Asymmetric Syntheses of the Naturally Occurring β-Amino Acids, β-Lysine, β-Leucine and β-Phenyl-β-alanine via Nitrone Cycloaddition

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A general asymmetric synthesis of β-amino acids is based on the dipolar cycloaddition of nitrones **7** (R* chiral) with vinyl acetate **8a**, ketene acetals **8b** or α-chloroacrylonitrile **8c**. The cycloadducts **9** are converted either directly (**9b**) or via the isoxazolidinones **10** (**9a, 9c**) into the free β-amino acids **11**. Diastereoselectivity at C-3 in the adducts **9** ranges between 2:1 and 11:1. The natural β-amino acids, β-lysine, β-leucine and β-phenyl-β-alanine, have been prepared in this way.

β-Amino acids have emerged in recent years as substances of considerable biological interest.[1-3] They are components of a growing list of important antibiotics. Thus, (3S)-β-lysine is widely produced by *Streptomyces* species and incorporated into a large family of broad-spectrum antibiotics.[4,5] Of these, strepto-thrycin F, which contains one β-lysine residue, has received most attention,[6,7] but the racemomycins[5,8] (RM-A = strep-tochrycin F) form a homologous series with up to seven β-lysine residues linked in a peptide chain. (3S)-β-Lysine also forms part of the cyclic peptide antibiotic viomycin,[9] while (3R)-β-lysine and its 5-hydroxy congeners are the sole amino acids in the unusual hydrazide antibiotics, the negamycins.[10] β-Tyrosine forms part of a group of large-peptide antibiotics, the edeins,[11] and β-arginine is part of the nucleoside antibiotic blasticidin S.[12,13]

The origin of β-amino acids in Nature and their role in primary metabolism are also of considerable interest. (3S)-β-Lysine is the first intermediate in the anaerobic fermentation of (2S)-α-lysine in *Clostridia*.[14] The stereochemistry of the lysine-2,3-aminomutase reaction has been established and the nitrogen migration shown to be intramolecular by NMR.[7] Poston has isolated leucine-2,3-aminomutase activity from a variety of sources and has proposed that it is the first intermediate in an alternative catabolic pathway for α-leucine.[15] It appears that the co-factor requirements and stereochemical characteristics for the lysine-,[7] leucine-,[15,16] tyrosine-[17] and arginine-2,3-aminomutase[13] reactions differ in important respects. Thus, although β-amino acids are probably formed from the corresponding α-amino acids, there may well be a variety of mechanisms for the amino group migration.

An effective and versatile stereocontrolled synthesis of β-amino acids seemed therefore worthwhile. Additionally, it might serve for the construction of peptides and peptide analogues and also lead to β-lactams. Two simple recent illustrations are syntheses of aspartame[18] and of a potential thienamycin intermediate.[19]

In previous asymmetric syntheses of β-amino acids the new chiral centre at C_β was generated either by nucleophile addition at sp² carbon or by hydrogenation of αβ-dehydro-β-amino esters. Examples are the diastereoselective Michael addition of amines to crotonates,[20,21] reaction of Reformatsky reagents with Schiff bases[22,23] and catalytic reduction of β-amino crotonates,[24,25] the chiral inducing element being in either reagents or catalysts. Optical yields have been disappointing, often not exceeding 20%. In a recent synthesis, the first of a naturally occurring β-amino acid, (S)-β-phenyl-β-alanine [a component of the cyclic spermidine alkaloid (S)-dihydro-periphylline] was obtained in 13 steps from L-diethyl tartrate. The enantioselective step went in 72% ee and the overall yield was about 5%.[26]

Results and Discussion

Our asymmetric synthesis of β-amino acids was based on two previous observations: (i) Belzecki and Panfil found[27] that 1,3-dipolar cycloaddition of nitrones **1**, bearing a chiral substituent at nitrogen, with mono-substituted alkenes **2** gives 3,5-substituted isoxazolidines **3** diastereoselectively; (ii) Huisgen observed[28] that C,N-diphenylnitrone **4** adds to ketene diethyl acetal **5** regioselectively to afford the 5,5-disubstituted iso-xazolidine **6** exclusively.


R* = (R)-(−)-α-methylbenzyl
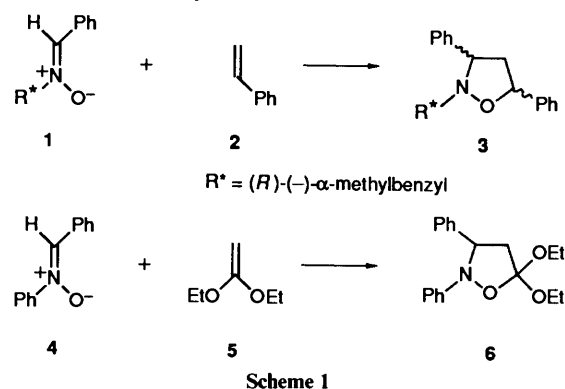
Scheme 1

On the basis of these experiments we chose the route shown in Scheme 1. Cycloaddition of the appropriate nitrone **7** with vinyl acetate **8a**, ketene acetals **8b** or α-chloroacrylonitrile **8c** afforded isoxazolidines **9** functionalised at C-5. The adducts **9a** from vinyl acetate required hydrolysis to the lactol and oxidation to the isoxazolidinone **10**. The latter step proved exceedingly troublesome, in that of the range of available oxidising agents none was generally applicable and the best worked in only

	X	Y
8a	OAc	H
8b	RO	OR
8c	Cl	CN
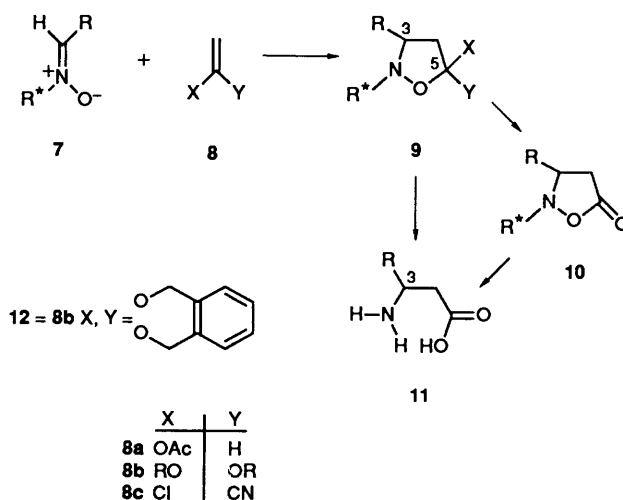
moderate yield. The use of α-chloroacrylonitrile **8c** circumvented this difficulty since the adducts **9c** were readily hydrolysed to the isoxazolidinones **10**. Hydrogenolysis of **10** cleaved both the weak N–O bond and also the N–R* bond (R* = benzylic), generally affording the free β-amino acids **11** in excellent yields. Experiments with the ketene acetals **8b** were confined to the special case of **12**, where both R groups are benzylic. Hydrogenolysis of **9b** here gave the β-amino acid direct. Chirality at C-3 in **11** was induced by the N-phenethyl group (R*) in nitrone **7**. Diastereoselectivity varied between 2:1 and 11:1.
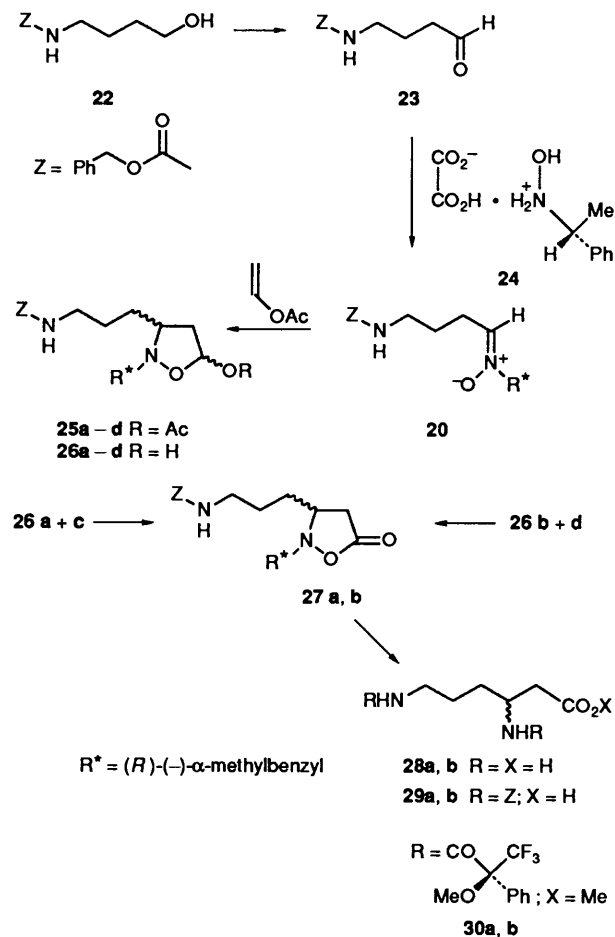
Cycloaddition of Nitrones with Vinyl Acetate.—The route to isoxazolidine-5-ones **10** was first explored with two achiral nitrones (Scheme 2). Addition of vinyl acetate to C-phenyl-N-
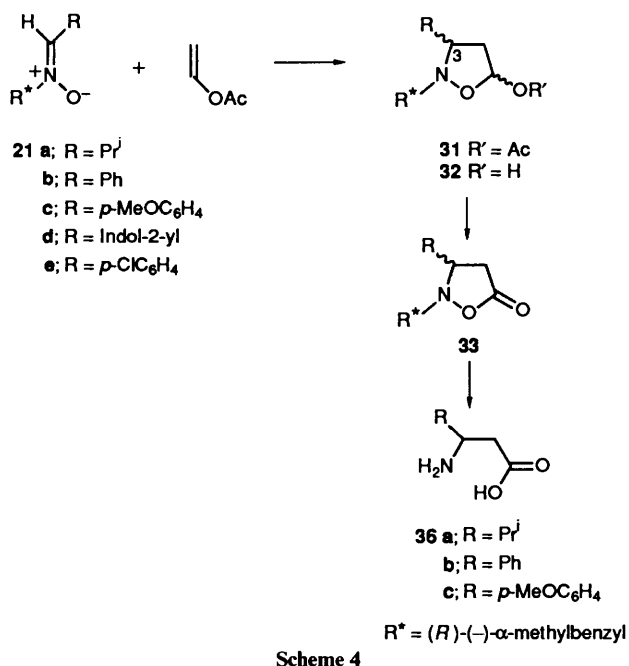
13 R = CH₂Ph
18 R = Me

17 R = CH₂Ph
19 R = Me

Scheme 2
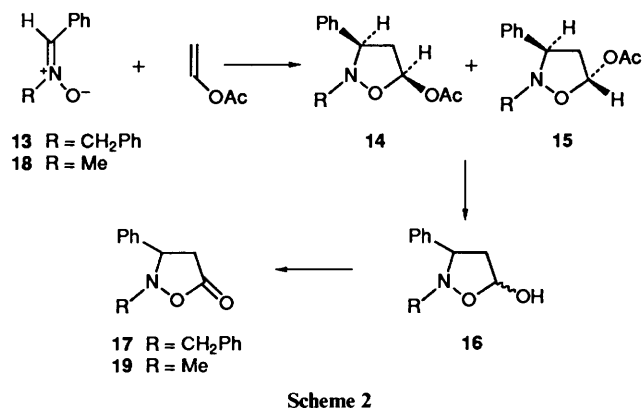
benzyl nitrone **13** afforded two diastereomeric isoxazolidines **14** and **15** (3.5:1 from OCOMe signals in the ¹H NMR). Cycloaddition was regiospecific in the sense shown (1 H multiplet at δ 6.3; overlapping 5-H's). The major isomer, separated by preparative TLC (PLC), showed a doublet of doublets at δ 6.35 (*J* 3, 6.5 Hz). It was assigned structure **14** and must have been formed via an exo-transition state, in accordance with previous work by DeShong.[29] Hydrolysis with potassium carbonate in aqueous methanol afforded the lactol mixture **16** (83%) (δ 5.50, 1 H, m; ν_max 3600 and 3450 cm⁻¹). Oxidation of **16** to the isoxazolidinone **17** proved to be the most difficult step in this sequence. Of the methods tried (PDC,[30] PCC,[31] Swern,[32] TMS-ether/Ph₃CBF₄,[33] NCS/Me₂S[34]), only the Jones[35] and Collins[36] reagents gave workable, if poor, yields (36 and 48%, respectively). Cinnamaldehyde was a major by-product, arising presumably from ring-opening of the lactol followed by β-elimination of the hydroxylamine. The isoxazolidinone **17** (ν_max 1780 cm⁻¹) was identical with a sample prepared by condensing C-phenyl-N-benzylnitrone with the Reformatsky reagent from ethyl α-bromoacetate, according to the procedure of Stamm.[37] C-Phenyl-N-methylnitrone **18** condensed with vinyl acetate similarly, affording a 2:1 mixture of the diastereoisomeric acetates, which was hydrolysed and oxidised (Collins; 21% yield) to the isoxazolidinone **19**.

Attention was next directed to the asymmetric synthesis of β-lysine, β-leucine, β-phenyl-β-alanine and β-tyrosine (methyl ether). To this end, the nitrones **20** and **21a–c** were condensed with vinyl acetate in the expectation that the chiral phenethyl group would induce chirality at C-3 of the isoxazolidine acetates **25** and **31** formed (Scheme 4). The synthesis of pure (*R*)- and (*S*)-β-lysine **28a**, **b** is described in detail[38] (Scheme 3).

