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Efficient synthesis of enantiomerically pure (*S*)-δ-azaproline starting from (*R*)-α-hydroxy-γ-butyrolactone via the Mitsunobu reaction

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ABSTRACT

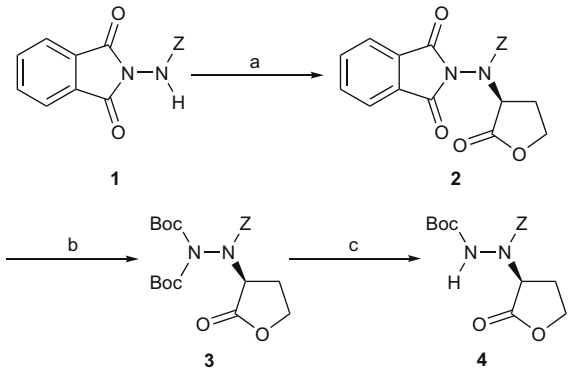
The synthesis of enantiomerically pure orthogonally protected δ-azaproline has been performed in five steps including two successive Mitsunobu reactions starting from benzyloxycarbonylaminophthalimide and the (*R*)-α-hydroxy-γ-butyrolactone.

1. Introduction

Among pseudopeptides and peptidomimetics, α-hydrazinopeptides have been used extensively for the elucidation of biological mechanisms.[1] From a structural point of view, the presence of an extra nitrogen in the backbone of a peptide chain generally induces specific conformations such as hydrazinoturn.[2] The family of azaprolines is of great interest in biology as several studies described dramatic conformational change and a concomitant alteration of biological response of α-azaproline-containing peptides.[3] Some syntheses of racemic δ-azaproline, a cyclic hydrazine analogous to proline, have been described in the literature.[4] However, none of them use α-hydrazinoacids as starting materials.[1,5] Carreira and co-workers reported that substituted Δ^2-pyrazoline, obtained via a dipolar cycloaddition of Me_3SiCHN_2 and camphor sultam-derived dipolarophiles, could give enantiomerically pure δ-azaprolines, after enantiomeric resolution.[6] Kim et al. have also synthesized enantiomerically pure δ-azaproline, as intermediate for the synthesis of a peptidic secondary structure mimetic, starting from malic acid.[7]

2. Results and discussion

A few years ago, we developed an easy and convenient method to replace a hydroxyl group by a hydrazino group by using a Mitsunobu[8] protocol using *N*-alkoxy-carbonylaminophthalimide derivatives as acidic partners. This pathway was used successfully in the synthesis of enantiomerically pure bis-nitrogen containing analogues such as α-hydrazinoacid and *N*-aminodipeptide derivatives.[9] We thought that the same kind of protocol could be adapted to obtain enantiomerically pure δ-azaproline. The main difficulty of this work was to find the appropriate alcohol partner of the Mitsunobu reaction. α-Hydroxy-γ-butyrolactone seemed to be the most suitable one as it was commercially available in an enantiomerically pure form and is not too hindered to allow the Mitsunobu substitution. As a result, we decided to perform the reaction between substituted *N*-benzyloxycarbonylaminophthalimide **1** with (*R*)-α-hydroxy-γ-butyrolactone via the Mitsunobu reaction. As this reaction proceeds with total inversion of configuration, we obtained the corresponding compound **2** in pure (*S*)-form with a very good yield of 80% (Scheme 1).



Scheme 1. Reagents and conditions: (a) (*R*)-α-hydroxy-γ-butyrolactone, DBAD, PPh_3, THF, rt, 80%; (b) (i) $MeNH_2$/MeOH, THF, rt; (ii) Boc_2O, cat. DMAP, THF, rt, 94%; (c) $Mg(ClO_4)_2$, CH_3CN, rt, 90%.

