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Enantiospecific Synthesis of (3*R*, 4*R*)-3-Amino-1-Hydroxy-4-Methyl Pyrrolidin-2-one (L-687,414), an NMDA Receptor Antagonist

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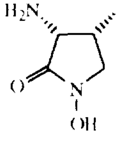
Abstract: An enantiospecific synthesis of the NMDA receptor antagonist (3*R*, 4*R*)-3-amino-1-hydroxy-4-methylpyrrolidin-2-one *via* ring opening of the chiral β-lactam (**9**) is reported.

INTRODUCTION

Intensive efforts to identify antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptors for the treatment of pathological conditions such as cerebral ischaemia and epilepsy have led to the discovery of functionalised pyrrolidin-2-ones as active leads. In particular (3*R*, 4*R*)-3-amino-1-hydroxy-4-methyl pyrrolidin-2-one (**1**) (L-687,414) has been claimed by groups at both Merck, Sharp and Dohme and Pfizer pharmaceutical companies to be one of the most potent antagonists of its class with its significant *in vivo* activity suggesting good penetration of the blood-brain barrier.[1-4] Moreover, it has been demonstrated that (**1**), which displays both anticonvulsant and neuroprotective properties, acts upon the glycine modulatory site of the NMDA receptor and that activity is confined only to the (3*R*, 4*R*) isomer. Although both Merck, Sharp and Dohme and Pfizer have described syntheses of (**1**) their routes lacked efficient stereochemical control and also they report inconsistent optical data for (**1**).[1,3,4] As such an independent, high yielding synthesis with controllable stereoselectivity and flexibility with respect to potentially useful analogues was desirable. Herein we describe such a synthesis.



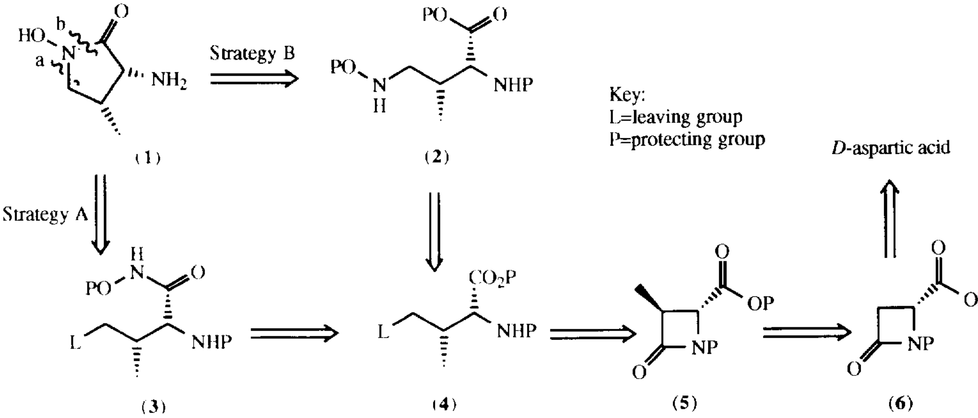
(**1**)

Figure 1

RESULTS AND DISCUSSION

Retrosynthetic Analysis

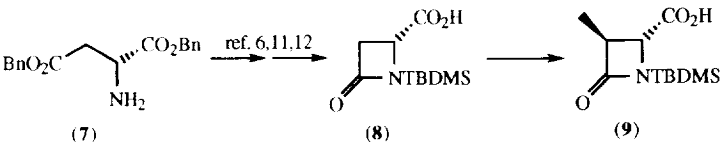
Our group has previously made a number of significant contributions into the use of simple β-lactams as precursors of amino acids and heterocycles.[5-10] As a continuation of this program it was envisaged that (**1**) and related analogues could be derived in a stereoselective manner from β-lactam (**6**)[6,7] (available from *D*-aspartic acid[6,11,12]) *via* one of two possible pathways, Scheme 1. Key to the overall approach would be the stereospecific *trans* alkylation of β-lactam (**6**) which would confer the correct 4*R* absolute configuration of (**1**). Subsequent cleavage of the lactam bond and the incorporation of a suitable leaving group at C-4, generating (**4**), could be followed by either conversion to the hydroxamic acid (**3**) (Strategy A) or to hydroxylamine (**2**) (Strategy B) from which (**1**) could be derived *via* suitable ring closure protocols.



Scheme 1

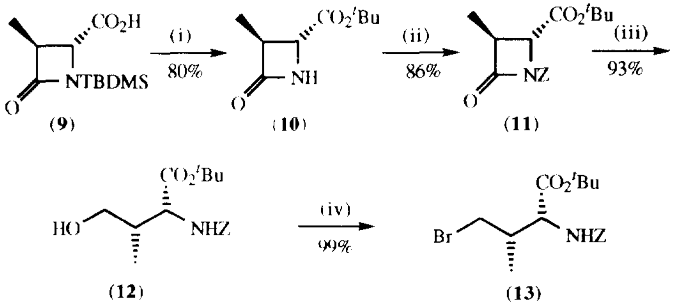
Preparation of a Suitably Protected form of Key Intermediate (4)

β-Lactam (**8**), prepared as previously described in four steps from the readily available *D*-aspartic acid, was subject to stereospecific *trans* methylation, Scheme 2. This was achieved by treatment of (**8**) with 2.2 equivalents of LDA and quenching of the resulting dianion with methyl iodide to afford, after work-up, (**9**).[9] The ^1H n.m.r. of the crude reaction mixture showed only one set of resonances attributable to the β-lactam and the stereochemistry of (**9**) was assigned as *trans* based upon the observed coupling constant for 3H-4H of 2.5Hz. In previous reports[13,14] $J_{3H\text{-}4H}$ for *trans* β-lactams systems was found to be in the range 1-3Hz, whereas for the *cis* orientation a coupling of 5-8Hz was observed.



Scheme 2

With the carbon skeleton in place cleavage of the amide bond of (**9**) would be required to generate key intermediate (**4**), Scheme 1. Previous experience with the nucleophilic ring opening of β-lactams has indicated the need for a sterically demanding ester function to inhibit products arising from attack at the ester carbonyl.[6,7] In addition the efficiency of the amide bond cleavage has been shown to be enhanced by activation of the nitrogen with an electron withdrawing group such as a carbamate. Thus treatment of (**9**) with *O*-(^{t}-butyl)trichloroacetimidate and catalytic $BF_3.Et_2O$ gave the ^{t}-butyl ester[15] and exposure of the resultant mixture of *N*-silylated and free amino ^{t}-butyl esters to CsF afforded (**10**) in 80% yield. Amide (**10**) was then activated towards nucleophilic attack by formation of the corresponding *N*-benzyloxycarbamate using dibenzyldicarbonate and catalytic DMAP[8] yielding (**11**) (86%). Reductive ring opening of (**11**) was smoothly accomplished using sodium borohydride in MeOH[9] to afford alcohol (**12**) as a colourless oil in 93% yield which was converted into the corresponding bromide using a carbon tetrabromide/triphenylphosphine protocol[16-18] in near quantitative yield, Scheme 3.

