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Amino Acid Synthesis Using (L)-Pyroglutamic Acid as a Chiral Starting Material

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Abstract: Deprotonation of protected pyroglutamates 1(c),1(d), and 1(e) with lithium di-isopropylamide (LDA) or lithium hexamethyldisilazide (LiHMDS) in THF, followed by reaction with electrophiles, leads to the formation of 4-substituted pyroglutamates in good yield. This approach has been used for the synthesis of the novel amino acid (4).

We have recently reported the application of L-glutamic acid to the synthesis of non-proteinogenic amino acids[1] using a strategy which involved deprotonation at the γ-carbon to generate an ester enolate, followed by reaction with a range of electrophiles. The yields from this procedure were moderate to good, and in a number of cases, diastereomeric induction was observed at the new chiral centre. As a means both to extend the utility, and to improve the selectivity of this process, the lactam enolate derived from L-pyroglutamic acid offered considerable potential, since its reaction with electrophiles would be expected to be preferred from the less hindered face. The preparation of enolates from carboxylic acids and their derivatives is well known, as are the generation of lactam enolates[2]. A recent study has investigated the generation and reactivity of lactam enolates of different ring sizes[3], and anions of this type have been used in the synthesis of a range of molecules of biological interest[4]. Although the generation of lactam enolates from variously modified forms of pyroglutamic acid (in which the carboxyl substituent was reduced to the corresponding alcohol, in order to remove its acidifying effect on the C2-proton) had been described prior to the commencement of our work[5], no reports of the deprotonation of a suitably protected pyroglutamic acid had been made. However, a recent report of the synthesis of (-)-bulgecinine by hydroxylation of a lactam enolate derived from protected L-pyroglutamic acid[6] and of work which has shown the versatility of pyroglutamates as useful synthetic intermediates[7] prompted this report of our investigation of the utility of such anions for general amino acid synthesis.

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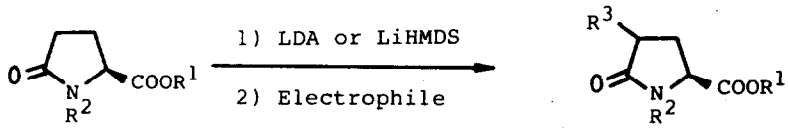
L-Pyroglutamic acid in variously protected forms is readily prepared from L-glutamic acid[8] or L-proline[9]. Our initial attempt to generate the dianion from ethyl pyroglutamate[10] (1a) by treatment with 2 equivalents of LDA, followed by reaction with various electrophiles, was not successful, and a similar reaction sequence using the N-silyl derivative (1b) gave none of the desired product. However, when the pyroglutamates (1c)-(1e) were treated with LDA or LiHMDS in tetrahydrofuran, and the resulting lactam enolate quenched with various electrophiles, the corresponding 4-substituted pyroglutamates (2a)-(2g) could be obtained (see Table). Addition to aldehydes gave low to good yields of the corresponding hydroxyalkylated products (2a)-(2f) as a mixture of diastereomers at the two new chiral centres, with the best yields being obtained from t-butyl N-BOCpyroglutamate (1e). Although reaction of the enolate derived from pyroglutamate (1e) with benzyl bromide gave the corresponding product (2g) in 51% yield, none of the desired products could be obtained with other alkyl halides (methyl iodide, allyl bromide) or esters (methyl benzoate). A similar lack of reactivity has been observed in the alkylation of the ester enolate derived from aspartic acid[11] and glutamic acid.[12] Reaction with cinnamyl bromide or ethyl acrylate gave products resulting from multiple alkylation at C2 and C4, probably as a result of the greater reactivity of these electrophiles. In all of these reactions, in addition to recovered starting material, minor products also arose due to multiple alkylation (at C2 and/or C4), as well as ring cleavage.



(1) (2)

(a) R^1 = Et, R^2 = H

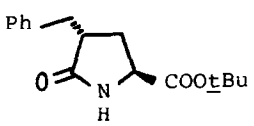
(b) R^1 = Et, R^2 = Me_2tBuSi

(c) R^1 = tBu, R^2 = $PhCH_2OC(O)$

(d) R^1 = $PhCH_2$, R^2 = $PhCH_2OC(O)$

(e) R^1 = tBu, R^2 = tBuOC(O)

Scheme 1



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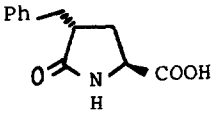

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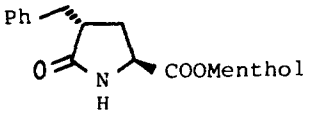

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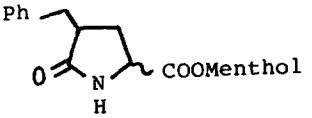

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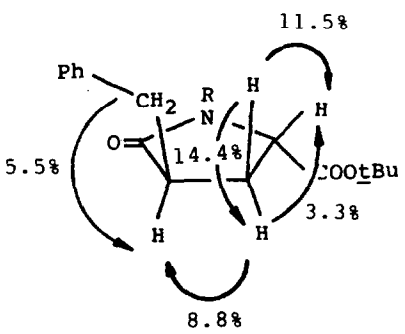
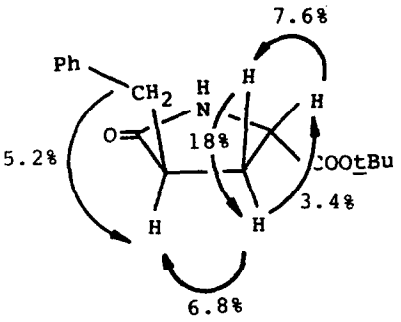


