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Enantioselective Synthesis of (2S,3S)- and (2R,3R)-Pyrrolidine-2,3-Dicarboxylic Acids: Conformationally Constrained (S)- and (R)-Aspartic Acid Analogues

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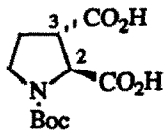
Abstract : The title compounds were prepared from the key intermediate **2** and its enantiomer at C2, derived from chiral synthons **1**- (R) and **1**- (S), respectively, by ethoxycarbonylation, desulfonylation and conversion to carboxylic acid.

Asymmetric synthesis of conformationally constrained α-amino acid analogues has gained considerable interest in recent years. This seems mainly due to the notion that the introduction of conformational constraints into peptides may provide useful informations on their bioactive conformation and may result in beneficial physiological effects such as optimization of peptide-receptor binding and resistance to peptidases[1]. Another reason derives from the search for a better understanding of conformational requirements for receptor binding of excitatory amino acids (EAA) like glutamate, aspartate, kainate and quisqualate and the eventual search for effective EAA antagonists[2].

N-Methyl-D-aspartate (NMDA) has been long known as a potent agonist which selectively activates one of the excitatory amino acid (EAA) receptors. Efforts to prepare a unified model for the explanation of the observed binding specificities of aspartate in terms of specific molecular conformations have been eclipsed by those made for glutamate[3]. Thus, we have been very interested in preparing aspartate analogues in which the functional groups presumably responsible for the binding are in well-defined positions, e.g., within a relatively rigid molecular framework.



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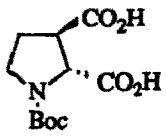

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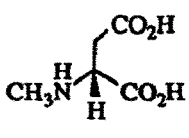
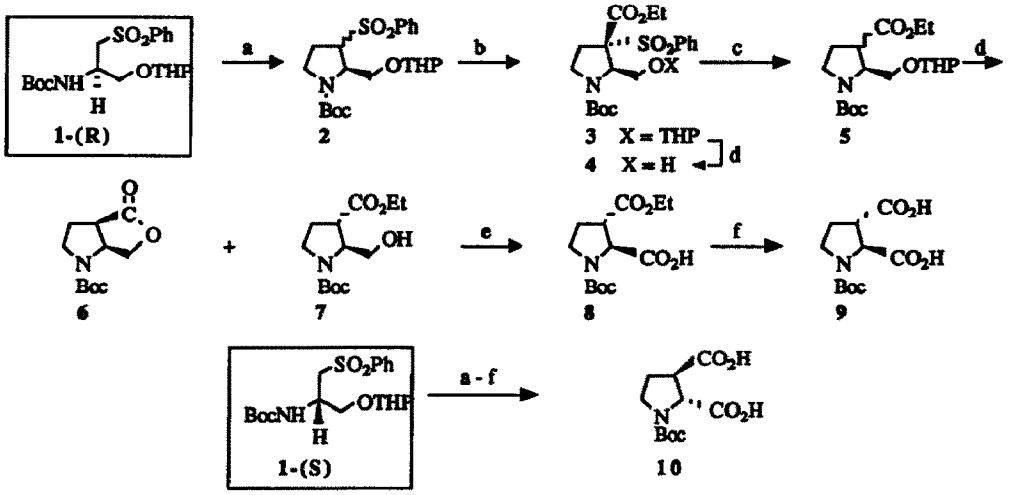


NMDA

In the preceeding communication, we demonstrated that L-serine derived **1**-(R) and **1**-(S) readily formed 5-, 6-, 7- and 8-membered heterocyclic ring systems in addition reaction with electrophiles possessing two different electrophilic centers, thus providing C2-monosubstituted chiral pyrrolidine, piperidine, hexahydro- azepine and azacyclooctane derivatives[4].

In this communication, we describe the first application of this new synthetic methodology for the enantioselective synthesis of (2S,3S)-N-Boc-pyrrolidine-2,3-dicarboxylic acid **9** and its (2R,3R)-enantiomer **10** a conformationally constrained L-and D-aspartic acid analogue, respectively, as depicted in Scheme 1.

The chiral synthon **1-(R)** was transformed into pyrrolidine sulfone **2** by treatment with 2 equiv of n-butyllithium and 1-bromo-2-chloroethane at -78°C. The resulting pyrrolidine **2** was then treated with n-butyllithium in the presence of HMPA (3 equiv), followed by addition of ethyl chloroformate at -78°C to afford the β-ester sulfone **3** in 93% yield as a single diastereomer.



