SYNTHESIS OF 6-ARYL-4-HYDROXYPIPERIDIN-2-ONES AND A POSSIBLE APPLICATION TO THE SYNTHESIS OF A NOVEL HMG-CoA REDUCTASE INHIBITOR

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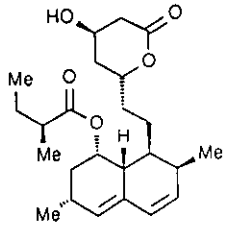
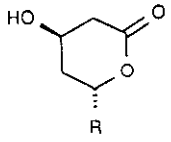
Abstract - A series of 6-aryl-4-hydroxypiperidin-2-ones (11a-11g) were synthesised with the key step being a Dieckmann cyclisation of the appropriate methyl 3-(ethoxycarbonylacetylamino)-3-(substituted) propionate (8a-8g) and this new synthetic route was successfully applied to the synthesis of 4-hydroxy-6-(2-phenylethyl)piperidin-2-one (11h). The application of this strategy to the synthesis of the putative HMG-CoA reductase inhibitor 6-[2-(2-benzyloxy-4,6-dichlorophenyl)ethyl]-4-hydroxypiperidin-2-one (11i) was attempted, but failed during the Dieckmann cyclisation of methyl 3-(ethoxycarbonylacetylamino)-3-[2-(2-benzyloxy-4,6-dichlorophenyl)-ethyl]propionate (8i). An alternative synthesis of a 1:1 diastereomeric mixture of (11i) was achieved by the reductive cleavage of the isoxazoline (24) with Raney nickel. The mixture of diastereoisomers (11i) was inactive *in-vitro* and *in-vivo* (rat) against HMG-CoA reductase

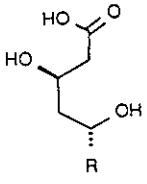
The fungal metabolite lovastatin (mevinolin) (1) is a potent reversible inhibitor of HMG-CoA reductase, which is the rate limiting enzyme in cholesterol biosynthesis.[1] Lovastatin (1) has been introduced recently as the first of a new generation of hypocholesterolaemic agents.



(1)

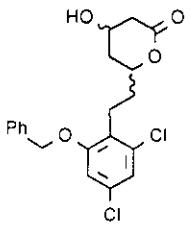


(2)

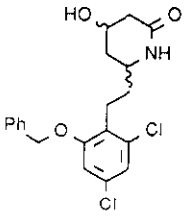


(3)

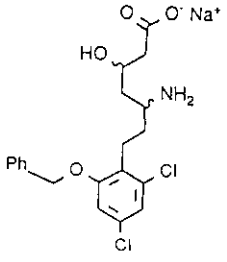
Simplified structures (2) have been synthesised as HMG-CoA reductase inhibitors, and the vast majority, like lovastatin, requires the 4-hydroxypyranone ring to elicit inhibitory activity.[2] It is known that the pyranone ring is a 'prodrug' form of the active dihydroxy acid (3).[3] In contrast to this seemingly specific requirement, the hexahydronaphthalene ring system of lovastatin (1) may be replaced by a variety of appropriately substituted aryl- and heteroaryl-ring systems,[4] and compound (4) is reported to have a similar inhibitory activity to that of lovastatin.[3]



(4)



(11i)

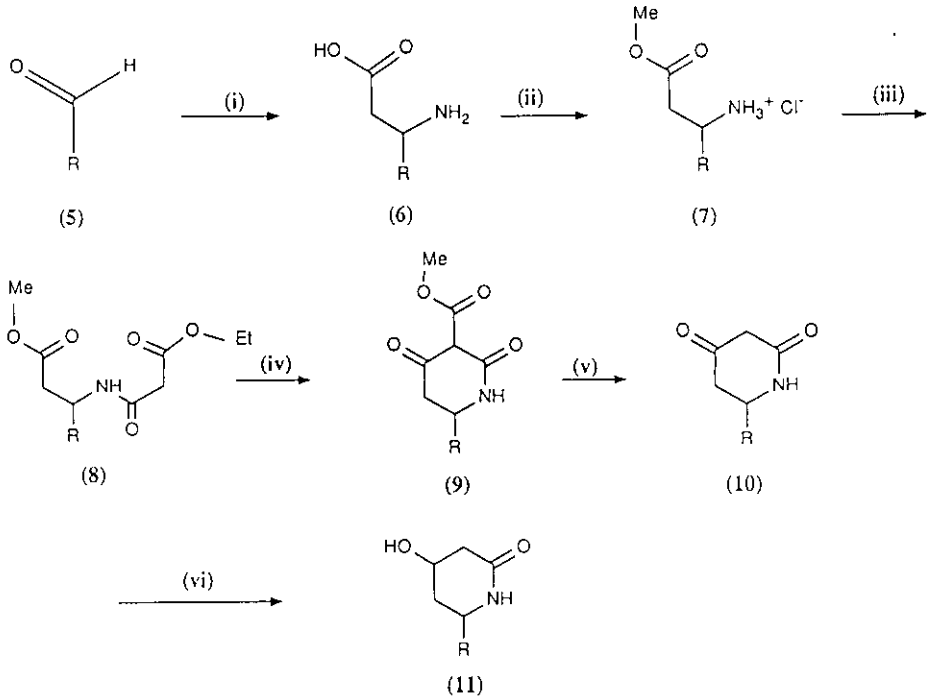


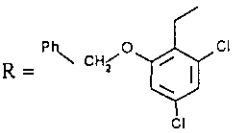
(26)

It was thus of interest to synthesise compounds bearing an appropriate aryl function e g. (11i) connected to a 4-hydroxy-6-lactam ring (4-hydroxypiperidin-2-one) as potential novel HMG-CoA reductase inhibitors. Such lactams could conceivably undergo hydrolytic ring opening *in-vivo* to the corresponding 5-amino-3-hydroxy acid (26) by a proteolytic mechanism.[5] 4-Hydroxypiperidin-2-ones have not been previously described, and a general synthetic route to such compounds, which might be applicable to a synthesis of compound (11i) was initially investigated. Retrosynthetically, the 4-hydroxypiperidin-2-one structure (11) could be derived by reduction of the corresponding piperidine-2,4-dione (10). A synthesis of the unsubstituted piperidine-2,4-dione (10, R=H) has been described,[6] and a variation on the reported route of access was used to prepare the 6-aryl derivatives (10a-10g) (Scheme 1).

The appropriate benzaldehyde (5a-5g) was condensed with ammonium acetate and malonic acid, yielding the β-amino acids[7] (6a-6g), which were esterified (thionyl chloride/methanol) to give the corresponding β-amino ester hydrochlorides (7a-7g). Treatment with base followed by coupling to ethyl hydrogen malonate, using N,N'-dicyclohexylcarbodiimide, yielded the diesters (8a-8g), in which the ester groups were correctly dispositioned to undergo Dieckmann cyclisation under methoxide catalysis, to give the methyl, 2,4-dioxopiperidine-3-carboxylates (9a-9g) after ester exchange. Hydrolysis and decarboxylation then gave the key intermediates (10a-10g). General experimental details and physical properties of the intermediates and products are collated in Table 1, and the sequence is fully described in the experimental section for the preparation of the 1-naphthyl derivative (10f).

Scheme 1



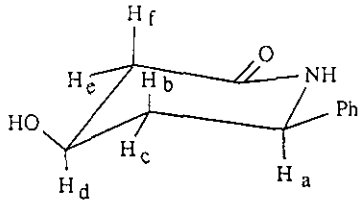
a R = C_6H_5-
b R = 4-MeO-C_6H_4-
c R = 2-$PhCH_2O$-C_6H_4-
d R = 4-Cl-C_6H_4-
e R = 3,4,Cl_2.C_6H_3-
f R = 1-naphthyl-
g R = 4-C_6H_5-C_6H_4-
h R = $C_6H_5CH_2CH_2$-
i R = 

Reagents: (i), NH_4OAc, $CH_2(CO_2H)_2$; (ii), $SOCl_2$, MeOH, (iii), Et_3N, $EtOOCCH_2COOH$, N,N-Dicyclohexylcarbodiimide; (iv), NaOMe, THF; (v), KOH, EtOH; (vi), $NaBH_4$, MeOH.

