Enantioselective synthesis of 2-substituted 3-aminopropanoic acid (β-alanine) derivatives which are β-analogues of aromatic amino acids

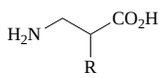
Elena Arvanitis, Holger Ernst, Alice A. Ludwig (*née* D'Souza), Andrew J. Robinson and Peter B. Wyatt *,†

Department of Chemistry, Queen Mary and Westfield College, University of London, Mile End Road, London, UK E1 4NS

3-Aminopropanoic acid derivatives with a phenyl, 4-hydroxyphenyl, benzyl or indol-3-yl substituent at C-2 can be prepared enantioselectively by routes involving electrophilic attack of synthetic equivalents of $[H_2NCH_2]^+$ upon enolates derived from chiral 3-acyl-1,3-oxazolidin-2-ones. *tert*-Butyl bromoacetate may be used as the electrophile, with subsequent introduction of nitrogen through the Curtius reaction, using the sequence of reagents (i) CF_3CO_2H; (ii) $(PhO)_2P(O)N_3$, Et_3N, $PhCH_2OH$; alternatively, direct electrophilic reaction with 1-[*N*-(benzyloxycarbonyl)aminomethyl]benzotriazole 4c or benzyl *N*-(acetoxymethyl)carbamate 2d introduces a protected aminomethyl group in a single step.

Introduction

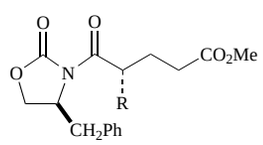
There is considerable interest in the enantioselective synthesis of β-amino acids, compounds which can have biological activity in their own right and which are useful building blocks for the preparation of modified peptides and other potential pharmaceuticals.[1] However, there have been few reports of asymmetric routes to β-alanine derivatives of general structure **1**, substituted *only* at the α-carbon. The known methods include



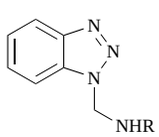
1

$RNHCH_2X$

2a R = PhCO; X = Cl
2b R = $PhCH_2OCO$ = Z; X = OH
2c R = Z; X = Cl
2d R = Z; X = OAc



3a R = H
3b R = $CH_2NHCOPh$



4a R = PhCO
4b R = $PhCH_2$
4c R = Z

stereoselective alkylations of chiral enolates that are synthetically equivalent to the enolate from β-alanine[2–4] and the conjugate addition of a carbon nucleophile to an α-methylene β-alanine derivative.[5] However, such approaches are unsuitable for the preparation of the β-amino acids **1** where R is an aryl group. In 1995 we described, in preliminary form, the first enantioselective synthesis of 3-amino-2-phenylpropanoic acid (α-phenyl-β-alanine, **13**).[6] Our key step was the asymmetric Mannich reaction of the benzotriazole derivative **4c** with the lithium enolate of the acyl oxazolidinone **6a**. Recently Williams and co-workers reported that α-aryl-β-alanines may also be prepared by sequences involving asymmetric Pd-catalysed reactions of allylic acetates with dimethyl malonate,[7] which in this context are equivalent to the $[RCHCO_2H]^+$ and $[H_2NCH_2]^-$ synthons respectively. Here we provide a full account of our complementary approaches to α-substituted-β-alanines **1**, in which chiral enolates undergo electrophilic attack by synthetic equivalents of the $[H_2NCH_2]^+$ cation.

† E-Mail: p.b.wyatt@qmw.ac.uk

Evans *et al.* have reported the use of *N*-(chloromethyl)-benzamide **2a** to amidomethylate the titanium enolate of the acyl oxazolidinone **3a**, leading to the stereoselective formation of the protected amino acid **3b** in high yield.[8] However, the reagent **2a** is known to be somewhat unstable.[9] Furthermore, the removal of the *N*-benzoyl group normally involves heating with mineral acid. These hydrolysis conditions could cause racemisation, particularly when enolisation is facilitated by the presence of an α-aryl group, and they are likely to destroy sensitive aromatic groups such as the indolyl moiety.

1-(Aminomethyl)benzotriazoles and their *N*-acyl derivatives can also function as aminomethylating agents.[10] Work by Page *et al.*[11] has shown that the reagents **4a** and **4b**, with *N*-benzoyl and *N*-benzyl protecting groups respectively, may be used to effect the stereoselective aminoalkylation of ketone enolates containing the 1,3-dithiane-1-oxide auxiliary. 2-(Bromomethyl)-phthalimide is commercially available and has been used for enolate alkylation, but again harsh conditions (*e.g.* refluxing 40% HBr) are needed for the *N*-deprotection.[12] We favoured the *N*-benzyloxycarbonyl (Z) protecting group for use in the synthesis of the amino acids **1**. The Z group survives the conditions for removal of common chiral auxiliaries, but may be cleaved by catalytic hydrogenolysis under mild conditions; because all the by-products of this deprotection are volatile, the final isolation of the amino acids is made extremely straightforward.

Results and discussion

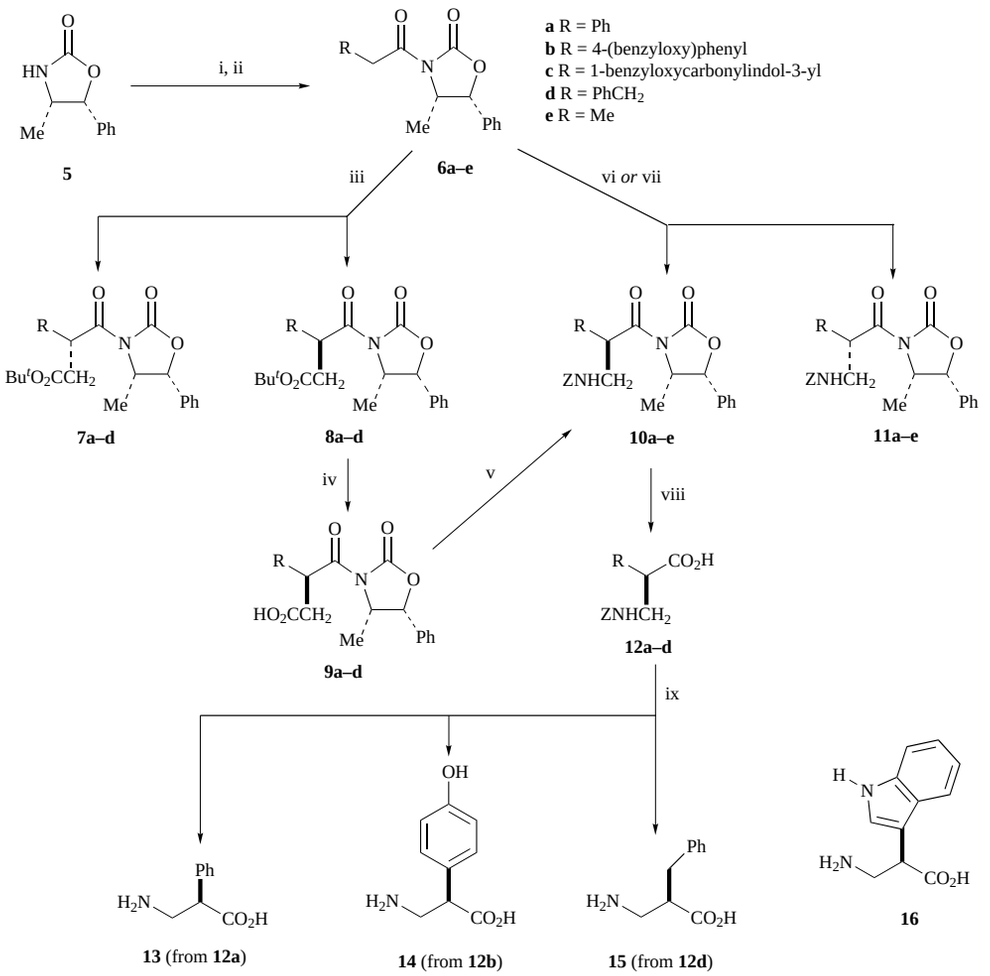
We elected to make use of the Evans oxazolidinone chiral auxiliary **5** to achieve stereoselectivity in attack upon the enolates (Scheme 1, Table 1). By analogy with simple alkylation,[13] this was predicted to lead to the preferential formation of precursors to the (*R*)-β-amino acids **13**–**16**; if the (*S*)-isomers of the amino acids were required, then they could be prepared using the enantiomer of **5**, which is readily available.

