *J* = 7.6 Hz, 1H, NH), 4.2–4.14 (q, *J* = 6.8 Hz, 2H, $OCH_2$), 4.0-3.99 (m, 1H, -CH-OH), 3.6 (m, 1H, CH), 3.39-3.38 (d, *J* = 3.6 Hz, 1H, OH), 2.48-2.42 (m, 2H, -$CH_2$CO), 1.59-1.49 (m, 2H, $CH_2$), 1.44 (s, 9H, C($CH_3$)$_3$, Boc), 1.36-133 (m, 1H, $CH_2$), 1.29-1.25 (t, *J* = 7.2 Hz, 3H, -$CH_3$), 0.94-0.91 (t, *J* = 7.6 Hz, 3H, -$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 172.8, 156.2, 79.5, 71.1, 60.7, 54.3, 38.1, 32.1, 28.3, 19.1, 14.1, 13.9; Mass (ESI): $C_{14}H_{27}NO_5$ $[M+H]^+$; calculated: *m/z:* 290.19; found: *m/z:* 290.13.

## 3. Results and Discussion

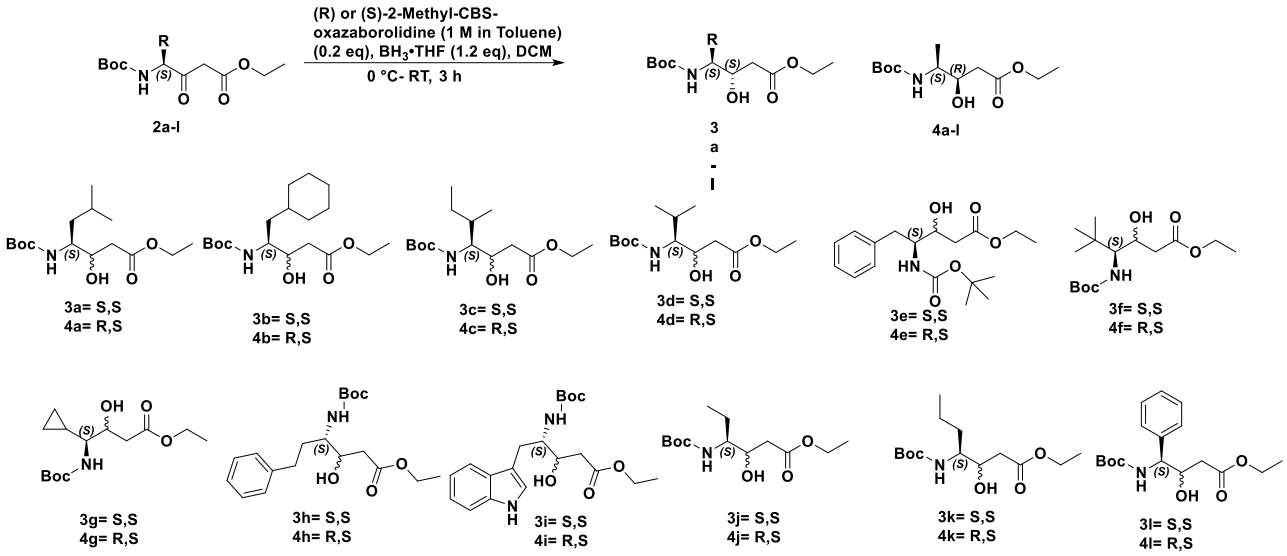
To expand the scope of the asymmetric reduction of α-amino-β-keto esters with (*R)* or (*S)* enantiomer of 2-Methyl-oxazaborolidine (mentioned as **R** or **S**-Me-CBS catalysts in remaining article), we prepared 12 different α-amino-β-keto esters **(2a-l,** Scheme-1**)** starting from Boc-protected amino acids via the reported procedure after slight modifications **(1a-l,** Scheme-1**)**.[19,20] Activation of the amino acid carboxyl with N,N'-carbonyldiimidazole (CDI), followed by treatment of the resulting activated ester with the nucleophilic magnesium enolate, and spontaneous decarboxylation during acidic workup provided compounds **2a-l** which were easily purified by flash chromatography on silica gel. Amino acids selected had different substituents at the 2-position varying from primary, secondary, tert-alkyl and cycloproyl chains to benzyl, homobenzyl and heteroaryl groups. Enantiomeric excess of the β-keto esters was established by chiral HPLC and was >98% in all the cases.




