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The Stereospecific Synthesis of (2*S*,3*R*) 3-Carboxyproline and (2*S*,3*R*) 3-Aminoproline

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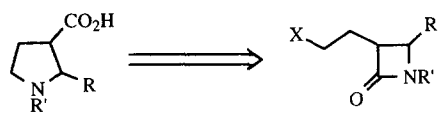
Abstract: Stereospecific syntheses of (2*S*,3*R*) 3-carboxyproline and (2*S*,3*R*) 3-aminoproline are reported which make use of the stereospecific alkylation of (4*S*)-*N*-(*t*-butyldimethylsilyl)azetidin-2-one 4-carboxylic acid with the cyclic sulfate derived from ethylene glycol.

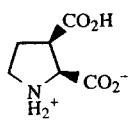
In continuation of work investigating the use of chiral functionalised monocyclic β-lactams for the synthesis of non-proteinogenic amino acids,[1-3] a general synthesis of 2,3-difunctional pyrrolidines **1** applicable to the specific synthesis of (2*S*,3*R*) 3-carboxyproline **2** and (2*S*,3*R*) 3-aminoproline **3** *via* the rearrangement of a 3-substituted azetidin-2-one, Scheme 1, was proposed.[4]



1

Scheme 1

Our interest in (2*S*,3*R*) 3-carboxyproline **2** arises from the development of the structure-activity relationships of excitatory amino acid receptor agonists and competitive antagonists, which indicate that such substituted prolines show activity at a number of different classes of receptor site.[5,6] (2*S*,3*R*) 3-Aminoproline **3** is a naturally occurring amino acid, which has been isolated from the *Morchella* genus of mushrooms, notably *Morchella esculenta*,[7] and has been described in the structural elucidation of viomycidine **4**.[8,9] In addition (2*S*,3*R*)-3-aminoproline **3** has been used as an adduct in film-forming dental cement.[10]



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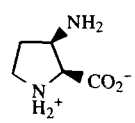

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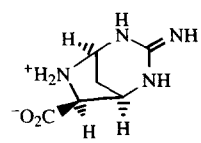
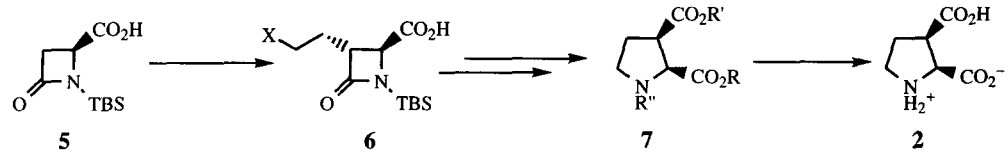
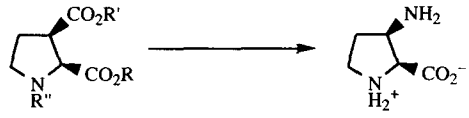


4

Our initial proposal for the synthesis of (*2S,3R*) 3-carboxyproline **2** was to stereospecifically elaborate the homochiral β-lactam, (*4S*) *N*-(*t*-butyldimethylsilyl)azetidin-2-one 4-carboxylic acid **5**, to an alkylated derivative **6**. Subsequent rearrangement to pyrolidine **7**, which contains the 3-carboxyproline nucleus, followed by global deprotection would afford (*2S,3R*) 3-carboxyproline **2**, Scheme 2. The protected proline derivative **7** could also be elaborated to (*2S,3R*) 3-aminoproline **3**, *via* a Curtius rearrangement on the 3-carboxyl group, whose characterisation should further confirm the stereochemical integrity of the synthetic sequence, Scheme 3.

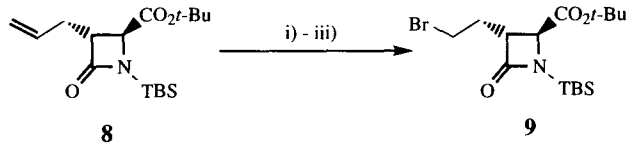


Scheme 2



Scheme 3

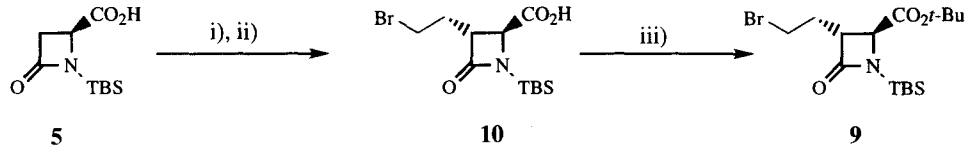
The first task was to synthesise a 3-functionalised β-lactam containing the necessary 2-carbon chain with terminal leaving group, i.e. **6**. Our initial approach was to consider the conversion of the previously reported allylated species **8**[1] to the primary bromide **9**, a sequence which was carried out in three steps with an overall yield of 35%, Scheme 4.



i) OsO_4, $NaIO_4$, dioxan: H_2O (86%); ii) BH_3.DMS, THF (75%);
iii) Br_2, PPh_3, Et_3N, CCl_4 (55%)

Scheme 4

Although this sequence did afford the necessary substituted β-lactam the unsatisfactory yield directed us to investigate the direct alkylation of the dianion derived from azetidin-2-one **5** with 2-carbon electrophiles. As precedent existed for epoxides acting as 2-carbon electrophiles with the enolates of both amides and esters,[11-18] the alkylation of the β-lactam enolate derived from **5** with ethylene oxide was investigated. This reaction proved unsuccessful. In addition, the reaction between the aluminium enolate,[11] formed by the reaction of the di-lithio enolate of **5** with diethylaluminium chloride, and ethylene oxide did not furnish any useful products. The alkylation of azetidin-2-one **5** with 2-bromoethyl triflate[19] was partially successful in that it afforded the *trans* alkylated β-lactam **10** which was isolated in only 25% yield as the *t*-butyl ester **9**, Scheme 5.



