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Efficient syntheses of enantioenriched (*R*)-pipecolic acid and (*R*)-proline via electrophilic organocatalytic amination

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ABSTRACT

Five-step syntheses of (*R*)-pipecolic acid and (*R*)-proline are described, respectively, from cyclohexene and cyclopentene. The key step involves the organocatalytic α-amination of functionalized aldehydes.

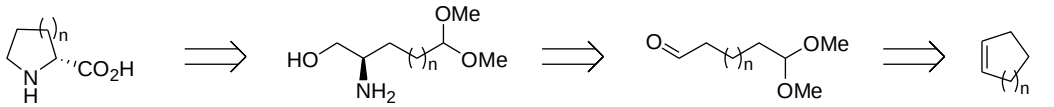
Cyclic amino acids are important building blocks in organic synthesis and occur in numerous natural products. For example, pipecolic acid moiety, also known as homoproline, is present in FK506,[1] Neamphamide[2] or Penasulfate A[3] whereas proline moiety can be found in Dolastatine 14[4] or Virginiamycin M2.[5] Incorporated into peptides, these cyclic amino acids confer rigidity[6] to the proteins thus modifying biological activities. In this context, the asymmetric synthesis of pipecolic acid and proline is of importance and several synthetic approaches have been reported in the literature[7] based on enzymatic reactions,[8] derivatization of natural amino acids or carbohydrates,[9] asymmetric reactions as alkylation of chiral glycine enolates,[10] Strecker reactions,[11] Sharpless epoxydation[12] or catalytic hydrogenation.[13]

In connection with our ongoing program on syntheses of cyclic amino acids via electrophilic amination[14] and organocatalysis,[15] we have been developing a new enantioselective synthesis of such cyclic amino acids using the organocatalytic amination reaction[16] of functionalized aldehydes and subsequent cyclization. We describe here the syntheses of (*R*)-pipecolic acid and (*R*)-proline in high enantiomeric purities and on possible multigram scales, from commercially available cyclohexene and cyclopentene, respectively.

The key step of our retrosynthetic approach is the organocatalytic α-amination of aldehydes **3** for the stereoselective formation of the C–N bond (Scheme 1).

The aldehydes **3**, functionalized with an acetal was derived from the corresponding cycloalkenes **4**. α-Amination of **3** and subsequent reduction of the aldehyde moiety led to the aminoalcohols **2** which are the direct precursors of the cyclic amino acids **1**. The cyclization is based on a reductive amination step which occurred without racemization of the newly created stereogenic center.

The functionalized aldehydes **3a** and **3b** were obtained, respectively, from cyclohexene and cyclopentene via an ozonolysis reaction in the presence of methanol as described in the literature.[17]



1a (n=2) **1b** (n=1) **2a** (n=2) **2b** (n=1) **3a** (n=2) **3b** (n=1) **4a** (n=2) **4b** (n=1)

Scheme 1.

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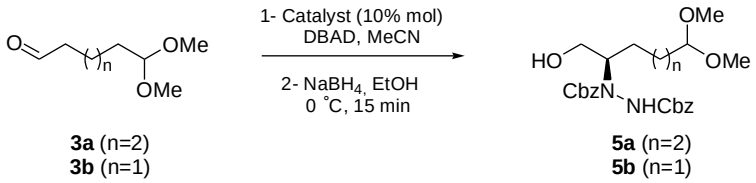

3a (n=2)
3b (n=1)

5a (n=2)
5b (n=1)

Scheme 2.

Table 1

Entry	Substrate	Catalyst	Time, temperature (°C)	Product	Yield (%)	ee[a] (%)
1	**3a**	L-Pro	25, 40 min	**5a**	72	91
2	**3a**	L-Pro	0, 16 h	**5a**	76	94
3	**3a**	L-ACA	25, 7h	**5a**	74	80
4	**3a**	L-ACA	0, 44 h	**5a**	32	70
5	**3b**	L-Pro	25, 1 h	**5b**	66	84
6	**3b**	L-Pro	0, 16 h	**5b**	73	84
7	**3b**	L-Pro	−10, 16 h	**5b**	33	85

[a] Determined by HPLC analysis using a JASCO PU 2089 plus apparatus and a CHIRACEL AD-H column.

Then, we examined the organocatalytic α-amination step of aldehydes **3** under various conditions. The reaction was carried out in acetonitrile, using dibenzylazodicarboxylate (DBAD) as a source of electrophilic nitrogen and different organocatalysts (10 mol %). The hydrazino aldehydes which are formed were reduced in situ after the amination step in order to avoid epimerization of the enolizable products giving the corresponding hydrazino alcohols **5**. After a flash chromatography purification, the enantiomeric excesses were determined by chiral HPLC analysis (Scheme 2, Table 1).

