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Research Article

The synthesis and characterisation of deuteriated amides

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Summary

Results are reported on the regioselective C-deuteriation of a series of enolates derived from the addition of sec-BuLi to a variety of substituted amides. The outcomes of the reactions are discussed in terms of the structural nature of the amides and the deuteriated sources employed. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: deuterium donor; deprotonation-deuteriation; kinetic deuteriation; D-amides and isotopic labels

Regioselective C-deuteriation adjacent to a carbonyl group to give perdeuteriated aldehydes,[1] ketones[2] and esters[3] is well documented. The majority of these methods rely on sequential deprotonation and deuteriation of an intermediate enolate under thermodynamic control.[4] Generally, the more acidic the carbonyl-based acid, the more efficient the deuteriation process.[5] For weakly acidic carbonyl-based acids, such as those derived from amides, it is unsurprising to find a limited number of reports into proton-deuterium exchange under thermodynamic

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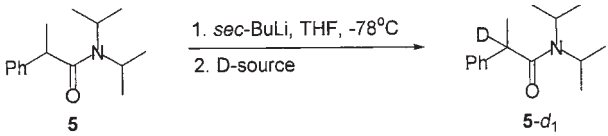
control.[6] In contrast, selective deuteriation has been shown to occur under kinetic control by pre-forming the intermediate enolate. However, the method chosen to generate the intermediate enolate has been shown to be important since the use of lithium amide bases, such as lithium diisopropylamide (LDA)[7] have been documented to lower the overall deuterium incorporation due to internal proton return involving the residual diisopropylamine base. However, in the absence of a competitive base,[9] the levels of *D*-incorporation were found to be significantly higher.[10] The structural nature of the deuterium donor is also important; the use of a weakly D-acidic deuterium donor, such as D_2O is preferred since this promotes efficient regioselective *C*-deuteriation to give the required deuteriated carbonyl derivative[11] rather than competitive *O*-deuteriation which has been shown to lead to loss of the newly incorporated D-label.[12]

We now report our study into the synthesis of deuteriated amides using a deprotonation–deuteriation strategy. We discuss the effects of amide substitution and the nature of the deuterium donor on the level of deuterium incorporation. For our study, we were required to synthesise a series of structurally related amides **1**,[13] **2**,[14] **3**,[15] **4**,[16] **5**,[17] **6**,[18] **7**,[19] **8**, **9**,[16] **10**, **11**,[20] **12**,[21] **13**, **14**, **15** and **16**. These were efficiently synthesised by the addition of two equivalents of an amine (e.g. diisopropylamine) to a stirred solution of the corresponding acid chloride in dichloromethane to give the required amides **1**, **2**, **3**, **4**, **6**, **7**, **8**, **9**, **10**, **12**, **14** and **16**. Further substitution at the C(2) position was easily achieved using classical deprotonation and alkylation methodology by treatment of the amides **4**, **12** and **16** with either LDA or *sec*-BuLi in THF at $-78^{\circ}C$, followed by the addition of methyl iodide, ethyl iodide, isopropyl iodide and benzyl bromide to give the corresponding 2-alkyl substituted amides **5**, **11**, **13** and **15**.

We first probed the structural nature of the deuterium donor on the efficiency of regioselective enolate *C*-deuteriation. We chose to use 2-phenylpropionyl diisopropylamide **5** as our model compound due to its UV activity, non-volatile nature and predictable enolate chemistry (Table 1).[17,22] To ensure efficient *C*-deuteriation, removal of the C(2) proton in the starting amide **5** is paramount. In a related study, Vedejs[17,22] have shown that deprotonation of this amide can efficiently occur when using *sec*-BuLi as the base. Under these conditions,[17,22] addition of an excess of *sec*-BuLi (1.7 equivalents) to a stirred solution of 2-phenylpropionyl diisopropylamide **5** in THF at $-78^{\circ}C$, followed by addition of the deuterium donor (DA) gave the required 2-deuterio-2-

Table 1.



Entry	D-source	[(D):(H)]	Yield (%)
1	Acetic acid-d_4	98:2	66
2	Nitromethane-d_3	98:2	61
3	Acetonitrile-d_3	〈1:〉99	81
4	D_2O	98:2	65
5	Ethyl glycol-d_2	77:23	64

phenylpropionyl amide **5**-d_1. The levels of deuterium incorporation were measured by ^{1}H NMR spectroscopy by integration of the singlet for methyl group (CH_3CD) in **5**-d_1 and the corresponding doublet (CH_3CH) for the unlabelled amide **5**. For mildly *D*-acidic sources, such as acetic acid-d_4, nitromethane-d_3 and D_2O the level of *D*-incorporation was near perfect (>98%) (Table 2), whereas, for simple diols, like ethylene glycol-d_2 the level of *D*-incorporation was significantly lower than that for D_2O.

For the remainder of this study, D_2O was chosen as our deuterium source primarily due to it being readily available, inexpensive and easy to remove during the purification process. The required 'base-free' enolates were formed by direct addition of *sec*-BuLi (1.7 equivalents) to a solution of the corresponding amides **1**, **2**, **3**, **4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15** and **16** in THF at −78°C. After stirring for 1 hour, two equivalents of D_2O were added, and the resulting solutions were stirred for a further 2 h to give the corresponding deuteriated amides **1**-d_1, **2**-d_1, **3**-d_1, **4**-d_1, **6**-d_1, **7**-d_1, **8**-d_1, **9**-d_1, **10**-d_1, **11**-d_1, **12**-d_1, **13**-d_1, **14**-d_1, **15**-d_1 and **16**-d_1 in moderate to good yield. The substitution pattern at both the C(2) and the *N*-position in the amides **1**–**16** appears to have little or no effect on the level of deuterium incorporation; all gave similar levels of *D*-incorporation (>98% *D*-incorporation). However, the substitution pattern at the C(2) position appears to have a significant effect on the overall yield; the presence of an electron-withdrawing substituent (such as a phenyl or aryl ring) adjacent to the carbonyl group improves the chemical yield. This is presumably due to the increased acidity at the C(2)-position favouring enolate formation rather than promoting direct nucleophilic addition to the carbonyl group which is known to lead to ketone formation.[23]

Table 2.

