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Synthesis of Homochiral 3-Substituted Glutamic Acids and Prolines from Pyroglutamic Acid

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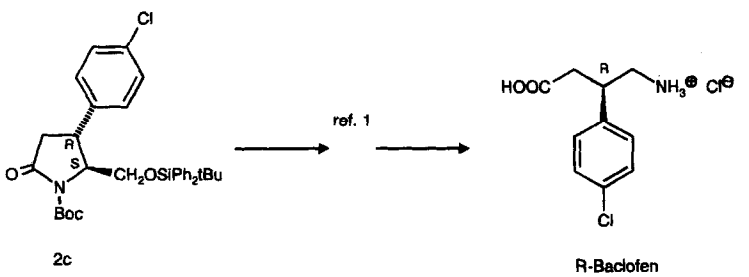
Abstract: Efficient syntheses of (2S,3S)-methylproline (**5a**) and (2S,3R)-phenylproline (**5b**) are described, starting from the readily available pyroglutaminol derivatives **2a** and **2b** via conjugate 1,4-addition of organocuprates to **1**. Catalytic hydrogenation of **3** from the least hindered α-side furnishes **6**, which is transformed to (2S,3R)-methylproline (**7**). 3-Substituted glutamic acids **8c,d** are provided by a four step procedure from **2c,d**.

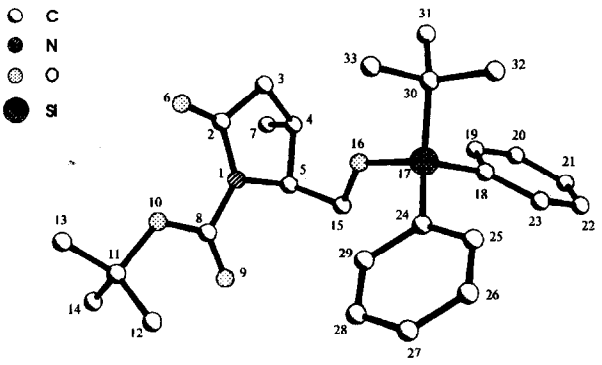
We recently reported that 1,4-conjugate additions of Grignard-and Gilman-cuprates to pyroglutaminole derivative **1** give **2a-d** in good yields without racemisation of the stereogenic centre in 5-position.[1] Excellent *trans*-selectivity was observed for this reaction. Pyroglutaminole **2c** was transformed to R-Baclofen, a derivative of the inhibitory neurotransmitter GABA (γ-aminobutyric acid)[1] (Scheme 1).



2c R-Baclofen

Scheme 1

Herein we report the transformation of pyroglutaminoles **2a,b** to *cis*-and *trans*-3-substituted proline[2] derivatives **7** and **5a,b**. On the other hand **2c,d** are converted to the 3-substituted glutamic acids[3] **8c,d**.



X-ray structure of 2a

For the synthesis of *trans*-3-substituted proline derivatives (Scheme 2), pyroglutamate **2a** (the *trans*-configuration was unambiguously assigned by x-ray structure analysis[10]) and **2b** were reduced with $BH_3 \cdot S(CH_3)_2$ to the protected prolinol derivatives **4a,b** with 89% and 60% yield respectively. Deprotection of the alcohol function with TBAF provided the N-Boc prolinols in 93% and 86% yield. Sharpless oxidation with $RuCl_3/NaIO_4$[4] gave N-Boc prolines **5a,b**. After deprotection with TFA, (2S,3S) 3-methylproline (**5a**)[9] and (2S,3R) 3-phenylproline (**5b**)[9] were obtained in 40% and 31% respectively.

