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An improved synthesis of deuterated Schöllkopf's bis-lactim ether and its use for the asymmetric synthesis of (*R*)-[α-^{2}H]-phenylalanine methyl esters

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Abstract—Treatment of (*S*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine with trifluoroacetic acid in MeOD results in regioselective deuteration at its C_6-position affording its corresponding (*S*)-[6-$^2H_2$]-isotopomer in excellent yield with no loss of stereochemical integrity at its C_3-stereocentre. The lithium *aza*-enolate of this deuterated chiral template has been alkylated with a range of substituted benzyl bromides to afford (3*S*,6*R*)-[6-^{2}H]-3-isopropyl-6-benzyl-bis-lactim ethers that were hydrolysed to afford their corresponding (*R*)-[α-^{2}H]-phenylalanine methyl esters as hydrochloride salts in good yield.

1. Introduction

Amino acid derivatives that contain stable isotopes[1] are important for studying biosynthetic pathways,[2] enzyme mechanisms[3] and for probing the secondary and tertiary structures of peptides and proteins by NMR spectroscopy.[4] Enantiopure α-amino acids that are labelled with deuterium at their α-position have often been used for these purposes, and as a consequence, a range of methods have been developed for their syntheses.[5] They may be prepared via kinetic resolution[6] or chiral chromatography[7] of readily available racemic [α-^{2}H]-amino acids or their derivatives. A range of enzymatic based protocols have also been developed using different synthetic strategies, including the resolution of racemic [α-^{2}H]-α-amino acid derivatives,[8] biocatalytic deuteration of α-amino acids,[9] reductive amination of α-keto acid substrates[10] or derivatisation of deuterated building blocks that have been prepared chemoenzymatically.[11] Alternative synthetic approaches to α-deuterated-α-amino acids include asymmetric alkylation of deuterated glycine enolate derivatives,[12] asymmetric deuteration of enolates,[13] reduction of 2,3-dehydroamino acid derivatives with D_2 or SmI_2/D_2O,[14] and photolysis of chiral chromium carbene complexes in MeOD.[15] Despite the availability of this diverse range of methodologies, there still remains a strong demand for the development of efficient synthetic routes for the preparation of enantiopure [α-^{2}H]-α-amino-acids that proceed in a reliable manner, since relatively few enantiopure [α-^{2}H]-α-amino-acids are available commercially.

Schöllkopf's bis-lactim ether **1**[16] is a chiral glycine enolate equivalent that has been widely used for the asymmetric synthesis of enantiopure α-amino acids, with over 200 reports having been described on its use to date.[17] In this approach, an enantiopure bis-lactim ether **1** is deprotonated with *n*-BuLi in THF at −78 °C, and the resultant *aza*-enolate **2** alkylated with an electrophile to afford a trans-alkylated bis-lactim ether **3** in high de. Subsequent purification of the trans-alkylated-bis-lactim ether **3** to homogeneity, followed by mild acid catalysed hydrolysis, affords a mixture of enantiopure valine methyl ester **4** and the target enantiopure α-amino methyl ester **5** as their hydrochloride salts, whose free amines may be separated by chromatography or fractional distillation in vacuo (Scheme 1).

Given its popularity, it is unsurprising that this versatile methodology has been adapted for the asymmetric synthesis of enantiopure [α-^{2}H]-α-amino acid methyl esters, which has been achieved using enantiopure [6-$^2H_2$]-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine **6** as a chiral template for synthesis.[18,19] We herein report on an improved

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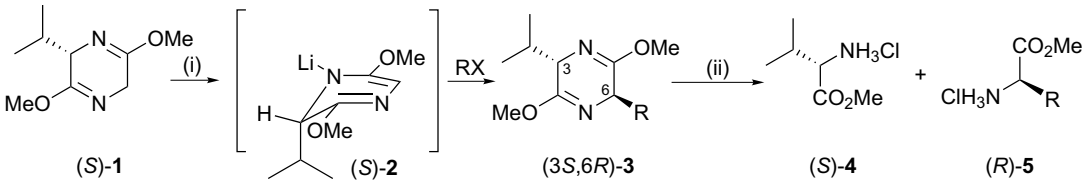


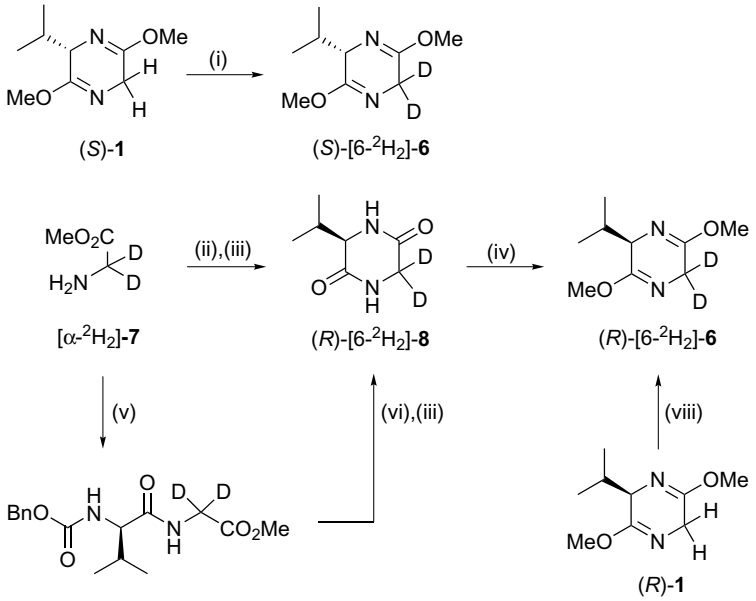
Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C; (ii) 0.1 M $HCl_{(aq)}$/CH_3CN.

synthesis of enantiopure [6-$^2H_2$]-bis-lactim ether **6** that may be used to prepare gram quantities of this isotopomer in excellent yield and further demonstrate its synthetic utility for the asymmetric synthesis of a series of enantiopure [α-^{2}H]-phenylalanine methyl esters.

