SYNTHESIS OF 2-OR/AND 6-METHYLATED ANALOGUES OF ISOGUVACINE (1,2,3,6-TETRAHYDROPYRIDINE-4-CARBOXYLIC ACID) A $GABA_A$ AGONIST

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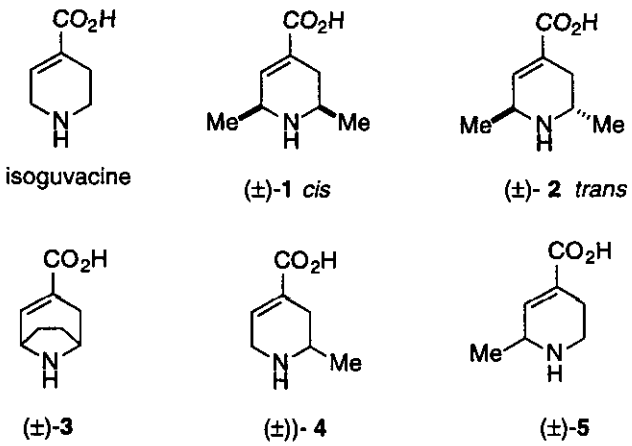
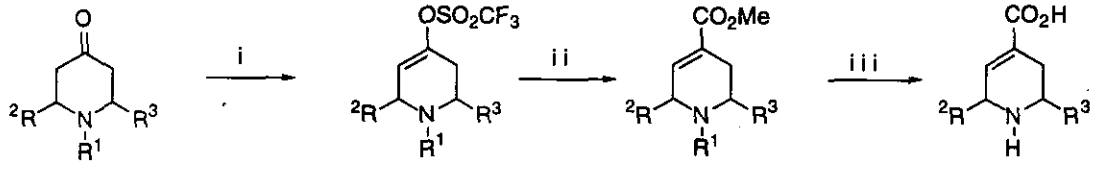
Abstract - 1,2,3,6-Tetrahydropyridine-4-carboxylic acid (isoguvacine) and related 2-and/or 6-methylated analogues (**1-4**) were synthesized using the methoxycarbonylation [$Pd(OAc)_2$, PPh_3, CO, MeOH)] of their corresponding vinylic triflates. Analogue (**5**), the 6-methyl-1,2,3,6-tetrahydropyridine-4-carboxylic acid was obtained after a reductive deoxygenation of the corresponding β-keto ester.

During the course of our investigation on compounds acting on the GABA receptor, we decided to prepare analogues of isoguvacine, a potent and selective $GABA_A$ agonist bearing either one or two methyl substituents in the 2- and/or 6-positions of the piperidine ring. A literature survey on the preparation of isoguvacine revealed that a regiospecific setting of substituents with respect to the double bond could not be achieved with the reported procedure.[1] Therefore we developed two new strategies : one which starts from substituted 4-piperidones using the alkoxycarbonylation of their corresponding vinyl triflates, the second which starts from a 4-carboxy-3-piperidone using a deoxygenation for the generation of the α,β-unsaturated carboxylate. In the present paper we report the straigthforward regioselective preparation of isoguvacine and of the methylated 1,2,3,6-tetrahydropyridine-



Scheme 1

4-carboxylic acids (**1-5**), as racemates (Scheme 1). First of all, in order to evaluate the experimental conditions of the methoxycarbonylation of the vinylic triflate of 4-piperidone, we prepared its triflate (**7a**) starting from the *N*-Boc piperidone (**6a**) (Scheme 2). The enolate of **6a** was prepared in THF with LDA at -78°C, and quenched with *N*-(5-chloro-2-pyridyl)triflimide.[2] This triflate could be purified by column chromatography and stored as a solution in Et_2O, to avoid decomposition. According to Cacchi, the oxidative insertion of palladium was performed using palladium acetate in presence of triphenyphosphine in a mixture of DMF and MeOH under a CO atmosphere (CO, balloon).[3] After stirring this mixture for 12 h at room temperature the expected methoxycarbonylation took place, and chromatography purification afforded the α,β-unsaturated carboxylate (**8a**) in 76% yield. Hydrolytic cleavage of the carbamate and ester functions with concentrated aqueous 48% hydrobromic acid gave isoguvacine as its HBr salt in 60% yield.[1] This sequence constitutes a new and short preparation of isoguvacine, an important ligand for studying the GABA receptors.[4] Now this route was further investigated for the preparation of the methylated analogues of isoguvacine. The above standard conditions (formation of the enolates, subsequent quenching to the corresponding triflates, methoxycarbonylation and hydrolytic cleavage) were applied to the known substituted piperidones (**6b**),[5] (**6c**)[6] and (**6d**),[7] and the expected racemic amino acids (**1-3**) were obtained uneventful in moderate overall yields (Scheme 2).