**Scheme-1.** Synthesis of substituted $\alpha$-amino- $\beta$ -keto esters starting from Boc protected amino acids.

As reported earlier by our group,[17] reduction of **2a** with **S**-Me-CBS has given the desired diastereomer **4a** almost exclusively and the reaction was reproducible. Further, we tried the reduction of **2a** with **R**-Me-CBS**.** As in case of **S**-Me-CBS, reaction was performed at 0 °C with 0.2 equivalents of **R**-Me-CBS and 1.2 equivalents of $BH_3$-THF. Under these conditions, starting material was completely consumed but diastereomeric ratio (*dr*) was only 83:17**(**entry-1, Table-1**)**. As expected, **3a** was the major diastereomer with **R**-Me-CBS **(**Scheme 2**)**. To improve *dr*, reaction was tried at -78 °C. However, at this temperature, the reaction was not complete, and no improvement in *dr* was observed (60% unreacted starting material, 30% **3a** and 7% **4a, (**entry-2, Table-1)). Increasing equivalents of borane at –78 °C led to the reduction of the ester as well. Changing the solvent to toluene and 1,4-dioxane gave disappointing conversion as well as *dr*. However, changing the solvent to DCM led to complete conversion and excellent *dr* (96:4, **(**entry-3, Table-1)). Then we studied the reduction of all the 12 $\beta$-keto esters with **R**-Me-CBS in DCM **(**entry-2-14, Table-1). To our disappointment, in most of the other cases, very moderate to poor *dr* was obtained in most of the cases. Only in case of **2a** (Leucine) and **2b** (cyclohexyl-L-alanine), diastereomeric purity obtained was more than 90% (entries-1,2; table-1). Most surprising result was obtained with the **2l**. Distereoselectivity obtained was almost in 1:1 ratio in case of **2I**. To improve diastereomeric purity further, we tried reaction in DCM at -78 °C as well as -20 °C. Although a small improvement in *dr* was observed but reaction did not go for completion at lower temperatures, as observed in the case of THF.

Stereoselective reduction of enantiopure $\alpha$-L-amino-$\beta$-keto esters using oxazaborolidine catalysts




**Scheme 2.** General scheme for the reduction of Boc protected $\alpha$-amino- $\beta$ -keto esters an its substrate scope

Under the same conditions, with **S**-Me-CBS catalyst, reduction of other $\beta$- keto esters **(2b-l)** gave diastereomeric purity in the range of 85-95%. Although diastereomeric purity obtained is better than what we obtained with **R**-Me-CBS but still lower than obtained with **2a**. All these results indicate that the substituent at chiral center of the $\beta$-keto esters plays very important role in determining the chiral purity of the newly formed chiral center.

