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Asymmetric Induction in Acyclic Radical Reactions: Enantioselective Syntheses of (*S*)-2-Deuterioglycine and (*R*)-2-Deuterioglycine.

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Abstract: The (-)-8-phenylmenthol esters of N-Boc-glycine and N-Boc-2,2-dideuterioglycine were brominated with N-bromosuccinimide and the bromo compounds were reduced with tri-n-butyldeuteriostannane and tri-n-butylstannane respectively, to give the chiral glycine derivatives in 90% optical yield. Hydrolysis yielded the amino acid without racemisation.

Recently we described[1] the asymmetric synthesis of amino acids *via* the addition of Grignard reagents to an imine derivative **1**. This derivative was formed *in situ* from a bromo compound **2** which was formed by a free radical bromination of an optically active glycine derivative **3**. By NMR spectroscopy the bromo compound appeared to be only one of two possible diastereoisomers. This suggested the exciting possibility that asymmetric induction could occur at a radical centre in an acyclic system and, since no such observation had been reported at that time,[2] it was important to confirm that observation.

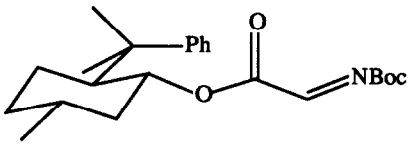
Because of the lability of the bromo derivative, it was recognised that the high diastereoselectivity of the bromination reaction may not be due, in fact, to the initial radical reaction. It may arise by a first order asymmetric transformation in which the first formed mixture of diastereoisomers equilibrates to a thermodynamically more stable product. However, regeneration of the radical from the bromo derivative should allow a study of the stereoselectivity of its subsequent reactions. It has been found that the reaction of this radical with tri *n*-butylstannanes is highly stereoselective. We present here the experimental details for a preliminary communication[3] which outlined the preparation, in high optical purity, of both (*S*)-2-deuterioglycine **4** and (*R*)-2-deuterioglycine **5**.

A short introduction to the importance of chiral glycines to biological studies, and the references to the previous methods of preparation of them, is available[4].

(S)-2-Deuterioglycine.

The bromination of 8-phenylmenthyl N-Boc-glycinate **3** with freshly recrystallised N-bromosuccinimide under UV irradiation in dry CCl_4, at reflux, proceeds rapidly to afford the bromide **2** as a colourless oil, in virtually quantitative yield. Tri-n-butyldeuteriostannane was synthesized by the method developed[5] to produce tri-n-butylstannane, except that lithium aluminium deuteride (99 atom%) was used to give tri-n-butyldeuteriostannane in 69% yield after distillation. The reduction of α-brominated dipeptides with tri-n-butyldeuteriostannane at room temperature, without the use of a radical initiator has been reported[6]. Presumably, the stability of capto-dative radicals of the type involved here is such that carbon-bromine bond homolysis occurs spontaneously even at ambient temperature. This observation, along with the general need for low temperatures in order to attain high diastereoselectivity in asymmetric reactions,

were considered important factors in the search for the optimum conditions for the reduction of the α-bromoglycinate **2**. The minimum temperature at which the thermally initiated tin hydride reduction of



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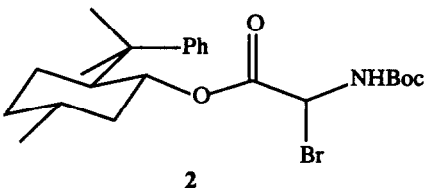

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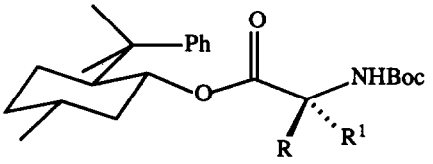
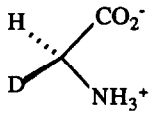


3 R = R^1 = H
6 R = D, R^1 = H
7 R = H, R^1 = D
12 R = R^1 = D



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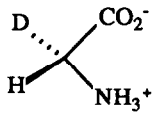

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α-bromoglycinates occurs is not certain. To ensure that the reduction occurred at the lowest possible temperature, the reaction was started at -78° and allowed to equilibrate to room temperature slowly overnight. Extension of the reaction time beyond sixteen hours did not improve the yield of the deuteriated product.

