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Enantioselective synthesis of (*S*,*S*)-ethambutol using proline-catalyzed asymmetric α-aminooxylation and α-amination

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Abstract—An efficient enantioselective synthesis of (*S*,*S*)-ethambutol, a tuberculostatic antibiotic, has been achieved in 99% ee via both proline-catalyzed α-aminooxylation and α-amination of *n*-butyraldehyde as the key step.

1. Introduction

Ethambutol **1** [(*S*,*S*)-2,2′-(ethylenediimino)-di-butanol] is among the frontline antimycobacterial chemotherapeutic agents, active against nearly all strains of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* as well as a number of strains of *Mycobacterium avium*.[1] The biological activity of ethambutol has been attributed to its inhibition of mycobacterial arabinosyl transferases involved in bacterial cell wall biosynthesis.[2] Ethambutol is administered as its (*S*,*S*)-enantiomer, which is 200–500 times more potent than the (*R*,*R*)-enantiomer and the *meso*-isomer.[3]

The literature methods for the synthesis of (*S*,*S*)-ethambutol involve resolution of racemic 2-amino-1-butanol,[1,4] palladium catalyzed regio- and stereoselective epoxide opening by pthalimide as the key step,[5] and a chiral pool approach by using L-methionine as a chiral material.[3b] As a part of our research program aimed at developing stereocontrolled synthesis of bioactive molecules,[6] we report a highly efficient synthesis of (*S*,*S*)-ethambutol **1** using both proline-catalyzed α-aminooxylation[9] and α-amination[10] of *n*-butyraldehyde (Schemes 1 and 2).

2. Results and discussion

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds.[7] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[8] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[9,10] of carbonyl compounds. We envisaged O-protected (*S*)-2-amino-1-butanol **7** as the precursor for an asymmetric synthesis of ethambutol. Thus, we have achieved the enantioselective synthesis of (*S*,*S*)-ethambutol by employing proline-catalyzed α-aminooxylation[9] and α-amination[10] of *n*-butyraldehyde; the results of which are presented in this paper.

2.1. α-Aminooxylation approach

Firstly, α-aminooxylation[9a] of *n*-butyraldehyde was carried out using nitrosobenzene and L-proline (25 mol %) at −20 °C to furnish an aminooxy aldehyde, which upon in situ reduction with sodium borohydride afforded the α-aminooxy alcohol **2** in 85% yield; $[\alpha]_D^{25} = +20.7$ (*c* 1, $CHCl_3$) {lit.[9e] $[\alpha]_D^{25} = +20.5$ (*c* 1, $CHCl_3$)}. Alcohol **2** was then protected with TBSCl to give the corresponding silyl ether **3** in 90% yield, which on hydrogenation over Pd/C (10 mol %) furnished monoprotected diol **4** in 88% yield. Tosylation of **4** using *p*-toluenesulfonyl chloride and pyridine followed by displacement of tosyl group with NaN_3 in DMF gave the azido product **6** in 75% yield. Subsequent catalytic hydrogenation of azide with Pd/C–H_2 (1 atm) afforded the protected amine **7** in 95% yield (Scheme 1).

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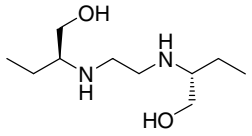
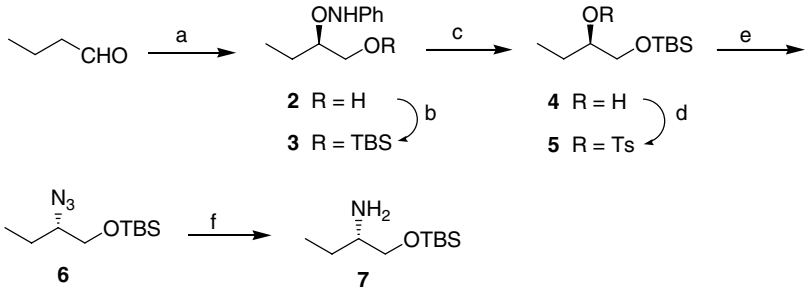
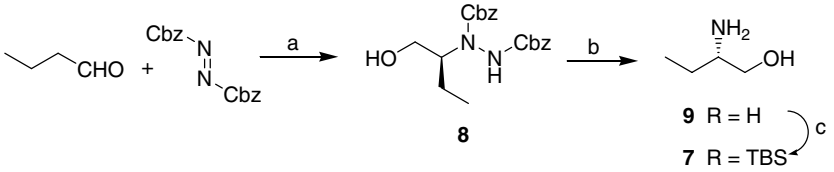


