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New Enantioselective Synthesis of 4-Hydroxy-2-Oxopyrrolidine-N-Acetamide (Oxiracetam) from Malic Acid

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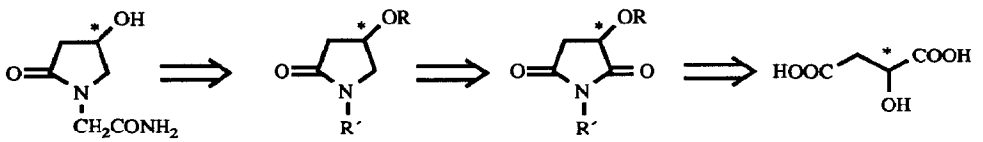
Abstract: The enantioselective synthesis of oxiracetam has been accomplished from readily available optically active D(+) and L(-) malic acids. The key step of the described method involves the selective reduction of a chiral cyclic diimide; in this way, both enantiomers of 4-hydroxy-2-oxopyrrolidine-N-acetamides were prepared.

Nootropic agents of the pyrrolidinone group[1,2] have been shown to enhance learning and long-term potentiation in hippocampal slices. The clinical effects of oxiracetam (4-hydroxy-2-oxopyrrolidine-N-acetamide, **1**) on cognitive processes have been demonstrated on many cases. Recently, it has been found that **1** enhances hippocampal synaptic transmission[3], indicating that the activation of excitatory aminoacid receptors is probably important as regards its nootropic properties. This effect can be explained since **1** increases the release of endogenous glutamate evoked by depolarization[4].

Several studies on the synthesis of these potential nootropic drugs for the treatment of Alzheimer´s disease have been reported[5–8]. However, only a few syntheses of optically active forms have been carried out from the expensive enantiomers (3*R*) and (3*S*) 4-amino-3-hydroxybutanoic acid (GABOB) with overall yields below 15%[9] or 44%[10].

We now report a short, convenient and efficient method for the parallel asymmetric synthesis of both enantiomers of **1** from the readily available D(+) and L(–) malic acids. The general strategy was to use an optically active alcohol as a source of chirality to establish the correct absolute stereochemistry in the target molecule (Scheme 1).



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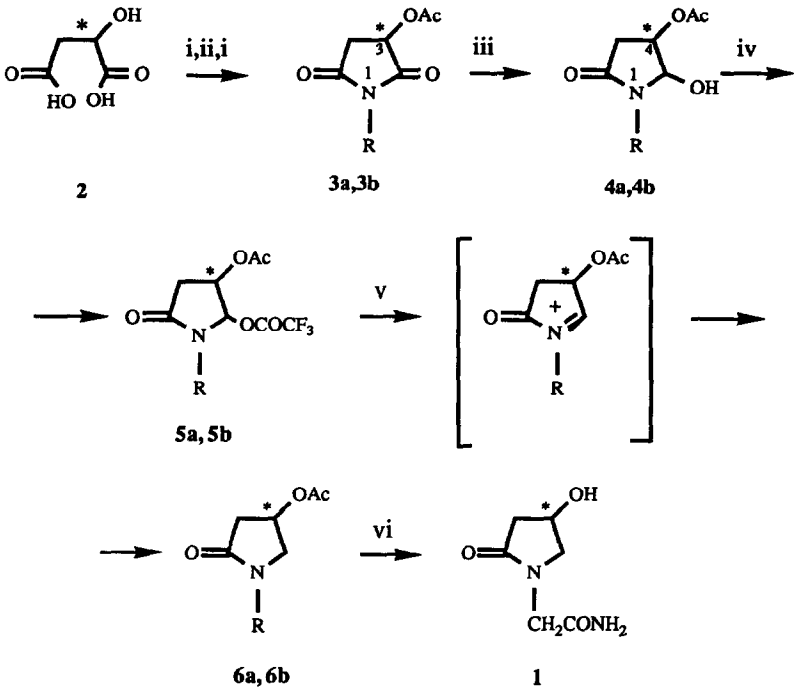
Scheme 1

We set about finding the best conditions for the synthesis using (±) malic acid and glycine methyl ester or aminoacetonitrile as starting materials. Thus, (±) malic acid was treated sequentially (Scheme 2) with acetyl chloride, glycine methyl ester and acetyl chloride again to give racemic **3a** in 70% yield after recrystallization. The same treatment was followed with aminoacetonitrile to give racemic **3b** in 60% yield. The first amine is easily prepared from glycine[11] [i) Cl_2SO/MeOH; ii) NH_3/Et_2O] but has to be used immediately owing to polymerization problems[12]. Aminoacetonitrile avoids this problem, but is bothersome to synthesize it[13].

