An Efficient Synthesis of Orthogonally Protected *trans*- and *cis*-4-Aminopipecolic Acid

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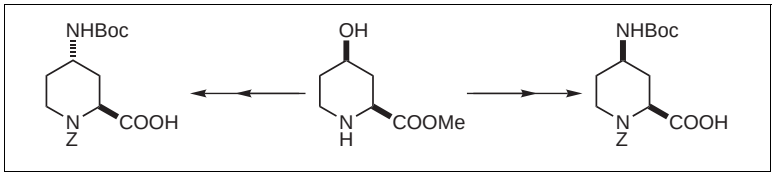
Received December 28, 2005



A straightforward synthesis of orthogonally N^{α}/N^{γ}-protected *trans*- and *cis*-4-aminopipecolic acid is reported, starting from methyl *cis*-4-hydroxypiperidine-2-carboxylate. The two diastereomers were synthesized with the aid of C-4 inversion (the *trans* isomer) or double C-4 inversion (the *cis* isomer).

J. Heterocyclic Chem., **43**, 1387 (2006).

Introduction

The incorporation of conformationally constrained amino acids into peptides is a powerful approach for the generation of structurally defined peptides as conformational probes and bioactive agents [1].

Pipecolic acid derivatives bearing amino functionalities at position C-4 are examples of endocyclic-N^{α}/exocyclic-N^{γ} basic constrained amino acids. Pipecolic acid substituted with an amino group at position C-4 is a naturally occurring non-proteinogenic α-amino acid found in some plants: 4-aminopipecolic acid is present in the leaves of *Strophantus scandens* (Apocinaceae) [2-4] and (2*S*,4*S*)-4-acetylaminopipecolic acid has been isolated from the leaves of *Calliandra hamatocephala* (Leguminosae) [5].

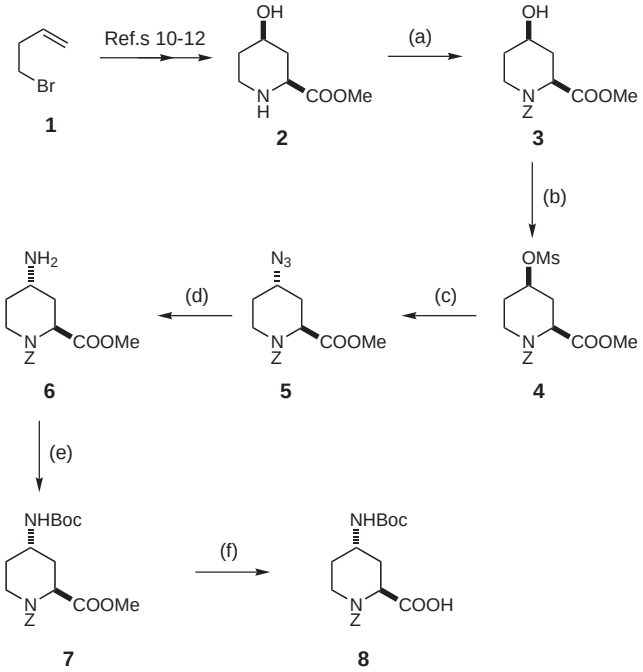
None of the earlier syntheses of 4-aminopipecolic acid derivatives seemed suitable for the preparation of orthogonally protected compounds [6-8]. Machetti *et. al*. published a simple method for the preparation of protected *trans*-4-aminopipecolic acid starting from methyl *cis*-4-hydroxypiperidine-2-carboxylate [9]. Our present aim was to develop a method suitable for the synthesis of both diastereomers of 4-aminopipecolic acid in the frame of an ongoing industrial research project.

Results and Discussion.

For the synthesis of the diastereomers of protected 4-aminopipecolic acid derivatives **8** and **13**, methyl *cis*-4-hydroxypiperidine-2-carboxylate (**2**) was used as starting material. The known synthetic pathway was applied to obtain **2** from 4-bromo-1-butene (**1**, Scheme I) [10-12].

