# Synthesis of functionalised oxazoles and bis-oxazoles[1]

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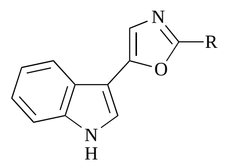
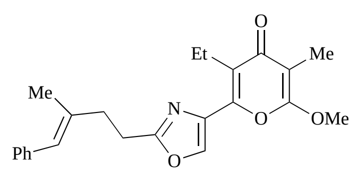
**A new method for the synthesis of oxazoles, and in particular chiral non-racemic oxazoles derived from amino acids, has been developed. Thus, rhodium(II) catalysed reaction of diazocarbonyl compounds 6 and 11 in the presence of amides 8 and 10 results in regioselective insertion of the carbenoid into the amide N–H bond with formation of the β-carbonyl amides 9 and 12. Cyclodehydration of amides 9 and 12 using triphenylphosphine–iodine–triethylamine gives functionalised oxazoles 7 and 13. The oxazoles 13c and 13f were converted into the bis-oxazoles 17a and 17b by a second rhodium(II) catalysed regioselective N–H insertion reaction on the amides 15, followed by cyclodehydration.**

## Introduction

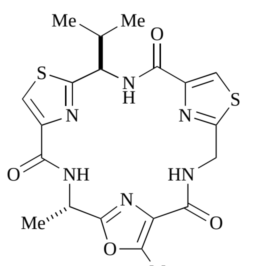
The isolation of many structurally diverse oxazole containing natural products has resulted in a renewed interest in the chemistry of oxazoles.[2–9] Naturally occurring oxazoles range in structure from relatively simple 2,5-disubstituted derivatives such as the 5-(indol-3-yl)oxazole alkaloids pimprinine **1a** and pimprinethine **1b**,[10] to the more complex 2,4-disubstituted compounds such as phenoxan **2**,[11–14] calyculin A[15–17] and rhizoxin.[18,19] The oxazole (and thiazole) ring systems also occur in biologically active cyclic peptides;[4] examples include nostocyclamide **3**[20] and bistratamide C.[21] Bis-oxazoles such as



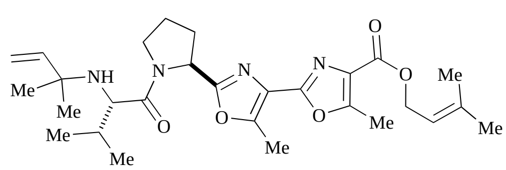
**1a** R = Me
**1b** R = Et



**2**



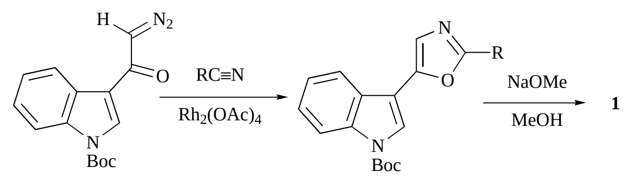
**3**



**4**

muscoride A **4**,[22–24] hennoxazole A[25,26] and tris-oxazoles such as the ulapualides and kabiramides are also known.[27–31]

From the many synthetic methods available for the construction of the heteroaromatic oxazole ring,[32–34] we have focused on the rhodium(II) catalysed reaction of diazocarbonyl compounds with nitriles,[35,36] as exemplified by our recent syntheses of the 5-(indol-3-yl)oxazole alkaloids **1** (Scheme 1).[37] Although this

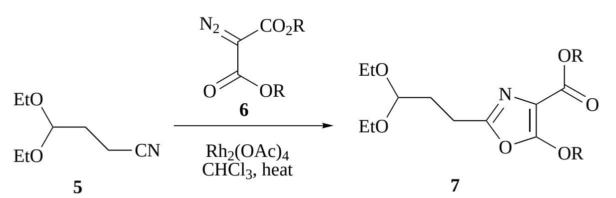


**Scheme 1**

method works well for simple nitriles, it is less satisfactory for complex nitriles containing additional functional groups. Therefore we have developed an alternative strategy based on the N–H insertion reactions of rhodium carbenoids.[38,39] This has proved an effective strategy, particularly for the synthesis of chiral, non-racemic oxazoles derived from α-amino acids, and the results are described in detail herein.[1] The following paper reports an application of this methodology in the total synthesis of (+)-nostocyclamide **3**.

## Results and discussion

It was in a projected synthesis of phenoxan **2** that the reaction of diazocarbonyl compounds with nitriles proved somewhat unsatisfactory. Thus reaction of the cyano acetal **5** with diazomalonates **6**, prepared by diazo transfer to the corresponding malonates,[40] gave poor yields of the oxazoles **7a** (33%) and **7b** (7%) (Scheme 2).



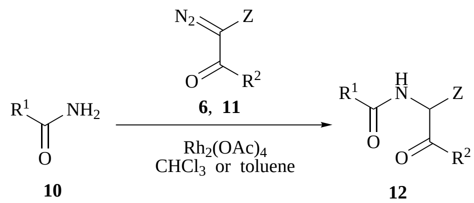
**Scheme 2** (**a**, R = Me; **b**, R = Bu$^t$)

The rhodium(II) catalysed addition of diazocarbonyl compounds to *N*-protected α-aminonitriles, derived by dehydration of α-amino acid amides (Path A, Scheme 3), also proved unsatisfactory. Therefore we investigated the possibility of reversing the order of steps by carrying out a rhodium carbenoid N–H insertion reaction on the amide followed by cyclodehydration to give the oxazole (Path B, Scheme 3).

Insertion reactions of metallocarbenoids are widely used in synthesis,[41–52] although, with the exception of the intramolecular insertion into the N–H bond of a β-lactam

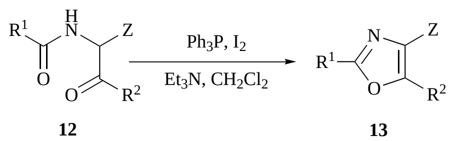
† A substantial part of this work was carried out by the authors in the Department of Chemistry, Loughborough University, Loughborough, Leics., UK LE11 3TU.

**Table 1**

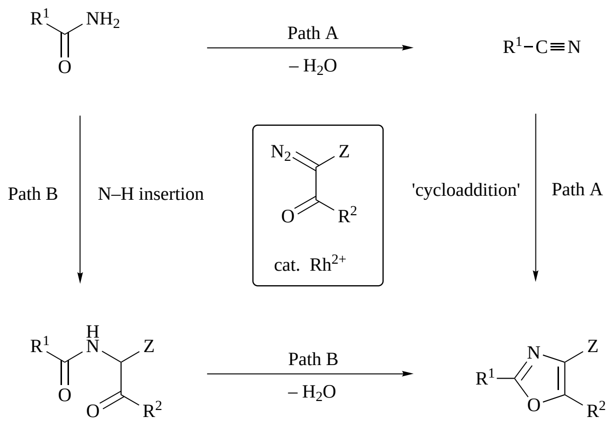


| Amide | $R^1$ | Diazo compound | $R^2$ | Z | Keto amide | Yield (%) |
|---|---|---|---|---|---|---|
| **10a** | CbzNHCH$_2$ | **11a** | Me | CO$_2$Me | **12a** | 71 |
| **10b** | (*S*)-CbzNHCHMe | **11a** | Me | CO$_2$Me | **12b** | 71 |
| **10c** | (*S*)-PhthNCHPr$^i$ | **6a** | OMe | CO$_2$Me | **12c** | 38 |
| **10d** | (*S*)-BocNHCHPr$^i$ | **6a** | OMe | CO$_2$Me | **12d** | 47 |
| **10d** | (*S*)-BocNHCHPr$^i$ | **11a** | Me | CO$_2$Me | **12e** | 30 |
| **10e** | (*S*)-CbzNHCHPr$^i$ | **6a** | OMe | CO$_2$Me | **12f** | 61 |
| **10e** | (*S*)-CbzNHCHPr$^i$ | **11a** | Me | CO$_2$Me | **12g** | 68 |
| **10e** | (*S*)-CbzNHCHPr$^i$ | **11b** | CH$_2$Cl | CO$_2$Me | **12h** | 67 |
| **10e** | (*S*)-CbzNHCHPr$^i$ | **11c** | Et | CO$_2$Me | **12i** | 48 |
| **10e** | (*S*)-CbzNHCHPr$^i$ | **11d** | Ph | CO$_2$Et | **12j** | 72 |
| **10f** | (*S*)-*N*-Cbz-pyrrolidin-2-yl | **11a** | Me | CO$_2$Me | **12k** | 74 |

**Table 2**

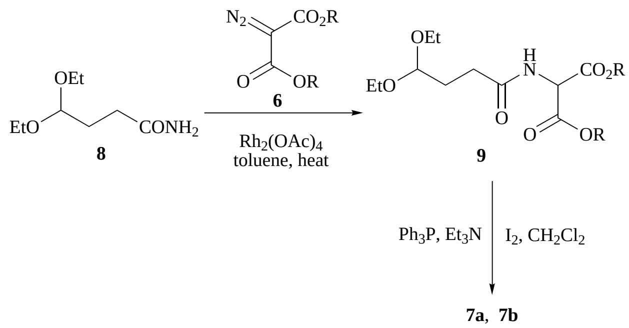


| Keto amide | $R^1$ | $R^2$ | Z | Oxazole | Yield (%) |
|---|---|---|---|---|---|
| **12a** | CbzNHCH$_2$ | Me | CO$_2$Me | **13a** | 56 |
| **12b** | (*S*)-CbzNHCHMe | Me | CO$_2$Me | **13b** | 66 |
| **12g** | (*S*)-CbzNHCHPr$^i$ | Me | CO$_2$Me | **13c** | 65 |
| **12i** | (*S*)-CbzNHCHPr$^i$ | Et | CO$_2$Me | **13d** | 88 |
| **12j** | (*S*)-CbzNHCHPr$^i$ | Ph | CO$_2$Me | **13e** | 31 |
| **12k** | (*S*)-*N*-Cbz-pyrrolidin-2-yl | Me | CO$_2$Me | **13f** | 73 |




**Scheme 3**

developed by Merck as a route to carbapenems and related compounds,[53] the N–H insertion reaction has found little use to date.[38,39] The initial substrate we investigated was the amide **8** which underwent reaction with the rhodium carbenoids derived from diazomalonates **6a** and **6b** to give the corresponding N–H insertion products **9a** and **9b** in 81 and 60% yield respectively (Scheme 4). Various methods, *e.g.* POCl$_3$, SOCl$_2$, PCl$_5$, P$_2$O$_5$, were tried to effect the cyclodehydration of the β-carbonyl amides **9** to the oxazoles **7**, but the triphenylphosphine–iodine–triethylamine protocol reported by Wipf proved the most satisfactory.[54] Using this method, the oxazoles **7a** and **7b** were obtained in 84 and 79% yield respectively from the amides **9a** and **9b** (Scheme 4).