The chemoselective reduction of the most electrophilic carbonyl group of **3**, was achieved by reacting a tetrahydrofuran solution of **3** with powdered sodium borohydride (1 mol) for 10 min at –20°C, followed by quenching with 2M HCl. With similar substances these hydride reductions were described to be highly regio- and stereoselective[14,15]. In our case, the resulting hydroxy lactams **4a** (75% yield) or **4b** (58% yield) were obtained as a *cis/trans* diastereomeric mixture in *ca* 95:5 ratio. The regioisomer resulting from the reduction of the C_5 carbonyl group was not detected in any of the performed experiments. The analysis of the reaction product was done by HPLC and the stereochemistry assignments of both isomers were based on the observed ^1H NMR coupling constants $J_{4,5}$[16,17].

When this reaction was carried out at temperature above –20°C, the reduction of the cyano or the ester groups attached to the nitrogen chain was also observed.



a. R= CH_2COOCH_3
b. R= CH_2CN

i. AcCl; ii. H_2NR; iii. $NaBH_4$ / THF ; iv. $(CF_3CO)_2O$ / CH_2Cl_2 ; v. Et_3SiH / CF_3COOH ; vi. MeO^-Na^+/ MeOH ,then $NH_3(g)$ / MeOH for **a** or HCl / MeOH for **b.**

Scheme 2

Attempts to reduce directly the diastereomers **4** with triethylsilane in trifluoracetic acid[18] were not successful, so the alcohols **4** were first esterified with trifluoracetic anhydride (1.1 mol) and then reduced *in situ* with Et_3SiH. The trifluoracetates **5a** and **5b** were characterized by ^1H NMR as a *cis-trans* mixture in *ca* 1:2.5 ratio.

The reduction of the crude trifluoracetates with triethylsilane (1.2 mol) in CF_3CO_2H to the pyrrolidones **6a** or **6b**, via an iminium ion[19], was achieved at room temperature in 80% or 48% yield from **4a** or **4b** respectively. Lastly, standard treatment of lactams **6**[8] gave the target molecule oxiracetam **1** in 56% and 44% yields from **6a** or **6b** respectively.

As shown above, better yields in some of these reactions were obtained in the series **2 - 3a - 4a - 6a - 1**, and therefore this series was chosen for the syntheses of enantiomerically pure molecules of oxiracetam. Starting from L-malic acid, $[\alpha]_D = -7.9$, we obtained (–) oxiracetam, $[\alpha]_D = -38.5$ in 21% overall yield; similarly, (+) oxiracetam, $[\alpha]_D = +36.0$, was prepared from D-malic acid, $[\alpha]_D = +8.1$, in 23% overall yield but the yield of the last step can presumably be increased. Although epimerization takes place during the formation of the trifluoracetates, it seems that the configuration of C_4 remains unaffected throughout the synthesis, according to the optical activity of the oxiracetam samples obtained which showed essentially identical optical activity to those reported for the samples prepared from GABOB[9].

This method constitutes a real improvement in respect to previous syntheses described for this drug and we are now applying it to the synthesis of some new related compounds.

Experimental Section

General methods. M.p. were determined on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60, 230-400 mesh, and TLC on silica gel Merck 60, F_{254}. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively. Chemical shifts (δ) are reported in ppm with TMS as internal standard; J values are quoted in Hz. IR spectra were determined on a Beckman Acculab-8 spectrophotometer. EIMS were measured on a VG-TS-250 spectrometer (70 eV). Elemental analyses were carried out on a Perkin-Elmer 240 B Analyser.

