Chemistry and X-ray crystallographic structure of *N*-protected (5-oxo-1,3-oxazolidin-4-yl)acetic acids: versatile intermediates in the synthesis of peptidomimetics

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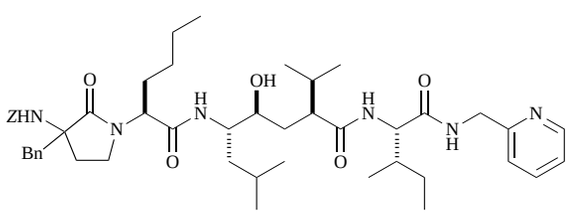
The X-ray crystal structures of [(2′*R*,4′*S*)-3′-benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl]acetic acid 16 and [(2′*S*,4′*R*)-3′-acetyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl]acetic acid 19 have been determined and their conformations compared to those of related oxazolidinones. Compounds of the type 16 and 19 have also been shown to be useful precursors to succinimide-based peptidomimetics possessing conformational restriction and latent reactivity.

Introduction

In recent years enormous effort has gone into the design and synthesis of peptidomimetics. These compounds maintain important structural features found in biologically active peptides while offering the advantage of increased bio-availability, bio-stability, bio-efficiency and bio-selectivity against the natural biological target of the parent peptide.[1] In extreme cases, peptidomimetics bear only a scant resemblance to the original parent peptide. Peptidomimetics can either inhibit (*i.e.* act as an antagonist or inhibitor) or enhance (*i.e.* act as an agonist) the effects of the original peptide and as a result they offer a high potential as medicinal agents.

The introduction of rings into peptidomimetics results in structures of well-defined conformation that can be used as biological probes to mimic and test the biological conformations adopted by peptides.[1,2] Examples of this include potent peptidomimetic inhibitors of renin[3] (*e.g.* **1**) and the HIV



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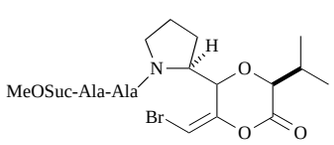

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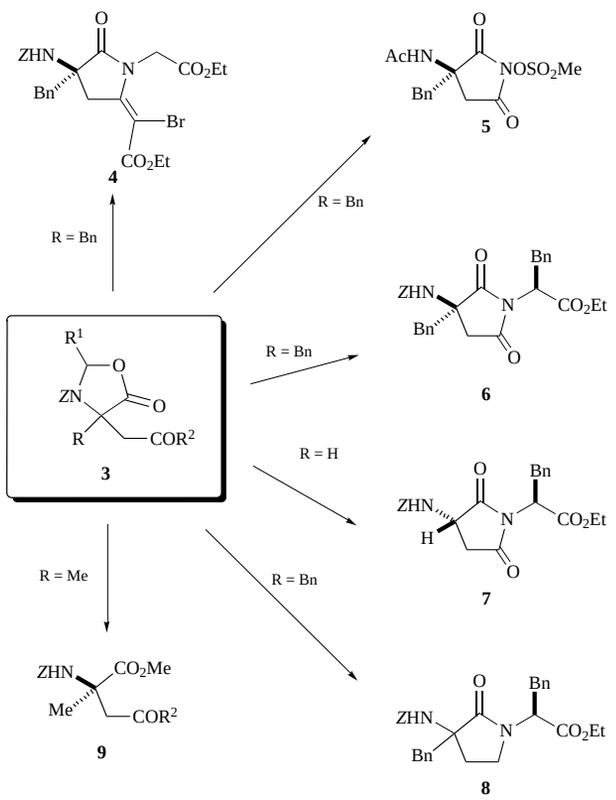
protease.[4] Functional groups possessing latent reactivity have also been incorporated into peptidomimetics to provide selective mechanism-based inactivators of enzymes.[5] For example, peptidomimetic halogeno enol lactones of the type **2** are potent inactivators of serine proteases.[6]

We and others have used *N*-protected (5-oxo-1,3-oxazolidin-4-yl)acetic acids[7,8] and their derivatives (see Scheme 1, structure **3**) as key synthetic intermediates to peptidomimetics with latent reactivity (*e.g.* **4** and **5**) and conformational restriction (*e.g.* **6**–**9**). Acylated enamino esters **4** are inactivators of serine proteases, a class of enzyme that catalyses the cleavage of peptides.[8] *N*-Methylsulfonyloxysuccinimides have been shown to be



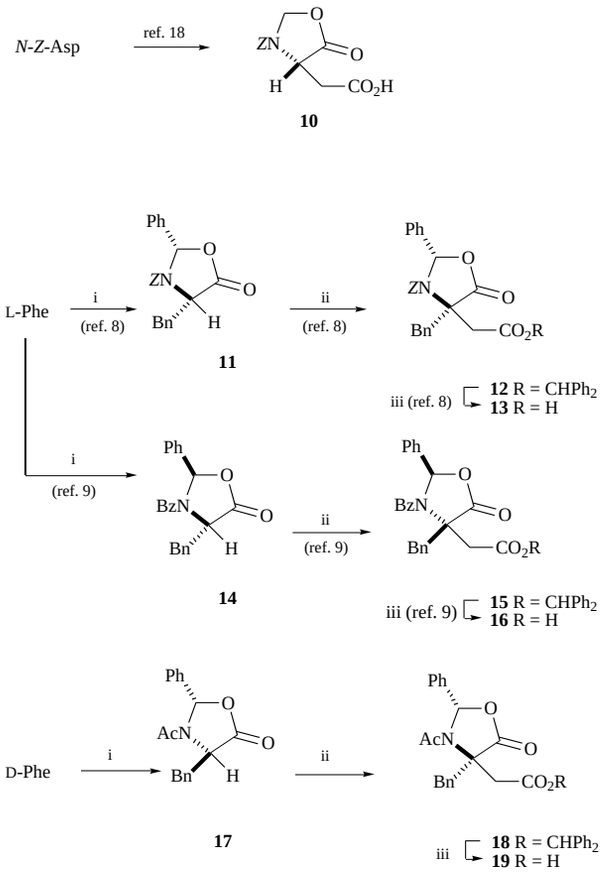
Scheme 1

potent mechanism-based inactivators of serine proteases.[9,10] These compounds function by an enzyme-mediated hydrolysis with subsequent Lossen rearrangement to release a highly reactive isocyanate which results in irreversible enzyme inactivation. We have attempted to increase the peptidic nature of these simple amino acid analogues, with a view to increasing potency and selectivity towards a given protease, by incorporating them into a peptidic sequence as in **5**. Amino succinimides of the type **7** have been reported to display anticonvulsant activity[11] and also to play a critical role in protein splicing and other post-translational protein modifications.[12] Amino succinimdes of the type **6**, reported for the first time here, are phenylalanine analogues of the known peptidomimetics **7**. Peptidomimetic lactams **8** have found wide application as conformationally restricted inhibitors of renin[3] (*e.g.* compound **1**) and other biological targets,[13,14] while α-methylated amino acids **9** display helix-inducing properties.[15]

Here we detail the synthesis and X-ray crystallographic structure analysis of *N*-protected (5-oxo-1,3-oxazolidin-4-yl)acetic acids and also their application to the preparation of imide-based peptidomimetics of the type **5**, **6** and **7**.

