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A facile enantioselective synthesis of (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol via proline-catalyzed asymmetric α-aminooxylation and α-amination of aldehyde

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ABSTRACT

A high-yielding enantioselective synthesis of the bioactive (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol (**1**), a Notch-1-sparing γ-secretase inhibitor metabolite (with EC_{50} = 28 nM) effective in reduction of Aβ production in vivo, has been realized starting from readily available 3-pentanone. The key steps of the synthesis are proline-catalyzed α-aminooxylation and α-amination of aldehyde; the latter contributing an overall yield of 45.2% and 98% ee.

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder which is characterized by a loss of cognitive ability, severe behavioral abnormalities, and ultimately death.[1] A key event in the pathogenesis of AD is now believed to be the deposition of β-amyloid (Aβ) plaques on the outside of the nerve cells in areas of the brain that are produced by the proteolytic cleavage of amyloid precursor protein (APP) by β and γ-secretase.[2] A 'β-amyloid cascade' hypothesis has emerged to account for various experimental facts including genetic variations related to the production and elimination of Aβ.[1a,3a] Recent studies have further shown that neuritic plaques and neurofibriliary tangles are accepted pathological hallmarks of AD as confirmed at autopsy.[3] γ-Secretase inhibitors like BMS-299897, LY-450139, and MK-0752 have entered clinical trials.[4,5] Recently (*S*)-*N*-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol **1** (**7.b.2**), a Notch-1-sparing γ-secretase inhibitor (with EC_{50} = 28 nM), has been found to be effective in reduction of Aβ production in vivo.[5]

Organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds.[6] In particular, proline, an abundant, inexpensive amino acid available in both enantiomeric forms has emerged arguably as the most practical and versatile organocatalyst.[7] In a continuation of our work on proline-catalyzed synthesis of bioactive molecules,[8] we wish to report a facile synthesis of **1** (Fig. 1), whose activity makes it an attractive synthetic target.[5] The synthetic sequence for **1**, wherein proline-catalyzed α-aminooxylation[9] and α-amination[10] reactions constitute key steps for the introduction of chirality, is presented in Schemes 1 and 2. Evidently, amino alcohol **9** has emerged as the key intermediate in the synthesis of **1**.

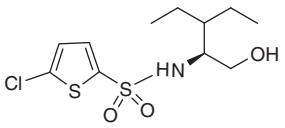

Figure 1. Compound **7.b.2** (**1**).

Thus, our synthesis of **1** commenced from 3-pentanone, which on Horner–Wardworth–Emmons olefination (triethyl phosphonoacetate, NaH, THF), gave the corresponding α, β-unsaturated ester **2** in 93% yield. Hydrogenation [10% Pd/C, H_2 (1 atm), MeOH] of the unsaturated ester **2** produced the crude saturated ester, which was directly subjected to reduction with $LiAlH_4$ in THF at 25 °C affording the saturated primary alcohol **3** in 83% yield over two-steps. Oxidation of primary alcohol **3** with IBX/DMSO mixture gave the key precursor aldehyde **4**, which was found to be highly volatile. Hence, upon solvent extraction, it was immediately (without purification) subjected to proline-catalyzed α-aminooxylation[9] and α-amination,[10] respectively (Schemes 1 and 2).

Firstly, the L-proline-catalyzed α-aminooxylation[9] of aldehyde **4** was carried out in a two-step reaction sequence: (i) reaction of aldehyde **4** with nitrosobenzene as the oxygen source in the

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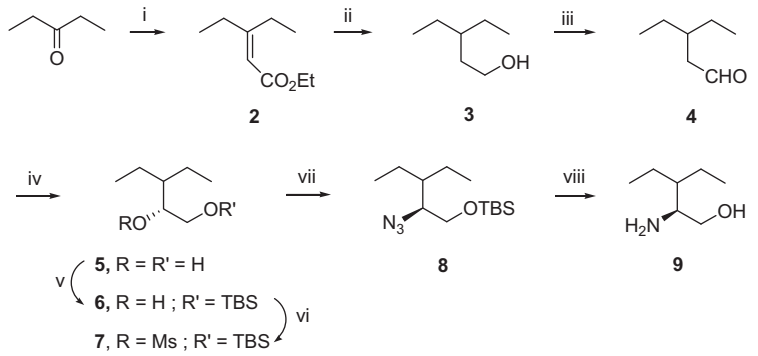
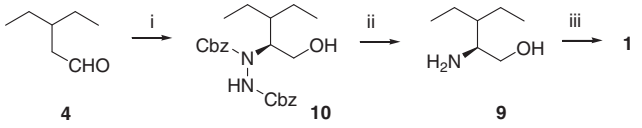