Reduction of the piperidinediones (10a-10g) was accomplished with sodium borohydride, and the products (11a-11g) were isolated by crystallisation. Examination of each of these seven products (11a-11g) by 200 MHz ^1H nmr showed that they had all been obtained as single diastereoisomers and the similarities in their spectra implied that the same diastereoisomers had been isolated in each case. Detailed analysis of the spectrum of the 6-phenyl derivative (11a) was performed and the coupling constants of protons H_a, H_b, H_d, H_e and H_f (Figure 1,

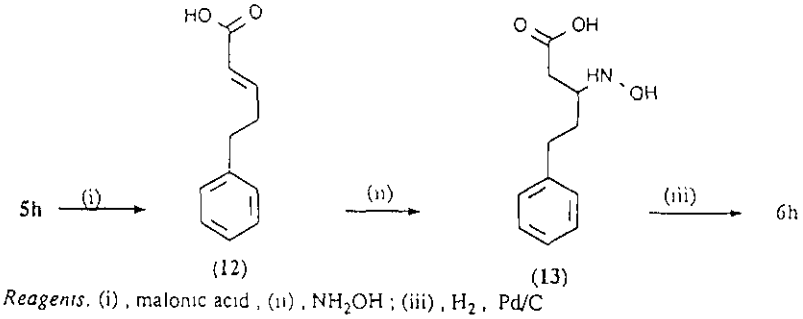
also see Table 2) determined. The coupling constants of H_a, H_b and H_d were diagnostic of protons in axial positions, and therefore the disposition of the 4-hydroxy and 6-phenyl groups were clearly equatorial (or pseudo-equatorial accounting for the slight flattening of the chair by the lactam group). Therefore the two substituents must be *cis* to each other on the ring.

Figure 1



Synthesis of the 6-(2-phenylethyl)piperidine-2,4-dione (11h) was next approached. Preparation of the β-amino acid (6h) was not possible directly from the phenylpropionaldehyde (5h), but was prepared conveniently in 3 steps from (5h) as depicted in Scheme 2.

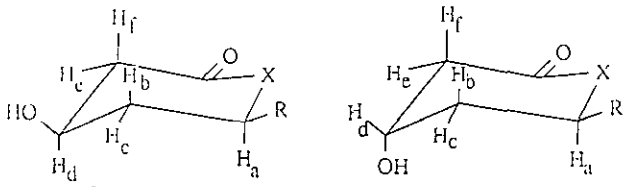
Scheme 2



Reagents. (i), malonic acid, (ii), NH_2OH; (iii), H_2, Pd/C

Thus condensation of (5h) with malonic acid gave the E-pentenoic acid (12). This reacted smoothly with hydroxylamine yielding (13), which was reductively cleaved to give the desired β-amino acid (6h). The previously described route (6→10, Scheme 1) was used to transform (6h) into the piperidinedione (10h), and reduction with sodium borohydride followed by crystallisation, yielded, as before, a single diastereoisomer of (11h). The ^1H nmr spectrum of (11h) was very similar to those of the 4-hydroxypiperidinones (11a-11g) previously described, particularly in terms of the coupling patterns of the protons on the piperidinone ring. This product was hence assigned the *cis*-stereochemistry (Figure 2, Isomer A, R=$PhCH_2CH_2$, X=NH).

Figure 2



R = Aryl or Aralkyl
X = O or NH

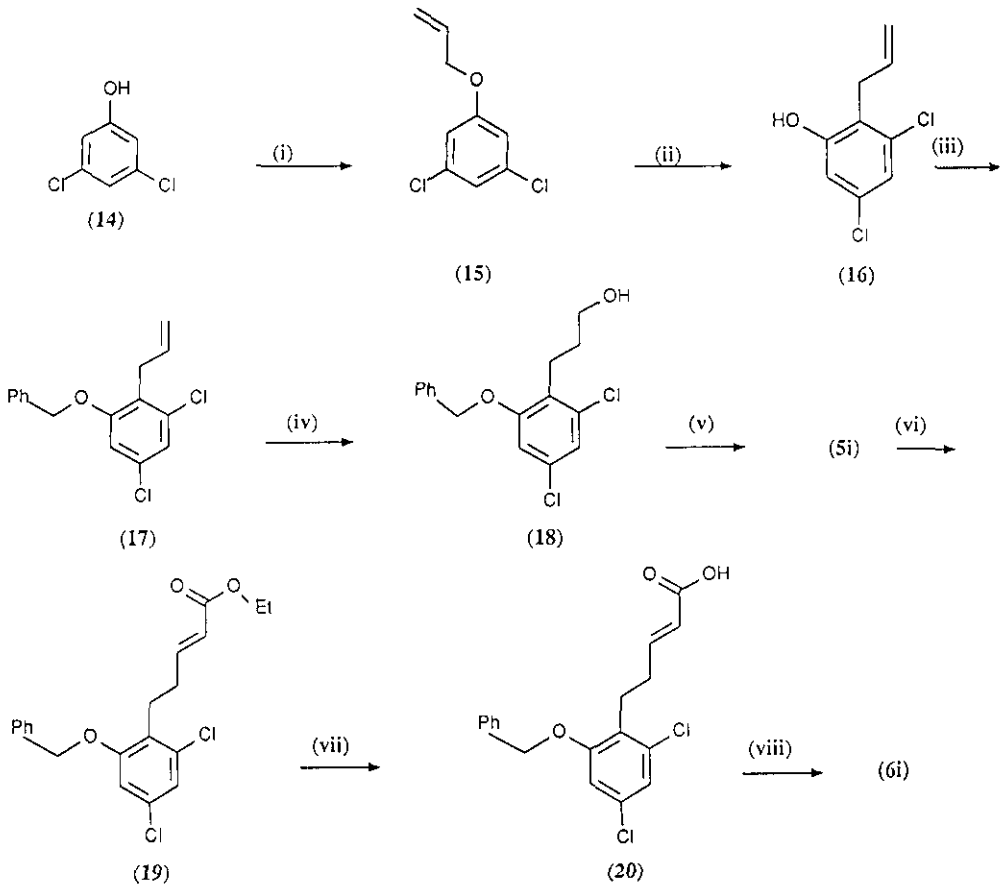
Examination of the mother liquors from the crystallisation of (11h), revealed that the second diastereoisomer (Figure 2, Isomer B, R=$PhCH_2CH_2$, X=NH) was indeed present, albeit in a minor amount, not isolable by tlc. Analysis of the ^1H nmr spectrum of the mixture clearly showed a second set of signals assignable to the *trans*-isomer (Figure 2, Isomer B, R=$PhCH_2CH_2$, X=NH). The ^1H nmr spectra of the well reported 4-hydroxy-6-(substituted) pyran-2-ones,[8] in which the group at the 6-position is equatorial and the hydroxy group at position-4 is either equatorial (*cis*) or axial (*trans*), showed that the *trans*-products have signals for H_d and H_a (Figure 2, Isomer B, X=O) at lower field relative to their *cis*-congeners. Satisfyingly, the observed extra pair of signals corresponding to protons attached to positions -4 and -6 (Figure 2, Isomer B, R=$PhCH_2CH_2$, X=NH) of the minor isomer of the 6-(2-phenylethyl)piperidinone (11h) were also at lower field than those of the major isomer further suggesting that our assignments were correct. Table 3 in the experimental section gives a partial description and assignment of the ^1H nmr spectrum of the mixture of diastereoisomers of (11h)

Attention was now turned to the preparation of compound (11i), in which the incorporation of the 2-benzyloxy-4,6-dichlorophenyl group (shown in the 4-hydroxypyranone series to confer good inhibitory activity against HMG-CoA reductase[3]) was designed to give a 4-hydroxypiperidinone with activity against HMG-CoA reductase.