Results and discussion

The required *N*-protected (5-oxo-1,3-oxazolidin-4-yl)acetic acids **13**,[8b] **16** and **19** were prepared (Scheme 2) using an extension of the methods pioneered by Seebach for the stereoselective preparation of α,α-disubstituted amino acids.[16]



Scheme 2 *Reagents and conditions:* i, NaOH, PhCHO, then RCOX, −20 to 4 °C; ii, LiHMDS, THF, −78 °C, then $BrCH_2CO_2CHPh_2$; iii, TFA

The starting oxazolidinones **11**, **14** and **17** were prepared from L- and D-phenylalanine under standard conditions[8,16] (Scheme 2), *i.e.* treatment of the Schiff base sodium salt of the amino acid/benzaldehyde with either benzyl chloroformate (to give **11**), benzoyl chloride (to give **14**) or acetyl chloride (to give **17**). It is interesting to note that the reaction conditions gave either the *syn* (*e.g.* **11**) or the *anti* (*e.g.* **14** and **17**) isomers as the major products depending on the nature of the acylating agent. The configurations of **11**,[8] **14**[7] and **17**[17] were assigned as shown based on NOE data and/or X-ray crystallographic studies. In addition, the X-ray crystal structure of **13** has been published[8] and the structures of **16** and **19** are reported here.

The precursor oxazolidinones **11**, **14** or **17** were deprotonated with lithium hexamethyldisilazide at −78 °C, and the resulting C4 anion was treated with diphenylmethyl bromoacetate to give **12**, **15** and **18** respectively. Hydrolysis then gave the desired compounds **13**, **16** and **19**.

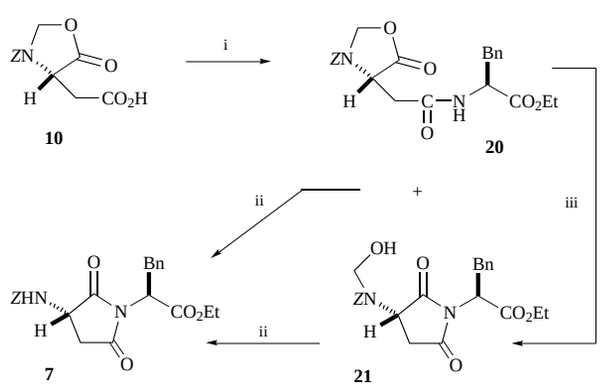
The *syn* and *anti* oxazolidinones **11** and **14**, both derived from L-phenylalanine, gave rise to products (**12** and **15**) of opposite configuration on alkylation (Scheme 2). For this reason, D-phenylalanine was used in the *N*-acetyl series to give **17** and hence **18**, which then has the same configuration as **12**. This allowed the preparation of **5** and **6** with the same configuration, a requirement for our biological studies.[18]

The unsubstituted oxazolidinone **10** was prepared by reaction of *N*-Z-L-aspartic acid with paraformaldehyde and toluene-*p*-sulfonic acid (PTSA) according to the method of Scholtz and Bartlett (Scheme 2).[19]

Synthesis of peptidomimetics

Amino succinimides, *e.g.* **7**, are traditionally prepared by reaction of an *N*-protected aspartic acid anhydride with an amine or an amino acid ester. The intermediate ring-opened α- and β-acid amides are then cyclised by reaction with acetic anhydride.[20] Alternatively, side chain-protected aspartyl-containing peptides can be cyclised with triethylamine to give amino succinyl peptides.[21] Amino succinimide formation of the second type is also involved in the biochemistry of a number of post-translational protein modification procedures.[12] Here, attack of a peptide amide nitrogen on an asparaginyl or aspartyl side chain gives an amino succinimde that can undergo ring opening to give two products, containing either an α- or β-linkage.

In the present study, an *N*,*N*-dicyclohexylcarbodiimide (DCC)-catalysed coupling of the Z-protected aspartic acid oxazolidinone **10** with L-phenylalanine ethyl ester, in the presence of 1-hydroxybenzotriazole (HOBT), gave a mixture of **20** and **21** which was separable by chromatography (Scheme 3).

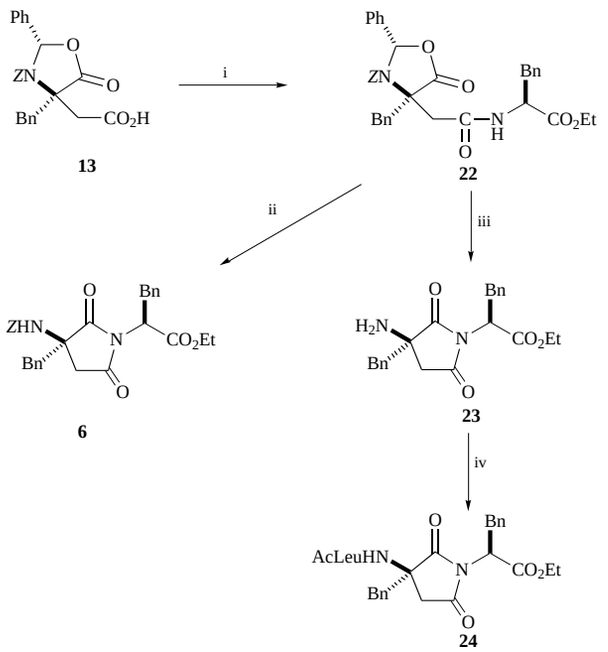


Scheme 3 *Reagents and conditions:* i, L-PheOEt·HCl, Et_3N, DCC, HOBT, CH_2Cl_2; ii, excess Et_3N, CH_2Cl_2, reflux; iii, Et_3N, CH_2Cl_2

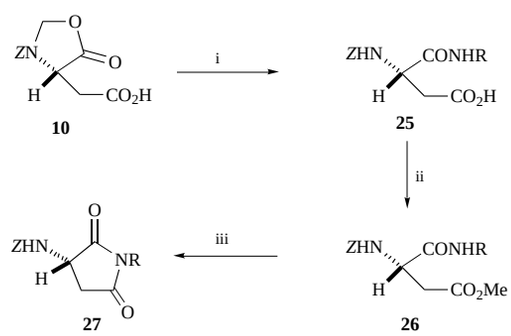
The reaction was carried out a number of times giving variable ratios of **20** and **21**. Treatment of **20** with triethylamine at room temp. gave compound **21** while the reaction of either a mixture of **20/21**, or a separate sample of **21**, with an excess of triethylamine at reflux gave the desired amino succinimide **7** and recovered starting material (Scheme 3).

The advantage of the current procedure over the existing literature procedures is not just that compounds of the type **7** can be prepared, but also that it can be extended to the preparation of substituted succinimides of the type **6**, a Phe-Phe dipeptidomimetic (Scheme 4). In this case, the phenylalanine-derived oxazolidinone **13** was coupled to L-phenylalanine ethyl ester to give **22** in 65% yield, which was either cyclised directly to give the dipeptidomimetic **6** (73%) or treated with toluene-*p*-sulfonic acid (PTSA) to give the amino succinimide **23** (58%). A DCC-catalysed coupling of **23** with *N*-acetyl-L-leucine then gave the tripeptidomimetic **24** (67%). An intermediate of the type **21** was not observed in this case, unlike the example given in Scheme 3. A complementary preparation of amino succinimides has been reported (Scheme 5).[11] Here the oxazolidinone ring, rather than the acid side chain of **10**, is reported to react with an amine to give **25** (step i, Scheme 5). Methylation (step ii) and cyclisation (step iii) then gave the succinimde **27**.

A related sequence to that given in Scheme 4 was used to prepare peptidomimetics of the type **5** (Scheme 6). To this end,



Scheme 4 *Reagents and conditions:* i, L-PheOEt·HCl, Et_3N, DCC, HOBT, CH_2Cl_2; ii, Et_3N, CH_2Cl_2, room temp.; iii, 4-$MeC_6H_4SO_3H$, toluene, reflux; iv, *N*-Ac-L-Leu, DCC, HOBT, CH_2Cl_2, 0 °C to room temp.



Scheme 5 *Reagents and conditions:* i, RNH_2, MeOH, reflux; ii, H_2SO_4, MeOH, reflux; iii, 4-$MeC_6H_4SO_3H$, toluene, reflux

reaction of the phenylalanine-derived oxazolidinone acid **19** with *O*-benzylhydroxylamine in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) gave a separable mixture of **28** (26%) and **29** (56%). The reaction of **28** with an excess of triethylamine at room temp. gave a quantitative conversion to **29**. Catalytic hydrogenation of **29** gave the hydroxysuccinimide **30** (96%) which was reacted with methanesulfonyl chloride, in the presence of diisopropylethylamine, to give the desired pseudo dipeptide **5** in 83% yield (Scheme 6).