By using a two-step one-pot protocol reaction developed in the laboratory,[10] we were able to transform the phthalimide protecting group into a bis-*tert*-butyloxycarbonyl group to obtain compound **3**. One of the two *tert*-butyloxycarbonyl groups can also be removed by using $Mg(ClO_4)_2$.[11] This trans-protection allowed the introduction of a Boc protecting group on the nitrogen which is one of the most used protecting groups in amino acid and peptide

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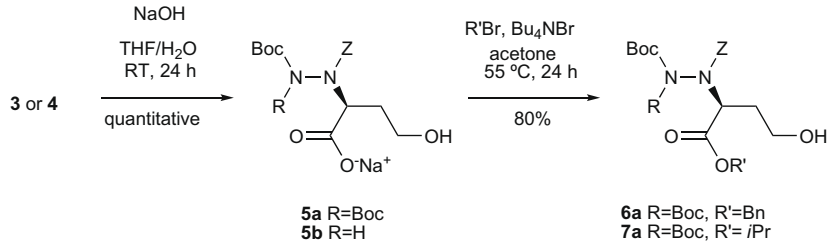
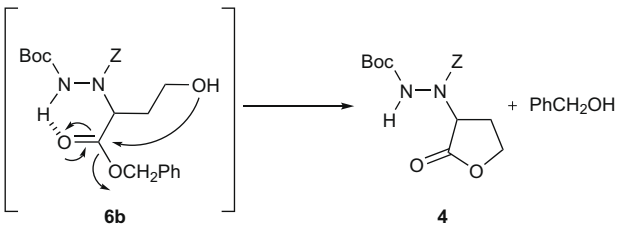


Scheme 2. Formation of carboxylates **5a**/**5b** and hydroxyesters **6a**/**7a**.

chemistry. As we chose a Z group to protect the *N*-aminophthalimide starting material, we obtained orthogonally protected compounds (Scheme 1).

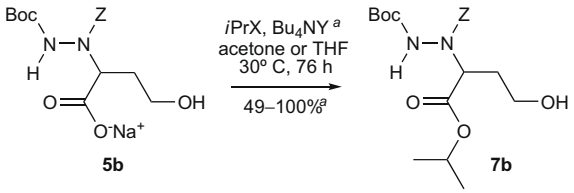
The next step consisted of finding the best conditions to open the lactone. Two possibilities were offered. The opening of the lactone can be performed either from bis-protected compound **3** or from mono-protected compound **4**. By using basic conditions, we were able to obtain the carboxylates **5a** and **5b** from lactone**s 3** or **4**, respectively, in quantitative yield. The greatest difficulty in this work was to find good conditions to transform the carboxylate groups of **5a** and **5b** in an ester group, stable enough to avoid retro reaction.[12] Starting from sodium salt **5a**, the esterification with benzyl bromide, in the dipolar aprotic solvent DMF, did not lead to the formation of benzyl ester **6a**. This was probably due to the low solubility of the carboxylate **5a** in DMF.[13] At the same time, the use of benzyl bromide in the presence of a catalytic amount of tetrabutylammonium bromide in acetone enabled us to obtain the corresponding stable benzyl ester **6a** (Scheme 2).[14]

Unfortunately, the Boc-monodeprotection of compound **6a** failed under whatever the conditions we used, catalytic or stoichiometric amounts of $Mg(ClO_4)_2$. Furthermore, using the same conditions of esterification on sodium salt **5b** gave the unwanted lactone **4**, quantitatively. An identical result was obtained when the Boc-monodeprotection of ester **6a** was carried out in basic conditions, using potassium carbonate in refluxing methanol.[15] In fact, we thought that the simultaneous presence of the free NH and the labile benzyl ester group was responsible for the retro lactonization (Scheme 3).



Scheme 3. Retro-lactonization of benzylester **6b**.

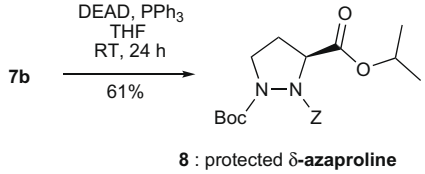
This problem could be prevented by replacing the benzyl ester group by the more stable isopropyl one. The corresponding isopropyl ester **7a** was obtained in 97% yield by adding 6 equiv of isopropyl bromide and a catalytic amount of tetrabutylammonium bromide in acetone at 55 °C (Scheme 2) to the carboxylate **5a**. Unfortunately, when the same reaction was applied to carboxylate **5b**, it led to the formation of a mixture of the desired ester **7b** (23%) and lactone **4**. A better yield (49%) was obtained when the esterification was performed at 30 °C. A quantitative amount of **7b** was finally produced when isopropyl iodide and tetrabutylammonium fluoride were used in THF at 30 °C (Scheme 4).[16]



[a] X = Br, Y = Br, acetone, 49%
X = I, Y = F, THF, 100%

Scheme 4. Formation of isopropyl ester **7b**.