Our synthetic route began from 2-methyl *cis*-1-benzyloxycarbonyl-4-hydroxypiperidine-2-carboxylate (**3**). We started by treating the *cis* alcohol with methanesulfonyl chloride in pyridine to afford compound **4**, which was reacted without further purification with sodium azide to obtain the azido compound **5** with C-4 inversion. Reduction of **5** with triphenylphosphine in THF/H_2O gave the 4-aminopipecolic acid methyl ester (**6**). The amino function at position 4 was then protected with a *tert*-butoxycarbonyl group (**7**). Hydrolysis of methyl ester **7**

Scheme I

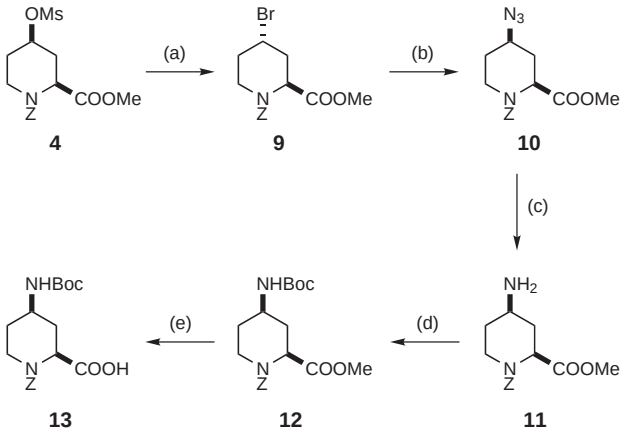


(a) Z-Cl, Et_3N, THF, 20 h, rt., 93%; (b) MsCl, DMAP, Py, 14 h, rt., 95%; (c) NaN_3, DMF, 16 h, 70 °C, 85%; (d) PPh_3, THF/H_2O, 2 days, rt., 75%; (e) $(Boc)_2O$, Et_3N, THF, 10 h, rt., 85%; (f) NaOH, dioxane/H_2O, 3 days, rt., 70%

with sodium hydroxide gave the desired orthogonally protected *trans*-4-aminopipecolic acid **8** (Scheme I).

The strategy for the preparation of the *cis*-4-aminopipecolic acid isomer was based on the double inversion of the configuration at C-4. The first inversion was carried out by substitution of the mesylate **4** with lithium bromide to give bromo compound **9**, and the second one involved the treatment of **9** with sodium azide, which led to azido compound **10** with a further inversion at C-4. The azido group could then be reduced with triphenylphosphine in THF/H_2O to give the diamino ester **11**. The desired orthogonally protected *cis*-4-aminopipecolic acid (**13**, Scheme II) was obtained by protection of the amino function at position 4 with a *tert*-butoxycarbonyl group (**12**), followed by hydrolysis of the ester group under alkaline conditions.

Scheme II



(a) LiBr, DMF, 2 days, 70 °C, 65%; (b) NaN_3, DMF, 3 days, 70 °C, 70%; (c) PPh_3, THF/H_2O, 2 days, 60 °C, 65%; (d) $(Boc)_2O$, Et_3N, THF, 10 h, rt., 90%; (e) NaOH, dioxane/H_2O, 3 days, rt., 60%

In conclusion, a simple and efficient method has been developed for the synthesis of both diastereomers of 4-aminopipecolic acid from methyl *cis*-4-hydroxypiperidine-2-carboxylate. The *trans* isomer was synthesized *via* an inversion at C-4, and the *cis* isomer through double inversion at C-4.

EXPERIMENTAL

Melting points were determined on a Kofler micro melting point apparatus and were not corrected. Compounds **2** and **3** were prepared according to the literature procedure [10-12].

2-Methyl *cis*-1-benzyloxycarbonyl-4-[(methylsulfonyl)oxy]-piperidine-2-carboxylate (**4**).

To a solution of **3** (17.58 g, 60 mmol) in dry pyridine (400 mL), methanesulfonyl chloride (13.67 g, 120 mmol) and 200 mg DMAP were added. The resulting mixture was stirred at room temperature for 14 h. 18% HCl was then added dropwise at 0 °C until pH 3, and the mixture was extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated.