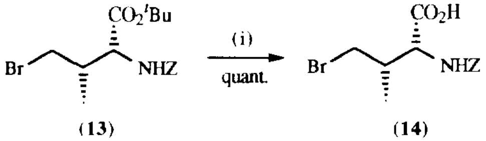


(i) $Cl_3CC(NH)O^tBu$ (2eq.), $BF_3.Et_2O$ (cat.), DCM:cyclohexane (1:2), RT, 1h. then CsF (1.5eq.), MeOH, RT, 1h.; (ii) Z_2O (2.1eq.), DMAP (cat.), MeCN, RT, 100min.; (iii) $NaBH_4$ (3eq.), MeOH, 0°C, 40min.; (iv) CBr_4 (1.25eq.), PPh_3 (1.5eq.), DCM, 0°C, 90min.

Scheme 3

Strategy A

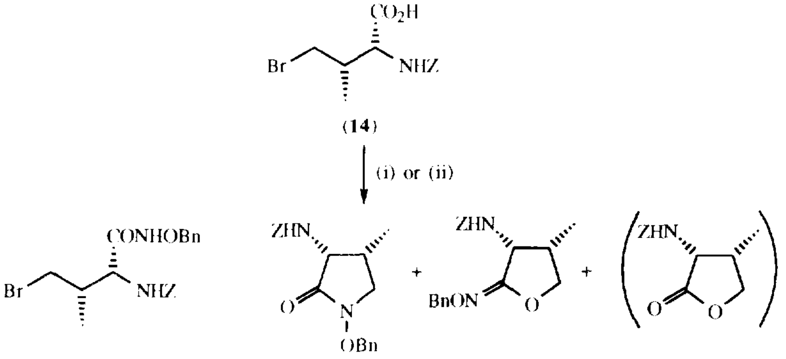
With a high yielding route to bromide (**13**) in hand its conversion into the target material (**1**) was investigated. *Strategy A* was studied initially. Deprotection of the ester functionality of (**13**) was achieved using TFA in high yield to afford the corresponding carboxylic acid, Scheme 4, which under basic conditions spontaneously lactonised to (**18**).



(i) TFA, RT, 45min.

Scheme 4

Attempts to couple acid (**14**) with the *O*-benzyl hydroxylamine proved problematic. A number of coupling reagents were investigated with DCC[19] in the presence of HOBt proving to be superior. Formation of the hydroxamate (**15**), obtained in highest yield using DCC (1.3eq.) and HOBt (1.3 eq.) in DCM (1.5 hours, RT), was, however, accompanied by imidate (**17**) presumably arising from cyclisation of (**15**) *via* the hydroxamic acid oxygen and lactone (**18**) arising from intramolecular cyclisation of acid (**14**), Scheme 5. Somewhat unexpectedly an increase in the quantity of both DCC and HOBt to 3 equivalents led to the generation, in 22% yield, of the protected target material (**16**), accompanied by (**15**) in 21% yield as well as lactone (**18**) and imidate (**17**).



	(**15**)	(**16**)	(**17**)	(**18**)
Procedure (i)	44%	—	14%	6%
Procedure (ii)	21%	22%	11%	3%

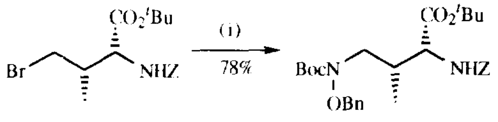
(i) NH$_2$OBn (1.2eq.), DCC (1.3eq.), HOBt (1.3eq.), DCM, RT, 90min.;
(ii) NH$_2$OBn (3eq.), DCC (3eq.), DCM, RT, 120min.

Scheme 5

The ambident behaviour of hydroxamates towards electrophiles is well established but the tendency of hydroxamate (**15**) to cyclise *via* oxygen as shown by the above results was unexpected. Indeed the alkylation of hydroxamates under neutral conditions has been little studied and the preferred mode of attack is unclear. However, under basic conditions it has been demonstrated that from the reaction of simple hydroxamates with alkyl halides the *N*-substituted product generally predominates, the exact ratio of the *N* and *O*-substituted products being largely dependent on the steric bulk of the halide, the solvent and the base employed.[20,21] Thus it was hoped that by the judicious choice of conditions that cyclisation of (**15**) to *via* nitrogen could be favoured. However, we were unable to effect ring closure of (**15**) to (**16**) *via* the hydroxamate nitrogen anion, despite having obtained (**16**) in low yield from the coupling reaction discussed above. Under conditions described by Johnson for *N*-alkylation of hydoxamic acids (K$_2$CO$_3$, MeOH, H$_2$O), for example, only (**17**) was isolated in a 42% yield from (**15**). Thus, *Strategy A* was abandoned.

Strategy B

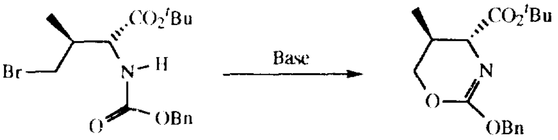
An alternative approach to (**1**), *Strategy B*-Scheme 1, involved the S$_N$2 displacement of the bromide of (**13**) with BocHNOBn in the presence of potassium carbonate to afford hydroxylamine (**19**). This reaction was found to be highly solvent dependent with good yields of the desired product being obtained only when DMF was employed, Scheme 6. The use of acetonitrile (as utilised by Pfizer in a similar procedure at reflux in their synthesis of (**1**),[4]) for example, led at 70°C to substantial quantities of a by-product consistent with oxazine (**20**) derived from cyclisation *via* the benzyloxycarbamate group, Scheme 7.



(**13**) (**19**)

(i) BocNHOBn (4eq.), K_2CO_3 (2eq.), KI (0.1eq.), DMF, RT, 55h.

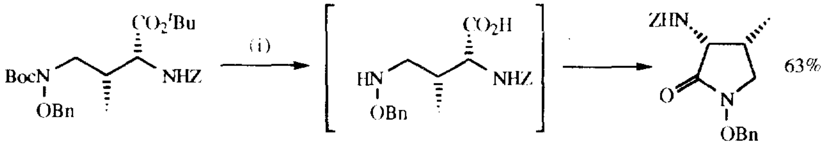
Scheme 6



(**13**) (**20**)

Scheme 7

Removal of the ^{t}butyl ester and Boc protecting groups of (**19**) was accomplished by treatment with TFA for 45 minutes at room temperature. Acid (**21**) was not routinely isolated as further exposure to TFA (up to 3 hours) brought about the desired acid catalysed cyclodehydration to generate the protected heterocycle (**16**) as a crystalline solid, Scheme 8.



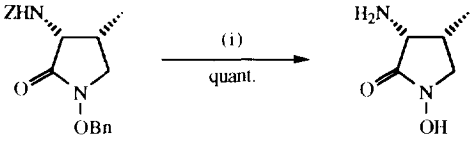
(**19**) (**21**) (**16**)

(i) TFA, RT, 3h.