(2g)



(3)

Figure 1: n.O.e. Spectroscopic Data for Pyroglutamates (2g) and (3)

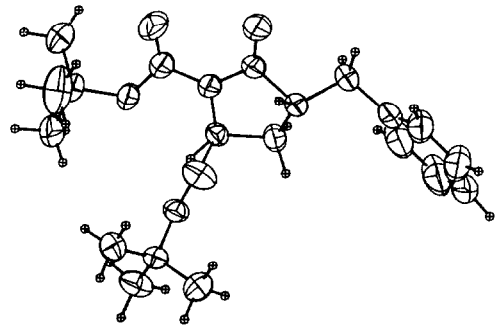


Figure 2: X-Ray structure of pyroglutamate (2g)

When benzyl bromide was used as the electrophile, the product (2g) was obtained as a single diastereomer, as shown by the ^{13}C n.m.r. spectrum. Minor products, resulting from multiple alkylation at C2 and C4, were also obtained. Results from n.O.e. experiments indicated the expected 2,4-trans-configuration (see Figure 1), and X-ray crystallographic

"Table: Products and yields for the Reactions of Lactam Enolates Derived from Pyroglutamates (1c)-(1e) (see Scheme 1)."

PYROGLUTAMATE	BASE[a]	ELECTROPHILE	PRODUCT	YIELD (%)
(1c)	LiHMDS	PhCHO	(2a), R^3 = PhCH(OH)-	38
(1c)	LiHMDS	CH_3CH_2CHO	(2b), R^3 = $CH_3CH_2CH(OH)$-	25
(1d)	LiHMDS	PhCHO	(2c), R^3 = PhCH(OH)-	35
(1e)	LDA	PhCHO	(2d), R^2 = PhCH(OH)-	62
(1e)	LiHMDS	PhCHO	(2d), R^3 = PhCH(OH)-	69
(1e)	LICA	CH_3CH_2CHO	(2e), R^3 = $CH_3CH_2CH(OH)$-	28
(1e)	LiHMDS	CH_2CHCHO	(2f), R^3 = $CH(OH)CHCH_2$	79
(1e)	LDA	$PhCH_2Br$	(2g), R^3 = $PhCH_2$-	51
(1e)	LDA	MeI	-	0
(1e)	LDA	CH_2CHCH_2Br	-	0
(1e)	LiHMDS	$PhCO_2CH_3$	-	0

[a] LDA = lithium diisopropylamide; LiHMDS, lithium hexamethyldisilazide; LICA, lithium isopropylcyclohexylamide.

analysis confirmed this assignment (Figure 2). Selective cleavage of the t-butyloxycarbonyl group of pyroglutamate (2g) with cold trifluoroacetic acid gave ester (3), and n.O.e. experiments confirmed the 2,4-trans-configuration (Figure 1). Deprotection of pyroglutamate (2g) in refluxing TFA gave the analytically pure amino acid (4) in good yield. The optical purity at C-2 of this product was determined by the method of Nozoe[7]. Thus, re-esterification of amino acid (4) with menthol/hydrochloric acid gave ester (5). When the ^{13}C n.m.r. spectrum of menthol ester (5) was compared with the corresponding ester (6) derived from racemic pyroglutamic acid, only a single diastereomer was present, indicating that the optical integrity at the C-2 centre had been retained.

Thus, pyroglutamic acid is a useful starting material capable of ready elaboration to more complex amino acids, with retention of configuration at the C2-centre. However, one limitation would appear to be the ease with which multiple alkylations can occur. The investigation of the application of this type of approach to the synthesis of more complex amino acids is currently in progress.

EXPERIMENTAL

Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter. Ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^1H nmr spectra were recorded on a Bruker WH 300 (300 MHz), or Varian Gemini 200 MHz spectrometer. ^{13}C nmr spectra were recorded at 62.85 MHz on a Bruker AM 250 spectrometer or at 50 MHz on a Varian Gemini 200 instrument. Mass spectra were recorded on VG Analytical Ltd., ZAB1F, or MM30F mass spectrometers using the techniques of (DCI) ammonia desorption chemical impact, or (CI) ammonia chemical ionisation. Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford.

Ethyl (S)-pyroglutamate (1a)

A mixture of (S)-pyroglutamic acid (3.0 g, 23 mmol), ethanol (2.9 g, 6.2 mmol) and conc. sulfuric acid (3 drops) in benzene (20 ml) was refluxed for 5 h, and water removed using a Dean-Starke apparatus. The mixture was cooled, and the solvent removed. The residue was dissolved in chloroform (23 ml), the solution washed with potassium carbonate, and the solvent evaporated. The crude product was distilled by Kugelrohr (200°C/1.5 mmHg) to give the title compound (1a) as a white solid (2.7 g, 73%), m.p. 46.5-47.5°C (lit.[10] m.p. 50°). $[\alpha]_D^{\beta\circ}$ - 3.1° (c 0.75, H_2O). ν_{max} (nujol) 3200, 1745, 1700 cm^{-1}, δ_H ($CDCl_3$) 1.30 (3H, t, J = 7.1 Hz, $CH_2\underline{CH_3}$), 2.26 and 2.41 (4H, m, H3, H3', H4 and H4'), 4.23 (2 H, q, J = 7.1 Hz, $\underline{CH_2}CH_3$), 6.14 (1H, br, s, NH). δ_C ($CDCl_3$) 13.9 ($CH_2\underline{CH_3}$), 24.6 and 29.2 (C3 and C4), 55.5 (C2), 61.5 ($\underline{CH_2}CH_3$), 172.4 ($\underline{C}(O)O$), 178.6 (C5). m/z 157 (M^+).

