Chemistry of the mycalamides: antiviral and antitumour compounds from a New Zealand marine sponge. Part 6.[1–3] The synthesis and testing of analogues of the C(7)–C(10) fragment

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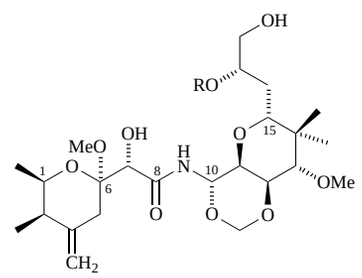
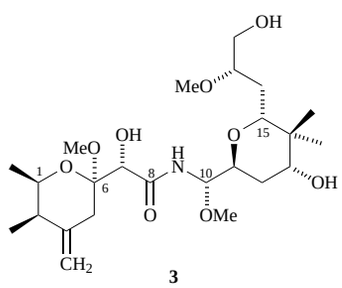
The key structural features associated with the potent cytotoxicity observed in the mycalamide, onnamide, pederin and theopederin series have been defined on the basis of structure–activity studies. A model pharmacophore structure has been proposed and selected examples, with modest bioactivity, synthesized.

Introduction

Mycalamides A **1**[1] and B **2**,[2] pederin **3**,[4] the onnamides[5] and the theopederins[6] are biologically active natural products characterised by the presence of the O(1)–C(10) pederic acid subunit (see structures **1**–**3** for atom numbering). The mycalamides, onnamides and theopederins were isolated from marine sponges while pederin, a potent insect toxin, was isolated from a beetle (*Paederus fuscipes*). Considerable synthetic interest has been generated in this class of compound due to its natural scarcity, novel structure and potent biological activity. Total syntheses of pederin,[7,8] the mycalamides and onnamide A[9] have been reported.



1 R = H
2 R = Me



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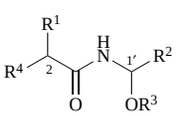


4

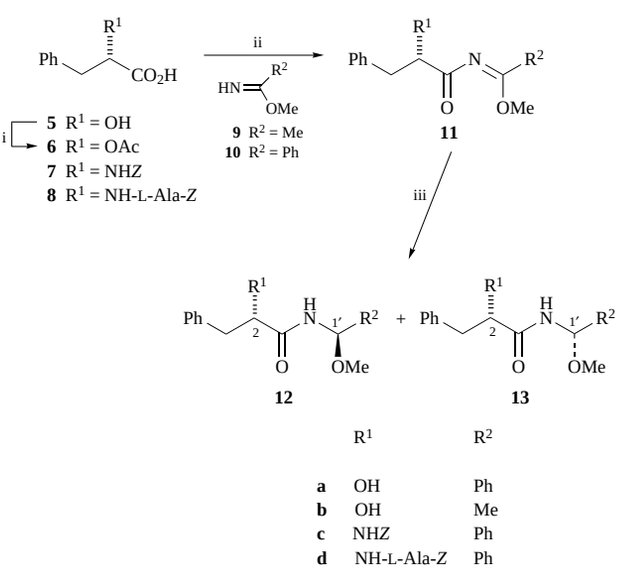
The biological activity of this class of compound is most likely a consequence of inhibition of protein synthesis.[10] We recently reported extensive microscale structure–activity studies[3] on **1** and **2** with a view to understanding the requirements for biological activity. These experiments demonstrated that the α-hydroxyamido acetal C(7)–C(10) functionality of **1** and **2** is essential for the *in vitro* P388 anti-leukaemia activity. Some of the more important structure–activity correlations from this study can be summarised as follows. Acylation or alkylation of the 7-OH group caused a 10–10^2-fold decrease in bioactivity as compared to **1**. Methylation of both the amide nitrogen and 7-OH resulted in a 10^3-fold less bioactive derivative. Cleavage of the C(8)–N(9) amide bond resulted in total loss of biological activity. The product of deoxygenation at C(10) was 40 times less bioactive than **1**, suggesting the crucial importance of the C(10) centre to the activity. Kocienski *et al.*[11] have also reported that the C(10) epimer of mycalamide B (**2**) is some three orders of magnitude less active than the parent compound. Further support for the critical importance of the C(10) oxygen came from studying the biological activity of the various onnamide and theopederin derivatives that have been isolated by the Fusetani group from *Theonella* sp. sponges.[5b,6] Most notable was the reported inactivity of an onnamide derivative lacking oxygenation at C(10).[5b]

The aim of the current study was to synthesise and test, *in vitro* against the P388 leukaemia cell line, simple analogues of the C(7)–C(10) functionality of parents **1**–**3**, *i.e.* compounds of the general structure **4** where R^1 to R^4 could be variously alkyl or aryl, and with defined stereochemistry at each of the two stereogenic centres.

Results and discussion

Synthesis

Two general synthetic routes were used to prepare the optically active analogues **12**, **13**, **27**–**36**, **42** and **43**. The selection of R^1 to R^4 was based initially on synthetic utility, then on aspects pertaining to the actual structure of the mycalamides and finally on aspects such as solubility. The method given in Scheme 1



5 R^1 = OH
6 R^1 = OAc
7 R^1 = NHZ
8 R^1 = NH-L-Ala-Z

9 R^2 = Me
10 R^2 = Ph

11

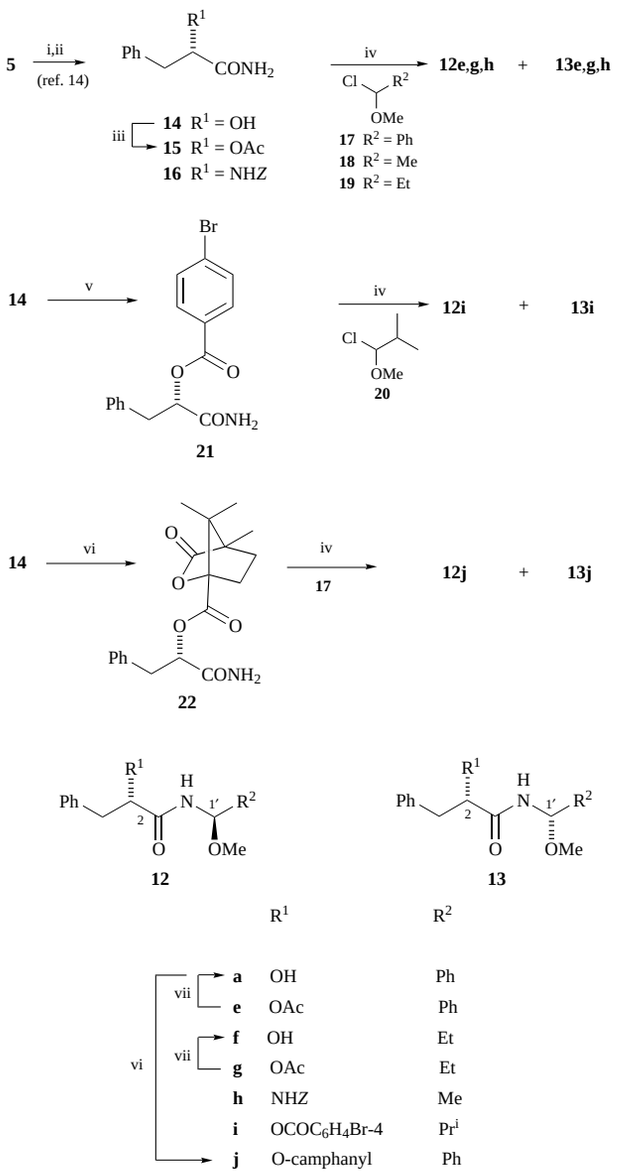
12 + **13**

	R^1	R^2
a	OH	Ph
b	OH	Me
c	NHZ	Ph
d	NH-L-Ala-Z	Ph

Scheme 1 *Reagents and conditions:* i, Ac_2O, pyridine; ii, DCC, HOBT, CH_2Cl_2; iii, $NaBH_4$, Pr^iOH

involved a dicyclohexylcarbodiimide (DCC)-mediated coupling of a suitable carboxylic acid **6**–**8** with methyl acetimidate **9**, or methyl benzimidate **10**, to form a methyl *N*-acylimidate **11**. Subsequent reduction of **11** with a large excess of sodium borohydride gave the desired compounds **12a**–**d** and the corresponding (1′)-epimers **13a**–**d**. The epimers were separated by silica-based radial chromatography. Similar methodologies have also been applied by Kocienski *et al.*[8] and Matsumoto and coworkers[12] in total syntheses of pederin. The reduction of **11** (where R^1 = OAc) gave **12a**/**13a** and **12b**/**13b** as the isolated products rather than the corresponding acetates. The starting compound **9** was commericially available while **10** was prepared by reaction of benzonitrile with methanol and gaseous hydrogen chloride.[13] Compound **6** was prepared by acetylation of (*S*)-3-phenylacetic acid **5** (Scheme 1, step i), while **7** and **8** were commercially available.