The last step of the synthesis of orthogonally protected δ-azaproline **8** consisted of a cyclization, which was performed via an intramolecular Mitsunobu reaction between the hydroxyl and the NH groups of compound **7b**. As we demonstrated before, the introduction of a hydrazine function on a molecule via an intermolecular Mitsunobu protocol necessitated the use of a hydrazine bearing three electron-withdrawing groups, which contributed to a decrease in the pK_a of the sole NH group around 11.[9b] For this reason, very good yields were obtained when *N*-alkoxy or benzyloxy carbonylaminophthalimides were used as acidic partner. On the contrary, no reaction occurred when only two electron-withdrawing groups were present on the hydrazino acidic partner. As intramolecular processes are generally easier to perform when compared to intermolecular ones, Mitsunobu reaction can give good results even if these rules are not respected. This behaviour was effectively described once in the literature for the synthesis of (*S*)-3-carbobenzoxyamino-1-amino-2-azetidinones.[17] Taking into account this result, we thought that the presence of only two electron-withdrawing groups, the Z and the Boc protecting groups, on compound **7b** could be sufficient to allow the substitution. Hence, by using classical Mitsunobu conditions we were able to obtain the desired enantiomerically pure protected δ-azaproline in 61% yield (Scheme 5).



Scheme 5. Formation of δ-azaproline.

3. Conclusion

In conclusion, we have developed a new and very convenient synthesis leading, in only five steps to orthogonally protected (*S*)-δ-azaproline with 41% overall yield. The presence of orthogonal protecting groups of both nitrogens allows the possibility of intro-

ducing this proline analogue into peptide chains either by the δ or by the ε nitrogen leading to different types of pseudopeptides. This work is currently under active investigation.

4. Experimental

4.1. General experimental

All reactions were carried out with dry solvents. Dry THF was obtained by distillation over sodium and benzophenone; MeCN and acetone were purchased in an anhydrous form. Reagents were obtained commercially and used without further purification. Reactions were monitored by Thin Layer Chromatography (TLC) using Kieselgel 60 with fluorescent indicator UV_{254} (purchased from Merck or Macherey-Nagel). Detection was performed by UV, phosphomolybdic acid or ninhydrine. Columns chromatography was carried out on Silica Gel 60 (70–200 μm). All yields have been calculated from pure isolated products. ^1H and ^{13}C NMR spectra were recorded on a spectrometer operating at 300 MHz, in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent signal for deuterated DMSO or to the signal of tetramethylsilane (TMS) as internal standard. Coupling constants (J values) are given in hertz. Peaks are described using the following abbreviations: br, broad; s, singlet; t, triplet; m, multiplet. HRMS spectra were obtained in ESI method. All melting points are uncorrected. $[\alpha]_D$ is given in units of deg dm^{-1} cm^2 g^{-1}; concentrations are quoted in g/100 mL.

4.2. (*S*)-α-(*N*-Benzyloxycarbonylaminophthamilido)-γ-butyrolactone 2

To a solution of compound **1** (5.15 g, 17.40 mmol), triphenylphosphine (5.48 g, 20.90 mmol) and (*R*)-α-hydroxy-γ-butyrolactone (1.36 mL, 17.40 mmol) in dry THF (80 mL), under nitrogen, were added, in one portion, di-*tert*-butyl azodicarboxylate (4.80 g, 20.90 mmol) with stirring at 0 °C. The resulting solution was stirred at room temperature for 4 h and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of petroleum ether and ethyl acetate as eluant to give butyrolactone **2** (5.29 g, 80%) as a white solid, mp = 136 °C. $[\alpha]_D^{22} = -2.6$ (*c* 0.760, EtOH). R_f = 0.27 (EP/EtOAc 6/4). IR (KBr) ν 1800, 1780, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.85–7.70 (m, 4H, H_{Pht}), 7.35–6.90 (m, 5H, H_{arom}), 5.25–4.91 (m, 2H, OCH_2), 4.82–4.68 (t, *J* 10.5 Hz, 1H, $CHCH_2$), 4.42–4.27 (m, 1H, OCH_2), 4.27–4.05 (m, 1H, OCH_2), 2.79–2.40 (m, 2H, $CHCH_2$). ^{13}C NMR ($CDCl_3$) δ 171.8 (CO), 165.8 (CO), 155.3 (CO), 154.0 (CO), 135.7 (CH), 135.6 (CH), 130.5 (C), 130.2 (2C), 129.2 (2CH), 129.1 (2CH), 127.9 (CH), 124.8 (CH), 124.7 (CH), 69.5 (OCH_2), 66.1 (OCH_2), 59.1 (CH), 28.1 (CH_2). ESI calcd for $C_{20}H_{16}N_2O_6$ $[M+Na]^+$ *m/z* = 403.0901, found 403.0886.

