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Synthesis of Kainoid Analogues

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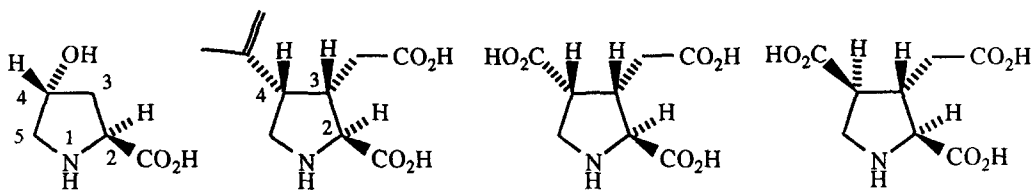
Abstract : 4-oxoproline has been used as a chiral template in a synthesis of kainoid analogues which are epimeric with the parent compound at C-3.

We are prompted by the recent publication of the work of Baldwin and Rudolf[2] to report our studies on the use of the cheap and readily available (2S, 4R)-4-hydroxyproline (**1**) as a template for the stereospecific synthesis of kainate analogues.

The kainoids are a class of excitatory non-proteinogenic amino acids which act at one of the sub-types of glutamate receptor.[3] The excitatory effects of the KAIN receptor are mediated by depolarisation of the post-synaptic membrane, the 'parent' agonist being kainic acid (**2**). The majority of active compounds in the series have the same (2S, 3S, 4S) stereochemistry as kainic acid (**2**), although it has been shown that the epimeric triacids (**3**) and (**4**) have similar potency as glutamate agonists.[4] We therefore wished to develop a reliable synthetic route to kainoids of varied but well-defined stereochemistry and chose L-*trans*-4-hydroxyproline (**1**) as our starting point. The potentiation of activity noted[5,6] when an aryl substituent was present at C-4 made 4-aryl analogues of especial interest.



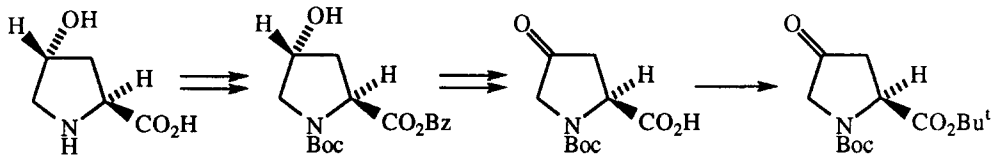
(**1**) (**2**) (**3**) (**4**)

Because of the medicinal interest in this series of compounds and the synthetic challenge presented by the three chiral centres, many syntheses of kainoids have been completed. The majority of these access the pyrrolidine ring by a variety of ingenious cyclisation reactions in which the three chiral centres are created in a controlled manner. The apparently simpler strategy of using a preformed pyrrolidine ring containing one chiral

centre to access the other side chains is rarer but both (2S)-pyroglutamic acid[7,8] and L-*trans*-4-hydroxyproline (**1**)[2,6] have been used in this way.

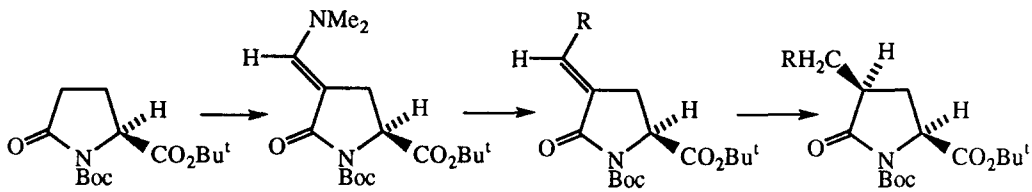
Our interest in glutamate agonists and antagonists[9,10] led us to consider kainoids as appropriate synthetic targets and we wished to prepare both the natural and epimeric series of compounds for structure / activity studies. L-*trans*-4-Hydroxyproline (**1**) was an attractive starting point, and our first target was to prepare compounds which are epimers of the naturally occurring series at C-3.

Since a carbonyl group at C-4 of L-proline should allow development of side chains at both C-3 and C-4, *tert*-butyl N-*tert*-butoxycarbonyl-4-oxoprolinate (**7**) was prepared from the corresponding acid (**6**), either by adaptation of the method of Witkop for the N-carbobenzyloxy compound[11] or by the method of Herdewijn.[12] Neither method proved reproducible on a large scale and we found a more reliable route[13] to be that shown in Scheme 1. Here the benzyl ester (**5**) was prepared from N-*tert*-butoxycarbonyl-4-hydroxyproline[14] and oxidised to the corresponding ketone using chromium trioxide and pyridine. Hydrogenolysis then gave the acid (**6**) which was converted to the *tert*-butyl ester (**7**) in 76% yield using *tert*-butanol, DMAP and dicyclohexylcarbodiimide in dichloromethane.



Scheme 1

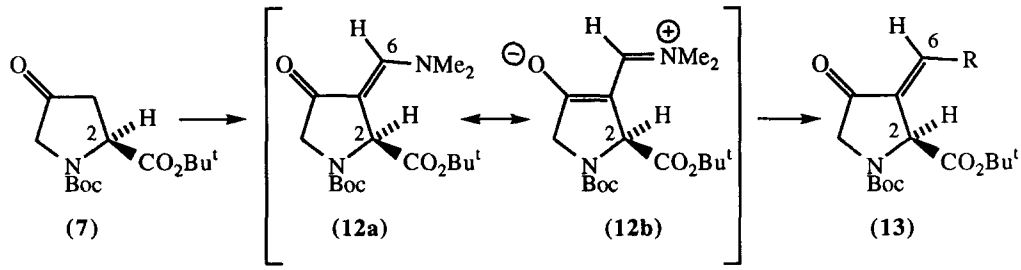
We have recently developed methods to prepare derivatives of pyroglutamic acid which are stereospecifically substituted at C-4 and have used these in the synthesis of naturally occurring non-proteinogenic amino acids as outlined in Scheme 2.[15,16] Here conversion of the protected proglutamic acid derivative (**8**) to the enaminone (**9**) and reaction with Grignard reagents yielded the 4-alkylidene derivatives (**10**). These could be reduced stereospecifically to the *cis*-4-substituted compounds (**11**).



Scheme 2

If this methodology were applicable to the 4-ketoproline derivative (**7**), then we would be able to synthesise compounds with a side chain at C-3 of known stereochemistry. We therefore reacted the ketone (**7**)

with Bredereck's reagent, as shown in Scheme 3, and obtained the enaminone **(12)** in 77% yield. The NMR spectra of this compound were complicated by the well known[17] conformational isomerism shown by N-acylproline derivatives but nOe experiments in the ^1H NMR spectrum showed an enhancement of the NMe_2 singlet when H-2 was irradiated, indicating that the compound was the E-isomer **(12)**.



Scheme 3

Reaction of the enaminone **(12)** with MeMgBr and PhMgBr respectively led to the 1,4-addition / elimination sequence which we had already observed[15] in Grignard reactions of vinylogous amides in the pyroglutamate series and no addition to the ketonic carbonyl group occurred. Since Grignard attack might be expected to be directed in a 1,2 sense, this may indicate the importance of the resonance form **(12b)** in directing the regiospecificity of these reactions. The ethylidene derivative **(13, R=Me)** was obtained in 50% yield from this reaction and nOe experiments showed it to be mainly the E-isomer, since irradiation of the proton H-2 at δ 5. 1 ppm caused an enhancement of 1. 3% in the methyl doublet at δ 2. 04 ppm. There was also *ca.* 8% of the Z-isomer present.

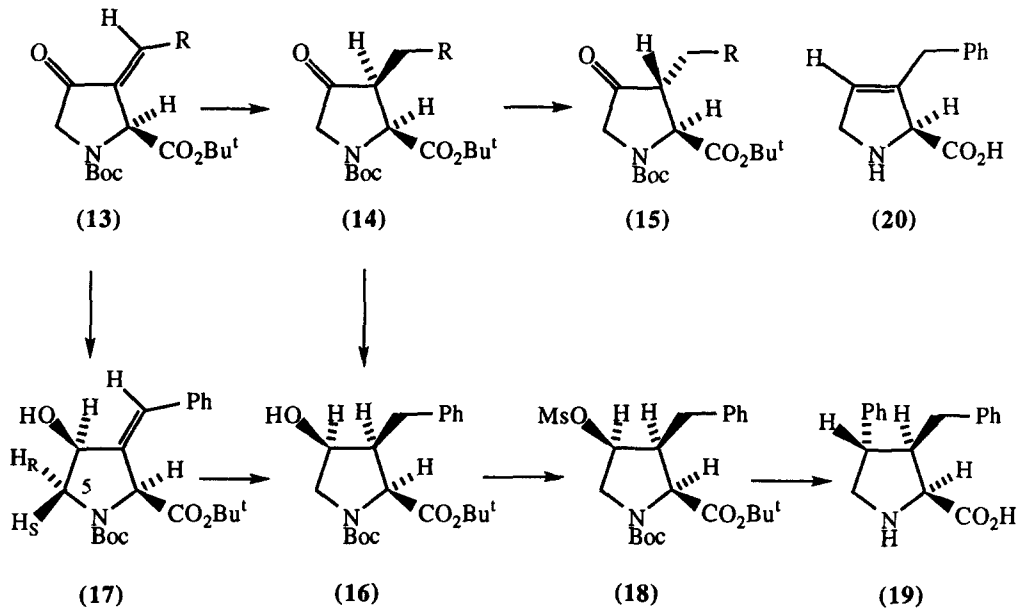
Hydrogenation using 10% palladium on carbon gave the 3-ethyl compound **(14, R=Me)** in 94% yield. The (3S)-stereochemistry for this compound was indicated by an nOe of 7. 4% at δ 2. 65 ppm for H-3 when the proton, H-2, at δ 4. 65 ppm was irradiated.

The 3-E-benzylidene compound **(13, R=Ph)** was obtained in 74% yield from the Grignard reaction using PhMgBr. This was uncontaminated with the Z-isomer and hydrogenation gave the (3S)-benzyl compound **(14, R=Ph)** in quantitative yield. Attempted purification by chromatography on silica gel caused epimerisation at C-3 giving a mixture of **(14, R=Ph)** and **(15, R=Ph)** which proved to be inseparable. The stereochemical instability at C-3 in such compounds had been indicated by other work[18] and the acidity at this centre is well known. Attempts to obtain the thermodynamically more stable (3R)-isomer in reasonable yield by equilibration under a variety of conditions was unsuccessful. The (3S)-diastereoisomer obtained directly from this reaction was very pure and it proved to be stable on storage. We considered the benzyl side chain to be a potential precursor of the acetate group found at C-3 in kainoids as we had effected conversion of a similar side chain to acetate in related compounds in the pyroglutamic acid series.[16]

Reduction of the unchromatographed (3S)-isomer **(14, R=Ph)** using sodium borohydride gave a mixture of diastereoisomers from which the major isomer **(16)** could be isolated in 32% yield. Irradiation of H-2 of the alcohol **(16)** at δ 4. 3 ppm caused an enhancement of 8. 3% at δ 2. 51 ppm due to H-3. The absorption for H-3

also showed an enhancement of 5. 8% when H-4 at δ 3. 95 ppm was irradiated. All three side chains were thus in a *cis* relationship and we had isolated the (2S, 3S, 4S) isomer.