Scheme 1. Synthesis of (*S*)-2-amino-3-ethylpentan-1-ol **(9)**. Reagents and conditions: (i) triethyl phosphonoacetate, NaH, dry THF, 0–25 °C, 8 h, 93%; (ii) (a) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 °C; (b) $LiAlH_4$, dry THF, 25 °C, 12 h, 83% (for two-steps); (iii) IBX, dry DMSO, 25 °C, 2 h; (iv) (a) PhNO, L-proline (20 mol %), CH_3CN, −20 °C, 24 h then MeOH, $NaBH_4$; (b) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 25 °C, 77% (over two-steps); (v) TBSCl, imid, CH_2Cl_2, 0–25 °C, 2 h, 81%; (vi) MsCl, Et_3N, 45 min; (vii) NaN_3, dry DMF, 60 °C, 30 h, 78% (for two-steps); (viii) $LiAlH_4$, dry THF, 50 °C, 12 h, 75%.



Scheme 2. Synthesis of **7**.**b**.**2** (**1**). Reagents and conditions: (i) dibenzyl azodicarboxylate, D-proline (10 mol %), CH_3CN, 0–20 °C, 3 h then MeOH, $NaBH_4$, 92%; (ii) H_2 (11.8 atm), Raney Ni, MeOH, AcOH, 70%; (iii) 5-chlorothiophene-2-sulfonyl chloride, Et_3N, dry CH_2Cl_2, 0 °C, 30 min, 91%.

presence of 20 mol % L-proline in CH_3CN at −20 °C followed by its treatment with $NaBH_4$ in MeOH gave the crude α-aminooxy alcohol in situ and (ii) subsequent reduction of the crude α-aminooxy alcohol with 10% Pd/C over H_2 (1 atm) furnished chiral diol **5** in 77% yield over two-steps with 99% ee (determined from its Mosher ester analysis). Selective protection of primary hydroxyl group in diol **5** (TBSCl, imid, CH_2Cl_2) was achieved to produce the TBS ether **6** in 81% yield, followed by mesylation (MsCl, Et_3N, CH_2Cl_2) of the secondary alcohol which gave the corresponding mesylate **7**. However, attempts to purify the mesylate via column chromatography proved problematic due to its instability. This crude mesylate was, therefore, treated immediately with sodium azide (DMF, 60 °C) to afford the corresponding azide **8** in 78% yield $\{[\alpha]_D^{25}$ −21.3 (*c* 1.6, $CHCl_3$)}. The $LiAlH_4$ reduction of TBS azide **8** in THF at 50 °C afforded the key intermediate (*S*)-2-amino-3-ethylpentan-1-ol **9** in 75% yield with 99% ee, which was accomplished with the simultaneous removal of TBS group (Scheme 1). Since the number of steps involved in the α-aminooxylation process is relatively too many thereby limiting the overall yield (25.5%), we have explored alternative chemistry that involved a direct α-amination approach.

Asymmetric α-amination of aldehydes using proline as the catalyst represents a burgeoning field of synthetic efforts toward synthesizing chiral building blocks, such as α-amino acids and alcohols.[10] Thus, α-amination of aldehyde **4** was carried out using List's protocol.[10a] Accordingly, aldehyde **4** was subjected to α-amination with dibenzyl azodicarboxylate in the presence of D-proline (10 mol %) to produce the α-amino aldehyde, which upon in situ reduction with $NaBH_4$ afforded the protected amino alcohol **10** in 92% yield and 98% ee (determined by chiral HPLC). The amino alcohol **10** was then hydrogenated [Raney Ni, H_2 (11.8 atm), MeOH, AcOH (five drops)] to give (*S*)-2-amino-3-ethylpentan-1-ol **9** in 70% yield (Scheme 2).[11] Finally, the amino alcohol **9** was condensed with 5-chlorothiophene-2-sulfonyl chloride in the presence of Et_3N to afford the target molecule **1** in 91% yield and 98% ee (determined by chiral HPLC)[12] (Scheme 2).

