Pergamon

Tetrahedron 57 (2001) 1399–1410

TETRAHEDRON

A concise method for the functionalisation of ethanolamine α to nitrogen using free radical methodology

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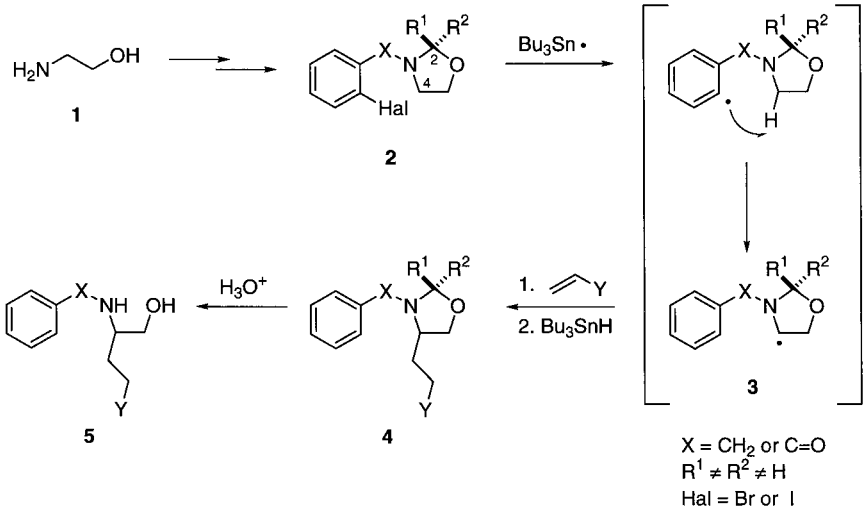
Received 2 October 2000; revised 9 November 2000; accepted 23 November 2000

Abstract—A method is described for the free radical functionalisation of ethanolamine at the carbon atom α to nitrogen. The key step of the methodology is a 1,5-hydrogen atom abstraction to produce an α-aminoalkyl radical at C-4 of a 1,3-oxazolidine.

We recently reported preliminary studies into the free–radical functionalisation of β-amino alcohols at the carbon atom α to nitrogen,[1] using 1,5-hydrogen atom abstraction as the key α-aminoalkyl radical[2] generating step. In developing this procedure, our aim was to produce a general method which would facilitate carbon–carbon bond formation at this carbon atom without the need for prior functionalisation. The methodology should also be compatible with a wide variety of functional groups to minimise the need for complex protection strategies, hence the choice of free radical based techniques. The experiments described herein concentrate on the functionalisation of ethanolamine **1** (Scheme 1) as a model system for more complex amino alcohols.

Ethanolamine derived 1,3-oxazolidines of general structure **2** containing an *N*-2-halobenzyl or *N*-2-halobenzoyl protecting–radical translocating (PRT) group,[3] when subjected to standard tin hydride mediated free radical generating conditions, represent a synthetically viable source of α-aminoalkyl radicals **3**. These radicals are produced via 1,5-hydrogen atom transfer and can be trapped with appropriate radicalphiles (Scheme 1). The lack of a hydrogen substituent at C-2 ensures that hydrogen atom abstraction



Scheme 1. Overall methodology.

Keywords: amino alcohols; oxazolidines; radicals.

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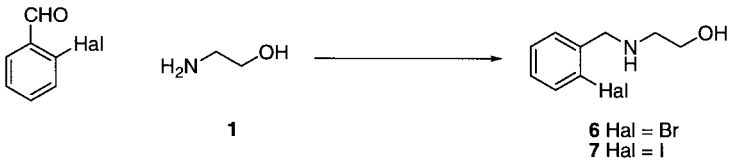
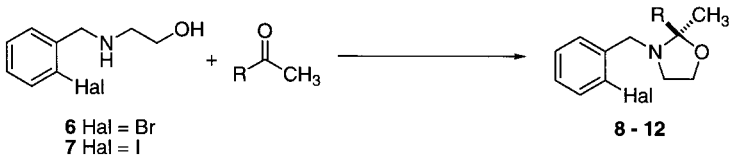


Scheme 2. *Reagents and conditions*: $NaBH_4$, EtOH (**6**, 89%; **7**, 91%).



Scheme 3. *Reagents and conditions*: see Table 1.[6,7]

Table 1. Results for Scheme 3 (*a*, $RCOCH_3$, TsOH (cat.), C_6H_6, Δ ($-H_2O$); *b*, EtO_2CCOCH_3, 4 Å mol. sieves, THF, RT)

Substrate	Hal	R	Method	Product	Yield (%)
6	Br	Ph-	*a*	**8**	83
6	Br	4-NO_2-C_6H_4-	*a*	**9**	100
6	Br	4-pyridyl-	*a*	**10**	72
7	I	4-pyridyl-	*a*	**11**	61
7	I	EtO_2C-	*b*	**12**	65

can only occur at C-4 as required and also gives an alkylated product **4** from which the functionalised, *N*-protected β-amino alcohol **5** can be obtained by mild hydrolytic cleavage.

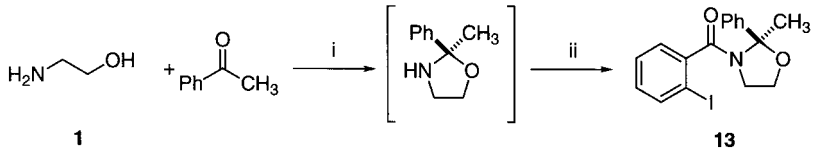
For more complex amino alcohols, already possessing an alkyl substituent α to nitrogen, the chiral centre in this starting material should offer the possibility for stereocontrol at C-2 during the 1,3-oxazolidine formation and, ultimately, transfer of stereochemical information back to C-4 during the intermediate radical trapping process, following Seebach's principle of self-reproduction of chirality.[4]

A variety of 1,3-oxazolidines **2** were prepared by two-step methods to investigate the structural features required to give them sufficient stability towards the typical reaction conditions and purification methods encountered in standard tin hydride based free radical procedures. *N*-2-Halobenzyl PRT groups (**2**, X=CH_2) were chosen initially to eliminate any possible amide configurational problems which could affect the efficiency of the 1,5-hydrogen atom abstraction in the corresponding *N*-2-halobenzoyl derivatives (**2**, X=C=O).[5] *N*-2-Halobenzoyl derivatives (**2**, X=C=O) were, however, also prepared for comparative purposes.

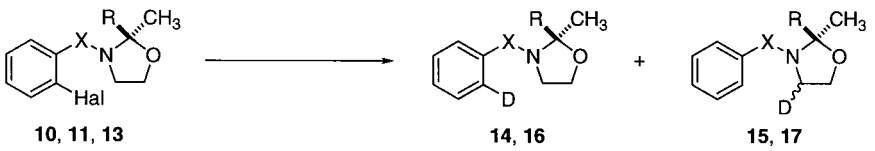
Firstly, the PRT group was introduced via a reductive amination procedure, leading to both the *N*-2-bromobenzyl **6** and *N*-2-iodobenzyl **7** derivatives as starting materials for ring closure (Scheme 2).

Condensation of **6** with acetophenone under Dean–Stark dehydrating conditions gave 1,3-oxazolidine **8** in good yield (83%, Scheme 3 and Table 1) but the heterocycle was found to be highly susceptible towards acidolytic cleavage, with repeated chromatography on silica gel resulting in substantial decomposition. Stability could be improved by the incorporation of an electron withdrawing group into the C-2 aromatic substituent, the 4-nitro derivative **9** proving to be stable towards chromatography on silica gel, but as expected, it proved to be incompatible with tin hydride mediated free radical procedures. It was found, however, that a 4-pyridyl or ethyl ester substituent at C-2 conferred adequate stability on compounds **10**, **11** and **12** which were used in preliminary studies.

N-2-Iodobenzoyl 1,3-oxazolidine **13** was also prepared for comparative purposes. For this example, the best yield (58%) was obtained by firstly condensing ethanolamine **1** with acetophenone under Dean–Stark dehydrating



Scheme 4. *Reagents and conditions*: i, $PhCOCH_3$, C_6H_6, Δ ($-H_2O$); ii, 2-iodobenzoyl chloride, Et_3N, C_6H_6, 0°C (58% over 2 steps).



Scheme 5. *Reagents and conditions*: see Table 2.

Table 2. Results for Scheme 5 (*a*, Bu_3SnD, AIBN, C_6H_6, Δ; *b*, Bu_3SnD, Et_3B, O_2, C_6H_6, RT)

Substrate	Hal	X	R	Method	Products (ratio)	Yield (%)
10	Br	CH_2	4-pyridyl-	*a*	**14**, **15** (1: 2)	74
11	I	CH_2	4-pyridyl-	*a*	**14**, **15** (1: 2)	92
13	I	C=O	Ph-	*a*	**16**, **17** (1: 1)	64
13	I	C=O	Ph-	*b*	**16**, **17** (1: 1)	100

conditions, followed by acylation of the crude reaction product with 2-iodobenzoyl chloride in the presence of triethylamine (Scheme 4). As expected, this derivative proved to be highly stable towards silica gel chromatography, particularly when compared with the corresponding *N*-2-iodobenzyl derivative **11**. Unfortunately, NMR spectra of **13** recorded at room temperature were complicated by the presence of amide rotamers.

In order to obtain a qualitative insight into the efficiency of the proposed hydrogen atom transfer step for both classes of PRT group equipped 1,3-oxazolidine, reductions of derivatives **10**, **11** and **13** were carried out using tributyltin deuteride under different initiation conditions. In all cases, all of the required tributyltin deuteride was added at the start of the reaction, resulting in conditions which would be expected to disfavour 1,5-hydrogen atom abstraction. Pleasingly, in all cases, significant levels of deuterium incorporation were found at C-4 in both of the final products **15** and **17**. The optimised results for these experiments are summarised in Scheme 5 and Table 2.

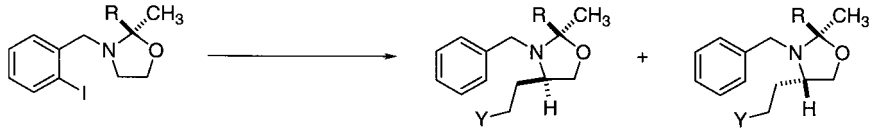
N-2-Iodobenzyl derivative **11** could be reduced more cleanly and efficiently than the corresponding bromide **10**, hence this derivative was used in all future experiments. Both **10** and **11** gave a 1: 2 ratio of deuterated products **14** and **15** (determined by ^2H NMR), in favour of the required C-4 deuterio derivative **15**, which was produced as a 1:1 mixture of diastereoisomers. **13** gave a 1:1 mixture of deuterated products **16** and **17** with quantitative reduction occurring under triethylborane/oxygen mediated initiation conditions. Mass spectrometry confirmed the presence of only one deuterium atom in all of the products **14**–**17**. (Note: all spectra were compared with the corresponding unlabelled samples.)