Scheme 8

Preparation of (3R, 4R)-3-amino-1-hydroxy-4-methylpyrrolidin-2-one (1)

Deprotection of (**16**) was readily accomplished by hydrogenolysis to afford the target material (**1**) in quantitative yield, Scheme 9. Appropriate n.O.e. studies were in agreement with those previously reported for (**1**)[22] and confirm the relative *cis* stereochemistry of the amine and methyl groups, Figure 2.



(16) **(1)**

(i) $Pd(OH)_2$ (cat.), H_2, MeOH, RT, 105min.

Scheme 9

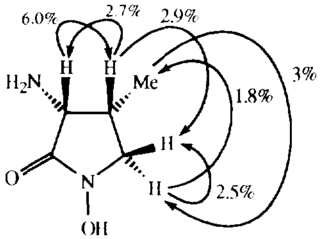


Figure 2

In summary an independent synthesis of (3*R*, 4*R*)-3-amino-1-hydroxy-4-methyl pyrrolidin-2-one (**1**) was accomplished in a stereospecific fashion from a readily available optically active starting material *via strategy B*, Scheme 1. The specific rotation of (**1**) was found to be +14.3 (*c* 0.49, MeOH) (literature values of 16.5 (*c* 0.48, MeOH)[2] and 10.4 (*c* 0.47, MeOH)[4] were reported by Merck, Sharp and Dohme and Pfizer respectively).

EXPERIMENTAL

Experimental Techniques

Melting points (m.p.) were obtained using a Thermogalen™ III melting point apparatus and are uncorrected.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at approximately 20°C with a pathlength of 1dm. Concentrations (*c*) are given in g/100ml.

Infrared (IR) spectra were recorded as thin films between NaCl plates, as KBr discs or in $CHCl_3$ solution on a Perkin-Elmer 1750 Fourier Transform spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Proton magnetic resonance spectra (^1H N.M.R.) were recorded at 200MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer and at 500MHz on a Bruker AM500 spectrometer. The nOes determined for (3*R*,4*R*)-3-amino-1-hydroxy-4-methylpyrrolidin-2-one (**1**) were recorded at 500MHz on a Bruker AMX500 spectrometer. For ^1H N.M.R. recorded in $CDCl_3$ and D_2O chemical shifts (δ_H) are quoted in parts per million (p.p.m.) and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5Hz.

Carbon magnetic resonance spectra (^{13}C N.M.R.) were recorded at 50.31MHz on a Varian Gemini 200 or Bruker AC200 spectrometer and at 125.77MHz on a Bruker AMX500 spectrometer using DEPT editing. Chemical shifts (δ_C) are quoted in p.p.m. and referenced to $CDCl_3$ unless otherwise stated. Spectra recorded in D_2O are referenced to internal 1,4-dioxane.

Low resolution mass spectra (m/z) were recorded on a V.G. Micromass ZAB 1F (CI/DCI/FAB), a V.G. Masslab 20-250 (CI/DCI) or a V.G. BIO Q (electrospray) spectrometer, with only molecular ions (M^+), fragments from molecular ions and major peaks being reported.

Accurate mass analyses were performed as accurate mass CI peak match on $(M+H)^+$ or $(M+NH_4)^+$ by EPSRC Mass Spectrometry Service Centre, Chemistry Department, University of Wales, Swansea.

Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford.

Flash chromatography was accomplished on silica gel using Sorbsil^{TM} C60. Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254} which were visualised by the quenching of UV fluorescence (λ_{max}=254nm), by staining with 10%w/v ammonium molybdate in 2M sulphuric acid, 5%w/v phosphomolybdic acid in 95% ethanol or ninhydrin, followed by heat.

All solvents were distilled before use. Anhydrous DCM was obtained by stirring over calcium hydride for 24 hours followed by distillation under argon. Anhydrous Et_2O and anhydrous THF were obtained by distillation from sodium/benzophenone ketyl under nitrogen. Anhydrous cyclohexane and anhydrous ^{t}BuOH were obtained by distillation from calcium hydride at atmospheric pressure and stored over 4Å molecular sieves. Anhydrous DMF and anhydrous *n*-octanol were obtained by distillation from calcium hydride under reduced pressure and stored over 4Å molecular sieves. P.E. 30-40 refers to the fraction of light petroleum ether boiling between 30-40°C. Solvents were evaporated at 30°C or below on a Büchi R Rotavapor; high boiling solvents were evaporated on a Büchi RE111 Rotavapor fitted with a dry ice condenser at <2mmHg. Et_3N, $^iPr_2NEt$ and $^iPr_2NH$ were distilled from calcium hydride and stored over 4Å molecular sieves. All other reagents were purified in accordance with the instructions in D.D. Perrin and W.L.F. Armarego, "Purification of Laboratory Chemicals", 3rd edition, Pergamon Press, London, 1988 or used as obtained from commercial sources. All chemicals were handled in accordance with the safety instructions identified in "Good Laboratory Practice" Dyson Perrins Laboratory, 1993-94.

Experimental Procedures

(3*S*,4*R*)-*N*-(^{t}-Butyldimethylsilyl)azetidine-3-methyl-2-one-4-carboxylic acid (**9**)

To a stirred solution of $^iPr_2NH$ (12.1cm^3, 0.086mol) in anhydrous THF (100cm^3) at 0°C under an inert atmosphere of argon was added ^{n}BuLi (40.9cm^3, 0.086mol) and the solution was stirred for 10 minutes. This solution was then added dropwise to a solution of (4*R*)-*N*-(^{t}-butyldimethylsilyl)azetidin-2-one-4-carboxylic acid (**8**) (8.96g, 0.039mol) in anhydrous THF (100cm^3) at 0°C under an inert atmosphere of argon and the solution was stirred for a further 10 minutes. To this solution was added MeI (7.3cm^3, 0.117mol) and the solution stirred for a further 1 hour. The reaction was quenched by the addition of a 1: 1 mixture of 1N aqueous $KHSO_4$: EtOAc (600cm^3). The phases were separated and the aqueous layer extracted with further EtOAc (2 x 250cm^3). The combined EtOAc layers were washed with distilled water (250cm^3), saturated brine (250cm^3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a yellow solid which was recrystallised (Et_2O, P.E. 30-40) to yield (3*S*,4*R*)-*N*-(^{t}-butyldimethylsilyl)azetidin-3-methyl-2-one-4-carboxylic acid (**9**) as colourless needles, (7.69g, 81%); R_f 0.2 (Et_2O: P.E. 30-40; 50: 50); m.p. 115-117°C; $[\alpha]^{22}_D$ +39.8 (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3439br w (OH), 2951m, 2930m and 2856m (CH), 1746s (β-lactam C=O), 1689m (acid C=O), 1295m, 1201m and 844m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.14 and 0.31 (2 x 3H, 2 x s, 2 x $SiC\underline{H}_3$), 0.97 (9H, s, $SiC(C\underline{H}_3)_3$), 1.42 (3H, d, *J* 7.5Hz, $CHC\underline{H}_3$) 3.34 (1H, dq, *J* 2.5Hz, *J* 7.5Hz, 3-H) and 3.71 (1H, d, *J* 2.5Hz, 4-H); δ_C (50.3MHz; $CDCl_3$) -6.56 and -6.07 (2 x $Si\underline{C}H_3$), 13.86 ($CH\underline{C}H_3$), 18.46 ($Si\underline{C}(CH_3)_3$), 26.07 ($SiC(\underline{C}H_3)_3$), 52.74 ($\underline{C}HCH_3$), 56.72 ($\underline{C}HCO_2$), 175.66 and 177.23 (2 x C=O); m/z (desorption chemical ionisation, NH_3) 358 [$(M+SiMe_2{}^tBu)^+$, 29%], 261 [$(M+NH_4)^+$, 15], 244 [$(M+H)^+$, 74], 216 [52], 143 [62] and 130 [100]; acc. mass found 244.1369; acc. mass required for [$C_{11}H_{21}NO_3Si$ + H] 244.1369; anal. found C 54.39, H 8.91, N 5.48; anal. required for $C_{11}H_{21}NO_3Si$ C 54.29, H 8.70, N 5.76%.