1, (*S,S*)-Ethambutol



Scheme 1. Reagents and conditions: (a) PhNO, L-proline (25 mol %), −20 °C, 24 h then MeOH, $NaBH_4$, 85%; (b) TBSCl, imidazole, CH_2Cl_2, 3 h, 90%; (c) H_2 (1 atm), Pd/C (10%), Et_3N, MeOH, 12 h, 88%; (d) *p*-TsCl, Py, 24 h, 95%; (e) NaN_3, DMF, 60 °C, 30 h, 75%; (f) H_2 (1 atm), Pd–C (10%), Et_3N, MeOH, 6 h, 95%.



Scheme 2. Reagents and conditions: (a) dibenzyl azodicarboxylate, D-proline (10 mol %), 0–20 °C, 3 h then $NaBH_4$, EtOH, 92%; (b) H_2 (12 bar), Raney-nickel, MeOH, AcOH, 70%; (c) TBSCl, imidazole, CH_2Cl_2, 0–20 °C, 3 h, 85%.

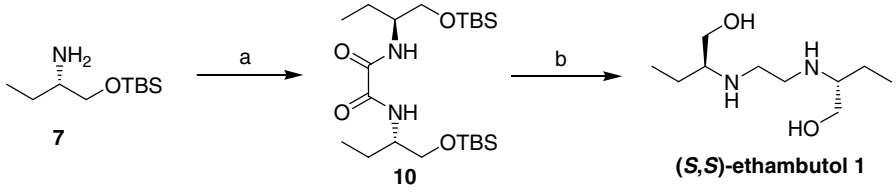
2.2. α-Amination approach

In the second approach, α-amination of *n*-butyraldehyde was carried out using List's protocol.[10a] Thus, *n*-butyraldehyde was treated with dibenzyl azodicarboxylate in the presence of D-proline (10 mol %) to furnish an aminoaldehyde, which upon in situ reduction with sodium borohydride afforded the protected aminoalcohol **8** in 92% yield. Aminoalcohol **8** was then hydrogenated using Raney-nickel[11] as a catalyst to give (*S*)-2-amino-1-butanol **9** in 70% yield; $[\alpha]_D^{25} = +10.1$ (neat), {lit.[12] $[\alpha]_D^{25} = +10$ (neat) for 96% ee}. Protection of the hydroxyl group in amino alcohol **9** with TBSCl afforded silyl ether **7** in 85% yield (Scheme 2).

Finally, protected aminoalcohol **7** was transformed into (*S,S*)-ethambutol in two steps. Thus, amine **7** on treatment with 0.5 equiv of oxalyl chloride and pyridine furnished oxalyldiamide **10** in 98% yield. The reduction of diamide and TBS deprotection were carried out in one-pot reaction using lithium aluminum hydride at reflux conditions to give (*S,S*)-ethambutol **1** in 80% yield and 99% ee (Scheme 3). The physical and spectroscopic data were in full agreement with the literature values.[3b]

3. Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies toward the synthesis of (*S,S*)-ethambutol, which was obtained in 99% ee. The operationally simple reactions are rapid, and require a relatively low amount of an inexpensive and non-toxic proline-catalyst that is available in both enantiomeric forms. The high overall yields (35.7% via α-aminooxylation and 43% via α-amination) and small number of steps renders our approach a good alternative to the known methods.