The analysis by NMR spectroscopy of the degree of stereoselectivity was expected to be straightforward. The signals due to the diastereotopic α-protons of the parent compound appear as the AB portion of an ABX system, with the X nucleus being the vicinal amide proton. Replacement of either of the diastereotopic protons by deuterium should be readily determined. However, although the two doublets of doublets due to the two diastereotopic α-protons of the starting material were separated to baseline resolution in deuteriochloroform, at 300 MHz, integration of the relative area of the upfield doublet of doublets (centred at δ 3.05) to the area of the downfield doublet of doublets (centred at δ 3.29) was not accurately1:1. An impurity which resonated under the upfield doublet of doublets was present, despite the analytical purity of the ester. Further purification of the ester by preparative HPLC failed to improve the integration. When the spectrum of this compound was run in d_6-benzene at 300 MHz, however, the impurity now resonated as a distinct, broadened singlet at δ 3.14. In this solvent, the two doublets of doublets were situated at δ 3.34 and δ 3.22. Geminal coupling was 18.2 Hz. The downfield doublet of doublets exhibited a 5.5 Hz coupling to the amide proton, whilst the upfield doublet of doublets exhibited a 6.0 Hz coupling to this nucleus. Unfortunately, the chemical shift difference between the two α–proton signals was now only 0.12 p.p.m. and baseline resolution was not obtained. For accurate analysis it was necessary to run the spectrum at higher field. At 500 MHz the resolution of the two multiplets was complete (see the figure) but the analysis had to be done elsewhere (see Acknowledgements).

The deuteriostannane reduction of the bromo compound **2** resulted in a mixture of two monodeuteriated diastereoisomeric products **6** and **7**, the α-protons of which, each gave a separate broadened doublet signal in the NMR spectrum. Each doublet arises due to coupling to the amide proton and broadening of each signal is due to the unresolved coupling to deuterium. In deuteriochloroform the major deuteriated diastereoisomer gave an α-proton doublet at δ 3.05 (J=5.4 Hz), whilst the α-proton of the minor deuteriated diastereoisomer resonated at δ 3.29 (J=4.7 Hz). Integration of each doublet allowed an estimate of the d.e. for the reaction. Reaction conditions such as solvent, temperature, concentration and the ratio of tri-n-butyldeuteriostannane to the α-bromoglycinate **2** were systematically varied in an effort to improve the diastereoselectivity of the reduction. These conditions, along with the experimental results, are summarized in the table. As can be seen, the diastereoselectivity of the reduction is markedly concentration

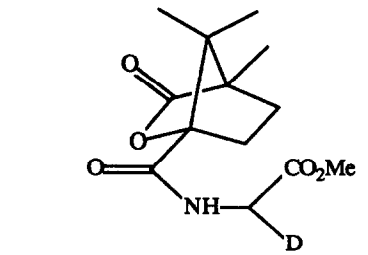
TABLE

	RATIO of Bu_3SnD: 2	CONC. 2 (mM)	SOLVENT	TEMP. (°C)	YIELD (%)	2-(*S*) : 2-(*R*)	d.e. (%)
1	1.1	70	ether	−78° → R.T.	85	84.5 : 15.5	69
2	1.1	128	ether	−78° → R.T.	71	90.5 : 9.5	81
3	2.0	245	ether	−78° → R.T.	70	95.0 : 5.0	90
4	2.0	490	ether	−78° → R.T.	60	94.0 : 6.0	88
5	2.0	245	toluene	−78° → R.T.	35	94.0 : 6.0	88
6	1.1	92	ether	R.T.	59	82.5 : 17.5	65
7	2.0	245	ether	R.T.	72	90.0 : 10.0	80
8	2.0	245	benzene	80°	41	69.0 : 31.0	38

and temperature dependent. The optimum conditions appear to be those of entry 3 and the region in the 500 MHz ^1H NMR spectrum for the α-proton for this product is shown in the figure (b).

