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Asymmetric synthesis of *syn*- and *anti*-α-deuterio-β^3-phenylalanine derivatives

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ABSTRACT

The conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of aryl substituted *tert*-butyl cinnamate esters followed by reaction of the resultant lithium β-amino enolates with D_2O provides access to *anti* configured α-deuterio-β-aminocinnamate esters in high dr. The corresponding *syn* configured diastereoisomers were also obtained with high diastereoselectivity via the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of *tert*-butyl α-deuteriocinnamate esters followed by reaction of the resultant lithium β-amino enolates with 2-pyridone. After deprotection both the *syn*- and *anti*-diastereoisomers of the corresponding α-deuterio-β^3-amino acids can be isolated in high dr.

1. Introduction

The synthesis of enantiopure β-amino acids has become an important area within organic synthesis. The pharmacological activities of a variety of β-amino acids and their derivatives have been well documented.[1] For example, the α-hydroxy-β-phenylalanine component of Taxol® was found to be essential to its antitumour activity,[2] (*S*)-β-tyrosine was found to be a key component of the antibiotic edeine A,[3] and its antipode (*R*)-β-tyrosine is the β-amino acid component of the cyclodepsipeptide jasplakinolide.[4] β-Amino acids are also precursors for β-lactam antibiotics[5] and various other compounds of biological interest.[6] In addition, the pharmacological and conformational properties of synthetic peptides derived from β-amino acids have been receiving increasing attention[7] and β-amino acids have become important building blocks for peptidomimetic studies.[8] Within this field, amino acids specifically labelled with stable isotopes are valuable tools for the investigation of proteins at the atomic level.[9] Methods for the synthesis of deuterium labelled amino acids include isotopic exchange[10] or deuteriogenation of a suitable precursor that incorporates a double bond.[11] One other common method for the incorporation of deuterium is through deuteration of enolates, typically generated by deprotonation with lithium amide bases. For example, Seebach et al. have reported the deuteration of enolates generated by deprotonation with LDA, although only partial deuterium incorporation was observed; a hydrogen bonded complex between the amine and the lithium enolate was proposed to account for this effect.[12] An alternative protocol was therefore presented in which BuLi is added to the preformed amine–enolate complex. This 'double deprotonation' strategy[13] removes the residual proton from the amine by reforming the lithium amide base (e.g., LDA) with subsequent deuteration of the enolate giving significantly improved levels of deuterium incorporation.[14]

Previous investigations from our laboratory have demonstrated that the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[15] This methodology has found numerous applications, including the total syntheses of natural products,[16] molecular recognition phenomena[17] and resolution protocols,[18] and has been reviewed.[19] While lithium β-amino enolates have been shown by us to undergo diastereoselective alkylation[20] and oxidation,[21] their diastereoselective deuteration has yet to be reported. It was envisaged that both *syn*- and *anti*-α-deuterio-β-amino esters **3** could be obtained via either a tandem conjugate addition/deuteration approach [i.e., conjugate addition of (*S*)-**4** to **1** followed by in situ deuteration of the resultant lithium (*Z*)-β-amino enolate] or a stepwise protocol [i.e., deprotonation of β-amino ester **2** followed by deuteration of the resultant lithium (*E*)-β-amino enolate] and we report herein our findings within this area (Scheme 1).

2. Results and discussion

2.1. Tandem conjugate addition/deuteration of α,β-unsaturated esters

tert-Butyl cinnamate **5** was selected as a model system with which to screen various 'D$^+$' sources for high levels of diastereoselectivity upon deuteration of the intermediate lithium β-amino

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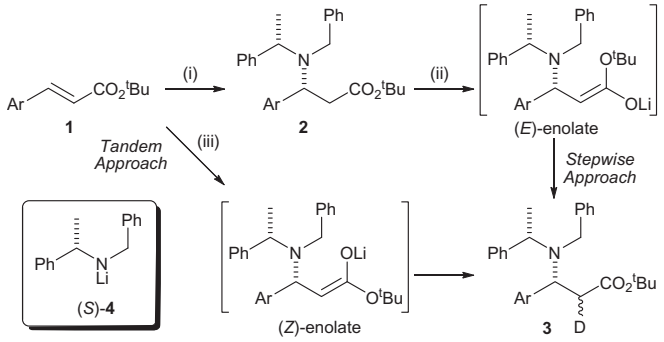


Scheme 1. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C then NH_4Cl (satd, aq); (ii) LHMDS, THF, −78 °C then 'D$^+$'; (iii) (*S*)-**4**, THF, −78 °C then 'D$^+$'.

enolate formed from the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **4**. Prior to the deuteration studies we sought to confirm that this conjugate addition reaction was highly diastereoselective such that any diastereoisomeric mixtures observed following deuteration would be a result of an unselective enolate deuteration [i.e., be C(2)-epimers] rather than mixtures arising from an unselective conjugate addition step giving rise to products with different configurations at C(3). Thus, a solution of *tert*-butyl cinnamate **5**[22] at −78 °C was added to a solution of lithium amide (*S*)-**4** in THF at −78 °C following our standard procedure for lithium amide conjugate addition; the resultant solution was stirred at −78 °C then quenched by the addition of satd aq NH_4Cl to give, as previously reported,[20b] **6** in >99:1 dr, and 89% isolated yield and >99:1 dr after chromatographic purification. The relative configuration within **6** had previously been assigned by analogy to the transition state mnemonic[23] developed by us to rationalise the diastereoselectivity exhibited by this class of lithium amide reagents upon conjugate addition to α,β-unsaturated esters; this assignment has now been unambiguously confirmed by single crystal X-ray diffraction analysis of the racemic analogue (*RS*,*SR*)-**6**, with the absolute configuration within (3*R*,α*S*)-**6** being assigned relative to the known (*S*)-configuration of the α-methylbenzyl group (Fig. 1). This result establishes that any diastereoisomeric mixtures observed following deuteration of the intermediate lithium β-amino enolate are epimeric at C(2) and not at C(3).[24] The corresponding α-deuteration reactions (employing a range of commercially available deuteron sources, viz. D_2O, MeOH-d_4 and AcOH-d_4) were next evaluated. The product distributions were analysed by both ^{1}H NMR spectroscopic and mass spectrometric analyses. As expected, the ^{1}H NMR spectra of the products were in accord with formation of the β-amino ester as a mixture of the two mono-deuterated diastereoisomers *anti*-**7** and *syn*-**8**, as well as a trace amount of α,α-diprotio-β-amino ester **6**. In each case, the reaction diastereoselectivity was judged by integration of the distinct resonances arising from the individual diastereoisomers *anti*-**7** and *syn*-**8**.[25] The degree of deuteration was determined by ^{1}H NMR spectroscopic analysis of the product mixture and comparison of specific integrals due to the C(2)*H* resonances. The relative intensities of the molecular ion peaks in the mass spectra provided by low resolution mass spectrometric analysis were found to be consistent with the degree of deuterium incorporation as judged by ^{1}H NMR spectroscopic analysis. In each case the maximum deuterium incorporation was expected to be less than 100% due to the suppliers' disclaimers that the deuterated solvents employed in this protocol were not 100% isotopically pure (Scheme 2).[26]

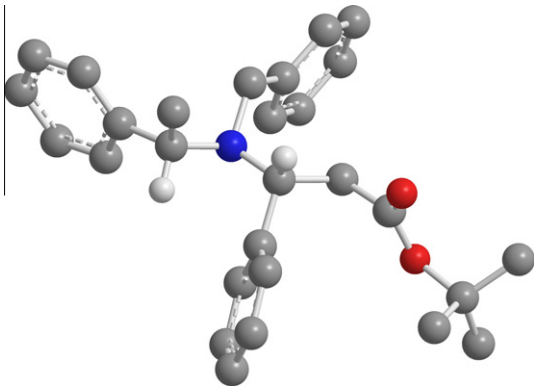
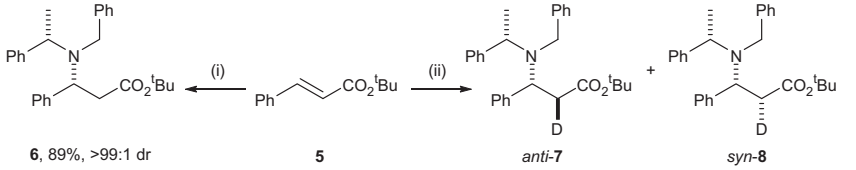


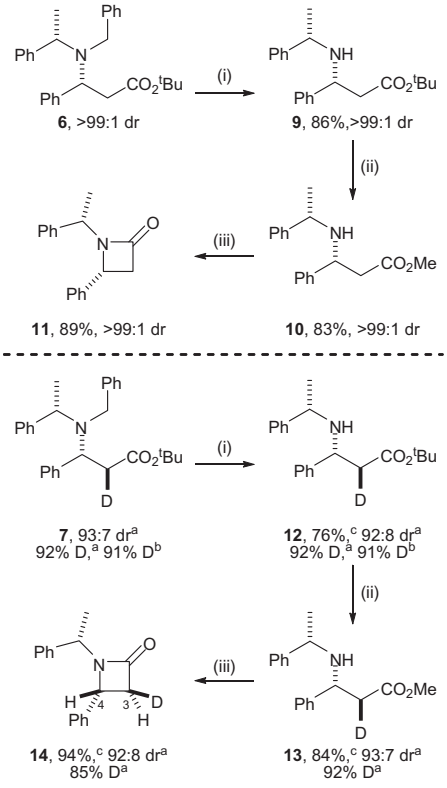
Figure 1. Chem3D representation of the single crystal X-ray structure of (*RS*,*SR*)-**6** (some H atoms are omitted for clarity).

The configuration at C(2) within *anti*-**7** (and therefore also that within *syn*-**8**) was established by conversion of *anti*-**7** (93:7 dr) into the corresponding β-lactam **14** as the ^{1}H NMR ^3J coupling constants between the C(3)*H* and C(4)*H* protons within 3,4-disubstituted β-lactams are known to be diagnostic of the stereochemical configuration.[27] The transformations were first performed on α,α-diprotio-β-amino ester **6** to confirm that epimerisation of the β-stereogenic centre was not occurring. The route involved the chemoselective debenzylation[28] of β-amino ester **6** with CAN[29] to give **9** in 86% yield and >99:1 dr, subsequent transesterification of **9** to give the corresponding methyl ester **10** in 83% yield and >99:1 dr, and finally cyclisation[30] of **10** to give β-lactam **11** in 89% yield and >99:1 dr upon treatment with MeMgBr, confirming that all reactions proceeded without compromising the stereochemical integrity at the β-stereocentre within this substrate. An analogous series of transformations were therefore applied to α-deuterio-β-amino ester *anti*-**7** (93:7 dr) giving β-lactam **14** in 60% overall yield (three steps) with a negligible decrease in deuterium incorporation or diastereoisomeric purity (Scheme 3). The value of the ^{1}H NMR ^3J coupling constant observed between the C(3)*H* and C(4)*H* protons within **14** (2.4 Hz) was indicative of an *anti* relationship between these protons. The *anti* relative configurations within β-amino esters **7**, **12** and **13** (and the *syn* configuration within **8**) could therefore be confidently assigned.



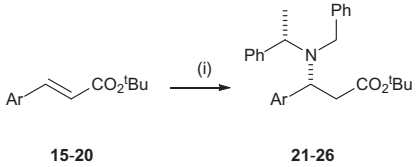
"D$^+$" Source	D Incorporation (%)	dr[a] (*anti*:*syn*)	Yield[c] (%)
D_2O	92[a] (91)[b]	93:7	91
CD_3OD	96[a] (96)[b]	88:12	90
CD_3CO_2D	53[a] (52)[b]	68:32	55

Scheme 2. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C, 2 h then NH_4Cl (satd, aq); (ii) (*S*)-**4**, THF, −78 °C, 2 h then 'D$^+$' [[a] ^{1}H NMR spectroscopic analysis; [b] mass spectrometric analysis; [c] combined isolated yield].



Scheme 3. Reagents and conditions: (i) CAN, MeCN/H_2O (v/v 5:1), rt, 18 h; (ii) MeOH, $SOCl_2$, reflux, 2 h; (iii) MeMgBr, Et_2O, 0 °C, 30 min [[a] ^{1}H NMR spectroscopic analysis; [b] mass spectrometric analysis; [c] combined isolated yield].

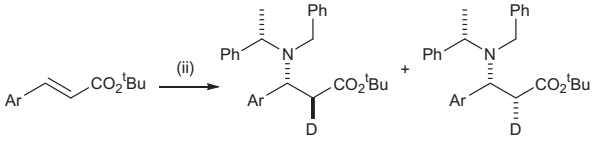
In order to validate the 'tandem' conjugate addition/deuteration reaction as a synthetically useful process the procedure was applied to a range of α,β-unsaturated esters incorporating alternative C(3)-aryl substitution. The lithium amide conjugate addition reactions to α,β-unsaturated esters **15–20**[31] were first quenched with satd aq NH_4Cl to give authentic samples of β-amino esters **21–26** in good yield. In each case very high levels of diastereoselectivity (⩾98:2 dr) were observed, confirming that any possible diastereoisomeric mixtures obtained from the corresponding tandem conjugate addition/deuteration reactions would be epimeric at C(2) rather than C(3) (Scheme 4).[32]



Acceptor	Ar	Product	dr[a,b]	Yield (%)
15	4-MeOC$_6$H$_4$	21	98:2	96
16	4-BrC$_6$H$_4$	22	98:2	92
17	3-BrC$_6$H$_4$	23	>99:1	86
18	3-FC$_6$H$_4$	24	98:2	83
19	2-BrC$_6$H$_4$	25	>99:1	89
20	2-IC$_6$H$_4$	26	>99:1	96

Scheme 4. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C, 2 h then NH_4Cl (satd, aq) [[a] ^{1}H NMR spectroscopic analysis; [b] crude and isolated].

