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Ring-opening of oxazolines derived from L-serine: a short and efficient stereoselective synthesis of all four diastereomers of 3-mercaptoaspartic acid derivatives

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Abstract—Facile methods are described for accessing four diastereomerically pure 3-mercaptoaspartic acid derivative from L-aspartic acid. In our synthesis, ring-opening reactions of oxazoline-4,5-dicarboxylate with thiolacetic acid as well as the stereochemical interconversion of both α- and β-configuration via oxazoline chemistry were utilized as key steps.

There is an ever-growing interest in the synthesis and biological evaluation of non-proteinogenic amino acids, peptides, and peptidomimetics.[1] One particular synthetic interest lies on the β-substituted aspartates, since their derivatives are found in many biologically active compounds, both synthetic and natural.[2] However, compared with other β-substituted derivatives such as β-hydroxy, amino, or alkyl, the synthesis of β-mercaptoaspartic acid has received little attention.[3,4] This is surprising since a thiol moiety has been extensively utilized as zinc chelating group in the development of potent inhibitors for numerous zinc-metalloproteases, such as angiotensin converting enzyme and matrix metalloproteinases, which play a crucial role in the activation or inactivation of regulatory peptides.[5,6]

General methods for the synthesis of β-amino-α-mercapto acids include the electrophilic sulfenylation of N-protected β-amino esters, which can be available via the Arndt–Eistert homologation of the corresponding α-amino acids derivatives.[5] Both the Baldwin[3] and Roques[6b,c] groups reported the stereoselective synthesis of protected *erythro* (2*R*,3*R*)-3-mercaptoaspartic acid from L-aspartic acid using electrophilic sulfenylation as a key step. Even though this approach is an efficient way of preparing β-amino-α-mercapto acids, only *erythro* isomers are accessible. It was also demonstrated that the nucleophilic ring-opening of N-activated *trans*-aziridine-2,3-dicarboxylate with alkylthiol afforded the *erythro* β-(alkylthio)aspartic acid derivatives.[4]

2-Oxazolines **1** are versatile building blocks in organic synthesis, and can be opened in two ways (Fig. 1).

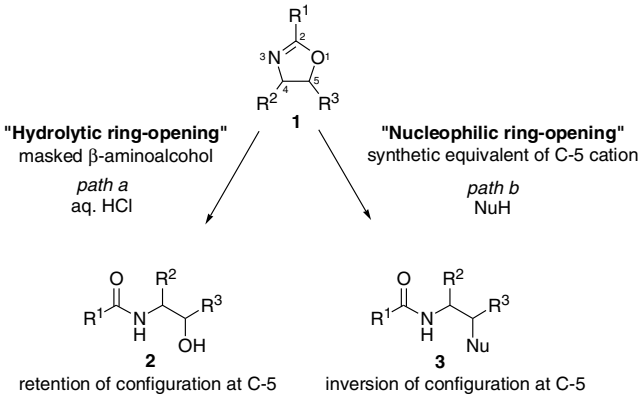

Figure 1. 2-Oxazoline: masked β-aminoalcohol or synthetic equivalent of C-5 cation.