The ^{13}C NMR spectrum of the deuteriated product was identical to that of the parent compound[1], with the exception of the signal due to the α-carbon. This shifted upfield by *ca.* 0.2 p.p.m. (42.26 to 42.05 p.p.m.) upon deuteriation, and now appeared as a 1 : 1 : 1 triplet (J=20 Hz) in the broad band decoupled spectrum.

Hydrolysis of the 95:5 mixture of α-deuterio diastereoisomers was accomplished under the conditions developed[1] for the hydrolysis of 8-phenylmenthyl *N*-*t*-Boc-alaninate without racemisation of the resultant amino acid. The α-deuterioglycinate was dissolved in neat trifluoroacetic acid, to remove the Boc group and the ester was cleaved by 6N HCl to give the crude deuterioglycine hydrochloride from which the amino acid was obtained by ion exchange chromatography. The overall yield for this process was 95%. Analysis of the 2-deuterioglycine by MS indicated that little or no deuterium had been lost in the hydrolysis step and therefore the product was still chiral glycine with the configuration unaffected.



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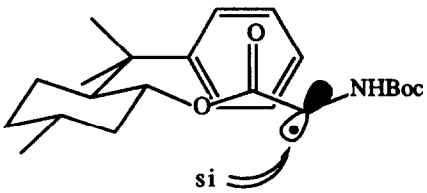

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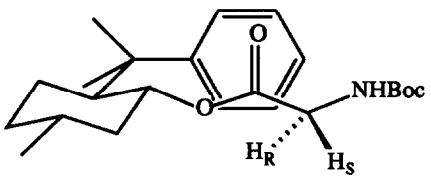

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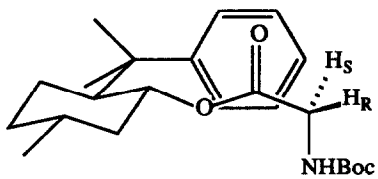

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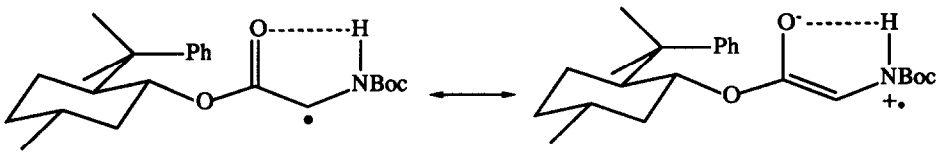

13 **14**

The free 2-deuterioglycine was converted, by a modified procedure, to the camphanamide ester derivative **8** which has been developed[7] for the determination of the configurations of the chiral deuterioglycines. The ^{1}H NMR spectrum (300 MHz) was consistent with the spectral data, obtained at 60MHz, reported for these compounds. Due to the higher field instrument used here, more detail was evident in the spectrum of the derivatives and it was unnecessary to utilize a shift reagent to increase the separation between the doublets, at δ 4.17 and δ 3.98, which arise from the α-protons of each of the diastereoisomers. The predominance of the doublet signal at δ 4.17 indicated that the majority of the chiral glycine had the (*S*) configuration.

Now that the majority of the product from the deuteriostannane reduction had been shown to be 2-deuterioglycinate **6**, a transition state model for the deuteriation of the α-centred radical could be

proposed. This model is shown in structure **9**. Adoption of the configuration shown, followed by delivery of deuterium to the *si* face of the radical (the face opposite the phenyl group) accounts for the 2-(*S*) stereochemistry of the reduction product.

Assignment of the 2-(*S*) configuration **6** to the major 2-deuterioglycinate, in turn, allows for the assignment of the doublet of doublets centred at δ 3.29 in the ^{1}H NMR spectrum of the undeuteriated compound **3**, as being due to the pro-(*S*) proton. When drawn as the *Z*-rotamer **10**, the pro-(*S*) proton points away from the phenyl ring of the 8-phenylmenthyl moiety. This is consistent with the observation that the pro-(*S*) proton resonates downfield of the pro-(*R*) proton, since the pro-(*R*) proton would be expected to experience greater magnetic shielding from the phenyl ring than would the pro-(*S*) proton. These observations indicate that the *Z*-rotamer **10** is preferred over the *E*-rotamer **11**. It was, therefore, of interest to investigate the selectivity of α-hydrogen abstraction, by the bromine atom, from the compound **3**. Since the *Z*-rotamer appeared to be predominant, we speculated that the pro-(*S*) hydrogen, which points away from the phenyl group in this conformation, may be stereoselectively removed in the bromination reaction.

