Pergamon

Tetrahedron Vol. 51, No. 31, pp. 8545-8554, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00455-6

The Asymmetric Synthesis of γ-Substituted Glutamic Acid Derivatives *via* a Glutamic Acid γ-Enolate Synthon.

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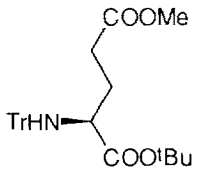
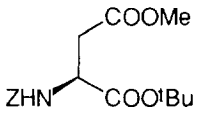
Abstract: *Treatment of α-t-butyl γ-methyl N-Z-glutamate with lithium hexamethyldisilazide gives the γ-enolate regioselectively. Reaction of this enolate with electrophiles gives γ-substituted glutamic acid derivatives including the conformationally constrained glutamate analogue trans-piperidine-2,4-dicarboxylic acid. No racemisation occurs during these reactions.*

There is currently considerable interest in the synthesis of unusual and unnatural amino acids.[1] Most work to date has concentrated on the formation of bonds at the α-centre, with particularly successful methods being developed for the generation of glycine anion[2] and cation[3] synthons, as well as for the formation of the carbon-nitrogen bond.[4] However, all of these methods necessitate the formation of a chiral centre. Over recent years therefore, we[5,6] and others[7] have been investigating the generation of β-anion synthons derived from aspartic acid, and γ-anion synthons derived from glutamic acid. An alternative approach to the same synthons has also been developed by Jackson *et al.*[8] These systems overcome the need to create a chiral centre (the homochiral α-centre is already in place and only needs to be preserved), at the expense of some loss of versatility. The γ-anion synthon developed previously by us was based upon the regiospecific γ-deprotonation of glutamate (**1**), however whilst this enolate reacted well with carbonyl compounds it was inert towards other electrophiles. In this paper therefore we report full details[9] of an alternative, more reactive γ-anion synthon which has been developed in analogy to our existing β-anion synthon derived from aspartate (**2**).



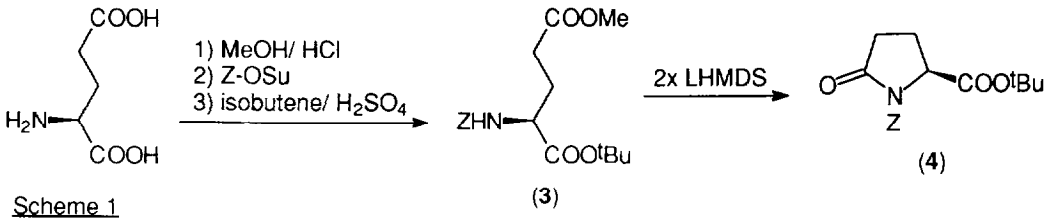
(**1**)



(**2**)

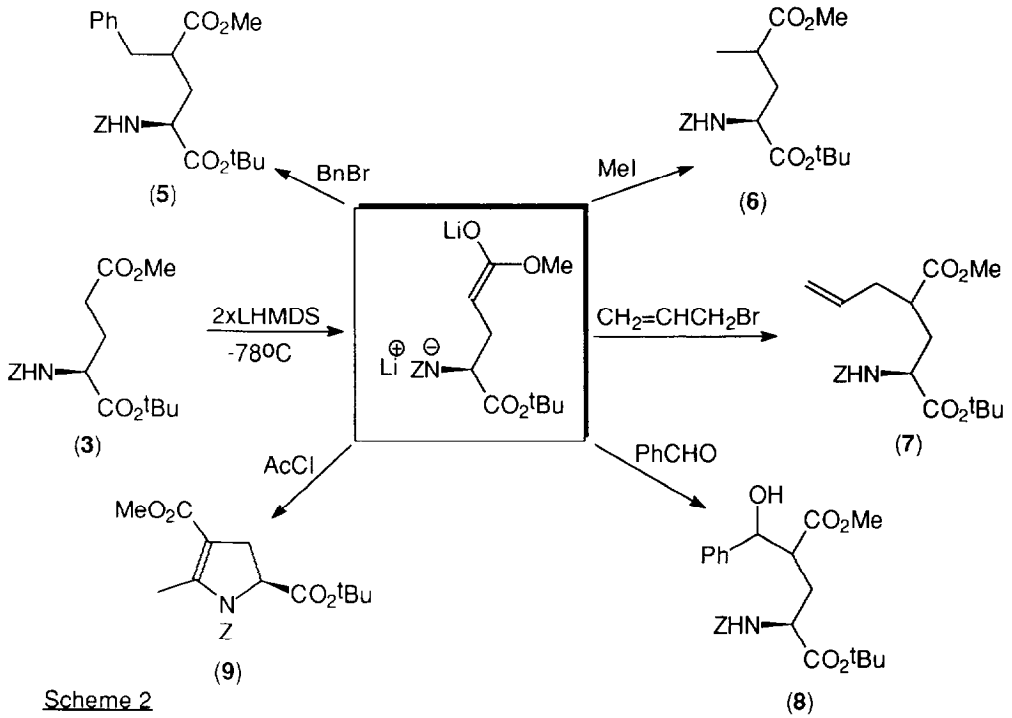
+Andrew Johnstone was a very talented and promising young chemist who died suddenly in March 1995. The work contained within this paper would have formed part of his PhD thesis.

