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Asymmetric synthesis of α,α-disubstituted α-amino acids

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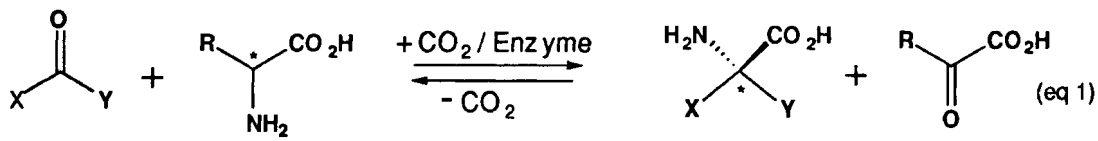
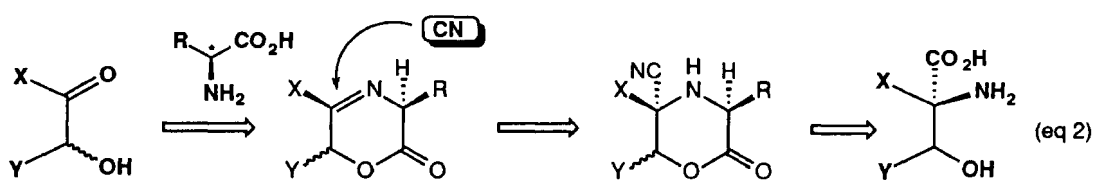
Abstract: A new method for the synthesis of each optically active α-methylserine (**1a**,**1b**) and α-methylthreonine (**2a**-**2d**) is described. Intramolecular Strecker synthesis of L-valine acetol ester **3** gave stereoselectively 5*S*-ketimine **5**, which upon oxidative removal of the L-valyl group furnished (*R*)-2-methylserine (**2b**). The use of D-valine afforded (*S*)-**1a**. The treatment of phenylalanine-*dl*-acetoin ester **7** gave a 4 / 1 mixture of 5*S*-ketimines, **9a** and **9b**. The mixture in the presence of trifluoroacetic acid was equilibrated to give **9b** as the major product (9 : 1). Deuterium exchange experiments using 2-propanol-D clearly indicated the presence of equilibrium between the ketimines **8a** and **8b** via an enamine **8c**. Removal of the phenylalanyl moiety from **9a** and **9b** afforded **2c** and **2d**, respectively, in 44-50% overall yields. The use of D-phenylalanine gave **2a** and **2b**.

α,α-Disubstituted α-amino acids, often found in nature, have attracted substantial synthetic interest because of its importance as enzyme inhibitors and as conformational modifiers in physiologically important peptides (1,2). Among these amino acids, their β-hydroxy congeners can be viewed as the analogous amino acids of serine or threonine (1), which should have marked effects on peptide conformation as well as biological activity (3). It has been proposed that the biosynthetic pathway of α,α-disubstituted α-amino acids involves an asymmetric transformation of the amino group from an α-amino acid and a carboxyl group to a ketone (4). As a result, the chirality of a strating amino acid was transferred to the ketone and that of the amino acid was destroyed to give a pyruvate derivative (eq 1). Most synthetic routes to these important class of amino acids are based on the alkylation of enolates from bislactims, oxazinones, imidazolidinones, and other procedures (2b). Along the hypothetical biosynthetic routes in eq 1, we wish to describe here a new method for the synthesis of each optically active α-methylserine (**1a**, **1b**) and α- methylthreonine (**2a**-**2d**) (5).



Enzyme: pyridoxal-P dependent α-dialkylamino acid transferase

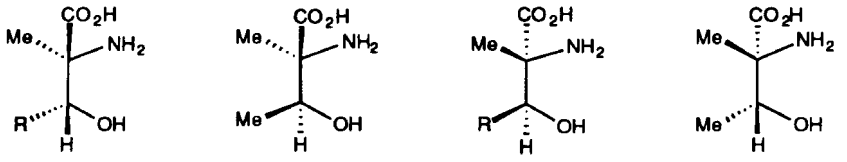
Transfer of chirality & N̲H̲



X = alkyl or aryl, Y=H, alkyl or aryl

Our synthetic plan to these amino acids was an intramolecular version of an asymmetric Strecker synthesis (6).

