Synthetic use of the primary kinetic isotope effect in hydrogen atom transfer: generation of α-aminoalkyl radicals†

Mark E. Wood,*[a] Sabine Bissiriou,[a] Christopher Lowe,[b] Andrew M. Norrish,[a] Katell Sénéchal,[a] Kim M. Windeatt,[a] Simon J. Coles[c] and Michael B. Hursthouse[c]

Received 4th June 2010, Accepted 5th July 2010
DOI: 10.1039/c0ob00205d

The extent to which deuterium can act as a protecting group to prevent unwanted 1,5-hydrogen atom transfer to aryl and vinyl radical intermediates was examined in the context of the generation of α-aminoalkyl radicals in a pyrrolidine ring. Intra- and intermolecular radical trapping following hydrogen atom transfer provides an illustration of the use of the primary kinetic isotope effect in directing the outcome of synthetic C–C bond-forming processes.

Introduction

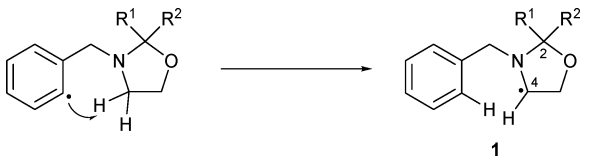
Traditionally, the observation of a primary kinetic isotope effect (or lack thereof) has provided an excellent, straightforward probe for the examination of reactions whose mechanisms involve the cleavage of a carbon–hydrogen bond. The magnitude of the isotope effect observed gives an estimate of the extent of hydrogen atom transfer in the transition state, thus providing insight into the rate-determining step of the reaction.[1] In some instances, the substitution of a hydrogen atom with deuterium may even be sufficient to divert a reaction predominantly along an alternative, normally minor pathway.[2] There are, however, comparatively few examples of this phenomenon being applied to routine synthetic procedures.

Clayden *et al.* have shown that the replacement of hydrogen with deuterium at positions of high kinetic acidity in benzamides can result in selectivity in the regiochemical course of deprotonation reactions with organolithium reagents, a deuterium atom effectively acting as a "protecting group" for a carbon–hydrogen bond.[3] Prior to this, Miyano reported the use of deuterium to invert the *exo*/*endo* selectivity in the generation of an alkene by a thionyl chloride-induced β-elimination of a 1-methylcyclobutanol moiety, as a key step in the synthesis of 18-oxoprogesterone,[4] and both Vedejs and Little[5] and Danishefsky *et al.*[6] have also used deuterium to prevent unwanted intramolecular deprotonation by key intermediate organolithium species (originally intended to act as nucleophiles) in cyclisation procedures.

Herein, we discuss the background to and provide the full experimental details of some of our recent studies[7] into the extent to which deuterium can be used to protect carbon–hydrogen bonds in radical procedures involving hydrogen atom transfer.[8]

Results and discussion

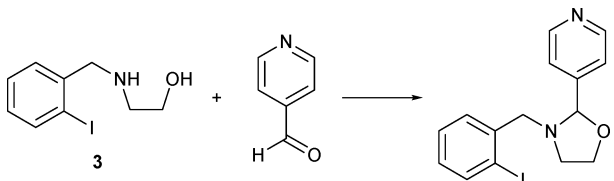
Our earlier studies into the preparation of highly substituted β-amino alcohols utilised a radical-based synthetic pathway, in which the key step was the generation of a 1,3-oxazolidine-derived C4 α-aminoalkyl radical **1** *via* a 1,5-hydrogen atom transfer step (Scheme 1).[9]



1

Scheme 1 α-Aminoalkyl radical generation by 1,5-hydrogen atom transfer.

During the course of this work, we encountered a problem with the regioselectivity of hydrogen atom transfer in the remote functionalisation process. Whilst attempting to maximise the stereoselectivity of the trapping of the intermediate radicals **1** at C-4, using the principle of "self-regeneration of stereocentres,"[10] we examined the radical reactions of a racemic, aldehyde-derived 1,3-oxazolidine **2** (with a large difference in C2 substituent size), prepared from 2-(2-iodobenzylamino)ethanol **3**[9] and 4-pyridinecarboxaldehyde **4** (Scheme 2). Although the aldehyde-derived 1,3-oxazolidines such as **2** were found to be more robust towards hydrolytic cleavage (particularly during the commonly non-trivial chromatographic purification of radical reaction products) than the ketone-derived species used in earlier work,[9] this substrate obviously introduced the issue of C2 *vs.* C4 regioselectivity in the hydrogen atom transfer, occurring after initial aryl radical generation.

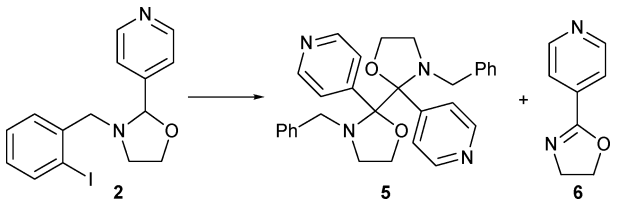


3 **4** **2**

Scheme 2 *Reagents and conditions*: $MgSO_4$, THF, rt, 18 h (85%).

[a]*School of Biosciences, University of Exeter, Geoffrey Pope Building, Stocker Road, Exeter, UK EX4 4QD. E-mail: m.e.wood@exeter.ac.uk; Tel: +44 1392 263450*
[b]*UCB Celltech, 208 Bath Road, Slough, Berkshire, UK SL1 3WE*
[c]*EPSRC X-ray Crystallography Service, Department of Chemistry, University of Southampton, Highfield, Southampton, UK SO17 1BJ*
† CCDC reference number 291244. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00205d

On reducing the aryl iodide moiety in **2** with tributyltin hydride (under standard conditions with AIBN as initiator), only two heterocyclic products could be isolated after repeated chromatography of the crude reaction product, required to remove all tin-containing residues. (The remainder of the material appeared to be a complex mixture of degradation products.) These products were identified as the C2-linked dimeric bioxazolidine **5** and the dihydrooxazole **6**, isolated in very low (8 and 3%, respectively) yields (Scheme 3).



Scheme 3 *Reagents and conditions*: Bu_3SnH (4.1 equiv.), AIBN (0.1 equiv.), C_6H_6, 80 °C, 18 h (**5**, 8%; **6**, 3%).

Both products had clearly arisen from the formation of the highly stabilised C2 radical intermediate **7** (Fig. 1) by either β-elimination of a benzyl radical for the formation of **6** or radical–radical combination in the case of **5**. No products could be identified as being derived from the required intermediate C4 radical **8** (Fig. 1).

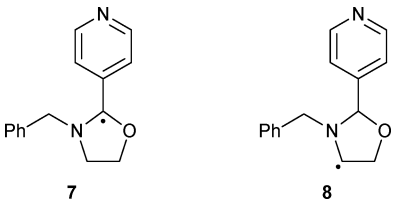


Fig. 1 Intermediate α-aminoalkyl radicals derived from **2**.

Despite the small quantity of material obtained, we were fortunate enough to be able to obtain an X-ray crystal structure of dimer **5**, thus providing confirmation of the product structure (Fig. 2).

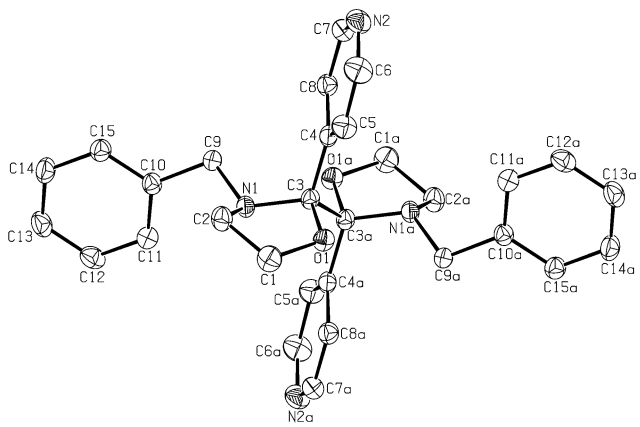
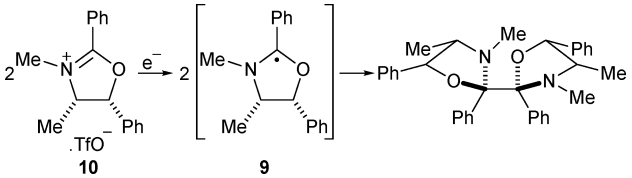


Fig. 2 ORTEP representation of **5**; ellipsoids drawn at 30% probability level.

Interestingly, Shono *et al.* have demonstrated an essentially identical dimerisation of oxazolidine C2 radicals such as **9**, derived from single electron reduction of a 2-aryl-2-oxazolinium salt **10** (Scheme 4).[11] Our observation of apparently exclusive formation of the *meso*-diastereoisomer of the dimer **5** is in contrast to the stereoselectivity proposed by Shono *et al.* (Scheme 4), although the reasons for this stereoselectivity are unclear. Indeed, it is not unfeasible that we were only able to isolate the minor diastereoisomer of **5**, with the major 2*R*,2′*R*/2*S*,2′*S* racemic mixture possibly being labile under the reaction and/or purification conditions. The ^{1}H NMR spectrum of **5** also revealed a remarkable *ca.* 2 ppm chemical shift difference between the diastereotopic methylene group protons at the benzylic and oxazolidine C4/C5 positions, as can be seen in the portion of the spectrum shown in Fig. 3.



Scheme 4 Reductive coupling of 2-aryl-2-oxazolinium salts.[11]

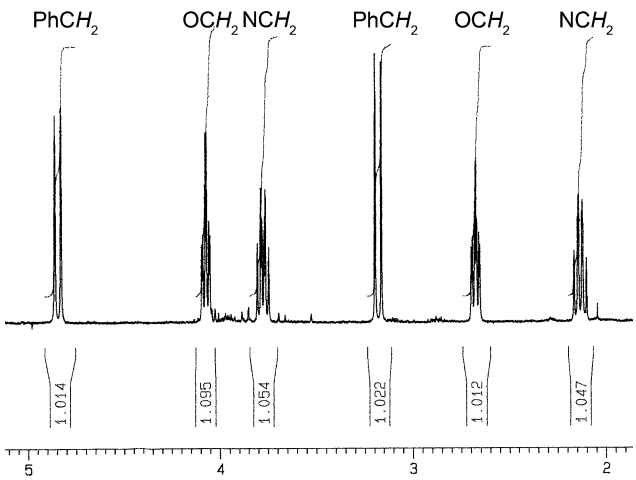
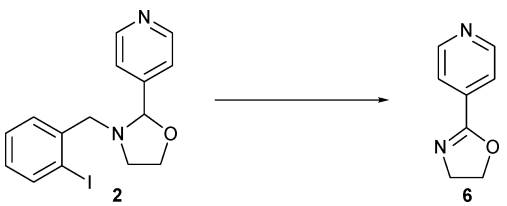


Fig. 3 400 MHz ^{1}H NMR spectrum of **5**.

From previous studies,[9] we were confident that should the desired intermediate C4 α-aminoalkyl radical **8** be formed during the hydrogen atom transfer step, we should be able to trap it with an appropriate radicalphile. To this end, we therefore carried out a tributyltin hydride reduction of **2** in the presence of a 3-fold excess of *tert*-butyl acrylate (Scheme 5).

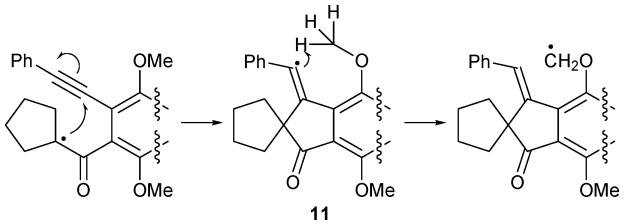


Scheme 5 *Reagents and conditions*: *tert*-butyl acrylate (3.0 equiv.), Bu_3SnH (3.5 equiv.), AIBN (0.5 equiv.), C_6H_6, 80 °C, 23 h, (59%).