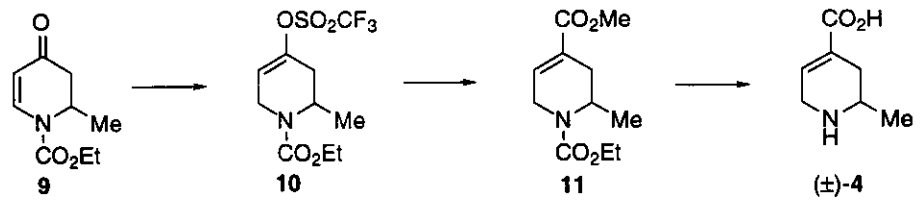
6a	$R^1 = CO_2tBu$, $R^2 = R^3 = H$	**7a**	(87%)	**8a**	(76%)	isoguvacine	(60%)
6b	$R^1 = CO_2Et$, $R^2 = R^3 = Me$ (*cis*)	**7b**	(65%)	**8b**	(80%)	**1**	(55%)
6c	$R^1 = CO_2$ t Bu, $R^2 = R^3 = Me$ (*trans*)	**7c**	(68%)	**8c**	(98%)	**2**	(62%)
6d	$R^1 = CO_2Et$, $R^2 = R^3 = CH_2CH_2$	**7d**	(75%)	**8d**	(95%)	**3**	(55%)

Reagents : i. LDA, *N*-(5-chloro-2-pyridyl)triflimide, THF, -78°C; ii. $Pd(OAc)_2$, PPh_3, NEt_3, CO (balloon), DMF, MeOH; iii. 48% HBr

Scheme 2

For the synthesis of the monomethylated analogue (**4**) a slightly different procedure was used. The conjugated double bond of the piperidone (**9**) was selectively reduced according to Comins with K-selectride and the transcient enolate quenched with *N*-(5-chloro-2-pyridyl)triflimide to yield the triflate (**10**).[8] The subsequent methoxycarbonylation delivered the fully protected amino acid (**11**), which was deprotected with 37% hydrochloric acid yielding the amino acid ((±)-**4**) (Scheme 3). For the synthesis of the monomethyl derivative

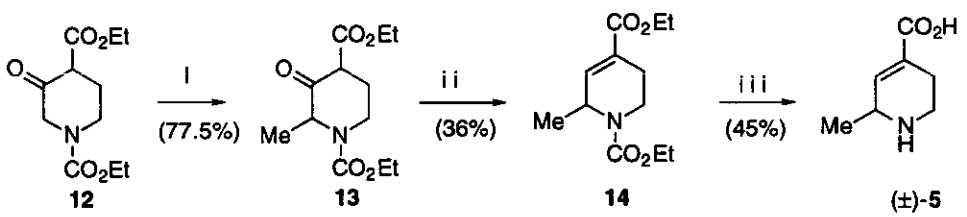
(**5**) we examined a route which started from the known β-keto ester(**12**).[9] At -78°C in a mixture of THF/HMPA, using two equivalents of LDA, a kinetic alkylation of **12** was obtained



Reagents : i. K-Selectride, THF, *N*-(5-chloro-2-pyridyl)triflimide; ii. $Pd(OAc)_2$, PPh_3, NEt_3, CO (balloon), DMF, MeOH. iii. 37% HCl

Scheme 3

with dimethyl sulfate as the electrophile to yield **13**. Thereafter the procedure of Ganem was followed to realize the deoxygenation of **13** in order to obtain with moderate yield the cyclic enoate (**14**).[10] Finally after hydrolytic cleavage, the amino acid ((±)-**5**) was obtained as hydrobromide (Scheme 4).



Reagents : i. LDA (2 equ.), THF/HMPA, $(MeO)_2SO_2$; ii. Li(H)MDS, Cp_2ZrHCl; iii. 48% HBr

Scheme 4

Compounds(**1-5**)were submitted to binding against [^{3}H]-muscimol and found without any detectable affinity at 10^{-4} M. Accordingly it seems that the GABA receptor is sensitive to substituents close to the nitrogen.[12] Our results are consistent with earlier findings on substituted THIP (4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol), which were also devoid of any affinity for $GABA_A$ receptor preparations.[13]

In conclusion we present here a general method for the synthesis of isoguvacine and related analogues, based on the mild and efficient methoxycarbonylation of 4-piperidone-triflates.