X-Ray molecular structures

Perspective drawings of compounds **16** and **19**, with atom labelling, are presented in Figs. 1 and 2. The phenyl and benzyl ring substituents are *syn*, as would be expected from the alkylation of precursor oxazolidinones **11** and **14**, respectively. The absolute configurations follow from the configuration of the starting amino acids (Scheme 2). The conformations adopted by **16**, **19**, the previously reported derivatives **13**, **31**–**33**[7] and related examples[22] are very similar. In particular, the oxazolidinone rings adopt a shallow envelope conformation (*e.g.* see Fig. 3) such that the phenyl substituent occupies a quasi-equatorial position. In this conformation the phenyl-substituted carbon atom is slightly out of the plane formed by the other four ring atoms. This is supported by the fact that the angles between the least-squares plane of O(1)–C(5)–C(4)–N(3) and the plane of

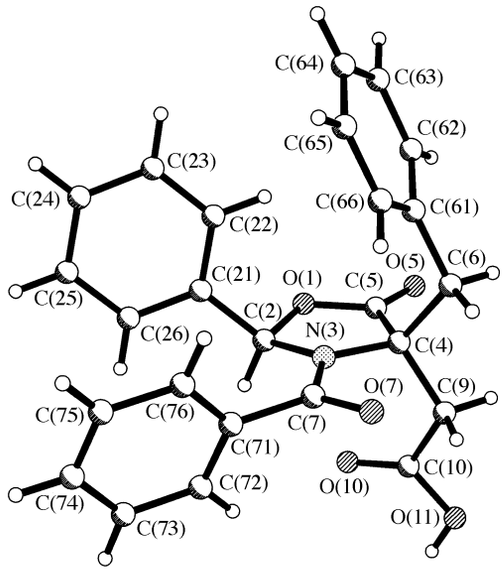


Fig. 1 X-Ray molecular structure of compound **16** with crystallographic numbering scheme

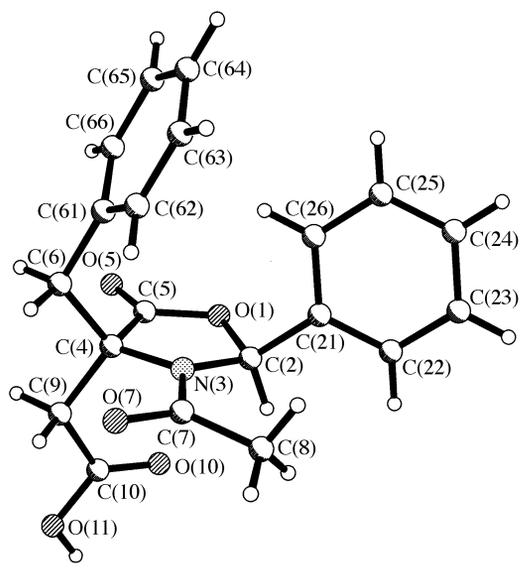
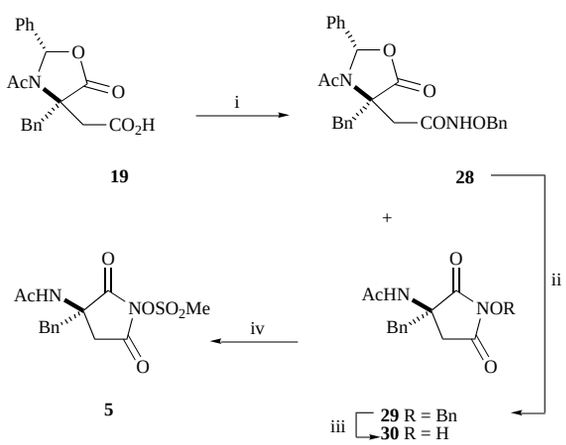


Fig. 2 X-Ray molecular structure of compound **19** with crystallographic numbering scheme



Scheme 6 *Reagents and conditions:* i, NH_2OBn, Et_3N, BOP, CH_2Cl_2; ii, Et_3N, CH_2Cl_2, room temp.; iii, 10% Pd–C, H_2; iv, Pr^i_2EtN, $MeSO_2Cl$, CH_2Cl_2, 0 °C

O(1)–C(2)–N(3) (see Figs. 1 and 2 for atom numbering) of **13**, **16**, **19** and **31**–**33** are in the range of 9–12° (Table 1).

The conformations adopted by the ring substituents of **16**

Table 1 Selected bond angles and bond lengths

Compound	Angle between planes (°)[a]	$\Sigma a_{N(3)}$[b] (°)	Torsion angles (°) τ_1[c]	τ_2[d]	N(3)–C(7)/Å
13	11.9	358.6	−9.6	6.5	1.346
16	10.3	359.1	0.9	10.6	1.343
19	10.9	358.8	2.9	−11.4	1.352
31	9.5	359.2	10.4	−1.7	1.359
32	12.4	359.0	−7.5	6.5	1.356
33	9.2	358.8	−8.8	4.4	1.407

[a] Angle between least-squares plane through atoms O(1)–C(5)–C(4)–N(3) and the plane of O(1)–C(2)–N(3). [b] Sum of the bond angles about N(3). [c] Torsion angle C(2)–N(3)–C(7)–C(8)/C(71). [d] Torsion angle C(4)–N(3)–C(7)–O(7).

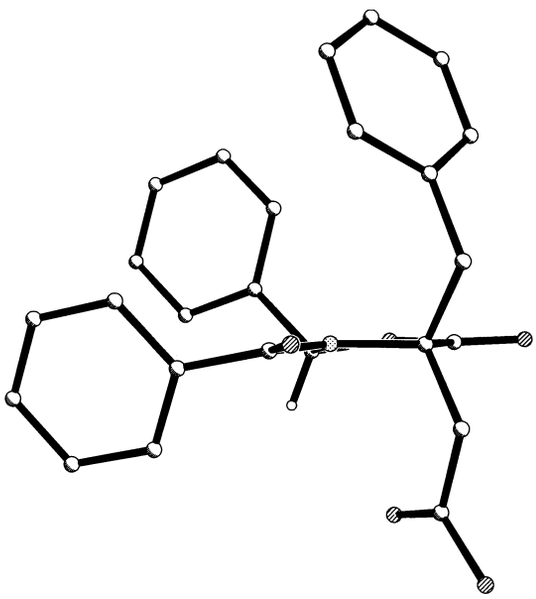
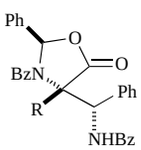
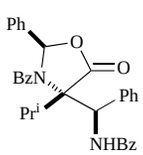


Fig. 3 X-Ray molecular structure of compound **16** showing ring conformation



31 R = Bn
32 R = Pr^i



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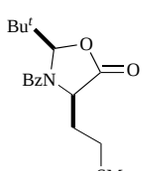

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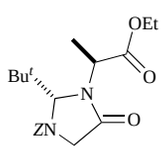

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and **19** (and the previously reported examples **13** and **31**–**33**)[7] are also very similar. The C(21)–C(26) and C(61)–C(66) aromatic rings of **16** (Fig. 1) and **19** (Fig. 2) show an edge-on π–π interaction[23] [the distance between C(22)/C(26) and the plane of C(61)–C(66) is 3.336 and 3.444 Å for **16** and **19**, respectively]. The C(21)–C(26) and C(71)–C(76) aromatic rings in the structure of **16** also show some evidence of π–π stacking[23] [angle between the aromatic ring planes defined by C(21)–C(26) and C(71)–C(76) is 23.8° and the distance between C(26) and the plane defined by C(71)–C(76) is 3.162 Å]. The structures of **16** and **19** also revealed intermolecular hydrogen bonds between the carboxylic acid group [O(11)] and the *N*-acyl carbonyl group [O(7)] of a second molecule [O(7)–O(11) distance is 2.604 and 2.625 Å for **16** and **19**, respectively].

