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Synthesis of (2*S*,4*S*) 2-Carboxy-4-Pyrrolidine Acetic Acid, a Conformationally Constrained 2-Amino Adipic Acid Analogue

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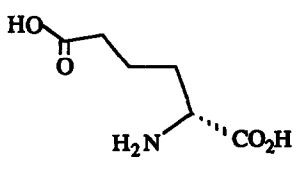
Key Words : pyroglutamic acid, excitatory amino-acids, alkyl bromoacetate, sodium cyanoborohydride.

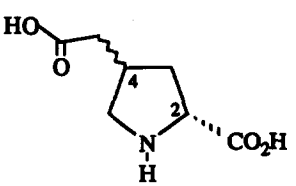
Abstract : (2S,4S) 2-carboxy-4-pyrrolidine acetic acid was synthesized from (S) pyroglutamic acid in 26% overall yield by a regiospecific deprotonation of the N-methoxycarbonyl benzylester 4.

(*S*) Glutamic acid acts as a major excitatory neurotransmitter in the central nervous system and conformationally restricted structural analogues were developed as agonists and antagonists at several receptor sites, particularly the most studied NMDA receptor. These "excitatory amino-acids" can indeed be useful as experimental tools for investigating central nervous system mechanisms.[1] Among them, the homologous 2-amino adipic acid was early recognized as an NMDA selective antagonist and (*R*) 2-amino adipic acid **1** was shown to be the more active enantiomer.[2]

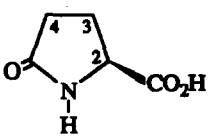
Thus, we planned to synthesize the analogues (2*R*) 2-carboxy-4-pyrrolidine acetic acids **2a** and **2b** with limited conformational flexibility. For this purpose, (*R*) pyroglutamic acid appeared to be an appropriate starting material taking advantage of specific deprotonation at C-4 of suitably N-protected pyroglutamates, as first demonstrated in the Bredereck reaction.[3]



1

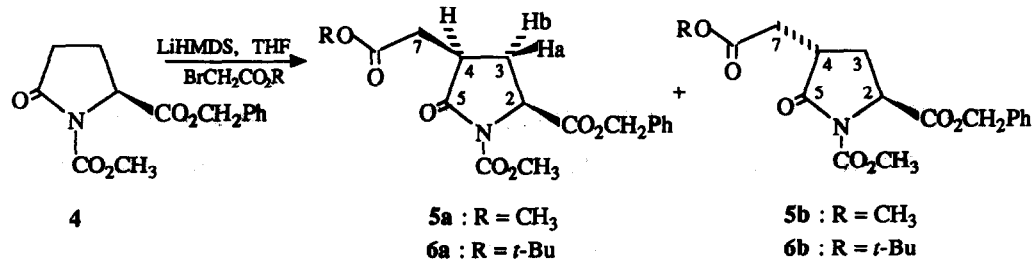


2a : 2*R*, 4*S*
2b : 2*R*, 4*R*



3

To ensure the validity of the synthetic route described in Scheme 1, we started from readily available (*S*) pyroglutamic acid **3** as synthetic precursor of diastereomers **2c** (2*S*, 4*R*) and **2d** (2*S*, 4*S*).[4]



