Substituent-dependent asymmetric synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]phenylalanine from chiral (*Z*)-dehydrophenylalanine

Makoto Oba, Shinji Nakajima and Kozaburo Nishiyama*

Department of Material Science and Technology, Tokai University, 317, Nishino, Numazu, Shizuoka 410-03, Japan

A stereo-divergent synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]-phenylalanine by a catalytic deuteriation of (*Z*)-dehydrophenylalanine included in a chiral diketopiperazine ring is accomplished simply by changing the substituents on the nitrogen atoms in the diketopiperazine ring.

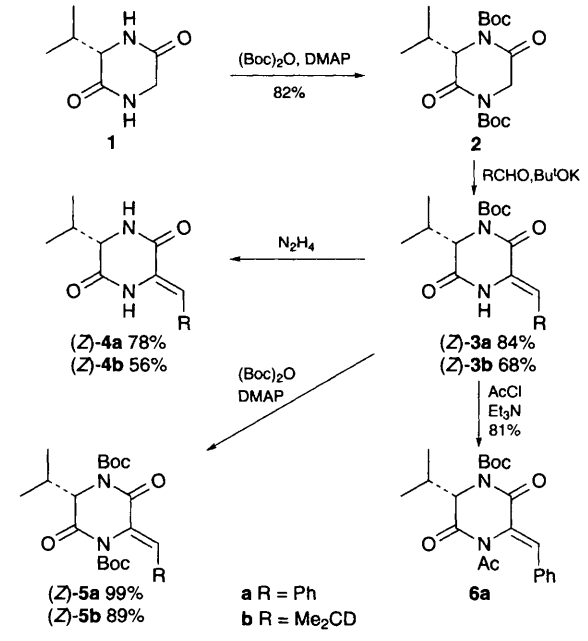
With a view to understanding the functions of peptide molecules, it is indispensable to clarify the three dimensional arrangement of their side chain groups, because their structural features significantly modulate their biological properties. The availability of L-amino acids regio- and stereo-selectively labelled with stable isotopes would allow the conformational analysis of peptide side chains by NMR spectroscopy, and proper assignment of the signals, the nuclear Overhauser effect (NOE), and the spin–spin coupling between the prochiral proton or methyl group and the other nuclei.[1] From this perspective, we previously reported the preparation of L-*threo*- and L-*erythro*-[1-^{13}C,2,3-$^2H_2$]amino acids as the probes, in which the stereoselective deuterium-labelling of the amino acids was accomplished by the catalytic deuteriation of (*Z*)-dehydroamino acids followed by a combination of enzymatic optical resolution and racemization at the α-position.[2] To circumvent such tedious processes, a direct synthesis of either diastereoisomer in high optical purity must be exploited. In this preliminary communication, we would like to describe an asymmetric synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]phenylalanine separately *via* a deuteriation of (*Z*)-dehydrophenylalanine included in a chiral diketopiperazine ring.[3] It is noteworthy that the diastereoselectivity of the deuteriation to give either the *threo* or the *erythro* isomer can be controlled only by the substituents on the nitrogen atoms in the diketopiperazine ring.

The chiral glycine template for this investigation was optically active *N,N'*-(diBoc)diketopiperazine derivative **2**, prepared by treatment of diketopiperazine **1**[4] derived from L-valine with $(Boc)_2O$–DMAP in 82% yield. As shown in Scheme 1, the protected diketopiperazine **2** was condensed with benzaldehyde in the presence of potassium *tert*-butoxide, affording cyclic 2,3-dehydrophenylalanine derivatives (*Z*)-**3a** and (*E*)–**3a** in 84 and 16% yields as a separable mixture by column chromatography on silica gel. During the reaction course, the Boc group on the dehydrophenylalanine residue was removed.[5] Deprotection of (*Z*)-**3a** with hydrazine, or reprotection using $(Boc)_2O$–DMAP, afforded dehydrophenylalanine derivatives (*Z*)-**4a** or (*Z*)-**5a** in 78 and 99% yields, respectively.