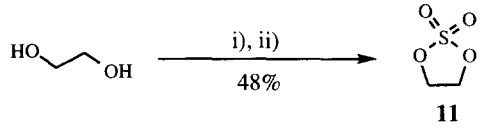
5 **10** **9**

25% from **5**

i) LDA (2.2eq.), THF, 0°C; ii) 2-bromoethyl triflate, -78°C;
iii) *t*-BuOC(=NH)CCl$_3$, $BF_3.Et_2O$ (cat.), DCM, cyclohexane.

Scheme 5

After these reactions the 1,2-cyclic sulfate **11** was considered as an electrophilic quench for a β-lactam enolate.[20] Thus, 2,2-dioxo-1,3-dioxathiolane **11**, a reported carcinogen,[21] was prepared from ethylene glycol *via* a modification of the reported general procedure, Scheme 6.[22]

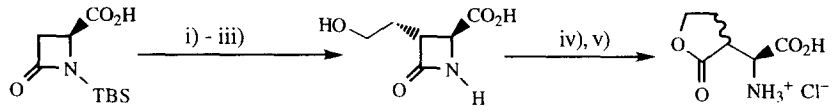


11

i) $SOCl_2$, DCM, reflux ; ii) $RuCl_3$, $NaIO_4$, MeCN, H_2O.

Scheme 6

After formation of the dianion of the carboxy azetidinone **5**, using LDA in THF at 0°C, the solution was cooled to -78°C prior to the addition of cyclic sulfate **11**. Subsequent warming to room temperature and stirring for 24 hours led to a yellow solution which was partitioned between ethyl acetate and 1N hydrochloric acid. ^{1}H NMR (200 MHz) analysis of the material obtained from the ethyl acetate extract did not show any resonances which could be attributed to a β-lactam containing product, however investigation of the aqueous phase suggested that in addition to a large quantity of the hydrogen chloride salt of diisopropylamine a quantity 3-(2'-hydroxyethyl)azetidin-2-one 4-carboxylic acid **12** had been formed. Purification by ion exchange (Dowex 50-X8) allowed the isolation of lactam **12** as a hydroscopic yellow oil, which was observed to undergo a facile rearrangement under acidic catalysis, albeit with some epimerisation, to a *ca.* 8:1 mixture of diastereoisomers of the novel δ-lactone α-amino acid **13**, in a 75% yield, Scheme 7.

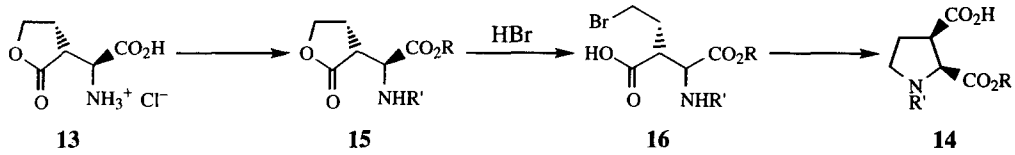


5 **12** **13**

i) LDA (2.2 equivalents), THF, 0°C → -78°C; ii) **11**, THF, -78°C → r.t.;
iii) Dowex 50-X8; iv) 6M hydrochloric acid (aq), 48 hrs; v) 1 week, neat.

Scheme 7

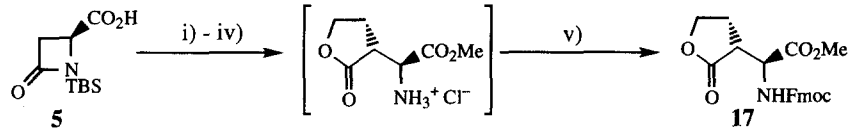
The efficient synthesis of the γ-lactone **13** prompted an alternative route to a protected *cis*-3-substituted proline **14**, Scheme 8. In this revised sequence the protected γ-lactone **15** would be converted to the aspartyl derivative **16** using hydrogen bromide which could then be cyclised to generate the requisite *cis*-substituted proline skeleton **14**, Scheme 8.



13 15 16 14

Scheme 8

In accord with the proposed sequence, Scheme 8, the free amino acid **13** required both amino and carboxyl protection. In practice, the carboxyl moiety of **13** was initially protected as a methyl ester (methanol, anhydrous hydrogen chloride) which was followed by amino protection with the 9-fluorenyloxycarbonyl (Fmoc) group (Fmoc-chloride, triethylamine, acetonitrile) to yield the protected lactone **17** with an overall yield of 50%, from **5**. Fortuitously, under these conditions no evidence of epimerisation was observed, Scheme 9.

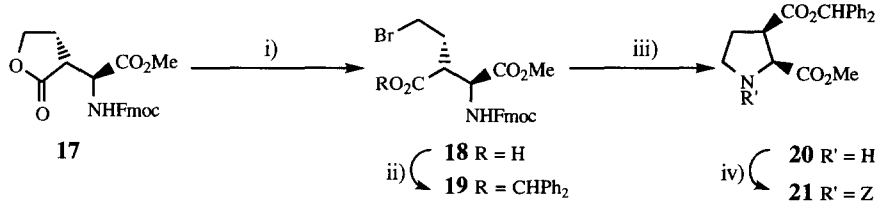


5 17

i) LDA (2.2 equivalents), THF, 0°C → -78°C; ii) **11**, THF, -78°C → r.t..;
iii) Dowex 50-X8; iv) MeOH, $HCl_{(g)}$; v) Fmoc-Cl, Et_3N, MeCN.

