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PAPER

Access to β,γ-diamino acids. Application to the synthesis of 3-deoxyaminostatine†

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The synthesis of orthogonally protected diastereo- and enantiopure β,γ-diamino acids starting from natural α-amino acids is described, as well as its application to the synthesis of fully protected 3-deoxyaminostatine.

Introduction

The design and synthesis of original amino acid derivatives is a continuous challenge in organic and bioorganic chemistry. Among the non proteinogenic amino acids, β-amino acids and γ-amino acids appear to be useful building blocks in peptide science, as their corresponding peptides possess interesting conformational properties and increased resistance to peptidolysis.[1] In this field, we are particularly involved for a few years in the synthesis of β,γ-diamino acids (of *syn* or *anti* configuration). These compounds[2] present several advantages: firstly, they possess the 1,2-diamine structural motif and 1,2-diamines are often used as ligands for transition metals, or as organic catalysts;[3] secondly they are present in several natural products such as pseudotheonamide A_1,[4] microsclerodermin[5] or aminocarnitine,[6] or in biologically active compounds such as 3-deoxyaminostatine **1** (Fig. 1),[7] which induces an enhancement of biological activity, when incorporated, instead of statine **2**, in renin inhibitor peptides;[8] thirdly, they can be precursors for both β- or γ-peptides, the second nitrogen being source of molecular diversity.

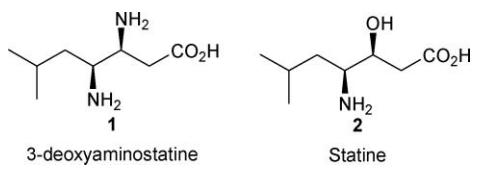
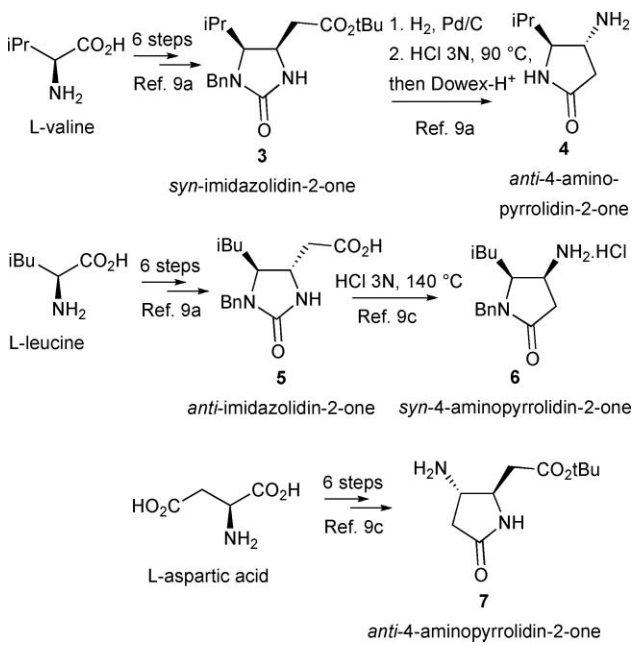


Fig. 1 Structures of 3-deoxyaminostatine and statine.

Results and discussion

We have previously reported our synthetic approach of β,γ-diamino acids starting from natural α-amino acids. The key steps were a Blaise Reaction onto an α-aminonitrile followed by diastereoselective reduction. We have thus described the diastereoselective synthesis of their cyclic form either 4-aminopyrrolidin-2-one or imidazolidin-2-one, obtained as single diastereomer and enantiomer (Scheme 1).[9] We would like to present here the final steps towards the orthogonally protected β,γ-diamino acids, ready for peptide synthesis and its application to the synthesis of protected 3-deoxyaminostatine. We have selected 3 amino acids as starting material: L-valine and L-leucine which give access to imidazolidin-2-one of opposite relative configuration and L-aspartic acid, which is a functionalized amino acid.



Scheme 1 Synthesis of imidazolidin-2-one and 4-aminopyrrolidin-2-one.

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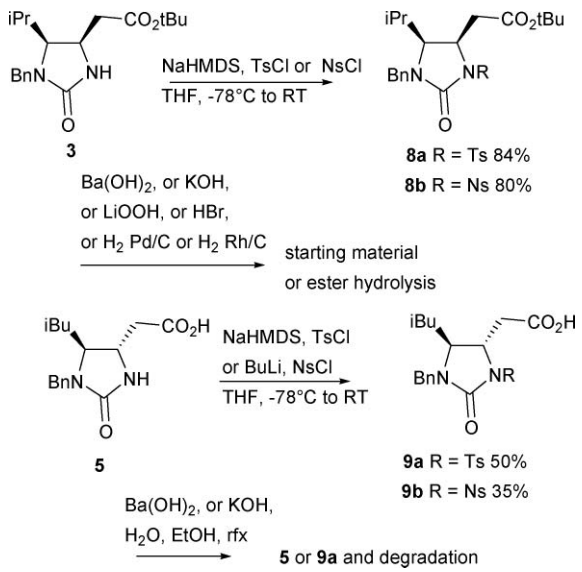
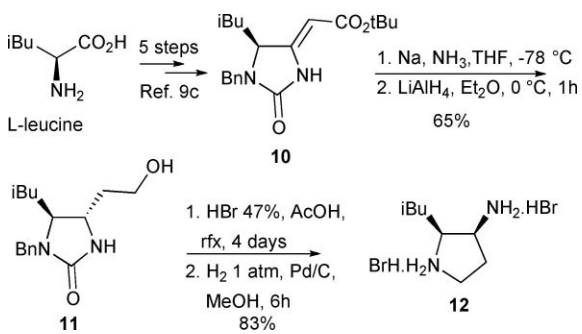
† Electronic supplementary information (ESI) available: Supplementary figures and tables, and ^{1}H and ^{13}C NMR spectra of compounds. CCDC reference numbers 780546. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00370k

