Tetrahedron: Asymmetry Vol. 4, No. 1, pp. 121-131, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Enantiopure DAVA-Derivatives-Part III.[1] Synthesis of All 4 Stereoisomers of 2-Methyl-4-hydroxy-5-aminopentanoic Acid (2-Me-4-OH-DAVA).

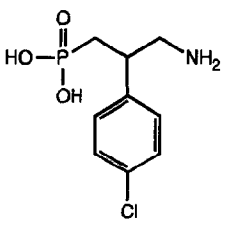
Claus Herdeis* and Karen Lütsch

Institut für Pharmazie und Lebensmittelchemie der
Universität 8700 Würzburg, Am Hubland,FRG

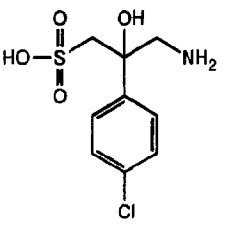
(*Received in UK 23 November* 1992)

Abstract: A stereoselective synthesis of the 4 stereoisomers of 2-methyl-4-hydroxy-5-amino-pentanoic acid namely **2R,4S-9a**, **2S,4S-9b**, **ent-9a** and **ent-9b** is presented, starting from the known lactones **S-1** and **R-1**, which are readily available from L- and D-glutamic acid. Only **ent-9b** shows affinity for $GABA_B$-receptor sites.

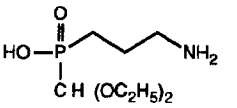
The neutral amino acid 4-aminobutanoic acid (γ-aminobutyric acid, GABA) is an inhibitory neurotransmitter which plays an important role in the control of neuronal activity in the mammalian central nervous system.[2] The neurotransmitter functions of GABA are mediated by at least two distinct subtypes of receptors, $GABA_A$ and $GABA_B$ receptors. $GABA_B$ receptors are characterized by their lack of affinity for $GABA_A$ agonists (e.g. isoguvacine and muscimol) and by their specific affinity for and activation by R(-) baclofen.[3] Understanding of the physiological and pharmacological role of $GABA_B$ receptor is facilitated by specific $GABA_B$ antagonists. Recently a number of $GABA_B$ antagonists like phaclofen[4] **I** 2-OH-saclofen[5] **II** and 3-aminopropyl-(diethoxymethyl)phosphinic acid[6] **III** were synthesized and tested.



I

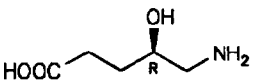


II



III

Recent data have shown that δ-aminovaleric acid (DAVA) is an antagonist of the central pharmacological actions of baclofen (Lioresal®)[7]. On the other hand the introduction of hydroxy groups into different positions of the carbon backbone of DAVA shows dissimilar agonistic and antagonistic affinity profiles to $GABA_B$ receptors[1b]. Recently we have synthesized R(-)-and S(+)-4-OH-DAVA from D-and L-glutamic acid[8].