Under the optimised conditions, conjugate addition of (*S*)-**4** to **15–20**, followed by deuteration of the resultant lithium β-amino enolates with D_2O at −78 °C, gave the corresponding *anti*-α-deuterio-β-amino esters **27–32** as the major products. In most cases ^{1}H NMR spectroscopic analysis of the crude reaction mixtures indicated that the reactions had all proceeded to full conversion giving



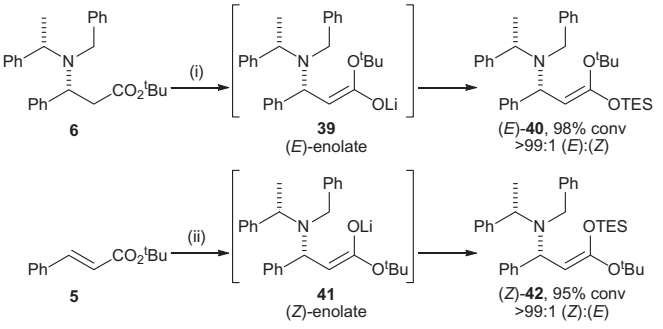
Acceptor	Ar	Products (*anti*:*syn*)	D Incorporation (%)	dr[a,c] (*anti*:*syn*)	Yield (%)
15	4-MeOC$_6$H$_4$	**27**:**33**	78[a] (77)[b]	>99:1	60
16	4-BrC$_6$H$_4$	**28**:**34**	81[a] (86)[b]	96:4	65
17	3-BrC$_6$H$_4$	**29**:**35**	74[a] (70)[b]	>99:1	72
18	3-FC$_6$H$_4$	**30**:**36**	80[a] (75)[b]	>99:1	67
19	2-BrC$_6$H$_4$	**31**:**37**	81[a] (90)[b]	>99:1	68
20	2-IC$_6$H$_4$	**32**:**38**	89[a] (92)[b]	95:5	70

Scheme 5. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C, 2 h then D_2O [[a] ^{1}H NMR spectroscopic analysis; [b] mass spectrometric analysis; [c] crude and isolated].

27–32 with very high levels of diastereoselectivity (⩾95:5 dr) and deuterium incorporation (⩾74%). In each case the configuration of the major product was assigned as 2,3-*anti* by analogy to that unambiguously proven for *anti*-**7** (Scheme 5).

2.2. Stepwise conjugate addition/deuteration of α,β-unsaturated esters

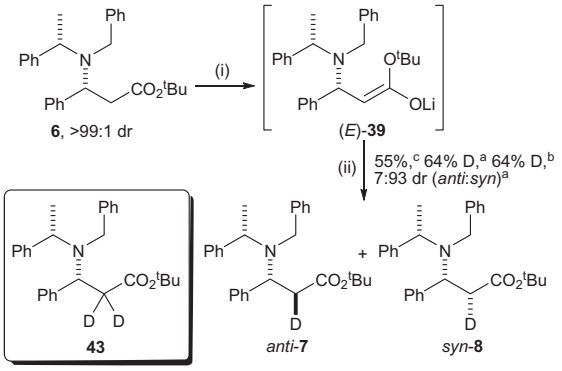
Following the alternative 'stepwise' conjugate addition/deuteration strategy, deprotonation of α,α-diprotio-β-amino ester **6** followed by diastereoselective deuteration upon the addition of a 'D$^+$' source was next investigated. We have previously established in a range of systems that deprotonation of a β-amino ester gives rise to (*E*)-enolates, whereas (*Z*)-enolates are formed as a result of a lithium amide conjugate addition reaction to an α,β-unsaturated ester.[33] In order to confirm that this trend was also observed in our model system the lithium β-amino enolates derived from both (i) deprotonation of β-amino ester **6**, or (ii) conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **4** to α,β-unsaturated ester **5**, were captured with TESCl to confirm their enolate geometries by ^{1}H NMR NOE analyses. Thus, in accordance with our previous results, α,α-diprotio-β-amino ester **6** was sequentially treated with LDA and TESCl to give triethylsilyl ketene acetal (*E*)-**40** in 98% conversion and >99:1 dr. Conversely, triethylsilyl ketene acetal (*Z*)-**42** was accessed in 95% conversion and >99:1 dr upon conjugate addition of (*S*)-**4** to **5** followed by treatment with TESCl (Scheme 6). ^{1}H NMR NOE analysis of (*Z*)-**42** revealed that when the C(2)*H* proton was irradiated, enhancements to the corresponding C(3)*H*, C(α)*Me* and C*Me*$_3$ protons were observed. Additionally, when the C*Me*$_3$ protons were irradiated, there was clearly a strong enhancement to the C(2)*H* proton. For (*E*)-**40**, however, irradiation of the C(2)*H* proton showed no enhancement to the *tert*-butyl group, but a large enhancement to the Si(C*H*$_2$CH$_3$)$_3$ protons was observed. In addition, when the Si(C*H*$_2$CH$_3$)$_3$ protons were irradiated the only enhancement that was observed was to the C(2)*H*



Scheme 6. Reagents and conditions: (i) LDA, THF, TESCl, −78 °C, 1 h; (ii) (*S*)-**4**, THF, TESCl, −78 °C, 1 h [TES = $SiEt_3$].

proton. This stereochemical outcome is consistent with other β-amino enolate trapping studies[34] and also that predicted by the Ireland chelation-controlled deprotonation transition state model[35] for deprotonation of **6** with LDA.

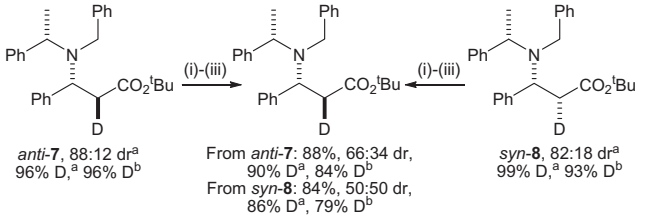
Lithium β-amino enolate (*E*)-**39**, generated by deprotonation of α,α-diprotio-β-amino ester **6** with LDA, was next treated with D_2O at −78 °C under a range of conditions to give α-deuterated products *anti*-**7** and *syn*-**8** with varying levels of deuterium incorporation and diastereoselectivity. Under optimised conditions α,α-diprotio-β-amino ester **6** was added to 1.0 equiv of LDA at −78 °C and the resultant mixture was allowed to warm to 0 °C over 1 h before being cooled to −78 °C prior to the addition of D_2O. This produced a 7:93 mixture of α-deuterio-β-amino esters *anti*-**7** and *syn*-**8**, respectively, which was isolated in relatively poor yield (55%) with incomplete deuterium incorporation (64%), as determined by ^{1}H NMR spectroscopic analysis. The corresponding α,α-dideuterio-β-amino ester **43**[36] was not detected (Scheme 7). Employing a 'double deprotonation' strategy[37] [i.e., whereby (*E*)-**39** was formed upon deprotonation of **6** with LDA, BuLi was then added, the reaction mixture was allowed to warm to 0 °C then cooled to −78 °C before the addition of D_2O] gave a 30:70 mixture of *anti*-**7** and *syn*-**8**, respectively, with 91% deuterium incorporation.



Scheme 7. Reagents and conditions: (i) LDA, THF, −78 to 0 °C, 1 h; (ii) D_2O, −78 °C to rt, 30 min [[a] ^{1}H NMR spectroscopic analysis; [b] mass spectrometric analysis; [c] combined isolated yield].

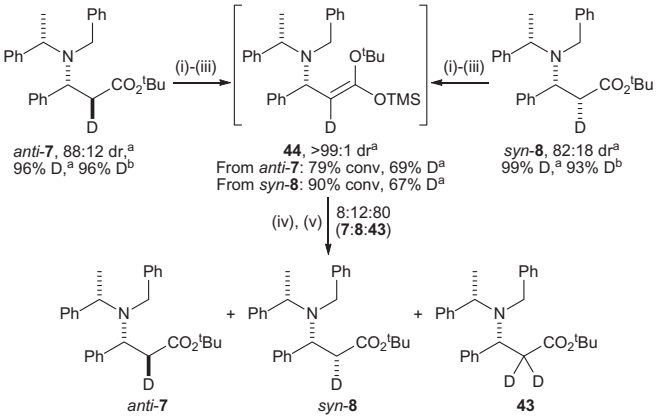
Having studied the diastereoselectivity of deuteration of lithium (*E*)-α-protio-β-amino enolates, the diastereoselectivity of deprotonation of α-deuterio-β-amino esters *anti*-**7** and *syn*-**8**[38] was next investigated. Thus, *anti*-**7** and *syn*-**8** were treated with LDA under 'double deprotonation' conditions at −78 °C followed by the addition of H_2O. When *anti*-**7** (88:12 dr, 96% D incorporation) was subjected to these conditions a 66:34 mixture of *anti*-**7** and *syn*-**8**, respectively, was formed with minimal loss of deuterium (90% D incorporation), indicating preferential removal of the *syn*-α-proton. If deprotonation was indeed *syn* diastereoselective, treatment of α-deuterio-β-amino ester *syn*-**8** would be predicted to afford a product with low deuterium incorporation. However, treatment of *syn*-**8** (82:18 dr, 93% D incorporation) with LDA under 'double deprotonation' conditions followed by the addition of H_2O gave a 50:50 mixture of *anti*-**7** and *syn*-**8**, again with minimal loss of deuterium (86% D incorporation). There are two possible explanations for this result: either full deprotonation is not occurring upon treatment with LDA, or a kinetic isotope effect is overriding any diastereoselective process, with a proton being more readily removed than a deuteron (Scheme 8).

To monitor whether full deprotonation was indeed occuring, and to investigate further the diastereoselectivity of deprotonation, it was envisaged that *anti*-**7** and *syn*-**8** could be treated with LDA under the 'double deprotonation' conditions, then the intermediate lithium β-amino enolates could be trapped by addition of TMSCl at



Scheme 8. Reagents and conditions: (i) LDA, THF, −78 to 0 °C; (ii) BuLi, −78 °C; (iii) H_2O, −78 °C to rt, 30 min.

−78 °C. Treatment of *anti*-**7** under these conditions gave silyl ketene acetal **44** in 79% conversion with 69% deuterium incorporation. The (*E*)-configuration within **44** was assigned by analogy to the previous results for capture of enolate (*E*)-**39** with TESCl. Treatment of *syn*-**8** under identical conditions also gave **44** (in 90% conversion with 67% D incorporation). An estimate of the kinetic isotope effect may be given by dividing the percentage of hydrogen removed by the percentage of deuterium removed: for deprotonation of *anti*-**7**, a kinetic isotope effect of 2.6 was calculated, whereas a kinetic isotope effect of 3.0 was calculated for deprotonation of *syn*-**8**. As deprotonation of both diastereoisomers gave silyl ketene acetal **44** with good conversion this confirms that LDA was effecting complete deprotonation. Silyl ketene acetal **44** (69% D incorporation; formed from *anti*-**7**) was next treated with BuLi at −78 °C (to remove the silyl moiety) followed by the addition of D_2O which gave a product mixture containing *anti*-**7**, *syn*-**8** and α,α-dideuterio **43** in the ratio of 8:12:80 respectively; there was no evidence of the corresponding α,α-diprotio-β-amino ester **6** (Scheme 9). The formation of 80% α,α-dideuterated product **43** reflects the observed 79% deuterium incorporation of intermediate **44**, and confirms that the proton is selectively removed from either β-amino ester *anti*-**7** or *syn*-**8** via a kinetic isotope effect. These data demonstrate that the reaction conditions are not, therefore, interfering with deuterium incorporation.

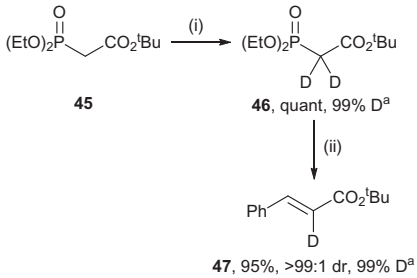


Scheme 9. Reagents and conditions: (i) LDA, THF, −78 to 0 °C; (ii) BuLi, −78 °C; (iii) TMSCl, −78 °C; (iv) BuLi, THF, −78 °C; (v) D_2O, −78 °C [[a] ^{1}H NMR spectroscopic analysis; [b] mass spectrometric analysis].

Given the limited success of this approach for the preparation of *syn*-α-deuterio-β-amino esters it was envisaged that an alternative protocol could be used to access these substrates. The conjugate addition of lithium amide (*S*)-**4** to an α-deuterio-α,β-unsaturated ester followed by diastereoselective protonation of the intermediate lithium β-amino enolate was therefore investigated as it was anticipated that superior levels of deuterium incorporation would be observed relative to the 'stepwise' conjugate addition/deuteration protocol.