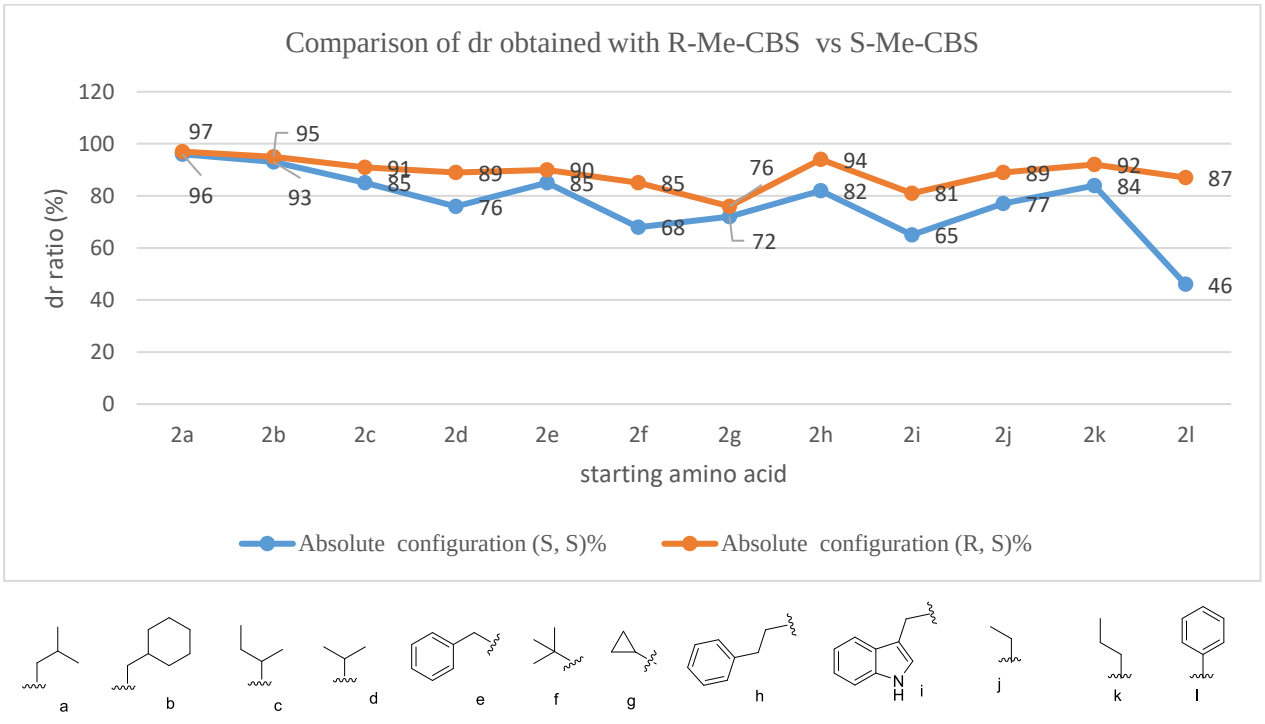


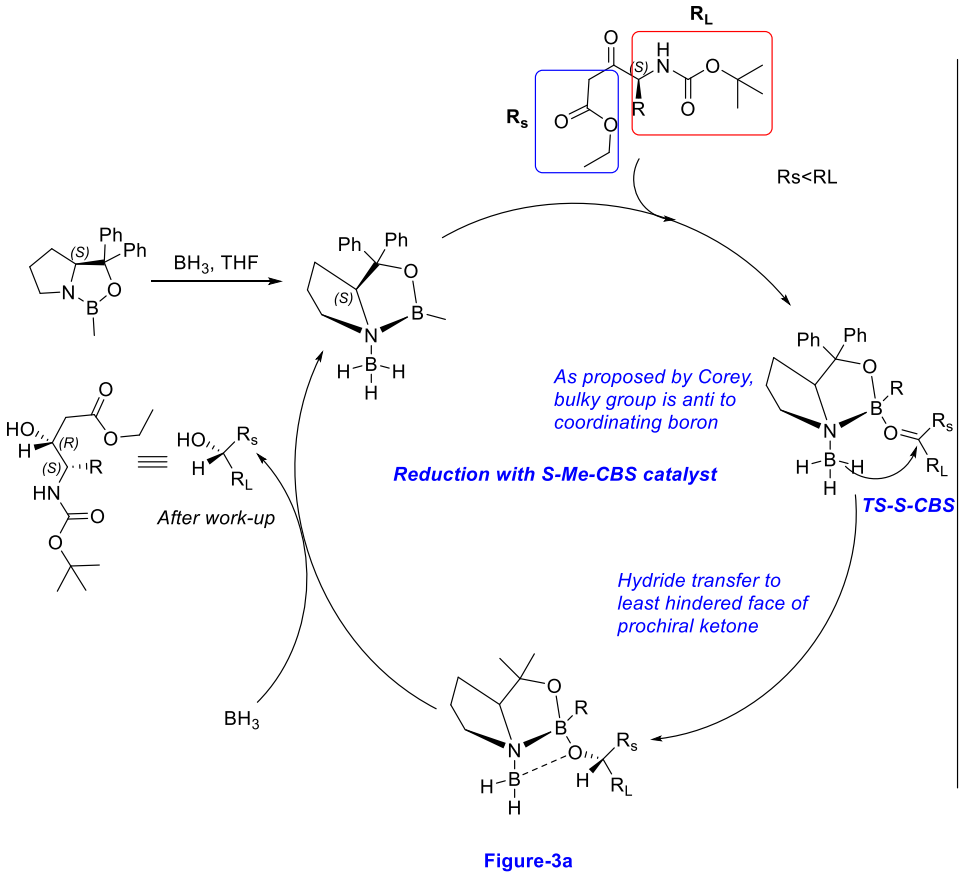

**Figure 2.** Plot of *dr* obtained with S-2-Methyl-CBS-oxazaborolidine vs. R-2-Methyl-CBS-oxazaborolidine.

**Table 1.** Diastereomeric ratio obtained with **R**-Me-CBS and **S**-Me-CBS catalysts*

| | | | **R-Me-CBS** | | | | **S-Me-CBS** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Entry** | **Starting material** | **Conditions** | **Absolute Configuration (S, S)%** | **Absolute Configuration (R, S)%** | **Optical Rotation** | **Yield%** | **Absolute Configuration (R, S)%** | **Absolute configuration (S, S)%** | **Optical Rotation** | **Yield (%)** |
| 1 | **2a** | 0 °C, 0.2 equiv, CBS catalyst, THF, 1.2 equiv borane | **3a, 83%** | **4a, 17%** | - | - | **4a, 97% (Ref-7b)** | **Not detected** | - | - |
| 2 | **2a** | -78 °C, 0.2 equiv, CBS catalyst, THF, 1.2 equiv borane | **3a, 30% (reaction not complete)** | **A, 7%** | - | - | **(--)**** | **(--)** | - | - |
| 3 | **2a** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3a**,*** 96% | **4a**, 4% | -36.8 | 81 | **4a**, 97% | **3a**, 3% | **-27.5** | **86** |
| 4 | **2b** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3b**, 93% | **4b**, 7% | **-31.1** | **76** | **4b**, 95% | **3b**, 5% | **-23.7** | **83** |
| 5 | **2c** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3c**, 85% | **4c,** 15% | **-36.1** | **61** | **4c**, 91% | **3c**, 9% | **-32.15** | **79** |