Scheme 3. Reagents and conditions: (a) oxalyl chloride (0.5 equiv), Py, CH_2Cl_2, 12 h, 98%; (b) LAH, THF, reflux, 24 h, 80%.

4. Experimental

4.1. General information

The solvents were purified and dried by standard procedures before use. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

4.2. (*R*)-2-(*N*-Phenylaminooxy)butan-1-ol 2

To a CH_3CN (60 mL) solution of *n*-butyraldehyde (4.5 mL, 50 mmol) and nitrosobenzene (2.67 g, 25 mmol) was added L-proline (718 mg, 6.2 mmol, 25 mol %) at −20 °C. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (25 mL) and $NaBH_4$ (2.8 g, 75 mmol) to the reaction mixture, which was stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (60 mL × 3) and the combined organic phases were dried over Na_2SO_4. Purification by column chromatography with silica gel (pet. ether–EtOAc = 80:20) afforded aminooxy alcohol **2** (3.8 g, 85% yield); $[\alpha]_D^{25} = +20.7$ (*c* 1, $CHCl_3$) {lit.[9e] $[\alpha]_D^{25} = +20.5$ (*c* 1, $CHCl_3$)}. IR ($CHCl_3$) ν_{max} 3375, 3012, 2933, 1955, 1689, 1605, 1596, 1483, 1298, 1217, 1070, 756 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.01 (t, $J = 6.9$ Hz, 3 H), 1.4–1.79 (m, 2H), 3.81 (m, 2H), 3.98 (m, 1H), 6.93 (m, 3H), 7.25 (m, 2H), 7.4 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 10.17, 26.0, 64.43, 85.23, 114.66, 122.2, 128.92, 148.51 ppm. Elemental analysis: $C_{10}H_{25}NO$ required C, 66.27; H, 8.34; N, 7.73. Found C, 66.15; H, 8.26; N, 7.80.

4.3. (*R*)-2-*N*-Phenylaminooxy(*tert*-butyl)dimethylsilane 3

To a solution of alcohol **2** (3.0 g, 16.5 mmol) dissolved in dry CH_2Cl_2 (30 mL) was added imidazole (1.34 g, 19.8 mmol, 1.2 equiv) at 0 °C. After stirring for 10 min, TBDMSCl (2.73 g, 18.2 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 25 °C for 3 h. After completion of the reaction as monitored by TLC, the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was then purified by column chromatography with silica gel (pet. ether–EtOAc = 98:2). Colorless liquid, yield = 4.4 g, 90%; $[\alpha]_D^{25} = +42.35$ (*c* 1, $CHCl_3$). IR (neat) ν_{max} 3412, 2929, 2856, 2360, 1718, 1600, 1471, 1255, 1097, 910, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 6H), 0.94 (s, 9H), 1.01 (t, $J = 7.45$ Hz, 3H), 1.61 (m, 2H), 3.77 (m, 2H), 3.78 (m, 1H), 6.97 (m, 2H), 7.24 (m, 2H), 7.25 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ −5.42, 10.17, 18.30, 23.01, 25.87, 64.46, 85.25, 114.30, 121.55, 128.80, 149.09. Elemental analysis: $C_{16}H_{29}NO_2Si$ required C, 65.03; H, 9.89; N, 4.74. Found C, 65.1; H, 9.85; N, 4.78.