Our initial efforts were oriented towards direct hydrolysis of the urea of the imidazolidin-2-ones. Performing hydrolysis under various acidic conditions (HCl, H_2SO_4 or HBr) on compounds **3** or **5** gave always access to the starting material (no reaction or only ester hydrolysis) or to the corresponding cyclized 4-aminopyrrolidin-2-one. Performing hydrolysis in basic conditions ($Ba(OH)_2$)[10] resulted in only recovered starting urea (without the ester function). We next decided to activate the urea with a nosyl or a tosyl group,[11,7c] but none of our attempts (basic, or acidic hydrolysis or hydrogenolysis) was successful (Scheme 2). We then chose to perform acidic hydrolysis onto the reduced compound **11**, which was a secondary product of the synthetic sequence (obtained during the Birch reduction step). This should avoid cyclization to 4-aminopyrrolidin-2-one. We thus performed direct reduction of the crude mixture obtained after the Birch reduction to get the alcohol **11**. The next steps, acidic hydrolysis and hydrogenolysis, did not lead to the expected diaminoalcohol but to the dehydrated product **12** (Scheme 3).[12] This provides an alternative route to 3-aminopyrrolidines.[9b] We therefore decided to change our strategy and to tackle hydrolysis of the cyclic 4-aminopyrrolidinones. Direct hydrolysis of 4-aminopyrrolidinones[2a] under basic conditions failed and we chose to activate the ring opening by a *tert*-butylcarbamate.[13] 4-Aminopyrrolidin-2-one derived from L-valine was first protected with a Cbz group and next amide protection was performed under standard condition to give compound **14**.

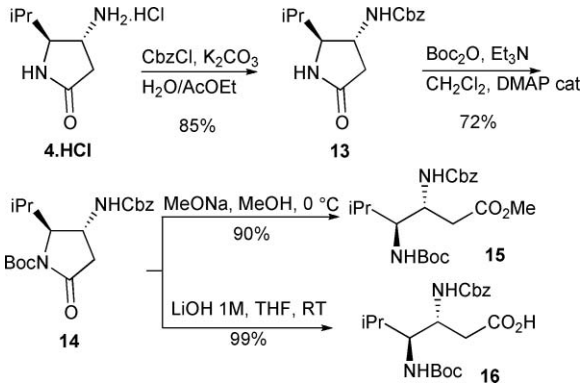


Scheme 2 Urea cleavage unsuccessful attempts.



Scheme 3 Synthesis of 3-aminopyrrolidine **12**.

Lactam opening was then easily achieved and led to either methyl ester **15** or carboxylic acid **16**, ready for Boc-solid phase peptide synthesis (Scheme 4).



Scheme 4 L-valine derivative: synthesis of β,γ-diamino acids **15** and **16**.

Compound **15** is crystalline and the molecules form hydrogen-bonded ladder structures (Fig. 2). Successive molecules in the ladder are parallel and the two N···O distances is around 2.94 Å, with N–H···O angles equal to 150 and 158°, which is indicative of an usual hydrogen bonding. Thus the molecules are linked into infinite chains *via* C=O···H–N hydrogen bonds and the chains form a parallel β-sheet-like arrangement.

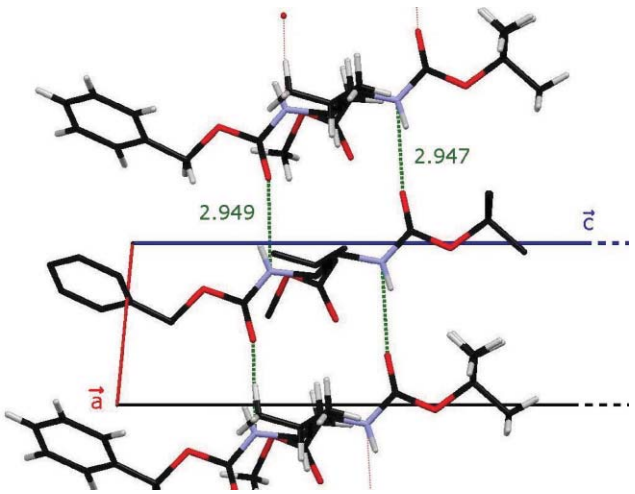
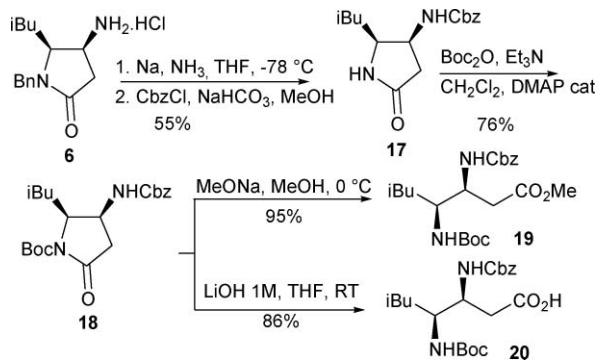


Fig. 2 A partial view of the packing of protected β,γ-diamino acid **15** along the b axis, showing the network of hydrogen bonds linking two molecules. Some H atoms have been omitted for clarity.