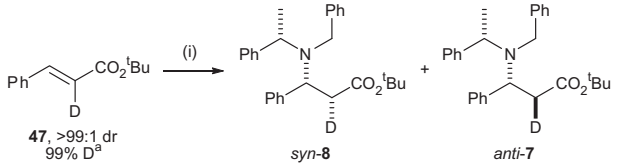
2.3. Tandem conjugate addition/protonation of α-deuterio-α,β-unsaturated esters

With a Wadsworth-Emmons protocol in mind (i.e., reaction of an aldehyde with a deuterated phosphonate), the synthesis of C(2) isotopically labelled *tert*-butyl cinnamate **47** commenced with the preparation of α,α-dideuterio phosphonate **46** from unlabelled phosphonate **45**. Initially, the base employed for deprotonation of phosphonate **45** was KO^{t}Bu in MeOH-d_4, although in this case a maximum of 89% deuterium incorporation was observed. The level of deuterium incorporation was increased to 95% by use of KO^{t}Bu in ^{t}BuOD.[39] However, full conversion of phosphonate **45** to phosphonate-d_2 **46** was obtained upon treatment of **45** with K_2CO_3 in D_2O.[40] Reaction optimisation indicated that 3.0 equiv of K_2CO_3 as a solution in D_2O provided phosphonate-d_2 **46** in quantitative yield with 99% deuterium incorporation. With phosphonate-d_2 **46** in hand, attention turned to developing the Wadsworth–Emmons olefination with benzaldehyde to give *tert*-butyl α-deuteriocinnamate **47** with high diastereoselectivity and deuterium incorporation. A range of conditions were screened and the combination of K_2CO_3 in D_2O was found to give **47** with the highest level of deuterium incorporation. Thus, under optimised conditions, reaction of 2.0 equiv of **46** with benzaldehyde at 50 °C gave **47** in 95% yield and >99:1 dr with 99% deuterium incorporation (Scheme 10).



Scheme 10. Reagents and conditions: (i) K_2CO_3, D_2O, rt, 24 h; (ii) PhCHO, D_2O, 50 °C, 30 h [^{a} ^{1}H NMR spectroscopic analysis].

The conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **4** to *tert*-buyl α-deuteriocinnamate **47** was performed at −78 °C, followed by protonation of the lithium α-deuterio-β-amino enolate with a range of proton sources, viz. H_2O, MeOH, AcOH and 2-pyridone. In each case a diastereoisomeric mixture of the two mono-deuterated-β-amino esters *anti*-**7** and *syn*-**8**, along with a trace amount of the α,α-diprotio-β-amino ester **6**, was observed. The highest level of diastereoselectivity was observed upon protonation of the intermediate lithium β-amino enolate with 2-pyridone, giving *syn*-**8** in >99:1 dr and 96% deuterium incorporation (Scheme 11). In each case, the level of deuterium incorporation of the product mixture of β-amino esters from each reaction was consistently high (⩾92%) although slightly lower than that of the starting material. When compared with the results obtained for the deuteration of lithium α-protio-β-amino enolates, the major difference between the two sets of data is the high degree of deuterium incorporation in the products arising from protonation with AcOH (95%), which is substantially greater than that for deuteration with AcOH-d_4 (53%). While each reaction demonstrated *anti*-diastereoselectivity to produce *syn*-**8** as the major product, the diastereoselectivity ranged from 73:27 to >99:1 dr. The levels of diastereoselectivity obtained upon protonation of the α-deuterio substituted enolate by H_2O, MeOH and AcOH were found to be comparable with those arising from deuteration of the corresponding α-protioenolate with D_2O, MeOH-d_4 and AcOH-d_4. While it is difficult to predict the mechanism that is operating upon addition of each of the proton/deuteron sources, consideration of the pK_a and structure of the proton/deuteron source is helpful for analysing

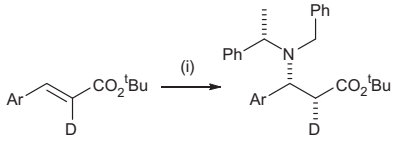


"H$^+$" Source	D Incorporation (%)	dr^{a,c} (*syn*:*anti*)	Yield (%)
H_2O	94^a (94)^b	90:10	85
MeOH	99^a (93)^b	82:18	90
AcOH	95^a (92)^b	73:27	26
2-pyridone	96^a (97)^b	>99:1	75

Scheme 11. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C, 2 h then 'H$^+$', −78 °C to rt, 30 min [^{a} ^{1}H NMR spectroscopic analysis; ^{b} mass spectrometric analysis; ^{c} crude and isolated].

the results. AcOH (pK_a 12.6 in DMSO[41]) may be preferentially protonating on oxygen, with subsequent loss of diastereoselectivity upon tautomerisation, and the greater diastereoselectivity of protonation by H_2O (pK_a 31.4 in DMSO[42]) may be rationalised via a mechanism in which protonation occurs directly at the C(2) carbon atom. We have previously demonstrated that high diastereoselectivity can be obtained during the protonation of lithium β-amino enolates by 2-pyridone via a 'proton relay' mechanism where the proton is delivered directly to the C(2) carbon atom of the enolate;[43] this rationale may also, therefore, account for the extremely high diastereoselectivity observed upon protonation of the intermediate lithium β-amino enolate with 2-pyridone in this case.

This approach represents a significant improvement upon the 'stepwise' protocol and was therefore applied to a range of α,β-unsaturated esters incorporating alternative C(3)-substitution. The requisite α-deuterio-α,β-unsaturated esters **48–52** were prepared in good yield from the corresponding aldehydes by treatment with phosphonate-d_2 **46** and K_2CO_3 in D_2O at 50 °C; in each case α-deuterio-α,β-unsaturated esters **48–52** were isolated in >99:1 dr with ⩾96% deuterium incorporation. Following the optimised conditions, conjugate addition of (*S*)-**4** to **48–52** gave the corresponding *syn*-α-deuterio-β-amino esters **34–38** as the sole products after protonation of the resultant lithium β-amino enolates with 2-pyridone at −78 °C.[44] In most cases ^{1}H NMR spectroscopic analysis of the crude reaction mixtures indicated that very high levels of diastereoselectivity (>99:1 dr) and deuterium incorporation (⩾89%) were observed (Scheme 12).



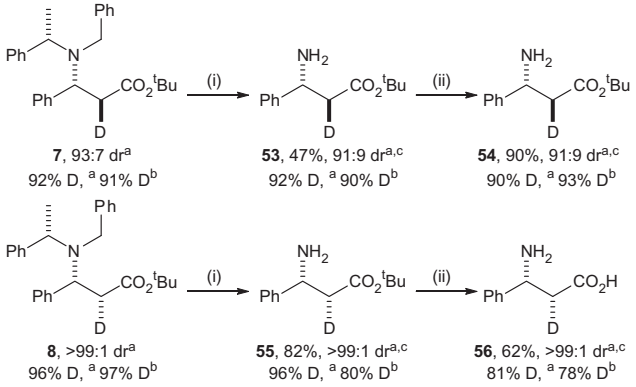
Acceptor^d	D Incorporation (%)	Ar	Product	D Incorporation (%)	dr^{a,c}	Yield (%)
48	99^a (99)^b	4-BrC_6H_4	**34**	92^a (96)^b	>99:1	53
49	99^a (98)^b	3-BrC_6H_4	**35**	92^a (96)^b	>99:1	59
50	99^a (98)^b	3-FC_6H_4	**36**	90^a (91)^b	>99:1	73
51	99^a (98)^b	2-BrC_6H_4	**37**	92^a (96)^b	>99:1	65
52	99^a (96)^b	2-IC_6H_4	**38**	89^a (95)^b	>99:1	53

Scheme 12. Reagents and conditions: (i) (*S*)-**4**, THF, −78 °C, 2 h then 2-pyridone, −78 °C to rt, 30 min [^{a} ^{1}H NMR spectroscopic analysis; ^{b} mass spectrometric analysis; ^{c} crude and isolated; ^{d} compounds **48**-**52** were isolated in >99:1 dr with ⩾96% D incorporation].

2.4. Deprotection to give α-deuterio-β-amino acids

The deprotection of *anti*-**7** and *syn*-**8** (as representative examples) to give the corresponding α-deuterio-β-amino acids was next undertaken. *N*-Benzyl deprotection of *anti*-**7** (93:7 dr) was

achieved by hydrogenolysis in the presence of Pearlman's catalyst [$Pd(OH)_2/C$] under 1 atmosphere of hydrogen giving **53** in 47% yield and 91:9 dr, without compromising the extent of deuterium incorporation.[45] Subsequent treatment of **53** with TFA followed by purification via ion exchange chromatography on Dowex 50WX8-200 resin gave α-deuterio-β-amino acid (2*S*,3*R*)-**54** in 90% yield and 91:9 dr, confirming that the stereochemical integrity of the α-centre was maintained during the deprotection sequence. Deprotection of *syn*-**8**[45] (>99:1 dr) was achieved by an analogous sequence of reactions to give α-deuterio-β-amino acid (*R*,*R*)-**56** in 51% yield (in two steps from *syn*-**8**) and >99:1 dr, following purification via ion exchange chromatography (Scheme 13).



Scheme 13. Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/H_2O/AcOH (v/v/v 40:4:1), rt, 24 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 24 h then HCl, Dowex 50WX8-200 [[a] ^1H NMR spectroscopic analysis; [b] mass spectrometric analysis; [c] crude and isolated].

3. Conclusion

In conclusion, the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of α,β-unsaturated esters followed by reaction of the resultant lithium (*Z*)-β-amino enolates with D_2O provides access to *anti* configured α-deuterio-β-amino esters in high dr. Attempted preparation of *syn* configured α-deuterio-β-amino esters via deprotonation of the corresponding α,α-diprotio-β-amino esters followed by reaction of the resultant lithium (*E*)-β-amino enolates with D_2O also proceeded with high diastereoselectivity, although in this case the extent of deuterium incorporation was poor. An alternative procedure for the preparation of *syn* configured α-deuterio-β-amino esters in high dr was therefore developed via the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of α-deuterio-α,β-unsaturated esters followed by reaction of the resultant lithium (*Z*)-β-amino enolates with 2-pyridone. After deprotection of two diastereoisomeric α-deuterio-β-amino esters, both the *syn*- and *anti*-diastereoisomers of the corresponding α-deuterio-β^3-amino acids were isolated in high dr.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[46] Water was purified by an Elix® UV-10 system. BuLi was purchased from Sigma–Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

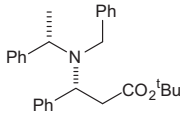
4.2. General procedure 1 for lithium amide conjugate addition

BuLi (1.55 equiv) was added dropwise to a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.6 equiv) in THF (0.5 mmol/mL) at −78 °C. The resultant pink solution was stirred at −78 °C for 30 min before the addition of the requisite α,β-unsaturated ester (1.0 equiv) in THF (0.3 mmol/mL) at −78 °C. The reaction mixture was then stirred at −78 °C for 2 h before the addition of either satd aq NH_4Cl, D_2O, MeOH-d_4, AcOH-d_4, H_2O, MeOH, AcOH or 2-pyridone, as specified. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O and Et_2O and the aqueous layer was extracted with Et_2O. The combined organic extracts were then sequentially washed with brine, 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.3. General procedure 2 for Wadsworth–Emmons olefination

The requisite aldehyde (0.5 equiv) was added to a solution of phosphonate-d_2 **46** (1.0 equiv) and K_2CO_3 (3.0 equiv) in D_2O (6.0 mmol/mL). The resultant solution was stirred for 30 h at 50 °C, then allowed to cool to rt and extracted with three portions of Et_2O. The combined organic extracts were washed with 10% aq $Na_2S_2O_3$, then dried and concentrated in vacuo.

4.3.1. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 6



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (8.19 g, 39.2 mmol) in THF (75 mL), BuLi (15.2 mL, 37.9 mmol) and **5**[22] (5.00 g, 24.5 mmol) in THF (75 mL), followed by satd aq NH_4Cl (25 mL), gave **6** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **6** as a colourless oil (9.07 g, 89%, >99:1 dr); $[\alpha]_D^{23}$

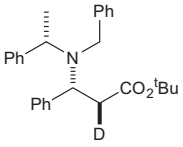
−2.2 (*c* 1.4 in CH_2Cl_2); {lit.[15b] for enantiomer $[\alpha]_D^{24}$ +3.9 (*c* 1.4 in CH_2Cl_2)}; δ_H (400 MHz, MeOH-d_4) 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.53 (1H, dd, *J* 14.4, 9.8, C(2)H_A), 260 (1H, dd, *J* 14.4, 5.4, C(2)H_B), 3.69 (2H, app s, NCH_2Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, dd, *J* 9.8, 5.4, C(3)*H*), 7.13–7.44 (15H, m, *Ph*).

