Investigation into direct use of protected 3,4-dehydropyroglutamates in synthesis

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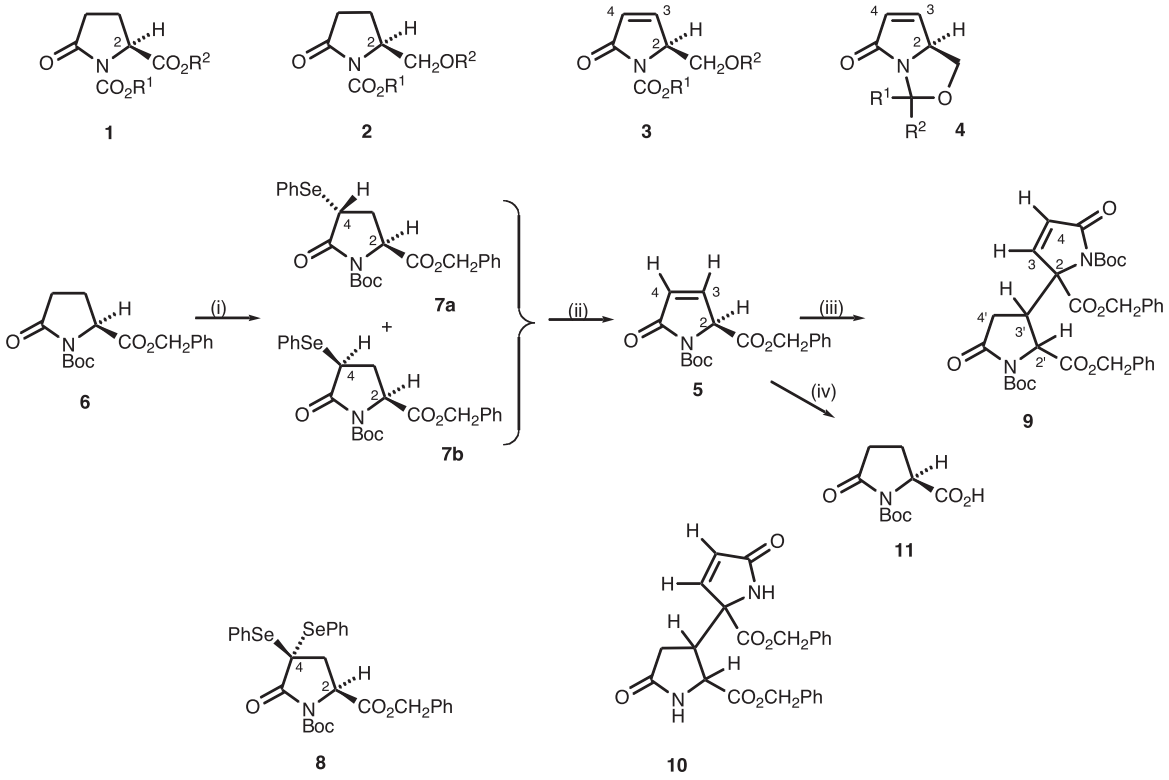
Synthesis of the 3,4-dehydropyroglutamate **5** has shown it to be unstable, forming the dimer **9** on chromatography and being too readily racemised to be considered as a useful chiral synthon.

Keywords: 3,4-dehydropyroglutamate

When protected pyroglutamic acids such as **1** were first used as chiral starting materials in synthesis, it was deemed necessary to reduce the ester to a protected alcohol such as **2** to prevent loss of chirality at C-2 through keto/enol tautomerism. This often led to a requirement for re-oxidation before completion of the synthesis.[1] It has since been shown by ourselves and others, that this reduction/re-oxidation sequence is unnecessary and protected pyroglutamic acids **1** have been used directly in synthesis, the centre at C-2 being used to direct stereochemistry at C-4.[1] For 3-substituted pyroglutamates, the 3,4-dehydro reduced esters **3** have proved to be excellent substrates for 1,4-addition, epoxidation and dihydroxylation reactions of great stereoselectivity and a variety of reduced esters **3** and **4** have been used to this end.[1,2] Although we would expect the 3,4-dehydro esters such as the pyroglutamate derivative **5** to be more acidic and therefore be more prone to racemisation than the pyroglutamate **2**, there have been no reports of its synthesis or properties. We have, therefore, prepared this compound and shown that it is easily racemised and dimerised, even on attempted purification by chromatography on silica gel.

