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Routes to 4-Substituted Analogues of the Glycine/NMDA Antagonist HA-966. Enantioselective Synthesis of (3R,4R) 3-Amino-1-Hydroxy-4-Methyl-2-Pyrrolidinone (L-687,414).

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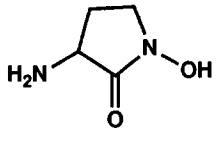
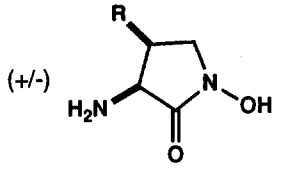
Abstract: Glycine anion (**4**) and glycine cation (**8**) synthons are used in efficient syntheses of 4-substituted analogues of HA-966 (**1**). A stereospecific route to *cis* derivatives involves hydrogenation of enamines such as **16**. Introduction of a chiral auxiliary leads to an enantioselective synthesis of **2a** (L-687,414).

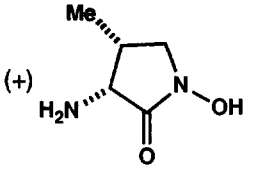
As part of a program to develop compounds for the treatment of cerebral ischæmia, we have been interested in the struture - activity relationships of analogues of 3-amino-1-hydroxy-2-pyrrolidinone (**1**, HA-966), an antagonist at the glycine modulatory site of the N-methyl D-aspartate (NMDA) subtype of excitatory amino acid receptor. Substitution with a methyl or hydroxyl group at various positions of the pyrrolidone ring showed biological activity only in the *cis* 4-substituted compounds, e.g. **2** and **3**.[1,2] We have previously shown that the glycine/NMDA antagonism of HA-966 (**1**) resides in the R-(+)-enantiomer,[3] and it is the (3R,4R)-(+)-isomer of **2** (**2a**, L-687,414) which is biologically active.[2]



1 (HA-966)



2 R = Me
3 R = OH

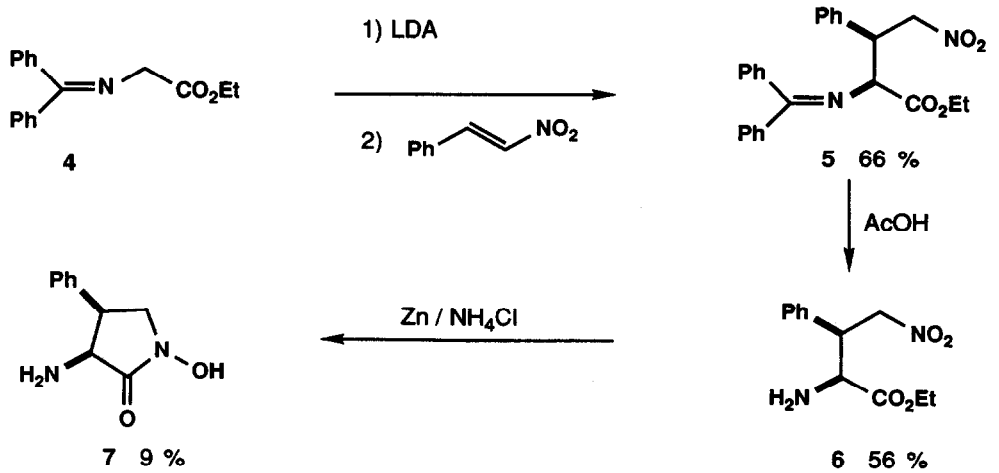


2a (L-687,414)

The route described to **2**[2] is not readily applicable to the synthesis of a large number of other analogues, due to the lack of availability of the corresponding starting materials. In addition the required *cis* substituted compounds are the minor products from the amination of 4-substituted pyrrolidinone enolates which predominantly gives the *trans* stereochemistry. A number of other routes to the desired compounds are described in this paper, with a representative example for

each approach, together with full experimental details of a diastereospecific and enantioselective synthesis of multigram quantities of **2a**.

An approach based on the use of a glycine anion equivalent is exemplified by the synthesis of the 4-phenyl analogue (7)(Scheme 1). Conjugate addition of the anion of 4 to β-nitrostyrene,[4] gave, after recrystallisation, a single diastereoisomer of the coupled product (5) whose relative stereochemistry is assigned by the fact that after cyclisation (see below) the product is *cis*. Removal of the nitrogen protecting group gave amino ester (6). This was partially reduced using zinc and ammonium chloride to the hydroxylamine, cyclising under the reaction conditions to give hydroxamate (7), which was purified by reverse phase HPLC. The relative stereochemistry of 7 was proved to be *cis* by nuclear Overhauser effect (nOe) experiments.

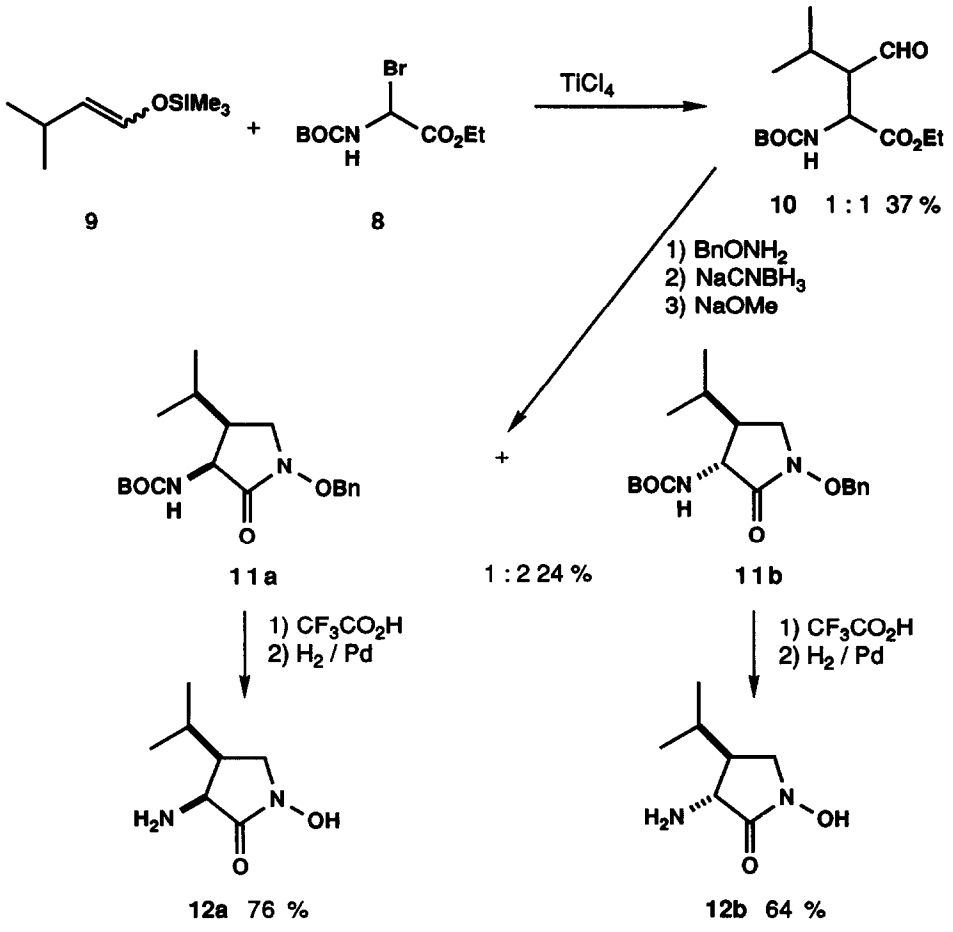


Scheme 1

This route is short but the low yield of the final step (although not optimised), and the difficulty in isolating the products, appears to preclude its use for synthesis of a large number of analogues.

A second approach explored (Scheme 2) makes use of a glycine cation synthon: Steglich[5] has reported the reaction of silyl enol ethers with protected α-bromoglycine (8), catalysed by Lewis acids, and we have used aldehydes as starting materials in this reaction. Thus, for example, the silyl enol ethers (9) (as a 1 : 1 mixture of *E* and *Z* isomers derived from 3-methylbutyraldehyde) were treated with 8 and titanium tetrachloride at -78 °C to give a 1 : 1 mixture of diastereoisomeric aldehydes (10). Although we have not extensively investigated the stereochemical outcome of this reaction, it seems not to be related to the ratio of starting enol ethers. The aldehydes were converted to the O-benzyl oximes and these reduced to the hydroxylamines with sodium cyanoborohydride under acidic conditons. Some cyclisation occured spontaneously during the reduction, so the hydroxylamines were not purified, but cyclised directly to the protected

hydroxamates (11), using a catalytic amount of sodium methoxide in methanol. The *cis* (11a) and *trans* (11b) isomers were separated at this stage, and their relative stereochemistries assigned by nOe experiments. A two step deprotection on each isomer using trifluoroacetic acid, then hydrogenolysis on a palladium catalyst gave the final aminohydroxamic acids (12).

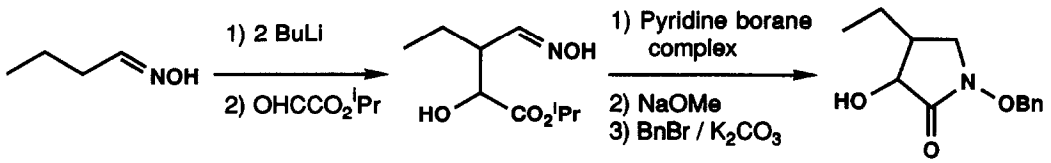


Scheme 2

Due to the ready availability of aldehydes, or direct precursors to them, and the brevity of the route, this is an attractive general approach for the synthesis of *cis* and *trans* 4-substituted analogues of HA-966. The lack of stereospecificity, and the need to prove which isomer is which in every case, however, makes this route less useful for the synthesis of the biologically important *cis* derivatives.

