Self-addition products from the alkylation of amino acid-derived oxazolidinones: X-ray molecular structures of (2*R*,4*S*,1′*S*)-3-benzoyl-4-[benzoylamino(phenyl)methyl]-4-benzyl-2-phenyl-1,3-oxazolidin-5-one, (2*R*,4*S*,1′*S*)- and (2*R*,4*S*,1′*R*)-3-benzoyl-4-[benzoylamino(phenyl)methyl]-4-isopropyl-2-phenyl-1,3-oxazolidin-5-one

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The alkylation of (2*R*,4*S*)-3-benzoyl-4-benzyl-2-phenyloxazolidin-5-one 7 with diphenylmethyl bromoacetate proceeded with high diastereoselectivity, and the resulting product was hydrolysed to give [(2′*R*,4′*S*)-3′-benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl]acetic acid 9. The self-addition by-product (2*R*,4*S*,1′*S*)-3-benzoyl-4-[benzoylamino(phenyl)methyl]-4-benzyl-2-phenyl-1,3-oxazolidin-5-one 11 was also isolated. The structures of compound of 11 and the related self-addition products (2*R*,4*S*,1′*S* and 1′*R*)-3-benzoyl-4-[benzoylamino(phenyl)methyl]-4-isopropyl-2-phenyl-1,3-oxazolidin-5-one 20 and 21 were determined by X-ray crystallography. The mechanism of formation of the self-addition products is discussed.

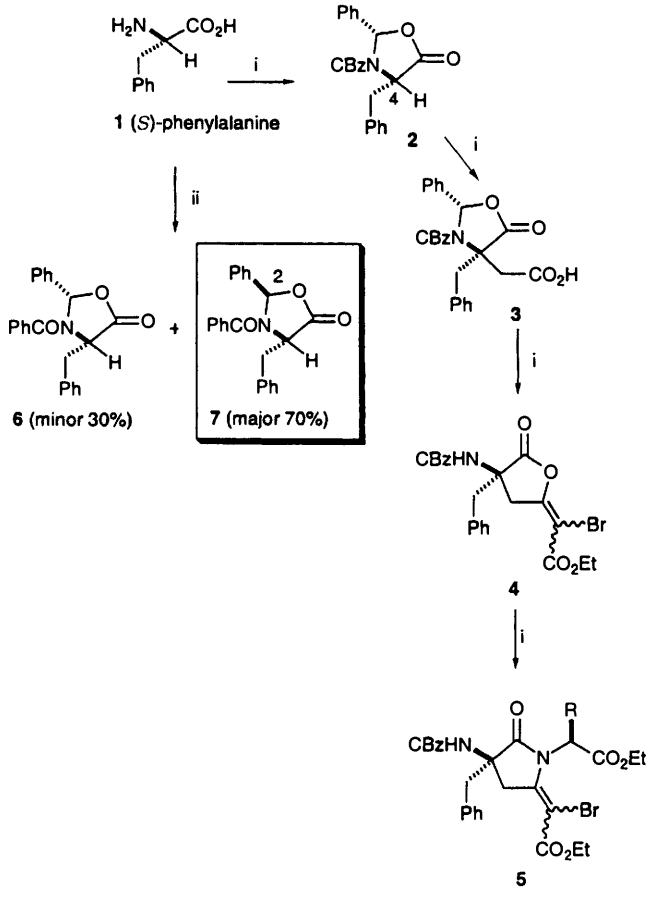
Introduction

Deprotonation at 4-H of an amino acid-derived oxazolidinone of the type **2** yields an enolate which can be alkylated, at C-4, by a range of electrophiles, with a very high degree of diastereoselectivity.[1-3] Subsequent hydrolysis of the oxazolidinone ring provides a convenient synthesis of α,α-dialkylated amino acids.[1-3] The overall sequence occurs by a process referred to as a self-reproduction of chirality, *i.e.* the initial amino acid stereocentre controls the relative stereochemistry of the alkylation and hence the absolute configuration of the final product.[1-3] Some additional diastereoselectivity has also been observed in reactions of related enolates with an electrophile where a second stereocentre is produced, such as in aldol reactions.[2-5]

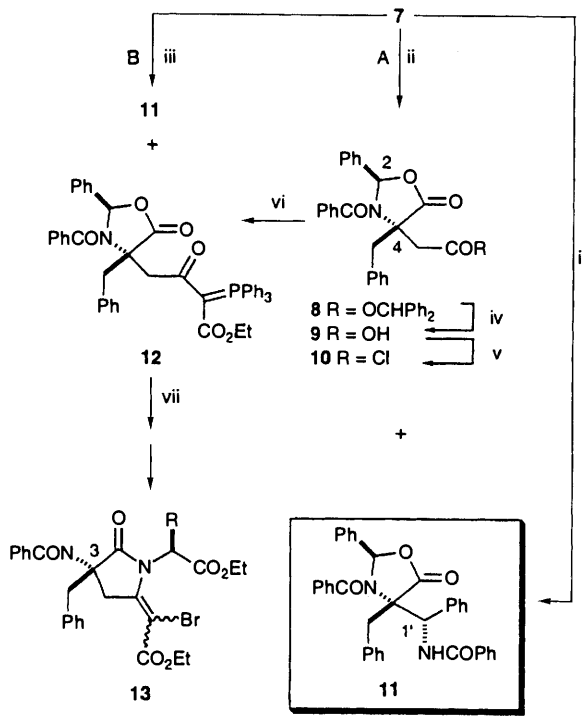
In previous work,[6] we reported a synthesis of compound **5**, a potential mechanism-based inhibitor of serine proteases, based on this methodology. Alkylation of the enolate derived from the *syn*-*N*-benzyloxycarbonyl (CBz)-substituted oxazolidinone **2**, with benzhydryl bromoacetate, followed by hydrolysis of the benzhydryl ester, gave the acid **3** (Scheme 1). A halolactonisation sequence then gave compounds of type **4**, precursors to compounds **5**. Here, we report the alkylation of an enolate, derived from the *anti*-*N*-benzoyloxazolidinone **7**, with benzhydryl bromoacetate (Scheme 2, pathway A) to give the product of self-addition, compound **11**, in addition to the expected adduct, compound **8**. The oxazolidinone **7** also gave rise to compound **11** on treatment with lithium hexamethyldisilazide (LiHMDS) in the absence of an alkylating agent. Compound **20**, and its 1′-epimer **21**, were obtained from a similar reaction of the oxazolidinone **19**. The structure and configuration of compounds **11**, **20** and **21** were confirmed by single-crystal X-ray structure analyses. This work is part of ongoing studies on the preparation of diesters **13**, compounds which have an alternative N-protecting group and an opposite C-3 configuration as compared with analogues **5**.