We first studied the organocatalytic electrophilic amination[18] of 6,6-dimethoxyhexanal **3a**. When L-proline was used as catalyst at room temperature, **5a**[19] was obtained in 72% yield and 91% ee (entry 1). Lowering the temperature to 0 °C improved slightly the enantioselectivity to 94% (entry 2). The use of L-azetidine carboxylic acid (L-ACA) as an efficient organocatalyst for the α-amination of aldehydes and ketones was previously reported.[15,16d] In this case, the enantiomeric excess was lower at room temperature (entry 3) and the kinetic of the reaction dropped at 0 °C with concomitant racemization (entry 4).

Reaction with 5,5-dimethoxypentanal **3b** was less enantioselective. Comparable results were observed when the reactions were run at room temperature or at 0 °C and **5b**[20] was obtained in good yields and 84% ee (entries 5 and 6). When the reaction was performed at −10 °C, the enantiomeric excess was identical to those previously observed but the chemical yield was very moderate (entry 7).

Thus, the hydrazino alcohols **5a** and **5b** were engaged in a three step hydrogenation sequence (Scheme 3).

The benzylcarbamates were removed by hydrogenolysis in the presence of Pd/C (5%) and the cleavage of N–N bond was achieved by addition of Raney-Ni to the reaction mixture. The crude amino alcohols were directly submitted to the cyclization step. The reductive amination was conducted in the presence of trifluoroacetic acid and $PtO_2{\cdot}H_2O$ in water under hydrogen atmosphere. 2-Hydroxymethyl piperidinium and pyrrolidinium trifluoroacetates **6a** and **6b** were both obtained in 95% yield from the corresponding hydrazino alcohols **5** completing the sequence without purification of the intermediates.[21] Final oxidation using $KMnO_4$ in aqueous 3 N H_2SO_4 provided the cyclic amino acids. (*R*)-Pipecolic acid **1a** and (*R*)-proline **1b** were isolated without racemization[22] in 69% and 66% yields, respectively, after elution on Dowex 50W-X4 ion-exchange column.

In conclusion, we have developed a green straightforward access to unnatural cyclic amino acids using natural proline as the source of chirality and as the organocatalyst for the stereoselective formation of the C–N bond. It is noteworthy that (*S*)-proline is involved in the synthesis of its enantiomer. (*R*)-Pipecolic acid and (*R*)-proline were obtained, respectively, in 50% yield and 94% ee from 6,6-dimethoxyhexanal and in 41% yield and 84% ee from 5,5-dimethoxypentanal. Wider application to the synthesis of elaborated cyclic amino acid derivatives is currently in progress.

Acknowledgments

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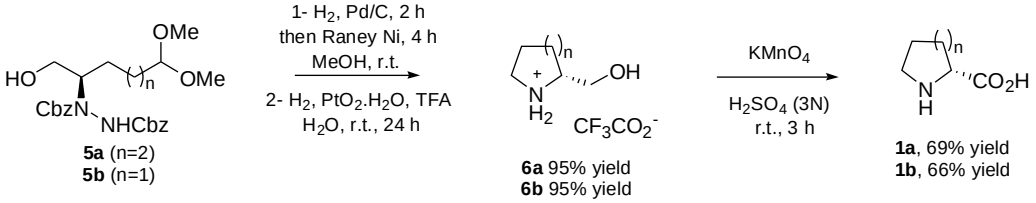

5a (n=2)
5b (n=1)

6a 95% yield
6b 95% yield

1a, 69% yield
1b, 66% yield

Scheme 3.

