Stereo-divergent synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]amino acids using optically active dioxopiperazine as a chiral template

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A stereo-divergent synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]amino acids from the same chiral auxiliary is described. Aldolization of *N*,*N*′-di(*tert*-butoxycarbonyl)dioxopiperazine 2, derived from L-valine, with various aldehydes followed by successive elaboration gives various 2,3-dehydroamino acid derivatives. Catalytic deuteriation of the derivatives then followed by acidic hydrolysis affords L-[2,3-$^2H_2$]amino acids in good yields with high optical purities. It becomes clear that diastereoselective deuteriation for either the *threo* or the *erythro* isomer depends upon the protective groups on the nitrogen atoms in the dioxopiperazine ring.

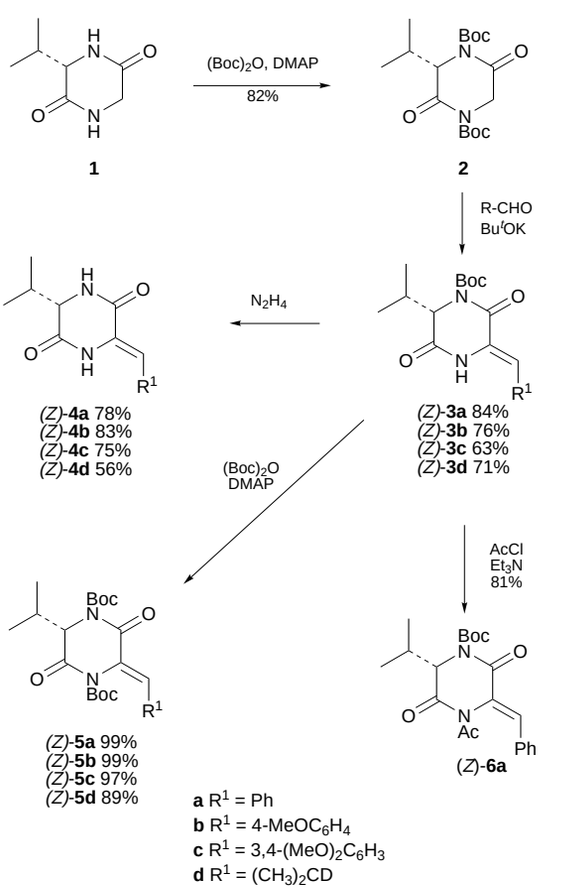
Recent advances in multi-dimensional nuclear magnetic resonance (NMR) spectroscopy have spurred the dynamic conformational analysis of peptides, DNA and their interactions with other molecules in solution.[1] However, the NMR spectra of high molecular weight compounds are generally too broad and complex to be assigned properly even at the higher field strengths currently available. In order to conquer these problems, positive (^{13}C, ^{15}N) and/or negative (^2H) stable isotope labelling has become one of a number of essential techniques now in use. Since it is impossible to incorporate these labelling atoms selectively into the macromolecules directly, it would be of great importance to establish an efficient route for the chemical synthesis of their components, such as amino acids and nucleosides, regio- and stereo-selectively labelled with stable isotopes.[2]

With a view to understanding the functions of peptide molecules, it is of overriding importance 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 stereoselectively labelled with isotopic hydrogen would allow the conformational analysis of peptide side chains to be assessed, because the structural information on the side chains could be mainly gleaned by observation of the nuclear Overhauser effect (NOE) and the spin-spin coupling between the prochiral proton or methyl group and the other nuclei. As far as the determination of the χ1-angle in a peptide is concerned, specimens of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]amino acids are necessary. For this reason, we previously established a method of preparing such amino acids based on the catalytic deuteriation of (*Z*)-dehydroamino acids followed by the combination of enzymatic optical resolution and racemization at the α-position.[3] To bypass such tedious processes, a direct synthesis of either diastereomer in high optical purity needs to be investigated. Although the chiral synthesis of L-*threo*-[2,3-$^2H_2$]amino acids is supposed to be easily achieved by the asymmetric deuteriation of (*Z*)-dehydroamino acids using a chiral auxiliary or a transition metal catalyst with a chiral phosphine ligand,[4] the corresponding L-*erythro* isomer is not easily accessible due to the lack of a general and efficient synthetic route to the thermodynamically unstable (*E*)-dehydroamino acids.

In our preliminary communication,[5] we briefly described a substituent-dependent asymmetric synthesis of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]phenylalanine by a catalytic deuteriation of a (*Z*)-dehydrophenylalanine moiety included in a chiral dioxopiperazine ring.[6] We report herein a full account of the work.

Results and discussion

The chiral glycine template employed for this study was the novel di-protected dioxopiperazine **2** as shown in Scheme 1. When the dioxopiperazine **2** was condensed with benzaldehyde in the presence of potassium *tert*-butoxide, cyclic 2,3-dehydrophenylalanine derivative (*Z*)-**3a** along with (*E*)-**3a** was obtained



Scheme 1

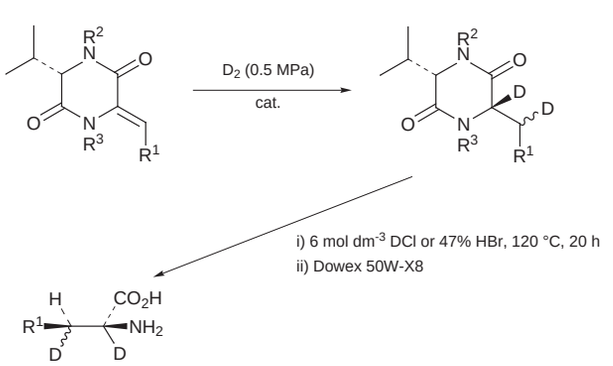
Table 1 Asymmetric deuteriation of chiral cyclic dehydroamino acids

	Dehydroamino acid				Conditions			Deuteriated amino acid		
Entry	R^1	R^2	R^3	Compound	Catalyst	Solvent	*t*/h	Yield[a] (%)	*threo*:*erythro*[b]	ee[c] (%)
1	Ph	H	H	(*Z*)-**4a**	Pd/C	MeOD + DMF[d]	2	85	97:3	91
2	Ph	Boc	H	(*Z*)-**3a**	Pd/C	MeOD	2	62	78:22	94
3	Ph	Boc	Ac	(*Z*)-**6a**	Pd/C	MeOD	2	69	16:84	98
4	Ph	Ac	Ac	(*Z*)-**8a**	Pd/C	MeOD	2	75	18:82	92
5	Ph	Ac	Boc	(*Z*)-**9a**	Pd/C	MeOD	2	67	6:94	93
6	Ph	Boc	Boc	(*Z*)-**5a**	Pd/C	MeOD	2	74	4:96	98
7	Ph	H	H	(*E*)-**4a**	Pd/C	MeOD + DMF[d]	2	100	11:89	92
8	Ph	Boc	Boc	(*E*)-**5a**[e]	Pd/C	MeOD	2	72	74:26	99
9	4-$MeOC_6H_4$[f]	H	H	(*Z*)-**4b**	Pd/C	MeOD + DMF[d]	2	74	96:4	83
10	4-$MeOC_6H_4$[f]	Boc	Boc	(*Z*)-**5b**	Pd/C	MeOD	1	72	3:97	95
11	3,4-$(MeO)_2C_6H_3$[f]	H	H	(*Z*)-**4c**	Pd/C	MeOD + DMF[d]	2	76	97:3	94
12	3,4-$(MeO)_2C_6H_3$[f]	Boc	Boc	(*Z*)-**5c**	Pd/C	MeOD	1	42	4:96	96
13	$(CH_3)_2CD$	H	H	(*Z*)-**4d**	PtO_2	MeOD	12	76	94:6	96
14	$(CH_3)_2CD$	Boc	Boc	(*Z*)-**5d**	Pd/C	MeOD	8	53	93:7	100
15	$(CH_3)_2CD$	H	H	(*E*)-**4d**	PtO_2	MeOD	7	58	10:90	95