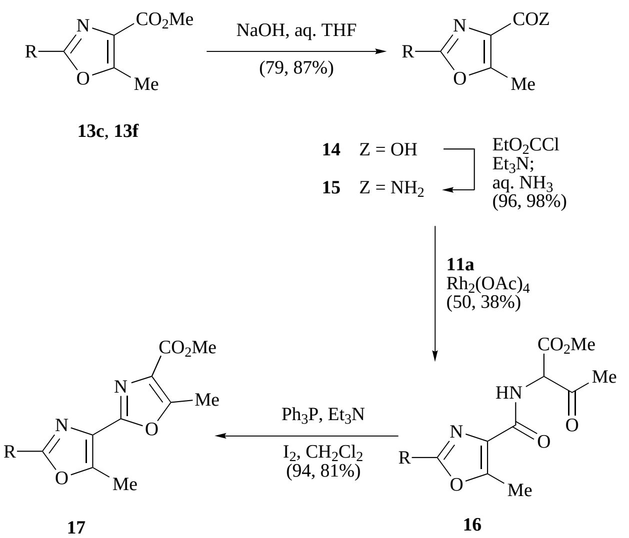

**Scheme 4** (**a**, R = Me; **b**, R = Bu$^t$)

The reaction was then extended to the *N*-protected amino acid amides **10** derived from glycine, (*S*)-alanine, (*S*)-valine and (*S*)-proline, and to other diazocarbonyl compounds **11**. The amides **10** were prepared from the corresponding *N*-protected amino acids by mixed anhydride formation with ethyl chloroformate followed by reaction with aqueous ammonia. The α-diazo β-keto esters **11** were prepared by diazo transfer reaction on the corresponding β-keto esters. The rhodium(II) acetate catalysed N–H insertion reactions proceeded readily in boiling chloroform and gave the desired products **12** in reasonable yield (Table 1). In the case of amides **10a**, **10b**, **10d** and **10e** no competing insertion into the carbamate N–H bond was observed.[55]

Cyclodehydration of the β-carbonylamides **12** gave the oxazoles **13** in modest to good yield (Table 2); the enantiomeric purity of the oxazoles **13b**, **13c** and **13f** was checked by HPLC

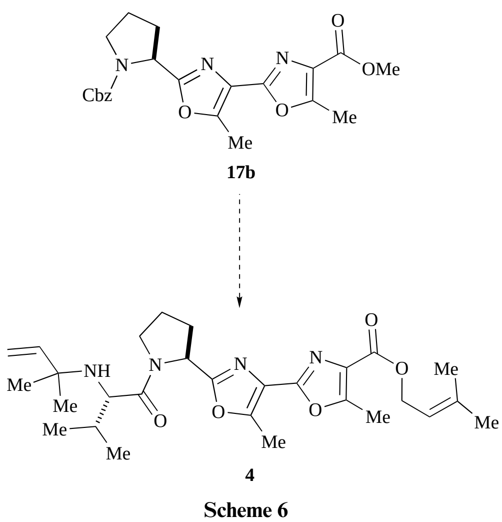
[Chiracel OD, hexane : propan-2-ol (19 : 1), 2 ml min$^{-1}$] and found to be >99%. The structure of oxazole **13c** was also confirmed by X-ray crystallography as reported previously.[1] Amide **12h** failed to give any oxazole under the cyclodehydration conditions, presumably because of competing attack of the triphenylphosphine on the $CH_2Cl$ group.

Finally the method was extended to the synthesis of bis-oxazoles. The oxazole-4-carboxylates **13c** and **13f**, derived from *N*-Cbz (*S*)-valine and (*S*)-proline respectively were converted into the corresponding acids **14** and hence amides **15** (Scheme 5). The amides **15** underwent regioselective N–H insertion in modest yield on treatment with methyl diazoacetoacetate and rhodium(II) acetate to give the insertion products **16**, cyclodehydration of which gave the bis-oxazoles **17** in good yield (Scheme 5).




**Scheme 5** (**13c**, **14**–**17a**; R = (*S*)-CbzNHCHPr$^i$; **13f**, **14**–**17b**; R = (*S*)-*N*-Cbz-pyrrolidin-2-yl)

The proline derived bis-oxazole **17b** comprises the heterocyclic core of the naturally occurring bis-oxazole muscoride A **4**,[22] and therefore **17b** was a key intermediate in our projected synthesis of the natural product (Scheme 6). However, our work was curtailed when Wipf,[23] and subsequently Pattenden[24] reported total syntheses of muscoride A.




**Scheme 6**

## Experimental

Commercially available reagents were used throughout without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 $GF_{254}$. Plates were visualised under UV light (at 254 and/or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60.

Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 cm$^{-1}$ using Nicolet FT-205 or Perkin-Elmer Paragon 1000 FT-IR spectrometers. $^1$H and $^{13}$C NMR spectra were recorded using Bruker AC-250 and Bruker DPX-400 instruments; *J* values were recorded in Hz. High and low resolution mass spectra were recorded on a Kratos MS80 instrument. Rotations were recorded on an Optical Activity PolAAR 2001 polarimeter; $[\alpha]_D$ values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$.

### Preparation of diazo compounds

**General method for diazo transfer**

To a solution of the substrate (37.8 mmol) and 4-acetamidobenzenesulfonyl azide[56] (10.0 g, 41.6 mmol) in acetonitrile (100 ml) at 0 °C was added triethylamine (15.8 ml, 113.4 mmol) dropwise. After stirring at room temperature for 16 h the reaction mixture was concentrated *in vacuo* and the resultant solid was triturated with ether–light petroleum. The filtrate was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with ether–light petroleum (1 : 4) to yield the desired product.

**Dimethyl diazomalonate 6a.** Prepared in 96% yield according to the literature procedure.[56]

**Di-*tert*-butyl diazomalonate 6b.** Prepared in 95% yield according to the literature procedure.[57]

**Methyl 2-diazo-3-oxobutanoate 11a.** According to the general procedure the title compound was obtained as a yellow oil (91%) (lit.,[58] no data given) (Found: M$^+$, 142.0377. $C_5H_6N_2O_3$ requires *M*, 142.0378); $\nu_{max}$(neat)/cm$^{-1}$ 2143, 1721, 1659 and 1367; $\delta_H$(250 MHz; $CDCl_3$) 3.85 (3 H, s, OMe) and 2.48 (3 H, s, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 189.9, 161.7, 52.1 and 28.0; diazo carbon not observed; *m*/*z* (EI) 142 (M$^+$, 20%), 83 (15) and 43 (100).

**Methyl 4-chloro-2-diazo-3-oxobutanoate 11b.** According to the general procedure the title compound was obtained as a yellow oil (56%) (Found: M$^+$, 175.9987. $C_5H_5ClN_2O_3$ requires *M*, 175.9989); $\nu_{max}$(neat)/cm$^{-1}$ 2140, 1719, 1658 and 1439; $\delta_H$(250 MHz, $CDCl_3$) 4.62 (2 H, s, $CH_2$) and 3.87 (3 H, s, OMe); $\delta_C$(100.6 MHz; $CDCl_3$) 184.0, 161.3, 75.8, 52.9 and 46.7; *m*/*z* (EI) 176 (M$^+$, 4%), 178 (M$^+$, 2), 127 (55), 119 (5), 117 (15), 113 (85) and 85 (42).

**Methyl 2-diazo-3-oxopentanoate 11c.** According to the general procedure the title compound was obtained as a yellow oil (90%) (lit.,[59] no data given) (Found: M$^+$, 156.0536. $C_6H_8N_2O_3$ requires *M*, 156.0535); $\nu_{max}$(neat)/cm$^{-1}$ 2982, 2145, 1725, 1660, 1438, 1365, 1309, 1220, 1139, 1081 and 1025; $\delta_H$(250 MHz; $CDCl_3$) 3.84 (3 H, s, OMe), 2.86 (2 H, q, *J* 7.3, $CH_2$) and 1.14 (3 H, t, *J* 7.3, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 193.2, 161.7, 52.0, 33.6 and 8.1; diazo carbon not observed; *m*/*z* (EI) 156 (M$^+$, 15%), 128 (13), 113 (25), 69 (45) and 57 (100).

**Ethyl 2-diazo-3-oxo-3-phenylpropanoate 11d.** Prepared in 98% yield according to the literature procedure.[57]

### Oxazole formation from nitriles

**Methyl 2-(3,3-diethoxypropyl)-5-methoxyoxazole-4-carboxylate 7a**

To a stirred boiling solution of 3-cyanopropionaldehyde diethyl acetal **5** (1.00 g, 6.36 mmol) and rhodium(II) acetate (2 mol%) in ethanol-free chloroform (15 ml) was added a solution of dimethyl diazomalonate (1.51 g, 9.54 mmol) in ethanol-free chloroform (10 ml) dropwise over a period of 24 h. After heating for a further 24 h the solvent was removed under reduced pressure to yield a dark brown oil. The crude product was subjected to flash silica gel column chromatography using ethyl acetate and light petroleum (1:1) as eluent to yield the title compound as a golden yellow oil (0.61 g, 2.13 mmol, 33%), data given below.

***tert*-Butyl 2-(3,3-diethoxypropyl)-5-*tert*-butoxyoxazole-4-carboxylate 7b**

To a stirred boiling solution of 3-cyanopropionaldehyde diethyl acetal **5** (1.00 g, 6.36 mmol) and rhodium(II) acetate (2 mol%) in ethanol-free chloroform (15 ml) was added di-*tert*-butyl diazomalonate (2.31 g, 9.54 mmol) in ethanol-free chloroform (10 ml) dropwise over a period of 24 h. After heating for a further 24 h the solvent was removed under reduced pressure to yield a dark brown oil. The crude product was subjected to flash silica gel column chromatography using ethyl acetate and light petroleum (1:2) as eluent to yield the title compound as a golden yellow oil (0.156 g, 0.42 mmol, 7%), data given below.

## Preparation of amides

**$N^2$-Benzyloxycarbonylglycinamide 10a ‡**

To a stirred solution of *N*-benzyloxycarbonylglycine (8.4 g, 40 mmol) and triethylamine (5.6 ml, 40 mmol, 1.0 equiv.) in dry THF (65 ml) was added ethyl chloroformate (3.85 ml, 40 mmol, 1.0 equiv.) dropwise at −10 °C. The reaction was stirred for 30 min, after which aqueous ammonia (35%; 10 ml) in THF (5 ml) was added and the resultant mixture was stirred at −10 °C for 45 min. The white precipitate was filtered, washed sequentially with water (25 ml), saturated aqueous sodium hydrogen carbonate (25 ml) and water (25 ml) and dried *in vacuo* to afford *N*-benzyloxycarbonylglycinamide (7.1 g, 85%) as colourless crystals, mp 136.5–137.5 °C (ethyl acetate) (lit.,[60] mp 136–138 °C) (Found: C, 57.3; H, 5.8; N, 13.3. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5%) (Found: M$^+$, 208.0849. $C_{10}H_{12}N_2O_3$ requires *M*, 208.0848); $\nu_{max}$(KBr)/cm$^{-1}$ 3379, 3325, 3189, 3063, 3037, 2979, 2943, 2775, 1693, 1651, 1537, 1455, 1410, 1344, 1290, 1266, 1150, 1117, 1058, 1003, 878, 818, 783, 733 and 695; $\delta_H$(400 MHz; [$^2H_6$]DMSO) 7.38 (5 H, m, ArH), 7.36 (2 H, s, exch. $D_2O$, $NH_2$), 7.00 (1 H, m, exch. $D_2O$, NH), 5.04 (2 H, s, $OCH_2$) and 3.57 (2 H, d, *J* 6, $NCH_2$); $\delta_C$(100.6 MHz; [$^2H_6$]DMSO) 172.0, 157.3, 137.9, 129.2, 128.6, 128.5, 66.3 and 44.1; *m*/*z* (EI) 208 (M$^+$, 5%), 108 (55) and 91 (100).