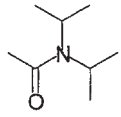
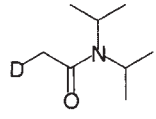
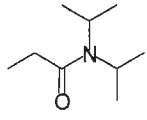
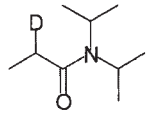
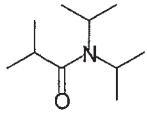
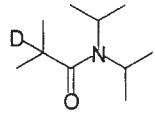
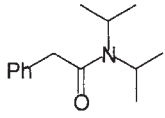
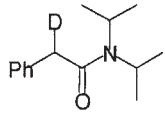
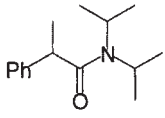
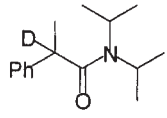
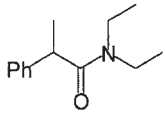
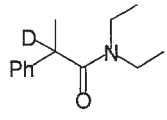
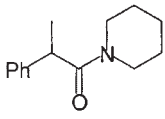
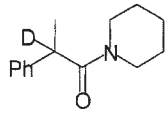
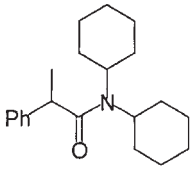
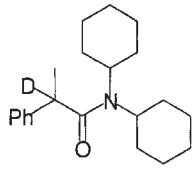
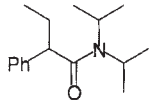
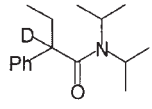
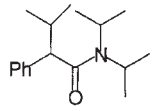
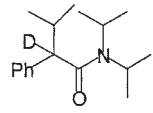
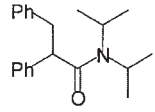
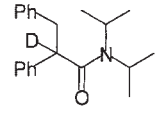
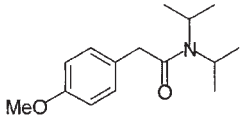
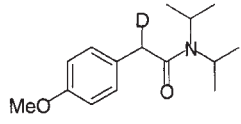
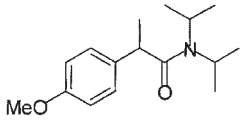
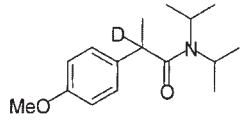
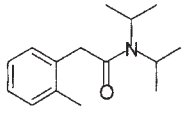
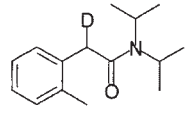
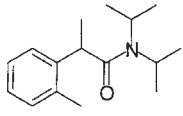
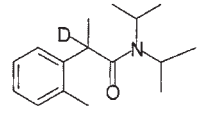
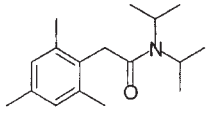
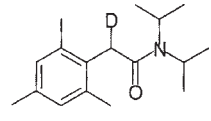
Entry	Starting material	Product	Yield	[(D):(H)]
1		**1** 	**1**-d_1 25%	>98:<2
2		**2** 	**2**-d_1 25%	>98:<2
3		**3** 	**3**-d_1 35%	>98:<2
4		**4** 	**4**-d_1 78%	>98:<2
5		**5** 	**5**-d_1 65%	>98:<2
6		**6** 	**6**-d_1 65%	>98:<2
7		**7** 	**7**-d_1 75%	>98:<2
8		**8** 	**8**-d_1 75%	>98:<2

Table 2. Continued.

Entry	Starting material		Product		Yield	[(D):(H)]
9		**9**		**9**-d_1	50%	>98:<2
10		**10**		**10**-d_1	65%	>98:<2
11		**11**		**11**-d_1	67%	>98:<2
12		**12**		**12**-d_1	73%	>98:<2
13		**13**		**13**-d_1	58%	>98:<2
14		**14**		**14**-d_1	89%	>98:<2
15		**15**		**15**-d_1	91%	>98:<2
16		**16**		**16**-d_1	72%	>98:<2

In conclusion, we have shown that efficient regioselective *C*-deuteriation of 'base-free' enolates (derived from carbonyl amides) can occur under kinetic control using D_2O as the deuterium donor. The levels of *D*-incorporation were shown to be near perfect ($>98\%$) for a wide variety of substituted amides. It appears that single *D*-incorporation preferentially occurs. This is presumably due to the conjugate base of the deuterium donor [lithium deuterium oxide (LiOD)] being not sufficiently basic enough to enable thermodynamic equilibration. The substitution pattern at the C(2) position appears to play a major role in the reaction pathway. An acidifying substituent at the C(2) position (such as a phenyl substituent) preferentially aids enolate formation – without it competitive addition to the carbonyl group occurs. We believe there are two main factors that are responsible for efficient amide *C*-deuteriation under 'base-free' conditions; (a) the presence of an electron-withdrawing substituent in the C(2) position to aid enolate formation and (b) the use of a mildly *D*-acidic deuterium donor (like D_2O) to prevent competitive *O*-deuteriation which is known to lower the overall level of D-incorportion.

Experimental

All solvents were distilled before use. Tetrahydrofuran (THF) and ether were freshly distilled from $LiAlH_4$. Triphenylmethane was used as the indicator for THF. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Proton and carbon NMR spectra were recorded on a JEOL EX 270 and Bruker AM 250, AMX 400 and AM 600 Fourier transform spectrometer (using an internal deuterium lock). Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR spectrometer machine and mass spectra were recorded on a Kratos 50MSTC instrument using a DS503 data system for high-resolution analysis.

N,N-Diisopropyl-ethanamide **1**[13]

A solution of acetyl chloride (2.91 g, 2.63 ml, 37.0 mmol) was added slowly to a stirred solution of diisopropylamine (7.69 g, 10.71 ml,

76 mmol) in dichloromethane (20 ml) at 0°C. The mixture was stirred for 12 h. The resulting solution was extracted with ether (10 ml) and water (10 ml). The organic layer was dried over magnesium sulphate and the filtrate was evaporated to give the amide **1** (5.01 g, 95%) as a yellow liquid; R_f [light petroleum : ether (7:3)] 0.15; ν_{max} (film) 1631 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 3.95–3.85 (1 H, m, NCH), 3.57–3.52 (1 H, m, NCH), 2.07 (3 H, s, $COCH_3$), 1.37 (6 H, d, *J* 6.8, 2 × CH_3) and 1.21 (6 H, d, *J* 6.7, 2 × CH_3); δ_C (63 MHz, $CDCl_3$) 169.4 (CO), 49.2 (CNH), 45.4 (CNH), 23.8 (*C*H_3CO), 20.9 (CH_3) and 20.6 (CH_3); (Found MH^+, 144.1382. $C_8H_{17}NO$ requires 143.2260).

N,N-Diisopropyl-2-deuterio-ethanamide **1**-d_1

A solution of *sec*-butyllithium (0.87 ml, 1.4 M in cyclohexane, 1.22 mmol) was added dropwise to a stirred solution of the amide **1** (0.1 g, 0.70 mmol) in THF (1 ml) at −78°C. The resulting solution was stirred for a further 1 h. Deuterium oxide (31 mg, 28 µl, 1.55 mmol) was added dropwise to this solution and stirred for a further 2 h. The reaction was quenched by the addition of water (10 ml). The solution was extracted with ether (3 × 10 ml), dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum ether–ether (7:3) to give the amide **1**-d_1 (25 mg, 25%) as an oil; R_f [light petroleum:ether (7:3)] 0.15; ν_{max} (film) 2116 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 3.89–3.78 (1 H, septet, *J* 6.7, NCH), 3.51–3.46 (1 H, m, NCH), 2.00 (1 H, *d*, *J* 3.6, CH_AH_B), 1.99 (1 H, d, *J* 4.3, CH_AH_B), 1.30 (6 H, d, *J* 6.8, 2 × CH_3) and 1.15 (6 H, d, *J* 6.8, 2 × CH_3); δ_C (62.5 MHz, $CDCl_3$) 169.5 (CO), 49.2 (CNH), 45.5 (CNH), 23.6 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 20.9 (CH_3) and 20.6 (CH_3); (Found MH^+, 145.1460. $C_8H_{17}DNO$ requires 145.1451).

