Synthesis of α-Alkyl-α-Benzyl Amino Acid Derivatives, *via* the Diastereoselective Alkylation of (3*S*,5*R*)-*N*,3-Dibenzyl-3,4,5,6-tetrahydro-5-phenyl-1,4-oxazin-2-one

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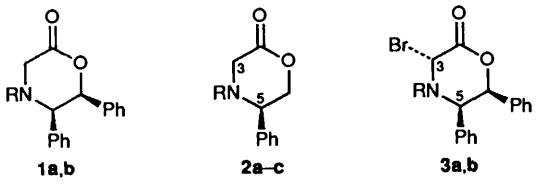
(3*S*,5*R*)-*N*,3-Dibenzyl-3,4,5,6-tetrahydro-5-phenyl-1,4-oxazin-2-one, derived from L-phenylalanine and phenacyl bromide, was alkylated in a diastereoselective manner to give a range of α-alkylated phenylalanine derivatives.

Recent reports have shown how homochiral 5,6-diphenyl-1,4-oxazin-2-ones **1**[1] and 5-phenyl-1,4-oxazin-2-ones **2**[2,3] can successfully be used as templates for the synthesis of optically active α-amino acids.

Previously[4] the 3-bromo-5,6-diphenyl-1,4-oxazin-2-ones **3**, generated by reaction of compounds **1** with *N*-bromosuccinimide, had been shown to be extremely versatile glycine cation equivalents. The enolate anions of compounds **1** or **2** on the other hand were extremely sensitive to the solvent–base conditions under which they were generated. Only the use of lithium or sodium hexamethyldisilazide (LiHMDS or NaHMDS) in tetrahydrofuran (THF) (−78 °C) generated the anions without significant decomposition. Subsequent quenching with an alkylating agent gave the monosubstituted derivatives with excellent stereocontrol, which upon deprotection gave the α-alkyl α-amino acids with high enantiomeric excess.

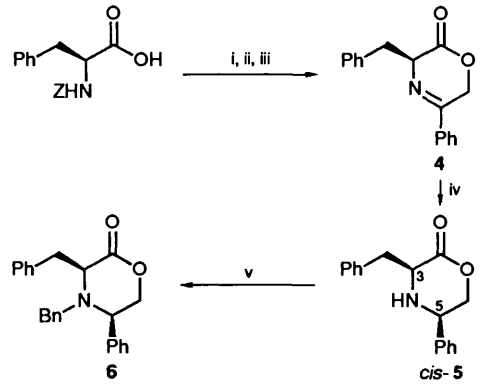


1a,b **2a–c** **3a,b**

a; R = CO_2CH_2Ph (Z)
b; R = CO_2Bu^t (Boc)
c; R = CH_2Ph (Bn)

Williams and Im,[5] and subsequently Baldwin,[6] have investigated the conversion of the monoalkylated 5,6-diphenyloxazinones into the dialkylated species, thus giving access to α,α-disubstituted α-amino acids. Not surprisingly the enolates of the monosubstituted derivatives are as unstable as their unsubstituted precursors, and again the disilazane bases must be used.

Our results reported herein show how the protected oxazinone **6**, derived from L-phenylalanine, can be alkylated to give access to the α,α-disubstituted α-amino acid derivatives. Starting from a proteinogenic amino acid other than glycine means that there is no need for a chiral auxiliary. D-Phenylglycinol (as used by Dellaria[2] and by Baker[3]) is by no means cheap and Williams' auxiliary[1,4,5] needs to be synthesized. Unfortunately, deprotection of these oxazinones to give the free amino acids destroys the chiral auxiliary. In our work we took advantage of Seebach's principle of self-reproduction of chirality.[7] By performing a highly stereoselective reduction of the imine **4**, 'chiral information' from C-3 is reproduced at C-5, and this centre can then direct the stereochemical outcome of the subsequent enolate alkylation.

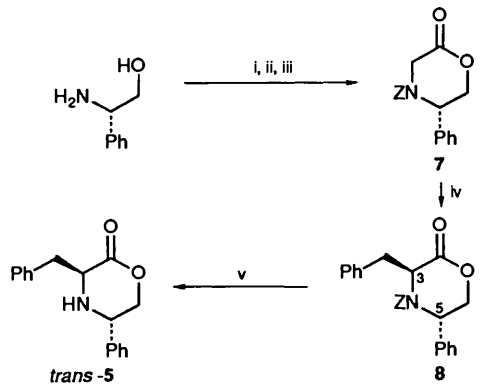


Scheme 1 *Reagents:* i, $PhCOCH_2Br$, NaOH; ii, HBr-AcOH; iii, NaOAc–HOAc; iv, $NaBH_3CN$; v, BnBr, K_2CO_3