4.3.1.1. X-ray crystal structure determination for (*RS*,*SR*)-6. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[47]

X-ray crystal structure data for (*RS*,*SR*)-**6** [$C_{28}H_{33}NO_2$]: M = 415.58, triclinic, space group $\bar{P}$, a = 10.2498(2) Å, b = 10.2921(2) Å, c = 12.7424(3) Å, α = 101.6433(7)°, β = 109.9610(9)°, γ = 95.8929(7)°, V = 1215.79(4) Å^3, Z = 2, μ = 0.070 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.23 × 0.23 mm^3. A total of 5480 unique reflections were measured for $5 < \theta < 27$ and 4642 reflections were used in the refinement. The final parameters were wR_2 = 0.119 and R_1 = 0.055 [$I > -3.0\sigma(I)$].

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 810336. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3.2. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 7



Method A: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.04 g, 7.83 mmol) in THF (15 mL), BuLi (3.04 mL, 7.59 mmol) and **5** (1.00 g, 4.90 mmol) in THF (15 mL), followed by D_2O (5 mL), gave a 93:7 mixture of **7** and **8**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave a 93:7 mixture of **7** and **8** as a colourless oil (1.87 mg, 91%, D incorporation 92% [^{1}H NMR], 91% [MS]).

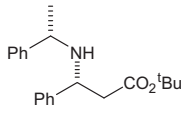
Data for *anti*-**7**: δ_H (400 MHz, MeOH-d_4) 1.26 (9H, s, C*Me*$_3$), 1.30 (3H, d, *J* 6.8, C(α)*Me*), 2.57 (1H, d, *J* 4.6, C(2)*H*), 3.72 (2H, app s, NCH_2Ph), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.44 (1H, d, *J* 4.6, C(3)*H*), 7.19–7.47 (15H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 16.3 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.3 (*C*(2)), 50.9 (NCH_2Ph), 57.1 (*C*(α)), 59.7 (*C*(3)), 80.1 (*C*Me$_3$), 126.5, 126.8, 126.9 (*p*-*Ph*), 127.1, 127.8, 128.1, 128.2, 128.3, 128.9, (*o*,*m*-*Ph*), 141.7, 141.8, 144.2, (*i*-*Ph*), 171.1 (*C*(1)).

Data for mixture: $[\alpha]_D^{22}$ −8.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1725 (C=O), 1453 (C–N), 1160 (C–O); *m*/*z* (ESI$^+$) 417 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}DNO_2^+$ ([M+H]$^+$) requires 417.2647; found 417.2667.

Method B: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (248 mg, 1.18 mmol) in THF (2 mL), BuLi (3.04 mL, 7.59 mmol) and **5** (150 mg, 0.734 mmol) in THF (2 mL), followed by MeOH-d_4 (1 mL), gave an 88:12 mixture of **7** and **8**. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 30:1) gave an 88:12 mixture of **7** and **8** as a colourless oil (275 mg, 90%, D incorporation 96% [^{1}H NMR], 96% [MS]).

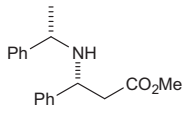
Method C: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (157 mg, 0.744 mmol) in THF (1.5 mL), BuLi (0.45 mL, 0.72 mmol) and **5** (95 mg, 0.47 mmol) in THF (1.5 mL), followed by AcOH-d_4 (0.5 mL), gave a 68:32 mixture of **7** and **8** in addition to returned starting material **5**. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 100:1) gave **5** as a colourless oil (37 mg, 41%). Further elution gave a 68:32 mixture of **7** and **8** as a colourless oil (106 mg, 55%, D incorporation 53% [^{1}H NMR], 52% [MS]).

4.3.3. *tert*-Butyl (3*R*,α*S*)-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 9



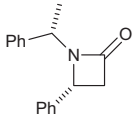
CAN (1.38 g, 2.52 mmol) was added to a solution of **6** (500 mg, 1.20 mmol) in a mixture of MeCN/H_2O (v/v 5:1, 13.8 mL). The resultant solution was stirred at rt for 18 h then satd aq $NaHCO_3$ (15 mL) was added and the product mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were then washed with brine, dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **9** as a yellow oil (226 mg, 86%, >99:1 dr);[29] $[\alpha]_D^{22}$ −15.8 (*c* 1.0 in $CHCl_3$); {lit.[30] $[\alpha]_D^{23}$ −16.3 (*c* 1.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.5, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 1.91 (1H, br s, N*H*), 2.59 (1H, dd, *J* 14.7, 6.2, C(2)H_A), 2.86 (1H, dd, *J* 14.7, 7.9, C(2)H_B), 3.70 (1H, q, *J* 6.5, C(α)*H*), 4.21 (1H, dd, *J* 7.9, 6.2, C(3)*H*), 7.21–7.32 (10H, m, *Ph*).

4.3.4. Methyl (3*R*,α*S*)-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 10



$SOCl_2$ (0.50 mL, 6.86 mmol) was added dropwise to a stirred solution of **9** (199 mg, 0.61 mmol) in MeOH (6 mL) at 0 °C. The resultant mixture was heated at reflux for 2 h then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo to give **10** as a yellow oil (144 mg, 83%, >99:1 dr);[30] $[\alpha]_D^{22}$ −20.0 (*c* 0.1 in $CHCl_3$); {lit.[30] $[\alpha]_D^{21}$ −16.3 (*c* 1.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.5, C(α)*Me*), 1.76 (1H, br s, N*H*), 2.67 (1H, dd, *J* 15.3, 6.2, C(2)H_A), 2.75 (1H, dd, *J* 15.3, 7.8, C(2)H_B), 3.63 (3H, s, O*Me*), 3.67 (1H, q, *J* 6.5, C(α)*H*), 4.22 (1H, dd, *J* 7.8, 6.2, C(3)*H*), 7.19–7.34 (10H, m, *Ph*).

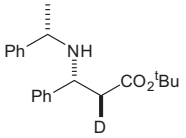
4.3.5. (4*R*,α*S*)-*N*(1)-(α-Methylbenzyl)-4-phenylazetidin-2-one 11



MeMgBr (2.13 M in Et_2O, 0.28 mL, 0.59 mmol) was added dropwise via syringe to a solution of **10** (140 mg, 0.49 mmol) in Et_2O (2.5 mL) at 0 °C. The resultant mixture was stirred for 30 min at 0 °C and then satd aq NH_4Cl (5 mL) was added. The reaction mixture was then extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried and concentrated in vacuo to give **11** as a yellow oil (111 mg, 89%, >99:1 dr);[30] $[\alpha]_D^{22}$ +40.0 (*c* 0.6 in $CHCl_3$); {lit.[30] $[\alpha]_D^{21}$ +57.9 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.2, C(α)*Me*), 2.84 (1H, dd, *J* 14.8, 2.5, C(3)H_A), 3.25

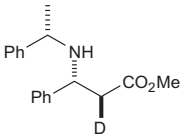
(1H, dd, *J* 14.8, 5.4, C(3)H_B), 4.30 (1H, dd, *J* 5.4, 2.5, C(4)*H*), 5.05 (1H, q, *J* 7.2, C(α)*H*), 7.19–7.42 (10H, m, *Ph*).

4.3.6. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 12



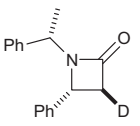
CAN (1.38 g, 2.52 mmol) was added to a solution of **7** (500 mg, 1.20 mmol, 93:7 dr, D incorporation 92% [^{1}H NMR], 91% [MS]) in a mixture of MeCN/H_2O (v/v 5:1, 11.8 mL). The resultant solution was stirred at rt for 18 h then satd aq $NaHCO_3$ (15 mL) was added and the product mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were then washed with brine, dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:5) gave **12** as a yellow oil (282 mg, 76%, 92:8 dr, D incorporation 92% [^{1}H NMR], 91% [MS]); $[\alpha]_D^{21}$ −18.3 (*c* 0.3 in $CHCl_3$); ν_{max} (film) 3333 (N–H), 1725 (C=O), 1452 (C–N), 1158 (C–O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.5, C(α)*Me*), 1.39 (9H, s, C*Me*$_3$), 1.88 (1H, br s, N*H*), 2.64 (1H, d, *J* 8.0, C(2)*H*), 3.68 (1H, q, *J* 6.5, C(α)*H*), 4.18 (1H, d, *J* 8.0, C(3)*H*), 7.20–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.3 (C(α)*Me*), 28.0 (C*Me*$_3$), 43.7 (*C*(2)), 54.5 (*C*(α)), 57.0 (*C*(3)), 80.5 (*C*Me$_3$), 126.6, 126.8, 127.1, 127.2, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 142.8, 146.1 (*i*-*Ph*), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 327 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}DNO_2^+$ ([M+H]$^+$) requires 327.2177; found 327.2172.

4.3.7. Methyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 13



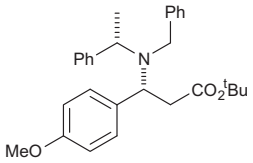
$SOCl_2$ (0.50 mL, 6.85 mmol) was added dropwise to a stirred solution of **12** (217 mg, 0.67 mmol, 92:8 dr, D incorporation 92% [^{1}H NMR], 91% [MS]) in MeOH (4 mL) at 0 °C. The resultant mixture was heated at reflux for 2 h then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **13** as a colourless oil (127 mg, 84%, 93:7 dr, D incorporation 92% [^{1}H NMR]); $[\alpha]_D^{21}$ −15.5 (*c* 0.4 in $CHCl_3$); {lit.[27] for enantiomer $[\alpha]_D^{20}$ +19.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, MeOH-d_4) 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.86 (1H, br d, *J* 6.6, C(2)*H*), 3.55 (3H, s, O*Me*), 3.68 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d, *J* 6.6, C(3)*H*), 7.20–7.36 (10H, m, *Ph*).

4.3.8. (3*S*,4*R*,α*S*)-*N*(1)-(α-Methylbenzyl)-3-deuterio-4-phenyl-azetidin-2-one 14



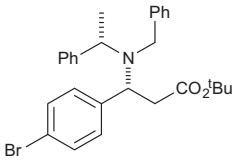
MeMgBr (2.13 M in Et_2O, 0.17 mL, 0.37 mmol) was added dropwise via syringe to a solution of **13** (88 mg, 0.31 mmol, 93:7 dr, D incorporation 92% [^{1}H NMR]) in Et_2O (2 mL) at 0 °C. The resultant mixture was stirred for 30 min at 0 °C and then satd aq NH_4Cl (2 mL) was added. The reaction mixture was then extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **14** as a colourless oil (73 mg, 94%, 92:8 dr, D incorporation 85% [^{1}H NMR]); $[\alpha]_D^{22}$ +27.9 (*c* 0.8 in $CHCl_3$); {lit.[27] for enantiomer $[\alpha]_D^{20}$ −15.8 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.2, C(α)*Me*), 2.85 (1H, d, *J* 2.4, C(3)*H*), 4.32 (1H, d, *J* 2.4, C(4)*H*), 5.07 (1H, q, *J* 7.2, C(α)*H*), 7.24–7.38 (10H, m, *Ph*).

4.3.9. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(4′-methoxyphenyl)propanoate 21



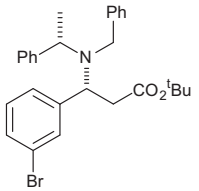
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (360 mg, 1.70 mmol) in THF (15 mL), BuLi (1.00 mL, 1.60 mmol) and **15**[31a] (249 mg, 1.14 mmol) in THF (15 mL), followed by satd aq NH_4Cl (5 mL), gave **21** in 98:2 dr. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 4:1) gave **21** as a colourless oil (453 mg, 96%, 98:2 dr); $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$); {lit.[31a] $[\alpha]_D^{20}$ −1.8 (*c* 3.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 2.46 (1H, dd, *J* 14.4, 10.2, C(2)H_A), 2.68 (1H, dd, *J* 14.4, 5.0, C(2)H_B), 3.67 (2H, app s, NCH_2Ph), 3.81 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.35 (1H, dd, *J* 10.2, 5.0, C(3)*H*), 6.85–6.89 (2H, m, *Ar*), 7.16–7.42 (12H, m, *Ar*, *Ph*).

4.3.10. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(4′-bromophenyl)propanoate 22



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (240 mg, 1.13 mmol) in THF (2.5 mL), BuLi (0.44 mL, 1.09 mmol) and **16**[31b] (200 mg, 0.70 mmol) in THF (2.5 mL), followed by satd aq NH_4Cl (5 mL), gave **22** in 98:2 dr. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 50:1) gave **22** as a colourless oil (321 mg, 92%, 98:2 dr);[48] $[\alpha]_D^{21}$ +2.8 (*c* 0.5 in $CHCl_3$); {lit.[49] $[\alpha]_D^{23}$ +3.6 (*c* 1.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.42–2.54 (2H, m, C(2)H_2), 3.66 (2H, app s, NCH_2Ph), 3.95 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, dd, *J* 10.1, 5.1, C(3)*H*), 7.17–7.48 (14H, m, *Ar*, *Ph*).

