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Self Reproduction of Chirality in Pyroglutamates: Reactions at α- Position with Electrophiles[1]

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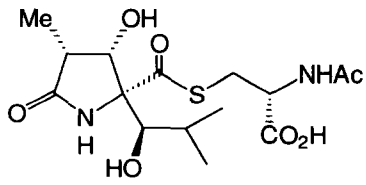
Abstract : *Condensation of pyroglutamic acid with trimethylacetaldehyde gave a bicyclic derivative which on deprotonation with LiHMDS and reaction with electrophiles gives chiral α-substituted pyroglutamate derivatives.*

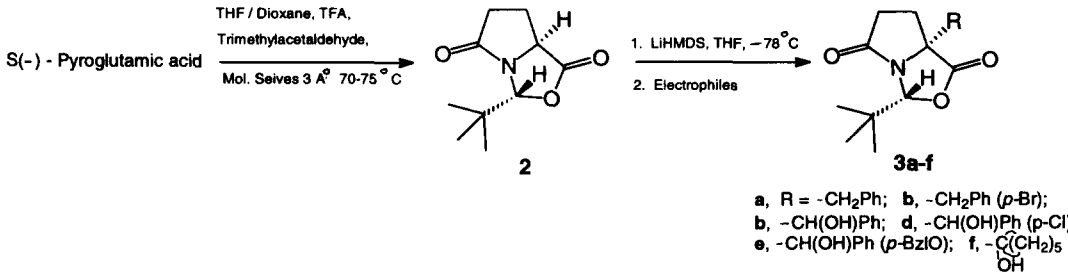
Natural α- amino acids constitute an important and inexpensive chiral pool for the synthesis of complex natural products[3]. Pyroglutamic acid, the cyclized form of glutamic acid, possesses two carbonyl groups whose differential reactivities have made pyroglutamic acid a starting material of choice for the synthesis of complex natural products such as Deoxynojirimicin[3d], Bulgecinine[3e], Domoic acid[3f] and Kainic acid[3g]. Stereoselective functionalisation of the pyroglutamate skeleton at position C-4[4] & C-5[5] (and the consequential functionalisation at position C-3[3a,6]) have been extensively reported. C-2 Substituted pyroglutamate skeleton is part of many a complex natural products such as Lactacystin (1), and approaches for the synthesis of C-2 substituted pyroglutamate skeleton have been recently described[7,8]. However, no synthetic procedure for the chiral functionalization at C-2 of the native pyroglutamate exists to date. We wish to report in the present paper the application of Seebach's methodology for 'self reproduction of chirality'[9] to S(-) pyroglutamic acid and some representative alkylation & aldol reactions at its C-2.



Lactacystin (1)

The condensation of N- protected amino acids with aldehydes is reported to give both *cis-* & *trans-*cyclic products[10], whereas the only published report in case of pyroglutamic acid condensation with aldehydes leads to a bis- adduct[11]. While our attempts to condense trimethylacetaldehyde with pyroglutamic acid using Seebach's procedure[9] were

unsuccessful, use of THF or dioxane as solvent, molecular sieves 3°A, and a Parr™ SS pressure vessel gave (2*R*,5*S*)-2-t-butyl-1-aza-3-oxabicyclo [3.3.0]octane-4,8-dione (**2**)[12] where the t-butyl group was assigned to be in pseudo equatorial position. Lack of positive nOe between 2-H & 5-H also supported the assignments.



Scheme–1

The C-5 of **2** was selectively deprotonated using LiHMDS in THF at -78°C . Reaction of the resultant enolate with benzylbromide gave the corresponding 5-benzyl derivative **3a**[13] where the benzyl group was assigned α- stereochemistry. The β- orientation of the benzyl group would have resulted in a strong nOe between 2-H and the benzylic protons, which was not observed experimentally. That the incoming electrophiles approached the enolate exclusively from the α-side was further evident by the recovery of **2** when the enolate was quenched with water[14]. Reaction of the enolate of **2** with other electrophiles gave **3b-f**[13] in moderate yields.

Thus we have successfully shown for the first time that pyroglutamates can react at α-position with retention of chirality. This approach may be of use for the synthesis of complex C-2 substituted pyroglutamates.

Synthesis of 2 : *S* (-)-Pyroglutamic acid (1.30g,10 mmol), molecular sieves 3A°(10 g), trimethylacetaldehyde (9 ml, 80 mmol) and trifluoroacetic acid (0.1 ml) were taken in dry dioxane (200 ml) in a Parr™ SS pressure vessel and The contents were stirred magnetically and heated at 70-75°C for 48 hr. The pressure vessel was cooled in an ice bath, molecular sieves were filtered off and the filtrate was concentrated to one fourth of its volume under reduced pressure. Water (100ml) was added to this and the organic material was extracted with EtOAc (3x100 ml). The EtOAc layer was washed with sat. $NaHCO_3$ solution (2x25 ml), sat. brine (2x25 ml), dried (Na_2SO_4) and concentrated. The crude product was chromatographed over a florisil column using hexane-EtOAc (80:20) to give **2** as white powder, yield 800 mg (40 %) m.p.134-6°C (hexane)