We decided to protect the phenolic hydroxy group of the tyrosine analogue **14** as a benzyl ether and so used the known[14] [4-(benzyloxy)phenyl]acetyl chloride in the acylation step. We also considered it appropriate to protect the indolyl system in tryptophan analogue **16** against deprotonation and electrophilic attack by using a group which could be cleaved by hydrogenolysis: we chose to use the *N*-(indolyl) benzyloxycarbonyl group. This protecting group has occasionally been used in tryptophan chemistry,[15] but the indole-3-acetic acid derivative **18** has not been described before and little has been said about the

Table 1 Percentage yields obtained in transformations depicted in Scheme 1 and diastereoselectivities (ds) observed in Mannich reactions.

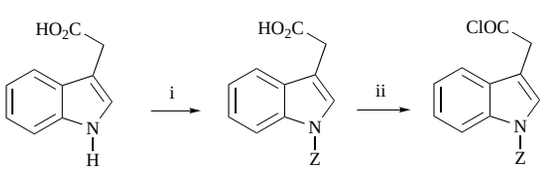
	Yields (%)							
	5 ⟶ **6**	**6** ⟶ **8**	**8** ⟶ **10**	**6** ⟶ **10**[a]	**6** ⟶ **10**[b]	**10** ⟶ **12**	**12** ⟶ (**13**–**15**)	Ds **10**:**11** from Mannich reaction
a	80	67	58	65	62	65	68[d]	96:4[a,e]
b	55	56	40	59	—	69	91	95:5[a,e]
c	48	49	52	58	—	84	—	93:7;[a,e] 95:5[a,f]
d	83	69	47	<10[f]	38	67	81	>90:10[b,f]
e	84	—	—	*ca.* 0	34	—	—	

[a] Using **4c**. [b] Using **2d**. [c] Yield based on **10a**. [d] Based on isolated yields of **10** and **11**. [e] Based on 250 MHz ^{1}H NMR spectrum of crude reaction mixture.



Scheme 1 *Reagents and conditions*: i, BuLi, THF, −78 °C; ii, RCH_2COCl; iii, $NaN(SiMe_3)_2$, THF, −78 °C, then $BrCH_2CO_2Bu^t$; iv, CF_3CO_2H, 20 °C, 1 h; v, $(PhO)_2P(O)N_3$, Et_3N, $PhCH_2OH$, PhMe, 20 °C, then reflux; vi, LDA *or* $LiN(SiMe_3)_2$, THF, −78 °C, then **4c**; vii, $TiCl_4$, $EtNPr^i_2$, $ZNHCH_2OAc$, CH_2Cl_2, 20 °C; viii, LiOH, H_2O_2, H_2O, 0 °C; ix, H_2, Pd–C, AcOH

compatibility of 1-(benzyloxycarbonyl)indole derivatives with strongly basic and nucleophilic reagents. The dilithium salt of indole-3-acetic acid was acylated with benzyl chloroformate, thus introducing a Z group onto the indole nitrogen (Scheme 2).



17 18 19

Scheme 2 *Reagents and conditions*: i, BuLi (2.2 equiv.), THF, −45 °C, then $PhCH_2OCOCl$ (1 equiv.); ii, $SOCl_2$, 20 °C, 14 h

The protected acid **18** was then converted into the acyl chloride **19**, prior to coupling with the chiral auxiliary **5** in the usual way.

It has been reported that sodium and lithium enolates bearing chiral auxiliaries such as **5** undergo alkylation by α-haloacetate esters with diastereoselectivity (ds) values usually ≥95:5 (ref. 16). We used this general method to convert the acyl oxazolidinones **6** into the *tert*-butyl esters **8**, all of which were highly crystalline compounds that could easily be obtained in isomerically pure form. We did not isolate the minor diastereoisomers **7**, but in each case the 250 MHz NMR spectrum of the crude reaction mixture was studied and it was concluded that the amount of the by-product **7** could not have exceeded 10% of the amount of the major product **8**. Treatment of the esters **8** with trifluoroacetic acid led to smooth deprotection to form the corresponding carboxylic acids **9**, which were transformed into the urethanes **10**, using diphenylphosphoryl azide, triethylamine and benzyl alcohol in the general procedure of Shioiri *et al.*[17] In this variant of the Curtius rearrangement the intermediate acyl azides and isocyanates need not be isolated. Com-

parison of the 250 MHz ^{1}H NMR spectrum of crude **10a** from the Curtius reaction with an authentic sample of the diastereoisomer *ent*-**11a** (formed by the Mannich reaction as described below) demonstrated that no detectable epimerisation had occurred during the former reaction. Having obtained reference samples of the *N*-(benzyloxycarbonyl)-β-amino acid derivatives **10**, we then sought methods for preparing these compounds directly from the acyloxazolidinones **6**.

The Mannich reagent **4c** was found to be stable, crystalline and easily prepared by refluxing commercially available 1-(hydroxymethyl)benzotriazole and benzyl carbamate together in toluene with a catalytic amount of toluene-4-sulfonic acid, using a Dean and Stark trap to remove water. The benzotriazolide anion is a relatively poor leaving group (pK_a of benzotriazole = 8.2)[18] and **4c** does not show high reactivity as an electrophile. Thus **4c** completely failed to react with the titanium enolate of **6a** at 20 °C. Reaction of **4c** with the Li and Na enolates of **6a**, which were quenched at temperatures of −10 and −5 °C respectively, gave Mannich product **10a** in yields of only 31 and 45%; again much of the acyl oxazolidinone **6a** remained unchanged. The highest yield (65%) of the desired product **10a** was obtained when a mixture containing **4c** and the lithium enolate of **6a** was allowed to warm up to 25 °C before being quenched; under these conditions the major oxazolidinone-containing by-product was the deacylated chiral auxiliary **5**, which can arise by the known decomposition of enolates at higher temperatures through a ketene mechanism.[13] Analysis of the crude product by 250 MHz ^{1}H NMR spectroscopy indicated that **10a**, **5** and unreacted **6a** were present in the approximate molar ratio 8 : 2 : 1. Very little of the diastereoisomeric Mannich product **11a** was formed and the similarity in the chemical shifts of **11a** to those of the main products made it difficult to detect **11a** in the NMR spectrum of the crude product. When we performed the Mannich reaction using *ent*-**6a** we were able to isolate the minor product *ent*-**11a** in 2% yield. Reagent **4c** was also successfully employed to effect the direct conversion of the lithium enolates of **6b** and **6c** into the urethanes **10b** and **10c** (yields 59 and 58% respectively). Again only small amounts (*ca*. 3%) of the minor diastereoisomers **11b** and **11c** were formed. Cleavage of the Z group from the indole nitrogen did not occur under these conditions. Attempted reactions of lithium enolates from the (3-phenylpropanoyl)oxazolidinone **6d** and the propanoyloxazolidinone **6e** with the benzotriazole derivative **4c** did not yield synthetically useful amounts of Mannich products **10** and **11**: the acyl oxazolidinones **6** were mainly recovered unchanged, although some of the chiral auxiliary **5** was observed as a minor product. Thus the Mannich reaction was successful in cases where R was an aryl group, but not when R was alkyl. This suggested that those lithium enolates which are not stabilised by conjugation with an α-aryl group may be sufficiently basic to abstract the N-H proton from the benzotriazole reagent **4c**. We therefore examined the possibility of introducing the $ZNHCH_2$ group in Lewis acid-promoted Mannich reactions.