EXPERIMENTAL

^{1}H-Nmr spectra were performed on a Bruker SY 200 (200 MHz) spectrometer and recorded in $CDCl_3$ solutions. The residual $CHCl_3$ present in $CDCl_3$ was used as internal standard at 7.27 ppm. ^{13}C Nmr (50 MHz) spectra were recorded on the same instrument with $CDCl_3$ (δ = 77 ppm) as reference. Tlc visualization was achieved by a uv lamp or spraying with 2%

ethanolic phosphomolybdic acid and charring. Melting points were measured in open capillary tubes using a Gallenkampf apparatus, and are uncorrected. Purifications and separations by column chromatography were performed on silica gel, using the flash chromatography procedure. DMF was used after drying with molecular sieves. MeOH was taken directly from a fresh bottle.

Procedure for the preparation of the triflates .

To a solution of the carbonyl compound (4.8 mmol) in dry THF (5 ml) was added at -78°C a solution of freshly prepared LDA (5.5 mmol) [BuLi (5.4 mmol, 3.4 ml from 1.6 M solution in hexane) and diisopropylamine (5.6 mmol, 0.56 g) in THF (15 ml)]. After stirring for 2 h, a solution of *N*-(5-chloro-2-pyridyl)triflimide (2.17 g, 5.1 mmol) in THF (5 ml) was added. The reaction mixture was stirred at -78°C for 12 h and slowly warmed up to room temperature. The solvent was evaporated in vacuo and the resulting oil purified by column chromatography on silica gel (hexane/AcOEt : 1/1) to yield the triflate, which was stored at -16°C in ether in order to avoid decomposition. Starting from the known piperidones (**6a**), (**6b**),[4] (**6c**)[5] and (**6d**),[6] the triflates (**7a-d**) were obtained following this procedure.

***N-tert*-Butoxycarbonyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (7a).**

Yield 87%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.45 (9 H, s, 3 x CH_3), 2.41 (2 H, m, CH_2), 3.60 (2 H, t, J = 5.8 Hz, CH_2), 4.02 (2 H, m, CH_2), 5.74 (1 H, m, CH=).

(±)-*cis*-*N*-Ethoxycarbonyl-2,6-dimethyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (7b).

Yield 65%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.25 - 1.39 (9 H, m, 3 x CH_3), 2.13 (1 H, m, CH), 2.78 (1 H, m, CH), 4.18 (2 H, m, CH_2), 4.60 - 4.90 (2 H, m, CH_2), 5.73 (1 H, dd, J = 6 and 1.5 Hz, CH=).

(±)-*trans*-*N*-*tert*-Butoxycarbonyl-2,6-dimethyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (7c).

Yield 68%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.22 (3 H, d, J = 6.5 Hz, CH_3), 1.35 (3 H, d, J 6.3 Hz, CH_3), 1.46 (9 H, s, 3 CH_3), 2.16 (1 H, m, CH), 2.84 (1 H, m, CH), 4.33 (2 H, m, 2 CH), 5.78 (1 H, m, CH=).

(±)-8-Ethoxycarbonyl-3-trifluoromethanesulfonyloxy-8-azabicyclo[3.2.1]oct-2-ene (7d).

Yield 75%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.40-1.42 (3 H, t, J = 7 Hz, CH_3), 1.80-3.10 (9 H, m), 4.02 (2 H, q, J = 7 Hz, CH_2), 4.50 (2 H, m, CH_2), 6.95 (1 H, dt, J = 7.3 and 1.5 Hz, CH=).

General procedure for the methoxycarbonylation

A mixture of the triflate (1 mmol), triethylamine (0.28 ml, 2 mmol), palladium acetate (6 mg, 0.03 mmol), triphenylphosphine (16 mg, 0.06 mmol), and MeOH (1.8 ml, 40 mmol) in

DMF (4 ml) was purged with CO for 5 min and stirred under a CO atmosphere (balloon) at room temperature for 12 h. Ether and water were then added. The ether layer was washed with water until neutral, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (hexane/ethyl acetate : 1/1) to give pure ester.