The requisite nitrone **20** was prepared as follows: Swern oxidation of the N-protected 4-aminobutan-1-ol **22** gave the aldehyde **23** as an unstable oil. This was reacted immediately with the hydroxylamine oxalate **24**[39] to furnish the nitrone **20**, m.p. 92–96 °C in 91% overall yield from **22**. Reaction of the nitrone **20** with vinyl acetate can result in four diastereomeric

Z = Ph

22 → **23**

24

25a – d R = Ac
26a – d R = H

20

26 a + c → ← **26 b + d**

27 a, b

R* = (*R*)-(-)-α-methylbenzyl

28a, b R = X = H
29a, b R = Z; X = H

R = CO—CF₃
      |
MeO   Ph ; X = Me

30a, b

Scheme 3

acetates **25a–d**. They arise from interaction of the reactants in an exo- or endo-manner and reaction at the Re or Si-face of vinyl acetate.[29] In the event, four acetates were formed (68%) and could be separated by flash chromatography into two pairs (7:3 = diastereoselectivity at C-3). Each pair consisted of C-5 epimers but had only one configuration at C-3 (see below) [δ 6.42 and 6.20 (OC*H*OAc)]. Hydrolysis of each acetate pair to the corresponding pair of alcohols (**26a, c,** δ 5.61 and **26b, d,** δ 5.35 OC*H*OH) and Collins oxidation gave the pure isoxazolidinones **27a, b**. Hydrogenolysis, as before, of **27a** afforded (*S*)-(−)-β-lysine **28a**, [α]_D + 18° (lit.,[40] +24°) and **27b** gave (R)-(+)-β-lysine **28b**, [α]_D − 19.5°, both characterised as the crystalline N,N-dibenzyloxycarbonyl derivatives **29a, b**, m.p. 153–156 °C. The optical purity of the (*R*)- and (*S*)-β-lysines from hydrogenolysis was checked by conversion of the total product into the methyl ester bis-(*S*)-methoxy(trifluoromethyl)phenyl-acetamides **30a, b**. They could not be clearly identified in the ¹⁹F NMR spectrum because other fluorine-containing products interfered, but they were readily separated by GC on a capillary OV-1 column. Each isomer was uncontaminated by the other. Authentic specimens of (*R*)- and (*S*)-β-lysine were prepared by Arndt–Eistert homologation of (*R*)- or (*S*)-dibenzyloxycarbon-ylornithine. Comparison of derivatives **29a, b** and **30a, b** showed complete identity of the (*R*) and (*S*)-β-lysines prepared by the two routes. β-Leucine **36a**, β-phenyl-β-alanine **36b** and β-tyrosine methyl ether **36c** were synthesised similarly (Scheme 4). Thus nitrone **21a** with vinyl acetate gave the isoxazolidinyl acetate **31a** as a mixture of four diastereoisomers, not separable by PLC (3:1:1:1 from integration of 5-H's; diastereoselectivity at C-3, 2:1). Hydrolysis and Swern oxidation afforded the isoxazolidinone **33a**, accompanied by the Δ⁴-isoxazolidine **34**,

21 a; R = Pr^i
b; R = Ph
c; R = p-MeOC$_6$H$_4$
d; R = Indol-2-yl
e; R = p-ClC$_6$H$_4$

31 R' = Ac
32 R' = H

33

36 a; R = Pr^i
b; R = Ph
c; R = p-MeOC$_6$H$_4$

R* = (R)-(−)-α-methylbenzyl

Scheme 4

from elimination of the intermediate 35. Hydrogenolysis of 33a gave β-leucine 36a quantitatively, m.p. 204–207 °C, [α]$_D$ −22.4° (lit.,[41] m.p. 201–202°, [α]$_D$ +55.2° for (S)-β-leucine). Formation of (R)-β-leucine in about 35% ee implies that the nitrone 21a underwent preferential cycloaddition to the Si face of vinyl acetate via an exo transition state. The nitrone 21b furnished the

34

35
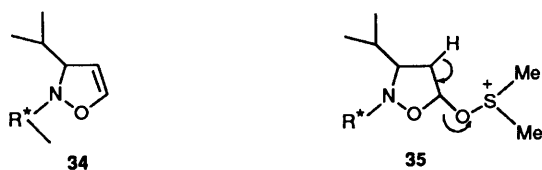
isomeric acetates 31b (1:8:5:5; diastereoselectivity at C-3, 2:1). Hydrolysis as before and Collins oxidation of the lactol mixture afforded the isoxazolidinone 33b, contaminated with cinnamaldehyde. PLC and crystallisation gave 33b as a mixture of diastereoisomers not resolvable in either the ^{1}H or ^{13}C NMR spectrum or by capillary GC. Hydrogenolysis gave (R)-β-phenyl-β-alanine 36b in 25% ee, m.p. 231–234 °C, [α]$_D$ −1.5° [(S)-β-phenyl-β-alanine, m.p. 232 °C, [α]$_D$ +6.2°[41]]. The initial cycloaddition thus proceeds with the same topology and diastereoselectivity as for nitrone 21a. Cycloaddition of the nitrone 21c and vinyl acetate was much slower than before, presumably because of the increased electron density at the C=N bond. Only two isomeric acetates 31c were formed (1:1). They were not separable but the acetal H's in the 200 MHz NMR spectrum showed well-resolved multiplets (δ 6.38, ddd, J 0.2 and 6.5 Hz; δ 6.32, ddd, J 1, 4 and 7 Hz). The small-range coupling in each case indicates that the 3- and 5-H's are syn. This implies that addition has occurred exclusively in an exo sense but with equal ease at the Re or Si face of the olefin. Oxidation of the lactol mixture 32c proved difficult with all the previous reagents but succeeded with anhydrous N-methylmorpholine N-oxide in presence of hydrated RuCl$_3$.[42] The ^{1}H NMR spectrum showed a 1:1 mixture of products 33c [δ 3.77 and 3.70, (OMe)], from which one, m.p. 127–128 °C could be crystallised (one isomer by ^{1}H and ^{13}C NMR). The same enantiomer was obtained as the only product from cycloaddition of α-chloroacrylonitrile with nitrone 21c (see Experimental section). Hydrogenolysis of this afforded (R)-β-tyrosine methyl ether 36c, m.p. 241–243 °C [α]$_D$ −7.2° [(S)-β-tyrosine has [α]$_D$ +7.8°[17]], optically pure

(Mosher amide ^{1}H and ^{19}F NMR and GC on two capillary columns).

An attempt to synthesise β-tryptophan was unsuccessful. The α-indolylnitrone 21d did not undergo cycloaddition with vinyl acetate under the previously successful conditions. The only product obtained was the (N-acetyl)indolylnitrone.

Cycloaddition of Nitrones with α-Chloroacrylonitrile.[*]—α-Chloroacrylonitrile (α-CAN) is an effective ketene equivalent in Diels–Alder additions.[43] The chloronitrile adduct is readily transformed into the corresponding ketone by alkaline hydrolysis.[44] It therefore seemed sensible to replace vinyl acetate with α-CAN in the cycloaddition with nitrones. Provided the reaction is regiospecific in the same sense, hydrolysis should afford the isoxazolidinone directly, thus circumventing the difficult oxidation step.

Reaction of the nitrone 37 with α-CAN afforded a mixture of products with very similar R_f values whose 200 MHz NMR spectrum showed the presence of at least four different methoxy

37 R = p-MeOC$_6$H$_4$
42 R = Me

38

41
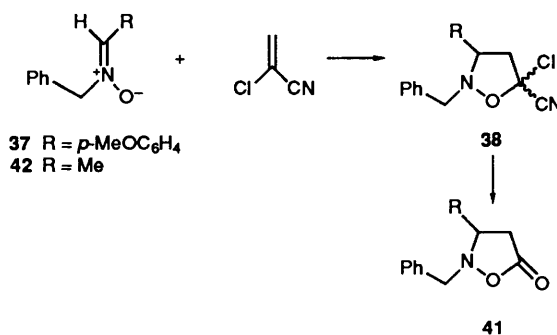
groups. In addition to the expected epimeric chloronitriles 38a, b, both the product of HCl loss 39 and the unsaturated keto nitrile 40 appear to be major products. The latter was recovered in 75% yield as a crystalline solid, m.p. 125–126 °C, when nitrone 37 was heated at reflux in α-CAN for 24 h. Attempts to hydrolyse the adduct mixture with KOH in DMSO were unsuccessful. However, triethylamine (1.5 equiv.) in aqueous THF solution

C$_6$H$_4$OMe-p

39

C$_6$H$_4$OMe-p

40

converted the adduct mixture into the isoxazolidinone 41 in 42% yield. C-Methyl-N-benzylnitrone 42 reacted much more rapidly and hence more cleanly (10 min; 74% yield), affording the isoxazolidinone 41 in 74% yield on hydrolysis.

The more facile reaction of C-alkyl as against C-aryl nitrones was mirrored in the preparation of the isoxazolidinones 43 and 44, previously transformed into β-phenyl-β-alanine and β-leucine, respectively. Thus nitrone 45 ≡ 21b and α-CAN afforded after hydrolysis 43 ≡ 33b in 20% yield. Its ^{1}H NMR spectrum suggested the presence of only one diastereoisomer. Hydrogenolysis gave β-phenyl-β-alanine, m.p. 231–233 °C, [α]$_D$ +5.4° [(S)-β-phenyl-β-alanine has [α]$_D$ +6.2°] in 80% ee.

The nitrone 46 ≡ 21a on cycloaddition gave 44 ≡ 33a in 48% yield after hydrolysis. However, hydrogenolysis in this case furnished (R)-β-leucine, m.p. 197–200 °C, [α]$_D$ −15° in only 46% ee. On the other hand, a change in the N-attached inducing group had a marked effect on the diastereoselectivity of the

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* For further applications of α-CAN in cycloadditions, see Refs. 18 and 19.

45 R = Ph   43
46 R = Pr^i 44

48   49
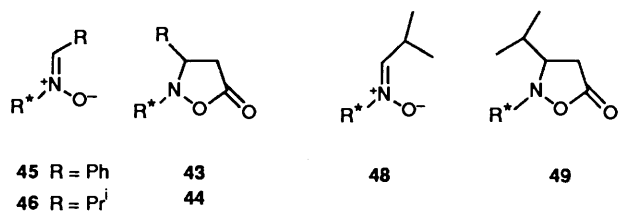
R* = (R)-(-)-α-methylbenzyl   R* = (R)-α-methoxylcarbonylbenzyl

cycloaddition. Thus the nitrone 48 gave the isoxazolidinone 49 in 30% yield as a 11:1 diastereomeric mixture in favour of the isomer corresponding to (R)-β-leucine, equivalent to 80% ee.

Cycloaddition of Nitrones with Ketene Acetals.—As previously mentioned, Huisgen had found that C,N-diphenylnitrone adds to ketene diethyl acetal regioselectivity to afford the 5,5-disubstituted isoxazolidine. The stable crystalline ketene acetal 50, introduced by Grewe,[45] seemed an attractive dipolarophile for our purpose, since, apart from its ease of handling, hydrogenolysis of the cycloaddition product should lead to the free amino acid directly.

50   51

52

53 R = Ph
56 R = ClC$_6$H$_4$-p
57 R = MeOC$_6$H$_4$-p
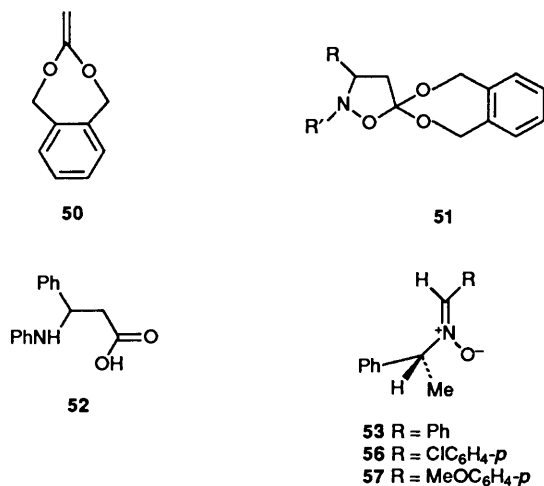
Cycloaddition of C,N-diphenylnitrone with the ketene acetal 50 afforded the isoxazolidine 51, m.p. 130–131 °C (63%). Hydrogenolysis at 20 °C afforded N-phenyl-β-phenyl-β-alanine 52, m.p. 118–120 °C in 80% yield. The chiral nitrone 21b reacted with 50 more sluggishly (12%) but chiral induction at C-3 was moderately good (diastereoisomer ratio 4:1). The yield improved with an electron-withdrawing substituent, as in compound 21e (28%; 3.5:1), but there was no reaction with 21c.

Experimental

M.p.s, determined on a Kofler hot-stage apparatus, are uncorrected. IR spectra were obtained on a Perkin-Elmer 580 spectrophotometer. ^{1}H NMR spectra were obtained in deuteriochloroform (unless otherwise stated) using tetramethylsilane (TMS) as internal standard on the Perkin-Elmer R.32 (90 MHz), Varian XL 100 (100 MHz) or Bruker WP 200 SY (200 MHz) spectrometers, the last employing a deuterium lock system setting either chloroform (CHCl$_3$) in CDCl$_3$ at δ 7.25 or methanol (CH$_3$OH) in CD$_3$OD at δ 3.35 as internal standard. ^{13}C NMR spectra were obtained on either the Varian XL 100 (25.2 MHz) or the Bruker WP 200 SY (55 MHz) spectrometers, either in deuteriochloroform (reference CDCl$_3$ signal at δ 77.0), deuteriomethanol (CD$_3$OD at δ 49.0) or in [^{2}H$_6$]DMSO [(CD$_3$)$_2$SO at δ 40.0]. All J values are in Hz. Mass spectra were obtained with the V.G./Kratos M.S. 12 or V.G./Kratos M.S. 9025 (high resolution) spectrometers.