The second method (Scheme 2) involved the reaction of a primary amide, either **15** or **16**, with an α-chloro ether (**17**, **18** or **19**) in the presence of an excess of triethylamine in dichloromethane at 0 °C. This procedure was used to prepare (1′)-epimeric mixtures of **12e**,**g**,**h**/**13e**,**g**,**h**. Silica-based radial chromatography was used to separate the (1′)-epimers **12e**,**h**/**13e**,**h**.

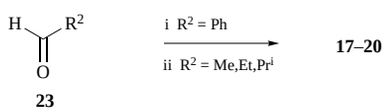


Scheme 2 *Reagents and conditions:* i, acetone, H_2SO_4, −10 °C; ii, NH_3; iii, Ac_2O, pyridine; iv, Et_3N, CH_2Cl_2, 0 °C; v, 4-BrC_6H_4COCl, DMAP, Et_3N, CH_2Cl_2; vi, (1*S*,4*R*)-camphanic chloride, DMAP, Pr^i_2NEt, CH_2Cl_2; vii, K_2CO_3, MeOH, H_2O

The mixture of **12g** and **13g** was hydrolysed to give **12f** and **13f**, which were then separated by silica-based radial chromatography. The (1′)-epimers **12e** and **13e** were also separately hydrolysed to give **12a** and **13a**, respectively. This method gave a 50% combined yield (from the acid **5**) of **12a**/**13a**. By comparison, the preparation of **12a**/**13a** as detailed in Scheme 1 (*via* the *N*-acylimidate **11**) gave a 33% combined yield of **12a**/**13a** (from the acid **5**).

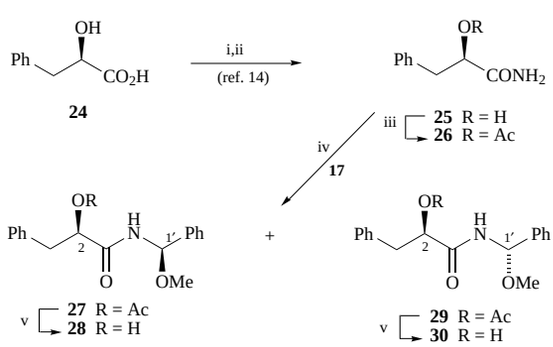
In general, the methods detailed in Scheme 2 proved superior to those given in Scheme 1 for the preparation of derivatives of the type **4**. In particular, the coupling of amides **15** and **16** with α-chloro ethers **17**–**19**, to form analogues of general structure **4**, gave typical yields ranging from 83 (for **12e**/**13e**) to 52% (for **12h**/**13h**). The corresponding two step procedure using **6**–**8** (Scheme 1) proved less satisfactory and gave typical yields ranging from 54 (for **12d**/**13d**) to 33% (for **12a**/**13a**). Separation of the mixtures of epimeric products **12** and **13**, by silica-based chromatography, resulted in a reduction in yield due to acid-catalysed degradation of the amido acetal functionality. However, sufficient material was obtained for biological testing.

The starting amide **15**, used in Scheme 2, was synthesized by acetylation of **14**, itself prepared by condensation of the α-hydroxy acid **5** with acetone followed by reaction with ammonia (Scheme 2, steps i–iii).[14] Compound **16**, which was used to prepare **12h** and **13h**, was isolated as a decomposition by-product of **12c** and **13c** on silica. The key α-chloro ethers **17**–**20** were prepared from the corresponding aldehyde **23** by reaction with gaseous hydrogen chloride and methanol (Scheme 3).[15]



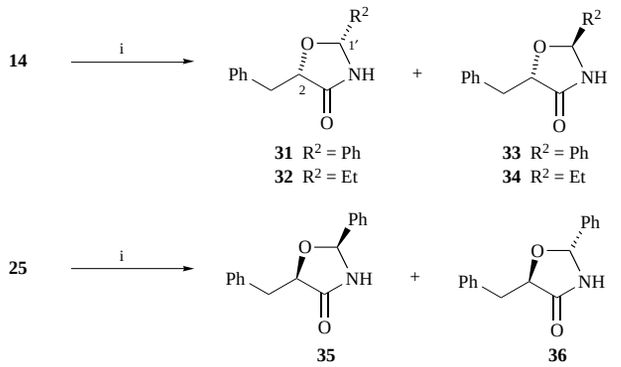
Scheme 3 *Reagents and conditions:* i, MeOH, HCl (g), EtCl, −60 °C; ii, MeOH, HCl (g), −30 °C

The general method detailed in step iv in Scheme 2 was also used to prepare a number of other derivatives of the general structure **4**. The reaction of **21** and **22** (prepared from **14** as shown in Scheme 2) with **20** and **17** respectively, gave the derivatives **12i**/**13i** and **12j**/**13j** as separable mixtures of epimers. These compounds were prepared for structure–activity studies and in an attempt to obtain a crystalline product suitable for X-ray analysis (*vide infra*). A mixture of **12j** and **13j** (9:1 by ^{1}H NMR spectroscopy) was also prepared in 69% yield from a mixture of **12a** and **13a** (9:1 by ^{1}H NMR spectroscopy) (Scheme 2). The enantiomers of **12a** and **13a**, compounds **30** and **28** respectively, were synthesized as detailed in Scheme 4 using (*R*)-3-phenyllactic acid **24** (*cf*. steps i–v in Scheme 2).



Scheme 4 *Reagents and conditions:* i, acetone, H_2SO_4, −10 °C; ii, NH_3; iii, Ac_2O, pyridine; iv, Et_3N, CH_2Cl_2, 0–18 °C; v, K_2CO_3, MeOH, H_2O

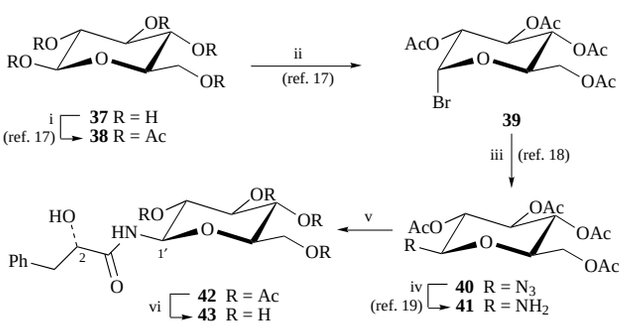
The oxazolidinone-based examples **31**–**36** were synthesized as mixtures of epimers by the direct reaction of **14** or **25** with the α-chloro ethers **17** or **19**, in the presence of gaseous hydro-



Scheme 5 *Reagents and conditions:* i, **17** or **19**, CH_2Cl_2, −10 °C

gen chloride (Scheme 5). A related cyclisation of an α-hydroxy amide with an aromatic or aliphatic aldehyde to give 1,3-oxazolidin-4-ones has been reported.[16]

The glucosyl derivative **42** was synthesized by a DCC-mediated coupling of the acid **5** with the glucopyranosyl amine **41** (Scheme 6, step v). The amine **41** was prepared[17–19] from D-



Scheme 6 *Reagents and conditions:* i, Ac_2O, H_2SO_4; ii, HBr in AcOH, 0–18 °C; iii, NaN_3, DMF, 80 °C; iv, H_2, PtO_2, EtOAc; v, **5**, DCC, HOBT, CH_2Cl_2; vi, K_2CO_3, MeOH, H_2O

glucose **37** as detailed in Scheme 6. Hydrolysis of **42** then gave **43** (Scheme 6, step vi). The glucosyl derivatives **42** and **43** were synthesized as compounds possessing the previously established, biologically active (1′*R*)-configuration. As well as modelling more closely the structural requirements of the mycalamide skeleton, *cf.* **1**, it was also considered that the sugar moiety might impart improved water solubility, which would be of assistance in the *in vitro* cytotoxicity assay.

Assignment of configuration

Compounds **12a–j** and **13a–j** were assigned the (1′*R*,2*S*)- and (1′*S*,2*S*)-absolute configurations, respectively. The relative configuration of the camphanate derivative **13j** was determined unambiguously by single crystal X-ray analysis (Fig. 1). The absolute configuration of **13j**, and hence its (1′)-epimer **12j**, followed from the known absolute configurations of **14** and (1*S*,4*R*)-camphanyl chloride, which were used to prepare **12j** and **13j** (Scheme 2). The absolute configuration of **12a**, and hence its (1′)-epimer **13a**, was assigned on the basis that **12a** was converted into **12j** (Scheme 2). Compounds **28** and **30** gave identical NMR data, but opposite optical rotations, to the reference compounds **13a** and **12a**, respectively.