(±)-*N-tert*-Butoxycarbonyl-4-methoxycarbonyl-1,2,3,6-tetrahydropyridine (8a).
Yield 76%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.45 (9 H, s, 3 x CH_3), 2.37 (2 H, m, CH_2), 3.49 (2 H, t, J = 5.7 Hz, CH_2), 3.74 (3 H, s, CH_3), 4.05 (2 H, q, J = 3.0 Hz, CH_2), 6.87 (1 H, m, =CH). ^{13}C-Nmr ($CDCl_3$) δ 23.7, 27.9, 43.4, 54.2, 52.6, 83.5, 130.7, 142.1, 163.1, 165. 4. Anal. Calcd for $C_{12}H_{19}NO_4$: C: 59.75; H: 7.94; N: 5.81. Found: C: 59.93; H: 8.23; N: 5.68.

(±)-*cis-N*-Ethoxycarbonyl-4-methoxycarbonyl-2,6-dimethyl-1,2,3,6-tetrahydropyridine (8b).
Yield 80%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.11 (3 H, d, J = 7.0 Hz, CH_3), 1.25 (3 H, t, J = 7.0 Hz, CH_3), 1.32 (3 H, d, J = 7.0 Hz, CH_3), 2.36 (2 H, s, CH_2), 3.74 (3 H, s, CH_3), 4.15 (2 H, q, J = 7.0 Hz, CH_2), 4.55 (1 H, m, -CH-), 4.70 (1H, m, -CH-), 6.82 (1H, m, =CH). ^{13}C-Nmr ($CDCl_3$) δ 14.6, 20.4, 20.6, 28.9, 43.8, 47.6, 51.8, 61.8, 125.1, 138.4, 152.2, 167.5. Anal. Calcd for $C_{12}H_{19}NO_4$: C: 59.75; H: 7.94; N: 5.81. Found: C: 59.63; H: 8.13; N: 5.98.

(±)-*trans-N*-tert-Butoxycarbonyl-2,6-dimethyl-4-methoxycarbonyl-1,2,3,6-tetrahydropyridine (8c).
Yield 98%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.06 (3 H, d, J = 6.5 Hz, CH_3), 1.32 (3 H, d, J = 6.5 Hz, CH_3), 1.48 (9 H, s, 3 CH_3), 2.48 (2 H, d, J = 3.8 Hz, CH_2), 3.76 (3 H, s, CH_3), 4.32 (2 H, m, 2 -CH-), 6.95 (1 H, d, J 5.0 Hz, =CH). ^{13}C-Nmr ($CDCl_3$) δ 18.9, 20.4, 28.3, 29.0, 46.9, 47.7, 51.7, 77.7, 125.6, 140.7, 154.9, 167.5. Anal. Calcd for $C_{12}H_{19}NO_4$: C: 59.75; H: 7.94; N: 5.81. Found: C: 59.93; H: 8.03; N: 5.68.

Methyl (±)-8-Ethoxycarbonyl-8-azabicyclo[3.2.1]oct-2-ene-3-carboxylate (8d).
Yield 95%; oil. bp 120°C/0.1 mm. ^{1}H-Nmr ($CDCl_3$) δ 1.20 (3 H, t, J = 7 Hz), 1.85-3.10 (6 H, m), 3.75 (3 H, s), 4.13 (2 H, q, J = 7 Hz), 4.55 (2 H, m), 7.15 (1 H, dd, J = 4 and 8 Hz). Anal. Calcd for $C_{12}H_{17}NO_4$: C: 60.32; H: 7.16; N: 5.85. Found: C: 60.10; H: 7.50; N: 5.58.

(±)-*N*-Ethoxycarbonyl-2-methyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (10).
To a solution of potassium tri-*sec*-butylborohydride (K-selectride, 1 M in THF, 6.5 mmol, 6.5 ml) in dry THF (20 ml) at -100°C and under argon, was added a solution of ketone (**9**) (1.1 g, 5.4 mmol) in dry THF (5 ml). The reaction mixture was stirred at -100°C for 2 h, quenched with a solution of *N*-(5-chloro-2-pyridyl)triflimide (2.17 g, 5.1 mmol) in THF (5 ml). The reaction mixture was stirred at -78°C for 12 h and slowly warmed up to room temperature. The solvent was evaporated in vacuo and the resulting oil purified by column chromatography on silica gel (hexane/AcOEt : 1/2) to yield the triflate as an oil (1.1 g, 58%)

which was stored at -16°C in ether in order to avoid decomposition. ^{1}H-Nmr ($CDCl_3$) δ 1.17 (3 H, d, J = 6.8 Hz,CH_3), 1.47 (9 H, s, 3 CH_3), 2.07 (1 H, m, CH), 2.81 (1 H, m, CH), 3.63 (1 H, m, CH), 4.42 (1 H, m, CH), 4.66 (1 H, m, CH), 5.75 (1 H, m, =CH).