Ethyl (S)-N-(t-butyldimethylsilyl)pyroglutamate (1b)

To a solution of t-butyldimethylsilyl chloride (1.1 g, 7.0 mmol) and DBU (1.1 ml, 7.6 mmol) in dry dichloromethane (40 ml) was added a solution of the pyroglutamate (1a) (1.0 g, 6.4 mmol) in dry dichloromethane (25 ml)[13], and then stirred for 2.5 days. The solution was washed with water (50 ml), hydrochloric acid (0.1N, 50 ml) and saturated sodium bicarbonate (30 ml). The organic solution was dried ($MgSO_4$) and evaporated to give a colourless oil. Distillation gave the pure product (1b) (1.0g, 59%), b.p. 110°C (1.5 mmHg). $C_{13}H_{25}NO_3Si$ requires C, 57.5; H, 9.3; N, 5.2%. Found: C, 57.7; H, 9.5; N, 5.4%. $[\alpha]_D^{\beta\circ}$ - 9.2° (c 0.75, $CHCl_3$). ν_{max} (nujol) 2910, 1745, 1700 cm^{-1}. δ_H ($CDCl_3$) 0.08 (3H, s, $Si(\underline{CH_3})$), 0.37 (3H, s, $Si(\underline{CH_3})$), 0.94 (9H, s, $Si(\underline{CH_3})_3$), 1.29 (3H, t, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.30 (4H, m, H3, H3' H4 and H4'), 4.21 (3H, m, $O\underline{CH_2}CH_3$ and C2). δ_C ($CDCl_3$) 5.58 ($Si\underline{CH_3}$), 5.75 ($Si\underline{CH_3}$), 13.9 ($CH_2\underline{CH_3}$), 19.0 (Si $\underline{C}$), 26.5 ($SiC(\underline{CH_3})_3$), 26.8 and 30.6 (C3 and C4), 60.6 and 61.2 (C2 and $\underline{CH_2}CH_3$), 174.0 (C5), 188.5 ($\underline{C}(O)O$). m/z 272 (MH^+).

(2S)-N-Carbobenzyloxypyroglutamic Acid

The title compound was prepared in 3 steps from (S)-N-carbobenzyloxyglutamic acid[14] according to the literature method[8] in 75% overall yield, and obtained as pale yellow crystals, m.p. 128.5-130°C (lit.[8] 125-128°C). $[\alpha]_D^{20}$ - 20° (c 0.75, $CHCl_3$) (lit.[8] - 29.1°, MeOH). δ_H ($CDCl_3$) 2.15 and 2.53 (4H, m, H3, H3', H4 and H4'), 4.72 (1H, dd, J 2.7 Hz, J' 10.7 Hz, H2), 5.32 (2H, s, CH_2Ph), 6.19 (1H, brs, OH), 7.35 (5H, m, ArH). δ_C ($CDCl_3$) 21.5 (C3), 30.9 (C4), 58.4 (C2), 68.5 (CH_2Ph), 128.2, 128.7, 135.0 (all ArC), 151.2 (NC(O)), 173.6 and 176.0 (C5 and C(O)O). m/z. (DCI) 281 ($M + NH_4^+$).

t-Butyl (2S)-N-carbobenzyloxypyroglutamate (1c)

To a solution of acetonitrile (11 ml), dimethylformamide (3.8 ml) and oxalyl chloride (1.6 ml) at -23°C was added the above acid (3.6 g, 13.6 mmol) in acetonitrile (5 ml) and the mixture stirred for 1h.[15] t-Butanol (3.8 g) and pyridine (3.4 g) were then added, the mixture stirred at room temperature for 18h, and poured into a 20% sodium carbonate solution (50 ml). The solution was extracted with ether, the combined ether layers washed with water, citric acid (10%), saturated sodium chloride, and saturated sodium bicarbonate. The ether layer was dried ($MgSO_4$), the solvent removed, and the crude product purified by flash chromatography (light petroleum/35% ethyl acetate) to give (1c) as a colourless oil (1.8 g, 41%). $[\alpha]_D^{20}$ - 20.4° (c 0.75, $CHCl_3$) ν_{max} ($CHCl_3$) 1800, 1740 cm^{-1}. δ_H ($CDCl_3$) 1.39 (9H, s, $OC(CH_3)_3$), 2.05 (1H, m, H3), 2.32 (1H, m, H3'), 2.60 (2H, m, H4 and H4'), 4.54 (1H, dd, J 2.7 Hz, 10.7 Hz, H2), 5.28 (2H, q, CH_2Ph), 7.39 (5H, m, ArH). δ_C ($CDCl_3$) 21.7 (C3), 27.6 ($C(CH_3)_3$), 30.8 (C4), 59.3 (C2), 68.1 (OCH_2Ph), 82.5 ($C(CH_3)_3$), 128.5, 135.2 (ArC), 151.1 (NC(O)), 170.3 and 173.4 (C5 and C(O)O). m/z 320 (MH^+).