[a] Isolated yield based on the starting olefin. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis. The value refers to the α-position. [d] DMF was added as a co-solvent to overcome the low solubility of the compound. [e] (*E*:*Z*) = 94:6. [f] Methyl aryl ether was cleaved during acidic hydrolysis.

in 84 and 16% yields, respectively, with concomitant removal of the Boc group attached to the dehydrophenylalanine residue.[7] Then, deprotection of the Boc group attached to the valine residue of (*Z*)-**3a** by hydrazine gave dehydrophenylalanine derivative (*Z*)-**4a**[6c] in 78% yield. Reprotection of compound (*Z*)-**3a** using $(Boc)_2O$–dimethylaminopyridine (DMAP) afforded di(Boc)-protected derivative (*Z*)-**5a** in 99% yield. Similar treatment of compound **2** with other aldehydes afforded the corresponding dehydroamino acid moieties included in the dioxopiperazine skeleton, such as tyrosine derivatives **3b**–**5b**, 3-(3,4-dihydroxyphenyl)alanine (DOPA) **3c**–**5c** and leucine derivatives **3d**–**5d**, in good to excellent yields. The representative results, mainly for the (*Z*)-isomers, are shown in Scheme 1.

To obtain sufficiently deuteriated compounds, a catalytic deuteriation of the dehydroamino acids **3**–**6**, **8**, **9** was performed in MeOD under medium pressure (0.5 MPa) deuterium gas. When a deuteriation of unprotected dehydrophenylalanine (*Z*)-**4a** was carried out in the presence of 10% Pd/C, the reaction was completed within 2 h to give a dideuteriated dioxopiperazine derivative as a single diastereomer almost exclusively. The stereoselectivity of the deuteriation was confirmed after conversion of the product into phenylalanine itself. As illustrated in Scheme 2, acidic hydrolysis of the product in 6 mol dm^{-3}



Scheme 2

DCl† followed by column chromatography on Dowex 50W-X8 gave [2,3-$^2H_2$]phenylalanine in 85% yield (Table 1, entry 1). A thorough analysis of the deuteriated phenylalanine by ^1H NMR (400 MHz) spectroscopy showed the ratio of *threo*:*erythro* was 97:3 with 99% deuterium content at the α-position. The absolute configuration at the α-position was determined to be L in 91% ee by HPLC analysis using a chiral stationary phase column. This stereochemical outcome can be attributed to a preference for delivery of deuterium atoms opposite to the isopropyl group on the almost planar dioxopiperazine ring in a *cis* fashion.

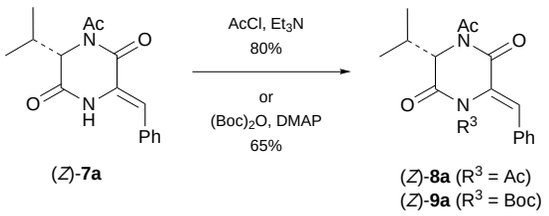
By treating di(Boc)-protected dehydrophenylalanine (*Z*)-**5a** in a similar manner, deuteriated phenylalanine was also obtained in 74% yield with an excellent optical yield (98% ee, entry 6). It was noteworthy that the ratio of *threo*:*erythro* was completely reversed to be 4:96, indicating that the deuteriation of the di(Boc)-protected derivative (*Z*)-**5a** had formally proceeded *via* a *trans* addition. From these findings, it was found that both diastereomers, L-*threo* and L-*erythro* isomers, of [2,3-$^2H_2$]phenylalanine were obtained from the same chiral auxiliary by changing the substituents on the dioxopiperazine ring.

Dehydrotyrosine derivatives **4b** and **5b** were also subjected to the above protocol. Thus, the catalytic deuteriation of unprotected dehydrotyrosine (*Z*)-**4b** followed by acidic hydrolysis with 47% HBr‡ afforded a 74% yield of L-[2,3-$^2H_2$]tyrosine (83% ee) in a ratio of 96:4 (*threo*:*erythro*) whereas a similar treatment of di(Boc)-protected dehydrotyrosine (*Z*)-**5b** gave a 3:97 (*threo*:*erythro*) mixture of L-[2,3-$^2H_2$]tyrosine (95% ee) in 72% yield (entries 9 and 10). Furthermore, stereoselective formation of L-*threo*- and L-*erythro*-[2,3-$^2H_2$]DOPA from the corresponding unprotected and di(Boc)-protected dioxopiperazine derivatives (*Z*)-**4c** and (*Z*)-**5c** was also achieved in diastereomeric ratios (*threo*:*erythro*) of 97:3 and 4:96, respectively (entries 11 and 12).

To throw some light on the relationship between the diastereoselectivity of the deuteriation and the protecting groups of the dioxopiperazine ring, several kinds of protected dehydrophenylalanines were prepared from dioxopiperazine derivatives (*Z*)-**3a** and (*Z*)-**7a**[8] with appropriate acylating agents (Schemes 1 and 3). A conversion of the obtained dehydrophenylalanine derivatives (*Z*)-**6a**, (*Z*)-**8a** and (*Z*)-**9a** as well as (*Z*)-**3a** into the deuteriated phenylalanine was similarly carried out and the results are also compiled in Table 1 (entries 2–5). As shown in the entries 1–6, the diastereoselectivity of the deuterium addition varied depending upon the substituents on the

† To minimize considerable H–D exchange at the α-position during the process, the deuteriated acid was used.

‡ 47% HBr was employed for the acidic hydrolysis of tyrosine and DOPA derivatives in order to achieve the simultaneous cleavage of the methyl aryl ether during the process. In these cases, the corresponding deuteriated acid, 47% DBr, could not be used due to the considerable H–D exchange at the 3,5-positions of the phenyl ring.[2b]



(*Z*)-**7a**

(*Z*)-**8a** (R^3 = Ac)
(*Z*)-**9a** (R^3 = Boc)

Scheme 3

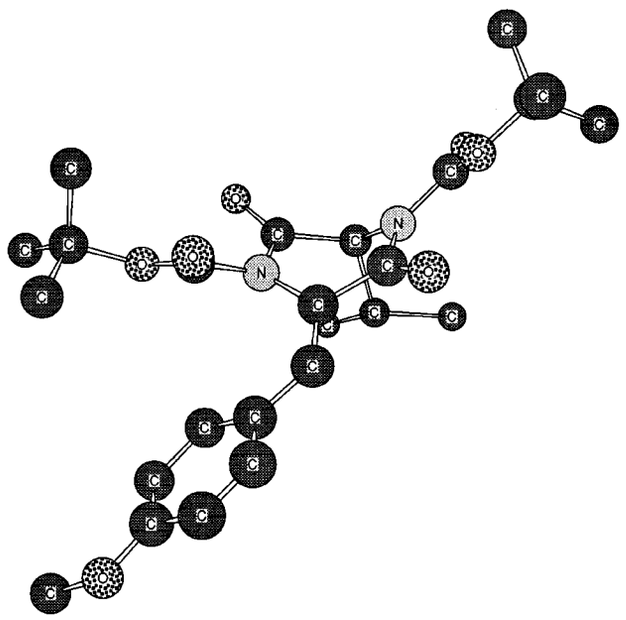


Fig. 1 X-Ray crystal structure (Chem3D drawing) of dehydrotyrosine derivative (*Z*)-**5b**. Hydrogen atoms are omitted for clarity.

