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SYNTHESIS OF HYDROXYMETHYL SIDE-CHAINED α-AMINOXY DIAMIDE

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Unnatural polar α-aminoxy acid residue with proteingenous hydroxymethyl side chain, a building block of the peptidomimetic foldamer of α-aminoxy peptide, was synthesized starting from natural amino acid L-serine. The starting material, L-serine, undergoes a reaction sequence to produce compound 1 in three steps: (1) the neighboring carboxyl group participates in diazotization/bromination to transform the amino group to a bromo group, (2) the C-terminal carboxyl group is protected, and (3) bromide is S_N2-displaced by N-hydroxyl phthalimide to introduce a N–O bond. After several conventional deprotection/coupling reactions, compound 1 is easily transformed to an α-aminoxy diamide, which can be widely used in peptidomimetics design.

Keywords: α-Aminoxy acid; diazotization/bromination; neighboring carboxyl group participation; peptide synthesis; polar side chain

Since the first report of an unusual turn and helix structure (so-called α N–O turn and α N–O helix) adopted by α-aminoxy peptides,[1] a kind of peptidomimetic foldamer,[2] their conformational studies[3] and bioactivities[4] have widely attracted researchers' interest. Because of the importance of the natural amino acid side chains' function in biosystems, for example, participation in molecular recognition, the synthesis of chiral α-aminoxy acid residues with various side chains have been reported.[5] Herein, we report another synthetic strategy for hydroxymethyl side-chained α-aminoxy acid residue, which can be incorporated into aminoxy peptide backbones for peptidomimetic studies.

α-Aminoxy acid residues have an oxygen atom inserted between the amino group and α-carbon of the natural α-amino acid backbone (Fig. 1). As shown in Scheme 1, a retrosynthetic analysis of hydroxymethyl side-chained α-aminoxy acid residue illustrates that the building block can be synthesized from α,β-dihydroxyl propanoic acid (glyceric acid) or α-bromo-β-hydroxyl propanoic acid. Both intermediates can be synthesized from the natural amino acid L-serine conveniently. The literature reports usually adopted the strategy to transform L-serine to glyceric

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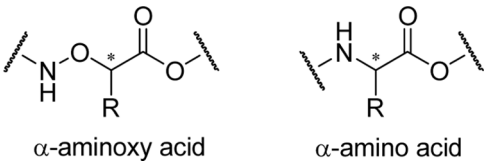


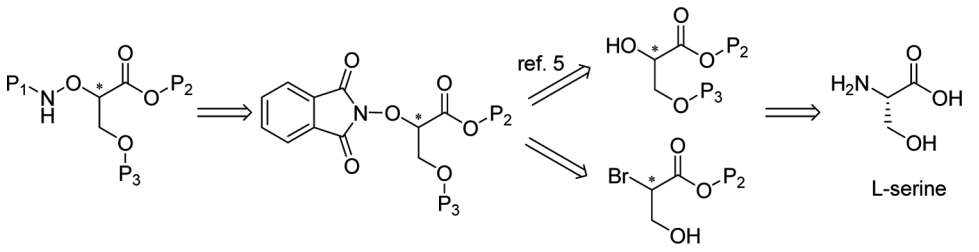
Figure 1. Chiral α-aminoxy acid residue.

acid with protected primary hydroxyl group, selectively protect the *C*-terminal carboxyl group, and introduce a N−O bond by the Mistunobu reaction.[5a,b]

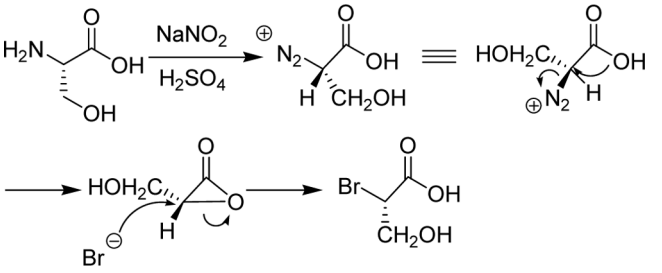
As shown in Scheme 2, the strategy to transform the amino group to a bromo group by diazotization/bromination provides α-bromo-β-hydroxyl propanoic acid, which can displace via the S_N2 mechanism without previously protecting the primary hydroxyl group of glyceric acid. Moreover, starting from L-serine, its carboxyl group as the neighboring group makes the retention of α-carbon's configuration while producing (*S*)-α-bromo-β-hydroxyl propanoic acid.[6]

Based on these two advantages, we prepared compound **1** in three sequential steps: (1) diazotization/bromination of L-serine, (2) protection of *C*-terminal carboxyl group by methyl ester, and (3) displacement of bromide by *N*-hydroxyl phthalimide via S_N2 mechanism to introduce an N−O bond in 44% yield over three steps (Scheme 3).

