Three approaches to the synthesis of L-leucine selectively labelled with carbon-13 or deuterium in either diastereotopic methyl group

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Three approaches to the synthesis of L-leucine selectively labelled with carbon-13 or deuterium in either diastereotopic methyl group as well as at C-3 and C-4 are described. In all three methods the stereogenic centre at C-2 was created with total stereocontrol *via* a one-pot, two-enzyme catalysed procedure involving hydrolysis and reductive amination of a 2-keto ester. However, the approaches vary in the synthesis of the isotopically labelled 2-keto esters and in the production of the stereogenic centre at C-4 which was achieved either *via* alkylation of a propionylated Evans' auxiliary with labelled iodomethane or by the diastereoselective conjugate addition of a labelled organocopper reagent to crotonate tethered to a chiral sultam. The latter approach proved most efficient and using the (1*R*,2*S*,3*R*)-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethyldiphenyl)aminobornan-2-ol ester **27**, [5-^{13}C]-L-leucine was prepared with >98% de at C-4 and in 49% overall yield from the first labelled intermediate **28**.

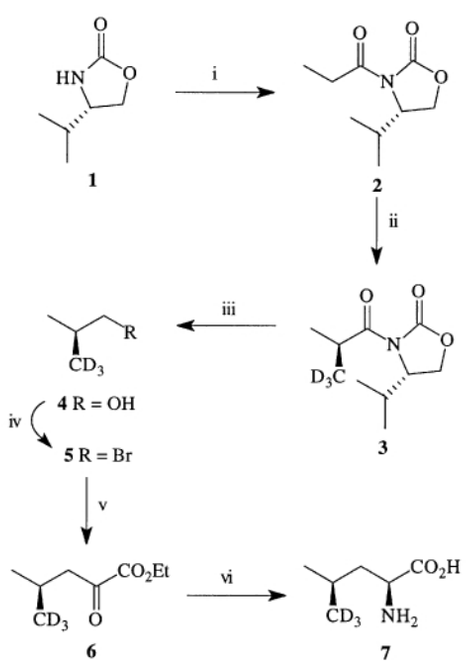
Introduction

Isotopically labelled L-amino acids serve a vital role in a variety of studies in bioorganic chemistry.[1,2] For example, the selective labelling of either diastereotopic methyl group of L-leucine has enabled the elucidation of their fate during secondary metabolic reactions.[3–7] Leucine is also important in protein tertiary structure formation due to its participation in hydrophobic interactions. Assignment of the leucine *pro-R* and *pro-S* methyl group resonances in protein NMR spectra allows more precise definition of protein structure and the study of stereochemical aspects of associated molecular recognition phenomena.[8,9] Thus several groups have investigated approaches to the synthesis of leucine selectively labelled in either diastereotopic methyl group for example *via* biosynthesis,[10,11] using chemical and enzymatic resolutions,[5,6,7,11,12] and using starting materials from the chiral pool.[13] Young and co-workers performed the first fully stereoselective synthesis of (2*S*,4*R*)-[5,5,5-$^{2}H_3$]-leucine using (2*S*)-pyroglutamic acid as a chiral template[14] and more recently a similar approach has been reported by Nishiyama and co-workers.[15] We have previously described a chemoenzymatic route for the synthesis of L-leucine selectively labelled with deuterium and/or carbon-13 in either diastereotopic methyl group.[16] Our strategy was versatile enabling the incorporation of isotopic labels at C-3 and C-4 as well as in either diastereotopic methyl group and gave total stereocontrol at C-2. However, there were technical difficulties in handling the volatile intermediates and only 86% de at C-4 was achieved. We now describe this approach in full as well as our more recent investigations which have led to the development of a new and efficient strategy for the synthesis of isotopically labelled L-leucine which not only overcomes the problems of handling volatile intermediates but also gives >98% de at C-4.

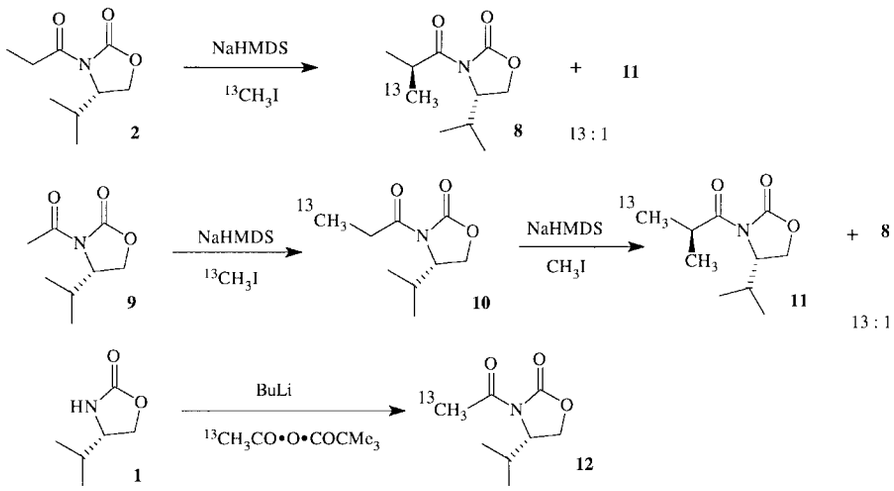
Results and discussion

Method 1. Synthesis of (2*S*,4*R*)-[5,5,5-$^{2}H_3$]leucine 7

Our initial route[16] to the synthesis of L-leucine selectively labelled with deuterium and/or carbon-13 in either diastereotopic methyl group is shown in Scheme 1. First it was necessary to create the stereogenic centre which was to become C-4 in L-leucine and this was formed *via* alkylation of the known[17,18] propionylated oxazolidinone **2** with CD_3I to give **3** (or $^{13}CH_3I$ to give **8**, Scheme 2). The optimum conditions for the reaction proved to be generation of the enolate with sodium hexamethyldisilazide (NaHMDS) and quenching with 10 equivalents of iodomethane giving the product in 90% yield. However, to minimise the quantity of expensive isotopically labelled iodomethane, further optimisation showed that 1.4 equivalents of $^{13}CH_3I$ giving 76% yield of **8** was the best compromise. The alternative diastereomer **11** was prepared from (4*S*)-3-acetyl-4-isopropyloxazolidinone **9** by an initial alkylation with $^{13}CH_3I$ followed by alkylation with iodomethane



Scheme 1 *Reagents*: i, BuLi, EtCOCl, 94%; ii, NaHMDS, CD_3I, 72%; iii, $LiAlH_4$, Et_2O; iv, Ph_3P, Br_2, $PhNO_2$; v, Mg, $(CO_2Et)_2$, Et_2O, THF, −78 °C, 14–60% from **3**; vii, CRL, leucine dehydrogenase, FDH, HCO_2NH_4, 85%.



Scheme 2

(Scheme 2). In the ^{1}H NMR spectra of **8** and **11** the signals assigned to 2′-CH_3 and 2′-$^{13}CH_3$ were well resolved due to the large ^{13}C–^{1}H coupling and integration of the signals at δ 1.22 (dd, *J* 128.3, 6.9 Hz in **8**; dd, *J* 6.9, 5.0 Hz in **11**) and at δ 1.15 (dd, *J* 6.7, 5.2 Hz in **8**; dd, *J* 127.9, 6.7 Hz in **11**) confirmed that selective alkylation of (4*S*)-3-propionyloxazolidinone had occurred giving a 13 : 1 mixture of diastereomers.

With the required stereogenic centre established, the next stage was to cleave the auxiliary and to effect a two-carbon homologation to the 2-keto ester **6**. Many methods are known for the synthesis of 2-keto esters and we favoured the reaction of a Grignard reagent with diethyl oxalate at low temperature.[19] Reduction of **3** with lithium aluminium hydride cleaved the chiral auxiliary and liberated the labelled alcohol **4** which was converted to the bromide **5** using triphenylphosphine and bromine. Both alcohol **4** (bp[20] *ca.* 108 °C) and bromide **5** (bp[20] *ca.* 91 °C) are rather volatile necessitating the use of manifold trap techniques for their efficient manipulation. Nitrobenzene was used as the solvent in the conversion of **4** to **5** so that bromide **5** could be distilled from the reaction mixture and then used immediately to form the Grignard reagent, which was reacted *in situ* with diethyl oxalate to give the 2-keto ester **6** in variable yields (14–60% from **3**).