(±)-*N*-Ethoxycarbonyl-4-ethoxycarbonyl-2-methyl-1,2,3,6-tetrahydropyridine (11).
The methoxycarbonylation was performed as described for **8a**. Yield : 76%; oil. ^{1}H-Nmr ($CDCl_3$) δ 1.06 (3 H, d, J = 6.8 Hz), 1.47 (9 H, s), 2.18-2.48 (2 H, m), 3.62-3.75 (1 H), 3.76 (3 H, s), 4.32-4.45 (1 H, m), 4.58 (1 H, m), 6.89 (1 H, m). ^{13}C-Nmr ($CDCl_3$) δ 16.4, 27.7, 28.9, 39.4, 42.9, 51.0, 79.1, 125.6, 133.6, 153.7, 166.1. Anal. Calcd for $C_{13}H_{21}NO_4$: C: 61.15; H: 8.29; N: 5.48. Found: C: 59.93; H: 8.35; N: 5.18.

Ethyl (±)-*N*-ethoxycarbonyl-2-methyl-3-oxopiperidine-4-carboxylate (13).
Under an atmosphere of argon at -78 °C a solution of **12** (488 mg, 2.0 mmol) and hexamethylphosphoramid (HMPA, 1.15 ml, 6.6 mmol) in dry THF (5 ml) was added to a solution of LDA (4.4 mmol) in THF (15 ml). The reaction mixture was stirred for 2 h at the same temperature and then dimethyl sulfate (0.2 ml, 2.1 mmol) is added. The reaction was stirred for 12 h and slowly warmed to room temperature. Addition of water and extraction with ether gave the crude product, which was purified by silica gel chromatography (hexane/ethyl acetate : 1/2) to give pure **13** (400 mg, 77.5% yield) as an oil. ^{1}H-Nmr ($CDCl_3$) δ 1.24 (3 H, t, J = 7.1 Hz, CH_3), 1.28 (3 H, t, J = 7.1 Hz, CH_3), 1.35 (3 H, d, J = 6.9 Hz, CH_3), 2.29 (2 H, m, CH_2), 2.90 (1 H, m, CH), 4.19 (5 H, m, 2 CH_2, CH), 4.57 (1 H, m, CH), 9.43 (1 H, s, CH). Anal. Calcd for $C_{12}H_{19}NO_5$: C: 56.01; H: 7.44; N: 5.44. Found: C: 55.83; H: 7.63; N: 5.78.

(±)-*N*-Ethoxycarbonyl-4-ethoxycarbonyl-6-methyl-1,2,3,6-tetrahydropyridine (14).
Under an atmosphere of argon at -78 °C a solution of **13** (304 mg, 1.18 mmol) in dry THF (5 ml) was added to a solution of lithium hexamethyldisilazane(1.4 mmol) in dry THF (10 ml). The reaction mixture was stirred for 2 h at the same temperature and then transferred into a vigorously stirred suspension of Cp_2ZrHCl (0.366 g, 1.4 mmol) in dry THF (10 ml) at 0 °C. The reaction was stirred for 12 h and slowly warmed to room temperature. The crude product was seperated from insoluble organozirconium byproducts by the addition of hexanes (2 - 3 volumes), filtration and concentration. Purification by silica gel chromatography (hexane/ethyl acetate : 2/1) gave pure **14** (163 mg, 56% yield) as an oil.
^{1}H-Nmr ($CDCl_3$) δ 1.18-1.28 (9 H, m, 3 CH_3), 2.19 - 2.41 (2 H, m, CH_2), 2.72 - 2.84 (1 H, m, CH), 4.05 - 4.22 (5 H, m, 2 CH_2, CH), 4.61 (1 H, m, CH), 6.76 (1 H, m, =CH). ^{13}C-Nmr ($CDCl_3$) δ 14.1, 14.5, 18.0, 24.2, 36.1, 48.0, 60.5, 61.2, 128.5, 139.8, 154.8, 166.2. Anal. Calcd for $C_{12}H_{19}NO_4$: C: 59.73; H: 7.93; N: 5.80. Found: C: 59.83; H: 7.63; N: 5.78.