The configurations of the other analogues given in Table 1 followed from a comparison of ^{1}H NMR data. The methoxy resonance of the (1′*R*,2*S*)-derivatives **12a–i**, was in a characteristic downfield position relative to the corresponding (1′*S*,2*S*)-diastereoisomers **13a–i**. The C*H*R^1 resonance of **12a**, **12b** and **12f** was also consistently 0.04–0.07 ppm downfield relative to **13a**, **13b** and **13f**. However, the corresponding resonances for **12c** and **12h** (where R^1 = NHZ) were upfield relative to those of **13c** and **13h**. An observed positive NOE between the ring protons labelled 1′ and 2 (Scheme 5, non-systematic numbering) of the oxazolidinones **31**, **32** and **35**, but not **33**, **34** and **36**, was consistent with the assignment of configuration of these derivatives.

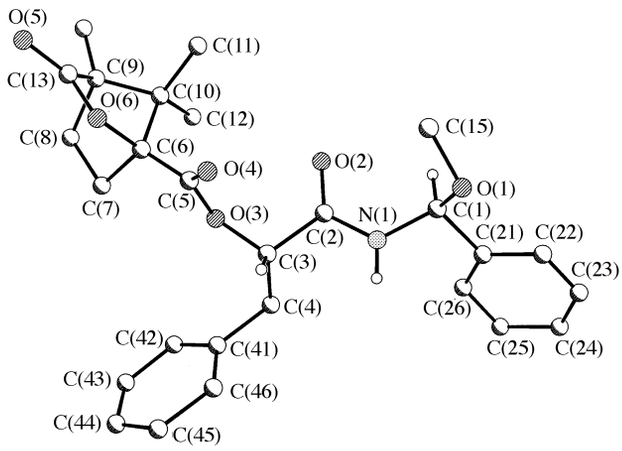


Fig. 1 X-Ray molecular structure of compound **13j** with crystallographic numbering scheme

Table 1 IC_{50} Values of derivatives against P388 cells

Compound	R^1	R^2	Configuration 1′[a]	Configuration 2[a]	IC_{50}/μg cm^{-3}
12a	OH	Ph	*R*	*S*	52
13a	OH	Ph	*S*	*S*	>340
12b	OH	Me	*R*	*S*	>125
13b	OH	Me	*S*	*S*	>188[b]
12c	NHZ	Ph	*R*	*S*	14
13c	NHZ	Ph	*S*	*S*	>188[c]
12d	NH-Ala-Z	Ph	*R*	*S*	36
13d	NH-Ala-Z	Ph	*S*	*S*	>125
12e	OAc	Ph	*R*	*S*	101
13e	OAc	Ph	*S*	*S*	>313
12f	OH	Et	*R*	*S*	176
13f	OH	Et	*S*	*S*	43
12h	NHZ	Me	*R*	*S*	>375
13h	NHZ	Me	*S*	*S*	>375
12i	$OCOC_6H_4Br$	Pr^i	*R*	*S*	105[d]
13i	$OCOC_6H_4Br$	Pr^i	*S*	*S*	105
12j	O-camphanyl	Ph	*R*	*S*	42[e]
13j	O-camphanyl	Ph	*S*	*S*	78[e]
28	OH	Ph	*R*	*R*	27
30	OH	Ph	*S*	*R*	102
31		Ph	*R*	*S*	57
33		Ph	*S*	*S*	37
32		Et	*R*	*S*	57
34		Et	*S*	*S*	47
36		Ph	*R*	*R*	8
35		Ph	*S*	*R*	12
42	OAc		*R*	*S*	267
43	OH		*R*	*S*	>375

[a] Atom numbering as shown in Schemes. [b] Activity obtained on 1:1 mixture of epimers. [c] Activity obtained on 3:1 mixture of epimers. [d] Activity obtained on 17:3 mixture of epimers. [e] Activity obtained on 9:1 mixture of epimers.

Biological activity

The analogues shown in Table 1 were each tested for *in vitro* cytotoxicity against P388, a murine leukaemia cell line. IC_{50} values for each sample were determined, after a 72 h incubation period, using an MTT endpoint.[20]

In general, compounds **12** with a (1′*R*,2*S*)-configuration show significantly greater *in vitro* cytotoxicity than the corresponding (1′*S*,2*S*)-derivatives **13**, such that a (1′*R*)-configuration would appear favourable towards activity. Notable exceptions were the parent natural products **1–3** [the equiv-

alent C(10) position is *S*] and **12f** and **13f** (see below for a discussion). The C(10) epimer of mycalamide B is reported to be significantly less active than the parent natural product **2**.[11] An analysis of the data for **28** and **30** (Table 1), which possess the alternative (2*R*)-configuration, also suggests that a (1′*R*)-configuration, as in **28**, is favoured over a (1′*S*)-configuration (**30**) for cytotoxic activity. The (1′*R*)-compounds **12a** and **28** show similar *in vitro* antitumour activity such that it seems that there is no marked preference for either an (*R*)- or (*S*)-configuration at position C(2). It is worth noting that the natural products **1**–**3** possess an (*S*)-configuration at the equivalent C(7) centre. A preference for a (1′*R*)-configuration over a (1′*S*)-configuration does not seem to be evident within the cyclic oxazolidinone series **31**–**36**, where the (1′*S*)- and (1′*R*)-compounds (non-systematic numbering) show similar *in vitro* cytotoxicity.

A variety of R^1 groups appear to be accommodated for the induction of *in vitro* cytotoxicity. For example, the corresponding acetates of **12a** and **13a**, compounds **12e** and **13e**, show comparable activity. By comparison, acylation of the 7-hydroxy group of **1** or **2** [analogous to C(2) in **12**/**13**] results in compounds with significantly decreased activity. The (1′)-epimeric pairs **12c**/**13c**, **12d**/**13d** and **12h**/**13h** were designed to give the derivatives more peptide character. This was done since the natural products (**1**–**3**), upon which the compounds in the current study were modelled, exert their biological activity by inhibiting protein biosynthesis. The most bioactive compounds in this series, compounds **12c** and **12d**, show activities comparable to, or better than, **12a**. Again a preference for a (1′*R*)-configuration is noted (Table 1, **12c**/**13c** and **12d**/**13d**).

A change from R^2 = Ph to Et appears to be tolerated, although in this case, contrary to the other compounds given in Table 1, a (1′*S*)-configuration seems to give the most potent *in vitro* bioactivity (see compounds **12f** and **13f**, Table 1). It should be noted that **13f** and the parent natural products, compounds **1**–**3**, possess the same relative configuration at this centre [(1′*S*) in **13f** and (10*S*) in **1**–**3**]. The configurations at C(2) of **13f** and C(7) of **1**–**3** are both *S*. The introduction of a methyl group at the R^2 position resulted in compounds with significantly reduced activity (see results for compounds **12b**, **13b**, **12h** and **13h**, Table 1). Finally, the glucosyl derivatives **42** and **43** show less activity than the corresponding R^2 = Et and Ph analogues (Table 1).

Conclusion

Structure–activity studies on the mycalamide/pederin/onnamide skeleton (*cf.* **1**–**3**) have established the key features which are necessary or essential for the bioactivity observed across this series of compounds. These structural requirements have been summarised in structure **4.** Examples of general structure **4** have been synthesized (Table 1) and shown to give modest *in vitro* antitumour activity. The level of activity appears to be more sensitive to changes at R^2 than R^1, and a (1′*R*)-configuration is favoured.

Experimental

Mps were taken using a Reichert hot-stage microscope and are uncorrected. Optical rotations were measured on a JASCO J-20C recording spectropolarimeter and $[\alpha]_D$ values are given in units of 10^{-1} degrees $cm^2\ g^{-1}$. IR Spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer. ^{1}H and ^{13}C NMR Spectra were recorded on Varian Unity and XL300 spectrometers, in $CDCl_3$ solution, using Me_4Si as an internal standard; *J* values are given in Hz. Mass spectra were obtained using a Kratos MS80RFA spectrometer. Radial chromatography was performed on a chromatotron (Harrison and Harrison) using Merck type 60 PF_{254} silica gel. Compounds **5**, **7**, **8**, **9** and **24** are commercially available. Compounds **10**,[13] **14**,[14] **17**–**20**[15] and **25**[14] were prepared by the general literature methods.

(*S*)-2-Acetoxy-3-phenylpropanoic acid 6

To a solution of (*S*)-3-phenyllactic acid **5** (106 mg, 0.64 mmol) in dry pyridine (1 cm^3) was added acetic anhydride (0.12 cm^3, 1.27 mmol) and the mixture was stirred for 18 h at room temp. Water (2 cm^3) was added and the solution was extracted with chloroform (3 × 5 cm^3), dried and the solvent was evaporated to give **6** (quant.) as a yellow oil which was not purified further. ^{1}H NMR Data were as previously reported.[21]

Preparation of compounds 12 and 13

The general methods A and B detailed below gave mixtures of **12** and **13** that were unstable to silica. However, for purposes of biological testing, rapid silica-based radial chromatography of the mixtures, where specified, gave samples of the separate epimers with some loss due to decomposition.