4.3. (*S*)-α-[N^{α}-(Benzyloxycarbonyl)-N^{β},N^{β}-bis(*tert*-butyloxycarbonyl)hydrazino]-γ-butyrolactone 3

To a solution of compound **2** (1.90 g, 5.00 mmol) in THF (100 mL) was added at room temperature a solution of methylamine (2 M) in MeOH (3.75 mL, 7.50 mmol). The mixture was stirred at room temperature for 1 h. The solvent and the excess of methylamine were removed in vacuo. The white solid obtained was dissolved in THF (100 mL) and di-*tert*-butyl dicarbonate (3.27 g, 15.00 mmol) and a catalytic amount of 4-dimethylaminopyridine were added. The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of petroleum ether and ethyl acetate as eluant to give butyrolactone **3** (2.12 g, 94%) as a yellow oil. $[\alpha]_D^{22} = -2.5$ (*c* 1.180, EtOH). R_f = 0.44 (EP/EtOAc 7/3). IR (NaCl) ν 1792, 1767, 1726 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.22 (m, 5H, H_{arom}), 5.31–5.14 (m, 2H, OCH_2), 4.54–4.32 (m, 2H, OCH_2), 4.32–4.07 (m, 1H, $CHCH_2$), 2.79–2.45 (m, 2H, $CHCH_2$), 1.61–1.26 (m, 18H, 2 $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 171.6 (CO), 154.3 (CO), 151.0 (CO), 150.8 (CO), 136.1 (C), 129.2 (2CH), 129.0 (CH), 128.7 (2CH), 85.4 (C), 85.3 (C), 69.1 (OCH_2), 66.1 (OCH_2), 59.9 (CH), 28.5 ($6CH_3$), 27.2 (CH_2). ESI calcd for $C_{22}H_{30}N_2O_8$ $[M+Na]^+$ *m/z* = 473.1894, found 473.1891.

4.4. (*S*)-α-[N^{α}-(Benzyloxycarbonyl)-N^{β}-(*tert*-butyl-oxycarbonyl)-hydrazino]-γ-butyrolactone 4

To a solution of compound **3** (1.55 g, 3.4 mmol) in CH_3CN (40 mL) was added magnesium perchlorate (150.00 mg, 0.68 mmol). The solution was stirred at room temperature overnight and then partitioned between water (100 mL) and diethylether (50 mL). The aqueous layer was extracted with diethylether (2×50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of petroleum ether and ethyl acetate (7/3) as eluant to give butyrolactone **4** (1.07 g, 90%) as a white solid, mp = 103 °C. $[\alpha]_D^{22} = -2.9$ (*c* 1.050, EtOH). R_f = 0.40 (EP/EtOAc 7/3). IR (KBr) ν 3263, 1781, 1742, 1701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.53–7.00 (m, 5H, H_{arom}), 6.52 (br s, 1H, N*H*), 5.43–4.75 (m, 3H, $CHCH_2$ and OCH_2), 4.40–4.08 (m, 2H, OCH_2), 2.61–2.29 (m, 2H, $CHCH_2$), 1.52–1.15 (m, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 172.9 (CO), 155.0 (CO), 154.8 (CO), 134.8 (C), 128.0 (2CH), 127.9 (CH), 127.5 (2CH), 81.6 (C), 68.3 (OCH_2), 65.3 (OCH_2), 57.4 (CH), 27.3 ($3CH_3$), 25.3 (CH_2). ESI calcd for $C_{17}H_{22}N_2O_6$ $[M+Na]^+$ *m/z* = 373.1370, found 373.1370.