The glutamic acid analogue (**3**) of aspartate (**2**) was prepared in three steps from glutamic acid by a slight modification of the literature procedure[10] as shown in Scheme 1. Initial attempts to generate and trap the *N,C*-dianion of compound (**3**) under the conditions developed for aspartate (**2**) were unsuccessful due to a competing intramolecular cyclisation leading to pyroglutamate (**4**). However, by careful control of the reaction temperature, in particular never allowing the solution to warm above -40°C, conditions were eventually found under which the γ-alkylated adducts (**5-9**) could be isolated in 21-80% yield as shown in Scheme 2.



(3) (4)

Scheme 1



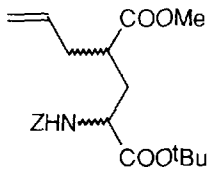
(5) (6) (3) (7) (9) (8)

Scheme 2

During the formation of compounds (**5-7**), a new chiral centre is generated at the γ-carbon. The diastereomeric ratio of compounds (**5-7**) formed during this reaction was found to be dependent upon the electrophile. Thus the γ-benzyl adduct (**5**) was obtained as a single stereoisomer, the γ-methyl adduct (**6**) as a 3:1 ratio of stereoisomers, and the γ-allyl adduct (**7**) as a 2.3:1 ratio of diastereomers. Formation of the

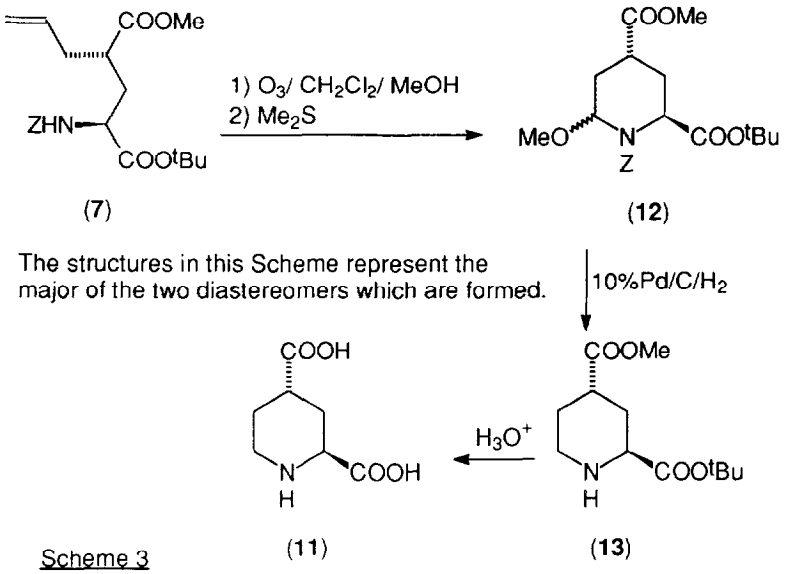
benzaldehyde adduct (**8**), creates two new chiral centres, however only two diastereomers are formed in a 1:1 ratio. The acetyl chloride adduct (**9**), is formed without the creation of a new chiral centre, and it is anticipated that this (and similar compounds) will be a key intermediates in our future work in this area. Compound (**9**) was optically active ($[\alpha]_D^{21}$ -24.4° (conc 1.0, $CHCl_3$)) thus providing the first indication that complete racemisation of the α-centre did not occur under the strongly basic reaction conditions.

The choice of lithium hexamethyldisilazide as the base for this reaction was based upon our previous results with the corresponding aspartate derivative (**2**), for which system the use of a less hindered base such as LDA caused significant racemisation. That no racemisation of the α-centre occurred during the generation or trapping of the enolate derived from compound (**3**), was shown by chiral HPLC. Thus the allyl derivative (**7**) derived from optically pure (**S**)-glutamic acid gave only two peaks when analysed on a chiral HPLC column. By comparison, the corresponding racemate (**10**), prepared from (**RS**)-glutamic acid by exactly the same route as for compound (**7**), gave 4 HPLC peaks when examined under identical conditions to compound (**7**). These results showed that the generation of the dianion of glutamate (**3**), and its trapping (at least with allyl bromide) proceeded without detectable racemisation of the α-centre.