Method A. Compound **6**, **7** or **8** (typically 0.60 mmol), 1-hydroxybenzotriazole (1 equiv.) and 1.5 equiv. of **10** (or the hydrochloride salt of **9** and 1.5 equiv. of triethylamine) were dissolved in dichloromethane (2.5 cm^3) at 0 °C and the mixture was stirred for 10 min. Dicyclohexylcarbodiimide (1 equiv.) was added and the mixture was stirred for a further 10 min at 0 °C and finally at 18 °C for 18 h. The reaction mixture was diluted with more dichloromethane (5 cm^3), filtered and the solvent was evaporated to give **11**, which was reduced without further purification. The residue was redissolved in dry isopropyl alcohol (5 cm^3), sodium borohydride (15 equiv.) was added and the suspension was stirred at 0 °C for 2 h. Brine (5 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 5 cm^3). The combined organic extracts were washed with water (5 cm^3), dried and evaporated to give **12a**–**d** and **13a**–**d** as mixtures.

Method B. Triethylamine (25 equiv.) and **17**, **18**, **19** or **20** (25 equiv.) were added to **15**, **16**, **21** or **22** (typically 0.30 mmol) dissolved in dry dichloromethane (2.5 cm^3) at 0 °C. The mixture was then stirred for 18 h at 5 °C. The reaction mixture was washed with water, dried and evaporated to give **12e**,**g**–**j** and **13e**,**g**–**j** as mixtures.

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Hydroxy-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 12a and 13a. The acid **6**, freshly prepared from **5** (96 mg, 0.58 mmol) as previously described, was reacted with **10** according to general method A to give a mixture of **12a** and **13a** (54 mg). Purification on a 1 mm silica chromatotron plate eluting with diethyl ether–dichloromethane (1:9 to 1:0) gave **13a** (6 mg) [HRMS: found $(M - Me)^+$, 270.1125. $C_{16}H_{16}NO_3$ requires 270.1130]; mp 104–105 °C; $[\alpha]_D^{23}$ −92 (*c* 3.8, dichloromethane); ν_{max}/cm^{-1} 3406, 1684, 1504, 1497 and 1092; $\delta_H(CDCl_3)$ 2.61 (1 H, d, *J* 4.9, OH), 2.96 (1 H, dd, *J* 14.0 and 8.5, C*H*$_2$Ph), 3.27 (1 H, dd, *J* 14.0 and 4.2, C*H*$_2$Ph), 3.37 (3 H, s, OMe), 4.32 (1 H, m, C*H*OH), 6.10 (1 H, d, *J* 9.3, C*H*OMe), 7.00 (1 H, d, *J* 9.8, NH) and 7.30–7.38 (10 H, m, ArH); $\delta_C(CDCl_3)$ 40.8, 55.9, 72.9, 81.2, 125.8, 127.1, 128.6, 128.6, 128.8, 129.6, 136.5, 139.9 and 172.8; *m/z* (EI) 270 $(M^+ - Me$, 15%), 253 $(M^+ - MeOH$, 22), 121 (99) and 106 (100).

Further elution gave a second fraction (7 mg) containing a mixture of **13a** and **12a** (3:2 by ^{1}H NMR spectroscopy).

The final fraction gave **12a** (9 mg) [HRMS: found $(M - Me)^+$, 270.1128. $C_{16}H_{16}NO_3$ requires 270.1130]; mp 66–68 °C; $[\alpha]_D^{23}$ −17 (*c* 3.6, dichloromethane); ν_{max}/cm^{-1} 3406, 1684, 1504, 1497 and 1090; $\delta_H(CDCl_3)$ 2.96 (1 H, dd, *J* 13.8 and 8.1, C*H*$_2$Ph), 3.27 (1 H, dd, *J* 13.9 and 4.1, C*H*$_2$Ph), 3.47 (3 H, s, OMe), 4.45 (1 H, dd, *J* 8.3 and 3.9, C*H*OH), 6.12 (1 H, d, *J* 9.3, C*H*OMe), 7.01 (1 H, d, *J* 9.3, NH) and 7.31 (10 H, m, ArH); $\delta_C(CDCl_3)$ 40.6, 56.1, 72.7, 81.1, 125.8, 127.1, 128.5, 128.5, 128.8, 129.6, 136.3, 138.8 and 172.9; *m/z* (EI) 270 $(M^+ - Me$, 7%), 253 $(M^+ - MeOH$, 17), 121 (77) and 106 (100).

Compounds **12a** and **13a** were also prepared by hydrolysing separate samples of **12e** (5 mg, 0.01 mmol) and **13e** (4 mg, 0.01 mmol) in methanol and water (2.5 cm^3 of a 9:1 mixture) with K_2CO_3 (0.2 equiv.) at room temp. for 2 h. The mixtures were evaporated and the residues were dissolved in dichloromethane

(0.5 cm^3). The organic solutions were washed with water (0.5 cm^3), dried and evaporated to give white crystalline solids **12a** (4 mg, 90%) and **13a** (4 mg, quant.).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Hydroxy-*N*-(1′-methoxyethyl)-3-phenylpropanamide 12b and 13b. The acid **6**, freshly prepared from **5** (100 mg, 0.60 mmol) as previously described, was reacted with **9** according to general method A to give a mixture of **12b** and **13b** (55 mg). Purification on a preparative silica column eluting with methanol–water (92:5) gave three fractions.

The first fraction contained a mixture of **12b** and **13b** (11 mg, 1:1 by ^{1}H NMR spectroscopy).

The second fraction contained a mixture of **12b** and **13b** (6 mg, 3:2 by ^{1}H NMR spectroscopy); data for **13b** (from the mixture) $\delta_H(CDCl_3)$ 1.30 (3 H, d, CH*Me*), 2.94 (1 H, m, CH_2Ph), 3.28 (1 H, m, CH_2Ph), 3.24 (3 H, s, OMe), 4.05 (1 H, d, OH), 4.36 (1 H, m, C*H*CO), 5.26 (1 H, m, C*H*OMe), 6.72 (1 H, d, NH) and 7.28 (5 H, m, ArH).

The final fraction gave **12b** as an oil (4 mg) [HRMS: found $(M - Me)^+$, 208.0966. $C_{11}H_{14}NO_3$ requires 208.0973]; $\delta_H(CDCl_3)$ 1.26 (3 H, d, *J* 5.8, CH*Me*), 2.90 (1 H, dd, *J* 9.6 and 8.3, CH_2Ph), 3.24 (1 H, m, CH_2Ph), 3.30 (3 H, s, OMe), 4.41 (1 H, dd, *J* 8.3 and 3.4, C*H*OH), 5.25 (1 H, dd, *J* 9.7 and 5.8, C*H*OMe), 7.03 (1 H, d, *J* 9.8, NH) and 7.25 (5 H, m, ArH); *m/z* (EI) 208 ($M^+ - Me$, 2%), 205 ($M^+ - H_2O$, 6), 191 ($M^+ -$ MeOH, 80) and 91 (100).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Benzyloxycarbonylamino-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 12c and 13c. The acid **7** (203 mg, 0.68 mmol) was reacted with **10** according to general method A. The crude product was subjected to repeated chromatography eluting with ethyl acetate–light petroleum mixtures to give (S)-N-*Z*-*phenylalaninamide*[22] **16** (73 mg, 37%), further mixtures of **12c**/**13c** (118 mg) and a sample of **12c** (2 mg), mp 151–153 °C (HRMS: found M^+, 418.1886. $C_{25}H_{26}N_2O_4$ requires 418.1893); $\delta_H(CDCl_3)$ 3.08 (2 H, d, *J* 6.8, CHCH_2), 3.40 (3 H, s, OMe), 4.53 (1 H, m, C*H*CH$_2$), 5.07 (2 H, s, PhCH_2O), 6.07 (1 H, d, *J* 9.7, C*H*OMe), 7.10–7.31 (15 H, m, ArH) and 7.45 (1 H, d, *J* 9.3, NH); $\delta_C(CDCl_3)$ 38.6, 55.8, 56.4, 66.8, 81.3, 125.7, 126.8, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 129.2, 129.3, 136.2, 138.7, 155.9 and 171.4; *m/z* (EI) 418 (M^+, 5%), 403 ($M^+ - Me$) and 386 (100).