The benzotriazole-derived reagent **4c** was found to be unreactive towards the titanium enolate of **6a**. Benzyl *N*-(hydroxymethyl)carbamate ($ZNHCH_2OH$) **2b** was easily prepared,[19] but our attempts to convert it into the chloride $ZNHCH_2Cl$ **2c**, using PCl_5, by analogy with the preparation of **2a**, led only to decomposition. However, the acetate **2d** is readily available and comparatively stable. We found that this reagent was able to bring about the stereoselective Mannich reactions on titanium enolates both when R was aryl (**6a** ⟶ **10a**, 62%) and when R was alkyl. In the latter cases the yields were rather low (**6d** ⟶ **10d**, 38%; **6e** ⟶ **10e**, 34%) and much of the starting acyl oxazolidinone remained unconverted, even when the reaction mixture was allowed to warm up to room temperature (*e.g* 42% of the starting acyl oxazolidinone **6d** was recovered after 1 h at 20 °C).

Removal of the chiral auxiliaries from compounds **10a**–**d** was performed under Evans' usual hydrolytic conditions (LiOH, H_2O_2, H_2O) and gave the carboxylic acids **12a**–**d** in yields of ⩾65% after recrystallisation; if mild conditions were used for the hydrolysis then the Z group on the indole system was not affected. Finally the free amino acids **13**, **14** and **15** were prepared by catalytic hydrogenolysis.

The specific rotation of the (*R*)-3-amino-2-phenylpropanoic acid **13** was equal in both sign and magnitude of that of resolved material which had been assigned the (*S*)-absolute configuration on the basis of a lengthy series of chemical correlations.[20] However, a single crystal X-ray diffraction study[6] of the salt of **13** with (1*S*)-(+)-camphor-10-sulfonic acid showed that we had indeed synthesised (*R*)-**13** and that the earlier assignment of absolute configuration by Garbarino and Nuñez was incorrect.

In our hands (*R*)-**15** had $[\alpha]_D$ +19 in 1 M HCl. This is somewhat larger than the literature value of +11.3, which has been reported by Juaristi *et al*.[2] Juaristi has observed that the specific rotations of free β-amino acids are rather sensitive to the conditions of measurement.[21] We wondered if it might be possible that partial racemisation occurred in the final step of Juaristi's synthesis (hydrolysis by 6 M HCl, 90–100 °C, 8 h). When we heated a sample of **15** in 6 M DCl in an NMR tube at 93–97 °C for 7 days and studied the 600 MHz NMR spectrum, we found that no decomposition of **15** had occurred, but that the changes in integration and appearance of the peaks in the region δ_H 2.5–3.2 were consistent with *ca*. 35% deuterium incorporation at the chiral centre. Thus there is a real possibility that small amounts of racemisation may occur when α-substituted β-alanine derivatives are exposed to hot hydrochloric acid.

Conclusions

We have established synthetically useful routes to enantiomerically pure, α-substituted β-alanine derivatives. These methods are especially attractive because they deliver the amino acids in Z-protected form, convenient for further synthesis or for deprotection under mild conditions by hydrogenolysis. They avoid the use of refluxing mineral acid for deprotection, thus minimising the risk of racemisation.

In cases where the α-substituent is an aryl group, the protected aminomethyl group is conveniently introduced by reaction of an appropriate chiral lithium enolate with the benzotriazole-derived Mannich reagent **4c**. This direct approach fails when the α-substituent is an alkyl group, but under such circumstances the alternative Mannich reagent **2d**, with acetate as the leaving group, can be used in conjunction with a titanium enolate. There may be scope for increasing the conversions obtained in these titanium-mediated reactions by further changing the leaving group.

β-Alanine derivatives with either alkyl or aryl substituents at the α-position are also available by reactions of chiral enolates with *tert*-butyl bromoacetate, which can be rendered synthetically equivalent to a Mannich electrophile by a sequence of steps including a Curtius rearrangement. This method is less direct than the Mannich approach, but it tolerates a range of substituents (both alkyl and aryl) and the major diastereoisomer from the asymmetric step tends to be amenable to purification by crystallisation.

Experimental

General experimental procedures have been described by us in an earlier publication.[22] $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Hydrogenations were performed using balloons. All reported compounds were homogeneous as judged by both TLC and NMR spectroscopy. Mass spectra were obtained by electron impact unless otherwise stated. The known acyl oxazolidinones **6a** (ref. 23), **6d** (ref. 24) and **6e** (ref. 25) were prepared from the appropriate acyl chlorides and the lithium

salt of **5**, according to the general procedure of Evans *et al.*[25] Petrol refers to light petroleum with bp 40–60 °C.

1-[*N*-(Benzyloxycarbonyl)aminomethyl]benzotriazole 4c

1-(Hydroxymethyl)benzotriazole (3.89 g, 26.1 mmol), benzyl carbamate (3.94 g, 26.1 mmol), toluene-*p*-sulfonic acid monohydrate (0.01 g) and toluene (70 ml) were refluxed together for 15 h in an apparatus fitted with a Dean and Stark water separator. The mixture was cooled and the crystals which separated were filtered off. Recrystallisation from toluene gave the *title compound* **4c** (4.53 g, 62%) as a white crystalline solid, mp 119–120 °C (Found: C, 64.0; H, 5.0; N, 20.0. $C_{15}H_{14}N_4O_2$ requires C, 63.8; H, 5.0; N, 19.85%); ν_{max}(KBr)/cm^{-1} 3255, 1725, 1531 and 1251; δ_H(80 MHz, $CDCl_3$) 5.15 (2 H, s), 6.05 (2 H, d, *J* 7), 6.5 (1 H, br t, *J* 7), 7.2–7.6 (7 H, m) and 7.8–8.1 (2 H, m); *m*/*z* 282 (M^+, 15%), 119 (54) and 91 (100) (Found: M^+, 282.1115. $C_{15}H_{14}N_4O_2$ requires *M*, 282.1117).

(4*S*,5*R*)-3-[4-(Benzyloxy)phenylacetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6b

A solution of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (5.10 g, 28.8 mmol) in THF (30 ml) was cooled to −78 °C and treated over 2 min with 2.5 M BuLi in hexane (12.7 ml, 31.7 mmol), followed by a solution of 4-(benzyloxy)phenylacetyl chloride[14] (7.52 g, 28.8 mmol) in THF (30 ml), which was added during 2 min. The reaction mixture was allowed to warm to 0 °C over 1 h, then was quenched with saturated aqueous NH_4Cl (5 ml) and partitioned between CH_2Cl_2 (100 ml) and water (100 ml). The organic phase was washed with aqueous $NaHCO_3$ (2 × 100 ml), dried ($MgSO_4$), and evaporated to leave an orange oil. Flash chromatography [CH_2Cl_2–petrol (1:1) to CH_2Cl_2–Et_2O (9:1); gradient elution] followed by recrystallisation from Et_2O–petrol gave (4S,5R)-3-[4-(*benzoyloxy*)*phenylacetyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **6b** (6.36 g, 55%) as white crystals, mp 97–98 °C (Found: C, 74.8; H, 5.7; N, 3.4. $C_{25}H_{23}NO_4$ requires C, 74.8; H, 5.7; N, 3.5%); $[\alpha]_D^{30}$ +6.3 (*c* 1.0, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1778 and 1698; δ_H(250 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 7), 4.21 (1 H, d, *J* 15), 4.28 (1 H, d, *J* 15), 4.75 (1 H, quintet, *J* 7), 5.05 (2 H, s), 5.64 (1 H, d, *J* 7), 6.92–6.98 (2 H, m) and 7.22–7.45 (14 H, m); *m*/*z* 401 (M^+, 4%), 224 (55) and 91 (100) (Found: M^+, 401.1638. $C_{25}H_{23}NO_4$ requires *M*, 401.1627).