Initially formed internal Schiff base (ketimine) from an amino ester would undergo stereoselective amino nitrile formation to give 1,4-oxazine; subsequent hydrolysis of the nitrile group and oxidative removal of the chirality transferring group would yield optically active β-hydroxy α-methyl α-amino acid (eq 2).



1a R = H
2a R = Me

2b (L-allo-form)

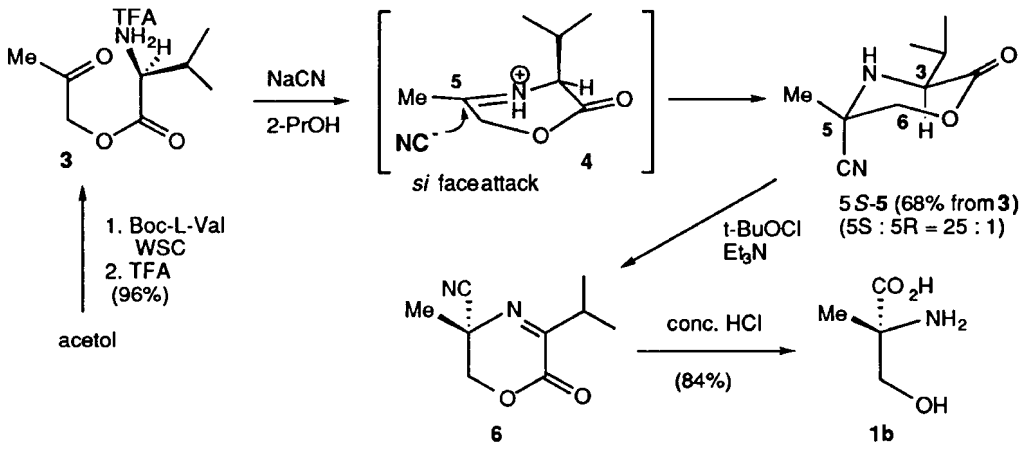
1b R = H
2c R = Me

2d (D-allo-form)

Figure 1.

Condensation of acetol with *N*-*tert*-butoxycarbonyl (Boc) -L-valine with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD) HCl salt gave *N*-Boc-valine acetol ester in 96% yield. After removal of the Boc group with trifluoroacetic acid (TFA), treatment of the resulting TFA salt **3** with 2 equiv of NaCN in 2-propanol for 2 h gave in 68% isolated yield the desired cyclic amino nitrile **5** which contained a small amount of its 5*R* isomer (5*S*-**5** : 5*R*-**5** = 25 : 1). The structure possessing a 5*S* configuration was determined by converting it to known (*R*)-α-methylserine (vide infra). In order to examine an extent of racemization of the valine residue under the reaction conditions, the reaction was performed using 2-propanol-*d* as the solvent. No racemization at C3 was occurred since any deuterium atom was not detected at the C3 position of **5**. On the other hand, significant amounts of D atom were incorporated into the C5 methyl (15%) and C6 methylene (25%) groups, indicating that the present reaction involved a small amount of imine-enamine equilibrium. Treatment of the mixture under the prolonged reaction time (24 h) or the presence of excess TFA did not affect to the product ratio. These results suggest that the 5*S* isomer is kinetically as well as thermodynamically more favored product than the 5*R* isomer. Therefore, the highly diastereoselective formation of 5*S*-**5** would be derived from an attack of cyanide ion to the sterically less hindered *si*-face of the ketimine where a boatlike conformation with the isopropyl group oriented to a pseudoaxial position seemed to be plausible. It is noted that the 5*S* / 5*R* ratio was decreased when the other amino acids with a sterically less bulky side chain was employed, e.g., L-alanine acetol ester gave a mixture of 5*S* and 5*R* cyclic amino nitriles in 3 : 1 ratio, and L-phenylalanine acetol ester afforded in 10 : 1 ratio, respectively. Thus, valine was found to be an excellent chirality transferring group in the stereoselective formation of **5**.