The 90% optically pure 8-phenylmenthyl *N*-*t*-Boc-2-deuterioglycinate **6** was brominated with *N*-bromosuccinimide under standard conditions[1]. In order to produce a stable derivative for analysis, the resultant bromide was immediately reduced with tri-*n*-butylstannane in ether from −78°C to room temperature (i.e., under the optimum stereoselective reduction conditions). If deuterium had been selectively removed in the bromination step, the product of reduction with the stannane would be mainly the undeuteriated ester **3**. A non-selective hydrogen abstraction would lead to a *ca.* 1:1 mixture of **3** and the 2-(*R*)-deuterioglycinate **7**. MS analysis of the reduction product indicated that the $d_0 : d_1$ ratio was 73 : 27, indicating that the bromination step removed three times as much deuterium as hydrogen. The α-proton region of the ^{1}H NMR spectrum of the reduction product is very similar to that of the authentic undeuteriated compound **3**. Electronic subtraction of the spectrum of compound **3** from the spectrum of the reduction product left a residual doublet centred at δ 3.29. This doublet is due to the α-proton of 2-(*R*)-deuterioglycinate **7**. A kinetic isotope effect ($k_H/k_D = 3.15$) in the bromination of similar (achiral) glycinates with *N*-bromosuccinimide has been reported[8]. The kinetic isotope effect may be the reason that the selectivity for the removal of the deuterium atom from the ester **6** is not even higher.

As both the chiral glycine ester **6** and the bromide **2** are produced by delivery of deuterium and bromine respectively to the same α-centred radical **9**, it is probable that the configuration at the α-carbon of the bromide is also (*S*).

(R)-2-Deuterioglycine.

The methodology used to produce (*S*)-2-deuterioglycine **4** could be used to synthesize (*R*)-2-deuterioglycine **5**, not by use of the enantiomeric chiral auxiliary, but by simply interchanging the roles of hydrogen and deuterium.

Commercially available 2,2-dideuterioglycine was converted to its *N*-*t*-Boc derivative, which was subsequently esterified with 8-phenylmenthol under standard conditions. Bromination of the ester **12** was accomplished by the same method as that used for the α,α-diprotio analogue **3**. The reduction step involved exactly the same conditions as those employed previously in obtaining the (*S*)-chiral glycinate **6** (Table, entry 3), except that tri-*n*-butylstannane was used. Analysis of the product, by 500 MHz ^{1}H NMR

spectroscopy, revealed that the low field doublet now predominated over the high field doublet as can be seen in the figure (c). However, the spectrum indicated that a significant amount of undeuteriated material

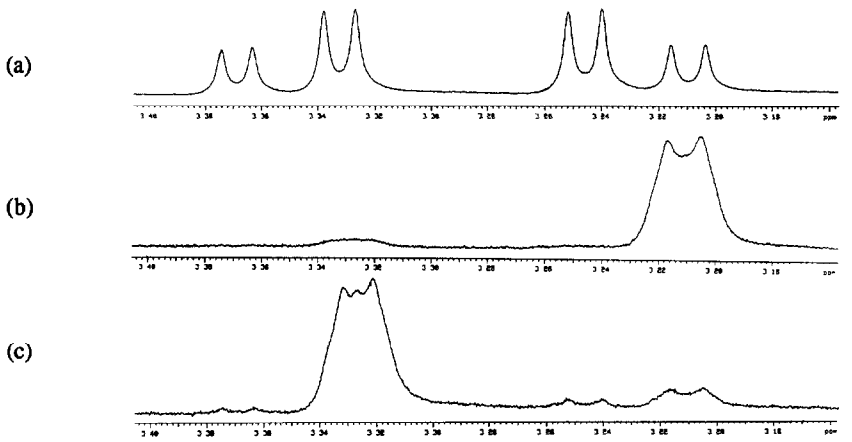

Figure. 500 MHz NMR spectra of the region for the α-protons in (a) compound **3** (b) compound **6** (c) compound **7**.