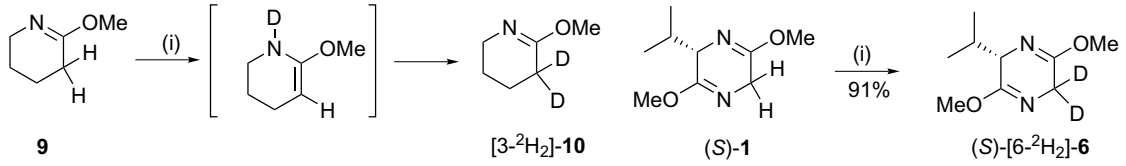
2. Results and discussion

We were interested in preparing a series of enantiopure (*R*)-[α-^{2}H]-phenylalanine methyl esters[20] as mechanistic probes and required access to gram quantities of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** for synthesis. Four approaches had previously been reported for its preparation in enantiopure form. In the first approach, Vederas et al. employed a deprotonation–deuteration protocol involving treatment of bis-lactim ether (*S*)-**1** with *n*-BuLi, followed by quenching of the resultant *aza*-enolate with CD_3OD. This deprotonation–deuteration process was repeated two further times on the same substrate to afford (*S*)-[6-$^2H_2$]-bis-lactim ether **6** in 77% yield (Scheme 2).[18] Gani et al. subsequently reported that they found this repeated deprotonation–deuteration strategy to be low-yielding, and as a consequence, investigated three alternative routes to [6-$^2H_2$]-bis-lactim ether **6**.[19] Their first two approaches employed the expensive [α-$^2H_2$]-glycine methyl ester **7** as a deuterated building block to prepare diketopiperazine (*R*)-[6-$^2H_2$]-**8**, which was then bis-O-methylated using Me_3OBF_4 to afford (*R*)-[6-$^2H_2$]-bis-lactim ether **6** (Scheme 2). They reported that both these multi-step approaches were expensive and inefficient, and as a consequence, developed an alternative synthesis of (*R*)-[6-$^2H_2$]-bis-lactim ether **6** involving treatment of (*R*)-bis-lactim ether **1** with potassium hydroxide in refluxing MeOD/D_2O. This approach resulted in regioselective bis-deuteration of bis-lactim ether (*R*)-**1** at its C_6-position to afford (*R*)-[6-$^2H_2$]-bis-lactim ether **6** in 80% yield, with no racemisation having occurred at its C_3-stereogenic centre (Scheme 2).

Whilst Gani's base catalysed deuteration strategy was practically appealing, our attempts to reproduce this capricious protocol to prepare (*S*)-[6-$^2H_2$]-bis-lactim ether **6** proved unsatisfactory, resulting in either incomplete incorporation of deuterium at its C_6-position, or low yields due to the prolonged reaction times required for complete deuterium incorporation. It has been reported that simple monolactim ethers tautomerise in protic solvents to afford their corresponding enamine tautomers, with *O*-ethyl-valerolactim ether undergoing bis-deuteration at its C_3-position in CD_3OD under acidic conditions.[21] This result was confirmed by carrying out a model study involving treatment of *O*-methyl-valerolactim ether **9** with trifluoroacetic acid in MeOD (20:80, v/v) over a period of 18 h, which resulted in quantitative incorporation of 2 equiv of deuterium to



Scheme 2. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C; CD_3OD; repeat deprotonation–deuteration protocol two further times; (ii) (*R*)-4-isopropyloxazolidin-2,4-dione, Et_3N, $CHCl_3$, −78 °C; (iii) toluene, Δ; (iv) Me_3OBF_4, CH_2Cl_2; (v) isobutyl chloroformate, *N*-methylmorpholine, (*R*)-*N*-benzyloxycarbonyl-valine, EtOAc–DMF; (vi) H_2, Pd/C, CH_2Cl_2–MeOH; (viii) MeOD–D_2O (10:1, v/v), KOH, Δ.



Scheme 3. Reagents and conditions: (i) trifluoroacetic acid, MeOD (20:80, v/v), 24 h.

afford [3-$^2H_2$]-*O*-methyl-valerolactim ether **10** (Scheme 3). Encouraged by this result, it was proposed that treatment of (*S*)-bis-lactim ether **1** under identical conditions might result in regioselective incorporation of deuterium at its C_6-position. Therefore, (*S*)-bis-lactim ether **1**[22] was dissolved in a mixture of trifluoroacetic acid and MeOD (20:80, v/v) over a period of 18 h, which after neutralisation with aqueous potassium carbonate solution afforded (*S*)-[6-$^2H_2$]-bis-lactim ether **6** in 91% yield (Scheme 3). This was evident from examination of its clean ^1H NMR spectra in $CDCl_3$, which clearly revealed that two atoms of deuterium had been regioselectively incorporated into its C_6-position, with no deuterium having been incorporated into the C_3-stereogenic position.[23] Analysis of a standard ^{13}C NMR spectra of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** in $CDCl_3$ revealed only eight resonances, with no resonance being observed for the C_6-^2H carbon due to quadropolar relaxation effects caused by the neighbouring deuterium nuclei, whilst mass spectroscopic analysis revealed a molecular ion for $C_9H_{14}{}^2H_2N_2O_2$. Measurement of the specific rotation of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** afforded an $[\alpha]_D^{23} = +72.0$ (*c* 1.0, EtOH), which compared favourably with that previously reported by Gani et al. of $[\alpha]_D^{23} = +65.6$ (*c* 1.38, EtOH).[19] Therefore, it was concluded that no deuterium incorporation or racemisation had occurred at the C_3-stereogenic centre of (*S*)-**1** under these acidic conditions.

In order to rationalise why deuteration of bis-lactim ether **1** had occurred selectively at its C_6-position, we considered the conformation of its dihydropyrazine ring that is known to adopt a half-boat ring conformation with its sterically demanding isopropyl group occupying a *pseudo*-axial position.[24] Deuterium incorporation at the C_6-position of bis-lactim ether **1** proceeds via an enamine-like tautomer whose formation requires one of the C_6–H σ-bonds to align itself *syn*-periplanar to the π orbitals of the N_4–C_5 imidic bond. This alignment can be achieved by either of the C_6-protons through conformational 'wagging' of the dihydropyrazine ring, which therefore results in stepwise incorporation of two atoms of deuterium into its C_6-position (Fig. 1). In contrast, the sterically demanding C_3-isopropyl group of bis-lactim ether **1** occupies a *pseudo*-axial conformation with its C_3-H proton in a *pseudo*-equatorial environment that is orthogonal to the π orbitals of the N_1–C_2-imidic bond. This prevents enamine formation from occurring, and as a consequence, no deuterium was incorporated into its C_3-position (Fig. 2).