Surprisingly, this reaction gave the dihydrooxazole **6** as the only isolable product, in a 59% yield, again suggesting efficient and apparently exclusive formation of the undesired C2 radical

intermediate **7**. At this stage, therefore, we were faced with a difficult regiochemical problem to solve in our key hydrogen atom transfer step.

During studies ultimately leading to the successful total synthesis of fredericamycin A, an antibiotic with antitumour activity, Clive *et al.* experienced similar problems with unwanted 1,6-hydrogen atom transfer from an aryl methyl ether (used as a phenol protecting group) to a vinyl radical **11**, generated from a 5-*exo dig* spirocyclisation (Scheme 6).[12]



Scheme 6 Unwanted 1,6-hydrogen atom transfer in fredericamycin A synthesis.[12]

Deuteration of this methyl ether was found to retard this hydrogen atom transfer sufficiently to ensure that the intermediate vinyl radical **11** was trapped with triphenyltin hydride before the problematic side reaction could occur.[13] Encouraged by this observation, we decided to investigate the reactivity of a C2 deuterated version of our 1,3-oxazolidine radical precursor **12** (Fig. 4).

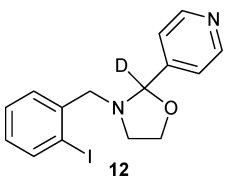
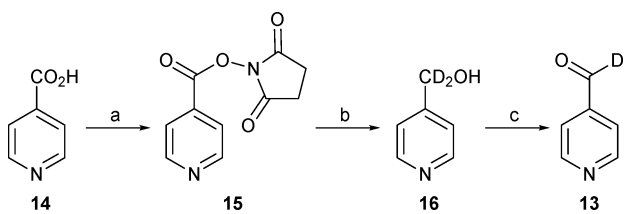


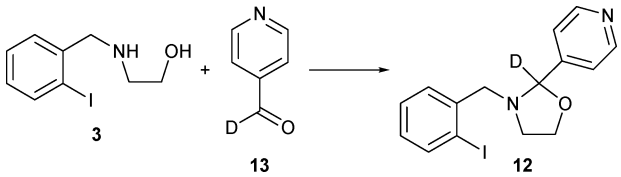
Fig. 4 C2 deuterated 1,3-oxazolidine radical precursor.

In order to access **12**, α-deutero-4-pyridinecarboxaldehyde **13** was firstly prepared by a three-step process. Isonicotinic acid **14** was converted into an active ester **15** by an EDCI-mediated coupling with *N*-hydroxysuccinimide.[14] Reduction of **15** with an excess of sodium borodeuteride gave the corresponding di-deuterated alcohol **16** which was then oxidised to the required aldehyde **13** under standard Swern conditions (Scheme 7).



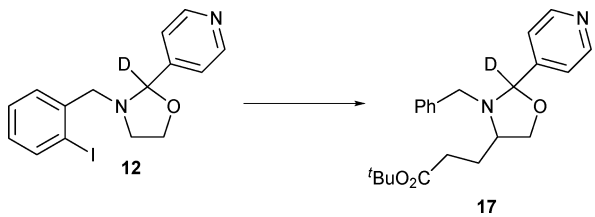
Scheme 7 *Reagents and conditions*: (a) *N*-hydroxysuccinimide, EDCI, DMF, 0 °C, 2 h, (60%); (b) $NaBD_4$ (4.0 equiv.), EtOH, rt, 18 h (98%); (c) DMSO (2.2 equiv.), $(COCl)_2$ (1.1 equiv.), CH_2Cl_2, –60 °C, 2 min, then **16**, –60 °C, 15 min, then Et_3N (5 equiv.), –60 °C, 5 min, then warm to rt (55%).

The overall yield of **13** from isonicotinic acid **14** was 32%, with the level of deuteration being at least 98%. Condensation of **13** with 2-(2-iodobenzylamino)ethanol **3** under previously developed conditions,[9] gave **12** in an excellent (89%) yield (Scheme 8).



Scheme 8 *Reagents and conditions*: $MgSO_4$, THF, rt, 18 h (89%).

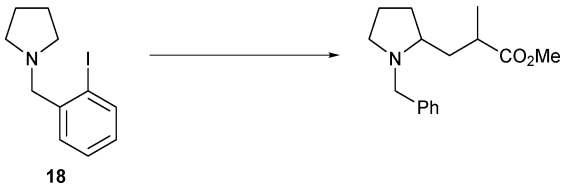
In contrast to the results obtained with 1,3-oxazolidine substrate **2**, on subjecting **12** to reduction with tributyltin hydride in the presence of a 3-fold excess of *tert*-butyl acrylate, this time with initiation using triethylborane,[15] we obtained the desired C-4 alkylated derivative **17** as the sole heterocyclic species from the crude reaction product (Scheme 9). This was obtained in a poor (13%) yield as a 6.5 : 1 ratio of inseparable diastereoisomers but most importantly, neither the dihydrooxazole **6** nor the bioxazolidine dimer **5** appeared to be produced, suggesting that hydrogen atom transfer to give the unwanted C2 radical **7** had been significantly suppressed as required.



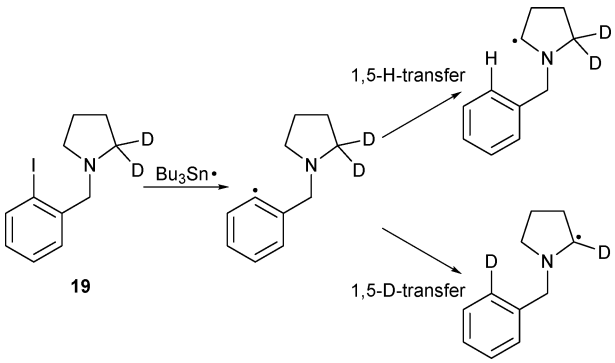
Scheme 9 *Reagents and conditions*: *tert*-butyl acrylate (3.0 equiv.), Bu_3SnH (3.5 equiv.), Et_3B (0.2 equiv.), C_6H_6, rt, 18 h (13%).

Although at this stage we had identified an alternative solution to our problem of regioselectivity of hydrogen atom transfer in 1,3-oxazolidines by using 2-iodobenzamide derivatives,[16] the importance of α-aminoalkyl radicals in synthesis[17] prompted us to undertake a more detailed, fundamental investigation into the effectiveness of deuterium in controlling the selectivity of this process. It is well established that quantum mechanical tunnelling can provide the principal mechanism for hydrogen atom transfer, resulting in much higher kinetic isotope effects than would have been predicted from a simple zero-point energy model, adding to the potential synthetic utility of such an approach.[18] We therefore felt it appropriate and important to assess the efficiency of deuterium as a "blocking group" in synthetically useful scenarios in a systematic manner.[7]

Our interest in the generation of α-aminoalkyl radicals *via* 1,5-hydrogen atom transfer highlighted studies carried out by Undheim *et al.* which investigated the radical-based α-alkylation of a number of nitrogen-containing heterocycles. Of particular relevance was the remote functionalisation of *N*-(2-iodobenzyl)pyrrolidine **18** shown in Scheme 10.[19] Our initial investigations were aimed at assessing the degree of selectivity (and hence, the extent of the kinetic isotope effect) between 1,5-hydrogen atom transfer and the competitive deuterium transfer in the di-deuterated analogue **19** of Undheim *et al.*'s radical reaction substrate **18** (Scheme 11).

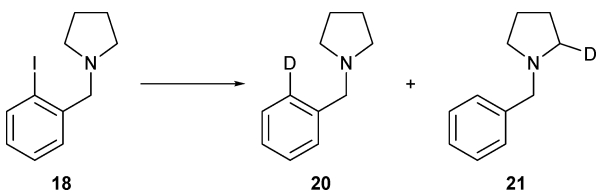


Scheme 10 *Reagents and conditions*: methyl methacrylate (3.2 equiv.), Bu_3SnH (2.0 equiv.), AIBN (0.1 equiv.), C_6H_6, 80 °C, 9 h (66%).[20]



Scheme 11 1,5-Hydrogen *vs.* deuterium atom transfer.

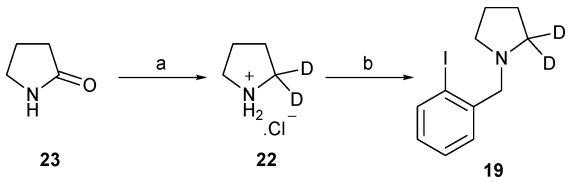
Having found in earlier studies with 1,3-oxazolidine substrates that the rate of 1,5-hydrogen atom transfer was sufficiently high that slow addition of tributyltin hydride and the radical initiator was not necessary,[9] we firstly confirmed that this was also the case in the pyrrolidine system **18** by carrying out its reduction with tributyltin deuteride. (Scheme 12; the reduction was carried out with 2.0 equiv. of tributyltin deuteride at a substrate concentration of 58 mM.)



Scheme 12 *Reagents and conditions*: Bu_3SnD (2.0 equiv.), AIBN (2.3 equiv.), C_6H_6, 80 °C, 6 h (23%; **20** : **21**, 1 : 19).

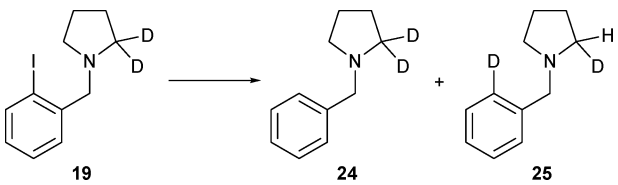
As is often the case, the repeated chromatography required for removal of the organotin residues from the reaction products resulted in a disappointing (23%) final isolated yield of the **20**/**21** product mixture. Fortunately, the product ratios could also be verified if required using ^{2}H NMR spectroscopy on the crude reaction product, the 1 : 19 ratio of **20** : **21** being confirmed before and after chromatography.‡ With 95% of the isolable reaction product originating from 1,5-hydrogen atom transfer, the high efficiency of this process was confirmed and similar conditions were used for all future radical reactions.

The required di-deuterated substrate **19** was prepared using 2,2-dideuteropyrrolidine, isolated as its hydrochloride salt **22** from a lithium aluminium deuteride reduction of 2-pyrrolidinone **23**. After reaction with 2-iodobenzyl bromide in the presence of an excess of Hünig's base, **19** was isolated in a 33% overall yield from **23** (Scheme 13).

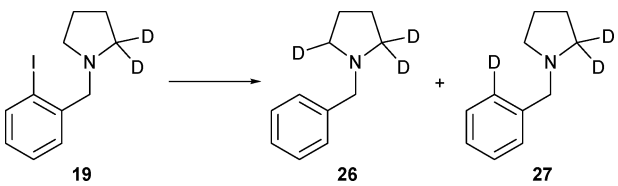


Scheme 13 *Reagents and conditions*: (a) $LiAlD_4$ (2.5 equiv.), THF, 0 °C then 67 °C, 14 h, then HCl, H_2O (62%); (b) 2-iodobenzyl bromide (1.1 equiv.), ^{i}PrNEt$_2$ (4.0 equiv.), CH_3CN, rt, 14 h (53%).

19 was then subjected to reduction reactions using 1.3 equiv. of both tributyltin hydride (Scheme 14) and tributyltin deuteride (Scheme 15), at three different temperatures (80, 25 and −50 °C), in order to estimate the extent to which the primary kinetic isotope effect could determine the regioselectivity of the hydrogen atom transfer. All reactions were carried out at our standardised substrate concentration of 50–60 mM, with benzene as solvent for the reactions at 80 and 25 °C and fluorobenzene at −50 °C. With AIBN as initiator, thermal decomposition at 80 °C was replaced by photochemical radical generation at the lower temperatures, using a medium pressure mercury vapour lamp. Chromatographic purification of the reduced products **24**–**27** was carried out on silica gel containing potassium fluoride (10% w/w),[20] which was found to significantly improve the isolated yields when compared with the tributyltin deuteride reduction of **18**, and this purification method was also used very successfully in later experiments. Table 1 summarises the results of these studies.‡



Scheme 14 *Reagents and conditions*: Bu_3SnH (1.3 equiv.), AIBN (0.7–2.4 equiv.), C_6H_6 or C_6H_5F, heat or UV irradiation, 80, 25 or −50 °C, 6–12 h.