4.4. ((*R*)-2-Hydroxy)(*tert*-butyl)dimethylsilane 4

To a solution of **3** (4.0 g, 13.5 mmol) in MeOH was added 10% Pd/C (200 mg) carefully followed by addition of 5–6 drops of Et_3N. The reaction mixture was then stirred in a hydrogen atmosphere (1 atm of H_2) for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad and then concentrated to near dryness. The crude product was then purified by silica gel chromatography (pet. ether–EtOAc 95:5). Yield = 2.4 g, 88%. Colorless liquid; $[\alpha]_D^{25} = -9.4$ (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3569, 3018, 2859, 2957, 2400, 1711, 1460, 1362, 1216, 1093, 927, 837, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.06 (s, 6H), 0.89 (s, 9H), 0.94 (t, $J = 7.32$ Hz, 3H), 1.44 (m, 2H), 2.42 (br s, 1H), 3.39–3.59 (m, 2H), 3.54 (m, 1H). ^{13}C NMR ($CDCl_3$): δ −5.45, 9.85, 18.21, 25.69, 25.80, 66.85, 73.15 ppm. Elemental analysis: $C_{10}H_{24}O_2Si$ required C, 58.77; H, 11.84. Found C, 58.66; H, 12.05.

4.5. (*R*)-1-(*tert*-Butyldimethylsilyloxybutan-3-yl)4-methylbenzenesulfonate 5

To a solution of alcohol **4** (2.4 g, 11.7 mmol) in pyridine (30 mL) kept at 0 °C was added *p*-toluenesulfonyl chloride (2.44 g, 12.8 mmol, 1.1 equiv) and the reaction mixture was allowed to stir at 25 °C for 24 h. After completion of the reaction (monitored by TLC), pyridine was removed under reduced pressure. To the residue was added water (30 mL) and extracted with EtOAc (3 × 30 mL). The crude product was then purified by silica gel chromatography (pet. ether–EtOAc = 97:3). Colorless liquid, yield = 4 g, 95%; $[\alpha]_D^{25} = +17.0$ (*c* 1, $CHCl_3$). IR ($CHCl_3$) ν_{max} 3030, 2955, 2930, 1598, 1496, 1463, 1362, 1255, 1188, 1099, 915, 835, 758, 665 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ −0.02 (s, 6H), 0.82 (s, 9H), 0.79 (t, $J = 7.45$ Hz, 3H), 1.63 (m, 2H), 2.42 (s, 3H), 3.61–3.65 (m, 2H), 4.38 (m, 1H), 7.29 (d, $J = 8.34$ Hz, 2H), 7.77 (d, $J = 8.35$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ −5.62, 9.02, 18.14, 24.03, 25.69, 63.52, 73.12, 84.34, 127.70, 129.58, 134.42, 144.34. Elemental analysis: $C_{17}H_{30}O_4SSi$ required C, 56.94; H, 8.43; S, 8.94. Found C, 56.82; H, 8.38; S, 8.75.

4.6. ((*S*)-2-Azidobutoxy)(*tert*-butyl)dimethylsilane 6

To a solution of **5** (4.0 g, 11.1 mmol) in DMF (40 mL) was added sodium azide (5.0 g, excess), and the reaction mixture was allowed to stir at 60 °C for 30 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 50 mL water and extracted with diethyl ether (3 × 50 mL) to give the crude product, which was purified, by column chromatography (pet. ether) as a colorless liquid, yield = 1.91 g, 75%; $[\alpha]_D^{25} = +21.9$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 0.96 (t, $J = 7.45$ Hz, 3H), 1.45 (m, 2H), 3.24 (m, 1H), 3.63–3.69 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −5.59, 10.56, 18.19, 23.47, 25.75, 65.30, 65.98. Elemental analysis: $C_{10}H_{23}N_3OSi$ required C, 52.36; H, 10.11; N, 18.32. Found C, 56.25; H, 10.10; N, 18.48.