Results and discussion

(*S*)-Phenylalanine **1** was converted into the oxazolidinones **6** and **7** (3:7 by ^{1}H NMR spectroscopy) by using the general method of Seebach and Fadel.[1] The desired *anti*-oxazolidinone **7**[7] was obtained in 25% yield from the crude mixture by crystallisation from dichloromethane and light petroleum. The assignment of an *anti*-configuration[7] to the major isomer **7** was supported by the observation of a nuclear Overhauser enhancement (NOE) between 2-H and CH_2Ph.



Scheme 1 *Reagents and conditions:* i, ref. 6; ii, ref. 7



Scheme 2 *Reagents and conditions:* i, LiHMDS, THF, −78 to 20 °C; ii, LiHMDS, THF, −78 °C, 30 min; then $BrCH_2CO_2CHPh_2$; iii, LiHMDS, THF, −78 °C, 10 min; then $BrCH_2COC(PPh_3)CO_2Et$; iv, TFA, CH_2Cl_2, 0 °C; v, $(COCl)_2$, DMF, CH_2Cl_2; vi, Ph_3PCHCO_2Et (2 mol equiv.), CH_2Cl_2; vii, for a related sequence see ref. 6

Compound **7** was dissolved in tetrahydrofuran (THF), at −78 °C, and the solution was treated with LiHMDS. After stirring of the mixture for 30 min at −78 °C, 1.1 mol equiv. of benzhydryl bromoacetate was added and the mixture was stirred at −78 °C for a further 2 h and then was warmed to 20 °C over a period of 16 h. A ^{1}H NMR spectrum of the crude product, which was not purified further, indicated a mixture of compounds **8** and **11** in the ratio 6:1. Treatment of the crude mixture with trifluoroacetic acid (TFA), followed by extraction with base and recrystallisation, gave the desired compound **9** in 44% yield. Compound **11** was not purified from the reaction mixture. An observed NOE between 2-H and $CH_2CO_2CHPh_2$ of compound **9** was consistent with the assigned configurations at C-2 and C-4. The absolute configuration follows from the configuration of the starting (*S*)-phenylalanine and the fact that the alkylation of an enolate of this type [1–3] is known to occur from the opposite face of the C-2 phenyl group.

The formation of compound **11** was suppressed in a second alkylation of compound **7** by using a reduced reaction time of 5 min, rather than 30 min, prior to the addition of a large excess (1.5 mol equiv.) of benzhydryl bromoacetate. In a third experiment, a THF solution of compound **7**, at −78 °C, was treated with LiHMDS and the solution was stirred at −78 °C for 2 h and was then allowed to warm to 20 °C over a period of 16 h. Compound **11** was isolated from this experiment in 62% yield and its structure and configuration were determined by a single-crystal X-ray analysis, Fig. 1. A ^{1}H NMR spectrum of the crude mixture from this reaction revealed ~5% of a second diastereoisomer of compound **11**. This compound, which was not purified, was tentatively assigned as the C-1′ epimer of compound **11** based on the downfield position of the 2-H resonance (δ 4.92) compared with **11** (δ 4.72) (see later for a discussion).

The reaction of compound **7** with LiHMDS at −78 °C for 40 min followed by the addition of ethyl bromoacetate (1.1 mol equiv.) gave compounds **14** and **11** (in the ratio 1:3 by ^{1}H NMR spectroscopy). Compounds **14** and **11** were subsequently

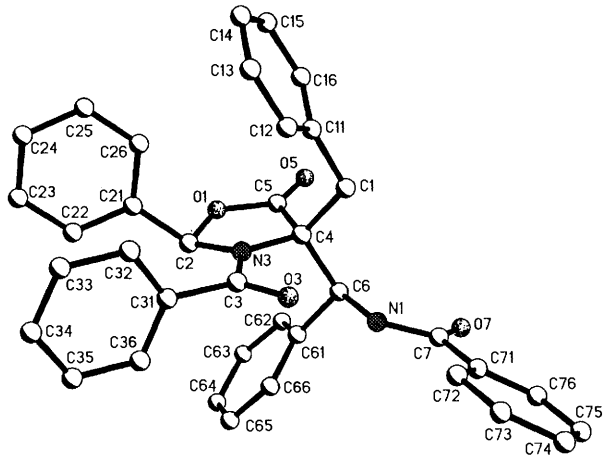
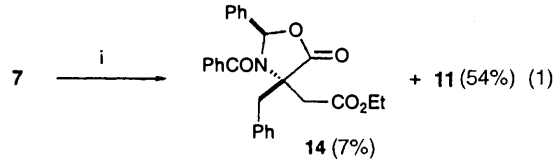