Benzyl (2S)-N-carbobenzyloxypyroglutamate (1d)

A mixture of (2S)-N-carbobenzyloxypyroglutamic acid (2.1 g, 8.0 mmol) and potassium bicarbonate (0.81 g, 8.0 mmol) in water was stirred for 2h at room temperature. The water was azeotroped off with toluene, and the potassium salt thus obtained stirred with benzyl bromide (0.84 ml, 7.1 mmol) in dimethylformamide (15 ml) at room temperature for 18h. The solution was filtered, and the solvent removed under high vacuum using toluene as an azeotroping agent, to give (1d) as a colourless solid (1.30 g, 51%), m.p. 104-6°C (Lit.[8] 106-107°C). $[\alpha]_D^{20}$ - 47.6° (c 1.1, $CHCl_3$), (lit[8]. -41.3°) ν_{max} ($CHCl_3$) 1800, 1750 cm^{-1}. δ_H ($CDCl_3$) 2.07 (1H, m, H3), 2.38 (1H, m, H3'), 2.62 (2H, m, H4 and H4'), 4.73 (1H, dd, J 2.7 Hz, 10.7 Hz, H2), 5.14 (2H, s, CH_2Ph), 5.23 (2H, s, CH_2Ph), 7.36 (10H, m, 10 x ArH). δ_C ($CDCl_3$) 21.6 (C3), 30.8 (C4), 58.7 (C2), 67.4 (CH_2Ph), 68.3 (CH_2Ph), 128.6 and 135.1 (ArC), 151.0 (NC(O)), 171.1 and 173.2 (C5 and C(O)O). m/z 354 (MH^+).

t-Butyl (2S)-N-t-butyloxycarbonylpyroglutamate (1e)

To a solution of (2S)-N-t-butyloxycarbonylpyroglutamic acid (4.8 g, 21 mmol) (prepared from N-t-butyloxycarbonyl (S)-glutamic acid) and N,N-dimethylaminopyridine (2.5 g, 20 mmol) and t-butanol (1.95 ml, 21 mmol) in dichloromethane (100 ml) was added a solution of 1,3-dicyclohexylcarbodiimide (5.1 g, 24 mmol) in dichloromethane (50 ml). The reaction mixture was stirred overnight at room temperature, the precipitated dicyclohexylurea was removed by filtration, and the solvent removed. The residue was dissolved in ethyl acetate, and filtered again; evaporation of the solvent gave a red oil. Purification by flash chromatography (hexane/30% ethyl acetate) gave the product (1e) a pale yellow oil (3.3 g, 56%). $[\alpha]_D^{20}$ -33.2° (c 0.9, $CHCl_3$) (lit.[9] $[\alpha]_D^{22}$ -35.1 (c 0.9, $CHCl_3$). ν_{max} ($CHCl_3$), 1790, 1690 cm^{-1}. δ_H ($CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 2.01 (1H, m, H3), 2.27 (1H, m, H3'), 2.53 (2H, m, H4 and H4'), 4.48 (1H, dd, J 2.7 Hz, J' 10.7 Hz, H2). δ_C ($CDCl_3$) 21.3 (C3), 27.6 (2 x $C(CH_3)_3$), 30.8 (C4), 59.4 (C2), 82.1 ($C(CH_3)_3$), 83.0 ($C(CH_3)_3$), 149.30 (NC(O)), 170.5 and 173.8 (C5 and C(O)O). m/z 286 (MH^+).

The compound (1e) was also prepared from t-butyloxycarbonylproline by the literature procedure[9] in 72% yield overall.

General Method for Reactions of Pyroglutamates with Electrophiles

To a solution of N,N-hexamethyldisilazane (1.2 -2equiv) in THF (20 ml) under an argon atmosphere and at -78°C was added dropwise butyl lithium (1 eq of 1.6M hexane solution). After 30 min, a solution of the pyroglutamate (0.5 g) in THF was added at -78°C, and the solution stirred for 1h. The aldehyde was then added, and the mixture stirred for 4h. The reaction mixture was quenched with a saturated solution of ammonium chloride (80 ml) at -78°C, and the solution allowed to warm to room temperature. The solution was extracted with ether, and the combined organic phases dried ($MgSO_4$), evaporated to dryness and the crude product purified by flash chromatography.

The following compounds were synthesised using the above general method:

(i) t-Butyl (2S)-1-benzyloxycarbonyl-4-(hydroxyphenylmethyl)pyroglutamate (2a) was prepared from pyroglutamate (1c) and benzaldehyde, and obtained as a white foam (254 mg, 38%). After further purification by flash chromatography (40% EtoAc/ light petroleum) a single diastereomer could be isolated. $[\alpha]_D^{\delta}$ - 11.4° (c 0.5, $CHCl_3$). ν_{max} ($CHCl_3$) 3490, 1790, 1735 cm^{-1}. δ_H ($CDCl_3$) 1.39 (9H, s, $OC(CH_3)_3$, 1.5-1.65 (1H, m, H3), 2.05-2.25 (1H, m, H3'), 2.93 (1H, m, H4), 4.38 (1H, m, H2), 4.54 (1H, s, OH), 4.84 (1H, d, J = 9.5Hz, CH(OH)), 5.31 (2H, s, OCH_2), 7.28-7.43 (10H, m, ArH). δ_C ($CDCl_3$) 24.9 (C3), 27.7 (CH_3)$_3$), 48.8 (C4), 57.8 (C2), 68.7 (OCH_2Ph), 75.1 (CHOH), 82.7 ($C(CH_3)_3$), 126.9, 128.5, 134.7, 140.1 (all ArC), 150.7 (NC(O)O), 169.8 (OC(O)), 175.3 (C5). m/z (DCI) 443, (M + NH_4^+).