Scheme 9

The ring cleavage of the protected lactone **17** with hydrogen bromide (48% in acetic acid) was found to proceed smoothly with the resultant acyclic ω-bromo acid **18** being directly derivatised with diphenyldiazomethane to yield the acyclic benzhydryl ester **19**, scheme 10. At this stage removal of the Fmoc group (piperidine, DMF) resulted in concomitant cyclisation to the *cis*-proline derivative **20**, Scheme 10, which was subsequently Z-protected (benzylchloroformate, sodium hydrogencarbonate, 1,4-dioxan: water) to facilitate its isolation as the fully protected 3-carboxyproline **21**, in a yield of 65% over the four steps. However in order to attain the target (*2S,3R*) 3-carboxyproline **2** more directly it was decided to isolate methyl 3-carboxyproline **22** by deprotection of the partially protected proline **20** with trifluoroacetic acid (TFA), Scheme 11. Unfortunately the $J_{2\text{-}3}$ value of 6.5 Hz observed in the ^1H NMR of the single diastereomeric product **22** failed to clearly indicate the C2-C3 stereochemistry as it fell between values previously observed for both *cis* and *trans* 3-substituted prolines (J_{cis} 7.2-9.0 Hz and J_{trans} 4.4-6.5 Hz).[23-25]



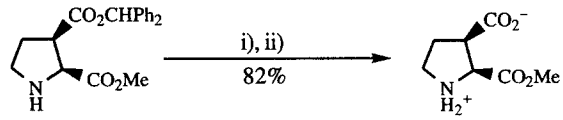
17

ii) **18** R = H, **19** R = $CHPh_2$

iv) **20** R' = H, **21** R' = Z

i) HBr, AcOH; ii) Ph_2CN_2, DCM; iii) piperidine, DMF; iv) Z-Cl, $NaHCO_3$, 1,4-dioxan: water.

Scheme 10

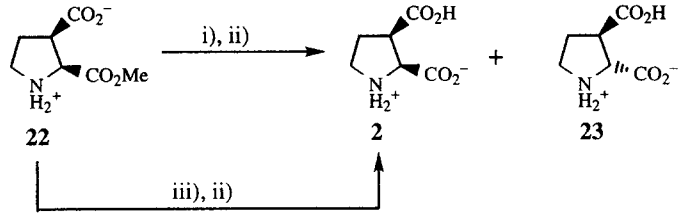


20 **22**

i) TFA, $MeOC_6H_5$, $CH_3C_6H_5$; ii) Dowex 50-X8.

Scheme 11

Successful removal of the final protecting group initially proved to be pH dependent. The initial gambit of lithium hydroxide afforded a 5:4 mixture of the two diasteromeric 3-carboxyprolines **2** and **23**, Scheme 12, showing $J_{2\text{-}3}$ values of 7.0 and 4.5 Hz respectively,[26,27] which suggested that **2** was indeed the required *cis* diastereoisomer.



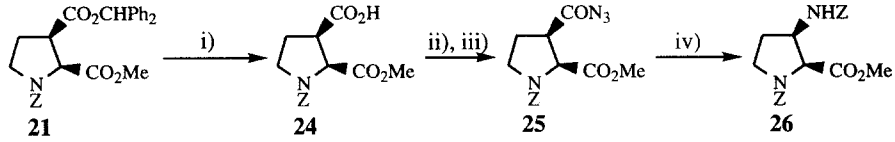
22 **2** **23**

i) LiOH, H_2O ii) Dowex 50-X8; iii) 6M HCl.

Scheme 12

Pleasingly, a simple acid mediated hydrolysis (6M hydrochloric acid) was found to give a good yield of a single diastereoisomer of 3-carboxyproline **2** with desired *cis*-geometry.

Having synthesised our initial goal, the amino diacid **2**, our attention turned to the synthesis of (2*S*,3*R*) 3-aminoproline **3**. The strategy chosen was to selectively deprotect the 3-carboxyl function of diester **21** and follow this with a Curtius rearrangement to generate the required 3-amino moiety. Deprotection of the 3-carboxyl group of **21** was carried out with TFA to afford the free acid **24** which was converted to its acid chloride (oxalyl chloride, DMF (cat.), benzene) prior to treatment with sodium azide to yield the acyl azide **25**. This acyl azide **25** was directly heated with benzyl alcohol, in benzene, leading to the formation of the di-Z-protected proline **26**, Scheme 13.

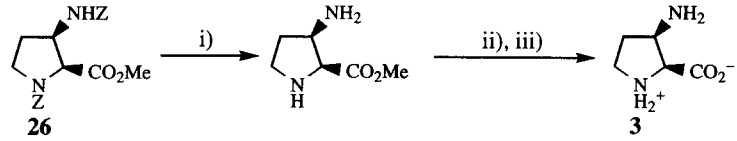


21 **24** **25** **26**

i) TFA; ii) $(COCl)_2$, DMF (cat.), benzene iii) NaN_3; iv) BnOH, benzene, reflux.

Scheme 13

Deprotection of the aminoproline **26** was carried out in two steps; hydrogenolysis of the benzyloxycarbonyl groups, followed by acid hydrolysis (6M hydrochloric acid). Purification by ion-exchange chromatography then afforded a single diastereoisomer of (*2S,3R*) 3-aminoproline **3** in a 94% yield ($J_{2\text{-}3}$ 7.5 Hz), Scheme 14.