(3*S*,4*R*)-^{t}Butyl azetidin-3-methyl-2-one-4-carboxylate (**10**)

To a stirred solution of (3*S*,4*R*)-*N*-(^{t}butyldimethylsilyl)azetidin-3-methyl-2-one-4-carboxylic acid (**9**) (7.69g, 0.032mol) in a 1: 1 mixture of anhydrous DCM: anhydrous cyclohexane (160cm^3) was added $BF_3.Et_2O$ (200cm^3) followed rapidly by a solution of ^{t}butyl trichloroacetimidate (13.81g, 0.063mol) in anhydrous cyclohexane (80cm^3). The reaction mixture was stirred for 1 hour, quenched by the addition of solid $NaHCO_3$ (10g), and concentrated *in vacuo*. The resulting solid material was triturated repeatedly with P.E. 30-40 (5 x 100cm^3). The P.E. 30-40 portions were filtered through a plug of Celite® and then concentrated *in vacuo* to yield a yellow oil. To a stirred solution of this crude material in methanol (250cm^3) was added CsF (7.29g, 0.048mol). The solution was stirred for 1 hour and then concentrated *in vacuo*. The residue was taken into DCM (250cm^3) and the DCM solution was washed with distilled water (2 x 250cm^3), saturated brine (250cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 70: 30) to yield (3*S*,4*R*)-^{t}butyl azetidin-3-methyl-2-one-4-carboxylate (**10**) as white crystalline solid, (4.71g, 80%); R_f 0.45 (Et_2O: P.E. 30-40; 80: 20); m.p. 89-91°C; $[\alpha]^{22}_D$ -18.7 (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3213br m (NH), 3006m, 2986m, 2936m and 2874m (CH), 1751s and 1725s (2 x C=O), 1370m, 1305m and 1160m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.44 (3H, d, *J* 7.5Hz, $CHC\underline{H}_3$), 1.50 (9H, s, $OC(C\underline{H}_3)_3$), 3.26 (1H, dq, *J* 2.5Hz, *J* 7.5Hz, 3-H), 3.74 (1H, d, *J* 2.5Hz, 4-H) and 5.96 (1H, br s, $N\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 13.18 ($CH\underline{C}H_3$), 27.85 ($OC(\underline{C}H_3)_3$), 52.22 ($\underline{C}HCH_3$), 55.88 ($\underline{C}HCO_2$), 82.48 ($O\underline{C}(CH_3)_3$), 170.49 and 170.89 (2 x C=O); m/z (chemical ionisation, NH_3) 203 [$(M+NH_4)^+$, 100%], 186 [$(M+H)^+$, 75], 158 [88], 147 [78], 102 [40] and 58 [48]; anal. found C 58.40, H 8.05, N 7.46; anal. required for $C_9H_{15}NO_3$ C 58.36, H 8.16, N 7.56%.

(3*S*,4*R*)-^{t}Butyl *N*-(benzyloxycarbonyl)azetidin-3-methyl-2-one-4-carboxylate (**11**)

To a stirred solution of (3*S*,4*R*)-^{t}butyl azetidin-3-methyl-2-one-4-carboxylate (**10**) (171mg, 0.92mmol) in anhydrous acetonitrile (10cm^3) under an inert atmosphere of argon was added dibenzyl dicarbonate (556mg, 1.94mmol) followed by DMAP (29mg, 0.24mmol). The reaction mixture was stirred for 1 hour 40 minutes, then diluted with DCM (220cm^3), washed with 1M $KHSO_4$ (2 x 75cm^3), saturated $NaHCO_3$ (440cm^3), saturated brine (440cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil which was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 25: 75) and extrusion of benzyl alcohol by heating on a vacuum line to 50°C for 7 hours to yield (3*S*,4*R*)-^{t}butyl *N*-(benzyloxycarbonyl)azetidin-3-methyl-2-one-4-carboxylate (**11**) as a pale yellow oil, (254mg, 86%); R_f 0.3 (Et_2O: P.E. 30-40; 30: 70); $[\alpha]^{22}_D$ +36.3 (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, NaCl plates) 2979w and 2937w (CH), 1825s (β-lactam C=O), 1733s (ester and carbamate C=O), 1391m, 1327m, 1306m and 1154m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.42 (9H, s, OC(C$\underline{H}_3$)$_3$), 1.44 (3H, d, *J* 7Hz, CHC$\underline{H}_3$), 3.23 (1H, dq, *J* 3Hz, *J* 7Hz, 3-H), 3.97 (1H, d, *J* 3Hz, 4-H), 5.23 and 5.32 (2H, ABq, *J* 12Hz, C$\underline{H}_2$(C_6H_5)) and 7.26-7.40 (5H, m, CH_2($C_6\underline{H}_5$)); δ_C (50.3MHz; $CDCl_3$) 12.83 (CH$\underline{C}H_3$), 27.71 (OC($\underline{C}H_3$)$_3$), 50.38 ($\underline{C}HCH_3$), 58.04 ($\underline{C}HCO_2$), 68.29 ($\underline{C}H_2$(C_6H_5)), 83.08 (O$\underline{C}$(CH_3)$_3$), 128.56 and 128.78 (aromatic CH), 135.04 (aromatic ipso C), 148.64, 166.41 and 168.12 (3 x C=O); m/z (chemical ionisation, NH_3) 337 [$(M+NH_4)^+$, 21%], 281 [48], 192 [29], 108 [53] and 91 [$(C_7H_7)^+$, 100]; acc. mass found 337.1763; acc. mass required for $[C_{17}H_{21}NO_5 + H]^+$ 337.1763.