(ii) t-Butyl (2S)-1-benzyloxycarbonyl-4-(1-hydroxypropyl)pyroglutamate (2b) was prepared from pyroglutamate (1c) and propanal, and obtained as a single diastereomer (152 mg, 25%) after purification by flash chromatrography (15% EtOAc/light petroleum). $C_{20}H_{27}NO_6$ requires C, 63.6; H, 7.2; N, 3.7%. Found: C, 63.2; H, 7.7; N, 3.5%. $[\alpha]_D^{\delta}$ -11.2° (c 0.5, $CHCl_3$). ν_{max} ($CHCl_3$) 3510, 1790, 1735 cm^{-1}. δ_H ($CDCl_3$) 0.98 (3H, t, J 7.2 Hz, CH_2CH_3), 1.30-1.75 (11H, m, $C(CH_3)_3$ and CH_2CH_3), 1.90-2.33 (2H, m, H3 and H3'), 2.6-2.8 (1H, m, H4), 3.60-3.75 (1H, m, CH(OH)), 4.08 (1H, s, OH), 4.52 (1H, m, H2), 5.26 (1H, d, J = 16Hz, CHPh), 5.28 (1H, d, J = 16Hz, CH'Ph), 7.36 (5H, m, ArH). δ_C ($CDCl_3$) 9.0 (CH_2CH_3), 25.6 (CH_2CH_3) 27.1 (C3), 27.6 ($C(CH_3)_3$), 45.7 (C4), 57.6 (C2), 68.5 (OCH_2Ph), 73.1 (CH(OH)), 83.0 ($C(CH_3)_3$), 128.5, 128.7, and 135.0 (all ArC), 150.8 (NC(O)O), 169.9 (OC(O)), 176.4 (C5). m/z (DCI) 393 (M + NH_4^+).

(iii) Benzyl (2S)-1-benzyloxycarbonyl-4-(hydroxyphenylmethyl)pyroglutamate (2c) was prepared from pyroglutamate (1d) and benzaldehyde and obtained as an oil (227 mg, 35%). After further purification by flash chromatography (20% EtOAc/ hexane) a single diastereomer could be obtained. $C_{27}H_{25}NO_6$ requires C, 70.6; H, 5.5; N, 3.0%. Found: C, 70.6; H, 5.7; N, 3.1%. $[\alpha]_D^{\delta}$ -2.7° (c 0.5, $CHCl_3$). ν_{max} ($CHCl_3$) 3470, 1790, 1745 cm^{-1}. δ_H 1.5-1.75 (1H, m, H3), 2.05-2.25 (1H, m, H3'), 2.85-3.00 (1H, m, H4), 4.45 (1H, s, OH), 4.50-4.60 (1H, m, C2), 4.77 (1H, t, J = 9.5Hz, CH(OH)), 5.09 (2H, s, CH_2Ph), 5.24 (2H, s, CH_2Ph), 7.20-7.50 (10H, m, 2 x ArH). δ_C ($CDCl_3$) 24.7 (C3), 48.8 (C4), 57.2 (C2), 67.5 (CH_2Ph), 68.8 (CH_2Ph), 75.0 (CH(OH)), 126.9, 128.7, 128.8, 140.0 (ArC), 172.5 (C(O)O), 175.5 (C5). m/z (DCI) 460 (MH^+).

(iv) t-Butyl (2S)-1-t-butoxycarbonyl-4-(hydroxyphenylmethyl)pyroglutamate (2d) was prepared from pyroglutamate (1e) and benzaldehyde, and obtained as a mixture of diastereomers. Chromatography (25% EtoAc/hexane) gave the product as a hygroscopic oil (427 mg, 62%). $C_{21}H_{29}NO_6$ requires C, 64.4; H, 7.5; N, 3.6%. Found: C, 63.5; 7.7; N, 3.9%. $[\alpha]_D^{\delta}$ -12.6° (c 0.9, $CHCl_3$). ν_{max} ($CHCl_3$) 3490, 1790, 1735 cm^{-1}. δ_H ($CDCl_3$) 1.4 - 1.65 (18H, m, 2 x $(CH_3)_3$), 1.8-2.15 (1H, m, H3), 2.38 - 2.59 (1H, m, H3'), 2.80-3.10 (1H, m, H4), 4.30-4.45 (1H, m, H2), 4.75-4.85 and 5.45-5.50 (1H, m, CHOH), 7.30-7.45 (5H, m, ArH). δ_C

($CDCl_3$) 21.1, 24.4 and 25.0 (C3), 27.7 (2 x $C(\underline{C}H_3)_3$), 47.8, 48.7, 49.7 (C4), 57.6-57.8 (C2), 70.21 and 75.1 ($\underline{C}H(OH)$), 82.2 - 84.1 (2 x $\underline{C}(CH_3)_3$), 125.5-128.8, 140.3, 141.8 (all ArC), 149.1 and 149.3 ($N\underline{C}(O)O$), 170.1 - 170.8 ($\underline{C}(O)$), 176.2 (C5). m/z (DCI) 409 ($M + NH_4^+$).