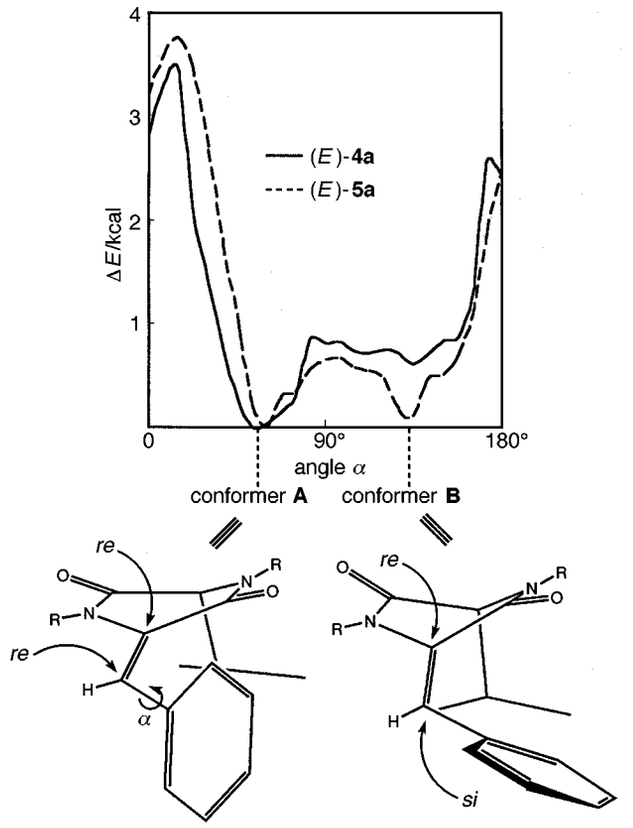


Fig. 2 Energy diagram for (*E*)-**4a** and (*E*)-**5a** as a function of angle *α*

nitrogen atoms of the dioxopiperazine ring and it appeared that the *erythro*-selective deuteriation, *i.e. trans* addition, had become predominant when bulky protective groups were attached to the nitrogen atoms of the dioxopiperazine ring. In particular, the substituents on the dehydrophenylalanine residue nitrogen atom exhibited remarkable effects on the diastereoselectivity.

As one of the important factors for the *trans* adduct selectivity, an interaction of the catalyst with the aryl ring is presumed. In order to clarify the three dimensional arrangement of the substituents on the di(Boc)-protected dioxopiperazine derivative, the structure of dehydrotyrosine derivative (*Z*)-**5b** was determined by X-ray crystallography. Fig. 1 shows a crystal structure (Chem3D§ drawing) of compound (*Z*)-**5b** in which the dioxopiperazine ring adopts a boat-like conformation induced by the bulky protective groups and the plane of the phenyl ring is deviated from that of the dioxopiperazine ring. Furthermore, the Boc group attached to the dehydrotyrosine residue occupies a very close position to the aromatic ring. In fact, the ^{1}H NMR spectrum of compound (*Z*)-**5b** shows that one of the Boc groups suffers a shift of −0.46 ppm relative to the other Boc group, indicating the former Boc group lies in the shielding region of the phenyl ring. Because of the steric hindrance around one side of the aromatic ring, the interaction of the catalyst occurs from the other side including the *re*-face of the benzylic position. However the deuteriation of the α-position still proceeds from the *re*-face opposite to the bulky isopropyl group and, consequently, the selective formation of the *trans* adduct would be observed.

Similar reversibility of the diastereoselectivity was also observed in the deuteriation of (*E*)-dehydrophenylalanines (*E*)-**4a** and (*E*)-**5a**, prepared from compound (*E*)-**3a** in an analogous manner to the corresponding (*Z*)-isomers as mentioned above, though the extent of the diastereoselectivities was not so remarkable (entries 7 and 8). Namely, the deuteriation of the unprotected dehydrophenylalanine (*E*)-**4a** proceeded mainly through a *cis* addition to give an 11 : 89 mixture of *threo* and *erythro* isomers whereas a similar treatment of the protected dehydrophenylalanine (*E*)-**5a** resulted in the predominant formation of the *trans* adduct (*threo* : *erythro* = 74 : 26). Coupled with the result obtained from the deuteriation of partially protected dehydrophenylalanine (*Z*)-**3a** (entry 2, *threo* : *erythro* = 78 : 22), these results demonstrate that the steric interaction between the phenyl ring and the protecting group on the dehydrophenylalanine residue is not the only factor causing the observed *trans* deuteriation, because such a steric constraint does not exist in compound (*Z*)-**3a** and is not so critical in the (*E*)-forms. The change in the conformational preference in the dehydroamino acid residue induced by the introduction of bulky protective groups must also be important.

In this respect, we next carried out the conformational analysis of dehydrophenylalanine derivatives (*E*)-**4a** and (*E*)-**5a** using AM1[9] calculations. Fig. 2 shows the conformational energy difference from the global minimum as a function of angle *α*. Examination of the molecular structures of conformers **A** and **B** illustrated in Fig. 2 reveals the origin of the *re*/*si* face selectivity in the D-atom transfer to the benzylic position. In conformer **A**, the interaction of the catalyst toward the phenyl ring is expected to occur from the less hindered side including the *re*-face of the benzylic position whereas the face preferred in the interaction with conformer **B** includes the *si*-face. Since the deuteriation of the α-position always occurs from the *re*-face, the *cis* and *trans* adducts (the *erythro* and *threo* isomer in this case), are obtained from conformers **A** and **B**, respectively. The energy diagram for compound (*E*)-**5a** clearly reveals the existence of conformer **B** as a local minimum and, consequently, the extent of *trans* addition would increase. A similar tendency is also observed for the corresponding (*Z*)-isomers (*Z*)-**3a**, (*Z*)-**4a** and (*Z*)-**5a** (Fig. 3). As the Boc group is introduced into the dioxopiperazine ring, conformer **B′**, which leads to the *trans*

§ CSC Chem3D Plus of Cambridge Scientific Computing, Inc.

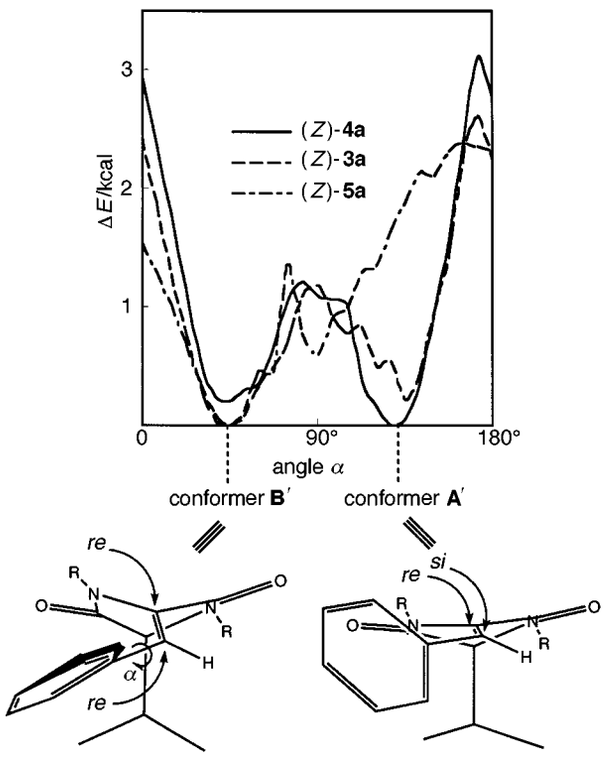


Fig. 3 Energy diagram for (*Z*)-**3a**, (*Z*)-**4a** and (*Z*)-**5a** as a function of angle *α*

adduct (*erythro* isomer), becomes predominant in the order of (*Z*)-**4a**, (*Z*)-**3a** and (*Z*)-**5a**. In the case of compound (*Z*)-**5a**, especially, the higher population of conformer **B′** is expected, showing good agreement with the X-ray result for the di(Boc)-protected dehydrotyrosine (*Z*)-**5b**. As described below, alkyl derivatives (*Z*)-**4d** and (*Z*)-**5d** did not show such stereodivergent selectivity.