This lack of stereospecificity is solved in the third route to these analogues (Scheme 3) designed to provide the *cis* derivatives. Treatment of an aldehyde

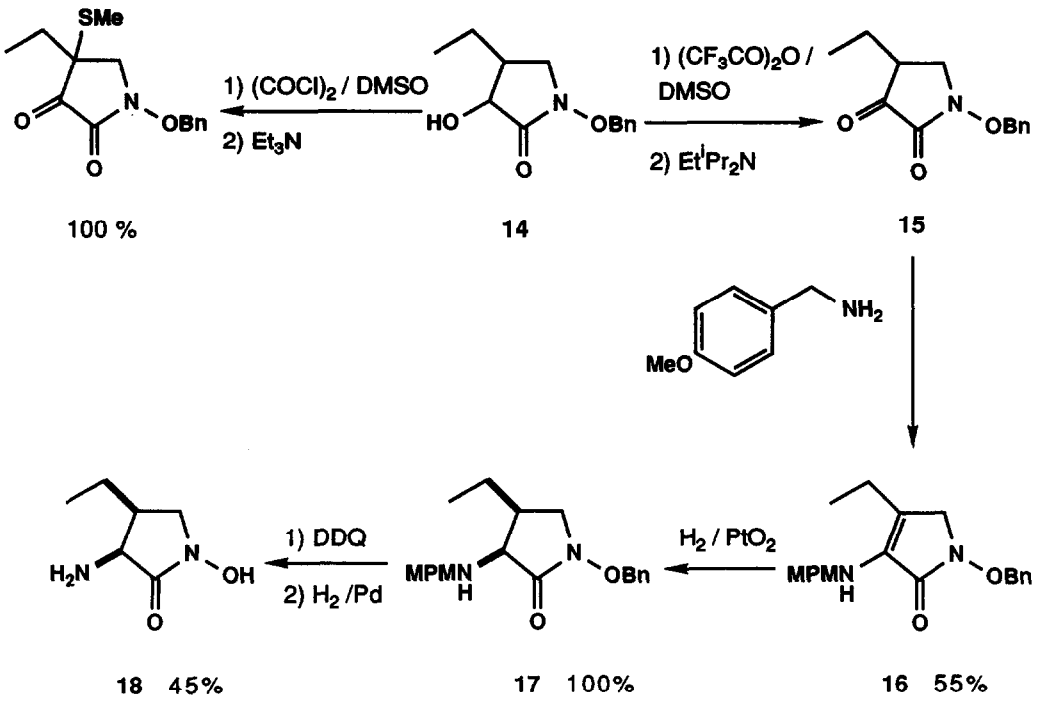
oxime (as a mixture of stereoisomers), for instance butyraldehyde oxime, with two equivalents of n-butyllithium at -78 °C in THF gives a white suspension of, presumably, the monoanion, which on warming to 0 °C becomes a yellow solution of the dianion. Recooling the solution to -78 °C and addition to a solution of *iso*-propyl glyoxalate gives a mixture of two isomers (3 : 2 by NMR) of the coupled products (13). Attempts to perform a similar reaction on the monoanion of an O-protected oxime (benzyl- or *tert*-butyldimethylsilyl-) were not successful.[6] Since it is known that ketoxime dianions alkylate regiospecifically *syn* to the oxime oxygen,[7] we presume that it is only the *syn* aldoxime that gives the desired products. This is supported by the facts that in the ^{1}H NMR spectra both isomers of the product have the proton α to the nitrogen at similar chemical shifts (∂ ~6.7 ppm), whereas the starting *syn* and *anti* oximes have this proton at markedly different shifts (∂ 6.72 and 7.42 respectively), and that after reduction of the oximes the product is still a mixture of diastereoisomers. Although the yield of this reaction is moderate (20% to 50% with a range of oximes), the ready availability of both starting materials makes this a viable route. No attempt was made to separate the mixture since all the stereochemistry is lost later in the route. Reduction of the oximes (13) with pyridine borane complex, cyclisation to the hydroxamic acid, and, for ease of handling, O-benzylation, gave the 3-hydroxyhydroxamates (14), again as a mixture of isomers (2 : 1).



13 25% 14 55%

Scheme 3

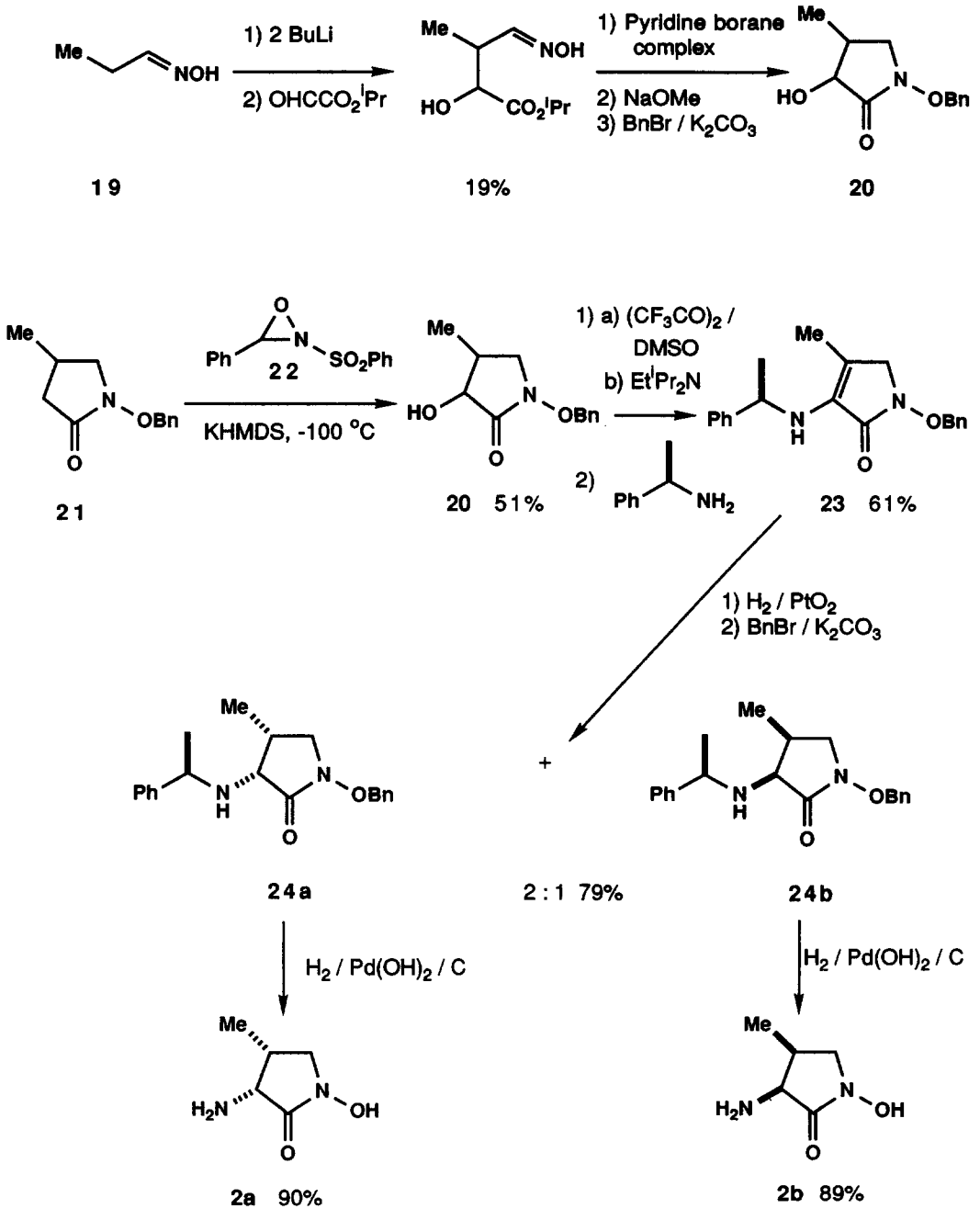
Swern oxidation using oxalyl chloride / DMSO followed by triethylamine[8] not only oxidised the alcohol, but also introduced a methylthio group next to the newly formed ketone (Scheme 4). However, using trifluoroacetic anhydride / DMSO then Hünig's base[9] gave the desired α-dicarbonyl (15), which exists as a 3:1 mixture of enol to keto tautomers in chloroform solution at room temperature. Compound 15 was readily converted to 16 with *p*-methoxybenzylamine in methanol, which existed entirely as the enamine tautomer, then the desired relative stereochemistry was introduced by hydrogenation of the double bond on platinum oxide to give a single diastereoisomer of the protected aminohydroxamate (17). This was deprotected in two steps: oxidative (DDQ) removal of the *p*-methoxybenzyl group from the nitrogen, and reductive (H_2 / Pd) removal of the O-benzyl group gave the final product (18). Alternatively, the deprotection of 17 could be done in one step by removal of both protecting groups by hydrogenolysis on Pearlman's catalyst.



Scheme 4 **MPM** = *p*-methoxybenzyl

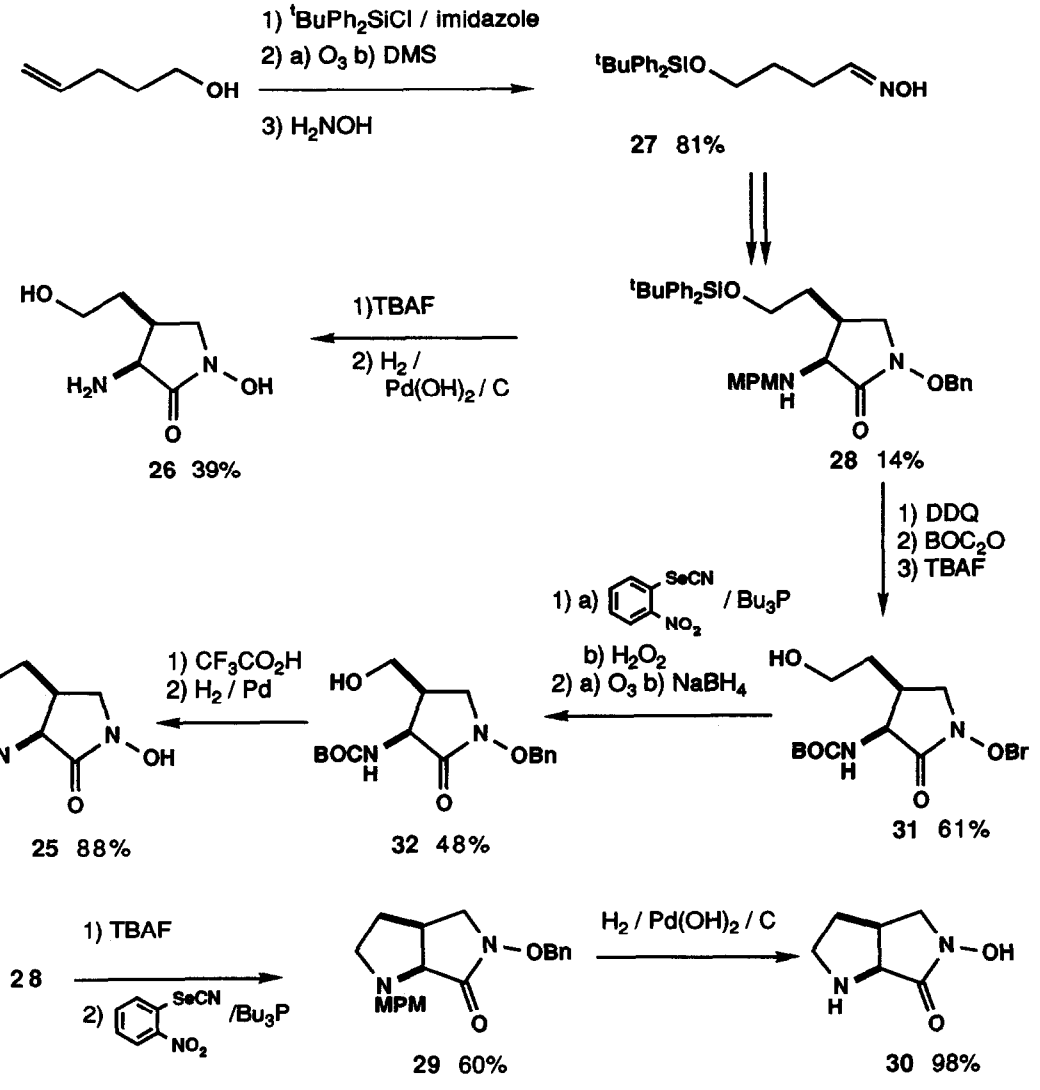
In order to fully evaluate the biological profile of the *cis* 4-methyl analogue (2) a route that gave multigram quantities of enantiomerically pure material was required. The route had to be able to supply both enantiomers, and was established by a modification of the third route above. Although it was possible to make the required intermediate, 3-hydroxyhydroxamate (20), in large quantities from propionaldehyde oxime (19)(Scheme 5), the poor first step, and subsequent tedious chromatography led us to investigate alternatives. The hydroxamate (21)[2] is readily availalable in >100 gram quantities, and it can be hydroxylated with the use of Davis's oxaziridine (22)[10] and potassium *bis*-trimethylsilylamide at -100 °C. This hydroxylation could also be performed on a large scale, giving multigram quantities of intermediate 20. Oxidation of 20, then formation of the enamine, this time with the chiral amine R-(+)-1-phenylethylamine gave enamine (23). (We found that commercially available (Aldrich) R-(+)-1-phenylethylamine had an enantiomeric excess (e.e.) of 97%, and we improved this to optical purity within the limits of detection by crystallisation of its D-(-)-tartrate salt from methanol). Hydrogenation of 23 on platinum oxide (followed by replacement of the O-benzyl group from the small amount of material that had been deprotected)