Precoated Merck Kiesel-gel 60-F254 20 × 20 cm, 0.2 mm plates were used for analytical TLC, and 20 × 20 cm, 0.25 mm plates for PLC. Flash column chromatography was done over Fluka Kieselgel GF-254 silica gel. Capillary GC was carried out on a Hewlett Packard 5880A GC with dual capillary columns and FID detectors. The capillary columns used were fused silica capillary 25 m × 0.32 mm (internal diameter) SE-54 (GC^2, Northwich, Chester) or CP Sil5B. The sample was injected via Grob-type injectors in split mode (50:1) using helium as both carrier and make up gas (flow rates 3 and 25 cm^3 min^{-1}, respectively). GC-MS was performed with an LKB 9000 instrument fitted with DB-1 fused silica capillary columns, 60 m × 0.3 mm I.D. (J. and W. Scientific, Rancho Cordova, CA, USA) and a falling needle injector. Helium was used as both carrier and make-up gas (flow rates 7 and 25 cm^3 min^{-1}, respectively, measured at ambient temperature). Mass spectra were recorded under electron impact conditions (20 eV); accelerating voltage 3.5 kV; trap current 60 μA; source and separator temperatures 260 °C. Optical rotations were measured at ambient temperature on an Optical Activity AA-100 polarimeter.

Solvents were dried and purified prior to use as follows: acetone [distilled from K$_2$CO$_3$, stored over molecular sieves (4 Å)]; benzene, toluene (dried and stored over sodium metal); carbon tetrachloride [filtered through alumina (basic, activity 1)]; dichloromethane [distilled from P$_2$O$_5$, stored over molecular sieves (4 Å)]; ether and tetrahydrofuran (THF) (distilled from sodium and benzophenone immediately before use); dimethylformamide (DMF) [distilled from blue silica gel, stored over molecular sieves (4Å)]; dimethyl sulphoxide (DMSO) [dried and stored over molecular sieves (4 Å)]; triethylamine [distilled from anhydrous KOH, stored over molecular sieves (4 Å)].

1,3-Dipolar Cycloadditions of Nitrones to Vinyl Acetate.— 5-Acetoxy-N-benzyl-3-phenylisoxazolidines 14 and 15 (R = CH$_2$Ph). N-(Benzylidene)benzylamine N-oxide 13, (1.03 g, 4.9 mmol) was dissolved in an excess of freshly distilled vinyl acetate (30 cm^3, 0.37 mmol) and heated at reflux with exclusion of light, under an argon atmosphere for 60 h. Excess of vinyl acetate was removed under reduced pressure and the residue purified by flash column chromatography (ether–hexane, 1:1) to give the isoxazolidines 14, 15 (0.98 g, 67%), as a colourless oil (Found: M$^+$, 297.1360. C$_{18}$H$_{19}$NO$_3$ requires M, 297.1365); $ν_{max}$(CHCl$_3$)/cm^{-1} 1738, 1498, 1458, 1378, 1240, 1010 and 970. Isomers 14 and 15 were separated by PLC (ether–hexane, 1:4, 3 × developed).

(a) Isoxazolidine 14 $δ_H$(200 MHz) 2.10 (3 H, s), 2.40 (1 H, ddd, J 3, 9.5 and 13.6), 3.03 (1 H, ddd, J 6.6, 8.0 and 13.6), 3.79 (1 H, d, J 14.8), 3.82 (1 H, dd, J 8 and 9.5), 4.07 (1 H, d, J 14.8), 6.35 (1 H, dd, J 3 and 6.5) and 7.20–7.51 (10 H, m); $δ_C$(^{1}H decoupled) 21.37, 46.36, 59.27, 69.51, 95.05, 127.14, 127.88, 128.06, 129.14, 128.75, 128.96, 136.86 and 170.60.

(b) Isoxazolidine 15 $δ_H$(200 MHz) 2.07 (3 H, s), 2.62 (2 H, m), 4.01 and 4.13 (2 H, AB q, J 14), 4.24 (1 H, t, J 8.5), 6.37 (1 H, m) and 7.20–7.45 (10 H, m); $δ_C$(^{1}H decoupled) 21.44, 29.69, 45.64, 62.27, 66.69, 96.54, 122.33, 127.52, 127.98, 128.18, 128.69, 129.27, 136.77, 138.34 and 169.98.

General Procedure for the Hydrolysis of Isoxazolidinyl Acetates.—The acetate (0.01 mol) was dissolved in aqueous methanol (ca. 10:1 MeOH–H$_2$O) containing potassium carbonate (0.005 mol) and the resulting solution stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue dissolved in water (50 cm^3). The aqueous solution was extracted with ether (3 × 50 cm^3) and the combined organic layers were dried (MgSO$_4$), filtered and evaporated to give crude lactol. The lactol was generally used without purification.

N-*Benzyl-5-hydroxy-3-phenylisoxazolidine* **16**. Acetate mixture **14**, **15** (3.0 g, 10 mmol) was hydrolysed with potassium carbonate (0.70 g, 5 mmol) in methanol (55 cm³)–water (5 cm³) according to the general procedure to give the crude isoxazolidine lactol mixture **16** (2.14 g, 83%) as a colourless oil (Found: M⁺, 255.1255. $C_{16}H_{15}NO_2$ requires M, 255.1349); v_{max}(CHCl₃)/cm⁻¹ 3600, 3450, 1500, 1460, 1068 and 1032; δ_H 2.08–2.55 (1 H, m), 2.75–3.30 (1 H, m), 3.41–4.40 (3 H, m), 5.50 (1 H, m) and 7.15–7.80 (10 H, m).

Jones Oxidation of the Lactol **16**.[35]—The crude lactol mixture **16** (0.2 g, 0.78 mmol) dissolved in dry acetone (5 cm³), was stirred at 0 °C and Jones reagent (0.8 mol dm⁻³ solution; 0.2 cm³, 1.5 mmol) was added. The solution became green after 5 min and was then diluted with aqueous sodium hydrogen carbonate (50 cm³, 10%) and extracted with ether (2 × 50 cm³). The combined ether extracts were dried with anhydrous MgSO₄, filtered and evaporated to give a yellow oil which was purified by PLC [1 × ether–hexane (1:4), 1 × ether–hexane (1:1)], to give N-*benzyl-3-phenylisoxazolidin-5-one* **17** as a light yellow oil (48 mg, 36%) (Found: M⁺, 253.1110. $C_{16}H_{15}NO_2$ requires M, 253.1103); v_{max}(CHCl₃)/cm⁻¹ 3580, 3280, 1780, 1498, 1458, 1198, 1165 and 705; δ_H 2.95 (2 H, d, J 9), 3.95 and 4.15 (2 H, AB q, J 15), 4.35 (1 H, t, J 9), 7.30 (5 H, s) and 7.35–7.60 (5 H, m).

Collins Oxidation of Lactol **16**.—The crude lactol mixture **16** (0.1 g, 0.39 mmol) was added to a solution of freshly prepared Collins reagent[36] (0.69 g, 2.35 mmol) in dry dichloromethane (15 cm³). The deep red solution immediately became dark brown and reaction appeared complete after 15 min (TLC) when the solution was washed successively with water (1 × 20 cm³) and dilute NaHCO₃ (1 × 20 cm³), dried (Na₂SO₄) and then filtered through Celite to remove the last traces of chromium salts. Evaporation of solvent under reduced pressure gave a brown oil, which was purified by PLC (ether–hexane, 2:3), to give *isoxazolidinone* **17**, (43 mg, 48%), as a light yellow oil. This was identical (IR, NMR, MS) with the material prepared above.

Synthesis of Isoxazolidinone **17** *via Reformatski Reaction*.[37]—Powdered zinc (0.28 g, 4.3 mmol) and ethyl α-bromoacetate (0.58 g, 3.5 mmol) were heated together with stirring (oil bath temp. 75–80 °C) in dry THF (30 cm³) until boiling occurred. The solution became green and boiling was continued for a further 5 min. N-(Benzylidene)benzylamine N-oxide (0.5 g, 2.4 mmol) in THF (10 cm³) was then added during 5 min. After the addition was complete, the solution was boiled for a further 20 min and then left to cool. Kieselgel HF254 silica gel (1.25 g) was added and the solvent removed under reduced pressure. The product was extracted from the silica gel with hot ether. Evaporation of the ether under reduced pressure gave a solid brown residue, which was purified by PLC (silica gel, ether–hexane, 1:1) to give N-*benzyl-3-phenylisoxazolidinone* **17** as a light yellow oil (82 mg, 14%). This was identical (IR, NMR, TLC) with the material obtained above by Jones and Collins oxidation of lactol **16**.

5-*Acetoxy*-N-*methyl-3-phenylisoxazolidine* **14** + **15** (R = CH₃).—N-(Benzylidene)methylamine N-oxide **18** (2.10 g, 17 mmol) dissolved in an excess of vinyl acetate (50 cm³, 0.62 mol) was heated at reflux for 48 h. Work-up as before gave *isoxazolidine* **14** + **15** (1.95 g, 68%) as a colourless oil (Found: M⁺, 221.1041. $C_{12}H_{15}NO_3$ requires M, 221.1055); v_{max}(CHCl₃)/cm³ 1735, 1455, 1375, 1360, 1235 and 975; δ_H 2.08 (2 H, m), 2.10 (3 H, s), 2.60 (2 H, s), 2.78 (1 H, s), 3.55 (0.69 H, dd, J 9 and 10), 4.02 (0.31 H, t, J 8), 6.35 (1 H, m) and 7.35 (5 H, m).

5-*Hydroxy*-N-*methyl-3-phenylisoxazolidine* **16** (R = CH₃).—Acetate **14** + **15** (R = Me) (0.37 g, 1.67 mmol) was hydrolysed

with potassium carbonate (0.12 g, 0.9 mmol) in methanol (20 cm³)–water (2 cm³) following the general procedure, to give the *crude lactol* **16** (R = Me) (0.21 g, 70%) as a light yellow oil (Found: M⁺, 179.0940. $C_{10}H_{13}NO_2$ requires M, 179.0945); δ_H 2.15–3.15 (2 H, m), 2.60 (2.21 H, s), 2.79 (0.79 H, s), 3.50 (0.76 H, dd, J 9 and 10), 4.10 (0.2 H, t, J 9), 5.55 (1 H, m) and 7.32 (5 H, m).

N-*Methyl-3-phenylisoxazolidin-5-one* **19**.—Crude lactol **16** (0.3 g, 1.67 mmol) was oxidised with Collins reagent (1.31 g, 4.42 mmol) as before to give the *isoxazolidinone* **19** as an oil (62 mg, 21%) (Found: M⁺, 177.0801. $C_{10}H_{11}NO_2$ requires M, 177.0790); v_{max}(CHCl₃)/cm⁻¹ 1770, 1455, 1235, 1170, 1122, 990, 915 and 700; δ_H 2.88 (3 H, s), 2.95 (2 H, d, J 9), 4.10 (3 H, t, J 9) and 7.38 (5 H, s).

4-(*Benzyloxycarbonylamino*)*butan*-1-*ol* **22**.—4-Aminobutan-1-ol (3 g, 33.7 mmol), dissolved in NaOH (5 mol dm⁻³; 5 cm³) was stirred at 0 °C whilst benzyl chloroformate (4.8 cm³, 33.7 mmol) was added dropwise over 15 min; the reaction mixture was kept at 0 °C for a further 90 min with the addition of sufficient methanol to maintain homogeneity. The solution was neutralised with HCl (1 mol dm⁻³), extracted with ethyl acetate (2 × 100 cm³) and the combined organic extracts were washed with water (100 cm³), dried (Na₂SO₄) and evaporated under reduced pressure to give a yellow solid. This was recrystallised from Et₂O–CHCl₃ to give the benzyl carbamate **22** (4.8 g, 64%), m.p. 58–61 °C (Found: M⁺, 223.1214. $C_{12}H_{17}NO_3$ requires M, 223.1208); v_{max}(CHCl₃)/cm⁻¹ 1515 and 1715; δ_H 1.50 (4 H, m, CH_2CH_2CH₂OH), 2.61 (1 H, br s, OH), 3.15 (2 H, m, CH_2OH), 3.58 (2 H, m, NHCH_2), 6.62 (1 H, s, NH), 5.06 (2 H, s, PhCH_2) and 7.30 (5 H, s, C₆H₅).

4-*Benzyloxycarbonylaminobutanal* **23**.—DMSO (1.41 cm³, 19.8 mmol) in dry CH₂Cl₂ (5 cm³) was added dropwise with stirring to oxalyl chloride (0.86 cm³, 9.9 mmol) during 10 min and the solution stirred for a further 3 min. The alcohol **22** (2 g, 9 mmol) dissolved in the minimum volume of CH₂Cl₂, was added dropwise during 15 min, and the solution stirred for a further 15 min, the temperature being maintained at −60 °C. Triethylamine (6.3 cm³, 45 mmol) was added dropwise during 10 min and then water (30 cm³) was added; the mixture was then shaken vigorously. The organic layer was separated, dried (Na₂SO₄), and evaporated under reduced pressure at 20 °C to afford the aldehyde **23** as an unstable pale-yellow oil (1.96 g, 98%) which was used *immediately* without purification; δ_H 1.85 (2 H, m, CH_2CH₂CHO), 2.54 (2 H, t, J 6.5, CH_2CHO), 3.25 (2 H, m, NHCH_2), 5.09 (2 H, s, PhCH_2), 5.54 (1 H, br s, NH), 7.31 (5 H, s, C₆H₅) and 9.80 (1 H, s, CHO).