Results and Discussion

The oxazinone *cis*-**5** was synthesized as depicted in Scheme 1. Following a literature procedure to give the dihydrooxazinone **4**[8,9] a highly stereoselective, sodium cyanoborohydride-mediated reduction of the imine bond gave the oxazinone *cis*-**5**. High-field ^1H NMR (400 MHz) spectroscopy of the crude product showed that only the *cis* diastereoisomer had been formed, albeit in the moderate yield of 41%. To confirm we had indeed made the *cis* diastereoisomer, the oxazinone *trans*-**5** was synthesized from L-phenylglycinol by a method similar to that of Dellaria[2] (Scheme 2). Alkylation of the oxazinone **7**[2] with lithium diisopropylamide (LDA) and benzyl bromide, followed by deprotection using catalytic hydrogenation gave the diastereoisomer *trans*-**5**. An X-ray determination of the structure of the N-BOC protected equivalent of oxazinone **8** had shown Dellaria that the relative configuration at C-5 and C-3 in this compound was *trans*. The ^1H NMR spectrum of the mixed products *trans*- and *cis*-**5** indicated that the oxazinone we had made from phenylalanine was indeed the *cis* diastereoisomer.

The method of formation of the oxazinone meant that protection of the nitrogen functionality had to be performed *after* the cyclisation, but this proved to be more of a problem than expected. Protection using the benzyloxycarbonyl (Z) or *tert*-butoxycarbonyl (Boc) groups was unsuccessful using a variety of reaction conditions, but the less bulky methoxycarbonyl group could be introduced using a pyridine/4-(dimethylamino)pyridine (DMAP) system. Alas, it turned out to be quite unsatisfactory as the protecting group was too labile under conditions of a trial alkylation reaction.

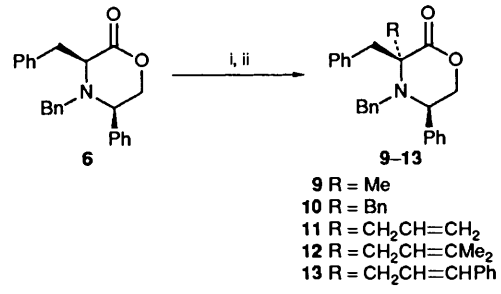


Scheme 2 *Reagents*: i, CH_2BrCO_2Et, Et_3N; ii, $PhCH_2OCOCl$, $NaHCO_3$; iii, *p*-TsOH; iv, LDA; then $PhCH_2Br$; v, HCO_2NH_4, Pd–C, EtOH

Table 1 Alkylation of oxazinone **6** – summary of results

Product	Base	Electrophile	Yield (%)
9	LDA	MeI	67
10	LDA	BnBr	68
	LDA	CH_2=$CHCH_2Br$	0
	LDA	Me_2C=$CHCH_2Br$	0
11	LiHMDS	CH_2=$CHCH_2Br$	43
12	LiHMDS	Me_2C=$CHCH_2Br$	57
13	LiHMDS	(*E*)-PhCH=$CHCH_2Br$	55

Eventually we found that reaction of *cis*-**5** with benzyl bromide and potassium carbonate yielded the *N*-protected oxazinone **6** in 61% yield after purification. This was alkylated with various electrophiles to give products **9–13** (Scheme 3),



Scheme 3 *Reagents*: i, Li Base/THF; ii, RX

by using either LDA or LiHMDS to generate the enolate (Table 1). It was interesting to note that alkylation could be achieved in good yield with LDA as base when using methyl iodide or benzyl bromide, to give **9** and **10** respectively, but with less reactive electrophiles the disilazide bases needed to be used. Reaction with allyl bromide, dimethylallyl bromide and cinnamyl bromide gave the alkylated products **11–13**. (When developing his reaction protocol, Dellaria [2] had reported total failure in the alkylation of the Boc-protected equivalent of compound **7** when using LDA and benzyl bromide in neat THF.) Enolate reactions are known to be sensitive to reaction conditions and one possible explanation for this observation relates to the stability of the enolate complex. Hexamethyldisilazane has been shown to be a poorer ligand than diisopropylamine,[10] because the nitrogen's lone pair is delocalised by the two $SiMe_3$ groups. This would suggest that the enolate complex with hexamethyldisilazane would be less stable, and more reactive, compared with that with diisopropylamine.

