Efficient Syntheses of the Four Enantiomers and Diastereomers of α-Methylthreonine and Both Enantiomers of α-Methylserine

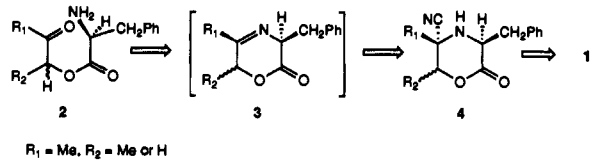
Sung-Hwan Moon and Yasufumi Ohfune*

Suntory Institute for Bioorganic Research Shimamoto-cho, Osaka 618, Japan

Received March 30, 1994

α,α-Disubstituted α-amino acids are often found in nature, either in the free form or as constituents of biologically active peptides.[1] In recent years, this class of amino acids has attracted substantial synthetic interest[2] because of its importance as enzyme inhibitors[3] and as conformational modifiers in physiologically important peptides.[4] Among these amino acids, their β-hydroxy congeners[1,5] can be viewed as the analogous amino acids of threonine or serine, which should have marked effects on peptide conformation as well as biological activity.[6] Most synthetic routes to these important amino acids are based on the alkylation of enolates from bis-lactims,[2b,7] oxazinones,[2b,8] imidazolidinones,[2b,9] and other procedures.[2b,10] We wish to describe here a new method for the synthesis of each optically active α-substituted threonine (**1a–1d**) and serine (**8a**, **8b**), which are characterized by their enantiomeric convergence (Figure 1).

Our synthetic plan was an intramolecular version of an asymmetric Strecker synthesis.[11] Initially formed internal Schiff base (ketimine **3**) from an amino ester **2** would undergo stereoselective amino nitrile formation to give **4**; subsequent hydrolysis and removal of the chirality transferring group would yield optically active β-hydroxy α-methyl α-amino acids **1** (eq 1).



Condensation of *dl*-acetoin with *N*-*tert*-butoxycarbonyl(Boc)-L-phenylalanine 2-pyridyl thiol ester[12] gave a diastereomeric mixture of *N*-Boc-phenylalanine acetoin esters. After removal of the Boc group with trifluoroacetic acid (TFA), treatment of the resulting TFA salt **2a** with 2 equiv of NaCN in 2-propanol gave a 4/1 mixture of cyclic amino nitriles, **4a** and **4b**.[13] The major isomer **4a** was not separable from the mixture by column chromatography on SiO_2 but was isolated by treatment of the mixture with 2,2-dimethoxypropane in the presence of 0.4 equiv of *dl*-camphorsulfonic acid (CSA). Only **4b** afforded its corresponding acetonide **5**, and **4a** (mp 107.5–108.5 °C; $[\alpha]^{26}_D$ –49.7° (*c* 0.31, $CHCl_3$)) was recovered unchanged. The structure of **4a** possessing the 5*S*,6*S* configuration was confirmed by its spectral data in combination with X-ray crystallographic analysis.[14] To our surprise, the mixture of **4a** and **4b**, upon prolonged exposure to an additional 1 equiv TFA in 2-propanol, was equilibrated to afford a 1/9 mixture of **4a** and **4b**. Recrystallization (ether/hexane) gave pure **4b**, mp 100–100.5 °C; $[\alpha]^{27}_D$ +30.8° (*c* 1.0, $CHCl_3$), whose structure was assigned to be (5*S*,6*R*)-**4b** by spectroscopic studies (^{1}H NMR and NOE experiments) of the corresponding acetonide **5** (Scheme 1).

The present reaction is characterized by the following points: (i) the reaction produced only two diastereomers, **4a** and **4b**, (ii) both isomers possessed the same 5*S* configuration, and (iii) the major product was the 6*S* isomer **4a**, which was equilibrated to the 6*R* isomer **4b** under acidic conditions.[13b] These results suggest that the reaction involves both ketimine-type intermediates, **3a** and **3b**, coexisting at equilibrium via an enamine-type intermediate **3c**.[15] This was proven by the fact that the reaction using 2-propanol-*d* as the solvent gave a 4/1 mixture of the monodeuterated products, **4a** and **4b**, in which the C6-H was completely

(1) (a) Barrett, G. C. *Amino acids, peptides and proteins*; The Chemical Society: London, 1980; Vol. 13, p 1. (b) Hunt, S. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55.

(2) (a) Coppola, G. M.; Shuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: New York, 1987; pp 20, 78, and 267. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: London, 1989; pp 1, 34, 62, 87, and 208, and references cited therein.