The amide nitrogens of **13**, **16**, **19** and **31**–**33** show a very slight pyramidalisation, with the angles at the nitrogen atom summing to a value slightly less than 360° (Table 1). This is further supported by small, but significant, τ_1 and τ_2 angles (Table 1). The limited pyramidalisation observation is consistent with electron delocalisation between the nitrogen and carbonyl centre (see N–C=O bond lengths, Table 1). A number of *syn N*-acylated oxazolidinones, *e.g.* **34**, and *N*-acylated imidazolidinones, *e.g.* **35**, are reported to show significantly greater pyramidalisation of the amide nitrogen.[24] In these cases, the acyl group and the other ring substituents are located on opposite sides of the ring and the *tert*-butyl group occupies a quasi-axial, rather than a quasi-equatorial, position.[24] Non-acylated analogues are reported to show even greater ring puckering.[24] This pyramidalisation is thought to contribute strongly to the steric bias between the two faces of the ring and hence influence the stereoselectivity of reactions of these heterocycles.

The *N*-acyl carbonyl oxygen atom [O(7)] of **16** and **19** occupies an approximate s-*trans* position with the phenyl substituent of the acetal carbon atom [C(2), Figs. 1–3]. A similar conformation was noted in the structures of **13** and **31**–**33** all of which, like **16** and **19**, are geminally disubstituted at C(4).[7] The X-ray crystal structures of less congested examples, which are mono-substituted at C(4), reveal the alternative s-*cis* conformation.[24]

The work described here gives an analysis of the X-ray structures of *N*-protected (5-oxo-1,3-oxazolidin-4-yl)acetic acids and provides a platform for their application to the synthesis of peptidomimetics with conformational restriction and latent reactivity.

Experimental

Mps were obtained using a Hot Stage Microscope and are uncorrected. NMR Spectra were obtained in $CDCl_3$ (unless otherwise stated) at 300 MHz for ^{1}H and 75 MHz for ^{13}C; *J* values are given in Hz. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were obtained on a Kratos MS80RFA magnetic sector double focusing mass spectrometer. 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}. Preparative chromatography was carried out using a Chromatotron (Harrison Research Inc.) using glass plates coated with silica gel (P.F. 254 60). Lithium hexamethyldisilazide (LiHMDS) was obtained as a 1.0 M solution in THF from the Aldrich chemical company.

(2*S*,4*R*)-(−)-3-Acetyl-4-benzyl-2-phenyl-1,3-oxazolidin-5-one 17 D-Phenylalanine (2.50 g, 15.1 mmol) was dissolved in 1 M aq. NaOH (15.2 cm^3, 15.2 mmol), with slight warming, to give the corresponding sodium salt. The solvent was removed under reduced pressure to give a white sticky solid. To this was added benzaldehyde (2.3 cm^3, 22.6 mmol) and cyclohexane (60 cm^3) and the mixture was refluxed for 23 h using a Dean and Stark apparatus for the azeotropic removal of water. The solvent was evaporated under reduced pressure and to the resultant white solid residue was added dichloromethane (50 cm^3) and the mixture was cooled to −20 °C under N_2. Acetyl chloride (1.5 cm^3, 21.1 mmol) was added and the mixture was stirred at −20 °C for a further 2 h and then at 4 °C for 4 days. The mixture was allowed to warm to room temp. over 3.5 h before the solvent was removed under reduced pressure. The pale orange oil residue was taken up into a mixture of ethyl acetate (60 cm^3) and 5% aq. $NaHCO_3$ (50 cm^3). The organic phase was separated and washed with 5% aq. $KHSO_4$ (50 cm^3) and water (50 cm^3). The organic phase was separated and after the addition of solid NaCl, dried (Na_2SO_4) and the solvent removed. The *anti* oxazolidinone **17**, which crystallised from the residue, was recrystallised from ethyl acetate and light petroleum (1.64 g, 37%), mp 148–150 °C (Found: C, 73.3; H, 5.9; N, 4.5. $C_{18}H_{17}NO_3$ requires

C, 73.2; H, 5.8; N, 4.7%); $[\alpha]_D^{20}$ −182 (*c* 1.3, dichloromethane); ν_{max}(KBr)/cm^{-1} 3447, 3032, 1798 and 1666; δ_H([$^2H_6$]DMSO, 100 °C) 1.78 (3 H, br s, CH_3), 3.21 (1 H, A part of ABX, J_{AB} 14.1, J_{AX} 2.7, CH_2Ph), 3.60 (1 H, B part of ABX, J_{AB} 14.1, J_{BX} 5.9, CH_2Ph), 5.20 (1 H, X part of ABX, H4), 6.08 (1 H, s, H2), 7.18 (2 H, m, ArH), 7.29 (3 H, m, ArH) and 7.42 (5 H, s, ArH); δ_C 23.4, 34.2, 58.6, 90.5, 126.8, 127.6, 128.8, 129.4, 129.7, 130.8, 134.9, 136.1, 168.3 and 171.0.

(2′*S*,4′*R*)-(+)-3′-Acetyl-4′-benzyl-5′-oxo-2′-phenyl-1′,3′-oxazolidin-4′-yl)acetic acid 19

LiHMDS (3.75 cm^3 of 1 M solution in THF, 3.75 mmol, 1.1 equiv.) was added to oxazolidinone **17** (1.00 g, 3.39 mmol) dissolved in THF (40 cm^3) at −78 °C under N_2. The mixture was stirred at −78 °C for 7 min, after which time a solution of $BrCH_2CO_2CHPh_2$ (1.50 g, 4.92 mmol) in dry THF (4 cm^3) was added. The mixture was stirred at −78 °C for a further 2 h and then at room temp. for 20 h. The solvent was evaporated under reduced pressure and the residue was taken up into a mixture of diethyl ether (50 cm^3) and saturated aq. NH_4Cl (40 cm^3). The aqueous phase was extracted with diethyl ether (3 × 30 cm^3) and the diethyl ether fractions were combined, dried (Na_2SO_4) and solvent removed. The resulting clear yellow oil was purified by radial chromatography using a 4 mm silica gel plate and eluting with ethyl acetate–light petroleum (1:4) to give **18** as a clear colourless oil (1.47 g, 83%), which was used in subsequent steps without further purification [HRMS: found (EI) M^+, 519.2048. $C_{33}H_{29}NO_5$ requires 519.2046]; $[\alpha]_D^{20}$ +10 (*c* 2.2, dichloromethane); ν_{max}(KBr)/cm^{-1} 3065, 3032, 2928, 1794, 1734 and 1666; δ_H 1.30 (3 H, s, CH_3), 3.17 and 4.09 (2 H, ABq, J_{AB} 17.1, CH_2CO), 3.32 and 3.78 (2 H, ABq, J_{AB} 13.7, CH_2Ph), 6.02 (1 H, s, H2), 6.05 (2 H, d, *J* 7.3, ArH), 6.89 (1 H, s, CHPh$_2$), 7.00 (2 H, t, *J* 7.8, ArH), 7.19 (1 H, t, *J* 7.4, ArH) and 7.22–7.39 (15 H, m, ArH); δ_C 24.2, 39.6, 41.9, 66.2, 77.9, 90.8, 126.7, 127.2, 127.6, 127.7, 127.9, 128.1, 128.5, 128.5, 128.5, 129.0, 129.9, 130.6, 134.8, 135.1, 139.1, 139.5, 169.3, 169.7 and 172.7.