The starting aldehyde (5i) was prepared as shown in Scheme 3, in which 3,5-dichlorophenol (14) was alkylated with allyl bromide giving (15). Claisen rearrangement gave the 2-allyl derivative (16) in good yield, which was benzylated on oxygen (17) before being subjected to oxidative hydroboration affording the primary alcohol (18). Oxidation with pyridinium chlorochromate then gave the aldehyde (5i).

Aldehyde (5i) was not directly transformable to the aminoacid (6i), and so (5i) was converted into the pentenoate (19), using triethylphosphonoacetate. The acid (20) was liberated, and aminated with liquid ammonia under pressure, giving the requisite β-aminoacid (6i) (Scheme 3).

Scheme 3

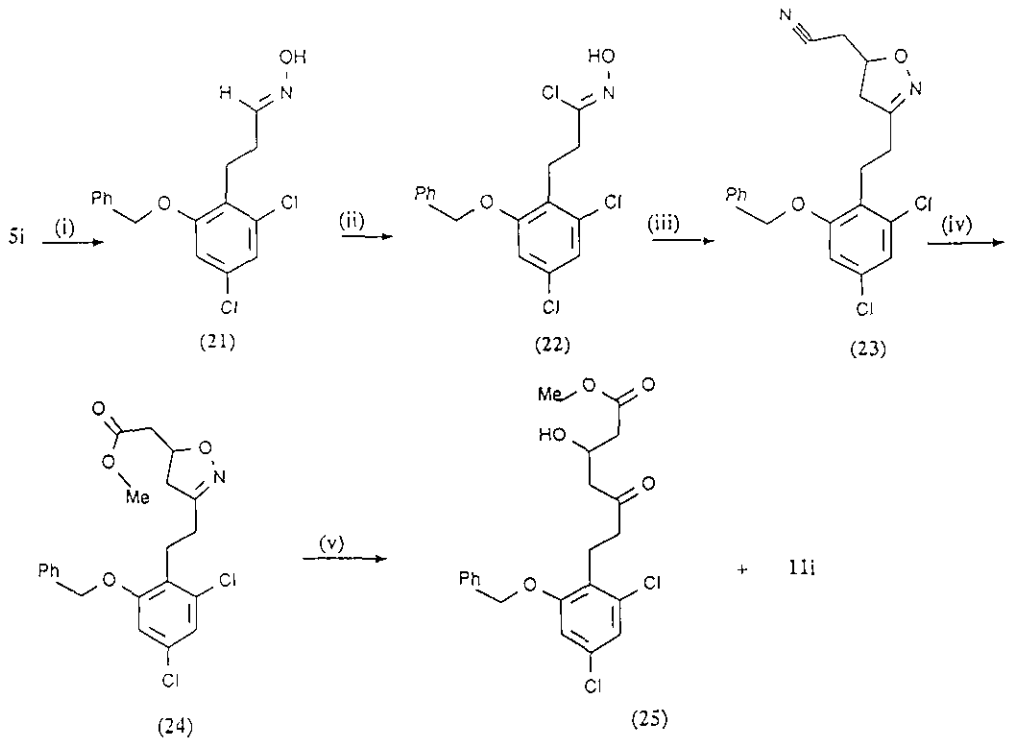


Reagents. (i), K_2CO_3, $CH_2{=}CHCH_2Br$; (ii), $Et_2NC_6H_5$ / Heat; (iii), K_2CO_3, $PhCH_2Br$; (iv), Borane-THF complex / H_2O_2, NaOH; (v), Pyridinium chlorochromate; (vi), Triethyl phosphonoacetate, THF, NaH; (vii), KOH, acetone, water; liquid NH_3 / Sealed vessel

The usual sequence (6i) to (10i) (Scheme 1) was now attempted with success until the Dieckmann condensation stage (8i→9i), when surprisingly neither under normal nor varied basic cyclisation conditions, could the cyclised product (9i) be obtained.

An alternative approach commencing with the aldehyde (5i) was investigated (Scheme 4) for the synthesis of the 4-hydroxypiperidinone (11i). Thus, oximation of (5i) yielded the oxime (21), which was chlorinated (N-chlorosuccinimide) to give (22). The nitrile oxide, derived

Scheme 4



Reagents: (i), NaOMe, $NH_2OH.HCl$, MeOH; (ii), N-Chlorosuccinimide, (iii) $CH_2=CHCH_2CN$, Et_3N; (iv), HCl, MeOH; (v), H_2 / Raney-Ni, MeOH

from dehydrochlorination of (22), underwent regiospecific cycloaddition with allyl cyanide to furnish the isoxazoline (23) in 61% yield. The nitrile group, on treatment with methanol/hydrogen chloride, gave the methyl ester (24), and then the isoxazoline ring was reductively cleaved over H_2 and Raney nickel. The intention was to liberate the 5-amino-3-hydroxy ester, which should cyclise spontaneously to the desired piperidinedione (11i). Two products were isolated from this reaction. The first product was the 3-hydroxy-5-keto ester (25) (49% yield),[9] presumably obtained by a reaction involving reductive fission of the N-O bond, followed by hydrolysis of the resulting 5-imino group. The second product, isolated in 32% yield, was an inseparable 1:1 mixture of diastereoisomers of the target 4-hydroxypiperidinone (11i), clearly identified by comparison of its 200 MHz ^1H nmr spectrum with that of the mixture of diastereoisomers of (11h), obtained by the previous route. Both *cis- and trans- isomers were identifiable* in the spectrum, with the *cis*-isomer having the characteristic pattern of signals for the piperidinone ring protons seen in the eight prior examples (11a-11h), and the *trans*-isomer corresponding well with the previously assigned *trans*-isomer of compound (11h).

All compounds (11a-11i) were inactive as inhibitors of HMG-CoA reductase *in-vitro*, and the mixture of diastereoisomers (11i) was inactive also in-vivo in the rat[10], establishing that the lactam is not a suitable bio-isostere for the lactone moiety in typical HMG-CoA reductase inhibitors.

EXPERIMENTAL

Melting points were determined on an 'Electrothermal' instrument.The ^1H nmr spectra were recorded on a Brucker 200 MHz spectrometer with TMS as the internal standard.

3-Amino-3-(1-naphthyl)propionic acid (6f). A mixture of ammonium acetate (30 g, 0.39 mol), malonic acid (20 g, 0.192 mol), and 1-naphthaldehyde (5f) (29.36 g, 0.188 mol) in ethanol (70 ml) was heated under reflux (5 h). The mixture was cooled and the precipitated solid collected and recrystallised from aqueous acetic acid (50% v/v), giving the amino acid (6f) (12.94 g, 32%) as colourless crystals, mp 225-227°C. Found: C, 72.1; H, 6.3; N, 6.5%. $C_{13}H_{13}NO_2$ requires: C, 72.5; H, 6.1; N, 6.5%.

Methyl 3-amino-3-(1-naphthyl)propionate hydrochloride (7f). Thionyl chloride (17 ml, 0.23 mol) was added dropwise to a stirred suspension of 3-amino-3-(1-naphthyl)propionic acid (6f) (12.94 g, 0.06 mol) in dichloromethane (21 ml) at room temperature. The mixture was allowed to stir at room temperature (1 h), and then concentrated. The residue was treated with methanol (31 ml) dropwise, and the mixture was stirred at room temperature (1 h). The solid was collected and recrystallised from methanol giving the ester hydrochloride (7f) 9.32 g, 58%) as colourless crystals, mp 200-202°C. Found: C, 63.2; H, 6.1; Cl, 13.4; N, 5.3%. $C_{13}H_{12}NO_2.HCl$ requires: C, 63.3; H, 6.1; Cl, 13.3; N, 5.3%.

Methyl 3-(ethoxycarbonylacetylamino)-3-(1-naphthyl)propionate (8f). Triethylamine (5.2 g, 0.051 mol) was added dropwise to a stirred solution of methyl 3-amino-3-(1-naphthyl)-propionate hydrochloride (7f) (13.27 g, 0.05 mol) in dichloromethane (100 ml) at 0°C. A solution of ethyl hydrogen malonate (6.6 g, 0.05 mol) in dichloromethane (40 ml) was added dropwise at 0°C, followed by a solution of N,N'-dicyclohexylcarbodiimide (10.4 g, 0.05 mol) in dichloromethane (20 ml) at 0°C. The mixture was stirred at 0°C (15 min) and then at room temperature (2 h). The reaction mixture was filtered and the filtrate concentrated.