Benzyl *N*-*tert*-butoxycarbonylpyroglutamate **6**[3] was converted into the anion using LHMDS and reacted with phenylselenium bromide to afford, on chromatography, a 45% yield of a mixture of the *trans*- and *cis*-selenides **7a** and **7b** in a ratio of 4:3, together with the *bis*-selenide **8** in 11% yield, as shown in Scheme 1. Further chromatography to isolate samples for NMR analysis allowed the *trans* isomer **7a** to be obtained in pure form together with a sample of the *cis*-isomer **7b** which was contaminated with a small amount of the *trans*-isomer **7a**. The ^{1}H NMR spectrum of the *cis*-compound **7b**, unlike that of the *trans*-isomer **7a**, exhibited distinct and separate signals for the protons H-3 and so the stereochemistry could be confirmed by the NOE experiments shown in Fig. 1. Irradiation of the signal for H-3 at 2.79 ppm caused, in addition to a 35% enhancement in the geminal proton signal at 2.83 ppm, a 16% enhancement in the signal for H-2 at 3.96 ppm and a 15% enhancement in the signal for H-4 at 4.65 ppm. Thus the signal at 2.79 ppm was assigned to the proton H-3*R* and the stereochemistry was defined as being that of the *cis* (2*S*,4*S*)-isomer. The amount of diselenide **8** produced could be minimised by using two equivalents of base.



Scheme 1 Reagents and conditions: (i) LHMDS/PhSeBr/THF 10 min –78°C (45% **7**, 11% **8**); (ii) 60% H_2O_2/ EtOAc/ 0°C and r.t. 30 min (87%); (iii) silica gel chromatography (42%); (iv) H_2/EtOAc/ 10% Pd–C/ r.t. 24 h (90%).

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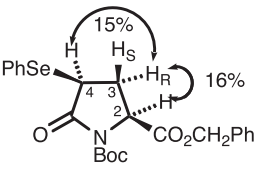

Fig. 1 NOE experiments on **7b**.

When the mixture of monoselenides was treated with 60% hydrogen peroxide in ethyl acetate at 0 °C, the desired 3, 4-dehydro-compound **5** was isolated in crude form in 87% yield. The compound was reasonably pue by ^{1}H NMR spectroscopy but, when an attempt was made to purify this compound by chromatography on silica gel, a new compound was obtained in 42% yield. The ^{1}H NMR spectrum indicated that this was the urethane dimer **9** with two nine-proton signals at 1.42 and 1.38 ppm, ten aromatic protons between 7.41 and 7.27 ppm and four benzylic protons at 5.32–5.08 ppm, indicating the presence of two benzyl esters and two Boc groups. There were two olefinic doublets for H-3 and H-4 (J 6.1 Hz) which showed none of the coupling between H-3 and H-2 which had been present in the spectrum of the endomethylene compound **5** before chromatography. Finally, there were three further protons as an ABX system at 2.69 ppm (dd, $J_{4'A,4'B}$=18.0, $J_{4'A,3'}$=8 Hz), 2.15 ppm (dd, $J_{4'B,4'A}$=18.0, $J_{4'B,3'}$=1.8 Hz) and 3.58 ppm (dd, $J_{3',4'A}$=8.0, $J_{3',4'B}$=1.6 Hz). The ^{13}C NMR spectrum was also compatible with this structure. In an NOE experiment, irradiation of the signal for H-2' caused a 6% enhancement in the signal for H-3 (Fig. 2a) and irradiation of the signal for H-3 caused a 15% enhancement of the signal for H-2' (Fig. 2b). The highest ion in the high resolution EI mass spectrum was that of the deurethenylated compound **10** formed by McLafferty rearrangement in the mass spectrometer.

Formation of the dimer **9** was evidently a result of the enhanced acidity of H-2 in **5** allowing the 2-anion to be formed under mild conditions and to attack a second molecule of **5** at C-3 in a 1,4-addition reaction. To check the stereochemical integrity of **5**, the crude product was hydrogenated using 10% palladium on carbon as catalyst. The product **11** had the expected spectra but $[\alpha]_D$ +0.7 (*c* 1, HOAc) indicated almost complete racemisation (literature[3] $[\alpha]_D$ –36.9 (*c* 1, HOAc).