Finally, we investigated the preparation of the corresponding deuteriated leucine derivatives. When dehydroleucine derivatives (*Z*)-**4d** and (*Z*)-**5d**, prepared from dioxopiperazine **2** and 2-methyl[2-^{2}H]propanal[10] as shown in Scheme 1, were employed as the starting materials, the desired L-[2,3,4-$^2H_3$]leucines¶ were obtained in 76 and 53% yields with 96 and 100% ees, respectively (entries 13 and 14). However, no significant difference in the ratio of *threo*:*erythro* was observed between the reactions (94:6 and 93:7), suggesting that the aromatic ring was indeed responsible for the reversal in the diastereoselectivity as described above. In order to obtain L-*erythro*-[2,3,4-$^2H_3$]leucine from a practical standpoint, dehydroleucine (*E*)-**4d** was subjected to similar processes to furnish the desired L-[2,3,4-$^2H_3$]leucine in 58% yield with 95% ee in a ratio of *threo*:*erythro* = 10:90 (entry 15). In the reduction of unprotected dehydroleucine derivatives, PtO_2 was used as a catalyst instead of Pd/C in order to avoid the substantial H–D scrambling.

The other noticeable result obtained in this work is that a higher degree of chiral induction is observed when both of the N–H moieties are protected with Boc groups (entries 6, 8, 10, 12 and 14). This can also be rationalized by considering the boat-like conformation of the protected dioxopiperazine ring which is considered to increase the steric hindrance around the *si*-face of the α-carbon.

In summary, the protocol described here allows for convenient access to either L-*threo*- or L-*erythro*-[2,3-$^2H_2$]amino acids from the corresponding (*Z*)-dehydroamino acid included in a chiral dioxopiperazine ring simply by changing the substituents on the nitrogen atoms in the ring.

¶ An introduction of a deuterium atom into the γ-position is necessary in order to cancel the spin-spin coupling and the overlapping between β- and γ-proton signals in leucine.

Experimental

Measurements and materials

Melting points were determined on a Yamato MP-21 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$, $(CD_3)_2SO$ or D_2O on a Varian UNITY-400 spectrometer. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (7.26 ppm), tetramethylsilane (0.00 ppm) or sodium 3-(trimethylsilyl)propanesulfonate (0.00 ppm); *J* values are in Hz. ^{13}C NMR spectra were also measured in $CDCl_3$ or $(CD_3)_2SO$ on a Varian UNITY-400 spectrometer using the central peak of $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (43.0 ppm) as an internal standard. High resolution mass spectra (EI) were obtained on a JEOL JMS-AX-500 spectrometer with DA7000 data system using perfluorokerosene as an internal standard. Optical purity was determined on a Senshu SSC-3100 high-pressure liquid chromatography system equipped with a chiral MCIGEL CRS10W column from Mitsubishi Kasei Co. or CROWNPAC CR(+) from Daicel Chemical Industries using 2 mol dm^{-3} $CuSO_4$ or $HClO_4$ (pH 2.0) solution as an eluent, respectively. Catalytic deuteriation was performed in an Ishii CHA-S medium-pressure catalytic hydrogenator.

(*S*)-3-(1-Methylethyl)piperazine-2,5-dione **1**,[11] (*Z*,*S*)-1-acetyl-3-benzylidene-6-(1-methylethyl)piperazine-2,5-dione **7a**[8] and 2-methyl[2-^{2}H]propanal[10] were prepared according to the reported procedure. All other reagents were of commercial grade and used as supplied.

(*S*)-1,4-Di(*tert*-butoxycarbonyl)-3-(1-methylethyl)piperazine-2,5-dione 2

To a mixture of (*S*)-3-(1-methylethyl)piperazine-2,5-dione **1** (4.00 g, 25.6 mmol) and $(Boc)_2O$ (11.7 g, 53.7 mmol) in DMF (30 cm^3) was added 4-dimethylaminopyridine (DMAP, 6.57 g, 53.8 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then, the reaction mixture was diluted with AcOEt, washed with aqueous $KHSO_4$, and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography on SiO_2, eluting with hexane–AcOEt (7:3), to give 7.51 g (82%) of compound **2** as a white solid, mp 129–131 °C; $\delta_H(CDCl_3)$ 1.04 (3 H, d, *J* 7), 1.10 (3 H, d, *J* 7), 1.53 (9 H, s), 1.54 (9 H, s), 2.07 (1 H, m), 4.15 and 4.73 (2 H, ABq, *J* 19) and 4.59 (1 H, d, *J* 10); $\delta_C(CDCl_3)$ 19.4, 19.5, 27.90, 27.94, 31.9, 49.1, 65.4, 84.7, 84.9, 150.1, 150.3, 164.7 and 165.6 (Found: M$^+$, 356.1980. $C_{17}H_{28}N_2O_6$ requires *M*, 356.1947).

(*Z*,*S*)- and (*E*,*S*)-3-Benzylidene-1-(*tert*-butoxycarbonyl)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-3a and (*E*)-3a]

To a chilled solution of dioxopiperazine **2** (1.77 g, 4.97 mmol) and benzaldehyde (555 mg, 5.24 mmol) in THF (20 cm^3) was added Bu^{t}OK (590 mg, 5.27 mmol), and the reaction mixture was stirred at room temperature for 0.5 h. Then, the reaction mixture was partitioned between AcOEt and aqueous NH_4Cl, and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with hexane–AcOEt (8:2) afforded (*Z*)-**3a** (1.43 g, 84%) as a viscous oil; $\delta_H(CDCl_3)$ 1.08 (3 H, d, *J* 7), 1.11 (3 H, d, *J* 7), 1.57 (9 H, s), 2.21 (1 H, m), 4.67 (1 H, dd, *J* 5 and 1), 7.14 (1 H, s), 7.37–7.47 (5 H, m) and 7.65 (1 H, br s); $\delta_C(CDCl_3)$ 18.4, 19.1, 28.0, 34.1, 64.0, 84.3, 119.1, 126.7, 128.7, 129.1, 129.4, 133.1, 151.3, 159.5 and 165.5 (Found: M$^+$, 344.1756. $C_{19}H_{24}N_2O_4$ requires *M*, 344.1736).

Further elution with hexane–AcOEt (7:3) yielded (*E*)-**3a** (274 mg, 16%) as a viscous oil; $\delta_H(CDCl_3)$ 1.10 (3 H, d, *J* 7), 1.11 (3 H, d, *J* 7), 1.53 (9 H, s), 2.22 (1 H, m), 4.59 (1 H, dd, *J* 7 and 1), 6.53 (1 H, s), 7.32 (3 H, m), 7.55 (2 H, m) and 9.22 (1 H, br s); $\delta_C(CDCl_3)$ 18.8, 19.2, 28.0, 33.7, 64.0, 84.2, 126.0, 126.1, 128.0, 128.6, 130.2, 133.2, 151.2, 158.7 and 167.7 (Found: M$^+$,

344.1720. $C_{19}H_{24}N_2O_4$ requires *M*, 344.1736). The following compounds were prepared by similar treatment of compound **2** with the appropriate aldehydes.