gave a 2 : 1 mixture of diastereoisomeric amines (24), that could be separated by chromatography.



Scheme 5

The absolute stereochemistry of the products was proved by an x-ray structure of the hydrochloride salt of the minor isomer **24b**. Deprotection of the separated isomers by hydrogenolysis on Pearlman's catalyst gave the (3R,4R)-(+)-enantiomer **2a**, and its enantiomer **2b**.



Scheme 6 **MPM = *p*-methoxybenzyl**

In order to further examine the structure - activity relationships, we required access to the hydroxymethyl (**25**) and hydroxyethyl (**26**) analogues (Scheme 6). Using the routes described above, protection of 4-penten-1-ol as a silyl ether,

ozonolysis, and oxime formation gave oximes (27), which were taken through to the *cis* amine (28). Deprotection of this compound gave the hydroxyethyl analogue (26). An attempt to remove one carbon atom from the hydroxyethyl side chain at this stage by elimination[11] of the selenide derived[12] from the deprotected primary alcohol, followed by ozonolysis, failed due to the presence or a nucleophilic nitrogen atom, leading to bicycle (29) which could be deprotected to aminohydroxamic acid (30). After some protecting group manipulation, the Grieco[12] procedure worked well on 31, leading to alcohol (32). At this stage the relative stereochemistry was checked by nOe experiments, before deprotection to 25.

The routes described in this paper have been applied to the synthesis of a large number of 4-substituted analogues of the glycine/NMDA antagonist HA-966, and allowed the structure-activity relationships for this type of substitution to be established. Large quantities of compound 2a (L-687,414) have been synthesised, which has enabled the biological evaluation of a potent systemically active excitatory amino acid antagonist. Biological results on these compounds will be published in full elsewhere.

Acknowledgements: We thank Miss S. Cross, Mr. J. McKenna, Dr. S. Young, and Dr. D Hands (MSDRL, Hoddesdon) for synthetic support, Dr. R. Herbert for NMR and mass spectra, Dr. K. Hoogsteen (MSDRL, Rahway, N.J.) for X-ray crystallography, and our colleagues in the Departments of Biochemistry and Pharmacology for biological assays.

Experimental: Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. NMR spectra were recorded using Brucker AM 360 and AC 250 spectrometers, and mass spectra on a VG 7250 spectrometer. Flash chromatography was performed on Fluka Kieselgel 60 (220 - 440 mesh). Dry solvents were bought from Aldrich Chemical Company. Microanalysis was performed by CHN Analysis, Leicester, UK.

(2RS, 3SR) *Ethyl 2-Diphenylmethyleneimino-4-nitro-3-phenylbutanoate* (5).- Lithium diisopropylamide (13.3 ml, 1.5 M in THF, 20 mmol) was added to a stirred solution of N-diphenylmethyleneglycine ethyl ester (5.34 g, 20 mmol) in THF (40 ml) at -78 °C. After 1 h b-nitrostyrene (2.98 g, 20 mmol) in THF (10 ml) was added, the mixture stirred at -78 °C for 1 h, then brought to room temperature. Ethyl acetate and water were added, the mixture separated, the organic layer washed with brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with hexanes : ethyl acetate (9 : 1 v/v), then recrystallised from ether to give the *ester* (3.95 g, 47 %) as a white solid, m.p. 86 - 88 °C; ∂ (360 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7.0 Hz, CH_3), 3.98 (2 H, d, *J* 8 Hz, CH_2NO_2), 4.1 - 4.3 (3 H, m, OCH_2 and PhCH), 6.07 (1 H, d, *J* 4.7 Hz, NCH), 6.78 (2 H, dd, *J* 2 and 7.7 Hz, ArH), 7.1 - 7.5 (11 H, m, ArH), 7.77 (2 H, d, *J* 7.7 Hz, ArH); *m/z* (EI^+) 417 (M^+).

(2RS, 3SR) *Ethyl 2-Amino-4-nitro-3-phenylbutanoate* (6).- The ester (5)(2 g, 4.8 mmol) was heated in acetic acid : water (5 : 1 v/v, 20 ml) at 60 °C for 4 h, then the solution stood at room temperature for 16 h. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (10 ml), then ethereal hydrogen chloride added. Cooling to 0 °C yielded the *amino ester* (776 mg, 57%) as its hydrochloride salt; ∂ (250 MHz, d_6-DMSO) 1.01 (3 H, t, *J* 7 Hz, CH_3), 3.9 - 4.1 (3 H, m, OCH_2 and PhCH), 4.43 (1 H, d, *J* 9 Hz, NCH), 5.20 (1 H, dd, *J* 11 and 14 Hz, $CH_AH_BNO_2$), 5.41 (1 H, dd, *J* 4.6 and 14 Hz, $CH_AH_BNO_2$), 7.3 - 7.5 (5 H, m, Ph), 8.9 (3 H, br s, NH's); *m/z* (CI^+, NH_3) 253(M^+ + H).

cis *2-Amino-1-hydroxy-3-phenyl-2-pyrrolidinone* (7).- Zinc dust (256 mg, 4 mmol) was added to a stirred solution of the amino ester (6)(577 mg, 2 mmol) and ammonium chloride (107 mg, 2 mmol) in ethanol (15 ml) and water (10 ml). After 8 h ammonium chloride (53 mg, 1 mmol) was added and the mixture stirred for a further 16 h. The mixture was filtered, evaporated *in vacuo*, and purified on an RP18 μ-Bondapak column, eluting with a gradient of 5 - 95% acetonitrile in 0.1% aqueous trifluoroacetic acid. The first compound to elute was the desired compound, and fractions containing it were evaporated *in vacuo*, then recrystallised from ethyl acetate to give the *pyrrolidinone* (56 mg, 9%) as its trifluoroacetate salt, m.p. 186 - 187 °C; (Found: C, 46.82; H, 4.38; N, 9.00. $C_{10}H_{12}N_2O_2$ + $C_2HF_3O_2$ requires C, 47.07; H, 4.30; N, 9.15%); ∂ (360 MHz, d_6-DMSO) 3.64 (1 H, dd, *J* 2 and 9.3 Hz, CH_AH_BNO), 3.8 - 3.85 (1 H, m, PhCH), 3.98 (1 H, dd, *J* 7.1 and 9.3 Hz, CH_AH_BNO), 4.35 (1 H, d, *J* 8.2 Hz, NCH), 7.2 - 7.4 (5 H, m, Ph); irradiation of either methine proton gave a positive nOe to the other; *m/z* (FAB^+) 193 (M^+ + H).

3-Methyl-1-trimethylsilyloxy-1-butene (9).- Chlorotrimethylsilane (38 ml, 0.28 mol) was added to a solution of 3-methylbutyraldehyde (21.5 g, 0.25 mmol) in DMF (300 ml) at room temperature, followed by dropwise addition of triethylamine (84 ml, 0.6 mol) over 10 min. The mixture was refluxed for 4 h, cooled to room temperature, and poured into pentane (200 ml). The pentane solution was washed with cold saturated sodium hydrogencarbonate (3 x 300 ml), cold 1M hydrochloric acid (300 ml), cold saturated sodium hydrogencarbonate (300 ml), brine (300 ml), dried ($MgSO_4$), evaporated *in vacuo*, and distilled to give the silyl enol ethers (9 g, 22%) as a 1 : 1 mixture of isomers by NMR, b.p. 117 - 119 °C; ∂ (360 MHz, $CDCl_3$) 0.06 (9 H, s, $SiMe_3$), 0.87 - 0.93 (6 H, m, $CH(CH_3)_2$), 2.11- 2.17 and 2.69 - 2.75 (1 H, m, $CH(CH_3)_2$), 4.23 (1 H, dd, *J* 6.3 and 8.9 Hz, $CHCH(CH_3)_2$, isomer A), 4.89 (1 H, dd, *J* 7.7 and 12.0 Hz, $CHCH(CH_3)_2$, isomer B), 5.95 (1 H, dd, *J* 1.1 and 6.3 Hz, CHO, isomer A), 6.12 (1 H, dd, *J* 1.1 and 12 Hz, CHO, isomer B).

