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Memory of Chirality in Diastereoselective α-Alkylation of Isoleucine and *allo*-Isoleucine Derivatives

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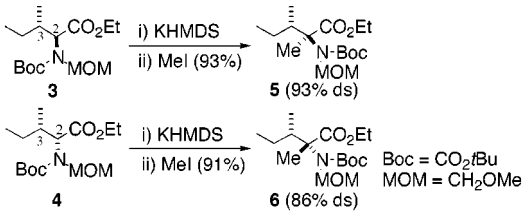
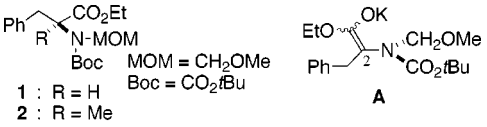
ABSTRACT



α-Methylation of 3 gave 5 as a major product whereas 4 gave 6 predominantly, although both 3 and 4 have an (*S*)-chiral center at C(3). This indicates that chirality at C(2) in 3 and 4 was memorized in the corresponding intermediate enolates and the induced chirality made a major contribution in the stereochemical course of the reaction, while chirality at the adjacent chiral center C(3) had little effect.

Nonproteinogenic α,α-disubstituted-α-amino acids have attracted considerable attention because of their utility as conformational modifiers of biologically active peptides and as enzyme inhibitors.[1] Typical methods for their asymmetric synthesis involve chiral auxiliary-based enolate chemistry.[2,3] However, we developed a direct asymmetric α-alkylation of α-amino acid derivatives without using any external chiral sources.[4,5] For example, phenylalanine derivative **1** undergoes α-methylation to give **2** in 81% ee and 96% yield upon treatment with potassium hexamethyldisilazide (KHMDS) followed by methyl iodide. We proposed the chiral nonracemic enolate intermediate **A**[6] with a chiral C(2)−N axis as a crucial intermediate for this asymmetric induction.[4c] We report here the stereochemistry of the α-alkylation of L-isoleucine derivative **3** and its C(2)-epimer, D-*allo*-isoleucine derivative **4**.



It is unclear whether the stereochemical course of the reaction of **3** and **4** is governed by the chirality at C(2) or C(3). If the chiral information at C(2) is completely lost with formation of the enolate, α-alkylation of either **3** or **4** should give products (e.g., **5** and **6**) with an identical diastereomeric

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(1) (a) Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. *J. Med. Chem.* **1991**, *34*, 404. (b) Altmann, K.-H.; Altmann, E.; Mutter, M. *Helv. Chim. Acta* **1992**, *75*, 1198. (c) Mendel, D.; Ellman, J.; Schultz, P. G.; *J. Am. Chem. Soc.* **1993**, *115*, 4359. (d) Stilz, H. U.; Jablonka, B.; Just, M.; Knolle, J.; Paulus, E. F.; Zoller, G. *J. Med. Chem.* **1996**, *39*, 2118. (e) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 995.

(2) For examples of *advanced* chiral auxiliaries which utilize chirality of parent α-amino acids, see: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612. (c) Ferey, V.; Toupet, L.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430. (d) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

(3) Recently, excellent catalytic methods for asymmetric synthesis of α,α-disubstituted-α-amino acid derivatives have been developed, see: (a) Kuwano, R. Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