Two radicalphiles, *tert*-butyl acrylate and acrylonitrile, were then introduced into the system in an attempt to form carbon–carbon bonds at C-4. Scheme 6 and Table 3 show the optimised results for these studies.

Slow addition of tributyltin hydride (3 eq.) and AIBN to a benzene solution of the C-2 4-pyridyl derivative **11** under reflux, in the presence of a 3-fold excess of *tert*-butyl acrylate, gave a reasonable (50%) isolated yield of the required product **18a/b** as an inseparable 2:1 diastereoisomer mixture.[8] Photochemical AIBN cleavage at room temperature resulted in a significant reduction in the number of minor side-products for the same process, using *tert*-butyl acrylate (5 eq.), whilst maintaining a comparable isolated yield (54%) of alkylated products **18a/b**. Most importantly, however, it was found, under these conditions, that slow addition of tributyltin hydride/AIBN was not necessary, despite the excess of tin hydride which was found to be required for optimal results. Similarly, the use of triethylborane/oxygen initiation gave rise to a very 'clean' reaction which gave a comparable yield of **18a/b** with an identical ratio of diastereoisomers. These results were echoed with acrylonitrile as the radicalphile with an isolated yield of 51% of **19a/b** as an inseparable 2:1 diastereoisomer mixture being obtained.

Ethyl pyruvate derived 1,3-oxazolidine **12** gave lower yields of alkylated products **20a/b** and **21a/b** with *tert*-butyl acrylate and acrylonitrile respectively (triethylborane/oxygen initiation), although with a slightly improved diastereoisomer ratio of 3:1 in both cases. The acrylonitrile trapped products **21a** and **21b** proved to be separable, allowing the assignment of relative stereochemistry using NOESY[9] experiments. The major stereoisomer proved to be that in which the newly introduced C-4 substituent and the C-2 ethyl ester were *cis* relative to each other. The key NOESY results obtained are summarised in Fig. 1. (Note: all other NOE enhancements support these stereochemical assignments.)

A possible explanation for the observed stereochemistry is that the intermediate α-aminoalkyl radical **22** could preferentially adopt an envelope conformation in which the C-2 ethyl ester is *pseudo*-equatorial and the methyl



10, 12 **18a - 21a** **18b - 21b**

Scheme 6. *Reagents and conditions*: CH_2=CH-Y (2.2–7.4 equiv.), Bu_3SnH, initiator (see Table 3), C_6H_6.

Table 3. Results for Scheme 6 (*a*, AIBN, Δ (slow addition); *b*, AIBN, hν, RT (no slow addition); *c*, Et_3B, O_2 (no slow addition))

Substrate	R	Y	Method	Isolated yield (%)	Products (dr[8])
11	4-pyridyl-	$-CO_2{}^tBu$	*a*	50	**18a/b** (2:1)
11	4-pyridyl-	$-CO_2{}^tBu$	*b*	54	**18a/b** (2:1)
11	4-pyridyl-	$-CO_2{}^tBu$	*c*	42	**18a/b** (2:1)
11	4-pyridyl-	-CN	*b*	51	**19a/b** (2:1)
11	4-pyridyl-	-CN	*c*	51	**19a/b** (2:1)
12	EtO_2C-	$-CO_2{}^tBu$	*c*	41	**20a/b** (3:1)
12	EtO_2C-	-CN	*c*	26	**21a/b** (3:1)

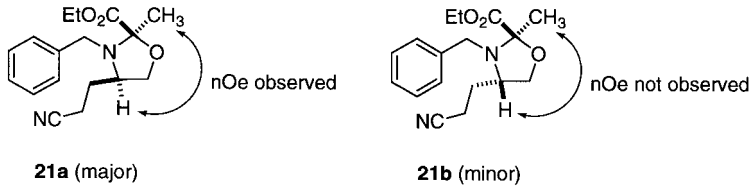


Figure 1. Key NOESY results.

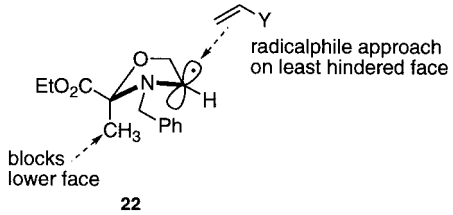
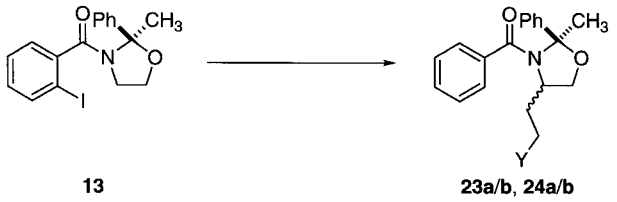


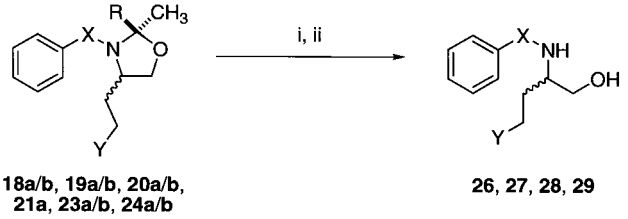
Figure 2. Possible explanation for observed diastereoselectivity.



Scheme 7. *Reagents and conditions*: CH_2=CH-Y (2.8–8.5 equiv.), Bu_3SnH, AIBN (see Table 4).

Table 4. Results for Scheme 7 (*a*, Bu_3SnH, AIBN, C_6H_6, Δ (slow addition); *d*, Bu_3SnCl (15 mol%), $NaBH_3CN$, AIBN, ^tBuOH, Δ)

Substrate	R	Y	Method	Isolated yield (%)	Products (dr[8])
13	Ph-	-$CO_2{}^t$Bu	*a*	70	**23a/b** (2.5:1)
13	Ph-	-CN	*a*	59	**24a/b** (1.7:1)
13	Ph-	-$CO_2{}^t$Bu	*d*	75	**23a/b** (2.0:1)
13	Ph-	-CN	*d*	61	**24a/b** (1.8:1)



Scheme 8. *Reagents and conditions*: i, see Table 5; ii, neutral alumina (for products **26** and **27** only).

group *pseudo*-axial (Fig. 2). Approach of the acrylonitrile radicalphile on the least hindered face, away from the methyl group, would give rise to the stereochemistry observed in the major product.

Similar NOESY experiments carried out on the mixture of diastereoisomers of **20a** and **20b** again suggested that the major diastereoisomer obtained was that in which the C-4 substituent was *cis* to the C-2 ethyl ester (**12a**).

Significantly improved yields were observed for analogous reactions using the *N*-2-iodobenzoyl 1,3-oxazolidine **13**. The optimised results, summarised in Scheme 7 and Table 4, were obtained under slow addition conditions using a 2.8 fold excess of *tert*-butyl acrylate and an 8.5 fold excess of acrylonitrile to give products **23a/b** and **24a/b** respectively. **24a/b** was obtained as a 2.5:1 mixture of diastereoisomers (70% yield) and **24a/b** as a 1.7:1 mixture (59% yield), neither of which proved to be readily separable. Again, NMR spectra were complicated by the presence of amide rotamers which unfortunately prevented definitive assignments of C-2/C-4 relative stereochemistry by NOE studies.

The improvement in isolated yield here can, to some extent, be attributed to the enhanced stability of the *N*-benzoylated 1,3-oxazolidine moiety compared with its *N*-benzylated counterpart towards silica gel chromatography.

Importantly, it was also found that the reaction conditions using *N*-2-iodobenzoyl substrate **13** could be modified to replace the excess of tributyltin hydride from the earlier experiments with a catalytic quantity (15 mol%) of tributyltin chloride and in situ reduction to the hydride using sodium cyanoborohydride. Good yields of **23a/b** and **24a/b** were obtained (75% and 61% respectively) with similar diastereoisomeric ratios to those obtained in the earlier experiments and a simplified purification procedure could now be employed. (Note: these conditions proved unsuitable with *N*-2-iodobenzyl substrate **11**, where reductive ring-opening of the 1,3-oxazolidine[10] proved to be the major competing reaction pathway.)

Table 5. Conditions and results for Scheme 8 (*a*, HCl, H_2O, THF, RT; *b*, Amberlite® IR-120 (H^+ form), CH_3CN, RT)

Substrate	X	R	Y	Method	Isolated yield (%)	Product
18a/b	CH_2	4-pyridyl-	-$CO_2{}^t$Bu	*a*	99	**26**
19a/b	CH_2	4-pyridyl-	-CN	*a*	99	**27**
20a/b	CH_2	EtO_2C-	-$CO_2{}^t$Bu	*a*	84	**26**
21a/b	CH_2	EtO_2C-	-CN	*a*	48	**27**
23a/b	C=O	Ph-	-$CO_2{}^t$Bu	*b*	76	**28**
24a/b	C=O	Ph-	-CN	*b*	89	**29**

All of the alkylated products could be cleaved efficiently to the corresponding alkylated, *N*-protected β-amino alcohols under mild acidolytic conditions (Scheme 8). Diastereoisomer mixtures **18a/b**, **19a/b** and **20a/b** and major diastereoisomer **21a** were all cleaved using aqueous hydrochloric acid in dilute tetrahydrofuran solutions to give the corresponding β-amino alcohols **26** and **27**. (Note: significant degradation of nitrile containing product **27** was observed with prolonged exposure to the hydrolysis conditions.) The free amines in each case could be released from their hydrochloride salts by chromatography using a neutral alumina stationary phase.[11]

N-Benzoyl derivatives **23a/b** and **24a/b** were hydrolysed using a suspension of Amberlite® IR-120 (H^+ form) ion exchange resin in acetonitrile solution, the acetophenone produced in these reactions being removed under high vacuum. Again, the hydrolysis procedure proved to be efficient, products **28** and **29** being obtained in 76% and 89% yields respectively. The results of all of these hydrolyses are summarised in Scheme 8 and Table 5.

In summary, we have developed a viable, mild method for the functionalisation of ethanolamine at the carbon α to the nitrogen which does not require prior functionalisation of the β-amino alcohol. The key step in this synthetic procedure is an efficient 1,5-hydrogen atom transfer using a nitrogen protecting, radical translocating (PRT) group and we are currently developing extensions of this methodology for the functionalisation of more complex β-amino alcohols, particularly those already containing one alkyl substituent α to nitrogen, where significant possibilities for stereocontrol exist. The methodology has the potential for development into a useful synthetic approach towards highly substituted amine derivatives including α,α-disubstituted α-amino acids.

1. Experimental

1.1. General

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

Infrared spectra were recorded using a Nicolet Magna 550 spectrometer with major absorbances being quoted using the abbreviations: w, weak; m, medium; s, strong and br, broad. Thin film samples were prepared by evaporation of a dilute chloroform solution of the compound on a sodium chloride plate.

^{1}H NMR spectra were obtained using either Brüker AM300 or Brüker Advance DRX400 spectrometers at operating frequencies of 300 and 400 MHz respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane as reference with coupling constants being given to the nearest 0.5 Hz. The abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad are used.