Data for **13c** (from the mixture) $\delta_H(CDCl_3)$ 3.15 (2 H, d, *J* 6.8, CHCH_2), 3.32 (3 H, s, OMe), 4.60 (1 H, m, C*H*CH$_2$), 5.04 (2 H, s, PhCH_2O), 6.09 (1 H, d, *J* 9.3, C*H*OMe) and 7.14–7.31 (15 H, m, ArH); $\delta_C(CDCl_3)$ 38.3, 55.7, 56.2, 66.7, 81.4, 125.7, 126.7, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 129.2, 136.1, 138.8, 155.9 and 171.5; *m/z* (EI) 403 ($M^+ - Me$, 32%) and 386 ($M^+ -$ MeOH, 100).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-[(*N*-Benzyloxycarbonyl-L-alaninyl)-amino]-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 12d and 13d. The acid **8** (50 mg, 0.13 mmol) was reacted with **10** according to general method A to give a mixture of **12d** and **13d** (36 mg) which was purified on a 1 mm chromatotron plate eluting with ethyl acetate–light petroleum (1:3 to 3:1) to give **12d** (9 mg) [HRMS: found $(M - MeOH)^+$, 457.1993. $C_{27}H_{27}N_3O_4$ requires 457.2002]; $\delta_H(CDCl_3)$ 1.20 (3 H, d, *J* 7.1, CH*Me*), 3.12 (2 H, d, *J* 3.6, CHCH_2), 3.30 (3 H, s, OMe), 4.17 (1 H, m, C*H*Me), 4.76 (1 H, m, C*H*CH$_2$), 4.92 (2 H, m, PhCH_2O), 5.38 (1 H, d, *J* 5.8, Ala-NH), 6.05 (1 H, d, *J* 8.8, C*H*OMe), 6.88 (1 H, d, *J* 7.8, Phe-NH) and 7.15–7.31 (15 H, m, ArH); $\delta_C(CDCl_3)$ 18.1, 37.7, 51.0, 54.3, 55.8, 67.1, 81.6, 125.9, 125.9, 126.9, 127.0, 128.1, 128.3, 128.5, 128.6, 129.3, 136.1, 138.5, 171.1 and 172.3; *m/z* (EI) 457 ($M^+ -$ MeOH, 2%), 352 (4) and 91.0 (100).

Further elution gave **13d** (21 mg) [HRMS: found $(M -$ MeOH)$^+$, 457.2005. $C_{27}H_{27}N_3O_4$ requires 457.2002]; $\delta_H(CDCl_3$, [$^2H_6$]DMSO) 1.23 (3 H, d, *J* 7.3, CH*Me*), 3.01–3.15 (2 H, m, CHCH_2), 3.39 (3 H, s, OMe), 4.12 (1 H, m, C*H*Me), 4.71 (1 H, m, Phe-CH), 5.05 (2 H, m, PhCH_2O), 6.04 (1 H, d, *J* 9.3, C*H*OMe), 6.86 (1 H, d, *J* 7.3, Ala-NH), 7.17–7.34 (15 H, m, ArH), 7.72 (1 H, d, *J* 9.3, Phe-NH) and 8.23 (1 H, d, *J* 9.3, CONH); $\delta_C(CDCl_3$, [$^2H_6$]DMSO) 17.2, 36.6, 49.9, 53.3, 54.5, 65.3, 80.2, 125.1, 125.4, 127.0, 127.1, 127.4, 128.4, 136.1, 138.2, 170.6 and 171.6.

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Acetoxy-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 12e and 13e. The amide **14** (87 mg, 0.53 mmol) was acetylated with acetic anhydride (0.15 cm^3, 1.59 mmol) in pyridine (3 cm^3) to give **15**[23] as a yellow oil (quant.), which was not purified further. The amide **15** (0.53 mmol) was reacted with **17** according to general method B to give a crude mixture of **12e** and **13e**. Repeated chromatography on a 2 mm silica chromatotron plate eluting with ethyl acetate–light petroleum mixtures gave a number of fractions.

The first fraction contained a mixture of **12e** and **13e** (21 mg, 9:1 by ^{1}H NMR spectroscopy) which was crystallised from ethyl acetate–light petroleum to give **12e** (6 mg), mp 122–125 °C [HRMS: found $(M - Me)^+$, 312.1233. $C_{18}H_{18}NO_4$ requires 312.1236]; $[\alpha]_D^{23}$ +89 (*c* 5.3, dichloromethane); ν_{max}/cm^{-1} 3419, 1747, 1693, 1506, 1454, 1373 and 1220; $\delta_H(CDCl_3)$ 2.07 (3 H, s, COMe), 3.21 (2 H, dd, *J* 5.6 and 2.2, CH_2Ph), 3.41 (3 H, s, OMe), 5.49 (1 H, dd, C*H*OAc), 6.11 (1 H, d, *J* 9.8, C*H*OMe), 6.46 (1 H, d, *J* 9.7, NH) and 7.12–7.30 (10 H, m, ArH); $\delta_C(CDCl_3)$ 20.9, 37.5, 56.1, 74.2, 80.8, 125.7, 126.9, 128.3, 128.4, 128.4, 129.7, 135.9, 138.6, 149.7 and 169.3; *m/z* (EI) 312 ($M^+ -$ Me, 8%), 296 ($M^+ -$ OMe, 15), 237 (50) and 106 (100).

Further elution gave mixtures of **12e** and **13e** (81 mg). Crystallisation of one such fraction from ethyl acetate–light petroleum gave **13e** (5 mg), mp 110–112 °C [HRMS: found $(M - Me)^+$, 312.1234. $C_{18}H_{18}NO_4$ requires 312.1236]; $[\alpha]_D^{23}$ −25 (*c* 5.3, dichloromethane); ν_{max}/cm^{-1} 3419, 1747, 1693, 1506, 1454, 1373 and 1220; $\delta_H(CDCl_3)$ 2.04 (3 H, s, COMe), 3.22 (2 H, m, CH_2Ph), 3.33 (3 H, s, OMe), 5.36 (1 H, m, C*H*OAc), 6.10 (1 H, d, *J* 9.2, C*H*OMe), 6.77 (1 H, d, NH) and 7.17–7.33 (10 H, m, ArH); $\delta_C(CDCl_3)$ 20.7, 37.5, 55.9, 74.5, 81.0, 123.6, 125.6, 126.9, 128.3, 128.4, 129.5, 135.9, 138.9, 149.6 and 169.3; *m/z* (EI) 312 ($M^+ - Me$), 296 ($M^+ -$ OMe, 8%), 252 (84) and 121 (100).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Hydroxy-*N*-(1′-methoxypropyl)-3-phenylpropanamide 12f and 13f. A mixture of **12g** and **13g** prepared by method B (12 mg of a 1:1 mixture by ^{1}H NMR spectroscopy) was hydrolysed in methanol and water (2.5 cm^3 of a 9:1 mixture) with K_2CO_3 (0.2 equiv.) at room temp. for 2 h. The mixture was evaporated and the residue was redissolved in dichloromethane (2 cm^3). The organic solution was washed with water (2 cm^3), dried and the solvent was evaporated to give an oil (11 mg) which was chromatographed on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (3:10) to give **13f** as an oil (2 mg) [HRMS: found $(M - Me)^+$, 222.1125. $C_{12}H_{16}NO_3$ requires 222.1130]; $[\alpha]_D^{23}$ +104 (*c* 0.2, dichloromethane); ν_{max}/cm^{-1} 3400, 2972, 1680, 1301 and 1085; $\delta_H(CDCl_3$, [$^2H_5$]pyridine) 0.91 (3 H, t, *J* 7.3, CH$_2$*Me*), 1.57 (1 H, m, C*H*$_2$Me), 1.65 (1 H, m, C*H*$_2$Me), 2.95 (1 H, dd, *J* 13.7 and 8.3, CH_2Ph), 3.22 (3 H, s, OMe), 3.28 (1 H, m, C*H*$_2$Ph), 4.38 (1 H, dd, *J* 8.3 and 3.9, C*H*OH), 5.03 (1 H, m, C*H*OMe), 6.98 (1 H, d, *J* 9.3, NH) and 7.21–7.30 (5 H, m, ArH); $\delta_C(CDCl_3$, [$^2H_5$]pyridine) 9.0, 28.6, 41.1, 55.6, 72.7, 81.8, 126.7, 128.5, 129.6 and 137.5; *m/z* (EI) 222 ($M^+ -$ Me, 2%), 208 ($M^+ - C_2H_5$, 13), 205 ($M^+ -$ MeOH, 64), 91 (63) and 73 (100).