Glycine methyl ester hydorchloride. Thionyl chloride (55 ml, 7.58 mol) was added dropwise under stirring to 200 ml of dist. methanol at –10°C, avoiding the rise of the temperture above –5°C. Glycine, (50 g, 0.66 mol) was then added in small portions and the mixture was heated at 40°C. Ten min later the solution was clear and a voluminous white precipitate had begun to appear. After two hours the reaction mixture was cooled to room temperature and the precipitate was collected and dried in air until the pungent smell disappeared. The methanolic solution was concentrated under vacuum and a second portion of the

hydrolchloride was isolated. Yield, 82g (98%) IR (Nujol): 1750 cm^{-1}. ^1H NMR (D_2O): 3.72(2H, s, -$C\underline{H}_2$-COO-); 3.70(3H, s, -COO-$C\underline{H}_3$).

Glycine methyl ester. A stream of dry ammonia was passed through an ice cooled suspension of fine grinded hydrochloride (27 g 21.5 mol) in Et_2O (300 ml) under vigorous stirring for one hour. The white precipitate of ammonium chloride was removed and the organic solution was dried on sodium sulphate and concentrated under vacuum until evaporation of the ammonia. Yield, 80%. ^1H NMR ($CDCl_3$): 3.0(2H, s, -$C\underline{H}_2$-COO-); 3.4(3H, s, -COO-$C\underline{H}_3$). A titrated solution of glycine methyl ester in ether or in methylene chloride was immediatly used in the next step.

3-Acetoxy-N-methoxycarbonylmethylsuccinimide (3a). A suspension of malic acid (8.0 g, 59.6 mmol) and acetyl chloride (30 ml, 420 mmol) was heated under reflux for 1.5 hours. The resulting solution was evaporated to dryness and the yellowish oil obtained was taken in methylene chloride (80 ml) and then poured into a recently prepared 1M solution of glycine methyl ester in Et_2O (60 ml, 60 mmol) or in CH_2Cl_2 at 5°C. The solvent was evaporated, acetyl chloride (15 ml, 210 mmol) was added and the mixture heated under reflux for three hours until the cyclization was complete (^1H NMR). The excess of acetic acid an acetyl chloride was removed under vacuum and the residue was taken in methylene chloride, washed with saturated Na_2CO_3 and the organic layer dryed and concentrated to give an oil which was purified by chromatography. Succinimide (±)**3a** was isolated from (±) malic acid in 77% yield. M.p., 58-59°C (ethyl acetate / hexane). IR (Nujol): 3269, 3188, 1746, 1726 cm^{-1}. ^1H NMR ($CDCl_3$): 5.56(1H, dd, J_1= 8.3 Hz, J_2= 4.9 Hz ; -C$\underline{H}$OAc-); 4.29(2H, s ; -N-$C\underline{H}_2$-); 3.74(3H, s ; -O$C\underline{H}_3$-); 3.24(1H, dd, J_1= 8.3 Hz, J_2= 18.4 Hz ; -$C\underline{H}_2$-CHOAc); 2.73(1H, dd, J_1= 4.9 Hz, J_2=18.4 Hz ; -$C\underline{H}_2$-CHOAc); 2.15(3H, s ; -CO-$C\underline{H}_3$). ^{13}C NMR ($CDCl_3$): 20.22(-CO-$\underline{C}H_3$), 35.57(-$\underline{C}H_2$-CHOAc), 39.38(-N-$\underline{C}H_2$-), 52.55(-O$\underline{C}H_3$), 67.43(d), 166.62(s), 169.56(s), 172.22(s), 172.51(s). EIMS ***m/e*** (%): 229(M^+, 12), 198(9), 187(42), 170(55), 158(56), 110(43), 100(52), 86(75).

(3S) 3-Acetoxy-N-methoxycarbonylmethylsuccinimide, (–)***3a.*** Prepared from (–) malic acid, $[\alpha]_D$ – 7.9 (c=1, MeOH), was isolated in 74% yield. Oily. $[\alpha]_D$ – 26.4 (c=1, MeOH).

(3R) 3-Acetoxy-N-methoxycarbonylmethylsuccinimide, **(+)*3a*.** Prepared from (+) malic acid, $[\alpha]_D$ +8.1 (c=1, MeOH), was isolated in 76% yield. Oily. $[\alpha]_D$: + 25.1 (c=1, MeOH).