When considering the alkylation of compound **6** with various electrophiles, models suggested that the intermediate enolate

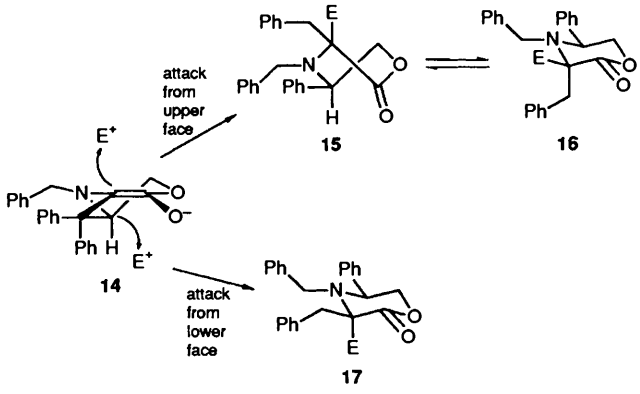
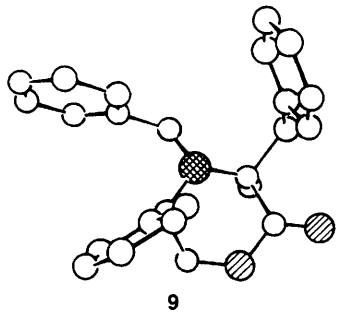


Fig. 1



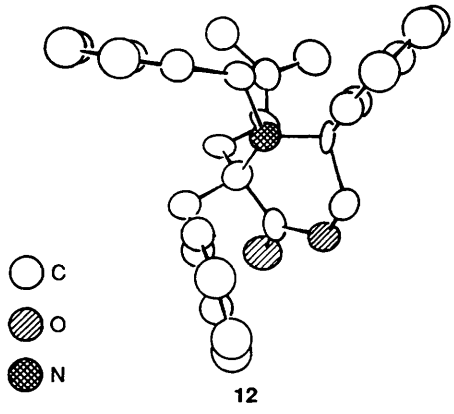


Fig. 2 Crystal structures of products **9** and **12** (hydrogen atoms omitted for clarity)

would adopt the half-chair conformation **14**, as shown in Fig. 1. Attack of the electrophile from the upper face would give the less stable twist-boat conformer as the initial product **15**, which would then flip into the chair conformation **16**, where the new substituent and C-5 phenyl group are *cis*. Attack from the bottom face would give directly the more stable chair conformation **17**, and would result in a *trans* relationship between the new substituent and the C-5 phenyl group. The incoming electrophile should not be affected by steric hindrance from the C-5 phenyl group, and so this would be the expected mode of alkylation.

The high-field ^1H NMR spectra of the products indicated in all cases that only one diastereoisomer had been formed, and crystal structures of the methyl and dimethylallyl derivatives **9** and **12** showed that alkylation of the enolates had indeed occurred from the least hindered face (Fig. 2). This resulted in the *trans* relationship between the C-5 phenyl group and the new substituent, which had been predicted by the models. It is interesting to note that the sense of diastereoselection observed is opposite to that reported by Dellaria [2] for the 3-unsubstituted

compound **2c**. In that example the 5-phenyl group and electrophile react so as to give a *cis* relationship between the two substituents. As yet no rational explanation can be put forward for this apparent contradiction.

The excellent stereocontrol observed in these alkylation reactions means that diastereoisomerically pure α,α-disubstituted α-amino acid derivatives could easily be obtained. Using Seebach's[7] principle of self-reproduction of chirality and an optically pure proteinogenic amino acid means that this can be achieved without the need of a chiral auxiliary. We hope that this method can be extended to α-amino acids other than phenylalanine with the same degree of success. If this is possible an even wider range of α,α-disubstituted amino acid derivatives can be made using this method.

Experimental

High-field ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using the high-field NMR service at the University of Warwick. Mass spectra were recorded at the SERC Mass Spectrometry Centre, University College of Swansea, and elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. IR spectra were recorded on a Perkin-Elmer 298 spectrometer, and m.p.s on a Kofler hot stage and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter, with values of $[\alpha]_D$ given in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was carried out according to the method of Still *et al.*,[11] using silica gel [Kiesel 60, 230–400 mesh (ASTM)] manufactured by Merck and Co. Light petroleum, unless otherwise stated, refers to the fraction boiling in the range 40–60 °C.