The apparent lack of stereospecificity in the borohydride reduction might in fact be ascribed to the inherent acidity at C-3 in the ketone (**14, R=H**) causing epimerisation at C-3. Since this epimerisation would be avoided by reducing the ketone function before the olefinic group, the benzylidene derivative (**13, R=Ph**) was first reduced with sodium borohydride in methanol and diethyl ether. A single diastereoisomeric product (**17**) was obtained in 82% yield from this reaction, together with 8% of the fully reduced compound (**16**). The stereochemistry of the alcohol (**17**) was indicated by an nOe experiment, since irradiation of H-2 at δ 5. 1 ppm caused a long range enhancement to H-5R at δ 3. 55 ppm. This same proton, H-5R exhibited an nOe of 4. 1% when H-4 at δ 4. 51 ppm was irradiated. The alcohol was therefore *cis* to the ester function at C-2 in the product (**17**). Hydrogenation then proceeded to give the single diastereoisomeric alcohol (**16**) in quantitative yield.

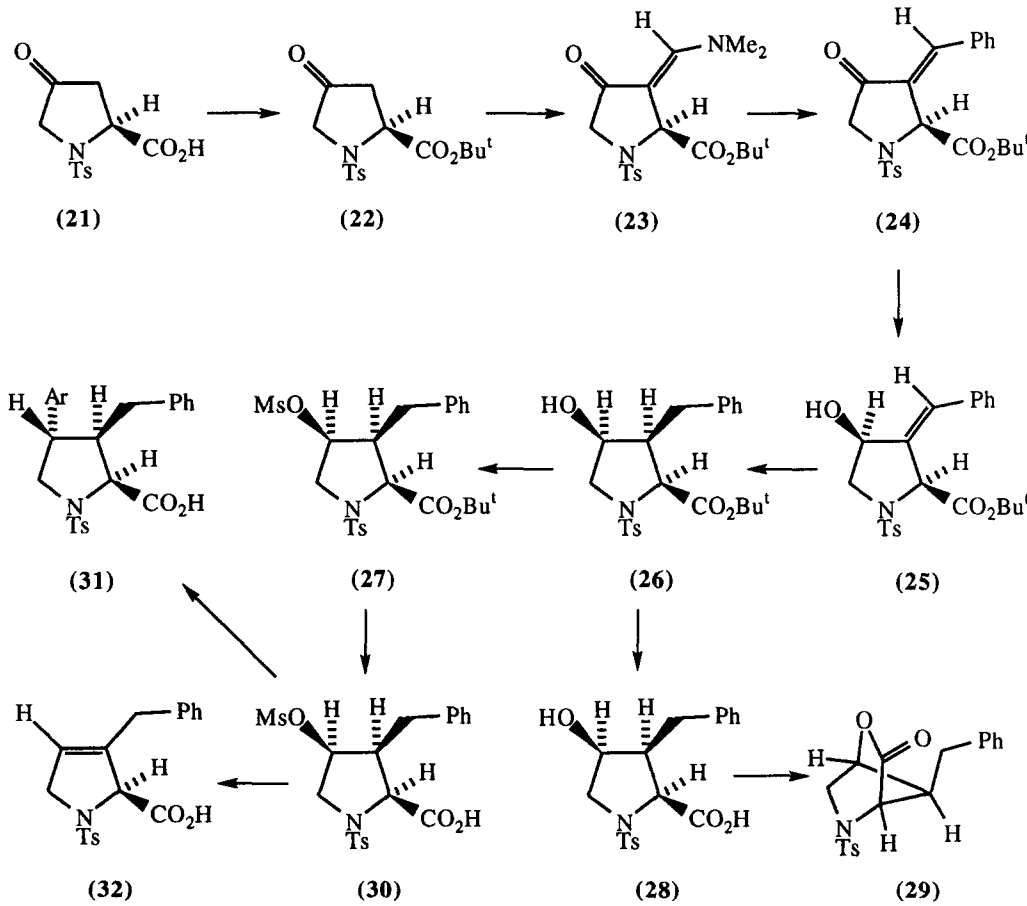


Scheme 4

The sequence was now entirely stereospecific, giving a compound (**16**) with three centres of well-defined stereochemistry and so we proceeded to investigate the introduction of an aromatic substituent at C-4. The alcohol (**16**) was therefore converted to the mesylate (**18**) in 48% yield using lithium hexamethyldisilazide and methanesulfonyl chloride. Attempted displacement of the mesylate by Grignard reagents or organocuprates to obtain kainoid analogues containing a variety of substituents at C-4 of well-defined stereochemistry proved unsuccessful. A report[19] that N-acylproline-4-mesylates underwent Friedel Crafts reaction with inversion of configuration, however, encouraged us to investigate this reaction on the 3-substituted ester (**18**). Reaction with aluminium chloride in benzene gave the aryl free acid (**19**) as a single diastereoisomer in 24% yield together with

a 23% yield of the product (**20**) of elimination. The coupling constants were in accord with assignment of (2S, 3R, 4S) stereochemistry to the product (**19**).

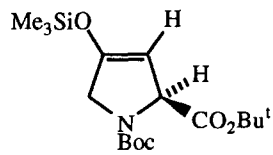
Neither protecting group had survived in the product (**19**) and, since the original high-yielding Friedel Crafts reaction had been conducted on an N-acyl free acid, we felt that the reaction might be improved if a free acid containing an alternative N-protecting group were used as a substrate for the reaction. We therefore prepared N-*para*-toluenesulfonyl-4-oxoproline (**21**) by the method of Andreatta *et al.*[20] and converted it to the corresponding (2S, 3S, 4S)-3-benzyl-4-mesylate (**27**) using a parallel series of reactions to that used in the N-*tert*-butoxycarbonyl protected series and shown in Scheme 5. The NMR spectra for the compounds in this series were uncomplicated by the conformational isomerism shown by the corresponding urethanes. The stereochemistry of all compounds in the scheme was confirmed by nOe experiments and that of the alcohol (**26**) was also defined by conversion to the acid (**28**) and cyclisation to the lactone (**29**).



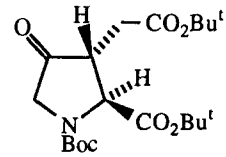
Scheme 5

The mesylate (**27**) was converted to the acid (**30**) using trifluoroacetic acid and this was reacted with benzene or anisole and aluminium chloride. The adducts (**31**) could not be purified from these reactions, the only identifiable product being the olefin (**32**). Reaction of Grignard reagents or organocuprates with the mesylates again failed to yield useful products.

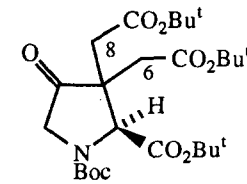
Having used the 4-oxoprolinate template to prepare kainate analogues with three chiral centres, we now turned our attention to the 3-*epi* series which has the same stereochemistry as natural kainic acid. Reaction of the anion of the ketone (**7**) with electrophiles might be expected to occur from the less hindered face to give this stereochemistry but attempts at direct alkylation with *tert*-butyl bromoacetate gave mixtures of products, a strong absorption at λ_{max} 256 nm suggesting that aldol self-condensation may have occurred. We therefore converted the ketone (**7**) to the silylenol ether (**33**) using lithium diisopropylamide and trimethylsilyl chloride in tetrahydrofuran. The enol ether was a single isomer and, since the characteristic absorption for the C-5 protons was still present in the ^{1}H NMR spectrum, it was evidently the $\Delta^{3,4}$ isomer (**33**). The enol ether (**33**) was reacted with *tert*-butyl bromoacetate in the presence of benzyltrimethylammonium fluoride . A small yield of the dialkylated product (**35**) was obtained, presumably due to the monoalkylated product (**34**) being sufficiently acidic to compete with the silylenol ether (**33**) for the *tert*-butyl bromoacetate.



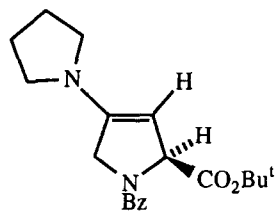
(**33**)



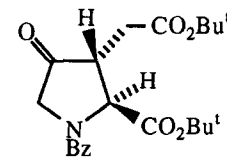
(**34**)



(**35**)



(**36**)



(**37**)

At this point, stereospecific alkylation of 4-oxoproline derivatives from the less hindered face was achieved by Baldwin and Rudolf,[2] who found that the enamine (**36**), on reaction with *tert*-butyl bromoacetate followed by hydrolysis, gave monoalkylated products with better stereospecificity than had been found for a related enamine by previous workers.[18] The *trans*-alkylated ketone (**37**) was obtained and so the enamine (**36**) was a better substrate for such reactions than we had found the silylenol ether (**33**) to be.

Experimental

Melting points were determined on a Kofler hot stage, and optical rotations on a Perkin Elmer PE 241 polarimeter using a 1 dm path length. IR-spectra were recorded on a Perkin Elmer 1710 Fourier transform instrument and U.V. spectra on Philips PU 8720 or Unicam UV 2-100 spectrophotometers. ^{1}H NMR spectra were determined on a Brucker WM 360 instrument (360 MHz) and ^{13}C-NMR spectra on Bruker AC-P 250 (62.88 MHz) and AMX-500 (125.76 MHz) instruments with INEPT experiments to help assign the spectra and residual solvent peaks as internal references. *J* values are given in Hz. Mass spectra were recorded on Kratos MF 80RF or Fisons VG-Autospec instruments by Mr A. M. Greenway and Dr. A. Abdul-Sada (Sussex) and on Kratos MS50 and Fisons VG BIO Q instruments by Drs D. Dell and D. Cooper at Wellcome Research Laboratories. Accurate mass measurements were run on a Kratos Concep 15 instrument by Dr. S. Chotai (Wellcome) and microanalyses were performed by Miss M. Patel (Sussex) and Miss W. C. Man and Mrs C. Lawless (Wellcome). Column chromatography was performed using Merck Kieselgel 60 (230-400 mesh - Art 9385).