The FTIR spectrum of compound **15** in the solid state was recorded and we observed a NH stretching band at 3346 cm^{-1}, characteristic of hydrogen bonded amide (below 3400 cm^{-1}) and two C=O streching bands at 1735 and 1679 cm^{-1}. The FTIR spectrum of the same compound was also recorded as 5 mM solution in dichloromethane to avoid aggregation. We observed a NH streching band at 3429 cm^{-1} and a C=O streching band at 1716 cm^{-1}. This excludes the formation of intramolecular hydrogen bond. We also performed ^1H NMR studies. In fact, compound **15** was present as a single conformer in $CDCl_3$ whereas several conformers were observed by switching to CD_3OD ($c > 30$ mM). After 30 min, the spectrum became more simple and only one

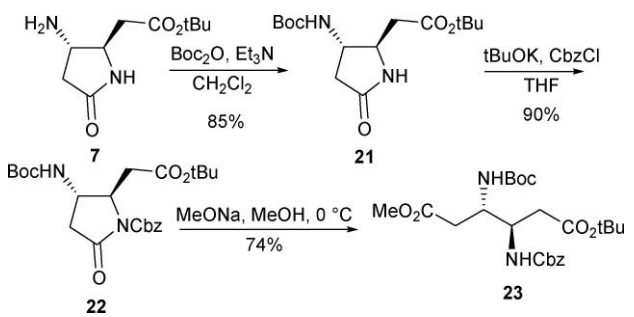
conformer was visible. Moreover, the signals of the NH were still present after several hours, showing a slow NH-ND exchange. For compound **16**, several conformers were observed in $CDCl_3$, and again the spectrum was much more simple in CD_3OD, showing only one conformer with a slow NH-ND exchange. In both cases, this is significant of hydrogen bonding. This behavior is under investigation.

The same strategy[14] was then successfully applied to L-leucine derivative **6** and fully protected 3-deoxyaminostatine **19** or **20** were obtained *enantio* and diastereopure (Scheme 5). Data for compounds **19** and **20** were identical in all respects to those reported in the literature.[8a,8c]



Scheme 5 L-Leucine derivative: synthesis of orthogonally protected 3-deoxyaminostatine **19** and **20**.

For the L-aspartic acid derivative **7**, we decided to test alternative protection.[15] In this case, the lactam was successfully activated by a benzylcarbamate and ring opening gave access to the highly functionalized β,γ-diamino acid **23** (Scheme 6).



Scheme 6 L-aspartic acid derivative: synthesis of β,γ-diamino acid **23**.

Conclusions

We have described the synthesis of fully protected diastereo- and enantiopure β,γ-diamino acids, starting from natural α-amino acids. This strategy has been successfully applied to the synthesis of orthogonally protected 3-deoxyaminostatine. For compound **15**, the interesting packing observed in crystals, and its original behavior in solution (NMR) encourage us to pursue its conformational studies. Incorporation of these β,γ-diamino acids in peptides and conformational studies of the resulting peptide are under investigation.

Experimental section

General methods

Dichloromethane was distilled over CaH_2 under argon. Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone ketyl under argon. All other reagents were used as received. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 glass precoated with a 0.25 mm thickness of silica gel. Flash chromatography was performed on Kieselgel 60 (230–400 mesh) silica gel. ^{1}H NMR spectra were measured at 400 MHz, 360 MHz, 300 MHz, and 250 MHz using $CDCl_3$, MeOD or D_2O (dioxane as internal reference) as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision with coupling constants reported to 0.1 Hz precision using residual chloroform (δ 7.27 ppm) as an internal reference. IR spectra were recorded on a FT-IR spectrometer. MS and HRMS experiments were performed on a high/low-resolution magnetic sector mass spectrometer. Optical rotations were performed on a precision automated polarimeter.

Compounds **3–7** were prepared according to procedures described in ref. 9a and 9c.

(4*S*,5*S*)-1-Benzyl-4-(2-hydroxyethyl)-5-isobutylimidazolidin-2-one (11)

NH_3 gas (15 mL) was passed through a tube containing NaOH pellets and condensed into a cooled (−78 °C) glass tube containing some pieces of sodium metal, giving a deep blue solution. The cooling bath was removed, and dried ammonia gas was transferred into a cooled (−78 °C) tri-necked flask containing a solution of enaminoester **10** (106 mg, 0.31 mmol) in dry THF (3 mL). Sodium pieces (41 mg, 1.87 mmol) were added and the deep blue solution was stirred for additional 30 min at −78 °C. The reaction was quenched by addition of solid NH_4Cl (167 mg, 3 mmol) and warmed to room temperature to remove NH_3 gas. The solution was then acidified to pH 1 with 2M HCl solution and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The crude mixture was dissolved in anhydrous Et_2O (1.5 mL) and a solution of $LiAlH_4$ (0.25 mmol) in Et_2O (1.5 mL) was added dropwise at 0 °C. The solution was stirred for 1 h at 0 °C and treated with Na_2SO_4, filtered and concentrated to give the desired compound **11** (56 mg, 0.20 mmol) without further purification. Yield: 65%