(3S,5R)-3-*Benzyl*-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* cis-**5**.—To a solution of freshly made imine **4**[8,9] (0.5 g, 1.9 mmol) in acetonitrile (40 cm^3) was added water (10 cm^3). Then 1 mol dm^{-3} HCl was added dropwise until the solution was at pH 5.0 (pH meter). After addition of sodium cyanoborohydride (0.13 g, 1.9 mmol) the pH was again adjusted to 5.0 by using 1 mol dm^{-3} HCl. The mixture was stirred at room temperature for 1.5 h, then stored at +4 °C overnight. A further portion of sodium cyanoborohydride (0.13 g, 1.9 mmol) was then added to the mixture and this was stirred at room temperature for 3 h, while the pH was kept at 5.0 by addition of 1 mol dm^{-3} HCl whenever necessary. The mixture was concentrated under reduced pressure, and the residue was dissolved in saturated aq. sodium hydrogen carbonate (100 cm^3). This was extracted with ethyl acetate (2 × 50 cm^3), and the organic fractions were then washed successively with saturated aq. sodium hydrogen carbonate (2 × 30 cm^3) and brine (2 × 30 cm^3). After being dried over potassium carbonate, the solution was evaporated under reduced pressure to give a clear oil. Purification of the product by flash chromatography, with (1:4) ethyl acetate–light petroleum (b.p. range 60–80 °C) as eluent, gave the title compound (0.204 g, 41%) as a microcrystalline solid, $[\alpha]_D^{22}$ −155.6 (*c* 2.28, $CHCl_3$) {lit.,[8,9] $[\alpha]_D^{22}$ −169 (*c* 2.28, $CHCl_3$)}; R_f 0.39 [(1:4) ethyl acetate–light petroleum (60–80 °C)]: ν_{max}(Nujol mull)/cm^{-1} 3310m, 1730s, 1380m, 1315m, 1190s, 1030m, 1010m, 760m, 745m, 720m and 700m; δ_H(400 MHz; $CDCl_3$) 1.875 (1 H, s, NH), 3.025 (1 H, dd, *J* 10.0 and 13.0), 3.570 (1 H, dd, *J* 3.0 and 13.0), 4.00 (1 H, dd, *J* 3.0 and 10.0), 4.160 (2 H, dd, *J* 11.0 and 19.0), 4.280 (1 H, dd, *J* 11.0 and 19.0) and 7.20–7.40 (10 H, m, Ph); δ_C(100 MHz; $CDCl_3$) 38.90 (CH), 57.10 (CH_2), 59.90 (CH_2), 74.60 (CH), 126.80 (CH), 126.85 (CH), 128.45 (CH), 128.55 (CH), 128.65 (CH), 129.25 (CH), 137.20 (C), 137.50 (C) and 168.90 (C).

(3S,5S)-*Benzyl* 3-*Benzyl*-2-*oxo*-5-*phenyl*-3,4,5,6-*tetrahydro*-2H-1,4-*oxazine*-4-*carboxylate* **8**.—To a solution of diisopropylamine (0.55 cm^3, 3.87 mmol) in THF (16 cm^3) at 0 °C under argon was added a 1.6 mol dm^{-3} solution of butyllithium in THF (2.2 cm^3; 3.52 mmol). The solution was stirred for 0.3 h, cooled to −78 °C, and added to a solution of compound **7**[2] (1.0 g, 3.2 mmol) in THF (16 cm^3) also at −78 °C. After the mixture had been stirred for 0.5 h, benzyl bromide (1.15 cm^3, 9.6 mmol) was added, and the mixture was allowed to warm up to room temperature over a period of 2 h. The resulting solution was then poured into water (30 cm^3), and extracted with methylene dichloride (3 × 30 cm^3). The organic layers were dried ($MgSO_4$) and evaporated to give a pale yellow solid. Purification by flash chromatography [ethyl acetate–hexane (3:7)], followed by recrystallisation from ethyl acetate–hexane, gave the *title compound* as a microcrystalline solid (0.9 g, 75%), m.p. 160–161 °C; $[\alpha]_D^{22}$ −40.0 (*c* 0.4 CH_2Cl_2); R_f 0.39 [(3:7) ethyl acetate–hexane] (Found: C, 74.7; H, 5.9; N, 3.5. $C_{25}H_{23}NO_4$ requires C, 74.81; H, 5.74; N, 3.49%); ν_{max}(Nujol)/cm^{-1} 1745s, 1688s, 1375s, 1335s, 1250m, 1240m, 1100s, 1080m, 960m, 750m and 700m; δ_H[300 MHz; $(CD_3)_2SO$; 343 K] 3.35 (1 H, dd, *J* 13.5 and 4.5), 3.48 (1 H, dd, *J* 13.5 and 7.5), 4.2–4.3 (1 H, m), 4.41 (1 H, dd, *J* 12.0 and 1.5), 5.07 (1 H, dd, *J* 7.5 and 4.5), 5.15–5.35 (3 H, m) and 7.10–7.45 (15 H, m, 3 Ph); *m/z* 419 [(M + NH_4)$^+$, 100%], 402 [(M + H)$^+$, 63], 358 (32), 266 (24), 108 (36) and 91 (75).

(3S,5S)-3-*Benzyl*-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* trans-**5**.—Ammonium formate (0.10 g, 1.56 mmol), 10% palladium-on-charcoal (0.50 g) and the ester **8** (0.105 g, 0.26 mmol) were stirred in ethanol (5 cm^3) at room temperature under argon for 0.3 h. The solution was then filtered through a Celite pad and this was washed with ethanol. Evaporation of the combined filtrate yielded a solid, and this was purified by flash chromatography [ethyl acetate–hexane (1:4)] and recrystallisation to give the product *trans*-**5** as crystals (0.044 g, 52%); R_f 0.56 [(3:7) ethyl acetate–hexane]; $[\alpha]_D^{22}$ −55.8 (*c* 3.0 in $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.58 (1 H, s, NH), 3.17 (1 H, dd, *J* 13.3 and 9.3), 3.30 (1 H, dd, *J* 13.3 and 3.7), 4.07 (1 H, dd, *J* 9.3 and 3.7), 4.25–4.45 (3 H, m) and 7.2–7.4 (10 H, m, 2 Ph); δ_C(75 MHz; $CDCl_3$) 37.9 (CH), 52.5 (CH_2), 57.2 (CH_2), 73.6 (CH), 127–129 (2 Ph) and 136.8 (C).