N-[4-(*Benzyloxycarbonylamino*)*butylidene*]-(R)-(−)-α-*methylbenzylamine* N-*Oxide* **20**.—The unstable aldehyde **23** above (1.96 g, 8.8 mmol) was immediately redissolved in CH₂Cl₂ (40 cm³). (R)-(+)-α-Methylbenzylhydroxylamine oxalate **24**[39] (2.0 g, 8.8 mmol) was added to the solution followed by triethylamine (1.4 cm³, 9.7 mmol). The solution was stirred at 20 °C for 5 h, diluted with more CH₂Cl₂ (50 cm³) and washed with water (3 × 50 cm³). The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure to leave a white solid which was recrystallised from Et₂O–CHCl₃ to give the N-*oxide* **20** (2.73 g, 91%), m.p. 92–96 °C; $[\alpha]_D$ −7.28 ° (c 0.02 in EtOAc) (Found: C, 70.8; H, 7.15; N, 8.15; M⁺, 340.1793. $C_{20}H_{24}N_2O_3$ requires C, 70.8; H, 7.1; N, 8.2%; M, 340.1787); v_{max}(CHCl₃)/cm⁻¹ 1515 and 1710; δ_H(200 MHz) 1.67 (2 H, quin, J 6.70, NHCH₂CH_2), 1.76 (3 H, d, J 7.0, MeCHPh), 2.47 (2 H, q, J 6.5, CH₂C=N), 3.12 (2 H, m, NHCH_2), 4.95 (1 H, q, J 7.0, MeCHPh), 5.06 (2 H, s, PhCH_2), 5.76 (1 H, br s, NH), 6.77 (1 H, t, J 6.70, H–C=N) and 7.15–7.50 (10 H, m, 2 × C₆H₅); δ_C

18.96 (MeCH), 23.50 (NHCH₂CH₂), 26.15 (CH₂CH=N), 40.05 (NHCH₂), 66.39 (PhCH₂), 73.51 (CH₃CH), 127.20–138.13 (C₆H₅), 136.64 (C=N) and 156.49 (CONH).

5-Acetoxy-3-(4-benzyloxycarbonylaminobutyl)-N-[(R)-(-)-α-methylbenzyl]isoxazolidine **25.**—The *N*-oxide **20** (1.5 g, 4.4 mmol) dissolved in vinyl acetate (50 cm³) was heated at reflux as before for 16 h. Work-up afforded the crude isoxazolidine **25** as a mixture of four diastereoisomeric C-5 acetates which were cleanly separable by silica gel chromatography into two pairs (overall yield 68%).

Thus, 35–40% EtOAc–hexane eluted the *major pair* **25b + d** (0.85 g) having the 3*R* configuration (Found: M⁺, 426.2185. C₂₄H₃₀N₂O₅ requires *M*, 426.2155); *v*ₘₐₓ(CCl₄)/cm⁻¹ 1510, 1730 and 1750; δ_H(200 MHz) 1.01–1.62 (2 H, 2 × m, CH₂-CHN + 3 H, 2 × d, CH₃CHN + 2 H, 2 × m, CH₂CH₂NH), 1.95 (1 H, 2 × m, CH_AH_BCOCO), 2.02 and 2.10 (3 H, 2 × s, COMe), 2.50 (1 H, 2 × m, CH_AH_BCOCO), 2.70–3.31 (2 H, 2 × m, NHCH₂ + 1 H, 2 × m, CHN), 3.78 and 4.00 (1 H, 2 × q, PhCHN), 4.68 (1 H, 2 × m, NH), 5.05 (2 H, 2 × s, PhCH₂), 6.42 (1 H, 2 × m, CH₂CHO) and 7.09–7.41 (10 H, 2 × m, C₆H₅); δ_C 20.68 and 19.90 (MeCHN), 21.28 and 21.41 (COMe), 26.75 and 26.33 (CH₂CH₂NH), 31.34 and 33.12 (CH₂CHN), 39.63 (CH₂COCO), 40.36 and 40.37 (CH₂NH), 60.66 and 61.51 (CH₂CHN), 66.42 (PhCH₂), 66.82 and 67.23 (CH₃CHN), 96.55 and 98.89 (CHOCO), 127.17–142.63 (C₆H₅), 156.19 (CONH), and 170.15 and 170.84 (COCH₃).

45–55% EtOAc–hexane eluted the *minor pair* **25a + c** (0.38g) having the 3*S* configuration (Found: M⁺, 426.2155. C₂₄H₃₀N₂O₅ requires *M*, 426.2155); *v*ₘₐₓ(CCl₄)/cm⁻¹ 1510, 1730 and 1750; δ_H(200 MHz) 1.28–1.86 (2 H, 2 × m, CH₂CHN + 3 H, 2 × d, MeCHN + 2 H, 2 × m, CH₂CH₂NH), 1.89 and 2.03 (3 H, 2 × s, COMe), 2.20 (1 H, 2 × m, CH_AH_BCOCO), 2.81 (1 H, 2 × m, CH_AH_BCOCO), 3.05–3.45 (2 H, 2 × m, NHCH₂ + 1 H, 2 × m, CH₂CHN), 3.95 and 4.05 (1 H, 2 × q, PhCHN), 4.91 (1 H, 2 × m, NH), 5.09 (2 H, 2 × s, PhCH₂), 6.20 (1 H, 2 × m, CH₂CHO) and 7.25–7.34 (10 H, 2 × m, C₆H₅); δ_C 19.90 and 21.90 (MeCHN), 21.33 and 21.17 (COMe), 27.08 and 26.62 (CH₂CH₂NH), 30.42 and 31.19 (CH₂CHN), 40.76 (CH₂-COCO), 41.38 and 41.48 (CH₂NH), 60.09 and 59.91 (CH₂-CHN), 64.05 and 65.13 (CH₃CHN), 66.53 (PhCH₂), 95.63 and 96.88 (CHOCO), 127.03–142.33 (C₆H₅), 156.30 and 156.37 (CONH), and 170.38 and 169.81 (COMe).

3-(4-Benzyloxycarbonylaminobutyl)-N-[(R)-(-)-α-methyl-benzyl]isoxazolidin-5-ol **26.**—The acetate (0.5 g, 1.17 mmol) was dissolved in aqueous methanol (*ca.* 10:1 MeOH–H₂O) containing potassium carbonate (0.083 g, 0.59 mmol) and the resulting solution stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue dissolved in water (30 cm³). The aqueous solution was extracted with Et₂O (3 × 40 cm³). The combined organic layers were dried (Na₂SO₄) and evaporated to leave the isoxazolidinol as a colourless foam (>90%) which was used without purification.

The acetate mixture **25b + d** afforded, by the general procedure described above, the corresponding isoxazolidinol mixture **26b + d** having the 3*R* configuration while the acetate mixture **25a + c** afforded isoxazolidinols **26a + c** having the 3*S* configuration. The ¹H NMR (90 MHz) spectra had multiplets at δ(CDCl₃) 5.35 (1 H, m, OCHOH) for **26b + d** and 5.61 (1 H, m, OCHOH) for **26a + c**. The IR spectra of both mixtures showed free and bonded hydroxy absorption at *v*ₘₐₓ/cm⁻¹ 3600 and 3400.

N-(4-Benzyloxycarbonylaminobutyl)-N[(R)-(-)-α-methyl-benzyl]isoxazolidin-5-ones **27a, b.**—*Collins oxidation* [36] *of iso-xazolidinols* **26.** A solution of dry pyridine (0.74 g, 9.36 mmol) in dry dichloromethane (20 cm³) was cooled to 0 °C with stirring.

Chromium trioxide (0.47 g, 4.68 mmol) was added and the deep burgundy solution stirred at 0 °C for a further 10 min and then allowed to warm to room temperature. The appropriate isoxazo-lidinol mixture (0.3 g, 0.78 mmol) in dichloromethane (5 cm³) was added all at once and the mixture stirred for a further 30 min. Saturated aqueous NaHCO₃ (15 cm³) was added to the solution. The organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure to leave a black residue. Ethyl acetate (50 cm³) was added and the solution filtered through a short column of silica gel. The residue was thoroughly washed with further portions of EtOAc (3 × 20 cm³) and filtered. The combined filtrates were evaporated to leave an orange oil which was purified by silica gel chromatography (40% EtOAc–hexane) affording the isoxazolidinones **27a, b.** Thus **26b + d** afforded *isoxazolidinone* (3*R*)-**27** (0.114 g, 38%) (Found: M⁺, 382.1894. C₂₂H₂₆N₂O₄ requires *M*, 382.1893); *v*ₘₐₓ(CCl₄)/cm⁻¹ 1510, 1725 and 1790; δ_H(200 MHz) 1.23–1.51 (2 H, m, CH₂CH₂NH + 2 H, m, CH₂CHN), 1.53 (3 H, d, *J* 7.0, MeCH), 2.35 (2 H, m, CH₂CO), 3.30 (2 H, m, CH₂NH), 3.54 (1 H, m, CH₂CHN), 4.00 (1 H, q, *J* 7.0, MeCH), 4.70 (1 H, m, NH), 5.06 (2 H, s, PhCH₂) and 7.36 (10 H, m, C₆H₅); δ_C(CDCl₃) 20.53 (MeCHN), 26.66 (CH₂CH₂NH), 31.57 (CH₂CHN), 39.69 (CH₂-CO), 40.27 (CH₂NH), 60.08 (CH₂CHN), 66.60 (PhCH₂), 66.83 (MeCHN), 127.23–140.44 (C₆H₅), 156.27 (CONH) and 176.52 (CH₂CO).

Isoxazolidinols (**26a + c**) afforded *isoxazolidinone* (3*S*)-**27** (0.13 g, 43%) (Found: M⁺, 382.1912. C₂₂H₂₆N₂O₄ requires *M*, 382.1893); *v*ₘₐₓ(CCl₄)/cm⁻¹ 1510, 1730 and 1790; δ_H(200 MHz) 1.40–1.78 (2 H, m, CH₂CH₂NH + 2 H, m, CH₂CHN), 1.60 (3 H, d, *J* 7.5, MeCH), 2.30 (2 H, m, CH₂CO), 3.21 (2 H, m, CH₂NH), 3.35 (1 H, m, CH₂CHN), 4.04 (1 H, q, *J* 7.5, MeCH), 4.81 (1 H, m, NH), 5.10 (2 H, s, PhCH₂), 7.26 (5 H, s, C₆H₅) and 7.33 (5 H, m, C₆H₅); δ_C 19.72 (MeCHN), 26.88 (CH₂CH₂NH), 31.89 (CH₂CHN), 40.58 (CH₂CO), 40.63 (CH₂NH), 60.74 (CH₂CHN), 65.31 (MeCHN), 66.72 (PhCH₂), 128.09–138.09 (C₆H₅), 156.41 (CONH) and 175.24 (CH₂CO).

(S)- *and* (R)-N,N-*Dibenzyloxycarbonylornithine.*[46]—(S)- or (R)-ornithine hydrochloride (1.68 g, 10 mmol) was dissolved in NaOH (5 mol dm⁻³; 25 cm³) and the solution cooled to 0 °C with stirring. Benzyl chloroformate (3.6 cm³, 25 mmol) was added dropwise over 10 min and the solution stirred for 1 h and then diluted with water (30 cm³) and extracted with EtOAc (50 cm³). The aqueous phase was acidified (approx. pH 5) with HCl (1 mol dm³) and extracted into EtOAc (3 × 50 cm³). This organic layer was washed with saturated brine (2 × 50 cm³), dried (Na₂SO₄) and evaporated under reduced pressure to leave a colourless viscous oil which was crystallised from Et₂O–light petroleum (40–60 °C). Thus (*S*)-ornithine hydrochloride afforded (*S*)-*N*,*N*-dibenzyloxycarbonylornithine (3.4 g, 85%), m.p. 113–116 °C (lit.,[45] 112–114 °C); *v*ₘₐₓ(CHCl₃)/cm⁻¹ 1515 and 1715; δ_H 1.69 (4 H, m, CH₂CH₂CHNH), 3.18 (2 H, m, NHCH₂), 4.40 (1 H, m, CH₂CHCO₂H), 5.10 (4 H, m, PhCH₂), 5.19 (1 H, m, NH), 7.31 (10 H, s, C₆H₅) and 9.45 (1 H, br s, CO₂H). (*R*)-Ornithine hydrochloride afforded (*R*)-*N*,*N*-di-benzyloxycarbonylornithine (3.12 g, 78%), m.p. 112–113 °C.