The oily product was used in the next step without further purification; ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.64-2.10 (3H, m); 2.72 (1H, t, J = 14.1 Hz); 2.98 (3H, s); 3.49 (1H, t, J = 13.1 Hz); 3.66-3.80 (3H, m); 3.99-4,20 (2H, m); 5.06 (1H, s); 5.12-5.21 (2H, m); 7.32-7.42 (5H, m)

Anal. Calcd. for $C_{16}H_{21}NO_7S$: C, 51.74; H, 5.70; N, 3.77. Found: C, 51.82; H, 5.72; N, 3.72.

2-Methyl *trans*-1-benzyloxycarbonyl-4-azidopiperidine-2-carboxylate (**5**).

The mesyl compound **4** (6.31 g, 17 mmol) and sodium azide (3.25 g, 50 mmol) were dissolved in DMF (100 mL). After stirring for 16 h at 70 °C, water (500 mL) was added to the mixture, which was then extracted with EtOAc (3 x 120 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated; Yield: 85%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.40-1.57 (1H, m); 1.59-1.75 (1H, m); 1.91-2.06 (1H, m); 2.48 (1H, t, J = 12.6 Hz); 3.12 (1H, t, J = 12.6 Hz); 3.30-3.41 (1H, m); 3.64-3.81 (3H, m); 4.10-4.30 (1H, m); 5.04-5.24 (3H, m); 7.23-7.46 (5H, m).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.82; H, 5.72; N, 17.65.

2-Methyl *trans*-1-benzyloxycarbonyl-4-aminopiperidine-2-carboxylate (**6**).

The azido compound **5** (4.14 g, 13 mmol) and triphenylphosphine (5.24 g, 20 mmol) were dissolved in THF (150 mL) and water (10 mL). After stirring for 48 h, the mixture was concentrated and chromatographed over silica gel ($CHCl_3$-MeOH 9:1); Yield: 75%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.17-1.36 (2H, m); 1.73-1.89 (1H, m); 2.36 (1H, t, J = 16.1 Hz); 2.68-2.79 (1H, m); 2.97-3.18 (1H, m); 3.65-3.79 (3H, m); 4.05-4.24 (1H, m); 4.89-5.20 (3H, m); 7.28-7.41 (5H, m).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.71; H, 6.87; N, 9.61.

2-Methyl *trans*-1-benzyloxycarbonyl-4-[(*tert*-butoxycarbonyl)-amino]piperidine-2-carboxylate (**7**).

To a solution of amino compound **6** (2.63 g, 9 mmol) and triethylamine (3 mL) in THF (80 mL), di-*tert*-butyl dicarbonate (2.61 g, 12 mmol) was added at 0 °C. After stirring for 10 h, the mixture was taken up in EtOAc (200 mL), washed with water, dried (Na_2SO_4) and concentrated; Yield: 85%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44-1.49 (11H, m); 1.94-2.04 (1H, m); 2.43-2.58 (1H, m); 3.03-3.24 (1H, m); 3.67-3.75 (3H, m); 4.09-4.27 (2H, m); 4.88-5.22 (3H, m); 7.31-7.43 (5H, m).

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.31; H, 7.15; N, 7.19.

trans-1-Benzyloxycarbonyl-4-[(*tert*-butoxycarbonyl)amino]-piperidine-2-carboxylic acid (**8**).

To a solution of amino ester **7** (2.35 g, 6 mmol) in dioxane (70 mL) NaOH (1.12 g, 48 mmol) in water (70 mL), was added. After stirring for 3 days, 10% HCl was added at 0 °C until pH 5. The mixture was then extracted with $CHCl_3$ (3 x 120 mL). The combined organic layers were dried (Na_2SO_4) and concentrated

under reduced pressure. The crude product was crystallized from *n*-hexane (50 mL); Yield: 70%; a white solid; mp 170-172° C; ^{1}H-NMR (400 MHz, DMSO): δ 1.20-1.44 (10H, m); 1.45-1.60 (1H, m); 1.78 (1H, d, *J* = 12.6 Hz); 2.23 (1H, d, *J* = 12.1 Hz); 2.94-3.12 (1H, om); 3.24-3.35 (1H, m); 3.97 (1H, d, *J* = 11.1 Hz); 4.77 (1H, d, *J* = 5.5 Hz); 5.11 (2H, s); 6.58 (1H, bs); 7.31-7.37 (5H, m); 12.12-13.43 (1H, bs).

Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.39; H, 6.90; S, 7.37.