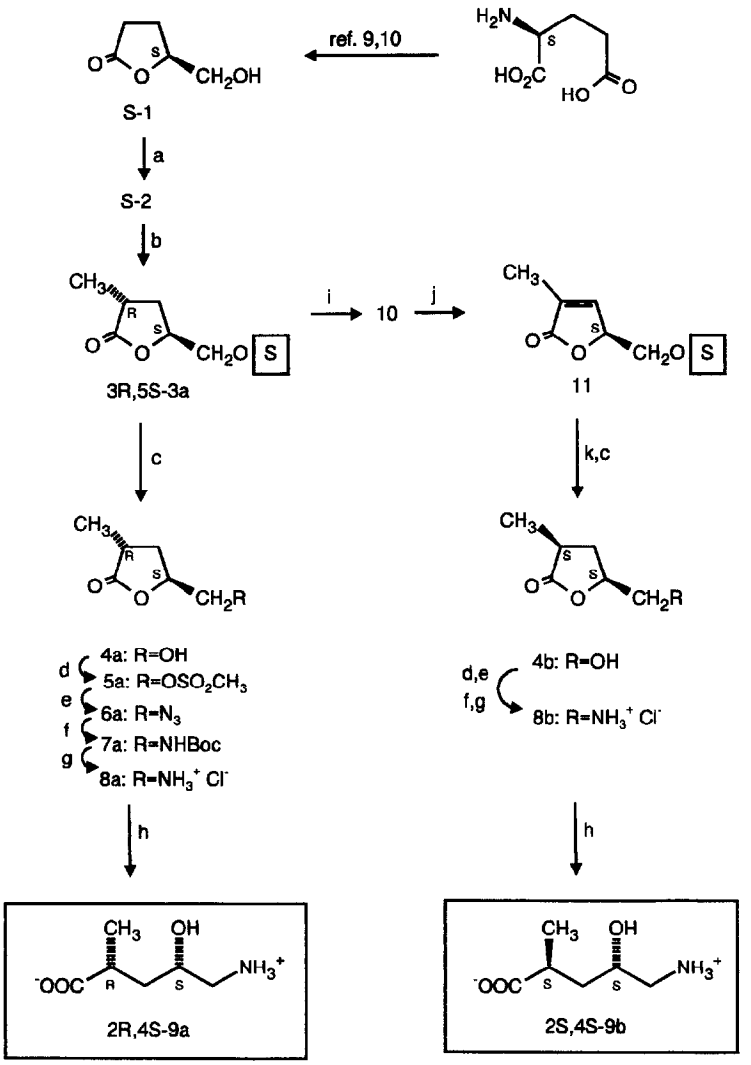


IV

R(-)-4-OH-DAVA (**IV**) has shown a moderately potent affinity for $GABA_B$ receptor sites in rat brain and $GABA_B$ antagonistic effects in guinea pig ileum preparation. The S-enantiomer did not affect $GABA_B$ receptor binding in both preparations[1b].

To study stereostructure-activity relations and the influence of the lipophilicity of derivatives of **IV** on $GABA_B$ receptor site, we started a synthetic program with the aim to introduce alkyl substituents in the 2-and (or) 3-position of **IV** in a stereoselective manner. The "lactone pathway"[1a,8] with **S-1** (**R-1**) as a starting material seemed to be best suited for this project; first, position 2 can be modified by enolate alkylation of **2** and second, position 3 via 1,4 conjugate addition of organo cuprates to the 3,4 dehydro derivative of **2**. In this paper we describe the synthesis of **9a** and **9b** from S-glutamic acid. **Ent-9a** and **ent-9b** is provided from R-glutamic acid in the same way.

Enantiopure **S-1**[9] was silylated to **S-2**[10a] which was methylated[11] to **3a** in excellent diastereoselectivity (d.e. greater 98% was determined by GC for **4a** on a Lipodex D column after desilylation of crude **3a**). One crystallization of **3a** from methanol furnished diastereopure material. On the other hand phenylselenenylation of the enolate of **3a** provided **10** as a single diastereomer, which could be transformed to the olefin **11** by oxidation with hydrogen peroxide at room temperature[10a]. Hydrogenation of **11** on Pd/C from the less hindered α-side gave **3b/a** in a cis/trans ratio of 96:4, detected with GC on a crude mixture of **4b/a**. After mesylation of **4a,b**, **5a,b** were reacted with sodium azide to **6a,b** which were hydrogenated in the presence of di-t-butyl dicarbonate to the Boc-protected amino lactones **7a,b**. Treatment of **7a,b** with methanolic hydrogen chloride solution furnished **8a,b** in an overall yield of 61% starting from **4a,b**. Only minor amounts of **8a,b** could be isolated, when **6a,b** was hydrogenated in the presence of methanolic HCl solution. After column chromatography, 3,5-dimethyltetrahydrofurane-2-one was isolated as an oil. The ringopening of the unexpectedly stable aminolactone hydrochlorides **8** and the isolation of the amino acids **9** turned out to be more difficult than anticipated. Higher base concentrations than 1M KOH caused extensive epimerisation on position 3. This could be determined by ^{13}C-NMR spectroscopy after relactonization of the amino acids in acidic media. This facile lactonization prohibited the isolation of the amino acids **9** as their hydrochlorides. Ultimately, after ringopening of the lactones **8** with 0.5M KOH at room temperature, the potassium salts of **9** were brought on a acidic ion exchange column (Dowex 50Wx2). The neutral amino acids were eluated with 0.5M NH_4OH solution and freeze dried. **Ent-9a/b** were produced from R-glutamic acid according to the same reaction sequence. Interestingly only one stereoisomer namely **ent-9b** showed affinity on $GABA_B$ receptor sites[12]. Receptor binding studies will be published elsewhere in due course.