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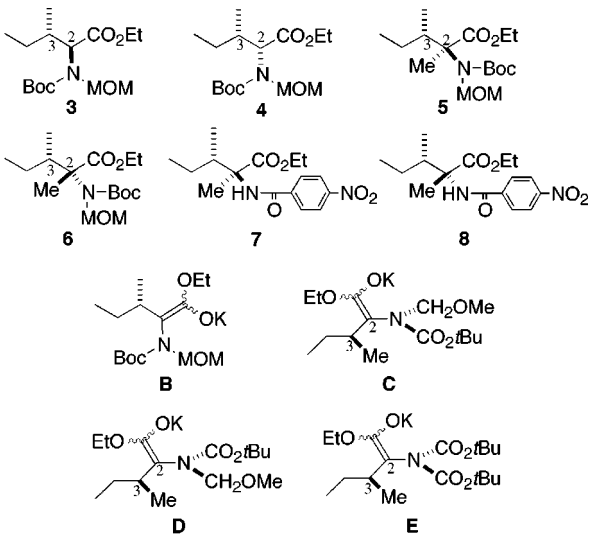
composition via common enolate intermediate **B**. On the other hand, if the chirality of C(2) is preserved in enolate intermediates (i.e., *memory of chirality*[7,8]), **3** and **4** should give products with different diastereomeric compositions via diastereomeric enolate intermediates such as **C** (a*S*, 3*S*) and **D** (a*R*, 3*S*), respectively. To test this hypothesis, the α-methylation of **3** and **4** was examined.



L-Isoleucine and D-*allo*-isoleucine derivatives **3** and **4** with *tert*-butoxycarbonyl (Boc) and methoxymethyl (MOM) groups at the nitrogen were prepared from the parent amino acids in respective yields of 92 and 75%. Treatment of **3** with 1.1 molar equiv of KHMDS in THF at −78 °C for 60 min followed by the addition of methyl iodide gave a mixture of diastereomers **5** and **6** in a ratio of 93:7 in a combined yield of 93%. On the other hand, the same treatment of **4** gave a mixture of **5** and **6** in a ratio of 14:86 with a combined yield of 91%. Although **5** and **6** were obtained as an inseparable mixture, the ratio was unambiguously determined by 400 MHz ^{1}H NMR, and each of the pure diastereomers was obtained after conversion to the corresponding *p*-nitrobenzamides **7** and **8**, respectively.[9] The stereochemistry of **8** was determined to be (2*R*,3*S*) by an X-ray crystallographic analysis (Figure 1).[10] α-Methylation of both **3** and **4** occurred

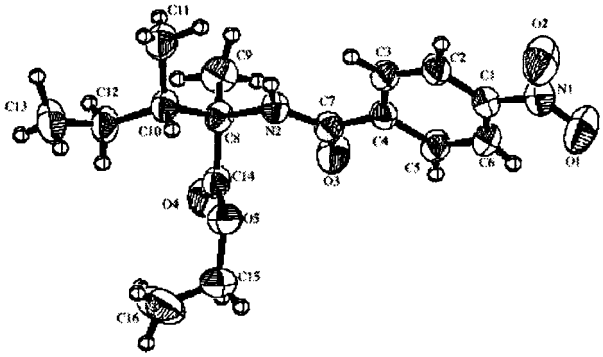


Figure 1. X-ray structure of **8**.

with retention of configuration at C(2) with comparable diastereoselectivities (93% ds for **3** vs 86% ds for **4**). Thus, the chirality at C(2) made a decisive contribution to the stereochemical course of α-methylation even in the presence of the adjacent chiral center C(3). We assume **C** and **D** for the possible structures of chiral enolate intermediates generated from **3** and **4**, respectively, by analogy with our recent results.[4c] The central chirality at C(2) in **3** and **4** appears to be preserved in **C** and **D** as dynamic axial chirality[6] due to restricted rotation of the C(2)−N bond.

Since the Boc and MOM groups at the nitrogen seem to be essential for the axial chirality in **C** and **D**, we next examined the reactions of *N*,*N*-di-Boc derivatives **9** and **10** that do not generate axially chiral enolates. Upon α-methylation under conditions identical to those for **3** and **4**, **9** gave a 54:46 mixture of **11** and **12** in 83% yield.[11] The exact same diastereomer ratio of **11** and **12** was observed in the α-methylation of **10** (87% yield). The stereochemical course of the α-methylation of **9** and **10** was totally controlled by the chirality at C(3), independent of the chirality at C(2), which is in sharp contrast to the reactions of **3** and **4**. These

(4) (a) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809. (b) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373. (c) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155.