Ethyl 2-tert.-Butyloxycarbonylamino-3-formyl-4-methylpentanoate. (10).- N-Bromosuccinimide (4.46 g, 24.8 mmol) was added to a solution of BOC-glycine ethyl ester (5 g, 24.6 mmol) in carbon tetrachloride (50 ml) at 5 °C, then stirred whilst being illuminated by a 60 watt light bulb for 1 h. The solution was filtered, evaporated *in vacuo*, the residue dissolved in dichloromethane (250 ml), cooled to -78 °C, and triethylamine (3.83 ml, 27.3 mmol) added. After 20 min titanium tetrachloride (3.02 ml, 28 mmol) in dichloromethane (20 ml) was added dropwise over 10 min, then the mixture stirred for 10 min. The silyl enol ethers (9)(4.65 g, 29.4 mmol) in dichloromethane (10 ml) were added, the reaction stirred at -78 °C for 1.5 h, then at room temperature for 30 min. The mixture was poured into ice water, separated, and the aqueous layer extracted with dichloromethane (2 x 100 ml). The combined organic layers were washed with water, saturated sodium hydrogencarbonate solution, and brine, dried ($MgSO_4$), evaporated *in vacuo* and purified by flash chromatography, eluting with hexanes : ethyl acetate (5 : 1 v/v) to give the *ester* as an oil (2.6 g, 37% as a 1 : 1 mixture of isomers by NMR); ∂ (360 MHz, $CDCl_3$) 1.0 - 1.1 (6 H, m, $CH(CH_3)_2$), 1.23 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.34 (9 H, s, ^tBu), 2.05 - 2.15 (1 H, m, $CH(CH_3)_2$), 2.45 - 2.55 (1 H, m, CHCHO, isomer A), 2.9 - 2.95 (1 H, m, CHCHO, isomer B), 4.14 - 4.23 (2 H, m, OCH_2), 4.60 - 4.65 (1 H, m, NCH), 5.17 (1 H, br s, NH, isomer A), 5.32 (1 H, br s, NH, isomer B), 9.73 (1 H, d, *J* 2.8 Hz, CHO, isomer A), 9.78 (1 H, d, *J* 2.8 Hz, CHO, isomer B); *m/z* (CI^+, NH_3) 288 ($M^+ + H$).

1-Benzyloxy-3-tert.-butyloxycarbonylamino-4-isopropyl-2-pyrrolidinone (11).- Triethylamine (0.58 ml, 4.2 mmol), 3Å molecular sieves (1 g), and O-benzylhydroxylamine hydrochloride (0.61 g, 3.8 mmol) were added to a solution of aldehyde (10)(1 g, 3.5 mmol) in THF (50 ml). After heating at 60 °C for 6 h, the mixture was cooled and poured into a mixture of ethyl acetate (100 ml) and 1 M citric acid (100 ml). The aqueous layer was extracted with ethyl acetate (2 x 50 ml), and the combined orgainc layers washed with water, saturated sodium hydrogencarbonate solution, and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give the oximes as an oil. Methanol (50 ml) was added to the oil, followed by sodium cyanoborohydride (0.36 g, 5.7 mmol) and to this mixture at room temperature was added hydrochloric acid in methanol (methanol : 1 M aqueous HCl, 1 : 1 v/v, 5 ml) dropwise over 2 h. Sodium cyanoborohydride (0.18 g, 2.9 mmol) was then added, followed by hydrochloric acid in methanol (2.5 ml) over 1 h. The reaction mixture was diluted with ethyl acetate (100 ml) and 1 M sodium hydroxide added. The aqueous layer was extracted with ethyl acetate (3 x 100 ml), and the combined organic layers washed with water, and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give the hydroxylamines as an oil. Methanol (100 ml) was added followed by sodium methoxide (20 mg, 0.37 mmol). After stirring for 4 h at room temperature the mixture was poured into 1 M citric acid and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water, saturated sodium hydrogencarbonate solution, and brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with hexanes : ethyl acetate (3 : 1 v/v) to give a mixture of the two isomers (2 : 1 by NMR) of the hydroxamates (0.29 g, 24 %). The isomers were separated by MPLC (LOBAR, LiChroprep Si 60) eluting with dichloromethane : methanol (99 : 1 v/v) to give the *cis* isomer (11a)(78 mg) as an oil; ∂ (360 MHz, $CDCl_3$) 0.69 (3 H, d, *J* 9.8 Hz, CH_3), 0.87 (3 H, d, *J* 9.8 Hz, CH_3), 1.45 (9 H, s, ^tBu), 1.7 - 1.8 (1 H, m, $CHMe_2$), 2.3 - 2.4 (1 H, m, NCHCH), 3.2 - 3.3 (2 H, m, CH_2NO), 4.2 - 4.3 (1 H, m, NCH), 4.9 (1 H, br s, NH), 4.99 (1 H, d, *J* 15.8 Hz, OCH_AH_B), 5.02 (1 H, d, *J* 15.8 Hz, OCH_AH_B), 7.35 - 7.45 (5 H, m, Ph); irradiation of either ring methine proton gave a positive nOe to the other; *m/z* (CI^+, NH_3) 350 ($M^+ + H$); and the *trans* isomer (11b)(120 mg) as an oil; ∂ (360 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 9.6 Hz, CH_3), 0.90 (3 H, d, *J* 9.6 Hz, CH_3), 1.45 (9 H, s, ^tBu), 1.7 - 1.8 (1 H, m, $CHMe_2$), 1.9 - 2.0 (1 H, m, NCHCH), 2.91 (1 H, t, *J* 12.3 Hz, CH_AH_BNO), 3.27 (1 H, t, *J* 12.3 Hz, CH_AH_BNO), 4.0 - 4.1 (1 H, m, NCH), 4.8 (1 H, br s, NH), 4.97 (1 H, d, *J* 15.7 Hz, OCH_AH_B), 5.02 (1 H, d, *J* 15.7 Hz, OCH_AH_B), 7.35 - 7.45 (5 H, m, Ph); *m/z* (CI^+, NH_3) 350 ($M^+ + H$).

trans *3-Amino-1-hydroxy-4-isopropyl-2-pyrrolidinone* (12b).- A solution of 11b (120 mg, 0.34 mmol) in trifluoroacetic acid (1 ml) was stirred at room temperature for 10 min, evaporated *in vacuo*, then the residue dissolved in ethanol (5 ml) and hydrogenated on palladium black (30 mg) at 50 psi for 2 h. After filtration and evaporation, the residue was dissolved in dilute hydrochloric acid and applied to a column containing DOWEX 50W-X8 (H^+ form, 100 - 200 mesh, 2 x 2 cm). After washing with water (100 ml), the product was eluted with 4% aqueous ammonia. Fractions containing the product were evaporated, redissolved in water, and freeze dried to give the *pyrrolidinone* (35 mg, 64%) as a hydroscopic solid; ∂ (360 MHz, D_2O) 0.93 (3 H, d, *J* 6.7 Hz, CH_3), 0.98 (3 H, d, *J* 6.8 Hz, CH_3), 1.85 - 1.90 (1 H, m, $CHMe_2$), 2.10 - 2.15 (1 H, m, $CHCH_2$), 3.58 (1 H, dd, *J* 6.6 and 9.9 Hz, NCH_AH_B), 3.70 - 3.75 (2 H, m, NCH and NCH_AH_B); *m/z* (FAB^+) 159 ($M^+ + H$); *m/z* (EI) 142 (M - NH_2)(Found: M - NH_2, 142.102 6. $C_7H_{12}NO_2$ requires M, 142.086 8).

cis 3-Amino-1-hydroxy-4-isopropyl-2-pyrrolidinone (12a).- As 12b, using 11a (70 mg, 0.20 mmol) to give the *pyrrolidinone* (24 mg, 76%) as a hydroscopic solid; ∂ (360 MHz, D_2O) 0.89 (3 H, d, *J* 6.6 Hz, CH_3), 0.98 (3 H, d, *J* 6.6 Hz, CH_3), 1.80 - 1.85 (1 H, m, $CHMe_2$), 2.30 - 2.35 (1 H, m, $CHCH_2$), 3.50 (1 H, dd, *J* 7.5 and 9.8 Hz, NCH_AH_B), 3.6 - 3.7 (2 H, m, NCH_AH_B and NCH); *m/z* (FAB$^+$) 159 (M^+ + H).

Iso-*Propyl 2-Hydroxy-3-hydroxyliminomethylpentanoate* (13):- n-Butyllithium (74 ml of a 1.6M solution in hexanes, 118 mmol) was added over 5 min to a solution of butyraldehyde oximes (5.12 g, 58.8 mmol) in THF (150 ml) at -78 °C. The thick white suspension was warmed to 0 °C for 30 min until the solid had dissolved. The yellow solution was then cooled to -78 °C and cannulated into a solution of *iso*-propyl glyoxalate (6.8 g, 58.6 mmol) in THF (100 ml) at -78 °C. After 30 min the mixture was warmed to room temperature, poured into brine, and extracted with ether (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (20 : 1 v/v) to give a mixture of two isomers (3:2 by NMR) of the *ester* (2.89 g, 25%) as an oil; ∂ (250 MHz, $CDCl_3$) 0.8 - 1.3 (3 H, m, CH_3CH_2), 1.2 - 1.3 [6H, m, $CH(CH_3)_2$], 1.5 - 2.0 (2 H, m, CH_2) 3.4 - 3.5 (1 H, m, $CHCH_2$), 4.24 (1 H, d, *J* 3.1 Hz, CHCO, minor isomer), 4.34 (1 H, d, *J* 4.0 Hz, CHCO, major isomer), 5.0 - 5.1 (1H, m, $CHMe_2$), 6.68 (1H, d, *J* 7.6 Hz, CHN, minor), 6.72 (1H, d, *J* 7.6 Hz, CHN, major); *m/z* (CI^+, NH_3) 204 (M^+ + H).