(3S,5R)-N,3-*Dibenzyl*-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* **6**[2].—To a solution of *cis*-**5** (0.091 g, 0.34 mmol) in dimethylformanide (DMF) (5 cm^3) were added potassium carbonate (0.040 g, 1.7 mmol) and benzyl bromide (0.22 cm^3, 1.7 mmol). The reaction mixture was refluxed for 3 h, cooled to room temperature, and then poured onto water (10 cm^3) and extracted with methylene dichloride (3 × 10 cm^3). The organic fractions were washed with water (3 × 10 cm^3), then dried over magnesium sulfate before being concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography [(3:17) ethyl acetate–hexane] gave compound **6** as a clear oil which solidified on storage (0.072 g, 61%), m.p. 95 °C, R_f 0.39 [(3:7) diethyl ether–light petroleum] (Found: C, 80.6; H, 6.4; N, 3.9. $C_{24}H_{23}NO_2$ requires C, 80.67; H, 6.44; N, 3.92%); ν_{max}(Nujol)/cm^{-1} 1730s, 1320m, 1260m, 1205m, 1150m, 1140m, 1060m, 1050m, 765m, 745m, 720m and 700s; δ_H(300 MHz; $CDCl_3$) 2.66 (1 H, dd, *J* 13.5 and 6.0), 3.02 (1 H, dd, *J* 13.5 and 3.6), 3.32 (1 H, dd, *J* 13.5 and 9.0), 3.47 and 3.81 (2 H, AB system, *J* 13.5), 3.78 (1 H, dd, *J* 9.0 and 6.0), 3.85 (1 H, dd, *J* 13.5 and 4.5), 4.04 (1 H, dd, *J* 3.6 and 4.5) and 7.0–7.5 (15 H, m, 3 Ph); δ_C(75 MHz; $CDCl_3$) 41.1 (CH_2), 57.7 (CH_2), 61.8 (CH), 63.9 (CH), 70.5 (CH_2), 126–138 (3 Ph) and 171.0 (C); *m/z* 356 [(M + H)$^+$ 16%], 267 (100), 208 (12), 207 (11), 166 (10), 118 (11), 117 (27), 105 (14), 104 (43), 103 (26), 102 (12) and 91 (77).

(3S,5R)-N,3-*Dibenzyl*-3-*methyl*-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* **9**.—To a solution of diisopropylamine (0.18 cm^3, 1.3 mmol) in THF (8 cm^3) under nitrogen at 0 °C was added 1.6 mol dm^{-3} butyllithium in hexanes (0.73 cm^3, 1.2 mmol). The mixture was stirred for 0.3 h, cooled to −78 °C, then added to a solution of compound **6** (0.309 g, 1.1 mmol) in THF (8 cm^3). After 0.75 h methyl iodide (0.2 cm^3, 3.3 mmol) was added and the mixture was allowed to warm up slowly to room temperature during 2 h. The reaction mixture was poured into water (10 cm^3), extracted with methylene dichloride (3 × 10 cm^3) and washed with water (3 × 10 cm^3). The organic fractions were dried ($MgSO_4$) and then concentrated to give a yellow oil. Purification by flash chromatography [(3:17) ethyl acetate–hexane], followed by recrystallisation from diethyl ether–hexane gave the *title product* **9** as microcrystals (0.260 g, 67%), m.p. 97–98 °C; $[\alpha]_D^{22}$ +81.2 (*c* 2.1, CH_2Cl_2); R_f 0.41 ($CHCl_3$) (Found: C, 80.6; H, 6.7, N, 3.6. $C_{25}H_{25}NO_2$ requires C, 80.86; H, 6.74; N, 3.77%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1738s, 1160s, 1140m, 1070s, 770m, 755m, 750s, 725m, 710m and 700s; δ_H(300 MHz; $CDCl_3$) 1.73 (3 H, s, Me), 2.98 and 3.13 (2 H, AB system, *J* 21.7), 3.75 and 3.91 (2 H, AB system, *J* 23.3), 3.88 (1 H, dd, $J_{5,6'}$ 16.3, $J_{5,6}$ 17.3), 3.97 (1 H, dd, $J_{6,6'}$ 5.0, $J_{6,5}$ 17.3), 4.11 (1 H, dd, $J_{6',6}$ 5.0, $J_{6',5}$ 16.3) and 7.0–7.4 (15 H, m, 3 Ph); *m/z* 372 [(M + H)$^+$, 100%], 280 (25) and 91 (30).