N,N-Diisopropylpropanamide **2**[14]

In the same way as the amide **1**, propionyl chloride (2.01 g, 1.92 ml, 22 mmol) and diisopropylamine (4.40 g, 6.12 ml, 44 mmol) in dichloromethane (15 ml) gave the amide **2** (3.15 g, 91%) as a yellow liquid; R_f [light petroleum:ether (7:3)] 0.33; ν_{max} (film) 1626 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 3.99–3.94 (1 H, m, NCH), 3.62–3.42 (1 H, m, NCH), 2.35–2.26 (2 H, q, *J* 7.4, CH_2CH_3), 1.38 (6 H, d, *J* 6.5, 2 × CH_3), 1.20 (6 H, d, *J* 6.4, 2 × CH_3) and 1.12 (3 H, t, *J* 7.4, CH_2CH_3); δ_C (62.5 MHz,

$CDC1_3$) 172.6 (CO), 48.0 (CNH), 45.4 (CNH), 28.3 (CH_2CO), 20.9 (CH_3), 20.7 (CH_3) and 9.5 (CH_2CH_3) (Found MH^+, 158.1550. $C_9H_{19}NO$ requires 157.2525).

N,N-Diisopropyl-2-deuterio-propanamide **2**-d_1

In the same way as the amide **1**-d_1, amide **2** (0.1 g, 0.63 mmol), *sec*-butyllithium (0.79 ml, 1.4 M in cyclohexane, 1.12 mmol) and deuterium oxide (28.8 mg, 26 µl, 1.44 mmol) gave the amide **2**-d_1 (25 mg, 25%) as an oil; R_f [light petroleum:ether (7:3)] 0.33; ν_{max} (film) 2173 cm^{-1} (C-D) and 1630 cm^{-1} (C = O); δ_H(250 MHz, $CDC1_3$) 3.88–3.77 (1 H, septet, *J* 6.6, NCH), 3.45–3.36 (1 H, m, NCH), 2.19–2.09 (1 H, m, CH), 1.23 (6 H, d, *J* 6.7, 2 × CH_3), 1.04 (6 H, d, *J* 6.7, 2 × CH_3) and 0.97 (3 H, d, *J* 7.3, CH_3); δ_C (62.5 MHz, $CDC1_3$) 172.7 (CO), 48.1 (CNH), 45.5 (CNH), 28.0 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 20.9 (CH_3), 20.7 (CH_3) and 9.5 (CH_2CH_3) (Found MH^+, 159.1614. $C_9H_{18}DNO$ requires 158.1535).

N,N-Diisopropyl-2-methylpropanamide **3**[15]

In the same way as the amide **1**, *iso*-butyric chloride (3 g, 28 mmol) and diisopropylamine (5.67 g, 7.9 ml, 56 mmol) in dichloromethane (30 ml) gave the amide **3** (2.55 g, 53%) as an orange solid; R_f [light petroleum:ether (7:3)] 0.24; ν_{max} (KBr) 1634 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 4.07–3.96 (1 H, m, NCH), 3.59–3.49 (1 H, m, NCH), 2.77–2.63 (1 H, septet, *J* 6.7, C(2)H), 1.35 (6 H, d, *J* 6.8, 2 × CH_3), 1.23 (6 H, d, *J* 6.8, 2 × CH_3) and 1.11 (6 H, d, *J* 6.7, 2 × CH_3); δ_C (62.5 MHz, $CDC1_3$) 176.1 (CO), 47.5 (CNH), 45.5 (CNH), 31.7 (*C*HCO), 21.4 (2 × CH_3). 20.7 (2 × CH_3) and 19.7 (2 × CH_3) (Found MH^+, 172.1693. $C_{10}H_{21}NO$ requires 171.2790).

N,N-Diisopropyl-2-deuterio-2-methylpropanamide **3**-d_1

In the same way as the amide **1**-d_1, amide **3** (0.1 g, 0.58 mmol), *sec*-butyllithium (0.73 ml, 1.4 M in cyclohexane, 1.02 mmol) and deuterium oxide (25.5 mg, 23 µl, 1.27 mmol) gave the amide **3**-d_1 (35 mg, 35%) as an oil; R_f [light petroleum: ether (7:3)] 0.24; ν_{max} (film) 2162 cm^{-1} (C–D) and 1634 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 3.91–3.80 (1 H, m, NCH), 3.57–3.44 (1 H, m, NCH), 1.20 (6 H, d, *J* 6.8, 2 × CH_3), 1.08 (6 H, d, *J* 6.8, 2 × CH_3) and 0.95 (6 H, s, $CD(CH_3)_2$); δ_C(62.5 MHz, $CDC1_3$) 176.2 (CO), 47.4 (CNH), 45.5 (CNH), 31.4 (1 C, triplet [1:1:1],

$J_{CD} = 19.8$, CD), 21.4 ($2 \times CH_3$), 20.7 ($2 \times CH_3$) and 19.6 ($2 \times CH_3$) (Found MH^+, 173.1770. $C_{10}H_{21}DNO$ requires 173.1764).

N,N-Diisopropyl-2-phenylethanamide **4**[16]

In the same way as the amide **1**, phenylacetyl chloride (24.53 g, 21.0 ml, 0.16 mol) and diisopropylamine (32.31 g, 45.0 ml, 0.34 mol) in dichloromethane (240 ml) gave the amide **4** (33.83 g, 95%) as a yellow solid; R_f [light petroleum: ether (7:3)] 0.18; m.p. 44–47°C; ν_{max} (KBr) 3001–2869 cm^{-1} (aromatic, C–H) and 1625 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.34–7.12 (5 H, m, $5 \times CH$; Ph), 4.04 (1 H, m, NCH), 3.69 (2 H, s, $PhCH_2$), 3.48–3.25 (1 H, m, NCH), 1 0.39 (6 H, d, *J* 6.8, $2 \times CH_3$) and 1.11 (6 H, d, *J* 6.8, $2 \times CH_3$); δ_C (62.5 MHz, $CDCl_3$) 169.9 (CO), 135.9 (Ph), 128.6 (Ph), 128.5 (Ph), 126.5 (Ph), 49.4 (NCH), 45.8 (NCH), 43.5 (CHCO) and 20.6 (CH_3) (Found MH^+, 220.1702. $C_{14}H_{21}NO$ requires 219.1622).

N,N-Diisopropyl-2-deuterio-2-phenylethanamide **4**-d_1

In the same way as amide **1**, amide **4** (0.1 g, 0.46 mmol), *sec*-butyllithium (0.57 ml, 1.4 M in cyclohexane. 0.81 mmol) and deuterium oxide (19.9 mg, 18 µl, 0.91 mmol) gave the amide **4**-d_1 (79 mg, 78%); as an oil; R_f [light petroleum: ether (7:3)] 0.18; ν_{max} (film) 2172 cm^{-1} (C–D) and 1632 cm^{-1} (C = O); δ_H(250 MHz, $CDC1_3$) 7.47–7.11 (5 H, m, $5 \times CH$; Ph), 3.94–3.84 (1 H, septet, *J* 6.7, NCH), 3.62 (1 H, s, CH), 3.33–3.27 (1 H, septet, *J* 6.7, NCH), 1.35 (6 H, d, *J* 6.8, $2 \times CH_3$) and 0.93 (6 H, d, *J* 6.7, $2 \times CH_3$); δ_C(62.5 MHz, $CDC1_3$) 170.0 (CO), 135.8 (Ph), 128.6 (Ph), 128.4 (Ph), 126.5 (Ph), 49.4 (CNH), 45.8 (CNH), 43.2 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.4$, CD) and 20.6 (CH_3); (Found MH^+, 221.1775. $C_{14}H_{20}DNO$ requires 220.1696).