In order to provide further evidence for this deuteration model, a sample of (3*S*,6*R*)-3-isopropyl-6-benzyl-bis-lactim ether **11** was prepared via treatment of (*S*)-bis-lactim ether **1** with *n*-BuLi in THF at −78 °C, followed by addition of benzyl bromide.[16] It was found that treatment of the resultant (3*S*,6*R*)-bis-lactim ether **11** with trifluoroacetic acid in MeOD (20:80, v/v) over a period of 7 days failed to result

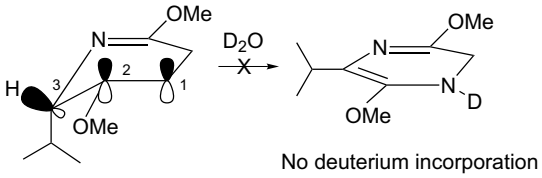


Figure 2. Tautomerisation of the C_3-proton of bis-lactim ether **1** does not occur because of poor orbital overlap between the equatorial C_3–H σ-bond and the N_1–C_2 π-bond.

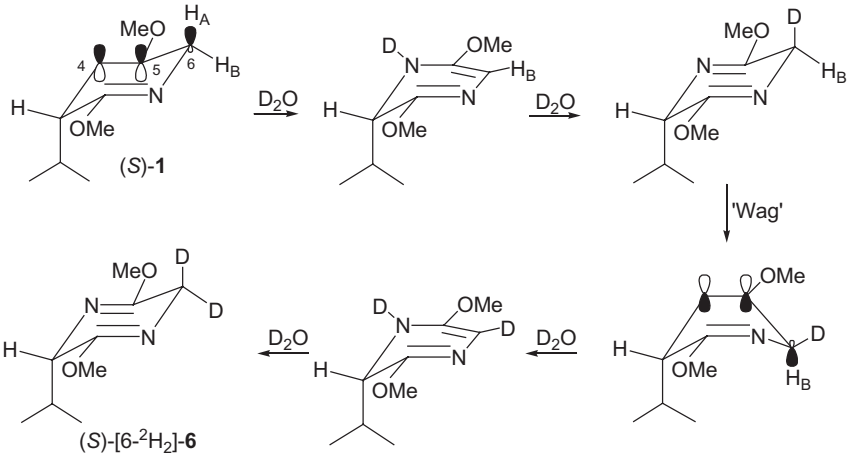


Figure 1. Conformational wagging of the dihydropyrazine ring of (*S*)-bis-lactim ether **1** enables stepwise incorporation of two deuterium atoms into its C_6-position to selectively afford (*S*)-[6-$^2H_2$]-bis-lactim ether **6**.

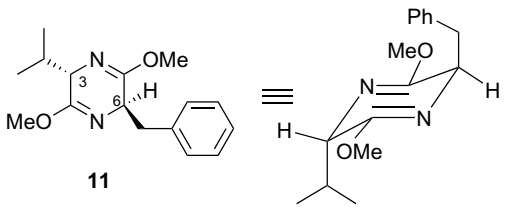


Figure 3.

in any deuterium being incorporated into either its C_3 or C_6 positions. This implies that the trans-diaxial conformation adopted by the isopropyl and benzyl substituents of lactim ether substrate **11** is sufficiently rigid to ensure that neither the C_3 nor C_6 protons can adopt *pseudo*-axial orientations required for tautomerisation, and as a consequence, deuterium incorporation does not occur (Fig. 3).

With a high yielding route to gram quantities of (*S*)-[6-$^2H_2$]-bis-lactim ether **6**, we next employed it for the asymmetric synthesis of a range of substituted (*R*)-[α-^{2}H]–phenylalanine methyl esters. Therefore, (*S*)-[6-$^2H_2$]-bis-lactim ether **6** was treated with 1.1 equiv of *n*-BuLi in THF in −78 °C for 1 h before the addition of 1.3 equiv of benzyl bromide to afford (3*S*,6*R*)-[6-^{2}H]-3-isopropyl-6-benzyl-2,5-dimethoxy-3,6-dihydropyrazine **12a** in >90% de, which was isolated in 80% yield and >95% de after chromatographic purification. Analysis of the ^{1}H and ^{13}C NMR spectra of (3*S*,6*R*)-[6-^{2}H]-**12a** revealed no evidence of any deuterium being present at its C_3-position, whilst its $[\alpha]_D^{25} = -41.2$ (*c* 1.3, CH_2Cl_2) compared well with the value previously reported by Gani et al. for its (3*R*,6*S*)-antipode of $[\alpha]_D^{23} = +40.4$ (*c* 1.55, CH_2Cl_2). These conditions were subsequently employed to react the *aza*-enolate of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** with five further benzyl bromide electrophiles containing different halide substituents at their *ortho*- and *para*-position, to afford a series of (3*S*,6*R*)-[6-^{2}H]-3-isopropyl-6-benzyl-bis-lactim ethers **12b–f** in >90% de that were isolated in 68–83% yield and in >95% de after chromatographic purification (Scheme 4 and Table 1).

Subsequent hydrolysis of these (3*S*,6*R*)-[6-^{2}H]-bis-lactim ethers **12a–f** was carried out by dissolving each substrate in a 1:1 mixture of acetonitrile:0.3 M $HCl_{(aq)}$ and stirring the resulting solutions for 30 min, which afforded clean mixtures of (*S*)-valine-methyl ester **4** and their respective (*R*)-[α-^{2}H]–phenylalanine methyl esters **13a–f** as hydrochloride salts. Purification of these 50:50 mixtures of α-amino-acid methyl esters hydrochloride salts was then achieved by neutralisation with aqueous sodium bicarbonate solution,

Table 1. Yields of (3*S*,6*R*)-[6-^{2}H]-bis-lactim ether **12a–f** and (*R*)-[α-^{2}H]-phenylalanine methyl ester hydrochlorides **13a–f**