(4*S*,5*R*)-3-[(1-Benzyloxycarbonylindol-3-yl)acetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6c

[1-(Benzyloxycarbonyl)indol-3-yl]acetic acid **18** (1.17 g, 3.79 mmol) was dissolved in $SOCl_2$ (11 ml) and the mixture was allowed to stir overnight. The excess of $SOCl_2$ and the side products were evaporated under vacuum to leave a dark coloured oil (1.27 g), considered to be [1-(benzyloxycarbonyl)-indol-3-yl]acetyl chloride **19** on the basis of the following data: ν_{max}(film)/cm^{-1} 1798 and 1737; δ_H(60 MHz, $CDCl_3$) 4.2 (2 H, s), 5.4 (2 H, s), 7.2–7.5 (8 H, m), 7.6 (1 H, s) and 8.1–8.3 (1 H, m). A portion of crude compound **19** (1.24 g, 3.79 mmol) was used to acylate the oxazolidinone **5** by analogy with the preparation of **6b**. Flash chromatography [CH_2Cl_2–petrol (7:3)] gave the *title compound* **6c** (0.854 g, 48%) as a white solid, mp 52–54 °C; $[\alpha]_D^{35}$ −0.4 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1778, 1732 and 1705; δ_H(250 MHz, $CDCl_3$) 0.90 (3 H, d, *J* 7), 4.36 (1 H, dd, *J* 17, 1), 4.44 (1 H, dd, *J* 17, 1), 4.77 (1 H, quintet, *J* 7), 5.45 (2 H, s), 5.67 (1 H, d, *J* 7), 7.24–7.64 (13 H, m), 7.70 (1 H, s) and 8.20 (1 H, d, *J* 8); *m*/*z* 468 (M^+, 19%), 291 (6), 247 (27), 220 (7), 157 (11), 91 (100), 65 (6) and 44 (11) (Found: M^+, 468.1683. $C_{28}H_{24}N_2O_5$ requires *M*, 468.1685).

(4*S*,5*R*,2′*S*)-3-(3-*tert*-Butoxycarbonyl-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 8a

A 1 M solution of $NaN(SiMe_3)_2$ in THF (Aldrich; 10.2 ml, 10.2 mmol) was diluted with dry THF (10 ml) and cooled to −72 °C. A solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-phenylacetyl-1,3-oxazolidin-2-one **6a**[23] (2.50 g, 8.5 mmol) in THF (20 ml) was then added by cannula over 5 min. The mixture was stirred during 30 min and then *tert*-butyl bromoacetate (1.65 ml, 10.2 mmol) was added by syringe. The mixture was allowed to attain −20 °C over 2 h and was then quenched with saturated aqueous NH_4Cl (5 ml).

The mixture was extracted with ethyl acetate (100 ml), washed with distilled water (100 ml), and the organic layer was dried. The solvent was evaporated under vacuum to yield an orange, viscous liquid, which was purified by flash chromatography [CH_2Cl_2–petrol (80:20) to (90:10); gradient elution] and crystallisation (EtOAc–petrol) to yield the *title compound* **8a** (2.18 g, 67%) as white crystals, mp 125 °C; $[\alpha]_D^{30}$ +63.8 (*c* 0.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1767, 1722 and 1700; δ_H(80 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 6), 1.45 (9 H, s), 2.60 (1 H, dd, *J* 17, 4.5), 3.28 (1 H, dd, *J* 17, 11), 4.70 (1 H, quintet, *J* 7), 5.4–5.7 (2 H, m) and 7.2–7.5 (10 H, m); *m*/*z* 409 (M^+, 10%), 336 (10), 292 (10), 178 (100), 134 (11), 104 (10) and 57 (40) (Found: M^+, 409.1894. $C_{24}H_{27}NO_5$ requires *M*, 409.1889).

(4*S*,5*R*,2′*S*)-3-[2-(4-Benzyloxyphenyl)-3-(*tert*-butoxycarbonyl)-propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 8b

This was prepared by analogy with **8a**, starting from (4*S*,5*R*)-3-[4-(benzyloxy)phenylacetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6b** (1.60 g, 4.0 mmol). The *title compound* **8b** (1.18 g, 56%) was obtained as white crystals, mp 158–160 °C (from EtOAc–petrol); ν_{max}(KBr)/cm^{-1} 1783, 1732 and 1701; δ_H(250 MHz, $CDCl_3$) 0.93 (3 H, d, *J* 7), 1.40 (9 H, s), 2.56 (1 H, dd, *J* 17.5, 5), 3.21 (1 H, dd, *J* 17.5, 11), 4.67 (1 H, quintet, *J* 7), 5.40 (2 H, s), 5.45 (1 H, dd, *J* 11, 5), 5.50 (1 H, d, *J* 7), 6.90–6.97 (2 H, m) and 7.25–7.45 (12 H, m); *m*/*z* 515 (M^+, 1%), 282 (21), 178 (15) and 91 (100) (Found: M^+, 515.2314. $C_{31}H_{33}NO_6$ requires *M*, 515.2308).

(4*S*,5*R*,2′*S*)-3-[2-(1-Benzyloxycarbonylindol-3-yl)-3-(*tert*-butoxycarbonyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 8c

This was prepared by analogy with **8a**, starting from (4*S*,5*R*)-3-[(1-benzyloxycarbonylindol-3-yl)acetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6c** (0.72 g, 1.53 mmol). Purification of the crude product by flash chromatography [CH_2Cl_2–petrol (4:1)] and recrystallisation (Et_2O–petrol) yielded the *title compound* **8c** (0.439 g, 49%) as white crystals, mp 145 °C (Found: C, 70.1; H, 5.9; N, 4.8. $C_{34}H_{34}N_2O_7$ requires C, 70.1; H, 5.9; N, 4.8%); $[\alpha]_D^{30}$ +78.5 (*c* 1.0, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1765, 1734 and 1705; δ_H(250 MHz, $CDCl_3$) 0.95 (3 H, d, *J* 7), 1.41 (9 H, s), 2.65 (1 H, dd, *J* 17, 5), 3.40 (1 H, dd, *J* 17, 11), 4.69 (1 H, quintet, *J* 7), 5.38–5.50 (3 H, m), 5.74 (1 H, dd, *J* 11, 5), 7.25–7.50 (12 H, m), 7.66 (1 H, s), 7.80 (1 H, d, *J* 8) and 8.20 (1 H, d, *J* 8); *m*/*z* 582 (M^+, 0.5%), 526 (3), 349 (7), 278 (3), 233 (5) and 91 (100).

(4*S*,5*R*,2′*R*)-3-[2-Benzyl-3-(*tert*-butoxycarbonyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 8d

This was prepared by analogy with **8a**, starting from (4*S*,5*R*)-4-methyl-5-phenyl-3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one **6d**[24] (2.50 g, 8.1 mmol). Recrystallisation from Et_2O–petrol yielded the *title compound* **8d** as white crystals (2.35 g, 69%), mp 79 °C; $[\alpha]_D^{30}$ +45 (*c* 0.2, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1766 and 1706; δ_H(250 MHz, $CDCl_3$) 0.87 (3 H, d, *J* 7), 1.38 (9 H, s), 2.37 (1 H, dd, *J* 17, 5), 2.71 (1 H, dd, *J* 13, 8), 2.82 (1 H, dd, *J* 17, 11), 2.99 (1 H, dd, *J* 13, 7), 4.48–4.59 (1 H, m), 4.60 (1 H, quintet, *J* 7), 5.30 (1 H, d, *J* 7) and 7.20–7.45 (10 H, m); *m*/*z* 423 (M^+, 3%), 367 (94), 308 (86), 178 (68), 117 (72) and 57 (100) (Found: M^+, 423.2040. $C_{25}H_{29}NO_5$ requires *M*, 423.2046).

(4*S*,5*R*,2′*S*)-3-(3-Carboxy-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 9a

(4*S*,5*R*,2′*S*)-3-(3-*tert*-Butoxycarbonyl-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **8a** (103 mg, 0.25 mmol) was dissolved in trifluoroacetic acid (1 ml) at room temperature. After 1 h, the pale pink solution was evaporated under vacuum.

The residue was dissolved in diethyl ether and was then re-evaporated. Recrystallisation from Et_2O–petrol yielded the *title compound* **9a** (101 mg, 98%) as white crystals, mp 151 °C; ν_{max}(KBr)/cm^{-1} 2700–3500, 1765, 1734 and 1694; δ_H(80 MHz, $CDCl_3$) 0.95 (3 H, d, *J* 7), 2.7 (1 H, dd, *J* 18, 4), 3.45 (1 H, dd, *J* 18, 12), 4.75 (1 H, quintet, *J* 7), 5.4–5.7 (2 H, m), 7.3–7.6 (10 H, m) and 8.4 (1 H, br s); *m*/*z* 353 (M$^+$, 30%), 177 (21), 148 (6) and 107 (100) (Found: M$^+$, 353.1259. $C_{20}H_{19}NO_5$ requires *M*, 353.1263).

