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Selective synthesis of dehydroamino acids from threonines

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Abstract—Dehydropeptides containing dehydroamino acid (ΔAA) are frequently found in natural resources with important biological activity. Herein, we report the selective synthesis of *Z*- and *E*-ΔAbu from L- and L-*allo*-threonine as starting materials through selenation and oxidative elimination. The detailed reaction mechanism of phosphine-assisted selenoether formation is also discussed.

Dehydropeptides containing α,β-unsaturated amino acid (or dehydroamino acid, ΔAA) residues, are frequently found in natural resources with important biological activity.[1,2] Their structures are rigid in both the backbones and the side chains of the peptides because of the presence of a double bond conjugated with a peptide linkage. In addition, dehydropeptides are known as fairly reactive Michael acceptors that react readily with 'soft' nucleophiles, such as thiols or amines of biological molecules. This reactivity is thought to be one of the molecular mechanisms underlying the biological activities of dehydropeptides. A number of molecules from this class were isolated from natural organisms, of which AM-toxins,[3,4] Sch-20561 (microorganisms)[5] and kahalalide-F (marine organism)[6] are known as typical examples. Biosynthetically, ΔAAs are derived from proteinogenic amino acids, such as ΔAla from serine and cystein, and α-dehydro-α-aminobutylic (ΔAbu) acid from threonine, by activation of the β-hydroxy or thiol function and posterior β-elimination. Chemical syntheses of such ΔAAs with eliminative formation of a double bond have been reported in numerous methods; for example, activation of β-hydroxy group by tosylation or other methods, followed by β-elimination;[7] permethylation of a β-amino group, followed by Hofmann elimination;[8] N-chlorination of an α-amino group by *tert*-butyl hypochlorite, followed by dehydrochlorination and isomerization under basic conditions.[9] However, selective synthesis of an *E*- or *Z*- unsaturated bond is rather difficult, though both *E*- and *Z*-ΔAbu have been found in natural products as dehydroamino acid components in cyclic depsipeptides.[10]

Recently, we developed new selenyl linkers for solid-phase synthesis of dehydropeptides.[11,12] Using these linkers, we achieved the solid-phase synthesis of ΔAla-containing dehydropeptides, AM-toxin,[11] and RGD-conjugate peptide[12] using a protected serine as a starting material. The novel linker (**1**) was designed for side-chain anchoring, which enabled amino acid elongation to both the N- and C-terminals of the starting amino acid by orthogonal protection. The construction of an unstable double bond could be realized simultaneously with oxidative cleavage by *syn*-elimination from the solid phase in the final stage of synthesis. We reported that the synthesis of selenoether derived from serine was readily carried out; however, threonine-derived selenoethers were much more troublesome. In particular, β-selenoether derived from L-threonine (*2S*,*3R*) could not be obtained under the described conditions.[12,13]

In the present study, selective synthesis of *Z*- and *E*-ΔAbu was attempted using L- and L-*allo*-threonine as starting materials. We carefully re-examined the reaction conditions for selenoether formation and established a sufficient condition using pyridine as a solvent under a cautious temperature control. We found that it was important to have a low temperature (−40 °C)

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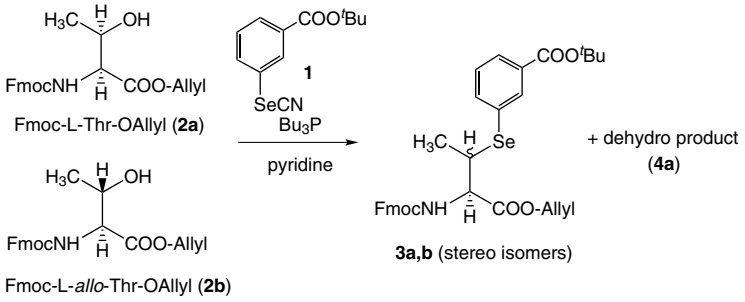

starting material	condition	product / yield*	byproduct / yield*
2a	-40° C / 40 min then r.t. / 90 min	**3a** / 29 % (38 %)	**4a** / 47 % (62 %)
2b	-40° C / 20 min then r.t. / 70 min	**3b** / 73 % (86 %)	**4a** / 12 % (14 %)

* yields in parentheses calculated based on consumed starting material.

Figure 1. Synthesis of selenoether.

for the induction of an active intermediate and that a much higher temperature (room temperature) was required to complete the selenium S_N2 substitution; that is, a bi-level temperature control was essential to obtain the desired products (**3a**,**b**).[14] In contrast, keeping the reactants at the lower temperature (−40 °C) or a higher temperature (0 °C or room temperature) led, respectively, to no reaction or to the product of only an undesired product, a dehydro derivative. Interestingly, the same dehydro product (**4a**) was obtained by β-elimination from two stereochemical isomers, L (**2a**) and L-*allo* (**2b**) (Fig. 1).