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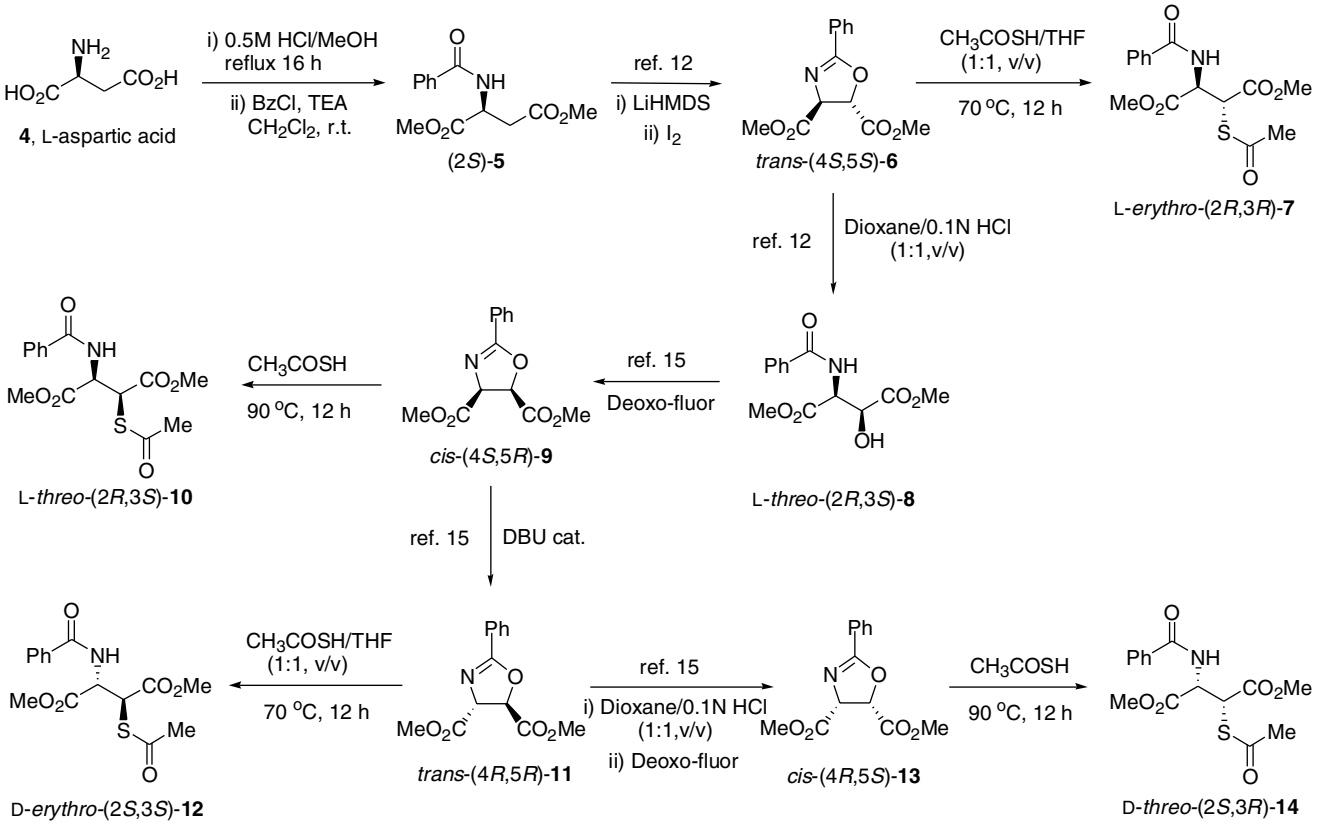
Firstly, the oxazoline ring can be considered as masked β-aminoalcohols **2** in the hydrolytic ring-opening, which does not involve the configurational change at the C-5 position (path a).[7] Secondly, oxazolines **1** can be considered as the synthetic equivalent of a C-5 cation in the synthesis of substituted amine **3** with inversion of C-5 configuration (path b).[8] The stereoselective nucleophilic ring-opening reactions of oxazoline-5-carboxylates developed by us has been successfully applied in the synthesis of both *syn* and *anti* α-substituted-β-amino acid derivatives, such as α,β-diamino acids,[8,9] phenylisocysteins,[8,10] and 2′-mercaptopaclitaxel derivatives.[11] Herein, we report an efficient stereoselective synthesis of the unnatural amino acids containing thiol moiety at the β-position, all four isomers of 3-mercaptoaspartic acid derivative, from L-aspartic acid (**4**) via ring-opening of oxazoline strategy (Scheme 1).

The key intermediate, *trans*-(4*S*,5*S*)-oxazoline-4,5-dicarboxylate **6**, was synthesized starting from L-aspartic acid (**4**). Esterification of both α- and β-carboxyl groups of **4** with dry HCl in methanol, followed by benzoylation of the resulting diester with benzoyl chloride resulted in the corresponding *N*-benzoyl diester **5** in 82% yield for the two steps. Following a known procedure reported by the Cardillo group,[12] *N*-benzoyl diester **5** was then treated with 2 equiv of LiHMDS, followed by quenching with I_2, to give *trans*-(4*S*,5*S*)-oxazoline **6** as the exclusive diastereomer.[13] The nucleophilic ring-opening reaction of *trans*-(4*S*,5*S*)-**6** with thiolacetic acid/THF (1:1) at 70 °C for 12 h afforded the desired L-*erythro*-(2*R*,3*R*)-3-mercaptoaspartic acid derivative **7** in 68% yield with a clean inversion of configuration at the C-5 position of the parent oxazoline **6**.[14] The Campiani group[15] recently reported the synthesis of D-*threo*-3-hydroxyaspartic acid from its L-*threo*-isomer in which inversion of both the α- and β-configuration was achieved by base-induced epimerization[16] and deoxo-fluor-catalyzed cylization,[17] respectively. Following this route, *trans*-(4*S*,5*S*)-**6** was hydrolyzed under mild acidic condition to afford L-threo-3-hydroxyaspartic acid derivative **8**, which in turn was transformed to *cis*-(4*S*,5*R*)-oxazoline-4,5-dicarboylate **9** by the treatment of deoxo-fluor with inversion of the C-5 configuration.[13] *cis*-(4*S*,5*R*)-Oxazoline **6**, which is less reactive compared to its *trans*-isomer,[8–10] was treated with neat thiolacetic acid at 90 °C for 12 h to provide the desired L-*threo*-(2*R*,3*S*)-**10** in 88% yield with a clean inversion of configuration at the C-5 position of the parent oxazoline **9**.[14]