4.5. Benzyl 2-[N^{α}-(benzyloxycarbonyl)-N^{β},N^{β}-bis-(*tert*-butyloxycarbonyl)hydrazino]-4-hydroxybutanoate 6a

To a solution of compound **3** (180 mg, 0.40 mmol, racemic mixture) in THF/H_2O (6 mL, 1:1) was added at room temperature a 1 M aqueous solution of sodium hydroxide (0.40 mL, 0.40 mmol). The mixture was stirred at room temperature for 24 h and concentrated in vacuo. The resultant white solid was suspended in toluene and concentrated to remove traces of water to give sodium carboxylate salt **5a**. Acetone (10 mL), tetrabutylammonium bromide (7.00 mg, 0.02 mmol) and a solution of benzyl bromide (0.05 mL, 0.44 mmol) in acetone (1 mL) were added. After stirring at reflux for 24 h, the reaction mixture was cooled and concentrated. The residue was partitioned between ethyl acetate (25 mL) and 0.5 M aqueous sodium bisulfate (10 mL). The organic phase was washed with portions of saturated aqueous sodium bicarbonate (1×10 mL) and brine (1×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of petroleum ether and ethyl acetate as eluant to give ester **6a** (178 mg, 80%) as an oil. R_f = 0.61 (EP/EtOAc 8/2). IR (NaCl) ν 3322, 1741 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45–7.25 (m, 10H, H_{arom}), 6.49 (br s, 1H, O*H*), 5.32–4.88 (m, 5H, $CHCH_2$ and $2OCH_2$), 4.43–4.10 (m, 2H, OCH_2), 2.40–2.22 (m, 1H, $CHCH_2$), 2.20–2.05 (m, 1H, $CHCH_2$), 1.50–1.27 (m, 18H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ 171.5 (CO), 157.0 (CO), 155.7 (CO), 154.0 (CO), 136.3 (C), 135.8 (C), 129.4–127.6 (10CH), 82.6 (2C), 69.2 (CH_2), 68.1 (CH_2), 64.1 (OCH_2), 58.6 (CH), 28.7 ($2CH_3$), 28.4 ($4CH_3$), 28.4 (CH_2). ESI calcd. for $C_{29}H_{38}N_2O_9$ $[M+Na]^+$ *m/z* = 581.2470, found 581.2470.

4.6. Isopropyl 2-[N^{α}-(benzyloxycarbonyl)-N^{β},N^{β}-bis-(*tert*-butyloxycarbonyl)hydrazino]-4-hydroxybutanoate 7a

To a solution of compound **3** (180 mg, 0.40 mmol, racemic mixture) in THF/H_2O (6 mL, 1:1) was added at room temperature, a

1 M aqueous solution of sodium hydroxide (0.40 mL, 0.40 mmol). The mixture was stirred at room temperature for 24 h and concentrated in vacuo. The resultant white solid was suspended in toluene and concentrated to remove trace of water to give sodium carboxylate salt **5a**. Acetone (10 mL), tetrabutylammonium bromide (7.00 mg, 0.02 mmol) and isopropyl bromide (0.22 mL, 2.4 mmol) were added. After stirring at reflux for 24 h, the reaction mixture was cooled and concentrated. The residue was partitioned between ethyl acetate (25 mL) and 0.5 M aqueous sodium bisulfate (10 mL). The organic phase was washed with portions of saturated aqueous sodium bicarbonate (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give ester **7a** (198 mg, 97%) as a yellow oil. R_f = 0.37 (EP/EtOAc 8/2). IR (NaCl) ν 3334, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.27 (m, 5H, H_{arom}), 6.54 (br s, 1H, O*H*), 5.35–4.75 (m, 4H, *CH*CH_2, O*CH*$_2$ and *CH*$(CH_3)_2$), 4.43–4.10 (m, 2H, O*CH*$_2$), 2.39–2.20 (m, 1H, CH*CH*$_2$), 2.20–1.95 (m, 1H, CH*CH*$_2$), 1.67–1.30 (m, 18H, C(*CH*$_3)_3$), 1.30–1.08 (m, 6H, CH(*CH*$_3)_2$). ^{13}C NMR ($CDCl_3$) δ 171.1 (CO), 157.2 (CO), 154.0 (2CO), 136.3 (C), 129.1 (2CH), 128.9 (CH), 128.5 (2CH), 82.6 (2C), 70.3 (CH), 69.1 (CH_2), 64.2 (OCH_2), 58.5 (CH), 28.7 (CH_2), 28.7 ($2CH_3$), 28.4 ($4CH_3$), 22.4 ($2CH_3$). ESI calcd for $C_{25}H_{38}N_2O_9$ $[M+H]^+$ m/z = 511.2650, found 511.2624.