| 6 | **2d** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3d**, 76% | **4d,** 24% | **-35.4** | **56** | **4d**, 89% | **3d,** 11% | **-26.1** | **77** |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 7 | **2e** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3e**, 85% | **4e,** 15% | **-36.2** | **62** | **4e**, 90% | **3e,** 10% | **-14.1** | **78** |
| 8 | **2f** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3f,** 68% | **4f,** 32% | **-27.7** | **63** | **4f,** 85% | **3f,** 15% | **-17.2** | **72** |
| 9 | **2g** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3g,** 72% | **4g,** 28% | **-24.7** | **52** | **4g**, 76% | **3g**, 24% | **-15.1** | **66** |
| 10 | **2h** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3h**, 82% | **4h,** 18% | **-42.5** | **71** | **4h**, 94% | **3h**, 6% | **-21.8** | **80** |
| 11 | **2i** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3i**, 65% | **4i,** 35% | **-2.2** | **53** | **4i**, 81% | **3i,** 19% | **-4.2** | **67** |
| 12 | **2j** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3j**, 77% | **4j,** 23% | **-26.5** | **66** | **4j**, 89% | **3j,** 11% | **-12.9** | **77** |
| 13 | **2k** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3k**, 84% | **4k,** 16% | **-32.2** | **74** | **4k**, 92% | **3k**, 8% | **-17.8** | **80** |
| 14 | **2l** | 0 °C, 0.2 equiv, CBS catalyst, DCM, 1.2 equiv borane | **3l,** 46% | **4l,** 54% | **-** | **-** | **4l,** 87% | **3l,** 12% | **-** | **-** |

*All diastereomeric ratios are based on the LCMS of direct reaction mixture. **(--) not tried. ***this reaction was scaled up to 1 g scale with reproducible yield and *dr*.