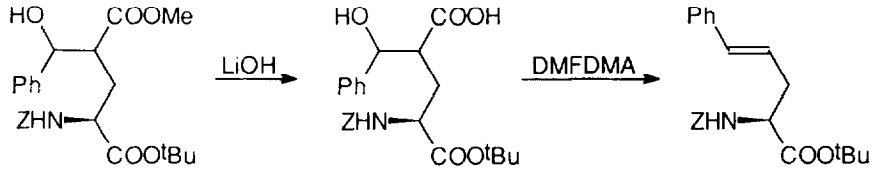
(**10**)

To illustrate the versatility of this approach in the preparation of unusual amino acids, and to determine which diastereomer was formed predominantly in compounds (**5-7**), the synthesis of the conformationally constrained glutamic acid analogue 2,4-dicarboxypiperidine (**11**) was undertaken as shown in Scheme 3. 4-Substituted, and 4,6-disubstituted pipecolic acids are of biological interest: for instance as antibiotics[11] and as *N*-methyl-D-aspartate antagonists,[12] and a number of synthetic approaches to this class of compounds have been reported.[13] Ozonolysis of the γ-allyl derivative (**7**) in a dichloromethane/ methanol solvent mixture gave 6-methoxypiperidine derivative (**12**), as a mixture of stereoisomers at the 6-position. Hydrogenation of compound (**12**), resulted in consecutive hydrogenolysis of the Z-group, elimination of methanol, and hydrogenation of the resulting imine to give piperidine diester (**13**). Deprotection of compound (**13**) was achieved by treatment with 6N hydrochloric acid, giving *trans*-(2S)-2,4-dicarboxypiperidine (**11**). The *trans*-relationship of the two carboxylic acid groups present in compound (**11**) was determined by comparison with the ^1H and ^{13}C nmr spectra of a commercially available sample of racemic-*cis*-2,4-dicarboxypiperidine. The resonances of the major diastereomer of compound (**11**) were clearly different to those of the commercial sample, whilst a minor set of resonances present in the spectra of compound (**11**) matched those of the commercial sample.



Scheme 3

As a further illustration of the synthetic utility of this approach, the synthesis of γ,δ-didehydroamino acid derivative (**14**) was undertaken as shown in Scheme 4. Thus selective saponification of the methyl ester of compound (**8**), followed by decarboxylative dehydration by treatment of the resulting hydroxy-acid with dimethylformamide dimethylacetal[14,15] gave only the *trans*-diastereomer of compound (**14**), the *trans*-stereochemistry being determined from the magnitude of the ^1H-^1H coupling constant between the two vinyl protons. If the decarboxylative dehydration reaction is a stereoselective *trans*-elimination as has previously been reported in at least some cases,[14] then the formation of only the *trans*-isomer of compound (**14**) would imply that the two stereocentres at C4 and C5 of compound (**8**) were formed with the *lk*-relative stereochemistry. However, cases have also been reported where this elimination reaction is not stereospecific,[15] so the observed *trans*-stereochemistry of compound (**14**) could also be due to equilibration to the thermodynamically more stable product under the reaction conditions. Attempts to achieve the decarboxylative dehydration with alternative reagents which are known to be more stereoselective such as DEAD/ PPh_3[16] or benzenesulphonyl chloride[17] were unsuccessful.



(**8**) (**14**)

Scheme 4

In conclusion, we have developed a versatile new γ-anion synthon for asymmetric amino acid synthesis, and have shown that this synthon can be utilised in the asymmetric synthesis of two unnatural amino acids. Our work in this area is continuing, and will be reported in due course.

Experimental

Chiral HPLC was performed on an (**R,R**)-Whelk column (25cm x 4.6mm) fitted to a Waters twin pump gradient HPLC system using a solvent system of 90% hexane and 10% propan-2-ol. Peaks were detected by their absorbance at 254nm. HPLC solvents were degassed immediately prior to use. Other experimental procedures were as previously reported.