Scheme 1



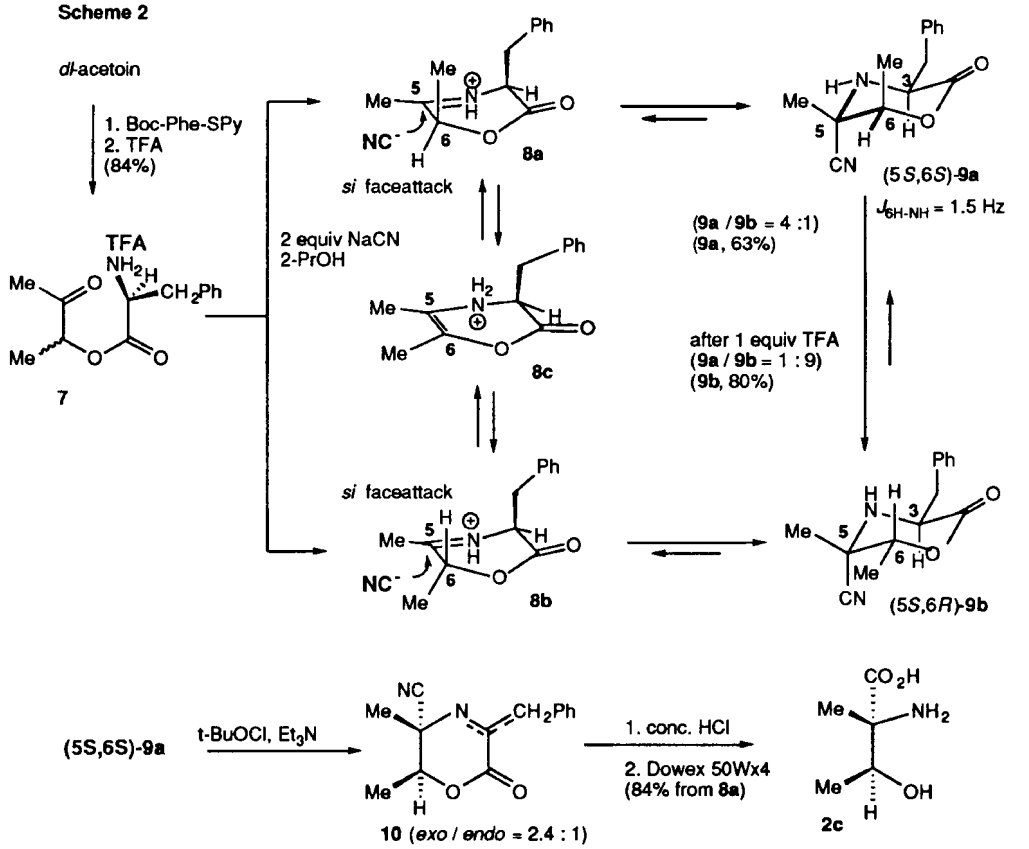
3 **4** **6** **1b**

Removal of the valyl moiety from **5** and its conversion into the amino acid **1b** were carried out by the following sequence of reactions. Treatment of **5** with *tert*-butyl hypochlorite and triethylamine gave exclusively imine **6**,

which, upon treatment with concentrated HCl, gave in 84% yield desired (*R*)-α-methylserine (**1b**). The spectroscopic data as well as physical constants of **1b** were in agreement with those reported (7,8): mp 262-267 °C dec; $[\alpha]^{22}_D$ -6.3° (*c* 1.05, H_2O). The use of D-valine afforded (*S*)-α-methylserine (**1a**): mp 261-265 °C dec; $[\alpha]^{22}_D$ +6.5 °(*c* 1.01, H_2O). Notice that the configuration of the new amino acid is opposite to that of valine. Thus, both enantiomers of α-methylserine were prepared in a few steps, and their overall yields were ~55%.