Scheme 15 *Reagents and conditions*: Bu_3SnD (1.3 equiv.), AIBN (2.1–2.4 equiv.), C_6H_6 or C_6H_5F, heat or UV irradiation, 80, 25 or −50 °C, 6–12 h.

The ambiguity in terms of the possible origins of compounds **24** (a product of direct reduction and/or 1,5-hydrogen atom transfer?) and **27** (a product of direct reduction and/or 1,5-deuterium atom transfer?) of course does not allow an accurate estimation of the actual k_H/k_D values from these experiments. The general preference for hydrogen atom transfer over deuterium atom transfer was, however, clear, as was the apparent increased

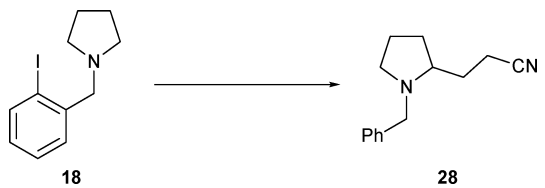
‡ Product ratios were determined by a combination of ^{1}H and ^{2}H NMR spectroscopy and mass spectrometry as appropriate.

Table 1 Product ratios and yields for reduction of **19**‡

Entry	Bu_3SnH/D	T/°C	Products	Ratio	Yield (%)
1	H	80	**24**, **25**	3 : 1	55
2	H	25	**24**, **25**	12 : 1	58
3	H	−50	**24**, **25**	49 : 1	66
4	D	80	**26**, **27**	1 : 2	58
5	D	25	**26**, **27**	7 : 1	71
6	D	−50	**26**, **27**	7 : 1	55

selectivity for hydrogen transfer as the reaction temperature was lowered.

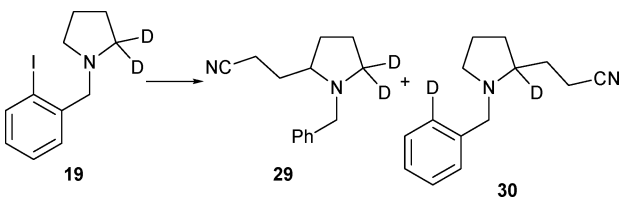
To investigate the degree to which deuterium "protection" of a carbon–hydrogen bond can be used to direct hydrogen atom transfer in a synthetically valuable carbon–carbon bond forming procedure, we chose the α-alkylation of the pyrrolidine moiety[19] in radical precursor **18** as our starting point. Acrylonitrile was chosen as the radicalphile on the basis of its high relative rate for trapping of alkyl radicals compared with other electron-deficient alkenes such as acrylate esters.[21] At a substrate concentration of 58 mM, **18** was reduced with tributyltin hydride in the presence of a 4.9-fold excess of acrylonitrile, with thermal AIBN initiation at 80 °C (Scheme 16). The α-alkylated derivative **28** was isolated as the only identifiable pyrrolidine-containing product, in a synthetically viable 56% yield.



18 28

Scheme 16 *Reagents and conditions*: Bu_3SnH (2.0 equiv.), acrylonitrile (4.9 equiv.), AIBN (2.1 equiv.), C_6H_6, 80 °C, 6 h (56%).

The same methodology was then transferred to di-deuterated substrate **19**. Again the temperatures chosen were 80, 25 and −50 °C, with a change of solvent to fluorobenzene for the −50 °C experiment and photochemical AIBN initiation at both 25 and −50 °C (Scheme 17).



19 29 30

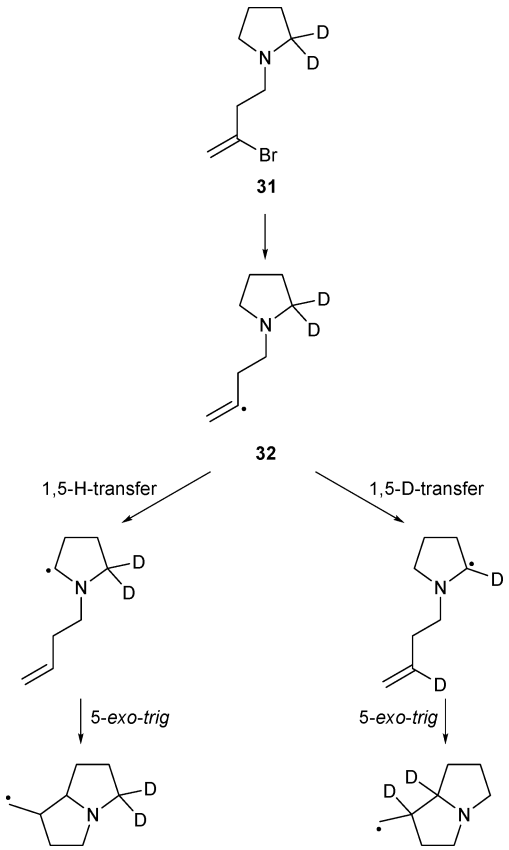
Scheme 17 *Reagents and conditions*: Bu_3SnH (2.0 equiv.), acrylonitrile (5.0–5.8 equiv.), AIBN (2.0–2.4 equiv.), C_6H_6 or C_6H_5F, heat or UV irradiation, 80, 25 or −50 °C, 6 h.

The results, summarised in Table 2, show a clear trend, with the maximum primary kinetic isotope effect of $k_H/k_D = 5.7$ being observed at −50 °C (entry 3) and the value dropping to 3.2 at 80 °C (entry 1).‡ The deviation from the normally expected maximum value of $k_H/k_D \sim 7$–8 is probably best rationalised by invoking a later, more "product-like" transition state for the hydrogen transfer process, stabilised by the adjacent nitrogen atom.

Table 2 Product ratios and yields for acrylonitrile trapping experiments‡

Entry	T/°C	Ratio **29** : **30**	Yield (%)
1	80	3.2 : 1	15
2	25	4.5 : 1	23
3	−50	5.7 : 1	56

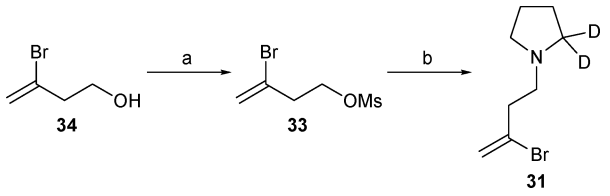
To further extend these studies to include intramolecular α-aminoalkyl radical trapping, an α-dideuterated analogue **31** of the radical precursor used by Robertson *et al.* for the synthesis of (±)-heliotridane[22] was then prepared. This substrate contains an appropriately positioned vinyl group for a 5-*exo*-*trig* cyclisation to follow 1,5-hydrogen (or deuterium) atom transfer to intermediate vinyl radical **32** (Scheme 18).



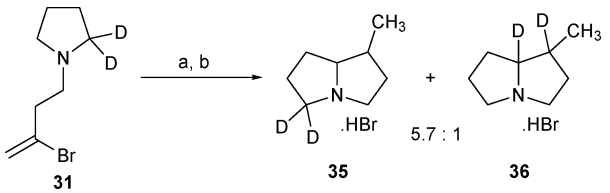
Scheme 18 Intramolecular radical trapping after 1,5-hydrogen or deuterium transfer.

31 was prepared by the *N*-alkylation of 2,2-dideuteropyrrolidine hydrochloride **22** with 3-bromobut-3-enyl methanesulfonate **33**[23] (prepared from 3-bromobut-3-en-1-ol **34**[24]), in the presence of potassium carbonate (Scheme 19).

At 80 °C, with an initial substrate concentration of 12 mM in benzene, **31** was reduced with a solution of tributyltin hydride and AIBN (also in benzene) added slowly over 1 h. Thiophenol was added to aid product purification[22] and the two di-deuterated products **35** and **36** were isolated in a 5.7 : 1 ratio as their hydrobromide salts (30% overall yield, Scheme 20).‡ Unfortunately, attempts to carry out the reaction at lower temperatures with



Scheme 19 *Reagents and conditions*: (a) CH_3SO_2Cl (1.2 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2, rt, 1 h (90%); (b) **22** (1.2 equiv.), K_2CO_3 (3.6 equiv.), CH_3CN, 82 °C, 24 h (28%).



Scheme 20 *Reagents and conditions*: (a) Bu_3SnH (2.7 equiv.), AIBN (0.2 equiv.), C_6H_6, 80 °C, 3 h; (b) PhSH (3.2 equiv.) (30% over 2 steps).

photochemical initiation did not give any of the desired products, but the result obtained at 80 °C shows a significant preference for hydrogen rather than deuterium transfer to intermediate vinyl radical **32** with an apparent value of $k_H/k_D = 5.7$.

A small quantity of the non-cyclised reduction product **37** (Fig. 5) was also produced (9% yield) during this reaction and this could not be separated from the **35**/**36** mixture.

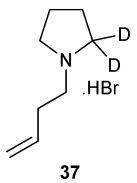


Fig. 5 1-(But-3-enyl)-2,2-dideuteropyrrolidine hydrobromide.

Conclusions

Successful implementation of 1,5-hydrogen atom transfer in the remote activation of carbon centres in synthetic methodologies involving radical intermediates, requires high regioselectivity. We have shown that for the generation of α-aminoalkyl radicals by such a process, deuterium can be used to block this atom transfer to a degree that could potentially be synthetically useful. The estimated values of k_H/k_D observed in these experiments suggest the likelihood of a later, product radical-like transition state for this process.

In order to use such a "protecting group" strategy, based on the primary kinetic isotope effect, either (i) the products which would ultimately arise from the different hydrogen atom transfer processes would need to be different in structure and, therefore, separable; (ii) the blocking deuterium atom(s) would need to be incorporated into a removable protecting group (as exemplified by the earlier studies of Clive *et al.*[13]); or (iii) the deuterium atoms would need to be readily exchangeable with hydrogen if isotopic labelling of the final product were not desired.

Experimental

General experimental

Melting points were determined with a Gallenkamp MPD350 apparatus and are uncorrected.

Infrared spectra were recorded using a Nicolet Magna 550 spectrometer. Generally, only major absorbances are quoted, using the abbreviations: (for intensity) w, weak; m, medium; and s, strong, with br indicating a broad peak. Thin film samples were produced by evaporation of a dilute chloroform or dichloromethane solution of the sample on a sodium chloride plate.

^{1}H NMR spectra were recorded at 300 and 400 MHz using Bruker ACF300 and Avance DRX400 spectrometers, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, the residual solvent peak being used for referencing purposes where possible. Coupling constants are quoted to the nearest 0.5 Hz with peak multiplicities for single resonances being labelled as: s, singlet; d, doublet; t, triplet; q, quartet; m, unresolved multiplet; AB, AB pattern; AA′BB′, AA′BB′ pattern and br, broad. Where delineation of individual resonances is not possible, the relevant peaks are grouped together, over a chemical shift range, as complex.

^{13}C NMR spectra were recorded at 75 and 100 MHz using Bruker ACF300 and Avance DRX400 spectrometers, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, the solvent peak being used for referencing. Where necessary, DEPT editing was used for assignment purposes.

^{2}H NMR spectra were recorded at 61.4 MHz using a Bruker DRX400 spectrometer. Where possible, the natural abundance deuterium resonance from the protonated solvent was used for referencing.

Mass spectra were obtained using Thermoquest Finnigan Trace 2000 GC-MS and Micromass GCT instruments or by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK. Ionisation modes are labelled as: EI, electron impact; CI, chemical ionisation and ES^+, positive ion electrospray.