1-Benzyloxy-4-ethyl-3-hydroxy-2-pyrrolidinone (14).- 10% Aqueous hydrochloric acid (30 ml) was added dropwise over 5 min to a stirred solution of 13 (1.74 g, 8.57 mmol) and pyridine-borane complex (3 ml, 2.7 g, 29 mmol) in ethanol (15 ml) at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 30 min, basified to pH 9 with solid sodium bicarbonate, and extracted with dichloromethane (3 x 25 ml). The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo*, the residue dissolved in methanol (20 ml), and sodium methoxide (0.56 g, 10.4 mmol) added. The solution was then refluxed for 2 h, cooled to room temperature, and benzyl bromide (2.16 g, 12.6 mmol) added. After stirring for 16 h, sodium methoxide (0.5 g) was added, and the mixture stirred for a further 30 min before being poured into water and extracted with ether (3 x 30 ml).The combined organic layers were washed with water and brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (96 : 4 v/v) to give a mixture of two isomers (2 : 1 by NMR) of the pyrrolidinone (1.10 g, 55%) as an oil; ∂ (360 MHz, $CDCl_3$) *major isomer:* 0.91 (3 H, t, *J* 7.4 Hz, CH_3), 1.2 - 1.3 and 1.7 - 1.8 (2 H, m, CH_2CH_3), 2.0 - 2.1 (1 H, m, $CHCH_2$), 2.87 (1 H, t, *J* 8.5 Hz, NCH_AH_B), 3.31 (1 H, t, *J* 8.5 Hz, NCH_AH_B), 3.91 (1 H, d, *J* 8.2 Hz, CHOH), 4.98 (1H, d, *J* 11.0 Hz, OCH_AH_B), 5.03 (1 H, d, *J* 11.0 Hz, OCH_AH_B), 7.4 - 7.5 (5 H, m, Ph); *minor isomer:* 0.84 (3 H, t, *J* 7.4 Hz, CH_3), 1.2 - 1.3 and 1.7 - 1.8 (2 H, m, CH_2CH_3), 2.1 - 2.2 (1 H, m, $CHCH_2$), 3.06 (1 H, dd, *J* 4.7 and 8.8 Hz, NCH_AH_B), 3.28 (1 H, dd, *J* 6.8 and 8.8 Hz, NCH_AH_B), 4.24 (1 H, d, *J* 8.2 Hz, CHOH), 5.00 (2 H, s, OCH_2), 7.4 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 236 (M^+ + H).

1-Benzyloxy-4-ethyl-2,3-pyrrolidinedione (15).- Trifluoroacetic anhydride (1.8 ml, 12.7 mmol) was added dropwise to a solution of dimethylsulphoxide (1 ml, 16.2 mmol) in dichloromethane (40 ml) at -78 °C. After 10 min 14 (0.94 g, 4 mmol) in dichloromethane (8 ml) was added, the mixture stirred for 30 min, then ethyldiisopropylamine (4.5 ml, 26.3 mmol) added. After 45 min methanol (1 ml) was added, and the solution brought to room temperature. Water was added, and the mixture extracted with ether (3 x 75 ml). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give the *dione* (0.69 g, 74%) as an oil. The ^1H NMR in $CDCl_3$ showed a mixture of enol and keto tautomers in a ratio of 3 : 1 in at room temperature; ∂ (250 MHz, $CDCl_3$) *enol form*: 1.04 (3 H, t, *J* 7.6 Hz, CH_3), 2.27 (2 H, q, *J* 7.6 Hz, CH_2CH_3), 3.63 (2 H, s, NCH_2) 5.03 (2 H, s, OCH_2), 7.3 - 7.5 (5 H, m, Ph); *keto form*: 0.84 (3 H, t, *J* 7.5 Hz, CH_3), 1.6 - 1.8 (2 H, m, CH_2CH_3), 2.5 - 2.6 (1 H, m, CH), 3.14 (1 H, dd, *J* 3.5 and 10 Hz, NCH_AH_B), 3.65 (1 H, dd, *J*, 7.6 and 10 Hz, NCH_AH_B), 5.17 (1 H, d, *J* 11.2 Hz, OCH_AH_B), 5.24 (1 H, d, *J* 11.2 Hz, OCH_AH_B), 7.3 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 234 (M^+ + H).

1-Benzyloxy-4-ethyl-4-methylthio-2,3-pyrrolidinedione.- Dimethylsulphoxide (110 µl, 1.8 mmol) was added to a solution of oxalyl chloride (80 µl, 0.92 mmol) in dichloromethane (4 ml) at -78 °C. After 10 min the alcohol (14)(27 mg, 114 µmol) in dichloromethane (500 µl) was added, then after a further 1 h triethylamine (350 µl, 2.8 mmol) was added. The mixture was brought to room temperature, diluted with ether, washed with water and brine, dried, evaporated *in vacuo*, and filtered through silica gel, eluting with dichloromethane : methanol (95 : 5 v/v) to give the *dione* (27 mg, 100 %) as an oil; n_{max}(film) 1705 and 1660 cm^{-1}; ∂ (250 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.6 - 1.8 (2 H, m, $CHCH_3$), 1.92 (3 H, s, SMe), 3.14 (1 H, d, *J* 11 Hz, NCH_AH_B), 3.48 (1 H, d, *J* 11 Hz, NCH_AH_B), 5.13 (1 H, d, *J* 12 Hz, OCH_AH_B), 5.17 (1 H, d, *J* 12 Hz, OCH_AH_B), 7.3 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 280 (M^+ + H).

1-Benzyloxy-4-ethyl-3-(4-methoxybenzylamino)-2-oxo-2,5-dihydropyrrole (16).- The ketone (15)(0.68 g, 2.9 mmol) and 4-methoxybenzylamine (1.1 ml) were kept in methanol (10 ml) overnight, evaporated *in vacuo*, and purified by flash chromatography, eluting with hexane: ethyl acetate (5:2 v/v) to give the *pyrrole* (0.75 g, 74%) as an oil: ∂ (250 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7 Hz, CH_3), 2.22 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.60 (2 H, s, CH_2NO), 3.78 (3 H, s, OMe), 4.32 (2 H, s, CH_2NH), 5.02 (2 H, s, OCH_2), 6.85 (2 H, d, *J* 9 Hz, ArH, H *o* to OMe), 7.22 (2 H, d, *J* 9 Hz, ArH, H *m* to OMe), 7.5 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 353 (M^+ + H).

cis *1-Benzyloxy-4-ethyl-3-(4-methoxybenzylamino)-2-pyrrolidinone.* (17).- The pyrrole (16)(72 mg, 205 µmol) was hydrogenated on platinum (IV) oxide (9.6 mg) in ethyl acetate (10 ml) and acetic acid (100 µl) at atmospheric pressure for 20 h. The mixture was filtered, washed with sodium hydrogencarbonate solution, water, and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give the *pyrrolidinone* (72 mg, 100%) as an oil; ∂ (250 MHz, $CDCl_3$) 0.74 (3 H, t, *J* 7.5 Hz, CH_3), 1.0 - 1.1 and 1.5 - 1.6 (2 H, m, CH_2CH_3), 2.0 - 2.1 (1 H, m, $CHCH_2$), 2.95 (1 H, dd, *J* 3 and 10 Hz, CH_AH_BNO), 3.25 (1 H, dd, *J* 6 and 10 Hz, CH_AH_BNO), 3.30 (1 H, d, *J* 8.5 Hz, NCH), 3.78 (3 H, s, OMe), 3.80 (2 H, s, CH_2NH), 4.98 (2 H, s, OCH_2) 6.84 (2 H, d, *J* 9 Hz, ArH, H *o* to OMe), 7.26 (2 H, d, *J* 9 Hz, ArH, H *m* to OMe), 7.3 - 7.5 (5 H, m, Ph); irradiation of either methine proton gave a positive nOe to the other; *m/z* (Cl^+, NH_3) 249 (M^+ - $MeOC_6H_4$ + H).

cis *3-Amino-1-hydroxy-4-ethyl-2-pyrrolidinone* (18).- Dichlorodicyanobenzoquinone (125 mg, 550 µmol) was added to a stirred solution of pyrrolidinone (17)(190 mg, 458 µmol) in dichloromethane (20 ml) and water (1 ml). After 90 min the mixture was evaporated, and purified firstly on DOWEX 50W-X8 then by flash chromatography, eluting with dichloromethane : methanol (95 : 5 v/v) to give the O-benzyl amine. The resulting oil (62 mg) was hydrogenated on palladium (30 mg) in ethanol (20 ml) and acetic acid (100 µl) at 50 p.s.i. for 2 h. After filtration and evaporation, the product was purified on DOWEX 50W-X8 and freeze dried to give the *pyrrolidinone* (29.1 mg, 45%) as a foam; ∂ (360 MHz, D_2O) 0.96 (3 H, t, *J* 7.3 Hz, CH_3), 1.3 - 1.4 and 1.5 - 1.6 2 H, m, CH_2CH_3), 2.45 - 2.55 (1 H, m, $CHCH_2$), 3.38 (1 H, dd, *J* 4.8 and 10.0 Hz, NCH_AH_B), 3.69 (1 H, dd, *J* 7.3 and 10 .0 Hz, NCH_AH_B), 3.82 (1 H, d, *J* 8.0 Hz, NCH); *m/z* (Cl^+, NH_3) 249 (M^+ + H).

1-Benzyloxy-3-hydroxy-4-methyl-2-pyrrolidinone (20).- Potassium *bis*-trimethylsilylamide (507 ml, 0.38 mol in toluene) was added over 1.5 h to a stirred solution of hydroxamate (21)(52.0 g, 0.25 mol) and oxaziridine (22)(70 g, 0.28 mol) in THF (750 ml) at -100 °C, keeping the internal temperature below -90 °C. After a further 30 min acetic acid (50 ml) was added, the mixture brought to room temperature, and the solvent removed *in vacuo*. Methanol (300 ml) and DOWEX 50W-X8 (150 g) were added, the mixture filtered,and the filtrate evaporated, then purified by flash chromatography, eluting with hexane : ethyl acetate (1 : 1 v/v) to give the *pyrrolidinones* (35.9 g, 64%) as a (3 : 2, *trans : cis*) mixture of isomers as a white solid; ∂ (250 MHz, $CDCl_3$) *trans*; 1.13 (3 H, d, *J* 6.7 Hz, CH_3), 2.1 - 2.2 (1 H, m, $CHCH_3$), 2.85 (1 H, t, *J* 8.7 Hz, NCH_AH_B), 3.27 (1 H, t, *J* 8.7 Hz, NCH_AH_B), 3.82 (1 H, d, *J* 8.4 Hz, OCH), 4.97 (1 H, d, *J* 11.0 Hz, OCH_AH_B), 5.03 (1 H, d, *J* 11.0 Hz, OCH_AH_B), 7.4 - 7.5 (5 H, m, Ph); *cis*; 0.98 (3 H, d, *J* 7.2 Hz, CH_3), 2.4 - 2.5 (1 H, m, $CHCH_3$), 2.93 (1 H, dd, *J* 3.0 and 8.7 Hz, NCH_AH_B), 3.35 (1 H, dd, *J* 6.5 and 8.7 Hz, NCH_AH_B), 4.24 (1 H, d, *J* 7.3 Hz, OCH), 4.99 (2 H, s, OCH_2), 7.4 - 7.5 (5 H, m, Ph). Crystallisation from ether gave the pure *trans* isomer, m.p. 112 - 113 °C.