a: TBDPSiCl, Imid., DMF; b: LDA, -78°C, MeI; c: TFA, H_2O, r.t.; d: MesCl, Et_3N; e: NaN_3,15-crown-5; f: H_2, Pd/C,Boc_2O; g: HCl/MeOH; h: OH^-/D 50W2/NH_4OH; i: PhSeCl, LDA -78°C; j: H_2O_2,Py; k: Pd/C, H_2;

Experimental

General:THF was distilled first from $LiAlH_4$ and then over sodium wire under N_2. Reactions with organometallic compounds were run in flame-dried glassware under dry and **oxygen-free N_2**. TLC: Merck precoated silica gel 60 F-254 plates. Reaction compounds were visualized by iodine vapor. Column chromatography was performed on silic gel 60. M.p.: Büchi 510 apparatus, values uncorrected. $[a]_D^{20}$: Perkin-Elmer 241 polarimeter. IR-spectra: Perkin-Elmer 681. ^{1}H-NMR and ^{13}C-NMR: Bruker AC 200.

3R,5S-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-4,5-dihydro-2(3H)-furanone (3a)

To a solution of LDA (21.05 mmol) in dry THF (50 ml) was added **2**[8,10a] (5.00g, 14.10 mmol) at -78° C. After 45 min the enolate was trapped with methyl iodide (3.58 ml, 56.40 mmol). After 15 min the reaction was quenched with sat. NH_4Cl solution and the mixture was extracted with ether (3x). After drying and evaporation of the solvent the yellow oil crystallized while standing overnight. Recrystallisation from MeOH furnished colorless crystals. Yield : 5.20 g (70%).- mp.: 75°C (MeOH).- $[\alpha]_D^{20}$: +37.7 (c=0.4, $CHCl_3$).- IR (KBr): 3060-2940, 1760, 1590, 1430, 1110 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.04 (9H,s,t-bu), 1.29 (3H,d,CH_3, $J_{Me,3}$= 7.3 Hz), 1.96 (1H,td,H-4, J_{gem}= 12.8 Hz, $J_{4,3cis}$= 9.0 Hz, $J_{4,5trans}$= 9.0 Hz), 2.44 (1H,m,H-4, J_{gem}= 12.8 Hz, $J_{4,3trans}$= 9.5 Hz, $J_{4,5cis}$= 3.1 Hz), 2.85 (1H,m,H-3, $J_{3,Me}$= 7.3 Hz, $J_{3,4trans}$= 9.5 Hz, $J_{3,4cis}$= 9.0 Hz), 3.68 (1H,dd,H-6, J_{gem}= 11.3 Hz, $J_{6,5}$= 3.2 Hz), 3.87 (1H,dd,H-6, J_{gem}= 11.3 Hz, $J_{6,5}$= 3.4 Hz), 4.55 (1H,m,H-5, $J_{5,6}$= 3.2,3.4 Hz, $J_{5,4cis}$= 3.1 Hz, $J_{5,4trans}$= 9.0 Hz), 7.43 (6H,m,H-arom.), 7.65 (4H,m,H-arom.).- ^{13}C-NMR ($CDCl_3$): δ(ppm)= 16.3 CH_3, 19.0 $\underline{C}(CH_3)$, 26.7 $C(\underline{C}H_3)$, 32.1 C-4, 34.1 C-3, 65.5 C-6, 77.4 C-5, 127.7, 129.8, 132.4, 132.8, 135.4 C-arom., 180.1 C-2.- $C_{22}H_{28}O_3Si$ (368.55) Calcd.: C 71.70 H 7.66 found: C 71.91 H 8.03.