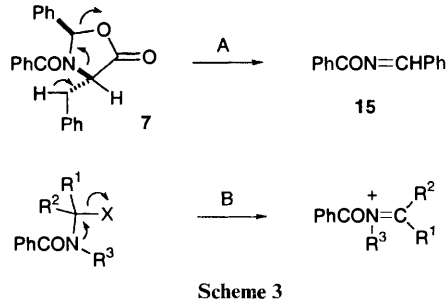
Fig. 1 X-Ray molecular structure of compound **11** with crystallographic numbering scheme



Reagents and conditions: i, LiHMDS, THF, −78 °C, 40 min; then $BrCH_2CO_2Et$ (1.1 mol equiv.)

isolated in 7 and 54% yield, respectively [equation (1)]. A related preliminary literature report on the reaction of the enolate of compound **7**, and related oxazolidinones,[7] with 1.6 mol equiv. of ethyl bromoacetate does not mention the formation of self-addition products of the type **11**. The alkylation of the LiHMDS-derived enolate of **7** with 1 mol equiv. of $BrCH_2COC(PPh_3)CO_2Et$ (pathway B, Scheme 2) gave a 1:1 mixture (by ^{1}H NMR spectroscopy) of phosphorane **12** and the self-addition product **11**. This mixture was not purified further; however, a sample of compound **12**, synthesized from the carboxylic acid **9** as shown in Scheme 2, was fully characterised. From these studies on the alkylation of oxazolidinones, it is clear that the use of a short reaction time (typically 7 min) between the addition of the base and electrophile (at least 1.5 mol equiv.) minimises the formation of self-addition by-products.

A possible mechanism for the formation of compound **11** would involve base-catalysed fragmentation of precursor **7** to give an *N*-acylimine of the type **15** which would then react with the oxazolidinone enolate at C-4 (see Scheme 3 and Fig. 2).



Scheme 3

However, it should be noted that cinnamic acid, the expected by-product from the fragmentation of compound **7**, could not be isolated from the crude product mixture. The proposed fragmentation is, nevertheless, analogous to the heterolytic cleavage of α-substituted amides to give *N*-acyliminium ions; see reaction B in Scheme 3.[8] The synthetic scope and mechanistic details of this reaction are under further study. Sketchy reports on the formation of other self-addition by-

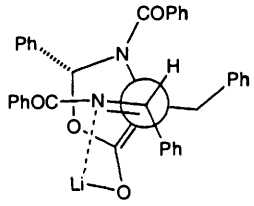


Fig. 2 Transition state for the formation of compound **11** *si,re* (relative topicity *ul*), *ul*-1,3-induction

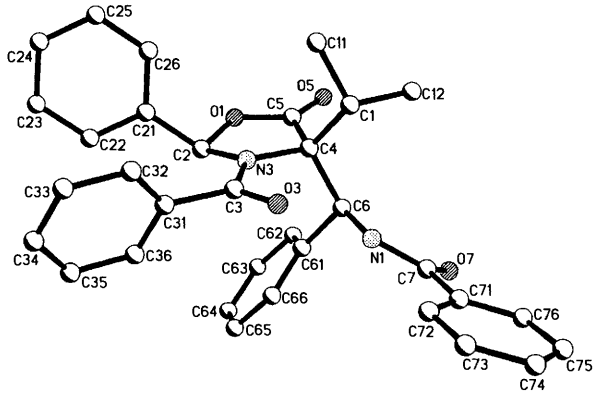
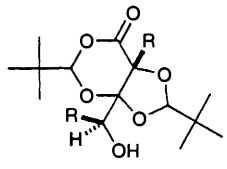


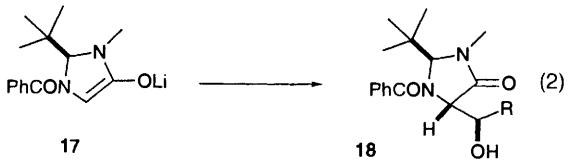
Fig. 3 X-Ray molecular structure of compound **20** with crystallographic numbering scheme

products in alkylation reactions of 1,3-oxazolidinones[9] and related 1,3-oxazolanones[5] have appeared in the literature. For example, compounds **16** have been isolated from the alkylation of phenylalanine- and alanine-derived 2-(*tert*-butyl)-1,3-dioxolanones.[5]



16a R = Me
16b R = CH_2Ph

The reaction of the oxazolidinone **7** with acylimine **15**, to give compound **11**, occurs from the side opposite to the C-2 phenyl group with *ul*-1,3-induction. A proposed transition state for this process is shown in Fig. 2 and is based on that reported for the related addition of an imidazolidinone enolate **17** to an aldehyde **18** [equation (2)].[4] The depicted staggered approach allows O–Li · · · N chelation and also maximum overlap of the synclinal double bonds of the donor and acceptor. The $PhCH_2$ group of the enolate is also antiperiplanar to the acceptor double bond.[4,10] The relative topicity for the coupling of the trigonal centres, to give compound **11** in > 90% diastereoselectivity (ds), is *ul*. This observation contrasts with literature reports [*e.g.*, equation (2)][4] on the addition of aldehydes to enolates of