Further elution gave mixtures of **12f** and **13f** and a sample **12f** as an oil (2 mg) [HRMS: found $(M - Me)^+$, 222.1095. $C_{12}H_{16}NO_3$ requires 222.1130]; $[\alpha]_D^{23}$ +423 (*c* 0.2, dichloromethane); ν_{max}/cm^{-1} 3400, 2972, 1680, 1301 and 1085; $\delta_H(CDCl_3$, [$^2H_5$]pyridine) 0.84 (3 H, t, *J* 7.3, CH$_2$*Me*), 1.48 and 1.65 (2 H, m, C*H*$_2$Me), 2.91 (1 H, dd, *J* 13.7 and 8.3, CH_2Ph), 3.28 (1 H, dd, *J* 13.7 and 3.4, CH_2Ph), 3.31 (3 H, s, OMe), 4.46 (1 H, dd, *J* 8.3 and 3.4, C*H*OH), 5.03 (1 H, m, C*H*OMe), 6.95 (1 H, br s, NH) and 7.18–7.33 (5 H, m, ArH); $\delta_C(CDCl_3$, [$^2H_5$]pyridine) 8.8, 28.2, 40.9, 55.5, 72.3, 81.7, 126.2, 128.1, 129.6, 137.9 and 174.3; *m/z* (EI) 222 ($M^+ -$ Me, 1%), 208 ($M^+ - C_2H_5$, 4), 205 (27), 91 (36) and 73 (100).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Acetoxy-*N*-(1′-methoxypropyl)-3-phenylpropanamide 12g and 13g. The amide **15** (0.25 mmol), prepared as described in the preparation of **12e** and **13e**, was reacted with **19** according to general method B. Purification of the crude product (49 mg) on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (1:5 to 1:3) gave a mixture of **12g** and **13g** (12 mg, 1:1 by ^{1}H NMR spectroscopy) which could not be separated; δ_H(of the mixture; $CDCl_3$) 0.78 and 0.83 (each 3 H, t, CH_2Me), 1.42 and 1.57 (each 2 H, m, CH_2Me), 2.09 and 2.11 (each 3 H, s, COMe), 3.14 and 3.24 (each 3 H, s, OMe), 3.15–3.22 (m, CH_2Ph), 4.99 (m, CHOMe), 5.35 and 5.40 (each 1 H, m, CHOAc), 6.10 (br m, NH) and 7.17–7.31 (m, ArH); δ_C($CDCl_3$) 8.8, 20.7, 20.9, 28.3, 28.5, 37.5, 37.6, 55.7, 55.9, 74.3, 74.4, 82.3, 127.0, 128.4, 128.4, 129.6, 129.6, 135.6, 135.7, 169.3 and 169.4.

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-Benzyloxycarbonylamino-*N*-(1′-methoxyethyl)-3-phenylpropanamide 12h and 13h. The amide **16**, isolated from the preparation of **12c** and **13c** (61 mg, 0.21 mmol), was reacted with **18** according to general method B. Purification of the crude product (38 mg) on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (1:5 to 1:1) gave three fractions.

The first fraction gave **12h** as a solid (18 mg) [HRMS: found $(M - MeOH)^+$, 324.1474. $C_{19}H_{20}N_2O_3$ requires 324.1474]; mp 136–138 °C; $[\alpha]_D^{23}$ −10 (*c* 0.1, dichloromethane); ν_{max}/cm^{-1} 3416, 3034, 1757, 1713, 1690 and 1497; δ_H($CDCl_3$, [$^2H_5$]pyridine) 1.12 (3 H, d, *J* 5.8, CH*Me*), 3.08 (2 H, d, *J* 7.4, CHCH_2), 3.24 (3 H, s, OMe), 4.47 (1 H, m, C*H*CH$_2$), 5.08 (2 H, s, PhCH_2O), 5.18 (1 H, m, C*H*OMe), 6.24 (1 H, d, *J* 7.4, BnOCON*H*) and 7.11–7.36 (10 H, m, ArH); δ_C($CDCl_3$, [$^2H_5$]pyridine) 20.9, 38.4, 55.1, 56.3, 66.5, 77.5, 126.6, 127.6, 127.8, 128.2, 128.3, 129.1 and 171.1; *m/z* (EI) 324 (M^+ − MeOH, 2%), 91 (100).

The second fraction contained a mixture of **12h** and **13h** (10 mg, 3:2 by ^{1}H NMR spectroscopy).

The final fraction gave **13h** (19 mg) [HRMS: found $(M - MeOH)^+$, 324.1474. $C_{19}H_{20}N_2O_3$ requires 324.1474]; mp 158–160 °C; $[\alpha]_D^{23}$ +3 (*c* 2, dichloromethane); ν_{max}/cm^{-1} 3416, 3034, 1757, 1713, 1690 and 1499; δ_H($CDCl_3$, [$^2H_5$]pyridine) 1.23 (3 H, d, *J* 6.8, CH*Me*), 3.06 (2 H, d, *J* 6.8, CHCH_2), 3.12 (3 H, s, OMe), 4.55 (1 H, m, C*H*CH$_2$), 5.06 (2 H, s, PhCH_2O), 5.20 (1 H, m, C*H*OMe), 6.24 (1 H, d, *J* 7.8, BnOCON*H*), 7.16–7.30 (10 H, m, ArH) and 7.39 (1 H, d, *J* 8.7, CONH); δ_C($CDCl_3$, [$^2H_5$]pyridine) 21.0, 38.2, 55.1, 56.2, 66.6, 77.8, 126.6, 127.6, 127.8, 128.2, 128.2, 129.1, 155.8 and 166.1; *m/z* (EI) 324 (M^+ − MeOH, 4%) and 91 (100).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-(4-Bromobenzoyloxy)-*N*-(1′-methoxy-2′-methylpropyl)-3-phenylpropanamide 12i and 13i. To a solution of amide **14** (55 mg, 0.33 mmol) and 4-dimethylaminopyridine (61 mg, 0.50 mmol) in dichloromethane (2.5 cm^3) was added triethylamine (92 μl, 0.66 mmol) and 4-bromobenzoyl chloride (81 mg, 0.57 mmol). After stirring the mixture at room temp. for 3 h the solvent was evaporated and benzene (5 cm^3) was added. The organic layer was washed with 2 M aqueous HCl (3 cm^3), saturated aqueous $NaHCO_3$ (3 cm^3) and water (3 cm^3), and dried. Evaporation under reduced pressure gave **21** (117 mg) which was used without further purification; δ_H($CDCl_3$) 3.31 (2 H, m, CH_2Ph), 5.60 (1 H, m, C*H*CH$_2$), 5.77 (1 H, br s, NH), 6.00 (1 H, br s, NH), 7.23–7.29 (5 H, m, ArH), 7.59 (2 H, m, ArH) and 7.82 (2 H, m, ArH).

The amide **21** was reacted with **20** according to general method B to give a crude mixture of **12i** and **13i** (quant.). The mixture was purified by two passes through a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (3:50) followed by ethyl acetate–light petroleum (1:50) to give **13i** (1 mg) [HRMS: found $(M - MeOH)^+$, 401.0635. $C_{20}H_{20}NO_3{}^{79}Br$ requires 401.0627]; δ_H($CDCl_3$) 0.75 (3 H, d, *J* 6.9, CH*Me*), 0.81 (3 H, d, *J* 6.4, CH*Me*), 1.68 (1 H, m, C*H*Me$_2$), 3.16 (3 H, s, OMe), 3.34 (2 H, d, CH_2Ph), 4.83 (1 H, dd, *J* 5.8 and 9.7, C*H*OMe), 5.60 (1 H, t, *J* 5.9, C*H*CH$_2$), 5.93 (1 H, d, *J* 9.3, NH), 7.22–7.28 (5 H, m, ArH), 7.62 (2 H, m, ArH) and 7.86 (2 H, m, ArH); *m/z* (EI) 403 [M^+(^{81}Br) − MeOH, 3%], 401 [M^+(^{79}Br) − MeOH, 4], 333 (9), 185 (95) and 183 (100).

Further elution gave fractions containing a mixture of **12i** and **13i** (13 mg).

The final fraction contained a mixture of **12i** and **13i** (3 mg, 17:3 by ^{1}H NMR spectroscopy) [HRMS: found $(M - MeOH)^+$, 401.0633. $C_{20}H_{20}NO_3{}^{79}Br$ requires 401.0627]; data for **12i** (from the mixture) δ_H($CDCl_3$) 0.76 (3 H, d, *J* 6.9, CH*Me*), 0.79 (3 H, d, *J* 6.4, CH*Me*), 1.68 (1 H, m, C*H*Me$_2$), 3.22 (3 H, s, OMe), 3.33 (2 H, d, CH_2Ph), 4.83 (1 H, dd, *J* 5.8 and 9.7, C*H*OMe), 5.64 (1 H, t, *J* 5.9, C*H*CH$_2$), 5.97 (1 H, d, *J* 9.3, NH), 7.22–7.27 (5 H, m, ArH), 7.62 (2 H, m, ArH) and 7.84 (2 H, m, ArH); *m/z* (EI) 403 [M^+(^{81}Br) − MeOH, 3%], 401 [M^+(^{79}Br) − MeOH, 3], 333 (8), 185 (87) and 183 (85).