^{13}C NMR spectra were obtained using either a Brüker ACF300 or Brüker Advance DRX400 spectrometer at operating frequencies of 75 and 100 MHz, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane as reference, assignments being derived from DEPT[9] editing.

^{2}H NMR spectra were obtained using a Brüker Advance DRX400 spectrometer operating at 61.4 MHz. Chemical shifts are quoted in ppm relative to tetramethylsilane with internal referencing to deuteriochloroform.

Mass spectra were determined using a Kratos Profile HV3 instrument, a Thermoquest Finnigan TRACE 2000 GC-MS instrument or by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK in electron impact (EI), ammonia chemical ionisation (CI) and positive ion electrospray (ES^+) modes.

Analytical thin layer chromatography was carried out using glass or aluminium backed plates coated with Merck Kieselgel 60 F_{254}, with developed plates being visualised by quenching of u.v. fluorescence or by staining with iodine or potassium permanganate as appropriate. Flash chromatography was carried out using BDH silica gel with particle size 40–63 μm.

Solvents and reagents were used as supplied or purified using standard procedures as described in Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, 1988 as appropriate. Petroleum ether refers to the fraction of light petroleum ether boiling between 40 and 60°C.

Solvents were removed under reduced pressure using a Büchi R110 Rotavapor equipped with a water or dry ice condenser as appropriate.

1.1.1. *N*-(2-Bromobenzyl)-2-aminoethanol (6). A mixture of ethanolamine **1** (1.28 cm^3, 21.3 mmol), 2-bromobenzaldehyde (3.90 g, 21.1 mmol) and anhydrous potassium carbonate (3.00 g, 21.7 mmol) in ethanol (10 cm^3) was heated under reflux for 1 h. After cooling to room temperature, the reaction mixture was filtered and sodium borohydride (960 mg, 25.4 mmol) was added, the resulting mixture being stirred at room temperature for 3 h. The reaction mixture was then concentrated in vacuo and the residue cooled in an ice bath before acidification by dropwise addition of hydrochloric acid (2 M). The resulting aqueous solution was extracted with ethyl acetate (2×15 cm^3) and concentrated in vacuo to a thick paste to which was added saturated aqueous sodium bicarbonate (30 cm^3). The resulting aqueous solution was extracted with ethyl acetate (3×20 cm^3) and the combined extracts were dried (magnesium sulfate), filtered and evaporated in vacuo to give the *title compound* as a colourless oil (4.30 g, 89%); R_f 0.15 (4:1 v/v EtOAc:petroleum ether); ν_{max}/cm^{-1} (thin film) 3520-3075brs (N-H, O-H), 2980–2730s (C-H), 1591w, 1568w, 1468s, 1441s, 1109m, 1053s, 1026s, 752s and 658m; δ_H (400 MHz; $CDCl_3$) 2.78 (2H, t, *J* 5, CH_2NH), 3.67 (2H, t, *J* 5, CH_2OH), 3.88 (2H, s, ArCH_2), 7.12 (1H, dt, *J* 8 and 1 Ar-*H*), 7.26–7.37 (2H, m, Ar-*H*) and 7.54 (1H, d, *J* 8, Ar-*H*); δ_C (100 MHz; $CDCl_3$) 50.3 (*C*H_2NH), 53.2 (*C*H_2OH), 61.0 (Ar*C*H_2), 124.1 (Ar*C*Br), 127.5, 128.8, 130.4 (Ar*C*H), 132.9 (Ar*C*H) and 138.7 (Ar$_{ipso}$*C*CH$_2$); *m/z* (CI) 232 (MH^+, 100%), 230 (MH^+, 100), 152 (61), 62 (17)

and 52 (20); *m/z* (EI) 200 (72%), 198 (70), 171 (100), 169 (98), 118 (25), 91 (52), 90 (52), 89 (66), 63 (40) and 51 (25); (Found MH^+ (ES^+) 230.0182, $C_9H_{13}{}^{79}BrNO$ requires 230.0180).

1.1.2. *N*-(2-Iodobenzyl)-2-aminoethanol (7). Using the procedure described above for the preparation of *N*-(2-bromobenzyl)-2-aminoethanol **6**, with ethanolamine **1** (690 μl, 11.5 mmol), 2-iodobenzaldehyde (2.30 g, 9.9 mmol), anhydrous potassium carbonate (3.00 g, 21.7 mmol) and sodium borohydride (470 mg, 12.4 mmol), the *title compound* was prepared as a colourless oil (2.50 g, 91%); R_f 0.14 (4:1 v/v EtOAc:petroleum ether); ν_{max}/cm^{-1} (thin film) 3500–3080brs (N-H, O-H), 3000–2750s (C-H), 1603w, 1588w, 1562w, 1455s, 1434s, 1107s, 1015s and 748s; δ_H (400 MHz; $CDCl_3$) 2.75 (2H, brs, N*H*, O*H*), 2.79 (2H, m, CH_2NH), 3.68 (2H, d, *J* 5, CH_2OH), 3.83 (2H, s, ArCH_2), 6.95 (1H, m, Ar-*H*), 7.31 (2H, m, Ar-*H*) and 7.82 (1H, dd, *J* 8 and 1, Ar-*H*); δ_C (100 MHz; $CDCl_3$) 50.3 (*C*H_2NH), 57.6 (*C*H_2OH), 61.0 (Ar*C*H_2), 99.7 (Ar*C*I), 128.4, 129.0, 129.8 (Ar*C*H), 139.6 (Ar*C*H) and 141.7 ($Ar_{ipso}CCH_2$); *m/z* (CI) 278 (MH^+, 31%), 134 (100), 108 (90) 106 (50) and 62 (29); *m/z* (EI) 277 (M^+, 4%), 246 (89), 217 (100), 118 (29), 91 (62), 90 (48) and 89 (44); (Found MH^+ (CI) 278.0045, $C_9H_{13}INO$ requires 278.0042).

1.1.3. 2-Phenyl-2-methyl-3-(2-bromobenzyl)-oxazolidine (8). A solution of *N*-(2-bromobenzyl)-2-aminoethanol **6** (1.42 g, 6.2 mmol), acetophenone (800 mg, 6.7 mmol) and 4-toluenesulfonic acid monohydrate (53 mg, 0.28 mmol) in benzene (50 cm^3) was heated under reflux using a Dean–Stark water separator for 12 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 3:1 v/v hexane: ethyl acetate) to give the *title compound* as a colourless oil (1.70 g, 83%); R_f 0.30 (3:1 v/v hexane:EtOAc); ν_{max}/cm^{-1} (thin film) 3127–2758m (C-H), 1653w, 1596s, 1559m, 1495m, 1456s, 1407m, 1375m, 1282w, 1210m, 1156m, 1065s, 1025s, 821s, 741w, 698s and 668w; δ_H (400 MHz; $CDCl_3$) 1.69 (3H, s, CH_3C), 2.87 (2H, m, NCH_2CH_2), 3.76, 3.95 (2×1H, ABq, J_{AB} 14, ArCH_2), 3.81 (1H, m, CH_2O), 4.02 (1H, ca. q, *J* 7.5, CH_2O), 7.13 (1H, dt, *J* 6 and 1, Ar-*H*), 7.25 (4H, complex, Ar-*H* and Ph-*H*), 7.56 (1H, dd, *J* 8 and 1, Ar-*H*) and 7.61–7.69 (3H, complex, Ar-*H* and Ph-*H*); δ_C (75MHz; $CDCl_3$) 24.2 (*C*H_3C), 50.3 (N*C*H_2CH_2), 53.1 (Ar*C*H_2), 98.7 (CH_3*C*), 124.3 (Ar*C*Br), 126.1, 127.4, 128.0, 128.4, 130.6, 132.8 (Ar*C*H and Ph*C*H) and 138.9, 145.3 ($Ar_{ipso}C$ and $Ph_{ipso}C$); *m/z* (EI) 318 ($[M-CH_3]^+$, 99%), 316 ($[M-CH_3]^+$, 100), 256 (44), 254 (45), 171 (90), 169 (91), 132 (12), 105 (27), 91 (51), 34 (77) and 51 (12).

1.1.4. 2-(4-Nitrobenzyl)-2-methyl-3-(2-bromobenzyl)-oxazolidine (9). A solution of *N*-(2-bromobenzyl)-2-aminoethanol **6** (2.33 g, 10.1 mmol), 4-nitroacetophenone (1.67 g, 10.1 mmol) and 4-toluenesulfonic acid monohydrate (2 crystals) in benzene (50 cm^3) was heated under reflux using a Dean–Stark water separator for 12 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 2:1 v/v hexane:ethyl acetate) to give the *title compound* as a yellow oil (3.83 g, 100%); R_f 0.30 (10:9:1 v/v/v hexane:EtOAc:Et_3N); ν_{max}/cm^{-1} (thin film) 3131–2761m (C-H), 1605w, 1521s, 1496w, 1456w, 1349s, 1279w, 1211w, 1082m, 1015w, 847m, 756w, 738w and 699m; δ_H (300 MHz; $CDCl_3$) 1.72 (3H, s, CH_3C), 2.76, 2.93 (2×1H, 2×m, NCH_2CH_2), 3.70–3.81, 4.02–4.12 (2×2H, 2×complex, CH_2CH_2O and ArCH_2), 7.19 (1H, t, *J* 7, Ar-*H*), 7.37 (1H, t, *J* 7, Ar-*H*), 7.59 (2H, t, *J* 7, Ar-*H*) and 7.84, 8.21 (2×1H, AA′BB′, *J* 9, Ar-*H* of 4-NO_2Ph-); δ_C (75 MHz; $CDCl_3$) 24.3 (*C*H_3C), 50.2 (N*C*H_2CH_2), 53.0 (CH_2*C*H_2O), 63.0 (Ar*C*H_2), 98.6 (CH_3*C*), 123.5 (Ar*C*-H), 124.5 (Ar*C*-Br), 127.1, 127.5, 128.8, 130.7, 133.0 (Ar*C*-H), 138.3 ($Ar_{ipso}C$, 2-I-Ph-), 147.4 (Ar*C*-NO_2) and 153.2 ($Ar_{ipso}C$, 4-NO_2Ph-); *m/z* (EI) 363 ($[M-CH_3]^+$, 36%), 361 ($[M-CH_3]^+$, 38), 256 (27), 254 (29), 171 (98), 169 (100), 90 (42) and 77 (17).

