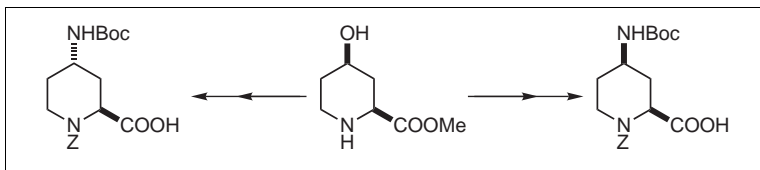


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A straightforward synthesis of orthogonally N^{α}/N^{γ} -protected *trans*- and *cis*-4-aminopiperic acid is reported, starting from methyl *cis*-4-hydroxypiperidine-2-carboxylate. The two diastereomers were synthesized with the aid of C-4 inversion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

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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].

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

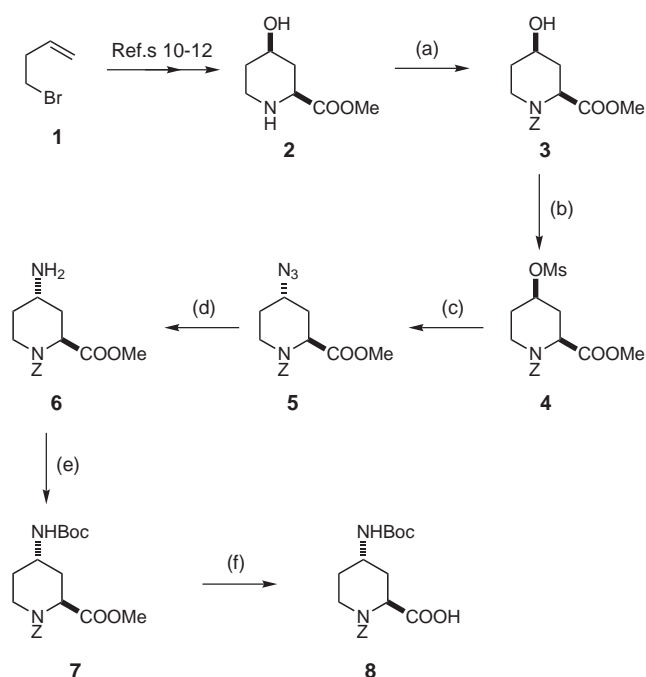
None of the earlier syntheses of 4-aminopiperic acid derivatives seemed suitable for the preparation of orthogonally protected compounds [6-8]. Machetti *et al.* published a simple method for the preparation of protected *trans*-4-aminopiperic acid starting from methyl *cis*-4-hydroxypiperidine-2-carboxylate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

Results and Discussion.

For the synthesis of the diastereomers of protected 4-aminopiperic 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 methane-

Scheme I



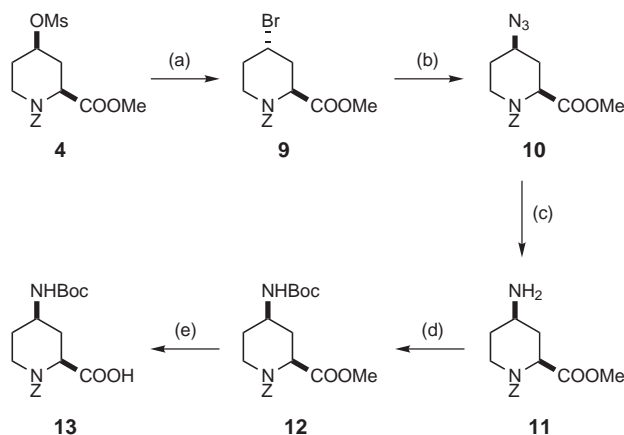
(a) Z-Cl, Et₃N, THF, 20 h, rt., 93%; (b) MsCl, DMAP, Py, 14 h, rt., 95%;
 (c) NaN₃, DMF, 16 h, 70 °C, 85%; (d) PPh₃, THF/H₂O, 2 days, rt., 75%;
 (e) (Boc)₂O, Et₃N, THF, 10 h, rt., 85%; (f) NaOH, dioxane/H₂O, 3 days, rt., 70%

sulfonyl 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/H₂O gave the 4-aminopiperic acid methyl ester (**6**). The amino function at position 4 was then protected with a *tert*-butoxycarbonyl group (**7**). Hydrolysis of methyl ester **7**

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

The strategy for the preparation of the *cis*-4-aminopipelic 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/H₂O to give the diamino ester **11**. The desired orthogonally protected *cis*-4-aminopipelic 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) NaN₃, DMF, 3 days, 70 °C, 70%;
(c) PPh₃, THF/H₂O, 2 days, 60 °C, 65%; (d) (Boc)₂O, Et₃N, THF, 10 h, rt., 90%; (e) NaOH, dioxane/H₂O, 3 days, rt., 60%

In conclusion, a simple and efficient method has been developed for the synthesis of both diastereomers of 4-aminopipelic 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 (Na₂SO₄) and concentrated.

The oily product was used in the next step without further purification; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₆H₂₁NO₇S: 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 (Na₂SO₄) and concentrated; Yield: 85%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₅H₁₈N₄O₄: 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 (CHCl₃-MeOH 9:1); Yield: 75%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₅H₂₀N₂O₄: 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 (Na₂SO₄) and concentrated; Yield: 85%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₂₀H₂₈N₂O₆: 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 CHCl₃ (3 x 120 mL). The combined organic layers were dried (Na₂SO₄) and concentrated

under reduced pressure. The crude product was crystallized from *n*-hexane (50 mL); Yield: 70%; a white solid; mp 170-172° C; ¹H-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 C₁₉H₂₆N₂O₆: 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 (Na₂SO₄) and concentrated; Yield: 65%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₅H₁₈BrN₂O₄: 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 (Na₂SO₄) and concentrated; Yield: 70%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₅H₁₈N₄O₄: 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 (CHCl₃-MeOH 9:1); Yield: 65%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₁₅H₂₀N₂O₄: 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 (Na₂SO₄) and concentrated; Yield: 90%; a colorless oil; ¹H-NMR (400 MHz, CDCl₃): 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 C₂₆H₂₈N₂O₆: 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 CHCl₃ (3 x 120 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was crystallized from *n*-hexane (50 mL); Yield: 60%; a white solid; mp 138-140° C; ¹H-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 C₁₉H₂₆N₂O₆: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.22; H, 6.95; N, 7.44.

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