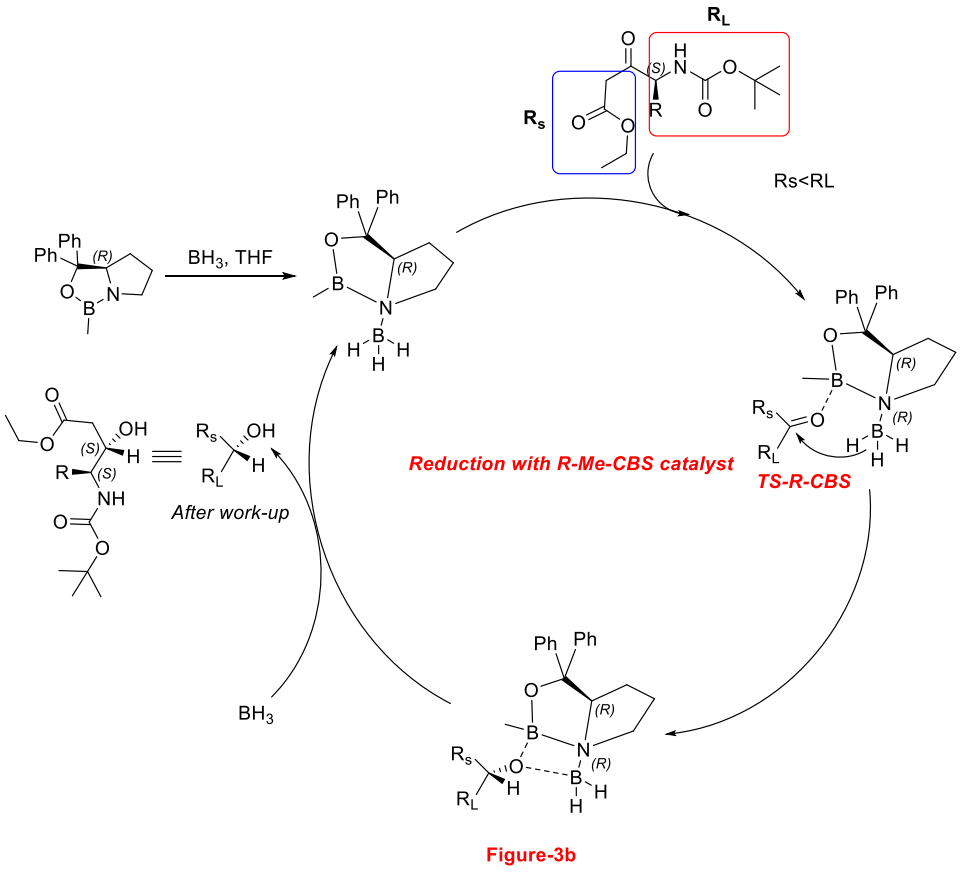




**Figure 3.** Plausible mechanism of reduction of Boc protected $\alpha$-amino-$\beta$-keto esters with (S) and (R)-enantiomers of 2-Methyl-CBS-oxazaborolidine catalyst

To visualize the trend of change in *dr* vis-à-vis structure, we plotted the *dr* obtained with **S**-Me-CBS and **R**-Me-CBS**,** and observed an interesting outcome (Figure 2). This plot indicated that change in *dr* with change in *β*- keto esters followed the same trend in both **S**-Me-CBS as **R**-Me-CBS catalysts. However, the change in *dr* with change in substituents is more pronounced in case of reduction with **R**-Me-CBS catalyst. In case of **S**-Me-CBS**,** it is clearly found that *dr* is >90% when we have a $CH_2$ or CH in alkyl side chain attached to C2 carbon (e.g. **2a, b, c, d, e, h, and k**). However, in case of tert-carbon or benzylic systems directly attached to C2 carbon, *dr* obtained is on the lower side (e.g. **2f and 2i**). *dr* obtained is worse when cyclopropyl ring is directly attached to the C2 carbon (e. g. **2g**). *dr* obtained with **R**-Me-CBS followed the same pattern, however (i) it was always lower than the **S**-Me-CBS and (ii) there was an unexplainable dip in *dr* in case of **2l**.