The residue was dissolved in acetone, filtered from a little undissolved solid , and concentrated. The residue was triturated with petroleum ether (bp 60-80°C) giving the diester (8f) (11.24 g, 65.5%) as colourless crystals, mp 76-78°C. Found: C, 66.7; H, 6.0; N, 4.2%. $C_{19}H_{21}NO_5$ requires: C, 66.5; H, 6.2; N, 4.1%

Methyl 6-(1-naphthyl)-2,4-dioxopiperidine-3-carboxylate (9f). Sodium methoxide (prepared from sodium (4.25 g, 0.184 mol) in methanol (172 ml) followed by evaporation) was dissolved in a solution of methyl,3-(ethoxycarbonylacetylamino)-3-(1-naphthyl)propionate (8f) 63.19 g, 0.104 mol) in tetrahydrofuran (307 ml), under an atmosphere of nitrogen, at room temperature. The mixture was heated under reflux (2 h), concentrated, and the residue partitioned between ethyl acetate and water. The aqueous phase was acidified to pH 1 (conc. HCl), and the precipitated solid collected and washed with water giving the ester (9f) (28.4 g, 52%) as a colourless solid, mp 179-181°C. Found: C, 69.7, H, 5.3; N, 4.7%. $C_{17}H_{15}NO_4$ requires: C, 68.7; H, 5.2; N, 4.7%.

6-(1-Naphthyl)piperidine-2,4-dione (10f). A mixture of methyl 6-(1-naphthyl)-2,4-dioxopiperidine-3-carboxylate (9f) (12 g, 0.04 mol) and potassium hydroxide (4.48 g, 0.08 mol) in ethanol (150 ml) was heated under reflux (6 h). .The mixture was acidified to pH 1 (conc. HCl), heated under reflux (15 min), cooled, and the precipitated product collected and washed with water, giving the piperidine-2,4-dione (10f) (4.01 g, 42%) as a colourless solid, mp 207-209°C. Found: C, 75.4; H, 5.6; N, 6.1%. $C_{15}H_{13}NO_2$ requires: C, 75.3; H, 5.5; N, 5.9%.

Cis-4-Hydroxy-6-(1-naphthyl)piperidin-2-one (11f). Sodium borohydride (3.36 g, 0.089 mol) was added portionwise to a solution of 6-(1-naphthyl)piperidine-2,4-dione (10f) (3.35 g, 0.014 mol) in methanol (150 ml) at 0°C. The solution was stirred at room temperature (1 h) and concentrated. The residue was partitioned between dichloromethane and water, and the organic phase was washed with water, dried ($MgSO_4$) and concentrated. The resulting gum was crystallised twice from water giving the *cis*-piperidinone (11f) (0.5g, 14.8%) as colourless crystals, mp 152-154°C. Found: C, 75.0; H, 6.1; N, 5.8%. $C_{15}H_{15}NO_2$ requires: C; 74.7; H, 6.3; N, 5.8%.

(E)-5-Phenyl-2-pentenoic acid (12). A solution of 3-phenylpropanal (6h) (197 ml, 1.49 mol) and malonic acid (155.2 g, 1.49 mol) in dry pyridine (120 ml) was stirred and heated at 100°C (7 h). The mixture was poured onto excess ice/HCl, and the precipitated solid was

collected and washed with water, giving the acid (12) (218.9 g, 83.5%) as a cream solid, mp 94-96°C. Found: C, 74.9; H, 6.9%. $C_{11}H_{12}O_2$ requires: C, 75.0; H, 6.7%.

3-Hydroxyamino-5-phenylpentanoic acid (13). A mixture of (E)-5-phenyl-2-pentenoic acid (12) (218.9 g, 1.24 mol), hydroxylamine hydrochloride (87.0 g, 1.25 mol) and anhydrous sodium acetate (102.9 g, 1.25 mol) in ethanol (2500 ml) was stirred and heated under reflux (90 mins) and then stirred at room temperature (3 h). The product was collected, and washed with water and dried giving the acid (13) (229.5 g, 88%) as a colourless solid, mp 155-157°C (decomp.). Found: C, 63.0; H, 7.1; N, 6.6%. $C_{11}H_{15}NO_3$ requires: C, 63.1; H, 7.2; N, 6.7%.

3-Amino-5-phenylpentanoic acid (6h). A solution of 3-hydroxyamino-5-phenylpentanoic acid (13) (10 g, 48 mmol) in glacial acetic acid (250 ml) was shaken and hydrogenated, warming occasionally with steam in the presence of 5% palladium on carbon (3.0 g) until the theoretical uptake of hydrogen had been reached. The mixture was filtered, and the filtrate concentrated to a colourless oil, which was triturated with ethanol, giving the acid (6h), (8.2 g, 89%) as a white solid, mp 226-228°C (decomp.). Found: C, 68.7; H, 8.0; N, 7.2%. $C_{11}H_{15}NO_2$ requires: C, 68.4; H, 7.8; N, 7.3%.

Methyl 3-amino-5-phenylpentanoate hydrochloride (7h). Thionyl chloride (35 ml, 0.48 mol) was added dropwise to stirred dry methanol (350 ml) maintaining the temperature at 0° to 5°C. 3-Amino-5-phenylpentanoic acid (6h) (66.4 g, 0.34 mol) was added portionwise, at 0° to 5°C, and the mixture was stirred at 0° to 5°C (15 min), and then at room temperature (5 h). The mixture was filtered and the filtrate concentrated. The residual oil was triturated with ether and then with ethyl acetate giving the ester hydrochloride (7h) (76.9 g, 92%) as a colourless solid, mp 87-89°C. Found: C, 58.4; H, 7.5; N, 5.5%. $C_{12}H_{17}NO_2.HCl$ requires: C, 59.1; H, 7.4; N 5.8%.

Methyl 3-(N-ethoxycarbonylacetylamino)-5-phenylpentanoate (8h). Triethylamine (41 ml, 0.29 mol) was added dropwise to a stirred solution of methyl 3-amino-5-phenylpropionate hydrochloride (4h) (70 g, 0.29 mol) in dichloromethane (867 ml) at 0°C. A solution of ethyl hydrogen malonate (41 g, 0.31 mol) in dichloromethane (481 ml) was added dropwise, followed by N,N'-dicyclohexylcarbodiimide (64.5 g, 0.31 mol) portionwise. The mixture was stirred at 0°C (15 min) and then at room temperature (3.5 h). The mixture was kept at room temperature (18 h) and then filtered from precipitated N,N'-dicyclohexylurea. The filtrate

was washed with water, dried ($MgSO_4$) and concentrated. The residual oil was triturated with acetone to remove further N,N'-dicyclohexylurea, and the filtrate was concentrated. The residual oil was triturated with petroleum ether (bp 40-60°C), giving the diester (8h) (70.5 g, 76%) as a pale brown oil. Found: C, 62.3; H, 7.1; N, 4.8%. $C_{17}H_{23}NO_5$ requires: C, 63.5; H, 7.2; N, 4.4%

Methyl 2,4-dioxo-6-(2-phenylethyl)piperidine-3-carboxylate (9h). Freshly prepared sodium methoxide (10.8 g, 0.2 mol) in dry tetrahydrofuran (140 ml) was treated with a solution of methyl 3-(ethoxycarbonylacetylamino)-5-phenylpentanoate (8h) (63.6 g, 0.2 mol) in dry tetrahydrofuran (340 ml) and the mixture was boiled under reflux (4 h). The mixture was evaporated, and the residue partitioned between ethyl acetate and water. The aqueous phase was separated, acidified to pH 1 (conc. HCl), and the oily product collected and crystallized from methanol, giving the piperidine ester (9h) (8.25 g, 15%) as colourless crystals, mp 113-115°C. Found: C, 65.5; H, 6.2; N, 5.2%. $C_{15}H_{17}NO_4$ requires: C, 65.4; H, 6.2; N, 5.1%.