(1′*R*,2*S*)- and (1′*S*,2*S*)-2-[(1*S*)-Camphanyloxy]-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 12j and 13j. A solution of (1*S*,4*R*)-camphanic acid (66 mg, 0.33 mmol) in thionyl chloride (5 cm^3) was refluxed for 2 h. Evaporation of the solvent under reduced pressure gave an oil which was dissolved in dichloromethane (1 cm^3). The solution was added to a stirred solution of **14** (24 mg, 0.15 mmol), 4-dimethylaminopyridine (18 mg, 0.15 mmol) and diisopropylethylamine (28 μl, 0.16 mmol) in dichloromethane (1 cm^3). After stirring for 18 h at room temp. the reaction mixture was washed with water (2 cm^3) and dried. Evaporation under reduced pressure gave **22** (65 mg), which was used without further purification.

Compound **22** (65 mg, 0.19 mmol) was reacted with **17** according to general method B. Purification of the crude product (44 mg) by two passes through a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (2:3) followed by ethyl acetate–light petroleum (1:4 to 3:7) gave a mixture of **12j** and **13j** (14 mg, 3:2 by ^{1}H NMR spectroscopy) [HRMS: found $(M - OMe)^+$, 434.1942. $C_{26}H_{28}NO_5$ requires 434.1968]; data for **12j** (from the mixture) δ_H($CDCl_3$, [$^2H_5$]pyridine) 0.71, 0.97 and 1.07 (each 3 H, s, camph-Me), 1.65 (1 H, m), 1.90 (2 H, m), 2.33 (1 H, m), 3.16 (1 H, dd, *J* 14.6 and 8.3, CH_2Ph), 3.33 (1 H, dd, *J* 14.6 and 4.6, CH_2Ph), 3.39 (3 H, s, OMe), 5.52 (1 H, dd, *J* 8.3 and 4.6, CHCO), 6.10 (1 H, d, *J* 9.3, C*H*OMe) and 7.19–7.37 (10 H, m, ArH); *m/z* (EI) 434 (M^+ − OMe, 11%), 329 (5), 273 (82) and 131 (100).

Further elution gave a mixture of **13j** and **12j** which was crystallised from ethyl acetate–light petroleum to give crystals of **13j** (11 mg) suitable for X-ray crystallography [HRMS: found $(M - OMe)^+$, 434.1974. $C_{26}H_{28}NO_5$ requires 434.1968]; δ_H($CDCl_3$, [$^2H_5$]pyridine) 0.76, 1.00 and 1.08 (each 3 H, s, camph-Me), 1.60 (1 H, m), 1.76 (1 H, m), 1.87 (1 H, m), 2.26 (1 H, m), 3.17 (1 H, dd, *J* 14.4 and 8.5, CH_2Ph), 3.30 (1 H, dd, *J* 14.2 and 5.4, CH_2Ph), 3.42 (3 H, s, OMe), 5.41 (1 H, dd, *J* 8.4 and 5.4, CHCO), 6.11 (1 H, d, *J* 9.3, C*H*OMe), 7.17–7.32 (10 H, m, ArH) and 7.99 (1 H, d, *J* 9.3, NH); *m/z* (EI) 434 (M^+ − OMe, 6%), 330 (7), 273 (70) and 131 (100).

A mixture (5 mg, 72%) of **12j** and **13j** (9:1 by ^{1}H NMR spectroscopy) was also prepared from a mixture (5 mg, 0.02 mmol) of **12a** and **13a** (9:1 by ^{1}H NMR spectroscopy) using (1*S*,4*R*)-camphanyl chloride as described for the preparation of **22** from **14**.

(1′*R*,2*R*)- and (1′*S*,2*R*)-2-Acetoxy-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 27 and 29

The amide **25** (40 mg, 0.24 mmol) was acetylated with acetic anhydride (69 μl, 0.73 mmol) in pyridine (3 cm^3) to give **26** as a yellow oil (quant.), which was not purified further. The amide **26** (0.24 mmol) was reacted with **17** according to general method B (see preparation of **12**/**13**). Purification of the crude mixture (33 mg) on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (2:25 to 1:3) gave a mixture of **27** and **29** (8 mg, 7:3 by ^{1}H NMR spectroscopy) which was recrystallised from ethyl acetate–light petroleum to give **27** (3 mg), mp 129–131 °C [HRMS: found (M^+ − Me), 312.1233.

$C_{18}H_{18}NO_4$ requires 312.1236]; $[\alpha]_D^{23}$ −37 (*c* 2.3, dichloromethane); δ_H and δ_C data identical to enantiomer **12e**.

Further elution gave a fraction containing a mixture of **29** and **27** (7 mg, 8:2 by ^{1}H NMR spectroscopy) which was recrystallised from ethyl acetate–light petroleum to give **29** (3 mg), mp 111–113 °C [HRMS: found $(M - Me)^+$, 312.1234. $C_{18}H_{18}NO_4$ requires 312.1236]; $[\alpha]_D^{23}$ +24 (*c* 0.7, dichloromethane); δ_H and δ_C data identical to enantiomer **13e**).

(1′*R*,2*R*)- and (1′*S*,2*R*)-2-Hydroxy-*N*-(1′-methoxy-1′-phenylmethyl)-3-phenylpropanamide 28 and 30

The acetates **27** (2.3 mg, 0.007 mmol) and **29** (1.3 mg, 0.004 mmol) were separately hydrolysed (as described for **12e** and **13e** in the preparation of **12a** and **13a**) to give **28** (1.7 mg, 84%) and **30** (0.7 mg, 60%), respectively. Compound **28**, mp 62–64 °C [HRMS: found $(M - Me)^+$, 270.1134. $C_{16}H_{16}NO_3$ requires 270.1130]; $[\alpha]_D^{23}$ +21 (*c* 0.1, dichloromethane); δ_H and δ_C data identical to enantiomer **12a**. Compound **30**, mp 99–101 °C [HRMS: found $(M - Me)^+$, 270.1128. $C_{16}H_{16}NO_3$ requires 270.1130]; $[\alpha]_D^{23}$ +76 (*c* 0.4, dichloromethane); δ_H and δ_C data identical to enantiomer **13a**.

(2*R*,5*S*)- and (2*S*,5*S*)-5-Benzyl-2-phenyl-1,3-oxazolidin-4-ones 31 and 33

An excess of **17** (25 equiv.) was added to the amide **14** (93 mg, 0.56 mmol) in dichloromethane (5 cm^3) and the mixture was stirred at −10 °C for 18 h. The solution was washed with 10% aqueous $NaHCO_3$ (5 cm^3) and water (5 cm^3), dried and the solvent was evaporated under reduced pressure to give a crude mixture of **31** and **33** (141 mg). Purification on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (2:3) gave a mixture of **31** and **33** (76 mg, 54%, 4:1 by ^{1}H NMR spectroscopy). Further purification on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (1:9 to 1:0) gave **33** as an oil (19 mg) (HRMS: found M^+, 253.1102. $C_{16}H_{15}NO_2$ requires 253.1103); $[\alpha]_D^{23}$ −17 (*c* 0.7, dichloromethane); ν_{max}/cm^{-1} 3429, 1756, 1728, 1278, 1247 and 1126; $\delta_H(CDCl_3)$ 3.13 (2 H, m, CH_2Ph), 4.77 (1 H, m, C*H*CH$_2$), 5.72 (1 H, d, *J* 2.4, NCH), 7.24–7.37 (10 H, m, ArH) and 7.86 (1 H, br s, NH); $\delta_C(CDCl_3)$ 37.6, 78.2, 87.8, 126.2, 126.8, 128.3, 128.7, 129.7, 129.7, 136.1, 138.3 and 166.4; *m/z* (EI) 253 (M^+, 76%), 106 (100).

Further elution gave **31** as an oil (11 mg) (HRMS: found M^+, 253.1105. $C_{16}H_{15}NO_2$ requires 253.1103); $[\alpha]_D^{23}$ −121 (*c* 0.1, dichloromethane); ν_{max}/cm^{-1} 3430, 1730, 1498, 1462, 1313 and 1081; $\delta_H(CDCl_3)$ 3.11 (2 H, m, CH_2Ph), 4.59 (1 H, m, C*H*CH$_2$), 5.96 (1 H, d, *J* 2.1, NC*H*), 7.03–7.07 (2 H, m, ArH), 7.18–7.36 (8 H, m, ArH) and 7.75 (1 H, br s, NH); $\delta_C(CDCl_3)$ 37.4, 78.5, 87.1, 126.6, 127.0, 128.3, 128.5, 129.8, 129.9, 136.5, 137.5 and 174.5; *m/z* (EI) 253 (M^+, 25%), 147 (90) and 106 (100).