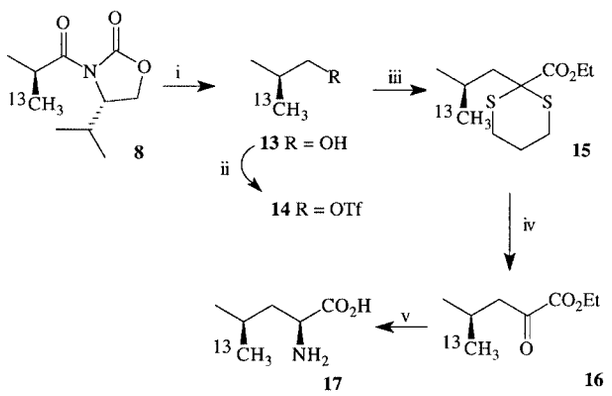
The final stages of the synthesis involved hydrolysis of the ester and the reductive amination of the resultant 2-keto acid catalysed by a commercially available amino acid dehydrogenase. These enzymes require NADH; the cofactor may be recycled efficiently *in situ* according to the protocol of Shaked and Whitesides using a second commercially available enzyme, formate dehydrogenase (FDH), with the consumption of formate ions and the evolution of carbon dioxide.[21] In our initial work[16] we converted α-keto ester **6** to the acid by saponification with sodium hydroxide. More recently we have adopted a milder procedure using a lipase isolated from *Candida rugosa* (CRL), as model reactions showed that it provides higher yields than saponification. Furthermore the reaction conditions of the lipase hydrolysis are compatible with those of the leucine dehydrogenase catalysed reductive amination.[22] Thus a one-pot dual enzyme catalysed hydrolysis of 2-keto ester **6** and reductive amination of the resultant 2-keto acid gave (2*S*,4*R*)-[5,5,5-$^2H_3$]-leucine **7** in 85% yield from **6**. The methyl region of the ^{1}H NMR spectrum of **7** displayed only the doublet corresponding to the lower frequency methyl resonance of unlabelled L-leucine; this is consistent with previous assignments of the lower frequency resonance to the 4-*pro*-*S* and the higher frequency resonance to the 4-*pro*-*R* leucine methyl groups.[12,14] The ^{13}C NMR spectrum of (2*S*,4*R*)-[5,5,5-$^2H_3$]leucine **7** showed a singlet at δ_C 20.8 due to the methyl group and a quintet at δ_C 20.7, assigned to the trideuteromethyl group. On first inspection these are confusing observations as, in common with the ^{1}H NMR spectrum, the lower frequency ^{13}C resonance has been assigned previously to the 4-*pro*-*S* and the higher frequency resonance to the 4-*pro*-*R* leucine methyl groups;[10,12,14] however, the apparent discrepancy is caused by an α-isotope shift[23] of the trideuteromethyl group resonance, as noted by Young and co-workers.[14]

In principle this approach may be used for the synthesis of the complementary diastereomer, (2*S*,4*S*)-[5,5,5-$^2H_3$]leucine by the route shown in part in Scheme 2 (using CD_3I). A more direct route would use the (+)-norephedrine derived auxiliary;[17] however we found that in this case the key alkylation step proceeds in lower yield than with the L-valine derived auxiliary **1**. Therefore for the synthesis of (2*S*,4*S*)-[5,5,5-$^2H_3$]leucine we suggest the use of the D-valine derived auxiliary (*i.e.* the enantiomer of **1**). This chemo-enzymatic approach to the synthesis of L-leucine has the further advantage that it enables the incorporation of carbon-13 at C-3 and/or C-4 using sodium [^{13}C]acetate as the source of isotopic label (Scheme 2). For example, treatment of sodium [2-^{13}C]acetate with pivaloyl chloride gives a mixed anhydride which on reaction with the lithium salt of **1** gives the acylated product **12** in 70% yield, the precursor to [4-^{13}C]-L-leucine. In addition, the approach may also be modified for the inclusion of nitrogen-15.[24]

Method 2. Synthesis of (2*S*,4*R*)-[5-^{13}C]leucine 17

When designing routes to the synthesis of expensive isotopically labelled compounds it is essential that each stage is high yielding and reproducible. Although the above approach is versatile and most of the steps are indeed high yielding and simple to perform, the route is not ideal due to the problems inherent in the preparation and purification of the volatile bromide **5**. Hence we required an alternative strategy for the two-carbon homologation of 2-methylpropanol to the key 2-keto ester. Our aim was to convert the alcohol to a good leaving group such as a sulfonate ester for coupling with the Umpolung 2-keto ester equivalent 2-ethoxycarbonyl-1,3-dithiane[25] and finally hydrolysis of the resultant dithiane.

First the carbon-13 labelled derivative **8** was converted into alcohol **13** using a two-step lithium hydroperoxide cleavage[26] – reduction sequence (Scheme 3), which gave a better yield than the direct reduction of **8** with lithium aluminium hydride and easy recovery of the Evans' auxiliary **1** by acid–base extraction after the first step. Model reactions were carried out in order to determine the best mode of activation for the hydroxy group of alcohol **13** for reaction with the salt of 2-ethoxycarbonyl-1,3-dithiane. We found that the toluene-*p*-sulfonate, methanesulfonate and *p*-bromobenzenesulfonate all proved insufficiently reactive whereas the bromide and triflate were suitable leaving groups. Given the difficulties we experienced



Scheme 3 *Reagents*: i, a, LiOH, H_2O_2; b, $LiAlH_4$, Et_2O, 88%; ii, Tf_2O, pyridine, CCl_4, 73%; iii, BuLi, CDT, 56%; iv, NBS, Me_2CO, H_2O, 80%; v, CRL, leucine dehydrogenase, FDH, HCO_2NH_4, 79%.

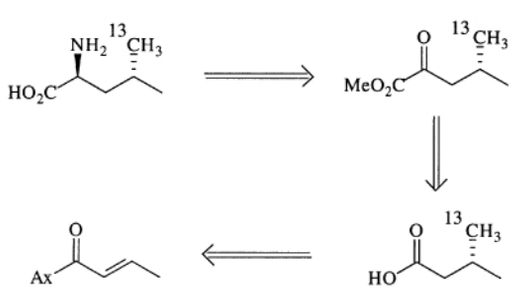
when using bromide **5** in Method 1, we chose triflate **14** as the alkylating agent. To our knowledge, the only previous example of the alkylation of a glyoxylic acid dithioacetal derivative with a triflate is found in Shiba and co-workers' synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO).[27] Treatment of alcohol **13** with triflic anhydride, pyridine and carbon tetrachloride at 0 °C gave the required triflate **14** in 73% yield. The triflate **14** was used to alkylate 2-ethoxycarbonyl-1,3-dithiane (CBT) to provide 2-ethoxycarbonyl-2-{(2*R*)-[3-^{13}C]-2-methylpropyl}-1,3-dithiane **15**. It was not necessary to fully purify **15** and oxidative hydrolysis of crude **15** with *N*-bromosuccinimide (NBS)[25,28] gave, after column chromatography, pure 2-keto ester **16** in 45% yield over the two steps.

2-Keto ester **16** was converted directly into (2*S*,4*R*)-[5-^{13}C]-leucine **17** in 79% yield, using our one-pot two-step hydrolysis–reductive amination sequence. As expected, the methyl region of the ^{1}H NMR spectrum of (2*S*,4*R*)-[5-^{13}C]leucine **17** featured two signals with the downfield signal (δ 0.95) displaying the larger coupling (*J* 125 Hz) to carbon-13. The ^{13}C NMR spectrum displayed one strongly enriched signal (δ 22.8) and, at higher field (δ 21.7), a weakly enriched signal {due to the minor diastereomer, (2*S*,4*S*)-[5-^{13}C]leucine **25**}, consistent with previous assignments of the leucine methyl groups.[10,12,14]

Method 3. (2*S*,4*S*)-[5-^{13}C]leucine 25

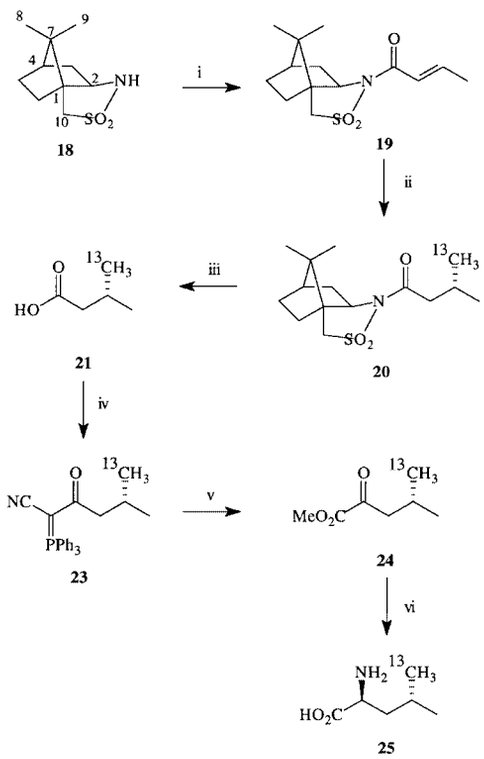
Although the second route to the synthesis of isotopically labelled L-leucine does overcome the problem of handling 1-bromo-2-methylpropane and each step of the synthesis is reliable and simple to perform, it is still not ideal. The diastereoselectivity at C-4 is only 86% and the overall yield for the synthesis of 2-keto ester **16** from the first isotopically labelled intermediate **8** is approximately 30%. Hence our third and final approach aimed to address these deficiencies and used different disconnections from the preceding two methods: the pivotal 2-keto ester came from a one-carbon homologation of labelled 3-methylbutanoic acid (isovaleric acid), itself ultimately derived from crotonic acid (Scheme 4).