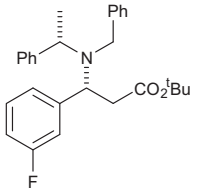
4.3.11. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′-bromophenyl)propanoate 23



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (307 mg, 1.45 mmol) in THF (4 mL), BuLi

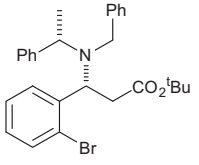
(0.56 mL, 1.41 mmol) and **17**[31b] (257 mg, 0.91 mmol) in THF (4 mL), followed by satd aq NH_4Cl (1.0 mL), gave **23** in >99:1 dr. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 50:1) gave **23** as a colourless oil (384 mg, 86%, >99:1 dr); $[\alpha]_D^{25}$ −6.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3027, 2975, 2932, 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 2.53 (1H, dd, *J* 14.7, 9.6, C(2)H_A), 2.58 (1H, dd, *J* 14.7, 5.3, C(2)H_B), 3.73 (2H, app br s, NCH_2Ph), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.47 (1H, dd, *J* 9.6, 5.3, C(3)*H*), 7.20–7.51 (13H, m, *Ar*, *Ph*), 7.62–7.65 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 28.0 (C*Me*$_3$), 38.0 (*C*(2)), 51.0 (NCH_2Ph), 57.5 (*C*(α)), 59.2 (*C*(3)), 80.6 (*C*Me$_3$), 122.4 (*C*(3′)), 126.8, 127.0, 127.1 (*Ar*, *p-Ph*), 127.9, 128.0, 128.3, 128.3, 129.8, 130.2, 131.3 (*Ar*, *o,m-Ph*), 141.3, 143.7, 144.7 (*i-Ph*, *C*(1′)), 170.9 (*C*(1)); *m/z* (ESI$^+$) 496 ([M(^{81}Br)+H]$^+$, 97%), 494 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}{}^{79}BrNNaO_2{}^+$ ([M(^{79}Br)+Na]$^+$) requires 516.1509; found 516.1493.

4.3.12. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′-fluorophenyl)propanoate 24



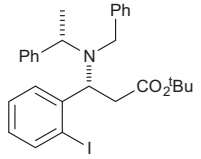
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.11 g, 4.32 mmol) in THF (10 mL), BuLi (1.80 mL, 4.18 mmol) and **18**[31b] (600 mg, 2.70 mmol) in THF (10 mL), followed by satd aq NH_4Cl (1 mL), gave **24** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **24** as a colourless oil (970 mg, 83%, 98:2 dr); $[\alpha]_D^{21}$ −0.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2976, 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 7.0, C(α)*Me*), 2.45–2.54 (2H, m, C(2)H_2), 3.69 (2H, app s, NCH_2Ph), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.43 (1H, app dd, *J* 9.6, 5.6, C(3)*H*), 6.93–7.45 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.9 (*C*(2)), 50.9 (NCH_2Ph), 57.3 (*C*(α)), 59.0 (*C*(3)), 80.4 (*C*Me$_3$), 114.4 (d, *J* 120), 114.6 (d, *J* 120), 123.7, 126.6, 127.0, 127.9, 128.2, 129.5 (*Ar*, *o,m,p-Ph*), 141.3, 143.7, (*i-Ph*), 144.9 (*C*(1′)), 161.4 (d, *J* 246.1, *C*(3′)), 171.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.6 (C(3′)*F*); *m/z* (ESI$^+$) 456 ([M+Na]$^+$, 100%), 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_2{}^+$ ([M+H]$^+$) requires 434.2490; found 434.2490.

4.3.13. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′-bromophenyl)propanoate 25



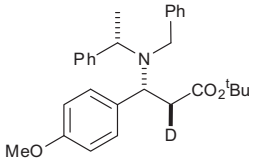
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (119 mg, 0.57 mmol) in THF (4 mL), BuLi (0.22 mL, 0.55 mmol) and **19**[31b] (100 mg, 0.35 mmol) in THF (4 mL), followed by satd aq NH_4Cl (1 mL), gave **25** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **25** as a pale yellow oil (155 mg, 89%, >99:1 dr); $[\alpha]_D^{25}$ −26.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061, 3028, 2975, 2931, 1723 (C=O); δ_H (400 MHz, $CDCl_3$); 1.21 (9H, s, C*Me*$_3$), 1.49 (3H, d, *J* 6.8, C(α)*Me*), 2.35 (1H, dd, *J* 13.9, 10.4, C(2)H_A), (1H, dd, *J* 13.9, 5.3, C(2)H_B), 3.78 (1H, d, *J* 15.4, NCH_AH$_B$Ph), 3.87 (1H, d, *J* 15.4, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.98 (1H, dd, *J* 10.4, 5.3, C(3)*H*), 7.11–7.46 (12H, m, *Ar*, *Ph*), 7.57 (1H, dd, *J* 8.0, 1.1, *Ar*), 7.71 (1H, dd, *J* 8.0, 1.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 42.2 (*C*(2)), 50.7 (NCH_2Ph), 56.9 (*C*(α)), 61.1 (*C*(3)), 80.4 (*C*Me$_3$), 125.4 (C(2′)), 126.4, 126.8, 127.5, 127.6, 128.0, 128.1, 128.8, 130.1, 133.0 (*Ar*, *o,m,p-Ph*), 141.9, 142.5, 143.8 (*C*(1′), *i-Ph*), 170.3 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 97%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}BrNNaO_2{}^+$ ([M(^{79}Br)+Na]$^+$) requires 516.1509; found 516.1509.

4.3.14. *tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′-iodophenyl)propanoate 26



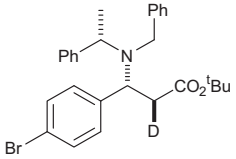
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.54 g, 7.27 mmol) in THF (20 mL), BuLi (2.82 mL, 7.04 mmol) and **20**[31b] (1.50 g, 4.54 mmol) in THF (20 mL), followed by satd aq NH_4Cl (10 mL), gave **26** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **26** as a white solid (2.45 g, 96%, >99:1 dr);[15] mp 86–87 °C ($CHCl_3$); {lit.[50] mp 88 °C}; $[\alpha]_D^{20}$ −20.0 (*c* 0.8 in $CHCl_3$); {lit.[50] $[\alpha]_D^{24}$ −24.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.51 (3H, d, *J* 6.7, C(α)*Me*), 2.17 (1H, dd, *J* 13.7, 9.7, C(2)H_A), 2.60 (1H, dd, *J* 13.7, 5.6, C(2)H_B), 3.72 (1H, d, *J* 15.5, NCH_AH$_B$Ph), 3.82 (1H, d, *J* 15.5, NCH$_A$$H_B$Ph), 3.92 (1H, q, *J* 6.7, C(α)*H*), 4.75 (1H, dd, *J* 9.7, 5.6, C(3)*H*), 6.93–6.97 (1H, m, C(4′)*H*), 7.11–7.44 (11H, m, C(6′)*H*, *Ph*), 7.67 (1H, dd, *J* 7.9, 1.1, C(5′)*H*), 7.82 (1H, dd, *J* 7.9, 1.1, C(3′)*H*).

4.3.15. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4′-methoxyphenyl)propanoate 27



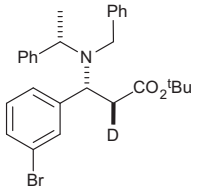
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (289 mg, 1.37 mmol) in THF (3 mL), BuLi (0.63 mL, 1.32 mmol) and **15**[31a] (200 mg, 0.85 mmol) in THF (3 mL), followed by D_2O (1 mL), gave **27** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **27** as a colourless oil (230 mg, 60%, >99:1 dr, D incorporation 78% [^{1}H NMR], 77% [MS]); $[\alpha]_D^{25}$ −2.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061, 3028, 3001, 2974, 2933, 2835 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 2.55 (1H, d, *J* 4.6, C(2)*H*), 3.68 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.72 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.82 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.38 (1H, d, *J* 4.6, C(3)*H*), 6.90 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.18–7.38 (10H, m, *Ph*), 7.45 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 27.9 (C*Me*$_3$), 38.5 (*C*(2)), 50.8 (NCH_2Ph), 55.3 (O*Me*), 57.1 (*C*(α)), 59.1 (*C*(3)), 80.1 (*C*Me$_3$), 113.5 (*C*(3′), C(5′)), 126.5, 126.8 (*p-Ph*), 127.9, 128.0, 128.1 (*o,m-Ph*), 129.4 (*C*(2′), C(6′)), 133.9 (*C*(1′)), 141.9, 144.4 (*i-Ph*), 158.7 (*C*(4′)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 447 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}DNO_3{}^+$ ([M+H]$^+$) requires 447.2752; found 447.2745.

4.3.16. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl]amino)-3-(4′-bromophenyl)propanoate 28



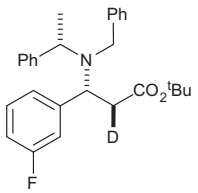
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (297 mg, 1.41 mmol) in THF (3 mL), BuLi (0.55 mL, 1.36 mmol) and **16**[31b] (250 mg, 0.880 mmol) in THF (3 mL), followed by D_2O (2 mL), gave **28** in 96:4 dr. Purification via flash column chromatography (eluent 40–60 °C petrol/Et_2O, 25:1) gave **28** as a colourless oil (282 mg, 65%, 96:4 dr, D incorporation 81% [^{1}H NMR], 86% [MS]); $[\alpha]_D^{24}$ +2.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1735 (C=O), 1594 (C=C), 1488 (C–N), 1157 (C–O), 699 (C–Br); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.49–2.50 (1H, m, C(2)*H*), 3.67 (2H, app s, NC*H*$_2$Ph), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.38 (1H, m, C(3)*H*), 7.20–7.48 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.5 (*C*(2)), 50.8 (NCH$_2$Ph), 57.3 (*C*(α)), 58.8 (*C*(3)), 80.4 (*C*Me$_3$), 120.9 (*C*(4′)), 127.0, 126.6 (*p-Ph*), 127.8, 127.9, 128.2, 128.2, 129.9, 131.2 (*Ar*, *o*,*m-Ph*), 141.1, 141.3, 143.8 (*C*(1′), *i-Ph*), 170.9 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 95%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1758.

4.3.17. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-bromophenyl)propanoate 29



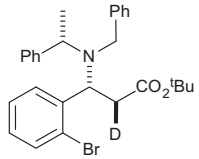
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (283 mg, 1.34 mmol) in THF (3 mL), BuLi (0.52 mL, 1.30 mmol) and **17**[31b] (237 mg, 0.84 mmol) in THF (3 mL), followed by D_2O (1 mL), gave **29** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **29** as a colourless oil (300 mg, 72%, >99:1 dr, D incorporation, 74% [^{1}H NMR], 70% [MS]); $[\alpha]_D^{25}$ −5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3085, 3062, 3028, 2976, 2932, 2877, 2839, 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.49 (1H, d, *J* 4.3, C(2)*H*), 3.66 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.70 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.40 (1H, d, *J* 4.3, C(3)*H*), 7.18–7.45 (13H, m, C(4′)*H*, C(5′)*H*, C(6′)*H*, *Ph*), 7.56–7.58 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.7 (*C*(2)), 51.0 (NCH$_2$Ph), 57.4 (*C*(α)), 59.1 (*C*(3)), 80.5 (*C*Me$_3$), 122.3 (*C*(3′)), 126.7, 127.0 (*C*(6′), *p-Ph*), 127.8, 128.0, 128.3 (*o*,*m-Ph*), 129.8, 130.2 (*C*(4′), *C*(5′)), 131.3 (*C*(2′)), 141.3, 143.7, 144.6 (*C*(1′), *i-Ph*), 170.9 (*C*(1)); *m/z* (ESI$^+$) 519 ([M(^{81}Br)+Na]$^+$, 95%), 517 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1752.

4.3.18. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-fluorophenyl)propanoate 30



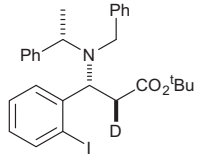
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (304 mg, 1.44 mmol) in THF (3 mL), BuLi (0.66 mL, 1.39 mmol) and **18**[31b] (200 mg, 0.9 mmol) in THF (3 mL), followed by D_2O (1 mL), gave **30** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **30** as a colourless oil (263 mg, 67%, >99:1 dr, D incorporation 80% [^{1}H NMR], 75% [MS]); $[\alpha]_D^{25}$ −2.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3028, 2974, 2931 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 2.57 (1H, d, *J* 4.3, C(2)*H*), 3.72 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.76 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.49 (1H, d, *J* 4.3, C(3)*H*), 6.97–7.04 (1H, m, *Ar*), 7.22–7.43 (11H, m, *Ar*, *Ph*), 7.46–7.50 (2H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.7 (*C*(2)), 51.0 (NCH$_2$Ph), 57.5 (*C*(α)), 59.0 (*C*(3)), 80.5 (*C*Me$_3$), 114.6 (d, *J* 97.5, *C*(4′), 114.6 (d, *J* 140.6, *C*(2′)), 123.5 (*C*(6′)), 126.7, 127.1 (*p-Ph*), 127.9, 128.0, 128.3 (*o*,*m-Ph*), 129.6 (*C*(5′)), 141.4, 143.8 (*i-Ph*), 145.1 (*C*(1′)), 162.9 (d, *J* 244.5, *C*(3′)), 171.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.6 (C(3′)*F*); *m/z* (ESI$^+$) 435 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}DFNO_2^+$ ([M+H]$^+$) requires 435.2553; found 435.2545.