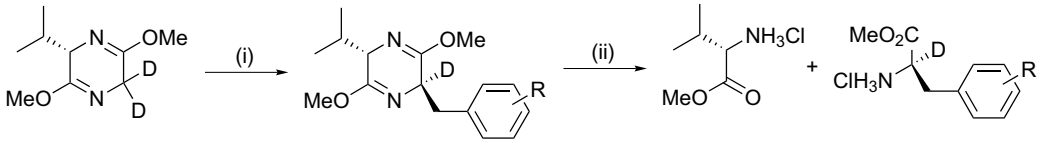
R	(3*S*,6*R*)-[6-^{2}H]-Bis-lactim ether **12a–f**	de (%)	Yield (%)	(*R*)-[α-^{2}H]-Phenylalanine methyl ester hydrochlorides **13a–f**	Yield (%)
H	**12a**	>90	80	**13a**	88
2-Br	**12b**	>90	73	**13b**	75
2-I	**12c**	>90	68	**13c**	77
4-F	**12d**	>90	71	**13d**	82
4-Br	**12e**	>90	75	**13e**	85
4-CF_3	**12f**	>90	83	**13f**	86

followed by chromatographic purification of the resultant mixture of free amines to afford (*R*)-[α-^{2}H]–phenylalanine methyl esters **13a–f** that were converted into their hydrochloride salts in 75–88% isolated yield (Scheme 4 and Table 1). Analysis of the ^{1}H NMR spectra of (*R*)-[α-^{2}H]–phenylalanine methyl esters **13a–f** revealed no α-proton resonances, and as a consequence, the level of α-deuterium incorporation was assigned as >95%.

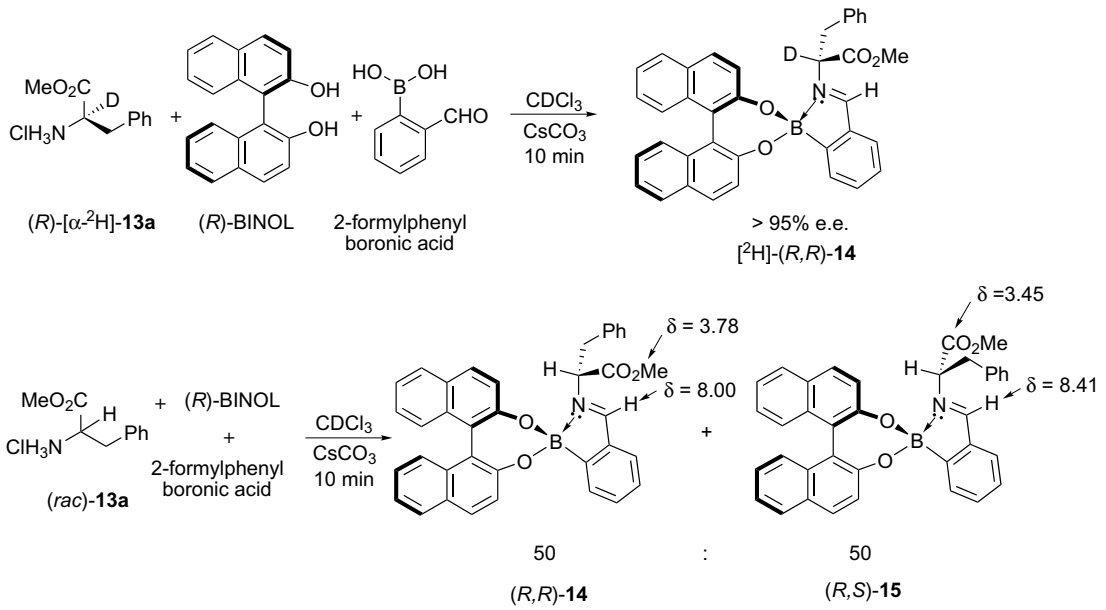
The enantiopurity of (*R*)-[α-^{2}H]-phenylalanine methyl ester **13a** was confirmed as >95% ee using a ^{1}H NMR chiral derivatisation protocol that we have recently developed for determining the enantiopurity of primary amines.[25] Therefore, (*R*)-[α-^{2}H]-phenylalanine methyl ester **13a** was treated with enantiopure (*R*)-BINOL and 2-formylphenylboronic acid in $CDCl_3$ to afford diastereoisomerically pure imino-boronate ester (*R*,*R*)-[α-^{2}H]-**14** as a single compound. This was confirmed by comparison with the ^{1}H NMR spectra of an authentic 50:50 mixture of diastereoisomeric imino-boronate esters (*R*,*R*)-**14** and (*R*,*S*)-**15** that were prepared in an analogous manner using racemic phenylalanine methyl ester hydrochloride as a substrate for derivatisation (Scheme 5). Finally, it follows that the value of >95% ee obtained for (*R*)-[α-^{2}H]-phenylalanine methyl ester **13a** confirms that the acidic deuteration protocol employed for the preparation of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** must have proceeded regioselectively, with no deuterium incorporation or racemisation occurring at its C_3 stereocentre (vide supra).

3. Conclusion

In conclusion, we have shown that treatment of (*S*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine with trifluoroacetic acid in MeOD results in regioselective deuteration at its C_6-position to afford its corresponding [6-$^2H_2$]-isotopomer in excellent yield with no loss in stereochemical



Scheme 4. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C; $ArCH_2Br$; (ii) 0.1 M $HCl_{(aq)}/CH_3CN$.



Scheme 5. Determination of the enantiomeric excess of (*R*)-[α-^{2}H]-phenylalanine methyl ester **13a** as >95% ee via derivatisation with (*S*)-BINOL and 2-formylphenyl boronic acid.

integrity at its C_3-stereocentre. The lithium *aza*-enolate of this deuterated chiral template has been alkylated with a range of substituted benzyl bromides to afford (3*S*,6*R*)-[6-^{2}H]-3-isopropyl-6-benzyl-bis-lactim ethers that were subsequently hydrolysed to give a series of (*R*)-[α-^{2}H]-phenylalanine methyl esters as their hydrochloride salts in good yield.