(2*R*,3*S*)-^{t}Butyl 2-*N*-(benzyloxycarbonyl)-4-hydroxy-3-methylbutanoate (**12**)

To a stirred solution of (3*S*,4*R*)-^{t}butyl *N*-(benzylcarbonyl)-azetidin-3-methyl-2-one-4-carboxylate (**11**) (300mg, 0.94mmol) in methanol (7cm^3) at 0°C was added $NaBH_4$ (107mg, 2.82mmol) in small portions. The solution was stirred for 40 minutes at 0°C before the reaction was quenched by the addition of flash silica (7cm^3) and methanol (18cm^3). The methanol was evaporated *in vacuo* and the silica triturated repeatedly with EtOAc (90cm^3). The EtOAc portions were filtered through a plug of Celite® and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 40: 60) to yield (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyloxycarbonyl)-4-hydroxy-3-methylbutanoate (**12**) as a colourless, thick oil, (283mg, 93%); R_f 0.15 (Et_2O: P.E. 30-40; 50: 50); $[\alpha]^{25}_D$ -8.6 (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, NaCl plates) 3374br m (OH), 2977m and 2936m (CH), 1718br s (2 x C=O), 1515m and 1157s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.02 (3H, d, *J* 7Hz, CHC$\underline{H}_3$), 1.48 (9H, s, OC(C$\underline{H}_3$)$_3$), 2.03-2.14 (1H, m, 3-H), 2.58 (1H, br s, O$\underline{H}$), 3.50-3.71 (2H, m, C$\underline{H}_2$OH), 4.27 (1H, dd, *J* 6Hz, *J* 8Hz, 2-H), 5.12 (2H, s, C$\underline{H}_2$(C_6H_5)), 5.73 (1H, d, *J* 8Hz, N$\underline{H}$) and 7.31-7.36 (5H, m, CH_2(C_6H_5)); δ_C (50.3MHz; $CDCl_3$) 13.58 (CH$\underline{C}H_3$), 27.82 (OC($\underline{C}H_3$)$_3$), 38.33 ($\underline{C}HCH_3$), 56.97 ($\underline{C}HCO_2$), 64.18 ($\underline{C}H_2$OH), 66.96 ($\underline{C}H_2$(C_6H_5)), 82.26 (O$\underline{C}$(CH_3)$_3$), 128.25 and 128.63 (aromatic C$\underline{H}$), 136.42 (aromatic ipso C), 156.87 and 171.47 (2 x C=O); m/z (chemical ionisation, NH_3) 341 [$(M+NH_4)^+$, 4%], 324 [$(M+H)^+$, 32], 268 [83], 224 [100], 178 [77], 108 [30] and 91 [$(C_7H_7)^+$, 97]; acc. mass found 324.1811; acc. mass required for $[C_{17}H_{25}NO_5 + H]^+$ 324.1811.

(2*R*,3*S*)-^{t}Butyl 2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**13**)

To a stirred solution of (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyloxycarbonyl)-4-hydroxy-3-methylbutanoate (**12**) (50mg, 0.15mmol) and CBr_4 (64mg, 0.19mmol) in anhydrous DCM (2cm^3) under an inert atmosphere of argon was added dropwise at 0°C a solution of PPh_3 (61mg, 0.23mmol) in anhydrous DCM (1cm^3). This mixture was stirred for 1 hour 30 minutes at 0°C and then concentrated *in vacuo* to yield a yellow oil which was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 20: 80) to yield (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyoxylcarbonyl)-4-bromo-3-methylbutanoate (**13**) as colourless oil, (59mg, 99%); R_f 0.25 (Et_2O: P.E. 30-40; 20: 80); $[\alpha]^{24}_D$ -18.1 (*c* 1.0 in $CHCl_3$); ν_{max} (FT IR, NaCl plates) 3340br m (NH), 2977m (CH), 1723br s (2 x C=O), 1520br m, 1369m, 1234br m and 1154s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.09 (3H, d, *J* 7Hz, CHC$\underline{H}_3$), 1.49 (9H, s, OC(C$\underline{H}_3$)$_3$), 2.34-2.37 (1H, m, 3-H), 3.31 (1H, dd, *J* 8Hz, *J* 10Hz, C$\underline{H}_A$$H_B$Br), 3.49 (1H, dd, *J* 5.5Hz, *J* 10Hz, $CH_A$$\underline{H}_B$Br), 4.41 (1H, dd, *J* 5Hz, *J* 8Hz, 2-H), 5.13 (2H, s, C$\underline{H}_2$(C_6H_5)), 5.52 (1H, d, *J* 8Hz, N$\underline{H}$) and 7.33-7.41 (5H, m, CH_2($C_6\underline{H}_5$)); δ_C (50.3MHz; $CDCl_3$) 14.87 (CH$\underline{C}H_3$), 27.93 (OC($\underline{C}H_3$)$_3$), 35.60 ($\underline{C}H_2$Br), 39.27 ($\underline{C}HCH_3$), 57.37 ($\underline{C}HCO_2$), 67.11 ($\underline{C}H_2$(C_6H_5)), 82.99 (O$\underline{C}$(CH_3)$_3$), 128.38 and 128.74 (aromatic CH), 136.38 (aromatic *ipso* C), 156.09 and 170.22 (2 x C=O); m/z (chemical ionisation,

NH_3) 403/5 [$(M+NH_4)^+$, 7/8%], 386/8 [$(M+H)^+$, 7/6], 108 [30] and 91 [$(C_7H_7)^+$, 100]; acc. mass found 386.0967; acc. mass required for [$C_{17}H_{24}{}^{79}BrNO_4 + H]^+$ 386.0967.

(2*R*,3*S*) 2-N-(Benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**14**)

(2*R*,3*S*)-^{t}Butyl-2-*N*-(benzyoxylcarbonyl)-4-bromo-3-methylbutanoate (**13**) (53mg, 0.14mmol) was dissolved in TFA (3cm^3). This solution was stirred for 45 minutes and then concentrated *in vacuo*. The residual TFA was removed azeotropically with toluene to yield (2*R*,3*S*)-2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**14**) as pale yellow semi-solid, (45mg, ca. quant.); $[\alpha]^{25}_D$ -16.0 (*c* 0.8 in $CHCl_3$); ν_{max} (FT IR, NaCl plates) 3318br m (NH), 3067m, 3034m and 2972m (CH), 1720br s (2 x C=O), 1524br s, 1455m, 1236br s and 697s cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.13 (3H, d, *J* 6Hz, $CHC\underline{H}_3$), 2.41-2.49 (1H, m, 3-H), 3.34-3.42 (1H, m, $C\underline{H}_ACH_BBr$), 3.48-3.57 (1H, m, $CH_AC\underline{H}_BBr$), 4.50-4.59 (1H, m, 2-H), 5.15 (2H, s, $C\underline{H}_2(C_6H_5)$), 5.50 (1H, br d, *J* 6Hz, N$\underline{H}$) and 7.37-7.39 (5H, m, $CH_2(C_6\underline{H}_5)$); δ_C (50.3MHz; $CDCl_3$) 15.22 ($CH\underline{C}H_3$), 35.24 ($\underline{C}H_2Br$), 38.46 ($\underline{C}HCH_3$), 56.84 ($\underline{C}HCO_2$), 67.53 ($\underline{C}H_2(C_6H_5)$), 128.42, 128.62 and 128.82 (aromatic CH), 136.01 (aromatic *ipso* C), 156.45 and 175.82 (2 x C=O); m/z (FAB+) 332/330 [$(M+H)^+$, 1/2%], 250 [$(M-Br)^+$, 8], 188 [11], 160 [7], 152 [9] and 91 [$(C_7H_7)^+$, 100].