(S)-N,N'-*Dibenzyloxycarbonyl-β-lysine* (S)-**29** via *Arndt–Eistert Homologation*[46] *of* (S)-N,N'-*Dibenzyloxycarbonyl-ornithine.*—(*S*)-*N*,*N*'-Dibenzyloxycarbonylornithine (0.74 g, 1.9 mmol) was dissolved in ethyl acetate (30 cm³) and the solution cooled in an ice–salt bath with stirring. *N*-Methylmorpholine (0.23 cm³, 2.09 mmol) was added followed by dropwise addition of ethyl chloroformate (0.2 cm³, 2.09 mmol) in EtOAc (3 cm³). After 3 h, the precipitated amine hydrochloride was rapidly filtered off in the cold. Excess of diazomethane (*ca.* 6 mmol, ethereal solution) was added to the filtrate at 0 °C and the solution was stirred overnight. Excess of diazomethane was

removed by warming to 50 °C and the solvent removed under reduced pressure to leave the oily diazo ketone (0.82 g, 98%) which could be crystallised from EtOAc–hexane to give a yellow solid, m.p. 94 °C (lit.,[46] 93–94 °C). The solid was dissolved in dry methanol (20 cm³) and the solution stirred at 20 °C in darkness. Freshly prepared silver benzoate (0.1 g) was dissolved in triethylamine (1.5 cm³), rapidly filtered and added to the solution. Two further portions of powdered silver benzoate (0.05 g) were added after 1 and 3 h and the mixture was stirred in the dark overnight and then concentrated under reduced pressure. The residue was dissolved in EtOAc (30 cm³) and filtered to remove insoluble material. The filtrate was washed successively with saturated aqueous $NaHCO_3$ (25 cm³), saturated brine (25 cm³), HCl (1 mol dm⁻³; 25 cm³) and finally saturated brine (3 × 25 cm³). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give (S)-N,N-dibenzyloxycarbonyl-β-lysine methyl ester (0.69 g, 85%), m.p. 105–107 °C (lit.,[46] 105–107 °C). The methyl ester (0.69 g, 1.6 mmol) was dissolved in a minimum volume of dioxane and aqueous NaOH (1.5 mol dm⁻³; 1.5 cm³) was added. After being stirred at 0 °C for 30 min and then at room temperature for 1 h, the reaction mixture was diluted with water (20 cm³) and extracted with EtOAc (20 cm³). The aqueous phase was acidified with HCl (1 mol dm⁻³) and extracted with EtOAc (5 × 20 cm³). The organic layer was washed with saturated brine (3 × 20 cm³), dried (Na_2SO_4), and evaporated under reduced pressure to give a white solid which was recrystalised from EtOAc to give (S)-N,N'-dibenzyloxycarbonyl-β-lysine (S)-29 (0.48 g, 72%), m.p. 152–154 °C (lit.,[46] 155 °C); ν_{max}(KBr disc)/cm⁻¹ 1550, 1650, 1695 and 1730; δ_H(CD₃OD) 1.55 (4 H, m, CH_2CH_2CHNH), 2.45 (2 H, d, J 6.5, CH_2CO_2H), 3.10 (3 H, m, $CHCH_2CO_2H$ + $NHCH_2$), 5.05 (4 H, s, $PhCH_2$) and 7.31 (10 H, s, C_6H_5).

(R)-N,N-*Dibenzyloxycarbonyl-β-lysine* (R)-29.—The title compound was prepared by Arndt–Eistert homologation of (R)-N,N'-dibenzyloxycarbonylornithine by the above procedure.

(S)-β-*Lysine* via *Hydrogenolysis of* (S)-29.—(S)-N,N'-Dibenzyloxycarbonyl-β-lysine (S)-29 (0.1 g, 0.24 mmol) prepared above was dissolved in ethanol (30 cm³) and hydrogenated over $Pd(OH)_2$ on charcoal (20%; 15 mg) for 6 h at 35 °C and atmospheric pressure. The catalyst was removed by filtration through a pad of Celite and was washed with ethanol. The combined filtrates were evaporated under reduced pressure to give (S)-β-lysine (S)-28 as a light yellow hygroscopic gum (35 mg, 100%) $[\alpha]_D$ +21° (c 0.035; 1 mol dm⁻³HCl) (lit.,[40] +24°).

(R)-β-*Lysine* via *hydrogenolysis of* (R)-29.—Hydrogenolysis of (R)-29 as for (S)-29 (above) afforded (R)-β-lysine (R)-28 (100%), $[\alpha]_D$ −20.5° (c 0.035; c 0.03, 1 mol dm⁻³ HCl).

(S)-β-*Lysine* via *Hydrogenolysis of the Isoxazolidinone* (3S)-27 *and Characterisation as* (S)-N,N'-*Dibenzyloxycarbonyl-β-lysine* (S)-29.—The isoxazolidinone (3S)-27 (0.2 g, 0.52 mmol) was dissolved in ethanol (50 cm³) and hydrogenated over $Pd(OH)_2$ on charcoal (20%; 30 mg) for 20 h at 20 °C then 5 h at 70 °C and atmospheric pressure. The catalyst was removed by filtration through Celite and washed thoroughly with ethanol. The combined filtrates were evaporated under reduced pressure to give (S)-β-lysine (S)-28 as a light yellow hygroscopic gum (76 mg, 100%), $[\alpha]_D$ +18° (c 0.076, 1 mol dm⁻³ HCl) (lit.,[40] + 24°). The ¹H NMR (90 MHz; D₂O) spectrum of the residue was virtually identical with the specimen of (3S)-β-lysine generated by Arndt–Eistert homologation of (S)-N,N'-dibenzyloxycarbonylornithine above. The gum was dissolved in NaOH (5 mol dm⁻³; 3 cm³) and the solution cooled to 0 °C with stirring. Benzyl chloroformate (0.16 cm³, 1.14 mmol) was added and the

mixture was stirred for 1 h at 0 °C then diluted with water (10 cm³) and extracted with EtOAc (10 cm³). The aqueous phase was acidified with HCl (1 mol dm⁻³) and extracted into EtOAc (5 × 10 cm³). The organic phase was washed with saturated brine (3 × 5 cm³), dried (Na_2SO_4) and evaporated under reduced pressure to give (S)-N,N-dibenzyloxycarbonyl-β-lysine (S)-29 (142 mg, 66%) which was identical (m.p., IR, ¹H NMR) with the specimen prepared by Arndt–Eistert homologation.

(R)-β-*Lysine* via *Hydrogenolysis of Isoxazolidinone* (3R)-27 *and Characterisation as* (R)-N,N'-*Dibenzyloxycarbonyl-β-lysine* 29.—Isoxazolidinone (3R)-27 was hydrogenated as for (3S)-27 (above) to give (R)-β-lysine as a hygroscopic gum (100%), $[\alpha]_D$ − 19.5° (c 0.1, 1 mol dm⁻³ HCl) (lit.,[40] +24°) for (S)-(+)-β-lysine. (R)-N,N'-Dibenzyloxycarbonyl-β-lysine (R)-29 was prepared as for (S)-29 (above) (61%) and was identical (m.p. 153–156 °C, IR, ¹H NMR) with the specimen prepared by Arndt–Eistert homologation.

Methyl Ester Bis 'Mosher' Amides 30.[47]—(a) via *Arndt–Eistert homologation*. (S)- or (R)-N,N'-Dibenzyloxycarbonyl-β-lysine methyl ester (50 mg, 0.12 mmol) was dissolved in ethanol (15 cm³) and hydrogenated over $Pd(OH)_2$ on charcoal at 35 °C and atmospheric pressure for 5 h. Removal of catalyst by filtration and evaporation of the filtrate under reduced pressure afforded the crude (S)- or (R)-β-lysine methyl ester as an oil (19 mg, 100%). The residue was dissolved in CCl₄–pyridine (10 cm³; 3:2). (S)-(−)-MTPA chloride (64 mg, 0.27 mmol) was added and the solution heated at reflux for 3 h. A few drops of water were added and the solution allowed to cool before dilution with CH₂Cl₂ (10 cm³) and washing with HCl (1 mol dm⁻³; 10 cm³), 10% NaHCO₃ (10 cm³) and water (2 × 10 cm³). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to leave the crude methyl ester bis 'Mosher' amides 30 [(S) or (R)]. GC-MS on OV-1; 25 m, 290 °C, 3 cm³ min⁻¹. Retention times/min (3S) 16.13, (3R) 16.68; m/z 592 (M⁺) and 403 (100, M − $C_9H_8F_3O$).

(b) via *Nitrone cycloadditions*. (S)- or (R)-N,N-Dibenzyloxycarbonyl-β-lysines were first converted into the methyl esters by treatment with an excess of CH₂N₂. The methyl ester bis 'Mosher' amides 30 (3S or 3R) were then generated as above. GC-MS: (3S) 16.12, (3R) 16.62; m/z 592 (M⁺) and 403 (100).

[N-(R)-5-*Acetoxy-3-isopropyl-α-methylbenzyl*]*isoxazolidine* 31a.—N-Isobutylidene[(R)-(−)α-methylbenzyl]amine N-oxide 21a (2.24 g, 11.7 mmol) was dissolved in vinyl acetate (100 cm³, 1.24 mmol) and heated at reflux with exclusion of light under an argon atmosphere for 48 h. After removal of excess of vinyl acetate under reduced pressure the residue was purified by flash column chromatography (ether–hexane, 1:4) to give the iso-xazolidine 31a (3.85 g, 81%) as a colourless oil (Found: C, 69.4; H, 8.4, N, 5.05; M⁺, 277.1680. $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.4; N, 5.05%; M, 277.1678); ν_{max}(CHCl₃)/cm⁻¹ 1735, 1495, 1468, 1455, 1378, 1305, 1240, 1015, 1000 and 988; δ_H(200 MHz) 0.64–0.96 (6 H, m), 1.28–2.41 (2 H, m), 1.44 (0.75 H, d, J 6.5), 1.49 (1.4 H, d, J 6.5), 1.55 (0.84 H, d, J 6.5), 2.01 (0.92 H, s), 2.02 (1.26 H, s), 2.09 (0.82 H, s), 2.61–2.87 (0.68 H, m), 2.98 (0.32 H, m), 3.76–4.06 (1 H, m), 6.20 (0.33 H, m), 6.41 (0.67 H, m) and 7.18–7.38 (5 H, m); δ_C(¹H decoupled) 17.91, 18.49, 19.43, 20.09, 20.31, 20.75, 20.85, 21.23, 21.31, 21.53, 29.77, 31.26, 35.97, 36.89, 64.93, 66.36, 67.14, 67.33, 67.63, 96.24, 96.74, 99.47, 125.84, 127.34, 127.46, 127.51, 127.65, 127.93, 127.99, 128.19, 128.25, 128.69, 128.87, 140.20, 142.13, 143.09, 170.99, 170.14 and 170.35.

3-*Isopropyl*-N-[(R)-α-*methylbenzylisoxazolidin-5-ol* 32a.—The acetate 31a (2.0 g, 8.5 mmol) was hydrolysed with potassium

carbonate (0.59 g, 4.24 mmol) in methanol (90 cm³)–water (5 cm³) following the general procedure to give the *crude lactol* **32a** (1.53 g, 91%) as a yellow oil (Found: M⁺, 235.1561. C₁₄-H₂₁NO₂ requires *M*, 235.1572); v_{max}(CHCl₃)/cm⁻¹ 3600, 3400, 1495, 1470, 1455, 1390, 1375, 1280, 1240, 1110 and 1060; δ_H 0.65–1.05 (6 H, m), 1.32–1.60 (3 H, m), 2.36–2.48 (2 H, m), 2.95–3.45 (1 H, m), 4.25 (1 H, q, *J* 6.5), 5.35–5.75 (1 H, m) and 7.35 (5 H, m).

3-Isopropyl-N-*(R)*-α-*methylbenzylisoxazolidin-5-one* **33a**.—A solution of DMSO (0.40 cm³, 4.66 mmol) in dichloromethane (10 cm³) was cooled to – 60 °C, and oxalyl chloride (0.54 cm³, 2.92 mmol), in dichloromethane (5 cm³), was added dropwise over a 5 min period.³² Stirring was continued at – 60 °C for 10 min, followed by dropwise addition of the crude lactol (0.63 g, 2.68 mmol) in dichloromethane (15 cm³); the reaction mixture was then stirred at – 60 °C for a further 15 min. Then triethylamine (1.98 cm³, 27 mmol) was added dropwise over *ca.* 10 min. The reaction was allowed to warm to room temperature, and washed with HCl (1 mol dm⁻³; 1 × 40 cm³), dilute NaHCO₃ (1 × 40 cm³), saturated brine (1 × 40 cm³) and water (1 × 40 cm³). The organic layer was dried (Na₂SO₄), filtered and evaporated to give a brown oil. PLC (ether–hexane, 1:1), gave the *isoxazolidinone* **33a** as a colourless oil (98 mg, 15%) (Found: C, 71.8; H, 8.2; N, 5.9%; M⁺, 233.1426. C₁₄H₁₉NO₂ requires C, 72.1; H, 8.2; N, 6.0%; *M*, 233.1416); v_{max}(CHCl₃)/cm⁻¹ 1778, 1492, 1455, 1415, 1390, 1375 and 910; δ_H(200 MHz) 0.75 (4.84 H, m), 0.92 (1.16 H, m), 1.51 (2.46 H, d, *J* 6.5 Hz), 1.60 (0.54 H, d, *J* 6.5 Hz), 2.02 (0.17 H, dd, *J* 9.5 and 17.5), 2.26 (0.19 H, dd, *J* 5 and 17.5), 2.31 (0.83 H, dd, *J* 4 and 19), 2.61 (0.81 H, dd, *J* 9 and 19), 3.12 (1 H, m), 4.02 (1 H, m) and 7.32 (5 H, m); δ_C(¹H decoupled) 17.34, 17.86, 18.42, 19.70, 19.94, 30.57, 31.07, 31.33, 31.59, 65.06, 65.85, 66.22, 66.86, 127.89, 128.04, 128.16, 128.52, 128.60, 129.17, 138.35, 140.34, 176.21 and 177.20.

3-Isopropyl-N-*(R)*-α-*methylbenzyl-2,3-dihydroisoxazole* **34** was obtained as a side product in the above oxidation in 28% yield (Found: M⁺, 217.1470. C₁₄H₁₉NO requires *M*, 217.1467); v_{max}(CHCl₃)/cm⁻¹ 1625, 1492, 1455, 1122 and 1052; δ_H 0.65 (6 H, m), 1.42 (1.36 H, d, *J* 6.5), 1.54 (1.64 H, d, *J* 6.5), 3.65 (1 H, m), 3.80 (1 H, m), 4.75 (1 H, m), 6.39 (1 H, m) and 7.35 (5 H, m).

β-*Leucine* **36a**.—The above isoxazolidinone **33a** (98 mg, 0.42 mmol) was dissolved in methanol (50 cm³) containing palladium hydroxide on charcoal (20%, 10 mg) and hydrogenated at room temperature and atmospheric pressure for 48 h. The catalyst was removed by filtration through a pad of Celite, and was thoroughly washed with warm methanol. The combined filtrate and washings were evaporated under reduced pressure to give β-leucine as colourless crystals (51 mg, 81%), m.p. 204–207 °C, [α]$_D^{21}$ – 22.4° (*c* 2.0, H₂O) [lit.,⁴¹ m.p. 201–202.5 °C, [α]$_D^{22}$ + 55.2°, for *(S)*-β-leucine].