26 **3**

i) 10% Pd/C, H_2, MeOH; ii) 6M hydrochloric acid (aq); iii) Dowex 50-X8

Scheme 14

In summary we have shown that alkylation of (*4S*) *N*-(*t*-butyldimethylsilyl)azetidin-2-one-4-carboxylic acid **5** with 2,2-dioxo-1,3-dioxothiolane **11** proceeds efficiently to exclusively produce a *trans*-alkylated product. A subsequently rearranged lactone **13** was then used to provide stereospecific syntheses of both (*2S,3R*) 3-carboxyproline **2** and (*2S,3R*) 3-aminoproline **3**.

Experimental

The general procedures used during this work have been previously described.[1]

***2,2-Dioxo-1,3-dioxathiolane* 11**

2,2-Dioxo-1,3-dioxathiolane **11** was prepared using a modification of the procedure of Sharpless and Gao.[22] Thionyl chloride (7.25 cm^3, 0.1 mol) in DCM (13.5 cm^3) was added to a solution of 1,2-ethanediol (5.0 g, 0.08 mol) in DCM (20 cm^3), with effervescence. The resulting solution was heated under reflux for 90 minutes. After cooling to room temperature, the solution was washed with water (2x50 cm^3), saturated sodium hydrogencarbonate (40 cm^3), water (50 cm^3), and brine (50 cm^3). The reaction mixture was dried ($MgSO_4$), filtered, and concentrated. The residual liquid containing 2-oxo-1,3-dioxathiolane (~5 cm^3) was dissolved in acetonitrile (70 cm^3). Ruthenium trichloride hydrate (2 mg) was added and the solution cooled to 0°C. Water (50 cm^3) and sodium periodate (25.0 g, 0.12 mol) were then added, with the formation of a precipitate, and the resulting orange mixture was then stirred for 60 minutes. Following filtration, the filtrate was diluted with diethyl ether (200 cm^3), washed with water (2x50 cm^3), saturated sodium hydrogencarbonate (25 cm^3), water (50 cm^3), and brine (50 cm^3). After drying ($MgSO_4$) and filtration, removal of the volatiles yielded *2,2-dioxo-1,3-dioxathiolane* **11** (4.76 g, 48%) (**CAUTION:** potential carcinogen)[21] as a white solid, which was used without further purification or characterisation, δ_H (200 MHz, $CDCl_3$) 4.77 (4H, s).

***(3R)-3-[(1'S)-1'-amino-1'-carboxymethyl]-γ-butyrolactone hydrochloride* 13**

(*4S*)-*N*-(*t*-butyldimethylsilyl)azetidin-2-one-4-carboxylic acid **5** (459 mg, 2.00 mmol) in THF (15 cm^3) was treated with freshly prepared lithium diisopropylamide [8.6 cm^3 of a 0.51M solution in THF: hexanes 5:3, 4.4 mmol], at 0°C, and then stirred for 15 minutes at 0°C. After cooling to -78°C, 2,2-dioxo-1,3-dioxathiolane **11** (372 mg, 3.00 mmol) was added and the solution was stirred for 4 hours. The solution was allowed to warm to room temperature and stirred for a further 24 hours whereupon the mixture was partitioned between ethyl acetate (20 cm^3) and 2M hydrochloric acid, the organic layer was removed and re-washed with a further

portion of 2M hydrochloric acid (15 cm^3). Evaporation of the combined aqueous layers yielded an off white gum. This residue was immediately dissolved in water (15 cm^3) and loaded onto a pre-washed column of Dowex 50-X8 (H-form, 200 mesh) which was then eluted with water (50 cm^3). Evaporation of the eluent yielded (*3R,4S*)-3-(2'-hydroxyethyl)azetidin-2-one-4-carboxylic acid **12** as a yellow oil; δ_H (500 MHz, D_2O) 1.83-1.90 & 2.04-2.10 (2x1H, 2xm, $HOCH_2C\underline{H}_2$), 3.26-3.30 (1H, m, 3-H), 3.95-4.05 (2H, m, $HOC\underline{H}_2CH_2$), and 4.25 (1H, d, J 4 Hz, 4-H). The partially purified **12** was dissolved in 6M hydrochloric acid (10 cm^3) and the solution was left to stand for 48 hours. Filtration and removal of the solvent yielded a brown oil which was allowed to stand for a week, after which time, the solid was dissolved in water (15 cm^3) and lyophilised to yield (*3R*)-3-[(*1'S*)-1'-amino-1'-carboxymethyl]-γ-butyrolactone hydrochloride **13** and a minor diastereoisomer, in a ratio of 8:1, as a pale brown solid (293 mg, 75%); ν_{max} (KBr disc)/cm^{-1} (both epimers) 3400-2650 (br s, CO_2H and NH_3^+), 1752 (s, C=O), 1618 (m), 1509 (m), 1452 (m), and 1225 (m); δ_H (500 MHz, D_2O, referenced to 1,4-dioxan δ 3.63) 2.08-2.17 & 2.45-2.52 (2x1H, 2xm, $OCH_2C\underline{H}_2$, major epimer), 2.30-2.44 (2H, m, $OCH_2C\underline{H}_2$, minor epimer), 3.33-3.38 (1H, m, 3-H, major epimer), 3.45-3.51 (1H, m, 3-H, minor epimer), and 4.26-4.31 & 4.39-4.44 (1H+2H, 2xm, $OC\underline{H}_2CH_2$ & 1'-H, both epimers); δ_C (125.8 MHz, D_2O, referenced to 1,4-dioxan δ 67.3, BB & ORD) (major epimer) 25.40 (t, $OCH_2\underline{C}H_2$), 41.40 (d, 3-C), 55.42 (d, 1'-C), 69.20 (t, $O\underline{C}H_2CH_2$), 171.84 (s, CO_2H), and 180.03 (s, lactone C=O); m/z [Direct CI(NH_3)] 160 (MH^+, 100%), and 114 (37).