3S,5R-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-4,5-dihydro-2(3H)-furanone (ent 3a)

From **ent 2** in the same manner as described for **3a**.

Yield: 5.27 g (71%).-. mp.: 73°C (MeOH).- $[\alpha]_D^{20}$: -37.1 (c=1.0, $CHCl_3$).- $C_{22}H_{28}O_3Si$ (368.55) Calcd.: C 71.70 H 7.66 found: C 71.15 H 7.86.

3R,5S-5-Hydroxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (4a)

3a (5.00g, 13.57 mmol) was treated with a mixture of trifluoroacetic acid (50 ml) and water (50 ml) for 2h at room temperature. After evaporation of the volatiles, **4a** was isolated as a colorless oil by column chromatography ($CHCl_3$/MeOH 9:1). Yield: 1.34g (77%).- $[\alpha]_D^{20}$: +36.2 (c=0.3, EtOH).- IR (neat): 3400, 2980-2880, 1760, 1200 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.26 (3H,d,CH_3, $J_{Me,3}$= 7.3 Hz), 1.97 (2H,m,OH,H-4, J_{gem}= 12.9 Hz, $J_{4,3cis}$= 8.5 Hz, $J_{4,5trans}$= 8.5 Hz), 2.40 (1H,m,H-4, J_{gem}= 12.9 Hz, $J_{4,3trans}$= 9.4 Hz, $J_{4,5cis}$= 3.8 Hz), 2.83 (1H,m,H-3, $J_{3,Me}$= 7.3 Hz, $J_{3,4trans}$= 9.4 Hz, $J_{3,4cis}$= 8.5 Hz), 3.62 (1H,dd,H-6, J_{gem}= 12.3 Hz, $J_{6,5}$= 4.3 Hz), 3.82 (1H,dd,H-6, J_{gem}= 12.3 Hz, $J_{6,5}$= 3.3 Hz), 4.60 (1H,m,H-5, $J_{5,6}$= 4.3,3.3 Hz, $J_{5,4cis}$= 3.8 Hz, $J_{5,4trans}$= 8.5 Hz).- ^{13}C-NMR ($CDCl_3$): δ(ppm)= 16.0 CH_3, 31.5 C-4, 34.3 C-3, 64.0 C-6, 78.6 C-5, 181.0 C-2 $C_6H_{10}O_3$ (130.14).- Calcd.: C 55.37 H 7.24 found: C 55.31 H 7.59.

3S,5R-5-Hydroxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 4a)

From **ent 3a** as described for **4a**. Yield: 1.48g (85%).- $[\alpha]_D^{20}$: -35.7 (c=0.3, EtOH).- $C_6H_{10}O_3$ (130.14) Calcd.: C 55.37 H 7.24 found: C 54.73 H 7.08.

3R,5S-5-Mesyloxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (5a)

4a (1.00g, 7.68 mmol) and triethylamine (1.17g, 8.45 mmol),were dissolved in dichloromethane (50 ml) and cooled to -30°C. To this solution mesylchloride (0.66 ml, 18.45 mmol) was added with stirring and

the mixture was gradually warmed to ambient temperature. After addition of 1N-HCl (20 ml) the organic phase was separated, and the aqueous layer was extracted with dichloromethane (2x). The combined organic extracts were washed with water (1x), dried and evaporated. The pale yellow oil crystallized after trituration with diisopropyl ether. Yield: 1.42g (89%).- mp.: 44°C (iPr_2O/EtOAc).- $[\alpha]_D^{20}$: +32.0 (c=0.2, EtOH).- IR (KBr): 3040-2940, 1770, 1350, 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.31 (3H,d,CH_3, $J_{Me,3}$= 7.2 Hz), 2.10 (1H,td,H-4, J_{gem}= 13.2 Hz, $J_{4,3cis}$= 8.6 Hz, $J_{4,5trans}$= 8.6 Hz), 2.41 (1H,m,H-4, J_{gem}= 13.2 Hz, $J_{4,3trans}$= 9.5 Hz, $J_{4,5cis}$= 4.0 Hz), 2.81 (1H,m,H-3, $J_{3,Me}$= 7.2 Hz, $J_{3,4trans}$= 9.5 Hz, $J_{3,4cis}$= 8.6 Hz), 3.08 (3H,s,CH_3-Mesyl), 4.30 (1H,dd,H-6, J_{gem}= 11.4 Hz, $J_{6,5}$= 4.3 Hz), 4.41 (1H,dd,H-6, J_{gem}= 11.4 Hz, $J_{6,5}$= 3.1 Hz), 4.77 (1H,m,H-5, $J_{5,6}$= 4.3,3.1 Hz, $J_{5,4cis}$= 4.0 Hz, $J_{5,4trans}$= 8.6 Hz).- $C_7H_{12}O_5S$ (208.18) Calcd.: C 40.38 H 5.81found: C 40.46 H 6.12.

