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An efficient synthesis of optically pure α-alkyl-β-azido- and α-alkyl-β-aminoalanines via ring opening of 3-amino-3-alkyl-2-oxetanones

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Abstract—*N*-Boc-α-alkylserine β-lactones on ring opening with sodium azide provide *N*-Boc-α-alkyl-β-azidoalanines, as N-protected amino acids are suitable for direct incorporation into peptides. *N*-Boc-α-alkyl-β-azidoalanines can be transformed by catalytic hydrogenation into the corresponding *N*-Boc-α-alkyl-β-aminoalanines.

1. Introduction

α,α-Disubstituted amino acids are often found in Nature either in free form or as constituents of biologically active natural products. Examples are peptaibol antibiotics such as alamethicine or emermicines,[1] and alkaloids with selective cytotoxicity against murine solid tumours like tantazole B.[2] Quaternary α-amino acids are an important class of compounds since they can induce physical and chemical changes in peptides. The amide linkages formed with these units are extremely resistant to both chemical and enzymatic hydrolyses.[3] The biological significance and synthetic utility of α,α-disubstituted amino acids continue to stimulate the development of new routes to these compounds. Synthetic α-substituted serine analogues have been widely applied in the synthesis of bioactive compounds such as salinosporamide A, a highly cytotoxic proteasome inhibitor,[4] endogenous opioid peptides (Leu-enkephalin,[5] deltorphin I[6] and endomorphin 2[7]) and cyclolinopeptide A analogues,[8] as well as a potent agonist of group II metabotropic glutamate receptor (+)LY-354740.[9] The α-hydroxymethylamino acids (α-alkyl serines) are readily available via the selective α-hydroxymethylation of proteinogenic amino acids.[10] Enantiomerically pure α,α-disubstituted amino acids have gained increasing interest as useful building blocks for enzyme inhibitors.[11]

In our laboratory, we have studied the synthesis of constrained amino acid building blocks and their incorporation into biologically active peptide analogues.[5–8] Recently, we reported the synthesis of optically pure 3-amino-3-alkyl-2-oxetanones **3** and the N-protected derivatives **2** of α-alkyl serines **1**.[12] We have proved that these β-lactones are useful starting materials for further derivatization yielding potentially interesting building blocks for medicinal chemistry. For example, the ring opening of the alkylserine lactones **2** with soft sulfur nucleophiles resulted in the corresponding S-protected *N*-Boc-α-alkylcysteines.[13]

Herein, we exemplify the use of the β-lactones of α-alkylserines in the preparation of N-protected α-alkyl-β-azidoalanines **4** and α-alkyl-β-aminoalanines **6**, as well as the free α-alkyl-β-azidoalanines **5**. Scheme 1 outlines our approach towards the preparation of α-alkyl-β-azido- and α-alkyl-β-aminoalanines. Recently, several approaches to the preparation of derivatives of α-alkyl-β-azidoalanines have been described. These include asymmetric syntheses based on ring opening of 2-alkylaziridine-2-carboxylates[14] or cyclic sulfonamides[15] with azide or by substitution of halogenated bis-lactim ethers with azide.[16]

Keywords: α-Alkyl-β-azidoalanines; α-Alkyl-β-aminoalanines; *N*-Boc-α-alkylserine β-lactones; α,α-Disubstituted amino acids; Mitsunobu reaction.
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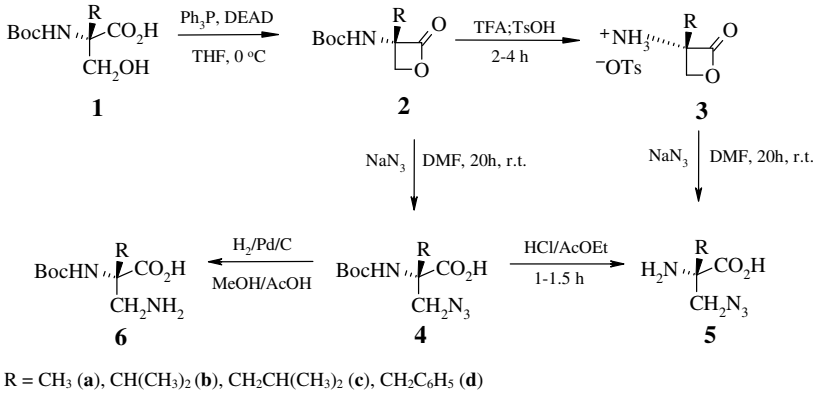