was also present. MS analysis revealed that the d_1 : d_0 ratio was *ca.* 95:5. The presence of undeuteriated material made accurate determination of the d.e. for this reaction difficult. However, integration of the total region covering the α-protons of both the deuteriated and undeuteriated compounds, yielded a 2-(*R*) : 2-(*S*) ratio of 89 : 11. This represents an apparent d.e. of 78%, but the actual d.e. must be significantly higher. There is no apparent reason why the inherent diastereoselectivity of the reduction of the deuteriated radical with tri-n-butylstannane should be lower than that for reduction of the undeuteriated radical with tri-n-butyldeuteriostannane. To estimate the true d.e. of the 2-(*R*) compound **7**, the deuterium content of the product (95%) must be taken into account. Subtracting the contribution made by the 5% of undeuteriated material to the integrals of the pro-(*S*) and pro-(*R*) signals in the ^{1}H NMR spectrum alters the 89 : 11 ratio to 84 : 6, which is equivalent to a *ca.* 93 : 7, 2-(*R*) : 2-(*S*) ratio. Hence the actual d.e. of the (*R*)-2-deuterioglycinate **7** is, within the accuracy of the method, the same as that of the (*S*)-2-deuterioglycinate.

The presence of undeuteriated material in the reduced product **7** was unexpected, as the 2,2-dideuterioglycine from which it was ultimately derived was 98 atom % deuteriated. The loss of

deuterium was traced to a small amount of exchange having taken place in the esterification step to give the ester **12**, as the MS of this derivative revealed a 92 : 8 d_2 : d_1 ratio.

The high selectivity in these radical reactions raises the question of why the inferred conformation (ester carbonyl and C-N bond *syn*) is preferrentially adopted by the α-centred radical **9**. Is it due to hydrogen bonding in the intermediate radical as shown in structure **13**, but for which the geometry is less than ideal, or perhaps more likely a combination of hydrogen bonding and electrostatic attraction[9] due to the resonance contributor **14** to the capto-dative radical intermediate? Alternatively, is it the geometry of the starting bromo compound **2** which dictates the configuration which the radical adopts? It is hoped that experiments which are underway will provide answers to these questions in the near future.

ACKNOWLEDGEMENTS

We would like to thank Professor F.J. Schmitz and Ms Aeri Park, Department of Chemistry, The University of Oklahoma, NORMAN, OK., U.S.A. for the determination of the 500 MHz NMR spectra. This work was supported financially, in part, by an Australian Research Committee grant to D.P.G.H. and R.A.M-W. The receipt of an Australian Post-graduate Reseach Award by P.R. is gratefully acknowledged.

EXPERIMENTAL

General

Melting points were determined using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada. Infrared Spectra were recorded, as films, on a Jasco A-102 Spectrophotometer using the 1603 cm^{-1} band of polystyrene as a reference. ^1H NMR and ^{13}C NMR spectra were recorded on either a Bruker CXP-300 or a Bruker ACP-300 spectrometer in $CDCl_3$ with TMS as internal standard. TLC was performed on Merck DC-Alufolien Kiselgel 60 F_{254} Art. 5554. and developed using a solution of 10% w/v ammonium molybdate in 1M HCl followed by heating. Flash Chromatography was performed on Merck Kieselgel 60 (230-400 mesh ASTM). Dry column chromatography was performed on Merck Kieselgel 60 HF_{254} Art. 7739. HPLC chromatography was carried out on a Waters 6000A solvent pump and a Waters Model 441 Absorbance Detector operating at 254 nm, in conjunction with an I.C.I. D.P-700 data station. A Waters Radial Pak normal phase 10 μm silica column (8 mm) was used. Electron impact mass spectra were recorded with an AEI MS-30 double focussing mass spectrometer operating at 70 eV. FAB mass spectra were recorded with a Vacuum Generators ZAB 2HF mass spectrometer with argon gas and a glycerol matrix. Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl.