N,N-Diisopropyl-2-phenylpropanamide **5**[17]

LDA (19.78 ml, 1.5 M in THF, 30 mmol) was added dropwise to a stirred solution of *N*,*N*-diisopropyl-2-phenylethanamide **4** (5 g, 23 mmol) in THF (60 ml) at −78°C and stirred for 1 h. Methyl iodide (3.41 g, 1.5 ml, 24 mmol) was added and the resulting solution was stirred for 12 h. Water (100 ml) was then added and the mixture was extracted with ether (3×200 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was

purified by flash column chromatography on silica gel eluting with light petroleum (b.p. 40–60°C)–ether (9:1) to give the amide **5** (3.36 g, 61%) as a yellow solid; R_f [light petroleum:ether (7:3)] 0.36; m.p. 39–40°C; ν_{max} (KBr) 3057–2872 cm^{-1} (aromatic, C–H) and 1638 cm^{-1} (C = O); δ_H(250 MHz, $CDC1_3$) 7.34–7.18 (5 H, m, 5 × CH; Ph), 4.10–3.95 (1 H, m, NCH), 3.83–3.75 (1 H, q, *J* 6.8, C(2)H), 3.32–3.25 (1 H, m, NCH), 1.45 (3 H, d, *J* 6.8, C(2)HCH3), 1.41 (3 H, d, *J* 76.8, CH_3), 1.38 (3 H, d, *J* 6.7, CH_3), 1.13 (3 H, d, *J* 6.7, CH_3) and 0.58 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDC1_3$) 172.2 (CO), 143.1 (Ph), 128.2 (Ph), 127.2 (Ph), 126.6 (Ph), 48.4 (CHN), 45.8 (CHN), 44.9 (CHCO), 21.1 (CH_3), 20.1 (CH_3) and 19.2 (CH_3) (Found MH^+, 234.1861. $C_{15}H_{23}NO$ requires 233.1782).

N,N-Diisopropyl-2-deuterio-phenylpropanamide **5**-d_1

A solution of *sec*-BuLi (0.54 ml, 1.4 M in cyclohexane, 0.75 mmol) was added to the amide **5** (0.1 g, 0.43 mmol) in THF (3 ml) at −78°C and stirred for 1 h. Deuterium oxide (19 mg, 17 µl 0.94 mmol) was added and the resulting solution was stirred for a further 1 h. The solution was quenched with water (10 ml) and extracted with ether (10 ml), dried (with $MgSO_4$) ands the organic layer was evaporated to give the amide **5**-d_1 (66 mg, 65%) as an oil; R_f [light petroleum:ether (7:3)] 0.36; ν_{max} (film) 2158 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 7.33–7.16 (5 H, m, 5 × CH; Ph), 4.06–3.92 (1 H, septet, *J* 6.7, NCH), 3.35–3.24 (1 H, septet, *J* 6.7, NCH), 1.45 (3 H, d, *J* 6.8, CH_3), 1.39 (3 H, s, CH_3), 1.38 (3 H, d, *J* 6.9, CH_3), 1.15 (3 H, d, *J* 6.7, CH_3) and 0.58 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.2 (CO), 143.0 (Ph), 128.8 (Ph), 127.2 (Ph), 126.5 (Ph), 48.3 (CNH), 45.8 (CNH), 44.4 (1 C, triplet [1:1:1], $^1J_{C.D} = 19.4$, CD), 21.0 (CH_3), 20.9 (CH_3), 20.0 (CH_3) and 19.6 (CH_3); (Found MH^+, 235.1912. $C_{15}H_{22}DNO$ requires 234.1833).

N,N-Diethyl-2-phenyl-propanamide **6**[18]

In the same way as the amide **1**, 2-phenylpropionyl chloride (3 g, 2.57 ml, 19 mmol) and diethylamine (2.78 g, 3.94 ml, 38 mmol) in dichloromethane (30 ml) gave the amide **6** (2.78 g, 71%) as a yellow liquid; R_f [light petroleum:ether (7:3)] 0.29; ν_{max} (KBr) 3061–2872 cm^{-1} (aromatic, CH) and 1639 cm^{-1} (C = O); δ_H(250 MHz, $CDC1_3$) 7.37–7.17 (5 H, m, 5 × CH; Ph), 3.87–3.79 (1 H, q, *J* 7.0, CH), 3.57–3.43 (1 H, dq, *J* 13.5, *J* 7.1, $CH_AH_BCH_3$), 3.39–3.04 (3 H, m, CH_AH_B and CH_2), 1.44

(3 H, d, *J* 6.9, C(2)HCH_3), 1.08 (3 H, t, *J* 7.1, CH_2CH_3) and 1.00 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.7 (CO), 142.5 (Ph), 128.8 (Ph), 127.3 (Ph), 126.6 (Ph), 43.2 (*C*HCO), 41.6 (CH_2N), 40.3 (CH_2N), 21.0 (CH_3), 14.2 (CH_3CH_2) and 12.8 (CH_3CH_2) (Found MH^+, 206.1542. $C_{13}H_{19}NO$ requires 205.1466).

N,N-Diethyl-2-deuterio-2-phenyl-propanamide **6**-d_1

In the same way as the amide **1**-d_1, amide **6** (0.1 g, 0.49 mmol), *sec*-butyllithium (0.61 ml, 1.4 M in cyclohexane, 0.86 mmol) and deuterium oxide (22.1 mg, 20 µl, 1.11 mmol) gave the amide **6**-d_1 (66 mg, 65%); R_f [light petroleum:ether (7:3)] 0.29; ν_{max} (film) 2156 cm^{-1} (C–D) and 1637 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.34–7.10 (5 H, m, 5 × CH; Ph), 3.49–2.97 (4 H,m,2 × CH_2), 1.36(3 H, s, CH_3), 1.02 (3 H, t, *J* 7.1, CH_2CH_3) and 0.91 (3 H, t, *J* 7.1, CH_2CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.7 (CO), 142.4 (Ph), 128.8 (Ph), 127.2 (Ph), 126.6 (Ph), 42.8 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.3, CD), 41.6 (CH_2N), 40.3 (CH_2N), 20.8 (CH_3), 14.2 (CH_3) and 12.8 (CH_3) (Found MH^+, 207.1598. $C_{13}H_{18}DNO$ requires 206.1519).

N-Cyclohexyl-2-phenyl-propanamide **7**[19]

In the same way as the amide **1**, 2-phenylpropionyl chloride (3 g, 2.57 ml, 19.4 mmol) and piperidine (3.30 g, 3.84 ml, 38.8 mmol) in dichloromethane (30 ml) gave the amide **7** (3.74 g, 89%) as a yellow liquid; R_f [light petroleum:ether (7:3)] 0.28; ν_{max} (KBr) 3061–2855 cm^{-1} (aromatic, CH) and 1639 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 7.38–7.17 (5 H, m, 5 × CH; Ph), 3.92–3.84 (1 H, q, *J* 6.6, CH), 3.76–3.71 (1 H, m, NCH_AH_B), 3.43–3.27 (3 H, m, NCH_AH_B and NCH_2), 1.54–1.36 (8 H, m, CH_3, CH_AH_B and 2 × CH_2) and 1.00–0.95 (1 H, m, CH_AH_B); δ_C (62.5 MHz, $CDCl_3$) 171.7 (CO), 142.5 (Ph), 128.8 (Ph), 127.3 (Ph), 126.6 (Ph), 46.6 (CH_2N), 43.2 (CH_2N), 43.1 (CHCO), 25.9 (CH_2), 25.5 (CH_2), 24.5 (CH_2) and 20.8 (CH_3) (Found MH^+, 218.1553. $C_{14}H_{19}NO$ requires 217.1466).