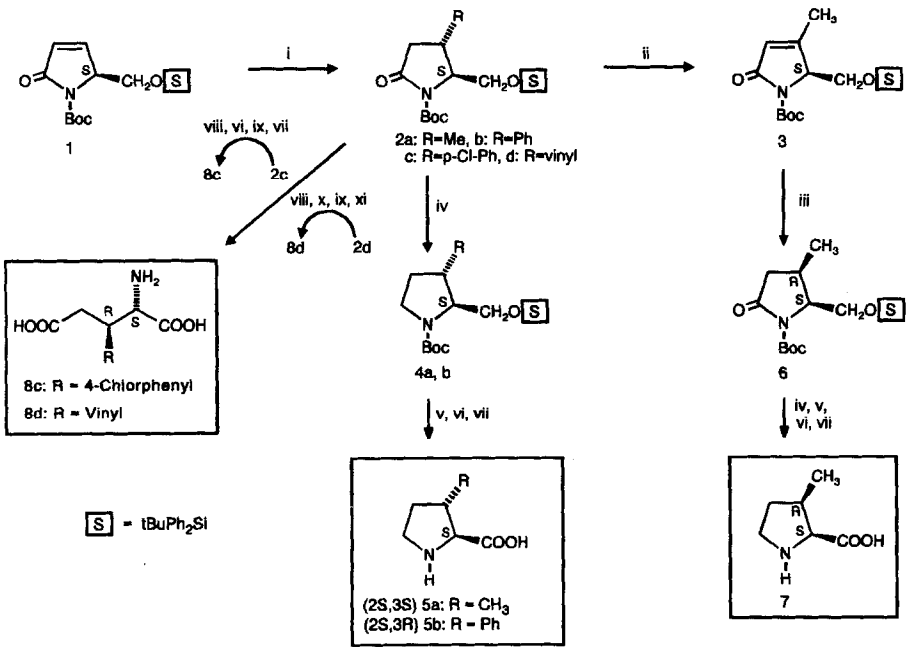
For the synthesis of glutamates **8c,d**, **2c,d** were deprotected with tetrabutylammonium fluoride in THF/AcOH. The addition of acetic acid was necessary to prevent ring expansion to the δ-lactone derivative.[5] With HF/CH_3CN only cleavage of the N-Boc protecting group was observed.

Oxidation of the pyroglutaminol **2c** with $RuCl_3/NaIO_4$[4] furnished the corresponding pyroglutamic acid derivative, which was ring opened with LiOH/THF[6] to the N-Boc protected glutamic acid derivative **8c**. Deprotection of with TFA provided glutamate **8c**[9] in 42% overall yield from **2c**.

As the vinyl group is sensitive to oxidation under the Sharpless conditions the alcohol of **2d** was oxidized to the t-butylester with CrO_3/Ac_2O/t-BuOH[7]. Extractive isolation of the product was facilitated by both protecting groups. Ring opening reaction according to Grieco's method[6] and cleavage of the protecting groups with 6M HCl furnished the glutamic acid derivative **8d**[9] in 25% combined yield from **2d**.

(2S,3R)-*cis*-3-Methylproline (**7**) was prepared in a similar reaction sequence as described for **5a** and **5b**. Starting with **2a**, the double bond was introduced via phenylselenylation and oxidative elimination[2l,8,1] to give **3** in 72% yield. Catalytic hydrogenation of **3** in ethyl acetate with Pd/C from the less-hindered α-side of **3** resulted in a single diastereomer **6** (73%). *Trans* isomer **2a** could not be detected with ^1H-and ^{13}C-NMR spectroscopy in the crude reaction product. After reduction of the amide group and O-deprotection, the alcohol was oxidized[6] to N-Boc-2S,3R-methylproline. N-Deprotection with TFA provided **7**[9] in 19% overall yield from **3**. Pharmacological studies with **8c,d** will be published elsewhere in due course.

In summary, the synthesis of enantiopure prolines and 3-substituted glutamic acids (> 98 % ee, in comparison with independently synthesized **5a**[2c], **5b**[2h], **7**[2c]) from inexpensive S-pyroglutamic acid has been accomplished. The synthetic strategy outlined in this report would be equally applicable for the synthesis of **ent 5a**, **5b**, **7**, **8c**, **8d**, starting with R-pyroglutamic acid.



Scheme 2

i: $5R_2LiCu$ or $5R_2MgBrCu$, $2Me_3SiCl$, Et_2O; **ii:** 1. HMDS/BuLi, PhSeCl -78°C, 2. H_2O_2; **iii:** $Pd/C/H_2$; **iv:** $BH_3{\cdot}S(CH_3)_2$; **v:** Bu_4NF; **vi:** $RuCl_3/NaIO_4$, CH_3CN/H_2O; **vii:** TFA; **viii:** Bu_4NF,AcOH,H_2O; **ix:** 1M LiOH/THF; **x:** CrO_3/Py/DMF, Ac_2O,t-BuOH; **xi:** 6M HCl.