We proposed to synthesise the stereoselectively labelled



Scheme 4

3-methylbutanoic acid by conjugate addition of a labelled organometallic reagent to a crotonic acid derivative, with a chiral auxiliary inducing the stereoselectivity. The application of Evans' type auxiliaries in this context is uncommon,[18,29,30] although some success has been reported both by Hruby and co-workers[31] and Williams and co-workers.[32] In contrast, Oppolzer and co-workers' camphorsultam **18** is well documented as a suitable chiral auxiliary for conjugate additions.[33] Method 3 therefore began with the crotonylation of (1*S*)-1,10-camphorsultam **18**[33b] to provide the conjugate addition substrate **19** in 84% yield (Scheme 5).

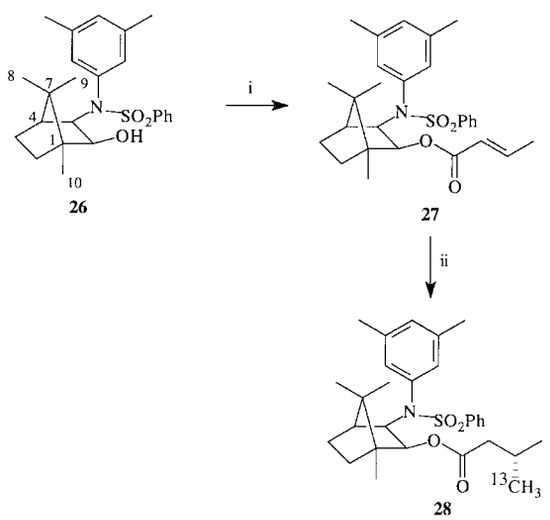


Scheme 5 *Reagents*: i, NaH, crotonyl chloride, 84%, ii, $(^{13}CH_3)_2$Cu-Li·PBu_3, 89%; iii, H_2O_2, LiOH, 93%; iv, Ph_3PCHCN **22**, EDCI, DMAP 80%; v, O_3, MeOH, CH_2Cl_2, 76%; vi, CRL, leucine dehydrogenase, FDH, HCO_2NH_4, 81%.

Oppolzer and co-workers have reported the highly diastereoselective conjugate addition of Grignard reagents and organocuprates to substrates similar to **19**.[33] However the addition of a methyl group is something of a special case: problems of 1,2 addition are suffered with Grignard reagents[33c] and low π-face discrimination with copper(I) catalysed Grignard reagents.[33e] Oppolzer and co-workers minimised these difficulties by employing phosphine stabilised Gilman reagents (3 equivalents), which give good regio- and stereo-selectivity.[33d,e] We needed to further optimise the conditions of our conjugate addition for we required not only maximum yield and maximum diastereoselectivity but also maximum isotope yield. Our investigations revealed that reduction of the quantity of Gilman reagent below 2.6 equivalents significantly lowered the reaction yield, as might be expected from inspection of the proposed mechanism.[33d] Our optimised conditions were thus treatment of chiral crotonyl derivative **19** with 2.6 equivalents of labelled Gilman reagent {prepared from [^{13}C]iodomethane, lithium metal and copper(I) iodide–tri-*n*-butylphosphine complex} at −78 °C, which gave the conjugate addition product **20** in 89% yield. The diastereoselectivity of this reaction was determined from integration of the signals assigned to 3′-CH_3 (δ 0.96, dd, *J* 6.6, 5.5 Hz) and 3′-$^{13}CH_3$ (δ 0.97, dd, *J* 125.2, 6.6 Hz) in the ^{1}H NMR spectrum which indicated that a 10:1 mixture of diastereomers (*ca.* 82% de) had been formed.

The auxiliary was cleaved with lithium hydroperoxide [33g] (and recovered in 85% yield) to liberate (*S*)-[4-^{13}C]-3-methylbutanoic acid **21** in 93% yield. The one-carbon homologation of **21** was achieved *via* formation and ozonolysis of the β-ketocyanophosphorane **23** under the conditions described by Wasserman and Ho [34] giving methyl (*S*)-[5-^{13}C]-4-methyl-3-oxopentanoate **24**. Finally the one-pot two-step enzymatic catalysed conversion of 2-keto ester **24** to (2*S*,4*S*)-[5-^{13}C]leucine **25** proceeded smoothly giving an 81% yield of pure product after ion exchange chromatography. This approach may be readily adapted to the synthesis of the complementary diastereomer (2*S*,4*R*)-[5-^{13}C]leucine **17** by starting from the commercially available (1*R*)-1,10-camphorsultam. This approach to the synthesis of either (2*S*,4*S*)- or (2*S*,4*R*)-[5-^{13}C]leucine is high yielding and each step is simple to perform and reliable. The only downside of this route was the poor diastereoselectivity at C-4; thus we sought to improve this by using a different chiral auxiliary.

Helmchen and co-workers have described the use of (1*R*,2*S*,3*R*)-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)-amino]bornan-2-ol **26** as a (commercially available) chiral auxiliary for conjugate addition reactions.[35] Acylation of chiral auxiliary **26** with crotonyl chloride [35b] gave enoate **27** in 81% yield (Scheme 6). As in the case of the Oppolzer auxiliary, we



Scheme 6 *Reagents*: i, Crotonyl chloride, molecular sieves, 81%; ii, $^{13}CH_3Cu{\cdot}BF_3$, 79%.

wished to optimise the conjugate addition conditions to produce maximum de and minimum isotopic label wastage. Following Helmchen and Wegner we employed the Yamamoto reagent,[36,37] $^{13}CH_3Cu{\cdot}BF_3$, in 7-fold excess (a 5-fold excess dramatically reduced the yield), derived from the organolithium with ether as solvent.[35a] Our optimum conditions gave the conjugate addition product **28** in 79% yields; inclusion of tri-*n*-butylphosphine (to dissolve and stabilise the Yamamoto reagent) [36,38] gave a similar result. NMR spectroscopy (in deuterochloroform, deuteroacetone or deuterobenzene) failed to detect the minor diastereomer (NMR spectroscopy of the conjugate addition product formed under sub-optimum reaction conditions revealed that the signals from each diastereomer's 3′-CH_3 and 3′-$^{13}CH_3$ are partially resolved) so we have achieved our objective and increased the de of the conjugate addition to above 98%.

The auxiliary was cleaved with aqueous potassium hydroxide in methanol [35a] (and recovered in 93% yield) to liberate (*R*)-[4-^{13}C]-3-methylbutanoic acid in quantitative yield. Thus, using Helmchen's auxiliary, we have improved Method 3 to produce a synthesis of (2*S*,4*R*)-[5-^{13}C]leucine **17** with greater than 98% de and 39% overall yield from the first labelled intermediate **28**. The complimentary diastereomer may be synthesised starting from the commercially available auxiliary (1*R*,2*R*,3*S*)-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanol.[35a]

Conclusions

We have described three enantioselective syntheses of L-leucine that permit the selective labelling of either diastereotopic methyl group with carbon-13 or deuterium. These routes are extremely versatile and allow incorporation of isotopic labels at other sites and the appropriate method may be chosen for maximum de or maximum isotope yield. We consider the conjugate addition route (Method 3 using Helmchen's auxiliary) the best of our three methods due to its comparative simplicity, high yields and excellent de.

Experimental

General experimental details have been described previously.[39] Cuprate reactions were conducted under argon. Copper(I) iodide was purified according to Taylor and Casy.[40] Copper(I) iodide–tri-*n*-butylphosphine complex was prepared according to the procedures of Taylor and Casy [40] and Kauffman and Teter [41] from purified copper(I) iodide and freshly distilled tri-*n*-butylphosphine in 66% yield; mp 74–75 °C (lit.,[41] 75 °C). All NMR spectra were run in $CDCl_3$ unless otherwise stated. *J* values are in Hz. $[\alpha]_D$ has units of 10^{-1} deg cm^2 g^{-1}. The enzymes were purchased and stored as follows: lipase from *Candida rugosa* (CRL), Sigma, stored at 4 °C as a 10000 eU ml^{-1} solution in tris buffer (5 mM); formate dehydrogenase (FDH) from *Candida boidinii*, Boerhinger, stored at 4 °C; leucine dehydrogenase from *Bacillus* species, Sigma, stored at −20 °C; β-nicotinamide adenine dinucleotide hydride (NADH), Genzyme, stored at −20 °C.