(*Z*,*S*)- and (*E*,*S*)-1-(*tert*-Butoxycarbonyl)-3-(4-methoxybenzylidene)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-3b and (*E*)-3b]. Treatment of **2** (2.14 g, 6.01 mmol) with 4-methoxybenzaldehyde (898 mg, 6.60 mmol) in the presence of Bu′OK (739 mg, 6.60 mmol) gave 1.70 g (76%) of (*Z*)-**3b** along with 352 mg (16%) of (*E*)-**3b**. (*Z*)-**3b**; $\delta_H(CDCl_3)$ 1.08 (3 H, d, *J* 7), 1.10 (3 H, d, *J* 7), 1.56 (9 H, s), 2.19 (1 H, m), 3.84 (1 H, s), 4.64 (1 H, d, *J* 7), 6.96 and 7.36 (4 H, AA′BB′q, *J* 9), 7.09 (1 H, s) and 7.62 (1 H, br s); $\delta_C(CDCl_3)$ 18.5, 19.1, 28.0, 33.9, 55.4, 64.0, 84.2, 115.0, 119.5, 125.2, 125.5, 130.4, 151.4, 159.8, 160.4 and 165.7 (Found: M^+, 374.1866. $C_{20}H_{26}N_2O_5$ requires *M*, 374.1842). (*E*)-**3b**; $\delta_H(CDCl_3)$ 1.08 (3 H, d, *J* 7), 1.09 (3 H, d, *J* 7), 1.53 (9 H, s), 2.17 (1 H, m), 3.82 (1 H, s), 4.56 (1 H, dd, *J* 8 and 1), 6.40 (1 H, s), 6.86 and 7.65 (4 H, AA′BB′q, *J* 9) and 8.13 (1 H, br s); $\delta_C(CDCl_3)$ 18.9, 19.2, 27.9, 33.4, 55.2, 63.9, 84.0, 113.5, 124.2, 125.5, 126.8, 132.5, 151.1, 159.2, 160.3 and 167.9 (Found: M^+, 374.1796. $C_{20}H_{26}N_2O_5$ requires *M*, 374.1842).

(*Z*,*S*)- and (*E*,*S*)-1-(*tert*-Butoxycarbonyl)-3-(3,4-dimethoxybenzylidene)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-3c and (*E*)-3c]. Treatment of **2** (1.17 g, 3.20 mmol) with 3,4-dimethoxybenzaldehyde (917 mg, 5.50 mmol) in the presence of Bu′OK (390 mg, 3.52 mmol) gave 813 mg (63%) of (*Z*)-**3c** along with 122 mg (9%) of (*E*)-**3c**. (*Z*)-**3c**; a pale yellow solid, mp 96–99 °C; $\delta_H(CDCl_3)$ 1.08 (3 H, d, *J* 7), 1.10 (3 H, d, *J* 7), 1.56 (9 H, s), 2.03 (1 H, m), 3.86 (3 H, s), 3.91 (3 H, s), 4.64 (1 H, dd, *J* 7 and 1), 6.85 (1 H, d, *J* 2), 6.91 (1 H, d, *J* 8), 7.02 (1 H, dd, *J* 8 and 2), 7.07 (1 H, s) and 7.69 (1 H, s); $\delta_C(CDCl_3)$ 18.4, 19.0, 27.9, 33.9, 56.0, 56.1, 64.0, 84.1, 112.3, 112.9, 119.3, 121.5, 125.5, 125.8, 150.0, 150.3, 151.3, 159.6 and 165.4 (Found: M^+, 404.1934. $C_{21}H_{28}N_2O_6$ requires *M*, 404.1947). (*E*)-**3c**; a pale yellow solid, mp 151–152 °C; $\delta_H(CDCl_3)$ 1.09 (6 H, d, *J* 7), 1.53 (9 H, s), 2.19 (1 H, m), 3.89 (3 H, s), 3.90 (3 H, s), 4.57 (1 H, d, *J* 8), 6.46 (1 H, s), 6.82 (1 H, d, *J* 8), 7.22 (1 H, d, *J* 8), 7.47 (1 H, d, *J* 2) and 9.19 (1 H, s); $\delta_C(CDCl_3)$ 18.8, 19.2, 27.9, 33.4, 55.9, 56.0, 63.9, 84.0, 110.9, 114.3, 124.3, 124.9, 125.7, 126.8, 148.5, 150.3, 151.3, 159.1 and 167.6 (Found: M^+, 404.1899. $C_{21}H_{28}N_2O_6$ requires *M*, 404.1947).

(*Z*,*S*)- and (*E*,*S*)-1-(*tert*-Butoxycarbonyl)-6-(1-methylethyl)-3-(2-methyl[2-^{2}H]propylidene)piperazine-2,5-dione [(*Z*)-3d and (*E*)-3d]. Treatment of **2** (859 mg, 2.41 mmol) with 2-methyl[2-^{2}H]propanal (876 mg, 12.0 mmol) gave 526 mg (71%) of (*Z*)-**3d** along with 81 mg (11%) of (*E*)-**3d**. (*Z*)-**3d**; $\delta_H(CDCl_3)$ 1.00 (3 H. d, *J* 7), 1.05 (3 H, d, *J* 7), 1.06 (3 H, s), 1.07 (3 H, s), 1.54 (9 H, s), 2.10 (1 H, m), 4.59 (1 H, dd, *J* 7 and 1), 6.12 (1 H, s) and 7.54 (1 H, br s); $\delta_C(CDCl_3)$ 18.3, 19.2, 21.6, 21.7, 25.5 (t, *J* 26), 27.9, 33.9, 63.6, 84.1, 125.4, 130.3, 151.3, 159.6 and 166.4 (Found: M^+, 311.1991. $C_{16}H_{25}{}^2HN_2O_4$ requires *M*, 311.1955). (*E*)-**3d**; $\delta_H(CDCl_3)$ 1.00 (3 H, s), 1.02 (3 H, d, *J* 7), 1.05 (3 H, d, *J* 7), 1.06 (3 H, s), 1.54 (9 H, s), 2.10 (1 H, m), 4.52 (1 H, dd, *J* 7 and 1), 5.44 (1 H, s) and 8.34 (1 H, br s); $\delta_C(CDCl_3)$ 18.7, 19.2, 22.4, 22.6, 26.0 (t, *J* 20), 28.0, 33.6, 63.7, 84.1, 124.6, 136.9, 151.1, 159.6 and 166.9 (Found: M^+, 311.1927. $C_{16}H_{25}{}^2HN_2O_4$ requires *M*, 311.1955).

(*Z*,*S*)-3-Benzylidene-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-4a]

To a solution of (*Z*)-**3a** (521 mg, 1.51 mmol) in THF (3 cm^3) was added hydrazine hydrate (150 mg, 3.00 mmol), and the solution was stirred at room temperature for 1 h. The precipitated solid was collected by suction to give 286 mg (78%) of (*Z*)-**4a** as a white solid, mp 232–234 °C (lit.,[6c] 232–234 °C); $\delta_H[(CD_3)_2SO]$ 0.89 (3 H, d, *J* 7), 0.96 (3 H, d, *J* 7), 2.10 (1 H, m), 3.79 (1 H, dd, *J* 4 and 4), 6.68 (1 H, s), 7.30 (1 H, m), 7.40 (2 H, m), 7.48 (2 H, m), 8.53 (1 H, br s) and 10.01 (1 H, br s); *m*/*z* 244 (M^+). The following compounds were similarly prepared.