Based on the seminal work of Corey on the asymmetric reduction of ketones[24] we have drawn a plausible mechanism for the asymmetric reduction of our substrates with both **S**-Me-CBS and **R**-Me-CBS as shown below in Figure 3a and 3b Borane first makes complex with N-atom of CBS catalyst and then electrophilic boron atom of this complex coordinates with the ketone carbonyl oxygen atom of the incoming substrate in such a way that bulky group is kept *anti* to B-O coordinative bond. Hydride transfer from the N-$BH_3$ unit to the most proximate and least hindered face of the ketone through 6-membered transition state gives rise to the desired product with the observed stereochemical outcome.

While looking at the structures of transition states (*TS-S-CBS* and *TS-R-CBS*, Figure 3a and 3b) it is evident that in *TS-R-CBS* the alkyl group at the chiral center of the substrate can offer some steric hindrance during hydride transfer. This steric hindrance justifies the lower *dr* observed with **R**-Me-CBS catalyst in comparison to **S**-Me-CBS catalyst.

Finally, relative *syn* and *anti*-configurations were assigned for few stanine analogues on the basis of coupling constant of the C2 methylene protons. Alejandro Preciado and Philip G. Williams have explained the *syn* and *anti* cconfigurational assignment of statine units by using a combination of chemical shift and coupling constant information.**[21]** On comparison, we found that coupling constants of the C2 methylene protons of our products were in complete agreement with the one reported by Alejandro et al (Figure 4). Secondly, for compound **3a** and **4a**, *syn* and *anti*-configuration was already confirmed by us by comparing with the reported $^1$H NMR values.[17] It was also observed in all cases that *syn* diastereomer is always polar on TLC system in comparison to *anti* diastereomer. Obtained mixtures of diastereomers can be easily purified by column chromatography to yield pure single diastereomers.