The remaining two diastereomers with D-configuration could be synthesized following the exactly same procedure utilized in the preparation of two L-diastereomers starting from D-aspartic acid. However, as shown in Scheme 1, the remaining two diastereomers could also be synthesized via further manipulation of both the 4- and 5-configuration of oxazoline-4,5-dicarboxylates.[15–17] Base-induced epimerization at C-4 configuration led to the formation of the thermodynamically more stable *trans*-(4*R*,5*R*)-isomer **11** in trans cis ratio of 95:5 dr, which was then purified by flash chromatography to give pure **11** in 77% yield.[13] The ring-opening of (4*R*,5*R*)-



Scheme 1.

trans-isomer with diluted thiolacetic acid afforded D-*erythro*-3-mercaptoaspartic acid derivative **12** in 84% yield.[14] Following the same two-step reaction sequence from trans-**6** to its cis-isomer **9**, *trans*-(4*R*,5*R*)-**11** was transformed to *cis*-(4*R*,5*S*)-isomer **13**,[13] which was then ring-opened with neat thiolacetic acid to provide the D-*threo*-(2*S*,3*R*)-**14** in 84% yield.

In conclusion, we have provided a convenient synthetic access to all four diastereomers of 3-mercaptoaspartic acid derivative **7**, **10**, **12**, and **14** from L-aspartic acid. In our synthesis, ring-opening reactions of oxazoline-4,5-dicarboxylates with thiolacetic acid as well as the stereochemical interconversion of α- and β-configuration via oxazoline chemistry were utilized as key steps.

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Supplementary data

^{1}H and ^{13}C spectra for the compounds **5**–**14**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.041.

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shows same spectral data and optical rotation with opposite sign compared with (4*S*,5*R*)-**9**.

14. L-*erythro*-(2*R*,3*R*)-**7**: $[\alpha]_D$ +60.7; mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 5.07 (d, $J =$ 3.7 Hz, 1H), 5.37 (dd, $J = 3.7$, 9.3 Hz, 1H), 7.27 (br d, $J = 9.3$ Hz, 1H), 7.40–7.60 (m, 3H), 7.75–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.05, 46.85, 53.05, 53.23, 53.38, 127.19, 128.61, 131.97, 133.44, 167.38, 169.66, 170.85, 192.21; HRMS (FAB) $m/z = 340.0849$ $(M+H)^+$, Calcd for $C_{15}H_{18}N_1O_6S_1 = 340.0855$. D-*erythro*-(2*S*,3*S*)-**12** shows same spectral data and optical rotation with opposite sign compared with L-*erythro*-**7**. L-*Threo*-(2*R*,3*S*)-**10**: $[\alpha]_D$ +11.3; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.86 (d, $J = 4.2$ Hz, 1H), 5.38 (dd, $J = 4.2$, 8.7 Hz, 1H), 6.98 (br d, $J = 8.7$ Hz, 1H), 7.40–7.58 (m, 3H), 7.74–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.02, 47.73, 53.13, 53.39, 53.84, 127.19, 128.65, 132.06, 133.24, 166.80, 169.62, 169.97, 192.92; HRMS (FAB) $m/z =$ 340.0860 $(M+H)^+$, Calcd for $C_{15}H_{18}N_1O_6S_1 = 340.0855$. D-*threo*-(2*S*,3*R*)-**14** shows same spectral data and optical rotation with opposite sign compared with L-*threo*-**10**.
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