1-Benzyloxy-4-methyl-2,3-pyrrolidinedione.- This was made in the same way as the dione (15), using the alcohol (20)(10 g, 45 mmol), dimethylsulphoxide (17.6 g, 259 mmol), trifluoroacetic anhydride (44 g, 212 mmol), and ethyldiisopropylamine (42 g, 330 mmol) and purified by flash chromatography, eluting with dichloromethane : methanol (98 : 2 v/v) to give the *dione* (7.8 g, 78%) as white needles, m.p. 129 - 132 °C (from ethyl acetate / hexane) as a 4 : 1 mixture of enol to ketone forms in $CDCl_3$ at room temperature; ∂(360 MHz, $CDCl_3$) *enol form*: 1.81 (3 H, t, *J* 0.9 Hz, CH_3), 3.61 (2 H, q, *J* 0.9 Hz, NCH_2), 5.01 (2 H, s, OCH_2), 7.3 - 7.5 (5 H, m, Ph); *keto form*: 1.51 (3 H, d, *J* 7 Hz, CH_3), 2.6 - 2.7 (1 H, m, CH), 3.11 (1 H, dd, *J* 3.9 and 10 .0 Hz, CH_AH_BN), 3.73 (1 H, dd, *J* 7.6 and 10.0 Hz, CH_AH_BN), 5.22 (1 H, d, *J* 11.0 Hz, OCH_AH_B), 5.26 (1 H, d, *J* 11.0 Hz, OCH_AH_B), 7.3 - 7.5 (5 H, m, Ph); *m/z* (Cl^+, isobutane) 220 (M^+ + H).

(R) *1-Benzyloxy-4-methyl-2-oxo-3-(1-phenylethylamino)-2,5-dihydropyrrole* (23).- This was made in the same way as the pyrrole (16) using the above ketone (7.8 g, 35.6 mmol) and R-(+)-1-phenylethylamine (crystallised from methanol as its D-(-)-tartrate salt, recrystallised from aqueous methanol, and liberated by ether extraction of an NaOH solution, then evaporation) to give the *pyrrole* (8.95 g, 78%) as an oil: $[\alpha]_D$ +59.7° (c = 1.8, $CHCl_3$); ∂ (360 MHz, $CDCl_3$) 1.45 (3 H, d, *J* 6.8 Hz, $PhCHCH_3$), 1.60 (3 H, s, CH_3CHCH_2), 3.43 (1 H, d, *J* 16.2 Hz, NCH_AH_B), 3.50 (1 H, d, *J* 16.2 Hz, NCH_AH_B), 4.1 (1 H, br s, NH), 4.64 (1 H, q, *J* 6.8 Hz, NCH), 5.00 (2 H, s, OCH_2), 7.2 - 7.5 (10 H, m, Ph); *m/z* (Cl^+, NH_3) 323 (M^+ + H).

1-Benzyloxy-4-methyl-3-[(R)-1-phenylethylamino]-2-pyrrolidinone (24).- 23 (8.95 g, 27.6 mmol) was hydrogenated on platinum (IV) oxide (900 mg) in ethyl acetate (300 ml) and acetic acid (30 ml) at atmospheric pressure for 14 h. The mixture was filtered, evaporated *in vacuo*, dissolved in methanol (250 ml), and potassium carbonate (19 g, 137 mmol) and benzyl bromide (4.3 g, 25 mmol) added. After stirring for 3 h, the mixture was poured into water, extracted with ether (3 x 100 ml), the combined organic layers washed with water, and brine, dried, evaporated *in vacuo*, and purified by flash chromatography, eluting with hexane : ethyl acetate (2 : 1 v/v) to give the *pyrrolidinones* (7.1 g, 79 %). The diastereoisomers were separated on a Waters PrepLC 500 eluting with 0.6% methanol in dichloromethane; (3R, 4R) isomer (24a)(major, less polar); $[\alpha]_D$ +103 (c = 1.6, $CHCl_3$); ∂ (360 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 7.0 Hz, CH_3CHCH_2), 1.43 (3 H, d, *J* 6.5 Hz, CH_3CHPh), 1.95 - 2.05 (1 H, m, $CHCH_2$), 2.80 (1 H, dd, *J* 0.5 and 8.6 Hz, NCH_AH_B), 3.20 (1 H, d, *J* 7.4 Hz, NCHCO), 3.27 (1 H, dd, *J* 2.7 and 8.6 Hz, NCH_AH_B), 4.24 (1 H, q, *J* 6.5 Hz, NCHPh), 4.99 (1 H, d, *J* 11 Hz, OCH_AH_B), 5.03 (1 H, d, *J* 11 Hz, OCH_AH_B), 7.3 - 7.6 (10 H, m, Ph); *m/z* (Cl^+, NH_3) 325 (M^+ + H); (3S, 4S) isomer (24b)(minor); $[\alpha]_D$ -19.7 (c = 1.3, $CHCl_3$); ∂ (360 MHz, $CDCl_3$) 0.95 (3 H, d, *J* 7.0 Hz, CH_3CHCH_2), 1.38 (3 H, d, *J* 6.7 Hz, CH_3CHPh), 2.3 - 2.4 (1 H, m, $CHCH_2$), 2.80 (1 H, dd, *J* 0.7 and 8.6 Hz, NCH_AH_B), 3.15 (1 H, d, *J* 7.3 Hz, NCHCO), 3.27 (1 H, dd, *J* 5.9 and 8.6 Hz, NCH_AH_B), 3.75 (1 H, q, *J* 6.7

Hz, NCHPh), 4.92 (1 H, d, *J* 11 Hz, OCH$_A$H$_B$), 4.97 (1 H, d, *J* 11 Hz, OCH$_A$H$_B$), 7.2 - 7.5 (10 H, m, Ph); *m/z* (Cl$^+$, NH$_3$) 325 (*M*$^+$ + H).

(3R, 4R) *3-Amino-1-hydroxy-4-methyl-2-pyrrolidinone* (2a).- The pyrrolidinone (24a)(6.4 g, 19.7 mmol) was hydrogenated on Pearlman's catalyst (1.6 g) in methanol (100 ml) and acetic acid (2 ml) at 50 p.s.i. for 2 h. After filtration and evaporation, the residue was purified on DOWEX 50W-X8 to give the *pyrrolidinone* (2.3 g, 90%) as a white foam; [α]$_D$ +16.5 (c = 0.48, MeOH)[lit.[2] +16.5 (c = 0.48, MeOH)]. D-(-)-tartaric acid (1.33 g) in water was added and the mixture freeze dried to give the tartrate salt; (Found: C, 38.09; H, 6.65; N, 12.65. $C_7H_{13}N_2O_5$ + 0.9 H_2O requires C, 37.97; H, 6.73; N, 12.65%); ∂ (360 MHz, D_2O) 1.74 (3 H, d, *J* 7.1 Hz, CH$_3$), 2.8 - 3.0 (1 H, m, CHCH$_3$), 3.34 (1 H, dd, *J* 2.2 and 9.5 Hz, NCH$_A$H$_B$), 3.90 (1 H, dd, *J* 6.6 and 9.5 Hz, NCH$_A$H$_B$), 4.24 (1 H, d, *J* 8.4 Hz, NCH), 4.36 (1 H, s, OCH); *m/z* (Cl$^+$, NH$_3$) 131 (*M*$^+$ + H). Analysis of the *bis*-DANSYL derivative on a Bakerbond DNPG (Pirkle) column, 5 µm, 100% EtOH, 1 ml / min, showed enantiomeric purity of 99.7%.

(3R, 4R) *3-Amino-1-hydroxy-4-methyl-2-pyrrolidinone* (2b).- This was made in the same way as 2a, using 24b, to give the *pyrrolidinone* (89%), identical to 2a, but [α]$_D$ -15.0 (c = 0.31, MeOH)[lit.[2] -15 (c = 0.31, MeOH)].

4-tert.-*Butyldiphenylsilyloxybutanal oximes* (27).- *tert.*-Butylchlorodiphenylsilane (69 g, 251 mmol) was added to a solution of 4-penten-1-ol (20 g, 232 mmol) and imidazole (31.5 g, 463 mmol) in dimethylformamide (350 ml) at 0 °C. After stirring at room temperature for 6 h the mixture was poured into water (1 l), extracted with ether (3 x 200 ml), the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give 1-*tert.*-butyldiphenylsilyloxy-4-pentene (84 g) as an oil; ∂ (250 MHz, $CDCl_3$) 1.06 (9 H, s, ^{t}Bu), 1.66 (2 H, quin, *J* 7 Hz, CH$_2$CH$_2$CH$_2$), 2.16 (2 H, q with other fine coupling, *J* 7 Hz, CH$_2$CH=C), 3.65 (2 H, t, *J* 7 Hz, OCH$_2$), 4.94 (1 H, d with other fine coupling, *J* 11 Hz, C=CH$_A$H$_B$), 5.00 (1 H, d with other fine coupling, *J* 17 Hz, C=CH$_A$H$_B$), 5.80 (1 H, ddt, *J* 11, 17, and 7 Hz, CH=C), 7.35 - 7.45 and 7.65 - 7.75 (10 H, m, Ph). This oil was dissolved in dichloromethane (500 ml) and methanol (500 ml), cooled to -78 °C, and ozone bubbled through for 6 h until a blue colour persisted. Nitrogen was then passed through until the colour dissipated, then dimethylsulphide (45 ml) added. The mixture was stirred at room temperature for 3 h, evaporated to 200 ml, poured into water (1 l), and extracted with ether (3 x 200 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give 4-*tert.*-butyldiphenylsilyloxybutanal (82 g) as an oil; ∂ (250 MHz, $CDCl_3$) 1.02 (9 H, s, ^{t}Bu), 1.8 - 2.0 (2 H, m, CH$_2$CH$_2$CH$_2$), 2.54 (2 H, dt, *J* 1 and 7 Hz, CH$_2$CHO), 3.65 (2 H, t, *J* 7 Hz, OCH$_2$), 7.25 - 7.35 and 7. 6 - 7.7 (10 H, m, Ph), 9.78 (1 H, t, *J* 1 Hz, CHO). This oil was dissolved in methanol (400 ml) with triethylamine (38 ml, 28.1 g, 280 mmol), then hydroxylamine hydrochloride (17.6 g, 255 mmol) added. After stirring for 17 h, the mixture was evaporated to 200 ml, poured into water (1 l), extracted with ether (3 x 200 ml), the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* . The resulting oil was purified by flash chromatography, eluting with hexane : ethyl acetate (4 : 1 v/v) to give the *oximes* (64 g, 81%) as a mixture of isomers (3 : 2 by NMR) as an oil; ∂ (250 MHz, $CDCl_3$) 1.05 (9 H, s, ^{t}Bu), 1.7 - 1.8 (2 H, m, CH$_2$CH$_2$CH$_2$), 2.32 (2 H, q, *J* 7 Hz, CH$_2$CHN, major isomer), 2.49 (2 H, q, *J* 7 Hz, CH$_2$CHN, minor isomer), 4.11 (2 H, t, *J* 7 Hz, OCH$_2$), 6.72 (1 H, t, *J* 7 Hz, CHN, minor isomer), 7.25 - 7.45 and 7.6 - 7.7 (m, Ph and CHN, major isomer); *m/z* (EI$^+$) 331 (*M*$^+$).