The benzhydryloxazolidinone **18** (250 mg, 0.48 mmol) was dissolved in dry THF (20 cm^3), trifluoroacetic acid (0.74 cm^3, 9.61 mmol) was added and the mixture was stirred for 3 h at room temp. under N_2. The mixture was evaporated under reduced pressure and the residue was taken up into ethyl acetate (75 cm^3) and washed with dilute aq. HCl (100 cm^3) and water (50 cm^3). The organic phase was dried (Na_2SO_4) and solvent was removed to give a residue that was washed with dichloromethane (3 cm^3) to give **19** as a white solid (106 mg, 62%), mp 228–229 °C (Found: C, 68.0; H, 5.5; N, 3.9. $C_{20}H_{19}NO_5$ requires C, 68.0; H, 5.4; N, 4.0%); $[\alpha]_D^{20}$ +16 (*c* 1.0, methanol); ν_{max}(KBr)/cm^{-1} 2932, 1794, 1726 and 1622; δ_H(CD_3OD) 1.52 (3 H, s, CH_3), 3.03 and 3.82 (2 H, ABq, J_{AB} 7.6, CH_2CO_2), 3.26 and 3.73 (2 H, ABq, J_{AB} 13.2, CH_2Ph), 6.25 (2 H, d, *J* 7.3, ArH) 6.49 (1 H, s, H2), 7.09 (2 H, t, *J* 7.8, ArH) and 7.20–7.46 (6 H, m, ArH); δ_C 24.9, 40.9, 43.3, 68.5, 92.9, 129.3, 129.7, 130.2, 130.5, 131.6, 132.0, 137.0, 137.3, 172.6, 174.1 and 175.2.

(2′*S*,4′*R*)-(−)-2-(3′-Acetyl-4′-benzyl-5′-oxo-2′-phenyl-1′,3′-oxazolidin-4′-yl)-*N*-benzyloxyacetamide 28 and (3*R*)-(+)-3-acetylamino-3-benzyl-1–benzyloxysuccinimide 29

Method A. Triethylamine (125 µl, 0.90 mmol, 1 equiv.) was added to a stirred suspension of **19** (316 mg, 0.89 mmol), BOP (442 mg, 0.10 mmol) and O-benzylhydroxylamine (142 mg, 1.15 mmol) in dichloromethane (12 cm^3) under N_2. After stirring at room temp. for 80 min., a further equivalent of triethylamine (125 µl, 0.9) was added and stirring was continued for a further 80 min. The solvent was evaporated under reduced pressure and the residue was taken up into ethyl acetate (20 cm^3). The organic phase was washed with 5% aq. HCl (20 cm^3), water (20 cm^3), 5% aq. $NaHCO_3$ (20 cm^3) and water (20 cm^3), and dried (Na_2SO_4). The solvent was removed and the residue was purified by radial chromatography on a 1 mm silica gel chromatotron plate eluting with ethyl acetate–light petroleum (1:1). Crystallisation from ethyl acetate and light petroleum gave **28** as fine white splintery crystals (108 mg, 26%), mp 160–162 °C (softens at 155 °C) (Found: C, 70.5; H, 5.6; N, 6.3. $C_{27}H_{26}N_2O_5$ requires C, 70.7; H, 5.7; N, 6.1%); $[\alpha]_D^{20}$ −20 (*c* 1.1, dichloromethane); ν_{max}(KBr)/cm^{-1} 3196, 3031, 1793 and 1667; δ_H([$^2H_8$]-dioxane, 90 °C) 1.66 (3 H, s, CH_3), 2.90 (1 H, d, *J* 16.1, CH_2CO), 3.43 and 3.84 (2 H, ABq, J_{AB} 13.6, CH_2Ph), 3.77 (1 H, br, CH_2CO), 4.99 and 5.02 (2 H, ABq, J_{AB} 11.2, OCH_2Ph), 6.55 (1 H, s, H2), 6.59 (2 H, d, *J* 7.3, ArH), 7.23 (2 H, t, *J* 7.3, ArH), 7.36–7.58 (11 H, m, ArH) and 9.64 (1 H, br s, NH); δ_C 24.3, 38.3, 42.0, 66.7, 78.2, 90.9, 127.7, 127.9, 128.5, 128.7, 129.1, 129.3, 130.1, 130.6, 134.8, 135.0, 135.04 166.7, 170.9 and 172.9.

Further elution with ethyl acetate gave **29** (177 mg, 56%), mp 186–189 °C (softens at 182 °C) (Found: C, 68.1; H, 5.9; N, 8.1. $C_{20}H_{20}N_2O_4$ requires C, 68.2; H, 5.7; N, 8.0%); $[\alpha]_D^{20}$ +80 (*c* 1.1, dichloromethane); ν_{max}(KBr)/cm^{-1} 3344, 3033, 1790, 1729, 1651 and 1538; δ_H 2.02 (3 H, s, CH_3), 2.96 and 2.98 (2 H, ABq, J_{AB} 17.6, CH_2CO), 3.00 and 3.13 (2 H, ABq, J_{AB} 13.2, CH_2Ph), 4.94 and 4.99 (2 H, ABq, J_{AB} 9.7, OCH_2Ph), 5.90 (1 H, s, NH), 7.16 (2 H, m, ArH), 7.35 (6 H, m, ArH) and 7.48 (2 H, m, ArH); δ_C 22.7, 37.4, 42.0, 57.3, 78.7, 128.3, 128.4, 129.09, 129.2, 129.7, 130.1, 132.0, 133.5, 168.5, 170.4 and 172.3.

Method B. Triethylamine (92 µl, 0.66 mmol) was added to a solution of **28** (30 mg, 0.07 mmol) in dichloromethane (0.8 cm^3) and the mixture stirred at room temp. for 1 h. The solution was diluted with dichloromethane (15 cm^3) and washed with 5% aq. HCl (10 cm^3), followed by water (2 × 10 cm^3). The organic phase was dried ($MgSO_4$) and the solvent removed to give a residue that was purified by radial chromatography using a 1 mm silica gel chromatotron plate eluting with ethyl acetate–light petroleum (3:1) to yield **29** as a clear colourless oil (23 mg, 100%).

(3*R*)-(+)-3-Acetylamino-3-benzyl-1-hydroxysuccinimide 30

A mixture of **29** (105 mg, 0.30 mmol) and 10% Pd on C (10 mg) in dry THF (5 cm^3) was stirred under a H_2 atmosphere for 2.5 h. The reaction mixture was filtered, the filtrate evaporated and the solid residue was washed with ethyl acetate to give **30** as a white solid (75 mg, 96%), mp 182–188 °C (softens at 112 °C) (Found: C, 55.6; H, 5.7; N, 9.8. $C_{13}H_{14}N_2O_4.H_2O$ requires C, 55.2; H, 5.8; N, 10.0%); $[\alpha]_D^{20}$ +90 (*c* 1.1, CH_3OH); ν_{max}(KBr)/cm^{-1} 3318, 1792, 1718, 1655 and 1543; δ_H(CD_3OD) 1.98 (3 H, s, CH_3), 2.82 and 2.87 (2 H, ABq, J_{AB} 17.6, CH_2CO), 2.99 and 3.22 (2 H, ABq, J_{AB} 13.2, CH_2Ph), 7.17 (2 H, m, ArH) and 7.23 (3 H, m, ArH); δ_C(CD_3OD) 22.4, 37.8, 42.6, 59.1, 129.2, 130.1, 131.6, 134.1, 171.9, 173.6 and 175.5.