N-Cyclohexyl-2-deuterio-2-phenyl-propanamide **7**-d_1

In the same way as the amide **1**-d_1, amide **7** (0.1 g, 0.46 mmol), *sec*-butyllithium (0.57 ml, 1.4 M in cyclohexane, 0.80 mmol) and deuterium oxide (19.9 mg, 18 µl, 1.0 mmol) gave the amide **7**-d_1; (75 mg, 75%); R_f

[light petroleum:ether (7:3)] 0.28; ν_{max} (film) 2158 cm^{-1} (C–D) and 1638 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.22–7.02 (5 H, m, 5 × CH; Ph), 3.61–3.54 (1 H, m, CH_AH_B), 3.29–3.08 (3 H, m, CH_2 and CH_AH_B) and 138–1.11 (9 H, m, 3 × CH_2 and CH_3); δ_C(62.5 MHz, $CDCl_3$) 171.8 (CO), 142.4 (Ph), 128.8 (Ph), 127.2 (Ph), 126.6 (Ph), 46.6 (CH_2N), 43.1 (CH_2N), 42.8 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 25.9 (CH_2), 25.5 (CH_2), 24.5 (CH_2) and 20.7 (CH_3); (Found MH^+, 219.1615. $C_{14}H_{19}DNO$ requires 218.1536).

N,N-Dicyclohexyl-2-phenyl-propanamide **8**

In the same way as the amide **1**, 2-phenylpropionyl chloride (2 g, 12 mmol) and dicyclohexyl amine (4.35 g, 4.77 ml, 24 mmol) in dichloromethane (20 ml) gave amide **8** (3.65 g, 98%) as a yellow solid; R_f [light petroleum:ether (7:3)] 0.44; m.p. 70–73°C; ν_{max} (KBr) 3061–2855 cm^{-1} (aromatic, CH) and 1639 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 7.37–7.11 (5 H, m, 5 × CH; Ph), 3.83–3.75 (1 H, q, *J* 6.7, CH), 3.59–3.50 (1 H, m, NCH), 2.82–2.59 (2 H, m, NCH and CH_AH_B) and 1.96–0.99 (22 H, m, CH_3, CH_AH_B and 9 × CH_2); δ_C (67.5 MHz, $CDCl_3$) 172.5 (CO), 143.4 (Ph), 128.8 (Ph), 127.3 (Ph), 126.5 (Ph), 57.4 (NCH), 56.2 (NCH), 45.2 (CHCO), 30.9 (CH_2), 30.3 (2 × CH_2), 30.2 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 25.3 (CH_2) and 21.0 (CH_3) (Found MH^+, 314.2492. $C_{21}H_{31}NO$ requires 313.2405).

N,N-Dicyclohexyl-2-deuterio-2-phenyl-propanamide **8**-d_1

In the same way as the amide **1**-d_1, amide **8** (0.1 g, 0.32 mmol), *sec*-butyllithium (0.40 ml, 1.4 M in cyclohexane, 0.56 mmol) and deuterium oxide (14.4 mg, 13 µl, 0.72 mmol) gave the amide **8**-d_1; (77 mg, 75%); R_f [light petroleum:ether (7:3)] 0.44; ν_{max} (film) 2191 cm^{-1} (C–D) and 1638 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.33–7.16 (5 H, m, 5 × CH; Ph), 3.62–3.50 (1 H, m, NCH), 2.90–2.68 (1 H, m, NCH), 2.66–2.44 (2 H, m, CH_2) and 1.90–0.52 (21 H, m, 9 × CH_2 and CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.6 (CO), 143.1 (Ph), 128.7 (Ph), 127.1 (Ph), 126.4 (Ph), 57.4 (CHN), 56.2 (CHN), 44.6 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 31.3 (CH_2), 30.2 (2 × CH_2), 29.2 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 25.2 (CH_2) and 20.7 (CH_3) (Found MH^+, 315.2555. $C_{21}H_{30}DNO$ requires 314.2476).

N,N-Diisopropyl-2-phenylbutanamide **9**[16]

In the same way as the amide **1**, 2-phenylbutyryl chloride (1 g, 5.4 mmol), diisopropylamine (1.09 g, 1.52 ml, 10.8 mmol) in dichloromethane (5 ml) gave the amide **9** (1.04 g, 77%) as a yellow solid; R_f [light petroleum:ether (7:3)] 0.44; m.p. 55–60°C; ν_{max} (KBr) 3064–2869 cm^{-1} (aromatic, C–H) and 1634 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.33–7.17 (5 H, m, Ph), 4.13–4.00 (1 H, m, NCH), 3.52–3.46 (1 H, t, *J* 7.2, C(2)H), 3.36–3.24 (1 H, m, NCH), 2.20–2.01 (1 H, septet, *J* 7.3. $CH_AH_BCH_3$), 1.75–1.58 (1 H, septet, *J* 7.1, $CH_AH_BCH_3$), 1.44 (3 H, d, *J* 6.8, $NCHCH_3$), 1.35 (3 H, d, *J* 6.8, $NCHCH_3$), 1.14 (3 H, d, *J* 6.7, $NCHCH_3$), 0.90–0.84 (3 H, t, *J* 7.4, CH_2CH_3) and 0.63 (3 H, d, *J* 6.6, $NCHCH_3$); δ_C(62.5 MHz, $CDCl_3$); 171.5 (CO), 141.2 (Ph), 128.5 (Ph), 127.7 (Ph), 126.4 (Ph), 52.5 (CHCO), 48.2 (CHN), 45.8 (CHN), 28.2 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 20.1 (CH_3), 19.8 (CH_3) and 12.4 (CH_3); (Found MH +, 248. $Ci_6H_{25}NO$ requires 247).

N,N-Diisopropyl-2-deuterio-2-phenylbutanamide **9**-d_1

In the same way as the amide **1**-d_1, the amide **9** (0.1 g, 0.40 mmol), *sec*-butyllithium (51 ml, 1.4 M in cyclohexane, 0.71 mmol) and deuterium oxide (17.7 mg, 16 µl, 0.88 mmol) gave the amide **9**-d_1 (50 mg, 50%); R_f [light petroleum:ether (7:3)] 0.44; ν_{max} (film) 2147 cm^{-1} (C–D) and 1637 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 7.33–7.16 (5 H, m, 5 × CH; Ph), 4.14–3.98 (1 H, septet, *J* 6.1 NCH), 3.33–3.27 (1 H, m, NCH), 2.17–2.03 (1 H, dq, *J* 13.6 and 7.3, CH_AH_B), 1.73–1.59 (1 H, dq, *J* 13.7 and 7.3, CH_AH_B), 1.44 (3 H, d, *J* 6.8, CH_3), 1.35 (3 H, d, *J* 6.8; CH_3), 1.15 (3 H, d, *J* 6.7, CH_3), 0.87 (3 H, t, *J* 7.3, CH_2CH_3) and 0.63 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.7 (CO), 141.2 (Ph), 128.6 (Ph), 127.8 (Ph), 126.5 (Ph), 52.1 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.4$, CD), 48.1 (CHN), 45.9 (CHN), 28.2 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.2 (CH_3), 19.9 (CH_3) and 12.4 (CH_3CH_2); (Found MH^+, 249.2062. $C_{16}H_{24}DNO$ requires 248.1983).