**(*S*)-$N^2$-Benzyloxycarbonylalaninamide 10b**

To a stirred solution of *N*-benzyloxycarbonylalanine (8.9 g, 40 mmol) and triethylamine (5.6 ml, 40 mmol, 1.0 equiv.) in dry THF (65 ml) was added ethyl chloroformate (3.85 ml, 40 mmol, 1.0 equiv.) dropwise at 0 °C. The reaction was stirred for 30 min and aqueous ammonia (35%; 10 ml) in THF (5 ml) was added. The resultant mixture was stirred at 0 °C for 45 min and partitioned between ethyl acetate (75 ml) and water (50 ml). The aqueous layer was further extracted with ethyl acetate (2 × 75 ml) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (100 ml), brine (100 ml), hydrochloric acid (1 M; 100 ml) and brine (2 × 100 ml), dried ($Na_2SO_4$) and evaporated *in vacuo* to afford (*S*)-*N*-benzyloxycarbonylalaninamide (6.0 g, 68%) as colourless crystals, mp 131–131.5 °C (lit.,[61] mp 129–130 °C), after recrystallisation (chloroform–light petroleum) (Found: C, 59.3; H, 6.4; N, 12.4. Calc. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.3; N, 12.6%) (Found: M$^+$, 222.1005. $C_{11}H_{14}N_2O_3$ requires *M*, 222.1004); $[\alpha]_D^{16.5}$ −12.8 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ −3.1 (*c* 1.0, MeOH) {lit.,[61] $[\alpha]_D^{16.5}$ −3.32 (*c* 2, MeOH)}; $\nu_{max}$(KBr)/cm$^{-1}$ 3393, 3312, 3198, 3067, 3034, 2982, 2955, 1699, 1653, 1539, 1455, 1251, 781 and 757; $\delta_H$(400 MHz, $CDCl_3$) 7.38 (5 H, m, ArH), 6.21 (1 H, s, exch. $D_2O$, $NH_2$), 5.75 (1 H, s, exch. $D_2O$, $NH_2$), 5.46 (1 H, d, *J* 7, exch. $D_2O$, NH), 5.13 (1 H, d, *J* 12, OCH*H*), 5.09 (1 H, d, *J* 12, OC*H*H), 4.27 (1 H, m, NCH) and 1.40 (3 H, d, *J* 7, Me); $\delta_C$(100.6 MHz; $CDCl_3$), 176.9, 158.2, 138.2, 130.7, 130.4, 130.2, 69.3, 52.2 and 20.6; *m*/*z* (EI) 222 (M$^+$, 2%), 178 (22), 134 (18), 107 (9) and 91 (100).

**(*S*)-$N^2$-(Phthaloyl)valinamide 10c**

To a stirred solution of (*S*)-*N*-phthaloylvaline (1.0 g, 5.04 mmol) and triethylamine (0.56 ml, 4.04 mmol) at 0 °C was added ethyl chloroformate (0.39 ml, 4.04 mmol) rapidly. The reaction mixture was stirred at 0 °C for 15 min. Aqueous ammonia (35%; 1 ml) was added and the reaction was stirred for 5 min and then concentrated *in vacuo*. Ethyl acetate (50 ml) was added to the crude residue and the resulting slurry was filtered. The filtrate was washed with saturated aqueous sodium hydrogen carbonate (50 ml), brine (50 ml), aqueous citric acid (1 M; 50 ml) and brine respectively. Concentration *in vacuo* followed by recrystallisation from dichloromethane–light petroleum yielded colourless needles (0.485 g, 30%), mp 191–192 °C (lit.,[62] mp 186–187 °C); $[\alpha]_D^{19}$ 76.0 (*c* 0.28, $CHCl_3$) (Found: C, 63.0; H, 5.4; N, 11.1. Calc. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4%) (Found: M$^+$, 246.1009. $C_{13}H_{14}N_2O_3$ requires *M*, 246.1004); $\nu_{max}$(Nujol)/cm$^{-1}$ 3399, 3197, 1773, 1711, 1692 and 1648; $\delta_H$(250 MHz; $CDCl_3$) 7.87 (2 H, m, ArH), 7.53 (2 H, m, ArH), 6.91 (1 H, s, NH), 5.52 (1 H, s, NH), 4.41 (1 H, d, *J* 11.3, CH), 2.83 (1 H, m, *J* 6.5, 11.3, Pr$^i$CH), 1.14 (3 H, d, *J* 6.5, Me) and 0.87 (3 H, d, *J* 6.5, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 171.5, 168.4, 134.4, 131.4, 123.6, 62.8, 27.6, 19.9 and 19.4; *m*/*z* (EI) 247 (MH$^+$, 30%), 202 (100) and 160 (34).

**(*S*)-$N^2$-(*tert*-Butoxycarbonyl)valinamide 10d**

To a stirred solution of (*S*)-*N*-(*tert*-butoxycarbonyl)valine (10.0 g, 46.0 mmol) and triethylamine (6.42 ml, 46.0 mmol) in dry THF (100 ml) at 0 °C was added ethyl chloroformate (4.40 ml, 46.0 mmol) rapidly. The reaction was stirred at 0 °C for 30 min and aqueous ammonia (35%; 10 ml) in THF (5 ml) was added. After stirring at 0 °C for a further 30 min the reaction mixture was partitioned between ethyl acetate (75 ml) and water (50 ml). The aqueous layer was extracted with ethyl acetate (2 × 75 ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (150 ml), brine (150 ml), aqueous citric acid (1 M; 150 ml) and brine respectively and dried over sodium sulfate. Concentration *in vacuo* yielded a colourless solid (8.85 g, 89%), mp 158–159 °C (dichloromethane–light petroleum) (lit.,[63] mp 160–161 °C); $[\alpha]_D^{19}$ 17.7 (*c* 1.33, DMF) {lit.,[63] $[\alpha]_D^{25}$ −4.73 (*c* 0.66, $CHCl_3$)} (Found: C, 55.5; H, 9.4; N, 12.7. Calc. for $C_{10}H_{20}N_2O_3$: C, 55.5; H, 9.3; N, 12.95%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3385, 3346, 3200, 1678, 1638, 1528 and 1459; $\delta_H$(250 MHz; [$^2H_6$]DMSO) 7.24 (1 H, s, $NH_2$), 6.98 (1 H, s, $NH_2$), 6.48 (1 H, d, *J* 8.8, NH), 3.72 (1 H, dd, *J* 7.0, 8.8, CH), 1.91 (1 H, m, *J* 6.7, 7.0, Pr$^i$CH), 1.38 (9 H, s, Bu$^t$), 0.85 (3 H, d, *J* 6.7, Me) and 0.81 (3 H, d, *J* 6.7, Me); $\delta_C$(100.6 MHz; [$^2H_6$]DMSO) 176.0, 158.0, 80.4, 62.0, 32.8, 30.7, 21.8 and 20.5; *m*/*z* (EI) 217 (MH$^+$, 35%), 172 (35), 161 (75), 117 (64) and 72 (100).

**(*S*)-$N^2$-(Benzyloxycarbonyl)valinamide 10e.**

To a stirred solution of (*S*)-*N*-(benzyloxycarbonyl)valine (10.0 g, 40.0 mmol) and triethylamine (5.55 ml, 40.0 mmol) in dry THF (100 ml) at 0 °C was added ethyl chloroformate (3.80 ml, 40.0 mmol) rapidly. The reaction was stirred at 0 °C for 30 min and aqueous ammonia (35%; 10 ml) in THF (5 ml) was added. After stirring at 0 °C for 30 min water (50 ml) was added and the resulting precipitate was filtered. The precipitate was washed with saturated aqueous sodium hydrogen carbonate (100 ml), water (100 ml), hydrochloric acid (1 M; 100 ml) and water (500 ml) respectively. The product was dried under vacuum over $P_2O_5$ to yield a colourless solid (7.20 g, 72%), mp 208–209 °C (methanol) (lit.,[64] mp 212 °C); $[\alpha]_D^{19}$ 24.3 (*c* 1.02, DMF) {lit.,[64] $[\alpha]_D^{25}$ 22.6 (*c* 1, DMF)} (Found: C, 61.9; H, 7.1; N, 10.8.

‡ In the names of amino acid amides, nitrogen atoms have the same numbers as the carbon atoms to which they are attached.

Calc. for $C_{13}H_{18}N_2O_3$: C, 62.4; H, 7.2; N, 11.2%) (Found: M$^+$, 250.1326. $C_{13}H_{18}N_2O_3$ requires *M*, 250.1317); $\nu_{max}$(Nujol)/cm$^{-1}$ 3379, 3318, 1682, 1658 and 1250; $\delta_H$(250 MHz; [$^2H_6$]DMSO) 7.35 (5 H, m, ArH), 7.16 (1 H, d, *J* 8.8, NH), 7.03 (2 H, s, $NH_2$), 5.03 (2 H, s, $OCH_2$), 3.80 (1 H, dd, *J* 6.5, 8.8, CH), 1.94 (1 H, m, *J* 7.2, 6.5, Pr$^i$CH), 0.86 (3 H, d, *J* 7.2, Me) and 0.83 (3 H, d, *J* 7.2, Me); $\delta_C$(62.9 MHz; [$^2H_6$]DMSO) 178.4, 161.2, 142.1, 133.3, 132.7, 132.6, 70.6, 65.1, 35.4, 24.4 and 22.9; *m/z* (EI) 250 (M$^+$, 2%), 206 (30), 162 (35) and 91 (100).

**(*S*)-*N*$^2$-Benzyloxycarbonylprolinamide 10f.**
To a stirred solution of (*S*)-*N*-benzyloxycarbonylproline (10.0 g, 40 mmol) and triethylamine (5.6 ml, 40 mmol, 1.0 equiv.) in dry THF (65 ml) was added ethyl chloroformate (3.85 ml, 40 mmol, 1.0 equiv.) dropwise at 0 °C. The reaction was stirred for 30 min and aqueous ammonia (35%; 10 ml) in THF (5 ml) was added. The resultant mixture was stirred at 0 °C for 45 min and partitioned between ethyl acetate (75 ml) and water (50 ml). The aqueous layer was further extracted with ethyl acetate (2 × 75 ml) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (100 ml), brine (100 ml), hydrochloric acid (1 M; 100 ml) and brine (2 × 100 ml), dried ($Na_2SO_4$) and evaporated *in vacuo* to afford (*S*)-*N*-benzyloxycarbonylprolinamide (6.0 g, 68%) as colourless crystals, mp 93–94 °C (decomp.), after recrystallisation (ethyl acetate–light petroleum) (lit.,[65] mp 90–91 °C) (Found: C, 62.7; H, 6.4; N, 11.2. Calc. for $C_{13}H_{16}N_2O_3$: C, 62.9; H, 6.5; N, 11.3%) (Found: M$^+$, 248.1162. $C_{13}H_{16}N_2O_3$ requires *M*, 248.1161); $[\alpha]_D^{16.5}$ −90.8 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ −36.0 (*c* 1.0, MeOH) {lit.,[65] $[\alpha]_D^{16.5}$ −31.8 (*c* 1.12, EtOH)}; $\nu_{max}$(KBr)/cm$^{-1}$ 3390, 3202, 2982, 2953, 2892, 1698, 1666, 1417, 1361, 1300, 1208, 1185, 1133, 1087, 1030, 767, 727 and 693; $\delta_H$(400 MHz; $CDCl_3$) 7.38 (5 H, m, ArH), 6.72 (1 H, s, exch. $D_2O$, N*H*H), 5.81 (1 H, s, exch. $D_2O$, NH*H*), 5.22 (1 H, d, *J* 12, OCH*H*), 5.17 (1 H, d, *J* 12, OC*H*H), 4.39 (1 H, m, NCH), 3.52 (2 H, m, $NCH_2$) and 2.48–1.80 (4 H, m, $CH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 175.7, 174.8, 156.4, 155.4, 136.8, 128.9, 128.5, 128.2, 67.7, 61.0, 60.6, 47.8, 47.4, 31.5, 28.9, 24.9 and 24.1; *m/z* (EI) 248 (M$^+$, 1%), 204 (72), 160 (59) and 91 (100).