(3) (a) Goodson, L. H.; Honigberg, I. L.; Lehman, J. J.; Burton, W. H. *J. Org. Chem.* **1960**, *25*, 1920. (b) Almond, H. R.; Manning, D. T.; Niemann, C. *Biochemistry* **1962**, *1*, 243. (c) Arnone, A.; Briley, P. D.; Rogers, P. H.; Hydge, C. C.; Metzler, C. M. *Molecular Structure and Biological Activity*; Griffin, J. F., Duax, W. L., Eds.; Elsevier: New York, 1985; p 57. (d) Abshire, C. J.; Ostiguy, M. *J. Med. Chem.* **1976**, *19*, 965. (e) Jung, M. J. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 227.

(4) For recent examples, see: (a) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1994**, *116*, 799. (b) Mendel, D.; Ellman, J.; Shultz, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 4359. (c) Boden, P. R.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; Hughes, J.; Rees, D. C.; Roberts, E.; Singh, L.; Suman-Chauhan, N.; Woodruff, G. N. *J. Med. Chem.* **1993**, *36*, 552. (d) Bourne, G. T.; Horwell, D. C.; Pritchard, M. C. *Tetrahedron* **1991**, *26*, 4763. (e) Smith, A. B., III.; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672. (f) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238 and references cited therein.

(5) For recent examples, see the following. (a) lactacystin: (i) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. (ii) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117. (b) Altermicidin: (i) Takahashi, A.; Kurasawa, S.; Ikeda, D.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 1556. (ii) Takahashi, A.; Ikeda, D.; Nakamura, H.; Naganawa, H.; Kurasawa, S.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 1562. (c) Thiazohalostatin: Shindo, S.; Yamagishi, Y.; Kato, S.; Matsuda, M.; Odagawa, A.; Kawai, H.; Mochizuki, J. *Abstracts of Papers*, 35th Symposium of Natural Products Chemistry, Kyoto, 1993; Koshimizu, K., Ed.; Taishodo: Kyoto, 1993; Symposium paper, p 298. (d) Conagenin: Yamashita, T.; Iijima, M.; Nakamura, H.; Isshiki, K.; Naganawa, H.; Hattori, S.; Hamada, S.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 557.

(6) (a) Mickos, H.; Sundberg, K.; Lüning, B. *Acta Chem. Scand.* **1992**, *46*, 989. (b) Flynn, E. H.; Hinman, J. W.; Caron, E. L.; Woolf, D. O., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 5867. (c) Altmann, E.; Altmann, K.-H.; Mutter, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *70*, 858.

(7) (a) Schöllkopf, U.; Groth, U.; Gull, M.-R.; Nozulak, J. *Liebigs Ann. Chem.* **1983**, 1133. (b) Schöllkopf, U.; Hartwig, W.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 212.

(8) (a) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976. (b) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Synlett* **1992**, 249.

(9) (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311. (b) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. (c) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.

(10) (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235. (b) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253.

(11) (a) Weinges, K.; Graab, G.; Nagel, D.; Stemmle, B. *Chem. Ber.* **1971**, *104*, 3594. (b) Weinges, K.; Stemmle, B. *Chem. Ber.* **1973**, *106*, 2291. (c) Weinges, K.; Gries, K.; Stemmle, B.; Schrank, W. *Chem. Ber.* **1977**, *110*, 2098. (d) Subramanian, P. K.; Woodard, R. W. *Synth. Commun.* **1986**, *16*, 337. (e) Kunz, H.; Sager, W.; Schanzenbach, D. *Tetrahedron Lett.* **1988**, *29*, 4397. (f) Inaba, T.; Kozono, I.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2359.

(12) Kurokawa, N.; Ohfune, Y. *Tetrahedron* **1993**, *49*, 6195.

(13) (a) The product ratio was analyzed by HPLC. Column: UNISIL PACK $5C_{18}$ (G. L. Sciences Inc., Tokyo, Japan); flow rate, 1.0 mL/min; eluent, CH_3CN/H_2O = 4.5/5.5. Retention time of each compound: **4a**, 19.7 min; **4b**, 18.9 min; **7**, 18.9 min; diastereomer of **7**, 17.8 min. (b) Upon cyclic imino nitrile formation, prolonged reaction time (room temperature, 24 h) resulted in a change of the product ratio (**4a**/**4b** = 1.3/1), suggesting that initially formed 6*S* isomer **4a** slowly isomerized to the 6*R* isomer **4b** under the reaction conditions. Addition of 1 equiv of TFA to the reaction mixture might accelerate the rate of isomerization from **4a** to **4b**.

(14) We thank Dr. N. Hamanaka, Director, Minase Research Institute of Ono Pharamaceutical Co. Ltd., for X-ray crystallographic analysis of **4a**.