(*E*,*S*)-3-Benzylidene-6-(1-methylethyl)piperazine-2,5-dione [(*E*)-4a]. Treatment of (*E*)-**3a** (225 mg, 0.654 mmol) with hydrazine hydrate (65 mg, 1.30 mmol) gave 101 mg (63%) of (*E*)-**4a** as a white solid, mp 231–233 °C; $\delta_H[(CD_3)_2SO]$ 0.90 (3 H, d, *J* 7), 0.95 (3 H, d, *J* 7), 2.12 (1 H, m), 3.74 (1 H, dd, *J* 4 and 4), 6.33 (1 H, s), 7.21 (1 H, m), 7.27 (2 H, m), 7.47 (2 H, m), 8.38 (1 H, br s) and 10.40 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 20.3, 21.6, 36.4, 63.6, 122.2, 130.4, 130.6, 130.7, 133.3, 137.8, 162.8 and 169.7 (Found: M^+, 244.1178. $C_{14}H_{16}N_2O_2$ requires *M*, 244.1212).

(*Z*,*S*)-3-(4-Methoxybenzylidene)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-4b]. Treatment of (*Z*)-**3b** (469 mg, 1.33 mmol) with hydrazine hydrate (260 mg, 5.32 mmol) gave 301 mg (83%) of (*Z*)-**4b** as a white solid, mp 220–225 °C; $\delta_H[(CD_3)_2SO]$ 0.88 (3 H, d, *J* 7), 0.95 (3 H, d, *J* 7), 2.08 (1 H, m), 3.75 (1 H, m), 3.78 (3 H, s), 6.64 (1 H, s), 6.97 and 7.84 (4 H, ABq, *J* 9), 8.44 (1 H, br s) and 9.91 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 20.4, 21.4, 36.7, 58.5, 64.0, 117.3, 117.6, 128.6, 129.2, 133.9, 162.4, 164.0 and 169.5 (Found: M^+, 274.1363. $C_{15}H_{18}N_2O_3$ requires *M*, 274.1317).

(*Z*,*S*)-3-(3,4-Dimethoxybenzylidene)-6-(1-methylethyl)-piperazine-2,5-dione [(*Z*)-4c]. Treatment of (*Z*)-**3c** (1.15 g, 2.86 mmol) with hydrazine hydrate (570 mg, 11.4 mmol) gave 651 mg (75%) of (*Z*)-**4c** as a white solid, mp 231–234 °C; $\delta_H[(CD_3)_2SO]$ 0.98 (3 H, d, *J* 7), 0.95 (3 H, d, *J* 7), 2.10 (1 H, m), 3.777 (3 H, s), 3.780 (3 H, s), 6.65 (1 H, s), 6.99 (1 H, d, *J* 8), 7.06 (1 H, s), 7.07 (1 H, d, *J* 8), 8.46 (1 H, d, *J* 3) and 9.97 (1 H, s); $\delta_C[(CD_3)_2SO]$ 20.4, 21.6, 31.6, 36.7, 59.0, 64.0, 115.5, 116.5, 117.8, 125.6, 128.7, 129.5, 152.1, 152.4, 164.1 and 169.7 (Found: M^+, 304.1407. $C_{16}H_{20}N_2O_4$ requires *M*, 304.1423).

(*Z*,*S*)-6-(1-Methylethyl)-3-(2-methyl[2-^{2}H]propylidene)-piperazine-2,5-dione [(*Z*)-4d]. Treatment of (*Z*)-**3b** (412 mg, 1.32 mmol) with hydrazine hydrate (132 mg, 2.64 mmol) gave 156 mg (56%) of (*Z*)-**4d** as a white solid, mp 238–241 °C; $\delta_H[(CD_3)_2SO]$ 0.81 (3 H, d, *J* 7), 0.91 (3 H, d, *J* 7), 0.91 (3 H, s), 0.94 (3 H, s), 2.09 (1 H, m), 3.75 (1 H, dd, *J* 3 and 3), 5.57 (1 H, s), 8.25 (1 H, br s) and 9.94 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 20.1, 21.5, 25.4, 25.6, 26.7 (t, *J* 20), 36.7, 63.6, 127.1, 128.8, 163.4 and 169.4 (Found: M^+, 211.1404. $C_{11}H_{17}{}^2HN_2O_2$ requires *M*, 211.1431).

(*E*,*S*)-6-(1-Methylethyl)-3-(2-methyl[2-^{2}H]propylidene)-piperazine-2,5-dione [(*E*)-4d]. Treatment of (*E*)-**3d** (500 mg, 1.61 mmol) with hydrazine hydrate (330 mg, 6.60 mmol) gave 230 mg (68%) of (*E*)-**4d** as a white solid, mp 236–242 °C; $\delta_H[(CD_3)_2SO]$ 0.82 (3 H, d, *J* 7), 0.900 (3 H, d, *J* 7), 0.902 (3 H, s), 0.93 (3 H, s), 2.07 (1 H, m), 3.66 (1 H, dd, *J* 3 and 3), 5.23 (1 H, s), 8.16 (1 H, br s) and 9.99 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 20.2, 21.6, 26.3, 26.4, 27.9 (t, *J* 20), 36.5, 63.5, 128.3, 132.3, 163.9 and 169.3 (Found: M^+, 211.1417. $C_{11}H_{17}{}^2HN_2O_2$ requires *M*, 211.1431).

(*Z*,*S*)-3-Benzylidene-1,4-di(*tert*-butoxycarbonyl)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-5a]

To a mixture of (*Z*)-**3a** (344 mg, 1.00 mmol) and $(Boc)_2O$ (240 mg, 1.10 mmol) in DMF (1 cm^3) was added DMAP (134 mg, 1.10 mmol), and the reaction mixture was stirred at room temperature for 2 h. Then, the reaction mixture was diluted with AcOEt, washed with aqueous $KHSO_4$ and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography on SiO_2, eluting with hexane–AcOEt (85:15), to give 441 mg (99%) of (*Z*)-**5a** as a viscous oil; $\delta_C(CDCl_3)$ 1.01 (3 H, d, *J* 7), 1.04 (9 H, s), 1.15 (3 H, d, *J* 7), 1.56 (9 H, s), 2.13 (1 H, m), 4.62 (1 H, d, *J* 11) and 7.35–7.45 (6 H, m); $\delta_C(CDCl_3)$ 19.3, 19.6, 27.1, 28.0, 31.6, 65.9, 84.5, 85.0, 126.9, 129.16, 129.19, 130.0, 131.0, 133.1, 147.0, 150.7, 162.0 and 165.4 (Found: M^+, 444.2278. $C_{24}H_{32}N_2O_6$ requires *M*, 444.2260). The following compounds were similarly prepared.

(*E*,*S*)-3-Benzylidene-1,4-di(*tert*-butoxycarbonyl)-6-(1-methylethyl)piperazine-2,5-dione [(*E*)-5a]. Reaction of (*E*)-**3a** (274 mg, 0.797 mmol) with $(Boc)_2O$ (217 mg, 1.00 mmol) in the presence of DMAP (117 mg, 0.959 mmol) afforded 307 mg (87%) of (*E*)-**5a** as a viscous oil; $\delta_H(CDCl_3)$ 1.04 (3 H, d, *J* 7), 1.10 (3 H, d, *J* 7), 1.54 (9 H, s), 1.57 (9 H, s), 2.18 (1 H, m), 4.57 (1 H, d, *J* 10), 6.91 (1 H, s), 7.36 (3 H, m) and 7.55 (2 H, m); $\delta_C(CDCl_3)$ 19.4, 19.6, 27.8, 27.9, 31.7, 65.9, 84.6, 85.3, 126.4,

128.3, 129.4, 129.9, 132.3, 135.3, 149.2, 150.6, 159.7 and 165.6 (Found: M^+, 444.2217. $C_{24}H_{32}N_2O_6$ requires *M*, 444.2260).