## Carbenoid N–H insertion reactions

**General procedure for dialkyl diazomalonate reactions**
A solution of the amide (12.65 mmol), the diazomalonate (6.32 mmol) and rhodium(II) acetate (2 mol%) in dry toluene (30 ml) was heated under reflux overnight under a nitrogen atmosphere. The solvent was then removed under reduced pressure to yield a dark oil. This crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1 : 15).

**4,4-Diethoxy-*N*-[bis(methoxycarbonyl)methyl]butanamide 9a.** According to the general method the title compound was obtained as a colourless solid (81%), mp 59–60 °C (ethyl acetate–light petroleum) (Found: M$^+$, 305.1460. $C_{13}H_{23}NO_7$ requires *M*, 305.1474); $\nu_{max}$($CH_2Cl_2$)/cm$^{-1}$ 3307, 2976, 1748, 1667, 1438 and 1127; $\delta_H$(250 MHz; $CDCl_3$) 6.78 (1 H, br d, *J* 6.9, NH), 5.21 (1 H, d, *J* 7.0, NCH), 4.54 (1 H, t, *J* 5.4, OCHO), 3.82 (6 H, s, OMe), 3.66 (2 H, m, $OCH_2$), 3.52 (2 H, m, $OCH_2$), 2.40 (2 H, t, *J* 7.3, $CH_2$), 1.97 (2 H, m, $CH_2$) and 1.20 (6 H, t, *J* 7.1, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 172.9, 167.2, 102.3, 62.2, 56.5, 53.7, 31.2, 29.5 and 15.6; *m/z* (EI) 305 (M$^+$, 1%), 214 (63), 103 (100), 85 (78) and 57 (33).

***N*-[Bis(*tert*-butoxycarbonyl)methyl]-4,4-diethoxybutanamide 9b.** According to the general method the title compound was obtained as a colourless solid (60%), mp 70–71 °C (light petroleum) (Found: M$^+$, 389.2415. $C_{19}H_{35}NO_7$ requires *M*, 389.2413); $\nu_{max}$($CH_2Cl_2$)/cm$^{-1}$ 3307, 2980, 1750, 1677, 1449 and 1144; $\delta_H$(250 MHz, $CDCl_3$) 6.56 (1 H, br d, *J* 6.9, NH), 4.95 (1 H, d, *J* 7.0, NCH), 4.54 (1 H, t, *J* 5.4, OCHO), 3.65 (2 H, m, $OCH_2$), 3.51 (2 H, m, $OCH_2$), 2.40 (2 H, t, *J* 7.3, $CH_2$), 1.97 (2 H, m, $CH_2$), 1.48 (18 H, s, Bu$^t$) and 1.20 (6 H, t, *J* 7.0, Me); $\delta_C$(100.6 MHz, $CDCl_3$) 172.9, 167.2, 102.4, 83.1, 62.1, 58.1, 31.4, 29.6, 28.2 and 15.7; *m/z* (EI) 389 (M$^+$, 1%), 344 (31), 242 (13), 214 (14), 187 (36), 103 (30), 85 (22), 57 (100) and 41 (40).

**General procedure for α-diazo β-keto ester reactions**
A solution of the diazo keto ester (1.0 g, 7.0 mmol) in dry chloroform (35 ml) was added dropwise over 6 h to a boiling solution of the amide (5.0 mmol) and rhodium(II) acetate (2 mol%) in ethanol-free chloroform (130 ml). The mixture was refluxed for a further 30 min, allowed to cool, evaporated *in vacuo* and purified by flash chromatography on silica gel, eluting with ethyl acetate–light petroleum (1 : 1).

***N*$^2$-Benzyloxycarbonyl-*N*$^1$-(1-methoxycarbonyl-2-oxopropyl)-glycinamide 12a.** According to the general procedure the title compound was obtained as an off-white solid (71%), mp 81.5–82 °C (ethyl acetate–light petroleum) (Found: C, 55.5; H, 5.6; N, 8.5. $C_{15}H_{18}N_2O_6$ requires C, 55.9; H, 5.6; N, 8.7%) (Found: M$^+$, 322.1166. $C_{15}H_{18}N_2O_6$ requires *M*, 322.1165); $\nu_{max}$(KBr)/cm$^{-1}$ 3401, 3325, 3035, 2958, 1744, 1721, 1656, 1529, 1284, 1265, 1233, 1223, 1156, 1135, 1047, 982, 784 and 724; $\delta_H$(400 MHz, $CDCl_3$) 7.37 (5 H, m, ArH), 7.19 (1 H, m, exch. $D_2O$, NH), 5.51 (1 H, m, exch. $D_2O$, NH), 5.29 (1 H, d, *J* 6.5, NHC*H*), 5.17 (2 H, s, $OCH_2$), 4.00 (2 H, d, *J* 6, NHC$H_2$), 3.84 (3 H, s, OMe) and 2.40 (3 H, s, COMe); $\delta_C$(100.6 MHz; $CDCl_3$) 200.9, 171.9, 169.0, 159.2, 138.7, 131.0, 130.7, 130.6, 69.7, 65.4, 55.9, 46.6 and 30.4; *m/z* (EI) 322 (M$^+$, 1%), 280 (3), 162 (26), 91 (100) and 43 (22).

***N*$^2$-Benzyloxycarbonyl-*N*$^1$-(1-methoxycarbonyl-2-oxopropyl)-alaninamide 12b.** According to the general procedure the title compound was obtained as colourless needles (71%), mp 122–123 °C (ethyl acetate–light petroleum) as an inseparable mixture of diastereomers (Found: C, 57.2; H, 6.0; N, 8.3. $C_{16}H_{20}N_2O_6$ requires C, 57.1; H, 6.0; N, 8.3%) (Found: M$^+$, 336.1322. $C_{16}H_{20}N_2O_6$ requires *M*, 336.1321); $\nu_{max}$(KBr)/cm$^{-1}$ 3293, 3065, 2959, 1738, 1725, 1687, 1649, 1532, 1449, 1437, 1360, 1329, 1263, 1232, 1216, 1174, 1136, 1075, 1057 and 698; $\delta_H$(400 MHz; $CDCl_3$) 7.43 (1 H, m, exch. $D_2O$, NH), 7.31 (5 H, m, ArH), 5.73 (1 H, d, *J* 6.5, exch. $D_2O$, NH), 5.26 (1 H, d, *J* 6.5, NHC*H*), 5.13 (1 H, d, *J* 12, OCH*H*), 5.06 (1 H, d, *J* 12, OC*H*H), 4.42 (1 H, m, NHC*H*Me), 3.76 (3 H, s, OMe), 2.33 (3 H, s, COMe) and 1.35 (3 H, d, *J* 7, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 197.8, 197.7, 171.9, 165.9, 165.8, 155.3, 135.7, 127.9, 127.6, 127.4, 66.4, 62.3, 52.6, 49.6, 27.2 and 17.8; *m/z* (EI) 336 (M$^+$, 0.5%), 294 (4), 178 (10), 162 (21), 134 (19), 91 (100) and 43 (23).

**(*S*)-*N*$^2$-Phthaloyl-*N*$^1$-[bis(methoxycarbonyl)methyl]valinamide 12c.** According to the general procedure the title compound was obtained as a colourless solid (38%), mp 98–99 °C (ethyl acetate–light petroleum) (Found: C, 56.1; H, 5.2; N, 7.1. $C_{18}H_{20}N_2O_7$·0.4$H_2O$ requires C, 56.4; H, 5.5; N, 7.3%) (Found: M$^+$, 376.1273. $C_{18}H_{20}N_2O_7$ requires *M*, 376.1270); $\nu_{max}$(Nujol)/cm$^{-1}$ 3354, 2960, 1762, 1721 and 1527; $\delta_H$(250 MHz; $CDCl_3$) 8.08 (1 H, d, *J* 6.5, NH), 7.88 (2 H, m, ArH), 7.76 (2 H, m, ArH), 5.16 (1 H, d, *J* 6.5, CH), 4.49 (1 H, d, *J* 11.3, CH), 3.81 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.91 (1 H, m, *J* 11.3, 6.5, Pr$^i$CH), 1.12 (3 H, d, *J* 6.5, Me) and 0.88 (3 H, d, *J* 6.5, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 168.7, 168.3, 166.30, 166.26, 134.5, 131.3, 123.8, 62.6, 56.4, 53.5, 53.4, 27.7, 19.6 and 19.5; *m/z* (EI) 377 (MH$^+$, 2%), 334 (40), 202 (100), 160 (25), 148 (33) and 130 (25).

**(*S*)-*N*$^2$-*tert*-Butoxycarbonyl-*N*$^1$-[bis(methoxycarbonyl)-methyl]valinamide 12d.** According to the general procedure the title compound was obtained as a colourless solid (47%), mp 118–118.5 °C (ethyl acetate–light petroleum) (Found: C, 51.7; H, 7.6; N, 8.1. $C_{15}H_{26}N_2O_7$ requires C, 52.0; H, 7.6; N, 8.1%) (Found: M$^+$, 346.1741. $C_{15}H_{26}N_2O_7$ requires *M*, 346.1740); $\nu_{max}$(Nujol)/cm$^{-1}$ 3315, 1759, 1747, 1687, 1656, 1539 and 1527; $\delta_H$(250 MHz; $CDCl_3$) 7.00 (1 H, d, *J* 6.5, NH), 5.19 (1 H, d, *J* 6.5, CH), 5.02 (1 H, d, *J* 8.5, NH), 4.06 (1 H, dd, *J* 5.3, 8.5, CH), 3.81 (6 H, s, OMe), 2.17 (1 H, m, *J* 7.0, 5.3, Pr$^i$CH), 1.45

(9 H, s, Bu$^t$), 0.98 (3 H, d, *J* 7.0, Me) and 0.93 (3 H, d, *J* 7.0, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 171.6, 166.5, 155.8, 83.2, 59.5, 56.1, 53.5, 30.9, 28.3, 19.2 and 17.5; *m*/*z* (EI) 347 ($MH^+$, 10%), 291 (25), 172 (40), 116 (75) and 72 (100).