Benzyl (2S,4R)-N-*tert*-Butoxycarbonyl-4-hydroxyprolinate (5)[13] - (2S,4R)-N-*tert*-butoxycarbonyl-4-hydroxyproline[14] (39. 1 g, 0. 17 mol) was dissolved in methanol (500 ml) at room temperature and distilled water (80 ml) was added. Sufficient 20% aqueous caesium carbonate was added to adjust the pH to 7. The solution was concentrated and dimethyl formamide (500 ml and 250 ml) was added to azeotrope the water leaving a white solid which was dissolved in dimethyl formamide (430 ml). Benzyl bromide (22. 29 ml, 0. 19 mol) was added and the mixture was stirred vigorously at room temperature for 20 h. The solvent was removed *in vacuo*, the residue was washed with water (250 ml) and dissolved in ethyl acetate (500 ml). The organic phase was washed with water (300 ml) and saturated aqueous sodium chloride (300 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to produce a colourless oil (53. 4 g, 95%), $[\alpha]_D^{25}$ - 63. 34 (*c* 1, $CHCl_3$); (Found m / z 321. 15858. $C_{17}H_{23}NO_5$ requires m / z 321. 15762); ν_{max} (film) / cm^{-1}, 1747 (ester), 1703 and 1690 (urethane); δ_H (360MHz, C^2HCl_3), 1. 31 and 1. 42 (9H, 2 x s, -C(C$\underline{H}_3$)$_3$), 2. 03 (1H, m, $J_{3A,2}$ 8. 6, $J_{3A,3B}$ 16. 3, $\underline{H}$-3$_A$), 2. 28 (1H, m, $J_{3B,3A}$ 16. 3, $\underline{H}$-3$_B$), 3. 0 (br, exch., 4-OH), 3. 45 (1H, m, $J_{5A,5B}$ 11. 6, $\underline{H}$-5$_A$), 3. 55 (1H, m, $J_{5B,4}$ 4. 2, $J_{5B,5A}$ 11. 6, $\underline{H}$-5$_B$), 4. 49 (2H, m, $J_{2,3A}$ 8. 6, $\underline{H}$-2 and $\underline{H}$-4), 5. 13 (2H, 2 x AB, $J_{A,B}$ 12. 23, C$\underline{H}_2$Ph) and 7. 38 (5H, m, Ar); δ_C (125. 76MHz, C^2HCl_3), 28. 03 and 28. 24 (C($\underline{C}H_3$)$_3$), 38. 19 and 38. 90 (3-$\underline{C}H_2$), 54. 48 and 54. 55 (5-$\underline{C}H_2$), 57. 62 and 57. 95 (2-$\underline{C}H$), 66. 64 ($\underline{C}H_2$Ph), 68. 6 and 69. 69 (4-$\underline{C}H$), 80. 11 and 80. 34 ($\underline{C}$(CH$_3$)$_3$), 127. 92, 128. 04, 128. 20, 128. 29, 128. 34 and 128. 47 (Ar, $\underline{C}H$), 135. 3 and 135. 55 (CH$_2\underline{C}$), 154. 0 and 154. 49 (N$\underline{C}O_2$R) and 172. 63 and 172. 90 (CO_2R).

Benzyl (2S)-N-*tert*-Butyloxycarbonyl-4-oxoprolinate[13] - Pyridine (270 ml) in dichloromethane (1 l) was cooled to 0 °C and CrO_3 (160 g, 1. 6 mol) was added slowly with stirring over a period of 30 min. The mixture was allowed to warm to room temperature and benzyl (2S,4R)-N-*tert*-butoxycarbonyl-4-hydroxyprolinate **(5)** (61. 5 g, 0. 192 mol) in dichloromethane (1 l) was added at once. The reaction was stirred vigorously for 4h at room temperature and the dark solid formed was decanted and washed with dichloromethane (2 x). The organic phases were washed with saturated aqueous $NaHCO_3$ (3 x), 10% aqueous citric acid (2 x) and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield an oily residue which was dissolved in

diethyl ether and filtered through Celite. Removal of the solvent *in vacuo* gave a brown oil (52. 4 g, 86%), a sample of which was purified by chromatography (silica gel - petroleum ether (60-80) : EtOAc, 5 : 1) to give a colourless oil (77.5%). This oil appeared to be unstable on standing for two weeks at room temperature, $[\alpha]_D^{20}$ -5. 4 (*c* 1, $CHCl_3$); m / z [FAB] 320 ($M + H^+$); ν_{max} (film) / cm^{-1} 1767 (ketone), 1747 (ester), 1703 (urethane); δ_H (360MHz, C^2HCl_3 -20°C) 1. 33 and 1. 46 (9H, 2 x s, $C(CH_3)_3$), 2. 58 and 2. 62 [1H, 2 x d x d,(*J* 2. 4 and 15. 5) and (*J* 2. 4 and 15. 5), H-3_A], 2. 97 and 3. 00 (1H, 2 x d x d, *J* 10. 6 and 15. 5, H-3_B), 3. 90 and 3.93 (2H, 2 x d, *J* 10. 3 and 13. 2, H-5), 4. 74 and 4. 86 [1H, 2 x d x d,(2 x *J* 2. 4 and 10. 6), H-2], (5. 09 and 5. 26) and (5. 15 and 5. 19) (2H, 2 x AB, *J* 12. 2, CH_2Ar), 7. 32 - 7. 40 (5H, m, Ar-H); δ_C (125. 76MHz, C^2HCl_3, -20 °C) 27. 84 and 28. 07 ($C(CH_3)_3$), 40. 58 and 41. 06 (C-3), 52. 36 and 52. 76 (C-5), 55. 33 and 55. 98 (C-2), 67. 34 and 67. 39 (CH_2-Ar), 81. 30 and 81. 34 ($C(CH_3)_3$), 128. 20, 128. 50, 128. 57, 128. 65 and 128. 70 (Ar, C-H), 134. 53 and 134. 60 (C-Ar), 153. 36 and 154. 13 (NCO_2R), 171. 49 and 171. 62 (CO_2R), 208. 37 and 209. 15 (C=O)

(2S)-N-*tert*-Butyloxycarbonyl-4-oxoproline (6)[13] - A solution of crude benzyl (2S)-N-*tert*-butyloxycarbonyl-4-oxoproline (42 g, 0. 132 mol) in ethyl acetate (500 ml) was hydrogenated for 24 h in the presence of 10% palladium on carbon (8. 4 g). The solution was filtered through Celite and the solvent was removed *in vacuo* to yield a residue which was recrystallised from diethyl ether as a white solid (27. 1 g, 90%); m.p 160-162°C (dec); $[\alpha]_D^{24}$ + 20. 9 (*c* 0. 49, $(CH_3)_2CO$), (Found C, 52. 5; H, 6. 8; N, 5. 9. $C_{10}H_{15}NO_5$ requires C, 52. 4; H, 6. 6; N, 6. 1%); m / z (FAB, glycerol) 230 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1769 (ketone), and 1752 (urethane); δ_H (360MHz, $(C^2H_3)_2CO$) 1. 39 and 1. 42 (9H, 2 x s, $C(CH_3)_3$), 2. 52 (1H, d x d, *J* 5. 5 and 18. 5, H-3_R), 3. 07 and 3. 11 (1H, 2 x d x d, *J* 10. 7 and 18. 5, H-3_S), 3. 69 and 3. 79 and 3. 71 and 3. 85 (2H, 2 x AB, *J* 18.5, H-5), 4. 70 and 4. 73 (1H, 2 x d x d, *J* 5. 5 and 10.7, H-2); δ_C (125. 76MHz, $(C^2H_3)_2CO$), 28. 41 [$C(CH_3)_3$], 41. 26 and 41. 78 (C-3), 53. 02 and 53. 41 (C-5), 56. 57 and 57. 20 (C-2), 80. 87 ($C(CH_3)_3$), 154. 36 and 155. 10 (NCO_2R), 173. 52 and 173. 74 (COOH), and 208. 41 and 209. 06 (C=O).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-4-oxoprolinate (7)** (2S)-N-*tert*-Butoxycarbonyl-4-oxoproline (**6**) (5 g, 21. 8 mmol) was dissolved in dry dichloromethane (100 ml) and cooled to 0 °C in an atmosphere of nitrogen. *tert*-Butanol (6. 3 ml, 68 mmol) and 4-dimethylaminopyridine (0. 265 g, 2. 1 mmol) were added followed by *N,N*-dicyclohexylcarbodiimide (4. 85 g, 22. 8 mmol) over 5 min. The mixture was stirred at room temperature for 3 h. The DCU was removed by filtration and the filtrate was washed with 0. 05% aqueous citric acid (2 x 60 ml), saturated aqueous sodium hydrogen carbonate (2 x 60 ml) and water (2 x 60 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by column chromatography (silica gel - dichloromethane : diethyl ether, 95 : 5) and recrystallisation from petroleum ether (60 - 80°) gave a white solid (4. 83 g, 78 %), m.p. 67-68 °C; $[\alpha]_D^{25}$ + 10. 65 (*c* 1.23, $CHCl_3$); (Found C, 58. 8; H, 8. 2; N, 4. 7. $C_{14}H_{23}NO_5$ requires C, 58. 9; H, 8. 1; N, 4. 9%); m / z [+ve FAB (3-nba)] 286 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1766 (ketone), 1733 and 1707 (ester) and 1692 (urethane); δ_H (360MHz, C^2HCl_3), 1. 42 (18H, 2 x s, $C(CH_3)_3$), 2. 5 (1H, d, $J_{3S,3R}$ 18. 8, H-3_S), 2. 89 (1H, m, $J_{3R,2}$ 10. 4, $J_{3R,3S}$ 18. 8, H-3_R), 3. 85 (2H, m, H-5) and 4. 55 and 4. 63 (1H, 2 x d, $J_{2,3R}$ 10. 4 H-2); δ_C (125. 76MHz, C^2HCl_3), 27. 88 and 28. 23