(3*R*,4*S*)-3-*N*-Benzyloxycarbonyl-4-methyltetrahydrofuran-2-one (**18**)

To a stirred solution of (2*R*,3*S*) 2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**14**) (43mg, 0.13mmol) in anhydrous MeCN (10cm^3) was added anhydrous K_2CO_3 (90mg, 0.65mmol) and this solution was stirred for 20 minutes. The solution was then concentrated *in vacuo* and the residue taken up in DCM (30cm^3) and distilled water (30cm^3) and the aqueous layer was washed with more DCM (2 x 30cm^3). The combined DCM layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 40: 60) to yield (3*R*,4*S*)-3-*N*-benzyloxycarbonyl-4-methyltetrahydrofuran-2-one (**18**) as white crystalline solid, (33mg, quant.); R_f 0.2 (Et_2O: P.E. 30-40; 50: 50); m.p. 98-102°C; $[\alpha]^{24}_D$ -53.2 (*c* 0.7 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3317m (NH), 2981w and 2913w (CH), 1770m (lactone C=O), 1690s (carbamate C=O), 1540m and 1266m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.00 (3H, d, *J* 7Hz, $CHC\underline{H}_3$), 2.91-3.08 (1H, m, $C\underline{H}CH_3$), 4.11 (1H, d, *J* 9Hz, $C\underline{H}_AH_BO$), 4.41 (1H, dd, *J* 5Hz, *J* 9Hz, $CH_A\underline{H}_BO$), 4.57 (1H, t, *J* 6Hz, $C\underline{H}NHZ$), 5.15 (2H, s, $C\underline{H}_2(C_6H_5)$), 5.25 (1H, br, N$\underline{H}$) and 7.30-7.44 (5H, m, $CH_2(C_6\underline{H}_5)$); δ_C (50.3MHz; $CDCl_3$) 12.68 ($CH\underline{C}H_3$), 34.05 ($\underline{C}HCH_3$), 54.49 ($\underline{C}HNHZ$), 67.35 ($\underline{C}H_2O$), 72.43 ($\underline{C}H_2(C_6H_5)$), 128.08, 128.31 and 128.56 (aromatic CH), 135.85 (aromatic *ipso* C), 156.09 and 174.58 (2 x C=O); m/z (chemical ionisation, NH_3) 267 [$(M+NH_4)^+$, 100%], 250 [$(M+H)^+$, 78], 159 [58], 116 [42], 108 [85] and 91 [$(C_7H_7)^+$, 84]; acc. mass found 250.1079: acc mass required for [$C_{13}H_{15}NO_4 + H]^+$ 250.1079; anal. found C 62.81, H 6.31, N 5.30; anal. required for $C_{13}H_{15}NO_4$ C 62.64, H 6.07, N 5.62%.

(2*R*,3*S*)-*N*-*O*-Benzyl-2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanamide (**15**)

To a stirred solution of (2*R*,3*S*) 2-N-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**14**) (492mg, 1.49mmol), DCCI (396mg, 1.94mmol) and HOBt (260mg, 1.94mmol) in anhydrous DCM (20cm^3) under an inert atmosphere of argon was added a solution of H_2NOBn (220mg, 1.79mmol) in anhydrous DCM (10cm^3). The reaction mixture was stirred for 1 hour 30 minutes, then diluted with DCM (100cm^3), washed with 1M HCl (100cm^3), saturated $NaHCO_3$ (100cm^3), saturated brine (100cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was twice dissolved in as little EtOAc as possible, filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; gradient elution 10: 90 to 50: 50) to yield (2*R*,3*S*)-*N*-*O*-benzyl-2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanamide (**15**) as a white crystalline solid, (285mg, 44%); R_f 0.15 (Et_2O: P.E. 30-40; 50: 50); m.p. 147-149°C; δ_H (200MHz; $CDCl_3$) 1.02 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 2.26-2.29 (1H, m, 3-H), 3.42 (2H, d, *J* 4.5Hz, $C\underline{H}_2Br$), 4.05 (1H, t, *J* 9Hz, 2-$\underline{H}$), 4.90 and 5.05 (2 x 2H, 2 x s, 2 x $C\underline{H}_2(C_6H_5)$), 5.65 (1H, d, *J* 9Hz, $N\underline{H}$), 7.33-7.37 (2 x 5H, m, 2 x $CH_2(C_6\underline{H}_5)$) and 9.37 (1H, s, $N\underline{H}OBn$); m/z (desorption chemical ionisation, NH_3) 435/437 [$(M+H)^+$, 67/69%], 141 [45], 108 [41] and 91 [$(C_7H_7)^+$, 100]; acc. mass found 435.0920; acc. mass required for $[C_{20}H_{23}N_2O_4{}^{79}Br + H]^+$ 435.0920.

(3*R*,4*S*)-2-*N*-Benzyloxyimino-3-*N*-benzyloxycarbonyl-4-methylfuran (**17**)

To a stirred solution of (2*R*,3*S*)-*N*-*O*-benzyl-2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanamide (**15**) (153mg, 0.35mmol) in a 1.5: 1 mixture of MeOH: distilled water (10cm^3) was added K_2CO_3 (73mg, 0.53mmol). This reaction mixture was stirred at 38°C for 15 hours and then concentrated *in vacuo*. The residue was taken up in DCM (50cm^3) and distilled water (50cm^3). The aqueous layer was washed with more DCM (3 x 50cm^3). The combined DCM layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 50: 50) to yield (3*R*,4*S*)-2-*N*-benzyloxyimino-3-*N*-benzyloxycarbonyl-4-methylfuran (**17**) as very fine white needles, (52mg, 42%); R_f 0.25 (Et_2O: P.E. 30-40; 50: 50); m.p. 125-127°C; $[\alpha]^{24}_D$ -33.1 (*c* 1.1 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3321br m (NH), 2967w and 2931w (CH), 1721m (C=O), 1672s (C=N), 1530s, 1261m, 1226m and 1023m cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.95 (3H, d, *J* 7Hz, $CHC\underline{H}_3$), 2.86-2.92 (1H, m, $C\underline{H}CH_3$), 4.11 (1H, d, *J* 9Hz, $C\underline{H}_ACH_BO$), 4.36 (1H, dd, *J* 5Hz, *J* 9Hz, $CH_AC\underline{H}_BO$), 4.74 (1H, t, *J* 6Hz, $C\underline{H}NHZ$), 5.00 and 5.13 (2 x 2H, 2 x s, 2 x $C\underline{H}_2(C_6H_5)$) and 7.31-7.79 (2 x 5H, m, 2 x $CH_2(C_6\underline{H}_5)$); δ_C (125.77MHz; $CDCl_3$) 11.68 ($CH\underline{C}H_3$), 35.17 ($\underline{C}HCH_3$), 54.28 ($\underline{C}HNHZ$), 67.09 ($\underline{C}H_2O$), 75.20 and 76.66 (2 x $\underline{C}H_2(C_6H_5)$), 127.85, 127.95, 128.04, 128.23, 128.33 and 128.52 (aromatic CH), 137.02 and 138.70 (2 x aromatic *ipso* C), 155.86 and 156.04 (C=O and C=N); m/z (desorption chemical ionisation, NH_3) 355 [$(M+H)^+$, 18%], 247 [100], 91 [$(C_7H_7)^+$, 54] and 70 [20]; acc. mass found 355.1658; acc. mass required for $[C_{20}H_{22}N_2O_4 + H]^+$ 355.1658; anal. found C 67.59, H 5.99, N 7.64; anal. required for $C_{20}H_{22}N_2O_4$ C 67.78, H 6.26, N 7.90%.