(4*S*,5*R*,2′*R*)-3-(2-Benzyl-3-carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 9d

By analogy with the preparation of **9a**, (4*S*,5*R*,2′*R*)-3-[2-benzyl-3-(*tert*-butoxycarbonyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **8d** (1.00 g, 2.36 mmol) was converted into the *title compound* **9d**, which was obtained as a white foam (682 mg, 79%), mp 62 °C; $[\alpha]_D^{30}$ +52 (*c* 0.2, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2800–3600 (br), 1781 and 1703; δ_H(250 MHz, $CDCl_3$) 0.84 (3 H, d, *J* 7), 2.47 (1 H, dd, *J* 17, 5), 2.68 (1 H, dd, *J* 13, 9), 2.92 (1 H, dd, *J* 17, 10), 3.03 (1 H, dd, *J* 13, 7), 4.45–4.59 (1 H, m), 4.63 (1 H, quintet, *J* 7), 5.36 (1 H, d, *J* 7) and 7.20–7.45 (10 H, m); *m*/*z* 367 (M$^+$, 15%), 308 (17), 177 (21), 148 (31) and 107 (100) (Found: M$^+$, 367.1420. $C_{21}H_{21}NO_5$ requires *M*, 367.1420).

(4*S*,5*R*,2′*R*)-3-(3-Benzyloxycarbonylamino-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 10a

(i) Preparation of 10a *via* the Curtius reaction. (4*S*,5*R*,2′*S*)-3-(3-Carboxy-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **9a** (404 mg, 1.14 mmol) was dissolved in toluene (5 ml). Triethylamine (320 μl, 2.3 mmol), diphenylphosphoryl azide (300 μl, 1.4 mmol) and benzyl alcohol (241 μl, 2.3 mmol) were added. The mixture was stirred for 1 h before being refluxed for 1 h. Evaporation of the solvent left a brown residue, which was dissolved in diethyl ether (14 ml) and washed with 2 M HCl (7 ml) and then with saturated aqueous $NaHCO_3$ (7 ml). The organic layer was dried and then evaporated under vacuum to yield a brown oil, which was purified by repeated flash chromatography [CH_2Cl_2–Et_2O (99:1)] to yield the *title compound* **10a** (309 mg, 59%) as a white foam, mp 50–51 °C; $[\alpha]_D^{29}$ +79 (*c* 1, EtOAc). This material was identical by IR and 250 MHz ^{1}H NMR spectroscopy to the major product **10a** obtained in the following experiment.

(ii) Preparation of 10a *via* the Mannich reaction with 1-[*N*-(benzyloxycarbonyl)aminomethyl]benzotriazole 4c. A solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-phenylacetyl-1,3-oxazolidin-2-one **6a** (295 mg, 1.0 mmol) in THF (4 ml) was added to LDA in THF (1.5 M, 0.73 ml, 1.1 mmol) and the mixture was stirred for 20 min. A solution of 1-[*N*-(benzyloxycarbonyl)aminomethyl]-benzotriazole **4c** (311 mg, 1.1 mmol) in THF (4 ml) was added and the mixture was stirred at −78 °C for 2 h, then allowed to warm to 20 °C. Saturated aqueous NH_4Cl (20 ml) was added and the product was extracted with Et_2O (3 × 30 ml). The Et_2O extracts were washed with 2 M HCl (20 ml), aqueous $NaHCO_3$ (2 × 20 ml) and brine (20 ml). Drying and evaporation of the combined Et_2O extracts gave a crude product whose ^{1}H NMR spectrum (250 MHz, $CDCl_3$) was consistent with the presence of (4*S*,5*R*,2′*R*)-3-(3-benzyloxycarbonylamino-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10a**, (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5** and the starting material **6a** as the three main components in an approximate molar ratio of 8:2:1.

Flash chromatography [EtOAc–petrol (1:4) to (2:3); gradient elution] gave (4S,5R,2′R)-3-(3-*benzyloxycarbonylamino*-2-*phenylpropanoyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **10a** (297 mg, 65%) as a foam, $[\alpha]_D^{30}$ +84 (*c* 1.1, EtOAc); ν_{max}(KBr)/cm^{-1} 3368, 1782, 1721 and 1698; δ_H(250 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 7), 3.56–3.67 (1 H, m), 3.74–3.85 (1 H, m), 4.68 (1 H, quintet, *J* 7), 5.00–5.13 (3 H, m), 5.22 (1 H, dd, *J* 8, 6), 5.46 (1 H, d, *J* 7) and 7.21–7.44 (15 H, m); *m*/*z* 458 (M$^+$, 1%), 307 (8), 295 (100), 177 (4) and 118 (25) (Found: M$^+$, 458.1854. $C_{27}H_{26}N_2O_5$ requires *M*, 458.1842).

A similar procedure to the above was used to convert *ent*-**6a** (414 mg, 1.40 mmol) into *ent*-**10a** (347 mg, 54%). Also isolated were: unreacted *ent*-**6a** (27 mg, 7%), *ent*-**5** (51 mg, 20%) and (4R,5S,2′R)-3-(3-*benzyloxycarbonylamino*-2-*phenylpropanoyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* ent-**11a** (14 mg, 2%), isolated as a colourless oil and purified by flash chromatography in CH_2Cl_2–Et_2O (97.5:2.5); $[\alpha]_D^{25}$ +96 (*c* 0.49, EtOAc); ν_{max}(KBr)/cm^{-1} 3359, 1781, 1721 and 1696; δ_H(250 MHz, $CDCl_3$) 0.75 (3 H, d, *J* 7), 3.58–3.80 (2 H, m), 4.81 (1 H, quintet, *J* 7), 5.05–5.13 (4 H, m), 5.62 (1 H, d, *J* 7) and 7.15–7.40 (15 H, m); *m*/*z* 458 (M$^+$, 1%), 414 (0.3), 367 (1), 295 (100) and 91 (54) (Found: M$^+$, 458.1843. $C_{27}H_{26}N_2O_5$ requires *M*, 458.1842).

(iii) Preparation of 10a *via* the Mannich reaction with benzyl *N*-(acetoxymethyl)carbamate. $TiCl_4$ (10% v/v in CH_2Cl_2; 0.97 ml, 0.88 mmol) was added to a solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-phenylacetyl-1,3-oxazolidin-2-one **6a** (240 mg, 0.81 mmol) in CH_2Cl_2 (10 ml) at 0 °C. The pale orange mixture was stirred at 0 °C for 10 min and then $EtNPr^i_2$ (167 μl, 0.96 mmol) was added. The purple solution was stirred at 0 °C for 1 h before being cooled to −78 °C and treated with a solution prepared from $TiCl_4$ (10% v/v in CH_2Cl_2; 1.16 ml, 1.06 mmol), benzyl *N*-(acetoxymethyl)carbamate[19] (230 mg, 0.96 mmol) and CH_2Cl_2 (10 ml) which had been kept at 0 °C for 30 min. The reaction mixture was allowed to warm from −78 to 20 °C over 6 h and then was stirred at 20 °C for 1 h, before being quenched with aqueous NH_4Cl (10 ml). The product was extracted with Et_2O (3 × 30 ml). Drying and evaporation of the combined Et_2O extracts gave a yellow oil, which was subjected to flash chromatography [EtOAc–petrol; gradient from 1:9 to 3:7] to yield (4S,5R,2′R)-3-(3-*benzyloxycarbonylamino*-2-*phenylpropanoyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **10a** (230 mg, 62%) as a pale yellow foam, identical by ^{1}H NMR spectroscopy (80 MHz, $CDCl_3$) to the sample prepared in the preceeding experiment.