Procedure for the hydrolytic cleavage.
A solution of the protected amino acids (0.25 mmol) in 48% aqueous hydrobromic acid (5 ml) or 37% aqueous hydrochloric acid (5 ml) was refluxed for 1 h. The reaction mixture was

evaporated and the residue was recrystallized (isopropanol/ether) to give the amino acid as bromhydrate or chlorhydrate, analytically pure after crystallization in a mixture of isopropanol and ether. This procedure was applied to the hydrolysis of **8a-d**, **11** and **14**.

1,2,3,6-Tetrahydropyridine-4-carboxylic acid hydrobromide (isoguvacine).
Yield : 60%; mp 268°-270°C (decomp.).

(±)-*cis*-2,6-Dimethyl-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrobromide (1).
Yield : 55.6% ; mp 252°C (decomp.). ^{1}H-Nmr (CD_3OD) δ 1.23 (3H, d, J = 7 Hz, CH_3), 1.31 (3H, d, J = 7.0 Hz, CH_3), 2.10 (1H, m, CH), 2.45 (1H, m, CH), 3.23 - 3.47 (1H, m, CH), 4.04 (1H, m, CH), 6.85 (1H, m, CH). Anal. Calcd for $C_8H_{14}NO_2Br$: C: 40.70; H: 5.98; N: 5.93. Found: C: 40.28; H: 5.45; N: 5.60.

(±)-*trans*-2,6-Dimethyl-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrobromide (2).
Yield : 62%; mp 232-234°C (decomp.). ^{1}H-Nmr (CD_3OD) δ 1.43 (3H, d, J = 6.5 Hz, CH_3), 1.51 (3H, d, J = 7.0 Hz, CH_3), 2.30 (1H, m, CH), 2.75 (1H, m, CH), 3.59 - 3.77 (1H, m, CH), 4.24 (1H, m, CH), 6.85 (1H, m, CH). ^{13}C-Nmr (CD_3OD) δ 17.5, 18.0, 29.7, 46.2, 49.2, 129.5, 135.7, 168.2. Anal. Calcd for $C_8H_{14}NO_2Br$: C: 40.70; H: 5.98; N: 5.93. Found: C: 40.45; H: 5.90; N: 6.01.

(±)-8-Azabicyclo[3.2.1]oct-2-ene-3-carboxylic acid hydrobromide (3).
Yield : 55%; mp 270°C (decomp.). ^{1}H-Nmr (D_2O) δ 2.10-3.20 (6 H, m), 4.55 (2 H, m), 7.15 (1 H, br d, J = 5 Hz). Anal. Calcd for $C_8H_{12}NO_2Cl$: C: 41.04; H: 5.16; N: 5.98. Found: C: 41.10; H: 5.40; N: 5.88.

(±)-2-Methyl-1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride (4).
Yield 47%; mp. 224-226°C (decomp.). ^{1}H-Nmr (CD_3OD) δ 1.47 (3 H, d, J = 7.0 Hz, CH_3), 2.60 (2 H, m, CH_2), 3.25 (1 H, m, CH), 3.50 (1 H, m, CH), 4.19 (1 H, m, CH), 6.81 (1 H, m, =CH). ^{13}C-Nmr (CD_3OD) δ 18.1, 29.4, 42.7, 49.7, 129.9, 130.7, 167.5. Anal. Calcd for $C_7H_{12}NO_2Cl$: C: 47.33; H: 6.81; N: 7.89. Found: C: 47.10; H: 6.60; N: 7.88.

(±)-6-Methyl-1,3,5,6-tetrahydropyridine-4-carboxylic acid hydrobromide (5).
Yield : 45%; mp. 207-212°C (decomp.).^{1}H-Nmr (CD_3OD) δ 1.45 (3 H, d, J = 6.6 Hz, CH_3), 2.15 - 2.81 (2 H, m, CH_2), 3.18-3.55 (1 H, m, CH), 4.16 (2 H, m, CH_2), 6.91 (1 H, m, CH). ^{13}C-Nmr (CD_3OD) δ 17.8, 22.2, 40.8, 50.7, 130.4 , 136.1, 168.2. Anal. Calcd for $C_7H_{12}NO_2Br$: C: 37.86; H: 5.45; N: 6.31. Found: C: 37.90; H: 5.46; N: 6.12.

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