Scheme 1. Synthesis of α-alkyl-β-azido- and β-aminoalanines.

Our method involves transformation of the *N*-Boc-α-alkylserines into β-lactones under modified Mitsunobu reaction conditions, followed by ring opening with sodium azide and further reduction of the azide group by catalytic hydrogenation. This method allowed us to obtain novel N^{α}-protected, α,α-disubstituted amino acids. Previously, 3-amino-2-oxetanone (R = H, serine β-lactone) and their N-protected derivatives were used in the synthesis of optically pure N-protected and free β-substituted alanines.[17,18]

The starting *N*-Boc-α-alkylserine lactones **2a–d** were synthesized as described previously.[12] The ring opening of *N*-Boc-α-methylserine lactone **2a** with sodium azide resulted in the formation of *N*-Boc-α-methyl-β-azidoalanine **4a** in 98% yield. Deprotection of the amine group of **4a** proceeded efficiently with 2 N HCl in ethyl acetate and afforded free amino acid **5a** in 88% yield (86% for two steps) without any side products. It is worth noting that according to Vederas and co-workers,[18] N-protected-β-azidoalanines are sensitive to most common deprotection conditions and the free β-azidoalanine can be obtained by ring opening of serine β-lactone with sodium azide. On the other hand, Kogan and Rawson used a TFA/CH_2Cl_2 mixture for Boc removal from Boc-azidoalanine benzyl ester without decomposition of the azide group.[19] Treatment of the *p*-toluenesulfonic acid salt of 3-amino-3-methyl-2-oxetanone (**3a**) with sodium azide gave free α-methyl-β-azidoalanine **5a** in 50% yield (overall yield 40% calculated from Boc-α-methylserine lactone **2a**).

We prepared azidoamino acids **5a–d** by opening of *N*-Boc-α-alkylserine lactones **2a–d** using sodium azide (95–98%) followed by N-deprotection resulting in azides **5a–d** in good to excellent yields (70–88%). The azide group in compounds **4a–d** and **5a–d** exhibits a characteristic IR absorbance band[20] between 2090 and 2120 cm^{-1}.

Azides **4a–d** were efficiently transformed into the corresponding free amines **6a–d**. Catalytic hydrogenation[21] yielded the *N*-Boc-α-alkyl-β-aminoalanines as useful, new building blocks, in 70–96% yields. Examples are presented in Table 1.

Table 1. Yields (%) of *N*-Boc-**4**, free α-alkyl-β-azidoalanine **5** and N^{α}-Boc-α-alkyl-β-aminoalanines **6**

R	4	5	6
CH_3 (**a**)	98	88	96
$CH(CH_3)_2$ (**b**)	97	70	76
$CH_2CH(CH_3)_2$ (**c**)	95	85	78
$CH_2C_6H_5$ (**d**)	98	83	70

2. General procedure for the preparation of (*S*)-2-alkyl-2-*N*-(*tert*-butyloxycarbonyl)-amino-3-azidopropionic acids (*N*-Boc-α-alkyl-β-azidoalanines 4)

Sodium azide (3 mmol) was added to a solution of *N*-Boc-α-alkyl-serine-β-lactone **2** (1 mmol) dissolved in 2 mL of dry DMF, and the mixture was stirred for 20 h at room temperature. DMF was removed in vacuo at 30 °C and the residue was dissolved in water, acidified to pH 3 with 1 N $NaHSO_4$ and extracted with AcOEt (3 × 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The crude material (yields 95–98%) was chromatographically pure and could be used without further purification. All the new compounds were characterized on the basis of ^1H, ^{13}C NMR and IR data.[22]