4.7. Isopropyl (2*S*)-2-[N^{α}-(benzyloxycarbonyl)-N^{β}-(*tert*-butyloxycarbonyl)hydrazino]-4-hydroxybutanoate 7b

To a solution of compound **4** (140 mg, 0.40 mmol) in a mixture of THF/H_2O (6 mL, 1:1) was added at room temperature a 1 M aqueous solution of NaOH (0.40 mL, 0.40 mmol). The mixture was stirred at room temperature for 24 h and concentrated in vacuo. The resultant white solid was suspended in toluene and concentrated to remove trace of water to give sodium carboxylate salt **5b**. THF (1.50 mL), tetrabutylammonium fluoride (0.48 mL, 0.48 mmol) and isopropyl iodide (0.05 mL, 0.48 mmol) were added. The solution was heated at 30 °C for 76 h. The reaction mixture was cooled and concentrated. The residue was partitioned between ethyl acetate (25 mL) and 0.5 M aqueous sodium bisulfate (10 mL). The organic phase was washed with portions of 0.5 M aqueous sodium bisulfate (2 × 10 mL), saturated aqueous sodium bicarbonate (3 × 10 mL) and brine (3x10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give ester **7b** (164 mg, 100%) as a yellow oil. $[\alpha]_D^{22} = -0.7$ (*c* 1.360, EtOH). R_f = 0.37 (EP/EtOAc 8/2). IR (NaCl) ν 3337, 3322, 1731 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.00 (br s, 1H, N*H*), 7.35–7.32 (m, 5H, H_{arom}), 5.33–5.06 (m, 2H, O*CH*$_2$), 5.06–4.76 (m, 2H, *CH*CH_2 and *CH*$(CH_3)_2$), 4.51 (br s, 1H, O*H*), 3.69–3.47 (m, 2H, O*CH*$_2$), 1.98–1.68 (m, 2H, CH*CH*$_2$), 1,52.1.24 (m, 9H, C(*CH*$_3)_3$), 1.24–1.05 (m, 6H, CH(*CH*$_3)_2$). ^{13}C NMR (DMSO-d_6) δ 170.1 (CO), 155.4 (3CO), 136.2 (C), 128.2 (2CH), 127.8 (CH), 127.2 (2CH), 79.6 (C), 68.3 (CH), 67.0 (OCH_2), 57.9 (CH), 57.2 (OCH_2), 31.4 (CH_2), 27.9 ($3CH_3$), 21.4 (CH_3), 21.3 (CH_3). ESI calcd for $C_{20}H_{30}N_2O_7$ $[M+H]^+$ m/z = 411.2126, found 411.2098.