4 **5a** : R = CH_3 **5b** : R = CH_3

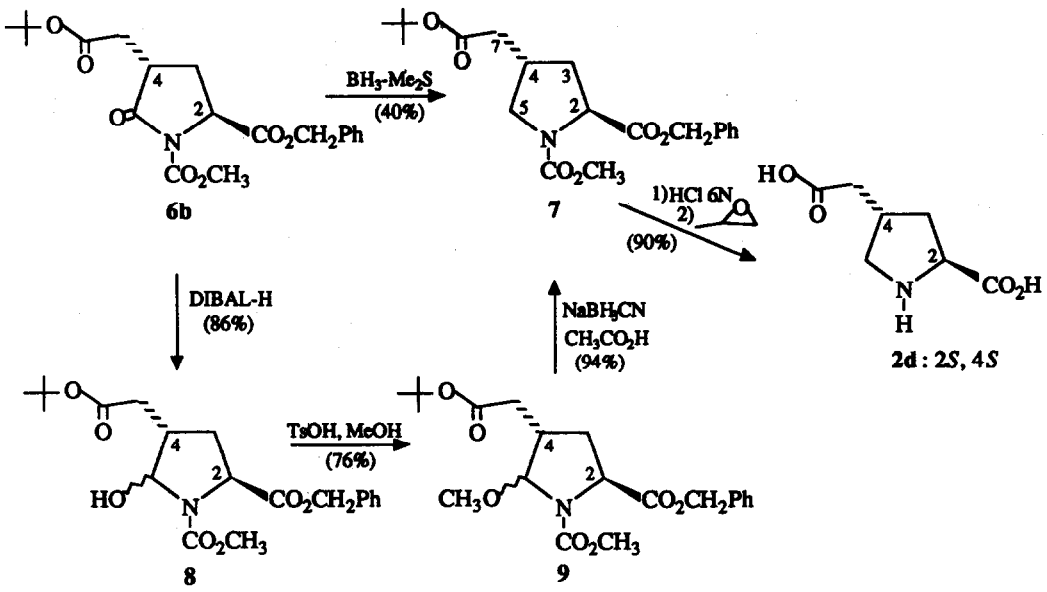
6a : R = *t*-Bu **6b** : R = *t*-Bu

Scheme 1

The *N*-methoxycarbonyl benzylester **4**, easily prepared without racemization,[5] was regiospecifically deprotonated with lithium bis(trimethylsilyl)amide (1 equiv., -78°C). The resulting lithium enolate was alkylated at the same temperature with methylbromoacetate (1.1 equiv., 1 h), leading to a mixture of diastereomers **5a** and **5b** in the ratio of 43 : 57 with a 56% yield. Predominant formation of *trans* 2,4-disubstituted pyrrolidones[6] could be expected from addition of the electrophile to the less hindered side of the enolate.[7] Therefore, a very poor diastereoselectivity was observed compared with the related alkylations using benzyl bromide.[8] It could be improved by the use of *tert*-butyl bromoacetate as the electrophile : under the same experimental conditions the diastereomers **6a** and **6b** were obtained after chromatography in a total yield of 82% in the ratio of 1 : 3 to 1 : 3.4.[9] When the reaction was quenched after five minutes at -78°C, **6a** and **6b** were isolated in the same ratio, together with 10% of the starting pyrrolidone **4**.

The optical purity of compound **6b** was preserved as demonstrated by ^1H NMR study in the presence of $Pr(hfc)_3$, by comparing with the racemic compound (±) **6b**.[10] The relative configurations indicated for **5** and **6** were confirmed by ^1H NMR analysis of diagnostic protons together with NOE experiments. The coupling constants between C2-H and C3-H differ in **6a** or **5a** (J = 9.5 Hz, J' = 1 Hz) and **6b** or **5b** ($J \simeq J' \simeq 8$ Hz), suggesting conformational differences between the *cis* and *trans* diastereomers. In the case of the diastereomers **5a** and **6a**, the small value of the coupling constants between C2-H and C3-Ha indicate a *trans* relationship in which the dihedral angle between them is close to 90°. The NOE observed between the other proton at C3, C3-Hb, and C4-H prove their proximity, hence a *cis* relationship between these two protons.

The synthesis of **2d** according to Scheme 2 involves the reduction of the C5 carbonyl into methylene before deprotection of the functional groups. The derivative **6b** was reduced to **7**[11] (40%) with BH_3-Me_2S in THF.[12] Attempts to improve this moderate yield failed and led us to try other stepwise methods, through the α-hydroxy carbamates **8**. Our previous work illustrated the utility of DIBAL-H (particularly in hexane solution) in partial chemoselective reduction of *N*-*o*-nitrobenzoyl[13] or *N*-methoxycarbonyl pyrrolidones.[5,14] Applied to **6b**, this method afforded, without any reduction of the ester groups, the α-hydroxy carbamates **8** (86%), which were directly converted into the more stable α-methoxy derivatives **9** (76%, Scheme 2). These compounds could not be reduced with large excess of sodium borohydride in acetic acid[15] and this lack of reactivity remained unexplained. However, the reduction of **9** with excess sodium cyanoborohydride in acetic acid[16] at 60°C gave the product **7** in 94% yield.



Scheme 2

Deprotection of **7** by acid hydrolysis (HCl 6N, 100°C), followed by treatment with propylene oxide afforded **2d** (90%).[17]

(*R*) 2-amino adipic acid analogues **2a** and **2b** could also be prepared following the above mentioned route, and tested for their affinity at the NMDA receptor. Therefore they could provide further insight into the structural requirements for activity at this receptor.