3. General procedure for the preparation of 2-alkyl-2-amino-3-azidopropionic acids (α-alkyl-β-azidoalanines 5)

A solution of 2-alkyl-2-*N*-Boc-amino-3-azidopropionic acid **4** (1 mmol) in AcOEt (1 mL) was treated with 2.5 N HCl in AcOEt (2 mL). The mixture was stirred for 1–1.5 h (TLC indicated the consumption of starting material) and then evaporated. The residue was dissolved in water, applied to an ion-exchange column (Amberlyst 15 in H^+ form) and eluted with MeOH/water (1:1) until the pH became neutral, followed by 25% ammonium hydroxide–MeOH–H_2O (1:2:2). The fractions, which gave a positive ninhydrin test, were collected. Evaporation of the chromatographically pure fractions in vacuo provided free amino acids[23] in 70–88% yields.

4. General procedure for the preparation of N^{β}-Boc-2-alkyl-2,3-diaminopropionic acids (N^{α}-Boc-α-alkyl-β-aminoalanines 6)

2-Alkyl-2-*N*-Boc-amino-3-azidopropionic acid **4** (1 mmol) was hydrogenated in 10 mL of methanol and 0.7 ml of AcOH in the presence of 60 mg of 10% Pd/C catalyst for 5–6 h at 1 atm. The mixture was filtered, and the filtrate concentrated in vacuo to give an oily residue. This was dissolved in water (for **6a**–**c**) or 5% AcOH (in the case of **6d**), washed with *n*-hexane (2 × 10 ml) and the aqueous phase evaporated in vacuo to give a white chromatographically pure solid,[24] in 70–96% yields.

In conclusion, we have demonstrated the utility of *N*-Boc-α-alkylserine lactones for the synthesis of novel, non proteinogenic multifunctional α,α-disubstituted amino acid derivatives. N-Protected α-alkyl-β-azidoalanines are excellent surrogates of α-alkyl-β-aminoalanines in peptide synthesis. *N*-Boc-α-alkyl-β-azidoalanines are suitable for direct incorporation into peptide chains using coupling methods for hindered residues.[25] The azido group can be reduced to an amino group in the last step of the peptide synthesis. Although asymmetric syntheses of free α-substituted α,β-diaminopropionic acids or precursors have been described earlier,[26–28] the incorporation of these residues into a peptide chain required masking of the side chain amino function. Efficient orthogonal protection of two amino groups in α-substituted α,β-diaminopropionic acids can be challenging. Our method enables diversification in the synthesis of peptides containing multifunctional α,α-disubstituted amino acids.