(v) t-Butyl (2S)-1-t-butoxycarbonyl-4-(1-hydroxypropyl)pyroglutamate (2e) was prepared from pyroglutamate (1e) and propanal, and obtained as a mixture of diastereoisomers. Chromatography (25% EtOAc/hexane) gave the product as an off-white solid (168 mg, 28%). $C_{17}H_{29}NO_6$ requires C, 59.5; H, 8.5; N, 4.1%. Found: C, 59.5; H, 8.8; N, 4.4%. $[\alpha]_D^{22}$° -15.7° (c 0.78, $CHCl_3$). ν_{max} ($CHCl_3$) 3490, 1780, 1735 cm^{-1}. δ_H ($CDCl_3$) 0.99 (3H, t, J 7.3 Hz, $CH_2\underline{CH_3}$), 1.35 -1.65 (20H, m, 2 x $C(\underline{CH_3})_3$ and $\underline{CH_2}CH_3$), 1.90 - 2.10 (2H, m, H3 and H3'), 2.5-2.75 (1H, m, H4), 3.55 - 3.80 (1H, m, CHOH), 4.12 and 4.23 (1H, s, OH), 4.30 - 4.55 (1H, m, H2). δ_C ($CDCl_3$) 8.90 and 10.1 ($CH_2\underline{CH_3}$), 24.5 and 25.2 ($\underline{CH_2}CH_3$), 27.7 ($C(\underline{CH_3})_3$), 45.8, 46.7 and 47.1 (C4), 57.7, 57.9 (C2), 70.1, 72.9, 73.1 (CHOH), 82.2, 82.3, 82.5, 83.2, 83.7 ($\underline{C}(CH_3)_3$), 149.4 ($N\underline{C}(O)O$), 170.2, 170.6 ($\underline{C}(O)O$), 173.8 (C5). m/z (DCI) 361 ($M + NH_4^+$).

(vi) 1-Butyl (2S)-1-t-butyloxycarbonyl-4-(1-hydroxyprop-2-en-1-yl)pyroglutamate (2f) was prepared from pyroglutamate (1e) and acrolein, and obtained as a mixture of diastereomers after flash chromatography (0.90 g, 79%). Re-purification allowed isolation of one of the diastereomers as an oil. $C_{17}H_{27}NO_6$ requires C, 59.8; H, 8.0; N, 4.1%. Found: (C, 59.8; H, 8.2; N, 4.4%. $[\alpha]_D^{22}$° - 7.0 (c 0.9, $CHCl_3$) . ν_{max} ($CHCl_3$) 1740, 1780, 3480 cm^{-1}. δ_H ($CDCl_3$) 1.47 and 1.51 (18H, 2 x s, 2 x $C(\underline{CH_3})_3$), 1.91 - 2.10 (2H, m, H3 and H3'), 2.64 - 2.90 (1H, m, H4). 4.20 (1H, s, OH), 4.21 -4.31 (1H, m, CHOH), 4.40 - 4.49 (1H, m, H2), 5.15 - 5.40 (2H, m, $CH\underline{=}CH_2$), 5.69 - 5.90 (1H, m, $C\underline{H}=CH_2$). δ_C ($CDCl_3$) 24.9 (C3), 27.1 ($(\underline{CH_3})_3$), 46.1 (C4), 57.8 (C2), 73.8 ($\underline{CH}(OH)$), 82.6 and 83.9 (2 x $O\underline{C}(CH_3)_3$), 117.7 ($CH=\underline{CH_2}$), 136.6 ($\underline{CH}=CH_2$), 149.1 ($N\underline{C}(O)O$), 170.1 ($\underline{C}(O)O$), 175.8 (C5). m/z (DCI) 359 ($M + NH_4^+$).

(vii) t-Butyl (2S)-1-t-butyloxycarbonyl-4-benzylpyroglutamate (2g) was prepared from pyroglutamate (1e) and benzyl bromide, and obtained as a colourless solid after flash chromatography (671 mg, 51%), m.p. 125.5-126.5°. $C_{21}H_{29}NO_5$ requires C, 67.2; H, 7.8; N, 3.7%. Found: C, 67.4; H, 8.1; N, 3.6%. $[\alpha]_D^{22}$° - 49.2° (c 0.9, $CHCl_3$). ν_{max} ($CHCl_3$) 1790, 1740, 1739 cm^{-1}. δ_H ($CDCl_3$) 1.45 and 1.52 (18H, 2 x s, 2 x $C(\underline{CH_3})_3$), 1.95-2.15 (2H, m, H3 and H3'), 2.65 - 2.73 (1H, m, $PhC\underline{H}$), 2.86 - 2.94 (1H, m, H4), 3.21-3.28 (1H, dd, $PhC\underline{H}'$) 4.35 (1H, dd, J 10.7 Hz, J' 8.3 Hz, C2), 7.15 -7.32 (5H, m, ArH). The relative stereochemistry of this compound was determined by n.O.e. spectroscopy, and the results are shown in Figure 1. δ_H (C_6D_6) 1.21 (9H, s, $C(\underline{CH_3})_3$), 1.24 - 1.37 (1H, m, H3), 1.41 (9H, s, $(\underline{CH_3})_3$), 1.59 - 1.70 (1H, m, H3'), 2.29 - 2.41 (1H, m, $PhC\underline{H}$), 2.67 - 2.85 (1H, m, H4), 3.01 - 3.10 (1H, m, $PhC\underline{H}'$), 4.22 (1H, d, J = 8.2Hz, C2), 6.75 - 7.15 (5H, m, ArH). δ_C ($CDCl_3$) 27.7 ($C(\underline{CH_3})_3$) 36.1 (C3), 43.2 (C4), 57.6 (C2), 82.3 and 83.2 (2 x $\underline{C}(CH_3)_3$), 126.7, 128.8, 129.1, 138.4 (all $Ar\underline{C}$), 149.5 ($N\underline{C}(O)O$), 170.5 ($O\underline{C}(O)$), 174.8 (C5). m/z (DCI) 393 ($M + NH_4^+$).