Reagent: RCHO

imidazolidinones,[4] dioxolanones[5] and oxazolidinones[4] where a ds of 55–95%, in favour of an *lk* approach, is reported. The relative configuration of compound **11** is, however, consistent with the observed products from the addition of lithium enolates of cyclic ketones to aldehydes.[4,11]

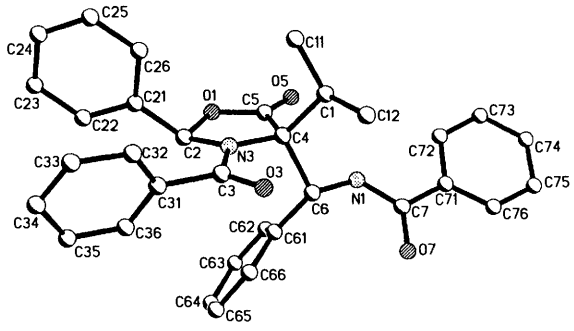
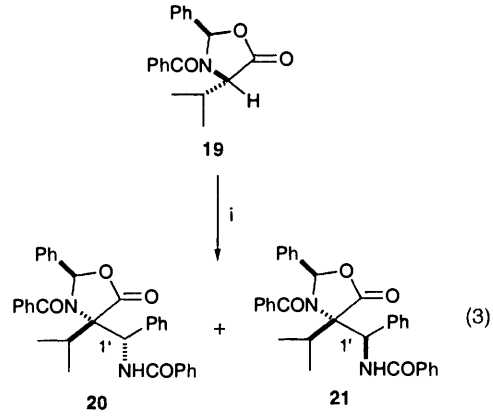


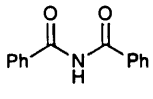
Fig. 4 X-Ray molecular structure of compound **21** with crystallographic numbering scheme

The valine-derived *anti*-*N*-benzoyloxazolidinone **19** was also treated with LiHMDS at −78 °C for 1 h, followed by warming to 18 °C over a period of 16 h, to ascertain the influence of a different amino acid on the reaction outcome. Purification of the crude product by chromatography gave starting material (42% recovery), compound **20** (analogous to compound **11**) (8%) and a third fraction containing a mixture of *N*,*N*-dibenzimide **22**[12] and the 1′-epimer of compound **20**, **21** (1 : 1 by ^1H NMR spectroscopy) [see equation (3)]. A ^1H NMR



Reagents and conditions: i, LiHMDS, THF, −78 to 18 °C

spectrum of the crude product revealed that epimers **20** and **21** were present in the ratio 1 : 1. The structure and configuration of epimers **20** and **21** were confirmed by X-ray crystallography, Figs. 3 and 4. The chemical shift of the 2-H resonances of epimers **20** (δ 4.78) and **21** (δ 5.32) was similar to that observed for corresponding resonances of compound **11** and its C-1′ epimer, respectively. This observation was used to assign the configuration of the minor C-1′ epimer of compound **11** (see earlier). The chemical shift of 2-H provides a means of assigning the configuration of C-1′ within a series of closely related compounds of this type.[5]



22

The valine-based oxazolidinone **19** gave a lower yield and a decrease in ds for the formation of the self-condensation products **20** and **21**, relative to reaction of the phenylalanine-based example, **7**, to give compound **11**. The lower yield may reflect a decrease in the ability of compound **19**, relative to analogue **7**, to form the electrophilic species, *e.g.* the *N*-acylimine **15**, although it has also been noted that LiHMDS is not the optimum base for the deprotonation of valine-based oxazolidinones.[7] Replacement of the CH_2Ph group of

compound **7** with the $CHMe_2$ group of compound **19**, in the transition state shown in Fig. 2, would appear to remove the preference for reaction of the enolate with the *re* face of *N*-acylimine **15**. Treatment of the phenylalanine-derived *syn*-*N*-CBz-oxazolidinone **2** with LiHMDS from −78 to 18 °C did not give rise to self-addition products. Further work is clearly required to enable us fully to elucidate those factors that influence the ease and the ds of self-addition reactions of this type.

Comparison of the X-ray molecular structures of compounds 11, 20 and 21

Perspective drawings of compounds **11**, **20** and **21**, with atom labelling, are presented in Figs. 1, 3 and 4. The C-2 *tert*-butyl analogues of oxazolidinones of types **2** and **7** have been shown[13,14] to have a slight envelope conformation for the oxazolidinone ring, with C-2 out of the plane of the other four atoms of the ring. These reports also reveal pyramidalisation of the amide N-atom and that the *N*-acyl carbonyl O-atom and the acetal substituent are in an s-*cis*-conformation.[13] The pyramidalization is thought to contribute to the steric bias of the oxazolidinone ring towards an incoming electrophile in Seebach alkylations of the type shown in Scheme 2.[13] The structures reported in the current study are of the products of C-4 alkylation and have an essentially planar oxazolidinone ring, little or no pyramidalisation of the amide N-atom, and do not have the *N*-acyl carbonyl O-atom in an s-*cis*-position relative to the acetal (C-2) substituent (see Figs. 1, 3 and 4). The three structures adopt very similar conformations, especially with regard to the C^{21-26}, C^{31-36} and C^{61-66} aromatic rings. This arrangement places the N-1 substituent of compound **21** [which has the opposite configuration at C-6 (crystallographic numbering) relative to compounds **11** and **20**] into an alternative conformation relative to that observed for compounds **11** and **20**.