1.1.5. 4-(3-(2-Bromobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine (10). A solution of *N*-(2-bromobenzyl)-2-aminoethanol **6** (3.73 g, 16.2 mmol), 4-acetylpyridine (1.94 g, 16.0 mmol) and 4-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) in benzene (50 cm^3) was heated under reflux, using a Dean–Stark water separator for 6 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 1:1 v/v petroleum ether: ethyl acetate) to give the *title compound* as a yellow oil (3.83 g, 72%); R_f 0.40 (1:1 v/v petroleum ether:EtOAc); ν_{max}/cm^{-1} (thin film) 3114–2767m (C-H), 1594m, 1562w, 1466m, 1439s, 1404w, 1367w, 1334w, 1155w, 1207m, 1156m, 1080s, 1025s, 815m and 751s; δ_H (400 MHz; $CDCl_3$) 1.64 (3H, s, CH_3C), 2.75 (1H, m, NCH_2CH_2), 2.90 (1H, m, NCH_2CH_2), 3.74 (1H, m, CH_2CH_2O), 3.75, 4.00 (2×1H, ABq, J_{AB} 14, ArCH_2), 4.03 (1H, *ca*. q, *J* 7.5, CH_2CH_2O), 7.12 (1H, t, *J* 7.5, Ar-*H*), 7.30 (1H, t, *J* 7.5, Ar-*H*), 7.48-7.58 (4H, complex, 2×Ar-*H* and 2×pyridine C*H*) and 8.59 (2H, part of AA′BB′, *J* 5, pyridine C*H*); δ_C (100 MHz; $CDCl_3$) 23.9 (*C*H_3C), 50.2 (N*C*H_2CH_2), 53.0 (CH_2*C*H_2O), 63.1 (Ar*C*H_2), 97.9 (CH_3*C*), 121.1 (pyridine *C*H), 124.4 (Ar*C*Br), 127.4, 128.7, 130.6, 133.0 (Ar*C*H), 138.4 ($Ar_{ipso}CCH_2$), 149.8 (pyridine *C*H) and 154.4 ($pyridine_{ipso}C$); *m/z* (CI) 335 (MH^+, 100%), 333 (MH^+, 100%), 256 (5) and 254 (5); *m/z* (EI) 319 (28%), 317 (29), 256 (67), 254 (70), 171 (100), 169 (100), 90 (55), 78 (40), 51 (40) and 43 (25); (Found MH^+ (ES^+) 333.0604, $C_{16}H_{17}{}^{79}BrN_2O$ requires 333.0602).

1.1.6. 4-(3-(2-Iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine (11). Using the procedure described above for the preparation of 4-(3-(2-bromobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **10**, with *N*-(2-iodobenzyl)-2-aminoethanol **7** (1.90 g, 6.90 mmol), 4-acetylpyridine (1.03 g, 8.50 mmol) and *p*-toluenesulfonic acid (52 mg, 0.27 mmol), the *title compound* was prepared as a colourless oil (1.61 g, 61%); R_f 0.40 (1:1 v/v hexane:EtOAc); ν_{max}/cm^{-1} (thin film) 3105-2765m (C-H), 1595m, 1559m, 1461m, 1439m, 1408m, 1375m, 1271m, 1218w, 1209m, 1147w, 1092w, 1058w, 1023s, 823m, 751s, 669m and 654m; δ_H (400 MHz; $CDCl_3$) 1.67 (3H, s, CH_3C), 2.74 (1H, m, NCH_2CH_2), 2.89 (1H, m, NCH_2CH_2), 3.68, 3.96 (2×1H, ABq, J_{AB} 14, ArCH_2), 3.73 (1H, m, CH_2O), 4.03 (1H, ca. q, *J* 7.5, CH_2O), 6.97 (1H, dt, *J* 8 and 1.5, Ar-*H*), 7.35 (1H, t, *J* 8, Ar-*H*), 7.53 (1H, d, *J* 8, Ar-*H*), 7.55, 8.58 (2×2H, AA′BB′, *J* 6, pyridine C*H*) and 7.86 (1H, dd, *J* 8 and 1, Ar-*H*); δ_C (100 MHz; $CDCl_3$) 24.1 (*C*H_3C), 50.0

(N*C*H$_2$CH$_2$), 57.6 (CH$_2$*C*H$_2$O), 63.0 (Ar*C*H$_2$), 97.9 (CH$_3$*C*), 100.2 (Ar*C*I), 121.1 (pyridine *C*H), 128.2, 128.9, 130.3, 139.7 (Ar*C*H), 141.2 (Ar$_{ipso}$*C*CH$_2$), 149.9 (pyridine *C*H) and 154.4 (pyridine$_{ipso}$*C*); *m/z* (CI) 381 (MH$^+$, 100%), 255 (63), 139 (37), 134 (81), 122 (97) and 108 (24); *m/z* (EI) 365 (37), 302 (81), 217 (100), 91 (57), 90 (49), 89 (33), 78 (28), 51 (29) and 43 (19); (Found MH$^+$ (ES$^+$) 381.0476, $C_{16}H_{18}IN_2O$ requires 381.0464).

1.1.7. 3-(2-Iodobenzyl)-2-methyl-oxazolidine-2-carboxylic acid ethyl ester (12). Ethyl pyruvate (540 μl, 4.86 mmol) was added dropwise to a vigorously stirred mixture of *N*-(2-iodobenzyl)-2-aminoethanol **7** (1.15 g, 4.15 mmol) and powdered 4 Å molecular sieves (3.00 g) in tetrahydrofuran (40 cm^3). After stirring at room temperature overnight, the molecular sieves were removed by filtration and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel (eluting with dichloromethane) to give the *title compound* as a yellow oil (1.01 g, 65%); R_f 0.40 (CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 3070–2750m (C-H), 1732s (C=O), 1564w, 1437m, 1375m, 1248s, 1200s, 1126s, 1109s, 1026s, 1013s, 901w, 752s and 650w; δ_H (400 MHz; $CDCl_3$) 1.36 (3H, t, *J* 7, C*H*$_3$CH$_2$), 1.59 (3H, s, C*H*$_3$C), 2.92 (1H, *ca*. q, *J* 8, C*H*$_2$N), 3.04 (1H, m, C*H*$_2$N), 3.63, 3.90 (2×1H, ABq, J_{AB} 14, ArC*H*$_2$), 4.02 (1H, *ca*. q, *J* 4, CH$_2$C*H*$_2$O), 4.14 (1H, m, CH$_2$C*H*$_2$O), 4.26 (2H, m, CH$_3$C*H*$_2$), 6.95 (1H, m, Ar-*H*), 7.33 (1H, m, Ar-*H*), 7.45 (1H, m, Ar-*H*) and 7.82 (1H, dd, *J* 8 and 1, Ar-*H*); δ_C (100 MHz; $CDCl_3$) 14.6 (*C*H$_3$CH$_2$), 21.3 (*C*H$_3$C), 49.8 (*C*H$_2$N), 57.5 (*C*H$_2$OCN), 60.9 (Ar*C*H$_2$), 65.8 (CH$_3$*C*H$_2$O), 94.5 (N*C*O), 99.4 (Ar*C*I), 128.3, 128.9, 129.8, 139.5 (Ar*C*H), 140.6 (Ar$_{ipso}$*C*CH$_2$) and 171.3 (*C*=O); *m/z* (CI) 376 (MH$^+$, 38%), 250 (32), 134 (100), 108 (39), 106 (63), 86 (43) and 61 (33); *m/z* (EI) 302 (100%), 217 (44), 91 (100) and 43 (93); (Found MH$^+$ (ES$^+$) 376.0415, $C_{14}H_{19}INO_3$ requires 376.0409).

1.1.8. (2-Iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone (13). A solution of ethanolamine **1** (593 μl, 9.82 mmol) and acetophenone (940 mg, 7.82 mmol) in benzene (100 cm^3) was heated under reflux using a Dean and Stark water separator for 24 h. The dark residue obtained from evaporation of the solvent in vacuo was dissolved in ethyl acetate (30 cm^3) and the resulting solution was washed with water (2×15 cm^3), dried (sodium sulfate), filtered and evaporated in vacuo. A solution of the residue in dichloromethane (10 cm^3) was added dropwise over 30 min to a stirred solution of 2-iodobenzoyl chloride (2.050 g, 7.69 mmol) and triethylamine (2.50 cm^3, 17.94 mmol) in benzene at 0°C under a nitrogen atmosphere. The stirred reaction mixture was allowed to attain room temperature over 3 h and after stirring at this temperature for a further 3 h, a saturated aqueous solution of sodium bicarbonate (15 cm^3) was added and the resulting biphasic mixture stirred for a further 30 min. The separated aqueous phase was extracted with dichloromethane (3×15 cm^3) and the combined organic extracts were dried (sodium sulfate), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluting with 3:1 v/v hexane:ethyl acetate) to give the *title compound* as a yellow oil which crystallised on standing to a yellow solid (1.740 g, 58%); m.p. 122–124°C; R_f 0.36 (3:1 v/v hexane:EtOAc); ν_{max}/cm^{-1} (thin film) 3138–2826w (C-H), 1653s (C=O), 1585m, 1559w, 1404s, 1226m, 1071m, 1046m, 766m, 698m and 639m; δ_H (400 MHz; $CDCl_3$) 2.20 (3H, s, C*H*$_3$C), 2.29-2.54 (2H, brm, NC*H*$_2$), 3.85 (1H, ca. q, *J* 7, NC*H*$_2$), 4.07 (1H, m, C*H*$_2$O), 7.09 (1H, dt, *J* 8 and 2, Ar-*H*), 7.24–7.46 (5H, complex, Ph-*H*), 7.68 (2H, brs, ArC-*H*) and 7.84 (1H, d, *J* 8, ArC-*H*); δ_C (100 MHz; $CDCl_3$) 25.1 (br, *C*H$_3$), 48.4 (*C*H$_2$N), 63.5 (*C*H$_2$O), 91.3 (CH$_3$*C*), 96.8 (Ar*C*I), 126.0, 126.6, 128.2, 128.9, 130.3, 139.4 (Ar*C*H and Ph*C*H), 143.7 (Ph$_{ipso}$*C*) and 167.3 (*C*=O); *m/z* (CI) 411 (MNH$_4^+$, 17%), 394 (MH$^+$, 15), 285 (43), 268 (100), 165 (35), 148 (29), 138 (26), 120 (22), 86 (8) and 61 (5); *m/z* (EI) 378 (32%), 316 (13), 231 (100), 203 (21), 117 (12), 105 (52), 77 (76), 76 (39), 51 (22) and 43 (14); (Found MH$^+$ (ES$^+$) 394.0303, $C_{17}H_{17}INO_2$ requires 394.0304).