($C(\underline{C}H_3)_3$), 40. 87 and 41. 40 (3-$\underline{C}H_2$), 52. 51 and 52. 95 (5-$\underline{C}H_2$), 56. 56 and 57. 03 (2-$\underline{C}H$), 81. 03 and 82. 36 ($\underline{C}(CH_3)_3$), 153. 65 and 154. 34 ($N\underline{C}O_2R$), 170. 84 and 170. 92 ($\underline{C}O_2R$) and 208. 18 and 209. 0 (4-$\underline{C}$=O).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-3-dimethylaminomethylene-4-oxoprolinate (12)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-4-oxoprolinate **(7)** (4. 8 g, 0. 017 mol) was dissolved in dry dimethoxyethane (200 ml) under an atmosphere of nitrogen and *tert*-butoxy-*bis*-(dimethylamino)-methane (6. 6 ml, 0. 032 mol) was added. The mixture was stirred at 70 °C for 4 h, cooled and the solvent was removed *in vacuo*. The resultant orange oil was purified by column chromatography (silica gel - ethyl acetate) and recrystallised from petroleum ether (60-80 °C) as a white solid (4. 4 g, 77%), m.p. 94 - 95 °C ; $[\alpha]_D^{27}$ + 44. 56 (*c* 0. 25, MeOH); (Found C, 60. 1 ; H, 8. 3 ; N, 8. 1. $C_{17}H_{28}N_2O_5$ requires C, 60. 0 ; H, 8. 2 ; N, 8. 2%); m / z [+ve FAB (3-nba)] 341 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1728 (ketone), 1688 (ester) and 1655 (urethane); λ_{max} (MeOH) / nm, 316 (ε 27, 509); δ_H (360MHz, C^2HCl_3), 1. 42 - 1. 48 (18H, 4 x s, -C($\underline{C}H_3)_3$), 3. 22 (6H, br s, N($\underline{C}H_3)_2$), 3. 85 (2H, m, $\underline{H}$-5), 5. 19 and 5. 29 (1H, 2 x s, $\underline{H}$-2) and 7. 37 (1H, m, $\underline{H}$-6); δ_C (62., 88MHz, C^2HCl_3), 27. 86, 27. 88 and 28. 36 (C($\underline{C}H_3)_3$), 52. 66 and 53. 13 (5-$\underline{C}H_2$), 61. 18 and 61. 65 (N($\underline{C}H_3)_2$), 77. 25 (2-$\underline{C}H$), 80. 34, 80. 55, 81. 70 and 81. 83 ($\underline{C}(CH_3)_3$), 98. 39 and 98. 65 (3-$\underline{C}$=CH), 147. 34 and 147. 38 (6-$\underline{C}H$) 156.2. 0 ($N\underline{C}O_2R$), 171. 38 ($\underline{C}O_2R$) and 195. 55 and 196. 03 (4-$\underline{C}$=O).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-3-ethylidene-4-oxoprolinate (13, R = Me)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-3-dimethylaminomethylene-4-oxoprolinate **(12)** (0. 7 g, 2. 05 mmol) was dissolved in dry diethyl ether (35 ml) under an atmosphere of nitrogen and cooled to -78 °C. Methylmagnesium bromide (3 *M* in diethyl ether; 2. 03 ml, 6. 09 mmol) was added dropwise and the mixture was stirred at -78 °C for 1 h, allowed to warm to room temperature and stirred for a further 5 h. The mixture was quenched with saturated aqueous ammonium chloride (20 ml) and the aqueous layer was separated and extracted with diethyl ether (2 x 40 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (20 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resultant orange oil was purified by column chromatography (silica gel - diethyl ether : petroleum ether (60-80 °C), 1 : 5) to yield a colourless oil (0. 32g, 50%),$[\alpha]_D^{26}$ + 101. 01 (*c* 0. 33, $CHCl_3$); (Found m / z 210. 11236. $C_{11}H_{16}NO_3$ [M-^{t}Boc] requires m / z 210. 11291); ν_{max} (film) / cm^{-1} 1742 (ketone), 1700 (ester) and 1659 (urethane); λ_{max} (MeOH) / nm , 242 (ε 9, 274); δ_H (360MHz, C^2HCl_3), *ca.* 1. 5 (18H, 3 x s, -C($\underline{C}H_3)_3$), 2. 04 (3H, d, $J_{7,6}$ 7. 4, 7-$\underline{C}H_3$), 4. 0 (2H, m, $\underline{H}$-5), 5. 08 and 5. 17 (1H, 2 x s, $\underline{H}$-2) and 6. 91 (1H, m, $J_{6,7}$ 7. 4, $\underline{H}$-6); δ_C (125. 76MHz, C^2HCl_3), 15. 54 and 15. 58 ($\underline{C}H_3$), 27. 84, 27. 89 and 28. 23 (C($\underline{C}H_3)_3$), 52. 98 and 53. 46 (5-$\underline{C}H_2$), 60. 69 and 61. 08 (2-$\underline{C}H$), 80. 90, 81. 01, 82. 37 and 82. 43 ($\underline{C}(CH_3)_3$), 132. 98 and 133. 38 ($\underline{C}$=$CHCH_3$), 137. 23 and 137. 32 (C=$\underline{C}HCH_3$), 153. 57 and 154. 35 ($N\underline{C}O_2R$), 168. 78 and 168. 80 ($\underline{C}O_2R$) and 196. 76 and 197. 42 (4-$\underline{C}$=O).

***tert*-Butyl (2S,3S)-N-*tert*-Butoxycarbonyl-3-ethyl-4-oxoprolinate (14, R = Me)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-3-ethylidene-4-oxoprolinate **(13, R = Me)** (0. 3 g, 0. 96 mmol) was dissolved in dry ethyl acetate (150 ml) under an atmosphere of nitrogen. 10% Palladium on carbon (*ca.* 10% w/w) was added and the mixture was flushed first with nitrogen and then three times with hydrogen gas before being stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was filtered and the solvent was removed *in*

vacuo to leave a white solid (0. 284 g, 94%), m.p. 61 - 64 °C ; $[\alpha]_D^{26}$ + 44. 42 (*c* 0. 5, $CHCl_3$); (Found C, 61. 05; H, 9. 4; N 4. 8. $C_{16}H_{27}NO_5$ requires C, 61. 3; H, 8. 6; N, 4. 5%); m / z [+ve FAB, (3-nba)] 314 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1764 (ketone), 1720 (ester) and 1707 (urethane); δ_H (360MHz, C^2HCl_3), 1. 06 (3H, t, J 7.2, C<u>H</u>$_3$), 1. 17 - 1. 28 (1H, m, <u>H</u>-6$_A$), 1. 41 - 1. 45 (18H, 3 x s, -C(C<u>H</u>$_3$)$_3$), 1. 83 - 1. 92 (1H, m, <u>H</u>-6$_B$), 2. 60 - 2. 69 (1H, m, $J_{3,2}$ 9. 2, <u>H</u>-3), 3. 81 - 3. 94 (2H, m, $J_{5B,5A}$ 18. 4, $J_{5A,5B}$ 18. 4, <u>H</u>-5), and 4. 63 and 4. 72 (1H, 2 x d, $J_{2,3}$ 9. 2, <u>H</u>-2); δ_C (125. 76MHz, C^2HCl_3), 12. 28 (<u>C</u>H$_3$), 17. 84 (6-<u>C</u>H$_2$), 27. 89 and 28. 18 (C(<u>C</u>H$_3$)$_3$), 52. 40 and 52. 84 (3-<u>C</u>H), 52. 95 and 53. 37 (5-<u>C</u>H$_2$), 60. 75 and 61. 24 (2-<u>C</u>H), 80. 94 and 82. 47 (<u>C</u>(CH$_3$)$_3$), 153. 64 and 154. 51 (N<u>C</u>O$_2$R), 169. 73 and 170. 06 (<u>C</u>O$_2$R), and 208. 93 and 209. 71 (4-<u>C</u>=O).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-3-benzylidene-4-oxoprolinate (13, R = Ph)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-3-dimethylaminomethylene-4-oxoprolinate **(12)** (3. 5 g, 10. 3 mmol) was dissolved in dry diethyl ether (180 ml) and cooled to -78 °C under an atmosphere of nitrogen. Phenyl magnesium bromide (3*M* in diethyl ether; 8. 82 ml, 27 mmol) was added dropwise and the mixture was stirred at -78 °C for 1 h. The mixture was allowed to warm to room temperature and was stirred for a further 4 h and quenched with saturated aqueous ammonium chloride (75 ml). The aqueous layer was separated and extracted with diethyl ether (2 x 100 ml). The combined organic layers were washed with saturated aqueous sodium chloride (75 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resultant orange oil was purified by column chromatography (silica gel - diethyl ether : petroleum ether (60-80 °C), 1 : 5) to yield a white solid which could be further purified by recrystallisation from petroleum ether (60-80 °C) (2. 84 g, 74%), m.p. 96 - 97 °C; $[\alpha]_D^{24}$ + 215. 1 (*c* 1, MeOH); (Found C, 67. 5; H, 7. 5; N, 3. 8. $C_{21}H_{27}NO_5$ requires C, 67. 5; H, 7. 2; N, 3. 75%); m / z [+ve FAB, (diethyl ether / 3-nba)] 374 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1735 (ketone), 1725 (ester), 1695 (urethane) and 1659 (C=C); λ_{max} (MeOH) / nm, 303 (ε 28, 915); δ_H (360MHz, C^2HCl_3), 1. 32 - 1. 53 (18H, 3 x s, -C(C<u>H</u>$_3$)$_3$), 4. 05 (2H, m, <u>H</u>-5), 5. 52 and 5. 67 (1H, 2 x s, <u>H</u>-2) 7. 46 (3H, m, Ar), 7. 56 (1H, s, <u>H</u>-6) and 7. 84 (2H, m, Ar); δ_C (125. 76MHz, C^2HCl_3), 27. 71, 27. 75 and 28. 31 (C(<u>C</u>H$_3$)$_3$), 52. 14 and 52. 64 (5-<u>C</u>H$_2$), 61. 41 and 61. 94 (2-<u>C</u>H), 81. 14, 81. 30 and 82. 83 (<u>C</u>(CH$_3$)$_3$), 128. 79, 128. 87, 129.14, 129. 61, 131. 09, 131. 57, 131. 65, 132. 72, and 136. 93 (Ar, <u>C</u> and <u>C</u>H), 153. 53 and 154. 42 (N<u>C</u>O$_2$R), 168. 55 and 168. 73 (<u>C</u>O$_2$R), and 198. 32 and 199. 02 (4-<u>C</u>=O).

***tert*-Butyl (2S,3S)-N-*tert*-Butoxycarbonyl-3-benzyl-4-oxoprolinate (14, R = Ph)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-3-benzylidene-4-oxoprolinate **(13, R = Ph)** (1. 91 g, 5. 13 mmol) was dissolved in dry ethyl acetate (500 ml) under an atmosphere of nitrogen . 10% Palladium on carbon (*ca.* 10% w/w) was added and the mixture was flushed first with nitrogen and then three times with hydrogen gas before being stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was filtered and the solvent was removed *in vacuo* to leave an oil which was purified by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 3) to yield a colourless oil (1. 82 g, 95%); (Found m / z 375. 20585, $C_{21}H_{29}NO_5$ requires m / z 375. 20457); ν_{max} (film) / cm^{-1} 1767 (ketone), 1745 (ester) and 1709 (urethane); δ_H (360MHz, C^2HCl_3), (sample before 'purification' by column chromatography) 1. 46 [18H, 2 x s, 2 x -C(C<u>H</u>$_3$)$_3$], 2. 44 - 2. 56 (1H, m, $J_{6A,6B}$ 15. 1, <u>H</u>-6$_A$), 3. 0 (1H, m, $J_{3,6B}$ 3. 6, $J_{3,2}$ 9. 1, <u>H</u>-3), 3. 30 (1H, m, $J_{6B,3}$ 3. 6, $J_{6B,6A}$ 15. 1, <u>H</u>-6$_B$), 3. 92 (2H, m, <u>H</u>-5), 4. 63 and 4. 76 (1H, 2 x d, $J_{2,3}$ 9. 1, <u>H</u>-2) and 7. 21 -

7. 34 (5H, m, Ar). Attempted purification by column chromatography yielded *tert*-butyl (2S,3RS)-N-*tert*-butoxycarbonyl-3-benzyl-4-oxoprolinate, δ_H (360MHz, C^2HCl_3) *ca.* 1. 5 (18H, 5 x s, $C(C\underline{H}_3)_3$), 2. 5 - 3. 4 (3H, 4 x m, 3-C<u>H</u> and 6-$C\underline{H}_2$), 3. 71 - 4. 0 (2H, m, <u>H</u>-5), 4. 3 (2 x s, br) and 4. 6 (2 x d, $J_{2,3}$ 9. 01) (1H, <u>H</u>-2) and 7. 25 (5H, m, Ar); δ_C (125. 76MHz, C^2HCl_3), 27. 15, 27. 63, 27. 75, 27. 86, 27. 94, 28. 02, 28. 06 and 28.20 ($C(\underline{C}H_3)_3$), 28. 28, 28. 33, 29. 91 and 30.98 (6-$\underline{C}H_2$), 48. 06, 49. 13, 52. 87 and 53. 53 (3-<u>C</u>H), 52. 06, 52. 63, 55. 48 and 55. 95 (5-$\underline{C}H_2$), 61. 30, 62. 37, 70. 80 and 71. 74 (2-<u>C</u>H), 80. 42, 80. 68, 81. 18 and 81. 34, 82. 89, 83. 15, 83. 36 and 83. 45 ($\underline{C}(CH_3)_3$),126. 34, 126.39, 126.55, 126. 92, 127. 19, 129. 38, 129. 47, 128. 51, 128. 58, 128. 60, 128. 83, 128.87, 128. 91, 129. 04, 129. 31, 129. 46 and 130.87 (Ar, <u>C</u>H), 138. 54, 139. 15 and 139. 25 (Ar, <u>C</u>) 153. 68, 153.91 and 154. 43 ($N\underline{C}O_2R$), 169. 41, 173. 84 and 174. 04 ($\underline{C}O_2R$) and 207. 72 (4-<u>C</u>=O).