(2*R*,3*S*)-^{t}Butyl 2-*N*-(benzyloxycarbonyl)-3-methyl-4-(*N*-^{t}butoxycarbonyl-*N*-*O*-benzyl) butanoate (**19**)

To a stirred solution of (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**13**) (69mg, 0.18mmol) and BocHNOBn (159mg, 0.71mmol) in anhydrous DMF (2cm^3) under an inert atmosphere of argon was added anhydrous K_2CO_3 (49mg, 0.36mmol) and KI (3mg, 0.018mmol). The reaction mixture was stirred for 55 hours and then concentrated *in vacuo*. The residue was taken up in Et_2O (40cm^3) and distilled water (40cm^3). The aqueous layer was washed with more Et_2O (4 x 40cm^3). The combined Et_2O layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; DCM) to yield (2*R*,3*S*) ^{t}butyl 2-*N*-(benzyloxycarbonyl)-3-methyl-4-(*N*-^{t}butoxycarbonyl-*N*-*O*-benzyl)butanoate (**19**) as colourless oil, (74mg, 78%); R_f 0.15 (DCM); $[\alpha]^{24}_D$ -10.7 (*c* 0.7 in $CHCl_3$); ν_{max} (FT IR, NaCl plates) 3340br w (NH), 3066w, 3033w, 2977m and 2934w (CH), 1723br s (3 x C=O), 1456m, 1494m, 1369m, 1269br m and 1157s cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.96 (3H, d, *J* 7Hz, $CHC\underline{H}_3$), 1.43 and 1.52 (2 x 9H, 2 x s, 2 x $OC(C\underline{H}_3)_3$), 2.46-2.59 (1H, m, 3-H), 3.37 (1H, dd, *J* 7.5Hz, *J* 14.5Hz, $C\underline{H}_AH_BN$), 3.50 (1H, dd, *J* 6.5Hz, *J* 14.5Hz, $CH_A\underline{H}_BN$), 4.29 (1H, dd, *J* 3.5Hz, *J* 9Hz, 2-H), 4.82

and 4.88 (2 x 1H, 2 x d, 2 x *J* 10Hz, $C\underline{H}_2(C_6H_5)$), 5.12 (2H, s, $C\underline{H}_2(C_6H_5)$), 5.61 (1H, d, *J* 9Hz, $N\underline{H}$) and 7.36-7.50 (2 x 5H, m, 2 x $CH_2(C_6\underline{H}_5)$); δ_C (50.3MHz; $CDCl_3$) 14.54 ($CH\underline{C}H_3$), 27.89 and 28.25 (2 x $OC(\underline{C}H_3)_3$), 34.63 ($\underline{C}HCH_3$), 51.04 ($\underline{C}H_2N$), 57.04 ($\underline{C}HCO_2$), 67.87 and 76.48 (2 x $\underline{C}H_2(C_6H_5)$), 81.65 and 82.37 (2 x $O\underline{C}(CH_3)_3$), 128.25, 128.66 and 129.60 (aromatic CH), 135.55 and 136.68 (2 x aromatic *ipso* C), 156.31, 156.62 and 170.60 (3 x C=O); m/z (desorption chemical ionisation, NH_3) 546 [$(M+NH_4)^+$, 73%], 529 [$(M+H)^+$, 12], 429 [82], 373 [98], 108 [32] and 91 [$(C_7H_7)^+$, 100]; acc. mass found 529.2914; acc. mass required for $[C_{29}H_{40}N_2O_7 + H]^+$ 529.2914.

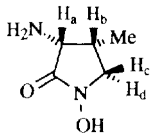
2-Benzyloxy-4-^{t}butoxycarbonyl-5-methyl-5,6-dihydro-1,3,4*H*-oxazine (**20**)

To a stirred solution of (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyloxycarbonyl)-4-bromo-3-methylbutanoate (**13**) (40mg, 0.10mmol) and BocHNOBn (93mg, 0.42mmol) in anhydrous MeCN (2cm^3) under an inert atmosphere of argon was added anhydrous K_2CO_3 (29mg, 0.21mmol) and KI (2mg, 0.01mmol). The reaction mixture was stirred at 70°C for 28 hours and then concentrated *in vacuo*. The residue was taken up in Et_2O (40cm^3) and distilled water (40cm^3), the aqueous layer separated and washed with more Et_2O (4 x 40cm^3). The combined Et_2O layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was purified by flash column chromatography (SiO_2; Et_2O: P.E. 30-40; 20: 80) to yield 2-benzyloxy-4-^{t}butoxycarbonyl-5-methyl-5,6-dihydro-1,3,4*H*-oxazine (**20**) as a white crystalline solid, (22mg, 69%); R_f 0.25 (Et_2O: P.E. 30-40; 20: 80); m.p. 85-88°C; $[\alpha]^{24}_D$ -26.4 (*c* 0.3 in $CHCl_3$); ν_{max} (FT IR, $CHCl_3$ solution) 1732br m (C=O), 1674br m (C=N), 1283m and 1154m cm^{-1}; δ_H (200MHz; $CDCl_3$) 1.06 (3H, d, *J* 7Hz, $CHC\underline{H}_3$), 1.50 (9H, s, $OC(C\underline{H}_3)_3$), 2.07-2.20 (1H, m, $C\underline{H}CH_3$), 3.73 (1H, d, *J* 7Hz, $C\underline{H}CO_2$), 3.86 (1H, dd, *J* 8.5Hz, *J* 10.5Hz, $C\underline{H}_AH_BO$), 4.26 (1H, dd, *J* 4Hz, *J* 10.5Hz, $CH_AC\underline{H}_BO$), 5.11 and 5.21 (2 x 1H, 2 x d, 2 x *J* 12Hz, $C\underline{H}_2(C_6H_5)$) and 7.29-7.42 (5H, m, $CH_2(C_6\underline{H}_5)$); δ_C (125.77MHz; $CDCl_3$) 14.62 ($CH\underline{C}H_3$), 28.06 ($OC(\underline{C}H_3)_3$), 28.75 ($\underline{C}HCH_3$), 62.29 ($\underline{C}HCO_2$), 69.12 ($\underline{C}H_2O$), 70.12 ($\underline{C}H_2(C_6H_5)$), 81.19 ($O\underline{C}(CH_3)_3$), 127.94, 128.08 and 128.34 (aromatic CH), 136.30 (aromatic *ipso* C), 152.98 and 171.82 (C=O and C=N); m/z (chemical ionisation, NH_3) 306 [$(M+H)^+$, 100%], 250 [17], 216 [22] and 91 [$(C_7H_7)^+$, 24]; acc. mass found 306.1705; acc. mass required for $[C_{17}H_{23}NO_4 + H]^+$ 306.1705. Two by-products were obtained: (3*R*,4*S*)-3-*N*-benzyloxycarbonyl-4-methyltetrahydrofuran-2-one (**18**) as white crystalline solid, (4mg, 15%), and (2*R*,3*S*)-^{t}butyl 2-*N*-(benzyloxycarbonyl)-3-methyl-4-(*N*-^{t}butoxycarbonyl-*N*-*O*-benzyl) butanoate (**19**) as colourless oil, (3mg, 5%).