1.1.9. 4-(3-(2-Deuteriobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine (14) and 4-(4-deuterio-3-benzyl-2-methyl-oxazolidin-2-yl)-pyridine (15). A de-gassed solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (380 mg, 1.00 mmol), tributyltin deuteride (554 μl, 2.05 mmol) and 2,2′-azobisisobutyronitrile (12 mg, 0.07 mmol) in benzene (25 cm^3) was heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (15 cm^3) and the resulting solution was stirred with aqueous sodium hydroxide solution (1.0 M, 5.0 cm^3) for 20 min before the separated organic phase was dried (sodium sulfate), filtered and evaporated to give a residue which was purified by flash chromatography on silica gel (eluting with 3:1 v/v hexane: ethyl acetate). This gave the *title compound* mixture (1:2, **14**:**15**) as a yellow oil (234 mg, 92%); R_f 0.40 (1:1 v/v hexane:EtOAc); δ_D (61.4 MHz; CCl_4) 2.66 (0.33D, s, NCH*D*CH$_2$), 2.78 (0.33D, s, NCH*D*CH$_2$) and 7.31 (0.33D, s, Ph-*D*); *m/z* (CI) 256 (MH$^+$, 24%), 153 (30), 122 (70), 121 (60), 109 (28), 108 (100), 106 (50) and 80 (33).

Key comparative data for unlabelled 4-(3-benzyl-2-methyl-oxazolidin-2-yl)-pyridine: ν_{max}/cm^{-1} (thin film) 3111–2755w (C-H), 1595m, 1551w, 1495w, 1453m, 1407m, 1375w, 1281w, 1210w, 1156w, 1065w, 1023m, 822m, 736w, 699m and 667w; δ_H (400 MHz; $CDCl_3$) 1.62 (3H, s, C*H*$_3$C), 2.76, 2.87 (2×1H, 2×m, NC*H*$_2$CH$_2$), 3.60, 3.91 (2×1H, ABq, J_{AB} 13, PhC*H*$_2$), 3.75 (1H, m, CH$_2$C*H*$_2$O), 3.98 (1H, *ca*. q, *J* 7.5, CH$_2$C*H*$_2$O), 7.22–7.45 (5H, complex, Ph-*H*), and 7.52, 8.59 (2×1H, AA′BB′, *J* 6, pyridine C*H*); δ_C (100 MHz; $CDCl_3$) 23.6 (*C*H$_3$C), 50.2 (N*C*H$_2$CH$_2$), 53.5 (CH$_2$*C*H$_2$O), 63.3 (Ph*C*H$_2$), 97.4 (CH$_3$*C*), 121.1 (pyridine *C*H), 127.1, 128.3, 128.4 (Ph*C*H), 139.4 (Ph$_{ipso}$*C*), 149.8 (pyridine *C*H) and 154.4 (pyridine$_{ipso}$*C*); *m/z* (CI) 255 (MH$^+$, 100%), 176 (5), 152 (5), 122 (4) and 108 (6); *m/z* (EI) 254 (M$^+$, 1%), 239 (42), 176 (65), 133 (10), 91 (100) and 65 (23); (Found MH$^+$ (ES$^+$) 255.1502, $C_{16}H_{19}N_2O$ requires 255.1497).

1.1.10. (2-Deuteriophenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone (16) and (2-phenyl)-(4-deuterio-2-phenyl-2-methyl-oxazolidin-3-yl)-methanone (17). Triethylborane (1.0 M solution on tetrahydrofuran, 100 μl, 0.1 mmol) was added to a solution of (2-iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone **13** (71.5 mg, 0.18 mmol) and tributyltin deuteride (148 μl, 0.55 mmol) in benzene (8 cm^3) at room temperature. After stirring for 12 h, aqueous sodium hydroxide solution (1.0 M, 20 cm^3) was

added and the biphasic mixture was stirred for 20 min before the separated organic phase was dried (sodium sulfate), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluting with 5:2 v/v petroleum ether:ethyl acetate) to give the *title compound* mixture (1:1, **16**:**17**) as a colourless oil (48.5 mg, 100%); R_f 0.31 (3:1 v/v hexane:EtOAc); δ_D (61.4 MHz; CCl_4) 3.57 (0.25D, s, NCH*D*CH_2), 3.69 (0.25D, s, NCH*D*CH_2) and 7.47 (0.5H, s, Ph-*D*); *m/z* (CI) 286 (MNH_4^+, 32%), 269 (MH^+, 100), 268 (27) and 149 (19).

Key comparative data for unlabelled (2-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone: ν_{max}/cm^{-1} (thin film) 3140–2833s (C-H), 1640s (C=O), 1602m, 1578m, 1494m, 1446m, 1403s, 1370m, 1272m, 1228m, 1176w, 1096w, 1071m, 1041m, 1028m, 869w, 764m, 699m, 726s and 657m; δ_H (400 MHz; $CDCl_3$) 2.12 (3H, brs, C*H*$_3$C), 3.70 (1H, brm, NC*H*$_2$CH$_2$), 3.77 (1H, brm, NC*H*$_2$CH$_2$), 3.87 (1H, m, CH$_2$C*H*$_2$O), 4.04 (1H, m, CH$_2$C*H*$_2$O) and 7.25–7.59 (10H, complex, Ph-*H*); δ_C (100 MHz; $CDCl_3$) 24.9 (*C*H$_3$C), 49.0 (N*C*H$_2$), 63.3 (*C*H$_2$O), 96.4 (CH$_3$*C*), 125.9, 126.4, 128.4, 128.3, 128.5, 129.8 (Ph*C*H), 137.7 (Ph$_{ipso}$*C*), 141.8 (Ph$_{ipso}$*C*) and 168.3 (*C*=O); *m/z* (CI) 285 (MNH_4^+, 37%), 268 (MH^+, 100) and 148 (18); *m/z* (EI) 267 (M^+, 13%), 253 (21), 252 (65, 190 (40), 147 (12), 117 (39), 105 (90) and 77 (100); (Found MH^+ (ES^+) 268.1336, $C_{17}H_{18}NO_2$ requires 268.1337).

1.1.11. 4-(2-*tert*-Butoxycarbonyl-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (18a/b)—method *a*. A de-gassed solution of tributyltin hydride (2.230 cm^3, 7.65 mmol) and 2,2′-azobisisobutyronitrile (28 mg, 0.17 mmol) in benzene (120 cm^3) was added dropwise over 8 h, to a stirred solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (940 mg, 2.47 mmol) and *tert*-butyl acrylate (1.017 cm^3, 6.94 mmol) in benzene (100 cm^3) under reflux and under a nitrogen atmosphere. The solvent was removed in vacuo and the residue was taken up in ethyl acetate (10 cm^3), the resulting solution being washed with saturated aqueous sodium fluoride solution (15 cm^3) followed by aqueous ammonia (2 M, 2×20 cm^3). The organic phase was dried (sodium sulfate), filtered and evaporated in vacuo, the residue being purified by flash chromatography on silica gel (eluting with 3:2 v/v hexane: ethyl acetate) to give the *title compound* (pale yellow oil) as an inseparable 2:1 mixture of diastereoisomers (472 mg, 50%); R_f 0.42 (1:1 v/v hexane: EtOAc); ν_{max}/cm^{-1} (thin film) 3124–2757m (C-H), 1731s (C=O), 1690w, 1593m, 1438w, 1419m, 1256m, 1194m, 1150m, 1039m, 835w and 769m; δ_H (400 MHz; $CDCl_3$) 1.33 (6H, s, (C*H*$_3$)$_3$C major diastereoisomer), 1.35–1.47 (2H, complex, C*H*$_2$CH$_2$CO$_2$^{t}Bu both diastereoisomers), 1.38 (3H, s, (C*H*$_3$)$_3$C minor diastereoisomer), 1.56 (2H, s, C*H*$_3$C major), 1.73 (1H, s, C*H*$_3$C minor), 1.89 (1.34H, m, C*H*$_2$CO$_2$^{t}Bu major), 2.14 (0.67H, m, C*H*$_2$CO$_2$^{t}Bu minor), 3.11 (0.33H, m, NC*H* minor), 3.20 (0.67H, m, NC*H* major), 3.35 (0.67H, dd, *J* 8 and 7, CHC*H*$_2$O major), 3.49, 3.61 (2×0.33H, ABq, J_{AB} 14, PhC*H*$_2$ minor), 3.67 (0.67H, part of ABq, J_{AB} 14.5, PhC*H*$_2$ major), 3.76 (0.33H, *ca*. t, *J* 8, CH$_2$C*H*$_2$O minor), 4.11–4.20 (1.67H, complex, PhC*H*$_2$ and CH$_2$C*H*$_2$O major and CH$_2$C*H*$_2$O minor), 7.20–7.38 (5.67H, complex, Ph-*H* both and pyridine C*H* minor), 7.47, 8.54 (2×1.34H, AA′BB′, *J* 6, pyridine C*H* major) and 8.59 (0.67H, part of AA′BB′, *J* 6, pyridine C*H* minor); δ_C (100 MHz; $CDCl_3$) 23.9 (*C*H$_3$C major), 26.4 (*C*H$_3$C and *C*H$_2$CH$_2$CO$_2$^{t}Bu minor), 28.0 ((*C*H$_3$)$_3$C major and (*C*H$_3$)$_3$C, CH$_2$*C*H$_2$CO$_2$^{t}Bu minor), 29.5 (*C*H$_2$CH$_2$CO$_2$^{t}Bu major), 32.1 (CH$_2$*C*H$_2$CO$_2$^{t}Bu major), 50.6 (Ph*C*H$_2$ minor), 55.6 (Ph*C*H$_2$ major), 61.3 (N*C*H minor), 64.1 (N*C*H major), 68.8 (CH*C*H$_2$O major), 70.0 (CH*C*H$_2$O minor), 80.1 ((CH$_3$)$_3$*C* major), 80.4 ((CH$_3$)*C* minor), 97.1 (CH$_3$*C* minor), 97.9 (CH$_3$*C* major), 121.3, 124.2, 126.1, 127.0, 127.9, 128.3, 128.7, 128.8 (Ph*C*H and pyridine *C*H both), 139.6 (Ph$_{ipso}$*C* major), 140.1 (Ph$_{ipso}$*C* minor), 149.7 (pyridine *C*H both), 152.1 (pyridine$_{ipso}$*C* minor), 155.6 (pyridine$_{ipso}$*C* major), 172.2 (*C*O$_2$^{t}Bu minor) and 172.3 (*C*O$_2$^{t}Bu major); *m/z* (CI) 383 (MH^+, 100%), 291 (13), 122 (76), 108 (85), 106 (41) and 80 (32); *m/z* (EI) 253 (10%), 91 (100), 57 (52) and 41 (49); (Found MH^+ (ES^+) 383.2336, $C_{23}H_{31}N_2O_3$ requires 383.2334).

1.1.12. 4-(2-*tert*-Butoxycarbonyl-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (18a/b)—method *b*. Tributyltin hydride (1.488 cm^3, 5.53 mmol) and 2,2′-azobisisobutyronitrile (36 mg, 0.22 mmol) were added to a de-gassed solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (700 mg, 1.84 mmol) and *tert*-butyl acrylate (1.257 cm^3, 8.58 mmol) in benzene (60 cm^3). After irradiation with a medium pressure mercury vapour lamp at room temperature under a nitrogen atmosphere for 6 h, the solvent was evaporated in vacuo and the reaction was worked-up as described in **method *a*** above to give the *title compound* (pale yellow oil) as an inseparable 2:1 mixture of diastereoisomers (378 mg, 54%); data as reported above in **method *a***.