In conclusion, it is clear that an enolate derived from the *N*-benzoyloxazolidinones **7**, and to a lesser extent compound **19**, undergoes a self-addition reaction to produce compounds **11** and **20/21**, respectively. The formation of these products can be suppressed in alkylations by employing a short reaction time between the addition of base and at least 1.5 mol equiv. of the electrophile. In some cases,[15] a reverse addition of the oxazolidinone to the base may prove beneficial in minimising self-addition reactions.

Experimental

General

Mps were obtained using a Hot Stage Microscope and are uncorrected. NMR spectra were obtained using a Varian CFT300 spectrometer for samples in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C. IR 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} deg cm^2 g^{-1}. Preparative chromatography was carried out using a Chromatotron (Harrison Research Inc.) with glass plates coated with silica gel (P.F. 254 60). LiHMDS was obtained as a 1.0 mol dm^{-3} solution in THF from the Aldrich® chemical company. Light petroleum refers to the fraction distilled in the range 60–70 °C.

[(2′*R*,4′*S*)-(+)-3′-Benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl]acetic acid 9

The oxazolidinone **7**[7] (2.00 g, 5.6 mmol, 1 mol equiv.) was dissolved in THF (200 cm^3) and the solution was cooled to −78 °C. LiHMDS (6.8 cm^3 of a 1 mol dm^{-3} solution in THF, 6.8 mmol, 1.2 mol equiv.) was added and the resulting yellow solution was stirred at −78 °C for 30 min. Benzhydryl bromoacetate (1.88 g, 6.2 mmol, 1.1 mol equiv.) was added and the solution was stirred at −78 °C for 2 h and was then allowed to warm to 20 °C over a period of 16 h. The THF was removed under reduced pressure and the residue was partitioned between saturated aq. NH_4Cl (150 cm^3) and diethyl ether (100 cm^3). The aqueous layer was separated, and extracted with diethyl ether (100 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4), and evaporated to give a yellow solid (1.60 g), used subsequently without further purification, which contained, by ^1H NMR spectroscopy, compounds **8** and **11** in the ratio 6:1; δ_H(**8**, from the mixture) 3.34 and 4.16 (2 H, ABq, *J* 17.6, $CH_2CO_2CHPh_2$), 3.41 and 4.02, (2 H, ABq, *J* 13.3, CH_2Ph), 5.42 (2 H, d, *J* 7.5, ArH), 6.13 (1 H, s, 2-H), 6.42 (2 H, m, ArH), 6.63 (2 H, t, *J* 7.8, ArH), 6.90 (3 H, m, ArH), 6.92 (1 H, s, $CHPh_2$) and 7.10–7.61 (16 H, m, ArH).

A repeat of this reaction using a reaction time of 5 min prior to the addition of benzhydryl bromoacetate (1.5 mol equiv.) gave a crude product which did not contain **11** by ^1H NMR spectroscopy.

The preceding mixture (1.60 g) was dissolved in dichloromethane (70 cm^3) and the solution was cooled to 0 °C. TFA (35 cm^3) was added and, after being stirred at 0 °C for 5 min, the solution was diluted with more dichloromethane (130 cm^3), washed with water (3 × 150 cm^3), and extracted with 5% aq. $NaHCO_3$ (2 × 100 cm^3). The $NaHCO_3$ extracts were combined, cooled to 0 °C, acidified to pH 1–3 (universal indicator paper) with 1 mol dm^{-3} HCl, and extracted with ethyl acetate (3 × 200 cm^3). The combined ethyl acetate extracts were dried (Na_2SO_4) and the solvent was evaporated off to give the *acid* **9** as a solid, which was recrystallised from dichloromethane–light petroleum (0.50 g, 44%), mp 207.5–211 °C (Found: C, 71.8; H, 5.4; N, 3.4. $C_{25}H_{21}NO_5$ requires C, 72.2; H, 5.1; N, 3.4%); $[\alpha]_D^{20}$ +64 (*c* 0.9, dichloromethane); ν_{max}(KBr)/cm^{-1} 1797, 1725, 1611 and 1595; δ_H 3.26 and 4.14 (2 H, ABq, *J* 18.0, CH_2CO_2H), 3.42 and 4.04 (2 H, ABq, *J* 13.4, CH_2Ph), 5.54 (2 H, d, *J* 7.2, ArH), 6.45 (**1** H, s, 2-H), 6.67 (2 H, t, *J* 7.8, ArH), 6.82 (2 H, m, ArH), 6.96 (1 H, m, ArH), 7.06 (2 H, t, *J* 7.5, ArH), 7.17 (1 H, m, ArH) and 7.42 (5 H, m, ArH); δ_C 38.7, 42.3, 66.1, 91.7, 125.3, 127.8, 127.9, 128.0, 128.3, 129.3, 130.9, 134.3, 135.0, 136.1, 170.3, 172.9 and 173.6.

(2*R*,4*S*,1′*S*)-3-Benzoyl-4-[benzoylamino(phenyl)methyl]-4-benzyl-2-phenyl-1,3-oxazolidin-5-one 11