Reaction of 2 with electrophiles *:* Using a syringe and rubber septa a solution of **2** (197 mg, 1 mmol) in THF (25 ml) was added over a period of 5 min to a magnetically stirred

solution of LiHMDS (1.1 ml, 1 mol soln in THF) in 20 ml. THF at -78°C. The reaction mixture was stirred at -78°C for 1.5 hr followed by the drop wise addition of electrophile (1.1 mmol) in 5 ml THF (5ml) and was stirred at the same temperature for additional 3 hrs. After quenching the reaction with a sat. NH_4Cl, THF was partially removed under reduced pressure at ambient temperature. Chilled water (50 ml) was added to it and the product was extracted with EtOAc (2x50 ml). EtOAc layer was washed with sat. brine (2x50 ml), dried (Na_2SO_4), concentrated and the product was chromatographed over florisil^R column using EtOAc-hexane (80:20) as eluant to give the C-2 substituted products.

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12. Data of **2**, white powder, yield 800 mg (40 %) m.p.134-6°C (hexane) $[\alpha]_D^{25}$ +29.6 (c,1.3, MeOH); IR(KBr) : 1730, 13780 cm^1, ^1H NMR($CDCl_3$) : δ 0.9 (s, 9H), 2.17 (m, 1H), 2.4 (m, 1H), 2.55 (m, 1H), 2.7 (m, 1H), 4.33 (t, J=8 Hz, 1H), 5.4 (s, 1H), ^{13}C NMR($CDCl_3$) : δ 24.06, 29.64, 32.02, 36.93, 57.28, 96.38, 173.55, 179.85, MS (m/z) 197, 152, 139, 112, 84, 57.

13. **Data of 3a** colourless oil, yield 125 mg (44%), $[\alpha]_D^{25}$ -7.6 (c, 0.8, MeOH), IR(Neat) 1700, 1780 cm^{-1}), ^1H NMR($CDCl_3$) δ 1.05 (s, 9H), 2.05-2.35 (m, 4H), 2.9 (d, J =14 Hz, 1H), 3.15 (d, J =14 Hz, 1H), 4.32 (s, 1H), 7.15 (m, 2H), 7.25 (m, 2H), 7.45 (m, 1H), FAB MS (m/z) 288, 287, 196, 174, 128, 91, 57.

Data of 3b,yield 210 mg (57%), mp 152-5°C, $[\alpha]_D^{25}$ +5.0 (c, 0.4, MeOH) IR(KBr): 1720, 1780 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.2 (s, 9H), 2.0-2.4 (m, 4H), 2.95 (d, J=15 Hz, 1H), 3.15 (d, J=15 Hz, 1H), 4.68 (s, 1H), 7.1 (m, 2H), 7.5 (m, 2H), MS (m/z): 368, 366, 197, 91, 57.

Data of 3c, yield 150 mg, 50%, mp 118-20°C, $[\alpha]_D^{25}$ +73.0(c,1.2, MeOH), IR(KBr): 1680, 1780 cm^{-1}, ^1H NMR($CDCl_3$): δ 1.15(s, 9H), 2.05-2.55 (m,4H), 4.55 (s,1H), 5.12(d, J =3Hz, 1H), 7.35-7.50 (m,5H), MS (m/z): 304 (M^+), 246,197,128,70

Data of 3d, yield 145 mg (43%), m.p.155-7°C, $[\alpha]_D^{25}$ +9.4 (c, 0.33, MeOH), IR(KBr) 1685, 1780 cm^{-1}, ^1H NMR($CDCl_3$): δ 1.15 (s, 9H), 2.0-2.15 (m, 2H), 2.30-2.45 (m, 2H), 4.70 (s, 1H), 5.10 (s, 1H), 7.40 (m, 4H), MS (m/z) 388, 337, 224, 197, 141, 128, 111, 70, 57.

Data of 3e,yield 200 mg, 51%, mp 125-7°C, $[\alpha]_D^{25}$ +31.8(c,1.1,MeOH), IR(KBr): 1680, 1760 cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.15 (s,9H), 2.0-2.4 (m,4H), 4.6 (s,1H), 5.05 (d, J = 3Hz, 1H), 5.1 (s,2H), 7.0 (d, J =11 Hz,2H), 7.3-7.45 (m,7H)

Data of 3f, yield 150 mg, 51%, mp 184-5°C, $[\alpha]_D^{25}$ +9.1(c,1.3, MeOH), IR(KBr): 1720, 1760 cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.2 (s,9H), 1.40-2.05 (m,10H), 2.08-2.80 (m,4H), 5.38 (s, 1H); MS (m/z): 297 (M^+), 198,129,128,70

14. In the PMR spectra of crude 2 & 3a-f there was no evidence for the β-isomer. The reported yields[13] are that of chromatographically pure isolated/crystallized materials.

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