X-Ray crystallographic data were recorded on a Nonius KappaCCD diffractometer driven by COLLECT[25] and DENZO[26] software. The structure was determined using the direct methods procedure in SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97.[27] Full details of data collection and structure determination have been deposited with the Cambridge Crystallographic Data Centre with deposition number CCDC 291244.†

Analytical thin layer chromatography was carried out using Merck Kieselgel 60 F_{254}, coated on aluminium plates, with visualisation of spots by quenching of UV (254 nm) fluorescence or staining with iodine or alkaline potassium permanganate solution as appropriate. Silica gel with particle size 40–63 μm was used for flash chromatography.

Solvents and reagents were used as commercially supplied or, when necessary, purified using standard procedures detailed in *Purification of Laboratory Chemicals*, 3rd edn, W. L. F. Armarego and D. D. Perrin, Pergamon Press, Oxford, 1998. The fraction of light petroleum ether boiling in the range 40 to 60 °C is referred to as "petroleum ether."

A Büchi R110 Rotovapor was used for the removal of solvents under reduced pressure, with a water or dry ice condenser being used as appropriate.

3-(2-Iodobenzyl)-2-(pyridin-4-yl)oxazolidine (2)

4-Pyridinecarboxaldehyde **4** (610 μl, 6.4 mmol) was added to a stirred solution of 2-(2-iodobenzylamino)ethanol[9] **3** (2.00 g, 7.2 mmol) in tetrahydrofuran (50 cm^3) containing anhydrous magnesium sulfate (2.00 g, 16.6 mmol), under a nitrogen atmosphere. After stirring for 18 h, the reaction mixture was filtered, the solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate (30 cm^3). The resulting solution was washed with aqueous sodium metabisulfite solution (20% w/v, 5 × 10 cm^3), dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **2** (2.25 g, 85%) as a yellow oil (Found MH^+ (CI) 367.0299, $C_{15}H_{16}IN_2O$ requires 367.0307); ν_{max}(thin film)/cm^{-1} 3112–2767 (m) (C–H), 1599 (s), 1562 (w), 1466 (m), 1437 (m), 1410 (s), 1385 (w), 1342 (m), 1317 (m), 1234 (m), 1200 (w), 1159 (w), 1124 (m), 1101 (m), 1063 (s), 1036 (s), 1013 (s), 993 (m), 904 (w), 814 (m), 784 (m), 752 (s) and 638 (m); δ_H (400 MHz; $CDCl_3$) 2.88 (1H, m, NC*H*HCH$_2$), 3.08 (1H, m, NCH*H*CH$_2$), 3.76, 3.86 (2 × 1H, AB, J = 14, ArCH_2), 3.96 (1H, m, C*H*HO), 4.07 (1H, m, CH*H*O), 5.27 (1H, s, NC*H*O), 6.95 (1H, dt, J = 1.5 and 7.5, arylC*H*), 7.31 (1H, dt, J = 1 and 7.5, arylC*H*), 7.41–7.47 (3H, complex, arylC*H* and 2 x pyridineC*H*), 7.83 (1H, dd, J = 1 and 8, arylC*H*) and 8.56 (2H, part of AA′BB′, J = 6, pyridineC*H*); δ_C (100 MHz; $CDCl_3$) 51.2 (NCH$_2$CH$_2$), 61.7 (*C*H$_2$O), 64.6 (ArCH$_2$), 95.4 (N*C*HO), 100.1 (aryl*C*I), 122.2 (pyridine*C*H), 128.2, 129.1, 130.2, 139.7 (aryl*C*H), 140.5 (aryl *ipso C*) and 149.8 (pyridine*C*H); m/z (EI) 366 (M^+, 3%), 288 (100), 217 (85), 149 (12), 135 (19), 119 (25), 91 (68), 90 (66), 89 (43), 78 (32, 77 (22), 65 (33), 63 (25), 51 (40) and 39 (26); m/z (CI) 367 (MH^+, 11%), 241 (21), 149 (100), 134 (12), 108 (31), 107 (23), 106 (17), 94 (43), 80 (19) and 72 (9).

3,3′-Dibenzyl-2,2′-di(pyridin-4-yl)-2,2′-bioxazolidine (5)

Tributyltin hydride (840 μl, 3.1 mmol) was added to a stirred, degassed solution of 3-(2-iodobenzyl)-2-(pyridin-4-yl)oxazolidine **2** (275.6 mg, 0.75 mmol) and 2,2′-azobisisobutyronitrile (12.0 mg, 73.1 μmol) in benzene (50 cm^3). After stirring under reflux under a nitrogen atmosphere for 18 h, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (50% petroleum ether–50% ethyl acetate) to give **5** (15.1 mg, 8%) as a pale yellow, crystalline solid (Found MH^+ (CI) 479.2439, $C_{30}H_{31}N_4O_2$ requires 479.2447); ν_{max}(thin film)/cm^{-1} 3127–2783 (m) (C–H), 1734 (m), 1635 (s), 1549 (w), 1497 (w), 1456 (m), 1426 (m), 1410 (m), 1369 (w), 1281 (s), 1217 (w), 1124 (w), 1065 (m), 833 (w), 756 (s), 700 (m) and 667 (m); δ_H (400 MHz; $CDCl_3$) 2.14 (2H, m, 2 × NC*H*HCH$_2$), 2.68 (2H, 2 × C*H*HO), 3.18, 4.84 (2 × 2H, AB, J = 13, 2 × PhCH_2), 3.78 (2H, m, NCH*H*CH$_2$), 4.07 (2H, m, CHH_2O), 6.83–6.88 (4H, complex, phenylC*H*), 7.13–7.18 (6H, complex, phenylC*H*) and 7.76, 8.71 (2 × 4H, AA′BB′, J = 6, pyridineC*H*); δ_C (100 MHz; $CDCl_3$) 48.3 (NCH$_2$CH$_2$), 53.6 (*C*H$_2$O), 66.1 (Ph*C*H$_2$), 99.2 (N*C*O), 124.3 (pyridine*C*H), 126.8, 127.7, 128.2 (phenyl*C*H), 139.2 phenyl *ipso C*), 148.0 (pyridine *ipso C*) and 149.0 (pyridine*C*H); m/z (EI) 239 (3%), 162 (18), 148 (14), 118 (27), 106 (21), 91 (100), 84 (24), 78 (30), 65 (19), 51 (39), 49 (41) and 41 (23); m/z (CI) 479 (MH^+, 1%), 241 (23), 239 (15), 149 (100), 134 (18), 108 (18), 106 (17), (94 (15) and 80 (25). A second fraction contained 2-(pyridin-4-yl)-4,5-dihydrooxazole **6** (3.8 mg, 3%), obtained as an orange oil (Found MH^+ (ES^+) 149.0716, $C_8H_9N_2O$ requires 149.0715); ν_{max}(thin film)/cm^{-1} 3128–2774 (m) (C–H), 1653 (s), 1601 (s), 1558 (m), 1497 (w), 1412 (s), 1367 (s), 1265 (s), 1217 (s), 1094 (m), 1080 (m), 1065 (m), 995 (w), 976 (w), 945 (s), 905 (w), 837 (m), 754 (s), 676 (s) and 667 (s); δ_H (400 MHz; $CDCl_3$) 4.09 (2H, t, J = 9.5, CH_2N), 4.46 (2H, t, J = 9.5, CH_2O) and 7.77, 8.70 (2 × 2H, AA′BB′, J = 6, pyridineC*H*); δ_C (100 MHz; $CDCl_3$) 55.1 (*C*H$_2$N), 68.0 (*C*H$_2$O), 121.9 (pyridine*C*H), 135.1 (pyridine *ipso C*), 150.2 (pyridine*C*H) and 163.0 (N = *C*–O); m/z (EI) 148 (M^+, 37%), 118 (100), 91 (32), 84 (35), 78 (44), 51 (60), 49 (53) and 40 (35); m/z (CI) 166 (MNH_4^+, 8%) and 149 (MH^+, 100).

Crystal structure determination for compound 5

Crystal data at 120(2) K with Mo-Kα (λ = 0.71073 Å). **5**: M = 478.58, monoclinic, $P2_1/c$, a = 8.9276(2), b = 14.35482(2), c = 10.1033(4) Å, β = 109.570(2)°, V = 1236.42(7) Å^3, Z = 2, 8639 measured reflections, 2801 unique reflections (R_{int} = 0.0467), R = 0.0412, wR = 0.1158.

2-(Pyridin-4-yl)-4,5-dihydrooxazole (6)

tert-Butyl acrylate (240 μl, 1.64 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-(pyridin-4-yl)oxazolidine **2** (200 mg, 0.55 mmol) in degassed benzene (10 cm^3) and the resulting solution was heated to reflux under a nitrogen atmosphere. A solution of tributyltin hydride (510 μl, 1.90 mmol) and 2,2′-azobisisobutyronitrile (44.8 mg, 0.27 mmol) in degassed benzene (10 cm^3) was added dropwise (using a syringe pump) over a period of 5 h, after which time heating under reflux was continued for a further 18 h. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (ethyl acetate) to give **6** (47.6 mg, 59%) as an orange oil. Data as reported above.

2,5-Dioxopyrrolidin-1-yl isonicotinate (15)[14]

N-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (5.00 g, 26.1 mmol) was added to a stirred solution of isonicotinic acid **14** (3.21 g, 26.1 mmol) in *N*,*N*-dimethylformamide (60 cm^3) at 0 °C, followed by *N*-hydroxysuccinimide (3.00 g, 26.1 mmol). After stirring at this temperature for 2 h, the reaction mixture was poured into ethyl acetate (70 cm^3) and the resulting solution was washed successively with water (30 cm^3), saturated aqueous sodium bicarbonate solution (30 cm^3) and saturated aqueous sodium chloride solution (30 cm^3). The separated organic phase was then dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **15** (3.47 g, 60%) as a white, crystalline solid (Found MH^+ (ES^+) 221.0560, $C_{10}H_9N_2O_4$ requires 221.0562); mp 115–120 °C; ν_{max}(KBr disc)/cm^{-1} 3331–2806 (s) (C–H), 1782 (m) (C═O), 1716 (s) (C═O), 1614 (w), 1521 (w), 1475 (w), 1412 (m), 1336 (w), 1306 (m), 1215 (s), 1078 (s), 1027 (s), 944 (m), 930 (m) and 856 (m); δ_H (400 MHz; $CDCl_3$) 2.93 (4H, s, CH_2CH_2) and 7.94, 8.88 (2 × 2H, AA′BB′, J = 6, pyridineC*H*); δ_C (100 MHz; $CDCl_3$) 25.7 (*C*H$_2$*C*H$_2$), 123.2 (pyridine*C*H), 132.6 (pyridine *ipso C*), 151.0 (pyridine*C*H), 160.8 (ester *C* = O) and 168.6 (imide *C* = O); m/z (EI) 220 (MH^+, 1%), 106 (100), 78 (79), 51 (63), 50 (33) and 42 (9); m/z (CI) 221 (MH^+, 88%), 141 (12), 138 (51), 124 (100), 123 (32), 108 (8), 91 (16), 80 (41) and 74 (9).

1,1-Dideutero(pyrid-4-yl)methanol (16)

2,5-Dioxopyrrolidin-1-yl isonicotinate **15** (1.00 g, 4.6 mmol) was added to a stirred solution of sodium borodeuteride (98 atom% D, 760 mg, 18.2 mmol) in ethanol at room temperature and stirring was continued at this temperature for 18 h. The solvent was removed *in vacuo* and the crude product was partitioned between water (40 cm^3) and ethyl acetate (30 cm^3), the separated aqueous phase being extracted with ethyl acetate (2 × 30 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **16** (500 mg, 98%) as a yellow oil (Found MH^+ (CI) 112.0729, $C_6H_6D_2NO$ requires 112.0731); ν_{max}(thin film)/cm^{-1} 3315 (br, m) (O–H), 3086–2806 (m) (C–H), 1608 (m), 1417 (s), 1313 (w), 1216 (s), 1113 (w), 1061 (w), 1006 (w), 921 (w), 758 (s) and 688 (s); δ_H (400 MHz; $CDCl_3$) 2.72 (1H, br s, O*H*) and 7.29, 8.51 (2 × 2H, AA′BB′, *J* = 6, pyridineC*H*); δ_D (61.4 MHz; CCl_4) 4.62 (s, CD_2OH); δ_C (100 MHz; $CDCl_3$) 121.2 (pyridine*C*H), 149.5 (pyridine*C*H) and 150.4 (pyridine *ipso C*); *m*/*z* (EI) 111 (M^+, 100%), 110 (92), 109 (31), 82 (56), 81 (94), 51 (53) and 40 (19); *m*/*z* (CI) 129 (MNH_4^+, 3%), 112 (MH^+, 100), 96 (66), 95 (14) and 80 (7).