4.3.19. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2′-bromophenyl)propanoate 31



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (239 mg, 1.13 mmol) in THF (3 mL), BuLi (0.52 mL, 1.09 mmol) and **19**[31b] (200 mg, 0.71 mmol) in THF (3 mL), followed by D_2O (1 mL), gave **31** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **31** as a colourless oil (238 mg, 68%, >99:1 dr, D incorporation 81% [^{1}H NMR], 90% [MS]); $[\alpha]_D^{25}$ −34.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061, 3028, 2976, 2933 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.69 (1H, d, *J* 5.3, C(2)*H*), 3.79 (1H, d, *J* 15.9, NC*H*$_A$H$_B$Ph), 3.89 (1H, d, *J* 15.9, NCH$_A$*H*$_B$Ph), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.99 (1H, d, *J* 5.3, C(3)*H*), 7.13–7.17 (1H, m, C(4′)*H*), 7.18–7.47 (11H, m, C(6′)*H*, *Ph*), 7.59 (1H, dd, *J* 8.1, 1.3, C(5′)*H*), 7.72 (1H, dd, *J* 7.8, 1.8, C(3′)*H*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 27.7 (C*Me*$_3$), 41.9 (*C*(2)), 50.8 (NCH$_2$Ph), 56.9 (*C*(α)), 61.1 (*C*(3)), 80.4 (*C*Me$_3$), 125.4 (*C*(2′)), 126.4, 126.8, 127.6, 128.0, 128.1, 128.8, 130.2, 133.0 (*C*(3′), *C*(4′), *C*(5′), *C*(6′), *o*,*m*,*p-Ph*), 141.9, 142.5, 143.8 (*C*(1′), *i-Ph*), 170.3 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 96%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1739.

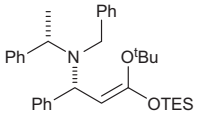
4.3.20. *tert*-Butyl (2*S*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2′-iodophenyl)propanoate 32



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (150 mg, 0.72 mmol) in THF (2 mL), BuLi (0.28 mL, 0.70 mmol) and **20** (150 mg, 0.454 mmol) in THF (2 mL), followed by D_2O (1 mL), gave **32** in 95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O,

40:1) gave **32** as a white solid (160 mg, 70%, 95:5 dr, D incorporation 89% [^{1}H NMR], 92% [MS]); $C_{28}H_{31}DINO_2$ requires C, 62.0; H/D, 5.95; N, 2.6. Found: C, 62.2; H/D, 5.9; N, 2.5; mp 84–85 °C ($CHCl_3$); $[\alpha]_D^{25}$ −24.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1724 (C=O), 1454 (C–N), 1159 (C–O); δ_H (400 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.8, C(α)*Me*), 2.62 (1H, d, *J* 5.8, C(2)*H*), 3.75 (1H, d, *J* 15.4, NC*H*$_A$H$_B$Ph), 3.85 (1H, d, *J* 15.4, NCH$_A$*H*$_B$Ph), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.77 (1H, d, *J* 5.8, C(3)*H*), 6.94–6.98 (1H, m, C(4′)*H*), 7.13–7.44 (11H, m, *Ph*, C(6′)*H*), 7.67–7.69 (1H, dd, *J* 8.0, 1.6, C(5′)*H*), 7.84 (1H, d, *J* 8.0, C(3′)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (C(α)*Me*), 27.8 (C*Me*$_3$), 42.5 (*C*(2)), 50.6 (NCH$_2$Ph), 56.7 (*C*(α)), 66.2 (*C*(3)), 80.3 (*C*Me$_3$), 101.7 (*C*(2′)), 126.3, 126.7 (*p-Ph*), 127.5, 127.9, 128.0, 128.1, 128.3 (*C*(5′), *o,m-Ph*), 129.1 (*C*(4′)), 129.9 (*C*(6′)), 139.6 (*C*(3′)), 142.6, 143.8, 145.3 (*i-Ph*, *C*(1′)), 170.2 (*C*(1)); *m/z* (ESI$^+$) 543 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}DINO_2^+$ ([M+H]$^+$) requires 543.1613; found 543.1613.

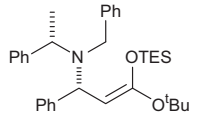
4.3.21. (3*R*,α*S*,*E*)-1-*tert*-Butoxy-1-triethylsiloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropene 40



BuLi (0.48 mL, 1.20 mmol) was added to a solution of diisopropylamine (0.17 mL, 1.25 mmol) in THF (2 mL) at −78 °C. The resultant solution was stirred at rt for 10 min, then cooled to −78 °C and stirred for another 5 min. A solution of **6** (100 mg, 0.24 mmol, >99:1 dr) in THF (2 mL) at −78 °C was then added dropwise via cannula. The reaction mixture was allowed to warm to 0 °C over 1 h then was cooled to −78 °C before a further portion of BuLi (0.19 mL, 0.48 mmol) was added. Stirring was continued at −78 °C for 1 h followed by the rapid injection of TESCl (0.06 mL, 0.38 mmol) via syringe. The reaction mixture was allowed to warm to rt over 30 min, then the solvent was removed under high vacuum to give the crude reaction mixture containing silyl ketene acetal **40**.

Data for **40**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.57–0.67 (6H, m, Si(C*H*$_2$CH$_3$)$_3$), 1.03 (9H, m, Si(CH$_2$C*H*$_3$)$_3$), 1.04 (3H, d, *J* 6.8, C(α)*Me*), 1.09 (9H, s, C*Me*$_3$), 3.49 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.13 (1H, d, *J* 9.4, C(2)*H*), 4.60 (1H, d, *J* 9.4, C(3)*H*), 7.11–7.57 (15H, m, *Ph*).

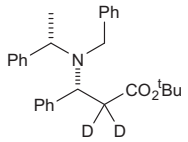
4.3.22. (3*R*,α*S*,*Z*)-1-*tert*-Butoxy-1-triethylsiloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropene 42



BuLi (0.20 mL, 0.49 mmol) was added dropwise to a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (103 mg, 0.490 mmol) in THF (2 mL) at −78 °C. The resultant pink solution was stirred at −78 °C for 30 min before the addition of a solution of **5** (100 mg, 0.49 mmol) in THF (2 mL) at −78 °C. The reaction mixture was then stirred at −78 °C for 2 h before the addition of TESCl (0.13 mL, 0.78 mmol). The reaction mixture was then allowed to warm to rt over 30 min and the solvent was removed under high vacuum to give the crude reaction mixture containing an 18:82 mixture of **6** and **42**.

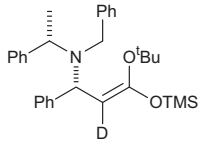
Data for **42**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.58–0.65 (6H, m, Si(C*H*$_2$CH$_3$)$_3$), 0.93 (9H, t, *J* 7.6, Si(CH$_2$C*H*)$_3$), 1.47 (9H, s, C*Me*$_3$), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 3.95 (1H, q, *J* 6.8, C(α)*H*), 4.04 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 4.18 (1H, d, *J* 9.8, C(2)*H*), 4.67 (1H, d, *J* 9.8, C(3)*H*), 7.26–7.73 (15H, m, *Ph*).

4.3.23. *tert*-Butyl (3*R*,α*S*)-2,2-dideuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 43



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (824 mg, 4.00 mmol) in THF (8 mL), BuLi (1.51 mL, 3.78 mmol) and **47** (500 mg, 2.44 mmol, D incorporation 99% [^{1}H NMR]) in THF (8 mL), followed by D_2O (7 mL), gave **43**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **43** as a colourless oil (1.01 g, 99%, >99:1 dr, D incorporation 92% [^{1}H NMR], 97% [MS]); $C_{28}H_{31}D_2NO_2$ requires C, 80.5; H/D, 7.97; N, 3.35. Found C, 80.15; H/D, 8.13; N, 3.32%; $[\alpha]_D^{25}$ −9.1 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1725 (C=O), 1453 (C–N), 1167 (C–O); δ_H (400 MHz, MeOH-d_4) 1.17 (3H, d, C(α)*Me*), 1.19 (9H, s, C*Me*$_3$), 3.65 (2H, app s, NC*H*$_2$Ph), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.34 (1H, s, C(3)*H*), 7.13–7.43 (15H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 16.4 (C(α)*Me*), 27.2 (C*Me*$_3$), 37.4 (*C*(2)), 50.8 (NCH$_2$Ph), 57.6 (*C*(α)), 59.9 (*C*(3)), 80.5 (*C*Me$_3$), 126.7, 127.0, 127.3 (*p-Ph*), 128.0, 128.1, 128.2, 128.2, 128.3, 128.6 (*o,m-Ph*), 142.0, 142.1, 144.7 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D_2NO_2^+$ ([M+H]$^+$) requires 418.2710; found 418.2722.

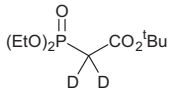
4.3.24. (3*R*,α*S*,*E*)-1-*tert*-Butoxy-1-trimethylsiloxy-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropene 44



From ***8****:* BuLi (0.26 mL, 0.66 mmol) was added to a solution of diisopropylamine (0.09 mL, 0.66 mmol) in THF (2 mL) at −78 °C. The resultant solution was stirred at rt for 10 min, then cooled to −78 °C and stirred for another 5 min. A solution of **8** (55 mg, 0.13 mmol, 82:18 dr, D incorporation 99% [^{1}H NMR], 93% [MS]) in THF (2 mL) at −78 °C was then added dropwise via cannula. The reaction mixture was allowed to warm to 0 °C over 1 h then was cooled to −78 °C before a further portion of (0.11 mL, 0.26 mmol) was added. Stirring was continued at −78 °C for 1 h followed by the rapid injection of TMSCl (0.02 mL, 0.16 mmol) via syringe. The reaction mixture was allowed to warm to rt over 30 min, then the solvent was removed under high vacuum to give the crude reaction mixture containing **44**.

Data for **44**: δ_H (400 MHz, $CDCl_3$) 0.25 (9H, s, Si*Me*$_3$), 1.03 (3H, d, *J* 6.8, C(α)*Me*), 1.09 (9H, s, C*Me*$_3$), 3.50 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.78 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.60 (1H, s, C(3)*H*), 7.10–7.57 (15H, m, *Ph*).

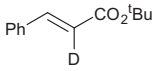
4.3.25. *tert*-Butyl 2,2-dideuterio-2-(diethoxyphosporyl)-ethanoate 46



tert-Butyl 2-(diethoxyphosporyl)ethanoate **45**[22] (6.00 g, 23.8 mmol) was added to a solution of K_2CO_3 (9.86 g, 71.4 mmol) in D_2O (15 mL) and the resultant mixture was stirred at rt for 24 h. The reaction mixture was then extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and

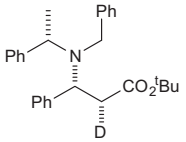
concentrated in vacuo to give **46** as a colourless oil (6.04 g, quant, D incorporation 99% [^{1}H NMR]);[39] δ_H (400 MHz, $CDCl_3$) 1.34 (6H, t, *J* 7.0, 2 × CH_2CH_3), 1.47 (9H, s, CMe_3), 4.20–4.12 (4H, m, 2 × CH_2CH_3).

4.3.26. *tert*-Butyl (*E*)-2-deuterio-3-phenylpropenoate 47



Following *general procedure 2*, **46** (2.63 mL, 11.1 mmol, D incorporation 99% [^{1}H NMR]) was reacted with K_2CO_3 (4.61 g, 33.3 mmol) and benzaldehyde (0.56 mL, 5.55 mmol) in D_2O (5.90 mL). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **47** as a colourless oil (1.08 g, 95%, >99:1 dr, D incorporation 99% [^{1}H NMR]);[51] ν_{max} (film) 1708 (C=O), 1164 (C–O); δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, CMe_3), 7.36–7.39 (3H, m, *Ph*), 7.50–7.53 (2H, m, *Ph*), 7.59 (1H, br s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 80.5 (CMe_3), 119.5 (*C*(2)), 127.9, 128.8 (*o,m-Ph*), 130.0 (*p-Ph*), 134.6 (*i-Ph*), 143.4 (*C*(3)), 166.3 (*C*(1)); *m/z* (CI$^+$) 206 ([M+H]$^+$, 100%); HRMS (GC ToF CI$^+$) $C_{13}H_{16}DO_2^+$ ([M+H]$^+$) requires 206.1286; found 206.1290.

4.3.27. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 8



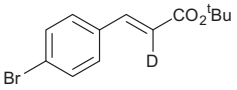
Method A: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (492 mg, 2.24 mmol) in THF (4 mL), BuLi (0.91 mL, 2.27 mmol) and **47** (300 mg, 1.46 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR]) in THF (4 mL), followed by H_2O (2 mL), gave a 90:10 mixture of **8** and **7**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave a 90:10 mixture of **8** and **7** as a colourless oil (610 mg, 85%, D incorporation 94% [^{1}H NMR], 94% [MS]).

Method B: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (165 mg, 0.780 mmol) in THF (1.5 mL), BuLi (0.30 mL, 0.76 mmol) and **47** (100 mg, 0.49 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR]) in THF (1.5 mL), followed by MeOH (1 mL), gave an 82:18 mixture of **8** and **7**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave an 88:12 mixture of **8** and **7** as a colourless oil (183 mg, 90%, D incorporation 99% [^{1}H NMR], 93% [MS]).

