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Stereoselective Functionalisation of N-Boc Pyroaminoadipic Acid: Synthesis of 5-Substituted Aminoadipic and Pipecolic Acids

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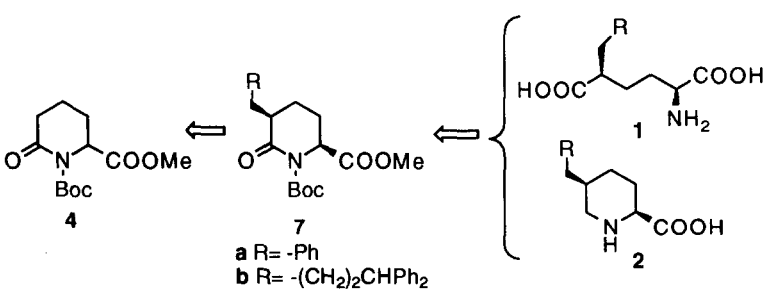
Abstract: 5-Alkylsubstituted aminoadipic and pipecolic acids were diastereoselectively synthetized from methyl *N*-Boc pyroaminoadipate.

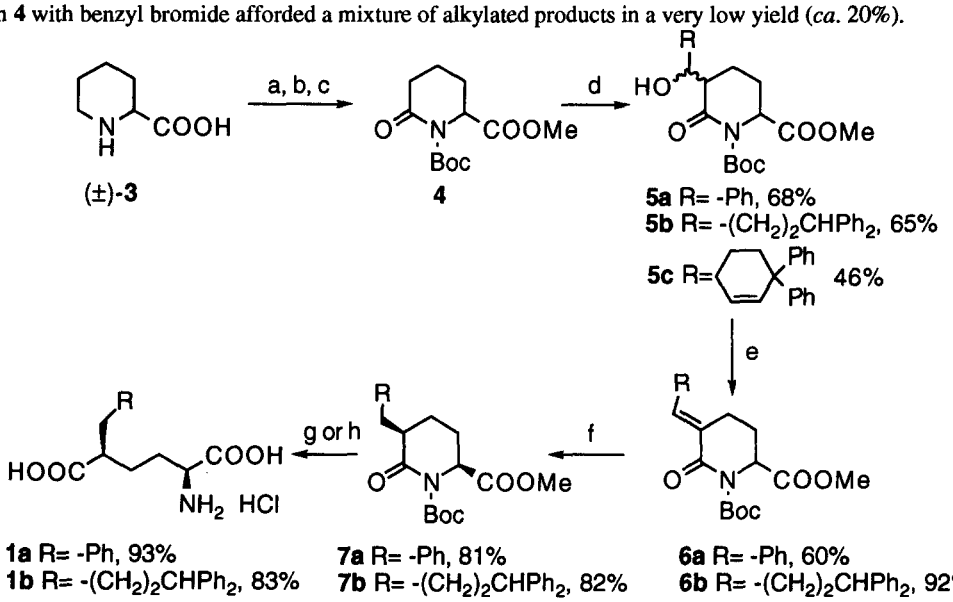
Competitive antagonists of the *N*-methyl-*D*-aspartate (NMDA) subtype of excitatory amino acid receptors[1] are potentially useful for treating a wide variety of neurodegenerative diseases.[2] Following the discovery of *D,L*-α-aminoadipic acid as a selective antagonist,[3] structurally related derivatives were prepared to study the structure activity relationship. Thus, the distance between the α-amino acid moiety and the distal carboxylic functionality has been modified by making higher homologues,[4] conformationally constrained compounds[5] or unsaturated derivatives.[5c,6] On the other hand, the replacement of the ω-carboxyl group by other acidic moieties such as the phosponic acids[5b-c,6] or tetrazoles[5a] has been shown to enhance the antagonist activity. In order to study substituent effects on the neuroexcitatory activity of α-aminoadipic acid, we decided to prepare different δ-substituted aminoadipic acids **1** as well as 5-substituted pipecolic acid derivatives **2** (Scheme 1). The synthetic approach used to obtain these compounds rests on the stereoselective functionalisation of pyroaminoadipate **4** through its lactam enolate. While the stereoselective alkylation[7] and aldol condensation[8] reactions of pyroglutamic acid derivatives has been quite successful, there are not many precedents[9] for the same kind of direct stereoselective reactions on the pyroaminoadipate counterpart **4**.



Scheme 1

Methyl *N*-Boc pyroaminoadipate **4** was prepared from *D,L*-pipecolic acid **3** by esterification with MeOH/HCl(g) and protected as the *N*-Boc derivative following Grieco's procedure.[10] Methyl *N*-Boc pipecolate was oxidised with ruthenium dioxide/sodium periodate giving rise to **4** in a 44% overall yield from **3** (Scheme 2). The enolate derived from **4** was generated with LiHMDS in anhydrous THF at -78°C and then treated with benzaldehyde or 4,4-diphenylbutyraldehyde in the presence of $Et_2O{\cdot}BF_3$,[11] affording the corresponding aldols

5a-b in 68% and 65% yield respectively. This is the first time that this reaction has been applied to the pyroaminoadipate system. The aldol condensation also took place with ketones, as in the case of 4,4-diphenyl-2-cyclohexen-1-one, although in a lower yield (46%). However, attempts to alkylate the lactam enolate derived from **4** with benzyl bromide afforded a mixture of alkylated products in a very low yield (*ca.* 20%).