Subsequent oxidative elimination readily proceeded by treatment with hydrogen peroxide. The two desired ΔAbu's (**4a** and **4b**)[14] with different geometries were selectively obtained from the respective isomers **3a** and **3b** through the corresponding selenoxides as solo products. Considering the well-known reaction mechanism, the selenoxide underwent precise *syn*-elimination by a [2,3]-sigmatropic rearrangement.[15] Therefore, the geometry of the double bond reflects the relative stereochemistry of the corresponding selenoxide. The geometries of the double bonds were determined by NOE experiments, depicted in Figure 2. Consequently, the relative stereochemistry of precursor selenoether (and selenoxide) could be also determined, as **5a** (*erythro*) led to *Z* olefin **4a** and **5b** (*threo*) led to *E* olefin **4b**, respectively. In addition, the undesired products at the selenation reaction could also be determined to have *Z* geometry, by comparison with both dehydroamino acids.[16]

Two reaction mechanisms can be assumed for phosphine-assisted selenoether formation: pentavalent intramolecular selenation (**A**) or a bi-molecular mechanism (**B**), as illustrated in Figure 3. In the former case, the starting chiral alcohol and the resultant selenoether should possess the same stereochemistry according to the S_Ni reaction mechanism, while in the latter case Walden inversion should be observed. According to our experimental results, (*threo*-)L-threonine derivatives gave *erythro*-selenoether, and (*erythro*-)L-*allo*-threonine gave *threo*-selenoether. These results mean that the selenation reaction underwent the stereo-inversion at the β-position. Therefore, we can conclude that the selenation reaction takes place via the phosphonium intermediate (mechanism B). It can be understood that bi-level temperature control is required for induction of the phosphonium intermediate at a lower temperature and the following nucleophilic substitution at an

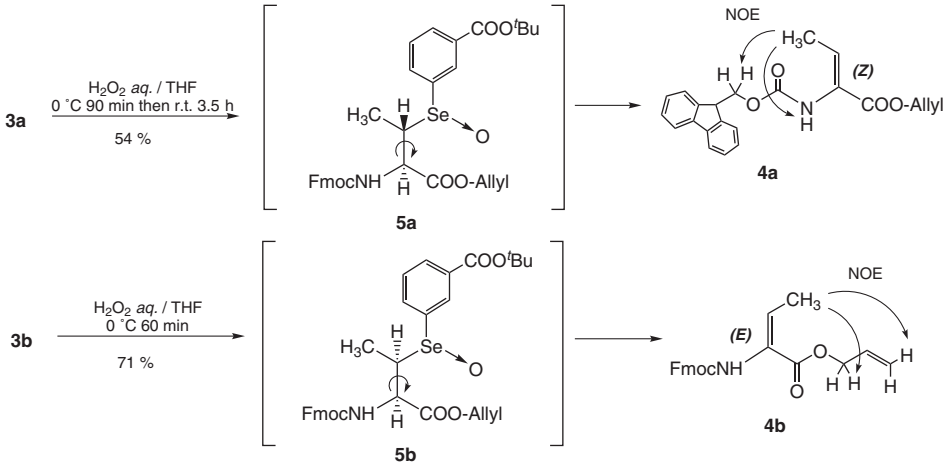

Figure 2. Synthesis of dehydroamino acids.

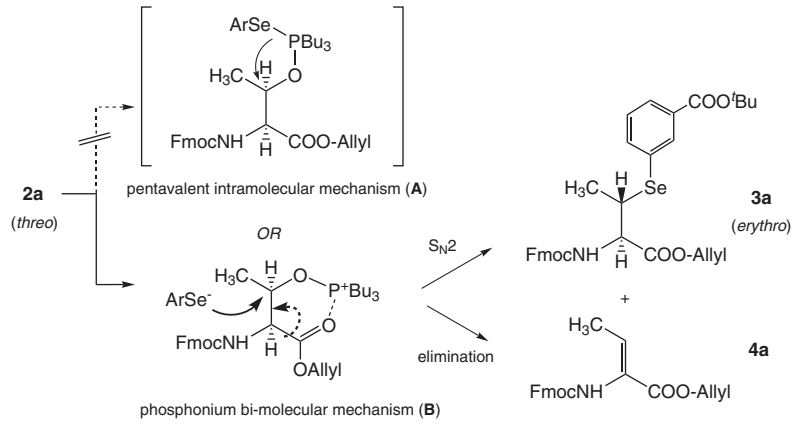

Figure 3. Reaction mechanism of selenoether formation.

elevated temperature. In addition, the dehydroamino acid as an undesired product can be produced through its elimination from the six-membered ring intermediate with the assistance of strong phosphorus–oxygen interaction. β-Elimination reaction would proceed through *trans*-relationship between the α-proton and the β-oxyphosphonium by formation of six-membered ring. The geometry of the double bond (*anti* relationship between the methyl and the ester) was clearly explained by this reaction model regardless of the relative stereochemistry at the α and β positions.