(15) The use of diastereomerically pure (2*S*)-acetoin ester **2a** or (2*R*)-**2a**, prepared by (i) condensation of (2*R*,3*R*)- or (2*S*,3*S*)-butanediol and phenylalanine 2-pyridyl thiol ester and (ii) Jones oxidation of the resulting mono ester, resulted in the formation of the same mixture of **4a** and **4b** as described in the text. No other diastereoisomers (5*R* isomers) were detected. Therefore, an enamine-type intermediate **3c** is certainly involved in the reaction.

0002-7863/94/1516-7405$04.50/0

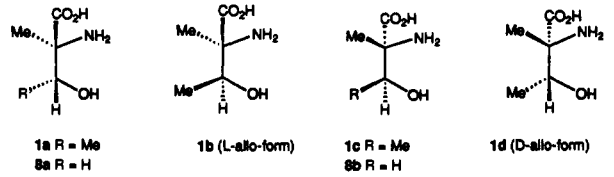
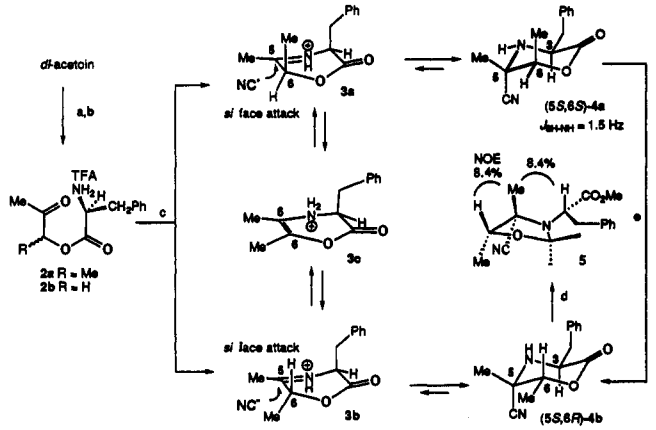


Figure 1.

Scheme 1[a]

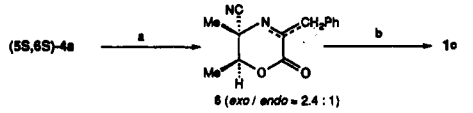


[a] (a) *N*-Boc-L-phenylalanine 2-pyridyl thiol ester, toluene, room temperature, 5 days (84%). (b) TFA, CH_2Cl_2, 0 °C, 30 min. (c) 2 equiv of powdered NaCN, 2-propanol, room temperature, 2 h (96% from step b as a mixture of **4a** and **4b**). (d) 2,2-Dimethoxypropane, 0.4 equiv of CSA, acetone, room temperature, 3 h (**5**, 19%, and recovered **4a**, 63%). (e) Mixture of **4a** and **4b** obtained in step c, 1 equiv of TFA, 2-propanol, room temperature, 5 h, then recrystallization from Et_2O/hexane (80% from step b).

exchanged with D atom.[16] 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 the benzyl group oriented to a pseudoaxial position seemed to be plausible (Scheme 1). The exclusive formation of 5*S* products would be derived from an attack of cyanide ion to the sterically less hindered *si*-face on C5 of the ketimines. Therefore, the attack of cyanide ion to **3a** might be kinetically more favored than the attack to **3b**, yielding **4a** as the major product.[17] The 6*R* isomer **4b** would be thermodynamically more favored than **4a** because its structure possesses all equatorial substituents.[18] Thus, the amino nitriles **4a** and **4b** were obtained from *dl*-acetoin in a stereoselective manner, respectively.

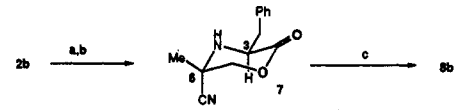
Removal of the phenylalanyl moiety from **4a** and **4b** and their conversion into the amino acids, **1c** and **1d**, were carried out by the following sequence of reactions. Treatment of **4a** with *tert*-butyl hypochlorite and triethylamine gave a mixture of isomers **6** [*exo* (enamine-type)/*endo* (imine-type) = 2.4/1],[19] which upon treatment with concentrated HCl, gave rise to the desired (2*R*,3*S*)-2-methylthreonine (**1c**): mp 211–213 °C; $[\alpha]^{25}_D$ +13.0° (*c* 0.95, H_2O) (Scheme 2). Phenylpyruvic acid was isolated in quantitative yield as the byproduct. (2*R*,3*R*)-2-Methylallothreonine (**1d**) was obtained from **4b** in the same manner as described above. The

Scheme 2[a]



[a] (a) 2 equiv of *t*-BuOCl, Et_2O, 0 °C, 30 min, then room temperature, 2 h, then triethylamine, room temperature, 8 h. (b) (1) Concentrated HCl, 0 °C, 4 h, room temperature, 24 h, then 80 °C, 24 h; (2) Dowex 50W × 4 (elution with 1 N NH_3), then recrystallized from H_2O/EtOH/Et_2O: **1c**, 84% from **4a**; **1d**, 73% from **4b**; **1a**, 88% from the enantiomer of **4a**; **1b**, 72% from the enantiomer of **4b**.