α-Deutero-4-pyridinecarboxaldehyde (13)

A solution of dimethyl sulfoxide (570 µl, 8.0 mmol) in dichloromethane (10 cm^3) was added slowly, over a period of 5 min, to a stirred solution of oxalyl chloride (360 µl, 4.1 mmol) in dichloromethane (10 cm^3) at –60 °C, under a nitrogen atmosphere. After stirring at this temperature for a further 2 min, a solution of 1,1-dideutero(pyrid-4-yl)methanol **16** (410 mg, 3.7 mmol) in dichloromethane (10 cm^3) was added slowly and after a further 15 min of stirring, triethylamine (2.58 cm^3, 18.5 mmol) was also added slowly. Stirring was continued at –60 °C for a further 5 min and then the reaction mixture was allowed to attain room temperature before the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (40% dichloromethane–60% ethyl acetate) to give **13** (220 mg, 55%) as an orange oil (Found MH^+ (CI) 109.0510, C_6H_5DNO requires 109.0512; ν_{max}(thin film)/cm^{-1} 3388–2791 (m) (C–H), 1697 (s) (C═O), 1675 (s), 1603 (s), 1563 (s), 1410 (s), 1388 (s), 1326 (w), 1302 (w), 1256 (m), 1223 (s), 1207 (s), 1196 (s), 1105 (s), 1061 (s), 992 (w), 945 (w), 889 (w), 854 (w), 789 (s), 722 (w), 667 (w) and 639 (s); δ_H (400 MHz; $CDCl_3$) 7.78, 8.86 (2 × 2H, AA′BB′, *J* = 6, pyridineC*H*); δ_D (61.4 MHz; CCl_4) 10.1 (s, C(O)*D*); δ_C (100 MHz; $CDCl_3$) 122.1 (pyridine*C*H), 141.4 (pyridine *ipso C*), 151.2 (pyridine*C*H) and 191.1 (t, *J* = 30, *C*(O)D); *m*/*z* (EI) 108 (M^+, 100%); 106 (43), 86 (19), 84 (32), 78 (50), 53 (40), 51 (94), 50 (52), 49 (70), 44 (42) and 43 (31); *m*/*z* (CI) 126 (MNH_4^+, 10%), 109 (MH^+, 100), 95 (35) and 80 (10).

3-(2-Iodobenzyl)-2-deutero-2-(pyridin-4-yl)oxazolidine (12)

α-Deutero-4-pyridinecarboxaldehyde **13** (210 mg, 1.9 mmol) was added to a stirred solution of 2-(2-iodobenzylamino)ethanol[9] **3** (440 mg, 1.6 mmol) in tetrahydrofuran (30 cm^3), containing anhydrous magnesium sulfate (2.00 g, 16.3 mmol), under a nitrogen atmosphere. After stirring for 18 h at room temperature, the reaction mixture was filtered, the solvent evaporated and the residue was purified by flash chromatography on silica gel (40% dichloromethane–60% ethyl acetate) to give **12** (520 mg, 89%) as a dark orange oil (Found MH^+ (ES^+) 368.0366, $C_{15}H_{15}DIN_2O$ requires 368.0370); ν_{max}(thin film)/cm^{-1} 3119–2741 (m) (C–H), 1599 (s), 1560 (m), 1466 (m), 1437 (m), 1408 (m), 1273 (m), 1234 (m), 1157 (m), 1065 (s), 906 (w), 818 (m), 787 (m), 752 (s) and 621 (m); δ_H (400 MHz; $CDCl_3$) 2.84–2.93 (1H, m, C*H*HN), 3.03 (1H, m, CH*H*N), 3.76, 3.86 (2 × 1H, AB, *J* = 14, ArCH_2), 3.96 (1H, *ca* q, *J* = 6, C*H*HO), 4.06 (1H, *ca* q, *J* = 6, CH*H*O), 6.95 (1H, dt, *J* = 2 and 7, arylC*H*), 7.31 (1H, t, *J* = 7, arylC*H*) and 7.40–8.92 (6H, complex, arylC*H* and pyridineC*H*); δ_D (61.4 MHz; CCl_4) 5.17 (s, C*D*); δ_C (100 MHz; $CDCl_3$) 51.2 (NCH_2CH_2), 61.7 (CH_2CH_2O), 64.6 (ArCH_2), 95.0 (m, *C*D), 100.1 (aryl*C*I) 122.2, 128.2, 129.1, 130.2, 139.7 (aryl*C*H and pyridine*C*H) 140.6 (aryl *ipso C*CH_2), 149.0 (pyridine *ipso C*) and 149.8 (pyridine*C*H); *m*/*z* (EI) 367 (M^+, 4%), 289 (100), 217 (71), 120 (19), 91 (31), 90 (46), 89 (30) and 51 (22); *m*/*z* (CI) 368 (MH^+, 84%), 242 (43) and 149 (100).

tert-Butyl-3-(3-benzyl-2-deutero-2-(pyridin-4-yl)oxazolidin-4-yl)propanoate (17)

Tributyltin hydride (510 µl, 1.90 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-deutero-2-(pyridin-4-yl)oxazolidine **12** (200 mg, 0.55 mmol) and *tert*-butyl acrylate (240 µl, 1.64 mmol) in benzene (40 cm^3), under a nitrogen atmosphere. Triethylborane (1 M solution in tetrahydrofuran, 100 µl, 0.10 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (40% petroleum ether–60% ethyl acetate) to give **17** as a 6.5 : 1 ratio of inseparable diastereoisomers (26 mg, 13%) as a yellow syrup (Found MH^+ (ES^+) 370.2250, $C_{22}H_{28}DN_2O_3$ requires 370.2241); ν_{max}(thin film)/cm^{-1} 3092–2773 (m) (C–H), 1726 (s) (C═O), 1593 (w), 1560 (w), 1456 (w), 1048 (w), 1367 (m), 1257 (m), 1153 (s), 1065 (w), 993 (w), 847 (w), 756 (s), 700 (w) and 667 (w); δ_H (400 MHz; $CDCl_3$; major diastereoisomer only) 1.41 (9H, s, $(CH_3)_3C$), 1.58 (2H, *ca* q, *J* = 7, $CH_2CH_2CO_2{}^tBu$), 2.23 (2H, *ca* dt, *J* = 3, 7, $CH_2CO_2{}^tBu$), 3.20 (1H, m, NC*H*), 3.64 (1H, *ca* dd, *J* = 6, 8, C*H*HO), 3.85 (2H, s, PhCH_2), 4.15 (1H, *ca* dd, *J* = 7.5 and 8, CH*H*O) and 7.18–8.48 (9H, complex, phenylC*H* and pyridine C*H*); δ_C (100 MHz; $CDCl_3$; major diastereoisomer) 28.1 ($(CH_3)_3C$), 29.1 ($CH_2CH_2CO_2{}^tBu$), 32.0 ($CH_2CO_2{}^tBu$), 58.7 (PhCH_2), 63.2 (N*C*H), 70.6 (CH_2O), 80.4 ($(CH_3)_3C$), 127.5, 128.4, 129.2 (phenyl*C*H), 138.1 (phenyl *ipso C*) and 172.5 (*C* = O) (note: N*C*D and pyridine carbon signals not visible owing to dilute sample and line broadening, respectively); δ_C (100 MHz; $CDCl_3$; minor diastereoisomer) 28.1 ($(CH_3)_3C$), 29.7 ($CH_2CH_2CO_2{}^tBu$), 32.6 ($CH_2CO_2{}^tBu$), 51.5 (PhCH_2), 60.6 (N*C*H), 68.8 (CH_2O) and 127.3, 128.4, 128.8 (phenyl*C*H) (note: other signals not visible owing to dilute sample); δ_D (61.4 MHz; CCl_4) 5.05 (0.87D, C*D*, major diastereoisomer) and 5.27 (0.13D, C*D*, minor diastereoisomer); *m*/*z* (EI) 369 (M^+, 1%), 240 (33), 91 (100) and 57 (34); *m*/*z* (CI) 370 (MH^+, 58%), 190 (10), 106 (20), 95 (100) and 80 (35).

N-(2-Iodobenzyl)pyrrolidine 18[19]

2-Iodobenzyl bromide (1.75 g, 5.9 mmol) and *N*,*N*-diisopropylethylamine (4.00 cm^3, 23.0 mmol) were added to a stirred solution of pyrrolidine (560 µl, 6.7 mmol) in acetonitrile (16 cm^3). After stirring for 48 h, the solvent was removed *in vacuo*

and the residue was partitioned between ethyl acetate (16 cm^3) and water (24 cm^3). The separated organic phase was washed with water (2 × 24 cm^3) and aqueous sodium chloride solution (saturated, 24 cm^3) before drying (magnesium sulfate), filtering and evaporation of the solvent *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient from 95% petroleum ether–5% ethyl acetate to 80% petroleum ether–20% ethyl acetate) to give **18** (1.38 g, 82%) as a colourless oil (Found MH^+ (CI) 288.0244, $C_{11}H_{15}IN$ requires 288.0244); ν_{max}(thin film)/cm^{-1} 3086–2644 (s) (C–H), 1697 (w), 1584 (w), 1459 (m), 1436 (m), 1374 (w), 1348 (m), 1326 (w), 1239 (w), 1201 (w), 1147 (w), 1129 (w) 1012 (s), 881 (w), 749 (s) and 650 (w); δ_H (300 MHz; $CDCl_3$) 1.81 (4H, m, $CH_2CH_2CH_2CH_2$), 2.60 (4H, m, $N(CH_2)_2$), 3.70 (2H, s, $ArCH_2$), 6.93 (1H, *ca* dt, J = 3.0, 7.5, arylC*H*), 7.32 (1H, *ca* dt, J = 1.5, 6.0, arylC*H*), 7.47 (1H, *ca* dd, J = 3.0, 6.0, arylC*H*) and 7.82 (1H, dd, J = 1.5, 7.5, arylC*H*); δ_C (75 MHz; $CDCl_3$) 23.6 ($CH_2CH_2CH_2CH_2$), 54.1 ($N(CH_2)_2$), 64.4 ($ArCH_2$), 100.1 (aryl*C*I), 128.0, 128.4, 129.8, 139.2 (aryl*C*H) and 141.6 (aryl *ipsoC*); *m*/*z* (CI) 288 (MH^+, 73%), 162 (100), 70 (75) and 52 (23). All data consistent with literature values.[19]

N-Benzyl-2-deuteropyrrolidine (20) and *N*-(2-deuterobenzyl)pyrrolidine (21)

Tributyltin deuteride (98 atom% D, 508 mg, 1.74 mmol) and 2,2′-azobisisobutyronitrile (81 mg, 0.49 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)pyrrolidine **18** (250 mg, 0.87 mmol) in benzene (15 cm^3), under a nitrogen atmosphere. The reaction mixture was heated to reflux and three further aliquots of 2,2′-azobisisobutyronitrile (81 mg, 0.49 mmol) were added at 1, 3.5 and 5 h. Reflux was continued for a further 1 h, after which time, the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 100% dichloromethane to 80% dichloromethane–20% ethyl acetate) to give a mixture of **20** and **21** (65 mg, 23%) in a 19 : 1 ratio as a colourless oil (Found MH^+ (ES^+) 163.1340, $C_{11}H_{15}DN$ requires 163.1340); ν_{max}(thin film)/cm^{-1} 3073–2503 (s) (C–H, C–D), 1667 (w), 1496 (w), 1456 (m), 1214 (w), 754 (w) and 701 (m); δ_H (300 MHz; $CDCl_3$) 1.96–2.05 (4H, complex, $CHDCH_2CH_2$), 2.96–3.06 (3H, complex, CH_2NCHD), 4.00 (2H, s, $PhCH_2$), 7.36–7.42 (3H, complex, phenylC*H*) and 7.53–7.61 (2H, complex, phenylC*H*); δ_C (75 MHz; $CDCl_3$) 23.1, 23.2 ($CHDCH_2CH_2$), 53.00 (*C*HD), 53.3 (NCH_2CH_2), 129.0, 130.2 (phenyl*C*H) and 132.8 (phenyl *ipsoC*); δ_D (61.4 MHz; CH_2Cl_2) 2.87 (0.95D, s, NCH*D*) and 7.52 (0.05D, s, phenylC*D*) *m*/*z* (EI) 162 (M^+, 20%), 161 ($(M–H)^+$, 45), 92 (17), 91 (100), 85 (49), 77 (15), 71 (30), 65 (37), 43 (42) and 42 (31); *m*/*z* (CI) 163 (MH^+, 100%), 108 (4), 91 (5), 85 (4), 73 (15) and 71 (6).