(4*S*,5*R*,2′*R*)-3-[3-Benzyloxycarbonylamino-2-(4-benzyloxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 10b

(i) Preparation of 10b *via* the Curtius reaction. (4*S*,5*R*,2′*S*)-3-[2-(4-Benzyloxyphenyl)-3-(*tert*-butoxycarbonyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **8b** (1.21 g, 2.35 mmol) was converted into the acid **9b** (1.02 g, 95%) by analogy with the preparation of **9a**. A portion of the crude acid **9b** (463 mg, *ca*. 1 mmol) was then transformed into the urethane **10b**, by analogy with the preparation of **10a** using the Curtius reaction. Flash chromatography [EtOAc–petrol (15:85) to EtOAc–petrol (25:75); gradient elution], afforded the *title compound* **10b** as a white foam (241 mg, 40% from **8b**), mp 50–51 °C; $[\alpha]_D^{35}$ +90 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3417, 1782, 1721 and 1694; δ_H(250 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 7), 3.51–3.83 (2 H, m), 4.67 (1 H, quintet, *J* 7), 5.01 (1 H, br s), 5.04 (2 H, s), 5.09 (2 H, s), 5.16 (2 H, dd, *J* 8, 6), 5.47 (1 H, d, *J* 7), 6.92–6.99 (2 H, m) and 7.24–7.47 (17 H, m); *m*/*z* (FAB *ex* Et_2O–nitrobenzyl alcohol) 565 (MH$^+$, 54%), 521 (47), 413 (100), 401 (99) and 224 (52).

(ii) Preparation of 10b *via* the Mannich reaction with 1-[*N*-(benzyloxycarbonyl)aminomethyl]benzotriazole 4c. A solution of (4*S*,5*R*)-3-[4-(benzyloxy)phenylacetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6b** (803 mg, 2.0 mmol) in THF (10 ml) was added by cannula to a 0.35 M solution of $LiN(SiMe_3)_2$ in THF (6.2 ml, 2.2 mmol) at −60 °C. The mixture was treated with a solution of 1-[*N*-(benzyloxycarbonyl)aminomethyl]-benzotriazole **4c** (565 mg, 2.0 mmol) in THF (8 ml) and was then allowed to warm up to 8 °C over 3 h. Saturated aqueous NH_4Cl (20 ml) was added, then the mixture was diluted with Et_2O (30 ml) and washed with 2 M HCl (30 ml) followed by aqueous $NaHCO_3$ (30 ml). Drying and evaporation of the organic phase gave a yellow oil (1.35 g). Flash chromatography [CH_2Cl_2 to CH_2Cl_2–Et_2O (96:4); gradient elution] gave two diastereoisomeric Mannich products as follows.

The *title compound* **10b** (661 mg, 59%), mp 51–54 °C, was obtained from the earlier chromatographic fractions and was identical by ^{1}H NMR spectroscopy to a sample of this compound prepared using the Curtius reaction, as described in the preceding experiment. Evaporation of the later fractions from the chromatography gave a colourless oil, which solidified upon standing and was considered to be (4S,5R,2′S)-3-[3-*benzyloxycarbonylamino*-2-(4-*benzyloxyphenyl*)*propanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **11b** (36 mg, 3%), on the basis of the following properties: mp 48–51 °C; $[\alpha]_D^{34}$ −129.5 (*c* 0.93, $CHCl_3$); ν_{max}(film)/cm^{-1} 3370, 1780, 1718 and 1700; δ_H(250 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 7), 3.55–3.80 (2 H, m), 4.81 (1 H, quintet, *J* 7), 5.00–5.15 (6 H, m), 5.63 (1 H, d, *J* 7), 6.95 (2 H, d, *J* 8) and 7.17–7.46 (17 H, m); *m*/*z* (FAB *ex* Et_2O–nitrobenzyl alcohol) 565 (MH^+, 31%), 520 (64), 412 (99) and 400 (100).

(4*S*,5*R*,2′*R*)-3-[3-Benzyloxycarbonylamino-2-(1-benzyloxycarbonylindol-3-yl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 10c

(i) Preparation of 10c *via* the Curtius reaction. This was performed by analogy with the preparation of **10b** by the Curtius reaction, starting from (4*S*,5*R*,2′*S*)-3-[2-(1-benzyloxycarbonylindol-3-yl)-3-(*tert*-butoxycarbonyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **8c** (192 mg, 0.33 mmol). Flash chromatography [CH_2Cl_2–EtOAc (99:1)] gave a colourless oil containing a mixture of **10c** and benzyl alcohol. Reprecipitation from diethyl ether with petrol afforded the *title compound* (108 mg, 52% from **8c**) as a white solid, mp 63–64 °C (Found: C, 70.4; H, 5.2; N, 6.4. $C_{37}H_{33}N_3O_7$ requires C, 70.35; H, 5.3; N, 6.65%); $[\alpha]_D^{30}$ +74.7 (*c* 0.79, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3400, 1784, 1731, 1696 and 1678; δ_H(250 MHz, $CDCl_3$) 0.93 (3 H, d, *J* 7), 3.68–3.96 (2 H, m), 4.70 (1 H, quintet, *J* 7), 5.05–5.12 (3 H, m), 5.39–5.52 (4 H, m), 7.25–7.50 (17 H, m), 7.67 (1 H, s), 7.76 (1 H, d, *J* 8) and 8.18 (1 H, d, *J* 8); *m*/*z* (FAB *ex* Et_2O–nitrobenzyl alcohol) 632 (MH^+, 100%), 588 (85), 467 (39) and 306 (8).

(ii) Preparation of 10c *via* the Mannich reaction with 1-[*N*-(benzyloxycarbonyl)aminomethyl]benzotriazole 4c. This was performed by analogy with the preparation of **10b** by method (ii), starting from (4*S*,5*R*)-3-[(1-benzyloxycarbonylindol-3-yl)acetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6c** (627 mg, 1.34 mmol). Evaporation of the crude product *in vacuo* left a pale yellow foam (894 mg). A portion of this residue (13 mg) was analysed by 250 MHz ^{1}H NMR spectroscopy, on the basis of which compounds **10c**, **5**, **6c** and **11c** were judged to be present in the approximate molar ratio 80:10:6:4. The remainder of the residue from the evaporation was purified by flash chromatography [CH_2Cl_2 to CH_2Cl_2–EtOAc (96:4); gradient elution] to yield the following three fractions. First fraction: (4*S*,5*R*)-3-[(1-benzyloxycarbonylindol-3-yl)acetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6c** (37.5 mg, 6%), identical to the starting material by ^{1}H NMR spectroscopy. Second fraction: (4*S*,5*R*,2′*R*)-3-[3-(Benzyloxycarbonylamino)-2-(1-benzyloxycarbonylindol-3-yl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10c** as a pale yellow foam (484 mg, 58%), mp 59–65 °C, identical by ^{1}H NMR spectroscopy (250 MHz, $CDCl_3$) to material prepared by the Curtius reaction, as described in the preceding experiment. Third fraction: considered to be (4S,5R,2′S)-3-[3-*benzyloxycarbonylamino*-2-(1-*benzyloxycarbonylindol*-3-*yl*)*propanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **11c** (36 mg, 3%), on the basis of the following data: off-white foam, mp 63–66 °C; $[\alpha]_D^{34}$ −95 (*c* 0.73, $CHCl_3$); ν_{max}(film)/cm^{-1} 3378, 1780, 1726 and 1698 (shoulder); δ_H(250 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 7), 3.65–3.90 (2 H, m), 4.80 (1 H, quintet, *J* 7), 5.06–5.18 (3 H, m), 5.39–5.50 (3 H, m), 5.66 (1 H, d, *J* 7), 7.16–7.52 (17 H, m), 7.60 (1 H, s), 7.78 (1 H, d, *J* 8) and 8.18 (1 H, d, *J* 8); *m*/*z* (FAB *ex* Et_2O–nitrobenzyl alcohol) 632 (MH^+, 47%), 588 (51), 479 (82) and 467 (100).

