# Regiospecific Deuteriation of Chiral 3-Isopropyl-2,5-dimethoxy-3,6-dihydropyrazines in the Stereospecific Synthesis of α-Deuteriated α-Amino Acids

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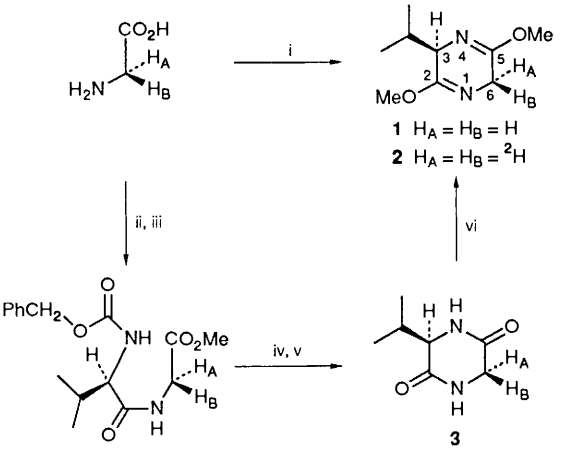
Base-catalysed deuteriation of (3*R*)- or (3*S*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine in refluxing $CH_3O^2H$–$^2H_2O$ gives the [6-$^2H_2$] isotopomer in excellent yield without disturbing the stereogenic centre at C-3, and thus providing convenient and efficient access to a range of (*R*)- and (*S*)-α-deuteriated α-amino acids.

The availability of labelled amino acids in enantiomerically pure form is of prime importance in many biosynthetic and metabolic studies and also in the delineation of enzyme mechanism. Access to some $C^{\alpha}$-deuteriated and titriated L-α-amino acids, for example, chiral glycines, L-aspartic acid and L-glutamic acid, has been facilitated through the use of enzymes in appropriately labelled buffer solution.[1,2] The preparation of labelled D-amino acids, however, has been much more difficult. Some D-α-amino acids (as well as the L-antipodes) have been prepared through the acylase-catalysed kinetic resolution of racemic mixtures of *N*-acetylated amino acids.[3] Here, deuterium or tritium can be introduced by exchanging the acidic hydrogen of azlactone intermediates during acetylation.[2] Unfortunately, the differential rates for the deacylation vary considerably for the two antipodes of different amino acids, so that enantiomeric excesses are variable. Furthermore, the technique is not applicable in several instances.

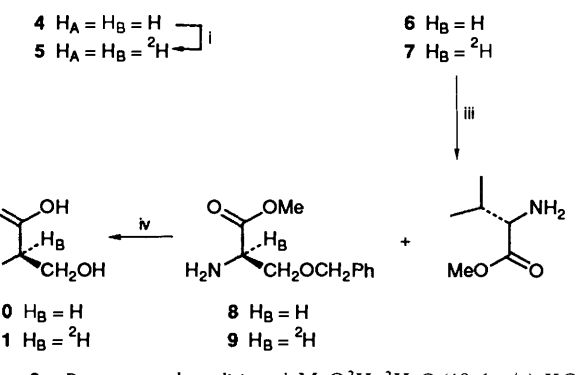
Schollkopf's bis-lactim ether methodology has proved to be of enormous utility in the preparation of a wide range of D- and L-α-amino acids[4] and the chiral dihydropyrazine precursors are now commercially available, for example, compound **1**. Nevertheless, to introduce deuterium at $C^{\alpha}$ of the amino acid product has hitherto required the synthesis of the [$^2H_2$]dihydropyrazine **2** from [$^2H_2$]glycine, Scheme 1, a rather expensive and inefficient practice, see below. Here we describe a facile and efficient method for preparing the [$^2H_2$]dihydropyrazine in excellent yield directly from the unlabelled material and demonstrate its use in the preparation of α-deuteriated α-amino acids. (3*R*)-3-Isopropyl-2,5-dimethoxy-3,6-dihydropyrazine **1** was prepared from glycine and (2*R*)-valine in up to a maximum overall yield of 62% (from glycine) or was obtained commercially. Note that in the synthesis of compound **1**, the conversion of the diketopiperazine **3** into the bis-lactim ether gave the most variable yields (66–89%) and was wasteful of trimethyloxonium tetrafluoroborate.