6-(2-Phenylethyl)piperidine-2,4-dione (10h). A mixture of methyl 2,4-dioxo-6-(2-phenylethyl)piperidine-3-carboxylate (9h) (49.6 g, 0.18 mol) and aqueous sodium hydroxide (2M, 500 ml) was heated at 100°C, (2h). The mixture was acidified (conc. HCl) and extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. The residue was crystallized from methanol giving the piperidine-2,4-dione (7h) (16.4 g, 42%) as a colourless solid, mp 138-140°C. Found: C, 71.7; H, 7.0; N, 6.5%. $C_{13}H_{15}NO_2$ requires: C, 71.9, H, 7.0; N, 6.5%.

4-Hydroxy-6-(2-phenylethyl)piperidin-2-one (11h). Sodium borohydride (5.2 g, 0.14 mol) was added portionwise to a stirred suspension of 6-(2-phenylethyl)piperidine-2,4-dione (10h) (4.72 g, 0.022 mol) in dry methanol (50 ml). The mixture was stirred (2h), and then filtered, giving pure *cis*-(11h) (2.79 g, 59%) as colourless crystals, mp 186-188°C (Found: C, 71.2; H, 8.10; N, 6.45%. $C_{13}H_{17}NO_2$ requires: C, 71.2; H, 7.81; N, 6.4%). The filtrate was concentrated, and the residue partitioned between water and dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated giving a white solid (0.62 g, mp 172-176°C) which was crystallized from isopropanol giving further *cis*-(11h) (0.62 g, 13%) mp 174-176°C. The isopropanol liquors were concentrated, giving a white solid (0.19 g, 4.0%), mp 160°C, which was shown to consist of a 1:1 mixture of *cis*-(11h) and *trans*-(11h). Found: C, 71.5; H, 7.8; N, 6.3%. $C_{13}H_{17}NO_2$ requires: C, 71.2; H, 7.8; N, 6.4%.

1-Allyloxy-3,5-dichlorobenzene (15). Potassium carbonate (233.6g, 1.69 mol) was added to a solution of 3,5-dichlorophenol (14) (250 g, 1.53 mol) in acetone (2500 ml) and the flask contents were stirred at room temperature (30 min). Allyl bromide (146 ml, 1.69 mol) was then added rapidly dropwise and the mixture was stirred and heated under reflux (4 h). The reaction mixture was left to stand at room temperature overnight, filtered and the filtrate was evaporated to dryness to give a golden oil which was distilled yielding the ether (15)

3-(4,6-Dichloro-2-hydroxyphenyl)prop-1-ene (16). A mixture of 1-allyloxy-3,5-dichlorobenzene (15) (220 g, 1.08 mol) and N,N-diethylaniline (500 ml) was stirred and heated under reflux (12 h). The N,N-diethylaniline was distilled off and the concentrated reaction mixture was poured onto concentrated hydrochloric acid (600 ml) and crushed ice (1 kg). The crude product was extracted with ether and the ethereal phase was washed with water (2x300 ml), brine (1x200 ml), dried ($MgSO_4$) and concentrated to dryness to give the propene (16) (213 g, 97%) as a brown oil.

3-(2-Benzyloxy-4,6-dichlorophenyl)prop-1-ene (17). A mixture of 3-(4,6-dichloro-2-hydroxyphenyl)prop-1-ene (16) (110 g, 0.54 mol), potassium carbonate (74.4 g, 0.54 mol) and dry dimethylformamide (750 ml) was stirred and heated on a steam-bath (1 h). Benzyl bromide (129 ml, 1.08 mol) was then added dropwise over a period of 60 mins. After the end of the addition, the flask contents were stirred and heated on a steam-bath (8 h). The reaction mixture was allowed to cool, poured onto water and extracted with ether. The ethereal phase was washed with water (2x100 ml), brine (1x100 ml) and dried ($MgSO_4$). This solution was evaporated to dryness to a brown oil which was distilled to give the ether (17) (123.3 g, 79%) as a pale yellow oil, bp 135-155°C (0.1-0.4 mm Hg). Found: C, 65.8, H, 4.7%. $C_{16}H_{14}Cl_2O$ requires: C, 65.6; H, 4.8%.

3-(2-Benzyloxy-4,6-dichlorophenyl)propan-1-ol (18). Borane-THF complex (1.0 M in THF, 57 ml, 0.057 mol) was added dropwise to a solution of 3-(2-benzyloxy-4,6-dichlorophenyl)prop-1-ene (17) (50 g, 0.17 mol) in dry THF (868 ml) maintaining the temperature below 6°C. The flask contents were then stirred (2 h) allowing the temperature to rise to room temperature. The solution was then cooled to 5°C and then treated with aqueous sodium hydroxide (3M, 19 ml) and aqueous hydrogen peroxide (30% v/v, 20 ml). The reaction mixture was warmed to 50°C and stirred at this temperature (1 h). The flask contents were then allowed to cool, and partitioned between ether and water. The ethereal phase was washed with aqueous sodium hydroxide (2M), aqueous hydrogen chloride (2M) and water, and then

dried ($MgSO_4$). The absence of peroxides was checked with starch-iodide paper and the solution was evaporated to a colourless oil which solidified on cooling. This solid was washed with petroleum ether (bp 40-60°C) to give the alcohol (18) (34.9 g, 66%) as a colourless solid, mp 60-62°C. ^1H Nmr ($CDCl_3$); 1.82 (2H, quintet, J=8 Hz, CH_2-CH_2-CH_2), 2.9 (2H, t, J=8 Hz, ArCH_2-CH_2), 3.59 (2H, t, J=8 Hz, CH_2-CH_2-OH), 5.06 (2H, s, C_6H_5-CH_2-O), 6.86 (1H, d, J=2 Hz, 3-H or 5-H), 7.05 (1H, d, J=2 Hz, 5-H or 3-H), 7.26-7.52 (5H, m, C_6H_5). Found: C, 61.9; H, 5.1%. $C_{16}H_{16}Cl_2O_2$ requires: C, 61.8; H, 5.2%.

3-(2-Benzyloxy-4,6-dichlorophenyl)propionaldehyde (5i). Pyridinium chlorochromate (90.9 g, 0.42 mol) was added portionwise to a stirred solution of 3-(2-benzyloxy-4,6-dichlorophenyl)propan-1-ol (18) (70.3 g, 0.22 mol) and sodium acetate (6.8 g, 0.08 mol) in dichloromethane (919 ml), the temperature being maintained below 10°C. The reaction mixture was stirred (1 h) at a temperature below 10°C, then allowed to warm to room temperature and stirred (1 h). The dark brown solution was poured onto ether (1500 ml). The ethereal solution was filtered through silica gel and the filtrate was evaporated to dryness to give a golden oil which solidified to yield the aldehyde (5i) (68.9 g, 98%) as a pale yellow solid, mp 59-62°C. ^1H Nmr ($CDCl_3$); 2.64 (2H, dt, J=7 Hz, 1 Hz, CH_2-CH_2-CHO), 3.14(2H, t, J=7 Hz, CH_2-CH_2-CHO), 5.06 (2H, s, CH_6H_5-$CH2$-O), 6.85 (1H, d, J=2 Hz, 3-H or 5-H); 7.04 (1H, d, J=2 Hz, 5-H or 3-H), 7.22-7.48 (5H, m, C_6H_5), 9.76 (1H, t, J=1 Hz, CHO). Found: C, 61.6; H, 4.5; Cl, 22.4%. $C_{16}H_{14}Cl_2O_2$ requires: C, 62.2; H, 4.6; Cl, 22.9%.