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.76 (d, J = 6.3, 3H), 0.88 (d, J = 6.3, 3H), 1.32–1.50 (m, 2H), 1.51–1.70 (m, 3H), 2.66–4.08 (br s, 1H), 3.06–3.16 (m, 1H), 3.45–3.55 (m, 1H), 3.61–3.73 (m, 1H), 3.73–3.85 (m, 1H), 3.97 (d, J = 15.8, 1H), 4.81 (d, J = 15.8, 1H), 5.91 (s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 21.9, 23.8, 24.0, 38.4, 41.3, 44.7, 54.5, 59.0, 59.6, 127.9, 128.3, 128.6, 137.2, 161.4; HRMS (electrospray) (M+Na) calculated 299.1727, found 299.1727; IR (CH_2Cl_2) ν/cm^{-1} 3293.0, 1683.9.

Analyses were in agreement with literature[9a]

(2*S*,3*S*)-2-Isobutylpyrrolidin-3-amine dihydrobromide (12)

Alcohol **11** was cleaved in the presence of aqueous HBr 47% and acetic acid (1 : 1) solution at 140 °C for 4 days. The mixture was washed three times with EtOAc and was concentrated

under reduced pressure. The crude product was dissolved in dry methanol (2 mL) and was hydrogenated at 1 bar for 15 h in the presence of 10% Pd/C (56 mg). Filtration of the catalyst through Celite pad and concentration under reduced pressure gave pure compound **12** (51 mg, 0.17 mmol).

Yield: 83% mp: 227 °C; ^{1}H NMR (300 MHz, D_2O) δ (ppm) 0.70 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H), 1.43–1.69 (m, 3H), 2.12 (m, 1H), 2.54 (m, 1H), 3.34 (m, 1H), 3.50 (m, 1H), 3.95 (m, 1H), 4.09 (m 1H); ^{13}C NMR (75 MHz, D_2O) δ (ppm) 20.7, 22.9, 25.4, 29.2, 35.3, 43.7, 52.4, 59.5; HRMS (electrospray) (M-2HBr+Na) calculated 143.1543, found 143.1544; IR (thin film, MeOH) ν (cm–1) 3428, 2963, 1622; $[\alpha]_D^{20}$ = –7.25 (c = 0.48, MeOH).

Benzyl (2*S*,3*R*)-2-isopropyl-5-oxopyrrolidin-3-ylcarbamate (13)

Aminopyrrolidinone **4**·**HCl** (obtained by omitting Dowex-H^+ purification, 243 mg, 1.7 mmol) was dissolved in MeOH (28 mL) and was treated with saturated aqueous $NaHCO_3$ (8.5 ml) and CbzCl (0.29 mL, 2.05 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc (20 mL) and was washed with H_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc) to afford pure compound **13** (400 mg, 1.44 mmol).

Yield: 85% white solid. mp: 109 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.88 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.70 (m, 1H), 2.13 (dd, J = 3.7 Hz, J = 17.6 Hz, 1H), 2.70 (dd, J = 8.3 Hz, J = 17.6 Hz, 1H), 3.15 (m, 1H), 4.16 (m, 1H), 5.07 (d, J = 12.1 Hz, 1H), 5.13 (d, J = 12.1 Hz, 1H), 5.80 (d, J = 7.0 Hz, 1H), 7.26–7.40 (m, 5H), 7.52 (br.s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 17.8, 18.8, 31.7, 37.9, 49.9, 66.8, 68.2, 128.1, 128.2, 128.5, 136.3, 155.7, 176.4; HRMS (electrospray) (M+Na) calculated 299.1366, found 299.1363; IR (thin film, CH_2Cl_2) ν (cm–1) 3294, 1690, 1536, 1272; $[\alpha]_D^{20}$ = +16.8 (c = 0.985, CH_2Cl_2).

Benzyl (2*S*,3*S*)-2-isobutyl-5-oxopyrrolidin-3-ylcarbamate (17)

Anhydrous ammonia (3 mL) was condensed into a two-necked flask containing a solution of compound **6** (50 mg, 0.177 mmol) in anhydrous THF (3 mL) maintained at –78 °C. Sodium metal was added to the mixture until a blue colour persisted. The reaction mixture was stirred at –78 °C for 30 min and quenched by addition of solid NH_4Cl. The ammonia was evaporated and the mixture was concentrated to dryness. Then, crude mixture was dissolved in MeOH (3 mL) and was treated with saturated aq $NaHCO_3$ (0.8 ml) and CbzCl (100 µL, 0.7 mmol). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc (20 mL) and was washed with H_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The crude product was purified by flash column chromatography (EtOAc) to afford compound **17** (28 mg, 0.096 mmol).