N,N-Diisopropyl-3-methyl-2-phenylbutanamide **10**

In the same way as the amide **1**, α-isopropylphenylacetyl chloride (2.27 g, 12 mmol) and diisopropylamine (2.43 g, 3.38 ml, 24 mmol) in dichloromethane (20 ml) gave the amide **10** (2.58 g, 85%) as a yellow solid; R_f [light petroleum:ether (7:3)] 0.54; m.p. 29–31°C; ν_{max} (KBr)

3061–2870 (aromatic, CH) and 1634 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 7.31–7.16 (5 H, m, 5 × CH; Ph), 4.25–4.14 (1 H, m, NCH), 3.35–3.27 (1 H, m, NCH), 3.20 (1 H, d, *J* 9.7, C(2)H), 2.50–2.36 (1 H, m, C(2)HCH), 1.43 (3 H, d, *J* 6.8, CH_3), 1.30 (3 H, d, *J* 6.7, CH_3), 1.18 (3 H, d, *J* 6.7, CH_3), 1.02 (3 H, d, *J* 6.4, CH_3), 0.74 (3 H, d, *J* 6.6, CH_3) and 0.65 (3 H, d, *J* 6.8, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.6 (CO), 140.0 (Ph), 128.4 (Ph), 126.5 (Ph), 58.0 (CHCO), 48.2 (CHN), 45.9 (CHN), 32.2 (CHCHCO), 22.3 (CH_3), 21.1 (CH_3), 20.8 (CH_3), 20.5 (CH_3). 20.3 (CH_3) and 20.2 (CH_3); (Found MH^+, 262.2163. $C_{17}H_{27}NO$ requires 262.4013).

N,N-Diisopropyl-2-deuterio-3-methyl-2-phenylbutanamide **10**-d_1

In the same way as the amide **1**-d_1, the amide **10** (0.1 g, 0.38 mmol), *sec*-butyllithium (0.48 ml, 1.4 M in cyclohexane, 0.67 mmol) and deuterium oxide (16.6 mg, 15 µl, 0.83 mmol) gave the amide **10**-d_1 (65 mg, 65%); R_f [light petroleum:ether (7:3)] 0.54; ν_{max} (film) 2158 cm^{-1} (C–D) and 1638 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.37–7.16 (5 H, m, 5 × CH; Ph), 4.25–4.14 (1 H, septet, *J* 6.7, NCH), 3.32–3.27 (1 H, m, NCH), 2.48–2.37 (1 H, septet, *J* 6.5, CDCH), 1.43 (3 H, d, *J* 6.8, CH_3), 1.30 (3 H, d, *J* 6.8, CH_3), 1.18 (3 H, d, *J* 6.7, CH_3), 1.02 (3 H, d, *J* 6.4, CH_3), 0.74 (3 H, d, *J* 6.6, CH_3) and 0.65 (3 H, d, *J* 6.8, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.7, 139.9, 128.4, 126.5, 57.5 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.8$, CD), 48.2 (CHN), 45.9 (CHN), 32.1 (CDCH), 22.3 (CH_3), 21.1 (CH_3), 20.8 (CH_3), 20.5 (CH_3), 20.3 (CH_3) and 20.2 (CH_3); (Found MH^+, 263.2243. $C_{17}H_{26}DNO$ requires 262.2164).

N,N-Diisopropyl-2,3-diphenylpropanamide **11**[20]

In the same way as the amide **5**, amide **4** (3.0 g, 14 mmol), *sec*-butyllithium (11 ml, 1.4 M in cyclohexane, 15 mmol) and benzyl bromide (2.59 g, 1.8 ml, 14 mmol) in THF (30 ml) gave the amide **11** (2.42 g, 56%) as a yellow solid; R_f [light petroleum:ether (7:3)] 0.18; m.p. 62–66°C; ν_{max} (film) 3084–2872 (aromatic, CH) and 1638 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 7.30–7.05 (10 H, m, 10 × CH; 2 × Ph), 4.04–3.96 (1 H, m, NCH), 3.71 (1 H, t, *J* 7.3, C(2)H), 3.54–3.44 (1 H, dd, *J* 13.3 and 7.2, CH_AH_B), 3.39–3.16 (1 H, m, NCH), 2.92–2.84 (1 H, dd, *J* 13.4 and 6.9, CH_AH_B), 1.36 (3 H, d, *J* 6.8, CH_3), 1.35 (3 H, d, *J* 6.7, CH_3), 0.98 (3 H, d, *J* 6.7, CH_3) and 0.63 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.1 (CO), 140.5 (Ph), 129.3 (Ph), 128.6 (Ph), 128.0 (Ph), 127.9

(Ph), 126.7 (Ph), 125.9 (Ph), 52.4 (CHCO), 48.4 (CHN), 45.9 (CHN), 41.4 (CH_2Ph), 20.8 ($2 \times CH_3$), 20.2 (CH_3) and 20.0 (CH_3) (Found MH^+, 310.2160. $C_{21}H_{27}NO$ requires 309.4441).

N,N-Diisopropyl-2-deuterio-2,3-diphenylpropanamide **11**-d_1

In the same way as the amide **1**-d_1, the amide **11** (0.1 g, 0.32 mmol), *sec*-butyllithium (0.41 ml, 1.4 M in cyclohexane, 0.57 mmol) and deuterium oxide (14.4 mg, 13 µl, 0.72 mmol) gave the amide **11**-d_1 (66 mg, 67%); R_f [light petroleum:ether (7:3)] 0.18; ν_{max} (film) 2148 cm^{-1} (C–D) and 1632 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 7.30–7.05 (10 H, m, $10 \times CH$; $2 \times Ph$), 4.03–3.92 (1 H, septet, *J* 6.7, NCH), 3.50 (1 H, d, *J* 13.4, CH_AH_B), 3.29–3.24 (1 H, m, NCH), 2.88 (1 H, d, *J* 13.4, CH_AH_B), 1.35 (3 H, d, *J* 6.8, CH_3), 1.34 (3 H, d, *J* 6.7, CH_3), 0.97 (3 H, d, *J* 67, CH_3) and 0.63(3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.1 (CO), 140.4 (Ph), 129.3 (Ph), 128.6 (Ph), 128.0 (Ph), 127.9 (Ph), 126.7 (Ph), 125.9 (Ph), 52.3 (1 C, triplet [1:1:1], $J_{C,D} = 19.2$, CD), 48.4 (CNH), 45.9 (CNH), 41.2 (CH_2Ph), 20.8 ($2 \times CH_3$), 20.2 (CH_3) and 20.0 (CH_3) (Found MH^+, 311.2226. $C_{21}H_{26}DNO$ requires 310.2147).