5-Acetoxy-N-*(R)*-α-*methylbenzyl-3-phenylisoxazolidine* **31b**.—*N*-Benzylidene[[*(R)*-(–)-α-methylbenzyl]amine *N*-oxide **21b** (2.24 g, 10.7 mmol) was dissolved in vinyl acetate (75 cm³, 0.93 mmol) and heated at reflux for 72 h. Working-up gave the *isoxazolidine* **31b** (2.14 g, 69%) as a colourless oil (Found: M⁺, 311.1523. C₁₉H₂₁NO₃ requires *M*, 311.1521); v_{max}(CHCl₃)/cm⁻¹ 1735, 1495, 1455, 1378, 1365, 1240, 1011, 1000, 990 and 970; δ_H(200 MHz) 1.49 (3 H, m), 2.07 (1.44 H, s), 2.13 (1.17 H, s), 2.16 (0.39 H, s), 2.26–2.46 (1 H, m), 2.62–3.04 (1 H, m), 3.77 (0.40 H, t, *J* 8.5), 3.81–4.34 (1.60 H, m), 6.27 (0.52 H, m), 6.42 (0.42 H, dd, *J* 2 and 8.5), 6.51 (0.06 H, dd, *J* 1.8 and 6.7) and 7.10–7.50 (10 H, m); δ_C(¹H decoupled) 18.92, 20.82, 20.94, 21.26, 21.32, 45.19, 46.00, 46.62, 62.68, 65.38, 65.55, 65.75, 66.22, 67.74, 94.58, 95.24, 97.68, 126.88, 127.09, 127.28, 127.43, 127.74, 127.82, 127.91, 128.02, 128.32, 128.59, 128.97, 129.59, 129.67, 139.09, 138.89, 140.40, 140.91, 141.34, 141.98, 170.48 and 170.56.

N-*(R)*-α-*Methylbenzyl-3-phenylisoxazolidin-5-ol* **32b**.—The acetate **31b** (2.04 g, 6.6 mmol) was hydrolysed with potassium carbonate (0.45 g, 3.3 mmol) in methanol (90 cm³)–water (10 cm³) following the general procedure to give the crude *lactol* **32b** (1.45 g, 82%) as a yellow oil (Found: M⁺, 269.1423. C₁₇H₁₉NO₂ requires *M*, 269.1416); v_{max}/cm⁻¹ 3600, 3180, 1604, 1495, 1455, 1125 and 1070; δ_H 1.18–1.58 (3 H, m), 2.05–2.90 (2 H, m), 3.50–4.50 (2 H, m), 5.30–5.70 (1 H, m) and 7.00–7.70 (10 H, m).

N-*(R)*-α-*Methylbenzyl-3-phenylisoxazolidin-5-one* **33b**.—The crude lactol **32b** (0.4 g, 1.49 mmol) was added to a solution of Collins reagent (1.0 g, 3.37 mmol) in dry dichloromethane (30 cm³), with stirring at 0 °C. The deep red solution immediately became dark brown and after being stirred for 2 min at 0 °C, the solution was decanted from the insoluble brown gum. The gum was quickly extracted with ether (3 × 50 cm³) and the ether and dichloromethane layers were combined. The resulting solution was washed successively with aqueous 5% aqueous NaOH (1 × 50 cm³), aqueous 5% HCl (1 × 20 cm³), saturated aqueous NaHCO₃ (2 × 100 cm³) and saturated brine (1 × 50 cm³). The organic layer was dried (Na₂SO₄), filtered and evaporated under reduced pressure to give a yellow oil, which was purified using PLC, (ether–hexane, 1:1) to give the *isoxazolidinone* **33b** (63 mg, 16%) as a light yellow oil. It crystallised from ether–hexane as prisms, m.p. 95–98 °C (Found: C, 76.3; H, 6.45; N, 5.2. C₁₇H₁₇NO₂ requires C, 76.35; H, 6.4; N, 5.25%); v_{max}-(CHCl₃)/cm⁻¹ 1775, 1495, 1455, 1380 and 1288; δ_H(200 MHz) 1.55 (3 H, d, *J* 6.5), 2.85 (1 H, dd, *J* 8 and 17.5), 3.06 (1 H, dd, *J* 8 and 17.5), 4.15 (1 H, q, *J* 6.5), 4.45 (1 H, t, *J* 8) and 7.22 (10 H, m); δ_C(¹H decoupled) 18.60, 39.18, 66.28, 126.99, 127.49, 127.87, 127.93, 128.02, 128.12, 128.40, 128.66, 128.76, 129.07, 129.13, 138.62, 140.10 and 173.85. Capillary GC: t_R 22.33 min [25 m, CPsil5-CB, 80 °C].

β-*Phenyl*-β-*alanine* **36b**.—The recrystallised isoxazolidinone **33b** (0.1 g, 0.37 mmol) was dissolved in dry ethanol (50 cm³), containing palladium hydroxide on charcoal (10 mg, 20%) and hydrogenated at atmospheric pressure and 70 °C for 5 h. The solid amino acid separated during hydrogenolysis. When hydrogen uptake was complete, distilled water (100 cm³) was added to dissolve the amino acid. The catalyst was removed by filtration through a pad of Celite, and this was thoroughly washed with warm water (100 cm³). The combined filtrate was evaporated under reduced pressure to give β-phenyl-β-alanine (56 mg, 92%), m.p. 231–234 °C, [α]$_D^{21}$ – 1.5° (*c* 1.0, H₂O) (lit.,⁴⁰ m.p. 236 °C, [α]$_D$ + 6.2°, for *(S)*-β-phenyl-β-alanine).

5-Acetoxy-3-(4-methoxyphenyl)-N-*(R)*-α-*methylbenzyl-isoxazolidine* **31c**.—*N*-(*p*-Methoxybenzylidene)[(*R*)-(–)-α-methylbenzyl]amine *N*-oxide **21c** (2.30 g, 8.9 mmol) in vinyl acetate (100 cm³, 1.09 mmol) was heated at reflux for 120 h. Work-up gave isoxazolidine **31c** (1.84 g, 60%) as a light yellow oil (Found: M⁺, 341.1634. C₂₀H₂₃NO₄ requires *M*, 341.1627); v_{max}(CHCl₃)/cm⁻¹ 1735, 1698, 1686, 1682, 1615, 1600, 1515, 1378, 1305, 1250, 1162, 1035, and 985; δ_H(200 MHz) 1.53 (1.54 H, d, *J* 6.5), 1.55 (1.46 H, d, *J* 6.5), 2.08 (1.54 H, s), 2.13 (1.46 H, s), 2.41 (1 H, m), 2.71–2.99 (1 H, m), 3.50 (0.53 H, t, *J* 9), 3.73–4.03 (1.47 H, m), 3.75 (1.6 H, s), 3.82 (1.4 H, s), 6.32 (0.54 H, ddd, *J* 1, 4 and 7), 6.38 (0.46 H, ddd, *J* 0.2, 2 and 6.5), 6.71 (0.97 H, d, *J* 9), 6.90 (0.97 H, d, *J* 9) and 7.08–7.38 (7.06 H, m); δ_C(¹H decoupled) 18.52, 20.99, 21.42, 21.46, 29.68, 46.07, 46.57, 55.20, 55.30, 62.37, 64.88, 65.30, 65.76, 94.66, 95.29, 113.61, 114.07, 127.10, 127.36, 127.97, 128.68, 129.01, 129.18, 130.61, 139.89, 141.60, 158.65, 159.26, 170.66 and 170.75.

N-*(R)*-α-*Methylbenzyl-3-(4-methoxyphenylisoxazolidin-5-ol* **32c**.—The acetate **31c** (1.59 g, 4.6 mmol) was hydrolysed with

potassium carbonate (0.64 g, 2.3 mmol) in methanol (50 cm³) and water (5 cm³), following the general procedure, to give the *crude lactol* 32c (1.27 g, 91%) as a yellow oil (Found: M⁺, 299.1530. $C_{18}H_{21}NO_3$ requires *M*, 299.1528); $v_{max}(CHCl_3)/cm^{-1}$ 3580, 3200, 1601, 1505, 1260, 1175, 1165 and 1035; δ_H 1.49 (3 H, m), 2.08–2.68 (2 H, m), 3.42–4.40 (2 H, m), 3.72 (1.68 H, s), 3.80 (1.32 H, s), 5.45–5.72 (1 H, m) and 6.50–7.68 (9 H, m).

3-(4-*Methoxyphenyl*)-N-(R)-α-*methylbenzylisoxazolidin-5-one* 33c.[42]—A 100 cm³, one-necked round bottomed flask equipped with a magnetic stirrer and drying tube was charged with dry acetone (50 cm³), lactol (1.2 g, 4 mmol) and anhydrous *N*-methylmorpholine *N*-oxide (0.93 g, 8 mmol). To this was added RuCl₃·3H₂O (2 mg, 0.08 mmol) and the resulting gold coloured solution was stirred for 45 min at room temperature, when the reaction mixture became dark brown. The acetone was removed under reduced pressure, the residue was transferred to a separating funnel with several portions of CH_2Cl_2 (100 cm³ total), and the organic layer was washed with HCl (2 mol dm⁻³; 2 × 50 cm³) and water (1 × 100 cm³), dried (Na₂SO₄), filtered and evaporated to give a brown oil (0.93 g), which was purified by flash column chromatography [hexane, hexane–ether (4:1), hexane–ether (1:1), ether], to give the oily *isoxazolidinone* 33c (0.23 g, 19%); δ_H(90 MHz) 1.50 (3 H, d, *J* 6.5), 2.56–3.24 (2 H, m), 3.70 (1.46 H, s), 3.70–4.48 (2 H, m), 3.77 (1.54 H, s) and 6.68–7.55 (9 H, m).

Recrystallisation of this material from ether–hexane gave the title compound 33c (97 mg), m.p. 127–128 °C (Found: C, 72.6; H, 6.65; N, 4.5%; M⁺, 297.1397. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.45; N, 4.7%; *M*, 297.1365); $v_{max}(CHCl_3)/cm^{-1}$ 1770, 1610, 1505, 1452, 1250, 1170 and 1032; δ_H(200 MHz) 1.53 (3 H, d, *J* 6.5), 2.83 (1 H, dd, *J* 9 and 17), 3.03 (1 H, dd, *J* 9 and 17), 3.77 (3 H, s), 4.12 (1 H, q, *J* 6.5), 4.42 (1 H, dd, *J* 9 and 17), 6.78 (2 H, d, *J* 9), 7.15 (2 H, d, *J* 9) and 7.21 (10 H, m); δ_C(¹H decoupled) 18.06, 39.15, 55.25, 65.57, 65.78, 114.05, 127.77, 128.23, 128.34, 130.28, 140.33, 159.32 and 173.84.

β-*Tyrosine Methyl Ether* 36c.—Isoxazolidinone 33c (90 mg, 0.3 mmol) in dry ethanol (30 cm³) containing palladium hydroxide on charcoal (10 mg, 20%) was hydrogenated at atmospheric pressure and 70 °C for 4 h. The solid amino acid separated during hydrogenolysis, and when hydrogen uptake was complete, distilled water (100 cm³) was added to dissolve the amino acid. The catalyst was removed by filtration through a pad of Celite and this was thoroughly washed with warm distilled water (100 cm³). The combined filtrate was evaporated under reduced pressure to give *β-tyrosine methyl ether* (53 mg, 90%), m.p. 241–244 °C, $[\alpha]_D^{21}$ −7.2°, (*c* 1.0, H₂O) (Found: C, 61.2; H, 6.9; N, 7.6. $C_{12}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%).

Attempted Cycloaddition of N-*Indol-2-ylmethylene*[(R)-(−)-α-*methylbenzyl*]*amine* N-*Oxide* 21d *with Vinyl Acetate*.—The indolyl *N*-oxide 21d (1.3 g, 5.2 mmol) was dissolved in an excess of vinyl acetate (50 cm³, 0.62 mmol) and heated at reflux for 120 h. Work-up gave the N-*acetyl nitrone* (1.21 g, 76%), m.p. 163 °C (Found: M⁺, 306.1377. $C_{19}H_{18}N_2O_2$ requires *M*, 306.1368); $v_{max}(CHCl_3)/cm^{-1}$ 1705, 1535, 1452, 1378, 1328 and 1150; δ_H 1.92 (3 H, d, *J* 6.5), 2.62 (3 H, s), 5.26 (1 H, q, *J* 6.5), 7.22–7.60 (8 H, m), 7.82 (1 H, s), 8.48 (1 H, m) and 9.24 (1 H, s).

N-*Benzyl*-3-*p*-*methoxyphenylisoxazolidin-5-one* 41 (R = *p*-MeOPh).—N-(*p*-*Methoxybenzylidene*)*benzylamine* N-*oxide* 37 (0.9 g, 3.73 mmol) was heated at reflux in neat α-chloroacrylonitrile (20 cm³, Aldrich, freshly distilled) under an argon atmosphere for 1 h. Excess of α-chloroacrylonitrile was evaporated under reduced pressure and the light brown residue chromatographed over silica gel [ethyl acetate – light petroleum ether (b.p. 40–60 °C), 1:4] to give the cycloaddition product mixture 38 as a pale yellow oil (0.95 g, 77%) [Found: M⁺,

328.0990 (4.45), 330.0949 (1.47). $C_{18}H_{17}N_2O_2{}^{35/37}Cl$ requires *M*, 328.0978, 330.0949].