2,2-Dideuteropyrrolidine hydrochloride (22)

Lithium aluminium deuteride (98 atom% D, 1.23 g, 29.3 mmol) was added to a stirred solution of 2-pyrrolidinone **23** (1.00 g, 11.8 mmol) in tetrahydrofuran (15 cm^3) at 0 °C, under a nitrogen atmosphere. The reaction mixture was heated at reflux for 14 h, after which time the solution was cooled in an ice bath and water (1.23 cm^3), aqueous sodium hydroxide solution (15% w/v, 1.23 cm^3) and water (3.7 cm^3) were added sequentially. The resulting solution was extracted with dichloromethane (4 × 10 cm^3) and the combined extracts were washed with hydrochloric acid (2 M, 3 × 30 cm^3). The combined aqueous extracts were evaporated to dryness *in vacuo* to give **22** (0.80 g, 62%) as a pale brown, hygroscopic solid (Found M–HCl (EI) 73.0864, $C_4H_7D_2N$ requires 72.0860); ν_{max}(thin film)/cm^{-1} 3600–3200 (s) (N–H), 3138–2488 (s) (C–H, C–D), 1664 (m), 1460 (w), 1304 (w), 1129 (w), 1080 (w) and 1030 (w); δ_H (300 MHz; $CDCl_3$) 1.95–2.13 (4H, complex, $NCH_2CH_2CH_2$), 3.29 (2H, br m, NCH_2) and 9.63 (2H, br s, $^+NH_2$); δ_C (75 MHz; $CDCl_3$) 24.6 (NCD_2CH_2), 24.4 (NCH_2CH_2), 44.5 (CD_2) and 45.0 (NCH_2); δ_D (61.4 MHz; H_2O) (s, 3.18 CD_2); *m*/*z* (EI) 73 (M–HCl, 100%).

N-(2-Iodobenzyl)-2,2-dideuteropyrrolidine (19)

2-Iodobenzyl bromide (2.10 g, 7.1 mmol) and *N*,*N*-diisopropylethylamine (4.44 cm^3, 25.5 mmol) were added to a stirred solution of 2,2-dideuteropyrrolidine hydrochloride **22** (700 mg, 6.4 mmol) in acetonitrile (20 cm^3). After stirring for 14 h, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate (20 cm^3) and water (20 cm^3) and the separated organic phase was washed with water (2 × 20 cm^3) and aqueous sodium chloride solution (saturated, 20 cm^3). After drying (magnesium sulfate), filtering and evaporation of the ethyl acetate *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient from 95% petroleum ether–5% ethyl acetate to 80% petroleum ether–20% ethyl acetate) to give **19** (970 mg, 53%) as a yellow oil (Found MH^+ (CI) 290.0370, $C_{11}H_{13}D_2NI$ requires 290.0369); ν_{max}(thin film)/cm^{-1} 3120–2642 (m) (C–H and C–D), 1583 (w), 1562 (m), 1460 (m), 1436 (m), 1363 (m), 1328 (m), 1305 (m), 1229 (w), 1205 (w), 1170 (m), 1134 (m), 1116 (m), 1044 (w), 1012 (s), 749 (s) and 651 (w); δ_H (300 MHz; $CDCl_3$) 1.82 (4H, complex, $CH_2CH_2CD_2$), 2.58 (2H, m, NCH_2CH_2), 3.67 (2H, s, $ArCH_2$), 6.94 (1H, *ca* dt, J = 3.0, 7.5, arylC*H*), 7.31 (1H, *ca* dt, J = 1.5, 6.0, arylC*H*), 7.44 (1H, *ca* dd, J = 3.0, 6.0, arylC*H*) and 7.82 (1H, dd, J = 1.5, 7.5, arylC*H*); δ_C (75 MHz; $CDCl_3$) 23.4, 23.6 ($CH_2CH_2CD_2$), 53.3 (CD_2), 54.1 (NCH_2CH_2), 64.4 ($ArCH_2$), 100.1 (aryl*C*I), 128.0, 128.4, 129.8, 139.2 (aryl*C*H) and 141.7 (aryl *ipsoC*); δ_D (61.4 MHz; H_2O) (s, 3.18 CD_2); 2.65 (s, CD_2); *m*/*z* (EI) 289 (M^+, 23%), 217 (22), 162 (12), 134 (12), 127 (10), 105 (10), 92 (30), 91 (50), 86 (100), 72 (18), 63 (15), 57 (12) and 44 (59); *m*/*z* (CI) 290 (MH^+, 81%), 164 (85), 72 (100), 52 (61) and 44 (56).

N-Benzyl-2,2-dideuteropyrrolidine (24) and *N*-(2-deuterobenzyl)-2-deuteropyrrolidine (25)

Reaction at 80 °C. Tributyltin hydride (240 µl, 0.89 mmol) was added to a degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in benzene (15 cm^3) under a nitrogen atmosphere. The reaction mixture was heated to reflux and 2,2′-azobisisobutyronitrile (20 mg, 0.12 mmol) was added. Reflux was continued for a further 12 h, during which time, three further aliquots of 2,2′-azobisisobutyronitrile (10 mg, 0.12 mmol) were added after 1.5, 3 and 10 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a

3 : 1 ratio (62 mg, 55%) as a colourless oil; ν_{max}(thin film)/cm^{-1} 3500–3000 (s) (C–D), 2970–2900 (s) (C–H), 1642 (m), and 1475 (m); δ_H (300 MHz; $CDCl_3$) 1.70 (4H, m, $NCH_2CH_2CH_2$), 2.45 (2.25H, m, NCH_2, NCHD), 3.62 (2H, s, $PhCH_2$) and 7.13–7.35 (4.75H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) 22.3, 22.5 ($NCH_2CH_2CH_2$), 58.3 (NCH_2CH_2), 65.0 ($PhCH_2$), 128.2, 128.8 (phenylCH), 131.7 (phenyl *ipso*C) and 132.6 (phenylCH); δ_D (61.4 MHz; $CHCl_3$) 2.53 (1.73D, s, NCD_2, NCHD) and 7.40 (0.27D, s, phenylCD); *m*/*z* (EI) 163 (M^+, 54%), 162 (72), 161 (12), 92 (42), 91 (100), 86 (58), 85 (39), 72 (48) and 65 (58); *m*/*z* (CI) 164 (MH^+, 100%), 163 (25) and 62 (14).

Reaction at 25 °C. Tributyltin hydride (300 µl, 1.12 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.86 mmol) in benzene (15 cm^3), under a nitrogen atmosphere at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a 12 : 1 ratio (81 mg, 58%) as a colourless oil; ν_{max}(thin film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.73 (4H, m, $NCH_2CH_2CH_2$), 2.45 (2.07H, m, NCH_2, NCHD), 3.55 (2H, s, $PhCH_2$) and 7.15–7.28 (4.93H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) as reported above; δ_D (61.4 MHz; $CHCl_3$) 2.85 (1.92D, s, NCD_2, NCHD) and 7.65 (0.08D, s, phenylCD); *m*/*z* (EI) 162 ((M–H)$^+$, 100%), 134 (29), 92 (8), 91 (73), 85 (68), 71 (85) and 65 (66).

Reaction at –50 °C. Tributyltin hydride (250 µl, 0.93 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (210 mg, 0.73 mmol) in fluorobenzene (12 cm^3), under a nitrogen atmosphere, at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **24** and **25** in a 49 : 1 ratio (78 mg, 66%) as a colourless oil; ν_{max}(thin film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.70 (4H, m, $NCH_2CH_2CH_2$), 2.48 (2.00H, m, NCH_2, NCHD), 3.55 (2H, s, $PhCH_2$) and 7.15–7.28 (5.00H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) as reported above; δ_D (61.4 MHz; $CHCl_3$) 2.75 (1.98D, s, NCD_2, NCHD) and 7.60 (0.02D, s, phenylCD); *m*/*z* (EI) 162 ((M–H)$^+$, 20%), 92 (10), 91 (30), 73 (30) and 57 (100); *m*/*z* (CI) 164 (MH^+, 20%), 153 (30) and 113 (58).

N-Benzyl-2,2-dideutero-5-deuteropyrrolidine (26) and *N*-(2-deuterobenzyl)-2,2-dideuteropyrrolidine (27)

Reaction at 80 °C. Tributyltin deuteride (98 atom% D, 210 µl, 0.78 mmol) was added to a degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (170 mg, 0.59 mmol) in benzene (12 cm^3), under a nitrogen atmosphere. The reaction mixture was heated to reflux and 2,2′-azobisisobutyronitrile (50 mg, 0.31 mmol) was added. Reflux was continued for a further 12 h, during which time three further aliquots of 2,2′-azobisisobutyronitrile (50 mg, 0.31 mmol) were added after 1, 3.5 and 10 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in a 1 : 2 ratio (56 mg, 58%) as a colourless oil; ν_{max}(thin film)/cm^{-1} 3500–3000 (w) (C–D), 2990–2900 (s) (C–H), 1665 (m) and 1494 (m); δ_H (300 MHz; $CDCl_3$) 1.73 (4H, NCHDCH_2CH_2), 2.43 (1.70H, m, NCHD, NCH_2), 3.54 (2H, s, $PhCH_2$) and 7.15–7.29 (4.30H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) 23.7, 23.8 ($NCH_2CH_2CH_2$), 54.2 (NCD_2), 54.6 ($NCHDCH_2$), 62.5 ($PhCH_2$), 127.4, 128.5, 128.7, 129.4 (phenylCH), 139.5 (phenyl *ipso*C); δ_D (61.4 MHz; $CHCl_3$) 2.45 (2.30D, s, NCD_2, NCHD) and 7.28 (0.70D, s, phenylCD); *m*/*z* (EI) 165 (MH^+, 20%), 164 (M^+, 32), 163 ((M–H)$^+$, 100), 162 (20), 136 (8), 135 (20), 134 (8), 92 (38), 91 (84), 86 (62), 73 (42), 72 (49) and 65 (50).

Reaction at 25 °C. Tributyltin deuteride (98 atom% D, 250 µl, 0.93 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in benzene (15 cm^3), under a nitrogen atmosphere at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in a 7 : 1 ratio (81 mg, 71%) as a colourless oil; ν_{max}(thin film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.71 (4H, m, $NCH_2CH_2CH_2$), 2.43 (1.15H, m, NCHD, NCH_2), 3.56 (2H, s, $PhCH_2$) and 7.16–7.28 (4.85H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) as reported above; δ_D (61.4 MHz; $CHCl_3$) 2.60 (2.87D, s, NCD_2, NCHD) and 7.65 (0.13D, s, phenylCD); *m*/*z* (EI) 164 (MH^+, 69%), 162 ((M–H)$^+$, 75), 162 (27), 92 (72), 91 (100), 87 (75), 73.2 (43), 72 (38) and 65 (66).