N,N-Diisopropyl-2-(4-methoxyphenyl)-ethanamide **12**[21]

In the same way as the amide **1**, 4-methoxyphenylacetyl chloride (2.5 g, 13 mmol) and diisopropylamine (2.69 g, 3.75 ml, 27 mmol) in dichloromethane (25 ml) gave the amide **12** (3 g, 92%) as a white solid; R_f [light petroleunrether (7:3)] 0.11; m.p. 53–61°C; ν_{max} (KBr) 3001–2837 (aromatic, CH) and 1634 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 7.15 (2 H, d, *J* 8.7, $2 \times CH$; Ar; 2,6-CH), 6.85 (2 H, d, *J* 8.7, $2 \times CH$; Ar; 3,5-CH), 4.06–3.87 (1 H, m, NCH), 3.79 (3 H, s, OCH_3), 3.61 (2 H, s, CH_2), 3.50–3.37 (1 H, m, NCH), 1.41 (6 H, d, *J* 6.8, $2 \times CH_3$) and 1.02 (6 H, d, *J* 6.7, $2 \times CH_3$); δ_C(62.5 MHz, $CDCl_3$) 170.2 (CO), 158.3 (Ph), 129.5 (Ph), 127.9 (Ph), 114.1 (Ph), 55.3 (CH_3O), 49.3 (CNH), 45.8 (CNH), 42.5 (CH_2CO), 20.7 (CH_3) and, 20.6 (CH_3) (Found MH^+, 250.1799. $C_{15}H_{23}NO_2$ requires 249.1728).

N,N-Diisopropyl-2-deuterio-2-(4-methoxyphenyl)-ethanamide **12**-d_1

In the same way as the amide **1**-d_1, amide **12** (50 mg, 0.20 mmol), *sec*-butyllithium (0.25 ml, 1.4 M in cyclohexane, 0.35 mmol) and deuterium oxide (11.1 mg, 10 µl, 0.55 mmol) gave the amide **12**-d_1, (36 mg, 73%); R_f

[light petroleum:ether (7:3)] 0.11; ν_{max} (film) 2144 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.15 (2 H, d, *J* 6.7, 2 × CH; Ar; 3,5-CH), 6.84 (2 H, d, *J* 6.6, 2 × CH; Ar; 2,6-CH), 4.02–3.88 (1 H, m, NCH), 3.78 (3 H, s, OCH_3), 3.59 (1 H, s, CH), 3.39–3.34 (1 H, m, NCH), 1.41 (6 H, d, *J* 6.8, 2 × CH_3) and 1.01 (6 H, d, *J* 6.7, 2 × CH_3): δ_C(62.5 MHz, $CDCl_3$) 170.3 (CO), 158.3 (Ph), 129.5 (Ph), 127.7 (Ph), 114.1 (Ph), 55.2 (CH_3O), 49.3 (CNH), 45.8 (CNH), 42.2 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 20.6 (CH_3) and 20.5 (CH_3) (Found MH^+, 251.1676. $C_{15}H_{22}DNO_2$ requires 250.1799).

N,N-Diisopropyl-2-(4-methoxyphenyl)-propanamide **13**

In the same way as the amide **5**, amide **12** (2.9 g, 12 mmol), LDA (12 ml, 1.5 M in THF, 18 mmol) and methyl iodide (2.05 g, 0.90 ml, 14 mmol) in THF (35 ml) gave the amide **13** (2.01 g, 67%) as a white solid; R_f [light petroleum:ether (7:3)] 0.27; m.p. 47–53°C; ν_{max} (KBr) 3001-2835 (aromatic, CH) and 1638 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.13 (2 H, d, *J* 8.7, 2 × CH; Ar; 3,5-CH), 6.82 (2 H, d, *J* 8.7, 2 × CH; Ar; 2,6-CH), 4.04–3.93 (1 H, m, NCH), 3.77–3.69 (4 H, m, OCH_3 and CH), 3.29–3.22 (1 H, m, NCH), 1.40 (3 H, d, *J* 6.8, CH_3), 1.37 (6 H, d, *J* 6.7, 2 × CH_3), 1.12 (3 H, d, *J* 6.7, CH_3) and 0.58 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.5 (CO), 158.2 (Ph), 135.2 (Ph), 130.1 (Ph), 128.2 (Ph), 114.2 (Ph), 55.2 (CH_3O), 43.2 (CHN), 45.8 (CHN), 43.8 (CHCO), 21.1 (CH_3), 21.0 (CH_3), 20.1 (CH_3) and 19.8 (CH_3) (Found MH^+, 260.1968. $C_{15}H_{25}NO_2$ requires 263.3742.)

N,N-Diisopropyl-2-deuterio-2-(4-methoxyphenyl)-propanamide **13**-d_1

In the same way as the amide **1**-d_1, amide **13** (50 mg, 0.19 mmol), *sec*-butyllithium (0.24 ml, 1.4 M in cyclohexane, 33 mmol) and deuterium oxide (11.1 mg, 10 µl, 0.55 mmol) gave the amide **13**-d_1 (29 mg, 58%); R_f [light petroleum:ether (7:3)] 0.27; ν_{max} (film) 2158 cm^{-1} (C–D) and 1638 cm^{-1} (C = O); δ_H (250 MHz, $CDC1_3$) 7.01 (2 H, d, *J* 6.6, 2 × CH; Ar; 3,5-CH), 6.78 (2 H. d *J* 6.7, 2 × CH; Ar; 2,6-CH), 4.00-3.89 (1 H, septet, *J* 6.7, NCH), 3.72 (3 H, s, OCH_3), 3.27-3.21 (1 H, m, NCH), 1.37 (3 H, d, *J* 6.8, CH_3), 1.31 (3 H, d, *J* 5.5, CH_3), 1.30 (3 H, s, CH_3), 1.07 (3 H, d, *J* 6.7, CH_3) and 0.57 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDC1_3$) 172.5 (CO), 158.2 (Ph), 135.1 (Ph), 128.2 (Ph), 128.1 (Ph), 114.2 (Ph), 55.2 (CH_3O), 48.2 (CHN), 45.8 (CHN), 43.1 (1 C, triplet [1:1:1],

$^1J_{C,D} = 19.7$, CD), 21.0 (CH_3), 20.1 (CH_3) and 19.8 (CH_3) (Found MH^+, 265.2020. $C_{16}H_{24}DNO_2$ requires 264.1941).

N,N-Diisopropyl-2-(2-methylphenyl)-ethanamide **14**

In the same way as the amide **1**, *o*-tolylacetyl chloride (1.5 g, 8.90 mmol) and diisopropylamine (1.82 g, 2.54 ml, 18 mmol) in dichloromethane (12 ml) gave the amide **14** (1.97 g, 47%); R_f [light petroleum:ether (7:3)] 0.17; m.p. 26–30°C; ν_{max} (KBr) 2999–2874 cm^{-1} (aromatic, CH) and 1639 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.23–7.06 (4 H, m, 4 × CH; Ar), 3.95–3.84 (1 H, m, NCH), 3.70 (2 H, s, CH_2), 3.45–3.39 (1 H, m, NCH), 2.26 (3 H, s, CH_3), 1.44 (6 H, d, *J* 6.8, 2 × CH_3) and 1.10 (6 H, d, *J* 6.8, 2 × CH_3); δ_C (63 MHz, $CDC1_3$) 169.9 (CO) 136.2 (Ar), 134.6 (Ar), 130.2 (Ar), 128.8 (Ar), 126.7 (Ar), 126.1 (Ar), 49.2 $(CNH)_5$ 4.5.9 (CNH), 40.8 (CHCO), 20.7 (CH_3) and 19.6 (CH_3) (Found MH^+, 234.1861 $C_{15}H_{23}NO$ requires 234.1782).