Ethyl (E)-5-(2-benzyloxy-4,6-dichlorophenyl)pent-2-enoate (19). A solution of triethyl phosphonoacetate (44 ml, 0.22 mol) in dry tetrahydrofuran (103 ml) was added dropwise to a stirred suspension of sodium hydride (80% dispersion in oil, 6.44 g, 0.22 mol) under an atmosphere of nitrogen, maintaining the temperature less than 25°C. A solution of 3-(2-benzyloxy-4,6-dichlorophenyl)propionaldehyde (5i) (66.44 g, 0.215 mol) in dry tetrahydrofuran (97 ml) was added dropwise at room temperature, and the reaction mixture was stirred (3 h) at room temperature. Glacial acetic acid (23 ml) was added dropwise, and the solution was concentrated. The oil was partitioned between water and ether, and the organic phase was washed twice with saturated sodium bicarbonate solution, water, and dried, giving the ester (19) (74.8 g, 92%) as a pale brown oil. ^1H Nmr ($CDCl_3$) 1.26 (3H, t, J=7 Hz, OCH_2CH_3), 2.40 (2H, q, J=8 Hz, $ArCH_2CH_2$), 2.94 (2H, t, J=8 Hz, $ArCH_2CH_2$), 4.18 (2H, q, J=7 Hz, OCH_2CH_3), 5.02 (2H, s, OCH_2Ar), 5.79 (1H, d, J=15 Hz, $CHCO_2Et$), 6.81 (1H, d, J=2 Hz, 3- or 5-Ar-H), 7.00(1H, d, J=2 Hz, 5- or 3-Ar-H), 7.04 (1H, dt, J=15 and 8 Hz, $ArCH_2CH_2CH$), and 7.25-7.40 (5H, m, C_6H_5).

(E)-5-(2-Benzyloxy-4,6-dichlorophenyl)-2-pentenoic acid (20). A mixture of ethyl (E)-5-(2-benzyloxy-4,6-dichlorophenyl)pent-2-enoate (19) (79 g, 0.21 mol) and potassium hydroxide (17.7 g, 0.32 mol) in acetone (371 ml) and water (557 ml) was heated under reflux (6 h). The acetone was removed under diminished pressure, and the aqueous phase was extracted with ether. The aqueous phase was acidified to pH 1 (conc. HCl), and extracted with ether. The ethereal extract was concentrated, giving the acid (20) (65.4 g, 90%) as a cream solid, mp 112-114°C. ^{1}H Nmr ($CDCl_3$) 2.46 (2H, q, J=7 Hz, $ArCH_2CH_2$), 2.97 (2H, t, J=7 Hz, $ArCH_2CH_2$), 5.04 (2H, s, OCH_2Ar), 5.65 (1H, d, J=15 Hz, $CHCO_2H$), 6.84 (1H, d, J=2 Hz, 3- or 5-Ar-H), 7.03 (1H, d, J=2Hz, 5- or 3-Ar-H), 7.10 (1H, dt, J=14 and 7 Hz), and 7.32-7.54 (5H, m, Ar-H). Found: C, 61.5; H, 4.6%. $C_{18}H_{16}Cl_2O_3$ requires: C, 61.4; H, 4.5%.

3-Amino-5-(2-benzyloxy-3,5-dichlorophenyl)pentanoic acid (6i). A mixture of (E)-5-(2-benzyloxy-4,6-dichlorophenyl)-2-pentenoic acid (20) (8.8 g, 0.025 mol) and liquid ammonia (98 ml) was heated at 120°C in a bomb (18 h). Evaporation of the ammonia gave a gum which was triturated with ethyl acetate, giving the amino acid (6i) (4.87 g, 53%) as a white solid, mp 205-207°C (decomp.). ^{1}H Nmr (DMSO-d_6) 1.50-1.80 (2H, br m, $ArCH_2CH_2$), 2.02 (1H, br dd, J=16 and 9 Hz, $CH_ACH_BCO_2H$), 2.30 (1H, br d, J=16 Hz, $CH_AH_BCO_2H$), 2.78 (2H, br t, J=7 Hz, $ArCH_2CH_2$), 3.00-3.10 (1H, br m, $CHNH_2$), 5.20 (2H, s, OCH_2Ar), 6.20 (2H, s, 3- and 5-Ar-H), 7.2-7.40 (5H, m, C_6H_5). Found: C, 58.5; H, 5.1; N, 3.7% $C_{18}H_{19}C_{12}NO_3$ requires: C, 58.7; H, 5.1; N, 3.7%.

Methyl 3-amino-5-(2-benzyloxy-4,6-dichlorophenyl)pentanoate hydrochloride (7i). Thionyl chloride (3 ml, 0.04 mol) was added dropwise to dry methanol (30 ml) maintaining the temperature at less than 10°C. 3-Amino-5-(2-benzyloxy-3,5-dichlorophenyl)pentanoic acid (6i) (10.58 g, 0.029 mol) was added portionwise at 0° to 5°C, and the solution was kept at room temperature (72 h). The precipitated solid was collected and washed with petroleum ether (bp 40-60°C), giving the hydrochloride (7i) (11.36 g, 94%) as a white solid, mp 172-174°C. ^{1}H Nmr (DMSO-d_6), 1.70-2.00 (2H, br m, $ArCH_2CH_2$), 2.70-2.90 (4H, br m, $ArCH_2$ and CH_2CO_2Me), 3.46 (1H, br, quintet, J=6 Hz, $CHNH_3^+$), 3.62 (3H, s, OCH_3), 5.24 (2H, s, OCH_2), 6.21 (2H, m, 3- and 5-Ar-H), 7.30-7.50 (5H, m, C_6H_5), and 8.46 (3H, br, s, NH_3^+). Found: 54.7; H, 5.2; N, 3.3%. $C_{19}H_{21}Cl_2NO_3$.HCl requires: C, 54.5; H, 5.30; N, 3.4%.

Methyl 3-(ethoxycarbonylacetylamino)-5-(2-benzyloxy-4,6-dichlorophenyl)pentanoate (8i). A stirred solution of methyl 3-amino-5-(2-benzyloxy-4,6-dichlorophenyl)pentanoate

hydrochloride (7i) (10.76 g, 0.026 mol) in dichloromethane (72 ml) was treated dropwise with triethylamine (3.6 ml, 0.026 mol). A solution of ethyl hydrogen malonate (3.6 g, 0.027 mol) in dichloromethane (43 ml) was added dropwise at 0°C. N,N'-Dicyclohexylcarbodiimide (5.74 g, 0.028 mol) was added portionwise at 0°C, and the mixture was stirred at 0°C (15 min) and room temperature (3.5 h). The mixture was kept (18 h), and then filtered from precipitated N,N'-dicyclohexylurea. The filtrate was washed with water, dried ($MgSO_4$), and concentrated. The resulting solid was triturated with acetone, filtered, concentrated, and retriturated with petroleum ether (bp 40-60°C), filtered and concentrated, giving the diester (8i) (9.52 g, 75%) as a colourless solid, mp 78-80°C. ^{1}H Nmr (DMSO-d_6), 1.08 (3H, t, J=6 Hz, OCH_2CH_3), 1.60-1.80 (2H, m, CH_2CH_2CH), 2.52 (2H, d, J=6 Hz, CH_2CO_2Me), 2.70-2.90 (2H, m, $ArCH_2CH_2$), 3.20 (2H, s, $COCH_2CO$), 3.58 (3H, s, OCH_3), 4.08 (2H, q, J=6 Hz, OCH_2CH_3), 4.16 (1H, m, CHNH), 5.22 (2H, s, OCH_2Ar), 6.18 (2H, m, 3- and 5-Ar-H), 7.30-7.50 (5H, m, Ar-H) and 8.16 (1H, d, J=7 Hz, NH). Found: C, 57.7; H, 5.2; N, 3.2%. $C_{24}H_{27}Cl_2NO_6$ requires: C, 58.1; H, 5.48: N, 2.8%.