***N*²-(*tert*-Butoxycarbonyl)-*N*¹-(1-methoxycarbonyl-2-oxopropyl)valinamide 12e.** According to the general procedure the title compound was obtained as a colourless solid (30%), mp 111–113 °C (ethyl acetate–light petroleum), as a mixture of diastereomers (Found: C, 54.5; H, 7.8; N, 8.5. $C_{15}H_{26}N_2O_6$ requires C, 54.5; H, 7.9; N, 8.5%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3323, 1751, 1727, 1687 and 1520; $\delta_H$(250 MHz; $CDCl_3$) 7.13 (1 H, d, *J* 6.3, NH), 7.06 (1 H, d, *J* 6.3, NH), 5.24 (1 H, d, *J* 6.3, CH), 5.01 (1 H, br d, *J* 6.0, NH), 4.04 (1 H, br dd, *J* 6.0, CH), 3.85 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.38 (3 H, s, Me), 2.35 (3 H, s, Me), 2.19 (1 H, m, *J* 7.0, Pr$^i$CH), 1.43 (9 H, s, Bu$^t$), 0.97 (3 H, d, *J* 7.0, Me) and 0.91 (3 H, d, *J* 7.0, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 198.1, 198.0, 171.5, 166.4, 166.3, 155.8, 80.1, 62.94, 62.89, 59.5, 53.3, 30.9, 30.7, 28.3, 28.2, 28.0, 19.2, 19.1, 17.5 and 17.3; *m*/*z* (EI) 331 ($MH^+$, 100%), 275 (30), 231 (30), 116 (25) and 72 (100).

**(*S*)-*N*²-Benzyloxycarbonyl-*N*¹-[bis(methoxycarbonyl)methyl]-valinamide 12f.** According to the general procedure the title compound was obtained as a colourless solid (61%), mp 161–162 °C (dichloromethane–light petroleum) (Found: C, 56.4; H, 6.3; N, 7.3. $C_{18}H_{24}N_2O_7$ requires C, 56.8; H, 6.4; N, 7.4%) (Found: $M^+$, 380.1582. $C_{18}H_{24}N_2O_7$ requires *M*, 380.1583); $\nu_{max}$(Nujol)/cm$^{-1}$ 3293, 1758, 1745, 1687, 1651, 1537 and 1249; $\delta_H$(250 MHz, $CDCl_3$) 7.35 (5 H, m, ArH), 6.88 (1 H, d, *J* 6.8, NH), 5.32 (1 H, d, *J* 8.8, NH), 5.18 (1 H, d, *J* 6.8, CH), 5.12 (2 H, s, $OCH_2$), 4.15 (1 H, dd, *J* 8.8, 5.5, CH), 3.81 (6 H, s, OMe), 2.17 (1 H, m, *J* 7.0, 5.5, Pr$^i$CH), 0.99 (3 H, d, *J* 7.0, Me) and 0.94 (3 H, d, *J* 7.0, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 171.1, 166.3, 156.2, 128.4, 128.1, 128.0, 67.0, 60.0, 56.0, 53.4, 53.3, 31.2, 19.0 and 17.4; *m*/*z* (EI) 380 ($M^+$, 4%), 206 (20), 162 (35) and 91 (100).

***N*²-(Benzyloxycarbonyl)-*N*¹-(1-methoxycarbonyl-2-oxopropyl)valinamide 12g.** According to the general procedure the title compound was obtained as a colourless solid (68%), mp 148–149.5 °C (dichloromethane–light petroleum), as a mixture of diastereomers (Found: C, 58.7; H, 6.6; N, 7.6. $C_{18}H_{24}N_2O_6 \cdot 0.25H_2O$ requires C, 58.6; H, 6.7; N, 7.6%) (Found: $M^+$, 364.1624. $C_{18}H_{24}N_2O_6$ requires *M*, 364.1634); $\nu_{max}$(Nujol)/cm$^{-1}$ 3299, 2923, 2854, 2360, 1725, 1692 and 1646; $\delta_H$(250 MHz, $CDCl_3$) 7.34 (5 H, m, ArH), 7.01 (1 H, d, *J* 6.3, NH), 5.30 (1 H, d, *J* 8.5, NH), 5.23 (1 H, d, *J* 6.3, CH), 5.13 (2 H, s, $OCH_2$), 5.12 (2 H, s, $OCH_2$), 4.14 (1 H, dd, *J* 6.0, 8.5, CH), 3.81 (3 H, s, OMe), 2.39 (3 H, s, Me), 2.38 (3 H, s, Me), 2.17 (1 H, m, *J* 6.0, 7.0, Pr$^i$CH), 0.97 (3 H, d, *J* 7.0, Me), 0.93 (3 H, d, *J* 7.0, Me) and 0.92 (3 H, d, *J* 7.0, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 171.14, 171.09, 166.2, 156.3, 136.1, 128.4, 128.1, 128.0, 67.0, 62.9, 62.8, 59.8, 53.3, 53.2, 31.2, 31.0, 28.0, 27.8, 19.1, 18.9, 17.5 and 17.3; *m*/*z* (EI) 365 ($MH^+$, 40%), 322 (15), 206 (45), 162 (75) and 91 (100).

***N*²-(Benzyloxycarbonyl)-*N*¹-(3-chloro-1-methoxycarbonyl-2-oxopropyl)valinamide 12h.** According to the general procedure the title compound was obtained as a colourless solid (67%), mp 146–147 °C (dichloromethane–light petroleum), as a mixture of diastereomers (Found: C, 53.7; H, 5.7; N, 7.0. $C_{18}H_{23}ClN_2O_6$ requires C, 54.2; H, 5.8; N, 7.0%) (Found: $M^+$, 398.1253. $C_{18}H_{23}ClN_2O_6$ requires *M*, 398.1244); $\nu_{max}$(Nujol)/cm$^{-1}$ 3292, 3036, 1761, 1737, 1687, 1650 and 1538; $\delta_H$(250 MHz, $CDCl_3$) 7.36 (5 H, m, ArH), 7.02 (1 H, d, *J* 6.5, NH), 5.41 (1 H, d, *J* 6.5, CH), 5.26 (1 H, d, *J* 8.0, NH), 5.13 (2 H, s, $OCH_2$), 5.12 (2 H, s, $OCH_2$), 4.48 (2 H, s, $CH_2Cl$), 4.14 (1 H, dd, *J* 8.0, 5.5, CH), 3.83 (3 H, s, OMe), 2.17 (1 H, m, *J* 7.0, 5.5, Pr$^i$CH), 0.99 (3 H, d, *J* 7.0, Me) and 0.94 (3 H, d, *J* 7.0, Me); $\delta_C$(100.6 MHz; [$^2H_6$]DMSO) 194.2, 194.1, 171.7, 166.5, 156.0, 136.8, 127.6, 127.5, 127.4, 65.3, 60.0, 59.9, 59.7, 52.6, 47.59, 47.55, 30.0, 29.9, 18.8, 17.9 and 17.7; *m*/*z* (EI) 400 ($M^+$, 1%), 398 ($M^+$, 1), 206 (14), 162 (25) and 91 (100).

***N*²-(Benzyloxycarbonyl)-*N*¹-(1-methoxycarbonyl-2-oxobutyl)-valinamide 12i.** The title compound was obtained as a solid (48%), mp 144–145 °C (dichloromethane–light petroleum), as a mixture of diastereomers (Found: C, 59.9; H, 6.8; N, 7.25. $C_{19}H_{26}N_2O_6$ requires C, 60.3; H, 6.9; N, 7.4%) (Found: $M^+$, 378.1795. $C_{19}H_{26}N_2O_6$ requires *M*, 378.1791); $\nu_{max}$(Nujol)/cm$^{-1}$ 3298, 1749, 1725, 1687, 1649 and 1536; $\delta_H$(250 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 7.05 (1 H, d, *J* 6.3, NH), 5.32 (1 H, d, *J* 8.8, NH), 5.22 (1 H, d, *J* 6.3, CH), 5.12 (1 H, s, $OCH_2$), 5.11 (1 H, s, $OCH_2$), 4.16 (1 H, dd, *J* 6.0, 8.8, CH), 3.79 (3 H, s, OMe), 2.75 (2 H, m, C*H*$_2$Me), 2.18 (1 H, m, *J* 7.0, 6.0, Pr$^i$CH), 1.10 (3 H, t, *J* 7.5, $CH_2$*Me*), 0.97 (3 H, d, *J* 7.0, Me), 0.93 (3 H, d, *J* 7.0, Me) and 0.91 (3 H, d, *J* 7.0, Me); $\delta_C$(100.6 MHz; [$^2H_6$]DMSO) 203.2, 203.1, 172.1, 172.0, 167.9, 156.6, 137.5, 128.8, 128.2, 128.07, 128.05, 65.9, 62.3, 60.4, 60.3, 52.98, 52.97, 33.3, 33.2, 30.8, 30.7, 19.52, 19.48, 18.5, 18.3, 7.8 and 7.7; *m*/*z* (EI) 378 ($M^+$, 1%), 206 (7), 162 (20) and 91 (100).

***N*²-(Benzyloxycarbonyl)-*N*¹-(1-benzoyl-1-ethoxycarbonyl-methyl)valinamide 12j.** According to the general procedure the title compound was obtained as a colourless solid (72%), mp 128–129 °C (dichloromethane–light petroleum), as a mixture of diastereomers (Found: C, 65.1; H, 6.2; N, 6.3. $C_{24}H_{28}N_2O_6$ requires C, 65.4; H, 6.4; N, 6.4%) (Found: $M^+$, 440.1947. $C_{24}H_{28}N_2O_6$ requires *M*, 440.1947); $\nu_{max}$(Nujol)/cm$^{-1}$ 3380, 3320, 1736, 1724, 1718, 1694, 1651, 1556, 1538, 1504 and 1454; $\delta_H$(250 MHz, $CDCl_3$, rotamers) 8.11 (2 H, d, *J* 7.3, ArH), 7.64 (1 H, m, ArH), 7.51 (2 H, t, *J* 6.5, ArH), 7.35 (5 H, m, ArH), 7.22 (1 H, d, *J* 7.0, NH), 6.15 (1 H, d, *J* 7.0, CH), 6.13 (1 H, d, *J* 7.0, CH), 5.32 (1 H, d, *J* 7.3, NH), 5.12 (2 H, s, $OCH_2$), 4.21 (1 H, br dd, *J* 7.3, 5.8, CH), 4.16 (2 H, q, *J* 6.5, $CH_2$), 2.19 (1 H, m, *J* 6.8, 5.8, Pr$^i$CH), 1.13 (3 H, t, *J* 6.5, Me) and 0.90–1.01 (6 H, m, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 191.2, 171.2, 166.2, 156.4, 136.3, 134.1, 130.1, 129.6, 129.2, 128.7, 128.5, 128.4, 128.1, 67.2, 62.6, 62.5, 60.1, 58.3, 31.4, 31.2, 19.1, 17.7, 17.5, 14.0 and 13.8; *m*/*z* (EI) 440 ($M^+$, 2%), 425 (5), 162 (15), 105 (55) and 91 (100).

***N*²-Benzyloxycarbonyl-*N*¹-(1-methoxycarbonyl-2-oxopropyl)-prolinamide 12k.** According to the general procedure the title compound (74%) was obtained as a pale yellow oil as an inseparable mixture of diastereomers (Found: $M^+$, 362.1486. $C_{18}H_{22}N_2O_6$ requires *M*, 362.1478); $\nu_{max}$(film)/cm$^{-1}$ 3307, 3063, 3033, 2955, 2884, 1755, 1726, 1703, 1680, 1500, 1415, 1357, 1273, 1210, 1119, 1090, 1029, 984, 919, 770, 737 and 699; $\delta_H$(400 MHz; $CDCl_3$) 7.60 (1 H, m, exch. $D_2O$, NH), 7.35 (5 H, m, ArH), 5.18 (3 H, m, $OCH_2$ and NHCH), 4.43 (1 H, m, NCH), 3.79 (3 H, s, OMe), 3.60 (2 H, m, $NCH_2$), 2.33 (3 H, s, COMe) and 2.25–1.86 (4 H, m, $CH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 198.6, 172.6, 172.2, 166.8, 156.3, 155.3, 136.9, 136.7, 129.0, 128.9, 128.6, 128.4, 128.3, 128.2, 67.71, 67.69, 63.4, 63.1, 60.9, 60.8, 53.9, 53.6, 47.9, 47.4, 31.4, 29.4, 28.2, 24.9 and 24.0; *m*/*z* (EI) 362 ($M^+$, 0.5%), 204 (15), 160 (23), 91 (100), 70 (13) and 43 (26).