(*Z*,*S*)-1,4-Di(*tert*-butoxycarbonyl)-3-(4-methoxybenzylidene)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-5b]. Reaction of (*Z*)-**3b** (868 mg, 2.32 mmol) with $(Boc)_2O$ (913 mg, 4.19 mmol) in the presence of DMAP (340 mg, 2.79 mmol) afforded 1.11 g (100%) of (*Z*)-**5b** as colourless prisms, mp 159–161 °C; $\delta_H(CDCl_3)$ 1.10 (3 H, d, *J* 7), 1.098 (9 H, s), 1.12 (3 H, d, *J* 7), 1.557 (9 H, s), 2.10 (1 H, m), 3.82 (3 H, s), 4.61 (1 H, d, *J* 11), 6.92 and 7.80 (4 H, AA′BB′q, *J* 9) and 7.32 (1 H, s); $\delta_C(CDCl_3)$ 19.3, 19.6, 27.3, 28.0, 31.6, 55.4, 66.0, 84.3, 84.8, 114.7, 125.2, 125.9, 131.1, 131.3, 147.4, 151.0, 161.3, 162.3 and 165.7 (Found: M^+, 474.2362. $C_{25}H_{34}N_2O_7$ requires *M*, 474.2366).

(*Z*,*S*)-1,4-Di(*tert*-butoxycarbonyl)-3-(3,4-dimethoxybenzylidene)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-5c]. Reaction of (*Z*)-**3c** (406 mg, 1.00 mmol) with $(Boc)_2O$ (261 mg, 1.20 mmol) in the presence of DMAP (146 mg, 1.20 mmol) afforded 488 mg (97%) of (*Z*)-**5c** as a viscous oil; $\delta_H(CDCl_3)$ 1.01 (3 H, d, *J* 7), 1.13 (3 H, d, *J* 7), 1.10 (9 H, s), 1.56 (9 H, s), 2.12 (1 H, m), 3.88 (3 H, s), 3.90 (3 H, s), 4.61 (1 H, d, *J* 11), 6.89 (1 H, d, *J* 8), 7.00 (1 H, d, *J* 2), 7.05 (1 H, dd, *J* 8 and 2) and 7.30 (1 H, s); $\delta_C(CDCl_3)$ 19.3, 19.5, 27.3, 28.0, 31.4, 55.9, 56.1, 66.0, 84.4, 85.0, 111.5, 111.6, 123.7, 125.3, 125.9, 131.0, 147.5, 149.4, 150.8, 150.9, 162.3 and 165.6 (Found: M^+, 504.2503. $C_{26}H_{36}N_2O_8$ requires *M*, 504.2472).

(*Z*,*S*)-1,4-Di(*tert*-butoxycarbonyl)-6-(1-methylethyl)-3-(2-methyl[2-^{2}H]propylidene)piperazine-2,5-dione [(*Z*)-5d]. Reaction of (*Z*)-**3d** (632 mg, 2.03 mmol) with $(Boc)_2O$ (531 mg, 2.44 mmol) in the presence of DMAP (297 mg, 2.43 mmol) afforded 728 mg (89%) of (*Z*)-**5d** as an amorphous solid; $\delta_H(CDCl_3)$ 0.98 (3 H, d, *J* 7), 0.98 (3 H, s), 1.04 (3 H, d, *J* 7), 1.09 (3 H, s), 1.54 (9 H, s), 1.55 (9 H, s), 1.93 (1 H, m), 4.50 (1 H, d, *J* 10) and 6.35 (1 H, s); $\delta_C(CDCl_3)$ 19.3 (2 C), 20.0, 21.4, 27.1 (t, *J* 19), 27.7, 27.9, 31.4, 65.6, 84.2, 85.1, 126.6, 142.1, 149.4, 150.9, 161.7 and 165.0 (Found: M^+, 411.2461. $C_{21}H_{33}{}^2HN_2O_6$ requires *M*, 411.2480).

(*Z*,*S*)-1-Acetyl-3-benzylidene-4-(*tert*-butoxycarbonyl)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-9a]. Reaction of (*Z*)-**7a** (659 mg, 2.30 mmol) with $(Boc)_2O$ (550 mg, 2.53 mmol) in the presence of DMAP (310 mg, 2.53 mmol) afforded 573 mg (65%) of (*Z*)-**9a** as a viscous oil; $\delta_H(CDCl_3)$ 0.93 (3 H, d, *J* 7), 1.08 (9 H, s), 1.17 (3 H, d, *J* 7), 2.10 (1 H, m), 2.62 (3 H, s), 5.03 (1 H, d, *J* 11) and 7.38–7.47 (6 H, m); $\delta_C(CDCl_3)$ 19.1, 19.4, 26.0, 27.2, 31.4, 62.1, 85.0, 126.9, 129.1, 129.2, 130.0, 131.0, 133.0, 147.2, 163.8, 164.9 and 171.1 (Found: M^+, 386.1861. $C_{21}H_{26}N_2O_5$ requires *M*, 386.1842).

(*Z*,*S*)-4-Acetyl-3-benzylidene-1-(*tert*-butoxycarbonyl)-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-6a]

To a solution of (*Z*)-**3a** (344 mg, 1.00 mmol) and triethylamine (202 mg, 2.00 mmol) in CH_2Cl_2 (5 cm^3) was added dropwise acetyl chloride (157 mg, 2.00 mmol). After stirring at room temperature for 0.5 h, the reaction mixture was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with hexane–AcOEt (8:2), to give 312 mg (81%) of (*Z*)-**6a** as an amorphous solid; $\delta_H(CDCl_3)$ 1.05 (3 H, d, *J* 7), 1.15 (3 H, d, *J* 7), 1.56 (9 H, s), 2.18 (1 H, m), 2.45 (3 H, s), 4.67 (1 H, d, *J* 10), 7.30–7.40 (5 H, m) and 7.54 (1 H, s); $\delta_C(CDCl_3)$ 19.3, 19.6, 27.3, 27.9, 31.8, 65.6, 84.5, 124.9, 128.7, 129.0, 130.1, 133.4, 133.8, 151.0, 162.0, 167.8 and 168.2 (Found: M^+, 386.1877. $C_{21}H_{26}N_2O_5$ requires *M*, 386.1842).

(*Z*,*S*)-1,4-Diacetyl-3-benzylidene-6-(1-methylethyl)piperazine-2,5-dione [(*Z*)-8a]

A similar reaction of (*Z*,*S*)-1-acetyl-3-benzylidene-6-(1-methylethyl)piperazine-2,5-dione **7a** (463 mg, 1.62 mmol) and acetyl chloride (254 mg, 3.24 mmol) in the presence of triethylamine (327 mg, 3.24 mmol) afforded 407 mg (80%) of (*Z*)-**8a** as a viscous oil; $\delta_H(CDCl_3)$ 0.96 (3 H, d, *J* 7), 1.17 (3 H, d, *J* 7), 2.48 (3 H, s), 2.60 (3 H, s), 5.09 (1 H, d, *J* 10), 7.38 (5 H, m) and 7.57 (1 H, s); $\delta_C(CDCl_3)$ 19.3, 19.6, 25.9, 27.3, 31.8, 62.8, 124.9, 128.8, 129.1, 133.5, 134.2, 164.1, 167.7, 168.4 and 171.2 (Found: M^+, 328.1425. $C_{18}H_{20}N_2O_4$ requires *M*, 328.1423).