Several methods for introducing deuterium at C-6 were considered using the known kinetic preference for 6-H abstraction.[4] Methods based upon repeatedly quenching the BuLi generated anion of **1** with $^2H_2O$ or $CH_3O^2H$ were quickly abandoned due to the formation of an array of by-products after the first cycle. This method also suffered from the potential problem of low selectivity for removing protium from the singly deuteriated compound in the second cycle of anion formation.

Compound **1** in $^2H_2O$ when stirred in the presence of KOH under a variety of conditions also proved to be of little or no utility. At room temperature, 6-H exchange was almost undetectable, and at higher temperatures, several by-products were formed. However, under optimised conditions, refluxing $CH_3O^2H$–$^2H_2O$ (10:1, v/v) in the presence of 1 equiv. of




**Scheme 1** *Reagents and conditions:* i, as per ref. 4; ii, $SOCl_2$ (1.2 equiv.), MeOH, 0 °C, then reflux 30 min; iii, isobutyl chloroformate (1 equiv.), *N*-methylmorpholine (2 equiv.), EtOAc–DMF, *N*-benzyloxycarbonyl-(2*R*)-valine (1 equiv.), stir, room temp., 16 h, 87%; iv, $H_2$, Pd/C, DCM/MeOH (3:1); v, PhMe, reflux, 16 h, 45% over 2 steps; vi, $[Me_3O]^+BF_4^-$ (3.5 equiv.), DCM, 66%




**Scheme 2** *Reagents and conditions:* i, $MeO^2H$–$^2H_2O$ (10:1, v/v), KOH (1 equiv.), reflux, 3 h, 80%; ii, BuLi (1 equiv.), THF, −90 °C to −60 °C, then $PhCH_2OCH_2Br$ (1.5 equiv.), THF, −90 °C, stir, 16 h, 56%; iii, 0.2 mol $dm^{-3}$ HCl (2 equiv.), room temp., stir, 16 h then separation on flash silica 19:1 $Et_2O$–EtOH, 70%; iv, 5 mol $dm^{-3}$ HCl, reflux, 3 h then EtOH, propylene oxide, reflux, 15 min, 89%

$KO^2H$, the C-6 dideuteriation of a 1 mol $dm^{-3}$ solution of compound **1** proceeded smoothly, without the formation of side

**Table 1**

| Compound[a] (stereochemistry and label at C$^{\alpha}$) | Overall yield (%) (from *R*- or *S*-**1** or **2**) | $[\alpha]_D$[b] | $[\alpha]_D$ Theory |
|---|---|---|---|
| Serine | | | |
| **10** (*R*-, H) | 20 | −13.6 (*c* 1.02, 1 mol dm$^{-3}$ HCl) | −14.3 (c 1.0, 1 mol dm$^{-3}$ HCl)[5,6] |
| **11** (*R*-, $^2$H) | 35 | −13.5 (*c* 1.025, 1 mol dm$^{-3}$ HCl) | |
| **20** (*S*-, H) | 25 | +13.2 (*c* 1.0, 1 mol dm$^{-3}$ HCl) | +14.5 (c 1.0, 1 mol dm$^{-3}$ HCl)[5,6] |
| **21** (*S*-, $^2$H) | 20 | +12.7 (*c* 1.01, 1 mol dm$^{-3}$ HCl) | |
| Phenylalanine | | | |
| **22** (*S*-, H) | 30 | −30.9 (*c* 2.035, $H_2O$) | −32.5 (*c* 2.0, $H_2O$)[7] |
| **23** (*S*-, $^2$H) | 35 | −28.2 (*c* 1.5, $H_2O$) | |
| Allylglycine | | | |
| **24** (*S*-, H) | 15 | −5.7 (*c* 2.0, 5 mol dm$^{-3}$ HCl) | +5.7 (*c* 2.0, 5 mol dm$^{-3}$ HCl) for *R* **24**[8] |
| **25** (*S*-, $^2$H) | 20 | −4.2 (*c* 1.87, 5 mol dm$^{-3}$ HCl) | |
| Aspartic acid | | | |
| **26** (*S*-, H) | 15 | +21.8 (*c* 0.495, 5 mol dm$^{-3}$ HCl) | +25.2 (*c* 2.0, 5 mol dm$^{-3}$ HCl)[6] |
| **27** (*S*-, $^2$H) | 15 | +19.5 (*c* 0.495, 5 mol dm$^{-3}$ HCl) | |