Method C: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.16 mL, 0.78 mmol) in THF (1.5 mL), BuLi (0.30 mL, 0.76 mmol) and **47** (100 mg, 0.49 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR]) in THF (1.5 mL), followed by AcOH (2 mL), gave a 73:27 mixture of **8** and **7** in addition to returned starting material **47**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave returned starting material **47** (18 mg, 18%). Further elution gave a 74:26 mixture of **8** and **7** as a colourless oil (53 mg, 26%, D incorporation 95% [^{1}H NMR], 92% [MS]).

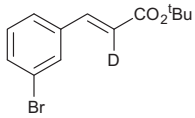
Method D: Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.16 mL, 0.78 mmol) in THF (1.5 mL), BuLi (0.30 mL, 0.76 mmol) and **47** (100 mg, 0.49 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR]) in THF (1.5 mL), followed by 2-pyridone (139 mg, 1.46 mmol), gave **8** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **8** as a colourless oil (153 mg, 75%, >99:1 dr, D incorporation 96% [^{1}H NMR], 97% [MS]); $[\alpha]_D^{21}$ −7.0 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1725 (C=O); δ_H (400 MHz, MeOH-d_4) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.19 (9H, s, CMe_3), 2.49 (1H, d, *J* 10.6, C(2)*H*), 3.65 (2H, app s, NCH_2Ph), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.36 (1H, d, *J* 10.6, C(3)*H*), 7.13–7.43 (15H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 16.4 (C(α)*Me*), 27.2 (CMe_3), 37.6 (*C*(2)), 50.8 (NCH_2Ph), 57.6 (*C*(α)), 59.9 (*C*(3)), 80.5 (CMe_3), 126.7, 126.8, 127.0 (*p-Ph*), 127.3, 128.0, 128.1, 128.2, 128.3, 128.6 (*o,m-Ph*), 142.0, 142.1, 144.7 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 417 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}DNO_2^+$ ([M+H]$^+$) requires 417.2647; found 417.2651.

4.3.28. *tert*-Butyl (*E*)-2-deuterio-3-(4′-bromophenyl)propenoate 48



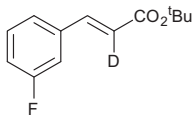
Following *general procedure 2*, **46** (600 mg, 2.36 mmol, D incorporation 99% [^{1}H NMR]), K_2CO_3 (978 mg, 7.08 mmol), D_2O (3 mL) and 4-bromobenzaldehyde (218 mg, 1.18 mmol) were reacted at 50 °C. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **48** as a white solid (289 mg, 86%, >99:1 dr, D incorporation 99% [^{1}H NMR], 99% [MS]); mp 45–51 °C; ν_{max} (film) 3004, 2978, 2931, 1707 (C=O), 1624 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, CMe_3), 7.34 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.48 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*), 7.49 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 80.7 (CMe_3), 124.1 (*C*(2), *C*(4′)), 129.3 (*C*(3′), *C*(5′)), 132.0 (*C*(2′), *C*(6′)), 133.6 (*C*(1′)), 142.0 (*C*(3)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 308 ([M(^{81}Br)+Na]$^+$, 95%), 306 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}D^{79}BrNaO_2^+$ ([M(^{79}Br)+Na]$^+$) requires 306.0210; found 306.0209.

4.3.29. *tert*-Butyl (*E*)-2-deuterio-3-(3′-bromophenyl)propenoate 49



Following *general procedure 2*, **46** (600 mg, 2.36 mmol, D incorporation 99% [^{1}H NMR]), K_2CO_3 (978 mg, 7.08 mmol), D_2O (3 mL) and 3-bromobenzaldehyde (0.14 mL, 1.18 mmol) were reacted at 50 °C. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **49** as a colourless oil (400 mg, quant, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]); ν_{max} (film) 3061, 2978, 2932, 1708 (C=O), 1624 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, CMe_3), 7.18 (1H, app t, *J* 7.8, C(5′)*H*), 7.36 (1H, d, *J* 7.8, C(6′)*H*), 7.42 (1H, app ddd, *J* 7.8, 2.8, 1.8, C(4′)*H*), 7.45 (1H, s, C(3)*H*), 7.60 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 80.7 (CMe_3), 121.4 (*C*(2)), 122.9 (*C*(3′)), 126.6 (*C*(6′)), 130.3, 130.6 (*C*(2′), *C*(5′)), 132.7 (*C*(4′)), 136.7 (*C*(1′)), 141.7 (*C*(3)), 165.7 (*C*(1)); *m/z* (ESI$^+$) 308 ([M(^{81}Br)+Na]$^+$, 95%), 306 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}D^{79}BrNaO_2^+$ ([M(^{79}Br)+Na]$^+$) requires 306.0210; found 306.0209.

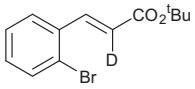
4.3.30. *tert*-Butyl (*E*)-2-deuterio-3-(3′-fluorophenyl)propenoate 50



Following *general procedure 2*, **46** (600 mg, 2.36 mmol, D incorporation 99% [^{1}H NMR]), K_2CO_3 (978 mg, 7.08 mmol), D_2O (3 mL)

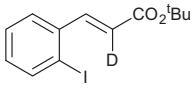
and 3-fluorobenzaldehyde (0.13 mL, 1.18 mmol) were reacted at 50 °C. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **50** as a colourless oil (322 mg, quant, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]); ν_{max} (film) 2979, 2933, 1708 (C=O), 1626 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, CMe_3), 7.00–7.06 (1H, m, *Ar*), 7.15–7.20 (1H, m, *Ar*), 7.22–7.34 (2H, m, *Ar*), 7.51 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 80.7 (CMe_3), 115.5 (d, *J* 241.3, *Ar*), 115.5 (d, *J* 284.4, *Ar*), 121.3 (*C*(2)), 123.9, 130.3 (*Ar*), 136.9 (*C*(1′)), 142.0 (*C*(3)), 163.0 (d, *J* 246.1, *C*(3′)), 165.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −112.7 (C(3′)*F*); *m/z* (ESI$^+$) 246 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}DFNaO_2^+$ ([M+Na]$^+$) requires 246.1011; found 246.1011.

4.3.31. *tert*-Butyl (*E*)-2-deuterio-3-(2′-bromophenyl)propenoate 51



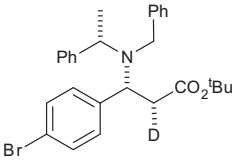
Following *general procedure 2*, **46** (600 mg, 2.36 mmol, D incorporation 99% [^{1}H NMR]), K_2CO_3 (978 g, 7.08 mmol), D_2O (3 mL) and 2-bromobenzaldehyde (0.14 mL, 1.18 mmol) were reacted at 50 °C. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **51** as a colourless oil (456 mg, quant, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]); ν_{max} (film) 3064, 3003, 2978, 2932, 1709 (C=O), 1620 (C=C); δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, CMe_3), 7.17 (1H, app dt, *J* 7.6, 1.5, C(4′)*H*), 7.24–7.30 (1H, m, C(5′)*H*), 7.54–7.58 (2H, m, C(3′)*H*, C(6′)*H*), 7.94 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 80.7 (CMe_3), 122.6 (*C*(2)), 125.2 (*C*(2′)), 127.7 (*C*(5′), *C*(6′)), 130.9 (*C*(4′)), 133.4 (*C*(3′)), 134.6 (*C*(1′)), 141.8 (*C*(3)), 165.7 (*C*(1)); *m/z* (ESI$^+$) 308 ([M(^{81}Br)+Na]$^+$, 95%), 306 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}D^{79}BrNaO_2^+$ ([M(^{79}Br)+Na]$^+$) requires 306.0210; found 306.0214.

4.3.32. *tert*-Butyl (*E*)-2-deuterio-3-(2′-iodophenyl)propenoate 52



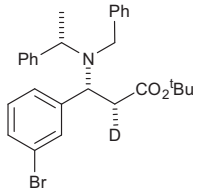
Following *general procedure 2*, **46** (600 mg, 2.36 mmol, D incorporation 99% [^{1}H NMR]), K_2CO_3 (978 mg, 7.08 mmol), D_2O (3 mL) and 2-iodobenzaldehyde (274 mg, 1.18 mmol) were reacted at 50 °C. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **52** as a colourless oil (370 mg, 95%, >99:1 dr, D incorporation 99% [^{1}H NMR], 96% [MS]); ν_{max} (film) 3060, 3003, 2977, 2931, 2871, 1708 (C=O), 1618 (C=C); $\delta\delta_H$ (400 MHz, $CDCl_3$) 1.54 (9H, s, CMe_3), 7.00 (1H, app dt, *J* 7.7, 1.6, C(4′)*H*), 7.31 (1H, app t, *J* 7.7, C(5′)*H*), 7.52 (1H, dd, *J* 7.7, 1.6, C(6′)*H*), 7.80 (1H, s, C(3)*H*), 7.85 (1H, dd, *J* 8.1, 1.0, C(3′)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CMe_3), 80.8 (CMe_3), 101.3 (*C*(2′)), 122.7 (*C*(2)), 127.3 (*C*(6′)), 128.5 (*C*(5′)), 131.0 (*C*(4′)), 137.8 (*C*(1′)), 140.0 (*C*(3′)), 146.6 (*C*(3)), 165.5 (*C*(1)); *m/z* (ESI$^+$) 354 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}DINaO_2^+$ ([M+Na]$^+$) requires 354.0072; found 354.0068.

4.3.33. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4′-bromophenyl)propanoate 34



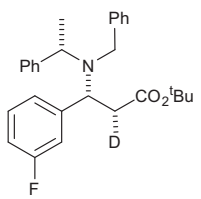
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (318 mg, 1.50 mmol) in THF (10 mL), BuLi (0.58 mL, 1.46 mmol) and **48** (267 mg, 0.94 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR], 99% [MS]) in THF (10 mL), followed by 2-pyridone (268 mg, 2.82 mmol), gave **34** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **34** as a colourless oil (248 mg, 53%, >99:1 dr, D incorporation, 92% [^{1}H NMR], 96% [MS]); $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3027, 2975, 2932, 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, CMe_3), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 2.48 (1H, d, *J* 10.5, C(2)*H*), 3.68 (1H, d, *J* 14.9, NCH_AH_BPh), 3.72 (1H, d, *J* 14.9, NCH_AH_BPh), 4.00 (1H, q, *J* 6.9, C(α)*H*), 4.42 (1H, d, *J* 10.5, C(3)*H*), 7.27–7.47 (10H, m, *Ph*) overlapping 7.34 (2H, d, *J* 8.3, C(2′)*H*, C(6′)*H*), 7.51 (2H, d, *J* 8.3, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.9 (CMe_3), 37.7 (*C*(2)), 50.9 (CH_2Ph), 57.4 (*C*(α)), 58.9 (*C*(3)), 80.5 (CMe_3), 121.0 (*C*(4′)), 126.7, 127.6 (*p-Ph*), 127.8, 128.0, 128.3 (*o,m-Ph*), 130.0 (*C*(2′), C(6′)), 131.2 (*C*(3′), C(5′)), 141.2, 141.4, 143.8 (*C*(1′), *i-Ph*), 171.0 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 97%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1735.

4.3.34. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-bromophenyl)propanoate 35



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (468 mg, 2.21 mmol) in THF (10 mL), BuLi (0.86 mL, 2.14 mmol) and **49** (393 mg, 1.38 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]) in THF (10 mL), followed by 2-pyridone (395 mg, 4.15 mmol), gave **35** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **35** as a colourless oil (402 mg, 59%, >99:1 dr, D incorporation, 92% [^{1}H NMR], 96% [MS]); $[\alpha]_D^{25}$ −5.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2975, 2931 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, CMe_3), 1.36 (3H, d, *J* 6.7, C(α)*Me*), 2.50 (1H, d, *J* 10.5, C(2)*H*), 3.70 (1H, d, *J* 15.2, NCH_AH_BPh), 3.74 (1H, d, *J* 15.2, NCH_AH_BPh), 4.03 (1H, q, *J* 6.7, C(α)*H*), 4.45 (1H, d, *J* 10.5, C(3)*H*), 7.23–7.49 (13H, m, C(4′)*H*, C(5′)*H*, C(6′)*H*, *Ph*), 7.62 (1H, br s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.9 (CMe_3), 37.7 (*C*(2)), 51.0 (NCH_2Ph), 57.5 (*C*(α)), 59.1 (*C*(3)), 80.6 (CMe_3), 122.3 (*C*(3′)), 126.8, 127.0, 127.1 (*C*(6′), *p-Ph*), 127.9, 128.0, 128.3 (*o,m-Ph*), 129.8, 130.2 (*C*(4′), *C*(5′)), 131.3 (*C*(2′)), 141.3, 143.7, 144.7 (*C*(1′), *i-Ph*), 170.9 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 97%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1740.