Crystal data for compound **9**. $C_{25}H_{25}NO_2$, M = 371.19, monoclinic, space group $P2_1$, a = 8.061(14), b = 9.570(20), c = 12.932(17) Å, β = 93.3(2)°, V = 995.9 Å^3, Z = 2, μ = 0.43 cm^{-1}, λ(Mo-Kα) = 0.7107 Å, F(000) = 396.0, D_c = 1.234 g cm^{-3}.

The data were collected for a triclinic cell and transformed to the monoclinic cell. The unit-cell parameters were determined by least-squares refinement of omega measurements for different layers.[12] The intensities of 2227 unique reflections with $2\theta < 5°$ and ($\pm h$, $\pm k$, $+l$) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite-monochromated Mo-Kα radiation using an omega-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1578 reflections with $I > 3\sigma(I)$.

The structure was solved using the TREF option of SHELXS-86.[13] All subsequent calculations were carried out using the computer program SHELX-76.[14]

Phenyl rings were included as rigid groups with D_{6h} symmetry and C–C distances of 1.395 Å. All hydrogen atoms were included in calculated positions (C–H 1.08 Å) with a fixed isotropic thermal parameter. All other atoms were refined with anisotropic thermal parameters.

Final cycles of refinement employed a weighting parameter g(0.00014) $\{w = 1/[\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices R $\{= \Sigma||F_o| - |F_c||/\Sigma|F_o|\}$ 0.0553 and R_w $\{=[\Sigma w(|F_o| - |F_c|)^2/\Sigma|F_o|^2]^{0.5}\}$ 0.0520.

The final difference Fourier map was featureless and an analysis of the weighting scheme over $|F_o|$ and sin θ/λ was satisfactory.

The geometry of the molecule is shown in Fig. 2. Final atomic positional and thermal parameters and lists of $|F_o|$- and $|F_c|$-values have been deposited as supplementary material with the Cambridge Crystallographic Data Centre.*

The derivative (5*R*)-*N*,3,3-tribenzyl-5-phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one **10** was prepared following the same general procedure as described for the methyl analogue **9** by using diisopropylamine (0.05 cm^3, 0.32 mmol), 1.6 mol dm^{-3} butyllithium (0.2 cm^3, 0.35 mmol), compound **6** (0.104 g, 0.29 mmol) and benzyl bromide (0.1 cm^3, 0.87 mmol). Yield was 0.089 g (68%); m.p. 160–161 °C; $[\alpha]_D^{22}$ −16.2 (*c* 2.1, CH_2Cl_2); R_f 0.41 [(1:4) ethyl acetate–light petroleum]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3060m, 3010m, 2920m, 1725s, 1495m, 1465m, 1335m, 1180s, 1160s, 1090m, 1070m and 700s; δ_H(300 MHz; $CDCl_3$) 3.05 and 3.21 (2 H, AB system, *J* 13.5), 3.42 and 3.63 (2 H, AB system, *J* 15.0), 3.80 (1 H, dd, $J_{6,6'}$ 3.0, $J_{6,5}$ 7.5), 3.90 and 4.24 (2 H, AB system, *J* 15.0), 3.93 (1 H, dd, $J_{6',6}$ 3.0, $J_{6',5}$ 10.5), 4.13 (1 H, dd, $J_{5,6}$ 7.5, $J_{5,6'}$ 10.5) and 6.8–7.4 (20 H, m, 4 Ph); δ_C(75 MHz; $CDCl_3$) 44.2 (CH_2), 45.1 (CH_2), 51.6 (CH_2), 58.1 (CH), 71.9 (CH_2), 72.1 (C), 125–140 (4 Ph) and 172.3 (C); *m/z* 447 [(M + H)$^+$, 5%), 357 (100), 103 (11) and 91 (100).