Borohydride Reduction of *tert*-Butyl (2S,3S)-N-*tert*-Butoxycarbonyl-3-benzyl-4-oxoprolinate (14, R = Ph) - *tert*-Butyl (2S,3S)-N-*tert*-butoxycarbonyl-3-benzyl-4-oxoprolinate **(14, R = Ph)** (0. 55 g, 1. 47 mmol) was dissolved in distilled methanol (4. 5 ml) and dry diethyl ether (5. 5 ml) under an atmosphere of nitrogen . The solution was cooled to 0 °C and sodium borohydride (0. 11 g, 2. 86 mmol) in distilled methanol (4. 5 ml) and dry diethyl ether (5. 5 ml) was added. The reaction was stirred at 0 °C for 5 min and allowed to warm to room temperature for 1 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (20 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 x 20 ml), water (2 x 20 ml) and saturated aqueous sodium chloride (2 x 20 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a mixture of diastereoisomeric alcohols. Purification by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 3) gave *tert*-butyl (2S,3S,4S)-N-*tert*-butoxycarbonyl-3-benzyl-4-hydroxy-prolinate **(16)** as the major product (0. 177 g, 32%), the ^{1}H-NMR spectrum of which was identical to that described below. The remaining material was an inseparable mixture of diastereoisomers (0. 109 g, 20%).

***tert*-Butyl (2S,4S)-N-*tert*-Butoxycarbonyl-3-benzylidene-4-hydroxyprolinate (17)** - *tert*-Butyl (2S)-N-*tert*-butoxycarbonyl-3-benzylidene-4-oxoprolinate **(13, R = Ph)** (2. 4 g, 6. 43 mmol), was dissolved in distilled methanol (24 ml) and dry diethyl ether (24 ml) under an atmosphere of nitrogen. The solution was cooled to 0 °C and sodium borohydride (0. 93 g, 24. 5 mmol) in distilled methanol (24 ml) and dry diethyl ether (24 ml) was added. The reaction was stirred at 0 °C for 5 min and then allowed to warm to room temperature for 1 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (40 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 x 40 ml), water (2 x 40 ml) and saturated aqueous sodium chloride (2 x 40 ml). The organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 3) gave a colourless oil (1. 98 g, 82%), $[\alpha]_D^{27}$ + 222. 15 (*c* 0. 2, $CHCl_3$); (Found m / z 375. 20124. $C_{21}H_{29}NO_5$ requires m / z 375. 20457); ν_{max} (film) / cm^{-1} 3442 (OH), 1740 (ester) and 1703 (urethane); λ_{max} (MeOH) / nm , 254 (ε 16, 500); δ_H (360MHz, C^2HCl_3), 1. 5 (18H, m, -C($C\underline{H}_3$)$_3$), 3. 55 (1H, m, $J_{5R,4}$ 5. 1, $J_{5R,5S}$ 11. 9, <u>H</u>-5$_R$), 3. 75 (1H, m, $J_{5S,5R}$ 11. 9, <u>H</u>-5$_S$), 4. 08 and 4. 3 (1H, 2 x d, exch., $J_{OH,4}$ 11. 3, 4-O<u>H</u>), 4. 51 and 4. 55 (1H, m, $J_{4,6}$, $J_{4,5R}$ 5. 1, $J_{4,OH}$ 11. 3, <u>H</u>-4), 5. 05 and 5. 13 (1H, 2 x s, <u>H</u>-2), 6. 83 (1H, d, $J_{6,OH}$ 4. 5, <u>H</u>-6) and 7. 38 - 7. 58 (5H, m, Ar); δ_C (125. 76MHz, C^2HCl_3), 27. 68, 27. 75, 28. 29 and 28. 33 ($C(\underline{C}H_3)_3$), 54. 22 and 54. 76 (5-$\underline{C}H_2$), 61. 06 and 61. 19 (2-<u>C</u>H), 75. 73 and 76. 66 (4-<u>C</u>H), 80. 43, 80.74, 83. 46 and 83. 57

(C(CH$_3$)$_3$), 125. 33 and 125. 44 (6-CH), 127. 53, 127. 76, 128. 30, 128. 38, 128.46, 128. 82, 129. 00 and 130. 42 (Ar, CH), 134.91, (Ar, C), 136. 30 and 137. 03 (3-CH), 153. 61 and 154. 23 (NCO$_2$R) and 171. 98 and 172. 30 (CO$_2$R).

***tert*-Butyl (2S,3S,4S)-N-*tert*-Butoxycarbonyl-3-benzyl-4-hydroxyprolinate (16)** - *tert*-Butyl (2S,4S)-N-*tert*-butoxycarbonyl-3-benzylidene-4-hydroxyprolinate **(17)** (1. 36 g, 3. 63 mmol) was dissolved in dry ethyl acetate (125 ml) under an atmosphere of nitrogen . 10% Palladium on carbon (*ca.* 10% w/w) was added and the mixture was flushed, first with nitrogen and then three times with hydrogen gas before being stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was filtered and the solvent was removed *in vacuo* to leave a colourless oil which crystallised on standing to give a white solid which could be recrystallised from petroleum ether 60-80 °C, (1. 11 g, 82%) m.p. 78 - 80. 5 °C; $[\alpha]_D^{28}$ + 23. 25 (*c* 0. 2, CHCl$_3$); (Found C, 66. 7; H, 8. 3; N, 3. 5. $C_{21}H_{31}NO_5$ requires C, 66. 8; H, 8. 2; N, 3. 7%); m / z [+ve FAB (3-nba)] 378 ([M+H]$^+$); ν_{max} (KBr) / cm^{-1} 1709 (ester); δ_H (360MHz, C^{2}HCl$_3$), *ca.* 1. 55 (18H, 3 x s, -C(CH$_3$)$_3$), 2. 51 (1H, m, H-3), 2. 83 (2H, m, H-6), 3. 45 (2H, m, $J_{5R,4}$ 4. 0, $J_{5R,5S}$ 12.1, H-5$_R$), 3. 73 (1H, 2 x d, $J_{5S,5R}$ 12. 1, H-5$_S$), 3. 80 and 4. 3 (1H, 2 x d, exch., $J_{OH,4}$ 12. 4, 4-OH), 3. 95 (1H, m, $J_{4,5R}$ 4. 0, $J_{4,OH}$ 12. 4, H-4), 4. 3 (1H, t, $J_{2,3}$ 8. 9, H-2) and 7. 2 - 7. 45 (5H, m, Ar); δ_C (125. 76MHz, C^{2}HCl$_3$), 27. 91, 28. 06, 28. 32 and 28. 37 (C(CH$_3$)$_3$), 30. 49 and 30. 69 (6-CH$_2$), 48. 14 and 49. 24 (3-CH), 55. 54 and 56. 0 (5-CH$_2$), 62. 37 and 62. 41 (2-CH), 70. 8 and 71. 8 (4-CH) 80. 19, 80. 39, 83. 23 and 83. 31 (C(CH$_3$)$_3$), 125. 35, 126. 33, 126. 39, 126. 69, 127. 81, 128. 35, 128. 48, 128. 52, 128. 93, 128. 96 and 129. 61 (Ar), 139. 29 and 139. 39 (Ar, C), 153. 74 and 154. 35 (NCO$_2$R) and 173. 87 and 174. 02 (CO$_2$R).

***tert*-Butyl (2S,3S,4S)-N-*tert*-Butoxycarbonyl-3-benzyl-4-oxymethanesulfonylprolinate (18)** - *tert*-Butyl (2S,3S,4S)-N-*tert*-butoxycarbonyl-3-benzyl-4-hydroxyprolinate **(16)** (1 g, 2. 65 mmol) was dissolved in dry tetrahydrofuran (15 ml) at -78 °C in an atmosphere of nitrogen and lithium hexamethyldisilazide (1. 0 *M* in tetrahydrofuran; 5. 26 ml, 5. 26 mmol) was added. The solution was stirred at -78 °C for 0. 5 h. Methanesulfonyl chloride (0. 827 ml, 10. 53 mmol) was added and the reaction was warmed to room temperature, stirred for 48 h and quenched with saturated aqueous ammonium chloride (15 ml). The tetrahydrofuran was removed *in vacuo* and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried (MgSO$_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 3) gave a white foamy solid (0. 58 g, 48%); m.p. 39 - 41 °C; $[\alpha]_D^{28}$ - 29. 87 (*c* 0. 1, CHCl$_3$); (Found m / z 455. 19857. $C_{22}H_{33}NO_7S$ requires m / z 455, 19778); ν_{max} (KBr) / cm^{-1} 1740 (ester), and 1702 (urethane); δ_H (500MHz, C^{2}HCl$_3$), 1. 5 (18H, m, C(CH$_3$)$_3$), 2. 78 - 2. 85 (2H, m, $J_{3,2}$ 8. 2, H-3 and H-6$_A$), 2. 92 and 2. 97 (3H, 2 x s, -CH$_3$), 3. 1 (1H, m, H-6$_B$), 3. 65 (1H, m, $J_{5R,4}$ 4. 3, $J_{5R,5S}$ 13. 7, H-5$_R$), 4. 0 (1H, 2 x d, $J_{5S,5R}$ 13. 7, H-5$_S$), 4. 33 and 4. 44, (1H, 2 x d, $J_{2,3}$ 8. 2, H-2), 4. 95 (1H, t, $J_{4,5R}$ 4. 3, H-4) and 7. 2 - 7. 4 (5H, m, Ar); δ_C (125. 76MHz, C^{2}HCl$_3$), 27. 7, 28. 01, 28. 31 and 28. 37 (C(CH$_3$)$_3$), 30. 61 and 30. 82 (6-CH$_2$), 39. 03 and 39. 49 (CH$_3$), 47. 33 and 48. 52 (3-CH), 52. 28 and 52. 80 (5-CH$_2$), 61. 34 and 61. 52 (2-CH), 79. 53 and 80. 2 (4-CH), 80. 42, 80. 50, 81. 88 and 81. 94 (C(CH$_3$)$_3$), 126. 77, 127. 55, 128. 64, 128. 72, 128. 78, 129. 01, 138. 42 and 138. 51 (Ar), 153. 51 and 153. 58 (NCO$_2$R) and 168. 77 and 168. 77 (CO$_2$R).