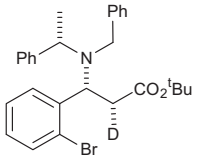
4.3.35. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-fluorophenyl)propanoate 36



Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (486 mg, 2.30 mmol) in THF (10 mL), BuLi

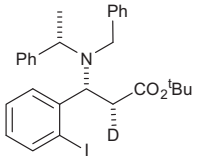
(0.89 mL, 2.23 mmol) and **50** (321 mg, 1.44 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]) in THF (10 mL), followed by 2-pyridone (410 mg, 4.31 mmol), gave **36** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **36** as a colourless oil (456 mg, 73%, >99:1 dr, D incorporation 90% [^{1}H NMR], 91% [MS]); $[\alpha]_D^{25}$ −1.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3085, 3063, 3028, 2976, 2933, 2877, 2841 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.38 (1H, d, *J* 6.8, C(α)*Me*), 2.56 (1H, d, *J* 10.4, C(2)*H*), 3.75 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.79 (1H, d *J* 14.8, NCH$_A$*H*$_B$Ph), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.52 (1H, d, *J* 10.4, C(3)*H*), 6.99–7.06 (1H, m, C(2′)*H*), 7.25–7.46 (11H, m, C(4′)*H*, C(6′)*H*, *Ph*), 7.49–7.53 (2H, m, C(5′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.7 (*C*(2)), 51.1 (NC*H*$_2$Ph), 57.5 (*C*(α)), 59.1 (*C*(3)), 80.5 (*C*Me$_3$), 114.7 (d, *J* 99.1, *C*(4′)) 114.7 (d, *J* 140.6, *C*(2′)), 123.9 (*C*(6′)), 126.8, 127.1 (*p-Ph*), 127.9, 128.1, 128.3 (*o,m-Ph*), 129.7 (*C*(5′)), 141.4, 143.9 (*i-Ph*), 145.1 (*C*(1′)), 162.9 (d, *J* 244.5, *C*(3′)), 171.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.6 (C(3′)*F*); *m/z* (ESI$^+$) 435 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}DFNO_2^+$ ([M+H]$^+$) requires 435.2553; found 435.2543.

4.3.36. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2′-bromophenyl)propanoate 37



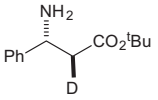
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (521 mg, 2.47 mmol) in THF (10 mL), BuLi (0.96 mL, 2.39 mmol) and **51** (438 mg, 1.54 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR], 98% [MS]) in THF (10 mL), followed by 2-pyridone (440 mg, 4.62 mmol), gave **37** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **37** as a white solid (500 mg, 65%, >99:1 dr, D incorporation 92% [^{1}H NMR], 96% [MS]); $[\alpha]_D^{25}$ −30.1 (*c* 1.0 in $CHCl_3$); mp 55–65 °C; ν_{max} (film) 3085, 2062, 3028, 2976, 2932, 2880 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 2.34 (1H, d, *J* 10.4, C(2)*H*), 3.78 (1H, d, *J* 15.4, NC*H*$_A$H$_B$Ph), 3.88 (1H, d, *J* 15.4, NCH$_A$*H*$_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.98 (1H, d, *J* 10.4, C(3)*H*), 7.12–7.17 (1H, m, C(4′)*H*), 7.18–7.46 (11H, m, C(6′)*H*, *Ph*), 7.58 (1H, dd, *J* 8.0, 1.1, C(5′)*H*), 7.72 (1H, dd, *J* 7.8, 1.5, C(3′)*H*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 27.7 (C*Me*$_3$), 42.0 (*C*(2)), 50.7 (NC*H*$_2$Ph), 56.9 (*C*(α)), 61.1 (*C*(3)), 80.4 (*C*Me$_3$), 125.4 (*C*(2′)), 126.4, 126.8 (*p-Ph*), 127.6, 128.0, 128.1 (*C*(6′), *o,m-Ph*), 128.8 (*C*(4′)), 130.2 (*C*(5′)), 133.0 (*C*(3′)), 141.9, 142.5, 143.8 (*C*(1′), *i-Ph*), 170.3 (*C*(1)); *m/z* (ESI$^+$) 497 ([M(^{81}Br)+H]$^+$, 97%), 495 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}D^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 495.1752; found 495.1738.

4.3.37. *tert*-Butyl (2*R*,3*R*,α*S*)-2-deuterio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2′-iodophenyl)propanoate 38



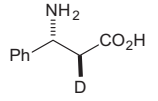
Following *general procedure 1*, reaction of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (376 mg, 1.78 mmol) in THF (10 mL), BuLi (0.69 mL, 1.72 mmol) and **52** (368 mg, 1.11 mmol, >99:1 dr, D incorporation 99% [^{1}H NMR], 96% [MS]) in THF (10 mL), followed by 2-pyridone (317 mg, 3.33 mmol), gave **38** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **38** as a white solid (318 mg, 53%, >99:1 dr, D incorporation 89% [^{1}H NMR], 95% [MS]); $[\alpha]_D^{25}$ −17.7 (*c* 1.0 in $CHCl_3$); mp 65–75 °C; ν_{max} (film) 3085, 3061, 3028, 2976, 2932 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.7, C(α)*Me*), 2.23 (1H, d, *J* 9.7, C(2)*H*), 3.78 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ph), 3.89 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 6.7, C(α)*H*), 4.81 (1H, d, *J* 9.7, C(3)*H*), 6.95–7.02 (1H, m, C(4′)*H*), 7.15–7.49 (11H, m, C(6′)*H*, *Ph*), 7.72 (1H, dd, *J* 7.8, 1.8, C(5′)*H*), 7.86 (1H, dd, *J* 8.0, 1.1, C(3′)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (C(α)*Me*), 27.9 (C*Me*$_3$), 42.7 (*C*(2)), 50.6 (NC*H*$_2$Ph), 56.8 (*C*(α)), 66.4 (*C*(3)), 80.4 (*C*Me$_3$), 101.8 (*C*(2′)), 126.4, 126.8 (*p-Ph*), 127.6, 128.0, 128.1, 128.4 (*C*(5′), *o,m-Ph*), 129.2 (*C*(4′)), 129.9 (*C*(6′)), 139.7 (*C*(3′)), 142.7, 143.8, 145.3 (*C*(1′), *i-Ph*), 170.2 (*C*(1)); *m/z* (ESI$^+$) 543 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}DINO_2^+$ ([M+H]$^+$) requires 543.1613; found 543.1600.

4.3.38. *tert*-Butyl (2*S*,3*R*)-2-deuterio-3-amino-3-phenylpropanoate 53



$Pd(OH)_2$/C (50% w/w of substrate, 105 mg) was added to a solution of **7** (210 mg, 0.48 mmol, 93:7 dr, D incorporation 92% [^{1}H NMR], 91% [MS]) in MeOH/H_2O/AcOH (v/v/v 40:4:1, 12 mL) and the resultant suspension was stirred at rt for 24 h under H_2 (1 atm). The reaction mixture was then filtered through a pad of Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq $NaHCO_3$, then dried and concentrated in vacuo. Purification via flash column chromatography (eluent Et_2O) gave *tert*-butyl (*S*)-2-deuterio-3-phenylpropanoate as a pale yellow oil (4 mg, 3%, D incorporation 99% [^{1}H NMR], 94% [MS]); $[\alpha]_D^{21}$ −12.0 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1730 (C=O), 1154 (C–O); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 2.59–2.53 (1H, m, C(2)*H*), 2.93 (2H, d, *J* 7.6, C(3)*H*$_2$), 7.40–7.21 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 31.1 (*C*(3)), 36.9 (*C*(2)), 80.4 (*C*Me$_3$), 128.9, 128.4, 128.4 (*o,m,p-Ph*), 140.8 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI$^+$) 208 ([M+H]$^+$, 100%); HRMS (FI$^+$) $C_{13}H_{17}DO_2^+$ ([M]$^+$) requires 207.1364; found 207.1371. Further elution gave **53** as a yellow oil (53 mg, 47%, 91:9 dr, D incorporation 92% [^{1}H NMR], 90% [MS]); $[\alpha]_D^{21}$ +24.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3382 (N–H), 3063, 3029, 3004, 2978, 2930 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.83 (2H, br s, N*H*$_2$), 2.53–2.56 (1H, m, C(2)*H*), 4.35 (1H, d, *J* 4.0, C(3)*H*), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 45.0 (*C*(2)), 52.7 (*C*(3)), 80.7 (*C*Me$_3$), 126.3 (*p-Ph*), 127.3, 128.5 (*o,m-Ph*), 144.8 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI$^+$) 223 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}DNO_2^+$ ([M+H]$^+$) requires 223.1551; found 223.1551.

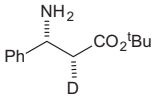
4.3.39. (2*S*,2*R*)-2-Deuterio-3-amino-3-phenylpropionic acid 54



A solution of **53** (100 mg, 0.45 mmol, 91:9 dr, D incorporation 92% [^{1}H NMR], 90% [MS]) in TFA/CH_2Cl_2 (v/v 1:1, 3 mL) was stirred at rt for 24 h. The reaction mixture was then concentrated in vacuo, HCl (2.0 M in Et_2O, 4 mL) was added to the residue, and the resultant mixture was stirred at rt for 5 min then concentrated in vacuo. This co-evaporation process was repeated once more then the residue was dissolved in H_2O and purified via ion exchange

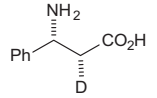
chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) to give **54** as a white foam (67 mg, 90%, 91:9 dr, D incorporation 90% [^{1}H NMR], 93% [MS]); $[\alpha]_D^{22}$ +0.7 (*c* 0.2 in H_2O); ν_{max} (film) 3372 br (N–H), 1711 (C=O); δ_H (400 MHz, D_2O) 2.79 (1H, br d, *J* 7.8 C(2)*H*), 4.55 (1H, d, *J* 7.8, C(3)*H*), 7.41–7.34 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 40.1 (*C*(2)) 52.6 (*C*(3)), 126.8 (*p*-*Ph*), 129.3, 129.2 (*o*,*m*-*Ph*), 135.9 (*i*-*Ph*), 177.2 (*C*(1)); *m*/*z* (ESI$^-$) 165 ([M−H]$^-$, 100%); HRMS (ESI$^-$) $C_9H_9DNO_2^-$ ([M−H]$^-$) requires 165.0780; found 165.0781.

4.3.40. *tert*-Butyl (*R*,*R*)-2-deuterio-3-amino-3-phenylpropanoate 55



$Pd(OH)_2/C$ (50% w/w of substrate, 272 mg) was added to a solution of **8** (545 mg, 1.31 mmol, >99:1 dr, D incorporation 96% [^{1}H NMR], 97% [MS]) in MeOH/H_2O/AcOH (v/v/v 40:4:1, 12 mL) and the resultant suspension was stirred at rt for 24 h under H_2 (1 atm). The reaction mixture was then filtered through a pad of Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq $NaHCO_3$, then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave *tert*-butyl (*R*)-2-deuterio-3-phenylpropanoate as a pale yellow oil (58 mg, 21%, D incorporation 96% [^{1}H NMR], 80% [MS]); $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$). Further elution gave **55** as a yellow oil (227 mg, 82%, >99:1 dr, D incorporation 96% [^{1}H NMR], 80% [MS]); $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3382 (N–H), 3063, 3029, 3004, 2978, 2930, 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.83 (2H, br s, N*H*$_2$), 2.53–2.56 (1H, m, C(2)*H*), 4.35 (1H, d, *J* 4.0, C(3)*H*), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 45.0 (*C*(2)), 52.7 (*C*(3)), 80.7 (*C*Me$_3$), 126.3 (*p*-*Ph*), 127.3, 128.5 (*o*,*m*-*Ph*), 144.8 (*i*-*Ph*), 171.3 (*C*(1)); *m*/*z* (ESI$^+$) 223 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}DNO_2^+$ ([M+H]$^+$) requires 223.1551; found 223.1551.

4.3.41. (*R*,*R*)-2-Deuterio-3-amino-3-phenylpropanoic acid 56



A solution of **55** (100 mg, 0.45 mmol, >99:1 dr, D incorporation 96% [^{1}H NMR], 80% [MS]) in TFA/CH_2Cl_2 (v/v 1:1, 4 mL) was stirred at rt for 24 h. The reaction mixture was then concentrated in vacuo, HCl (2.0 M in Et_2O, 4 mL) was added to the residue, and the resultant mixture was stirred at rt for 5 min then concentrated in vacuo. This co-evaporation process was repeated once more then the residue was dissolved in H_2O and purified via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) to give **56** as a white solid (46 mg, 62%, >99:1 dr, D incorporation 81% [^{1}H NMR], 78% [MS]); mp 208–215 °C; $[\alpha]_D^{25}$ +6.0 (*c* 1.0 in H_2O); ν_{max} (KBr) 2961, 2920, 2839, 2659 (O–H), 1627 (C=O); δ_H (400 MHz, D_2O) 2.72 (1H, d, *J* 6.4, C(2)*H*), 4.55 (1H, d, *J* 6.4, C(3)*H*), 7.33–7.43 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 40.2 (*C*(2)), 52.7 (*C*(3)), 126.9 (*p*-*Ph*), 129.2, 129.3 (*o*,*m*-*Ph*), 136.0 (*i*-*Ph*), 177.3 (*C*(1)); *m*/*z* (ESI$^+$) 189 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{10}DNNaO_2^+$ ([M+Na]$^+$) requires 189.0745; found 189.0745.

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