General procedure for the one-pot hydrolysis and reductive amination of 2-keto esters

Potassium phosphate buffer (5 mM, 25 mL per mmol of substrate) was deoxygenated by bubbling through nitrogen for 0.5 h. CRL (10000 eU per mmol of substrate) and the keto ester (1 eq.) in ethanol (1 mL per mmol of substrate) were added and the reaction mixture stirred at rt, maintaining the pH between 7.0 and 8.5 by the periodic addition of sodium hydroxide (1.0 or 0.1 M). Once the pH had stopped changing (*ca.* 5 h, *ca.* 1 eq. of sodium hydroxide having been added), ammonium formate (10 eq.), 1 M dithiothreitol (DTT) (1 μL per mmol of substrate), formate dehydrogenase (8 mg, 4 eU for less or 16 mg, 8 eU for more than 3 mmol of substrate), NADH (8 mg, 12 μmol for less or 16 mg, 24 μmol for more than 3 mmol of substrate) and leucine dehydrogenase (5 eU for less or 10 eU for more than 3 mmol of substrate) were added. The resultant solution was stirred at rt and maintained between pH 7.0 and 7.5 by the periodic addition of hydrochloric acid (1.0 or 0.1 M) until the pH remained static (*ca.* 7 days, *ca.* 0.8 eq. of hydrochloric acid having been added). The reaction mixture was concentrated *in vacuo* and the product isolated by ion exchange chromatography on Dowex® 50WX8-100 (20 g per mmol of substrate), eluting first with water (3 × 40 mL per mmol of substrate) then conc. ammonia (2 × 100 mL per mmol of substrate). The conc. ammonia eluent was evaporated to dryness to yield the pure α-amino acid.

(4*S*)-4-Isopropyl-3-{(2*R*)-[3,3,3-$^2H_3$]-2-methylpropanoyl}-oxazolidin-2-one 3. A solution of (4*S*)-4-isopropyl-3-propanoyloxazolidin-2-one **2** (558 mg, 3.0 mmol) in THF (6 mL) was added dropwise to a stirred solution of sodium hexamethyldisilazide (1.0 M in THF, 3.3 mL, 3.3 mmol) in THF (15 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h then [$^2H_3$]-iodomethane (0.37 mL, 6.0 mmol) was added

dropwise. The reaction mixture was stirred at −78 °C for 4 h then sat. ammonium chloride solution (15 mL) and water (6 mL) were added and the aqueous phase acidified to pH 2 with sulfuric acid. The product was extracted with ethyl acetate (3 × 60 mL). The combined extracts were washed successively with sat. sodium hydrogen carbonate solution (15 mL), sodium thiosulfate solution (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an oil. The product was purified by column chromatography eluting with 2–10% ethyl acetate in light petroleum to afford a 13 : 1 mixture of (4*S*)-4-isopropyl-3-{(2*R*)-[3,3,3-$^2H_3$]-2-methylpropanoyl}oxazolidin-2-one **3** and (4*S*)-4-isopropyl-3-{(2*S*)-[3,3,3-$^2H_3$]-2-methylpropanoyl}oxazolidin-2-one (437 mg, 72%) as a pale yellow oil; $[\alpha]_D$ +94.6 (*c* 4.1 in CH_2Cl_2) [lit.,[42] unlabelled material +94.2 (*c* 1.1 in CH_2Cl_2)]; δ_H (270 MHz) 0.88 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 0.91 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 1.15, 1.22 [3 H, 2 × (d, *J* 6.8), major and minor diastereomer CH_3CHCO respectively], 2.34 [1 H, septet d, *J* 7.0 and 4.0, $CH(CH_3)_2$], 3.76 (1 H, br q, *J* 6.8, CHCO), 4.20 (1 H, dd, *J* 9.0 and 3.3, CH_2O), 4.28 (1 H, dd, *J* 9.0 and 8.2, CH_2O) and 4.45 (1H, ddd, *J* 8.2, 4.0 and 3.3, CHN); δ_C 14.2 [$(CH_3)_2CH$], 17.3 [$(CH_3)_2CH$], 18.3 (CH_3CHCO), 19.1 (quin, *J* 20, CD_3), 28.0 [$CH(CH_3)_2$], 31.8 (*C*HCO), 58.1 (CHN), 62.9 (CH_2O), 153.2 (NCO_2) and 176.9 (CON); *m*/*z* 202 (M^+, 20%, 97% incorporation of three deuteriums), 159 (14), 130 (27), 86 (24), 74 (100) and 58 (60).

The above reaction was repeated using [^{13}C]iodomethane as the electrophile to give a 13 : 1 mixture of (4*S*)-4-isopropyl-3-{(2*R*)-[3-^{13}C]-2-methylpropanoyl}oxazolidin-2-one **8** and (4*S*)-4-isopropyl-3-{(2*S*)-[3-^{13}C]-2-methylpropanoyl}oxazolidin-2-one **11** as a pale yellow oil; $[\alpha]_D$ +89.9 (*c* 5.0 in CH_2Cl_2); δ_H (500 MHz) 0.88 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 0.91 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 1.15 (0.2 H, dd, *J* 127.9 and 6.9, **11** $^{13}CH_3$), 1.15 (2.8 H, dd, *J* 6.9 and 5.2, **8** $CHCH_3{}^{13}CH_3$), 1.22 (2.8 H, dd, *J* 128.3 and 6.9, **8** $^{13}CH_3$), 1.22 (0.2 H, dd, *J* 6.9 and 5.0, **11** $CHCH_3{}^{13}CH_3$), 2.34 [1 H, septet d, *J* 7.0 and 4.0, $CH(CH_3)_2$], 3.79 (1 H, septet d, *J* 6.9 and 5.0, $CHCH_3{}^{13}CH_3$), 4.20 (1 H, dd, *J* 9.2 and 3.1, CH_2O), 4.27 (1 H, dd, *J* 9.2 and 8.4, CH_2O), and 4.45 (1 H, ddd, *J* 8.4, 4.0 and 3.1, CHN); δ_C 14.6 [$CH(CH_3)_2$], 17.8 [$CH(CH_3)_2$], 18.2 ($CHCH_3{}^{13}CH_3$), 19.5 ($CHCH_3{}^{13}CH_3$), 28.3 [$CH(CH_3)_2$], 32.5 (d, *J* 34, $CHCH_3{}^{13}CH_3$), 58.3 (CHN), 63.2 (CH_2O), 153.6 (NCO_2) and 177.5 (d, *J* 2, CON); *m*/*z* 200 (M^+, 24%, 93% incorporation of carbon-13), 185 (5), 157 (14), 130 (52), 86 (44), 78 (15), 72 (100) and 58 (66).

The above reaction was repeated using (4*S*)-4-isopropyl-3-{[3-^{13}C]propanoyl}oxazolidin-2-one **10** and iodomethane giving a 13 : 1 mixture of (4*S*)-4-isopropyl-3-{(2*S*)-[3-^{13}C]-2-methylpropanoyl}oxazolidin-2-one **11** and (4*S*)-4-isopropyl-3-{(2*R*)-[3-^{13}C]-2-methylpropanoyl}oxazolidin-2-one **8** as a pale yellow oil; $[\alpha]_D$ +84.0 (*c* 3.5 in $CHCl_3$); δ_H (500 MHz) 0.88 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 0.91 [3 H, d, *J* 7.0, $(CH_3)_2CH$], 1.15 (2.8 H, dd, *J* 128.3 and 6.9, **11** $^{13}CH_3$), 1.15 [0.2 H, dd, *J* 6.9 and 5.0, **8** $CH_3(^{13}CH_3)CH$], 1.22 (0.2 H, dd, *J* 127.9 and 6.9, **8** $^{13}CH_3$), 1.22 [2.8 H, dd, *J* 6.9 and 5.2, **11** $CH_3(^{13}CH_3)CH$], 2.34 [1 H, septet d, *J* 7.0 and 4.0, $CH(CH_3)_2$], 3.79 (1 H, septet d, *J* 6.9 and 5.0, $CHCH_3{}^{13}CH_3$), 4.20 (1 H, dd, *J* 9.2 and 3.1, C*H*HO), 4.27 (1 H, dd, *J* 9.2 and 8.4, CH*H*O), and 4.45 (1 H, ddd, *J* 8.4, 4.0 and 3.1, CHN); δ_C 14.6 [$(CH_3)_2CH$], 17.8 [$(CH_3)_2CH$], 18.2 ($CHCH_3{}^{13}CH_3$), 19.6 ($CHCH_3{}^{13}CH_3$), 28.4 [$CH(CH_3)_2$], 32.5 (d, *J* 34.9, $CHCH_3{}^{13}CH_3$), 58.3 (CHN), 63.2 (CH_2O), 153.6 (NCO_2) and 177.5 (d, *J* 1.5, CON); *m*/*z* 200 (M^+, 18%, 87% incorporation of carbon-13), 173 (3), 157 (15) 130 (52), 86 (42), 72 (100) and 58 (60).