3-Acetoxy-N-cyanomethylsuccinimide, **(±)*3b*.** Prepared as (±)**3a** but changing the glycine methyl ester by aminoacetonitrile. The succinimide (±)**3b** was isolated in 62% yield. M.p., 123-4°C (ethyl acetate/hexane). IR (Nujol): 3269, 3187, 1748, 1724 cm^{-1}. ^1H NMR ($CDCl_3$): 5.43(1H, dd, J_1= 4.7 Hz, J_2= 8.5 Hz; -CHOAc); 4. 36(2H, s; -CH_2-CN); 3.20(1H, dd, J_1= 8.5 Hz, J_2= 18.5 Hz; -CH_2-CHOAc); 2.69(1H, dd, J_1= 4.7 Hz, J_2= 18.5 Hz; -CH_2-CHOAc); 2.10(3H, s; -CO-CH_3). ^{13}C NMR ($CDCl_3$): 20.18(-CO-CH_3), 25.78(-CH_2-CN), 35.33(-CH_2-CHOAc), 67.40(-CHOAc), 113.12(-CN), 169.81(s), 171.53(s), 171.83(s). EIMS *m/e* (%): 197(M^+, 10), 171(19), 154(40), 137(38), 111(100).

4-Acetoxy-5-hydroxy-N-methoxycarbonylmethyl-2-pyrrolidinone, **(±) *4a*.** To a solution of succinimide (±)**3a** (1.9 g, 8 mmol) in THF (20 ml) and water (1 ml) at –20°C, powdered $NaBH_4$ (350 mg, 9 mmol) was added in portions for one minute. The suspension was stirred for ten min and then acidified (pH 5-6) with 2M HCl. The solution was allowed to slowly warm to room temp, the solvent was removed and the residue extracted with chloroform. The organic layer was dried, evaporated and chromatographed (ethyl acetate/hexane, 1:1) to give **4a** (1.4 g, 75%) as a *cis/trans* 95:5 diastereomeric mixture which was purified by further chromatography.

(±) Cis 4a. M.p. 78-79°C (ethyl acetate/hexane). IR (Nujol): 3269, 1761, 1737, 1724, 1699 cm^{-1}. ^1H NMR ($CDCl_3$): 5.36(1H, d, J= 5.3 Hz, -N-CHOH-); 5.30(1H. dt, J_1= 5.3, J_2= 5.3, J_3= 7.3 Hz, -CHOAc); 4.14(2H, s, -N-CH_2); 3.75(3H, s, -OCH_3); 2.76(1H, dd, J_1= 16.8, J_2= 7.3 Hz, -CH_2-CHOAc); 2.61(1H, dd, J_1= 16.8, J_2= 5.3 Hz, -CH_2-CHOAc); 2.13(3H, s, -CO-CH_3). ^{13}C NMR ($CDCl_3$): 20.67(-CO-CH_3), 34.85(-CH_2-CHOAc), 41.57(-N-CH_2-), 52.49(-OCH_3), 68.01(-CHOAc), 82.35(-CHOH-), 169.76(s), 170.26(s), 171.35(s). EIMS *m/e* (%): 231(M^+, 78), 212(20), 201(41), 187(100), 170(38). *Trifluoracetate,* (±)***cis* 5a,** [$(CF_3CO)_2O$ / $CHCl_3$]: ^1H NMR ($CDCl_3$): 6.55(1H, d, J= 5.3 Hz, -CHOCOCF_3); 5.50(1H, m, -CHOAc); 4.46(1H, d, J= 17.8 Hz, -N-CH_2-); 4.00(1H, d, J= 17.8 Hz, -N-CH_2-); 3.63(1H, s, -OCH_3); 3.02(1H, m, -CO-CH_2-CHOAc); 2.91(1H, m, -CO-CH_2-CHOAc); 2.15(3H, s, -CO-CH_3).