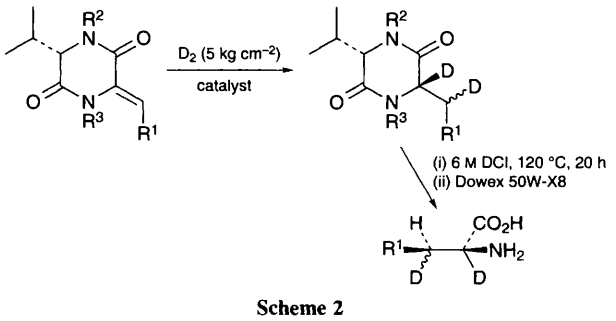
The catalytic deuteriation of the dehydrophenylalanine derivatives was performed in MeOD under a medium pressure (5 kg cm^{-2}) of deuterium gas. When the deuteriation of unprotected dehydrophenylalanine (*Z*)-**4a** was carried out in the presence of 10% Pd/C, the reaction was complete within 2 h to give a dideuteriated diketopiperazine derivative as almost a single diastereoisomer. The stereochemistry of the deuteriation was confirmed after conversion into phenylalanine itself. As illustrated in Scheme 2, acidic hydrolysis of the product in 6 M DCl followed by column chromatography on Dowex 50W-X8[6] gave [2,3-$^2H_2$]phenylalanine in 85% yield (Table 1, entry 1). A thorough analysis of the deuteriated phenylalanine by ^{1}H NMR (400 MHz) spectroscopy showed the ratio of *threo*:*erythro*† was 97:3, with satisfactory deuterium content (99%D at α-position). The optical yield was determined with HPLC using chiral stationary phase column to be 91% ee (L-form). The stereochemical outcome can be attributed to a selective addition of deuterium atoms to opposite sides of the isopropyl group on the almost planar diketopiperazine ring in a *cis* fashion.

From diBoc-protected dehydrophenylalanine (*Z*)-**5a** in a similar manner, L-[2,3-$^2H_2$]phenylalanine was also obtained in 74% yield with an excellent optical yield (98% ee, entry 4). Surprisingly, the ratio of *threo*:*erythro* was completely reversed, at 4:96, indicating the deuteriation of the protected diketopiperazine derivative (*Z*)-**5a** would mainly proceed *via* a *trans* addition.

To throw some light on the relationships between the diastereoselectivities and the protective groups, the deuteriation of dehydrophenylalanine derivatives (*Z*)-**3a** and its acetyl



Scheme 1



Scheme 2

Table 1 Asymmetric deuteriation of chiral cyclic dehydroamino acids

		Dehydroamino acid			Conditions			Deuteriated amino acid		
Entry	Compound	R^1	R^2	R^3	Catalyst	Solvent	*t*/h	Yield[a] (%)	*threo* : *erythro*[b]	ee[c] (%)
1	(*Z*)-**4a**	Ph	H	H	Pd/C	MeOD + DMF[d]	2	85	97:3	91
2	(*Z*)-**3a**	Ph	Boc	H	Pd/C	MeOD	2	62	78:22	94
3	(*Z*)-**6a**	Ph	Boc	Ac	Pd/C	MeOD	2	69	16:84	98
4	(*Z*)-**5a**	Ph	Boc	Boc	Pd/C	MeOD	2	74	4:96	98
5	(*E*)-**4a**	Ph	H	H	Pd/C	MeOD + DMF[d]	2	100	11:89	92
6	(*E*)-**5a**[e]	Ph	Boc	Boc	Pd/C	MeOD	2	72	74:26	99
7	(*Z*)-**4b**	Me_2CD	H	H	PtO_2[f]	MeOD	12	76	94:6	96
8	(*Z*)-**5b**	Me_2CD	Boc	Boc	Pd/C	MeOD	8	53	93:7	100

[a] Isolated yield based on the starting alkene. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis. The value refers to α-position. [d] DMF was added as a co-solvent to overcome the low solubility of the compound. [e] (*E* : *Z*) = 94 : 6. [f] PtO_2 was used instead of Pd/C in order to avoid the substantial H/D scrambling.