Attempted cyclization of methyl 3-(ethoxycarbonylacetylamino)-5-(2-benzyloxy-4,6-dichlorophenyl)pentanoate (8i) using sodium methoxide in tetrahydrofuran at reflux , sodium methoxide in toluene at reflux , sodium methoxide in methanol at reflux , sodium methoxide in methanol at room temperature , 4-dimethylaminopyridine in toluene at reflux , 4-dimethylaminopyridine in tetrahydrofuran, sodium hydride in tetrahydrofuran at room temperature , triethylamine in tetrahydrofuran at reflux , potassium *tert*-butoxide in tetrahydrofuran at room temperature, sodium 2,4,6-trimethylphenoxide in dimethyl sulphoxide at room temperature, and potassium carbonate in methanol at reflux , gave no material identifiable as the cyclised product (9i)

3-(2-Benzyloxy-4,6-dichlorophenyl)propionaldoxime (21). A solution of sodium methoxide (5.4 g, 0.1 mol) in methanol (100 ml) was added to hydroxylamine hydrochloride (7.0 g, 0.1 mol). A solution of 3-(2-benzyloxy-4,6-dichlorophenyl)propionaldehyde (5i) (31.3 g, 0.1 mol) in methanol (70 ml) was then added dropwise to the stirred suspension. The flask contents were stirred at room temperature (30 min). The solvent was then evaporated and the crude product was partitioned between ether and water. The ethereal phase was dried ($MgSO_4$) and evaporated to dryness. The solid was triturated with petroleum ether (bp 40-60°C) giving the oxime (as a 1:1 mixture of (Z)- and (E)- isomers) (21) (19.3 g, 59%) as a

colourless solid, mp 75-79°C. ^{1}H Nmr ($CDCl_3$) 2.44 and 2.66 (each 1H, q, J=6 Hz, CH_2CHNOH), 3.01, (2H, t, J=6 Hz, CH_2CH_2CHNOH), 5.05 (2H, s, CH_2O), 6.79 (1H, t, J=6 Hz, CHNOH), 6.84 (1H, m, Ar-H), 7.03 (1H, m, Ar-H), and 7.26-7.56 (5H, m, C_6H_5). Found: C, 59.8; H, 4.8; N, 4.1. $C_{16}H_{15}C_{12}NO_2$ requires: C, 59.3; H, 4.7; N, 4.3%.

3-[2-(2-Benzyloxy-4,6-dichlorophenyl)ethyl]-4,5-dihydroisoxazol-5-yl)acetonitrile (23). N-Chlorosuccinimide (2.64 g, 19.7 mmol) was stirred in a flask containing dry chloroform (18 ml) and dry pyridine (0.1 ml). 3-(2-Benzyloxy-4,6-dichlorophenyl)propionaldoxime (21) (6.4 g, 19.7 mmol) was added at room temperature in one portion. The flask contents were stirred (1 h), and then allyl cyanide (2.7 ml, 33.5 mmol) was added and the temperature raised to 40-50°C. A solution of triethylamine (2.75 ml, 19.7 mmol) in chloroform (3 ml) was added dropwise (30 min). The mixture was stirred at 45°C (45 min), washed with water (2x35 ml), dried ($MgSO_4$) and evaporated to dryness to a colourless oil which was triturated with petroleum ether (bp 40-60°C) to yield compound (23) (4.7 g, 61%) as a colourless solid, mp 60-62°C. ^{1}H Nmr ($CDCl_3$) 2.51 (1H, dd, J=16.8 and 6.8 Hz, CH_ACH_BCN), 2.58 (2H, t, J=7.6 Hz, $ArCH_2CH_2$), 2.63 (1H, dd, J=16.8 and 5.4 Hz, CH_AH_BCN), 2.73 (1H, dd, J=17.4 and 6.4 Hz, $CH_AH_BCH(O)$), 3.06 (2H, t, J=7.6 Hz, $ArCH_2CH_2$), 3.12 (1H, dd, J=17.4 and 10 Hz, $CH_AH_BCH(O)$), 4.73 (1H, dddd, J=10, 6.8, 6.4 and 5.4 Hz, $CH_AH_BCH(O)$), 5.06 (2H, s, CH_2O), 6.96 (1H, d, J=2 Hz, 3- or 5-Ar-H), 7.04 (1H, d, J=2 Hz, 5- or 3-Ar-H), and 7.28-7.50 (5H, m, Ar-H). Found: C, 61.6; H, 4.7; Cl, 18.2; N, 7.0%. $C_{20}H_{18}Cl_2N_2O_2$ requires: C, 61.7; H, 4.7; Cl, 18.2; N, 7.2%.

Methyl 3-[2-(2-benzyloxy-4,6-dichlorophenyl)ethyl]-4,5-dihydroisoxazol-5-yl acetate (24). Dry hydrogen chloride was bubbled (30 min) through a solution of 3-[2-(2-benzyloxy-4,6-dichlorophenyl)ethyl]-4,5-dihydroisoxazol-5-yl)acetonitrile (23) (2 g, 5.1 mmol) in methanol (50 ml) and ether (50 ml) and the mixture was left to stand at room temperature (18 h). Water (120 ml) was then added carefully and the reaction mixture was stirred (10 mins). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography [eluant: petroleum ether (bp 40-60°C)-ethyl acetate (3:2 v/v], yielding the ester (24) (1.5 g, 69%) as a colourless oil. ^{1}H Nmr ($CDCl_3$) 2.40-2.80 (5H, m, CH_AH_BCN, $ArCH_2CH_2$, and $CH_AH_BCH(O)$), 3.06 (2H, t, J=7 Hz, $ArCH_2CH_2$), 3.08 (1H, dd, J=16 and 8 Hz, $CH_AH_BCH(O)$), 3.68 (3H, s, OCH_3), 4.76-4.96 (1H, m, CH(O)), 5.04 (2H, s, CH_2O), 6.83 (1H, d, J=2 Hz, 3- or 5-Ar-H), 7.01 (1H, d, J=2 Hz, 5- or 3-Ar-H), 7.26-7.46 (5H, m, Ar-H). Found: C, 59.0; H, 5.0; N, 3.0%. $C_{21}H_{21}Cl_2NO_4$ requires: C, 59.7; H, 5.1; N, 3.3%.

6-[2-(2-Benzyloxy-4,6-dichlorophenyl)ethyl]-4-hydroxypiperidine-2-one and Methyl 7-(2-benzyloxy-4,6-dichlorophenyl)-3-hydroxy-5-oxoheptanoate (25). A solution of methyl 3-[2-(2-benzyloxy-4,6-dichlorophenyl)ethyl-4,5-dihydroisoxazol-5-yl]acetate (24) (2 g, 4.7 mmol) in methanol (40 ml) was shaken and hydrogenated at room temperature and atmospheric pressure in the presence of Raney Nickel (2 g) (5h). After removal of the catalyst by filtration, the filtrate was dried ($MgSO_4$) and concentrated. The residue was fractionated by flash chromatography (eluant: ethyl acetate, and the ethyl acetate/methanol (9:1 v/v), giving 1) the hydroxypiperidinone (11i) (0.6 g, 32%) as a colourless solid, mp 137-139°C. Found: C, 60.5; H, 5.3; N, 3.56%. $C_{20}H_{21}Cl_2NO_3$ requires: C, 60.9; H, 5.37; N, 3.55%; and 2) the hydroxy keto ester (25) (1.0 g, 49%) as a colourless solid, mp 53-55°C. ^1H Nmr ($CDCl_3$), 2.26 (2H, d, J=6 Hz, $CHCH_2$), 2.61 (2H, d, J=6 Hz, $CHCH_2$), 2.62 (2H, t, J=8 Hz, $ArCH_2CH_2$), 3.06 (2H, t, J=8 Hz, $ArCH_2$), 4.44 (1H, quintuplet, J=6 Hz, CH_2CHCH_2), 5.05 (2H, s, OCH_2), 6.82 (1H, d, J=2 Hz, 3- or 5-Ar-H), 7.01 (1H, d, J=2 Hz, 5- or 3-Ar-H), 7.38 (5H, s, Ar-H). Found: C, 59.2; H, 5.1; Cl, 17.1%. $C_{21}H_{22}Cl_2O_5$ requires: C, 59.3; H, 5.2; Cl, 16.7%.