(2S,3R,4S)-3-benzyl-4-phenylproline (19) - A solution of *tert*-butyl (2S,3S,4S)-N-*tert*-butoxycarbonyl-3-benzyl-4-oxymethanesulfonylprolinate **(18)** (0. 1 g, 0. 22 mmol) in dry benzene (2 ml) was added to a suspension of aluminium chloride (0. 106 g, 0. 8 mmol) in dry benzene (2 ml) in an atmosphere of nitrogen and stirred at room temperature for 5 h. The solution was filtered and the solvent was removed *in vacuo*. The residue was partitioned between 0. 2 M aqueous HCl (5 ml) and ethyl acetate (10 ml) and the aqueous layer was lyophilised *in vacuo*. The residue was dissolved in distilled water (5 ml), the pH was adjusted to 7 with 2N aqueous ammonium hydroxide and the solution was added to a Dowex 50X8 (H^+) ion exchange column. The column was washed with distilled water until the pH of the eluant was 5-6. The product was eluted with 2N aqueous ammonium hydroxide and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel- {dichloromethane : methanol : water : acetic acid, 7 : 3 : 0. 6 : 0. 3} : ethyl acetate, 3 : 1) to give two products. The desired product was an off-white solid (0. 015 mg, 24%), m.p. (dec.) 190 °C ; (Found m / z 281. 19066. $C_{18}H_{19}NO_2$ requires m / z 281.14199); ν_{max} (KBr) / cm^{-1}, 1634 (acid); δ_H (360MHz, $C^2H_3O^2H$), 2. 21 (1H, t, $J_{6A,6B}$ 13. 8, H-6_A), 2. 82 (1H, m, $J_{3,6B}$ 4. 0, $J_{3,2}$ 6. 3, H-3), 2. 92 (1H, dxd, $J_{6B,3}$ 4. 0, $J_{6B,6A}$ 13. 8, H-6_B), 3. 15 (1H, d, $J_{5R,5S}$ 12. 7, H-5_R), 3. 69 (1H, dxd, $J_{5S,4}$ 3. 8, $J_{5S,5R}$ 12. 7, H-5_S), 4. 1 (1H, d, $J_{4,5S}$ 3. 8, H-4), 4. 41 (1H, d, $J_{2,3}$ 6. 3, H-2) and 7. 10 - 7. 36 (10H, m, Ar.). The second product, (2S)-3-benzyl-3,4-dehydroproline **(20)** was an off-white solid (0. 01 g, 23%); m.p. (dec.) 176 °C; (Found m / z 203. 09280. $C_{12}H_{13}NO_2$ requires m / z 203. 09463); ν_{max} (KBr) / cm^{-1}, 1632 (acid); δ_H (500MHz, $C^2H_3O^2H$), 3. 6 (2H, 2 x AB, $J_{6A,6B}$ 15. 88, H-6), 3. 9 (1H, d, $J_{5A,5B}$ 14. 8, H-5_A), 4. 0 (1H, d, $J_{5B,5A}$ 14. 8, H-5_B), 4. 5 (1H, s, H-2), 5. 28 (1H, d, $J_{4,5}$ 1. 8, H-4) and 7. 25 (5H, m, Ar.).

***tert*-Butyl (2S)-N-*para*-Toluenesulfonyl-4-oxoprolinate (22)** - (2S)-N-*para*-Toluenesulfonyl-4-oxoproline **(21)**[20] (24 g, 85 mmol) was dissolved in dry dichloromethane (400 ml) and tetrahydrofuran (100 ml) and cooled to 0 °C under an atmosphere of nitrogen. *tert*-Butanol (26. 5 ml, 281 mmol) and 4-dimethylaminopyridine (1. 1 g, 9 mmol) were added to the solution followed by *N,N*-dicyclohexylcarbodiimide (20. 1 g, 96 mmol) over 5 min. The mixture was stirred at room temperature for 3 h and the DCU was removed by filtration. The filtrate was washed with 10% aqueous citric acid (2 x 150 ml), saturated aqueous sodium hydrogen carbonate (2 x 150 ml), water (2 x 150 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography using a gradient solvent system (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 5; 1 : 4; and 1 : 3) gave a white solid (13. 88 g, 48%), m.p. 90 - 91 °C; $[\alpha]_D^{31}$ + 12. 58 (*c* 0. 5, $CHCl_3$) ; (Found C, 56. 3; H, 6. 3; N, 4. 05. $C_{16}H_{21}NO_5S$ requires C, 56. 6; H, 6. 2; N, 4. 1%); m / z [+ve FAB (3-nba)] 340 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1766 (ketone), and 1720 (ester); δ_H (360MHz, C^2HCl_3), 1. 38 (9H, s, -C(CH_3)$_3$), 2. 45 (3H, s, -CH_3), 2. 5 (1H, d x d, $J_{3A,2}$ 2. 4, $J_{3A,3B}$ 18. 2, H-3_A), 2. 75 (1H, d x d, $J_{3B,2}$ 9. 4, $J_{3B,3A}$ 18. 2, H-3_B), 3. 8 (2H, 2 x AB, $J_{5A,5B}$ 17. 3, H-5), 4. 63 (1H, d x d, $J_{2,3A}$ 2. 4, $J_{2,3B}$ 9. 4, H-2), 7. 35 (2H, d, *J* 8. 1, Ar) and 7. 86 (2H, d, *J* 8. 1, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 50 (CH_3), 27. 70 (C(CH_3)$_3$), 40. 71 (3-CH_2), 52. 60 (5-CH_2), 58. 42 (2-CH), 83. 12 (C(CH$_3$)$_3$), 127. 42 and 129. 88 (Ar, CH), 135. 22 (CCH$_3$), 144. 25 (CSO_2), 169. 42 (CO_2R) and 206. 68 (4-C=O).

***tert*-Butyl (2S)-N-*para*-Toluenesulfonyl-3-dimethylaminomethylene-4-oxoprolinate (23)** - *tert*-Butyl (2S)-N-*para*-toluenesulfonyl-4-oxoprolinate **(22)** (7 g, 0. 02 mol) was dissolved in dry dimethoxyethane

(350 ml) under an atmosphere of nitrogen and *tert*-butoxy-*bis*-(dimethylamino)methane (11. 34 ml, 0. 05 mol) was added. The mixture was stirred at 70 °C for 2 h, cooled and the solvent was removed *in vacuo*. The resultant orange oil was purified by column chromatography using a gradient solvent system (silica gel - ethyl acetate : petroleum ether 60-80 °C, 1 : 3, 1 : 2) to give a pale brown solid (5. 17 g, 64%), m.p. 122 - 125 °C; $[\alpha]_D^{31}$ - 22. 44 (*c* 0. 5, $CHCl_3$); (Found C, 58. 1; H, 6. 9; N, 7. 2. $C_{19}H_{26}N_2O_5S$ requires C, 57. 85; H, 6. 6; N, 7. 1%); m / z [+ve FAB (3-nba)] 395 ($[M+H]^+$) ; ν_{max} (KBr) / cm^{-1} 1723 (ketone), and 1687 (ester); λ_{max} (MeOH) / nm 318 (ε 11, 460); δ_H (360MHz, C^2HCl_3), 1. 4 (9H, s, -C(CH_3)$_3$), 2. 43 (3H, s, -CH_3), 3. 13 (6H, br s, N(CH_3)$_2$), 3. 85 (2H, 2 x AB, $J_{5S,5R}$ 15. 6, H-5), 5. 38 (1H, s, H-2), 7. 27 (1H, s, H-6), 7. 28 (2H, d, *J* 8. 1, Ar) and 7. 8 (2H, d, *J* 8. 1, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 40 (CH_3), 27. 60 (C(CH_3)$_3$), 52. 86 (5-CH_2), 62. 58 (N(CH_3)$_2$), 82. 43 (C(CH_3)$_3$), 98. 12 (3-C), 127. 02 and 129. 63 (Ar, CH), 136. 23 (CCH_3), 143. 55 (CSO_2), 147. 15 (6-CH), 170. 32 (CO_2R) and 194. 46 (4-C=O).

***tert*-Butyl (2S)-N-*para*-Toluenesulfonyl-3-benzylidene-4-oxoprolinate (24)** - *tert*-Butyl (2S)-N-*para*-toluenesulfonyl-3-dimethylaminomethylene-4-oxoprolinate **(23)** (8. 5 g, 21 mmol) was dissolved in dry diethyl ether (350 ml) and cooled to -78 °C under an atmosphere of nitrogen. Phenylmagnesium bromide (3 *M* solution in diethyl ether; 21. 6 ml, 65 mmol) was added dropwise; the mixture was stirred at -78 °C for 1 h, allowed to warm to room temperature and stirred for a further 2 h. The mixture was quenched with saturated aqueous ammonium chloride (100 ml). The aqueous layer was separated and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with saturated aqueous sodium chloride (100 ml) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resultant orange oil was purified by column chromatography (silica gel - diethyl ether : petroleum ether (60-80 °C), 1 : 2) to yield a white solid which could be further purified by recrystallisation from petroleum ether (60-80 °C) (7. 1 g, 77%), m.p. 102 - 104 °C; $[\alpha]_D^{32}$ + 126. 82 (*c* 1, $CHCl_3$); (Found C, 64. 3; H, 5. 9; N, 3. 2. $C_{23}H_{25}NO_5S$ requires C, 64. 6; H, 5. 9; N, 3. 3%); m / z [+ve FAB (3-nba)] 428 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1727 (ketone), 1625 (ester), and 1600 (C=C); λ_{max} (MeOH) / nm 304 (ε 21, 183); δ_H (360MHz, C^2HCl_3), 1. 3 (9H, s, -C(CH_3)$_3$), 2. 45 (3H, s, -CH_3), 4. 05 (2H, 2 x AB, $J_{5S,5R}$ 17. 1, H-5), 5. 63 (1H, s, H-2) and 7. 25 - 7. 70 (9H, 3 m, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 52 (-CH_3), 27. 60 (C(CH_3)$_3$), 52. 52 (5-CH_2), 62. 92 (2-CH), 83. 61 (C(CH_3)$_3$), 127. 26, 129. 01, 129. 09, 129. 86, 131. 38 and 132. 54, (Ar), 135. 54 (CCH_3), 136. 99 (-C=CH), 144. 15 (CSO_2), 167. 55 (CO_2R) and 197. 50 (4-C=O).