(±) Trans 4a. Spectral data from enriched samples: IR (film): 3375(broad), 2961, 1742, 1711, 1697 cm^{-1}. ^1H NMR ($CDCl_3$): 5.12(1H, s, -N-CHOH-); 5.04(1H. d, J= 7 Hz, -CHOAc); 4.29(1H, d, J= 18 Hz, -CH_2COOCH_3); 4.05(1H, d, J= 18 Hz, -CH_2COOCH_3); 3.75(3H, s, -OCH_3); 3.00(1H, dd, J_1= 18, J_2= 7 Hz, -CH_2-CHOAc); 2.38(1H, dd, J_1= 18, J_2= 2 Hz, -CH_2-CHOAc);2.08(3H, s, -CO-CH_3). ^{13}C NMR ($CDCl_3$): δ : 20.76(-CO-CH_3), 35.21(-CH_2-CHOAc), 42.15(-CH_2COOCH_3), 52.59(-OCH_3), 73.69 (-CHOAc), 87.57(-CHOH-), 170.34(s), 170.48(s), 172.52(s). *Trifluoracetate,* (±)*trans* **5a**, [$(CF_3CO)_2O$ / $CHCl_3$]: ^1H NMR ($CDCl_3$): 6.32(1H, s, -$CHOCOCF_3$); 5.34(1H, d, J= 6.3 Hz, -CHOAc); 4.40(1H, d, J= 17.8 Hz, -N-CH_2-); 4.00(1H, d, J=17.8 Hz, -N-CH_2-); 3.76(3H, s, -OCH_3); 3.18(1H, dd, J_1= 6.3, J_2= 18.6 Hz, -CO-CH_2-CHOAc); 2.66(1H, d, J= 18.6 Hz, -CO-CH_2-CHOAc); 2.18(3H, s, -CO-CH_3).

(4S, 5S) 4-Acetoxy-5-hydroxy-N-methoxycarbonylmethyl-2-pyrrolidinone,* (–) *cis 4a. Starting from (–) **3a** the enantiomer (–)*cis* **4a** was isolated in 73% yield, $[\alpha]_D$ – 26.6 (c=1, MeOH).

(4R, 5R) 4-Acetoxy-5-hydroxy-N-methoxycarbonylmethyl-2-pyrrolidinone,* (+) *cis 4a. Starting from (+) **3a** the enantiomer (+)*cis* **4a** was isolated in 75% yield, $[\alpha]_D$ + 24.7 (c=1, MeOH).

4-Acetoxy-5-hydroxy-N-cyanomethyl-2-pyrrolidinone,* (±) *4b. The sodium borohydride reduction of (±) **3b** was done following the same procedure as described before, to give crude hydroxylactam (±) **4b** in 58% yield as a *cis/trans* 95:5 diastereomeric mixture which was purified by chromatography (ethyl acetate/hexane, 1:1).

(±) Cis 4b: M.p., 135-138°C (ethyl acetate/hexane). IR (Nujol): 3173, 1728, 1682 cm^{-1}. ^1H NMR (DMSO d_6): 6.45(1H, d, J= 7.5 Hz, -OH); 5.22(1H, d, J= 7.5 Hz, -CHOH-); 5.18(1H, m, -CHOAc); 4.34(1H, d, J= 17.7 Hz, -CH_2-CN); 4.20(1H, d, J= 17.7 Hz, -CH_2-CN); 2.65(1H, dd, J_1= 7.9, J_2= 17.1 Hz, -CH_2-CHOAc); 2.45(1H, dd, J_1= 6.4, J_2= 17.1 Hz, -CH_2-CHOAc); 2.04(3H, s, -CO-CH_3). ^{13}C NMR (DMSO d_6): 20.43(-CO-CH_3). 27.97(-CH_2-CN). 33.60(-CH_2-CHOAc). 67.58(-CHOAc). 81.14(-CHOH-). 116.08(-CN). 169.83(s). 170.43(s). EIMS *m/e* (%): 198(M^+, 62), 181(45), 155(24), 138(100), 127(75), 111(37). *Trifluoracetate,* (±)*cis* **5b** [$(CF_3CO)_2O$ / $CHCl_3$]: ^1H NMR ($CDCl_3$): 6.61(1H, d, J= 5.2 Hz, -$CHOCOCF_3$);

5.50(1H, m, -CHOAc); 4.45(1H, d, J= 18 Hz, -N-CH_2-); 4.19(1H, d, J= 18 Hz, -N-CH_2-); 2.78- 3.01(2H, m, -CO-CH_2-CHOAc); 2.10(3H, s, -CO-CH_3).