## Oxazole formation by cyclodehydration

### General procedure [54]

Triethylamine (4.1 equiv.) and a solution of the keto amide substrate (~3 mmol, 1.0 equiv.) in dry dichloromethane (10 ml) were added sequentially to a stirred solution of triphenylphosphine (2.0 equiv.) and iodine (2.0 equiv.) in dry dichloromethane (40 ml) at room temperature under $N_2$. The mixture was stirred until TLC analysis indicated that the reaction was complete, evaporated *in vacuo*, purified by flash chromatography on silica eluting with ethyl acetate–light petroleum.

**Methyl 2-(3,3-diethoxypropyl)-5-methoxyoxazole-4-carboxylate 7a.** According to the general procedure the title compound was obtained as a golden yellow oil (84%) (Found: $M^+$, 287.1363. $C_{13}H_{21}NO_6$ requires *M*, 287.1369); $\nu_{max}$(neat)/cm$^{-1}$ 2976, 1721, 1637, 1598, 1454 and 1126; $\delta_H$(250 MHz, $CDCl_3$) 4.54 (1 H, t, *J* 5.4, OCHO), 4.15 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.66 (2 H, m, $OCH_2$), 3.49 (2 H, m, $OCH_2$), 2.76 (2 H, t,

$J$ 7.8, $CH_2$), 2.06 (2 H, m, $CH_2$) and 1.19 (6 H, t, $J$ 7.0, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 162.3, 162.1, 154.0, 106.3, 102.1, 62.0, 60.1, 52.0, 31.0, 23.8 and 15.6; $m/z$ (EI) 287 ($M^+$, 1%), 242 (21), 214 (41), 85 (53), 69 (100) and 57 (48).

***tert*-Butyl 2-(3,3-diethoxypropyl)-5-*tert*-butoxyoxazole-4-carboxylate 7b.** According to the general procedure the title compound was obtained as a golden yellow oil (79%) (Found: $M^+$, 371.2317. $C_{19}H_{33}NO_6$ requires $M$, 371.2308); $\nu_{max}$(neat)/cm$^{-1}$ 2978, 1718, 1626, 1582, 1445 and 1142; $\delta_H$(250 MHz; $CDCl_3$) 4.54 (1 H, t, $J$ 5.4, OCHO), 3.66 (2 H, m, $OCH_2$), 3.50 (2 H, m, $OCH_2$), 2.74 (2 H, t, $J$ 8.1, $CH_2$), 2.05 (2 H, m, $CH_2$), 1.57 (9 H, s, $Bu^t$), 1.48 (9 H, s, $Bu^t$) and 1.20 (6 H, t, $J$ 7.0, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 161.3, 158.6, 156.0, 114.4, 102.3, 85.6, 81.4, 62.0, 31.0, 28.9, 28.7, 24.2 and 15.6; $m/z$ (EI) 371 ($M^+$, 1%), 242 (18), 214 (15), 187 (64), 84 (37), 57 (100), 41 (56) and 29 (46).

**Methyl 2-(*N*-benzyloxycarbonylaminomethyl)-5-methyloxazole-4-carboxylate 13a.** According to the general procedure the title compound was obtained as pale yellow needles (56%), mp 86–87 °C (ethyl acetate–light petroleum) (Found: C, 59.2; H, 5.1; N, 8.9. $C_{15}H_{16}N_2O_5$ requires C, 59.2; H, 5.3; N, 9.2%) (Found: $M^+$, 304.1051. $C_{15}H_{16}N_2O_5$ requires $M$, 304.1059); $\nu_{max}$(KBr)/cm$^{-1}$ 3323, 3067, 3036, 2954, 1719, 1690, 1622, 1545, 1439, 1345, 1273, 1217, 1198, 1154, 1098, 1055, 980, 786 and 698; $\delta_H$(400 MHz; $CDCl_3$) 7.26 (5 H, m, ArH), 5.30 (1 H, m, exch. $D_2O$, NH), 5.07 (2 H, s, $OCH_2$), 4.43 (2 H, d, $J$ 6, $NCH_2$), 3.83 (3 H, s, OMe) and 2.53 (3 H, s, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 162.8, 159.2, 157.3, 156.5, 136.5, 128.9, 128.6, 128.5, 127.8, 67.7, 52.4, 38.6 and 12.3; $m/z$ (EI) 304 ($M^+$ 12%), 169 (14), 155 (18), 137 (11), 108 (15), 91 (83) and 43 (100).

**(*S*)-Methyl 2-[1-(benzyloxycarbonylamino)ethyl]-5-methyloxazole-4-carboxylate 13b.** According to the general procedure the title compound was obtained as colourless needles (66%), mp 125.5–126 °C (ethyl acetate–light petroleum) (Found: C, 60.2; H, 5.7; N, 8.8. $C_{16}H_{18}N_2O_5$ requires C, 60.4; H, 5.7; N, 8.8%) (Found: $M^+$, 318.1218. $C_{16}H_{18}N_2O_5$ requires $M$, 318.1216); $[\alpha]_D^{16.5}$ −34.4 ($c$ 1.0, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 3292, 3063, 2985, 2955, 2934, 1720, 1684, 1619, 1541, 1448, 1347, 1329, 1273, 1253, 1206, 1100, 1065, 782, 749, 698, 577 and 544; $\delta_H$(400 MHz, $CDCl_3$) 7.26 (5 H, m, ArH), 5.41 (1 H, d, $J$ 7, exch. $D_2O$, NH), 5.07 (1 H, d, $J$ 12.3, OCH*H*), 5.02 (1 H, d, $J$ 12.3, OC*H*H), 4.94 (1 H, dq, $J$ 7, 7, NCH), 3.82 (3 H, s, OMe), 2.53 (3 H, s, Me) and 1.49 (3 H, d, $J$ 7, Me); $\delta_C$(100.6 MHz, $CDCl_3$) 163.0, 162.9, 157.1, 155.9, 136.5, 128.9, 128.6, 128.5, 127.7, 67.4, 52.4, 45.5, 20.5 and 12.4; $m/z$ (EI) 318 ($M^+$, 12%), 248 (5), 183 (20), 130 (22), 91 (100) and 70 (25).

**(*S*)-Methyl 2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylate 13c.** According to the general procedure the title compound was obtained as a colourless solid (65%), mp 113–114 °C (ethyl acetate–light petroleum) (lit.,[54] mp 110–110.5 °C); $[\alpha]_D^{19}$ −53.7 ($c$ 0.82, MeOH) {lit.,[54] $[\alpha]_D^{22}$ −35.9° ($c$ 0.4, $CH_2Cl_2$)} (Found: C, 62.0; H, 6.3; N, 8.1. Calc. for $C_{18}H_{22}N_2O_5$: C, 62.4; H, 6.4; N, 8.1%) (Found: $M^+$, 346.1529. $C_{18}H_{22}N_2O_5$ requires $M$, 346.1529); $\nu_{max}$(Nujol)/cm$^{-1}$ 3305, 2955, 2923, 2854, 1718, 1688, 1615 and 1536; $\delta_H$(250 MHz; $CDCl_3$) 7.35 (5 H, m, ArH), 5.50 (1 H, d, $J$ 9.3, NH), 5.11 (2 H, s, $OCH_2$), 4.80 (1 H, dd, $J$ 6.0, 9.3, CH), 3.90 (3 H, s, OMe), 2.60 (3 H, s, Me), 2.20 (1 H, m, $J$ 6.0, 7.5, $Pr^iCH$), 0.86 (3 H, d, $J$ 7.5, Me) and 0.85 (3 H, d, $J$ 7.5, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 162.4, 161.5, 156.2, 155.9, 136.1, 128.4, 128.0, 127.9, 127.1, 67.0, 54.7, 51.8, 32.6, 18.7, 17.9 and 11.9; $m/z$ (EI) 346 ($MH^+$, 10%), 303 (8), 259 (12) and 91 (100).

**(*S*)-Methyl 2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-5-ethyloxazole-4-carboxylate 13d.** According to the general procedure the title compound was obtained as a colourless solid (88%), mp 73–74 °C (ethyl acetate–light petroleum); $[\alpha]_D^{19}$ −43.2 ($c$ 0.53, MeOH) (Found: C, 63.3; H, 6.7; N, 7.8. $C_{19}H_{24}N_2O_5$ requires C, 63.3; H, 6.7; N, 7.8%); $\nu_{max}$(Nujol)/cm$^{-1}$ 3305, 1713, 1691, 1603, 1547, 1296, 1250, 1207, 1098 and 1038; $\delta_H$(250 MHz, $CDCl_3$) 7.33 (5 H, m, ArH), 5.49 (1 H, d, $J$ 9.3, NH), 5.11 (2 H, s, $OCH_2$), 4.81 (1 H, dd, $J$ 6.5, 9.3, CH), 3.90 (3 H, s, OMe), 3.04 (2 H, q, $J$ 7.5, $CH_2$), 2.20 (1 H, m, $J$ 6.5, 6.8, $Pr^iCH$), 1.26 (3 H, t, $J$ 7.5, Me), 0.94 (3 H, d, $J$ 6.8, Me) and 0.91 (3 H, d, $J$ 6.8, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 162.5, 161.5, 161.1, 155.9, 136.1, 128.4, 128.0, 127.9, 126.3, 67.0, 54.7, 51.9, 32.8, 19.5, 18.6, 17.9 and 11.9; $m/z$ (EI) 360 ($MH^+$, 5%), 317 (6), 273 (10), 210 (10), 178 (12) and 91 (100).

**(*S*)-Ethyl 2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-5-phenyloxazole-4-carboxylate 13e.** According to the general procedure the title compound was obtained as an off white sticky solid (31%) (Found: $M^+$, 422.1813. $C_{24}H_{26}N_2O_5$ requires $M$, 422.1842); $\nu_{max}$(Nujol)/cm$^{-1}$ 3321, 1723, 1693, 1589, 1572, 1547 and 1513; $\delta_H$(250 MHz; $CDCl_3$) 7.97 (2 H, t, ArH), 7.46 (3 H, m, ArH), 7.35 (5 H, m, ArH), 5.54 (1 H, d, $J$ 9.3, NH), 5.13 (2 H, s, $OCH_2$), 4.93 (1 H, dd, $J$ 6.3, 9.3, CH), 4.41 (2 H, q, $J$ 7.3, $OCH_2Me$), 2.27 (1 H, m, $J$ 6.3, 6.8, $Pr^iCH$), 1.38 (3 H, t, $J$ 7.3, Me), 1.00 (3 H, d, $J$ 6.8, Me) and 0.98 (3 H, d, $J$ 6.8, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 163.1, 162.3, 157.0, 155.0, 137.8, 131.2, 129.3, 129.2, 129.1, 128.7, 128.5, 127.4, 127.2, 66.5, 61.6, 55.9, 32.0, 19.8, 19.5 and 14.8; $m/z$ (EI) 422 ($M^+$, 15%), 335 (14), 287 (20), 105 (25) and 91 (100).