Yield: 55% white solid. mp: 143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.86 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 1.21–1.36 (m, 2H), 1.59 (m, 1H), 2.19 (dd, J = 3.7 Hz, J = 16.9 Hz, 1H), 2.63 (dd, J = 7.7 Hz, J = 16.9 Hz, 1H), 3.80 (m, 1H), 4.49 (m, 1H), 5.05 (d, J = 12.3 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.28 (d, J = 8.4 Hz, 1H), 6.72 (br.s, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.9, 23.6, 25.2, 38.1, 38.7, 50.4, 55.9, 67.2, 128.3, 128.4, 128.7, 136.5, 156.1, 175.7; HRMS (electrospray) (M+H) calculated 291.1703, found 291.1702; IR (thin film, CH_2Cl_2) ν (cm–1) 3306, 1689, 1542, 1266, 1044; $[\alpha]_D^{20}$ = –41.7 (c = 0.890, CH_2Cl_2).

(2*S*,3*R*)-*tert*-Butyl 3-(benzyloxycarbonylamino)-2-isopropyl-5-oxopyrrolidine-1-carboxylate (14)

To a solution of **13** (345 mg, 1.25 mmol) in CH_2Cl_2 (9 mL) were added triethylamine (0.19 mL, 1.37 mmol), di-*tert*-butyl dicarbonate (544 mg, 2.49 mmol) and 4-(dimethylamino)pyridine (30 mg, 0.24 mmol). The solution was stirred for 6 h at room temperature. The reaction mixture was diluted with EtOAc, washed with aqueous 10% citric acid and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the desired compound, which was purified *via* column chromatography (heptane/EtOAc 7 : 3) to yield compound **14** (339 mg, 0.90 mmol).

Yield: 72% colourless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 0.95 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 6.0 Hz, 3H), 1.53 (s, 9H) 2.11 (m, 1H), 2.39 (br d, 1H), 2.90 (dd, J = 7.2 Hz, J = 18.3 Hz, 1H), 3.92 (m, 1H), 4.11 (m, 1H), 5.10 (d, J = 11.6 Hz, 1H), 5.15 (d, J = 11.6 Hz, 1H), 5.34 (br.d, 1H), 7.31–7.41 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 17.2, 19.2, 28.2, 30.7, 40.2, 45.6, 67.2, 70.8, 83.5, 128.4, 128.5, 128.8, 136.2, 150.1, 155.5, 172.3; HRMS (electrospray) (M+Na) calculated 399.1890, found 399.1885; IR (thin film, CH_2Cl_2) ν (cm–1) 3331, 1788, 1708, 1538, 1303, 1247; $[\alpha]_D^{20}$ = + 55.8 (c = 0.650, CH_2Cl_2).

(2*S*,3*S*)-*tert*-Butyl 3-(benzyloxycarbonylamino)-2-isobutyl-5-oxopyrrolidine-1-carboxylate (18)

To a solution of **17** (362 mg, 1.25 mmol) in CH_2Cl_2 (9 mL) were added triethylamine (0.19 mL, 1.37 mmol), di-*tert*-butyl dicarbonate (544 mg, 2.49 mmol) and 4-(dimethylamino)pyridine (30 mg, 0.24 mmol). The solution was stirred for 6 h at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with aqueous 10% citric acid and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the desired compound, which was purified *via* column chromatography (heptane/EtOAc 7 : 3) to yield compound **18** (370 mg, 0.95 mmol).

Yield: 76% white solid. mp: 144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.89 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.26–1.69 (m, 3H), 1.54 (s, 9H), 2.44 (dd, J = 11.0 Hz, J = 16.8 Hz, 1H), 2.70 (dd, J = 8.0 Hz, J = 16.8 Hz, 1H), 4.36–4.58 (m, 2H), 4.94 (d, J = 7.6 Hz, 1H), 5.09 (d, J = 11.9 Hz, 1H), 5.17 (d, J = 11.9 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 22.9, 23.3, 25.2, 28.2, 37.2, 38.7, 47.5, 57.8, 67.4, 83.7, 128.5, 128.6, 128.8, 136.2, 149.8, 155.8, 170.7; HRMS (electrospray) (M+Na) calculated 413.2047, found 413.2043; IR (thin film, CH_2Cl_2) ν (cm–1) 3351, 1781, 1721, 1538, 1275, 1253, 1151; $[\alpha]_D^{20}$ = +20.3 (c = 0.400, CH_2Cl_2).

(3*R*,4*S*)-Methyl 3-(benzyloxycarbonylamino)-4-(*tert*-butoxycarbonylamino)-5-methylhexanoate (15)

A solution of protected aminopyrrolidinone **14** (170 mg, 0.45 mmol) in dry MeOH (4 mL) was cooled to 0 °C under

an argon atmosphere. Then a solution of sodium methoxide in methanol 30% wt. (42 µL) was added. After 2 h at 0 °C, the reaction was quenched with a saturated solution of NH_4Cl. MeOH was evaporated and the crude product was diluted with EtOAc, washed with water and brine. After drying over $MgSO_4$, filtration and concentration, the crude material was purified by flash chromatography (heptane/AcOEt: 1/1) to give the pure compound **15** (165 mg, 0.4 mmol).

Yield: 90% colourless crystals. mp: 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.86 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 1.40 (s, 9H) 1.90 (m, 1H), 2.46–2.52 (m, 2H), 3.50–3.69 (m, 1H), 3,67 (s, 3H), 4.02 (m, 1H), 4.41 (d, J = 9.9 Hz, 1H), 5.01–5.14 (m, 2H), 5.57 (d, J = 9.3 Hz, 1H), 7.19–7.39 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 16.4, 20.3, 28.5, 36.2, 50.0, 52.0, 58.1, 66.9, 79.8, 128.2, 128.7, 136.7, 156.0, 156.3, 172.6; HRMS (electrospray) (M+Na) calculated 431.2166, found 431.2145; IR (thin film, CH_2Cl_2) ν (cm−1) 3346, 1736, 1680, 1523; $[\alpha]_D^{20}$ = + 1.5 (c = 0.425, CH_2Cl_2).