LiHMDS (0.55 cm^3 of a 1 mol dm^{-3} solution in THF, 0.55 mmol, 1.1 mol equiv.) was added to a solution of the oxazolidinone **7** (180 mg, 0.50 mmol) in THF (15 cm^3) at −78 °C. The resulting yellow solution was stirred at −78 °C for 2 h and then at 20 °C for 16 h. The solution was poured onto cold, saturated aq. NH_4Cl (15 cm^3) and extracted with diethyl ether (2 × 15 cm^3). The combined extracts were washed with water (15 cm^3), dried ($MgSO_4$), and evaporated. A ^1H NMR spectrum of the crude product revealed that compound **11** and its C-1′ epimer were present in the ratio ~95:5. Purification by radial chromatography using a 1 mm silica gel chromatotron plate, and development with a gradient of (1–20%) ethyl acetate in dichloromethane gave *compound* **11** as a yellow oil, which crystallised from ethyl acetate–light petroleum (89 mg, 62%), mp 237–238 °C (Found: C, 78.5; H, 5.7; N, 4.9. $C_{37}H_{30}N_2O_4$ requires C, 78.4; H, 5.3; N, 4.9%); ν_{max}(film)/cm^{-1} 3350, 1791 and 1667; δ_H 3.61 and 4.46 (2 H, ABq, *J* 13.9, CH_2Ph), 4.72 (1 H, s, 2-H), 5.26 (2 H, dd, *J* 1.3 and 8.5, ArH), 6.22 (1 H, d, *J* 8.8, $CHPhNH$), 6.55 (2 H, t, *J* 7.8, ArH), 6.67 (2 H, m, ArH), 6.86 (1 H, m, ArH), 6.98 (2 H, t, *J* 7.6, ArH), 7.08 (1 H, m, ArH), 7.42–7.63 (13 H, m, ArH), 8.08 (2 H, m, ArH) and 9.52 (1 H, d, *J* 8.8, NH); δ_C 30.1, 60.8, 74.6, 90.7, 124.7, 127.5, 127.5, 127.7, 127.9, 128.3, 128.7, 129.0, 129.2, 129.3, 129.4, 131.1, 131.8, 133.6, 133.8, 135.1, 135.7, 137.6, 166.2, 171.5 and 172.6.

Minor C-1′ epimer (in part from the crude mixture) δ_H (*inter alia*) 3.90 and 4.41 (2 H, ABq, *J* 13.6, CH_2Ph), 4.92 (1 H, s, 2-H) and 5.31 (2 H, dd, *J* 1.3 and 7.2, ArH).

Ethyl (2′*R*,4′*S*)-(+)-4-(3′-benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl)-3-oxo-2-(triphenylphosphoranylidene)butanoate 12

Method A. The acid **9** (66 mg, 0.16 mmol) was dissolved in dichloromethane (6 cm^3) and the solution was cooled to 0 °C. Freshly distilled oxalyl dichloride (0.69 mm^3, 0.79 mmol) and a catalytic quantity of dimethylformamide (DMF) were added. The mixture was stirred at 0 °C for 2 h and at 20 °C for 16 h. The solvent was evaporated off and more dichloromethane (2 cm^3) was added and evaporated off (repeated 3 times). Final traces of oxalyl dichloride were removed at 1 mmHg to yield acid chloride **10** as a solid (69 mg, quant), which was used in subsequent steps without further purification; δ_H 3.38 and 3.98 (2 H, ABq, *J* 13.4, CH_2Ph), 3.76 and 4.65 (2 H, ABq, *J* 19.1, CH_2COCl), 5.54 (2 H, dd, *J* 1.1 and 8.4, ArH), 6.39 (1 H, s, 2-H), 6.69 (2 H, m, ArH), 6.80 (2 H, m, ArH), 6.98 (1 H, m, ArH), 7.09 (2 H, m, ArH), 7.20 (1 H, m, ArH) and 7.36–7.47 (5 H, m, ArH).

The acid chloride **10** (69 mg, 0.16 mmol) was dissolved in dichloromethane (5 cm^3) and the solution was cooled to 0 °C. [(Ethoxycarbonyl)methylene]triphenylphosphorane [ethyl(triphenylphosphoranylidene)acetate] (111 mg, 0.32 mmol, 2 mol equiv.) was added and the solution was stirred at 0 °C for 1.5 h and at 20 °C for 4.5 h. The solvent was evaporated off under reduced pressure and the residue was purified by radial chromatography on a 1 mm silica gel chromatotron plate, with dichloromethane–ethyl acetate (94:6) as developer to give *compound* **12** (122 mg, quant), mp 187–188.5 °C (from ethyl acetate–light petroleum) (Found: C, 75.6; H, 5.5; N, 1.8. $C_{47}H_{40}NO_6P$ requires C, 75.7; H, 5.4; N, 1.9%); $[\alpha]_D^{20}$ +67 (*c* 20, dichloromethane); ν_{max}(KBr)/cm^{-1} 1787, 1668, 1652 and 1554; δ_H 0.72 (3 H, t, *J* 7.1, CH_3), 3.41 and 4.12 (2 H, ABq, *J* 13.5, CH_2Ph), 3.77 (2 H, m, OCH_2), 4.05 and 4.59 (2 H, ABq, *J* 18.5, CH_2CO), 5.33 (2 H, d, *J* 7.5, ArH), 6.06 (1 H, s, 2-H), 6.38 (2 H, d, *J* 7.5, ArH), 6.55 (2 H, t, *J* 7.7, ArH), 6.85 (3 H, t, *J* 7.7, ArH), 7.05 (1 H, t, *J* 7.5, ArH) and 7.32–7.74 (20 H, m, ArH); δ_P 18.3; δ_C 13.7, 42.9, 45.9 (d, *J* 7.1), 58.5, 66.7, 70.8 (d, *J* 110.6), 90.7, 125.4, 126.3 (d, *J* 93.2), 127.2. 127.7, 128.0, 128.2, 128.5 (d, *J* 12.6), 128.7, 128.8, 131.0, 131.7 (d, *J* 2.9), 133.4 (d, *J* 10.0), 135.1, 136.4, 137.2, 167.4 (d, *J* 14.4), 169.0, 174.5 and 192.9 (d, *J* 4.6).