(5) For related asymmetric α-substitution of α-amino acid derivatives without using external chiral sources, see: (a) Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971. (b) Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Chem. Commun.* **1991**, 924. (c) Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1067.

(6) Chiral properties of **A** are time- and temperature-dependent. Therefore, we call this type of chirality "dynamic chirality". Half-life to racemization of **A** is 22 h at −78 °C: see ref 4c.

(7) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694−9697.

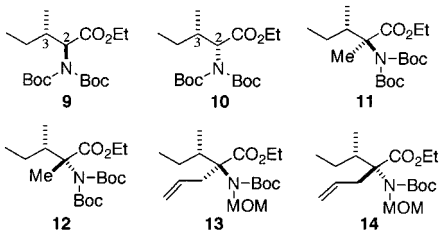
(8) The term "memory of chirality" and the related expressions have recently been used by us[4b,7] and others, see: (a) Schmalz, H.-G.; Konig, C. B.; Bernicke, D.; Siegel, S.; Pflectschinger, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1620. (b) Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586. (c) Yashima, E.; Maeda, K.; Okamoto, Y. *Nature* **1999**, *399*, 449. (d) Mizuno Y.; Aida, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 5278.

(9) (a) **Typical experimental procedure for α-alkylation:** A solution of **3** (152 mg, 0.5 mmol) in THF (4.5 mL) was added a to a solution of KHMDS[9b] (0.50 M in THF, 1.1 mL, 0.55 mmol) at −78 °C, and the mixture was stirred for 60 min. Methyl iodide (0.31 mL, 5.0 mmol) was added, and the solution was stirred at −78 °C for 20 h. The reaction mixture was poured into saturated aqueousNH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate:hexane = 1:12) to give an inseparable mixture (154 mg) of **5** and **6** (93% combined yield) and a trace amount (≤4%) of **3**. The diastereomeric ratio of **5** to **6** was determined by 400 MHz ^{1}H NMR to be 93:7. The mixture was treated with 4 M HCl in ethyl acetate followed by *p*-nitrobenzoyl chloride/*i*PrNEt_2 to give a crude mixture which was purified by column chromatography (SiO_2, $CHCl_3$:acetone = 60:1), giving a mixture of **7** and **8** (94% yield). Recrystallization from ether−hexane gave diastereomerically and analytically pure **7**. (b) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

(10) Crystal data for **8**: $C_{16}H_{22}N_2O_5$, MW = 322.36, orthorhombic, space group $P2_12_12_1$, a = 11.841(2) Å, b = 19.796(2) Å, c = 7.119(2) Å, V = 1668.7(6) Å$_3$, Z = 4, D_{calcd} = 1.283 g/cm^3, m(Cu Kα) = 7.98 cm^{-1}, R = 0.052.

(11) The stereochemistry of **11** and **12** was determined after their conversion to **7** and **8**.

results suggests that the reactions of both **9** and **10** share a common enolate intermediate, **E**.[12]



α-Allylation of **3** and **4** gave stereochemical results that paralleled those of α-methylation. Treatment of **3** with KHMDS for 60 min followed by the addition of allyl bromide in THF at −78 °C gave **13** and **14** in a 92:8 ratio with a combined yield of 78%, while the same treatment of **4** gave **13** and **14** in an 18:82 ratio with a combined yield of 73%.

(12) Enolate **E** is not axially chiral along the C(2)−N axis even if the bond rotation is restricted at −78 °C.

In conclusion, the stereochemical course of the α-alkylation of both L-isoleucine and D-*allo*-isoleucine derivatives **3** and **4** was controlled predominantly by the chirality at C(2), while that at the adjacent chiral center C(3) had little effect. The chirality at C(2) in **3** and **4** is assumed to be memorized in the intermediate enolates in the form of dynamic axial chirality along the C(2)−N axis.

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Supporting Information Available: Experimental procedure and characterization data of compounds **3**−**10**. This material is available free of charge via Internet at http://pubs.acs.org.

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