t-Butyl (2S)-4-benzylpyroglutamate (3)

To pyroglutamate (2g) (0.46 g, 1.2 mmol) in dry CH_2Cl_2 (20 ml) was added trifluoroacetic acid (0.2 ml). The reaction mixture was stirred at room temperature for 24h, then washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and the solvent evaporated to give a yellow oil. Trituration with petroleum ether yielded the product (3) as a white solid (196 mg, 58%), m.p. 145-145.5°C. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7; N, 5.1%. Found: C, 70.0; H, 8.0; N, 5.0%. $[\alpha]_D^{22}$° - 47.5° (c 0.75, $CHCl_3$). ν_{max} ($CHCl_3$) 1705, 1735 cm^{-1}. δ_H ($CDCl_3$) 1.47 (9H, s, $C(\underline{CH_3})_3$), 1.75 - 1.95 (1H, m, H3), 2.35 - 2.85 (3H, m, H3' and H4 and $C\underline{H}Ph$), 3.24 - 3.39 (1H, m, $PhC\underline{H}'$), 4.08 (1H, t, J=7.9 Hz, H2), 5.94 (1H, bs, $N\underline{H}$), 7.10 - 7.45 (5H, m, $Ar\underline{H}$). m/z (FD) 293 ($M + NH_4^+$).

(2S)-4-Benzylpyroglutamic Acid (4)

A solution of pyroglutamate (2g) (0.15 g, 0.54 mmol) and trifluoroacetic acid (1 ml) in toluene (15 ml) was refluxed for 6.5h. The solvent was removed in vacuo and the residue triturated with ether. The product (4) was obtained as a grey solid (83 mg, 71%), m.p. 161°C. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%. Found: C, 66.0; H, 6.2; N, 6.2%. $[\alpha]_D^{25}$ - 96.3° (c 0.77 in MeOH). ν_{max} (KBr) 3360, 3230,, 1725, 1640, 1665 cm^{-1}. δ_H (300 MHz, CD_3OD) 1.81 - 1.86 (1H, m, H3), 2.38 - 2.48 (1H, m, H3'), 2.56 - 2.64 (1H, dd, J 10.3Hz, J' 13.6 Hz, PhCH), 2.72 - 2.82 (1H, m, H4), 3.13 - 3.19 (1H, dd, J = 3.9 Hz, J = 13.6 Hz, PhCH'), 4.16 (1H, t, J=7.4 Hz, H2), 7.15 - 7.29 (5H, m, ArH). δ_C (62.85 MHz, $CDCl_3/(CD_3)_2SO$) 30.8 (C3), 36.5 (CH_2Ph), 43.1 (C4), 53.5 (C2), 126.2, 128.3, 128.6, 139.1 (all ArC), 173.7 (OC(O)), 178.1 (C5). m/z (DCI) 237 ($M + NH_4^+$).

Menthol(2S)-4-benzylpyroglutamate (5)

A mixture of pyroglutamic acid (4) (0.06 g, 0.20 mmol), L-menthol (0.09 g, 0.58 mmol) and 2 drops of conc. sulfuric acid were refluxed in toluene for 5h, and water collected in a Dean-Starke trap. The reaction mixture was cooled, the solvent removed, and the crude product purified by flash chromatography (CH_2Cl_2/10% ethyl acetate) to give the product (5) as a yellow oil (6 mg, 7%), along with a 59% recovery of unreacted starting material. δ_H ($CDCl_3$) 0.69 - 2.05 (17 H, m), 2.17 - 2.31 (2H, m, H3 and H3'), 2.59 - 2. 91 (2H, m, CH_2Ph), 3.05 - 3.34 (1H, m, H4), 3.90 - 4.05 (1H, m, CHOC(O)), 4.62 - 4.81 (1H, m, H2), 5.85 (1H, br s, NH), 7.08 - 7.50 (5H, m, ArH). δ_C ($CDCl_3$) 16.2, 20.7, 21.9, 23.4, 26.4, 29.7, 30.5, 31.4, 31.5, 34.1, 36.5, 40.7, 41.3, 46.9, 53.6 (C2), 76.7 (CHOC(O)), 126.6, 128.3, 129,0, 138.7 (all ArC), 171.6 (C(O)O), 178.6 (C5). m/z (EI) 357.2305 (M^+) (calculated for $C_{22}H_{31}NO_3$, 357.2304).