(2*R*,5*S*)- and (2*S*,5*S*)-5-Benzyl-2-ethyl-1,3-oxazolidin-4-ones 32 and 34

Prepared as described for **31** and **33** using the amide **14** (124 mg, 0.73 mmol) and **19** (25 equiv.). Purification of the crude mixture on a 1 mm silica chromatotron plate eluting with ethyl acetate–dichloromethane (0:1 to 3:10) gave **34** as an oil (6 mg) (HRMS: found M^+, 205.1103. $C_{12}H_{15}NO_2$ requires 205.1103); $\delta_H(CDCl_3)$ 0.90 (3 H, t, *J* 7.5, Me), 1.60 (2 H, m, CH_2Me), 3.05 (2 H, m, CH_2Ph), 4.57 (1 H, m, C*H*CO), 4.85 (1 H, m, NC*H*), 6.46 (1 H, br s, NH) and 7.29 (5 H, m, ArH); $\delta_C(CDCl_3)$ 7.2, 29.5, 37.8, 77.9, 87.7, 126.7, 128.3, 129.8, 136.5 and 176.0; *m/z* (EI) 205 (M^+, 54%), 176 ($M^+ - C_2H_5$, 49), 131 (87) and 91 (100).

Further elution gave a second fraction containing a mixture of **32** and **34** (6 mg, 1:4 by ^{1}H NMR spectroscopy).

The final fraction gave **32** as an oil (13 mg) (HRMS: found M^+, 205.1106. $C_{12}H_{15}NO_2$ requires 205.1103); $\delta_H(CDCl_3)$ 0.87 (3 H, t, *J* 7.6, Me), 1.46 (2 H, m, CH_2Me), 3.07 (2 H, m, CH_2Ph), 4.49 (1 H, m, C*H*CO), 5.10 (1 H, m, C*H*OMe), 6.88 (1 H, br s, NH) and 7.28 (5 H, m, ArH); $\delta_C(CDCl_3)$ 7.3, 29.1, 37.9, 78.2 87.2, 126.7, 128.2, 129.7, 136.9 and 174.1; *m/z* (EI) 205 (M^+, 40%), 176 ($M^+ - C_2H_5$, 78), 131 (73) and 91 (100).

(2*S*,5*R*)- and (2*R*,5*R*)-5-Benzyl-2-phenyl-1,3-oxazolidin-4-ones 35 and 36

Prepared as described for **31** and **33** using the amide **25** (40 mg, 0.24 mmol) and **17** (25 equiv.). Purification of the crude mixture (141 mg) by flash silica chromatography, eluting with ethyl acetate–dichloromethane (1:20 to 1:5) gave two fractions. The first fraction contained a mixture of **36** and **35** (16 mg, 7:3 by ^{1}H NMR spectroscopy). The second fraction gave **35** as an oil (16 mg) (HRMS: found M^+, 253.1105. $C_{16}H_{15}NO_2$ requires 253.1103); δ_H data identical to **31**. The first fraction was further purified on a 1 mm silica chromatotron plate eluting with ethyl acetate–light petroleum (1:3 to 1:1) to give **36** as an oil (2 mg) (HRMS: found M^+, 253.1102. $C_{16}H_{15}NO_2$ requires 253.1103); δ_H data identical to **33**. Further elution gave more **35** (3 mg).

(2*S*)-2-Hydroxy-3-phenyl-*N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)propanamide 42

A solution of the acid **5** [17–19] (50 mg, 0.30 mmol), glucosylamine **41** (104 mg, 0.30 mmol), 1-hydroxybenzotriazole (42 mg, 0.30 mmol) and dicyclohexylcarbodiimide (61 mg, 0.30 mmol) in dichloromethane (10 cm^3) was stirred at room temp. for 5 d. The mixture was filtered and evaporated to give the crude amide **42** (quant.). Purification on a 1 mm chromatotron plate eluting with ethyl acetate–light petroleum (1:1) gave **42** (87 mg, 59%), mp 172.5–174.5 °C (from ethyl acetate–light petroleum) (HRMS: found MH^+, 496.1810. $C_{23}H_{30}NO_{11}$ requires 496.1820); $[\alpha]_D^{23}$ +46 (*c* 0.1, dichloromethane); ν_{max}/cm^{-1} 3052, 1756, 1225 and 1043; $\delta_H(CDCl_3)$ 1.94, 2.02, 2.03, 2.07 (each 3 H, s, COMe), 2.78 (1 H, dd, *J* 13.6 and 8.5, CH_2Ph), 2.86 (1 H, d, *J* 4.8, OH), 3.18 (1 H, dd, *J* 13.7 and 2.9, CH_2Ph), 3.82 (1 H, m, H-5), 4.11 (1 H, m, H-6a), 4.31 (1 H, m, H-6b), 4.33 (1 H, m, C*H*CO), 4.94 (1 H, t, *J* 9.5, H-2), 5.06 (1 H, t, *J* 9.5, H-4), 5.21 (1 H, t, *J* 9.2, H-1), 5.30 (1 H, t, *J* 9.3, H-3), 7.23–7.34 (4 H, m, ArH) and 7.46 (1 H, m, ArH); $\delta_C(CDCl_3)$ 20.5, 20.6, 40.3, 61.5, 68.0, 70.4, 72.6, 72.7, 73.6, 77.8, 127.0, 128.6, 129.5, 136.4, 169.5, 170.5 and 173.6; *m/z* (FAB) 496 (MH^+, 53%) and 168 (100).

(2*S*)-2-Hydroxy-3-phenyl-*N*-(β-D-glucopyranosyl)propanamide 43

The amide **42** (37 mg, 0.08 mmol) and K_2CO_3 (2 mg, 0.02 mmol) were dissolved in methanol and water (4 cm^3 of a 9:1 solution) and the mixture was stirred at room temp. for 1 h. The methanol was removed under reduced pressure and the aqueous layer was washed with dichloromethane (3 × 5 cm^3) and evaporated to give **43** (24 mg, 96%) (HRMS: found MK^+, 366.0960. $C_{15}H_{21}NO_7K$ requires 366.0955); $\delta_H(D_2O)$ 1.77 (1 H, s, OH), 2.84 (1 H, dd, *J* 14.2 and 7.8, CH_2Ph), 3.02 (1 H, dd, *J* 14.1 and 4.9, CH_2Ph), 3.25–3.77 (6 H, m, H-2–H-6), 4.36 (1 H, dd, *J* 7.8 and 4.9, C*H*CO), 4.81 (1 H, d, *J* 9.3, H-1) and 7.16–7.26 (5 H, m, ArH); *m/z* (FAB) 366 (MK^+, 8%), 307 (10) and 153 (100).

Crystal structure determination for 13j

Crystal data. $C_{27}H_{31}NO_6$, $M = 465.53$, triclinic, $a = 6.2953(13)$, $b = 12.667(3)$, $c = 15.522(3)$ Å, $\alpha = 88.73(3)$, $\beta = 86.45(3)$, $\gamma = 85.19(3)°$, $V = 1230.9(4)$ Å^3 [by refinement against setting angles for 25 reflections with $106 \leq 2\theta \leq 115°$, $\lambda = 1.541\,84$ Å, $T = 293(2)$ K], space group *P*1 (No. 1), $Z = 2$, $D_x = 1.256$ g cm^{-3}, colourless needle 0.7 × 0.2 × 0.08 mm, μ(Cu-Kα) = 0.722 mm^{-1}.

Data collection and processing. Rigaku AFC four-circle diffractometer, ω–2θ scans, graphite-monochromated Cu-Kα X-radiation; 4056 reflections measured ($5.7 \leq 2\theta \leq 120.2°$, $+h$, $\pm k$, $\pm l$); 3665 had $F \geq 4\sigma(F)$ and all 4056 were retained in all calculations. Three intensity standards, monitored every 150 reflec-

tions, showed slight variations (1.3%). Corrections for absorption (min., 0.883; max., 1.000) were made using the ψ-scan method.

Structure solution and refinement. Automatic direct methods[24] (all non-H atoms). Full-matrix least-squares refinement[25] with all non-H atoms anisotropic; hydrogen atoms were introduced at geometrically calculated positions and thereafter allowed to ride on their parent atoms. The weighting scheme $w^{-1} = [\sigma^2(F_o^2) + (0.045P)^2 + 0.044P]$, $P = \frac{1}{3}[\mathrm{MAX}(F_o^2,0) + 2F_c^2]$ gave satisfactory agreement analyses. Final R_1 $[F \geq 4\sigma(F)] = 0.0282$, wR_2 (all data) = 0.102, $S(F^2) = 1.12$ for 621 refined parameters and 3 restraints. An absolute structure (Flack[26]) parameter refined to 0.3(2); no extinction correction was required; and the final ΔF synthesis showed no peaks above ± 0.15 e Å^{-3}.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/108.

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