(±) Trans 4b. Spectral data from enriched samples: ^{1}H NMR (DMSO d_6): 6.73(1H, d, J= 7 Hz, -OH); 5.01(1H, d, J= 7 Hz, -CHOH-); 4.87(1H, m, -CHOAc); 4.29(2H, m , -CH_2-CN); 2.92(1H, dd, J_1= 7, J_2= 18 Hz, -CH_2-CHOAc); 2.23(1H, dd, J_1= 1, J_2= 18 Hz, -CH_2-CHOAc); 2.01(3H, s, -CO-CH_3). *Trifluoracetate,* (±)***ttrans*** **5b** [$(CF_3CO)_2O$ / $CHCl_3$]: ^{1}H NMR ($CDCl_3$): 6.32(1H, s, -CHOCOCF$_3$); 5.34(1H, d, J= 6.2 Hz, -CHOAc); 4.51(1H, d, J= 18 Hz, -N-CH_2-); 4.25(1H, d, J=18 Hz, -N-CH_2-); 3.11(1H, dd, J_1= 6.2, J_2= 18.6 Hz, -CO-CH_2-CHOAc); 2.62(1H, d, J= 18.6 Hz, -CO-CH_2-CHOAc); 2.16(3H, s, -CO-CH_3).

4-Acetoxy-N-methoxycarbonylmethyl-2-pyrrolidinone, (±) ***6a.*** To a solution of (±) **4a** (1.15 g, 5 mmol) in chloroform (15 ml) at room temp., trifloracetic anhydride (0.84 ml, 6 mmol) was added. After 30 min the esterification was finished and the solvent evaporated. A solution of the crude reaction product in trifloracetic acid (5 ml, 65 mmol) and triethylsilane (0.95 ml, 6mmol) was left at room temp for one hour. The solution was concentrated under vacuum until a viscous oil was obtained. The oily residue taken in chloroform was washed with a saturated soln. of $NaHCO_3$ and water, dried and the solvent was evaporated. The reaction product was percolated through silica gel (ethyl acetate/hexane 1:1) to give (±) **6a** (0.86 g, 80% yield). Oily. IR (film): 3401, 2957, 1751, 1724 cm^{-1}. ^{1}H NMR ($CDCl_3$): 5.10(1H, m, -CHOAc); 3.98(1H, d, J= 17.6 Hz, -N-CH_2-$COOCH_3$); 3.76(1H, d, J= 17.6 Hz, -N-CH_2-$COOCH_3$); 3.67(1H, dd, J_1= 6.0, J_2= 11.2 Hz, -N-CH_2-CHOAc); 3.50(3H, s, -OCH_3); 3.23(1H, dd, J_1= 11.2 , J_2= 2.5 Hz, -N-CH_2-CHOAc); 2.60(1H, dd, J_1= 6.2, J_2= 18 Hz, -CO-CH_2-CHOAc); 2.25(1H, dd, J_1= 3, J_2= 18 Hz, -CO-CH_2-CHOAc); 1.85(3H, s, -CO-CH_3). ^{13}C NMR ($CDCl_3$): 20.80(-CO-CH_3), 37.08(-CO-CH_2-CHOAc), 43.50(-N-CH_2-$COOCH_3$), 52.17(-OCH_3), 53.78(-N-CH_2-CHOAc), 66.78(-CHOAc), 168.66(s), 170.45(s), 172.30(s). EIMS *m/e* (%): 215(M^+, 4), 184(20), 171(38), 156(100), 128(22).

(4S) 4-Acetoxy-N-methoxycarbonylmethyl-2-pyrrolidinone, (–) ***6a.*** Prepared from (–) **4a**, was isolated in 81% yield. $[\alpha]_D$ –38.6 (c=1, MeOH).

(4R) 4-Acetoxy-N-methoxycarbonylmethyl-2-pyrrolidinone, (+) ***6a.*** Prepared from (+) **4a**, was isolated in 77% yield. $[\alpha]_D$ +37.1 (c=1, MeOH).