1.1.13. 4-(2-*tert*-Butoxycarbonyl-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (18a/b)—method *c*. Triethylborane (1.0 M solution in tetrahydrofuran, 100 μl, 0.1 mmol) was added to a de-gassed solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (340 mg, 0.90 mmol), tributyltin hydride (481 μl, 1.79 mmol) and *tert*-butyl acrylate (263 μl, 1.80 mmol) in benzene (50 cm^3). The reaction flask was opened to the air and the mixture was stirred at room temperature for 12 h before removal of the solvent in vacuo and work-up as described in **method *a*** above. This gave the *title compound* (pale yellow oil) as an inseparable 2:1 mixture of diastereoisomers (143 mg, 42%); data as reported above in **method *a***.

1.1.14. 4-(2-Cyano-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (19a/b)—method *b*. Tributyltin hydride (832 μl, 3.09 mmol) and 2,2′-azobisisobutyronitrile (24 mg, 0.15 mmol) were added to a de-gassed solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (487 mg, 1.28 mmol) and acrylonitrile (186 μl, 2.83 mmol) in benzene (50 cm^3). After irradiation with a medium pressure mercury vapour lamp at room temperature under a nitrogen atmosphere overnight, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 1:3 hexane:ethyl acetate) to give the *title compound* (colourless oil) as an inseparable 2:1 mixture of diastereoisomers (200 mg, 51%); R_f 0.25 (2:3 v/v hexane:EtOAc); ν_{max}/cm^{-1} (thin film) 3120–2797w (C-H), 2228s (CN), 1608s, 1503m, 1453m, 1410s, 1372m, 1339w, 1282w, 1206m, 1120w, 1092s, 1014m, 900w and

839s; δ_H (400 MHz; $CDCl_3$) 1.61 (2H, s, CH_3C major diastereoisomer), 1.65 (1H, s, CH_3C minor), 1.65–1.95 (4H, complex, CH_2CH_2CN both diastereoisomers), 3.22–3.38 (2.33H, complex, NC*H* both, $PhCH_2$ minor, CH_2O both), 3.61 (0.67H, part of ABq, J_{AB} 13, $PhCH_2$ major), 4.19–4.33 (2H, complex, $PhCH_2$ both, CH_2O both), 7.23–7.42 (5.67H, complex, Ph-*H* both and pyridine C*H* minor), 7.49, 8.59 (2×1.34H, AA′BB′, *J* 6, pyridine C*H* major) and 8.62 (0.67H, part of AA′BB′, pyridine C*H* minor); δ_C (100 MHz; $CDCl_3$) major diastereoisomer: 13.6 (CH_2CH_2CN), 24.6 (CH_3C), 30.1 (CH_2CH_2CN), 55.9 ($PhCH_2$), 63.0 (N*C*H), 68.2 (CH_2O), 98.5 (CH_3C), 119.1 (*C*N), 120.9, 127.8, 128.6, 129.2, 149.9 (Ph*C*H and pyridine *C*H), 139.0 ($Ph_{ipso}C$) and 155.4 ($pyridine_{ipso}C$); *m/z* (CI) 308 (MH^+, 94%), 187 (21), 139 (20), 122 (92), 108 (100), 106 (46) and 80 (34); *m/z* (EI) 292 (3%), 229 (9), 91 (100), 78 (20), 65 (21), 51 (23) and 43 (12); (Found MH^+ (ES^+) 308.1766, $C_{19}H_{22}N_3O$ requires 308.1763).

1.1.15. 4-(2-Cyano-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (19a/b)—method *c*. Triethylborane (1.0 M solution in tetrahydrofuran, 100 μl, 0.1 mmol) was added to a de-gassed solution of 4-(3-(2-iodobenzyl)-2-methyl-oxazolidin-2-yl)-pyridine **11** (175 mg, 0.46 mmol), tributyltin hydride (250 μl, 0.93 mmol) and acrylonitrile (223 μl, 3.39 mmol) in benzene (25 cm^3). The reaction flask was opened to the air and the mixture was stirred at room temperature for 6 h before removal of the solvent in vacuo and work-up as described in **method *a*** above. This gave the *title compound* (colourless oil) as an inseparable 2:1 mixture of diastereoisomers (72 mg, 51%); data as reported above in **method *b***.

1.1.16. 4-(2-*tert*-Butoxycarbonyl-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester (20a/b)—method *c*. *tert*-Butyl acrylate (230 μl, 1.57 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-methyl-oxazolidine-2-carboxylic acid ethyl ester **12** (200 mg, 0.53 mmol) and tri-*n*-butyltin hydride (490 μl, 1.82 mmol) in benzene (45 cm^3) at room temperature. Triethylborane (1.0 M solution in tetrahydrofuran, 100 μl, 0.1 mmol) was added and, after stirring overnight, the solvent was evaporated in vacuo. A solution of the resulting oil in ethyl acetate (30 cm^3) was stirred vigorously with an aqueous solution of sodium fluoride (20% w/v, 50 cm^3) for 2 h, after which, the separated organic phase was dried (magnesium sulfate), filtered and evaporated in vacuo to give a yellow oil. The product was purified by flash chromatography on silica gel (eluting with dichloromethane) to give the *title compound* (yellow oil) as an inseparable 3:1 mixture of diastereoisomers (81 mg, 41%); R_f 0.22 (CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 3100–2800m (C-H), 1730s (C=O), 1456m, 1367m, 1257m, 1213m, 1153s, 1028w and 701w; δ_H (400 MHz; $CDCl_3$) 1.24 (0.75H, t, *J* 7, CH_3CH_2 minor diastereoisomer), 1.32 (2.25H, t, *J* 7, CH_3CH_2 major diastereoisomer), 1.37 (2.25H, s, $(CH_3)_3C$ minor), 1.38 (6.75H, s, $(CH_3)_3C$ major), 1.44 (2.25H, s, CH_3C major), 1.49 (0.75H, s, CH_3C minor) 1.63–1.74 (2H, complex, $CH_2CH_2CO_2{}^tBu$ both diastereoisomers), 2.01–2.16 (2H, complex, $CH_2CO_2{}^tBu$ both), 3.15 (0.25H, m, NC*H* minor), 3.35 (0.75H, ca. dq, *J* 8 and 3, NC*H* major), 3.62, 3.86 (2×0.75H, ABq, J_{AB} 15, $PhCH_2$ major), 3.69 (0.75H, dd, *J* 7 and 8, $CHCH_2O$ major), 3.74–3.80 (0.5H, complex, $PhCH_2$ and $CHCH_2O$ minor), 4.06–4.30 (3.25H, complex, $PhCH_2$ minor, $CHCH_2O$ both, CH_3CH_2O both) and 7.18–7.36 (5H, Ph-*H* both); δ_C (100 MHz; $CDCl_3$) major diastereoisomer: 14.5 (CH_3CH_2), 22.9 (CH_3C), 28.0 ($(CH_3)_3C$), 28.1 ($CH_2CH_2CO_2{}^tBu$), 31.3 ($CH_2CO_2{}^tBu$), 52.1 ($PhCH_2$), 60.7 CH_3CH_2), 62.0 (N*C*H), 71.0 ($CHCH_2O$), 80.2 ($(CH_3)_3C$), 96.2 (N*C*O), 126.9, 127.0, 128.1, 128.2 (Ph*C*H), 139.9 ($Ph_{ipso}C$) and 171.4, 172.5 (*C*=O); δ_C (100 MHz; $CDCl_3$) minor diastereoisomer: 14.1 (CH_3CH_2), 20.0 (CH_3C), 27.3 ($CH_2CH_2CO_2{}^tBu$), 28.1 ($(CH_3)_3C$), 31.7 ($CH_2CO_2{}^tBu$), 52.5 ($PhCH_2$), 61.0 CH_3CH_2), 62.0 (N*C*H), 70.2 ($CHCH_2O$), 80.2 ($(CH_3)_3C$), 95.2 (N*C*O), 126.9, 127.0, 128.1, 128.2 (Ph*C*H), 139.9 ($Ph_{ipso}C$) and 171.4, 172.5 (*C*=O); *m/z* (CI) 378 (MH^+, 100%), 304 (8) 214 (10), 134 (16) and 106 (19); *m/z* (EI) 304 (10%), 248 (25), 91 (100), 57 (22) and 43 (18); (Found MH^+ (ES^+) 378.2281, $C_{21}H_{31}NO_5$ requires 378.2280).

1.1.17. 4-(2-Cyano-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester (21a/b)—method *c*. Acrylonitrile (260 μl, 3.95 mmol) was added to a stirred solution of 3-(2-iodobenzyl)-2-methyl-oxazolidine-2-carboxylic acid ethyl ester **12** (500 mg, 1.33 mmol) and tri-*n*-butyltin hydride (1.230 cm^3, 4.57 mmol) in benzene (45 cm^3) at room temperature. Triethylborane (1.0 M solution in tetrahydrofuran, 100 μl, 0.1 mmol) was added and after stirring overnight, the solvent was evaporated in vacuo. A solution of the resulting oil in ethyl acetate (30 cm^3) was stirred vigorously with an aqueous solution of sodium fluoride (20% w/v, 50 cm^3) for 2 h, after which, the separated organic phase was dried (magnesium sulfate), filtered and evaporated in vacuo to give a yellow oil. (Note: ^1H NMR of the crude product indicated a 3:1 mixture of diastereoisomers of the *title compound*.) The product was purified by flash chromatography on silica gel (eluting with dichloromethane) to give the *title compound* as two diastereoisomers; major diastereoisomer: yellow oil (86 mg, 21%): R_f 0.40 (3:2 v/v petroleum ether:EtOAc); ν_{max}/cm^{-1} (thin film) 3100–2780m (C-H), 2445w (CN), 1730s (C=O), 1456m, 1377m, 1254s, 1213s, 1171s, 1128s, 899w, 746m and 701m; δ_H (400 MHz; $CDCl_3$) 1.33 (3H, t, *J* 7, CH_3CH_2), 1.37 (1H, m, CH_2CH_2CN), 1.53 (3H, s, CH_3C), 1.57 (1H, m, CH_2CH_2CN), 2.15 (2H, m, CH_2CN), 3.46 (1H, m, C*H*N) 3.51, 3.93 (2×1H, ABq, J_{AB} 14, $PhCH_2$), 3.69 (1H, dd, *J* 8 and 5, $CHCH_2O$), 4.24 (2H, ca. dq, *J* 7 and 2, CH_3CH_2), 4.38 (1H, ca. t, *J* 8, $CHCH_2O$) and 7.24–7.36 (5H, complex, Ph-*H*); δ_C (100 MHz; $CDCl_3$) 12.1 (CH_2CN), 14.4 (CH_3CH_2), 22.6 (CH_3C), 22.8 (CH_2CH_2CN), 53.0 ($PhCH_2$), 61.0 (CH_3CH_2), 61.5 (N*C*H), 70.5 ($CHCH_2O$), 96.5 (N*C*O), 119.6 (*C*N), 127.6, 128.2, 128.6 (Ph*C*H), 139.1 ($Ph_{ipso}C$) and 170.9 (*C*=O); *m/z* (CI) 303 (MH^+, 100%), 139 (40) and 106 (16); *m/z* (EI) 229 (15%), 91 (100), 65 (12) and 43 (18); (Found MH^+ (ES^+) 303.1710, $C_{17}H_{23}N_2O_3$ requires 303.1708); minor diastereoisomer: yellow oil (18 mg, 5%); R_f 0.23 (3:2 v/v petroleum ether: EtOAc); ν_{max}/cm^{-1} (thin film) 3120–2770m (C-H), 2445w (CN), 1736s (C=O), 1497w, 1454m, 1375m, 1263m, 1211m, 1173m, 1124s, 1026m, 743w and 701m; δ_H (400 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7, CH_3CH_2), 1.45 (1H, m, CH_2CH_2CN), 1.55 (1H, s, CH_3C), 1.61 (1H, m, CH_2CH_2CN), 2.10 (2H, m, CH_2CN), 3.26 (1H, m, NC*H*), 3.67, 4.21 (2×1H, ABq, J_{AB} 14, $PhCH_2$), 3.77 (1H, dd, *J* 8 and 7, $CHCH_2O$, 4.14 (1H, dd, *J* 8 and 7, $CHCH_2O$), 4.20 (2H, m, CH_3CH_2) and 7.22–7.35 (5H, complex, Ph-*H*); δ_C