***(3R)-3-[(1'S)-Methyl 1'-(fluorenylmethyloxycarbonylamino)-1'-carboxymethyl]-γ-butyrolactone* 17**

Freshly prepared lithium diisopropylamide [39 cm^3 of a 0.51M solution in THF: hexanes (5:3), 20.0 mmol] was added dropwise to a solution of (*4S*)-*N*-(*t*-butyldimethylsilyl)-azetidin-2-one-4-carboxylic acid **5** (2.08 g, 9.1 mmol) in THF (50 cm^3) at 0°C, the resulting pale yellow solution being stirred for 20 minutes at 0°C. After cooling to -78°C, 2,2-dioxo-1,3-dioxathiolane **11** (1.67g, 13.5 mmol) was added and the solution was stirred for 6 hours. The cooling bath was removed, the solution allowed to warm to room temperature, and stirred for a further 18 hours whereupon the mixture was diluted with ethyl acetate (150 cm^3) and 1M hydrochloric acid (150 cm^3). The organic layer was removed and re-washed with a further portion of 1M hydrochloric acid (150 cm^3). Evaporation of the combined aqueous layers yielded an off-white solid. This residue was immediately dissolved in water (15 cm^3) and loaded onto a pre-washed column of Dowex 50-X8 (H-form, 100 mesh) which was then eluted with water (300 cm^3). Evaporation of the eluent yielded (*3R,4S*)-3-(2'-hydroxyethyl)azetidin-2-one-4-carboxylic acid **12** as a yellow oil. The crude oil was dissolved in methanol (70 cm^3), cooled to 0°C, and then anhydrous hydrogen chloride was bubbled through the solution for 35 minutes. The flask was stoppered and stirred for 2 days, after which time, removal of the solvents yielded a brown oil. This oil was immediately dissolved in acetonitrile (30 cm^3) and triethylamine (2.50 cm^3, 18 mmol), and 9-fluorenylmethyl chloroformate (Fmoc-Cl) (3.50 g, 13.5 mmol) added. The resulting suspension was stirred for 70 minutes. The reaction mixture was then diluted with ethyl acetate (100 cm^3) and washed with 0.5M hydrochloric acid (120 cm^3), water (2x100 cm^3), and brine (150 cm^3). The resulting solution was then dried ($MgSO_4$), filtered, and the solvents removed to yield the single diastereomer of the crude *(3R)-3-[(1'S)-methyl 1'-(fluorenylmethyloxycarbonylamino)-1'-carboxymethyl]-γ-butyrolactone* **17** as a brown oil. Flash chromatography [SiO_2, graded elution from diethyl ether: petroleum ether, (40-60) 1:1 to diethyl ether] yielded (*3R*)-3-[(*1'S*)-methyl 1'-(fluorenylmethyloxycarbonylamino)-1'-carboxymethyl]-γ-butyrolactone **17** as a white foam (1.77g, 50%); $[\alpha]_D^{20}$ +10.2 (c 1.12, $CHCl_3$); (Found C, 66.92; H, 5.33; N, 3.48, $C_{22}H_{21}NO_6$ requires C,

66.83; H, 5.35; N, 3.54%); ν_{max} ($CHCl_3$)/cm^{-1} 3016 (m), 1773 (s, lactone C=O), 1725 (C=O), 1511 (s), and 1379 (s); δ_H (200 MHz, $CDCl_3$) 2.07-2.48 (2H, m, $OCH_2C\underline{H_2}$), 3.41-3.52 (1H, m, 3-H), 3.84 (3H, s, $CO_2C\underline{H_3}$), 4.15-4.50 (5H, 2×m, $OC\underline{H_2}CH_2$ & FmocC$\underline{H}$C$\underline{H_2}$), 4.75 (1H, dd, *J* 3, 10 Hz, 1'-H), 5.62 (1H, d, *J* 10 Hz, NHFmoc), and 7.28-7.83 (8H, m, FmocAr-H); δ_C (50.3 MHz, $CDCl_3$, BB & DEPT) 25.05 ($OCH_2\underline{C}H_2$), 42.80 (3-C), 47.00 (1'-C), 52.69 (Fmoc$\underline{C}$HCH$_2$), 53.07 ($CO_2\underline{C}H_3$), 66.89 & 67.33 ($O\underline{C}H_2CH_2$ & FmocCH$\underline{C}$H$_2$), 120.17, 125.22, 127.25 & 127.94 (FmocAr-C), 141.50, 143.66 & 143.91 (FmocAr *ipso* C), and 157.06, 170.45 & 176.41 (C=O); *m/z* [DCI(NH_3)] 413 (MNH_4^+, 2%), 396 (MH^+, 5), 196 (25), 178 (100), 166 (32), and 114 (36).