4. Experimental

4.1. General experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques, and glassware that was oven dried and cooled under nitrogen. THF was distilled from sodium/benzophenone ketyl. All other reagents were used as supplied without further purification. Flash column chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F254. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infrared spectra were recorded as thin films or KBr discs using a Perkin–Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in cm^{-1}. ^{1}H, ^{2}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent peak, with coupling constants (*J*) measured in Hertz. Low resolution mass spectra (*m*/*z*) were recorded on either a Finnigan MAT 8340 instrument or a Finnigan MAT 900 XLT instrument. Selected peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a Finnigan MAT 900 XLT instrument. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter, using a path length of 10 cm, in spectroscopic grade solvents (Aldrich), with concentrations (*c*) given in g per 100 cm^3. (*S*)-3-Isopropyl-2,5-dimethoxy-3,6-dihydropyrazine **1** and (3*S*,6*R*)-3-isopropyl,6-benzyl-2,5-dimethoxy-3,6-dihydropyrazine **11** were prepared according to previously published procedures.[16,22]

4.1.1. (*S*)-[6-$^2H_2$]-3-Isopropyl-2,5-dimethoxy-3,6-dihydropyrazine 6.[19] A solution of (*S*)-bis-lactim ether **1** (12.54 g, 68.0 mmol) was dissolved in a mixture of MeOD (24.0 ml) and trifluoroacetic acid (6.0 ml) and the resultant solution stirred for 24 h. Aqueous 1 M potassium carbonate solution was added to the reaction mixture until pH >7.0, which was then extracted with Et_2O (3 × 50 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the title compound **6** (11.53 g, 62.0 mmol) in 91% yield. $[\alpha]_D^{23} = +72.0$ (*c* 1.0, EtOH) [lit.[19] $[\alpha]_D^{23} = +65.6$ (*c* 1.38, EtOH)]; ν_{max}/cm^{-1} 1694 (C=N); δ_H (300 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.8 Hz, $CH_3(CH_3)CH$), 0.96 (3H, d, *J* 6.8 Hz, $CH_3(CH_3)CH$), 2.16 (1H, m, $CH(CH_3)_2$), 3.61 (3H, s, OMe), 3.65 (3H, s, OMe), 3.92 (1H, d, *J* 3.5 Hz, H_3); δ_C (75 MHz, $CDCl_3$) 16.8, 18.9, 32.3, 52.3, 52.4, 60.8, 162.2, 164.7; *m*/*z* (CI) 187 (MH^+, 62%), 173 (MH^+−Me, 100%); HRMS (FAB$^+$) [MH^+] for $C_9H_{14}{}^2H_2N_2O_2$ requires 187.1410, found 187.1409.

4.2. General procedure for the synthesis of (3*S*,6*R*)-[6-^{2}H]-bis-lactim ethers 12a–f

n-BuLi in hexanes (1.1 equiv) was added dropwise to a stirred solution of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (1.0 equiv) in THF under nitrogen at −78 °C and the reaction mixture

allowed to stir for 1 h. A solution of benzyl bromide (1.3 equiv) in THF was then added dropwise and the reaction mixture allowed to stir for a further 16 h whilst slowly warming to room temperature. Aqueous potassium carbonate solution (pH >8) was then added and the reaction extracted with Et_2O (×3). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the corresponding (3*S*,6*R*)-[6-^{2}H]-bis-lactim ethers **12a**–**f** in >90% de that were then purified to >95% de via column chromatography.

4.2.1. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-benzyl-2,5-dimethoxy-3,6-dihydropyrazine 12a.[19] The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.5 ml, 1.18 mmol) and benzyl bromide (0.240 g, 1.40 mmol) in THF (2 ml) according to the general procedure gave the title compound **12a** as a clear oil (0.238 g, 0.865 mmol) in 80% yield and >95% de; $[\alpha]_D^{25} = -41.2$ (*c* 1.3, CH_2Cl_2) [lit.[19] for (3*R*,6*S*)-**12a**, +40.4 (*c* 1.55, CH_2Cl_2)]; ν_{max}/cm^{-1} 1681 (C=N); δ_H (300 MHz, $CDCl_3$) 0.53 (3H, d, *J* 6.8 Hz, C*H*$_3$(CH$_3$)CH), 0.87 (3H, d, *J* 6.8 Hz, CH$_3$(C*H*$_3$)CH), 2.07 (1H, m, C*H*(CH$_3$)$_2$), 3.01 (2H, app s, C*H*$_2$Ph), 3.18 (1H, d, *J* 3.2 Hz, *H*$_3$), 3.61 (3H, s, OMe), 3.65 (3H, s, OMe), 6.99–7.20 (5H, br m, Ar*H*); δ_C (75 MHz, MeOD) 16.8, 19.4, 31.5, 40.3, 52.5, 52.8, 60.6, 126.7, 128.2, 130.4, 137.7, 162.8, 164.4; *m*/*z* (CI) 276 (MH^+, 100%); HRMS (FAB^+) [MH^+] for $C_{16}H_{21}{}^2HN_2O_2$ requires 276.1817, found 276.1814.

4.2.2. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-(2-bromobenzyl)-2,5-dimethoxy-3,6-dihydropyrazine 12b. The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.5 ml, 1.18 mmol) and 2-bromobenzyl bromide (0.358 g, 1.43 mmol) in THF (2 ml) according to the general procedure afforded the title compound **12b** as a clear oil (0.279 g, 0.79 mmol) in 73% yield and >95% de; $[\alpha]_D^{25} = -7.5$ (*c* 1.0, EtOAc); ν_{max}/cm^{-1} 1694 (C=N); δ_H (300 MHz, $CDCl_3$) 0.58 (3H, d, *J* 6.8 Hz, C*H*$_3$(CH$_3$)CH), 0.94 (3H, d, *J* 6.8 Hz, CH$_3$(C*H*$_3$)-CH), 2.14 (1H, m, C*H*(CH$_3$)$_2$), 2.86 (1H, d, *J* 14.0 Hz, C*H*$_A$H$_B$Ph), 3.39 (1H, d, *J* 14.0 Hz, CH$_A$H$_B$Ph), 3.57 (3H, s, OMe), 3.59 (1H, d, *J* 3.6 Hz, *H*$_3$), 3.66 (3H, s, OMe), 6.99 (1H, ddd, *J* 9.0, 5.8 and 3.2 Hz, Ar*H*), 7.06–7.26 (2H, br m, Ar*H*), 7.37–7.50 (1H, m, Ar*H*); δ_C (75 MHz, MeOD) 16.9, 19.5, 31.8, 40.6, 52.9, 56.3, 60.8, 125.8, 127.2, 128.3, 132.3, 133.0, 138.2, 163.5, 164.2; *m*/*z* (CI) 356 ($MBr^{81}H^+$, 98%), 354 (100%, $MBr^{79}H^+$); HRMS (FAB^+) [MH^+] for $C_{16}H_{20}{}^2H^{79}BrN_2O_2$ requires 354.0921, found 354.0922.