Menthol (2RS)-4-benzylpyroglutamate (6)

The title compound was prepared from the corresponding (2RS)-pyroglutamic acid using the method as described for the pyroglutamate (5) above, and obtained in 24% yield, along with a 45% recovery of unreacted starting material. δ_H ($CDCl_3$) 0.50 - 2.08 (17H, m), 2.12 - 2.40 (2H, m, H3 and one other) 2.65 - 2.85 (2H, m, PhCH and H3', 3.0 - 3.25 and 3.42 - 3.49 (2H, m, PhCH'- and H4), 3.90 - 4.10 (1H, CHOC(O)), 4.70 - 4.75 (1H, m, H2), 5.95 (1H, brs, NH), 7.18 - 7.50 (5H, m, ArH). δ_C ($CDCl_3$) 16.1 - 47.0 (12C), 53.7 and 53.9 (2 x C2), 76.4 and 76.8 (2 x CHOC(O)), 127.1, 128.6, 129.1, 139.0 (all ArC), 170.6 (C(O)O), 179.0 (C5). m/z (EI) 357 (M^+).

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REFERENCES

1. J.E. Baldwin, M. North, A. Flinn and M.G. Moloney, J.Chem.Soc., Chem.Commun., 1988, 828- 829 ; J.E. Baldwin, M. North, A. Flinn and M.G. Moloney, Tetrahedron, 1989, 1453-1464 and 1465-1474.

2. See, for example, B.M. Trost and R.A. Kunz, J.Org.Chem., 1974, 39, 2475-2476.

3. A.I. Meyers, K.B. Kunnen and W.C. Still, J.Am.Chem.Soc., 1987, 109, 4405-4407.

4. For example, A.G.M. Barrett, H.B. Broughton, S.V. Attwood and A.A.L. Gunatilaka, J.Org.Chem., 1986, 51, 495-503; J.E. Baldwin, R.M. Adlington, R.H. Jones, C.J. Schofield, C. Zaracostas and C.W. Greengrass, Tetrahedron, 1986, 42, 4879-4888; A.P. Craven, H.J. Dyke and E.J. Thomas, Tetrahedron, 1989, 45, 2417-2430; H.J. Dyke, P.G. Steel and E.J. Thomas, J.Chem.Soc., Perkin I, 1989, 525-528; W.S. Klaver, H. Hiemstra, and W.N. Speckhamp, Tetrahedron. 1988, 44, 6729-6738.

5. J.K. Thottathil, J.L. Moniot, R.H. Mueller, M.K.Y. Wong and T.P. Kissick, J.Org.Chem., 1986, 51, 3140-3143; Y. Ohfune and M. Tomita, J.Am.Chem.Soc., 1982, 104, 3511-3513; M. Yanagida, K. Hashimoto and M. Ishida, Tetrahedron Lett., 1989, 30, 3799-3802; K. Shimamoto and Y. Ohfune, Tetrahedron Lett., 1989, 30, 3803-3804.

6. T. Ohta, A. Hosoi and S. Nozoe, Tetrahedron Lett., 1988, 29, 329-332.

7. T. Ohta, T. Kimura, N. Sato and S. Nozoe, Tetrahedron Lett., 1988, 29, 4303-4304; T. Ohta, A. Hosoi, T. Kimura and S. Nozoe, Chem.Lett., 1987, 2091-2094; T. Nagasaka, A. Tsukada and F. Hamaguchi, Heterocycles, 1986, 24, 2015-2022; A. Giovannini, D. Savoia and A. Umani-Ronchi, J.Org.Chem., 1989, 54, 228-234; A.M.P. Koskinen and H. Rapoport, J.Org.Chem., 1989, 54, 1859-1866; N. Ikota, and A. Hanaki, Heterocycles, 1988, 27, 2535-2537; P.F. Keusenkothen and M.B. Smith, Tetrahedron Lett., 1989, 30, 3369-3372; F.G. Fang and S.J. Danishefsky, Tetrahedron Lett., 1989, 30, 3621-3624; F.G. Fang, M. Prato, G. Kim and S.J. Danishefsky, Tetrahedron Lett., 1989, 30, 3625-3628.

8. H. Gibian and E. Klieger, Annalen der Chemie., 1961, 640, 145-156.

9. S. Yoshifugi, K.-I. Tanaka, T. Kawai and Y. Nitta, Chem.Pharm.Bull., 1986, 34, 3873-3878.

10. U. Schmidt and R. Scholm, Synthesis, 1978, 752-753; M. Caswell, R.K. Chaturvedi, S.M. Lane, B. Zvilichovsky and G.L. Schmir, J.Org.Chem., 1981, 46, 1585-1593.

11. J.E. Baldwin, M.G. Moloney, and M. North, Tetrahedron, 1989, in press.

12. A.R.M.P. Koskinen and H. Rapoport, J.Org.Chem., 1989, 54, 1859.

13. J.M. Aizpurua and C. Palomo, Tetrahedron Lett., 1985, 26, 475-476.

14. S. Goldschmidt and C. Jutz, Chem.Ber., 1953, 86, 1116-1117.

15. J.S. Peterson, G. Fels and H. Rapoport, J.Am.Chem.Soc., 1984, 106, 4539-4547.