Ethyl (4*R*)-[5,5,5-$^2H_3$]-4-methyl-2-oxopentanoate 6. A solution of (4*S*)-4-isopropyl-3-{(2*R*)-[3,3,3-$^2H_3$]-2-methylpropanoyl}oxazolidin-2-one **3** (1.01 g, 5.0 mmol) in ether (5 mL) was added to a suspension of lithium aluminium hydride (380 mg, 10 mmol) in ether (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h then water (1 mL) was added carefully. The resultant mixture was filtered through a sinter funnel containing Celite, silica and magnesium sulfate, eluting with ether (100 mL). The filtrate was carefully concentrated *in vacuo* to *ca.* 10 mL. The product **4** and ether were distilled using a high vacuum manifold leaving behind the chiral auxiliary **1** (416 mg, 64%). The distillate was carefully concentrated *in vacuo* giving (2*R*)-[3,3,3-$^2H_3$]-2-methylpropanol **4** as a colourless liquid. Bromine (0.26 mL, 5.0 mmol) was added dropwise to a solution of triphenylphosphine (1.31 g, 5.0 mmol) in nitrobenzene (25 mL). The bromine colour disappeared almost immediately, giving a yellow solution from which a white solid precipitated after *ca.* 5 min. A solution of the (2*R*)-[3,3,3-$^2H_3$]-2-methylpropanol **4** in nitrobenzene (1 mL) was added and the flask was then connected to a trap at −78 °C and heated to 80 °C for 1 h, giving an orange solution. The reaction mixture was cooled to rt and quinoline (0.59 mL, 5.0 mmol) was added. The reaction mixture was stirred at rt for 15 min. The crude (2*R*)-[3,3,3-$^2H_3$]-2-methylpropyl bromide **5** was distilled into a trap (−196 °C) under reduced pressure (0.04 mmHg). The distillate was redistilled under reduced pressure through a phosphorus pentoxide bulb and into a collection flask. THF (4 mL) was immediately added to the flask and the solution was warmed to rt. This solution of bromide **5** was added to vigorously stirred magnesium turnings (140 mg, 5.8 mmol). The Grignard reaction was heated under reflux for 10 minutes then added to a solution of diethyl oxalate (0.54 ml, 4.0 mmol) in ether (10 mL) and THF (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 5 h then sat. ammonium chloride solution (4 mL) was added. The mixture was acidified to pH 2 with 1 M hydrochloric acid and the product extracted with ether (3 × 15 mL). The combined extracts were washed successively with sat. sodium hydrogen carbonate solution (4 mL) and brine (4 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The product was purified by column chromatography, eluting with 1% ethyl acetate in light petroleum, to give ethyl (4*R*)-[5,5,5-$^2H_3$]-4-methyl-2-oxopentanoate **6** (175 mg, 22%) as a colourless oil; $[\alpha]_D$ +2.1 (*c* 1.0 in $CHCl_3$) (lit. data on unlabelled material[43,44]); δ_H (270 MHz) 0.89 (3 H, d, *J* 6.8, CH_3CH), 1.30 (3 H, t, *J* 7.1, OCH_2CH_3), 2.09 (1 H, m, 4-H), 2.64 (2 H, d, *J* 6.8, 3-H_2), and 4.24 (2 H, q, *J* 7.1, OCH_2CH_3); δ_C (68 MHz) 13.9 (OCH_2CH_3), 21.3 (quin, *J* 19, CD_3), 22.3 (CH_3CH), 23.9 (C-4), 47.7 (C-3), 62.3 (OCH_2), 161.3 (C-1), and 194.4 (C-2); *m*/*z* 161 (M^+, 3%, 97% incorporation of 3 deuterium atoms), 116 (2), 97 (44), 88(44), 85 (50), 71 (72), 60 (39) and 57 (100).

(2*S*,4*R*)-[5,5,5-$^2H_3$]Leucine 7. The reaction was carried out as described in the general procedure using ethyl (*R*)-[5,5,5-$^2H_3$]-2-oxo-4-methylpentanoate **6** (79 mg, 0.49 mmol) and ammonium formate (63 mg, 1.0 mmol). Purification by ion exchange chromatography gave (2*S*,4*R*)-[5,5,5-$^2H_3$]leucine **7** (56 mg, 85%) as a white solid; $[\alpha]_D$ +12.5 (*c* 1.0 in 1 M HCl) [lit.,[12] (2*R*,4*S*)-diastereomer $[\alpha]_D$ −12.8 (*c* 0.47 in 6 M HCl)]; δ_H (500 MHz, D_2O) 0.87 (3 H, d, *J* 6.4, CH_3), 1.66 (2 H, m, 3-H_2), 1.76 (1 H, m, 4-H) and 3.97 (1 H, dd, *J* 8.1 and 6.4, C*H*NH_2); δ_C [68 MHz, D_2O + $(CD_3)_2CO$] 20.7 (quin, *J* 19, CD_3), 20.8 (CH_3), 23.6 (C-4), 38.7 (C-3), 51.3 (C-2), and 172.5 (C-1); *m*/*z* 134 (M^+, 3%, 96% incorporation of 3 deuterium atoms), 117 (1), 89 (100) and 74 (39).

(4*S*)-4-Isopropyl-3-{[3-^{13}C]propanoyl}oxazolidin-2-one 10. A solution of sodium hexamethyldisilazide (1.0 M in THF, 1.1 ml, 1.1 mmol) was added to a stirred solution of (4*S*)-3-acetyl-4-isopropyloxazolidin-2-one **9** (345 mg, 2.0 mmol) in 1,2-dimethoxyethane (4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min. [^{13}C]Iodomethane (0.25 mL, 4.0 mmol) was added dropwise and the reaction mixture stirred at −78 °C for 3 h. Sat. ammonium chloride solution (5 mL) and water (2 mL) were added and the aqueous phase acidified to pH 2 with sulfuric acid (1 M). The product was extracted with ethyl

acetate (3 × 20 mL). The combined organic extracts were washed with sat. sodium hydrogen carbonate solution (5 mL), sodium thiosulfate solution (5 mL) and brine (5 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow oil. The crude product was purified by column chromatography to give (4*S*)-4-isopropyl-3-{[3-^{13}C]propanoyl}-oxazolidin-2-one **10** (203 mg, 54%) as a pale yellow oil; $[\alpha]_D$ +94.5 (*c* 4.0 in CH_2Cl_2) [lit.,[17] unlabelled material +96.8 (*c* 8.7 in CH_2Cl_2)]; δ_H (500 MHz) 0.88 [3 H, d, *J* 6.8, $(CH_3)_2CH$], 0.92 [3 H, d, *J* 6.8, $(CH_3)_2CH$], 1.17 (3 H, dt, *J* 128.3 and 7.3, $^{13}CH_3CH_2$), 2.38 [1 H, septet d, *J* 7.3 and 3.9, $CH(CH_3)_2$], 2.91 (1 H, ddq, *J* 17.7, 7.3 and 4.4, $^{13}CH_3CH_2$) 2.98 (1 H, ddq, *J* 17.7, 7.3 and 4.4, $^{13}CH_3CH_2$), 4.22 (1 H, dd, *J* 9.1 and 3.0, CH_2O), 4.27 (1 H, dd, *J* 9.1 and 8.3, CH_2O) and 4.44 (1 H, ddd, *J* 8.3, 3.8 and 3.0, CHN); δ_C 8.4 ($^{13}CH_3$), 14.6 (CH_3), 17.9 (CH_3), 28.3 [$CH(CH_3)_2$], 29.1 (d, *J* 35.2, $^{13}CH_3CH_2$), 58.3 (CHN), 63.3 (CH_2O), 154.1 (NCO_2) and 174.0 (d, *J* 3.1, CON); *m*/*z* 186 (M^+, 7%, 88% incorporation of carbon-13), 143 (17), 113 (13), 85 (9), 71 (19) and 58 (100).

2-Ethoxycarbonyl-2-{(2*R*)-[3-^{13}C]-2-methylpropyl}-1,3-dithiane 15. Hydrogen peroxide solution (30%, 5.9 mL, 52 mmol) and lithium hydroxide monohydrate [875 mg, 21 mmol, in water (25 mL)] were added successively to a solution of (4*S*)-4-isopropyl-3-{(2*R*)-[3-^{13}C]-2-methylpropanoyl}oxazolidin-2-one **8** (2.61 g, 13 mmol) in THF (50 mL) and water (25 mL) at 0 °C. After 2 h sodium sulfite [6.5 g in water (25 mL)] was added and the solution stirred at 0 °C for a further 15 min. The solution was adjusted to pH 9–10 with sat. sodium hydrogen carbonate solution, the THF evaporated and the residual aqueous solution extracted with dichloromethane (2 × 125 mL). The organic extracts were dried over sodium sulfate and evaporated to yield (4*S*)-4-isopropyloxazolidin-2-one **1** (1.50 g, 89%).