Iso-*Propyl* 5-tert.-*Butyldiphenylsilyloxy-2-hydroxy-3-hydroxyliminomethylpentanoate*.- This was made in the same way as the ester (13) using oximes (27)(20.7 g, 60.6 mmol), butyllithium (76 ml, 1.6 M, 121 mmol), and *iso*-propyl glyoxalate (21 g, 181 mmol) and purified by flash chromatography, eluting with dichloromethane : methanol (98 : 2 v/v) to give the *esters* (11.5 g, 42 %) as a mixture of two isomers (7 : 5 by NMR) as an oil; ∂ (250 MHz, $CDCl_3$) 1.04 (9 H, s, ^{t}Bu, major isomer), 1.05 (9 H, s, ^{t}Bu, minor isomer), 1.2 - 1.3 (6 H, m, ^{i}Pr) 1.6 - 2.0 (2 H, m, CH$_2$CH), 3.1 - 3.2 (1 H, M, CH$_2$CH), 3.6 - 3.8 (2 H, m, OCH$_2$), 4.29 (1 H, br s, CHOH, major isomer), 4.39 (1 H, br s, CHOH, minor isomer), 5.05 - 5.10 (1 H, m, CHMe$_2$), 6.70 (1 H, d, *J* 7 Hz, CHN, minor isomer), 6.73 (1 H, d, *J* 7.4 Hz, CHN, major isomer), 7.3 - 7.4 and 7.6 - 7.7 (10 H, m, Ph); *m/z* (Cl$^+$, NH$_3$) 458 (*M*$^+$ + H).

*1-Benzyloxy-4-(2-*tert.*-butyldiphenylsilyloxyethyl)-3-hydroxy-2-pyrrolidinone*.- This was made in the same way as the pyrrolidinone (14), using the above esters (11.3 g, 24.9 mmol), pyridine - borane complex (9 ml, 8.1 g, 87 mmol), 10% aqueous hydrochloric acid (90 ml), sodium methoxide (1.6 g, 29.6 mmol), and benzyl bromide (4 ml, 5.8 g, 33.7 mmol) to give the *pyrrolidinones* (6.4 g, 53 %) as a mixture of isomers (7 : 5 by NMR) as an oil; ∂ (360 MHz, $CDCl_3$) major isomer: 1.04 (9 H, s, ^{t}Bu), 1.53 - 1.62 and 1.61 - 1.70 (2 H, m, OCH$_2$ CH$_2$), 1.65 (1 H, s, OH), 2.22 (1 H, dquin, *J* 6.0 and 8.6 Hz, CHCH$_2$), 2.95 (1 H, t, *J* 8.6 Hz, NCH$_A$H$_B$), 3.32 (1 H, t, *J* 8.6 Hz, NCH$_A$H$_B$), 3.67 (2 H, t, *J* 6 Hz, OCH$_2$), 3.90 (1 H, d, *J* 8.6 Hz, CHOH), 4.97 (1 H, d, *J* 11 Hz, OCH$_A$H$_B$), 5.02 (1 H, d, *J* 11 Hz, OCH$_A$H$_B$), 7.3 - 7.5 and 7. 6 - 7.65 (15 H, m, Ph). Minor isomer: 1.05 (9 H, s, ^{t}Bu), 1.40 - 1.50 and 1.90 - 2.00 (2 H, m, OCH$_2$CH$_2$), 1.65 (1 H, s, OH), 2.44 - 2.56 (1 H, m, CHCH$_2$), 3.09 (1 H, dd, *J* 5.3 and 8.8 Hz, NCH$_A$H$_B$), 3.25 (1 H, dd, *J* 7.0 and 8.8 Hz, NCH$_A$H$_B$), 3.5 - 3.6 (2 H, m, OCH$_2$), 4.21 (1 H, d *J* 7.3 Hz, CHOH), 4.98 (2 H, s, OCH$_2$), 7.3 - 7.5 and 7. 6 - 7.65 (15 H, m, Ph); *m/z* (Cl$^+$, NH$_3$) 490 (*M*$^+$ + H).

*1-Benzyloxy-4-(2-*tert.*-butyldiphenylsilyloxyethyl)-3-(4-methoxybenzylamino)-2-oxo-2,5-dihydropyrrole*.- This was made in the same way as the pyrrole (16) using the above pyrrolidinones (6.11 g, 12.5 mmol), dimethylsulphoxide (3.1 ml, 3.4 g, 50 mmol), trifluoroacetic anhydride (5.3 ml, 7.09 g, 37 mmol), ethyldiisopropylamine (13 ml, 9.7 g, 75 mmol), and 4-methoxybenzylamine (3.4 g, 25 mmol), and purified by flash chromatography, eluting with hexane :

ethyl acetate (5 : 1 v/v) to give the *pyrrole* (5.31 g, 70 %) as an oil; ∂ (250 MHz, $CDCl_3$) 1.01 (9 H, s, ^tBu), 2.40 (2 H, t, *J* 8.3 Hz, $OCH_2C\underline{H}_2$), 3.60 (2 H, t, *J* 8.3 Hz, $OC\underline{H}_2CH_2$), 3.63 (2 H, s, CH_2NO), 3.78 (3 H, s, OMe), 4.22 (2 H, s, $ArCH_2N$), 5.00 (2 H, s, $PhCH_2O$), 6.81 (2 H, d, *J* 8.7 Hz, ArH, H *o* to OMe), 7.12 (2 H, d, *J* 8.7 Hz, ArH, H *m* to OMe), 7.3 - 7.4 and 7.5 - 7.6 (15 H, m, Ph); *m/z* (CI^+, NH_3) 607 ($M^+ + H$).

cis *1-Benzyloxy-4-(2-*tert.*-butyldiphenylsilyloxyethyl)-3-(4-methoxybenzylamino)-2-pyrrolidinone* (28).- This was made in the same way as the pyrrolidinone (17) using the above pyrrole (5.21 g, 8.59 mmol) and platinum (IV) oxide (1 g) to give the *pyrrolidinone* (4.71 g, 90%) as an oil; ∂ (360 MHz, $CDCl_3$) 1.04 (9 H, s, ^tBu), 1.2 - 1.3 and 1.9 - 2.0 (2 H, m, $OCH_2C\underline{H}_2$), 2.35 - 2.45 (1 H, m, $C\underline{H}CH_2$), 2.97 (1 H, dd, *J* 3.0 and 8.9 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.19 (1 H, dd, *J* 6.3 and 8.9 Hz, $CH_A\underline{H}_BNO$), 3.29 (1 H, d, *J* 7.6 Hz, $C\underline{H}NH$), 3.5 - 3.7 (2 H, m, $OC\underline{H}_2CH_2$), 3.74 (2 H, s, $ArCH_2N$), 3.79 (3 H, s, OMe), 4.92 (1 H, d, *J* 11 Hz, $OC\underline{H}_A\underline{H}_BPh$), 4.95 (1 H, d, *J* 11 Hz, $OCH_A\underline{H}_BPh$), 6.83 (2 H, d, *J* 8 Hz, ArH, H *o* to OMe), 7.20 (2 H, d, *J* 8 Hz, ArH, H *m* to OMe), 7.3 - 7.5 and 7.6 - 7.7 (15 H, m, Ph); *m/z* (CI^+, NH_3) 609 ($M^+ + H$).

cis *3-Amino-1-benzyloxy-4-(2-*tert.*-butyldiphenylsilyloxyethyl)-2-pyrrolidinone.*- The pyrrolidinone (28)(3.67 g, 6.04 mmol) and dichlorodicyanobenzoquinone (1.51 g, 6.65 mmol) were stirred together in dichloromethane (50 ml) and water (2 ml) for 1 h. Dichlorodicyanobenzoquinone (0.30 g, 1.3 mmol) and water (7 ml) were added and the mixture stirred for a further 1h, then poured into water and extracted with dichloromethane (5 x 30 ml). The organic layers were filtered, the solids washed thoroughly with methanol (1 l in total) then the combined organic layers evaporated *in vacuo* and purified by flash chromatography, eluting with dichloromethane : methanol (97.5 : 2.5 v/v) to give the *amine* (1.98 g, 67%) as an oil; ∂ (360 MHz, $CDCl_3$) 1.02 (9 H, s, ^tBu), 1.2 - 1.3 and 1.8 - 1.9 (2 H, m, $OCH_2C\underline{H}_2$), 2.3 - 2.35 (1 H, m, $C\underline{H}CH_2$), 3.06 (1 H, dd, *J* 5.0 and 8.7 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.23 (1 H, dd, *J* 6.9 and 8.7 Hz, $CH_A\underline{H}_BNO$), 3.4 - 3.6 (3 H, m, $OC\underline{H}_2CH_2$ and CHN), 4.98 (1 H, d, *J* 11 Hz, $OC\underline{H}_A\underline{H}_BPh$), 5.01 (1 H, d, *J* 11 Hz, $OCH_A\underline{H}_BPh$), 7.3 - 7.7 (15 H, m, Ph); *m/z* (CI^+, NH_3) 489 ($M^+ + H$).

cis *1-Benzyloxy-3-*tert.*-butyloxycarbonylamino-4-(2-hydroxyethyl)-2-pyrrolidinone* (31). The above amine (140 mg, 0.29 mmol), di-*tert.*-butyldicarbonate (0.70 g, 3.2 mmol) and 4-dimethylaminopyridine (25 mg, 0.2 mmol) were stirred in dichloromethane (5 ml) overnight. N,N-Dimethylaminoethylenediamine (3 ml) was added and the mixture stirred for 5 min, diluted with ether, and washed with 1 M citric acid, saturated aqueous sodium hydrogencarbonate, and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting oil was dissolved in THF (3 ml) and tetrabutylammonium fluoride (0.5 ml, 1 M in THF) added. After 1 h the mixture was evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (97.5 : 2.5 v/v) to give the *pyrrolidinone* (103 mg, 90%) as an oil; ∂ (250 MHz, $CDCl_3$) 1.52 (9 H, s, ^tBu), 1.6 - 1.8 (2 H, m, $OCH_2C\underline{H}_2$), 2.6 - 2.7 (1 H, m, $C\underline{H}CH_2$), 3.36 (1 H, dd, *J* 6 and 9 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.6 - 3.7 (3 H, m, $OC\underline{H}_2CH_2$ and $CH_A\underline{H}_BNO$), 4.86 (1 H, d, *J* 10 Hz, CHN), 4.95 (2 H, s, OCH_2Ph), 7.3 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 351 ($M^+ + H$).