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18. *General procedure for the amination step*: Dibenzylazodicarboxylate (1 mmol) and (*S*)-proline (0.1 mmol, 10 mol %) in CH_3CN (10 mL) were treated with an aldehyde (1.2 mmol) at the indicated temperature. The reaction mixture was stirred until the yellow color of the azodicarboxylate disappeared. The mixture was treated with ethanol (10 mL) and NaBH4 (1.05 mmol) and was stirred for 5 min at 0 °C. The reaction was worked up with aqueous ammonium chloride solution and ethyl acetate. The organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (EtOAc/pentane 1/2) afforded the alcohols **5** as white solids.
19. *Compound* **5a**: (rotamers mixture) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19–1.73 (m; 6H); 3.26 (br s; 6H); 3.39–3.57 (m; 2H); 4.22–4.49 (m; 2H); 5.14 (m; 4H); 6.64 (br s; 1H); 7.33 (m; 10H). MS (ESI) *m/z* 483.3 (M+Na$^+$). IR ν 3447, 2986, 1716, 1629, 1265, 754 cm^{-1}. $[\alpha]_D^{25}$ +3.8 (*c* 0.53; MeOH). Mp 76–77 °C. Anal. calcd for $C_{24}H_{32}N_2O_7$: C, 62.59; H, 7.00; N, 6.08. Found: C, 62.38; H, 6.81; N, 6.11. ee = 94%, HPLC analysis: Chiralpack AD-H; Eluant heptane/propan-2-ol: 90/10 + 0.2% TFA; flow 0.5 mL/min; λ 206 nm; *T* 25 °C; $\tau_{(S)}$ = 45.6 min, $\tau_{(R)}$ = 48.8 min.
20. *Compound* **5b**: (rotamers mixture) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30–1.80 (m; 4H); 3.22–3.32 (m; 6H); 3.38–3.62 (m; 2H); 3.90–4.53 (m; 2H); 5.04–5.35 (m; 4H); 6.62–6.74 (m; 1H); 7.29–7.43 (m; 10H). MS (ESI) *m/z* 469.1 (M+Na$^+$). IR ν 3460, 3262, 2952, 1716, 1264, 752 cm^{-1}. $[\alpha]_D^{25}$ +3.0 (*c* 1.05; CH_2Cl_2). Mp 78–79 °C. Anal. calcd for $C_{24}H_{32}N_2O_7$: C, 61.87; H, 6.77; N, 6.27. Found: C, 61.16; H, 6.77; N, 6.14. ee = 84%, HPLC analysis: Chiralpack AD-H; Eluant heptane/propan-2-ol: 90/10 + 0.2% TFA; flow 0.5 mL/min; λ 260 nm; *T* 25 °C; $\tau_{(R)}$ = 50.2 min, $\tau_{(S)}$ = 55.5 min.
21. *General procedure for the cyclization step*: A solution of hydrazino alcohol **5** (0.4 mmol) in dry methanol (4 mL) containing 5% Pd/C was stirred for 2 h under hydrogen at atmospheric pressure. Raney Ni was added to the reaction mixture, which was vigorously stirred for 4 h under hydrogen atmosphere. The crude mixture was filtered through a pad of Celite and concentrated. The residue was dissolved in aqueous TFA (4 mL, pH 1), 5% $PtO_2{\cdot}H_2O$ was added, and the mixture was stirred for 20 h under hydrogen atmosphere. The crude mixture was filtered through pad of Celite and concentrated. Cyclic products **6** were used for the oxidation step without purification. *Compound* **6a**: ^{1}H NMR (200 MHz, D_2O) δ: 1.26–1.99 (m; 6H); 2.90 (m; 2H); 3.13 (m; 1H); 3.21–3.39 (br s; 2H); 3.50 (m, 1H); 3.70 (dd, *J* = 3.8 and 11.9 Hz, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 21.1; 21.8; 24.4; 44.4; 58.0; 61.7. MS (ESI) *m/z* 116.0 (M+H$^+$). *Compound* **6b:** ^{1}H NMR (200 MHz, D_2O) δ: 1.45–1.70 (m; 1H); 1.75–2.25 (m; 3H); 2.92–3.33 (m; 2H); 3.40–3.85 (m; 3H). ^{13}C NMR (75 MHz, MeOD) δ: 25.6; 27.9; 47.4; 62.4; 63.7. MS (ESI) *m/z* 101.9 (M+H$^+$).
22. *General procedure for the oxidation step*: To a solution of cyclic alcohol **6** (0.1 mmol) in 3N H_2SO_4 (1 mL) at 10 °C was slowly added $KMnO_4$ (0.16 mmol). The reaction mixture was stirred at room temperature for 3 h, filtered through a pad of Celite, and concentrated. (*R*)-Pipecolic acid **1a** and (*R*)-proline **1b** were isolated after elution on Dowex 50W-X4 ion-exchange column (NH_4OH, 1 N). Analytical data of **1a** and **1b** were in agreement with the literature[8a,9a] and the ees were confirmed by HPLC analysis on their carbamates derivatives: Chiralpack AD-H; Eluant heptane/propan-2-ol: 90/10 + 0.2% TFA; flow 0.5 mL/min; λ 260 nm; *T* 25 °C; **N–Cbz 1a**: $\tau_{(R)}$ = 25.0 min, $\tau_{(S)}$ = 13.0 min; **N–Cbz 1b**: $\tau_{(R)}$ = 20.7 min, $\tau_{(S)}$ = 26.0 min.