[a] All compounds and intermediates gave the expected spectral and analytical data. [b] Values, determined at 23–25 °C, are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.

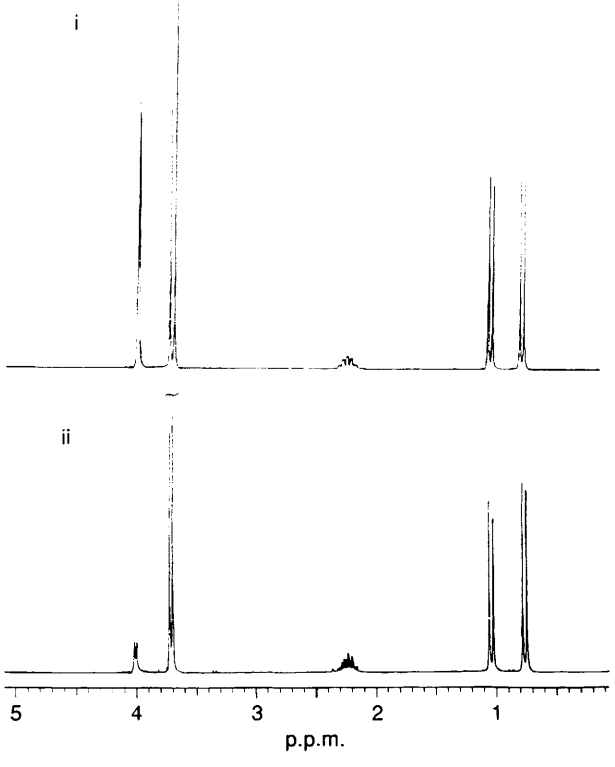
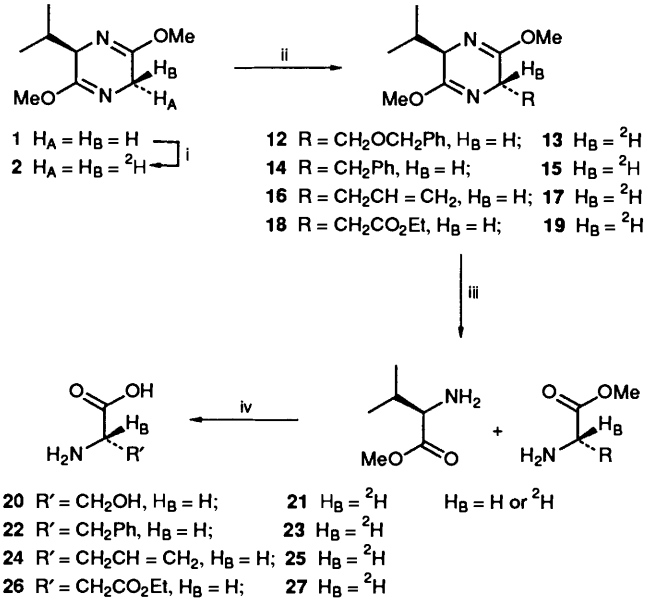



**Fig. 1** i, 200 MHz $^1$H NMR spectrum of compound **1** in $C^2H_3O^2H$. The signals at 4.02 ppm are due to 3-H (1 H, d, *J* 3.8 Hz) and 6-H (2 H, s); ii, $^1$H NMR spectrum of compound **2** formed as described in the text.