γ-Methyl N-Z-(S)-Glutamate

γ-Methyl (**S**)-glutamate (1.0g, 5.1mmol) was dissolved in water (20ml) and potassium carbonate (1.0g, 7.6mmol) was added. To the resulting mixture was added a solution of Z-OSu (1.4g, 5.6mmol) in acetone (20ml). The solution was stirred at room temperature for 90 minutes, then washed with ether (20ml), and acidified (to pH 1) with conc. hydrochloric acid. The resulting solution was then extracted with ethyl acetate (3x30 ml), and the combined organic phases dried ($MgSO_4$), filtered, and evaporated to give γ-methyl N-Z-(**S**)-glutamate as a yellow oil. Yield 1.33g (89%).

t-Butyl 2-benzyloxycarbonylamino-4-carbomethoxy-5-phenyl-(2S)-pentanoate (5)

α-*t*-Butyl γ-methyl *N*-Z-(**S**)-glutamate (**3**) (0.5g, 1.4mmol) was dissolved with THF (4ml), cooled to -78°C, and LHMDS (3.6ml of a 1.0M THF solution) was added. The resulting solution was stirred for 1 hour at -40°C, then recooled to -78°C. Benzyl bromide (0.33 ml, 2.8mmol) was added, and the solution was stirred for two hours at -78°C. Hydrochloric acid (1M, 20ml) was added at -78°C, and the solution was then extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$), and the solvent removed *in vacuo*. The product was purified by flash chromatography (20% EtOAc /80% Petrol), which gave compound (**5**) as a cloudy white oil. Yield 0.13g (21%); $[\alpha]_D^{21}$ -3.0° (conc 1.0, $CHCl_3$); υ_{max} (neat) 3354 s, 3064 m, 3031 m, 2978 s, 1696 s, and 1536cm^{-1} s; δ_H 1.35 (9H, s, $C(CH_3)_3$), 2.00 (2H, t *J* 7.8Hz, βCH_2), 2.8-3.0 (3H, m, γCH+ CH_2Ph), 3.53 (3H, s, OCH_3), 4.34 (1H, q *J* 7.8Hz, αCH), 5.13 (2H, s, CH_2Ph), 5.20 (1H, d *J* 8.0Hz, NH), 7.10-7.40 (10H, m, ArH) (Peak assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 27.91 (q, $OC(\underline{C}H_3)_3$), 34.56 (t, $CH\underline{C}H_2Ph$), 38.27 (t, βCH_2), 44.33 (d, γCH), 51.62 (d, αCH), 53.09 (q, OCH_3), 66.98 (t, OCH_2Ph), 82.39 (s, CMe_3), 126.55, 128.11, 128.41, 128.49, and 128.95 (5xd, ArCH), 136.52, and 138.31 (2xs, ArC), 156.32 (s, NCO_2), 170.91 and 175.40 (2xs, CO_2); m/z (CI) 459 (bp, $M+NH_4^+$), 442 (75, MH^+), 403 (45), 386 (55), 295 (99), 276 (55); Found 442.2230 ($C_{25}H_{32}NO_6$ requires 442.2230).

t-Butyl 2-benzyloxycarbonylamino-4-carbomethoxy-(2S)-pentanoate (6)

α-*t*-Butyl γ-methyl *N*-Z-(**S**)-glutamate (**3**) (0.5g, 1.41mmol) was dissolved with THF (4ml), cooled to -78°C, and LHMDS (3.6ml of a 1.0M THF solution) was added. The resulting solution was stirred for 1 hour at -40°C, then recooled to -78°C. Methyl iodide (0.35ml, 5.64mmol) was added, and the solution was stirred for two hours at -78°C. Hydrochloric acid (1M, 20ml) was added at -78°C, and the solution was extracted with ether (3x20ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to

give a reddish oil. The oil was subjected to flash chromatography (30% ether/ 70% Petrol) which gave compound (**6**) as an oil. Yield 150mg (28%); υ_{max} ($CHCl_3$) 2975 s, 1715 s, 1520 m, 1456 m and 1154cm^{-1} s; δ_H 1.22 (3H, d *J* 7.3, $CHCH_3$) 1.43 (9H, s, $OC(CH_3)_3$), 1.8-2.0 (2H, m, βCH_2), 2.3-2.6 (1H, m, γCH), 3.64, and 3.71 (3H, s, OCH_3), 4.25-4.35 (1H, m, NCH), 5.12 (2H, s, CH_2Ph), 5.21 and 5.43 (1H, d *J* 7.8Hz and 7.6Hz, NH), 7.3-7.4 (5H, s, ArH); δ_C 17.19, and 20.29 (q, CH_3), 27.92, and 29.96 (q, $OC(\underline{C}H_3)_3$), 36.33, and 36.38 (t, βCH_2), 51.76 (q, OCH_3), 52.98 (d, γCH), 53.82 (d, NCH), 66.95 (t, $PhCH_2$), 82.29, and 82.45 (s, $OCMe_3$), 128.07, 128.12, and 128.48 (d, ArCH), 136.24 (s, ArC), 156.06, and 156.34 (s, NCO_2), 171.29, and 176.56 (s, CO_2); m/z (CI) 383 (40, M+NH_4^+), 366 (50, MH^+), 327 (bp), 310 (95); Found 366.1917 ($C_{19}H_{28}NO_6$ requires 366.1917).