Scheme 1

Reagents and conditions: a) 2 eq n-Buli, THF, 1.2 eq Br-$(CH_2)_2$-Cl, -78°C to rt (90%); b) 1 eq n-BuLi,THF, 3 eq HMPA, 1.2 eq Cl-CO_2Et, -78°C to rt (93%); c) 5 eq 6 % Na-Hg (portionwise addition), EtOH, -10°C, 5h (50 -60%); d) EtOH, 0.1 eq pyridinium p-toluenesulfonate, 60°C, 3h (90%); e) Jones oxidation, acetone, 0°C, 1h (78%); f) 1N NaOH, MeOH, rt, 1h (92 %).

The reductive desulfonylation performed on **3** was sluggish. Among the reported methods[5], the highest yield of **5** was attained by reducing **3** with 6% Na-Hg in ethanol at -10°C and buffering with acetic acid (55%). Even under this condition, undesired cleavage of the ester group was observed (approximately 30%). Changes such as the use of methanol as solvent, sodium hydrogenphosphate as buffer, reaction temperature at 25°C, all suffered from inferior yields of **6** and **7**. Removal of THP group provided a mixture of **6** and **7** (2:3 mixture) in 90% yield. Although the mixture was separable by careful flash chromatography (SiO_2; heptane/EtOAc =2/1), direct Jones oxidation was more practical to furnish **6** (18% yield from **3**) and **8** (20% from **3**), separable via an extractive procedure. Alkaline hydrolysis of **8** gave **9** in 85% yield. Following the same synthetic sequence, (2R,3R)-enantiomer **10** was obtained from **1-(S)**.

Attempts to convert **6** to the *cis* dicarboxylic acid were unsuccessful. Base hydrolysis followed by Jones oxidation or reduction to diol by treatment with $LiAlH_4$ in refluxing THF and then followed by oxidation resulted in the reverse formation of **6**. Assignment of the absolute C2-C3 stereochemistry is based on the small values of the coupling constants between C2-H and C3-H of ^1H NMR spectra (3.8 Hz and 4.0 Hz for **9** and the methyl ester of **8**, respectively) which clearly indicate the *trans* relationship between the two carboxylic groups. This is confirmed by X-ray structure analysis (Figure 1)[6].

We were intrigued by the stereochemical outcome of the alkoxycarbonylation on 2 since the removal of THP group from 3 gave a single diastereomer 4, the absolute stereochemistry of which was determined by X-ray structure analysis (Figure 2)[6]. Due to the formation of a complex between the oxygen atom of THP group and the lithium atom localized on sulfonyl group[7], the phenyl group would be oriented down to α-face. This would hinder the nucleophilic attack from the same face and probably account for the observed stereoselectivity.

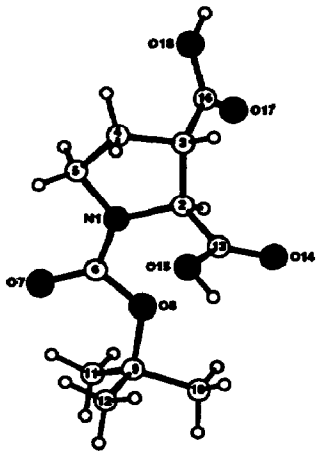


Figure 1 X-ray structure analysis of 9

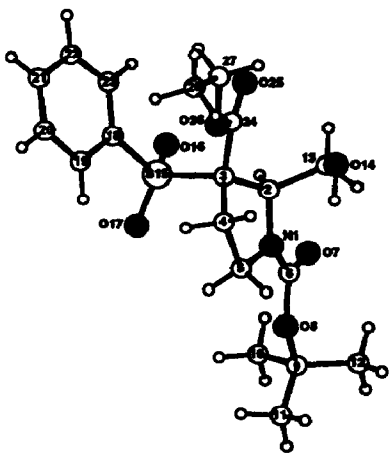


Figure 2 X-ray structure analysis of 4

Although the desulfonylation of 3 was rather disappointing, our preliminary studies indicate facile alkylation of 2 and desulfonylation thereof. Since saponification of a mixture of *cis*- and *trans*-3-alkylproline methyl ester is reported to provide selectively *trans*-isomer[1c], further application and optimization of the present approach in chiral synthesis of 2,3-disubstituted pyrrolidine derivatives are currently underway[8].