4-Acetoxy-N-cyanomethyl-2-pyrrolidinone, (±) ***6b.*** Prepared from (±) **4b** in dry acetonitrile as described above for (±)**6a**. Yield, 48%. Oily. IR (film): 3453, 2940, 1740, 1707 cm^{-1}. ^1H NMR ($CDCl_3$): 5.31(1H, m, -CHOAc); 4.23(2H, s, -CH_2-CN); 3.84(1H, dd, J_1= 11.1, J_2= 6 Hz, -N-CH_2-CHOAc); 3.45(1H, dd, J_1= 11.1, J_2= 2.1 Hz, -N-CH_2-CHOAc); 2.77(1H, dd, J_1= 7.2, J_2=18.1 Hz, -CO-CH_2-CHOAc); 2.45(1H, dd, J_1= 2.5, J_2= 18.1 Hz, -CO-CH_2-CHOAc ; 2.04(3H, s, -CO-CH_3). ^{13}C NMR ($CDCl_3$): 20.75(-CO-CH_3), 36.61(-CO-CH_2-CHOAc), 30.34(-CH_2-CN), 52.89(-N-CH_2-CHOAc), 66.20(-CHOAc), 114.09(-CN), 170.35(s), 171.82(s). EIMS *m/e* (%): 182(M^+, 1), 156(0.7), 138(3), 122(100), 112(9).

4-Hydroxy-2-oxopyrrolidine-N-acetamide, (±) ***1 (Oxiracetam).*** To a solution of (±) **6a** (430 mg, 2mmol) in dry methanol (5 ml), a few drops of a recently prepared solution of sodium methoxide in methanol was added to pH= 8.5-9.0. After five min. glacial acetic acid was dropped to netralize the solution and the solvent was evaporated. The white solid obtained was taken in dry methanol and the solution saturated with ammonia. After one hour the solvent was evaporated and the resudue chromatographed (Silica gel, chloroform/methanol 8:2) to give (±) **1** (177 mg; 56% yield). M.p.172-173°C (MeOH). IR (nujol): 3400, 3310, 3280, 3200, 1720, 1670 cm^{-1}.^1H NMR (DMSO d_6): 7.33(1H, s, -NH_2); 7.13(1H, s, -NH_2); 5.25(1H, s, -OH); 4.31(1H, m, -CHOH-); 3.88(1H, d, J= 16.6 Hz, -CH_2-$COOCH_3$); 3.69(1H, d, J= 16.6 Hz, -CH_2-$COOCH_3$); 3.62(1H, dd, J_1= 9.6, J_2= 5.5 Hz, -N-CH_2-CHOH-); 3.16(1H, d, J= 9.6 Hz, -N-CH_2-CHOH-); 2.57(1H, dd, J_1= 16.9, J_2= 6.4 Hz, -CO-CH_2-CHOH-); 2.09(1H, d, J= 16.9 Hz, -CO-CH_2-CHOH-). ^{13}C NMR (DMSO d_6): 39.91(-CO-CH_2-CHOH-), 44.20(-N-CH_2-$CONH_2$), 56.59(-N-CH_2-CHOH-), 63.24(-CHOH-), 169.66 ($CONH_2$), 172.90(-CO-N-). EIMS *m/e* (%): 158 (M^+, 2), 140(81), 123(19), 114(93), 96(100).

(4S) 4-Hydroxy-2-oxopyrrolidine-N-acetamide, (–) ***1.*** Prepared from (–) **6a**, was isolated in 56% yield. M.p. 135-6°C (MeOH), $[\alpha]_D$ –38.5 (c=1, H_2O). Lit.[9] –38.8 (c 1.0, H_2O). *Anal.*: Calc.for $C_6H_{10}N_2O$: C 45.56, H 6.37, O 30.35, N 17.71. Found C 45.45, H 6.40, O 30.54, N 17.61.

***(4R) 4-Hydroxy-2-oxopyrrolidine-N-acetamide*, (+) *1*.** Prepared from (+) **6a**, was isolated in 52%.yield. M.p.135-6°C (MeOH). $[\alpha]_D$ + 36.0 (c=1, H_2O). Lit.[9] +36.4 (c 1.0, H_2O). *Anal.*: Found. C 45.63, H 6.36, O 30.41, N 17.60.

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