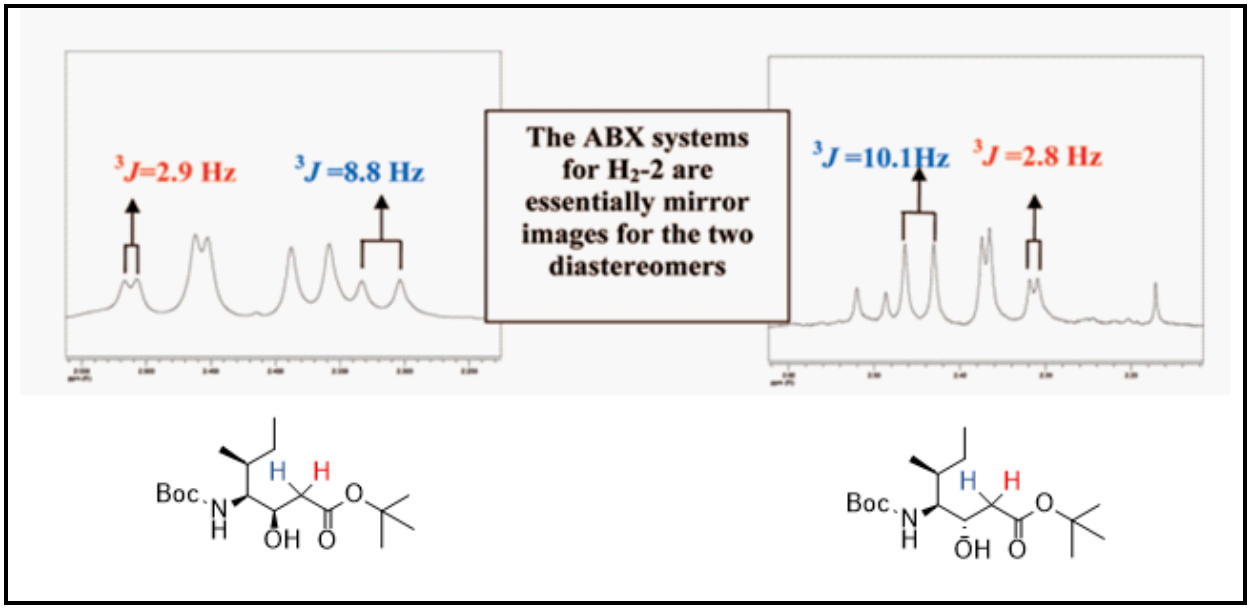



**Figure 4a.** Expansion of splitting pattern of C2 methylene of *Syn* and *Anti* diastereomers of stanine derived from isoleucine (reproduced from reference 9)

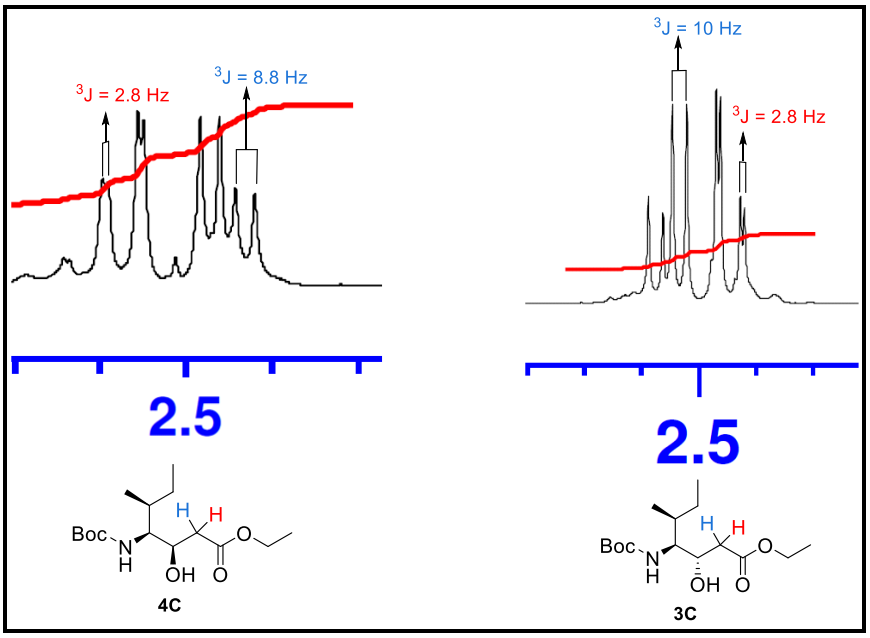



**Figure 4.** Expansion of splitting pattern of C2 methylene of *syn* and *anti* diastereomers from **3C** and **4C** $^{1}$H NMR.

## 4. Conclusion

In conclusion, we have successfully synthesized the statine analogues via the reduction of different *α*-L-amino-*β*-keto esters with both **R** and **S**-Me-CBS and tried to understand the variation in *dr* with change in substituents on amino acids. We have depicted a plausible mechanism which fairly explains the diastereoselectivity of the reactions with the use of different enantiomers of 2-Methyl-CBS-oxazaborolidine. However, to understand the results more comprehensively, further theoretical, and experimental studies are warranted. Irrespective of the diastereomeric outcome, all the diastereomers can be easily purified by column chromatography to obtain the pure diastereomers. This methodology gives an easy and reliable method to obtain the substituted stanines.

## Supporting Information

Experimental Details, $^{1}$H NMR, $^{13}$C NMR and LCMS of all the synthesized compounds can be found in the Electronic Supplementary Content of this article.

## Competing Interests

The authors declare no conflict of interest either of a financial or personal nature.

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**ORCID**
Malapati Venkateswara Reddy: 0009-0009-7753-5496
Shyamala Pulipaka: 0000-0001-8271-2607
Arvind Kumar Sharma: 0009-0009-2622-8357

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