In summary, we succeeded in the selective synthesis of *Z*- and *E*-ΔAbu by selecting L- and L-*allo*-threonine as starting materials and using selenation and oxidative elimination processes with a selenyl linker. Since the usefulness of this linker for solid-phase synthesis of dehydropeptides has been demonstrated,[12,13] it should be possible to synthesize natural dehydropeptides including both *E*- and *Z*-ΔAbu by a solid-phase method.

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14. Compound **3a**: HRMS calcd for $C_{33}H_{35}NO_6{}^{78}Se$ *m/z* 619.1635, found *m/z* 619.1657; $[\alpha]_D^{25}$ +3.6 (*c* 1.0, $CHCl_3$); IR (film) 1716, 1508, 1303, 1216, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (3H, d, J = 6.8 Hz), 1.58 (9H, s), 3.72 (1H, m), 4.23 (1H, t, J = 7.5 Hz), 4.38 (2H, d, J = 7.5 Hz), 4.63 (2H, d, J = 5.9 Hz, overlapped), 4.67 (1H, m, overlapped), 5.27 (1H, br d, J = 10.5 Hz), 5.34 (1H, br d, J = 18.2 Hz), 5.53 (1H, br d, J = 8.7 Hz, NH), 5.90 (1H, m), 7.32 (1H+2H, arom), 7.40 (2H, arom), 7.59 (2H, arom), 7.76 (1H+2H, arom), 7.91 (1H, arom), 8.22 (1H, arom). Compound **3b**: HRMS calcd for $C_{33}H_{35}NO_6{}^{78}Se$ *m/z* 619.1635, found *m/z* 619.1641; $[\alpha]_D^{24}$ +44.3 (*c* 1.2 $CHCl_3$); IR (film) 1718, 1508, 1301, 1216, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (3H, d, J = 6.8 Hz), 1.59 (9H, s), 3.91 (1H, m), 4.25 (1H, t, J = 4.7 Hz), 4.40 (3H, overlapped), 4.68 (1H, dd, J = 3.2, 9.1 Hz), 5.18 (1H, br d, J = 10.5 Hz), 5.23 (1H, br d, J = 16.9 Hz), 5.66 (1H, d, J = 9.1 Hz, NH), 5.72 (1H, m), 7.33 (1H+2H, arom), 7.41 (2H, arom), 7.61 (2H, arom), 7.74 (1H, arom), 7.78 (2H, arom), 7.91 (1H, arom), 8.19 (1H, arom). Compound **4a**: colorless needles mp 73–74 °C (hexane–EtOAc); HRMS calcd for $C_{22}H_{21}NO_4$ *m/z* 363.1468, found *m/z* 363.1458; IR (film) 1716, 1503, 1272, 1216, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (3H, d, J = 7.2 Hz), 4.26 (1H, t, J = 6.9 Hz), 4.45 (2H, d, J = 6.9 Hz), 4.68 (2H, d, J = 5.9 Hz), 5.26 (1H, dd, J = 1.4, 10.5 Hz), 5.34 (1H, dd, J = 1.4, 16.9 Hz), 5.94 (1H, m), 6.30 (1H, br s, NH), 6.83 (1H, q, J = 7.2 Hz), 7.32 (2H, arom), 7.41 (2H, arom), 7.67 (2H, arom), 7.77 (2H, arom). Compound **4b**: colorless needles mp 113–115 °C (hexane–EtOAc); HRMS calcd for $C_{22}H_{21}NO_4$ *m/z* 363.1468, found *m/z* 363.1465; IR (KBr) 1726, 1705, 1529, 1260, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (3H, d, J = 7.3 Hz), 4.25 (1H, t, J = 7.2 Hz), 4.42 (2H, d,

$J = 7.2$ Hz), 4.76 (2H, d, $J = 5.5$ Hz), 5.30 (1H, d, $J = 10.5$ Hz), 5.38 (1H, d, $J = 17.4$ Hz), 5.98 (1H, m), 6.86 (1H, br s, NH), 6.91 (1H, br m), 7.32 (2H, arom), 7.41 (2H, arom), 7.61(2H, arom), 7.77 (2H, arom).

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