4.2.3. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-(2-iodobenzyl)-2,5-dimethoxy-3,6-dihydropyrazine 12c. The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.50 ml, 1.18 mmol) and 2-iodobenzyl bromide (0.414 g, 1.40 mmol) in THF (2 ml) according to the general procedure afforded the title compound **12c** as a clear oil (0.295 g, 0.74 mmol) in 68% yield and >95% de; $[\alpha]_D^{25} = -15.5$ (*c* 1.0, EtOAc); ν_{max}/cm^{-1} 1692 (C=N); δ_H (300 MHz, $CDCl_3$) 0.58 (3H, d, *J* 7.0 Hz, C*H*$_3$(CH$_3$)CH), 0.94 (3H, d, *J* 7.0 Hz, CH$_3$(C*H*$_3$)CH), 2.15 (1H, m, C*H*(CH$_3$)$_2$), 2.86 (1H, d, *J* 13.6 Hz, C*H*$_A$H$_B$Ph), 3.35 (1H, d, *J* 13.6 Hz, CH$_A$*H*$_B$Ph), 3.57 (3H, s, OMe), 3.64 (1H, d, *J* 3.4 Hz, *H*$_3$), 3.66 (3H, s, OMe), 6.80 (1H, ddd, *J*, 7.9, 6.4 and 2.6 Hz, Ar*H*), 7.10–7.19 (2H, br m, Ar*H*), 7.73 (1H, d, *J* 7.9 Hz, Ar*H*); δ_C (75 MHz, $CHCl_3$) 15.5, 18.1, 30.4, 43.7, 51.5, 51.6, 59.5, 100.8, 126.7, 127.0, 130.0, 138.3, 140.2, 162.0, 162.8; *m*/*z* (CI) 402 (MH^+, 17%), 358 (M^+-i-Pr, 100%); HRMS (FAB^+) [MH^+] for $C_{16}H_{20}{}^2HIN_2O_2$ requires 402.0783, found 402.0783.

4.2.4. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-(4-fluorobenzyl)-2,5-dimethoxy-3,6-dihydropyrazine 12d. The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.5 ml, 1.18 mmol) and 4-fluorobenzyl bromide (0.265 g, 1.40 mmol) in THF (2 ml) according to the general procedure afforded the title compound **12d** as a clear oil (0.225 g, 0.77 mmol) in 71% yield and >95% de; $[\alpha]_D^{25} = -62.4$ (*c* 1.0, EtOAc); ν_{max}/cm^{-1} 1694 (C=N); δ_H (300 MHz, $CDCl_3$) 0.53 (3H, d, *J* 6.8 Hz, C*H*$_3$(CH$_3$)CH), 0.88 (3H, d, *J* 6.8 Hz, CH$_3$(C*H*$_3$)CH), 2.08 (1H, m, C*H*(CH$_3$)$_2$), 2.98 (2H, app t, *J* 14.0 Hz, C*H*$_2$Ph), 3.25 (1H, d, *J* 3.0 Hz, *H*$_3$), 3.59 (3H, s, OMe), 3.63 (3H, s, OMe), 6.82 (2H, app t, *J* 8.1 Hz, Ar*H*), 6.97 (2H, dd, *J* 8.1, 5.8 Hz, Ar*H*); δ_C (75 MHz, MeOD) 16.8, 19.4, 31.6, 39.4, 52.5, 52.7, 60.7, 115.0 (d, *J* 10.5 Hz), 131.7 (d, *J* 3.8 Hz), 133.4, 162.6, 164.4;[26] *m*/*z* (CI) 294 (MH^+, 32%), 278 (M^+-Me, 100%); HRMS (FAB^+) [MH^+] for $C_{16}H_{20}{}^2HFN_2O_2$ requires 294.1723, found 294.1721.

4.2.5. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-(4-bromobenzyl)-2,5-dimethoxy-3,6-dihydropyrazine 12e.[27] The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.5 ml, 1.18 mmol) and 4-bromobenzyl bromide (0.354 g, 1.42 mmol) in THF (2 ml) according to the general procedure afforded the title compound **12e** as a amorphous solid (0.287 g, 0.81 mmol) in 75% yield and >95% de; mp = 58–64 °C; $[\alpha]_D^{25} = -5.2$ (*c* 1.0, EtOAc); ν_{max}/cm^{-1}1694 (C=N); δ_H (300 MHz, $CDCl_3$) 0.54 (3H, d, *J* 6.8 Hz, C*H*$_3$(CH$_3$)CH), 0.88 (3H, d, *J* 6.8 Hz, CH$_3$(C*H*$_3$)CH), 2.08 (1H, m, C*H*(CH$_3$)$_2$), 2.96 (2H, app s, C*H*$_2$Ph), 3.32 (1H, d, *J* 3.0 Hz, *H*$_3$), 3.49 (3H, s, OMe), 3.63 (3H, s, OMe), 6.89 (2H, d, *J* 7.9 Hz, Ar*H*), 7.25 (2H, d, *J* 7.9 Hz, Ar*H*); δ_C (75 MHz, $CDCl_3$) 16.8, 19.4, 31.7, 39.6, 52.6, 56.7, 60.7, 120.7, 131.3, 132.0, 136.8, 162.5, 164.4; *m*/*z* (CI) 356 ($M^{81}BrH^+$, 33%), 354 ($M^{79}BrH^+$, 34%), 340 ($M^{81}Br^+-$Me, 100%), 338 ($M^{79}Br^+-$Me, 100%); HRMS (FAB^+) [MH^+] for $C_{16}H_{20}{}^2H^{79}BrN_2O_2$ requires 354.0921, found 354.0922.