(3*R*,4*R*)-3-Amino-3-*N*-(benzyloxycarbonyl)-1-benzyloxy-4-methylpyrrolidin-2-one (**16**)

(2*R*,3*S*)-^{t}Butyl 2-*N*-(benzyloxycarbonyl)-3-methyl-4-(*N*-^{t}butoxycarbonyl-*N*-*O*-benzyl)butanoate (**19**) (108mg, 0.20mmol) was dissolved in TFA (3cm^3) and stirred for 3 hours. The solution was then concentrated *in vacuo* and the residual TFA was removed azeotropically with toluene. This crude product was purified by flash column chromatography (SiO_2; acetone: P.E. 30-40; 25: 75) to yield (3*R*,4*R*)-3-amino-3-*N*-(benzyloxycarbonyl)-1-benzyloxy-4-methylpyrrolidin-2-one (**16**) as a white crystalline solid, (46mg, 64%); R_f 0.35 (acetone: P.E. 30-40; 25: 75); m.p. 94-97°C; $[\alpha]^{24}_D$ +1.1 (*c* 0.7 in $CHCl_3$); ν_{max} (FT IR, KBr disc) 3338m (NH), 3033w, 3019w, 2954w and 2881w (CH), 1730s and 1713s (2 x C=O), 1526m, 1275w, 1250m, 1013m, 753m and 701w cm^{-1}; δ_H (200MHz; $CDCl_3$) 0.83 (3H, d, *J* 7Hz, $CHC\underline{H}_3$), 2.63-2.79 (1H, m, 4-H), 2.89 (1H, d, *J* 9Hz, $C\underline{H}_AH_BN$), 3.43 (1H, dd, *J* 6Hz, *J* 9Hz, $CH_A\underline{H}_BN$), 4.30 (1H, dd, *J* 5Hz, *J* 7.5Hz, 3-H), 4.98 and 5.04 (2 x 1H, 2 x d, 2 x *J* 11Hz, $C\underline{H}_2(C_6H_5)$), 5.12 (2H, s, $C\underline{H}_2(C_6H_5)$), 5.25 (1H, d, *J* 5Hz, NH) and 7.30-7.48 (2 x 5H, m, 2 x $CH_2(C_6\underline{H}_5)$); δ_C (50.3MHz; $CDCl_3$) 13.88 ($CH\underline{C}H_3$), 29.73 ($\underline{C}HCH_3$), 52.18 ($\underline{C}H_2N$), 53.62 ($\underline{C}HNHZ$), 67.06 and 76.77 (2 x $\underline{C}H_2(C_6H_5)$), 128.01, 128.15, 128.50, 128.57, 129.06 and 129.58 (aromatic CH), 134.77 and 136.10 (2 x *ipso* C), 156.37 and 166.67 (2 x C=O); m/z (chemical ionisation, NH_3) 355 [$(M+H)^+$, 22%], 247 [35], 158 [100], 141 [57], 108 [32] and 91 [$(C_7H_7)^+$, 28]; acc. mass found 355.1658; acc. mass required for [$C_{20}H_{22}N_2O_4$ + H]$^+$ 355.1658.

(3*R*,4*R*)-3-Amino-1-hydroxy-4-methylpyrrolidin-2-one (**1**)



To a stirred solution of (3*R*,4*R*)-3-amino-3-*N*-(benzyloxycarbonyl)-1-benzyloxy-4-methylpyrrolidin-2-one (**16**) (76mg, 0.21mmol) in MeOH (4cm^3) under an inert atmosphere of argon was added $Pd(OH)_2$ (20mg). This suspension was placed under a balloon of hydrogen and stirred for 1 hours 45 minutes. The suspension was then filtered through a plug of Celite® and concentrated *in vacuo* to yield (3*R*,4*R*)-3-amino-1-hydroxy-4-methylpyrrolidin-2-one (**1**) as a light brown solid, (28mg, ca. quant.); $[\alpha]^{24}_D$ +14.3 (*c* 0.49 in MeOH); ν_{max} (FT IR, KBr disc) 3438br m (OH), 2968m and 2929m (CH), 1693s (C=O), 1550w and 999w cm^{-1}; δ_H (200MHz; D_2O, $\underline{H}OD$ 4.60) 0.84 (3H, d, *J* 7Hz, $CH\underline{C}H_3$), 2.38-2.60 (1H, m, $C\underline{H}_bCH_3$), 2.97 (1H, A of ABX, J_{AB} 10Hz, J_{AX} 3Hz, $CH_c\underline{H}_dN$), 3.52 (1H, B of ABX, J_{AB} 10Hz, J_{BX} 7Hz, $C\underline{H}_cH_d$), 3.63 (1H, d, *J* 8Hz, $C\underline{H}_aNH_2$); δ_C (50.3MHz; $CDCl_3$) 13.02 ($CH\underline{C}H_3$), 28.25 ($\underline{C}HCH_3$), 53.21 and 55.80 ($\underline{C}H_2N$ and $\underline{C}HNH_2$) and 164.44 (C=O), m/z (chemical ionisation, NH_3) 148 [$(M+NH_4)^+$, 8], 131 [$(M+H)^+$, 95], 115 [100], 113 [$(M-OH)^+$, 40] and 57 [23].

proton irratiated	nOe shown (>1%)
H_a	H_b (6%)
H_b	H_a (2.7%), H_c (2.9%)
Me	H_d (3%)
H_d	Me (1.8%), H_c (2.5%)

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