The aqueous solution was adjusted to pH 1–2 with 1 M sulfuric acid and extracted with ether (3 × 125 mL). The combined extracts were dried over sodium sulfate and evaporated to yield (2*R*)-[3-^{13}C]-2-methylpropanoic acid[45] (1.27 g, quantitative) as a colourless liquid; δ_H 1.20 (3 H, dd, *J* 128.1 and 7.0, $^{13}CH_3$), 1.20 (3 H, dd, *J* 7.0 and 5.2, CH_3), 2.59 (1 H, septet d, *J* 7.0 and 4.6, CH) and 5.96 (br s, CO_2H); δ_C 18.7 ($^{13}CH_3$), 33.8 (d, *J* 34, CH) and 183.4 (CO_2H).

A solution of (2*R*)-[3-^{13}C]-2-methylpropanoic acid (1.16 g, 13.0 mmol) in ether (25 mL) was added dropwise to a stirred slurry of lithium aluminium hydride (0.99 g, 26 mmol) in ether (40 mL) at 0 °C and the resultant mixture stirred at 0 °C for 6 h. Water (6 mL) was added slowly to the mixture and the pH of the resultant grey slurry adjusted to 2–3 with 1 M sulfuric acid. The layers were separated and the aqueous layer extracted with ether (4 × 65 mL). The combined organic extracts were washed with 1 M sodium hydrogen carbonate solution (120 mL), dried over magnesium sulfate and filtered. This solution was distilled (50 °C, atmospheric pressure) to yield, as the residue, a mixture of (2*R*)-[3-^{13}C]-2-methylpropan-1-ol **13** (861 mg, 88%, calculated from the ^{1}H NMR spectrum) and ether as a colourless liquid (lit. data on deuterated material[46]), δ_H (270 MHz) 0.91 (3 H, dd, *J* 124.8 and 6.7, $^{13}CH_3$), 0.91 (3 H, dd, *J* 6.8 and 5.3, CH_3), 1.21 (9 H, t, *J* 7.0, ether CH_3), 1.75 (1 H, nonet d, *J* 6.6 and 3.7, CH), 2.76 (1 H, br s, OH), 3.37 (2 H, dd, *J* 6.5 and 3.8, CH_2) and 3.48 (6 H, q, *J* 7.0, ether CH_2).

A solution of (2*R*)-[3-^{13}C]-2-methylpropan-1-ol **13** [*ca.* 625 mg, *ca.* 8.3 mmol, carried through from the preceding step in ether–deuterochloroform (*ca.* 3 mL)] and pyridine (1.2 mL, 15 mmol) in carbon tetrachloride (17 mL) was added dropwise over *ca.* 40 min to a stirred solution of trifluoromethanesulfonic anhydride (2.4 mL, 14 mmol) in carbon tetrachloride (13 mL) at 0 °C. The resultant solution was stirred at 0 °C for a total of 55 min then water (30 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL), the combined organic extracts dried over magnesium sulfate, filtered and evaporated until just dry, to yield crude (2*R*)-[3-^{13}C]-2-methylpropyl trifluoromethanesulfonate **14** (1.26 g, *ca.* 73%) as a cloudy brown oil (lit. data on unlabelled material[47]), δ_H (270 MHz) 1.03 (3 H, dd, *J* 126.4 and 6.7, $^{13}CH_3$), 1.03 (3 H, dd, *J* 6.6 and 5.1, CH_3), 2.13 (1 H, nonet d, *J* 6.7 and 4.1, CH) and 4.31 (2 H, ddd, *J* 6.4, 3.8 and 0.5, CH_2).

A solution of 2-ethoxycarbonyl-1,3-dithiane (0.96 mL, 6.1 mmol) in THF (2.5 mL) was added dropwise to *n*-butyllithium (2.8 mL, 2.44 M solution in hexanes) in THF (5 mL) at −78 °C for 20 min. Crude (2*R*)-[3-^{13}C]-2-methylpropyl trifluoromethanesulfonate **14** (1.26 g, *ca.* 6.1 mmol) was added dropwise and the mixture stirred at −78 °C for 15 min then at rt overnight. Sat. sodium hydrogen carbonate solution (50 mL) was added and the mixture extracted with ethyl acetate (5 × 60 mL). The combined organic extracts were washed successively with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated. Column chromatography of the resultant yellow oil with 1–5% ethyl acetate–light petroleum as eluent yielded pure 2-ethoxycarbonyl-2-{(2*R*)-[3-^{13}C]-2-methylpropyl}-1,3-dithiane **15** (820 mg, 56%) as a colourless oil; δ_H (270 MHz) 0.94 (3 H, dd, *J* 125.1 and 6.4, $^{13}CH_3$), 0.94 (3 H, dd, *J* 6.5 and 5.4, $CHCH_3$), 1.33 (3 H, t, *J* 7.1, OCH_2CH_3), 1.86 (1 H, dtt, *J* 14.0, 12.5 and 3.3, $SCH_2CH^{ax}H$), 1.94–2.06 (3 H, m, 3-H_2 and 4-H), 2.14 (1 H, dtt, *J* 14.0, 4.5 and 2.5, $SCH_2CH^{eq}H$), 2.65 (2 H, ddd, *J* 14.5, 4.5 and 3.3, 2 × $SCH^{eq}H$), 3.26 (2 H, ddd, *J* 14.5, 12.5 and 2.5, 2 × $SCH^{ax}H$) and 4.24 (2 H, q, *J* 7.1, $CO_2CH_2CH_3$); δ_C 14.1 (CH_2CH_3), 23.7 ($^{13}CH_3$ and CH_3), 24.8 (SCH_2CH_2), 25.2 (d, *J* 35, C-4), 27.9 (SCH_2), 47.0 (C-3), 53.1 (d, *J* 3, CS_2), 61.8 (OCH_2CH_3) and 171.4 (CO); followed by mixed fractions containing both **15** (319 mg, 21%) and 2-ethoxycarbonyl-1,3-dithiane, then pure 2-ethoxycarbonyl-1,3-dithiane.

Ethyl (4*R*)-[5-^{13}C]-4-methyl-2-oxopentanoate 16. A solution of 2-ethoxycarbonyl-2-{(2*R*)-[3-^{13}C]-2-methylpropyl}-1,3-dithiane **15** (299 mg, 1.2 mmol) in acetone (4 mL) was added dropwise over *ca.* 5 min to a solution of *N*-bromosuccinimide (2.2 g, 12 mmol) in acetone (30 mL) and water (1.5 mL) at −5 °C and the solution stirred at −5 °C for a further 5 min. Sat. sodium sulfite solution (40 mL) was added and the solution extracted with light petroleum–dichloromethane (1:1, 3 × 40 mL). The combined organics were washed successively with 1 M sodium hydrogen carbonate solution (40 mL), water (40 mL) and brine (40 mL), dried over magnesium sulfate, filtered and evaporated to yield ethyl (4*R*)-[5-^{13}C]-4-methyl-2-oxopentanoate **16** (150 mg, 80%), as a colourless oil; δ_H 0.97 (3 H, dd, *J* 125.4 and 6.7, $^{13}CH_3$), 0.97 (3 H, dd, *J* 6.6 and 5.4, $CHCH_3$), 1.37 (3 H, t, *J* 7.2, OCH_2CH_3), 2.15–2.25 (1 H, m, 4-H), 2.72 (2 H, dd, *J* 6.9 and 4.1, 3-H_2) and 4.32 (2 H, q, *J* 7.2, OCH_2CH_3); δ_C 14.0 (OCH_2CH_3), 22.4 ($^{13}CH_3$), 24.1 (d, *J* 29, C-4), 47.8 (C-3), 62.3 (OCH_2CH_3), 161.3 (C-1) and 194.4 (C-2).

(2*S*,4*R*)-[5-^{13}C]Leucine 17. The reaction was carried out as described in the general procedure using ethyl (4*R*)-[5-^{13}C]-4-methyl-2-oxopentanoate **16** (340 mg, 2.1 mmol). Purification by ion-exchange chromatography gave (2*S*,4*R*)-[5-^{13}C]leucine **17** (220 mg, 79%), as an off-white solid; mp 280–285 °C (decomp.) (lit.,[20] unlabelled leucine 293–295 °C); $[\alpha]_D$ +11.3 (*c* 1.56 in 6 M HCl) [lit.,[48] unlabelled leucine + 15.2 (*c* 1.58 in 6 M HCl)]; δ_H (400 MHz, D_2O) 0.94 (3 H, br t, *J* 5.5, CH_3), 0.95 (3 H, dd, *J* 125.1 and 5.7, $^{13}CH_3$), 1.63–1.77 (3 H, m, 3-H_2 and 4-H) and 3.71 (1 H, m, 2-H); δ_C (D_2O) 21.7 (slightly enriched CH_3), 22.8 (enriched CH_3), 25.0 (d, *J* 35, C-4), 40.6 (C3), 54.2 (d, *J* 3, C-2) and 176.3 (C-1); *m*/*z* (CI, aqueous methanolic solution) 133 [$(M + H)^+$, 133.1057, $C_5{}^{13}CH_{14}NO_2$ requires 133.1058, 28%] and 87 (100).