***(2S,3R)-Methyl-5-bromo-3-carboxy-2-[(Fmoc)amino]pentanoate* 18**

(*3R*)-3-[(*1'S*)-methyl 1'-(fluorenylmethyloxycarbonylamino)-1'-carboxymethyl]-γ-butyrolactone **17** (225 mg, 0.57 mmol) was treated with 48% hydrogen bromide in acetic acid (20 cm^3) for 18 hours. Removal of the volatile components yielded a red oil which was dissolved in dichloromethane (50 cm^3) and the resulting solution was washed with water (2×25 cm^3), 0.1M sodium thiosulphate (20 cm^3), and brine (20 cm^3). After drying ($MgSO_4$) and filtering, the solvent was removed to yield crude *(2S,3R) methyl-5-bromo-3-carboxy-2-[(Fmoc)amino]pentanoate* **18** (273 mg, quantitative) as a pale brown foam; ν_{max} ($CHCl_3$)/cm^{-1} 3600-2850 (br, CO_2H), 3020 (s, NH), 1720 (s, C=O), 1450 (s), and 1435 (m); δ_H (200 MHz, $CDCl_3$) 2.07-2.17 & 2.30-2.41 (2×1H, 2×m, $BrCH_2C\underline{H_2}$), 3.55-3.68 (2H, m, $BrC\underline{H_2}CH_2$), 3.72-3.85 (4H, m, CO_2CH_3 & 3-H), 4.32-4.54 (3H, 2×m, FmocC$\underline{H}$CH$_2$ & FmocCHC$\underline{H_2}$), 4.68 (1H, dd, *J* 2, 10 Hz, 2-H), 5.85 (1H, d, *J* 10 Hz, NHFmoc), and 7.28-7.80 (8H, m, FmocAr-H); δ_C (125.8 MHz, $CDCl_3$, BB & ORD) 30.28 (t, $BrCH_2\underline{C}H_2$), 31.23 (t, $Br\underline{C}H_2CH_2$), 45.13 (d, 3-C), 47.31 (d, 2-C), 53.15 (q, $CO_2\underline{C}H_3$), 54.30 (d, Fmoc$\underline{C}$HCH$_2$), 68.48 (t, FmocCH$\underline{C}$H$_2$), 119.99, 124.99, 127.10 & 127.75 (d, FmocAr-C), 141.38 & 143.6 (s, FmocAr *ipso* C), and 156.68, 170.84 & 175.71 (s, C=O); *m/z* [DCI(NH_3)] 493, 495 (MNH_4^+, 5%), 476, 478 (MH^+,10), 396 [$(M-Br)^+$, 15], and 178 (100).

***(2S,3R)-Methyl-5-bromo-3-(diphenylmethylcarboxy)-2-[(Fmoc)amino]pentanoate* 19**

The crude (*2S,3R*)-methyl-5-bromo-3-carboxy-2-[(Fmoc)amino]pentanoate **18** (273 mg, 0.57 mmol) was dissolved in acetonitrile (10 cm^3) and a solution of diphenyldiazomethane (*ca.* 0.63 mmol) in dichloromethane was added, with stirring, until evolution of nitrogen ceased and the reaction mixture showed a persistent purple colouration. After removal of the solvent the residue was purified by flash chromatography [SiO_2, eluting with diethyl ether: petroleum ether (40-60), 4:1] to yield *(2S,3R)-methyl-5-bromo-3-(diphenylmethylcarboxy)-2-[(Fmoc)amino]pentanoate* **19** (257 mg, 70%) as fine white needles, m.p. 140-141°C [Et_2O, petroleum ether (40-60)]; R_f 0.5 (Et_2O:petrol 1:1); $[\alpha]_D^{20}$ +23.6 (c 1.0, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 2.02-2.19 & 2.29-2.48 (2×1H, 2×m, $BrCH_2C\underline{H_2}$), 3.45-3.56 (2H, m, $BrC\underline{H_2}CH_2$), 3.62 (3H, s, CO_2CH_3), 3.63-3.72 (1H, m, 3-H), 4.20-4.27 (1H, m, FmocC$\underline{H}$CH$_2$), 4.33-4.47 (2H, m, FmocCHC$\underline{H_2}$), 4.25 (1H, dd, *J* 3, 10 Hz, 2-H), 5.65 (1H, d, *J* 10 Hz, NHFmoc), 6.91 (1H, s, $CO_2C\underline{H}Ph_2$), 7.25-7.81 (18H, m, Ar-H); δ_C (125.8 MHz, $CDCl_3$, BB & ORD) 30.33 (t, $BrCH_2\underline{C}H_2$), 31.39 (t, $Br\underline{C}H_2CH_2$), 45.36 (d, 3-C), 47.22 (d, 2-C), 52.66 (q, $CO_2\underline{C}H_3$), 53.69 (d, Fmoc$\underline{C}$HCH$_2$), 67.34 (t, FmocCH$\underline{C}$H$_2$), 78.33 (d, $CO_2\underline{C}HPh_2$),

119.99, 125.08, 127.01, 127.08, 127.25, 127.73, 128.25 & 128.65 (d, FmocAr-C), 139.38, 141.36, 143.62 & 143.86 (s, FmocAr *ipso* C and Ph_2C *ipso* C), and 165.62, 170.73 & 171.72 (s, C=O); *m/z* (FAB$^+$) 642, 644 (MH^+, 18%).