**(*S*)-Methyl 2-(1-benzyloxycarbonyltetrahydropyrrol-2-yl)-5-methyloxazole-4-carboxylate 13f.** According to the general procedure the title compound was obtained as light brown prisms (73%), mp 84–85 °C (decomp.) (ethyl acetate–light petroleum) (Found: C, 62.9; H, 5.8; N, 8.1. $C_{18}H_{20}N_2O_5$ requires C, 62.8; H, 5.85; N, 8.1%) (Found: $M^+$, 344.1371. $C_{18}H_{20}N_2O_5$ requires $M$, 344.1372); $[\alpha]_D^{16.5}$ −79.2 ($c$ 1.0, $CHCl_3$); $\nu_{max}$(KBr)/cm$^{-1}$ 2977, 2957, 2879, 1710, 1698, 1620, 1429, 1351, 1210, 1195, 1120, 1100, 770, 755, 699 and 608; $\delta_H$(400 MHz; $CDCl_3$, 50 °C) 7.19 (5 H, m, ArH), 5.09 (1 H, d, $J$ 12.4, OCH*H*), 4.91 (2 H, m, OC*H*H and NCH), 3.80 (3 H, s, OMe), 3.65–3.40 (2 H, m, $NCH_2$), 2.39 (3 H, s, Me), 2.30–1.78 (4 H, m, $CH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 163.2, 163.1, 162.9, 162.8, 156.8, 156.6, 155.2, 154.7, 137.0, 136.8, 128.9, 128.7, 128.43, 128.36, 128.32, 128.29, 127.9, 127.6, 67.4, 67.3, 55.3, 55.0, 52.3 (2 carbons), 47.4, 47.0, 32.9, 31.9, 24.7, 24.0, 12.5 and 12.3; $m/z$ (EI) 344 ($M^+$, 15%), 209 (12), 168 (27), 91 (100) and 51 (17).

## Preparation of bis-oxazoles

### (*S*)-2-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylic acid 14a

To a stirred solution of the oxazole ester **13c** (0.300 g, 0.866 mmol) in THF (15 ml) and water (5 ml) was added sodium hydroxide (0.173 g, 4.33 mmol). After stirring overnight at room temperature the reaction mixture was concentrated *in vacuo* and partitioned between water and dichloromethane. The aqueous layer was acidified to pH 1 with hydrochloric acid and extracted with dichloromethane. The combined organic extracts were washed with brine and dried over sodium sulfate. Concentration *in vacuo* yielded an off white solid which was recrystallised from ethyl acetate and light petroleum to give the *title compound* as a colourless solid (0.227 g, 79%); mp 176–177 °C; $[\alpha]_D^{24}$ −54.6 ($c$ 1.0, MeOH) (Found: C, 60.9; H, 5.9; N, 8.3. $C_{17}H_{20}N_2O_5 \cdot 0.1H_2O$ requires C, 61.1; H, 6.1; N, 8.4%) (Found: $M^+$, 332.1371. $C_{17}H_{20}N_2O_5$ requires $M$, 332.1372); $\nu_{max}$(Nujol)/cm$^{-1}$ 3413, 3281, 1713, 1543 and 1247; $\delta_H$(250 MHz; $CDCl_3$) 7.27 (5 H, m, ArH), 7.20 (1 H, br d, NH), 5.06 (2 H, s, $OCH_2$), 4.86 (1 H, dd, $J$ 6.5, 10.0, CH), 2.49 (3 H, s, Me), 2.24 (1 H, m, $J$ 6.8, 6.5, $Pr^iCH$), 0.98 (3 H, d, $J$ 6.8, Me) and 0.95 (3 H, d, $J$ 6.8, Me); $\delta_C$(62.9 MHz; $CDCl_3$) 164.2, 163.7, 157.1, 156.7, 136.2, 127.9, 128.2, 126.8, 66.9, 54.9, 32.6, 18.9, 18.1 and 11.6; 1 Ar C unobserved; $m/z$ (EI) 332 ($M^+$, 10%), 289 (5), 245 (7), 197 (5), 164 (10), 108 (12) and 91 (100).

### (*S*)-2-[1-(Benzyloxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxamide 15a

To a stirred solution of the oxazole acid **14a** (0.20 g, 0.602 mmol) and triethylamine (0.08 ml, 0.602 mmol) in THF (10 ml) at 0 °C was added ethyl chloroformate (0.06 ml, 0.602 mmol). After stirring at 0 °C for 15 min, aqueous ammonia (30%; 5 ml) in THF (5 ml) was added. The reaction was stirred for a further 15 min and then concentrated *in vacuo*. The crude residue was partitioned between dichloromethane and water, the aqueous layer was extracted with dichloromethane and the combined organic extracts washed with saturated aqueous sodium hydrogen carbonate, brine and dried over sodium sulfate. Purification by flash chromatography (ethyl acetate–light petroleum) gave the *title compound* as a solid (0.191 g, 96%); mp 84–86 °C (ethyl acetate–light petroleum) (Found: $M^+$, 331.1534. $C_{17}H_{21}N_3O_4$ requires *M*, 331.1519); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3344, 3062, 2972, 2930, 1722 and 1265; $\delta_H$(250 MHz; $CDCl_3$) 7.36 (5 H, m, ArH), 6.62 (1 H, s, NH), 6.06 (1 H, s, NH), 5.74 (1 H, d, *J* 9.1, NH), 5.12 (2 H, s, $OCH_2$), 4.71 (1 H, dd, *J* 6.0, 9.1, CH), 2.60 (3 H, s, Me), 2.19 (1 H, m, *J* 6.8, 6.0, $Pr^iCH$) and 0.94 (6 H, 2 d, *J* 6.8, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 166.7, 163.0, 158.5, 156.5, 138.7, 131.0, 130.8, 130.7, 130.6, 69.8, 57.3, 35.0, 21.2, 20.5 and 14.2; *m*/*z* (EI) 331 ($M^+$, 15%), 288 (10), 244 (10), 196 (12), 136 (5), 115 (10) and 91 (100).

**(*S*)-Methyl 2-{2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-5-methyloxazol-4-ylcarbonylamino}-3-oxobutanoate 16a**

To a stirred solution of the oxazole amide **15a** (0.242 g, 0.730 mmol) and rhodium(II) acetate (0.006 g, 0.015 mmol, 2 mol%) in anhydrous chloroform (10 ml) heating under reflux was added methyl diazoacetoacetate (0.156 g, 1.1 mmol) in chloroform (10 ml) dropwise *via* a syringe pump over 3 h. The reaction mixture was heated under reflux overnight and then concentrated *in vacuo*. The crude residue was purified by flash chromatography (ethyl acetate–light petroleum) to give the *title compound* as an oily solid (0.163 g, 50%) (Found: $M^+$, 445.1847. $C_{22}H_{27}N_3O_7$ requires *M*, 445.1849); $\nu_{max}$(Nujol)/$cm^{-1}$ 3392, 3326, 1727, 1669, 1634, 1504, 1234, 1159, 1095 and 1026; $\delta_H$(250 MHz; $CDCl_3$) 7.89 (1 H, d, *J* 6.6, NH), 7.35 (5 H, m, ArH), 5.35 (2 H, m, NH and CH), 5.15 and 5.14 (2 H, 2 × s, $OCH_2$, both diastereomers), 4.79 (1 H, dd, *J* 6.0, 9.3, CH), 3.85 (3 H, s, OMe), 2.59 (3 H, s, Me), 2.42 (3 H, s, Me), 2.20 (1 H, m, *J* 6.8, 6.0, $Pr^iCH$), 0.95 (3 H, d, *J* 6.8, Me) and 0.94 (3 H, d, *J* 6.8, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 199.1, 167.0, 161.2, 160.6, 156.1, 153.1, 136.9, 128.3, 127.8, 127.7, 127.6, 65.6, 62.5, 55.0, 52.9, 30.9, 27.6, 19.0, 18.7 and 11.3; *m*/*z* (EI) 446 ($MH^+$, 5%), 445 ($M^+$, 3), 403 (15), 312 (17), 294 (12), 225 (20), 207 (5), 162 (7), 137 (5), 110 (12) and 91 (100).

**(*S*)-Methyl 2-{2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-5-methyloxazol-4-yl}-5-methyloxazole-4-carboxylate 17a**

To a stirred solution of triphenylphosphine (0.148 g, 0.566 mmol) and iodine (0.144 g, 0.566 mmol) in anhydrous dichloromethane (10 ml) was added triethylamine (0.16 ml, 1.132 mmol) followed by a solution of the oxazole **16a** (0.126 g, 0.283 mmol) in dichloromethane (10 ml). The reaction mixture was stirred for 1 h at room temperature and then concentrated *in vacuo*. The crude residue was purified by flash chromatography (ethyl acetate–light petroleum) to yield the *title compound* (0.113 g, 94%); mp 163–164 °C (ethyl acetate–light petroleum); $[\alpha]_D^{24}$ −40.0 (*c* 1.0, $CHCl_3$) (Found: C, 61.2; H, 5.8; N, 9.6. $C_{22}H_{25}N_3O_6 \cdot 0.25H_2O$ requires C, 61.2; H, 5.9; N, 9.7%) (Found: $M^+$, 427.1742. $C_{22}H_{25}N_3O_6$ requires *M*, 427.1743); $\nu_{max}$(Nujol)/$cm^{-1}$ 3289, 2957, 2937, 2860, 1734, 1694, 1545, 1300, 1264, 1202 and 1177; $\delta_H$(400 MHz, $CDCl_3$) 7.32 (5 H, m, ArH), 5.48 (1 H, d, *J* 9.1, NH), 5.13 (2 H, s, $OCH_2$), 4.83 (1 H, dd, *J* 6.5, 9.1, CH), 3.92 (3 H, s, OMe), 2.70 (3 H, s, Me), 2.67 (3 H, s, Me), 2.21 (1 H, m, $Pr^iCH$) and 0.95 (6 H, 2 overlapping d, *J* 6.8, Me); $\delta_C$(100.6 MHz; $CDCl_3$) 162.7, 162.4, 156.0, 155.9, 154.0, 150.5, 136.2, 128.5, 128.3, 128.14, 128.08, 124.5, 67.1, 54.8, 51.9, 32.8, 18.8, 18.0, 12.0 and 11.7; *m*/*z* (EI) 427 ($M^+$, 2%), 340 (1), 319 (100), 276 (77), 259 (10), 244 (66), 222 (12), 190 (17), 162 (7), 135 (4), 108 (80), 107 (66), 91 (41), 79 (86), 77 (50) and 55 (41).