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22. Spectral data: **4a** (*N*-Boc-α-methyl β-azidoalanine)[29] white solid; mp108–110 °C (dec); $[\alpha]_D^{20}$ −10.4 (*c* 1, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) *δ*: 1.46 (s, 9H) Boc; 1.57 (s, 3H) CH_3; 3.79 (d, $^2J = 11.5$ Hz, 1H) –CH_2–N_3, 3.88 (d, $J = 11.5$ Hz, 1H) –CH_2–N_3; ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 21.6; 28.2; 54.3; 59.8; 80.5; 154.4; 176.8; **4b** (*N*-Boc-α-*iso*-propyl-β-azidoalanine) colourless oil, $[\alpha]_D^{20}$ −71.0 (*c* 1, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) 1.00 (d, $J = 7.5$ Hz, 6H) (CH_3)$_2$–CH; 1.45 (s, 9H) Boc; 2.40–2.53 (m, 1H) –CH═; 3.87 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 4.19 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 5.48 (s, 1H) –NH–; ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 17.3; 17.5; 28.3; 32.3; 51.9; 66.7; 80.2; 154.6; 175.1; **4c** (*N*-Boc-α-*iso*-butyl-β-azidoalanine) colourless oil, $[\alpha]_D^{20}$ −23.5 (*c* 1, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) *δ*: 0.87 (d, $J = 7.5$ Hz, 3H) (CH_3)$_2$–CH; 0.95 (d, $J = 7.5$ Hz, 3H) (CH_3)$_2$–CH; 1.45 (s, 9H) Boc; 1.56–1.71 (m, 2H) –CH_2–CH; 2.22–2.26 (m, 1H) ═C*H*–CH_2; 3.48 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 4.20 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 5.66 (s, 1H) –NH–; ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.0; 23.4; 28.3; 40.7; 54.5; 63.8; 80.1; 154.0; 176.3; **4d** (*N*-Boc-α-benzyl-β-azidoalanine) colourless oil, $[\alpha]_D^{20}$ −32.7 (*c* 1, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) *δ*: 1.47 (s, 9H) Boc; 3.01 (d, $J = 15$ Hz, 1H) –CH_2–C_6H_5; 3.36 (d, $J = 15$ Hz, 1H) –CH_2–C_6H_5; 3.63 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 3.94 (d, $J = 12.5$ Hz, 1H) –CH_2–N_3; 7.12–7.68 (m, 5H) C_6H_5; ^{13}C NMR(75 MHz, $CDCl_3$) *δ*: 29.6; 36.2; 54.2; 81.9; 125.5; 127.7; 125.5; 134.9; 154.4; 177.9.
23. Spectral data: **5a** ((*S*)-α-methyl-β-azidoalanine) white solid; mp 128–130 °C (dec); $[\alpha]_D^{20}$ 51.5 (*c* 1, MeOH); ^{1}H NMR (250 MHz, D_2O) *δ*: 1.36 (s, 3H) –CH_3; 3.40 (d, $J = 13.5$ Hz, 1H) –CH_2–N_3; 3.72 (d, $J = 13.5$ Hz, 1H) –CH_2–N_3; ^{13}C NMR (75 MHz, D_2O) *δ*: 18.0; 53.8; 58.9; 172.8; **5b** ((*S*)-2-*iso*-propyl-β-azidoalanine) white solid; mp 122–124 °C (dec); $[\alpha]_D^{20}$ 22.6 (*c* 1, H_2O); ^{1}H NMR (250 MHz, D_2O) *δ*: 0.78 (d, $J = 7.0$ Hz, 6H) (CH_3)$_2$CH–; 1.96 (sept., $J = 7.0$ Hz, 1H) ═C*H*–; 3.48 (d, $J = 13.0$ Hz,

1H) –CH_2–N_3; 3.75 (d, $J = 13.0$ Hz, 1H) –CH_2–N_3; ^{13}C NMR (75 MHz, D_2O) δ: 13.8; 14.9; 29.6; 52.6; 65.7; 171.8; **5c** ((*S*)-2-*iso*-butyl-β-azidoalanine) white solid; mp 140–142 °C (dec); $[\alpha]_D^{20}$ 22.0 (*c* 1, H_2O); ^{1}H NMR (250 MHz, D_2O) δ: 0.85 (d, $J = 5.75$ Hz, 3H) $(CH_3)_2CH$–; 0.89 (d, $J = 5.5$ Hz, 3H) $(CH_3)_2CH$–; 1.62–1.78 (m, 3H) –CH_2–CH═; 3.52 (d, $J = 13.25$ Hz, 1H) –CH_2–N_3; 3.84 (d, $J = 13.25$ Hz, 1H) –CH_2–N_3; ^{13}C NMR (75 MHz, D_2O) δ: 19.9; 21.4; 21.8; 40.0; 54.2; 61.1; 172.0; **5d** ((*S*)-2-benzyl-β-azidoalanine) white solid; mp 139–141 °C (dec); $[\alpha]_D^{20}$ 44.7 (*c* 1, H_2O); ^{1}H NMR (250 MHz, D_2O) δ: 3.03 (d, $J = 17.0$ Hz, 1H) CH_2–C_6H_5; 3.15 (d, $J = 17.0$ Hz, 1H) CH_2–C_6H_5; 3.63 (d, $J = 17$ Hz, 1H) CH_2–N_3; 3.97 (d, $J = 17$ Hz, 1H) CH_2–N_3; 7.34 (m, 5H) C_6H_5; ^{13}C NMR (75 MHz, D_2O) δ: 28.9; 40.5; 51.5; 61.7; 125.5; 126.4; 127.2; 128.7; 171.9.