(3*S*,4*S*)-Methyl 3-(benzyloxycarbonylamino)-4-(*tert*-butoxycarbonylamino)-6-methylheptanoate (19). A solution of protected aminopyrrolidinone **18** (45 mg, 0.115 mmol) in dry MeOH (1 mL) was cooled to 0 °C under an argon atmosphere. Then a solution of sodium methoxide in methanol 30% wt. (11 µL) was added. After 1 h 30 min at 0 °C, the reaction was quenched with a saturated solution of NH_4Cl. MeOH was evaporated and the crude product was diluted with EtOAc, washed with water and brine. After drying over $MgSO_4$, filtration and concentration, the crude material was purified by flash chromatography (heptane/AcOEt: 1/1) to give the pure compound **19** (46 mg, 0.109 mmol).

Yield: 95% colourless oil; ^{1}H NMR (300 MHz, MeOD) δ (ppm) 0.90 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.28–1.37 (m, 2H), 1.44 (s, 9H) 1.65 (m, 1H), 2.44 (dd, J = 8.1 Hz, J = 15.6 Hz, 1H), 2.58 (dd, J = 5.9 Hz, J = 15.6 Hz, 1H), 3.63 (s, 3H), 3.81 (m, 1H), 4.10 (m, 1H), 5.03–5.13 (m, 2H), 7.25–7.42 (m, 5H); ^{13}C NMR (75 MHz, MeOD) δ (ppm) 21.0, 22.2, 24.6, 27.3, 36.7, 41.0, 50.8, 51.2, 51.9, 66.1, 78.7, 127.3, 127.6, 128.1, 137.0, 156.9, 157.0, 171.9; HRMS (electrospray) (M+Na) calculated 445.2309, found 445.2305; IR (thin film, CH_2Cl_2) ν (cm−1) 3354, 2956, 1739, 1692, 1521; $[\alpha]_D^{20}$ = −44.6 (c = 2.20, CH_2Cl_2).

(3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(*tert*-butoxycarbonylamino)-5-methylhexanoic acid (16)

To a solution of the protected aminopyrolidinone **14** (62 mg, 0.16 mmol) in THF (1 mL) was added 0.5 mL of a 1 N aqueous solution of lithium hydroxide. The solution was stirred for 4 h at room temperature. After removal of THF *in vacuo*, the basic aqueous residue was acidified by the addition of 10% acetic acid and extracted with ether. After drying over $MgSO_4$, filtration and concentration, the pure compound **16** is obtained without further purification (64 mg, 0.162 mmol).

Yield: 99% white solid; mp: 170 °C.; ^{1}H NMR (250 MHz, MeOD) δ (ppm) 0.88 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.46 (s, 9H) 1.87 (m, 1H), 2.39 (dd, J = 4.0 Hz, J = 15.4 Hz, 1H), 2.58 (dd, J = 9.0 Hz, J = 15.4 Hz, 1H), 3.55 (m, 1H), 4.11 (m, 1H), 5.07–5.13 (m, 2H), 7.28–7.44 (m, 5H); ^{13}C NMR (62.5 MHz, MeOD) δ (ppm) 15.6, 19.2, 27.4, 28.4, 36.0, 49.7, 58.2, 65.9, 78.7, 127.2, 127.4, 128.0, 137.1, 156.7, 157.3, 173.9; HRMS (electrospray) (M+Na) calculated 417.1996, found 417.1989.

IR (thin film, CH_2Cl_2) ν (cm−1) 3351, 1685, 1527; $[\alpha]_D^{20}$ = +13.3 (c = 0.745, CH_2Cl_2).

(3*S*,4*S*)-3-(Benzyloxycarbonylamino)-4-(*tert*-butoxycarbonylamino)-6-methylheptanoic acid (20)

To a solution of the protected aminopyrolidinone **18** (38 mg, 0.097 mmol) in THF (1 mL) was added 0.5 mL of a 1 N solution of lithium hydroxide. The solution was stirred for 4 h at room temperature. After removal of THF *in vacuo*, the basic aqueous residue was acidified by the addition of 10% acetic acid and extracted with ether. After drying over $MgSO_4$, filtration and concentration, the pure compound **20** is obtained without further purification (34 mg, 0.083 mmol).

Yield: 86%; white solid; mp: 130 °C; ^{1}H NMR (360 MHz, MeOD) δ (ppm) 0.92 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 1.24–1.39 (m, 2H), 1.46 (s, 9H) 1.70 (m, 1H), 2.43 (dd, J = 7.9 Hz, J = 15.5 Hz, 1H), 2.58 (dd, J = 5.7 Hz, J = 15.5 Hz, 1H), 3.83 (m, 1H), 4.13 (m, 1H), 5.07 (d, J = 12.7 Hz, 1H), 5.13 (d, J = 12.7 Hz, 1H), 7.27–7.46 (m, 5H); ^{13}C NMR (90 MHz, MeOD) δ (ppm) 22.5, 23.7, 26.1, 28.9, 38.2, 42.5, 52.9, 53.4, 67.6, 80.2, 128.8, 129.1, 129.6, 138.5, 158.5, 158.6, 174.8; HRMS (electrospray) (M+Na) calculated 431.2158, found 431.2142; IR (thin film, CH_2Cl_2) ν (cm−1) 3340, 1692, 1522; $[\alpha]_D^{20}$ = −45.3 (c = 0.63, MeOH).