We have thus shown that the endomethylene compound **5** is extremely labile and will readily racemise or dimerise. Use of a synthetic strategy involving stereoselective reaction at C-3 of 3,4-dehydropyroglutamates will, therefore, continue to be restricted to reduced ester derivatives such as **2** and **3**.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations (given in units of 10^{-1}deg cm^2 g^{-1}) were obtained using a Perkin Elmer PE241 polarimeter with a 1 dm path length micro cell. IR spectra were recorded on a Perkin Elmer 1720 Fourier transform instrument. ^{1}H NMR spectra were recorded on Bruker AMX500 (500 MHz) and WM360 (360 MHz) Fourier transform instruments. ^{13}C NMR spectra were recorded on a Bruker AMX500 (125.8 MHz) Fourier transform instrument. INEPT experiments were used to help assign ^{13}C NMR resonances. Residual solvent peaks were used as internal reference for all NMR spectra. *J* values are in Hz. Mass spectra were recorded on Kratos MS80RF and MS25 double focusing spectrometers by Mr A.M. Greenway and on a Kratos MS50 spectrometer by Dr S. Chotai (Wellcome Research Laboratories). The high resolution mass measurement was recorded on a V67070 spectrometer by Dr S. Chotai (Wellcome Research Laboratories). Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh - ART 9385). Petroleum ether refers to that fraction of alkanes, b.p. 40–60°C.

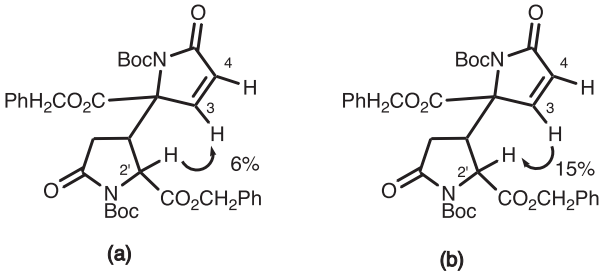

Fig. 2 (a) NOE on irradiation at H-2'; (b) NOE on irradiation at H-3.