(4*S*,5*R*,2′*R*)-3-(3-Benzyloxycarbonylamino-2-benzylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 10d

(i) Preparation of 10d *via* the Curtius reaction. This was performed by analogy with the preparation of **10a** by method (i), starting from (4*S*,5*R*,2′*R*)-3-(2-benzyl-3-carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **9d** (336 mg, 0.9 mmol). The crude product was purified by flash chromatography [CH_2Cl_2–Et_2O (19:1)] to give a colourless oil which was recrystallised from diethyl ether and petrol to yield the *title compound* **10d** as white crystals (252 mg, 60%), mp 91–93 °C; $[\alpha]_D^{31}$ +11.0 (*c* 1, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3377, 1778, 1737 and 1690; δ_H(250 MHz, $CDCl_3$) 0.83 (3 H, d), 2.86 (1 H, dd, *J* 14, 7), 3.02 (1 H, dd, *J* 13, 8), 3.43–3.64 (2 H, m), 4.39 (1 H, br quintet, *J* 7), 4.54 (1 H, quintet, *J* 7), 5.09 (2 H, s), 5.12–5.22 (1 H, br), 5.27 (1 H, d, *J* 7) and 7.20–7.45 (15 H, m); *m*/*z* 472 (M^+, 4%), 381 (6), 335 (10), 308 (59), 160 (30), 131 (46) and 91 (100) (Found: M^+, 472.1997. $C_{28}H_{28}N_2O_5$ requires *M*, 472.1998).

(ii) Preparation of 10d *via* the Mannich reaction with benzyl *N*-(acetoxymethyl)carbamate. This was performed analogously to the preparation of **10a** by method (iii), starting from **8d** (691 mg, 2.23 mmol). The reaction mixture was allowed to warm up from −78 to 0 °C over 3 h, then was kept at 0 °C for 3 h and at 20 °C for 1 h after which work up was performed as before. Analysis of the crude product by 250 MHz ^{1}H NMR spectroscopy indicated that the starting material **8d** and the Mannich product **10d** were present in a *ca*. 1:1 molar ratio. Flash chromatography [CH_2Cl_2–Et_2O (97:3)] gave first **8d** (292 mg, 42% recovery) followed by **10d** (446 mg) as an oil. Recrystallisation of the latter compound from diethyl ether–petrol gave **10d** (400 mg, 38%; 66% based on recovered **8d**) as white crystals, mp 90–93 °C, identical by 250 MHz ^{1}H NMR spectroscopy with material prepared by the Curtius reaction according to the preceding experiment.

(4*S*,5*R*,2′*R*)-3-(3-Benzyloxycarbonylamino-2-methylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 10e *via* the Mannich reaction with benzyl *N*-(acetoxymethyl)carbamate

This was prepared analogously to the preparation of **10a** by method (iii), starting from (4*S*,5*R*)-4-methyl-5-phenyl-3-propanoyl-1,3-oxazolidin-2-one **6e**.[25] The reaction mixture was allowed to warm from −78 to 20 °C over 8 h and then was stirred at 20 °C for 1 h, before being worked up as before. Flash chromatography [EtOAc–petrol; gradient from (2:1) to (1:1)] yielded (4S,5R,2′R)-3-(3-*benzyloxycarbonylamino*-2-*methylpropanoyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **10e** (130 mg, 34%) as a clear glass. Recrystallisation from petrol gave white crystals, mp 91–93 °C; $[\alpha]_D^{29}$ −33.7 (*c* 2.1, CH_2Cl_2); δ_H(250 MHz, $CDCl_3$) 0.86 (3 H, d, *J* 7), 1.23 (3 H, d, *J* 7), 3.41–3.54 (2 H, m), 3.96 (1 H, sextet, *J* 7), 4.73 (1 H, quintet, *J* 7), 5.08 (2 H, s), 5.19–5.29 (1 H, br t), 5.65 (1 H, d, *J* 7) and 7.25–7.45 (10 H, m); *m*/*z* 369 (M^+, 9%), 289 (5), 219 (8) and 91 (100) (Found: M^+, 396.1692. $C_{22}H_{24}N_2O_5$ requires *M*, 396.1685).

(*R*)-3-Benzyloxycarbonylamino-2-phenylpropanoic acid 12a

(4*S*,5*R*,2′*R*)-3-(3-Benzyloxycarbonylamino-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10a** (212 mg, 0.46 mmol) was dissolved in a mixture of THF (4 ml) and H_2O (1.3 ml) and cooled to 0 °C. $LiOH·H_2O$ (49 mg, 1.16 mmol), and aqueous H_2O_2 (30% solution, 0.25 ml) were added. The reaction was quenched after 30 min with saturated aqueous Na_2SO_3 (10 ml) and diluted with brine (10 ml).

The reaction mixture was extracted with CH_2Cl_2 (3 × 15 ml). The aqueous layer was then acidified with 2 M HCl (to pH 2) and extracted into EtOAc (3 × 15 ml). The combined organic layers were dried and evaporated under vacuum to yield a viscous oil, which was recrystallised from diethyl ether and petrol to yield the title compound as white crystals (89.4 mg, 65%), mp 95–97 °C (lit.,[26] 100–102 °C); $[\alpha]_D^{36}$ +92.5 (*c* 1.0 in EtOH) [lit.,[26] +93.6 (*c* 1.0, EtOH)]; ν_{max}(KBr)/cm^{-1} 3390, 1720 and 1654; δ_H(250 MHz, $CDCl_3$) 3.65–4.15 (3 H, m), 5.15–5.35 (3 H,

m) and 7.35–7.55 (10 H, m). The broadness of the peaks in the ^{1}H NMR spectrum was attributed to the presence of interconverting rotamers.

(*R*)-3-Benzyloxycarbonylamino-2-(4-benzyloxyphenyl)propanoic acid 12b

This was prepared by analogy with **12a**, starting from (4*S*,5*R*,2′*R*)-3-[3-benzyloxycarbonylamino-2-(4-benzyloxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10b** (571 mg, 1.01 mmol). Recrystallisation from Et_2O–petrol yielded the *title compound* **12b** as a white solid (283 mg, 69%), mp 105–108 °C (from Et_2O–petrol) (Found: C, 71.0; H, 5.6; N, 3.3. $C_{24}H_{23}NO_5$ requires C, 71.1; H, 5.7; N, 3.45%); $[a]_D^{28}$ +113 (*c* 1.1, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3350, 2400–3500 (br) and 1697; δ_H(250 MHz; $CDCl_3$, broad spectrum, probably as a result of the presence of interconverting rotamers) 3.5–3.9 (3 H, m), 5.05 (2 H, s), 5.05–5.20 (2 H, m), 6.05 (1 H, br s, exchanges with D_2O), 6.93 (2 H, d, *J* 8), 7.13–7.22 (2 H, m) and 7.30–7.45 (10 H, m); *m*/*z* 405 (M^+, 0.1%), 254 (11) and 91 (100) (Found: M^+, 405.1576. $C_{24}H_{23}NO_5$ requires *M*, 405.1564).

(*R*)-3-Benzyloxycarbonylamino-2-(1-benzyloxycarbonylindol-3-yl)propanoic acid 12c

(4*S*,5*R*,2′*R*)-3-[3-Benzyloxycarbonylamino-2-(1-benzyloxycarbonylindol-3-yl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10c** (50.2 mg, 0.079 mmol) was dissolved in THF (1 ml) and the solution was cooled to 0 °C; $LiOH·H_2O$ (4.0 mg, 0.095 mmol), aqueous H_2O_2 (30%, 0.1 ml) and water (0.3 ml) were then added. After 25 min aqueous Na_2SO_3 (1 ml) was added followed by 2 M HCl to pH 3. The mixture was partitioned between EtOAc (10 ml) and water (10 ml). Drying and evaporation of the EtOAc phase gave an off-white solid which was recrystallised from CH_2Cl_2–petrol to give the *title compound* **12c** (31.5 mg, 84%), mp 163–164 °C (Found: C, 68.5; H, 5.1; N, 5.9. $C_{27}H_{24}N_2O_6$ requires C, 68.6; H, 5.1; N, 5.9%); $[a]_D^{35}$ +58 (*c* 1.0, acetone); ν_{max}(KBr)/cm^{-1} 3331, 2500–3300 (br), 1743, 1719 and 1684; δ_H(250 MHz, $CDCl_3$) 3.5–3.8 (2 H, m), 4.0–4.3 (1 H, m), 5.0–5.3 (3 H, m), 5.4–5.5 (2 H, m), 7.05–7.7 (14 H, m) and 8.17 (1 H, d, *J* 8); *m*/*z* (FAB *ex* petrol–glycerol) 473 (MH^+, 16%), 429 (17), 283 (17) and 214 (100).