t-Butyl 2-benzyloxycarbonylamino-4-carbomethoxy-(2S)-hept-6-enoate (7)

α-*t*-Butyl γ-methyl *N*-Z-(**S**)-glutamate (**3**) (0.5g, 1.41mmol) was dissolved with THF (4ml), cooled to -78°C, and LHMDS (3.6ml of a 1.0M THF solution) was added. The resulting solution was stirred for 1 hour at -40°C, then recooled to -78°C. Allyl bromide (0.5ml, 5.64mmol) was added, and the solution was stirred for two hours at -78°C. Hydrochloric acid (1M, 20ml) was added at -78°C and the solution was extracted with ether (3x20 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a reddish oil. The oil was subjected to flash chromatography (20% EtOAc/ 80% Petrol) which gave compound (**7**) as an oil. The two diastereomers could be separated by further flash chromatography (20% EtOAc/ 80% Petrol). Yield 0.42g (75%); υ_{max} ($CHCl_3$) 3018 s, 1728 s, 1511 m, 1453 m, and 1369cm^{-1} m; δ_H 1.40 (9H, s, $C(CH_3)_3$), 1.95 (2H, t *J* 7.2Hz, βCH_2), 2.3-2.4 (2H, m, $=CHCH_2$), 2.5-2.6 (1H, m, γCH), 3.54, and 3.60 (3H, s, OCH_3), 4.27 (1H, m, αCH), 5.0-5.1 (4H, m, CH_2Ph and $CH_2=$), 5.30, and 5.50 (1H, d *J* 6.6, and 6.4Hz, NH), 5.50-5.60 (1H, m, CH=), 7.30-7.35 (5H, m, ArCH) (Peak assignments were confirmed by a ^1H-^1H COSY spectrum); δ_C 27.68, and 27.81 (q, $OC(\underline{C}H_3)_3$), 29.74, and 33.83 (t, βCH_2), 36.11, and 36.37 (t, $=CH\underline{C}H_2$), 41.65, and 42.51 (d, γCH), 51.39, and 51.48 (q, OCH_3), 52.95, and 53.63 (d, NCH), 66.68 (t, $Ph\underline{C}H_2$), 82.02, and 82.14 (s, $OCMe_3$), 117.14, and 117.33 (t, $\underline{C}H_2=$), 127.86, 127.88, and 128.25 (3xd, ArCH), 134.19, and 134.37 (d, =CH), 136.09 (s, ArC), 155.77, and 156.16 (s, NCO_2), 170.82, 170.90, 172.94, and 175.16 (4xs, CO_2); m/z (CI) 409 (80, M+NH_4^+), 392 (90, MH^+), 353 (66), 336 (bp); Found 392.2073 ($C_{21}H_{30}NO_6$ requires 392.2073).

t-Butyl 2-benzyloxycarbonylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2S)-pentanoate (8)

α-*t*-Butyl γ-methyl *N*-Z-(**S**)-glutamate (**3**) (0.5g, 1.41mmol) was dissolved with THF (4ml), cooled to -78°C, and LHMDS (3.6ml of a 1.0M THF solution) was added. The resulting solution was stirred for 1 hour at -40°C, then recooled to -78°C. Benzaldehyde (0.5ml, 5.9mmol) was added, and the solution was stirred for two hours at -78°C. Hydrochloric acid (1M, 20ml) was added at -78°C and the solution was extracted with ether (3x20 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography (20% EtOAc/ 80% Petrol), which gave compound (**8**) as an oil. Yield 0.30g (47%); υ_{max} ($CHCl_3$) 3426 br, 3018 s, 2955 m, 1729 s, 1512 m, 1455 m, and 1370cm^{-1} m; δ_H 1.60 and 1.70 (2x 9H, s, $C(CH_3)_3$), 1.9-2.2 (2H, m, βCH_2), 2.8-3.0 (1H, m, γCH), 3.50, and 3.68 (3H, s, OCH_3), 4.30 (1H, br, αCH), 4.89, and 4.95 (1H, d *J* 6.5Hz, and 6.1Hz, NH), 5.10, and 5.12 (2H, s, CH_2Ph), 5.46, and 5.52 (1H, d *J* 7.6Hz and 7.7Hz, $C\underline{H}$-OH), 7.3-7.4 (10H, m, ArCH); δ_C 27.95, and 28.01 (2xq, $OC(\underline{C}H_3)_3$), 30.91, and 32.83 (2xt, βCH_2), 49.90, and 50.28 (2xd, γCH), 51.95, and 52.01 (2xq, OCH_3),