4.7. ((*S*)-2-Aminobutoxy)(*tert*-butyl)dimethylsilane 7

To the solution of azide **6** (1.9 g, 8.2 mmol) in MeOH (15 mL) was added 10% Pd/C (100 mg) carefully followed by addition of 5–6 drops of Et_3N. The reaction mixture was then stirred in a hydrogen atmosphere (1 atm of H_2)

for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad, concentrated to near dryness to get amine **7** which was purified by column chromatography with neutral Al_2O_3 (pet. ether–EtOAc = 70:30). Yield = 1.6 g, 95%. $[\alpha]_D^{25} = +9.7$ (*c* 1, $CHCl_3$). IR (neat) ν_{max} 3355, 2952, 2927, 2856, 1739, 1589, 1471, 1253, 1103, 837, 775, 667 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 0.91 (t, $J = 7.33$ Hz, 3H), 1.34 (m, 2H), 1.78 (br s, 2H), 2.70 (m, 1H), 3.27–3.59 (m, 2H). ^{13}C NMR ($CDCl_3$): δ −5.48, −3.56, 10.46, 18.23, 25.84, 54.33. Elemental analysis: $C_{10}H_{25}NOSi$ required C, 59.05; H, 12.39; N, 6.89. Found C, 59.2; H, 12.44; N, 6.88.

4.8. (*S*)-2-(1,2-Dibenzyloxycarbonylhydrazinyl)-1-butanol 8

A mixture of dibenzyl azodicarboxylate (90%, 8.25 g, 25 mmol, 1 equiv) and D-proline (287 mg, 2.49 mmol, 10 mol %) in CH_3CN (200 mL) was taken and cooled to 0 °C, *n*-butyraldehyde (2.7 g, 37.5 mmol, 1.5 equiv) was added to it and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 °C within 1 h. After the reaction mixture became colorless it was cooled to 0 °C, treated with EtOH (150 mL) and $NaBH_4$ (1.2 g), and was stirred for 5 min at 0 °C. The reaction mixture was worked up by adding half-concentrated aq ammonium chloride solution and extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pet. ether–ethyl acetate = 85:15), which furnished a white solid, mp = 65 °C, yield = 8.6 g, 92%; $[\alpha]_D^{25} = +14.3$ (*c* 1, $CHCl_3$). IR (Nujol) ν_{max}: 3550, 3261, 2954, 2875, 1720, 1681, 1537, 1456, 1377, 1263, 1062 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.81 (m, 3H), 1.36 (m, 2H), 3.46 (m, 2H), 4.5 (br s, 1H), 5.15 (m, 4H), 6.53 (s, 1H), 7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 10.36, 20.82, 61.74, 61.78, 68.02, 68.08, 128.08, 135.06, 157.28. Elemental analysis: $C_{20}H_{24}N_2O_5$ required C, 64.50; H, 6.50; N, 7.52. Found C, 64.52; H, 6.45; N, 7.44.

4.9. (*S*)-2-Aminobutan-1-ol 9

Alcohol **8** (6.0 g, 16 mmol) was dissolved in MeOH (40 mL), AcOH (10 drops) and treated with Raney nickel (10.0 g, excess) for 24 h under 12 bar of hydrogen. The reaction mixture was filtered over Celite and concentrated to give the corresponding aminoalcohol **9** as a colorless liquid (1.0 g, 70%); $[\alpha]_D^{25} = +12.3$ (*c* 2, EtOH), {lit.[4b] $[\alpha]_D^{25} = +12.5$ (*c* 2, EtOH)}. IR ($CHCl_3$) ν_{max} 3450, 3560, 2960, 1650, 1420, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (t, $J = 7.58$ Hz, 3H), 1.44 (m, 2H), 3.40 (m, 1H), 3.57 (m, 1H), 4.07 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ 9.92, 25.87, 66.11, 73.60; MS (*m*/*z*, % RI) 89 (M+), 71, 60, 58, 56, 41.

4.10. ((*S*)-2-Aminobutoxy)(*tert*-butyl)dimethylsilane 7

To a solution of amino alcohol **5** (1.0 g, 11.2 mmol) dissolved in dry CH_2Cl_2 (50 mL) kept at 0 °C was added imidazole (0.916 g, 13.4 mmol, 1.2 equiv) after stirring for 10 min, TBSCl (1.8 g, 12.3 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 25 °C for 3 h. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was then purified by column chromatography on neutral Al_2O_3 (pet. ether–EtOAc = 70:30) as colorless liquid (yield = 1.87 g, 85%) $[\alpha]_D^{25} = +9.5$ (*c* 1, $CHCl_3$).