Analysis were in agreement with literature[8a]

tert-Butyl 2-((2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-5-oxopyrrolidin-2-yl)acetate (21)

To a solution of **7** (100 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) were added triethylamine (72 µL, 0.51 mmol) and di-*tert*-butyl dicarbonate (204 mg, 0.93 mmol). The solution was stirred for 2 h at room temperature. The reaction mixture was diluted with excess amount of EtOAc, washed with aqueous 10% citric acid and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give the desired compound, which was purified *via* column chromatography (CH_2Cl_2–MeOH 7 : 3) to yield pure compound **21** (125 mg, 0.40 mmol).

Yield: 85% white solid; mp: 155 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.48 (s, 18H), 2.21 (dd, J = 5.7 Hz , J = 16.9 Hz, 1H), 2.37 (dd, J = 10.5 Hz, J = 16.9 Hz, 1H), 2.63–2.84 (m, 2H), 3.75 (m, 1H), 4.00 (m, 1H), 5.26 (d, J = 6.4 Hz, 1H), 6.47 (br.s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 28.2, 28.5, 36.8, 40.4, 51.7, 58.1, 80.2, 81.9, 155.4, 170.7, 174.7; HRMS (electrospray) (M+Na) calculated 337.1739, found 337.1739; IR (thin film, CH_2Cl_2) ν (cm−1) 3305, 2978, 1701, 1159; $[\alpha]_D^{20}$ = +31.4 (c = 1.03, CH_2Cl_2).

(2*R*,3*S*)-Benzyl 2-(2-*tert*-butoxy-2-oxoethyl)-3-(*tert*-butoxycarbonylamino)-5-oxopyrrolidine-1-carboxylate (22)

A solution of compound **21** (100 mg, 0.32 mmol) in THF (3 mL) was added directly on sublimated tBuOK (57 mg, 0.51 mmol). The mixture was stirred 15 min at room temperature then benzyl chloroformate (67 µL, 0.48 mmol) was added. After 4 h, the reaction was quenched with a saturated solution of NH_4Cl. The crude product was diluted with EtOAc, washed with water and brine.

After drying over $MgSO_4$, filtration and concentration, the crude material was purified by flash chromatography (heptane/AcOEt: 6/4) to give the pure compound **22** (129 mg, 0.29 mmol).

Yield: 90%; white solid; mp: 132 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.39 (s, 9H), 1.40 (s, 9H), 2.41 (dd, J = 1.6 Hz, J = 18.4 Hz, 1H), 2.62 (dd, J = 8.3 Hz, J = 15.7 Hz, 1H), 2.77 (dd, J = 2.6 Hz, J = 15.7 Hz, 1H), 3.01 (dd, J = 7.9 Hz, J = 18.4 Hz, 1H), 4.05 (m, 1H), 4.29 (m, 1H), 4.88 (d, J = 6.2 Hz, 1H), 5.24 (d, J = 12.4 Hz, 1H), 5.31 (d, J = 12.4 Hz, 1H), 7.29–7.43 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 28.2, 28.5, 38.4, 39.0, 48.7, 62.3, 68.2, 80.7, 82.0, 128.3, 128.7, 128.8, 135.3, 151.3, 155.1, 169.3, 171.6; HRMS (electrospray) (M+Na) calculated 449.2282, found 449.2269; IR (thin film, CH_2Cl_2) ν (cm−1) 3358, 1792, 1721, 1294; $[\alpha]_D^{20} = -29.1$(c = 0.56, CH_2Cl_2).

(3*R*,4*S*)-1-*tert*-Butyl 6-methyl 3-(benzyloxycarbonylamino)-4-(*tert*-butoxycarbonylamino)hexanedioate (23)

A solution of protected aminopyrrolidinone **22** (58 mg, 0.13 mmol) in dry MeOH (1.5 mL) was cooled to 0 °C under an argon atmosphere. Then a solution of sodium methoxide in methanol 30% wt. (12 μL) was added. After 30 min. at 0 °C, the reaction was quenched with a saturated solution of NH_4Cl. MeOH was evaporated and the crude product was diluted with EtOAc, washed with water and brine. After drying over $MgSO_4$, filtration and concentration, the crude material was purified by flash chromatography (CH_2Cl_2: MeOH 97/3) to give the pure compound **23** (46 mg, 0.096 mmol).

Yield: 74% white solid; mp: 145 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.40 (s, 18H), 2.47–2.62 (m, 4H), 3.63 (s, 3H), 3.99–4.12 (m, 2H), 5.02–5.08 (m, 2H), 5.35 (m, 1H), 5.72 (m, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 28.2, 28.5, 36.1, 37.2, 50.4, 51.1, 51.9, 67.0, 79.8, 81.5, 128.3, 128.6, 136.6, 155.4, 156.2, 171.1, 172.4; HRMS (electrospray) (M+Na) calculated 503.2364, found 503.2355; IR (thin film, CH_2Cl_2) ν (cm−1) 3324, 1732, 1686, 1540; $[\alpha]_D^{20} = -4.8$(c = 0.48, CH_2Cl_2).