53.25, and 53.76 (2xd, NCH), 65.94, and 67.07 (2xt, CH_2Ph), 74.68, and 75.03 (2xd, CHOH), 82.40, and 82.55 (s, $OC(CH_3)_3$), 126.23, 126.38, 126.66, 128.01, 128.26, 128.29, 128.50, 128.62, and 128.73 (9xd, ArCH), 136.42, 141.48, and 141.56 (3xs, ArC), 156.11, and 156.49 (2xs, NCO_2), 170.94, 171.08, 174.60, and 174.99 (4xs, CO_2); m/z (CI) 475 (75, $M+NH_4^+$), 458 (81, MH^+), 402 (48), 340 (82), 108 (77), 91 (bp); Found 458.2179 ($C_{25}H_{32}NO_7$ requires 458.2179).

*t-Butyl N-Z-4-carbomethoxy-5-methyl-4,5-didehydro-(2S)-Proline (**9**)*

α-*t*-Butyl γ-methyl *N*-Z-(**S**)-glutamate (**3**) (0.5g, 1.41mmol) was dissolved with THF (4ml), cooled to -78°C, and LHMDS (4.2ml of a 1.0M THF solution) was added. The resulting solution was stirred for 1 hour at -40°C, then recooled to -78°C. Acetyl chloride (0.5ml, 4eq) was added, and the solution was stirred for 90 minutes at -78°C. Hydrochloric acid (1M, 20ml) was added at -78°C and the solution was extracted with ether (3x20 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (20% EtOAc/ 80% Petrol) gave compound (**9**) as a colourless oil. Yield 0.3g (54%); $[\alpha]_D^{21}$ -24.4° (conc. 1.0, $CHCl_3$); υ_{max} (neat) 3033 w, 2978 m, 2951 m, 1742 s, 1697 s, 1636 s, 1402 s, and 1233cm^{-1} s; δ_H 1.40 (9H, s, $C(CH_3)_3$), 2.62 (3H, s, CH_3), 2.6-2.7 (1H, m, βCH_2), 3.0-3.1 (1H, m, βCH_2), 3.71 (3H, s, OCH_3), 4.65 (1H, dd *J* 8.6, and 5.2Hz, αCH), 5.15 (2H, s, CH_2Ph), 7.3-7.4 (5H, m, ArCH) (Peak assignments were confirmed by a COSY experiment); δ_C 14.33 (q, CH_3), 27.77 (q, $OC(\underline{C}H_3)_3$), 32.23 (t, βCH_2), 51.01 (q, OCH_3), 59.84 (d, αCH), 67.71 (t, CH_2Ph), 81.95 (s, $OCMe_3$), 107.11 (s, C=$\underline{C}$Me), 127.33, 128.10, and 128.50 (3xd, ArCH), 135.42 (s, ArC), 152.31 (s, C=$\underline{C}CO_2Me$), 153.47 (s, NCO_2), 165.92 (s, CO_2), 170.29 (s, CO_2); m/z (CI) 376 (40 MH^+), 320 (bp); Found 376.1760 ($C_{20}H_{26}NO_6$ requires 376.1760).

*t-Butyl 2-benzyloxycarbonylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2**RS**)-pentanoate (**10**)*

Compound (**10**) was prepared in 52% yield from α-*t*-butyl γ-methyl *N*-Z-(**RS**)-glutamate exactly as described for compound (**8**). Spectroscopic data as reported for compound (**8**).

*N-Z-2-t-Butyloxycarbonyl-4-methoxycarbonyl-6-methoxy-(2S,4S)-piperidine (**12**)*