N,N-Diisopropyl-2-deuterio-2-(2-methylphenyl)-ethanamide **14**-d_1

In the same way as the amide **1**-d_1, amide **14** (0.1 g, 0.43 mmol), *sec*-butyllithium (0.54 ml, 1.4 M in cyclohexane, 0.75 mmol) and deuterium oxide (18.8 mg, 17 µl, 0.94 mmol) gave the amide **14**-d_1, (90 mg, 89%); R_f [light petroleum: ether (7:3)] 0.17; ν_{max} (film) 2163 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.19–7.13 (4 H, m, 4 × CH; Ar), 3.95–3.84 (1 H, m, NCH), 3.60 (1 H, s, CH), 3.48–3.37 (1 H, septet, *J* 6.7, NCH), 2.25 (3 H, s, CH_3). 1 44 (6 H. d, *J* 6.8, 2 × CH_3) and 1.09 (6 H, d, *J* 6.7, 2 × CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.0 (CO), 136.2 (Ar), 134.4 (Ar), 130.2 (Ar), 128.7 (Ar), 126.8 (Ar), 126.1 (Ar), 49.3 (CNH), 45.9 (CNH), 40.4 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.4$, CD), 20.6 (CH_3) and 19.6 (CH_3); (Found MH^+, 235.1910. $C_{15}H_{22}DNO$ requires 234.1831).

N,N-Diisopropyl-2-(2-methylphenyl)-propanamide **15**

In the same way as the amide **5**, amide **14** (1.5 g, 6.44 mmol), LDA (4.7 ml, 1.5 M in THF, 7.08 mmol) and methyl iodide (0.91 g, 0.40 ml, 6.42 mmol) in THF (20 ml) gave the amide **15** (1.05 g, 66%) as a white solid; R_f [light petroleum: ether (7:3)] 0.37; m.p. 72–76°C; ν_{max} (film) 2999–2866 cm^{-1} (aromatic, CH) and 1634 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 7.21–7.01 (4 H, m, 4 × CH, Ar), 3.86–3.80 (1 H, q, *J* 6.8,

C(2)H), 3.71–3.53 (1 H, m, NCH), 3.32–3.14 (1 H, m, NCH), 2.34 (3 H, s, CH_3; Ar), 1.43 (3 H, d, *J* 6.8, CH_3), 1.41 (3 H, d, *J* 6.8, CH_3), 1.26 (3 H, d, *J* 6.8, CH_3), 1.08 (3 H, d; *J* 6.7, CH_3) and 0.46 (3 H, d, *J* 6.6, CH_3); δ_C (62.5 MHz, $CDCl_3$) 172.8 (CO), 141.3 (Ar), 134.0 (Ar), 130.5 (Ar), 126.7 (Ar), 126.5 (Ar), 48.2 (CHN), 45.7 (CHN), 41.0 (CHCO), 21.0 (CH_3), 20.9 (CH_3), 19.9 (CH_3), 19.2 (CH_3) and 18.9 (CH_3) (Found MH^+, 248.2021. $C_{16}H_{25}NO$ requires 247.1935).

N,N-Diisopropyl-2-deuterio-2-(2-methylphenyl)-propanamide **15**-d_1

In the same way as the amide **1**, amide **15** (0.1 g, 0.40 mmol), *sec*-butyllithium (0.51 ml, 1.4 M in cyclohexane, 0.70 mmol) and deuterium oxide (17.7 mg, 16 µl, 0.88 mmol) gave the amide **15**-d_1, (91 mg, 91%); R_f [light petroleum: ether (7:3)] 0.37; ν_{max} (film) 2162 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H(250 MHz, $CDC1_3$) 7.20–7.07 (4 H, m, 4 × CH; Ph), 3.76–3.60 (1 H, septet, *J* 6.7, NCH), 3.31–3.20 (1 H, septet, *J* 6.8, NCH), 2.35 (3 H, s, CH_3) 1.46 (3 H, d, *J* 6.8, CH_3), 1.41 (3 H, d, *J* 6.8, CH_3), 1.32 (3 H, s, CH_3), 1.12 (3 H, d, *J* 6.7, CH_3) and 0.50 (3 H, d, *J* 6.6, CH_3); δ_C(62.5 MHz, $CDCl_3$) 172.8 (CO), 141.3 (Ar), 133.9 (Ar), 130.5 (Ar), 126.7 (Ar), 126.6 (Ar), 126.5 (Ar), 48.2 (CHN), 45.7 (CHN), 40.7 (1 C, triplet [1:1:1], $^1J_{C,D} = 19.4$, CD), 21.0 (CH_3), 20.9 (CH_3), 19.9 (CH_3), 19.2 (CH_3) and 18.8 (CH_3); (Found MH^+, 249.2070. $C_{15}H_{24}DNO$ requires 248.1991.)

N,N-Diisopropyl-2-(2,4,6-trimethylphenyl)-ethanamide **16**

In the same way as the amide **1**, mesitylacetyl chloride (1.50 g, 8.13 mmol) and diisopropylamine (1.65 g, 2.29 ml, 16 mmol) in dichloromethane (15 ml) gave the amide **16** (1.69 g. 85%) as a white solid; R_f [light petroleum: ether (7:3)] 0.16; m.p. 85–92°C; ν_{max} (film) 2999–2866 cm^{-1} (aromatic, CH) and 1638 cm^{-1} (C = O); δ_H (250 MHz, $CDCl_3$) 6.83 (2 H, s, 2 × CH; Ar; 3,5-CH), 4.21-4.10 (1 H, m, NCH), 3.58 (2 H, s, CH_2), 3.49–3.41 (1 H, m, NCH), 2.33 (3 H, s, CH_3; Ar, 4-CH_3), 2.20 (6 H, s, 2 × CH_3; Ar; 2,6-CH_3), 1.38 (6 H, d, *J* 6.7, 2 × CH_3) and 1.24 (6 H, d, *J* 6.7, 2 × CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.9 (CO), 136.6 (Ar), 135.7 (Ar), 130.7 (Ar), 128.8 (Ar), 48.5 (CNH), 46.0 (CNH), 35.7 (CHCO), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3) and 20.2 (CH_3) (Found MH^+, 262.2162. $C_{17}H_{27}NO$ requires 261.2092).

N,N-Diisopropyl-2-deuterio-2-(2,4,6-trimethylphenyl)-ethanamide **16**-d_1

In the same way as the amide **1**-d_1, amide **16** (50 mg, 0.19 mmol), *sec*-butyllithium (0.24 ml, 1.4 M in cyclohexane, 33 mmol) and deuterium oxide (11.1 mg, 10 µl, 0.55 mmol) gave the amide **16**-d_1 (36 mg, 72%); R_f [light petroleum: ether (7:3)] 0.16; ν_{max} (film) 2155 cm^{-1} (C–D) and 1636 cm^{-1} (C = O); δ_H(250 MHz, $CDCl_3$) 6.76 (2 H, s, 2 × CH; Ar; 3,5–CH), 4.14-4.03 (1 H, septet, *J* 6.8, NCH), 3.49 (1 H, s, CH), 3.42–3.32 (1 H, m, NCH), 2.17 (3 H, s, CH_3), 2.14 (6 H, s, 2 × CH_3), 1.32 (6 H, d, *J* 6.8, 2 × CH_3) and 1.17 (6 H, d, *J* 6.7, 2 × CH_3); δ_C (62.5 MHz, $CDCl_3$) 168.9 (CO), 136.6 (Ph), 135.7 (Ph), 130.7 (Ph), 128.7 (Ph), 48.4 (CHN), 46.0 (CHN), 35.4 (1 C, triplet [1:1:1], $^1J_{C,D}$ = 19.4, CD), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3) and 20.2 (CH_3); (Found MH^+, 263.2240. $C_{17}H_{26}DNO$ requires 262.2161).

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