(3*R*)-(+)-3-Acetylamino-3-benzyl–1-methylsulfonyloxysuccinimide 5

Methanesulfonyl chloride (27 µl, 0.35 mmol) was added to a solution of **30** (60 mg, 0.30 mmol) and diisopropylethylamine (44 µl, 0.25 mmol) in dichloromethane (1 cm^3) at 0 °C and the mixture was stirred at 0 °C for 20 min and then at room temp. for 1 h. The mixture was diluted with dichloromethane (15 cm^3) and washed successively with cold water (10 cm^3), cold 5% aq. HCl (10 cm^3) and cold 10% aq. $NaHCO_3$ (10 cm^3). The organic phase was dried (Na_2SO_4) and the solvent removed to give **5** as a clear colourless oil which crystallised from diethyl ether (65 mg, 83%), mp 64–67 °C (Found: C, 47.6; H, 4.9. $C_{14}H_{16}N_2O_6S{\cdot}3/4H_2O$ requires C, 47.5; H, 5.0%); $[\alpha]_D^{20}$ +36 (*c* 0.8, dichloromethane); ν_{max}(KBr)/cm^{-1} 3269, 3036, 2936, 1809, 1747, 1661 and 1531; δ_H 2.03 (3 H, s, CH_3CO), 3.04 and 3.11 (2 H, ABq, J_{AB} 17.6, CH_2CO), 3.06 and 3.23 (2 H, ABq, J_{AB} 13.2, CH_2Ph), 3.35 (3 H, s, SCH_3), 5.95 (1 H, s, NH), 7.19 (2 H, m, ArH) and 7.39 (3 H, m, ArH); δ_C 22.2, 37.4, 39.6, 41.5, 57.8, 128.3, 129.0, 130.2, 131.4, 166.6, 170.5 and 171.1 [HRMS: found (EI) M^+, 340.0725. $C_{14}H_{16}N_2O_6S$ requires 340.0729].

(2*S*,4′*S*)-(+)-Ethyl 2-[(3′-benzyloxycarbonyl-5′-oxo-1′,3′-oxazolidin-4′-yl)methylcarbonylamino]-3-phenylpropanoate 20 and (2*S*,3′*S*)-(−)-ethyl 2-{3′-[benzyloxycarbonyl(hydroxymethyl)amino]succinimido}-3-phenylpropanoate 21

Method A. L-Phenylalanine ethyl ester hydrochloride (50 mg, 0.22 mmol), triethylamine (31 μl, 0.22 mmol) and HOBT·1H_2O (34 mg, 0.22 mmol) were added to **10**[18] (61 mg, 0.22 mmol) dissolved in dichloromethane (0.45 cm^3) and the solution was cooled to 0 °C under N_2. After stirring for 10 min, DCC (45 mg, 0.22 mmol) was added and the mixture was stirred for a further 10 min at 0 °C and then for 18 h at room temp. The mixture was filtered and the filtrate diluted with dichloromethane (15 cm^3) and washed with 3.5% aq. HCl (20 cm^3) and water (2 × 20 cm^3). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate, filtered and evaporated to give a mixture of **20** and **21** (19:1 by ^{1}H NMR spectroscopy) which was not purified further (89 mg, 90%) [HRMS: found: (FAB) MH^+, 455.1808. $C_{24}H_{27}N_2O_7$ requires 455.1818]; $[\alpha]_D^{20}$ +71 (*c* 2.2, dichloromethane); ν_{max}(KBr)/cm^{-1} 3354, 2928, 1801, 1717 and 1531; δ_H(for **20**) ([$^2H_6$]DMSO, 60 °C) 1.08 (3 H, t, *J* 7.1, CH_3), 2.71 (1 H, dd, *J* 2.9, 16.7, CHC*H*$_2$CO), 2.92 (1 H, dd, *J* 8.4, 13.8, CHC*H*$_2$Ph), 3.01 (1 H, dd, *J* 6.2, 13.8, CHC*H*$_2$Ph), 3.04 (1 H, dd, *J* 4.7, 16.7, CHC*H*$_2$CO), 4.02 (2 H, q, *J* 7.1, OC*H*$_2$$CH_3$), 4.42 (2 H, m, 2 × CH), 5.08 (1 H, dd, *J* 1.0, 3.4, NC*H*$_2$O), 5.15 (2 H, s, OC*H*$_2$Ph), 5.44 (1 H, d, *J* 3.4, NC*H*$_2$O), 7.17–7.39 (10 H, m, ArH) and 8.45 (1 H, d, *J* 7.3, NH); δ_C 13.7, 35.0 (br), 37.2, 51.4, 53.1, 61.2, 67.4, 77.9 (br), 126.7, 127.7, 128.1, 128.2, 128.3, 128.9, 135.2, 135.4, 152.3, 168.4, 170.9 and 172.0.

A separate large scale preparation as described above, using L-phenylalanine ethyl ester hydrochloride (247 mg, 1.08 mmol), triethylamine (0.15 cm^3, 1.08 mmol,) and HOBT·1H_2O (165 mg, 1.08 mmol), gave a mixture of **20** and **21** in a ratio of 1:2 by ^{1}H NMR spectroscopy (455 mg, 94%). A sample (395 mg) of this was purified by radial chromatography using a 2 mm silica plate and eluting with ethyl aetate–light petroleum (1:1) to give **20** (113 mg, 27%, data as recorded above).

Further elution gave **21** (207 mg, 50%) {HRMS: found (EI) $[M - CH_2O]^+$, 424.1630. $C_{23}H_{24}N_2O_6$ requires 424.163 42}; $[\alpha]_D^{20}$ −64 (*c* 1.15, dichloromethane); ν_{max}(KBr)/cm^{-1} 3479, 2939, 1788 and 1715; δ_H([$^2H_8$]-1,4-dioxane, 90 °C) 1.37 (3 H, t, *J* 7.3, CH_3), 2.91 (1 H, A part of ABX, J_{AB} 17.6, J_{AX} 6.4, CH_2CO), 3.02 (1 H, B part of ABX, J_{AB} 17.6, J_{BX} 9.3, CH_2CO), 3.44 (1 H, A part of ABX, J_{AB} 14.4, J_{AX} 10.0, CHC*H*$_2$Ph), 3.62 (1 H, B part of ABX, J_{AB} 14.4, J_{AX} 5.7, CHC*H*$_2$Ph), 4.33 (2 H, q, OC*H*$_2$$CH_3$), 4.42 (1 H, br s, OH), 4.56 (1 H, X part of ABX, C*H*CH_2CO), 4.92 (2H, m, C*H*$_2$OH), 5.17 (1 H, X part of ABX, C*H*CH_2Ph), 5.24 and 5.30 (2 H, br ABq, *J* 12.3, OC*H*$_2$Ph) and 7.30–7.48 (10 H, m, ArH); δ_C(mixture of conformational isomers) 14.0, 33.8, 34.0, 34.3, 35.1, 53.9, 54.1, 54.8, 55.9, 62.2, 68.2, 72.2, 72.6, 127.0, 128.2, 128.5, 128.6, 128.6, 128.7, 129.0, 135.5, 136.4, 136.6, 154.7, 154.8, 168.0, 168.2, 173.2, 174.3 and 174.8.

Method B. A solution of compound **20** (15 mg, 0.03 mmol) in dichloromethane (0.4 cm^3) was treated with triethylamine (46 cm^3, 0.33 mmol, 10 equiv.) for 28 min at room temp. The mixture was diluted with dichloromethane (10 cm^3), washed successively with 5% aq. HCl (10 cm^3) and water (2 × 10 cm^3), dried ($MgSO_4$) and the solvent removed. ^{1}H NMR spectral analysis of the residue revealed the presence of **20** and **21** in an approximate ratio of 1:2.