Compound (**7**) (1.2g, 3.1mmol) was dissolved in a 10:1 methanol: dichloromethane solvent system, and glacial acetic acid (0.2ml, 3.1mmol) was added. The resulting solution was cooled to -78°C, and O_3 was bubbled through the solution until a persistent blue colour was observed. The supply of ozone was then disconnected, and the solution allowed to warm to room temperature. Dimethyl sulphide (0.7ml, 9.3mmol) was added, and the solution was stirred at room temperature for three days. Dichloromethane (30ml) was then added, and the resulting solution was washed with 10% sodium carbonate solution (2x20 ml), and then with water (2x20 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. to give compound (**12**) as a yellow oil. Yield 0.96g (69%); $[\alpha]_D^{21}$ -21.1° (conc. 1.0, $CHCl_3$); υ_{max}. (neat) 3032 m, 2977 s, 1729 s, and 1414cm^{-1} s; δ_H 1.45, and 1.48 (9H, s, $OC(CH_3)_3$), 1.6-1.8 (2H, m, δCH_2 and βCH_2), 2.1-2.2 (1H, m, δCH_2), 2.5-2.65 (1H, m, βCH_2), 3.0-3.1 (1H, t *J* 8.2Hz, γCH), 3.38, and 3.49 (3H, s, OCH_3), 3.68, and 3.71 (3H, s, OCH_3), 4.82, and 4.97 (1H, dd *J* 4.5, 1.8Hz, and 6.0, 2.2Hz, αCH), 5.1-5.3 (2H, m, OCH_2Ph), 5.4-5.6 (1H, m, εCH), 7.35-7.45 (5H, m, ArH) (Peak assignments were confirmed by a ^1H-^1H COSY experiment); δ_C 27.51 (t, δCH_2), 27.81, and 27.93 (q, $OC(\underline{C}H_3)_3$), 32.20, and 32.31 (d, γCH), 33.10, and 33.25 (t, βCH_2), 51.28, 51.68, 51.80, and 53.80 (q, OCH_3), 56.52, and 57.04 (d, αCH), 67.62, and 67.86 (t, CH_2Ph), 81.61, (s, $OCMe_3$), 81.73, and 81.96 (d, $\underline{C}H(OMe)$), 127.86, 128.12, 128.19, and 128.50 (4xd, ArCH), 136.18, and

136.23 (s, ArC), 155.46, and 156.33 (s, NCO_2), 169.68 (s, CO_2), 175.18 (CO_2); m/z (CI) 425 (1, $M+NH_4^+$), 376 (bp, $M-OMe^+$); Found 425.2288 ($C_{21}H_{33}N_2O_7$ requires 425.2288).

*2-t-Butyloxycarbonyl-4-methoxycarbonyl-(2S,4S)-piperidine (**13**)*

Compound (**12**) (0.7g, 1.7mmol) was dissolved in ethanol (20ml), and added to a suspension of 10% palladium on charcoal (0.1g) in ethanol (5ml). The solution was then stirred under an atmosphere of hydrogen at room temperature for 18 hours. The reaction mixture was filtered through celite, and the filtrate was evaporated *in vacuo*. to leave compound (**13**) as an oil. Yield 0.38g (93%); $[\alpha]_D^{21}$ +7.4° (conc. 1.0, MeOH); $\upsilon_{max.}$ (neat) 3435 br, 2928 s, 1732 s, and 1574cm^{-1} m; δ_H 1.35 (9H, s, $OC(CH_3)_3$), 2.05-2.25 (2H, m, $C(5)H_2$), 2.25-2.4 (2H, m, $C(3)H_2$), 2.55-2.7 (1H, m, C(4)H), 3.25-3.5 (2H, m, NCH_2), 3.65 (3H, s, OCH_3), 4.15-4.25 (1H, m, NCH); (Peak assignment were confirmed by a ^1H-^{13}C COSY experiment); δ_C 22.58 (t, $C(5)H_2$), 27.92 (t, $C(3)H_2$), 27.92 (q, $OC(\underline{C}H_3)_3$), 35.97 (d, C(4)H), 40.97 (t, NCH_2), 52.65 (q, OCH_3), 54.08 (NCH), 84.84 ($O\underline{C}(CH_3)_3$), 166.82 (CO_2), 172.95(CO_2); m/z (CI) 244 (bp, MH^+), 218 (20), 188 (30), 142 (80); Found 244.1549 ($C_{12}H_{22}NO_4$ requires 244.1549).

*(2S,4S)-Piperidine 2,4-dicarboxylic acid hydrochloride (**11**)*

Compound (**13**) (97mg, 0.4mmol) was dissolved in 6M hydrochloric acid (4ml), and stirred at 60°C for 18 hours. The solvent was evaporated *in vacuo*., leaving (2**S**,4**S**)-piperidine 2,4-dicarboxylic acid hydrochloride (**11**) as a white solid. Yield 83mg (86%); $\upsilon_{max.}$ (Nujol) 2568 br, 1730 s, and 1444cm^{-1} m; $[\alpha]_D^{20}$ -5° (conc. 0.1 H_2O/DMSO); δ_H (D_2O) 1.7-2.0 (3H, m, βCH_2 + δCH_2), 2.11 (1H, dt *J* 15.0, 4.9Hz, βCH_2), 2.69 (1H, pent *J* 5.0Hz, γCH), 2.9-3.0 (1H, m, NCH_2), 3.1-3.2 (1H, m, NCH_2), 4.00 (1H, dd *J* 9.7, 4.1Hz, NCH); δ_C (D_2O) 25.81 (t, βCH_2), 29.02 (t, δCH_2), 38.10 (d, γCH), 43.55 (t, NCH_2), 56.41 (d, αCH), 173.29, and 179.36 (2xs, CO2).