(3S,5R)-N,3-*Dibenzyl*-5-*phenyl*-3-(*prop*-2-*enyl*)-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* **11**.—To a solution of oxazinone **6** (0.044 g, 0.12 mmol) in THF (2 cm^3) under nitrogen at −78 °C was added 1 mol dm^{-3} LiHMDS (0.14 cm^3, 0.14 mmol). The mixture was stirred for 0.5 h, then 3-bromopropene (allyl bromide) (0.03 cm^3, 0.36 mmol) was added and the mixture was allowed to warm up slowly to room temperature during 2 h. The solution was then poured into water (100 cm^3), extracted with methylene dichloride (3 × 10 cm^3) and the combined organic fractions were washed with water (3 × 10 cm^3). After being dried over $MgSO_4$ the solution was concentrated under reduced pressure to give a yellow oil. This was purified using flash chromatography [ethyl acetate–light petroleum (1:19)] to yield *compound* **11** as an oil (0.021 g, 43%); $[\alpha]_D^{22}$ +55.8 (*c* 2.3, CH_2Cl_2); R_f 0.45 [(1:9) ethyl acetate–light petroleum] (Found: [M + H$^+$], 398.212. $C_{27}H_{27}NO_2$ requires [M + H$^+$], 398.204); $\nu_{max}(CHCl_3)/cm^{-1}$ 3040m, 3000m, 2840m, 1725s, 1495m, 1450s, 1440m, 1330s, 1185s, 1165s, 1090m, 1065s, 920m and 700s; δ_H(300 MHz: $CDCl_3$) 2.77 and 2.98 (2 H, AB system, *J* 12.0), 2.96 (1 H, dd, *J* 6.6 and 16.5), 3.10 (1 H, dd, *J* 6.6 and 15.0), 3.74 (1 H, dd, *J* 9.0 and 12.0), 3.83 and 4.11 (2 H, AB, system, *J* 15.0), 3.97 (1 H, dd, *J* 3.0 and 12.0), 4.23 (1 H, dd, *J* 3.0 and 9.0), 5.23–5.35 (2 H, m, CH_2=CH), 5.95–6.10 (1 H, m, CH_2=C*H*) and 6.90–7.40 (15 H, m, 3 Ph); δ_C(75 MHz; $CDCl_3$) 43.0 (CH_2), 45.2 (CH_2), 51.4 (CH_2), 60.4 (CH), 71.3 (CH_2), 71.7 (C), 119.5 (CH_2), 134.0 (CH), 126–140 (3 Ph) and 173.2 (C); *m/z* 307 [(M + H)$^+$, 100%], 358 (30), 357 (89), 105 (11), 104 (29), 103 (15) and 91 (77).

The derivative (3S,5R)-N,3-*dibenzyl*-3-(3-*methylbut*-2-*enyl*)-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* **12** was prepared following the same general procedure as described for compound **11**, by using 1 mol dm^{-3} LiHMDS (1.63 cm^3, 1.63 mmol), compound **6** (0.485 g, 1.36 mmol) in THF (15 cm^3), and 1-bromo-3-methylbut-2-ene (dimethylallyl bromide) (0.6 cm^3, 4.08 mmol): Yield was 0.330 g (57%); $[\alpha]_D^{22}$ +75.2 (*c* 2.3, CH_2Cl_2); R_f 0.47 [(1:9) ethyl acetate–light petroleum] (Found: [M + H$^+$], 426.243. $C_{29}H_{31}NO_2$ requires [M + H$^+$], 426.243); δ_H(300 MHz; $CDCl_3$) 1.74 (3 H, s, Me), 1.82 (3 H, s, Me), 2.73 and 2.97 (2 H, AB system, *J* 13.5), 2.9–3.0 (2 H, m), 3.65 (1 H, dd, *J* 9.0 and 10.5), 3.78 and 3.99 (2 H, AB system, *J* 15.0), 3.95 (1 H, dd, *J* 3.0 and 10.5), 4.25 (1 H, dd, *J* 3.0 and 9.0), 5.30–5.38 (1 H, m, CH=C) and 7.1–7.4 (m, 3 Ph); δ_C(75 MHz; $CDCl_3$) 18.6 (Me), 26.2 (Me), 37.2 (CH_2), 45.8 (CH_2), 51.8 (CH_2), 61.1 (CH), 71.1 (CH_2), 71.5 (C), 119.8 (CH), 134.6 (C), 126–142 (3 Ph) and 173.0 (C).

Crystal data for compound **12**. $C_{29}H_{31}NO_2$, M = 425.54, orthorhombic, space group $P2_12_12_1$, a = 22.215(21), b = 10.189(9), c = 10.575(6) Å, V = 2393.64 Å^3, Z = 4, μ = 0.40 cm^{-1}, λ(Mo-Kα) = 0.71069 Å, F(000) = 912.0, D_c = 1.18 g cm^{-3}.

The unit-cell parameters were determined by least-squares refinement of omega measurements for different layers. The intensities of 3095 reflections were measured from layers ($\pm h$, $+k$, 0–13l) in the range $7 \leqslant 2\theta \leqslant 45°$ on a Stoe STADI-2 Weissenberg diffractometer, with an omega-scan technique using the monoclinic cell a = 14.685, b = 22.215, c = 14.685,

* Supplementary data (see section 5.6.3 of Instructions for Authors, issue 1).

$\beta = 92.13$. The data were corrected for Lorentz and polarisation effects to give 1353 reflections with $I \geqslant 3\sigma(I)$. The monoclinic cell was transposed to the orthorhombic cell by using the transformation matrix 0 1 0, 0.5 0 0.5, 0.5 0 −0.5.

The structure was solved by direct methods using SHELXS-86.[13] All subsequent calculations were carried out using the computer program SHELX-76.[14]

Phenyl rings were included as rigid groups with D_{6h} symmetry and C–C distances of 1.395 Å. The hydrogen atoms were included in calculated positions (C–H 1.08 Å). All non-hydrogen atoms, with the exception of the phenyl C atoms, were refined anisotropically.