(2*S*,3′*S*)-(−)-Ethyl 2-[3′-(benzyloxycarbonylamino)succinimido]-3-phenylpropanoate 7

Method A. A solution of **20** (containing 5% **21**, prepared as described above) (13 mg, 0.03 mmol) and triethylamine (50 cm^3, 0.36 mmol) in dichloromethane (0.5 cm^3) was gently refluxed for 1 h under N_2. The mixture was cooled, diluted with dichloromethane (10 cm^3) and washed with 5% aq. HCl (10 cm^3) and water (2 × 10 cm^3), dried ($MgSO_4$) and solvent removed. The residue was purified by preparative silica TLC eluting with ethyl acetate–light petroleum (1:1) to give **21** (4.3 mg, 33%) and **7** (5.1 mg, 42%) [HRMS: found (EI) M^+, 424.1634. $C_{23}H_{24}N_2O_6$ requires 424.1634]; $[\alpha]_D^{20}$ −72 (*c* 0.5, dichloromethane); ν_{max}(KBr)/cm^{-1} 3358, 2937, 1786, 1717 and 1526; δ_H 1.28 (3 H, t, *J* 7.3, CH_3), 2.56 (1 H, dd, *J* 6.3, 17.8, CH_2CO), 3.04 (1 H, dd, *J* 8.9, 17.8, CH_2CO), 3.40 (1 H, A part of ABX, J_{AB} 14.1, J_{AX} 11.3, CHC*H*$_2$Ph), 3.50 (1 H, B part of ABX, J_{AB} 14.1, J_{BX} 5.6, CHC*H*$_2$Ph), 4.24 (3 H, m, OC*H*$_2$ and C*H*CH_2CO), 5.00 (1 H, X part of ABX, C*H*CH_2Ph), 5.11 (2 H, s, OC*H*$_2$Ph), 5.27 (1 H, br d, *J* 4.8, NH) and 7.13–7.39 (10 H, m, ArH); δ_C 14.1, 34.0, 36.0, 50.0, 54.1, 62.2, 67.5, 127.2, 128.3, 128.4, 128.6, 129.0, 135.7, 136.3, 155.8, 167.9, 173.0 and 174.6.

Method B. Triethylamine (0.5 cm^3, 0.36 mmol) was added to **21** (11.5 mg, 0.03 mmol) dissolved in dichloromethane (0.5 cm^3) and the mixture was refluxed for 1 h. Work up and purification as described above gave recovered **21** (7 mg, 61%) and **7** (4 mg, 38%).

(2*S*,2′*S*,4′*R*)-(+)-Ethyl 2-[(4′-benzyl-3′-benzyloxycarbonyl-5′-oxo-2′-phenyl-1′,3′-oxazolidin-4′-yl)acetamido]-3-phenylpropanoate 22

L-Phenylalanine ethyl ester hydrochloride (93 mg, 0.41 mmol), triethylamine (58 μl, 0.42 mmol) and HOBT·H_2O (62 mg, 0.41 mmol) were added to **13**[8] (178 mg, 0.40 mmol) dissolved in dichloromethane (1 cm^3) and the solution was cooled to 0 °C under N_2. After stirring for 10 min at 0 °C, DCC (85 mg, 0.41 mmol) was added and the mixture was stirred for a further 40 min at 0 °C and then for 18 h at room temp. The mixture was filtered and the filtrate diluted with dichloromethane (25 cm^3), washed with 5% aq. HCl (25 cm^3) and water (2 × 20 cm^3). The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by radial chromatography on a 1 mm silica gel chromatotron plate, eluting with ethyl acetate–light petroleum (1:3) to give **22** as a clear colourless oil (162 mg, 65%) [HRMS: found (EI) M^+, 620.2527. $C_{37}H_{36}N_2O_7$ requires 620.2522]; $[\alpha]_D^{20}$ +46 (*c* 0.5, dichloromethane); ν_{max}(KBr)/cm^{-1} 3360, 3033, 2934, 1794, 1711, 1674 and 1527; δ_H([$^2H_8$]-1,4-dioxane, 90 °C) 0.95 (3 H, t, *J* 7.1, CH_3), 3.05 (1 H, d, *J* 16.2, C*H*$_2$CO), 3.19 (2 H, m, C*H*$_2$Ph), 3.36 and 3.59 (2 H, ABq, *J* 13.2, C4′-C*H*$_2$Ph), 3.64 (1 H, br, C*H*$_2$CO), 4.27 (2 H, q, *J* 7.3, OC*H*$_2$$CH_3$), 4.92 (1 H, q, *J* 6.8, 1 H, CH), 4.99 (1 H, br s, OC*H*$_2$Ph), 5.18 (1 H, d, *J* 12.7, OC*H*$_2$Ph), 6.43 (1 H, s, H2′), 6.50 (2 H, d, *J* 7.3, ArH), 7.04 (2 H, br s, ArH), 7.10 (2 H, t, *J* 7.4, ArH) and 7.26–7.48 (14 H, m, ArH); δ_C 13.9, 37.9, 40.9, 53.2, 61.5, 65.4, 67.0, 90.2, 126.9, 127.3, 127.4, 127.7, 127.9, 128.0, 128.4, 128.8, 129.0, 129.1, 130.6, 134.9, 135.1, 135.7, 152.2, 168.2, 170.9 and 172.9.

(2*S*,3′*R*)-(−)-Ethyl 2-(3′-benzyl-3′-aminosuccinimido)-3-phenylpropanoate 23

Toluene-*p*-sulfonic acid (50 mg, 0.26 mmol) was added to a solution of **22** (68 mg, 0.11 mmol) in toluene (2 cm^3) and the mixture was refluxed for 1 h under N_2. The solvent was removed under reduced pressure and the residue taken up into ethyl acetate (20 cm^3) and water (20 cm^3). The organic phase was separated and washed with water (2 × 20 cm^3), dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by radial chromatography on a 1 mm silica gel chromatotron plate, eluting with ethyl acetate–light petroleum (1:1) to give **23** as an oil (24 mg, 58%) [HRMS: found (EI) M^+, 380.1734. $C_{22}H_{24}N_2O_4$ requires 380.1736]; $[\alpha]_D^{20}$ −54 (*c* 0.1, dichloromethane); ν_{max}(KBr)/cm^{-1} 3368, 2982, 2934, 1780, 1743 and 1711; δ_H 1.19 (3 H, t, *J* 7.1, CH_3), 2.23 and 2.71 (2 H, ABq, *J* 18.3, CH_2CO), 2.77 and 2.88 (2 H, ABq, *J* 13.6, C3′-C*H*$_2$Ph), 3.32 (1 H, A part of ABX, J_{AB} 14.2, J_{AX} 11.7, CHC*H*$_2$Ph), 3.47 (1 H, B part of ABX, J_{AB} 14.2, J_{BX} 5.4, CHC*H*$_2$Ph), 4.18 (2 H, m, OCH_2), 4.94 (1 H, X part of ABX, CH), 7.09 (5 H, m, ArH) and 7.25 (5 H, m, ArH); δ_C 14.0, 33.8, 40.0, 42.8, 53.1, 59.1, 61.9, 127.0, 127.3, 128.5, 128.6, 129.1, 130.3, 134.7, 136.5, 168.04 173.7 and 180.4.

(2*S*,3′*R*)-(−)-Ethyl 2-[3′-benzyl-3′-(*N*-acetyl-L-leucylamino)-succinimido]-3-phenylpropanoate 24