**1** $H_A = H_B = H$; **2** $H_A = H_B = {}^2H$

**12** R = $CH_2OCH_2Ph$, $H_B$ = H; **13** $H_B = {}^2H$
**14** R = $CH_2Ph$, $H_B$ = H; **15** $H_B = {}^2H$
**16** R = $CH_2CH=CH_2$, $H_B$ = H; **17** $H_B = {}^2H$
**18** R = $CH_2CO_2Et$, $H_B$ = H; **19** $H_B = {}^2H$

**20** R' = $CH_2OH$, $H_B$ = H; **21** $H_B = {}^2H$ $H_B$ = H or $^2$H
**22** R' = $CH_2Ph$, $H_B$ = H; **23** $H_B = {}^2H$
**24** R' = $CH_2CH=CH_2$, $H_B$ = H; **25** $H_B = {}^2H$
**26** R' = $CH_2CO_2Et$, $H_B$ = H; **27** $H_B = {}^2H$

**Scheme 3** *Reagents and conditions:* i, $MeO^2H$–$^2H_2O$ (10:1, v/v), KOH (1 equiv.), reflux, 3 h; ii, BuLi (1 equiv.), THF, −90 to −60 °C, then RBr (1.5 equiv.), THF, −90 °C, stir, 5–20 h; iii, 0.2 mol dm$^{-3}$ HCl (2 equiv.), room temp., stir, 16 h; then separation (chromatography for R=$CH_2OCH_2Ph$, $CH_2CH=CH_2$, $CH_2CO_2Et$, distillation for R= $CH_2Ph$); iv, 5 mol dm$^{-3}$ HCl, reflux, 3 h then ethanol, propylene oxide, reflux, 15 min

products or C-3 deuteriated material, and was complete within 3 h (Fig. 1).

The exchange at C-6 did not display biphasic kinetics, as assessed by $^1$H NMR spectroscopy, indicating that each diastereotopic 6-H exchanges hydrogen with the solvent at a similar rate and that a chiral [6-$^2H_1$]dihydropyrazine is not an intermediate.

This pleasing selectivity for C-6 anion formation over C-3 anion formation was further probed by refluxing compound **1** under the optimised exchange conditions for 6 h, twice as long as that required for exchange at C-6. Very little deuterium (<10 atom%) was incorporated at C-3 as judged by $^1$H NMR spectroscopy and mass spectrometry. Note that 6-alkyldihydropyrazines were resistant to base-catalysed deuteriation at C-6 under the same conditions, in accord with expectations.

To confirm that the chiral centre at C-6 of the [$^2H_2$]material **2** was intact, since measuring the extent of deuteriation at C-3 (which is subject to a primary isotope effect) might underestimate racemisation, the dihydropyrazine ring was cleaved (0.1 mol dm$^{-3}$ HCl, 16 h) to give methyl valinate and glycinate. These were separated, and the former ester was hydrolysed (5 mol dm$^{-3}$ HCl, reflux, 3 h) and then converted into its free base form with propylene oxide. The optical rotation of the re-

crystallised valine was −24.2 (*c* 1.01, 5 mol $dm^{-3}$ HCl)* which compared favourably to that for an authentic sample of (2*R*)-valine [−24.95 (*c* 1.09, 5 mol $dm^{-3}$ HCl)], indicating an enantiomeric excess of ≥97%. Thus, the deuteriation had proceeded highly selectively and without disturbing the stereogenic centre at C-3.

The utility of the enantiomers of the [$^2H_2$]dihydropyrazine **2** in the synthesis of α-deuteriated D-serine (Scheme 2) and L-serine, and some other L-amino acids (Scheme 3) is summarised in Table 1. In all cases the extent of $C^{\alpha}$-deuteriation was >95% and typical enantiomeric excesses were of the order of 95%.

## Acknowledgements

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* [α] Values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$.

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