To a portion of the cycloadduct mixture (0.4 g, 1.2 mmol) dissolved in aqueous THF (10 cm³ H₂O, 20 cm³ THF) was added triethylamine (0.18 g, 1.8 mmol, 1.5 equiv.) and the resulting mixture stirred at room temperature overnight. The THF was then evaporated under reduced pressure, and the residue taken up in chloroform (50 cm³). The organic layer was washed with water, dried (Na₂SO₄), filtered and evaporated under reduced pressure to give a residue which was chromatographed over silica gel (ethyl acetate–light petroleum (pp. 40–60 °C), 1:5) to afford *isoxazolidinone* 41 (0.145 g, 42%) as a pale yellow oil (Found: M⁺, 283.1221. $C_{17}H_{17}NO_3$ requires *M*, 283.1208); $v_{max}(CHCl_3)/cm^{-1}$ 1769, 1610, 1510, 1400, 1300, 1250, 1105, 1030, 920, 895 and 830; δ_H 2.91 (2 H, d, *J* 9), 3.8 (3 H, s), 4.0 (2 H, AB q, *J* 14.2), 4.28 (1 H, t, *J* 9), 6.9 (2 H, d, *J* 9), 7.26 (5 H, s) and 7.38 (2 H, d, *J* 9).

4-(*p*-*Methoxyphenyl*)-2-*oxobut*-3-*enenitrile* 40.—The N-benzyl *N*-oxide 37 (1 g, 4.15 mmol) was heated at reflux in neat α-chloroacrylonitrile (20 cm³) under an argon atmosphere for 24 h. Excess of α-chloroacrylonitrile was evaporated under reduced pressure, and the dark brown residue chromatographed over silica gel (hexane–ethyl acetate, 3:2) to afford the keto nitrile 40 (0.58 g, 75%) as a pale yellow crystalline solid, m.p. 125–126 °C (Found: C, 70.35; H, 4.7; N, 7.3%; M⁺, 187.0632. $C_{11}H_9NO_2$ requires C, 70.55; H, 4.85; N, 7.5%; *M*, 187.0633); $v_{max}(CHCl_3)/cm^{-1}$ 2230, 1659, 1570, 1510, 1430, 1340, 1310, 1260, 1239, 1200, 1171, 1031, 979 and 835; δ_H 3.91 (3 H, s), 6.75 (1 H, d, *J* 16), 7.0 (1 H, d, *J* 8.4), 7.6 (1 H, d, *J* 8.4) and 7.95 (1 H, d, *J* 16); δ_C 55.53 (MeO), 112.63 (CN), 114.96 (CH=CH–CO), 122.95 (Ar–H), 125.58 (Ar), 131.7 (Ar–H), 154.72 (Ar–CH=CH), 163.74 (Ar–H) and 175.59 (C=O).

N-*Benzyl*-3-*methylisoxazolidin-5-one* 41 (R = Me).—N-(*Ethylidene*)*benzylamine* N-*oxide* 42 (1.2 g, 8.05 mmol) was heated at reflux in neat α-chloroacrylonitrile (30 cm³) under an argon atmosphere for 10 min. Excess of α-chloroacrylonitrile was evaporated under reduced pressure and the light brown residue chromatographed over silica gel (hexane–ethyl acetate, 2:3) to give the cycloaddition product mixture as a pale yellow oil (1.41 g, 74%) [Found: M⁺, 236.0732 (2.33), 238.0699 (0.7). $C_{12}H_{13}N_2O^{35/37}Cl$ requires *M*, 236.0716, 238.0687].

To a portion of the cycloadduct mixture (0.8 g, 3.38 mmol) in aqueous THF (10 cm³ H₂O, 30 cm³ THF) was added triethylamine (0.5 g, 4.95 mmol, 1.5 equiv.) and the resulting mixture was stirred at room temperature overnight. Work-up as above gave a residue which was chromatographed over silica gel (ethyl acetate–hexane, 1:4) to afford the *isoxazolidinone* 41 (R = Me) (0.48 g, 74%) as a light yellow oil (Found: M⁺, 191.0961. $C_{11}H_{13}NO_2$ requires *M*, 191.0946); $v_{max}(CHCl_3)/cm^{-1}$ 1770, 1490, 1410, 1380, 1320, 1255, 1220, 1170, 1045, 1025, 910, 900 and 700; δ_H(100 MHz) 1.16 (3 H, d, *J* 6.2), 2.4 (1 H, dd, *J* 11 and 17), 2.68 (1 H, dd, *J* 7 and 17), 3.35 (1 H, m), 4.0 (2 H, AB q, *J* 13.8) and 7.2–7.5 (5 H, m); δ_C 17.06 (Me), 37.81 (CH₂CHCO), 61.084 (CHN and PhCH₂), 127.48 (Ar–H), 128.17 (Ar–H), 128.73 (Ar–H), 135.35 (Ar) and 173.31 (C=O).

N-(R)-α-*Methylbenzyl*-3-*phenylisoxazolidin-5-one* 43 ≡ 33b.—The *N*-Benzylidene *N*-oxide 45 ≡ 21b (2.5 g, 11.1 mmol) was heated at reflux in neat α-chloroacrylonitrile (40 cm³) under an argon atmosphere for 1 h. Excess of α-chloroacrylonitrile was evaporated under reduced pressure and the pale brown residue chromatographed over silica gel (ethyl acetate–hexane, 1:2) to give the cycloaddition product mixture (2.1 g, 60%) as a pale yellow oil [Found: M⁺, 312.1037 (1.13), 314.1020 (0.41). $C_{18}H_{17}N_2O^{35/37}Cl$ requires *M*, 312.1029, 314.0999].

To a portion of the cycloadduct mixture (1.5 g, 4.8 mmol),

dissolved in aqueous THF (10 cm³ H₂O, 20 cm³ THF), was added triethylamine (0.73 g, 7.2 mmol, 1.5 equiv.) and the resulting mixture was stirred at room temperature overnight. Work-up as before gave a residue which was chromatographed over silica gel (hexane–ethyl acetate, 5:1) to afford the *isoxazolidinone* **43** ≡ **33b** (0.43 g, 34%) as a pale yellow crystalline solid, m.p. 93–96 °C (Found: M⁺, 267.1265. C₁₇H₁₇NO₂ requires *M*, 267.1259); v_{max}(CHCl₃)/cm⁻¹ 1765, 1600, 1489, 1449, 1410, 1371, 1281, 1225, 1195, 1160, 1030, 905 and 700; δ_H(100 MHz) 1.6 (3 H, d, *J* 7), 2.86 (1 H, dd, *J* 8 and 17.8), 3.15 (1 H, dd, *J* 8 and 17.8), 4.21 (1 H, q, *J* 7), 4.55 (1 H, t, *J* 8) and 7.2–7.6 (10 H, m).

β-*Phenyl*-β-*alanine* **36b**.—To the isoxazolidinone **43** (0.3 g, 1.12 mmol) dissolved in absolute ethanol (50 cm³) was added palladium hydroxide on charcoal (20%; 30 mg) and the mixture hydrogenated at atmospheric pressure and 70 °C overnight. The solid amino acid separated during hydrogenolysis. Distilled water (50 cm³) was added to dissolve the amino acid, and the catalyst was removed by filtration through a pad of Celite, and this was thoroughly washed with warm water (100 cm³). The combined filtrate was evaporated under reduced pressure to give β-phenyl-β-alanine **36b** (0.18 g, 97%), m.p. 231–233 °C, [α]_D +5.43° (*c* 1.16, H₂O) (lit.,⁴⁰ m.p. 236 °C, [α]_D +6.2° for (*S*)-β-phenyl-β-alanine).

3-*Isopropyl*-N-(R)-α-*methylbenzylisoxazolidin*-5-*one* **44** ≡ **33a**.—N-α-Methylbenzyl N-oxide **46** ≡ **21a** (0.5 g, 2.62 mmol) was heated at reflux in neat α-chloroacrylonitrile under an argon atmosphere for 25 min. Excess of α-chloroacrylonitrile was evaporated under reduced pressure and the residue chromatographed over silica gel [ethyl acetate–light petroleum (b.p. 40–60 °C), 2:3] to give the cycloaddition product mixture as a light brown oil (0.52 g, 71%) [Found: M⁺, 278.1190 (0.34), 280.1160 (0.16). C₁₅H₁₉N₂O³⁵/³⁷Cl requires *M*, 278.1186, 280.1156].

To the cycloadduct mixture (0.51 g, 1.83 mmol) dissolved in aqueous THF (10 cm³ H₂O, 20 cm³ THF) was added triethylamine (0.28 g, 2.8 mmol) and the resulting mixture was stirred at room temperature overnight. Work-up as before gave a residue which was chromatographed over silica gel (ethyl acetate–light petroleum, 1:4) to afford the *isoxazolidinone* **44** ≡ **33a** (0.28 g, 66%) as a colourless oil (Found: M⁺, 233.1413. C₁₄H₁₉NO₂ requires, *M*, 233.1416); v_{max}(CHCl₃)/cm⁻¹ 1770, 1630, 1488, 1445, 1390, 1280, 1225, 1180, 1100, 915, 870 and 700; δ_H(200 MHz) 0.75 (4.125 H, m), 0.92 (1.875 H, m), 1.52 (2.06 H, d, *J* 6.6), 1.6 (0.94 H, d, *J* 6.9), 1.7 (0.31 H, m), 2.03 (0.31 H, dd, *J* 8.9 and 17.7), 2.28 (0.31 H, dd, *J* 5.5 and 18.3), 2.26 (0.69 H, dd, *J* 3.1 and 17.9), 2.62 (0.69 H, dd, *J* 8.8 and 17.95), 3.15 (1 H, m), 4.04 (1 H, m) and 7.32 (5 H, m); δ_C 17.34 [(*Me*)₂CH], 17.86 [(*Me*)₂CH], 18.43 [(*Me*)₂CH], 19.71 (PhCHCH₃), 19.95 (PhCHCH₃), 30.58 (CH₂CO), 31.07 [(Me)₂*CH*], 31.34 (CH₂CO), 31.59 [(Me)₂-*CH*], 65.07 (CHN), 65.86 (CHN), 66.23 (Ph*C*H), 66.88 (Ph*C*H), 127.89 (Ar–H), 128.05 (Ar–H), 128.16 (Ar–H), 128.53 (Ar–H), 128.61 (Ar–H), 138.35 (Ar), 140.34 (Ar), 176.19 (C=O) and 177.19 (C=O).

β-*Leucine* **36a**.—To the isoxazolidinone **44** (0.13 g, 0.56 mmol) dissolved in methanol (50 cm³) was added palladium hydroxide on charcoal (20 mg, 20%) and the resulting mixture hydrogenated at atmospheric pressure and room temperature for 48 h. The catalyst was removed by filtration through a pad of Celite, this being thoroughly washed with warm methanol (100 cm³). The combined filtrates were evaporated under reduced pressure to give β-leucine as colourless crystals (69 mg, 94%), m.p. 197–200 °C, [α]_D −15.1° (*c* 0.81, H₂O) (lit.,⁴⁰ m.p. 201–202 °C, [α]_D +55.2° for (*S*)-β-leucine).

3-*Isopropyl*-N-(R)-α-*methoxycarbonylbenzyl*)*isoxazolidin*-5-

one **49**.—N-Isobutylidene[(R)-α-methoxycarbonylbenzyl]-amine N-oxide **48** (1 g, 4.25 mmol) was heated at reflux in neat α-chloroacrylonitrile (20 cm³) under an argon atmosphere for 30 min. Excess of α-chloroacrylonitrile was evaporated under reduced pressure and the residue chromatographed over silica gel (hexane–ethyl acetate, 3:2), to give the cycloaddition product mixture as a pale yellow oil (0.81 g, 59%).

To a portion of the cycloadduct mixture (0.6 g, 1.86 mmol) was added aqueous HCl (0.4 equiv.) and the mixture stirred at room temperature overnight. Work-up as before gave a residue which was chromatographed over silica gel (ethyl acetate–hexane, 2:3) to afford the *isoxazolidinone* **49** (0.27 g, 52%) as a pale yellow oil (Found: M⁺, 277.1321. C₁₅H₁₉NO₄ requires *M*, 277.1314); v_{max}(CHCl₃)/cm⁻¹ 1731, 1658, 1600, 1575, 1504, 1475, 1430, 1355, 1259, 1195, 1165, 1005, 830 and 690; δ_H(200 MHz) 0.76 (5.5 H, m), 0.95 (0.5 H, m), 1.55 (1 H, m), 2.45 (1 H, m), 2.7 (1 H, m), 3.16 (1 H, m), 3.67 (2.75 H, s), 3.68 (0.5 H, s), 4.62 (0.92 H, s), 4.95 (0.08 H, s) and 7.3–7.6 (5 H, m); δ_C 17.51 [(*Me*)₂CH], 18.44 [(*Me*)₂CH] 30.28 (CH₂CO), 31.34 [(Me)₂*CH*], 52.34 (CO₂*Me*), 65.64 (CHN), 77.0 (PhCH-CO₂Me), 128.8 (Ar–H), 128.99 (Ar–H), 129.5 (Ar–H), 132.78 (Ar), 169.13 (CH₂C=O) and 176.11 (*C*O₂Me).

3-p-*Methoxyphenyl*-N-(R)-α-*methylbenzylisoxazolidin*-5-*one* **33c**.—The N-α-Methylbenzyl N-oxide **21c** (0.2 g, 0.78 mmol) was heated at reflux in neat α-chloroacrylonitrile (15 cm³) under an argon atmosphere for 1 h. Excess of α-chloronitrile was evaporated under reduced pressure and the residue chromatographed over silica gel (hexane–ethyl acetate, 4:1) to give the cycloaddition product mixture as a yellow oil (0.2 g, 75%); TLC, R_f *ca.* 0.72 (silica gel, hexane–ethyl acetate, 1:1) [Found: M⁺, 342.1145 (0.87), 344.1124 (0.42). C₁₉H₁₉N₂O₂³⁵/³⁷Cl requires *M*, 342.1135, 344.1105].