***tert*-Butyl (2S,4S)-N-*para*-Toluenesulfonyl-3-benzylidene-4-hydroxyprolinate (25)** - *tert*-Butyl (2S)-N-*para*-toluenesulfonyl-3-benzylidene-4-oxoprolinate **(24)** (6. 8 g, 16 mmol), was dissolved in distilled methanol (60 ml) and dry diethyl ether (60 ml). The solution was cooled to 0 °C under an atmosphere of nitrogen and sodium borohydride (2. 3 g, 60 mmol) in distilled methanol (60 ml) and dry diethyl ether (60 ml) was added. The reaction was stirred at 0 °C for 5 min, warmed to room temperature and stirred for 20 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 x 60 ml), water (2 x 60 ml), saturated aqueous sodium chloride (2 x 60 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 2) gave a colourless oil (5. 69 g, 83%), $[\alpha]_D^{34}$ + 35. 72 (*c* 0. 5, $CHCl_3$); (Found C, 63. 2; H, 6. 3; N, 3. 0. $C_{23}H_{27}NO_5S$. 0. 5 H_2O requires C, 63. 0; H, 6. 4; N, 3. 2%); m / z

[+ve FAB (3-nba)] 430 ([M+H]$^+$); ν_{max} (film) / cm^{-1}, 1719 (ester), and 1598 (C=C); λ_{max} (MeOH) / nm 253 (ε 20, 837); δ_H (360MHz, C^2HCl_3), 1. 45 (9H, s, -C(C<u>H</u>$_3$)$_3$), 2. 41 (3H, s, -C<u>H</u>$_3$), 3. 38 (1H, d x d, $J_{5R,4}$ 4. 6, $J_{5R,5S}$ 10. 2, <u>H</u>-5$_R$), 3. 64 (1H, d x d, $J_{5S,4}$ 0. 91, $J_{5S,5R}$ 10. 2, <u>H</u>-5$_S$), 4. 28 (1H, d, exch., $J_{OH,4}$ 11. 2, 4-O<u>H</u>), 4. 55 (1H, br d x d, $J_{4,5R}$ 4. 37, $J_{4,OH}$ 11. 2, <u>H</u>-4), 5. 0 (1H, s, <u>H</u>-2), 6. 75 (1H, s, <u>H</u>-6), 7. 21 - 7. 41 (7H, m, Ar) and 7. 69 (2H, d, J 8. 07, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 48 (<u>C</u>H$_3$), 27. 62 (C(<u>C</u>H$_3$)$_3$), 55. 76 (5-<u>C</u>H$_2$), 62. 21 (2-<u>C</u>H), 75. 96 (4-<u>C</u>H), 84. 02 (<u>C</u>(CH$_3$)$_3$), 127. 51, 128. 52, 128. 80, 129. 73 and 130. 46 (<u>C</u>H Ar), 134. 62 (<u>C</u>CH$_3$), 136. 8 (<u>C</u>=CH), 143. 93 (<u>C</u>SO$_2$) and 170. 9 (<u>C</u>O$_2$R).

***tert*-Butyl (2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-hydroxyprolinate (26)** - *tert*-Butyl (2S,4S)-N-*para*-toluenesulfonyl-3-benzylidene-4-hydroxyprolinate **(25)** (5. 69 g, 13 mmol) was dissolved in dry ethyl acetate (150 ml) under an atmosphere of nitrogen. 10% Palladium on carbon (*ca.* 10% w/w) catalyst was added and the mixture was first flushed with nitrogen and then three times with hydrogen gas before being stirred at room temperature under a hydrogen atmosphere for 24 h. The solution was filtered and the solvent was removed *in vacuo* to leave an oil which was purified by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 2) to yield a colourless oil which crystallised on standing as a white solid that could be recrystallised from petroleum ether (60-80 °C) (3. 43, 62%), m.p. 108 - 110 °C; $[\alpha]_D^{29}$ - 21. 32 (*c* 0. 5, $CHCl_3$); (Found C, 63. 8; H, 7. 0; N, 3. 0. $C_{23}H_{29}NO_5S$ requires C, 64. 0; H, 6. 8; N, 3. 25%); m / z [+ve FAB (3-nba)] 432 ([M+H]$^+$)); ν_{max} (KBr) / cm^{-1} 1711 (ester); δ_H (360MHz, C^2HCl_3), 1. 5 (9H, s, -C(C<u>H</u>$_3$)$_3$), 2. 28 (1H, m, $J_{3,6A}$ 4. 3, $J_{3,2}$ 9. 7, $J_{3,6B}$ 11. 0, <u>H</u>-3), 2. 34 (3H, s, -C<u>H</u>$_3$), 2. 66 (1H, d x d, $J_{6A,3}$ 4. 3, $J_{6A,6B}$ 13. 3, <u>H</u>-6$_A$), 2. 80 (1H, d x d, $J_{6B,3}$ 11. 0, $J_{6B,6A}$ 13. 3, <u>H</u>-6$_B$), 3. 2 (1H, d x d, $J_{5R,4}$ 3. 8, $J_{5R,5S}$ 10. 0, <u>H</u>-5$_R$), 3. 63 (1H, d, $J_{5S,5R}$ 10. 0, <u>H</u>-5$_S$), 3. 92 (1H, m, $J_{4,5R}$ 3. 8, $J_{4,3}$ 7. 5, $J_{4,OH}$ 12. 4, <u>H</u>-4), 4. 13 (1H, d, exch., $J_{OH,4}$ 12. 4, 4-O<u>H</u>), 4. 24 (1H, d, $J_{2,3}$ 9. 7, <u>H</u>-2), 7. 25 - 7. 36 (7H, m, Ar) and 7. 7 (2H, d, J 8. 2, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 52 (3-<u>C</u>H), 27. 86 (C(<u>C</u>H$_3$)$_3$), 30. 36 (6-<u>C</u>H$_2$), 49. 23 (<u>C</u>H$_3$), 56. 81 (5-<u>C</u>H$_2$), 63. 13 (4-<u>C</u>H), 71. 41 (2-<u>C</u>H), 83. 9 (<u>C</u>(CH$_3$)$_3$), 126. 5, 127. 44, 128. 51, 128. 87 and 129. 77 (Ar, <u>C</u>H), 134. 46 (Ar, <u>C</u>), 138. 69 (<u>C</u>CH$_3$), 143. 9 (<u>C</u>SO$_2$) and 172. 5 (<u>C</u>O$_2$R).

***tert*-Butyl (2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-oxymethanesulfonylprolinate (27)** - *tert*-Butyl (2S,3S,4S)-N-*para*-toluenesulfonyl-3-benzyl-4-hydroxyprolinate **(26)** (1 g, 2. 32 mmol) was dissolved in dry tetrahydrofuran (15 ml) at -78 °C under an atmosphere of nitrogen and lithium hexamethyldisilazide (1. 0 *M* solution in tetrahydrofuran; 4. 6 ml, 4. 6 mmol) was added. The mixture was stirred for 0. 5 h and methanesulfonyl chloride (0. 724 ml, 9. 2 mmol) was added. The reaction was warmed to room temperature, stirred for 48 h and quenched with saturated aqueous ammonium chloride (15 ml). The tetrahydrofuran was removed *in vacuo* and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 2) gave a white foamy solid (0. 992 g, 84%), m.p. 119 - 121 °C; $[\alpha]_D^{32}$ - 53. 06 (*c* 0. 5, $CHCl_3$); (Found C, 56. 9; H, 6. 2; N, 2. 6. $C_{24}H_{31}NO_7S_2$ requires C, 56. 6; H, 6. 1; N, 2. 7%); m / z [+ve FAB (3-nba)] 510 ([M+H]$^+$); ν_{max} (KBr) / cm^{-1} 1745 (ester); δ_H (360MHz, C^2HCl_3), 1. 46 (9H, s, C(C<u>H</u>$_3$)$_3$), 2. 49 (3H, s, CC<u>H</u>$_3$), 2. 59 (1H, m, $J_{3,4}$ 4. 2, $J_{3,6B}$ 4. 6, $J_{3,2}$ 8. 8, <u>H</u>-3), 2. 69 (1H, m, $J_{6A,6B}$ 14. 1, <u>H</u>-6$_A$), 2. 90 (3H, s, -SC<u>H</u>$_3$), 3. 0 (1H, d x d, $J_{6B,3}$ 4. 6, $J_{6B,6A}$ 14. 1, <u>H</u>-6$_B$), 3. 55 (1H, d x d, $J_{5R,4}$ 4. 3, $J_{5R,5S}$ 12. 2, <u>H</u>-5$_R$), 3. 87 (1H, d, $J_{5S,5R}$ 12. 2, <u>H</u>-5$_S$), 4. 46 (1H,

d, $J_{2,3}$ 8. 8, H-2), 4. 87 (1H, t, $J_{4,3}$ 4. 2, $J_{4,5R}$ 4. 3, H-4), 7. 15 - 7. 38 (7H, m, Ar) and 7. 74 (2H, d, *J* 8. 2, Ar); δ_C (62. 88MHz, C^2HCl_3), 21. 52 (CCH_3), 27. 87 ($C(CH_3)_3$), 30. 58 (6-CH_2), 39. 33 (3-CH), 48. 57 (SCH_3) 53. 19 (5-CH_2), 62. 65 (2-CH), 79. 42 (4-CH), 82. 58 ($C(CH_3)_3$), 126. 87, 127. 46, 128. 66, 128. 79 and 129. 78 (Ar), 135. 14 (C-Ar), 137. 84 (CCH_3), 143. 97 (CSO_2) and 168. 10 (CO_2R).