(100 MHz; $CDCl_3$) 12.9 (CH_2CN), 14.2 (CH_3CH_2), 19.8 (CH_3C), 28.3 (CH_2CH_2CN), 53.7 (PhCH_2), 61.3 (CH_3CH_2), 61.6 (NCH), 69.1 ($CHCH_2O$), 95.9 (NCO), 119.5 (CN), 127.5, 128.4, 128.5 (PhCH), 139.1 ($Ph_{ipso}C$) and 172.2 (C=O); *m/z* (CI) 303 (MH^+, 45%), 139 (100) and 106 (67); *m/z* (EI) 229 (27%), 91 (100), 65 (12) and 43 (17); (Found MH^+ (ES^+) 303.1706, $C_{17}H_{23}N_2O_3$ requires 303.1708).

1.1.18. 3-(3-Benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionic acid *tert*-butyl ester (23a/b)—method *a*. A de-gassed solution of tributyltin hydride (924 μl, 3.44 mmol), 2,2′-azobisisobutyronitrile (18 mg, 0.11 mmol) and *tert*-butyl acrylate (690 μl, 4.71 mmol) in benzene (18 cm^3) was added dropwise over 6 h to a stirred, de-gassed solution of (2-iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone **13** (660 mg, 1.68 mmol) in benzene (20 cm^3) under reflux under a nitrogen atmosphere. After heating under reflux for a further 3 h, the cooled reaction mixture was diluted with ethyl acetate (10 cm^3) and the resulting solution was stirred with aqueous sodium hydroxide solution (2.0 M, 10 cm^3) for 30 min before being dried (sodium sulfate), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluting with 2:1 v/v hexane:ethyl acetate) to give the *title compound* (colourless oil) as an inseparable 2.5:1 mixture of diastereoisomers (461 mg, 70%); R_f 0.40 (3:1 v/v hexane: EtOAc); ν_{max}/cm^{-1} (thin film) 3123–2833m (C-H), 1728 (C=O), 1695m, 1681w, 1648s, 1633s, 1451m, 1438m, 1395s, 1364s, 1241m, 1154s, 1073w, 1025w, 876w, 759m and 701s; δ_H (400 MHz; d_8 toluene; 100°C) 1.23 (2.6H, s, $(CH_3)_3C$ minor diastereoisomer), 1.31 (6.4H, s, $(CH_3)_3C$ major diastereoisomer), 1.45–2.15 (4H, complex, $CH_2CH_2CO_2{}^tBu$ both diastereoisomers), 1.98 (0.86H, s, CH_3C minor), 2.09 (2.14H, s, CH_3C major), 3.42 (0.29H, ca. dd, *J* 9 and 5.5, CH_2O minor), 3.55 (0.71H, ca. dd, *J* 9 and 3, CH_2O major), 3.73 (0.71H, ca. dd, *J* 9 and 6, CH_2O major), 3.91 (0.29H, ca. dd, *J* 9 and 7, CH_2O minor) 4.02–4.12 (1H, complex, NCH both) and 6.95–7.76 (10H, complex, Ph-H); δ_C (100 MHz; $CDCl_3$) principal peaks for major diastereoisomer only, 26.2 (CH_3C), 28.0 ($(CH_3)_3C$), 28.1 ($CH_2CH_2CO_2{}^tBu$), 32.0 ($CH_2CH_2CO_2{}^tBu$), 58.5 (NCH), 67.2 ($CHCH_2O$), 80.6 ($(CH_3)_3C$), 125.8, 126.3, 126.5, 127.1, 128.2, 128.6, 131.6, 137.8 (PhCH and $Ph_{ipso}CH$), 171.7 (PhC(O)N) and 174.1 ($CO_2{}^tBu$); *m/z* (CI) 396 (MH^+, 100%), 276 (62) and 139 (13); *m/z* (EI) 219 (21%), 202 (28), 105 (100), 77 (46), 57 (27) and 41 (16); (Found MH^+ (ES^+) 396.2176, $C_{24}H_{30}NO_4$ requires 396.2175).

1.1.19. 3-(3-Benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionitrile (24a/b)—method *a*. A de-gassed solution of tributyltin hydride (600 μl, 2.23 mmol), 2,2′-azobisisobutyronitrile (15 mg, 0.09 mmol) and acrylonitrile (498 μl, 7.56 mmol) in benzene (15 cm^3) was added dropwise over 6 h to a stirred, de-gassed solution of (2-iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone **13** (350 mg, 0.89 mmol) in benzene (15 cm^3) under reflux under a nitrogen atmosphere. After heating under reflux for a further 6 h, work-up as described for 3-(3-benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionic acid *tert*-butyl ester **(23a/b)** above gave the *title compound* (colourless oil) as an inseparable 1.7:1 mixture of diastereoisomers (168 mg, 59%); R_f 0.30 (1:1 v/v hexane: EtOAc); ν_{max}/cm^{-1} (thin film) 3135–2790m (C-H), 2246w (CN), 1636s (C=O), 1601m, 1493m, 1446s, 1396s, 1372s, 1271m, 1237s, 1075s, 1027m, 765s, 700s and 660m; δ_H (400 MHz; d_8 toluene; 100°C) 1.12–1.61 (4H, complex, CH_2CH_2CN both diastereoisomers), 1.87 (1.11H, s, CH_3C minor diastereoisomer), 1.96 (1.89H, s, CH_3C major diastereoisomer), 3.24 (0.37H, ca. dd, *J* 9 and 5, CH_2O minor), 3.35 (0.63H, ca. dd, *J* 9 and 3, major), 3.63 (0.63H, ca. dd, *J* 9 and 6, CH_2O major), 3.82 (0.37H, ca. dd, *J* 9 and 7, CH_2O minor), 3.91–4.02 (1H, complex, NCH both) and 6.93–7.60 (10H, complex, Ph-H both); δ_C (100 MHz; d_8 toluene; 100°C) major diastereoisomer: 13.0 (CH_2CN), 26.4 (CH_3C), 29.5 (CH_2CH_2CN, 57.6 (NCH), 66.6 (CH_2O), 96.8 (CH_3C), 117.6 (CN), PhCH region obscured by overlap with solvent peaks, 138.2, 142.6 ($2\times Ph_{ipso}C$) and 168.5 (C=O); δ_C (100 MHz; d_8 toluene; 100°C) minor diastereoisomer: 13.2 (CH_2CN), 26.1 (CH_3C), 29.6 (CH_2CH_2CN), 57.8 (NCH), 67.5 (CH_2O), 97.6 (CH_3C), 117.3 (CN), PhCH region obscured by overlap with solvent peaks, 137.9, 143.4 ($2\times Ph_{ipso}C$) and 168.5 (C=O); *m/z* (CI) 338 (MNH_4^+, 100%), 321 (MH^+, 47), 201 (46), 139 (22), 82 (22) and 52 (18); *m/z* (EI) 305 (10%), 105 (100), 77 (70) and 51 (16); (Found MH^+ (ES^+) 321.1605; $C_{20}H_{21}N_2O_2$ requires 321.1603).

1.1.20. 3-(3-Benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionic acid *tert*-butyl ester (23a/b)—method *d*. A de-gassed solution of (2-iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone **13** (260 mg, 0.66 mmol), *tert*-butyl acrylate (447 μl, 3.12 mmol), tributyltin chloride (27 μl, 0.1 mmol), sodium cyanoborohydride (82 mg, 1.31 mmol) and 2,2′-azobisisobutyronitrile (8 mg, 0.05 mmol) in *tert*-butanol (25 cm^3) was heated under reflux for 2 h under a nitrogen atmosphere. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (40 cm^3), the resulting solution being washed with water (2×10 cm^3). The separated organic phase was dried (sodium sulfate), filtered and evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 2:1 v/v hexane:ethyl acetate) to give the *title compound* (colourless oil) as an inseparable 2.0:1 mixture of diastereoisomers (280 mg, 75%); data as reported above in **method *a***.

1.1.21. 3-(3-Benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionitrile (24a/b)—method *d*. A de-gassed solution of (2-iodo-phenyl)-(2-phenyl-2-methyl-oxazolidin-3-yl)-methanone **13** (460 mg, 1.17 mmol), acrylonitrile (645 μl, 9.80 mmol), tributyltin chloride (48 μl, 0.18 mmol), sodium cyanoborohydride (145 mg, 2.31 mmol) and 2,2′-azobisisobutyronitrile (8 mg, 0.05 mmol) in *tert*-butanol (25 cm^3) was heated under reflux for 2 h under a nitrogen atmosphere. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (40 cm^3) and the resulting solution was washed with water (2×10 cm^3). The separated organic phase was dried (sodium sulfate), filtered and evaporated in vacuo and the residue was purified by flash chromatography on silica gel (eluting with 2:1 v/v hexane:ethyl acetate) to give the *title compound* (colourless oil) as an inseparable 1.8:1 mixture of diastereoisomers (160 mg, 61%); data as reported above in **method *a***.

1.1.22. 4-Benzylamino-5-hydroxy-pentanoic acid-*tert*-butyl ester (26)—from 4-(2-*tert*-butoxycarbonyl-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (18a/b).