4.8. Isopropyl (3*S*)-3-[2-(benzyloxycarbonyl)-(*tert*-butyloxycarbonyl)pyrazolidine]-carboxylate 8

To a solution of compound **7b** (266 mg, 0.66 mmol) and triphenylphosphine (259.00 mg, 0.99 mmol) in dry THF (10 mL), under nitrogen, was added, in one portion, diethyl azodicarboxylate (170.00 mg, 0.99 mmol) with stirring at 0 °C. The resulting solution was stirred at room temperature overnight and concentrated in vacuo. The residue was chromatographed on silica gel with a mixture of petroleum ether and ethyl acetate as eluant to give (*S*)-δ-azaproline **8** (156 mg, 61%) as an oil. $[\alpha]_D^{22} = -12.94$ (*c* 0.850, EtOH). R_f = 0.62 (EP/EtOAc 70/30). IR (NaCl) ν 1708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39–7.27 (m, 5H, H_{arom}), 5.27–5.13 (m, 2H, O*CH*$_2$), 5.13–4.90 (m, 1H, *CH*$(CH_3)_2$), 4.72–4.58 (br s, 1H, *CH*CH_2), 4.07 (br s, 1H, N*CH*$_2$), 3.22–3.20 (br s, 1H, N*CH*$_2$), 2.43–2.14 (m, 2H, CH*CH*$_2$), 1.52–1.30 (m, 9H, C(*CH*$_3)_3$), 1.30–1.10 (m, 6H, CH(*CH*$_3)_2$). ^{13}C NMR ($CDCl_3$) δ 170.6 (CO), 156.9 (2CO), 136.6 (C), 129.1 (2CH), 128.7 (CH), 128.5 (2CH), 82.2 (C), 69.7 (CH), 68.6 (OCH_2), 60.4 (CH), 46.9 (NCH_2), 31.0 (CH_2), 28.6 ($3CH_3$), 22.3 ($2CH_3$). ESI calcd for $C_{20}H_{28}N_2O_6$ $[M+Na]^+$ m/z = 415.1840, found 415.1840.

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References

1. Marraud, M.; Vanderesse, R.. In *Synthesis of Peptides and Peptidomimetics*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Houben-Weyl: Stuttgart, 2003; Vol. E22c, pp 423–453.
2. (a) Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Stérin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793–801; (b) Zerkout, S.; Dupont, V.; Aubry, A.; Vidal, J.; Collet, A.; Vicherat, A.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *44*, 378–387; (c) Aubry, A.; Mangeot, J. P.; Vidal, J.; Collet, A.; Zerkout, S.; Lecoq, A.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 305–311; (d) Marraud, M.; Boussard, G.; Vanderesse, R.; Collet, A.; Vidal, J.; Aubry, A. *Actualités Chim. Thér. 22nd Ser.* **1996**, 67–82.
3. (a) Zhang, W. J.; Berglund, A.; Kao, J. L. F.; Couty, J. P.; Gershengorn, M. C.; Marshall, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 1221–1235; (b) Che, Y.; Marshall, G. R. *J. Org. Chem.* **2004**, *69*, 9030–9042; (c) Che, Y.; Marshall, G. R. *J. Med. Chem.* **2006**, *49*, 11–124.
4. (a) Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 2199–2204; (b) Moody, C. J.; Pearson, C. J.; Lawton, G. *Perkin Trans. I* **1987**, 885–897; (c) Kanemasa, S.; Tomoshige, N.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3944–3949.
5. For recent preparations of α-hydrazino acid derivatives, see: (a) Bouillon, I.; Brosse, N.; Vanderesse, R.; Jamart-Grégoire, B. *Tetrahedron* **2007**, *63*, 2223–2234; (b) Oguz, U.; Guilbeau, G. G.; McLaughlin, M. L. *Tetrahedron Lett.* **2002**, *43*, 2873–2875; (c) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845–6847.
6. Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379–8380.
7. Kim, H.-O.; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935–4938.
8. Mitsunobu, O. *Synthesis* **1981**, 1–28.
9. (a) Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Org. Chem.* **2000**, *65*, 4370–4374; (b) Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem.* **2001**, *66*, 2869–2873.
10. Brosse, N.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2001**, *43*, 249–251.
11. Stafford, J. A.; Brackeen, M. F.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873–7876.
12. Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839–9846.
13. Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3775–3782.
14. Weber, A. E.; Halgren, T. A.; Doyle, J. J.; Lynch, R. J.; Siegl, P. K. S.; Parsons, W. H.; Grennlee, W. J.; Patchett, A. A. *J. Med. Chem.* **1991**, *34*, 2692–2701.
15. Schlosser, M.; Heiss, C.; Marzi, E.; Scopelliti, R. *Eur. J. Org. Chem.* **2006**, 4398–4404.
16. Wu, C. Y.; Brik, A.; Wang, S. K.; Chen, Y. H.; Wong, C. H. *ChemBioChem* **2005**, *6*, 2176–2180.
17. Iwagami, H.; Yasuda, N. *Heterocycles* **1990**, *31*, 529–536.