(2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-oxymethanesulfonylproline (30) - *tert*-Butyl (2S,3S,4S)-N-*para*-toluenesulfonyl-3-benzyl-4-oxymethanesulfonylprolinate **(27)** (0. 5 g, 0. 98 mmol) was dissolved in trifluoroacetic acid (10 ml), stirred for 1 h at room temperature and the solvent was removed *in vacuo*. The final traces of solvent were removed azeotropically with diethyl ether (3 x 20 ml) to produce a pink foam which was purified by column chromatography (silica gel - {dichloromethane : methanol : acetic acid : water, 7 : 3 : 0. 6 : 0. 3} : ethyl acetate, 1 : 6) to give a white foamy solid (0. 43g, 97%), m.p. 64 - 67 °C; $[\alpha]_D^{31}$ - 67. 3 (*c* 0. 5, $CHCl_3$); (Found C, 52. 5; H, 5. 1; N, 2. 9. $C_{20}H_{23}NO_7S_2$ requires C, 52. 9; H, 5. 1; N, 3. 1%); m / z [+ve FAB (3-nba)] 454 ($[M+H]^+$); ν_{max} (KBr) / cm^{-1} 1635 (acid); δ_H (360MHz, C^2HCl_3), 2. 46 (3H, s, -CCH_3), 2. 5 (1H, m, H-3), 2. 78 (1H, d x d, $J_{6A,3}$ 10. 6, $J_{6A,6B}$ 14. 3, H-6_A), 2. 98 (3H, s, -SCH_3), 3. 07 (1H, d x d, $J_{6B,3}$ 4. 7, $J_{6B,6A}$ 14. 3, H-6_B), 3. 37 (1H, d x d, $J_{5R,4}$ 3. 7, $J_{5R,5S}$ 12. 1, H-5_R), 3. 5 (br, exch., CO_2H), 4. 0 (1H, d, $J_{5S,5R}$ 12. 1, H-5_S), 4. 51 (1H, d, $J_{2,3}$ 9. 35, H-2), 4. 88 (1H, t, $J_{4,3}$ 3. 6, $J_{4,5R}$ 3. 7, H-4), 7. 15 - 7. 37 (7H, m, Ar) and 7. 76 (2H, d, *J* 8. 2, Ar); δ_C (125 MHz, C^2HCl_3), 21. 87 (3-CH), 30. 65 (6-CH_2), 39. 68 (CCH_3), 49. 02 (SCH_3) 53. 74 (5-CH_2), 61. 87 (2-CH), 78. 89 (4-CH), 127. 24, 127. 91, 128. 98, 129. 11 and 130. 36 (Ar), 133. 7 (C-Ar), 137. 5 (CCH_3), 144. 8 (CSO_2) and 172. 0 (CO_2H).

(2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-hydroxyproline (28) - *tert*-Butyl (2S,3S,4S)-N-*para*-toluenesulfonyl-3-benzyl-4-hydroxyprolinate **(26)** (0. 5 g, 1. 16 mmol) was dissolved in tetrahydrofuran (10 ml) and 6N aqueous HCl (5 ml) was added. The mixture was stirred for 5 h at room temperature and the solvent was removed *in vacuo*. The aqueous phase was extracted with chloroform (3 x 20 ml) to produce a white foam which was purified by column chromatography (silica gel - {dichloromethane : methanol : acetic acid : water, 7 : 3 : 0. 6 : 0. 3} : ethyl acetate, 1 : 3) to give a white foamy solid (0. 430g, 98%), m.p. 91 - 95 °C; $[\alpha]_D^{31}$ - 35. 02 (*c* 0. 5, $CHCl_3$); (Found m / z 375. 10786. $C_{19}H_{21}NO_5S$ requires m / z 375. 11398); ν_{max} (KBr) / cm^{-1} 1636 (acid); δ_H (360MHz, C^2HCl_3), 2. 31 (1H, m, H-3), 2. 49 (3H, s, -CH_3), 2. 79 (2H, m, H-6), 3. 15 (1H, d x d, $J_{5R,4}$ 3. 4, $J_{5R,5S}$ 10. 2, H-5_R), 3. 73 (2H, m, $J_{5S,5R}$ 10. 2, H-5_S and OH), 4. 03 (1H, t, $J_{4,3}$ 3. 3, $J_{4,5R}$ 3. 4, H-4), 4. 33 (1H, d, $J_{2,3}$ 10. 6, H-2), 5. 0 (br, exch., CO_2H), 7. 13 - 7. 28 (5H, m, Ar), 7. 36 (2H, d, *J* 8. 1, Ar) and 7. 79 (2H, d, *J* 8. 1, Ar); δ_C (125. 76MHz, C^2HCl_3), 21. 48 (CCH_3), 30. 42 (6-CH_2), 49. 19 (3-CH) 56. 79 (5-CH_2), 63. 57 (2-CH), 71. 16 (4-CH), 126. 25, 127. 53, 128. 4, 129. 0 and 129. 94 (Ar, CH), 133. 48 (Ar, C), 139. 0 (CCH_3), 144. 10 (CSO_2) and 176. 09 (CO_2H).

(2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-hydroxyproline Lactone (29) - (2S,3S,4S)-N-*para*-Toluenesulfonyl-3-benzyl-4-hydroxyproline **(28)** (0. 45 g, 1. 2 mmol) was dissolved in dry dichloromethane (40 ml) and stirred with anhydrous magnesium sulphate (0. 204 g) for 0. 5 h at room temperature in an atmosphere of nitrogen. *N,N*-Dicyclohexylcarbodiimide (0. 245 g, 1. 2 mmol) was added and the mixture was stirred for 16 h and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel - ethyl acetate : petroleum ether (60-80 °C), 1 : 2) to give the lactone **(29)** as a

white solid (0. 257g, 60%), m.p. 142 - 143.5 °C; $[\alpha]_D^{31}$ + 32. 94 (*c* 0. 5, $CHCl_3$); (Found C, 63. 85; H, 5. 4; N, 3. 9. $C_{19}H_{19}NO_4S$ requires C, 63. 85; H, 5. 3; N, 3. 9%); m / z [+ve FAB (3-nba)] 358 ($[M+H]^+$) ; ν_{max} (KBr) / cm^{-1} 1811 (lactone); δ_H (360MHz, C^2HCl_3), 2. 45 (3H, s, $C\underline{H}_3$), 2. 53 (1H, m, $J_{3,4}$ 1. 4, $\underline{H}$-3), 2. 73 (2H, 2 x s, H-6), 3. 43 (1H, d, $J_{5A,5B}$ 10. 4, $\underline{H}$-5_A), 3. 63 (1H, d x d, $J_{5B,4}$ 1. 3, $J_{5B,5A}$ 10. 4, $\underline{H}$-5_B), 4. 25 (1H, t, $J_{4,5B}$, 1. 3, $J_{4,3}$ 1. 4, $\underline{H}$-4), 4. 68 (1H, s, $\underline{H}$-2), 7. 08 (2H, d, *J* 8.2, Ar), 7. 25 (5H, m, Ar) and 7. 70 (2H, d, *J* 8. 2, Ar); δ_C (125. 76MHz, C^2HCl_3), 30. 6 (6-$\underline{C}H_2$), 51. 53 (5-$\underline{C}H_2$), 52. 49 (-$\underline{C}H_3$), 62. 29 (4-$\underline{C}H$), 80. 05 (2-$\underline{C}H$), 127. 13, 127. 94, 128. 49, 129. 01 and 129. 79 ($\underline{C}H$-Ar), 133. 33 ($\underline{C}$-Ar), 137. 21 ($\underline{C}CH_3$), 144. 56 ($\underline{C}SO_2$) and 169. 53 ($\underline{C}O_2R$).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-3,4-dehydro-4-trimethylsilyloxyprolinate (33)** - Di-isopropylamine (0. 116 ml, 0. 84 mmol) was dissolved in dry tetrahydrofuran (1 ml), at -78 °C in an atmosphere of nitrogen. *n*-Butyl lithium (1. 6 *M* in hexane; 0. 46 ml, 0. 74 mmol) was added and the solution was stirred for 0. 5 h. A solution of *tert*-butyl (2S)-N-*tert*-butoxycarbonyl-4-oxoprolinate **(7)** (0. 2 g, 0. 7 mmol) in tetrahydrofuran (1 ml) was added and the mixture was stirred for 1 h at -78 °C. Chlorotrimethylsilane (0. 152 ml, 1. 2 mmol) was added slowly over a period of 5 min. The reaction was warmed to room temperature, stirred for 1 h and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml) and the solid lithium chloride was removed by filtration. The solvent removed *in vacuo*. The resultant pale yellow oil was used unpurified (0. 197 g, 79%); ν_{max}(film) / cm^{-1} 1746 (ester) 1709 (urethane) and 1655 (enol ether); δ_H (360MHz, C^2HCl_3), 0. 2 (9H, 2 x s, -Si($C\underline{H}_3$)$_3$), 1. 45 (18H, 3 x s, -C($C\underline{H}_3$)$_3$), 3. 9 - 4. 2 (2H, m, $\underline{H}$-5) and 4. 6 (2H, m, $\underline{H}$-2 and $\underline{H}$-3).

***tert*-Butyl (2S)-N-*tert*-Butoxycarbonyl-3,3-*bis*-(*tert*-butoxycarbonylmethyl)-4-oxoprolinate (35)** - Benzyltrimethylammonium fluoride hydrate (0. 039 g, 0. 23 mmol) and 4Å sieves were suspended in dry tetrahydrofuran (1 ml) under nitrogen and stirred at room temperature for 20 h. A solution of *tert*-butyl bromoacetate (0. 031 ml, 0. 2 mmol) and *tert*-butyl N-*tert*-butoxycarbonyl-3,4-dehydro-3-trimethylsilyloxy-prolinate **(33)** (0. 08 g, 0. 21 mmol) in dry tetrahydrofuran (1 ml) was added to the suspension over a period of 5 min. The mixture was stirred at room temperature for 16 h, filtered through Celite and the solvent was removed *in vacuo* to yield an oil which was purified by column chromatography (silica gel - diethyl ether : petroleum ether (60-80 °C), 1 : 2) to afford a colourless oil which solidified on standing (0. 03 g) m.p. 38-41 °C; $[\alpha]_D^{27}$ + 4. 95 (*c* 0. 27, MeOH); (Found m / z 513. 28975. $C_{26}H_{43}NO_9$ requires m / z 513. 29364); ν_{max} (film) / cm^{-1} 1769 (ketone), 1729 (br, ester) and 1695 (urethane); δ_H (500MHz, C^2HCl_3), 1. 42 - 1. 49 (36H, 5 x s, -C($C\underline{H}_3$)$_3$), 2. 44 (1H, 2 x d, $J_{6A,6B}$ 18, $\underline{H}$-6_A), 2. 6 (1H, t, $J_{8A,8B}$ 14. 2, $\underline{H}$-8_A), 2. 86 - 2. 94 (2H, m, $J_{8B,8A}$ 14. 2, $J_{6B,6A}$ 18, $\underline{H}$-6_B and $\underline{H}$-8_B), 4. 0 (2H, AB, $J_{5A,5B}$ 18. 4, $\underline{H}$-5) and 4. 56 (1H, 2 x s, $\underline{H}$-2); δ_C (125. 76MHz, C^2HCl_3), 27. 93, 27. 99, 28. 08 and 28. 31 (C($\underline{C}H_3$)$_3$), 36. 55 and 37. 48 (6-$\underline{C}H_2$), 41. 92 and 42. 46 (8-$\underline{C}H_2$), 51. 15 and 52. 05 (3-$\underline{C}$), 52. 24 and 52. 93 (5-$\underline{C}H_2$), 65. 36 and 65. 72 (2-$\underline{C}H$), 80. 77, 81. 07, 81. 59, 81. 72, 81. 97, 82. 49 and 82. 96 ($\underline{C}(CH_3)_3$), 153. 89 and 154. 57 (N$\underline{C}O_2R$), 168.39, 168. 59, 168. 73, 168. 83, 168. 95 and 169. 15 ($\underline{C}O_2R$), and 209. 02 and 210. 22 (4-$\underline{C}$=O).

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