4.2.6. (3*S*,6*R*)-[6-^{2}H]-3-Isopropyl-6-(4-trifluoromethylbenzyl)-2,5-dimethoxy-3,6-dihydropyrazine 12f. The reaction of (*S*)-[6-$^2H_2$]-bis-lactim ether **6** (0.200 g, 1.08 mmol) in THF (10 ml) with 2.36 M *n*-BuLi in hexanes (0.5 ml, 1.18 mmol) and 4-trifluoromethylbenzyl bromide (0.330 g, 1.39 mmol) in THF (2 ml) according to the general procedure afforded the title compound **12f** as a crystalline solid (0.308 g, 0.90 mmol) in 83% yield and >95% de; mp = 57–58 °C; $[\alpha]_D^{25} = -20.7$ (*c* 1.0, EtOAc); ν_{max}/cm^{-1} 1694 (C=N); δ_H (300 MHz, $CDCl_3$) 0.54 (3H, d, *J* 7.2 Hz, C*H*$_3$(CH$_3$)CH), 0.87 (3H, d, *J* 7.2 Hz, CH$_3$(C*H*$_3$)CH), 2.08 (1H, m, C*H*(CH$_3$)$_2$), 2.99 (1H, d, *J* 13.2 Hz, C*H*$_A$H$_B$Ph), 3.11 (1H, d, *J* 13.2 Hz, CH$_A$*H*$_B$Ph), 3.33 (1H,

d, J 3.2 Hz, H_3), 3.58 (3H, s, OMe), 3.63 (3H, s, OMe), 7.14 (2H, d, J 8.0 Hz, ArH), 7.39 (2H, d, J 8.0 Hz, ArH); δ_C (75 MHz, MeOD); 16.7, 19.3, 31.9, 40.2, 52.5, 52.7, 60.8, 124.8 (q, J 270 Hz), 125.0 (q, J 3.8 Hz), 131.0 (q, J 32.3 Hz), 130.6, 142.2, 162.5, 164.5; m/z (CI) 344 (MH^+, 15%) 300 (M^+-i-Pr, 100%); HRMS (FAB$^+$) [MH^+] for $C_{17}H_{20}{}^2HF_3N_2O_2$ requires 344.1691, found 344.1692.

4.3. General procedure B: synthesis of (*R*)-[α-^{2}H]-phenylalanine methyl esters 13a–f

(3*S*,6*R*)-[6-^{2}H]-Bis-lactim ethers **12a–f** (1.0 equiv) were dissolved in a 1:1 solution of 0.3 M HCl and MeCN and the resultant solution stirred vigorously for 30 min. The reaction mixture was then concentrated in vacuo to afford a 50:50 mixture of (*S*)-valine methyl ester hydrochloride and the respective (*R*)-[α-^{2}H]-phenylalanine methyl esters **13a–f** as their hydrochloride salts. The resultant mixture of α-amino acid methyl ester hydrochloride salts was dissolved in $CHCl_3$, neutralised via treatment with concentrated $NaHCO_3$ solution (1.5 equiv), before being purified by column chromatography. The (*R*)-[α-^{2}H]-phenylalanine methyl ester obtained was then reacidified via treatment with 0.3 M $HCl_{(aq)}$ (2 ml) and the solvent removed in vacuo to afford the desired (*R*)-[α-^{2}H]-phenylalanine methyl esters **13a–f** as their hydrochloride salts.

4.3.1. (*R*)-[α-^{2}H]-Phenylalanine methyl ester hydrochloride 13a.[28] The reaction of a solution of **12a** (0.022 g, 0.08 mmol) in CH_3CN (1.2 ml) and 0.3 M HCl (1.2 ml) followed by chromatographic purification according to the general procedure afforded the title compound **13a** (0.015 g, 0.070 mmol) as its hydrochloride salt in 88% yield; $[\alpha]_D^{25} = -28.3$ (c 1.0, EtOH);[28] ν_{max}/cm^{-1} 3412 (NH), 1740 (C=O); δ_H (300 MHz, D_2O) 3.24 (1H, d, J 14.5 Hz, CH_AH$_B$Ph), 3.35 (1H, d, J 14.5 Hz, CH$_A$$H_B$Ph), 3.85 (3H, s, OMe), 7.26–7.49 (5H, br m, ArH); δ_D (60 MHz, EtOH) 4.22 (1 × ^{2}H, s, 6-^{2}H); δ_C (75 MHz, $CDCl_3$) 35.7, 53.8, 128.3, 129.5, 129.7, 134.0, 170.3; m/z (CI) 181 (MH^+, 100%); HRMS (FAB$^+$) [MH^+] for $C_{10}H_{12}{}^2HNO_2$ requires 181.1082, found 181.1080.

4.3.2. (*R*)-[α-^{2}H]-2-Bromophenylalanine methyl ester hydrochloride 13b. The reaction of a solution of **12b** (0.021 g, 0.060 mmol) in CH_3CN (1.2 ml) and 0.3 M HCl (1.2 ml) followed by chromatographic purification according to the general procedure afforded the title compound **13b** (0.013 g, 0.044 mmol) as its hydrochloride salt in 75% yield; $[\alpha]_D^{25} = -20.1$ (c 1.0, EtOH); ν_{max}/cm^{-1} 3435 (NH), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 3.21 (1H, d, J 14.7 Hz, CH_AH$_B$Ph), 3.53 (1H, d, J 14.7 Hz, CH$_A$$H_B$Ph), 3.81 (3H, s, OMe), 7.25–7.44 (3H, br m, ArH), 7.70 (1H, dd, J 7.9 and 1.0 Hz, ArH); δ_D (60 MHz, H_2O) 4.35 (1 × ^{2}H, s, 6-^{2}H); δ_C (75 MHz, $CDCl_3$) 34.6, 52.1, 122.7, 126.8, 128.5, 130.3, 131.8, 131.9, 168.3; m/z (CI) 261 (MH^+, 100%); MS (FAB$^+$) [MH^+] for $C_{10}H_{11}{}^2H^{79}BrNO_2$ requires 259.0187, found 259.0184.

4.3.3. (*R*)-[α-^{2}H]-2-Iodophenylalanine methyl ester hydrochloride 13c.[29] The reaction of a solution of **12c** (0.026 g, 0.065 mmol) in CH_3CN (0.7 ml) and 0.3 M HCl (0.7 ml) followed by chromatographic purification according to the general procedure afforded the title compound **13c** (0.017 g, 0.05 mmol) as its hydrochloride salt in 77% yield; $[\alpha]_D^{25} = -13.3$ (c 1.0, EtOH); ν_{max}/cm^{-1} 3420 (NH), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 2.84 (1H, d, J 13.6 Hz, CH_AH$_B$Ph), 3.16 (1H, d, J 13.6 Hz, CH$_A$$H_B$Ph), 3.70 (3H, s, OMe), 6.87 (1H, td, J 7.5 and 1.5 Hz, ArH), 7.14 (1H, dd, J 7.5 and 1.5 Hz, ArH), 7.22 (1H, td, J 7.5 and 1.1 Hz, ArH), 7.78 (1H, dd, J 7.5 and 1.1 Hz, ArH); δ_D (60 MHz, EtOH) 4.32 (1 × ^{2}H, s, 6-^{2}H); δ_C (75 MHz, $CDCl_3$) 40.8, 54.0, 130.2, 131.2, 131.3, 132.1, 137.0, 140.5, 170.0; m/z (CI) 307 (MH^+, 65%), 181 (MH^+-I, 100%); HRMS (FAB$^+$) [MH^+] for $C_{10}H_{11}{}^2HINO_2$ requires 307.0048, found 307.0049.