Comp. No.	General Experimental Method	Yield%	mp. °C	Anal. Calc			Found		
				C	*H*	*N*	*C*	*H*	*N*
6a (Ref. 7)	A	54	228-230						
6b	A	33	240-242	61.5	6.7	7.2	61.9	6.9	7.1
6c	A	26	197-200	70.9	6.3	5.2	70.6	6.3	4.9
6d	A	65	230-232	54.1	5.0	7.0	53.8	5.0	7.1
6e	A	61	235-237	46.2	3.9	6.0	45.8	3.8	6.0
6f	A	54	225-227	72.5	6.1	6.5	72.1	6.3	6.5
6g	A	62	230	74.7	6.2	5.8	75.5	6.2	5.1
7a	B	96	146	55.7	6.5	6.5	55.8	6.0	6.4
7b	B	85	45	53.8	6.5	5.7	53.6	6.4	5.8
7c	B	hygroscopic used directly in next stage							
7d	B	68	90	48.0	5.2	5.6	45.7	5.4	4.6
7e	B	86	163	not determined					
7f	B	70	200-202	63.3	6.1	5.3	63.2	6.1	5.3
7g	B	75	215-216	65.9	6.2	4.8	64.4	6.2	5.2
8a	C	78	52-53	61.4	6.5	4.8	61.5	6.6	4.8
8b	C	62	98-101	59.4	6.5	4.3	59.0	6.3	4.3
8c	C	52	73-75	66.2	6.3	3.5	66.1	6.3	3.4
8d	C	93	45-47	55.0	5.5	4.3	54.9	5.6	4.3
8e	C	94	oil	not determined					
8f	C	66	76-78	66.5	6.2	4.1	66.7	6.0	4.2
8g	C	52	80	68.3	6.2	3.8	68.1	6.4	4.0
9a	D	60	128-130	63.2	5.3	5.7	64.2	5.3	5.9
9b	D	47	115-118	60.7	5.4	5.1	60.9	5.6	5.1
9c	D	42	171-173	68.0	5.4	4.0	67.9	5.3	3.8
9d	D	46	183-185	55.4	4.3	5.0	55.3	4.3	5.0
9e	D	36	188-190	49.4	3.5	4.4	49.3	3.6	4.3
9f	D	52	179-181	68.7	5.1	4.7	69.7	5.2	4.7
9g	D	49	175-180	70.6	5.2	4.3	70.8	5.2	4.0
10a	E	53	167-169	69.8	5.8	7.4	69.7	5.9	7.4
10b	E	52	174-175	65.8	5.9	6.4	65.9	6.0	5.4
10c	E	48	138-142	73.2	5.8	4.8	73.4	5.9	4.7
10d	E	22	175	59.1	4.5	5.9	59.1	4.7	6.1
10e	E	33	167-169	51.2	3.5	5.4	51.1	3.5	5.3
10f	E	42	207-209	75.3	5.5	5.9	75.4	5.6	6.1
10g	E	30	210-212	77.0	5.7	5.3	76.6	5.7	5.3
11a	F	38	212-214	69.1	6.8	7.3	69.1	6.8	7.3
11b	F	11	193-197	65.2	6.8	6.3	64.8	7.0	6.3
11c	F	44	99-101	72.7	6.4	4.7	72.4	6.5	4.6
11d	F	81	213-215	58.6	5.3	6.2	58.5	5.4	6.1
11e	F	77	182-184	50.8	4.2	5.4	50.5	4.2	5.0
11f	F	15	152-154	74.7	6.3	5.8	75.0	6.1	5.8
11g	F	20	218-220	76.4	6.4	5.2	76.3	6.4	5.2

Table 2

^{1}H Nmr Assignment for Compound (11a) (DMSO-d_6)

Chemical shift ppm	Assignment
cis-isomer	
1.44	(1H, ddd, J=11.8, 11.8 and 11.4 Hz, H_b axial)
2.04-2.20	(1H, m, H_c equatorial)
2.13	(1H, dd, J=11.9 and 10.6 Hz, H_f axial)
2.47	(1H, ddd, J=16.9, 5.5 and 2.0 Hz, H_e equatorial)
3.95	(1H, br m, after D_2O shake: dddd, J=11.8, 10.6, 5.5 and 3.7 Hz H_d axial)
4.45	(1H, dd, J=11.4 and 4.4 Hz, H_a axial)
4.97	(1H, br d, removed by D_2O, OH)
7.2-7.4	(5H, m, phenyl-H)
7.65	(1H, br, s, NH, removed by D_2O)

Table 3

^{1}H Nmr Assignment for Compounds (11h) - mixture of *cis*- and *trans*-compounds (DMSO-d_6)

Chemical shift ppm	Assignment
cis-isomer	
1.26	(1H, ddd, J=12, 12 and 11 Hz, H_b axial)
1.58-1.90	(2H, m, $PhCH_2CH_2$)
2.00	(1H, dd, J=17 and 11 Hz, H_f axial)
2.00-2.16	(1H, m, H_c equatorial)
2.38	(1H, ddd, J=17, 6, and 2 Hz, H_e equatorial)
2.63	(2H, t, J=6 Hz, $PhCH_2CH_2$)
3.25	(1H, dd, J=12 and 4 Hz, H_a axial)
3.80	(1H, br m, after D_2O shake, dddd, J=12, 11, 6 and 4 Hz, H_d axial)
5.00	(1H, br d, OH, signal removed by D_2O)
7.1-7.35	(5H, m, phenyl-H)
7.54	(1H, br, s, NH, signal removed by D_2O)
trans-isomer	
3.48	(1H, C6-H equatorial)
4.08	(1H, C4-H axial)
4.87	(1H, OH)
7.46	(1H, NH)

Figure 3

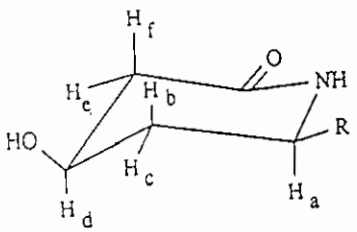


Table 4

^{1}H Nmr Assignment for Compounds (11i)-mixture of *cis*- and *trans*-compounds ($CDCl_3$)

Chemical shift ppm	Assignment
cis-isomer	
1.38	(1H, ddd, J=12, 12 and 11 Hz, H_b axial)
1.60-1.80	(2H, m, $PhCH_2CH_2$)
2.06-2.20	(1H, m, H_c equatorial)
2.22	(1H, dd, J=17 and 11 Hz, H_f axial)
2.61	(1H, ddd, J=17, 6, and 2 Hz, H_e equatorial)
2.84	(2H, t, J=6 Hz, $PhCH_2CH_2$)
3.30	(1H, dd, J=11 and 4 Hz, H_a axial)
3.98	(1H, br m, after D_2O shake, dddd, J=12, 11, 6, and 4 Hz, H_d axial)
5.06	(2H, s, CH_2O)
5.66	(1H, br s, OH)
6.84	(1H, d, J=2 Hz, Ar-H)
7.02	(1H, d, J=2 Hz, Ar-H)
7.30-7.50	(5H, br m, Ph-H)
trans-isomer	
3.64	(1H, m, C6-H axial)
4.26	(1H, m, C4-H equatorial)
7.88	(1H, br s, OH)
6.83	(1H, d, J=2 Hz, Ar-H)
7.01	(1H, d, J=2 Hz, Ar-H)

Table 5

^{1}H Nmr Assignment for Compounds (11b)-(11g) (DMSO-d_6)

(Piperidine-ring protons: c.f. Figure 1)

	Chemical Shift ppm					
Compound	h_b (ddd)	H_c (m)	H_f (dd)	H_e (ddd)	H_d (m)	H_a (dd)
11b	1.42	2.02-2.16	2.10	2.44	3.94	4.36
11c	1.40	2.18-2.30	2.08	2.46	3.95	4.83
11d	1.41	2.06-2.18	2.13	2.45	3.95	4.45
11e	1.45	2.04-2.20	2.16	2.46	3.94	4.48
11f	1.49	2.15-2.42	2.10	2.55	4.14	5.43
11g	1.47	2.10=2.24	2.15	2.48	3.98	4.48

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