2-Methyl *trans*-1-benzyloxycarbonyl-4-bromopiperidine-2-carboxylate (**9**).

To a solution of mesyl compound **4** (12.63 g, 34 mmol) in DMF, LiBr was added (4.43 g, 51 mmol). The mixture was stirred for 2 days at 70 °C, then taken up in EtOAc (200 mL), washed with water, dried (Na_2SO_4) and concentrated; Yield: 65%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.62-2.09 (5H, m); 2.32-2.40 (1H, m); 3.66-3.81 (4H, m); 4.20-4.26 (1H, m); 5.11-5.23 (2H, m); 7.32-7.42 (5H, m).

Anal. Calcd. for $C_{15}H_{18}BrNO_4$: C, 50.58; H, 5.09; N, 3.93. Found: C, 50.62; H, 5.11; N, 3.88.

2-Methyl *cis*-1-benzyloxycarbonyl-4-azidopiperidine-2-carboxylate (**10**).

Bromide derivative **9** (7.12 g, 20 mmol) and sodium azide (3.57 g, 55 mmol) were dissolved in DMF (100 mL). After stirring for 3 days at 70 °C, water (500 mL) was added to the mixture, which was then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated; Yield: 70%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ : 1.58-2.30 (6H, m); 3.62-3.81 (4H, m); 4.10-4.33 (1H, m); 5.07-5.26 (2H, m); 7.28-7.44 (5H, m).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.55; H, 5.68; N, 17.62.

2-Methyl *cis*-1-benzyloxycarbonyl-4-aminopiperidine-1,2-carboxylate (**11**).

The azido compound **10** (4.14 g, 13 mmol) and triphenylphosphine (5.24 g, 20 mmol) were dissolved in THF (150 mL) and water (10 mL). After stirring for 2 days at 60 °C, the mixture was concentrated and chromatographed over silica gel ($CHCl_3$-MeOH 9:1); Yield: 65%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.60-2.01 (5h, m); 2.11-2.29 (1H, m); 3.31-3.37 (1H, m); 3.60-3.94 (4H, m); 4.69 (1H, s); 5.05-5.26 (2H, m); 7.28-7.34 (5H, m).

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.65; H, 6.91; N, 9.53.

2-Methyl *cis*-1-benzyloxycarbonyl-4-[(*tert*-butoxycarbonyl)-amino]piperidine-2-carboxylate (**12**).

To a solution of amino compound **11** (2.34 g, 8 mmol) and triethylamine (3 mL) in THF (80 mL), di-*tert*-butyl dicarbonate (2.62 g, 12 mmol) was added at 0 °C. After stirring for 10 h, the mixture was taken up in EtOAc (200 mL), washed with water, dried (Na_2SO_4) and concentrated; Yield: 90%; a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39-1.45 (10H, m); 1.69-1.96 (3H, m); 2.44-2.54 (1H, m); 3.72 (3H, s); 3.81-4.18 (3H, m); 5.12-5.20 (2H, m); 7.31-7.42 (5H, m)

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.28; H, 7.20; N, 7.11.

cis-1-Benzyloxycarbonyl-4-[(*tert*-butoxycarbonyl)amino]piperidine-2-carboxylic acid (**13**).

To a solution of amino ester **12** (2.36 g, 6 mmol) in dioxane (70 mL) NaOH (1.92 g, 48 mmol) in water (70 mL), was added. After stirring for 4 days 10% HCl was added at 0 °C until pH 5. The mixture was then extracted with $CHCl_3$ (3 x 120 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was crystallized from *n*-hexane (50 mL); Yield: 60%; a white solid; mp 138-140° C; ^{1}H-NMR (400 MHz, DMSO): δ 0.83-0.91 (1H, m); 1.24-1.54 (11H, m); 1.64-1.82 (2H, m); 2.15 (1H, d, *J* = 12.6 Hz); 3.64 (1H, s); 3.73 (1H, d, *J* = 12.6 Hz); 4.33 (1H, d, *J* = 4.5 Hz); 5.03-5.09 (2H, m); 7.16 (1H, bs); 7.26-7.44 (5H, m).

Anal. Calcd. for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.22; H, 6.95; N, 7.44.

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