Benzyl (2S,4R)- and (2S,4S)-N-tert-butoxycarbonyl-4-phenylselenopyroglutamates **(7a)** *and* **(7b)***:* Butyl lithium (2.3*M* in hexane, 1.0 ml, 2.3 mmol) was added to a solution of hexamethyldisilazane (370 mg, 2.28 mmol) in tetrahydrofuran (3.0 ml) at –78 °C under nitrogen. The mixture was stirred at –78 °C for 20 min, followed by addition of a solution of benzyl (2*S*)-*N-tert*-butoxycarbonyl-pyroglutamate **6**[3] (638 mg, 2.00 mmol) in tetrahydrofuran (5.0 ml). The mixture was stirred for 40 min and allowed to warm to –20 °C to ensure formation of the anion. On cooling to –78 °C, a solution of phenylselenyl bromide (566 mg, 2.40 mmol) in tetrahydrofuran (5.0 ml) was added. The mixture was stirred for 10 min at –78 °C and 10% aqueous ammonium chloride (4 ml) was added. The mixture was allowed to warm to room temperature, ethyl acetate (30 ml) was added and the organic layer was separated, washed with water (2 × 30 ml), 10% aqueous sodium chloride (30 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford a yellow oil which was purified by column chromatography on silica gel using petroleum ether : diethyl ether (1:1) as eluant to afford a mixture of the *trans* and *cis* monoselenides **7a** and **7b** as a pale yellow foam (429 mg, 45%) with *m/z* [+ve FAB (3-NBA / $CHCl_3$)] 475 $[M+H]^+$ as the nearest ion to the parent and the *bis*-selenide **8** as a pale yellow oil (133 mg, 11%). The mixed monoselenides were further chromatographed to yield samples for identification by NMR spectroscopy. A pure sample of the *trans*-selenide **7a** was obtained together with a sample of the *cis*-selenide **7b** which contained a small amount of the *trans*-isomer **7a**. *Benzyl (2S,4R)-N-tert-butoxycarbonyl-4-phenylselenopyroglutamate* **7a**; δ_H (360 MHz, C^2HCl_3) 7.66–7.27 (10H, m, ArH), 5.16 (1H, AB, J_{AB} 12.1, OCH_APh), 5.11 (1H, BA, J_{BA}=12.1, OCH_BPh), 4.29 (1H, dd, $J_{4,3S}$=8.4, $J_{4,3R}$=5.3, H-4), 3.98 (1H, dd, $J_{2,3A}$=8.6, $J_{2,3B}$=7.9, H-2), 2.38 (2H, m, H-3) and 1.40 (9H, s, $C(CH_3)_3$); δ_C (125.8 MHz, C^2HCl_3) 171.4 (amide), 170.4 (ester), 148.7 (urethane), 126.1–135.0 (Ar), 83.7 ($OC(CH_3)_3$), 67.2 (OCH_2Ph), 57.5 (C-2), 39.9 (C-4), 29.7 (C-3) and 27.6 ($C(CH_3)_3$). *Benzyl (2S,4S)-N-tert-butoxycarbonyl-4-phenylselenopyroglutamate* **7b**; δ_H (360 MHz, C^2HCl_3) 7.60–7.27 (10H, m, ArH), 5.30 (1H, AB, J_{AB}=12.1, OCH_APh), 5.11 (1H, BA, J_{BA}=12.1, OCH_BPh), 4.65 (1H, dd, $J_{4,3R}$=9, $J_{4,3S}$=3.6, H-4), 3.96 (1H, dd, $J_{2,3R}$=9, $J_{2,3S}$=3.6, H-2), 2.79 (1H, tt, $J_{3R,3S}$=14.6, $J_{3R,2}$ = $J_{3R,4}$ 9, H-3*R*), 2.23 (1H, tt, $J_{3S,3R}$=14.6, $J_{3S,2}$ = $J_{3S,4}$=3.6, H-3*S*) and 1.42 (9H, s, $C(CH_3)_3$). *Benzyl (2S)-N-tert-butoxycarbonyl-4,4-diphenylselenopyroglutamate* **8**; *m/z* [+ve FAB (3-NBA / $CHCl_3$)] 630 $[M+H]^+$; δ_H (360 MHz, C^2HCl_3) 7.67–7.22 (15H, m, ArH), 5.10 (1H, AB, J_{AB}=12.1, OCH_APh), 5.03 (1H, BA, J_{BA}=12.1, OCH_BPh), 4.09 (1H, dd, $J_{2,3R}$=8.5, $J_{2,3S}$=6.4, H-2), 2.53 (1H, dd, $J_{3R,3S}$=14.6, $J_{3R,2}$=8.5, H-3*R*), 2.35 (1H, dd, $J_{3S,3R}$=14.6, $J_{3S,2}$=6.4, H-3*S*) and 1.37 (9H, s, $C(CH_3)_3$); δ_C (125.8 MHz, C^2HCl_3) 170.2 (amide), 169.9 (ester), 149.0 urethane), 128.5–137.3 (Ar), 83.9 ($OC(CH_3)_3$), 67.3 (OCH_2Ph), 56.6 (C-2), 49.1 (quin, $J_{C4,Se}$=96.9, $J_{C4,Se}$=94.7 (C-4), 36.0 (C-3) and 27.7 ($C(CH_3)_3$).

Benzyl (2S)-N-tert-butoxycarbonyl-3,4-dehydropyroglutamate **(5)**: A solution of the benzyl (2*S*)-*N-tert*-butoxycarbonyl-4-phenylselenopyroglutamates **7** (212 mg, 0.445 mmol) in ethyl acetate (5.0 ml) was treated with 60% hydrogen peroxide (0.63 ml) at 0°C and the mixture was allowed to warm to room temperature and stirred for 30 min. The organic layer was separated and washed with water (2 × 10 ml), saturated aqueous sodium hydrogen carbonate (2 × 10 ml), saturated aqueous sodium chloride (2 × 10 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford *benzyl (2S)-N-tert-butoxycarbonyl-3,4-dehydropyroglutamate* **5** as a pale yellow solid (123 mg, 87%), m.p. 67–69 °C, $[\alpha]_D^{22}$ +4.04 (*c* 0.67, $CHCl_3$), *m/z* [+ve FAB (3-NBA / $CHCl_3$)] 318 $[M+H]^+$; ν_{max} (KBr/cm^{-1}) 1786, 1718 (urethane), 1752 (ester) and 1604 (C=C); δ_H (360 MHz, C^2HCl_3) 7.37–7.33 (5H, m, ArH), 7.07 (1H, dd, $J_{3,4}$=6.0, $J_{3,2}$=2.4, H-3), 6.23 (1H, dd, $J_{4,3}$=6.0, $J_{4,2}$=2.0, H-4), 5.25–5.15 (3H, m, J_{AB}=12.1, OCH_2Ph and H-2) and 1.43 (9H, s, $C(CH_3)_3$); δ_C (125.8 MHz, C^2HCl_3) 167.9 (amide), 166.1