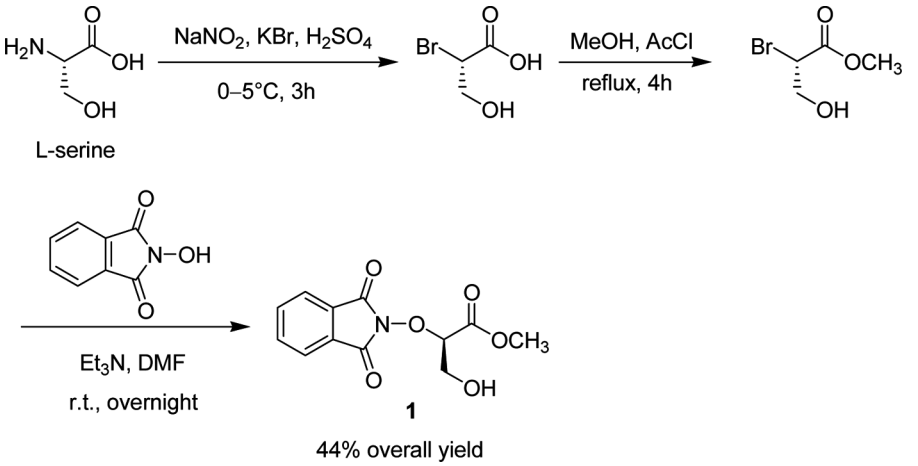
The primary hydroxyl group of compound **1** was then protected by *tert*-butyldimethyl chlorosilane (TBDMSCl) to produce compound **2** in 82% yield (Scheme 4). The protective groups of three functional groups of compound **2** can be removed under different reaction conditions. That means this building block can be incorporated into aminoxy peptide backbone by a conventional peptide synthesis procedure. To prove it, we synthesized the hydroxymethyl side-chained α-aminoxy acid monomer **5** from building block **2** with the general deprotection/coupling methods. As shown in Scheme 4, compound **2** was deprotected by hydrazine hydrate first to provide *N*-terminal free amine, which coupled with pivalyl chloride to produce compound **3**. Then, the *C*-terminal of compound **3** was deprotected by $LiOH \cdot H_2O$ O followed by coupling with isobutylamine using 1-hydroxy-7-azabenzotriazole (HOAt) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) as coupling reagent. At last, the TBDMS group bonded to the hydroxyl group was removed by tetra-*n*-butylammonium fluoride (TBAF) in 90% yield.



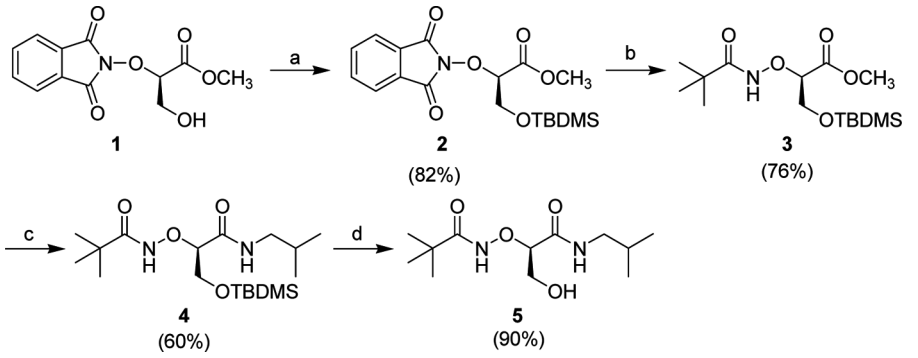
Scheme 1. Retrosynthetic analysis of aminoxy acid residue with hydroxymethyl side chain.



Scheme 2. Mechanism for retention of configuration through neighboring carboxyl group participation during the key diazotization/bromination sequence of L-serine.



Scheme 3. Three-step sequence to introduce N–O bond starting from L-serine, which reverses the α-carbon's configuration.



Scheme 4. Synthesis of α-aminoxy diamide **5** with hydroxymethyl side chain. Reagents and conditions: (a) TBDMSCl, DMAP, DMF, rt, overnight; (b) (i) $NH_2NH_2 \cdot H_2O$, MeOH, rt, 2.5 h; (ii) pivalyl chloride, K_2CO_3, CH_2Cl_2, 0 °C, 4 h; (c) (i) $LiOH \cdot H_2O$, H_2O/THF, rt, 2 h; (ii) isobutylamine, EDCI, HOAt, CH_2Cl_2, rt, overnight; and (d) TBAF, THF, rt, 2 h.