N-Acetyl-L-leucine (8.5 mg, 0.05 mmol) and HOBT (7.5 mg, 0.05 mmol) were added to a stirred solution of **23** (18 mg, 0.05 mmol) in dichloromethane (0.4 cm^3) at 0 °C under N_2. After 7 min, DCC (10 mg, 0.05 mmol) was added and the resulting mixture was stirred for 15 min at 0 °C and then at room temp. for 60 h. The reaction mixture was filtered, diluted with CH_2Cl_2 (15 cm^3), washed with 5% aq. HCl (20 cm^3) and water (2 × 20 cm^3), the solvent was evaporated under reduced pressure and the residue was purified by radial chromatography on a 1 mm silica gel chromatotron plate, eluting with ethyl acetate–light petroleum (3:2) to give **24** as a clear colourless oil (17 mg, 67%) [HRMS: found (FAB) MH^+, 536.2775. $C_{30}H_{38}N_3O_6$ requires 536.2761]; $[\alpha]_D^{20}$ −75 (*c* 1.5, dichloromethane); ν_{max}(KBr)/cm^{-1} 3271, 2959, 1786, 1747, 1717, 1643 and 1549; δ_H 0.90 (3 H, d, *J* 5.9, CHCH_3), 0.92 (3 H, d, *J* 5.9, CHCH_3), 1.20 (3 H, t, *J* 7.1, CH_2CH_3), 1.42 (1 H, m, CHCH_2CH), 1.60 (2 H, m, CH_2C*H*Me_2), 1.96 (3 H, s, CH_3CO), 2.78 and 2.92 (2 H, ABq, *J* 13.7, C3′-CH_2Ph), 2.85 and 2.94 (2 H, ABq, *J* 18.1, CH_2CO), 3.21 (1 H, A part of ABX, J_{AB} 14.5, J_{AX} 9.2, CHCH_2Ph), 3.53 (1 H, B part of ABX, J_{AB} 14.5, J_{BX} 6.6, CHCH_2Ph), 4.16 (2 H, m, OCH_2), 4.34 (1 H, dt, *J* 5.8, 8.3, NHC*H*), 4.99 (1 H, X part of ABX, C*H*CH_2Ph), 5.71 (1 H, d, *J* 7.8, N*H*CH), 6.53 (1 H, s, NH), 7.09 (2 H, m, ArH) and 7.18–7.33 (8 H, m, ArH); δ_C 14.0, 22.1, 22.8, 23.1, 24.6, 34.1, 39.1, 40.6, 41.9, 51.2, 53.4, 59.5, 61.8, 126.8, 127.9, 128.4, 128.9, 129.1, 130.2, 133.0, 136.8, 168.0, 170.3, 171.8, 173.1 and 176.0.

A second minor fraction (tentatively assigned as the leucine epimer of **24**) was obtained (1.6 mg, 6%) [HRMS: found (FAB) MH^+, 536.2761. $C_{30}H_{38}N_3O_6$ requires 536.2761]; $[\alpha]_D^{20}$ −13 (*c* 0.13, dichloromethane); δ_H 0.86 (3 H, d, *J* 5.8, CHCH_3), 0.88 (3 H, d, *J* 5.8, CHCH_3), 1.21 (3 H, t, *J* 7.1, CH_2CH_3), 1.30–1.65 (3 H, m, CH_2C*H*Me_2), 2.03 (3 H, s, CH_3CO), 2.60 and 2.92 (2 H, ABq, *J* 13.9, C3′-CH_2Ph), 2.81 and 2.96 (2 H, ABq, *J* 18.1, CH_2CO), 3.25 (1 H, A part of ABX, J_{AB} 14.4, J_{AX} 9.5, CHCH_2Ph), 3.54 (1 H, B part of ABX, J_{AB} 14.4, J_{BX} 6.6, CHCH_2Ph), 4.18 (2 H, m, OCH_2), 4.35 (1 H, m, NHC*H*), 5.20 (1 H, X part of ABX, C*H*CH_2Ph), 5.69 (1 H, d, *J* 7.8, N*H*CH), 6.79 (1 H, s, NH) and 7.10–7.34 (10 H, m, ArH).

(2*S*,3′*R*)-(−)-Ethyl 2-(3′-benzyl-3′-benzyloxycarbonylamino-succinimido)-3-phenylpropanoate 6

A solution of **22** (25 mg, 0.04 mmol) in dichloromethane (0.55 cm^3) was treated with triethylamine (0.06 cm^3, 0.43 mmol) for 3 h at room temp. under N_2. The reaction mixture was then diluted with dichloromethane (15 cm^3) and washed with 5% aq. HCl (20 cm^3) and water (20 cm^3). The organic phase was dried ($MgSO_4$), the solvent was evaporated under reduced pressure and the residue was purified by preparative silica TLC eluting with ethyl acetate–light petroleum (1:2) to give **6** (15 mg, 73%) [HRMS: found (EI) M^+, 514.2105. $C_{30}H_{30}N_2O_6$ requires 514.2104]; $[\alpha]_D^{20}$ −46 (*c* 1.2, dichloromethane); ν_{max}(KBr)/cm^{-1} 3358, 3032, 2930, 1786 and 1715; δ_H 1.21 (3 H, t, *J* 7.3, CH_3), 2.80 and 2.91 (2 H, ABq, *J* 13.8, C3′-CH_2Ph), 2.89 and 3.06 (2 H, ABq, *J* 18.3, CH_2CO), 3.26 (1 H, dd, *J* 10.2, 14.6, CHCH_2Ph), 3.53 (1 H, dd, *J* 6.3, 14.6, CHCH_2Ph), 4.18 (2 H, m, OCH_2CH_3), 5.04 (3 H, m, 3 H, CH and OCH_2Ph), 7.02 (2 H, m, ArH) and 7.15–7.39 (13 H, m, ArH); δ_C 14.0, 33.9, 39.4, 42.0, 53.4, 59.7, 62.0, 67.2, 126.9, 127.9, 128.3, 128.4, 128.5, 128.6, 128.9, 129.1, 130.2, 133.3, 135.8, 136.6, 154.7, 168.1, 173.2 and 176.6.

X-Ray crystallographic determination for compounds 16 and 19

General. Intensity data were collected on a Siemens Four-circle diffractometer, graphite monochromatised Mo-Kα radiation (λ 0.7107 Å) being used. The structures were solved by direct methods with the SHELXS86.[25] Hydrogen atoms were fixed in idealised positions. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton.[26] 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 207/107.

Data for compound 16. $C_{25}H_{21}NO_5$, M = 415.43, crystal dimensions 0.60 × 0.28 × 0.22 mm, orthorhombic, a = 6.8350(10), b = 16.178(2), c = 19.308(2) Å, α = 90, β = 90, γ = 90°, V = 2135.0(5) $Å^3$, space group $P2_12_12_1$, Z = 4, F(000) = 872, D_c = 1.292 Mg m^{-3}, absorption coefficient = 0.090 mm^{-1}, θ range for data collection = 2.11–24.96, index ranges = $0 \le h \le 7$, $0 \le k \le 19$, $0 \le l \le 20$, data/restraints/parameters = 1668/0/281, goodness-of-fit on F^2 = 1.084, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0427, wR_2 = 0.0904, R indices (all data): R_1 = 0.0688, wR_2 = 0.1036, largest difference peak and hole = 0.225 and −0.197 e $Å^{-3}$. The unit cell parameters were obtained by least-squares refinement of the setting angles of 32 reflections with $2 \le 2\theta \le 22.5°$. A unique data set was measured at 130(2) K within $2\theta_{max}$ = 57° limit (ω scans). Of the 1724 reflections obtained, 1668 were unique (R_{int} = 0.0361) and were used in the full-matrix least-squares refinement.[27] The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed 0% decay.

Data for compound 19. $C_{20}H_{19}NO_5$, M = 353.36, crystal dimensions 0.74 × 0.62 × 0.46 mm, orthorhombic, a = 7.3920(10), b = 15.1810(10), c = 15.7410(10) Å, α = 90, β = 90 γ = 90°, V = 1766.4(3) $Å^3$, space group $P2_12_12_1$, Z = 4, F(000) 744, D_c = 1.329 Mg m^{-3}, absorption coefficient = 0.096 mm^{-1}, θ range for data collection = 2.59 to 30.00, index ranges = $-10 \le h \le 3$, $0 \le k \le 21$, $0 \le l \le 22$, data/restraints/parameters = 3932/0/237, goodness-of-fit on F^2 = 0.890, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0352, wR_2 = 0.0710, R indices (all data): R_1 = 0.0517, wR_2 = 0.0846, largest difference peak and hole = 0.166 and −0.184 e $Å^{-3}$. The unit cell parameters were obtained by least-squares refinement of the setting angles of 42 reflections with $9.563 \le 2\theta \le 25.020°$. A unique data set was measured at 168(2) K within $2\theta_{max}$ = 57° limit (ω scans). Of the 4058 reflections obtained, 3933 were unique (R_{int} = 0.0222) and were used in the full-matrix least-squares refinement.[27] The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed 6.18% decay for which the data were scaled accordingly.

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