Reaction at –50 °C. Tributyltin hydride (200 µl, 0.74 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (200 mg, 0.69 mmol) in fluorobenzene (12 cm^3), under a nitrogen atmosphere at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **26** and **27** in 7 : 1 ratio (62 mg, 55%) as a colourless oil; ν_{max}(thin film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.73 (4H, m, $NCH_2CH_2CH_2$), 2.44 (1.15H, m, NCHD, NCH_2), 3.55 (2H, s, $PhCH_2$) and 7.15–7.28 (4.85H, complex, phenylCH); δ_C (75 MHz; $CDCl_3$) as reported above; δ_D (61.4 MHz; $CHCl_3$) 2.58 (2.88D, s, NCD_2, NCHD) and 7.46 (0.12D, s, phenylCD); *m*/*z* (EI) 163 ((M–H)$^+$, 30%), 162 (59), 92 (6), 91 (79), 86 (100), 72 (90) and 65 (58).

3-(*N*-Benzylpyrrolidin-2-yl)propanenitrile (28)

Tributyltin hydride (470 µl, 1.75 mmol) and 2,2′-azobisisobutyronitrile (85 mg, 0.52 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)pyrrolidine **18** (250 mg, 0.87 mmol) and acrylonitrile (280 µl, 4.25 mmol) in benzene (15 cm^3), under a nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 90% dichloromethane–10% petroleum ether to 80%–20% dichloromethane) to give **28** (104 mg, 56%) as a colourless oil (Found MH^+ (EI^+) 215.1544, $C_{14}H_{19}N_2$ requires 215.1543); ν_{max}(thin film)/cm^{-1} 3122–2726 (s) (C–H), 2244 (m) (CN), 1686 (m), 1530 (w), 1495 (m), 1453 (s), 1425 (m), 1369 (m), 1210 (w), 1154 (w), 1125 (m), 1075 (w), 740 (m) and 700 (m); δ_H (300 MHz; $CDCl_3$) 1.47 (1H, m, pyrrolidine NCHCH_aH_b), 1.59–1.79 (3H, complex, pyrrolidine $NCH_2CH_aH_b$, CH_2CH_2CN), 1.89–2.06 (2H, complex, pyrrolidine $NCHCH_aH_b$, pyrrolidine $NCH_2CH_aH_b$), 2.19 (1H, *ca* q, $J = 6.5$, pyrrolidine NCH_aH_b), 2.41 (2H, m, CH_2CN), 2.62 (1H, m, NC*H*), 2.93 (1H, m, pyrrolidine NCH_aH_b), 3.29, 3.93 (2 × 1H, AB, J = 12.0, PhCH_2) and 7.20–7.38 (5H, complex, phenylC*H*); δ_C (75 MHz; $CDCl_3$) 13.1 (CH_2CN), 22.4 (CH_2CH_2CN), 29.4 (NCH_2CH_2), 29.6 ($CHCH_2$), 53.4 (pyrrolidine NCH_2), 58.9 (PhCH_2), 120.3 (*C*N), 127.0, 128.3, 128.6 (phenyl*C*H) and 139.2 (phenyl *ipso C*); *m*/*z* (CI) 215 (MH^+, 100%), 160 (14), 123 (10) and 58 (15).

3-(*N*-Benzyl-2,2-dideuteropyrrolidin-2-yl)propanenitrile (29) and 3-(*N*-(2-deuterobenzyl)-2-deuteropyrrolidin-2-yl)propanenitrile (30)

Reaction at 80 °C. Tributyltin hydride (460 µl, 1.71 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.87 mmol) and acrylonitrile (280 µl, 4.25 mmol) in benzene (15 cm^3), under a nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (20% w/w) (gradient from 90% dichloromethane–10% petroleum ether to 80%–20% dichloromethane) to give a mixture of **29** and **30** in a 3.2 : 1 ratio (29 mg, 15%) as a colourless oil (Found MH^+ (ES^+) 217.1667, $C_{14}H_{17}D_2N_2$ requires 217.1668); ν_{max}(thin film)/cm^{-1} 3104–2692 (s) (C–H, C–D), 2245 (m) (CN), 1604 (w), 1495 (m), 1453 (s), 1425 (m), 1368 (m), 1201 (m), 1181 (m), 1119 (m), 1028 (w), 739 (m) and 701 (m); δ_H (400 MHz; $CDCl_3$) 1.51 (1H m, pyrrolidine NCH(orD)CH_aH_b both products), 1.57–1.79 (3H, complex, pyrrolidine $NCH(orD)_2CH_aH_b$, CH_2CH_2CN both products), 1.82–2.03 (2H, complex, pyrrolidine $NCH(orD)CH_aH_b$, pyrrolidine $NCH(or\ D)_2CH_aH_b$ both products), 2.19 (0.24H, q, J = 6.5, pyrrolidine NCH_aH_b minor product), 2.33, 2.45 (2 × 1H, 2 × m, CH_2CN both products), 2.62 (0.74H, m, NC*H* major product), 2.91 (0.24H, m, pyrrolidine NCH_aH_b minor product), 3.28, 3.91 (2 × 1H, AB, J = 12, PhCH_2 both products) and 7.07–7.42 (4.76H, complex, phenylC*H* both products); δ_C (100 MHz; $CDCl_3$; with DEPT editing) 13.6 (CH_2CN), 22.7 (CH_2CH_2CN), 29.8 (pyrrolidine NCD_2CH_2), 30.1 (pyrrolidine $NCHCH_2$), 54.7 (pyrrolidine NCH_2 minor product), 59.2 (PhCH_2), 62.7 (N*C*H) and 127.4, 128.7, 129.1 (phenyl*C*H); δ_D (61.4 MHz; CH_2Cl_2) 2.15 (0.76D, s, pyrrolidine NCD_aD_b major product), 2.60 (0.24D, s, N*C*D minor product), 2.85 (0.76D, s, pyrrolidine NCD_aD_b major product) and 7.35 (0.24D, s, phenylC*D* minor product); *m*/*z* (EI) 216 (M^+, 1%), 162 (98), 92 (37), 91 (100), 65 (17), 54 (12) and 41 (22); *m*/*z* (CI) 217 (MH^+, 100%), 162 (8), 127 (3) and 52 (1).

Reaction at 25 °C. Tributyltin hydride (460 µl, 1.71 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (250 mg, 0.87 mmol) and acrylonitrile (280 µl, 4.25 mmol) in benzene (15 cm^3), at 25 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **29** and **30** in a 4.5 : 1 ratio (44 mg, 23%) as a colourless oil (Found MH^+ (ES^+) 217.1669, $C_{14}H_{17}D_2N_2$ requires 217.1668); ν_{max}(thin film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.50 (1H m, pyrrolidine NCH(orD)CH_aH_b both products), 1.61–1.81 (3H, complex, pyrrolidine $NCH(orD)_2CH_aH_b$, CH_2CH_2CN both products), 1.85–2.05 (2H, complex, pyrrolidine $NCH(orD)CH_aH_b$, pyrrolidine $NCH(or\ D)_2CH_aH_b$ both products), 2.19 (0.18H, q, J = 6.5, pyrrolidine NCH_aH_b minor product), 2.34, 2.46 (2 × 1H, 2 × m, CH_2CN both products), 2.62 (0.82H, m, NC*H* major product), 2.93 (0.18H, m, pyrrolidine NCH_aH_b minor product), 3.28, 3.92 (2 × 1H, AB, J = 12, PhCH_2 both products) and 7.07–7.42 (4.82H, complex, phenylC*H* both products); δ_C (75 MHz; $CDCl_3$) 13.1 (CH_2CN), 22.2 (CH_2CH_2CN), 29.4 (pyrrolidine NCD_2CH_2), 29.6 (pyrrolidine $NCHCH_2$), 53.4 (pyrrolidine NCH_2 major product), 54.2 (pyrrolidine NCH_2 minor product), 58.8 (PhCH_2), 62.2 (N*C*H), 120.2 (*C*N), 126.9, 128.2, 128.6 (phenyl*C*H) and 139.2 (phenyl *ipso C*); δ_D (61.4 MHz; CH_2Cl_2) 2.14 (0.82D, s, pyrrolidine NCD_aD_b major product), 2.60 (0.18D, s, N*C*D minor product), 2.85 (0.82D, s, pyrrolidine NCD_aD_b major product) and 7.35 (0.18D, s, phenylC*D* minor product); *m*/*z* (EI) 216 (M^+, 1%), 215 ($(M–H)^+$, 3), 162 (53), 92 (30), 91 (100) and 65 (11); *m*/*z* (CI) 217 (MH^+, 100%), 162 (10), 127 (18) and 106 (21).

Reaction at –50 °C. Tributyltin hydride (390 µl, 1.45 mmol) and 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) were added to a stirred, degassed solution of *N*-(2-iodobenzyl)-2,2-dideuteropyrrolidine **19** (210 mg, 0.73 mmol) and acrylonitrile (280 µl, 4.25 mmol) in fluorobenzene (13 cm^3), at –50 °C. The reaction mixture was irradiated with a medium pressure mercury vapour lamp for 6 h, with three further aliquots of 2,2′-azobisisobutyronitrile (70 mg, 0.43 mmol) being added after 1, 3.5 and 5 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel containing potassium fluoride (10% w/w) (gradient from 100% petroleum ether to 80% petroleum ether–20% ethyl acetate) to give a mixture of **29** and **30** in a 5.7 : 1 ratio (89 mg, 56%) as a colourless oil (Found MH^+ (ES^+) 217.1667, $C_{14}H_{17}D_2N_2$ requires 217.1668); ν_{max}(thin

film)/cm^{-1} as reported above; δ_H (300 MHz; $CDCl_3$) 1.51 (1H m, pyrrolidine NCH(orD)CH_aH$_b$ both products), 1.64–1.81 (3H, complex, pyrrolidine NCH(orD)$_2$CH_aH$_b$, CH_2CH$_2$CN both products), 1.87–2.06 (2H, complex, pyrrolidine NCH(orD)CH$_a$$H_b$, pyrrolidine NCH(or D)$_2CH_a$$H_b$ both products), 2.21 (0.15H, q, J = 6.5, pyrrolidine NCH_aH$_b$ minor product), 2.34, 2.47 (2 × 1H, 2 × m, CH_2CN both products), 2.63 (0.85H, m, NCH major product), 2.93 (0.15H, m, pyrrolidine NCH$_a$$H_b$ minor product), 3.29, 3.94 (2 × 1H, AB, J = 12, PhCH_2 both products) and 7.17–7.35 (4.85H, complex, phenylCH both products); δ_C (75 MHz; $CDCl_3$) 13.1 (*C*H$_2$CN), 22.2 (*C*H$_2$CH$_2$CN), 29.4 (pyrrolidine NCD$_2$*C*H$_2$), 29.6 (pyrrolidine NCH*C*H$_2$), 54.3 (pyrrolidine N*C*H$_2$ minor product), 58.8 (Ph*C*H$_2$), 62.3 (N*C*H), 120.3 (*C*N), 127.0, 128.3, 128.7 (phenyl*C*H) and 139.3 (phenyl *ipso C*) - major product N*C*D and other signals or minor product not observed; δ_D (61.4 MHz; CH_2Cl_2) 2.15 (0.85D, s, pyrrolidine NCD_aD$_b$ major product), 2.59 (0.15D, s, N*C*D minor product), 2.85 (0.85D, s, pyrrolidine NCD$_a$$D_b$ major product) and 7.35 (0.15D, s, phenylCD minor product); *m/z* (EI) 216 (M$^+$, 3%), 215 ((M–H)$^+$, 5), 162 (100), 92 (24), 91 (83), 65 (10) and 40 (39); *m/z* (CI) 217 (MH$^+$, 100%), 162 (10), 127 (8), 106 (6), 52 (18) and 77 (7).