24. Spectral data: **6a** (*N*-Boc-(*S*)-α-methyl-β-aminoalanine) white solid, mp 197–199 °C (dec); $[\alpha]_D^{20}$ 10.2 (*c* 1, MeOH) ^{1}H NMR (250 MHz, D_2O–NaOD) δ: 1.22 (s, 3H) CH_3–; 1.40 (s, 9H) Boc; 2.75 (d, $J = 12.0$ Hz, 1H) –CH_2–NH_2; 2.89 (d, $J = 12.0$ Hz, 1H) –CH_2–NH_2; ^{13}C NMR (75 MHz, D_2O–NaOD) 23.0, 28.0, 44.4, 57.6, 78.9, 154.7, 179.6; **6b** (*N*-Boc-(*S*)-α-*iso*-propyl-β-aminoalanine) white solid, mp 145–147 °C (dec); $[\alpha]_D^{20}$ −4.4 (*c* 1, MeOH); ^{1}H NMR (250 MHz, D_2O–NaOD) δ: 0.80 (d, $J = 7.0$ Hz, 3H) $(CH_3)_2CH$–; 0.87 (d, $J = 6.8$ Hz, 3H) $(CH_3)_2CH$–; 1.20 (s, 9H) Boc; 1.87–2.04 (m, 1H) $(CH_3)_2CH$–; 2.71 (d, $J = 10.0$ Hz, 1H) –CH_2–NH_2; 2.99 (d, $J = 10.0$ Hz, 1H) –CH_2–NH_2; ^{13}C NMR (75 MHz, D_2O–NaOD) 13.3; 14.9; 27.9; 32.7; 45.1; 67.8; 79.2; 156.0; 179.1; **6c** (*N*-Boc-(*S*)-2-*iso*-butyl-β-aminoalanine) white solid, mp 136–138 °C (dec); $[\alpha]_D^{20}$ −4.9 (*c* 1, MeOH); ^{1}H NMR (250 MHz, D_2O–NaOD) δ: 0.77 (d, $J = 4.9$ Hz, 3H) $(CH_3)_2CH$–; 0.84 (d, $J = 5.1$ Hz, 3H) $(CH_3)_2CH$–; 1.39 (s, 9H) Boc; 1.48–1.59 (m, 3H) ═CH–CH_2–; 2.77 (d, $J = 13.5$ Hz, 1H) –CH_2–NH_2; 2.99 (d, $J = 13.5$ Hz, 1H) –CH_2–NH_2; ^{13}C NMR (75 MHz, D_2O–NaOD) 20.9; 20.8; 26.1; 28.0; 39.2; 44.5; 64.1; 79.9; 155.1; 179.2; **6d** (*N*-Boc-(*S*)-2-benzyl-β-aminoalanine) white solid, mp 147–149 °C (dec); $[\alpha]_D^{20}$ −118.8 (*c* 1, MeOH) ^{1}H NMR (250 MHz, D_2O–NaOD) δ: 1.42 (s, 9H) Boc; 2.92–3.29 (m, 4H) –CH_2–NH_2, CH_2–C_6H_5; 7.14–7.64 (m, 5H) C_6H_5; ^{13}C NMR (75 MHz, D_2O–NaOD) δ: 26.0; 36.5; 44.7; 65.9; 78.9; 123.9; 125.2; 126.6; 128.0; 133.2; 178.2.

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