4.11. (*S*,*S*)-N^1,N^2-Bis(1-*tert*-butyldimethylsilyloxybutan-3-yl)oxamide 10

To a solution of amine **7** (1.21 g, 6 mmol) in dry CH_2Cl_2 (10 mL), pyridine (1.04 g, 13.2 mmol) was added and the reaction mixture was cooled to 0 °C, followed by dropwise addition of oxalyl chloride (378 mg, 3 mmol, 0.5 equiv dissolved in CH_2Cl_2). On stirring the reaction mixture at 25 °C overnight, it was quenched with water (10 mL) and was extracted with EtOAc (20 mL × 3). The crude product was purified by column chromatography over silica gel (pet. ether) as a white solid, mp 86 °C; yield = 2.6 g, quantitative; $[\alpha]_D^{25} = -60.3$ (*c* 1, $CHCl_3$) for α-aminooxylation and $[\alpha]_D^{25} = -59.8$ (*c* 1, $CHCl_3$) for α-amination approach. IR ($CHCl_3$) ν_{max} 3629, 3547, 2985, 2086, 1888, 1739, 1507, 1458, 1374, 1241, 1047, 917, 846, 607 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.88 (s, 18H), 0.90 (t, $J = 7.3$ Hz, 6H), 1.57 (m, 2H), 3.61 (m, 1H), 3.63 (br s, 2H). ^{13}C NMR ($CDCl_3$): δ −5.60, 10.40, 18.17, 24.11, 25.78, 52.70, 63.73, 159.47. Elemental analysis: $C_{22}H_{48}N_2O_4Si_2$ required C, 57.34; H, 10.50; N, 6.08. Found C, 57.48; H, 10.66; N, 6.24.

4.12. (*S*,*S*)-Ethambutol 1

To a solution of lithium aluminum hydride (1.2 g, 30 mmol) in dry THF at 0 °C was added amide **10** (in THF) (2.5 g, 5.4 mmol) carefully. The mixture was refluxed for 24 h. After completion (TLC), the reaction mixture was quenched by 10% NaOH (2 mL) and water (2 mL). The precipitate formed was filtered off and washed with EtOAc (3 × 10 mL). The combined organic layers were concentrated under reduced pressure, dried (Na_2SO_4), and recrystallized (ethyl acetate/hexane) to furnish ethambutol as a white solid (mp = 88 °C, lit.[12] mp 87.5–88.8 °C). Yield = 0.87 g, 80%; $[\alpha]_D^{25} = +13.6$ (*c* 2, H_2O) (99% ee) for α-aminooxylation and $[\alpha]_D^{25} = +13.4$ (*c* 2, H_2O) (97% ee) for α-amination approach {lit.[13] $[\alpha]_D^{25} = +13.7$ (*c* 2, H_2O)}. IR ($CHCl_3$) ν_{max}: 3465, 2984, 1567, 1447, 1374, 1242, 1047, 758 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (t, $J = 7.55$ Hz, 6 H), 1.42 (m, 4H), 2.55 (m, 2H), 2.71 (m, 2H), 2.84 (m, 2H), 2.99 (br s, 2H), 3.34 (dd, $J = 7.23$, 10.88, 2H), 3.59 (dd, $J = 3.74$, 10.97, 2H). ^{13}C NMR ($CDCl_3$): δ 10.33, 23.96, 46.52, 60.42, 62.99. Elemental analysis: $C_{10}H_{24}N_2O_2$ required C, 58.79; H, 11.84; N, 13.71. Found C, 58.85; H, 11.74; N, 13.55.

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