t-Butyl 2-benzyloxycarbonylamino-4-carboxy-5-hydroxy-5-phenyl-(2S)-pentanoate

To a solution of t-butyl 2-benzyloxycarbonylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2**S**)-pentanoate (**8**) (0.3g, 0.66mmol) in THF (3ml) was added 1M lithium hydroxide solution (1.3ml, 1.3mmol). The resulting solution was stirred at room temperature for 45 minutes, after which time TLC (1:1 EtOAc/ petrol) showed the absence of compound (**8**). The reaction mixture was then diluted with dichloromethane (20ml), and washed with 1M hydrochloric acid (2x20ml). The organic layer was dried ($MgSO_4$), and evaporated *in vacuo*., to leave *t*-butyl 2-benzyloxycarbonylamino-4-carboxy-5-hydroxy-5-phenyl-(2**S**)-pentanoate as a colourless oil which could be used without further purification. Yield 0.25g (84%); δ_H 1.40 (9H, s, $OC(CH_3)_3$), 2.3-2.5 (2H, m, βCH_2), 2.9-3.1 (1H, m, γCH), 4.2-4.4 (1H, m, NCH), 5.0-5.2 (2H, m, $PhCH_2O$), 5.4-5.5 (1H, m, PhCHO), 7.3-7.4 (10H, m, ArCH); m/z (CI) 461 (8, $M+NH_4^+$), 444 (10, MH^+), 299 (80), 108 (bp); Found 444.2022 ($C_{24}H_{30}NO_7$ requires 444.2022).

*t-Butyl 2-benzyloxycarbonylamino-5-phenyl-(2S, 4E)-pent-4-enoate (**14**)*

To a solution of *t*-butyl 2-benzyloxycarbonylamino-4-carboxy-5-hydroxy-5-phenyl-(2**S**)-pentanoate (0.24g, 0.54mmol) in toluene (10ml) was added dimethylformamide dimethylacetal (1.5ml, excess). The resulting solution was stirred at room temperature for 1 hour, then at 100°C for 18 hours. The solvents were evaporated *in vacuo*., and the residue subjected to flash chromatography (40% CH_2Cl_2/ petrol) to give alkene

(**14**) as a colourless oil. Yield 150mg (73%); $\upsilon_{max.}$ (neat) 2976 w, 1746 s, 1498 m, and 11152cm^{-1} s; $[\alpha]_D^{20}$ -44° (conc. 0.5, $CHCl_3$); δ_H 1.37 (9H, s, $OC(CH_3)_3$), 2.5-2.7 (2H, m, CH_2), 4.2-4.4 (1H, m, NCH), 5.07 (2H, s, OCH_2Ph), 5.2-5.4 (1H, br, NH), 6.05 (1H, dt *J* 15.8, 7.6Hz, =CH), 6.42 (1H, d *J* 15.8Hz, PhCH=), 7.1-7.4 (10H, m, ArCH); δ_C 28.04 (q, $OC(\underline{C}H_3)_3$), 54.06 (t, CH_2), 65.32 (d, NCH), 66.89 (t, OCH_2Ph), 82.32 (s, $OCMe_3$), 123.72 (d, =CH), 127.49, 127.62, 128.14, 128.26, 128.35, 128.56 (6xd, ArCH), 133.90, and 134.09 (2xs, ArC), 140.94 (d, PhCH=), 155.72 (s, NCO_2), 170.75 (s, CO_2) m/z (CI) 399 (4, $M+NH_4^+$), 382 (3, MH^+), 343 (25), 235 (bp); Found 382.2018 ($C_{23}H_{28}NO_4$ requires 382.2018).

Acknowledgements

The authors thank ZENECA Pharmaceuticals PLC and the EPSRC for a CASE award to ANCJ, and the EEC Erasmus exchange program for grants to GB, SL and MDB. Z-OSu was generously donated by Peboc Ltd., and mass spectra were recorded by the EPSRC service at the University of Wales, Swansea.

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(*Received in UK* 15 *May* 1995; *revised* 5 *June* 1995; *accepted* 9 *June* 1995)