**(*S*)-2-(1-Benzyloxycarbonyltetrahydropyrrol-2-yl)-5-methyloxazole-4-carboxylic acid 14b**

Sodium hydroxide (1.42 g, 35.6 mmol) was added in one portion to a stirred solution of the oxazole ester **13f** (2.13 g, 6.19 mmol) in THF–water (3:1) (52 ml) at room temperature. The reaction was stirred overnight, the THF was evaporated *in vacuo* and the mixture was partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous layer was acidified to pH 2 with hydrochloric acid (1 M) and extracted with ethyl acetate (2 × 100 ml). The combined organic extracts were washed with brine (100 ml), dried ($Na_2SO_4$) and evaporated *in vacuo* to afford the title compound (1.79 g, 87%) as a colourless solid, mp 168–168.5 °C. A small portion was recrystallised to afford the *title compound* as colourless prisms, mp 168.5–169.5 °C (ethyl acetate); $[\alpha]_D^{20}$ −80.0 (*c* 1.0, $CHCl_3$) (Found: C, 61.7; H, 5.4; N, 8.5. $C_{17}H_{18}N_2O_5$ requires C, 61.8; H, 5.5; N, 8.5%) (Found: $M^+$, 330.1215. $C_{17}H_{18}N_2O_5$ requires *M*, 330.1216); $\nu_{max}$(KBr)/$cm^{-1}$ 3255, 2977, 2956, 2887, 1722, 1667, 1614, 1585, 1447, 1411, 1361, 1195, 1171, 1133, 1089, 768, 760, 729, 705, 677 and 612; $\delta_H$(400 MHz; $CDCl_3$, 20 °C) 9.15 (1 H, br s, exch. $D_2O$, $CO_2H$), 7.25 (5 H, m, ArH), 5.19 (1 H, m, $NCHCH_2$), 5.01 (2 H, m, $OCH_2$), 3.70 (1 H, m, $NCHHCH_2$), 3.61 (1 H, m, $NCHHCH_2$), 2.61 (1.34 H, s, Me), 2.46 (1.66 H, s, Me) and 2.38–1.88 (4 H, m, $NCHCH_2CH_2$); $\delta_H$(400 MHz, $CDCl_3$, 50 °C) 7.28 (5 H, m, ArH), 6.60 (1 H, br s, exch. $D_2O$, $CO_2H$), 5.17 (1 H, m, $NCHCH_2$), 5.11 (2 H, br s, $OCH_2$), 3.67 (1 H, m, $NCHHCH_2$), 3.59 (1 H, m, $NCHHCH_2$), 2.51 (3 H, s, Me) and 2.38–1.88 (4 H, m, $NCHCH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 165.7, 163.0, 157.5, 155.3, 154.7, 137.0, 136.7, 128.7, 128.4, 128.3, 127.2, 67.5, 55.3, 54.9, 47.4, 46.9, 32.7, 31.7, 24.7, 24.0, 12.6 and 12.4; *m*/*z* (EI) 330 ($M^+$, 8%), 149 (21), 91 (100) and 43 (50).

**(*S*)-2-(1-Benzyloxycarbonyltetrahydropyrrol-2-yl)-5-methyloxazole-4-carboxamide 15b**

To a stirred solution of the carboxylic acid **14b** (1.79 g, 5.40 mmol) and triethylamine (0.90 ml, 6.46 mmol) in dry THF (15 ml) was added ethyl chloroformate (0.60 ml, 6.28 mmol) dropwise at 0 °C. The reaction was stirred for 30 min and aqueous ammonia (35%; 1.5 ml) was added. The resultant mixture was stirred at 0 °C for 45 min and partitioned between ethyl acetate (100 ml) and water (50 ml). The aqueous layer was further extracted with ethyl acetate (2 × 50 ml) and the organic extracts were combined, washed sequentially with aqueous sodium hydrogen carbonate (100 ml), brine (100 ml), hydrochloric acid (1 M; 75 ml), and brine (100 ml), dried ($Na_2SO_4$), and evaporated *in vacuo* to afford the *title compound* (1.75 g, 98%) as a pale yellow foam that was used without further purification; $[\alpha]_D^{19}$ −71.7 (*c* 1.0, $CHCl_3$) (Found: $M^+$, 329.1378. $C_{17}H_{19}N_3O_4$ requires *M*, 329.1376); $\nu_{max}(CHCl_3)/cm^{-1}$ 3522, 3404, 1680, 1633, 1575, 1418, 1357, 1119, 984 and 910; $\delta_H$(400 MHz; $CDCl_3$, 20 °C) 7.33–7.00 (5 H, m, ArH), 6.75 (0.45 H, s, exch. $D_2O$, CONHH), 6.67 (0.55 H, s, exch. $D_2O$, CONHH), 5.86 (1 H, s, exch. $D_2O$, CONHH), 5.15–4.80 (3 H, m, $NCHCH_2$ and $OCH_2$), 3.61 (1 H, m, $NCHHCH_2$), 3.49 (1 H, m, $NCHHCH_2$), 2.52 (1.35 H, s, $OCCH_3$), 2.43 (1.65 H, s, $OCCH_3$) and 2.30–1.85 (4 H, m, $NCHCH_2CH_2$); $\delta_H$(400 MHz, $CDCl_3$, 50 °C) 7.27 (5 H, m, ArH), 6.66 (1 H, br s, exch. $D_2O$, CONHH), 5.56 (1 H, br s, exch. $D_2O$, CONHH), 5.16 (1 H, m, $NCHCH_2$), 4.95 (2 H, br s, $OCH_2$), 3.65 (1 H, m, $NCHHCH_2$), 3.56 (1 H, m, $NCHHCH_2$), 2.53 (3 H, s, Me) and 2.35–1.90 (4 H, m, $NCHCH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 165.1, 162.2, 162.1, 158.3, 155.6, 155.1, 154.4, 154.2, 129.64, 129.58, 129.2, 129.1, 128.8, 128.7, 128.5, 67.8, 55.6, 55.2, 47.7, 47.2, 35.0, 33.0, 24.9, 24.2, 12.5 and 12.4; *m*/*z* (EI) 329 ($M^+$, 13%), 194 (17), 153 (16), 91 (100), 70 (45) and 43 (46).

**(*S*)-Methyl 2-[2-(1-benzyloxycarbonyltetrahydropyrrol-2-yl)-5-methyloxazol-4-ylcarbonylamino]-3-oxobutanoate 16b**

A solution of methyl 2-diazoacetoacetate (0.439 g, 3.07 mmol) in dry chloroform (12 ml) was added dropwise over 6 h to a refluxing solution of the amide **15b** (0.715 g, 2.17 mmol) and rhodium(II) acetate (19 mg, 0.044 mmol, 2 mol%) in dry chloroform (60 ml). The reaction mixture was allowed to cool, evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1 : 1), to afford the *title compound* (0.36 g, 38%) as a mixture of diastereomers as a colourless oil (Found: $M^+$, 443.1691. $C_{22}H_{25}N_3O_7$ requires *M*, 443.1692); $\nu_{max}(CHCl_3)/cm^{-1}$ 3399, 2958, 2890, 1758, 1730, 1700, 1670, 1635, 1501, 1419, 1357, 1277, 1201, 1164 and 1119; $\delta_H$(400 MHz; $CDCl_3$, 20 °C) 7.88 (1 H, m, exch. $D_2O$, CONH), 7.40–7.05 (5 H, m, ArH), 5.36 (1 H, d, *J* 6.8, $MeO_2CCH$), 5.19–4.90 (3 H, m, $NCHCH_2$ and $OCH_2$), 3.74 (3 H, s, OMe), 3.68 (1 H, m, $NCHHCH_2$), 3.58 (1 H, m, $NCHHCH_2$), 2.58 (1.5 H, s, Me), 2.45 (1.5 H, s, Me), 2.42 (3 H, s, Me) and 2.30–1.85 (4 H, m, $NCHCH_2CH_2$); $\delta_H$(400 MHz; $CDCl_3$, 50 °C) 7.83 (1 H, m, exch. $D_2O$, CONH), 7.40–7.05 (5 H, m, ArH), 5.36 (1 H, d, *J* 6.8, $MeO_2CCH$), 5.19–4.90 (3 H, m, $NCHCH_2$ and $OCH_2$), 3.74 (3 H, s, $CH_3O$), 3.68 (1 H, m, $NCHHCH_2$), 3.58 (1 H, m, $NCHHCH_2$), 2.50 (3 H, br s, Me), 2.38 (3 H, s, Me) and 2.30–1.85 (4 H, m, $NCHCH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 198.3, 198.1, 166.5, 161.7, 161.5, 154.8, 154.3, 153.8, 153.6, 136.6, 136.4, 128.4, 128.3, 127.9, 127.8, 67.0, 66.9, 62.5, 54.8, 54.4, 53.3, 46.9, 46.5, 32.2, 31.2, 27.9, 24.2, 23.5, 11.7 and 11.5; *m/z* (EI) 443 ($M^+$, 3%), 401 (10), 310 (17), 223 (22), 160 (12), 91 (100), 70 (31) and 43 (55).

**(*S*)-Methyl 2-[(1-benzyloxycarbonyltetrahydropyrrol-2-yl)-5-methyloxazol-4-yl]-5-methyloxazole-4-carboxylate 17b**

Triethylamine (0.33 ml, 2.37 mmol) and a solution of the oxazole **16b** (252 mg, 0.568 mmol) in dry dichloromethane (5 ml) were added successively to a stirred solution of triphenylphosphine (298 mg, 1.14 mmol) and iodine (289 mg, 1.14 mmol) in dry dichloromethane (12 ml) at room temperature. The mixture was stirred overnight, evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (3 : 2) to afford the *title compound* (195 mg, 81%) as a colourless oil. A small portion was recrystallised from ethyl acetate–light petroleum to afford the title compound as colourless needles, mp 122–122.5 °C; $[\alpha]_D^{19}$ −71.1 (*c* 1.0, $CHCl_3$) (Found: C, 61.8; H, 5.15; N, 9.7. $C_{22}H_{23}N_3O_6$ requires C, 62.1; H, 5.45; N, 9.9%) (Found: $M^+$, 425.1592. $C_{22}H_{23}N_3O_6$ requires *M*, 425.1587); $\nu_{max}(CHCl_3)/cm^{-1}$ 3011, 2977, 2895, 1702, 1618, 1442, 1420, 1353, 1108, 1058 and 985; $\delta_H$(400 MHz, $CDCl_3$, 20 °C) 7.33 (2 H, m, ArH), 7.15 (3 H, m, ArH), 5.14 (1 H, d, *J* 12.4, $NCHCH_2$), 4.99 (2 H, m, $OCH_2$), 3.89 (3 H, s, OMe), 3.68 (1 H, m, $NCHHCH_2$), 3.56 (1 H, m, $NCHHCH_2$), 2.67 (3 H, s, Me), 2.64 (1.3 H, s, Me), 2.52 (1.7 H, s, Me) and 2.37–1.88 (4 H, m, $NCHCH_2CH_2$); $\delta_H$(400 MHz, $CDCl_3$, 50 °C) 7.35–7.00 (5 H, m, ArH), 5.09 (1 H, d, *J* 12.4, $NCHCH_2$), 4.95 (2 H, s, $OCH_2$), 3.84 (3 H, s, OMe), 3.61 (1 H, m, $NCHHCH_2$), 3.53 (1 H, m, $NCHHCH_2$), 2.61 (3 H, s, Me), 2.51 (3 H, s, Me) and 2.35–1.85 (4 H, m, $NCHCH_2CH_2$); $\delta_C$(100.6 MHz; $CDCl_3$) 163.2, 162.7, 155.8, 154.8, 154.3, 154.1, 154.0, 150.4, 150.2, 136.6, 136.4, 128.4, 128.3, 128.2, 127.9, 127.8, 124.7, 124.5, 67.0, 66.9, 55.0, 54.6, 51.8, 47.0, 46.5, 32.4, 31.4, 24.3, 23.6, 12.0, 11.8 and 11.6; *m/z* (EI) 425 ($M^+$, 11%), 290 (8), 237 (7), 160 (23), 91 (100) and 43 (32).

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