Method B. The oxazolidinone **7** (30 mg, 0.08 mmol) was dissolved in THF (10 cm^3) and the solution was cooled to −78 °C. LiHMDS (0.09 cm^3, 0.09 mmol, 1.1 mol equiv.) was added and the resulting yellow solution was stirred at −78 °C for 10 min. $BrCH_2COC(PPh_3)CO_2Et$ (39 mg, 0.08 mmol) was added and the solution was stirred at −78 °C for 2 h and was then allowed to warm to 20 °C over a period of 16 h. The THF was evaporated off and the residue was partitioned between saturated aq. NH_4Cl (10 cm^3) and dichloromethane (10 cm^3). The aqueous layer was separated, and extracted with dichloromethane (2 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give a residue (59 mg) containing, by ^{1}H NMR spectroscopy, compounds **12** and **11** in the ratio 1:1. The reaction mixture was not purified further.

Ethyl [(2′*R*,4′*S*)-3′-benzoyl-4′-benzyl-5′-oxo-2′-phenyloxazolidin-4′-yl]acetate 14

The oxazolidinone **7**[7] (350 mg, 1.0 mmol, 1 mol equiv.) was dissolved in THF (50 cm^3) and the solution was cooled to −78 °C. LiHMDS (2.35 cm^3 of a 1 mol dm^{-3} solution in THF, 2.4 mol equiv.) was added and the resulting yellow solution was stirred −78 °C for 40 min. Ethyl bromoacetate (328 mg, 1.1 mmol, 1.1 mol equiv.) was added and the solution was stirred at −78 °C for 2 h and was then allowed to warm to 20 °C over a period of 16 h. The THF was removed under reduced pressure and the residue was partitioned between saturated aq. NH_4Cl (50 cm^3) and diethyl ether (35 cm^3). The aqueous layer was separated, and extracted with diethyl ether (2 × 35 cm^3). The combined extracts were washed with water (2 × 15 cm^3), dried ($MgSO_4$), and evaporated to give a yellow solid (329 mg), which contained, by ^{1}H NMR spectroscopy, compounds **14** and **11** in the ratio 1:3. The residue was purified by radial chromatography with dichloromethane followed by dichloromethane–ethyl acetate (94:4) as developer to give compounds **14**[7] (30 mg, 7%) and **11** (152 mg, 54%).

(2*R*,4*S*,1′*S*)-3-Benzoyl-4-[benzoylamino(phenyl)methyl-4-isopropyl-2-phenyl-1,3-oxazolidin-5-one 20 and (2*R*,4*S*,1′*R*)-3-benzoyl-4-[benzoylamino(phenyl)methyl]-4-isopropyl-2-phenyl-1,3-oxazolidin-5-one 21

The oxazolidinone **19** (125 mg, 0.404 mmol, 1 mol equiv.) was dissolved in dry THF (15 cm^3) and the solution was cooled to −78 °C. LiHMDS (0.45 cm^3 of a 1.0 mol dm^{-3} solution in THF, 0.45 mmol, 1.1 mol equiv.) was added and the mixture was stirred at −78 °C under N_2 for 1 h and was then allowed to warm to 20 °C over a period of 18 h. The reaction mixture was washed with cold, saturated aq. NH_4Cl (15 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The organic fractions were combined, and washed with water (20 cm^3), dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a solid. Further purification by radial chromatography on a 1 mm silica plate and development with a solvent mixture of ethyl acetate–light petroleum (30:70) yielded the starting material oxazolidinone **19** (53 mg, 42% recovery) followed by compound **20** (8 mg, 8%), mp 277–279 °C (from ethyl acetate–pentane) [Found: (EI) M^+ + 1, 519.240 00. $C_{33}H_{31}N_2O_4$ requires *m*/*z*, 519.228 51]; δ_H 1.38 (3 H, d, *J* 6.8, CH_3), 1.45 (3 H, d, *J* 6.8, CH_3), 3.74 [1 H, hept, *J* 6.8, $CH(CH_3)_2$], 4.78 (1 H, s, 2-H), 6.18 [1 H, d, *J* 8.8, CH(Ph)NH], 6.72 (4 H, m, ArH), 6.93–7.17 (6 H, m, ArH), 7.43–7.60 (8 H, m, ArH), 8.01 (2 H, m, ArH) and 9.69 (1 H, d, *J* 8.8, NH). Further elution gave a fraction containing a mixture of *N*,*N*-dibenzamide **22** and compound **21** (15 mg of a 1:1 mixture by ^{1}H NMR spectroscopy) which was crystallised from ethyl acetate–pentane. Two separate crystals, selected from the mixture, were shown to be *N*,*N*-dibenzamide[12] and compound **21**, by X-ray crystallography. Compound **21**, mp 218 (softens)–232 °C; δ_H 1.33 (3 H, d, *J* 6.9, CH_3), 1.54 (3 H, d, *J* 6.9, CH_3), 3.11 [1 H, hept, *J* 6.9, $CH(CH_3)_2$], 5.32 (1 H, s, 2-H), 6.42 (2 H, d, *J* 6.8, ArH), 6.60 [1 H, d, *J* 8.8, CH(Ph)NH], 6.85 (2 H, d, *J* 7.8, ArH), 6.94 (2 H, t, *J* 7.8, ArH), 7.01–7.16 (4 H, m, ArH), 7.45–7.54 (6 H, m, ArH), 7.61 (2 H, m, ArH), 7.90 (2 H, d, *J* 6.8, ArH) and 8.16 (1 H, d, *J* 8.8, NH).