(1R, 2S, 5R)-*2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl* (S)-*2-[(tert-butoxycarbonyl)amino]-2-deuterioacetate* **6**.

The reactions given in the table were all conducted in essentially the same manner, except for the differences noted. The procedure for the optimum conditions (entry 3) are given. Tri-*n*-butyldeuteriostannane (133 μl, 0.491 mmol, 2.0 equivalents) was added rapidly to a stirred solution of freshly prepared (1*R*, 2*S*, 5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]bromoacetate **2**[1] (115 mg, 0.246 mmol, 1.0 equivalent) in anhydrous ether (1.00 ml) cooled to −78°C. The cold bath was left to equilibrate to room temperature over 16 h. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (74 mg, 0.189 mmol, 74%). ^{1}H NMR (300 MHz) δ: 0.87, d, *J* 6.6 Hz, 3H (ring CH_3); 1.18, s, 3H (CH_3CPh); 1.29, s, 3H (CH_3CPh); 1.43, s, 9H (*t*Bu CH_3); 0.8-2.1, complex, (methylene envelope); δ 3.05, br. d, *J* 5.4 Hz 0.95 H; δ 3.29, br. d, *J* 4.7 Hz, 0.05 H; 4.38, br. m, 1H (NH); 4.87, dt, *J* 4.2, 10.7 Hz, 1H (HC-O); 7.1-7.4, complex, 5H (ArH).

(S)-*Deuterioglycine* **4**.

(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(*tert*-butoxycarbonyl)amino]-2-deuterioacetate **6** (95 : 5 2-(*S*) : 2-(*R*) by ^{1}H NMR analysis) was dissolved in trifluoroacetic acid (0.5 ml) and the mixture left to stand at room temperature for 10 min. 6N HCl (1 ml) was then added and the mixture refluxed for 15 h. After cooling to room temperature, water was added and the resultant solution washed with $CHCl_3$ (2X). The aqueous layer was evaporated to dryness *in vacuo*. The residue was purified by ion exchange chromatography on Amberlite 1R-120 (H) to yield the *title compound* (6.0 mg, 0.079 mmol, 92%), mp 235-236°C; lit.[7] 234°C. M.S. 77 (21) 76 (M^+) (100) 75 (13). ^{1}H NMR (300 MHz, D_2O, internal reference 3-(trimethylsilyl)-1-propane-sulphonic acid sodium salt) δ : 3.53, t, *J* 2 Hz. Lit.[10] (270 MHz, D_2O, no internal reference quoted) δ : 3.65, t.

Methyl (1S,4R)-ω-camphanoylglycinate **8**.

(*S*)-Deuterioglycine **4** (95:5 *S*:*R*, 3.8 mg, 50.0 μmol) was dissolved in MeOH (5 ml) which had been treated with $SOCl_2$ (20 mg). After standing for 16 h, the solvent was evaporated and the residue dissolved in water (200 μl) and $KHCO_3$ (25.0 mg, 0.250 mmol), and ethyl acetate (130 μl) were added. To the stirred mixture was added a solution of (1*S*,4*R*)-ω-camphanoyl chloride[11] (11.9 mg, 55.0μmol) in ethyl acetate (100 μl). Stirring was continued for a further 2 h and the organic layer was separated and successively washed with dil. HCl and water. The organic layer was dried($MgSO_4$) and the ethyl acetate evaporated to yield the *title compound* as a colourless oil which later solidified. Yield : 7.4 mg, 27.5 μmol, 55%), mp 80-82°C; lit[7] 84°C. ^{1}H NMR data consistent with that reported[7]. ^{1}H NMR (300 MHz) δ: 0.98, s, 3H, (7' *gem.* CH_3); 1.11, s, 3H, (7' *gem.* CH_3); 1.12, s, 3H, (4' CH_3); 1.6-2.6, complex, 4H (5' and 6' CH_2); 3.77, s, 3H (CH_3O); 4.17, d, *J* 2.6 Hz, 0.08H (α-CH *(R)*); 3.98, d, *J* 2.6 Hz, 0.92H (α-CH *(S)*); 6.94, br. s, 1H (NH).