In conclusion, an α-aminoxy monomer with polar hydroxymethyl side chain was synthesized from L-serine in 15% overall yield. The first strategy contains three steps: neighboring carboxyl group participation in the diazotization/bromination of L-serine, carboxyl group protection, and introduction of an N−O bond by S_N2 displacement with *N*-hydroxyl phthalimide. This provides a convenient method to prepare both *N*-terminal and *C*-terminal protected α-aminoxy residue with polar hydroxymethyl side chains.

EXPERIMENTAL

All reagents and solvents for the reactions were of analytical grade and were dried and distilled if necessary. Flash-column chromatography was performed on Qing Dao Hai Yang silica gel 60 (230–400 mesh, ASTM) using ethyl acetate/*n*-hexane as eluting solvents. Optical rotations were measured with a Perkin-Elmer 341MC automatic polarimeter. NMR spectra were recorded on Jeol ECA-400 or Bruker DMX-400 instruments. Mass spectra were recorded with a Finningan MAT 95 or a Finnigan MAT 96 mass spectrometer for both low-resolution and high-resolution mass spectra.

(*R*)-Methyl 2-(*N*-Phthalimidoxy)-3-hydroxypropanoate (1)

Aqueous sulfuric acid (220 ml, 2.5 N) was added to the mixture of 10.5 g of L-serine (100 mmol) and 41.7 g of KBr (350 mmol) and cooled to 0 °C. A solution of $NaNO_2$ (10.9 g, 158 mmol) in 50 ml of water was added to this mixture dropwise while the reaction temperature was less than 5 °C. Then the mixture was stirred at 0 °C for 3 h. Upon completion, the reaction mixture was extracted with ethyl ether (50 ml × 3), dried over anhydrous $MgSO_4$, and concentrated. The crude product was dissolved in 80 ml of dried methanol. Eleven ml of acetyl chloride (156 mmol) were added dropwise to this mixture with stirring at room temperature. Then it was refluxed for 4 h, the volatiles were removed under vacuum, and the residue was dissolved in 100 ml of ethyl acetate. The organic solution was washed with saturated $NaHCO_3$ solution (30 ml) and brine (30 ml), dried over anhydrous $MgSO_4$, and concentrated to provide a colorless oil. This colorless oil was dissolved in 100 ml of DMF, and 16.0 g of *N*-hydroxy phthalimide (100 mmol) and 14 ml of triethylamine (100 mmol) were added to the solution. The mixture was then stirred at room temperature overnight. Upon completion, the solution was concentrated and purified by column chromatography to give **1** (11.62 g, 44%, over three steps) as colorless oil. $R_f = 0.30$ (EtOAc/hexane = 1:2); $[\alpha]_D^{20} + 55.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.80 (m, 4H), 4.76 (dd, $J = 4.8$, 2.5 Hz, 1H), 4.08–3.92 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 164.3, 135.2, 128.7, 124.2, 85.9, 60.8, 52.9; EI-MS (20 eV) *m/z* 148 (100), 266 ($M^+ + 1$, 1); HRMS-EI *m/z* for $C_{12}H_{11}NO_6$ (M^+) calcd. 265.0586, found 265.0612.

(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-2-(*N*-phthalimidoxy)propanoate (2)

To a solution of 9.40 g of compound **1** (35.4 mmol) in 80 ml of DMF, 9.8 ml of triethylamine (70.7 mmol), 0.31 g of DMAP (2.5 mmol), and 5.90 g of TBDMSCl

(39.2 mmol) were added. The mixture was stirred at room temperature overnight and then concentrated. The residue was purified by column chromatography to give **2** (11.02 g, 82%) as yellow solid. $R_f = 0.30$ (EtOAc/hexane = 1:6); mp 100.5–103.5 °C; $[\alpha]_D^{20} + 15.2°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.74 (m, 4H), 4.85 (t, $J = 5.5$ Hz, 1H), 4.15 (ABd, $J = 11.0$, 5.5 Hz, 2H), 3.82 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 163.1, 134.7, 128.9, 123.8, 85.9, 62.5, 52.6, 25.9, 25.6, 18.3, −5.4; ESI-MS *m/z* 274 (100); HRMS-ESI *m/z* for $C_{18}H_{25}NO_6SiNa$ ($M^+ + Na$) calcd. 402.1349, found 402.1368.