***(2S,3R)-Methyl-N-benzyloxycarbonyl-3-(diphenylmethylcarboxy)proline* 21**

(*2S,3R*)-Methyl-5-bromo-3-(diphenylmethylcarboxy)-2-[(Fmoc)amino]pentanoate **19** (159 mg, 0.25 mmol) was dissolved in a solution of piperidine (2 cm^3) in DMF (10 cm^3). The solution was stirred for 45 minutes before the solvents were removed to yield a yellow solid. This solid was then stirred with benzylchloroformate (100 µl, 0.70 mmol), and saturated sodium hydrogencarbonate (2 cm^3) in 1,4-dioxan: water 5:2 (7 cm^3) for 16 hours. The resulting mixure was diluted with ethyl acetate (25 cm^3) and the mixture was washed with water (30 cm^3), 1M hydrochloric acid (20 cm^3), water (2×10 cm^3), and brine (30 cm^3). After drying ($MgSO_4$), filtration, and solvent removal the crude product was purified by flash chromatography [SiO_2, eluting with diethyl ether: petroleum ether (40-60), 1:4] to yield *(2S,3R)-methyl N-benzyloxycarbonyl-3-(diphenylmethylcarboxy)proline* **21** (110 mg, 93%) as a colourless oil; (Found C, 71.28; H, 5.38; N, 2.79. $C_{28}H_{27}NO_6$ requires C, 71.01; H, 5.75; N, 2.96%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (s, C=O), 1703 (s, C=O), 1420 (s), 1349 (m), and 1175 (m); δ_H (500 MHz, $CDCl_3$, two rotamers) 2.17-2.26 & 2.44-2.50 (2×1H, 2×m, 4-H), 3.23 (1.35H, s, CO_2CH_3), 3.30 (1.65H, s, CO_2CH_3), 3.32-3.52 (2H, m, 5-H), 3.58-3.63 (0.45H, m, 3-H), 3.78-3.84 (0.55H, m, 3-H), 4.67 (0.45H, d, *J* 8 Hz, 2-H), 4.76 (0.55H, d, *J* 8 Hz, 2-H), 5.07-5.21 (2H, m, $PhCH_2CO_2$), 6.88 (0.45H, s, Ph_2CHCO_2), 6.90 (0.55H, s, Ph_2CHCO_2), and 7.19-7.38 (15H, m, Ar-H); δ_C (125.8 MHz, $CDCl_3$, BB & ORD) 26.25 & 26.97 (t, 4-C), 45.38 & 45.86 (t, 5-C), 46.42 & 47.41 (d, 3-C), 51.75 (q, $CO_2\underline{C}H_3$), 60.19 & 60.62 (d, C-2), 67.16 (t, $Ph\underline{C}H_2CO_2$), 77.81 (d, $CO_2\underline{C}HPh_2$), 127.06, 127.31, 127.76, 127.99, 128.40 & 128.48 (d, Ar-C), 136.43, 139.53 & 139.74 (s, Ar *ipso* C), and 153.93, 154.55, 169.05 & 170.17 (s, C=O); *m/z* [Probe CI(NH_3)] 491 (MNH_4^+, 2%), 474 (MH^+, 7) 308 (5), 262 (10), and 167 ($C_{13}H_{10}^+$, 100).

***(2S,3R)-Methyl 3-carboxyproline* 22**

(*2S,3R*)-Methyl-5-bromo-3-(diphenylmethylcarboxy)-2-[(Fmoc)amino]pentanoate **19** (92 mg, 0.14 mmol) was added to a solution of piperidine (2 cm^3) in DMF (10 cm^3) and the mixture was stirred for 30 minutes. Filtration and removal of the solvents yielded a yellow solid which was immediately dissolved in toluene: trifluoroacetic acid: anisole 16:3:1 (10 cm^3) and the solution was stirred for 45 minutes. The solvent mixture was removed and the residue dissolved in ethyl acetate (10 cm^3) and the resulting solution was washed with water (3×5 cm^3). The combined aqueous portion was again washed with ethyl acetate (10 cm^3) and removal of the water yielded an off-white solid which was purified by ion-exchange chromatography [Dowex 50-X8 (H-form, 200 mesh), desalting with water and eluting with 1M ammonia solution] to yield *(2S,3R)-methyl 3-carboxyproline* **22** (20 mg, 82%) as a white solid; R_f 0.2 (*n*-BuOH: AcOH: water 3:1:1); δ_H (500 MHz, D_2O, referenced to 1,4-dioxan δ 3.63) 2.11-2.17 & 2.26-2.34 (2×1H, 2×m, 4-H), 3.30-3.45 (3H, m, 3-H & 5-H), 3.68 (3H, s, CO_2CH_3), and 4.36 (1H, d, *J* 6.5 Hz, 2-H); δ_C (125.8 MHz, D_2O, referenced to 1,4-dioxan δ 67.3, BB & ORD) 29.37 (t, 4-C), 45.41 (t, 5-C), 48.52 (d, 3-C), 54.25 (q, $CO_2\underline{C}H_3$), 63.14 (d, 2-C), and 170.18 & 178.65 (s, C=O); *m/z* [DCI(NH_3)] 174 (MH^+, 100%), 142 (20), 128 (20), and 114 (38).

***(2S,3R)-3-Carboxyproline* 2**

(*2S,3R*)-Methyl 3-carboxyproline **22** (44 mg, 0.25 mmol) was dissolved in 6M hydrochloric acid (10 cm^3) and heated at 70°C for 24 hours. The solution was cooled, concentrated and loaded onto a column of Dowex 50-X8 (H-form, 100 mesh), desalted with water and then eluted with 1M ammonium hydroxide. The eluent was lyophilised to afford *(2S,3R)-3-carboxyproline* **2** (30 mg, 75%) as a white solid, $[\alpha]_D^{27}$ -12.2 (c 1, 1M HCl), $[\alpha]_D^{27}$ -43.1 (c 1, H_2O) [lit., for (2R,3S)-3-carboxyproline[27] +42.2 (c 1.15, $CHCl_3$)] ν_{max} (KBr disc)/cm^{-1} 3400-2800 (br s, CO_2H and NH_2^+), 1617 (s), 1407 (s); δ_H (500 MHz, D_2O), 2.09-2.18 & 2.23-2.35 (2H, 2xm, 4-H), 3.25-3.43 (3H, m, 3-H & 5-H), and 4.38 (1H, d, *J* 7.0 Hz, 2-H); *m/z* [DCI(NH_3)] 160 (MH^+, 10%), 142 [$(M-H_2O)H^+$, 15), 114 (50), and 70 (100).