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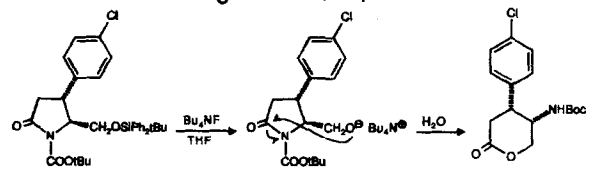
5. With **2c** the lactone **i** was isolated. With $Et_3NH^+F^-$/THF deprotection was extremely slow (see ref. 6).



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9. **5a**: mp.: 245°C (ref.[2c]: 240°-249°C).- $[\alpha]_D^{20}$ = -30 (c = 0.27/H_2O); +5 (c = 0.24/0.1 M HCl) (ref.[2c]: -30 (c = 0.1/ H_2O)].- ^{1}H-NMR (D_2O/d_4-methanol): δ (ppm) = 1.31 (3H, d, J = 6.7 Hz, CH_3), 1.70 (1H, dq, $J_{3,4a} \approx J_{4a,5a} \approx J_{4a,5b}$ = 8.5 Hz, J_{gem} = 13.0 Hz, 4a-H), 2.24 (1H, m, 4b-H), 2.47 (1H, sept, J = 7.2 Hz, 3-H), 3.34 (2H, m, 5-H), 3.65 (1H, d, $J_{2,3}$ = 8.1 Hz, 2-H).- **5b**: mp.: >250°C (ref.[2h]: 242°C.- $[\alpha]_D^{20}$ = +65 (c = 0.2/ 1 M HCl) [ref.[2h]: +69 (c = 0.75/ 6 M HCl)].- ^{1}H-NMR (D_2O/D_2SO_4/d_6-acetone): δ (ppm) = 2.16 (1H, m, 4-H), 2.41 (1H, m, 4-H), 3.51 (3H, m, 3-H und 5-H), 4.35 (1H, d, J = 9.9 Hz, 2-H), 7.26 (5H, m, Ar-H).- **7**: mp.: 225°C.-$[\alpha]_D^{20}$ = -30.5 (c = 0.19/0.1 M HCl).- ^{1}H-NMR (D_2O/D_2SO_4/d_6-acetone): δ (ppm) = 0.93 (3H, d, J = 7.1 Hz, CH_3), 1.70 (1H, sext, J = 6.3 Hz, 4-H), 2.18 (1H, m, 4-H), 2.72 (1H, sept, J = 7.1 Hz, 3-H), 3.27 (1H, m, 5-H), 3.46 (1H, m, 5-H), 3.65 (1H, d, $J_{2,3}$ = 7.7 Hz, 2-H).- **8c**: mp.: 182°C.- $[\alpha]_D^{20}$ = -1 (c = 0.2/1 M HCl).- ^{1}H-NMR (D_2O/D_2SO_4/d_6-acetone): δ (ppm) = 3.00 (2H, m, 4-H), 3.66 (1H, m, 3-H), 4.34 (1H, d, J = 5 Hz, 2-H), 7.17 (2H, d, J_{AB} = 8.65 Hz, Ar-H), 7.28 (2H, d, J_{AB} = 8.66 Hz, Ar-H).- **8d**: mp: 179°C.- $[a]_D^{20}$ = +13 (c = 0.27/H_2O).- ^{1}H-NMR (D_2O/d_6-acetone): δ (ppm) = 2.57 (1H, dd, $J_{3,4a}$ = 8.7 Hz, J_{gem} = 16.4 Hz, 4-H), 2.80 (1H, dd, $J_{3,4b}$ = 6.1 Hz, J_{gem} = 16.5 Hz, 4-H), 3.03 (1H, m, 3-H), 4.09 (1H, d, $J_{2,3}$ = 3.9 Hz, 2-H), 5.23 (2H, m, =CH_2), 5.66 (1H, m, -CH=).

10. X-ray structure determination of **2a**: colorless transparent platelets of size 0.5x0.7x0.1 mm, space group $P2_1$, a = 9.831, b = 13.088, c = 11.213Å, β = 105.2°, z = 2.1971 (1883 observed) reflections measured on a Siemens R3m/V diffractometer with CuK_α-radiation. Direct methods (SHELXTL), wR = 7.5% (unit weights). Atomic distances and angles as well as coordinates are deposited at the Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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