Bromination of (S)-2-deuterioglycinate **6** *followed by reduction with tri-n-butyltin hydride.*

(1*R*, 2*S*, 5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(*tert*-butoxycarbonyl)amino]-2-deuterioacetate **6** (95 : 5 *S* :*R*) (18.1 mg, 46.3 μmol) was treated with *N*-bromosuccinimide (8.3 mg, 46.8 μmol) by the same procedure used[1] for the undeuteriated compound **3**. Tri-*n*-butylstannane (25 μl, 92.6 μmol, 2.0 equivalents) was added rapidly to a stirred solution of the intermediate bromide in anhydrous ether (500 μl) cooled to –78°C. The cold bath was left to equilibrate to room temperature over 16h. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (9.7 mg, 24.9 μmol, 54%). MS indicated that the d_1:d_0 ratio was *ca.* 26 : 74, based on the relative intensities of the ions of m/z 391, 390 and 389. ^{1}H NMR (300 MHz) : identical to that of **3**, except for the presence of a doublet at δ 3.29 (*J* 4.7 Hz) lying under the doublet of doublets centred at δ 3.29, which was detected by subtraction of the spectrum of **3**.

N-*tert-Butoxycarbonyl-2,2-dideuterioglycine.*

Following the method of Itoh *et al.*[12], 2,2-dideuterioglycine (400 mg, 5.19 mmol) was converted to the *title compound.*. Yield = 788 mg, 4.45 mmol, 86% ; m.p. = 75-76°C (cf. 77-78°C for the undeuteriated compound). ^{1}H NMR (300 MHz, d_6 D.M.S.O.) δ: 1.38, s, 9H (*t*-Boc CH_3); 7.06, s, 1H (NH); 10.61, br. s, 1H (CO_2H). Electron impact MS indicated that the d_2:d_1:d_0 ratio was *ca.* 96.9 : 2.5 : 0.6, based on the relative intensities of the molecular ions of m/z 177, 176 and 175 respectively.

(*1*R, 2S, 5R)-*2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(tert-butoxycarbonyl)amino]-2,2-dideuterioacetate* **12**.

N-tert-Butoxycarbonyl-2,2-dideuterioglycine (245 mg, 1.384 mmol) was esterified with (–)-8-phenylmenthol (296 mg, 1.272 mmol) after the method of Hassner and Alexanian[13]. Purification of the crude product by flash chromatography gave the *title compound* as a colourless oil (434 mg, 1.108 mmol, 93%). The ^{1}H NMR (300 MHz) was identical to that of **3** except for the diminishment of the integrals of the two doublets of doublets centred at δ 3.05 and δ 3.29 from 1 H each to *ca.* 0.05 H and 0.03 H respectively. In addition, the amide proton resonated as a singlet at δ 4.33. MS indicated that the d_2:d_1 ratio was *ca.* 92 : 8, based on the relative intensities of the ions of m/z 392, 391 and 390.

(1R, 2S, 5R)-*2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl* (R)-*2-[(tert-butoxycarbonyl)amino]-2-deuterioacetate* **7**.

(1*R*, 2*S*, 5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyl 2-[(*tert*-butoxycarbonyl)amino]-2,2-dideuterioacetate **12** (75 mg, 0.192 mmol) was treated with *N*-bromosuccinimide (34 mg, 0.192 mmol) in the same manner as the undeuteriated compound **3**[1]. Tri-*n*-butylstannane (103 μl, 0.384 mmol, 2.0 equivalents) was added rapidly to a stirred solution of the uncharacterized bromide in anhydrous ether (740 μl) cooled to –78°C. The cold bath was left to equilibrate to room temperature over 16 h. The ether was then evaporated *in vacuo* and the residue purified by flash chromatography to yield the *title compound* (49 mg, 0.127 mmol, 66%). MS indicated that the d_1:d_0 ratio was *ca.* 94.6 : 5.4, based on the relative intensities of the ions of m/z 391, 390 and 389. ^{1}H NMR (300 MHz) : identical to that of **3** except for : δ 3.05, d, *J* 5.4 Hz 0.11 H; δ 3.29, br. d, *J* 4.7 Hz, 0.89 H.

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