cis *1-Benzyloxy-3-*tert.*-butyloxycarbonylamino-4-hydroxymethyl-2-pyrrolidinone* (32).- Tributylphosphine (740 µl, 2.97 mmol) was added to the pyrrolidinone (31)(694 mg, 1.98 mmol) and *o*-nitrophenylselenocyanate (675 mg, 2.97 mmol) in THF (15 ml) at room temperature. After 40 min hydrogen peroxide (500 µl, 30%) was added and the mixture stirred for 3 h. Ether was added and the mixture washed with saturated aqueous sodium hydrogencarbonate solution, water, and brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (99 : 1 v/v) to give *cis* 1-benzyloxy-3-*tert.*-butyloxycarbonylamino-4-vinyl-2-pyrrolidinone (436 mg, 67%) as an oil; ∂ (250 MHz, $CDCl_3$) 1.42 (9 H, s, ^tBu), 3.08 (1 H, d, *J* 9 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.1 - 3.2 (1 H, m, $C\underline{H}CH_2$), 3.45 (1 H, dd, *J* 6 and 9 Hz, $CH_A\underline{H}_BNO$), 4.32 (1 H, t, *J* 7 Hz, CHN), 4.98 (1 H, d, *J* 7 Hz, NH), 5.00 (1 H, d, *J* 12 Hz, $OC\underline{H}_A\underline{H}_BPh$), 5.01 (1 H, d, *J* 12 Hz, $OCH_A\underline{H}_BPh$), 5.1 - 5.2 (2 H, m, $C{=}CH_2$), 5.46 (1 H, ddd, *J* 8, 10, and 16 Hz, $C\underline{H}{=}C$), 7.3 - 7.4 (5 H, m, Ph). 419 mg (1.26 mmol) of this oil was dissolved in methanol (15 ml) and dichloromethane (15 ml), cooled to -78 °C, then ozone passed through until a blue colour persisted. Nitrogen was passed through until the colour dissipated, then sodium borohydride (200 mg, 5.3 mmol) was added and the mixture stirred at room temperature for 3 h. The mixture was diluted with dichloromethane, washed with 1 M citric acid, saturated aqueous sodium hydrogencarbonate solution, water, and brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (97 : 3 v/v) to give the *alcohol* (297 mg, 71%) as an oil; ∂ (360 MHz, $CDCl_3$) 1.45 (9 H, s, ^tBu), 2.6 - 2.7 (1 H, m, $C\underline{H}CH_2$), 3.26 (1 H, dd, *J* 2.1 and 9.2 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.38 (1 H, dd, *J* 7.2 and 9.2 Hz, $CH_A\underline{H}_BNO$), 3.48 (1 H, dd, *J* 5.4 and 11.2 Hz, $C\underline{H}_A\underline{H}_BOH$), 3.59 (1 H, dd, *J* 4.7 and 11.2 Hz, $CH_A\underline{H}_BOH$), 4.32 (1 H, t, *J* 8 Hz, $C\underline{H}N$, goes to d, *J* 8 Hz on D_2O shake), 5.01 (2 H, s, OCH_2Ph), 5.10 (1 H, d, *J* 8 Hz, NH, disappears on D_2O shake), 7.3 - 7.5 (5 H, m, Ph); irradiation of either methine proton gives a positive nOe to the other; *m/z* (CI^+, NH_3) 337 ($M^+ + H$).

cis *3-Amino-1-hydroxy-4-hydroxymethyl-2-pyrrolidinone* (25).- The pyrrolidinone (31)(60 mg, 178 µmol) was dissolved in trifluoroacetic acid (3 ml). After 30 min the acid was evaporated, and the residue dissolved in methanol (15 ml) then hydrogenated on palladium (20 mg) at 50 p.s.i. for 3 h. The mixture was filtered, evaporated *in vacuo*, and purified on DOWEX 50W-X8, and freeze dried to give the *pyrrolidinone* (23 mg, 88%) as a white foam; ∂ (360 MHz, D_2O) 2.7 - 2.8 (1 H, m, $C\underline{H}CH_2$), 3.44 (1 H, dd, *J* 3.4 and 10.2 Hz, $C\underline{H}_A\underline{H}_BNO$), 3.74 (1 H, dd, *J* 6.5 and 11.4 Hz, $C\underline{H}_A\underline{H}_BOH$), 3.75 (1 H, dd, *J* 6.8 and 10.2 Hz, $CH_A\underline{H}_BNO$), 3.82 (1 H, dd, *J* 6.0 and 11.4 Hz, $CH_A\underline{H}_BOH$), 3.93 (1 H, d, *J* 8.6 Hz, CHN); *m/z* (CI^+, NH_3) 147 ($M^+ + H$).

cis *1-Benzyloxy-4-(2-hydroxyethyl)-3-(4-methoxybenzylamino)-2-pyrrolidinone*.- The silyl ether (28)(4.71 g, 7.7 mmol) and tetrabutylammonium fluoride (10 ml, 1M in THF) were stirred in THF (100 ml) for 1 h. Ether was added, the mixture washed with water, and brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with dichloromethane : methanol (96 : 4 v/v) to give the *alcohol* (1.98 g, 69%) as an oil; ∂ (250 MHz, $CDCl_3$) 1.4 - 1.5 and 1.8 - 1.9 (2 H, m, OCH_2CH_2), 2.4 - 2.5 (1 H, m, $CHCH_2$), 2.96 (1 H, dd, *J* 4 and 10 Hz, CH_AH_BNO), 3.4 - 3.8 (4 H, m, CH_AH_BNO, CHN, and OCH_2CH_2), 3.80 (3 H, s, OMe), 3.84 (2 H, s, NCH_2), 5.02 (2 H, s, OCH_2), 6.87 (2 H, d, *J* 8 Hz, ArH, H *o* to OMe), 7.28 (2 H, d, *J* 8 Hz, ArH, H *m* to OMe), 7.3 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 371 ($M^+ + H$).

cis *3-Amino-1-hydroxy-4-(2-hydroxyethyl)-2-pyrrolidinone* (26).- The above alcohol (70 mg, 0.19 mmol) was hydrogenated on Pearlman's catalyst (70 mg) in methanol (20 ml) and acetic acid (30 µl) at 50 p.s.i. for 20 h, filtered, evaporated in vacuo, purified on DOWEX 50W-X8, and freeze dried to give the pyrrolidinone (18.5 mg, 56%) as a white foam. Toluenesulphonic acid (24.7 mg) in water was added and the solution freeze dried to give the tosylate salt as a foam; ∂ (360 MHz, D_2O) 1.7 - 1.9 (2 H, m, OCH_2CH_2), 2.39 (3 H s, ArMe), 2.9 - 3.0 (1 H, m, $CHCH_2$), 3.52 (1 H, dd, J 3.7 and 9.9 Hz, CH_AH_BNO), 3.6 - 3.8 (2 H, m, OCH_2), 3.86 (1 H, dd, J 7.2 and 9.9 Hz, CH_AH_BNO), 4.25 (1 H, d, J 8.8 Hz, NCH), 7.36 (2 H, d, J 8.1 Hz, ArH), 7.68 (2 H, d, J 8.1 Hz, ArH); m/z (FAB^+) 161 ($M^+ + H$).

cis *3-Benzyloxy-6-(4-methoxybenzyl)-4-oxo-3,6-diazabicyclo[3.3.0]octane* (29).- Tributylphosphine (26 mg, 129 µmol) was added to a solution of *cis* 1-benzyloxy-4-(2-hydroxyethyl)-3-(4-methoxybenzylamino)-2-pyrrolidinone (32 mg, 86 µmol) and *o*-nitrophenylselenocyanate (29 mg, 130 µmol) in THF (0.5 ml) at room temperature. After 1 h the mixture was evaporated *in vacuo* and purified by preparative thin layer chromatography, eluting with methanol : dichloromethane (95 : 5 v/v) to give the *bicyclooctane* (18.3 mg, 60 %) as an oil; ∂ (250 MHz, $CDCl_3$) 1.3 - 1.5 (1 H, m, H-8), 2.0 - 2.1 (1 H, m, H-1), 2.35 - 2.45 (1 H, m, H-8), 2.6 - 2.8 (2 H, m, H-7), 2.98 (1 H, dd, *J* 4 and 10 Hz, H-2), 3.32 (1 H, d, *J* 11 Hz, H-5), 3.46 (1 H, t, *J* 10 Hz, H-2), 3.74 (1 H, d, *J* 13 Hz, NCH_AH_BAr), 3.81 (3 H, s, OMe), 4.18 (1 H, d, *J* 13 Hz, NCH_AH_BAr), 5.00 (1 H, d, *J* 12 Hz, OCH_AH_B), 5.02 (1 H, d, *J* 12 Hz, OCH_AH_B), 6.86 (2 H, d, *J* 8 Hz, ArH, H *o* to OMe), 7.27 (2 H, d, *J* 8 Hz, ArH, H *m* to OMe), 7.4 - 7.5 (5 H, m, Ph); *m/z* (CI^+, NH_3) 353 ($M^+ + H$).

cis *3-Hydroxy-4-oxo-3,6-diazabicyclo[3.3.0]octane* (30).- Bicyclooctane (29)(57 mg, 162 µmol) was hydrogenated at 50 p.s.i. on Pearlman's catalyst (60 mg) in methanol (10 ml) and acetic acid (30 µl) for 17 h. The catalyst was removed by filtration, the solution evaporated, and the product purified on DOWEX 50W-X8 to give the *bicyclooctane* (22.6 mg, 98 %) as a white foam. *p*-Toluenesulphonic acid hydrate (30.2 mg) was added to a solution of the product in water, and the mixture freeze dried to give the tosylate salt; ∂ (250 MHz, D_2O) 1.9 - 2.0 (1 H, m, H-8), 2.38 (3 H, s, $ArCH_3$), 2.4 - 2.5 (1 H, m, H-8), 3.1 - 3.2 (1 H, m, H-1), 3.3 - 3.4 (2 H, m, H-7), 3.52 (1 H, d, *J* 10 Hz, H-2), 3.93 (1 H, dd, *J* 8 and 10 Hz, H-2), 4.56 (1 H, d, *J* 10 Hz, H-5), 7.36 (2 H, d, *J* 8 Hz, ArH), 7.68 (2 H, d, *J* 8 Hz, ArH); *m/z* (FAB^+) 143 ($M^+ + H$).

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