Final cycles of refinement employed a weighting parameter k (2.2920) g (0.000373) $\{w = k/[\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices R $\{=\Sigma||F_o| - |F_c||/\Sigma|F_o|\}$ 0.0853 and R_w $\{=[\Sigma w||F_o| - |F_c|)^2|/\Sigma|F_o|^2]^{0.5}\}$ 0.0773.

The final difference Fourier map and an analysis of the weighting scheme over $|F_o|$ and sin θ/λ was satisfactory.

The geometry of the molecule is shown in Fig. 2. Final atomic positional and thermal parameters and lists of $|F_o|$- and $|F_c|$-values have been deposited as supplementary material with the Cambridge Crystallographic Data Centre.*

The derivative (3S,5R)-N,3-*dibenzyl*-3-[(E)-*cinnamyl*]-5-*phenyl*-3,4,5,6-*tetrahydro*-1,4-*oxazin*-2-*one* **13** was prepared by following the same general procedure as described for *compound* **11**, using 1 mol dm^{-3}, LiHMDS (1.57 cm^3, 1.57 mmol), *compound* **6** (0.468 g, 1.31 mmol) in THF (15 cm^3) and (*E*)-cinnamyl bromide (0.77 cm^3, 3.93 mmol). Yield was 0.342 g (55%); $[\alpha]_D^{22}$ −24.5 (*c* 2.5, CH_2Cl_2); R_f 0.38 [(1:9) ethyl acetate–light petroleum] (Found: [M + H$^+$], 474.243. $C_{33}H_{31}NO_2$ requires [M + H$^+$], 474.235); $\nu_{max}(CHCl_3)$/cm^{-1} 3080m, 3060m, 2920m, 1725s, 1490m, 1450m, 1185m, 1150m, 1065m, 970m, 915m and 700s; δ_H(300 MHz; $CDCl_3$) 2.88 and 3.05 (2 H, AB system, *J* 13.5), 3.10–3.25 (2 H, m), 3.75 (1 H, dd, *J* 9.0 and 10.8), 3.89 and 4.17 (2 H, AB system, *J* 15.0), 3.98 (1 H, dd, *J* 10.8 and 3.0), 4.23 (1 H, dd, *J* 9.0 and 3.0), 6.25–6.38 (1 H, m), 6.57 (1 H, d, *J* 16.5) and 7.1–7.5 (20 H, m, 4 Ph); δ_C(75 MHz; $CDCl_3$) 45.1 (CH_2), 51.3 (CH_2), 60.3 (CH), 71.4 (CH_2), 71.8 (C), 125.4 (CH), 126.2 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 129.9 (CH), 130.1 (CH), 130.8 (CH), 134.0 (CH), 137.0 (C), 137.1 (C), 137.9 (C), 139.9 (C) and 172.3 (C); *m/z* 474 [(M + H)$^+$, 15%], 383 (17), 356 (100), 355 (60), 354 (38), 266 (100), 238 (13), 220 (11), 208 (17), 207 (18), 206 (26), 205 (12) and 193 (11).

* Supplementary data (see section 5.6.3 of Instructions for Authors, issue 1).

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References

1 R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989.
2 J. F. Dellaria and B. D. Santarsiero, *Tetrahedron Lett.*, 1988, **29**, 6079; *J. Org. Chem.*, 1989, **54**, 3916.
3 W. R. Baker, S. L. Condon and S. Spanton, *Tetrahedron Lett.*, 1992, **33**, 1573.
4 For example, see: R. M. Williams, P. J. Sinclair, D. Zhai and J. Reibenspies, *J. Am. Chem. Soc.*, 1986, **108**, 1103; R. M. Williams, P. J. Sinclair, D. Zhai and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547.
5 R. M. Williams and M.-N. Im, *Tetlahedron Lett.*, 1988, **29**, 6075; *J. Am. Chem. Soc.*, 1991, **113**, 9276.
6 J. E. Baldwin, V. Lee and C. J. Schofield, *Synlett*, 1992, 249.
7 M. Boes, R. Naef, W. B. Schweizer and D. Seebach, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
8 G. Schulz and W. Steglich, *Chem. Ber.*, 1977, **110**, 3615.
9 V. Caplar, A. Lisini, F. Kajfez, D. Kolbah and V. Sunjic, *J. Org. Chem.*, 1978, **43**, 1355.
10 L. Duhamel, S. Fouquay and J.-C. Plaquevent, *Tetrahedron Lett.*, 1986, **27**, 4975.
11 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
12 W. Clegg and G. M. Sheldrick, *Z. Kristallogr.*, 1984, **167**, 23.
13 G. M. Sheldrick, SHELXS-86, Program for Crystal Structure Solution, University of Göttingen, Germany, 1986.
14 G. M. Sheldrick, SHELX–76, Program for Crystal Structure Determination. University of Cambridge, 1976.

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