(*2R, 3R*)-3-Carboxyproline was isolated from a lithium hydroxide mediated deprotection of (*2S,3R*)-methyl 3-carboxyproline **22**; δ_H (500 MHz, D_2O) 2.01-2.15 & 2.20-2.28 (2H, 2xm, 4-H), 3.00-3.03 (1H, m, 3-H), 3.22-3.36 & 3.40-3.45 (2H, 2xm, 5-H), 4.29 (1H, d, *J* 4.5 Hz, 2-H).

***(2S,3R)-Methyl* N-*benzyloxycarbonyl-3-(benzyloxycarbonylamino)proline* 26**

(*2S,3R*)-Methyl *N*-benzyloxycarbonyl-3-(diphenylmethylcarboxy)proline **21** (140 mg, 0.29 mmol) was treated with toluene: trifluoroacetic acid: anisole 16:3:1 (10 cm^3) and the mixture was stirred for 30 minutes. After this time, the volatile components were removed and the residue placed under vacuum (0.05 mmHg) for 18 hours. The resulting solid was dissolved in benzene (6 cm^3), the solution was cooled to 0°C, and DMF (100 µl) and oxalyl chloride (38 µl, 0.43 mmol) were added. After stirring for 30 minutes, sodium azide (28 mg, 0.43 mmol) was added and the solution was allowed to warm to room temperature, followed by stirring for a further 60 minutes. Dilution with benzyl alcohol (1 cm^3) followed by heating under reflux for 2 hours yielded a yellow solution which was allowed to cool to room temperature before being further diluted with ethyl acetate (15 cm^3) and washed with water (2x10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). Subsequent solvent removal yielded a yellow liquid. Excess benzyl alcohol was then removed by Kugelröhr distillation (80°C @ 0.4 mmHg) and the residual oil was purified by flash chromatography [SiO_2, eluting with diethyl ether: petroleum ether (40-60), 1:2] to yield *(2S,3R)-methyl* N-*benzyloxycarbonyl-3-(benzyloxycarbonylamino)proline* **26** (69 mg, 58%) as a colourless oil; R_f 0.3 (Et_2O:petrol 1:1); $[\alpha]_D^{20}$ +13.1 (c 0.88, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3032 (m), 1741 & 1703 (s, C=O), and 1389 (s); δ_H (500 MHz, $CDCl_3$, rotamers) 2.13-2.19 & 2.42-2.46 (2x1H, 2xm, 4-H), 3.31-3.36 (1H, m, 5-H), 3.45 (1.5H, s, CO_2CH_3), 3.46-3.52 (1H, m, 5-H), 3.57 (1.5H, s, CO_2CH_3), 3.78-3.84 (1H, m, 3-H), 4.64 (0.5H, d, *J* 8Hz, 2-H), 4.70 (0.5H, d, *J* 8Hz, 2-H), 5.06-5.20 (4H, m, $PhCH_2CO_2$), and 7.28-7.40 (10H, m, Ar); δ_C (125.8 MHz, $CDCl_3$, BB & DEPT) 26.06 & 26.93 (4-C), 45.41 & 45.84 (5-C), 46.27 & 47.25 (3-C), 51.90 & 52.03 ($CO_2\underline{C}H_3$), 60.35 & 60.73 (2-C), 67.00 & 67.13 ($Ph\underline{C}H_2CO_2$), 127.75, 127.93, 128.34 & 128.50 (Ar), 135.26 & 136.41 (Ar *ipso* C), and 153.88, 154.51, 169.81 & 170.39 (C=O); *m/z* [Probe CI(NH_3)] 413 (MH^+, 5%), 398 (82), 354 (55), 294 (43), 262 (38), and 91 (100).

***(2S,3R)-3-Aminoproline* 3**

(*2S,3R*)-Methyl *N*-benzyloxycarbonyl-3-(benzyloxycarbonylamino)proline **26** (44.1 mg, 0.11 mmol) was dissolved in a suspension of 10% Pd/C (5 mg) in methanol (4 cm^3) and placed under a balloon of

hydrogen for 14 hours. The catalyst was removed by filtration and the filtrate concentrated to yield a white solid (13 mg). The solid was then dissolved in 6M hydrochloric acid and stirred for 48 hours. The acid was removed and the resulting yellow solid dissolved in water (1 cm^3) and placed on a pre-washed Dowex 50-X8 (H-form, 200 mesh) column. The column was washed with water (20 cm^3) then eluted with 2M ammonium hydroxide (30 cm^3). The aqueous ammonia was removed and the residue re-dissolved in water (5 cm^3) and lyophilised to yield *(2S,3R)-3-aminoproline* **3** as a pale yellow powder (13.1 mg, 94%), m.p. 190°C (H_2O) [lit.,[7] 215°C (MeOH, water)]; $[\alpha]_D^{20}$ +22.5 (c 0.9, 6M HCl) [lit.,[7] +23.0 (c 2, 5M HCl)]; δ_H (500 MHz, D_2O, referenced to HOD δ 4.63) 2.28-2.34 & 2.40-2.46 (2H, 2×m, 4-H), 3.41-3.53 (2H, m, 5-H), 3.57-3.62 (1H, m, 3-H), and 4.50 (1H, d, *J* 7.5 Hz, 2-H); δ_C (125.8 MHz, D_2O, referenced to 1,4-dioxan δ 67.3, ORD) 30.04 (t, 4-C), 45.65 (t, 5-C), 46.09 (d, 3-C), 63.45 (d, 2-C), and 170.95 & 176.82 (C=O); *m/z* [FAB$^+$] 131 (MH^+, 100%).

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