(*R*)-Methyl 3-(*tert*-Butyldimethylsilyloxy)-2-(*N*-pivaloylamidoxy)propanoate (3)

Hydrazine hydrate (24.0 mmol, 1.5 g, 80%) was added to a solution of 3.0 g of compound **2** (7.9 mmol) in 40 ml of methanol. The mixture was stirred at room temperature for 2.5 h and then concentrated. The residue was dissolved in 20 ml of CH_2Cl_2. The organic solution was washed with 3% $NaHCO_3$ aqueous solution (5 ml × 2), dried over anhydrous $MgSO_4$, and concentrated to provide colorless oil. This colorless oil was dissolved in 15 ml of CH_2Cl_2 and 8 ml of water. K_2CO_3 (2.51 g, 18.2 mmol) was added to the solution and cooled to 0 °C. Pivalyl chloride (1.25 ml, 10.2 mmol) was added to this mixture with vigorous stirring. The mixture was stirred at room temperature for 4 h, and then 20 ml of CH_2Cl_2 was added. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The mixture was concentrated and purified by column chromatography to give **3** (2.0 g, 76% over two steps) as colorless oil. $R_f = 0.30$ (EtOAc/hexane = 1:3); $[\alpha]_D^{20} + 50.0°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 4.54 (t, $J = 3.2$ Hz, 1H), 4.13–4.03 (m, 2H), 3.80 (s, 3H), 1.18 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 170.3, 84.2, 62.7, 52.1, 38.0, 27.1, 25.7, 18.2, −5.4; ESI-MS *m/z* 356 ($M^+ + Na$, 100), 274 (90); HRMS-ESI *m/z* for $C_{15}H_{31}NO_5SiNa$ ($M^+ + Na$) calcd. 356.1869, found 356.1883.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-(*N*-pivaloylamidoxy)-*N*-isobutylpropanamide (4)

$LiOH \cdot H_2O$ (190 mg, 4.5 mmol) was added to a solution of 501 mg of **3** (1.5 mmol) in 8 ml of THF and 1 ml of water. The mixture was stirred at room temperature over 2 h. Upon completion, the mixture was extracted by ethyl acetate (15 ml × 2). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in 10 ml of CH_2Cl_2. 1-Hydroxy-7-azobenzotriazole (HOAt, 264 mg, 1.9 mmol) and isobutyl amine (0.22 ml, 2.2 mmol) were added to this solution at room temperature. After stirring the reaction mixture for 5 min, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI, 431 mg, 2.2 mmol) was added and stirred overnight. Upon completion, the reaction mixture was washed by 0.5 N hydrochloride aqueous solution (10 ml), water (10 ml), saturated $NaHCO_3$ aqueous solution (10 ml), water (10 ml), and brine (10 ml); dried over anhydrous $MgSO_4$; and then concentrated. The crude product was purified by flash chromatography to give **4** (337 mg, 60% over two steps) as colorless oil. $R_f = 0.30$

(EtOAc/hexane = 1:3); $[\alpha]_D^{20} + 16.0°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.37 (s, br, 1H), 4.28–4.19 (m, 2H), 3.91 (dd, $J = 11.5$, 4.0 Hz, 1H), 3.14–3.05 (m, 2H), 1.84–1.79 (m, 1H), 1.20 (s, 9H), 0.93 (d, $J = 6.4$ Hz, 6H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 168.4, 86.5, 61.5, 46.4, 38.0, 28.2, 26.9, 19.9, −0.2; ESI-MS *m/z* 375 ($M^+ + 1$, 100), 274 (50); HRMS-ESI *m/z* for $C_{18}H_{39}N_2O_4Si$ ($M^+ + 1$) calcd. 375.2679, found 375.2695.

(*R*)-3-Hydroxy-2-(*N*-pivaloylamidoxy)-*N*-isobutylpropanamide (5)

One ml of 1 M TBAF was added to a solution of 301 mg of compound **4** (0.8 mmol) in 5 ml of THF. The reaction mixture was stirred for 2 h. Upon completion, the mixture was concentrated and purified by flash chromatography to give **5** (187 mg, 90%) as colorless oil. $R_f = 0.30$ (EtOAc/hexane = 1:2); $[\alpha]_D^{20} + 23.6°$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.83 (s, br, 1H), 4.28 (t, $J = 4.9$ Hz, 1H), 3.98–3.89 (m, 2H), 3.47 (s, br, 1H), 3.14–3.10 (m, 2H), 1.86–1.79 (m, 1H), 1.23 (s, 9H), 0.93 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 168.8, 86.9, 61.7, 46.7, 38.2, 28.5, 27.2, 20.1; ESI-MS *m/z* 242 (100), 283 ($M^+ + Na$, 44); HRMS-ESI *m/z* for $C_{12}H_{24}N_2O_4Na$ ($M^+ + Na$) calcd. 283.1634, found 283.1645.

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