(ester), 148.2 (urethane), 142.6 (C-4), 134.4 (C-3), 128.8–128.3 (Ar), 83.5 (O*C*(CH_3)$_3$), 67.8 (*C*H_2Ph), 64.4 (C-2) and 27.7 (C(*C*H_3)$_3$).

2-Benzyl 1-tert-butyl 2-(5-(benzyloxycarbonyl)-1-(tert-butoxycarbonyl)-2-oxopyrrolidin-3-yl)-5-oxo-2H-pyrrole-1,2(5H)-dicarboxylate **(9)**: Benzyl(2S)-N-tert-butoxycarbonyl-3,4-dehydropyroglutamate **5** (1.76 g, 5.5 mmol) was passed through a column of silica gel using petroleum ether : diethyl ether (2:1) as eluant to yield the dimer **9** as a white foam (746 mg, 42%), m/z [EI] Found: 434.1521 $C_{24}H_{22}N_2O_6$ [M-($CO_2C_4H_9$)$_2$+2H]$^+$ requires: 434.1478; ν_{max} (film/cm^{-1}) 1739 (ester); δ_H (500 MHz, C^2HCl_3) 7.41–7.27 (10H, m, ArH), 6.84 (1H, d, $J_{3,4}$=6.1, H-3), 6.34 (1H, d, $J_{4,3}$=6.1, H-4), 5.32–5.08 (4H, m, (2 × OCH_2Ph), 4.94 (1H, d, $J_{2',3'}$=1.3, H-2'), 3.58 (1H, d×d, $J_{3',4'A}$=8.0, $J_{3',4'B}$=1.7, H-3'), 2.69 (1H, d×d, $J_{4'A,4'B}$=18.0, $J_{4'A,3'}$=8, H-4'A), 2.15 (1H, d×d, $J_{4'B,4'A}$=18.0, $J_{4'B,3'}$=1.8, H-4'B), 1.42 (9H, s, C(CH_3)$_3$) and 1.38 (9H, s, C(CH_3)$_3$); δ_C (125.8 MHz, C^2HCl_3) 171.0 (amide), 170.1 (amide), 167.2 (ester), 167.1 (ester), 149.0 (urethane), 148.9 (urethane), 143.9 (C-3), 135.1 (Ar), 134.4 (Ar), 130.8 (C-4), 128.5 (Ar), 84.8 (OC(CH_3)$_3$), 84.3 (OC(CH_3)$_3$), 73.2 (C-2), 68.4 (OCH_2Ph), 67.7 (OCH_2Ph), 60.6 (C-2'), 37.5 (C-3'), 32.6 (C-4') and 27.8 (C(CH_3)$_3$).

N-tert-Butoxycarbonylpyroglutamate **(11)**: Benzyl (2*S*)-*N-tert*-butoxycarbonyl-3,4-dehydropyroglutamate **5** (42 mg, 0.131 mmol) was dissolved in ethyl acetate (10 ml) and 10% palladium on carbon (4.2 mg, 10% w/w) was added. The mixture was stirred under an atmosphere of hydrogen for 24 h at room temperature and filtered. The solvent was removed *in vacuo* to afford *N-tert-butoxycarbonylpyroglutamate* **11** as a white solid (27 mg, 90%) with spectral properties identical to those of an authentic sample[3] but having $[\alpha]_D^{18}$ +0.7 (*c* 1.2, HOAc) (literature[3] $[\alpha]_D^{29}$ –36.9 (*c* 1, HOAc)).

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