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Notes and references

1 (*a*) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893–4012; (*b*) D. Seebach, D. F. Hook and A. Glättli, *Biopolymers*, 2006, **84**, 23–37; (*c*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173–180; (*d*) W. S. Horne and S. H. Gellman, *Acc. Chem. Res.*, 2008, **41**, 1399–1408.
2 Examples of other syntheses of β,γ–diamino acids: (*a*) D.-H. Yoon, H.-J. Ha, B. C. Kim and W. K. Lee, *Tetrahedron Lett.*, 2010, **51**, 2181–2183; (*b*) N. Giri, M. Petrini and R. Profeta, *J. Org. Chem.*, 2004, **69**, 7303–7308; (*c*) J. M. Bartolomé-Nebreda, M. T. Garcia-Lopez, R. Gonzalez-Muniz, E. Cenarruzabeitia, M. Latorre, J. Del, Rio and R. Herranz, *J. Med. Chem.*, 2001, **44**, 4196–4206.
3 Reviews on 1,2-diamines: (*a*) D. Lucet, T. Le, Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580–2627; (*b*) S. R. S. S. Kotti, C. Timmons and G. Li, *Chem. Biol. Drug Des.*, 2006, **67**, 101–114.
4 T. Shiori and N. Irako, *Chem. Lett.*, 2002, 130–133.
5 (*a*) J. Zhu and D. Ma, *Angew. Chem., Int. Ed.*, 2003, **42**, 5348–5351; (*b*) A. Qureshi, P. L. Colin and D. J. Faulkner, *Tetrahedron*, 2000, **56**, 3679–3685.
6 (*a*) S. Shinagawa, T. Kanamaru, S. Harada, M. Asai and H. Okazaki, *J. Med. Chem.*, 1987, **30**, 1458–1463; (*b*) G. Calvisi, N. Dell'Uomo, F. De Angelis, R. Dejas, F. Giannessi and M. O. Tinti, *Eur. J. Org. Chem.*, 2003, 4501–4505.
7 Asymmetric synthesis: (*a*) H. J. Schostarez, *J. Org. Chem.*, 1988, **53**, 3628–3631; (*b*) D. Yoo, S. Kwon and Y. G. Kim, *Tetrahedron: Asymmetry*, 2005, **16**, 3762–3766; (*c*) R. Seo, T. Ishizuka, A. A.-M. Abdel-Aziz and T. Kunieda, *Tetrahedron Lett.*, 2001, **42**, 6353–6355; (*d*) E. Gomez-Bengoa, A. Linden, R. Lopez, I. Mugica-Mendiola, M. Oiarbide and C. Palomo, *J. Am. Chem. Soc.*, 2008, **130**, 7955–7966.
8 Biological activity: (*a*) R. J. Arrowsmith, K. Carter, J. G. Dann, D. E. Davies, C. J. Harris, J. A. Morton, P. Lister, J. A. Robinson and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1986, 755–757; (*b*) S. Thaisrivongs, H. J. Schostarez, D. T. Pals and S. R. Turner, *J. Med. Chem.*, 1987, **30**, 1837–1842; (*c*) D. M. Jones, J. Sueiras-Diaz, M. Szelke, B. J. Leckie, S. R. Beattie, J. Morton, S. Neidle and R. J. Kuroda, *J. Pept. Res.*, 2009, **50**, 109–121.
9 (*a*) C. T. Hoang, V. Alezra, R. Guillot and C. Kouklovsky, *Org. Lett.*, 2007, **9**, 2521–2524; (*b*) C. T. Hoang, V. H. Nguyen, V. Alezra and C. Kouklovsky, *J. Org. Chem.*, 2008, **73**, 1162–1164; (*c*) C. T. Hoang, F. Bouillère, S. Johannesen, A. Zulauf, C. Panel, D. Gori, A. Pouilhès, V. Alezra and C. Kouklovsky, *J. Org. Chem.*, 2009, **74**, 4177–4187 for related strategy in the synthesis of 4-aminopyrrolidones: (*d*) S. Pinheiro, R. C. da Silva Jr., A. S. de Souza, J. W. de M. Carneiro, E. M. F. Muri and O. A. C. Antunes, *Tetrahedron Lett.*, 2009, **50**, 2402–2404.
10 R. C. F. Jones and J. Schofield, *J. Chem. Soc., Perkin Trans. 1*, 1990, 375–383.
11 B. Zhao, H. Du and Y. Shi, *J. Org. Chem.*, 2009, **74**, 7577–7580.
12 For a similar cyclization with HBr, see : J. H. Swango, B. S. Bhatti, M. M. Qureshi and P. A. Crooks, *Chirality*, 1999, **11**, 316–318.
13 D. Farran, L. Toupet, J. Martinez and G. Dewynter, *Org. Lett.*, 2007, **9**, 4833–4836.
14 For compound **6**, only sodium in liquid nitrogen lead to cleavage of the benzyl group.
15 L. E. Burgess and A. I. Meyers, *J. Am. Chem. Soc.*, 1991, **113**, 9858–9859.