[^{13}C]Methyllithium. A solution of [^{13}C]iodomethane (6.0 g, 42 mmol) in ether (26 mL) was added slowly to stirred lithium

metal (wire, 1% sodium, freshly cut into small pieces and washed with light petroleum, 787 mg, 113 mmol) floating on ether (4 mL), at 0 °C, under an argon atmosphere. Effervescence occurred during the addition. The reaction mixture was stirred under an argon atmosphere at 0 °C for 30 min and then at rt for 4.5 h. The resultant [^{13}C]methyllithium solution was left to settle (stored in a refrigerator) and its concentration (1.25 M) determined by quenching an aliquot (100 μL) with 0.1 M hydrochloric acid (5 mL) and back titration with 0.0926 M sodium hydroxide (phenolphthalein).

(1*S*)-*N*-{(3*R*)-[4-^{13}C]-3-Methylbutanoyl}-1,10-camphorsultam 20. A solution of [^{13}C]methyllithium (0.46 M solution in Et_2O, 30.9 mL, 18.4 mmol) in ether (37 mL) was added dropwise to a stirred solution of copper(I) iodide–tri-*n*-butylphosphine complex (3.62 g, 9.2 mmol) in toluene (25 mL) at −5 °C. During the addition the reaction mixture became bright yellow then faded until colourless. The solution was stirred at −5 °C for 0.5 h, then cooled to −78 °C. A solution of (1*S*)-*N*-(*E*)-crotonyl-1,10-camphorsultam **19**[49] (1.06 g, 3.5 mmol) in toluene (40 mL) was added slowly to the homocuprate solution (during the addition the reaction mixture turned yellow again) and the resultant mixture was stirred at −78 °C for 6 h. The reaction was quenched at −78 °C with a suspension of sat. ammonium chloride (40 mL) in THF (40 mL) and warmed to rt. The layers were separated and the aqueous layer extracted with ether (3 × 50 mL). The combined organic extracts were washed with sat. ammonium chloride solution (30 mL), dried over magnesium sulfate, filtered and evaporated. Column chromatography of the resultant cloudy white oil yielded a 10 : 1 mixture of (1*S*)-*N*-{(3*S*)-[4-^{13}C]-3-methylbutanoyl}-1,10-camphorsultam **20** and (1*S*)-*N*-{(3*R*)-[4-^{13}C]-3-methylbutanoyl}-1,10-camphorsultam (1.0 g, 89%) as a white solid; mp 126–127 °C (lit.,[50] unlabelled material 129–130 °C); $[\alpha]_D$ −88.57 (*c* 1.18 in $CHCl_3$) [lit.,[50] unlabelled material −89.16 (*c* 1.14 in $CHCl_3$)]; δ_H (400 MHz) 0.95–0.99 (6 H, overlapping signals, 8-H_3 or 9-H_3 and CHCH_3), 0.96 (0.5 H,† dd, *J* 125.2 and 6.6, $^{13}CH_3$ minor diastereomer), 0.97 (3 H, s, CH_3), 0.97 (2.5 H,† dd, *J* 125.2 and 6.8, $^{13}CH_3$ major diastereomer), 1.16 (3 H, s, 8-H_3 or 9-H_3), 1.32–1.44 (2 H, m, 5-H and 6-H), 1.87–1.96 (3 H, m, 4-H, 5-H and 6-H), 2.08–2.10 (2 H, m, 3-H_2), 2.23 (1 H, nonet d, *J* 6.8 and 3.8, C*H*CH_3), 2.52 (1 H, ddd, *J* 15.6, 6.8 and 3.4, COC*H*H), 2.66 (1 H, ddd, *J* 15.7, 7.1 and 4.6, COCH*H*), 3.43 (1 H, d, *J* 13.9, 10-*H*H), 3.49 (1 H, d, *J* 13.9, 10-H*H*) and 3.88 (1 H, t, *J* 6.4, 2-H); δ_C (100 MHz) 19.9, 20.8 (C-8 and C-9), 22.3 (slightly enriched CH_3), 22.3 (enriched CH_3), 25.6 (d, *J* 35, *C*HCH_3), 26.5, 32.9 (C-5 and C-6), 38.6 (C-3), 44.2 (CO*C*H_2), 44.7 (C-4), 47.7, 48.3 (C-1 and C-7), 53.1 (C-10), 65.2 (C-2) and 171.5 (CO); *m*/*z* 300 (M^+, 300.1574, $C_{14}{}^{13}CH_{25}NO_3S$ requires 300.1589, 3%), 285 (1), 257 (22), 151 (12), 135 (25), 134 (25), 108 (17), 93 (16), 86 (100) and 58 (57).

(*S*)-[4-^{13}C]-3-Methylbutanoic acid 21. Hydrogen peroxide solution (30%, 3.3 mL, 29 mmol) and lithium hydroxide monohydrate (816 mg, 19 mmol) were added successively to a solution of (1*S*)-*N*-{(3*S*)-[4-^{13}C]-3-methylbutanoyl}-1,10-camphorsultam **20** (3.65 g, 9.7 mmol) in THF (9 mL) and water (3 mL) at 0 °C. After stirring for 2 h at 0 °C and overnight at rt, the solution was cooled to 0 °C, sodium sulfite [3.7 g in water (20 mL)] was added and the solution stirred at 0 °C for a further 15 min. The solution was adjusted to pH 9–10 with sat. sodium hydrogen carbonate solution, the THF evaporated and the residual aqueous solution extracted with dichloromethane (2 × 100 mL). The organic extracts were dried over sodium sulfate and evaporated to yield crude (1*S*)-1,10-camphorsultam **18** (1.77 g, 85%). The aqueous solution was adjusted to pH 1–2 with 1 M sulfuric acid and extracted with ether (3 × 40 mL). The combined extracts were dried over sodium sulfate and evaporated to yield (*S*)-[4-^{13}C]-3-methylbutanoic acid **21**[51] (930 mg, 93%) as a colourless liquid; δ_H (270 MHz) 0.99 (3 H, dd, *J* 6.6 and 5.3, CH_3), 0.99 (3 H, dd, *J* 125.2 and 6.6, $^{13}CH_3$), 2.05–2.17 (1 H, m, CH), 2.21–2.26 (2 H, m, CH_2) and 8.85 (1 H, br s, CO_2H); δ_C 22.4 (enriched CH_3), 25.5 (d, *J* 35, CH), 43.2 (CH_2) and 179.6 (d, *J* 3, CO_2H) .

† Integral determined from decoupling experiment (irradiation at δ_H 2.23).

Methyl (*S*)-[5-^{13}C]-4-Methyl-3-oxopentanoate 24. (Cyanomethylene)triphenylphosphorane hydrochloride (prepared as previously described[52]) (9.45 g, 28 mmol) was dissolved in water (60 mL) and the solution washed with dichloromethane (60 mL). The aqueous layer was stirred with sodium hydroxide [1.68 g, 42 mmol in water (30 mL)] and dichloromethane (60 mL) for 10 min at rt. The layers were separated and the aqueous layer extracted with dichloromethane (60 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated until a precipitate just formed. Sufficient dichloromethane was added to redissolve the precipitate.

A mixture of (*S*)-[4-^{13}C]-3-methylbutanoic acid **21** (0.96 g, 9.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (2.7 g, 14 mmol) and 4-dimethylaminopyridine (DMAP) (110 mg, 0.9 mmol) in dichloromethane (120 mL) was stirred at 0 °C for 10 min before the solution of (cyanomethylene)triphenylphosphorane **22** was added dropwise over *ca.* 20 min. The mixture was warmed to rt and stirred overnight. Water (200 mL) was added, the layers separated and the aqueous layer extracted with dichloromethane (2 × 200 mL). The combined organic extracts were washed successively with sat. sodium hydrogen carbonate solution (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated. Column chromatography of the resultant yellow oil with 5–10% ethyl acetate in dichloromethane as eluent yielded (*S*)-[6-^{13}C]-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanenitrile **23** (2.87 g, 80%) as an off-white solid; δ_H (270 MHz) 0.96 (3 H, dd, *J* 6.6 and 5.3, CH_3), 0.96 (3 H, dd, *J* 124.7 and 6.6, $^{13}CH_3$), 2.21 (1 H, nonet d, *J* 6.8 and 3.7, 5-H), 2.58 (2 H, dd, *J* 7.1 and 4.3, 4-H_2) and 7.46–7.66 (15 H, m, Ph); δ_C (67.9 MHz) 22.5 (enriched, CH_3), 25.8 (d, *J* 36, C-5), 48.1 (d, *J* 8, C-4), 49.3 (d, *J* 126, C-2), 122.6 (d, *J* 16, C-1), 123.3 (d, *J* 94, Ph *ipso*-C), 128.9 (d, *J* 13, aromatic), 132.8 (d, *J* 2, aromatic), 133.4 (d, *J* 10, aromatic) and 196.7 (C-2).