3-Bromobut-3-enyl methanesulfonate (33)[23]

Methanesulfonyl chloride (1.05 cm^3, 13.6 mmol) was added dropwise to a stirred solution of 3-bromobut-3-en-1-ol **34** (1.70 g, 11.3 mmol) and triethylamine (1.82 cm^3, 13.6 mmol) in dichloromethane (38 cm^3) at 0 °C. After stirring for a further 1 h at this temperature, water (38 cm^3) was added and the separated aqueous phase was extracted with dichloromethane (3 × 22 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered and evaporated *in vacuo* to give **33** (2.33 g, 90%) as a pale yellow oil (Found MH$^+$ (^{79}Br, CI) 228.9457, $C_5H_{10}{}^{79}BrO_3S$ requires 228.9534); ν_{max}(thin film)/cm^{-1} 3037–2832 (w) (C–H), 1632 (m) (C=C), 1468 (w), 1414 (w), 1355 (s), 1265 (w), 1227 (w), 1176 (s), 1145 (m), 1057 (w), 987 (m), 964 (m), 910 (m), 805 (m) and 734 (w); δ_H (300 MHz; $CDCl_3$) 2.81 (2H, t, J = 6.0, CH_2CH$_2$O), 3.00 (3H, s, CH_3), 4.35 (2H, t, J = 6.0, CH_2O), 5.54 (1H, d, J = 1.2, CHH=C) and 5.72 (1H, d, J = 1.2, CHH = C); δ_C (75 MHz; $CDCl_3$) 37.2 (*C*H$_3$), 40.7 (*C*H$_2$CH$_2$O), 66.7 (*C*H$_2$O), 120.4 (*C*H$_2$=C) and 127.5 (CH$_2$ = *C*); *m/z* (CI) 231 (MH$^+$ (^{81}Br), 3%), 229 (MH$^+$ (^{79}Br), 3), 149 (13), 135 (98), 133 (100), 115 (21), 97 (12), 85 (10), 79 (10), 71 (4), 53 (7) and 51 (7). (Note: Although the preparation of **33** has been reported,[23] no isolation method or characterisation was presented.)

1-(3-Bromobut-3-enyl)-2,2-dideuteropyrrolidine (31)

Anhydrous potassium carbonate (1.000 g, 7.24 mmol) and 3-bromobut-3-enyl methanesulfonate **33** (686 mg, 3.00 mmol) were added sequentially to a stirred solution of 2,2-dideuteropyrrolidine hydrochloride **22** (395 mg, 3.60 mmol) in dry acetonitrile (15 cm^3). After heating the stirred reaction mixture under reflux for 12 h, additional anhydrous potassium carbonate (500 mg, 3.62 mmol) was added and reflux was continued for a further 12 h. The solid was filtered off and washed with dichloromethane (2 × 15 cm^3) and the combined filtrate/washings were evaporated to dryness *in vacuo*. The residue produced was purified by flash chromatography on silica gel (gradient from 100% chloroform to 95% chloroform–5% methanol) to give **31** (175 mg, 28%) as a colourless oil (Found MH$^+$ (^{79}Br, CI) 206.0505, $C_8H_{13}{}^{79}BrD_2N$ requires 206.0508); ν_{max}(thin film)/cm^{-1} 3022–2338 (s) (C–H and C–D), 1672 (w), 1629 (m) (C=C), 1448 (w), 1317 (w), 1292 (w), 1240 (w), 1158 (m) and 913 (w); δ_H (300 MHz; $CDCl_3$) 1.83 (4H, br complex, CD$_2$CH_2CH_2), 2.59–2.79 (6H, br complex, pyrrolidine NCH_2 and C(Br)CH_2CH_2), 5.46 (1H, s, CHH=C) and 5.68 (1H, s, CHH = C); δ_C (75 MHz; $CDCl_3$) 23.1, 23.4 (CD$_2$*C*H$_2$*C*H$_2$), 40.5 (C(Br)*C*H$_2$CH$_2$), 53.3 (*C*D$_2$), 54.1 (pyrrolidine N*C*H$_2$), 54.5 (C(Br)CH$_2$*C*H$_2$N), 118.0 (*C*H$_2$=C) and 131.5 (CH$_2$ = *C*); δ_D (61.4 MHz; CH_2Cl_2) 3.20 (CD_2); *m/z* (CI) 208 (MH$^+$ (^{81}Br), 100%), 206 (MH$^+$ (^{79}Br), 98), 128 (25), 86 (24), 74 (10) and 52 (10).

(±)-5,5-Dideutero-1-methylhexahydro-(1*H*-pyrrolizine) hydrobromide (35) and (±)-1,7a-dideutero-1-methyl-hexahydro-1*H*-pyrrolizine hydrobromide (36)

A degassed solution of tributyltin hydride (250 µl, 0.93 mmol) and 2,2′-azobisisobutyronitrile (6 mg, 0.04 mmol) in benzene (12 cm^3) was added dropwise (*via* a syringe pump) to a degassed solution of 1-(3-bromobut-3-enyl)-2,2-dideuteropyrrolidine **31** (70 mg, 0.34 mmol) and 2,2′-azobisisobutyronitrile (6 mg, 0.04 mmol) in benzene (28 cm^3), at reflux under a nitrogen atmosphere, over a period of 1 h. After a further 2 h at reflux, the solvent was removed *in vacuo* and thiophenol (112 µl, 1.09 mmol) was added to the resulting residue. The crude product thus obtained was purified by flash chromatography on silica gel (75% petroleum ether–25% diethyl ether, then a gradient from 99% dichloromethane–1% methanol to 95% dichloromethane–5% methanol) to give a mixture of **35** and **36** in a 5.7 : 1 ratio (21 mg, 30%) as a colourless syrup (Found (MH–Br)$^+$ (ES$^+$) 128.1402, $C_8H_{14}D_2N$ requires 128.1403; ν_{max}(thin film)/cm^{-1} 3436 (br, m) ($^+$N–H), 3122–2417 (s) (C–H), 1641 (w), 1460 (m), 1385 (w) and 1033 (w); δ_H (300 MHz; $CDCl_3$) 1.07 (3H, d, J = 7.0, CH_3), 1.60–1.80 (2H, complex, C(2)H and C(7)H), 1.89–2.21 (4H, complex, C(2)H, C(7)H and C(6)H_2), 2.50 (0.85H, m, C(1)H), 2.69 (0.15H, m, C(5)H), 3.01 (1H, dd, J = 7, 10, C(3)H), 3.57 (1H, m, C(3)H), 3.92 (0.15H, m, C(5)H) and 4.24 (0.85H, *ca* q, J = 9, C(7a)H) (Note: The ^{1}H NMR spectrum showed the presence of a small quantity (*ca* 9%) of 1-(but-3-enyl)-2,2-dideuteropyrrolidine hydrobromide **37**, with distinguishable resonances at 5.16 (1H, d, J = 8, CH=CH_2 *cis*), 5.17 (1H, d, J = 16, CH=CH_2 *trans*) and 5.73 (1H, m, CH = CH$_2$)); δ_D (61.4 MHz; CH_2Cl_2) 2.47 (0.15D, s, C(1)D), 2.70 (0.85D, s, C(5)D), 3.88 (0.85D, s, C(5)D) and 4.20 (0.15D, s, C(7a)D); δ_C (75 MHz; $CDCl_3$) 13.4 (*C*H$_3$), 25.6 (*C*(6)), 25.7 (*C*(7)), 30.6 (*C*(2)), 34.6 (*C*(1)), 53.7 (*C*(3)) and 70.2 (C(7a)) (Note: *C*(5)D$_2$ not distinguishable.); *m/z* (CI) 128 (MH$^+$ (–Br), 100%), 58 (10), 52 (51) and 44 (18).

Acknowledgements

For funding, the authors gratefully acknowledge the support of EPSRC (Project Studentship to S. B. and DTA funding to K. M. W.) and UCB Celltech (CASE funding to K. M. W.). Dr Jeremy Roberston (Oxford, UK) generously provided essential advice on the preparation and isolation of (±)-heliotridane. For NMR studies, we thank the late Dr Vladimir Sik, Dr Ivan Prokes and Dr Stephen J. Simpson (all Exeter, UK) and for mass spectra,

the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) and Mr Eric Underwood (Exeter, UK).

Notes and references

1 T. H. Lowry and K. S. Richardson in *Mechanism and Theory in Organic Chemistry*, HarperCollins, New York, 3rd edn, 1987, 232.
2 J. E. Baldwin, R. M. Adlington, R. T. Aplin, N. P. Crouch, G. Knight and C. J. Schofield, *J. Chem. Soc., Chem. Commun.*, 1987, 1651.
3 J. Clayden, J. H. Pink, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1998, **39**, 8377.
4 M. Miyano, *J. Org. Chem.*, 1981, **46**, 1854.
5 E. Vedejs and J. Little, *J. Am. Chem. Soc.*, 2002, **124**, 748.
6 G. B. Dudley, S. J. Danishefsky and G. Sukenick, *Tetrahedron Lett.*, 2002, **43**, 5605.
7 M. E. Wood, S. Bissiriou, C. Lowe and K. M. Windeatt, *Org. Biomol. Chem.*, 2008, **6**, 3048.
8 J. Robertson, J. Pillai and R, K. Lush, *Chem. Soc. Rev.*, 2001, **30**, 94.
9 R. Gosain, A. M. Norrish and M. E. Wood, *Tetrahedron Lett.*, 1999, **40**, 6673; R. Gosain, A. M. Norrish and M. E. Wood, *Tetrahedron*, 2001, **57**, 1399.
10 D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2708.
11 T. Shono, N. Kise, R. Nomura and A. Yamanami, *Tetrahedron Lett.*, 1993, **34**, 3577.
12 D. L. J. Clive, Y. Tao, A. Khodabocus, Y.-J. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, G. Gleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson and P. G. Vernon, *J. Am. Chem. Soc.*, 1994, **116**, 11275.
13 D. L. J. Clive, A. Khodabocus, M. Cantin and Y. Tao, *J. Chem. Soc., Chem. Commun.*, 1991, 1755; D. L. J. Clive, M. Cantin, A. Khodabocus, X. Kong and Y. Tao, *Tetrahedron*, 1993, **49**, 7917.
14 H. Tsumoto, C. Murata, N. Miyata, R. Taguchi and K. Kohda, *Chem. Pharm. Bull.*, 2003, **51**, 1399. Other than melting point for which there was a discrepancy, our analytical data for **15** matched those reported in; J. B. Christensen, *Molecules*, 2001, **6**, 47.
15 K. Nozaki, K. Oshima and K. Utimoto, *Tetrahedron*, 1989, **45**, 923.
16 M. E. Wood, M. J. Penny, J. S. Steere, P. N. Horton, M. E. Light and M. B. Hursthouse, *Chem. Commun.*, 2006, 2983.
17 C. J. Easton, *Chem. Rev.*, 1997, **97**, 53.
18 G. Brunton, D. Griller, L. R. C. Barclay and K. U. Ingold, *J. Am. Chem. Soc.*, 1976, **98**, 6803; G. Brunton, J. A. Gray, D. Griller, L. R. C. Barclay and K. U. Ingold, *J. Am. Chem. Soc.*, 1978, **100**, 4197.
19 L. Williams, S. E. Booth and K. Undheim, *Tetrahedron*, 1994, **50**, 13697.
20 D. C. Harrowven and I. L. Guy, *Chem. Commun.*, 2004, 1968.
21 A. Citterio, A. Arnoldi and F. Minisci, *J. Org. Chem.*, 1979, **44**, 2674.
22 J. Robertson, M. A. Peplow and J. Pillai, *Tetrahedron Lett.*, 1996, **37**, 5825.
23 A. Padwa and A. G. Waterson, *Tetrahedron*, 2000, **56**, 10159.
24 T. J. Barton, J. Lin, S. Ijadi-Maghsoodi, M. D. Power, X. Zhang, Z. Ma, H. Shimizu and M. S. Gordon, *J. Am. Chem. Soc.*, 1995, **117**, 11695.
25 R. Hooft, *Collect: Data Collection Software*, Nonius B.V., Delft, The Netherlands, 1998.
26 Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307.
27 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112.