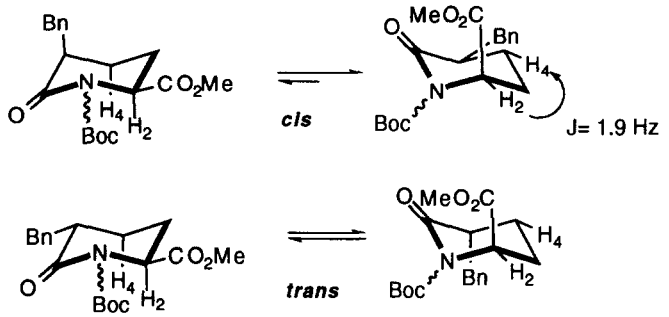
a: MeOH, HCl_g, 60%; **b**: $(Boc)_2O$, DMAP, Et_3N, 77%; **c**: RuO_2(10%), $NaIO_4$, EtOAc, 94%; **d**: LiHMDS, THF, RCHO, $Et_2O.BF_3$, 2h, -78°C; **e**: $MeSO_2Cl$, Et_3N (10 eq.), CH_2Cl_2, 48h, r.t.; **f**: PtO_2 (0.1 eq.), H_2, EtOAc, 2-6 h, r.t.; **g**: (for **7a**) 6N HCl, reflux, 24h; **h**: (for **7b**) i). LiOH 2.5N, 4h, r.t. ii). EtOAc, HCl_g, 1h, r.t.

Scheme 2

The diastereomeric mixture **5** was treated with mesyl chloride (1.2 eq) with an excess of triethylamine in dichloromethane. After two days at room temperature, the alkylidene compounds **6** were obtained in good yields (60-92%). In the case of the benzyl derivative (**6a**),[12] the double bond had *E* stereochemistry, while the alkyl compound **6b** was obtained as a *Z/E* mixture in 1:3 ratio. In both cases the methyl 5-alkylidenepyroaminoadipates **6** were further hydrogenated with platinum oxide as catalyst, delivering the 5-substituted pyroaminoadipates. Although the double bond reduction is highly stereoselective with the pyroglutamate derivatives,[13] the catalytic hydrogenation of **6** was less stereoselective. The *cis*-isomer **7**[14] was the major product in the reaction mixture, but it was possible to observe *ca.* 5% of the *trans*-isomer by ^{1}H-NMR spectroscopy in the crude reaction mixture. However, both diastereomers were easily separated by flash chromatography delivering pure compounds **7a,b** in good yields (81-82%).

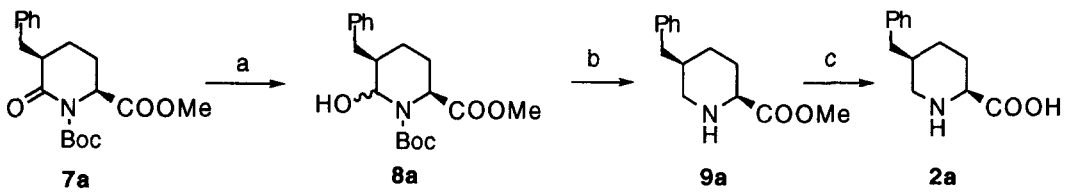
These *cis*-methyl-5-alkylpyroaminoadipates **7** were easily hydrolyzed to the corresponding δ-substituted aminoadipic acids **1**. Compound **1a**[15] (93% yield) was obtained by refluxing **7a** with 6N HCl for 24 h. Compound **1b** (83% yield) was obtained by treating **7b** with LiOH (2.5N) solution for 4 h at r.t. followed by acid hydrolysis with $HCl_{(g)}$ saturated ethyl acetate solution.

Stereochemical assigments of **7a,b** were made on the basis of the ^{1}H-NMR coupling constants between H_2 and H_{4eq}. Proton H_2 (ddd, 4.66 ppm) in the *cis*-isomer **7a**, shows a long range coupling constant $J_{2\text{-}4eq}$ = 1.9 Hz with H_{4eq} (m, 1.70-1.61 ppm) due to the W coplanar arrangement between both protons. This coupling pattern was not observed in the corresponding *trans*-isomer (Scheme 3).



Scheme 3

A highly chemoselective reduction method[16] was used to convert the methyl pyroaminoadipate derivative **7a** to the pipecolic acid **2a** (Scheme 4).



a: $LiBEt_3H$, THF, -78°C, 30 min.; **b**: Et_3SiH, $Et_2O{\cdot}BF_3$, -78°C —> r.t., 2h.; **c**: i. 6N HCl, 60°C, 24h. ii. Propylene oxide, MeOH.