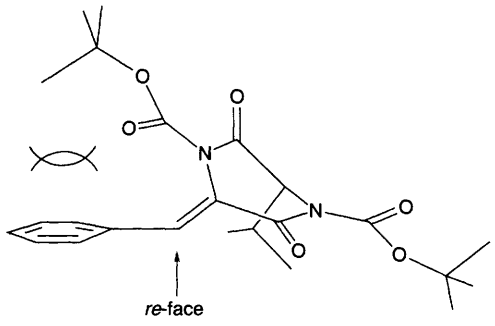


Fig. 1 Plausible molecular structure of protected diketopiperazine (*Z*)-**5a**

analogue (*Z*)-**6a**, were similarly carried out and the results are also shown in Table 1 (entries 2 and 3). With different substituents on the nitrogen atoms in the diketopiperazine ring, the diastereoselectivity varied as shown in the entries 1–4, and it appears that the *erythro*-selective deuteriation, *i.e. trans* addition, becomes predominant when bulky protective groups were present.

Such a tendency of the diastereoselectivity was also observed in the deuteriation of (*E*)-dehydrophenylalanines (*E*)-**4a** and (*E*)-**5a**, prepared from compound (*E*)-**3a**, but the extent was less remarkable (entries 5 and 6). Namely, the deuteriation of non-protected dehydrophenylalanine (*E*)-**4a** proceeded mainly through a *cis* addition to give a mixture of *threo* and *erythro* isomers (11 : 89) whereas a similar treatment of diBoc-protected dehydrophenylalanine (*E*)-**5a** resulted in the predominant formation of *trans* adducts (*threo* : *erythro* = 74 : 26). Coupled with the results of the deuteriation of (*Z*)-**3a** (entry 2), these results demonstrate that the steric repulsion between the phenyl ring and the protective group on the dehydrophenylalanine residue is not the only factor causing the observed *trans* addition, because such a steric constraint does not exist in the compound (Z)-**3a** and is not so critical in the (*E*)-forms.

The reason for the marked reversal in the diastereoselectivity is not clear but it may be due to an opposite face selectivity in an adsorption of the phenyl ring on a catalyst during the D-atom transfer to the benzylic position. For instance, the ^1H NMR signal for the Boc group on the dehydrophenylalanine residue of (*Z*)-**5a** shifted 0.52 ppm to upfield compared with the other one and it indicates the former Boc group lies in the region shielded by the phenyl ring. From these findings, it is assumed the structure of the compound prefers a boat-like conformation‡ due to the bulky protective groups and thus the phenyl ring is oriented in the neighbourhood of the Boc group as depicted in Fig. 1. Therefore, the deuteriation of the benzylic position should occur from the *re*-face opposite to the α-deuterium, and consequently, the selective formation of *trans* adducts would be observed.

On the other hand, when the corresponding dehydroleucine derivatives (*Z*)-**4b** and (*Z*)-**5b**, prepared from diketopiperazine **2** and 2-methyl[2-^2H]propanal[7] as shown in Scheme 1, were employed as the starting materials, the desired L-[2,3,4-$^2H_3$]leucine§ was obtained in 76 and 53% yields with 96 and 100% ees, respectively (entries 7 and 8). However, no significant difference in the ratio of *threo* : *erythro* was observed between the reactions, suggesting that the aromatic ring was indeed responsible for the reversal in the diastereoselectivity as described above.

Another notable result obtained in this work is that the degree of chiral induction is improved when both of the N–H moieties are protected (entries 3, 4, 6, and 8). This can also be rationalized by the boat-like conformation of the protected diketopiperazine ring, which is considered to increase the steric hindrance around the *si*-face of the α-carbon.

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Footnotes

† The ratio was determined by integration of the ^1H NMR signals corresponding to β-protons. In this case, the signals of *pro-R* and *pro-S* protons, observed in the *threo* and *erythro* isomers, resonate at δ 3.12 and 3.25, respectively.

‡ The preference for the boat-like conformation is also supported by MM2 calculations performed using the CSC CHEM3D program from Cambridge Scientific Computing, Inc.

§ The incorporation of deuterium to the γ-position of leucine is necessary in order to cancel the spin–spin coupling and the overlapping between β- and γ-proton signals.

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