Aqueous hydrochloric acid (2.0 M, 2 drops) was added to a stirred solution of 4-(2-*tert*-butoxycarbonyl-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine **18a/b** (54 mg, 0.14 mmol) in tetrahydrofuran (5 cm^3) at room temperature. After stirring for 3 h, the reaction mixture was evaporated to dryness in vacuo and the residue was applied to a neutral alumina chromatography column in chloroform. After elution of the by-product, 4-acetylpyridine with chloroform, elution with 9:1 v/v chloroform:methanol gave the *title compound* as a colourless oil (39 mg, 99%); R_f 0.30 (19:1 v/v $CHCl_3$:CH_3OH); ν_{max}/cm^{-1} (thin film) 3580–3140brw (N-H, O-H), 3090–2770m (C-H), 1728s (C=O), 1456m, 1392m, 1367s, 1256m, 1153s, 1049m, 847w and 700m; δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s, $(CH_3)_3C$), 1.74, 1.85 (2×1H, 2×m, $CH_2CH_2CO_2{}^tBu$), 2.28 (2H, m, $CH_2CO_2{}^tBu$), 2.73 (1H, m, NC*H*), 2.82 (2H, brs, N*H*, O*H*), 3.39 (1H, dd, *J* 11 and 6, $CHCH_2O$), 3.66 (1H, dd, *J* 11 and 4, $CHCH_2O$), 3.82, 3.86 (2×1H, ABq, J_{AB} 13, $PhCH_2$) and 7.20–7.41 (5H, complex, Ph-*H*); δ_C (100 MHz; $CDCl_3$) 26.2 ($CH_2CH_2CO_2{}^tBu$), 28.1 ($(CH_3)_3C$), 31.9 ($CH_2CO_2{}^tBu$), 50.8 ($PhCH_2$), 57.8 (N*C*H), 62.4 (CH_2OH), 80.6 ($(CH_3)_3C$), 127.3, 128.3, 128.5 (Ph*C*H), 139.3 ($Ph_{ipso}C$) and 172.8 (*C*=O); *m/z* (CI) 280 (MH^+, 100%), 108 (37) and 106 (22); *m/z* (EI) 91 (100%), 57 (43) and 41 (46); (Found MH^+ (CI) 280.1909, $C_{16}H_{26}NO_3$ requires 280.1912).

1.1.23. 4-Benzylamino-5-hydroxy-pentanenitrile (27)—from 4-(2-cyano-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine (19a/b). Aqueous hydrochloric acid (2.0 M, 2 drops) was added to a stirred solution of 4-(2-cyano-ethyl)-3-benzyl-2-(4-pyridyl)-2-methyl-oxazolidine **19a/b** (94 mg, 0.31 mmol) in tetrahydrofuran (5 cm^3) at room temperature. After stirring for 3 h, the reaction mixture was evaporated to dryness in vacuo and the residue was applied to a neutral alumina chromatography column in chloroform. After elution of the by-product, 4-acetylpyridine with chloroform, elution with 9:1 v/v chloroform:methanol gave the *title compound* as a colourless oil (62 mg, 99%); R_f 0.53 (9:1 v/v $CHCl_3$: CH_3OH); ν_{max}/cm^{-1} (thin film) 3570–3120brm (N-H, O-H), 3040–2780s (C-H), 2247w (CN), 1456m, 1217m, 1053m, 756s and 700m; δ_H (400 MHz; $CDCl_3$) 1.82 (2H, m, CH_2CH_2CN), 2.46 (2H, ca. dt, *J* 7 and 2, CH_2CN), 2.82 (1H, m, NC*H*), 3.48 (1H, ca. dd, *J* 11 and 5, CH_2O), 3.72 (1H, ca. dd, *J* 11 and 4, CH_2O), 3.80, 3.83 (2×1H, ABq, J_{AB} 13, $PhCH_2$) and 7.20–7.41 (5H, complex, Ph-*H*). (Note: N-*H* and O-*H* signals were broadened to a degree such that their chemical shifts could not be readily determined); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_2CN), 27.6 (CH_2CH_2CN), 51.1 ($PhCH_2$), 56.9 (N*C*H), 62.4 (CH_2OH), 119.7 (*C*N), 127.3, 128.1, 128.6 (Ph*C*H) and 140.0 ($Ph_{ipso}C$); *m/z* (CI) 205 (MH^+, 100%), 173 (27), 108 (22) and 52 (60); *m/z* (EI) 173 (19%), 91 (100), 65 (20) and 41 (23); (Found MH^+ (CI) 205.1338, $C_{12}H_{17}N_2O$ requires 205.1341).

1.1.24. 4-Benzylamino-5-hydroxy-pentanoic acid-*tert*-butyl ester (26)—from 4-(2-*tert*-butoxycarbonyl-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester (20a/b). Aqueous hydrochloric acid (2 M, 2 cm^3) was added at room temperature to a stirred solution of the 3:1 mixture of diastereoisomers of 4-(2-*tert*-butoxycarbonyl-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester **20a/b** (100 mg, 0.27 mmol) in tetrahydrofuran (50 cm^3). After stirring overnight, the reaction mixture was evaporated to dryness in vacuo, the final traces of water being removed by co-evaporation with benzene. The residue was purified by chromatography on neutral alumina, eluting with 9:1 v/v chloroform:methanol, giving the *title compound* as a yellow oil (63 mg, 84%); data as reported above.

1.1.25. 4-Benzylamino-5-hydroxy-pentanenitrile (27)—from 4-(2-cyano-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester (21a). Aqueous hydrochloric acid (2 M, 2 cm^3) was added, at room temperature, to a stirred solution of the major diastereoisomer of 4-(2-cyano-ethyl)-3-benzyl-2-methyl-oxazolidine-2-carboxylic acid ethyl ester **21a** (73 mg, 0.24 mmol) in tetrahydrofuran (50 cm^3). After stirring overnight, the reaction mixture was evaporated to dryness in vacuo, the final traces of water being removed by co-evaporation with benzene. The residue was purified by chromatography on neutral alumina, eluting with 9:1 v/v chloroform:methanol, giving the *title compound* as a yellow oil (24 mg, 48%); data as reported above.

1.1.26. 4-Benzoylamino-5-hydroxy-pentanoic acid *tert*-butyl ester (28). Amberlite® IR-120 (H^+ form, ca. 5 mg) was added to a stirred solution of 3-(3-benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionic acid *tert*-butyl ester **23a/b** (220 mg, 0.56 mmol) in acetonitrile (5 cm^3) at room temperature. After stirring at this temperature for 12 h, the ion-exchange resin was removed by filtration and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (eluting with 3:7 v/v hexane:ethyl acetate) to give the *title compound* as a colourless oil (124 mg, 76%); R_f 0.20 (1:1 v/v hexane: EtOAc); ν_{max}/cm^{-1} (thin film) 3612–3135brm (N-H, O-H), 3090–2791m (C-H), 1727s (ester C=O), 1641 (amide C=O), 1579w, 1539m, 1489m, 1392w, 1368m, 1293m, 1255m, 1152s, 713w and 694w; δ_H (400 MHz; $CDCl_3$) 1.40 (9H, s, $(CH_3)_3C$), 1.94 (2H, ca. q, *J* 7, $CH_2CH_2CO_2{}^tBu$), 2.38 (2H, m, $CH_2CH_2CO_2{}^tBu$), 3.40 (1H, brs, O*H*), 3.70 (2H, m, CH_2OH), 4.11 (1H, m, N*C*H), 7.02 (1H, brd, *J* 7.5, N*H*), 7.39 (2H, ca. t, *J* 8, Ph-*H*), 7.47 (1H, ca. t, *J* 8, Ph-*H*) and 7.79 (2H, ca. d, *J* 8, Ph-*H*); δ_C (100 MHz; $CDCl_3$) 25.4 ($CH_2CH_2CO_2{}^tBu$), 28.0 ($(CH_3)_3C$), 32.1 ($CH_2CH_2CO_2{}^tBu$), 52.5 (N*C*H), 65.2 (CH_2OH), 81.1 ($(CH_3)_3C$), 127.1, 128.5, 131.6 (Ph*C*H) and 174.0 ($CO_2{}^tBu$); *m/z* (CI) 294 (MH^+, 100%), 264 (15), 238 (26), 237 (42), 220 (33) and 139 (73); *m/z* (EI) 206 (7%), 105 (100), 77 (73), 57 (50), 43 (30) and 41 (46); (Found MH^+ (ES^+) 294.1710, $C_{16}H_{24}NO_4$ requires 294.1705).

1.1.27. *N*-(3-Cyano-1-hydroxymethyl-propyl)-benzamide (29). Amberlite® IR-120 (H^+ form, ca. 5 mg) was added to a stirred solution of 3-(3-benzoyl-2-phenyl-2-methyl-oxazolidin-4-yl)-propionitrile **24a/b** (120 mg, 0.38 mmol) in acetonitrile (5 cm^3) at room temperature. After stirring at this temperature for 12 h, the ion-exchange resin was removed by filtration and the solvent and acetophenone were removed in vacuo. The residue was purified by flash chromatography on silica gel (eluting with 3:7 v/v hexane: ethyl acetate) to give the *title compound* as a yellow oil (74 mg, 89%); R_f 0.30 (1:4 v/v hexane: EtOAc); ν_{max}/cm^{-1} (thin film) 3544–3141brm (N-H, O-H), 3010–2816w

(C-H), 2228w (CN), 1636s (C=O), 1586s, 1540s, 1462m, 1424m, 1306m, 1165w, 1066m, 1015m and 747m; δ_H (300 MHz; $CDCl_3$) 2.05 (2H, ca. q, *J* 7, CH_2CH$_2$CN), 2.25 (1H, brs, O*H*), 2.48 (2H, ca. t, *J* 7, CH_2CN), 3.78 (2H, m, CH_2OH), 4.23 (1H, m, NC*H*), 6.77 (1H, brd, *J* 8, N*H*), 7.42 (2H, dt, *J* 7 and 1.5, Ph-*H*), 7.51 (1H, dt, *J* 7 and 1.5, Ph-*H*) and 7.78 (2H, dd, *J* 7 and 1.5, Ph-*H*); δ_C (75 MHz; $CDCl_3$) 14.4 (*C*H$_2$CN), 27.5 (*C*H$_2$CH$_2$CN), 50.9 (N*C*H), 64.0 (*C*H$_2$OH), 127.1, 128.6, 133.8 (Ph*C*-H), 137.0 (Ph$_{ipso}$*C*) and 168.4 (*C*=O); *m/z* (CI) 236 (MNH_4^+, 100%), 219 (MH^+, 38), 206 (16) and 139 (45); *m/z* (EI) 146 (13%), 105 (100), 77 (85) and 51 (35); (Found MH^+ (ES^+) 219.1130, $C_{12}H_{15}N_2O_2$ requires 219.1133).

Acknowledgements

The authors gratefully acknowledge the Leverhulme Trust for a postdoctoral fellowship to R. G., Dr V. Sik, Exeter, UK for NMR spectroscopy and the EPSRC National Mass Spectrometry Service Centre, Swansea, UK for mass spectrometric work.

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