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6. Crystal data for compound **9** : $C_{11}H_{17}NO_6$, molecular weight 259.26, monoclinic system, space group $P2_1$, $Z = 2$, $a = 6.115$ (6), $b = 6.343$ (6), $c = 16.570$ (15) Å, $\beta = 95.30$ (4)°, $V = 640$ Å^3, $d_c = 1.34$ g cm^{-3}, $F(000) = 274$, λ (Cu Kα) = 1.5418 Å, $\mu = 0.89$ mm^{-1}, 2269 Nonius diffractometric intensities measured, 1171 observed with $I > 3.0\,\sigma(I)$.
Crystal data for compound **4** : $C_{19}H_{27}NO_7S$, molecular weight 413.49, orthorhombic system, space group $P2_12_12_1$, $Z = 4$, $a = 6.096$ (4), $b = 13.925$ (8), $c = 24.640$ (12) Å, $V = 2091$ Å^3, $d_c = 1.31$ g cm^{-3}, $F(000) = 880$, λ (Cu Kα) = 1.5418 Å, $\mu = 1.67$ mm^{-1}; 2028 Nonius diffractometric intensities measured, 1530 observed with $I > 2.5\,\sigma$ (I).
The structures were solved by direct methods using *SHELXS86* and refined by full matrix least-squares, minimizing the function $\Sigma w(Fo - |Fc|)^2$, with *SHELX76*. The hydrogen atoms, located in difference Fourier maps, were reajusted in the refinement at theoretical positions (C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at $R = 0.059$ and $R_w = 0.080$ for **4**; $R = 0.041$, $R_w = 0.061$ for **9** (with $R_w = \{\Sigma w(Fo - |Fc|)^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo)+kFo^2]$ ($k = -0.001252$ for **4**, -0.001723 for **9**). No residual was higher than 0.33 e Å^{-3} for **4**, 0.25 for **9** in the final difference maps. In the crystal structure of **9**, the molecules are linked in chains by hydrogen bonds established from the hydroxy groups HO15 and HO18 (O15H···O7' = 2.619 Å, angle O15-H···O7' = 172°; O18H···O14' = 2.706 Å, angle O18-H···O14' = 169°). Atomic scattering factors taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Lists of the fractional atomic coordinates, bond distances and angles, thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

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8 All isolated compounds described in this communication had satisfactory analytical and/or spectroscopic data.
6 : mp 96-97°C; $[\alpha]_D^{20} = -255$ (c = 1.0, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 4.55 (m, 1H, C2-H), 4.40 (m, 2H, -CH_2O-), 3.70 (m, 1H, C3-H), 3.22 (m, 2H, C5-H, H'), 2.33 (m, 1H, C4-H), 2.17 (m, 1H, C4-H'), 1.46 (s, 9H, ^{t}Bu). **7** : viscous oil; $[\alpha]_D^{20} = -126$ (c = 1.25, MeOH); MS (CI) m/e 274 ($(M+H)^+$), 218 (base); ^{1}H NMR (250 MHz, $CDCl_3$) 4.28 (m, 1H, C2-H), 4.18 (q, 2H, $J = 7.0$ Hz, -O-C$\underline{H}_2$CH$_3$), 3.75 (m, 1H, C3-H), 3.65 (m, 2H, -CH_2-O-), 3.37 (m, 2H, C5-H, H'), 2.10 (m, 2H, C4-H, H'), 1.46 (s, 9H, ^{t}Bu), 1.27 (t, 3H, -CH$_2$C$\underline{H}_3$). **8** : $[\alpha]_D^{20} = +47$ (c = 0.70, MeOH); MS (CI) m/e 288 ($(M+H)^+$), 232, 188 (base); ^{1}H NMR (250 MHz, $CDCl_3$) two conformers, 4.71 (d, 0.6H, $J = 1.6$ Hz, C2-H), 4.38 (d, 0.4H, $J = 2.8$Hz, C2-H), 4.20 (q, 2H, $J = 7.0$ Hz), 3.50 (m, 2H, C5-H, H'), 3.20 (m, 1H, C3-H), 2.21 (m, 2H, C4-H, H'), 1.48 (s, 6H, ^{t}Bu), 1.43 (s, 3H, ^{t}Bu), 1.28 (t, 3H). Methyl ester of **8** : ^{1}H NMR (400 MHz, Me_2SO-d_6, 70°C) 4.43 (d, 1H, $J = 4.0$ Hz, C2-H), 4.17 (q, 2H, $J = 7.0$ Hz, -C$\underline{H}_2$CH$_3$), 3.70 (s, 3H), 3.41 (m, 2H, C5-H, H'), 3.16 (m, 1H, C3-H), 2.12 (m, 2H, C4-H, H'), 1.45 (s, 9H, ^{t}Bu), 1.25 (t, 3H). **9** : mp 155-157°C; $[\alpha]_D^{20} = +29$ (c = 1.0, MeOH); MS (CI) m/e 260($(M+H)^+$), 204 (base), 160; ^{1}H NMR (400 MHz, CD_3OD, 50°C) 4.50 (d, 1H, $J = 3.8$ Hz, C2-H), 3.48 (m, 2H, C5-H, H'), 3.15 (m 1H, C3-H), 2.18 (m, 2H, C4-H, H'), 1.43 (s, 9H, ^{t}Bu); Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.95; H, 6.60; N, 5.40. Found: C, 50.85; H, 6.53; N, 5.39. **10** : mp 155-157°C; $[\alpha]_D^{20} = -29$ (c = 1.0, MeOH); MS (CI) and ^{1}H NMR (400 MHz, CD_3OD, 50°C) were identical in all respects with those of enantiomer **9**.

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