(*R*)-3-Benzyloxycarbonylamino-2-benzylpropanoic acid 12d

This was prepared by analogy with **12a**, from (4*S*,5*R*,2′*R*)-3-(3-benzyloxycarbonylamino-2-benzylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10d** (225 mg, 0.5 mmol). The crude product was crystallised from Et_2O–petrol to yield the *title compound* **12d** (99.6 mg, 67%) as white crystals. After a further recrystallisation from Et_2O–petrol the crystals (61 mg) had mp 74–75 °C (Found: C, 68.8; H, 6.0; N, 4.4. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5%); $[a]_D^{27}$ +9.7 (*c* 0.15, CH_2Cl_2); $[a]_D^{27}$ −1.4 (*c* 0.4, EtOH); ν_{max}(KBr)/cm^{-1} 3348, 2400–3600 (br), 1792 and 1695; δ_H(250 MHz, $CDCl_3$) 2.62–3.55 (5 H, m), 5.02–5.22 (3 H, m) and 7.10–7.40 (10 H, m); the peaks in the NMR spectrum were broad, probably as a consequence of the presence of interconverting rotamers; *m*/*z* 313 (M^+, 0.3%), 222 (0.4), 131 (7), 91 (100) and 65 (21) (Found: M^+, 313.1317. $C_{18}H_{19}NO_4$ requires *M*, 313.1314).

(*R*)-3-Amino-2-phenylpropanoic acid 13

(4*S*,5*R*,2′*R*)-3-(3-Benzyloxycarbonylamino-2-phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **10a** (459 mg, 1 mmol) was hydrolysed using $LiOH·H_2O$ (104 mg, 2.5 mmol) as in the preparation of **12a**. The crude (*R*)-3-benzyloxycarbonylamino-2-phenylpropanoic acid **12a** was not recrystallised, but was dissolved in glacial acetic acid (10 ml). 10% Palladium on carbon (300 mg) was added and the mixture was hydrogenated overnight. Filtration through Celite, repeated evaporation with water and recrystallisation from water–ethanol gave the title compound **13** as white crystals (112 mg, 68% from **10a**), mp 222–224 °C (lit.,[20] 224–225 °C, lit.,[26] 223–226 °C); $[a]_D^{30}$ +94 (*c* 0.2, H_2O) [lit.,[20] +95 (*c* 0.2 in H_2O), lit.,[26] +85 (*c* 0.2 in H_2O)]; δ_H(250 MHz, D_2O) 3.30 (1 H, dd, *J* 12, 7), 3.49 (1 H, dd, *J* 12, 8), 3.81 (1 H, 't', *J* 7) and 7.34–7.48 (5 H, m).

(*R*)-3-Amino-2-phenylpropanoic acid, (1*S*)-(+)-camphorsulfonate salt

A solution of (*R*)-3-amino-2-phenylpropanoic acid **13** (32.0 mg, 0.19 mmol) in water (4 ml) was treated with (1*S*)-(+)-camphor-10-sulfonic acid (49.0 mg, 0.21 mmol) in EtOH (1 ml). The solvents were evaporated and the residue was twice recrystallised from EtOH–Et_2O to give the title compound (52.5 mg, 68%) as white needles, mp 183–189 °C (lit.,[26] 190–192 °C); $[a]_D^{26}$ +61 (*c* 0.5 in H_2O) [lit.,[26] +63 (*c* 0.5, H_2O)]. The relative configuration of the title compound was proven by single crystal X-ray diffraction.[6]

(*R*)-3-Amino-2-(4-hydroxyphenyl)propanoic acid 14

(*R*)-3-(Benzyloxycarbonylamino)-2-(4-benzyloxyphenyl)propanoic acid **12b** (107.7 mg) was dissolved in glacial acetic acid (2 ml) and hydrogenated over Pd black (15 mg) for 1 h, during which time white crystals formed in the reaction mixture. Water (2 ml) was added and the mixture was filtered through Celite, which was then washed with 50% aqueous AcOH (10 ml). Evaporation of the combined filtrate and washings, then crystallisation from water, yielded the *title compound* **14** (43.7 mg, 91%) as a white solid, mp *ca*. 270 °C (decomp.) (Found: C, 59.2; H, 6.0; N, 7.5. $C_9H_{11}NO_3$ requires C, 59.7; H, 6.2; N, 7.6%); $[a]_D^{30}$ +16.7 (*c* 1.2, HCO_2H); ν_{max}(KBr)/cm^{-1} 3225, 2400–3300 (br), 1653, 1589 and 1510; δ_H(250 MHz, CF_3CO_2D) 3.62–3.76 (1 H, m), 3.84–3.95 (1 H, m), 4.33 (1 H, t, *J* 7), 6.8 (2 H, d, *J* 8), 7.1 (1 H, br s) and 7.32 (2 H, d, *J* 8); *m*/*z* 181 (M^+, 2%), 164 (15), 152 (100) and 107 (64) (Found: M^+, 181.0737. $C_9H_{11}NO_3$ requires *M*, 181.0739).

(*R*)-3-Amino-2-benzylpropanoic acid 15

This was prepared by analogy with **13**, starting from (*R*)-3-benzyloxycarbonylamino-2-benzylpropanoic acid **12d** (53.2 mg, 0.17 mmol). Crystallisation from H_2O–EtOH yielded the *title compound* **15** (24.6 mg, 81%) as white crystals, mp 227–229 °C (lit.,[2] 225–226 °C); $[a]_D^{35}$ +18.9 (*c* 0.88, 1 M HCl), $[a]_D^{33}$ +19.2 (*c* 0.65, 1 M HCl) {lit.,[2] $[a]_D^{29}$ +11.3 (*c* 1, 1 M HCl)}; δ_H(250 MHz, D_2O) 2.90–3.27 (5 H, m) and 7.41–7.57 (5 H, m); δ_C(63 MHz, D_2O) 39.2, 43.8, 50.1, 129.7, 131.8, 132.0, 141.7 and 182.7; *m*/*z* 179 (M^+, 53%), 162 (51), 144 (9), 117 (75), 103 (22), 91 (100), 78 (30) and 65 (29) (Found: M^+, 179.0947. $C_{10}H_{13}NO_2$ requires *M*, 179.0946).

(1-Benzyloxycarbonylindol-3-yl)acetic acid 18

Indole-3-acetic acid **17** (4.20 g, 24 mmol) was dissolved in dry THF (100 ml) and the solution was cooled to −45 °C. A 2.2 M solution of BuLi in hexane (24 ml, 53 mmol) was added over 5 min. After a further 5 min benzyl chloroformate (3.6 ml, 24 mmol) was added and the reaction mixture was allowed to attain −5 °C over 2 h before being quenched with saturated aqueous NH_4Cl (10 ml). Water (100 ml) was added and the mixture was extracted with Et_2O (2 × 60 ml). The aqueous phase was acidified with 2 M HCl to pH 3 and was then extracted with diethyl ether (3 × 60 ml). The ether extracts from after the acidification were combined, diluted with sufficient EtOAc to dissolve any precipitate, dried, filtered and evaporated. Recrystallisation from EtOAc–petrol, together with flash chromatography [CH_2Cl_2–EtOAc (4:1) to CH_2Cl_2–EtOAc (2:1); gradient elution] of the residue from evaporation of the mother liquors, and further recrystallisation (CH_2Cl_2–petrol) yielded the *title compound* **18** (5.14 g, 69%) as white crystals, mp 153–154 °C (Found: C, 69.8; H, 4.9; N, 4.55. $C_{18}H_{15}NO_4$ requires C, 69.9; H, 4.9; N, 4.5%); ν_{max}(KBr)/cm^{-1} 2400–3600 (br), 1733 and 1696; δ_H(250 MHz, $CDCl_3$) 3.75 (2 H, s), 5.46 (2 H, s), 7.23–7.55 (8 H, m) and 8.17 (1 H, d, *J* 8); *m*/*z* 309

(M^+, 18%), 265 (5), 220 (18) and 91 (100) (Found: M^+, 309.1000. $C_{18}H_{15}NO_4$ requires *M*, 309.1001).

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