In conclusion, we have described a short synthetic route to **1** incorporating a successful application of D-proline-catalyzed asymmetric α-amination of aldehyde **4** to give the corresponding amino alcohol **9** in 98% ee[12] with an overall yield of 45.2%. The operationally simple reactions with less number of steps, high overall yields requiring a relatively low amount of inexpensive and non-toxic proline as catalyst make this approach an attractive and useful process.

Acknowledgments

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12. Spectral data of:
((S)-2-Azido-3-ethylpentyloxy)(tert-butyl)dimethylsilane (**8**): $[\alpha]_D^{25}$ −21.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3064, 2896, 2110, 1600 1496, 1454, 1255, 1217, 967, 837; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6*H*), 0.84–0.92 (m, 15*H*), 1.33–1.37 (m, 5*H*), 3.40–3.45 (m, 1*H*), 3.64–3.77 (m, 2*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.6, 11.2, 11.3, 18.2, 21.8, 22.5, 25.8, 41.8, 65.0, 66.2; Anal. Calcd for $C_{13}H_{29}N_3OSi$ requires C, 57.52; H, 10.77; N, 15.48; found C, 57.67; H, 10.83; N, 15.45%.
(S)-2-(1,2-Dibenzyloxycarbonylhydrazinyl)-3-ethylpentan-1-ol (**10**): Colorless crystalline solid; mp 121 °C (crystallized from ethanol); $[\alpha]_D^{25}$ +20.0 (*c* 1.0, $CHCl_3$); 98% ee HPLC analysis: Column: ODH, mobile phase: hexane/isopropyl alcohol (9/1), flow rate: 0.5 mL/min, retention time: 12.59 min (−)-isomer, 15.59 min (+)-isomer. IR ($CHCl_3$, cm^{-1}): 3510, 3258, 2959, 2878, 1721, 1681, 1537, 1455, 1380, 1267; ^1H NMR (200 MHz, $CDCl_3$) δ 0.69–0.87 (m, 6*H*), 1.26–1.43 (m, 5*H*), 3.38–3.80 (m, 2*H*), 4.14–4.22 (m, 1*H*), 4.33 (br s, 1*H*), 5.12–5.27 (m, 4*H*), 6.39 (br s, 1*H*), 7.26–7.36 (m, 10*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 10.1, 20.5, 21.3, 38.9, 60.4, 62.9, 68.2, 68.5, 127.8, 128.1, 128.3, 128.4, 128.5, 128.6, 135.1, 135.7, 157.3; Anal. Calcd for $C_{23}H_{30}N_2O_5$ requires C, 66.65; H, 7.30; N, 6.76; found C, 66.53; H, 7.10; N, 6.89%.
(S)-N-(5-Chlorothiophene-2-sulfonyl)-β,β-diethylalaninol (**1**): Colorless crystalline solid; mp 115–117 °C (crystallized from heptane:ethylacetate 4:1) {lit.[5b] mp 115–117.6 °C}; $[\alpha]_D^{25}$ +10.3 (*c* 0.3, MeOH) {lit.[5b] $[\alpha]_D^{25}$ +10.81 (1% solution, MeOH)}; 98% ee HPLC analysis: Column: ODH, mobile phase: hexane/isopropyl alcohol (9/1), flow rate: 0.5 mL/min: retention time: 13.01 min (+)-isomer, 13.56 min (−)-isomer). IR ($CHCl_3$, cm^{-1}): 3519, 3301, 3068, 3034, 2957, 2881, 1615, 1456, 1337, 1130, 1090; ^1H NMR (200 MHz, $CDCl_3$) δ 0.77–0.87 (m, 6*H*), 1.18–1.34 (m, 5*H*), 1.93 (br s, 1*H*), 3.31–3.42 (m, 1*H*), 3.57–3.60 (m, 2*H*), 4.93 (br s, 1*H*), 6.92 (d, *J* = 4.0 Hz, 1*H*), 7.42 (d, *J* = 4.0 Hz, 1*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.4, 11.6, 22.7, 21.9, 42.8, 57.7, 62.6, 126.5, 131.5, 137.2, 140.1; Anal. Calcd for $C_{11}H_{18}ClNO_3S_2$ requires C, 42.37; H, 5.82; N, 4.49; found C, 42.26; H, 5.76; N, 4.50%.