4.3.4. (*R*)-[α-^{2}H]-4-Fluorophenylalanine methyl ester hydrochloride 13d.[30] The reaction of a solution of **12d** (0.029 g, 0.099 mmol) in CH_3CN (1.0 ml) and 0.3 M HCl (1.0 ml) followed by chromatographic purification according to the general procedure afforded the title compound **13d** (0.019 g, 0.081 mmol) as its hydrochloride salt in 82% yield; $[\alpha]_D^{25} = -34.3$ (c 1.0, EtOH); ν_{max}/cm^{-1} 3389 (NH), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 3.22 (1H, d, J 14.0 Hz, CH_AH$_B$Ph), 3.32 (1H, d, J 14.0 Hz, CH$_A$$H_B$Ph), 3.86 (3H, s, OMe), 7.13 (2H, m, ArH), 7.31 (2H, m, ArH); δ_D (60 MHz, EtOH) 4.14 (1 × ^{2}H, s, 6-^{2}H); δ_C (75 MHz, $CDCl_3$) 35.0, 53.9, 116.3 (J 21.8 Hz), 131.5 (J 6.8 Hz), 168.2;[26] m/z (CI) 199 (MH^+, 100%); HRMS (FAB$^+$) [MH^+] for $C_{10}H_{11}{}^2HFNO_2$ requires 199.0988, found 199.0987.

4.3.5. (*R*)-[α-^{2}H]-4-Bromophenylalanine methyl ester hydrochloride 13e.[31] The reaction of a solution of **12e** (0.021 g, 0.060 mmol) in CH_3CN (0.6 ml) and 0.3 M HCl (0.6 ml) followed by chromatographic purification according to the general procedure afforded the title compound **13e** (0.015 g, 0.051 mmol) as its hydrochloride salt in 85% yield; $[\alpha]_D^{25} = -18.5$ (c 1.0, EtOH); ν_{max}/cm^{-1} 3420 (NH), 1740 (C=O); δ_H (300 MHz, $CDCl_3$) 3.21 (1H, d, J 14.7 Hz, CH_AH$_B$Ph), 3.31 (1H, d, J 14.7 Hz, CH$_A$$H_B$Ph), 3.84 (3H, s, OMe), 7.20 (2H, d, J 8.5 Hz, ArH), 7.58 (2H, d, J 8.5 Hz, ArH); δ_D (60 MHz, EtOH) 4.35 (1 × ^{2}H, s, 6-^{2}H); δ_C (75 MHz, $CDCl_3$) 35.2, 53.9, 121.8, 131.5, 132.5, 133.2, 170.2; m/z (CI) 261 ($MBr^{81}H^+$, 100%), 259 ($MBr^{79}H^+$, 99%); HRMS (FAB$^+$) [MH^+] for $C_{10}H_{11}{}^2H^{79}BrNO_2$ requires 259.0187, found 259.0184.

4.3.6. (*R*)-[α-^{2}H]-4-Trifluoromethylphenylalanine methyl ester hydrochloride 13f.[30] The reaction of a solution of **12f** (0.031 g, 0.090 mmol) in CH_3CN (1.0 ml) and 0.3 M HCl (0.9 ml, 0.27 mmol) followed by chromatographic purification according to the general procedure afforded the title compound **13f** (0.022 g, 0.077 mmol) as its hydrochloride salt in 86% yield; $[\alpha]_D^{25} = -24.8$ (c 1.0, EtOH); ν_{max}/cm^{-1} 3402 (NH), 1742 (C=O); δ_H (300 MHz, $CDCl_3$) 3.33 (1H, d, J 14.5 Hz, CH_AH$_B$Ph), 3.43 (1H, d, J 14.5 Hz, CH$_A$$H_B$Ph), 3.83 (3H, s, OMe), 7.46 (2H, d, J 7.9 Hz, ArH), 7.74 (2H, d, J 7.9 Hz, ArH); δ_D (60 MHz, EtOH) 4.23 (1 × ^{2}H, s, 6-^{2}H); m/z (CI) 249 (MH^+, 100%); HRMS (FAB$^+$) [MH^+] for $C_{11}H_{11}{}^2HF_3NO_2$ requires 249.0956, found 249.0955.

4.4. Determination of the enantiomeric excess of (*R*)-[α-^{2}H]-phenylalanine methyl ester hydrochloride 13a[25]

(*R*)-[α-^{2}H]-Phenylalanine methyl ester hydrochloride **13a** (5 mg), (*R*)-BINOL (1.05 equiv), 2-formyl-phenylboronic acid (1.05 equiv) and caesium carbonate (2.00 equiv) were dissolved in $CDCl_3$ (0.5 ml). The resultant solution was filtered after 10 min and the ^{1}H NMR spectra of the resultant (*R*,*R*)-imino-boronate ester **14** were acquired. A similar derivatisation experiment was carried out using commercially available (*rac*)-phenylalanine methyl ester hydrochloride salt to afford a 50:50 mixture of (*R*,*R*)-imino-boronate ester **14** and (*R*,*S*)-imino-boronate ester **15**. The enantiomeric excess of (*R*)-[α-^{2}H]-**13a** was assigned via comparison of the integrals of the methoxy resonances for (*R*,*R*)-**14** at δ_H 3.78 with those for (*R*,*S*)-**15** at δ_H 3.45, as well as comparison of the imine resonances for (*R*,*R*)-**14** at δ_H 8.00 with those for (*R*,*S*)-**15** at δ_H 8.41, both of which revealed that (*R*)-[α-^{2}H]-**13a** had been formed in >95% ee.

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