Scheme 4

Compound **7a** was reduced to the hemiaminal **8a** with $LiBEt_3H$ in THF at -78°C for 30 min and without isolation further reduced with Et_3SiH and $Et_2O{\cdot}BF_3$ at -78°C, allowing the reaction mixture to reach r.t. after 2 h. The pipecolate **9a** was obtained in 78% yield, with the $Et_2O.BF_3$ simultaneously removing the BOC protecting group. Finally, acidic hydrolysis of **9a** with 6N HCl at 60°C for 24 h and further treatment of the hydrochloride salt with propylene oxide gave, after recrystallization from H_2O/acetone, the (±)-5-*cis*-benzylpipecolic acid **2a**[17] in 35% yield.

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11. In the absence of the catalyst the reaction did not take place. For a study of the role of the catalyst in the aldol condensation of pyroglutamate lactam enolates with aldehydes and ketones, see *ref.* 8.
12. All new compounds described in this paper were characterized on the basis of their ^{1}H-NMR (200 MHz), ^{13}C-NMR (50.3 MHz) spectroscopic data. **6a:** M.p.: 80-2°C. ^{1}H-NMR ($CDCl_3$) δ: 7.93 (t, J= 1.6 Hz, 1H, HC=C), 7.41-7.27 (m, 5H, Ph), 4.85 (t, J= 4.6 Hz, 1H, CH-CO_2Me), 3.79 (s, 3H, CO_2CH_3), 2.89 (dt, J=4.3 and 16.1 Hz, 1H, CH_2), 2.69-2.51 (m, 1H, CH_2), 2.31-2.19 (m, 1H, CH_2), 2.14-2.01 (m, 1H, CH_2), 1.54 (s, 9H, $(CH_3)_3$). ^{13}C-NMR ($CDCl_3$) δ: 171.0, 164.0, 151.7, 138.3, 134.6, 129.4 (2C), 128.9, 128.2, 127.8 (2C), 82.8, 57.3, 51.9, 27.3 (3C), 24.2, 22.6. Anal: calcd, C, 66.07; H, 6.71; N, 4.06; found, C, 65.84; H, 6.49; N, 4.06%.
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14. **7a:** M.p.: 90-2°C. ^{1}H-NMR ($CDCl_3$) δ: 7.32-7.14 (m, 5H, Ph), 4.66 (ddd, J= 1.9, 2.7 and 5.9 Hz, 1H, CH-CO_2Me), 3.71 (s, 3H, CO_2CH_3), 3.51 (m, 1H, CH_2Ph), 2.72-2.20 (m, 2H, CH_2Ph and CH), 2.15 (dq, 1H, J= 3.7 Hz and 14.1 Hz, CH_2), 1.96 (m, 1H, CH_2), 1.70-1.61 (m, 1H, H_{4eq}), 1.51 (s, 9H, $(CH_3)_3$), 1.48-1.35 (m, 1H, H_{4ax}). ^{13}C-NMR ($CDCl_3$) δ: 172.3, 171.9, 152.7, 139.2, 129.2 (2C), 128.3 (2C), 126.1, 83.3, 58.8, 52.3, 45.8, 37.0, 27.8 (3C), 25.2, 23.5. IR ($CHCl_3$): 2980, 1720, 1745, 1670, 1295, 1145. Anal: calcd, C, 65.68; H, 7.25; N, 4.03; found, C, 65.29; H, 7.20; N, 3.97%.
15. **1a:** M.p.: 175-7°C. ^{1}H-NMR (CD_3OD) δ: 7.31-7.12 (m, 5H, Ph), 3.94 (t, 1H, J= 6.1 Hz, CH-NH_2), 3.02-2.64 (m, 3H), 2.02-1.54 (m, 4H). ^{13}C-NMR (CD_3OD) δ: 178.3, 171.5, 140.2, 130.0 (2C), 129.4 (2C), 127.5, 53.7, 48.3, 39.3, 29.4, 28.0. IR (KBr): 2928, 1740, 1705, 1496, 1188 cm^{-1}.
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17. **2a:** M.p.: >240°C (dec.). ^{1}H-NMR (CD_3OD/KOD) δ: 7.27-7.11 (m, 5H, Ph), 3.19 (t, 1H, J= 4.6 Hz, CH-CO_2H), 2.70-2.65 (m, 2H, CH_2-N), 2.55 (d, 2H, J= 7.4 Hz, CH_2-Ph), 2.05-1.90 (m, 1H), 1.76-1.56 (m, 3H), 1.40-1.25 (m, 1H). ^{13}C-NMR (CD_3OD/KOD) δ: 181.3, 141.9, 130.1 (2C), 129.3 (2C), 126.9, 59.9, 48.9, 40.4, 37.9, 29.3, 27.3. IR (KBr): 3439, 1604, 1317cm^{-1}.

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