Scheme 3[a]



[a] (a) *N*-Boc **2b**, TFA/CH_2Cl_2 (1/1), 0 °C, 1.5 h. (b) 2 equiv of powdered NaCN, 2-propanol, room temperature, 2 h (97% from step a). (c) (1) 2 equiv of *t*-BuOCl, Et_2O, 0 °C, 30 min, room temperature, 2 h, then triethylamine, room temperature, 8 h; (2) concentrated HCl, 0 °C, 4 h, room temperature, 48 h, then 80 °C, 24 h; (3) Dowex 50W × 4 (elution with 1 N NH_3), then recrystallized from H_2O/EtOH/Et_2O: **8b**, 84% from **7**; **8a**, 84% from the enantiomer of **7**.

spectroscopic data as well as physical constants of **1d** were in agreement with those reported: **1d**, mp 267–268 °C dec; $[\alpha]^{24}_D$ −13.0° (*c* 0.3, H_2O).[9c] The use of D-phenylalanine afforded (2*S*,3*R*)-**1a**, mp 214–219 °C; $[\alpha]^{20}_D$ −14.1° (*c* 1.08, H_2O), and (2*S*,3*S*)-**1b**, mp 265–267 °C dec; $[\alpha]^{21}_D$ −12.6° (*c* 0.98, H_2O),[9c] respectively, in the same manner as the D isomers, **1c** and **1d**. Notice that the configuration of the new amino acids is opposite to that of phenylalanine.[20] Thus, α-methylated threonine and its allo compounds (**1a–1d**) were prepared in a few steps, and their overall yields were 44–50%.

To extend this method for further applications, the synthesis of each enantiomer of 2-methylserine was next examined. The key transformation from L-phenylalanine acetol ester **2b**, prepared by the condensation of acetol and *N*-Boc-L-phenylalanine 2-pyridyl thiol ester followed by TFA treatment, to amino nitrile **7** was achieved in quantitative yield with high stereoselectivity (~98% diastereomeric excess).[13] Recrystallization (Et_2O/hexane) afforded pure **7**: mp 114.5–115.0 °C; $[\alpha]^{20}_D$ +22.5° (*c* 1.06, $CHCl_3$). This was converted into 2-methyl-D-serine (**8b**), mp 262–267 °C dec; $[\alpha]^{22}_D$ −6.3° (*c* 1.05, H_2O),[7b,9c] in the same manner as described above (Scheme 3). The use of D-phenylalanine gave 2-methyl-L-serine (**8a**), mp 261–265 °C dec; $[\alpha]^{22}_D$ +6.5° (*c* 1.01, H_2O).[7b,9c] The overall yield of this process was 70%.

In summary, asymmetric amino carboxylation to α-hydroxy ketones has been accomplished to give optically active β-hydroxy α,α-disubstituted α-amino acids.

Acknowledgment. We thank New Energy and Industrial Technology Development Organization (NEDO), Ministry of International Trade and Industry, Japan, for financial support.

Supplementary Material Available: Description of experimental details and X-ray crystallographic data of **4a** (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) No D atom was incorporated at C3 of the products, indicating that no racemization at C3 accompanied the reaction process. The use of other cyanide ion sources was also effective for this transformation: (a) diethyl cyanophosphonate (DECP), imidazole, in DMF/THF, room temperature, 18 h (95% yield; **4a**/**4b** = 1.5/1) and (b) trimethylsilyl cyanide (TMSCN) in 2-propanol, room temperature, 18 h (40% yield; **4a**/**4b** = 2.2/1). However, partial exchange with D atom at both the C3-H and the C6-H was observed under these conditions: DECP/imidazole-*d* (~40% D at C3 and ~50% D at C6) and TMSCN/2-propanol-*d* (>20% D at C3 and ~90% D at C6).

(17) If L-valine instead of phenylalanine was used, the ratio of the cyclic amino nitriles **4a** and **4b** was 1/2 (82% yield). After equilibration of this mixture with TFA, the ratio changed to 1/8.

(18) For an isomerization of α-amino nitrile: (a) Weinges, K.; Blackholm, H. *Chem. Ber.* **1980**, *113*, 3098. (b) Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, *48*, 5369.

(19) In the case of **4b**, ratio of the enamine/imine **6** was 1/19.

(20) For the biosynthesis of α,α-disubstituted α-amino acids, see: Walsh, C. *Enzyme Reaction Mechanisms*; Freeman: San Francisco, CA, 1979; p 804.