To the cycloadduct mixture above (0.2 g, 0.58 mmol) dissolved in aqueous THF (5 cm³ H₂O, 20 cm³ THF) was added pyridine (0.07 g, 0.89 mmol, 1.5 equiv.) and the resulting mixture stirred at room temperature overnight. Work-up as before gave a residue which was chromatographed over silica gel (ethyl acetate–hexane, 1:4) to afford the *isoxazolidinone* **33c** (30 mg, 17%) as a pale yellow crystalline solid, m.p. 125–127 °C (Found: M⁺, 297.1387. C₁₈H₁₉NO₃ requires *M*, 297.1365); v_{max}-(CHCl₃)/cm⁻¹ 1775, 1615, 1515, 1455, 1410, 1300, 1251, 1210, 1175, 1160, 1035, 912, 885 and 701; δ_H(200 MHz) 1.55 (3 H, d, *J* 6.6), 2.82 (1 H, dd, *J* 9.1 and 17.3), 3.03 (1 H, dd, 7.7 and 17.3), 3.77 (3 H, s), 4.12 (1 H, q, *J* 6.6), 4.42 (1 H, t, *J* 7.9), 6.78 (1 H, d, *J* 9.4), 7.15 (1 H, d, *J* 9.4) and 7.21 (10 H, m); δ_C 18.06 (PhCH*Me*), 39.12 (CH₂CO), 55.23 (OMe), 65.56 (Ph*C*HMe), 65.75 (*p*-MeOPh*C*H), 14.04 (Ar–H), 127.76 (Ar–H), 128.22 (Ar–H), 128.33 (Ar–H), 130.28 (Ar), 140.34 (Ar), 159.32 (Ar) and 173.82 (C=O). This compound was identical with the compound m.p. 127–128 °C, prepared from the same nitrone and vinyl acetate.

3-*Methylene*-1,5-*dihydro*-2,4-*benzodioxepine* **50**.—This was prepared according to ref. 45 (85% yield) and had b.p. 140–143 °C at 0.2 mmHg, m.p. 46–47 °C (lit.,⁴⁵ m.p. 49 °C); δ_H(CDCl₃) 3.7 (2 H, s), 5.02 (4 H, s) and 6.98–7.4 (4 H, m).

General Procedure for the Synthesis of Isoxazolidinone (*o*-*Xylyl*) *Acetals*.—The appropriate N-oxide (1 equiv.) and (*o*-xylyl) ketene acetal (1.5 equiv.) were dissolved in anhydrous toluene and heated at reflux together for the specified period of time. Excess of solvent was evaporated at the oil pump and the isoxazolidinone acetal obtained from the residue by flash column chromatography (ether–hexane, 4:1) over silica gel.

2′,3′-*Diphenylspiro*[1,5-*dihydro*-2,4-*benzodioxepine*-3,5′-*iso-xazolidine*] **51** (R = R′ = Ph). N-(Benzylidene)phenylamine N-oxide (1.3 g, 6.6 mmol) and ketene acetal **50** (2.2 g, 13.5 mmol) by the general procedure (24 h), gave *isoxazolidine* **51** (R =

R' = Ph) (1.5 g, 63%), m.p. 130–131 °C (from ether) (Found: C, 76.9; H, 5.85; N, 3.9%; M⁺, 359.1516. $C_{23}H_{21}NO_3$ requires C, 76.9; H, 5.9; N, 3.9%; M, 359.1521); δ_H(CDCl$_3$) 2.65 (1 H, dd, J 9 and 13), 3.02 (1 H, dd, J 7 and 13), 4.6–4.95 (4 H, m), 5.25 (2 H, d, J 14) and 6.9–7.6 (14 H, m).

N-*Phenyl*-β-*phenyl*-β-*alanine* **52**.—The above isoxazolidine (0.15 g, 0.42 mmol) was hydrogenated in ethyl acetate (40 cm³)–ethanol (10 cm³) containing palladium on charcoal (40 mg, 20%) at atmospheric pressure and room temperature until hydrogen uptake was complete (3 equiv., 3 h). The catalyst was removed by filtration through a pad of Celite, which was washed with ethanol (20 cm³). The filtrate was evaporated under reduced pressure and the residue chromatographed over silica gel (hexane–ethyl acetate, 2:3) to afford the β-*amino acid* **52** (80 mg, 80%), m.p. 118–120 °C (Found: C, 74.6; H, 6.2; N, 5.8%; M⁺, 241.1103. $C_{15}H_{15}NO_2$ requires C, 74.65; H, 6.25; N, 5.8%; M, 241.1106); v_{max}(CHCl$_3$)/cm⁻¹ 3400–2500, 1709, 1601, 1501, 1450, 1420, 1315, 1265, 1225 and 701; δ_H(100 MHz) 2.86 (2 H, d, J 7), 4.88 (1 H, t, J 7), 6.5–7.4 (10 H, m) and 7.5 (2 H, br s, D_2O exchangeable); δ_C 42.17 (CH$_2$CO$_2$H), 55.3 (PhCH), 114.51 (Ar–H), 118.74 (Ar–H), 128.79 (Ar–H), 129.15 (Ar–H), 141.245 (Ar), 145.81 (Ar) and 176.7 (CO$_2$H).

N-[(R)-α-*Methylbenzyl*]-3′-*phenylspiro*[1,5-*dihydro*-2,4-*benzodioxepine*-3,5′-*isoxazolidine*] **51** (R = Ph, R′ = (R)-α-*methylbenzyl*).—The nitrone **21b** (0.50 g, 2.4 mmol) and ketene acetal **50** were heated at reflux in toluene (25 cm³) for 60 h, to give the oily *title isoxazolidine* (0.11 g, 12%) (Found: M⁺, 387.1834. $C_{25}H_{25}NO_3$ requires M, 387.1834); v_{max}(CHCl$_3$)/cm⁻¹ 1605, 1495, 1380, 1312, 1300, 1275, 1265, 1215, 1170, 1100 and 1038; δ_H(200 MHz) 1.38 (0.59 H, d, J 6.5), 1.56 (2.41 H, d, J 6.5), 2.52 (0.21 H, m), 2.60 (0.79 H, dd, J 7.5 and 12.5), 2.88 (0.18 H, dd, J 7.5 and 12.5), 2.95 (0.82 H, dd, J 7.5 and 12.5), 3.96 (0.21 H, q, J 6.5), 4.18 (0.79 H, q, J 6.5), 4.32 (1 H, t, J 7.5), 4.62–5.28 (4 H, m) and 6.98–7.56 (10 H, m); δ_C(¹H decoupled) 20.16, 21.36, 45.46, 47.35, 64.28, 65.96, 66.13, 66.31, 66.86, 67.17, 67.31, 67.42, 120.87, 123.49, 126.19, 126.44, 126.78, 126.87, 126.97, 127.01, 127.19, 127.27, 127.39, 127.80, 127.89, 128.11, 128.18, 128.41, 128.59, 128.93, 137.08, 137.18, 137.28, 140.79, 141.27 and 142.27.

3′-(4-*Chlorophenyl*)-N-[(R)-α-*methylbenzyl*]*spiro*[1,5-*dihydro*-2,4-*benzodioxepine*-3,5′-*isoxazolidine*] **51** (R = p-*ClPh*, R′ = (R)-α-*methylbenzyl*).—N-(p-Chlorobenzylidene)[(R)-(−)-α-methyl-benzyl]amine N-oxide **21e** (0.5 g, 1.9 mmol) and the ketene acetal **50** (0.37 g, 2.3 mmol) were heated at reflux in toluene (25 cm³) for 48 h, to give the oily *isoxazolidine* of the title (0.23 g, 28%) (Found: M⁺, 421.1455. $C_{25}H_{24}NO_3Cl$ requires M, 421.1445); v_{max}(CHCl$_3$)/cm⁻¹ 1730, 1595, 1488, 1452, 1380, 1372, 1305, 1150, 1088, 1075, 1030 and 1012; δ_H 1.54 (0.65 H, d, J 6), 1.72 (2.35 H, d, J 6), 2.58–3.24 (2 H, m), 4.09–4.52 (2 H, m), 4.85–5.46 (4 H, m) and 7.05–7.98 (9 H, m).

Acknowledgements

References

1 C. N. C. Drey, in *The Chemistry and Biochemistry of Amino Acids*, ed. B. Weinstein, Dekker, New York, 1976, vol. 4, p. 241.

2 C. N. C. Drey, in *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barnett, Chapman and Hall, London, 1984, p. 25.

3 O. W. Griffith, *Ann. Rev. Biochem.*, 1986, **55**, 855.

4 A. S. Khoklov, *J. Chromat. Libr.*, 1987, **15**, 617.

5 *Dictionary of Antibiotics and Related Substances*, ed. B. W. Bycroft, Chapman and Hall, London, 1988, p. 665.

6 S. J. Gould and T. K. Thiruvengadam, *J. Am. Chem. Soc.*, 1981, **103**, 6752.

7 T. K. Thiruvengadam, S. J. Gould, D. J. Aberhart and H.-J. Liu, *J. Am. Chem. Soc.*, 1983, **105**, 5470.

8 Y. Sawada and H. Taniyama, *Chem. Pharm. Bull.*, 1977, **25**, 1302.

9 J. H. Carter, R. H. DuBus, J. R. Dyer, J. C. Floyd, K. C. Rice and P. D. Shaw, *Biochemistry*, 1974, **13**, 1227.

10 Dictionary of Antibiotics and Related Substances, ed. B. W. Bycroft, Chapman and Hall, London, 1988, p. 504.

11 Dictionary of Antibiotics and Related Substances, ed. B. W. Bycroft, Chapman and Hall, London, 1988, p. 299.

12 Dictionary of Antibiotics and Related Substances, ed. B. W. Bycroft, Chapman and Hall, London, 1988, p. 176.

13 P. C. Prabhakaran, N.-T. Woo, P. Yorgey and S. J. Gould, *Tetrahedron Lett.*, 1986, 3815.

14 T. C. Stadtman, *Adv. Enzymol.*, 1970, **38**, 413.

15 J. M. Poston, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1986, **58**, 173.

16 I. Freer, G. Pedrocchi-Fantoni, D. J. Picken and K. H. Overton, *J. Chem. Soc., Chem. Commun.*, 1981, 80.

17 R. J. Parry and Z. Kurylo-Borowska, *J. Am. Chem. Soc.*, 1980, **102**, 836.

18 D. Keirs and K. Overton, *Heterocycles*, 1989, **28**, 841.

19 A. Freer, K. Overton and R. Tomanek, *Tetrahedron Lett.*, 1990, 1471.

20 M. Furukawa, T. Okawara and Y. Terawaki, *Chem. Pharm. Bull.*, 1977, **25**, 1319.

21 D. F. C. Moffat, Ph.D. Thesis, University of Glasgow, 1986.

22 M. Furukawa, T. Okawara, Y. Noguchi and Y. Terawaki, *Chem. Pharm. Bull.*, 1978, **26**, 260.

23 M. Furukawa, T. Okawara, Y. Noguchi and Y. Terawaki, *Heterocycles*, 1977, **6**, 1323.

24 K. Achiwa and T. Soga, *Tetrahedron Lett.*, 1987, 1119.

25 M. Furukawa, T. Okawara, Y. Noguchi and Y. Terawaki, *Chem. Pharm. Bull.*, 1979, **27**, 2223.

26 T. Kaseda, T. Kikuchi and C. Kibayashi, *Tetrahedron Lett.*, 1989, 4539.

27 C. Belzecki and I. Panfil, *J. Chem. Soc., Chem. Commun.*, 1977, 303; *J. Org. Chem.*, 1979, **44**, 1212.

28 R. Huisgen, R. Grashey, H. Seidl and H. Hauck, *Chem. Ber.*, 1968, **101**, 2559.

29 C. M. Dicken, P. DeShong, R. R. Staib, A. J. Freyer and S. M. Weinreb, *J. Org. Chem.*, 1982, **47**, 4397.

30 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.

31 E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 1987, 2461.

32 A. J. Mancuso, D. S. Brownfain and D. Swern, *J. Org. Chem.*, 1979, **44**, 4148.

33 M. E. Jung, *J. Org. Chem.*, 1976, **41**, 1479.

34 E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, 1972, **94**, 7586.

35 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley, New York, 1967, vol. 1, p. 142.

36 J. C. Collins and W. W. Hess, *Org. Synth.*, 1972, **52**, 5.

37 H. Stamm and H. Steudle, *Tetrahedron*, 1979, **35**, 647.

38 Preliminary communication: D. Keirs, D. Moffat and K. Overton, *J. Chem. Soc., Chem. Commun.*, 1988, 654.

39 P. M. Wovkulich and M. R. Uskokovic, *Tetrahedron*, 1985, **41**, 3455; ref. 14 therein.

40 H. E. Carter, W. R. Hearn and W. R. Taylor, Abstracts of Papers, 119th Meeting, American Chemical Society, Cleveland, Ohio, April 1951, p. 25A.

41 T. Yamada, S. Kumata and H. Watanabe, *Tetrahedron Lett.*, 1978, 1813.

42 K. B. Sharpless, K. Akashi and K. Oshima, *Tetrahedron Lett.*, 1976, 2503.

43 S. Ranganathan, D. Ranganathan and A. K. Mehrotra, *Synthesis*, 1977, 289.

44 P. K. Freeman, D. M. Balls and D. J. Brown, *J. Org. Chem.*, 1968, **33**, 2211.

45 R. Grewe and A. Struve, *Chem. Ber.*, 1963, **96**, 2819.

46 T. Wakamiya, H. Uritani, T. Tashima and T. Shiba, *Bull. Chem. Soc. Japan*, 1975, **48**, 2401.

47 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.