X-Ray crystallographic determination for compounds 11, 20 and 21

General. Intensity data were collected on a Siemens four-circle diffractometer, graphite-monochromatized Mo-Kα radiation (λ 0.7107 Å) being used. The structures were solved by direct methods with SHELXS-86.[16] Least-squares refinements on F^2 and all subsequent calculations were performed using the SHELXL-93 program system.[17] Tabulations of non-hydrogen-atom coordinates, bond lengths, bond angles, hydrogen-atom coordinates and anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC).†

Data for compound 11. $C_{37}H_{30}N_2O_4$, M = 566.63, crystal dimensions 0.30 × 0.65 × 0.17 mm, orthorhombic, a = 11.078(2), b = 12.609(3), c = 20.681(4) Å, α = 90, β = 90, γ = 90°, V = 2888.8(10) $Å^3$, space group $P2_12_12_1$, Z = 4, F(000) = 1192. Cell parameters were determined by least-squares refinement of accurately centred reflections in the range $5 < 2\theta < 12.5°$. Using 2.1° ω scans at a scan rate of 4.00° min^{-1}, 2590 unique reflections were collected in the range $4 < 2\theta < 50°$, and 2589 of these having $I > 3\sigma(I)$ were used in the structural analysis, R = 0.0294, R_w = 0.0548. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions. Data were corrected for Lorentz and polarisation effects but not for absorption.

† *Supplementary material:* see Instructions for Authors, in the January issue.

Data for compound 20. $C_{33}H_{30}N_2O_4$, $M = 518.59$, crystal dimensions $0.62 \times 0.28 \times 0.28$ mm, orthorhombic, $a = 11.718(5)$, $b = 13.008(2)$, $c = 18.063(5)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 2753.3(15)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $F(000) = 1096$. Cell parameters were determined by least-squares refinement of 11 accurately centred reflections in the range $9.6 < 2\theta < 20.7°$. Using 1.2° ω-scans at a scan rate of 5.00° min^{-1}, 2454 unique reflections were collected in the range $4 < 2\theta < 48°$ and 1259 of these having $I > 4\sigma(I)$ were used in the structural analysis, $R = 0.0383$, $R_w = 0.0721$. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions. Data were corrected for Lorentz and polarisation effects but not for absorption.

Data for compound 21. $C_{33}H_{30}N_2O_4$, $M = 518.59$, crystal dimensions $0.80 \times 0.15 \times 0.13$ mm, monoclinic, $a = 8.290(2)$, $b = 16.033(5)$, $c = 10.467(5)$ Å, $\alpha = 90$, $\beta = 104.65(3)$, $\gamma = 90°$, $V = 1346.0(10)$ Å^3, space group $P2_1$, $Z = 2$, $F(000) = 548$. Cell parameters were determined by least-squares refinement of 29 accurately centred reflections in the range $5.7 < 2\theta < 25.6°$. Using 1.8° ω-scans at a scan rate of 9.00° min^{-1}, 1834 unique reflections were collected in the range $4 < 2\theta < 45°$, and 1049 of these having $I > 4\sigma(I)$ were used in the structural analysis, $R = 0.0605$, $R_w = 0.1264$. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions. Data were corrected for Lorentz and polarisation effects but not for absorption.

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References

1 D. Seebach and A. Fadel, *Helv. Chim. Acta.*, 1985, **68**, 1243.
2 R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Organic Chemistry Series, ed. J. Baldwin and P. D. Magnus, Pergamon Press, Oxford, 1989, vol. 7.
3 D. Seebach, R. Imwinkelried and T. Weber, *Mod. Synth. Methods*, 1986, **4**, 128.
4 D. Seebach, E. Juaristi, D. D. Miller, C. Schicklin and T. Weber, *Helv. Chim. Acta.*, 1987, **70**, 237.
5 D. Seebach, R. Naef and G. Calderari, *Tetrahedron*, 1984, **40**, 1313.
6 A. D. Abell and J. M. Taylor, *J. Org. Chem.*, 1993, **58**, 14; A. D. Abell, M. D. Oldham and J. M. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1995, 953; *J. Org. Chem.*, 1995, **60**, 1214.
7 A. Fadel and J. Salaün, *Tetrahedron Lett.*, 1987, **28**, 2243.
8 W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367.
9 K. Nebel and M. Mutter, *Tetrahedron*, 1988, **44**, 4793.
10 D. Seebach and J. Golinski, *Helv. Chim. Acta*, 1981, **64**, 1413.
11 C. H. Heathcock, *Stereodifferentiating Addition Reactions* in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Orlando, Florida, 1984, vol. 3.
12 A. D. Abell and M. D. Oldham, unpublished work; V. Mizrahi and M. L. Niven, *S. Afr. J. Chem.*, 1983, **36**, 137.
13 D. Seebach, B. Lamatsch, R. Amstutz, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradón, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mouriño, E. Pfammatter, D. A. Plattner, C. Schickli, W. B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravitlles and E. Molins, *Helv. Chim. Acta*, 1992, **75**, 913.
14 A. C. Willis, A. L. J. Beckwith and M. J. Tozer, *Acta Crystallogr., Sect. C*, 1991, **47**, 2276.
15 T. M. Zydowsky, E. de Lara and S. G. Spanton, *J. Org. Chem.*, 1990, **55**, 5437.
16 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
17 G. M. Sheldrick, Program for Crystal Structure Solution, University of Göttingen, 1993.

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