Ozone was passed through a stirred solution of (5*S*)-[6-^{13}C]-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanenitrile **23** (2.87 g, 7.4 mmol) in dichloromethane (60 mL) and methanol (30 mL) at −78 °C until the solution remained blue (*ca.* 2 h). The solution was then purged with oxygen, at −78 °C, until colourless and finally warmed to rt. The reaction mixture was evaporated to dryness and the resultant yellow solid purified by column chromatography with 25% light petroleum in chloroform as eluent to yield methyl (4*S*)-[5-^{13}C]-4-methyl-3-oxopentanoate **24** (810 mg, 76%) as a colourless liquid (lit. data on unlabelled material[53]); δ_H (270 MHz) 0.97 (3 H, dd, *J* 6.6 and 5.3, CH_3), 0.97 (3 H, dd, *J* 125.4 and 6.7, $^{13}CH_3$), 2.20 (1 H, nonet d, *J* 6.7 and 3.8, 4-H), 2.73 (2 H, dd, *J* 6.8 and 4.2, 3-H_2) and 3.87 (3 H, s, CO_2CH_3); δ_C (67.9 MHz) 22.4 (enriched, CH_3), 24.2 (d, *J* 35, C-4), 47.9 (C-3), 52.8 (OCH_3), 161.7 (C-1) and 193.9 (C-2).

(2*S*,4*S*)-[5-^{13}C]Leucine 25. The reaction was carried out as described in the general procedure using methyl (4*S*)-[5-^{13}C]-4-methyl-2-oxopentanoate **24** (810 mg, 5.6 mmol). Purification by ion-exchange chromatography gave (2*S*,4*S*)-[5-^{13}C]leucine **25** (600 mg, 81%), as a pale yellow solid, mp 286 °C (decomp.); $[\alpha]_D$ −10.5 (*c* 2.0 in water) [lit.,[54] unlabelled leucine −10.7 (*c* 2.0 in water)]; δ_H (400 MHz, D_2O) 0.95 (3 H, dd, *J* 125.0 and 6.1, $^{13}CH_3$), 0.96 (3 H, br t, *J* 5.5, CH_3), 1.63–1.78 (3 H, m, 3-H_2 and 4-H) and 3.71 (1 H, m, 2-H); δ_C (67.9 MHz, D_2O) 20.8 (enriched

CH_3), 22.0 (slightly enriched CH_3), 23.7 (d, *J* 35, C-4), 40.7 (C-3), 53.4 (C-2) and 175.4 (C-1).

(1*R*,2*S*,3*R*)-2-[(*E*)-Crotonyl]-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)amino]bornan-2-ol 27. Crotonyl chloride (2.0 mL, 21 mmol) was added to (1*R*,2*S*,3*R*)-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)amino]bornan-2-ol **26** (1.19 g, 2.9 mmol) in carbon tetrachloride (100 mL) and the solution heated under reflux in the presence of 4 Å molecular sieves overnight. After the reaction mixture had been cooled to rt, the carbon tetrachloride was removed *in vacuo*. The residual oil was dissolved in ethyl acetate (20 mL) and washed with sat. sodium hydrogen carbonate solution (30 mL). The aqueous layer was extracted with ethyl acetate (30 mL). The combined organic extracts were dried over sodium sulfate, filtered and evaporated. The crude product was recrystallised from dichloromethane and light petroleum to give (1*R*,2*S*,3*R*)-2-[(*E*)-crotonyl]-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)amino]bornan-2-ol **27** (1.12 g, 81%) as a white solid, mp 166–167 °C (data not previously reported[33b]); $[\alpha]_D$ +1.51 (*c* 1.96 in $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 1719 (CO), 1660 (C=C), 1607 and 1593 (C=C, Ar), δ_H (300MHz) 0.65, 0.78 and 0.99 (3 × 3 H, 3 × s, 8-H_3, 9-H_3 and 10-H_3), 1.08, 1.35, 1.53, 1.72 (each 1 H, m, 5-H_2 and 6-H_2), 1.93 (3 H, dd, *J* 7, 2, CHCH_3), 2.07 (3 H, br s, Ar-CH_3), 2.16 (1 H, m, 4-H), 2.26 (3 H, br s, Ar-CH_3), 3.82 (1 H, d, *J* 7, 3-H), 5.21 (1 H, d, *J* 7, 2-H), 5.91 (1 H, dq, *J* 15.5, 2, COCH), 6.03 (1 H, br s, Ar-H), 6.83 (2 H, br s, Ar-H), 7.03 (1 H, dq, *J* 15.5, 7, COCHC*H*), 7.44 (5 H, m, Ar-H); δ_C 11.2, 20.8 and 21.2 (C-8, C-9 and C-10), 18.1 (CH*C*H_3), 21.1 (Ar-CH_3), 27.6 and 32.0 (C-5 and C-6), 47.4 and 50.2 (C-1 and C-7), 48.6 (C-4), 67.3 (C-3), 80.4 (C-2), 123.1 (CO*C*H), 128.1, 128.3, 129.2, 132.4, 137.0 and 139.2 (C-Ar), 144.1 (COCH*C*H) and 165.4 (CO); *m*/*z* (CI) 482 $[(M + H)^+$, 482.2372, $C_{28}H_{36}NO_4S$ requires 482.2365, 12%], 396 (74), 341 (100), 254 (70), 226 (8).

(1*R*,2*S*,3*R*)-2-{(3*R*)-[4-^{13}C]-3-Methylbutanoyl}-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)-amino]bornan-2-ol 28. Freshly prepared [^{13}C]methyllithium (3.0 mmol) was added dropwise to copper(I) iodide (571 mg, 3.0 mmol) in ether (5.5 mL) at −10 °C. The mixture turned yellow and was stirred at −10 °C for 20 min, before cooling to −78 °C. Boron trifluoride–diethyl ether (0.37 mL, 3.0 mmol) was added dropwise and the yellow solution stirred at −78 °C for 15 min. A solution of (1*R*,2*S*,3*R*)-2-[(*E*)-crotonyl]-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)amino]bornan-2-ol **26** (204 mg, 0.42 mmol) in ether (8 mL) was added dropwise and the reaction mixture stirred at −78 °C for 1 h, −40 °C for 3 h and finally −20 °C for 3 h. The reaction was quenched at −20 °C with sat. ammonium chloride solution (50 mL), before warming to rt. The layers were separated and the aqueous layer extracted with ether (3 × 50 mL). The combined organic extracts were washed with sat. ammonium chloride solution (50 mL), dried over sodium sulfate, filtered and evaporated to yield a yellow solid. Purification by column chromatography, eluting with 0–10% ethyl acetate in light petroleum gave (1*R*,2*S*,3*R*)-2-{(3*R*)-[4-^{13}C]-3-methylbutanoyl}-3-[*N*-phenylsulfonyl-*N*-(3,5-dimethylphenyl)-amino]bornan-2-ol **28** as a white solid (165 mg, 79%); mp 173–174 °C; $[\alpha]_D$ −3.8 (*c* 1.05 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1733 (CO); δ_H [500 MHz; $(CD_3)_2CO$] 0.63, 0.79 and 0.94 (3 × 3 H, 3 × s, 8-H_3, 9-H_3 and 10-H_3), 0.99 (3 H, dd, *J* 125, 6.5, ^{13}CH_3), 1.00 (3 H, dd, *J* 6.4, 5.3, CHCH_3), 1.22, 1.28, 1.54 and 1.70 (each 1 H, each m, 5-H_2 and 6-H_2), 2.04–2.34 (10 H, m, 2 × Ar-CH_3, 4-H, and COCH_2C*H*), 4.00 (1 H, d, *J* 7.0, 3-H), 5.17 (1 H, d, *J* 7.0, 2-H), 6.05 (1 H, br s, Ar-H), 6.90 (1 H, br s, Ar-H), 6.95 (1H, br s, Ar-H), 7.43–7.64 (5 H, m, Ar-H); δ_C [75MHz, $(CD_3)_2CO$] 11.9, 21.1, 21.2, 21.8 and 25.5 (C-8, C-9, C-10 and 2 × Ar-CH_3), 22.9 (^{13}CH_3), 23.0 (CH*C*H_3), 28.0 and 32.8 (C-5 and C-6), 44.2 (CO*C*H_2), 48.0 and 50.7 (C-1 and C-7), 49.4 (C-4), 68.0 (C-3), 81.6 (C-2), 129.0, 129.2, 129.8, 133.5, 138.5 and 140.3 (C-Ar), 172.0 (CO); *m*/*z* (CI) 499 $[(MH)^+$, 499.2714, $C_{28}{}^{13}CH_{40}NO_4S$ requires 499.2712, 13%], 396 (50), 358 (100), 254 (90), 85 (36).

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