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9. **6a** : Mp 76-8°C, $[\alpha]_D^{20}$ = -27 (c = 1.0, $CHCl_3$), IR : 1790, 1722 cm^{-1}; ^1H NMR [250 MHz, $CDCl_3$, δ = 0 ppm, TMS, *J* (Hz)] : 7.36 (bs, 5H, aromatic), 5.23 (2d, 2H, J_{AB} = 12, $C\underline{H}_2Ph$), 4.71 (bd, 1H, $J_{2,3b}$ = 9.5, $J_{2,3a} \simeq 1$, C2-H), 3.82 (s, 3H, *N*-CO_2CH_3), 2.98 (m, 1H, C4-H), 2.77 (dd, 1H, J_{AB} = 17, *J'* = 3.6, C7-Ha), 2.45 (dd, 1H, J_{AB} = 17, *J'* = 8, C7-Hb), 2.39 (m, 1H, $J_{3a,3b}$ = 13, $J_{3a,4}$ = 9, C3-Ha), 2.16 (m, 1H, $J_{3a,3b}$ = 13, $J_{3b,4} \simeq 12$, $J_{2,3b}$ = 9.5, C3-Hb), 1.43 (s, 9H, *t*-Bu) ; MS (m/z) : 335 $(M\text{-}t\text{-}Bu)^{+\cdot}$, 318, 200, 182, 154, 91 (100%), 57. Anal. Calcd for $C_{20}H_{25}NO_7$: C: 61.37, H: 6.44, N: 3.58, Found: C: 61.28, H: 6.32, N: 3.43. **6b** : Mp 74°C, $[\alpha]_D^{20}$ = -6 (c = 1.0, $CHCl_3$); IR : 2957, 1800, 1728 cm^{-1}; ^1H NMR (250 MHz) : 7.38 (bs, 5H, aromatic), 5.23 (d, 2H, J_{AB} = 12, $C\underline{H}_2Ph$), 4.61 (dd, 1H, $J_{2,3a} \simeq J_{2,3b} \simeq 8$, C2-H), 3.78 (s, 3H, *N*-CO_2CH_3), 3.00 (m, 1H, C4-H), 2.82 (dd, 1H, J_{AB} = 16.6, *J'* = 4, C7-Ha), 2.70 (m, 1H, C3-Ha), 2.38 (dd, 1H, J_{AB} = 16.6, *J'* = 9.4, C7-Hb), 1.74 (m, 1H, C3-Hb), 1.44 (s, 9H, *t*-Bu), MS (m/z) : 392 ($M^{+\cdot}$, very weak), 335, 290, 200 (100%), 182, 154, 91, 57; Anal. Calcd for $C_{20}H_{25}NO_7$: C: 61.37, H: 6.44, N: 3.58, Found C: 61.21, H: 6.41, N: 3.42.
10. Prepared from (±) pyroglutamic acid (splitting of the *N*-CO_2CH_3 signal by addition of Pr(hfc)$_3$).
11. **7** : $[\alpha]_D^{20}$ = -68 (c = 0.4, $CHCl_3$); IR : 3017, 1722 cm^{-1} ; ^1H NMR (300 MHz) : 7.33 (bs, 5H, aromatic), 5.16 (s, 2H, $C\underline{H}_2Ph$), 4.38 and 4.30 (2dd, 1H, $J_{2,3a} \simeq 8$, C2-H), 3.86 (m, 1H, C5-Ha), 3.71 and 3.50 (2s, 3H, *N*-CO_2CH_3), 3.13 (m, 1H, C5-Hb), 2.53 (m, 2H, C4-H and C3-Ha), 2.33 (m, 2H, C7-H2), 1.61 (m, 1H, C3-Hb), 1.43 (s, 9H, *t*-Bu). Ms (m/z) : 377 ($M^{+\cdot}$), 320, 276, 262, 242, 188 (100%). Anal. Calcd for $C_{20}H_{27}NO_6$: C: 63.64, H: 7.21, N: 3.71, Found C: 63.36, H: 7.19, N: 3.74.
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17. **2d** : $[\alpha]_D^{24}$ = -69 (c = 0.5, H_2O), ^1H NMR (250 MHz, D_2O), 4.16 (dd, 1H, C2-H), 3.60 (dd, 1H, C5-Ha), 3.07 (dd, 1H, C5-Hb), 2.55 (m, 4H, C7-H2, C3-Ha, C4-H), 1.72 (m, 1H, C3-Hb) ; CIMS : 174 $(M+H)^+$, 130.

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