L-*threo*-[2,3-$^2H_2$]Phenylalanine

A solution of (*Z*)-**4a** (101 mg, 0.414 mmol) in MeOD (10 cm^3) and DMF (10 cm^3) was deuteriated using D_2 gas (0.5 MPa) in the presence of 10% Pd/C (28 mg) for 2 h. After removal of the catalyst by filtration through a Celite pad, the solution was evaporated to give a dideuteriated dioxopiperazine derivative which was directly subjected to acidic hydrolysis with 6 mol dm^{-3} DCl at 120 °C for 20 h to afford a mixture of valine and deuteriated phenylalanine. On a 30 × 200 mm Dowex 50W-X8 column operated in the sodium form, separation of valine and phenylalanine was effected by using buffers of gradually increasing pH from 3.3 to 5.0 as eluents. The second fraction containing the deuteriated phenylalanine was then acidified to pH 1.0 with conc. HCl and treated with Dowex 50W-X8 (H^+ form) in order to separate the phenylalanine from citric acid to yield L-*threo*-[2,3-$^2H_2$]phenylalanine (59 mg, 85%). The ratio of *threo*:*erythro* (97:3) was determined by integration of the β-proton region in the ^1H NMR spectrum and the optical purity was checked by HPLC to be 91% ee; $\delta_H(D_2O)$ 3.09 (0.97 H, s), 3.25 (0.03 H, s) and 7.25–7.45 (5 H, m). The following amino acids were similarly prepared.

L-*erythro*-[2,3-$^2H_2$]Phenylalanine. Treatment of (*Z*)-**5a** (560 mg, 1.26 mmol) afforded 155 mg (74%) of L-*erythro*-[2,3-$^2H_2$]phenylalanine with 98% ee; $\delta_H(D_2O)$ 3.09 (0.04 H, s), 3.25 (0.96 H, s) and 7.29–7.44 (5 H, m).

L-*threo*-[2,3-$^2H_2$]Tyrosine. Treatment of (*Z*)-**4b** (394 mg, 1.44 mmol) afforded 194 mg (74%) of L-*erythro*-[2,3-$^2H_2$]tyrosine with 83% ee; $\delta_H(D_2O)$ 2.63 (0.99 H, s), 2.82 (0.01 H, s), 6.57 and 6.98 (4 H, ABq, *J* 8).

L-*erythro*-[2,3-$^2H_2$]Tyrosine. Treatment of (*Z*)-**5b** (365 mg, 0.770 mmol) afforded 102 mg (72%) of L-*threo*-[2,3-$^2H_2$]tyrosine with 95% ee; $\delta_H(D_2O)$ 2.63 (0.02 H, s), 2.82 (0.98 H, s), 6.57 and 6.98 (4 H, ABq, *J* 8).

L-*threo*-[2,3-$^2H_2$]DOPA. Treatment of (*Z*)-**4c** (208 mg, 0.684 mmol) afforded 104 mg (76%) of L-*erythro*-[2,3-$^2H_2$]DOPA with 94% ee; $\delta_H(D_2O)$ 2.98 (0.88 H, s), 3.14 (0.12 H, s), 6.74 (1 H, d, *J* 8), 6.83 (1 H, s) and 6.90 (1 H, d, *J* 8) (Found: M^+, 199.0829. $C_{21}H_{33}{}^2HN_2O_6$ requires *M*, 199.0814).

L-*erythro*-[2,3-$^2H_2$]DOPA. Treatment of (*Z*)-**5c** (498 mg, 0.988 mmol) afforded 82 mg (42%) of L-*threo*-[2,3-$^2H_2$]DOPA with 96% ee; $\delta_H(D_2O)$ 2.98 (0.08 H, s), 3.14 (0.92 H, s), 6.74 (1 H, d, *J* 8), 6.83 (1 H, s) and 6.90 (1 H, d, *J* 8) (Found: M^+, 199.0845. $C_{21}H_{33}{}^2HN_2O_6$ requires *M*, 199.0814).

L-*threo*-[2,3,4-$^2H_3$]Leucine. Treatment of (*Z*)-**5d** (270 mg, 0.657 mmol) afforded 47 mg (53%) of L-*threo*-[2,3,4-$^2H_3$]leucine with 100% ee; $\delta_H(D_2O)$ 0.93 (3 H, s), 0.95 (3 H, s), 1.64 (0.93 H, s) and 1.70 (0.07 H, s).

L-*erythro*-[2,3,4-$^2H_3$]Leucine. Treatment of (*E*)-**4d** (230 mg, 1.00 mmol) afforded 78.0 mg (58%) of L-*erythro*-[2,3,4-$^2H_3$]leucine with 95% ee; $\delta_H(D_2O)$ 0.93 (3 H, s), 0.95 (3 H, s), 1.64 (0.10 H, s) and 1.70 (0.90 H, s).

X-Ray structure determination of (*Z*)-5b

Data collection and processing. A colourless prismatic crystal of $C_{25}H_{33}N_2O_7$, $M = 437.54$, having approximate dimensions of 0.30 × 0.50 × 0.40 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα ($\lambda = 0.710\,69$ Å) radiation. Monoclinic, $a = 13.475(3)$, $b = 15.646(6)$, $c = 12.492(2)$ Å, $\beta = 95.73(2)°$, $V = 2620(1)$ Å^3 (by least-squares refinement using the setting angles of 25 carefully centred reflections in the range $22.33 < 2\theta < 24.73°$), space group $P2_1/n$ (#14), $Z = 4$, $D_{calc} = 1.200$ g cm^{-3}. The data were collected at 23 °C using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.38° with a take-

off angle of 6.0°. Scans of (1.10 + 0.30 tan θ)° were made at a speed of 8.0° min^{-1} (in ω). Of the 6477 reflections measured, 6223 were unique (R_{int} = 0.022).‖ The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards increased by 0.06%. The linear absorption coefficient, μ, for Mo-Kα radiation is 0.88 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.98 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure solution and refinement. The structure was solved by direct methods using SHELXS86.[12] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 2414 observed reflections [$I > 3.00\sigma(I)$] and 308 variable parameters and converged with unweighted and weighted agreement factors of $R = 0.060$ and $R_w = 0.067$. The standard deviation of an observation of unit weight was 2.47. The weighting schemes were based on counting statistics and included a factor ($p = 0.023$) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.25 and −0.34 e Å^{-3}, respectively. Neutral atom scattering factors were taken from ref. 13. Anomalous dispersion effects were included in F_{calc};[14] the values for $\Delta f'$ and $\Delta\varphi''$ were those of ref. 15. All calculations were performed using the TEXSAN ** program on a Silicon Graphics INDY computer.

Computational procedure. AM1[9] calculations were performed using CAChe WorkSystem ver. 3.9 from Oxford Molecular Group, Inc. on an Apple Power Macintosh 7600/132 computer. The initial geometry was created by a modification of the X-ray result for compound (*Z*)-**5b**. To create a map of the heat of formation with respect to the variation of the dihedral angle α, the energy is computed at each geometry defined by the angle α with optimizing other internal coordinates, where the angle α was varied by stepping through 0–180° at 7.5°.

‖ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/199.

** TEXSAN Crystal Structure Analysis Package of Molecular Structure Corporation.

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