In order to extend this method for general applications, we next synthesized 4 enantiomers and diastereomers of β-substituted α-methylserine, i.e., α-methylthreonine and α-methylallothreonine (**2a-2d**). Thus, *dl*-acetoin was chosen as the starting material. Treatment of a diastereomeric mixture of *N*-Boc-L-phenylalanine D- and L-acetoin esters, prepared by the condensation of *N*-Boc-L-phenylalanine 2-phyridyl thiol ester, with TFA followed by 2 equiv of NaCN in 2-propanol for 2 h gave a 4 / 1 mixture of cyclic amino nitriles, **9a** and **9b**. The structure of the major isomer **9a** possessing the 5*S*,6*S* configuration was confirmed by its spectral data in combination with X-ray crystallographic analysis. The mixture, upon prolonged reaction time at room temperature for 24 h, resulted in a change of the product ratio (**9a** / **9b** = 1.3 : 1). In the presence of an additional 1 equiv TFA in 2-propanol, the mixture was further equilibrated to afford a 1 / 9 mixture of **9a** and **9b**.

Scheme 2



The reaction produced only the two diastereomers, **9a** and **9b**, both possessing the same 5*S* configuration as that of **5**, and the major product was the 6*S*-isomer **9a** which was equilibrated to the 6*R*-isomer **9b** under acidic conditions. These results suggest that the reaction involves an enamine type intermediate **8c** and that both ketimine-type intermediates, **8a** and **8b**, coexist at equilibrium via **8c**. This was proven by the facts that (i) the reaction using diastereomerically pure **7** also afforded a 4 / 1 mixture of **9a** and **9b** in the same ratio as that of the mixture of the diastereomers **7**, and (ii) the reaction using 2-propanol-D as the solvent gave a 4 / 1 mixture of the mono-deuterated products, **9a** and **9b**, in which the C6-H was completely exchanged with D atom (no D atom was incorporated at C3 of the products). From these results, the rate determining step of the reaction would be an attack of cyanide ion to

the ketimine intermediates, where a boatlike conformation with a pseudoaxial benzyl group might sterically hinder the *re*-face. Therefore, an attack of cyanide ion to *si*-face on C5 of the ketimines would yield, exclusively, the 5*S* products (Scheme 2). The 6*R* isomer **9b** would be thermodynamically more favoured than **9a** since **9b** possessed all equatorial substituents on the cyclohexane ring. In view of obtaining both diastereomers, **9a** and **9b**, other chirality transferring groups such as L-valine were examined. However, this group was not satisfactory because the treatment of L-valyl acetoin ester gave **9a** as the minor isomer (**9a** / **9b** = 1 : 2, 82%), which, upon exposure to an additional TFA, affoded a mixture of **9a** and **9b** in 1 : 8 ratio. Thus, the amino nitriles **9a** and **9b** were obtained from *dl*-acetoin using phenylalanine in an enantiomerically convergent manner, respectively.

Removal of the phenylalanyl moiety from **9a** and **9b** and their conversions into the amino acids, **2c** and **2d**, were carried out in a manner similar to the preparation of **1b**: (2*R*,3*S*)-**2c**, mp 211-213 °C, $[\alpha]^{25}_{D}$ +13.0 °(*c* 0.95, H_2O); (2*R*,3*R*)-**2d**, mp 267-268 °C dec, $[\alpha]^{24}_{D}$ -13.0 °(*c* 0.3, H_2O) (8). The use of D-phenylalanine as the chiral auxiliary afforded (2*S*,3*R*)-**2a**; mp 214-219 °C, $[\alpha]^{20}_{D}$ -14.1 °(*c* 1.08, H_2O), and (2*S*,3*S*)-**2b**; mp 265-267 °C dec; $[\alpha]^{21}_{D}$ +12.6 °(*c* 0.98, H_2O) (8), respectively, in the same manner as the D-isomers, **2c** and **2d**. Thus, α-methylated threonine and its allo isomers (**2a**-**2d**) were prepared in a short numbers of steps and their overall yields were 44-50%.

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