3S,5R-5-Mesyloxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 5a)

From **ent 4a** as described for **5a**. Yield: 1.03g (65%).- mp.: 42°C (iPr_2O/EtOAc).- $[\alpha]_D^{20}$: -36.9 (c=0.2, EtOH).- $C_7H_{12}O_5S$ (208.18) Calcd.: C 40.38 H 5.81found: C 40.22 H 5.91.

3R,5S-5-Azidomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (6a)

To a solution of **5a** (1.00g, 4.80 mmol) in acetonitrile (50 ml), sodium azide (474 mg, 7.20 mmol) and 15-crown-5 (100 mg) were added and refluxed for 16h. After evaporation of the solvent and column chromatography ($CHCl_3$/MeOH 9:1) **6a** was isolated as a colorless oil. Yield: 700 mg (94%).- $[\alpha]_D^{20}$: +94.2 (c=0.3, EtOH).- IR (neat): 2980-2880, 2110, 1770, 1290, 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.30 (3H,d,CH_3, $J_{Me,3}$= 7.3 Hz), 2.04 (1H,td,H-4, J_{gem}= 13.2 Hz, $J_{4,3cis}$= 8.3 Hz, $J_{4,5trans}$= 8.3 Hz), 2.31 (1H,m,H-4, J_{gem}= 13.2 Hz, $J_{4,3trans}$= 9.4 Hz, $J_{4,5cis}$= 4.2 Hz), 2.81 (1H,m,H-3, $J_{3,Me}$= 7.3 Hz, $J_{3,4trans}$= 9.4 Hz, $J_{3,4cis}$= 8.3 Hz), 3.47 (1H,dd,H-6, J_{gem}= 12.7 Hz, $J_{6,5}$= 4.8 Hz), 3.60 (1H,dd,H-6, J_{gem}= 12.7 Hz, $J_{6,5}$= 3.9 Hz), 4.65 (1H,m,H-5, $J_{5,6}$= 4.8,3.9 Hz, $J_{5,4cis}$= 4.2 Hz, $J_{5,4trans}$= 8.3 Hz).- $C_6H_9O_2N_3$ (155.16) Calcd.: C 46.45 H 5.85 N 27.08 found: C 46.32 H 5.57 N 27.40.

3S,5R-5-Azidomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 6a)

From **ent 5a** as described for **6a**. Yield: 693 mg (93%).- $[\alpha]_D^{20}$: -95.6 (c=0.6, EtOH).- $C_6H_9O_2N_3$ (155.16) Calcd.: C 46.45 H 5.85 N 27.08 found: C 46.20 H 5.80 N 27.14.

3R,5S-5-(N-t-Butoxycarbonyl)aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (7a)

A solution of **6a** (500 mg, 3.22 mmol) and Boc_2O (775 mg, 3.55 mmol) in methanol (20 ml) was hydrogenated over Pd/C 10% (60 mg) for 2.5h at r.t. and 8 bar pressure. After filtration, evaporation of the solvent and column chromatography ($CHCl_3$/MeOH 9:1) **7a** was isolated as a colorless oil. Yield: 709 mg (96%).- $[\alpha]_D^{20}$: +35.9 (c=1.8, $CHCl_3$).- IR (neat): 3360, 2980,-2880, 1770, 1710, 1520, 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.28 (3H,d,CH_3, $J_{Me,3}$= 7.3 Hz), 1.45 (9H,s,t-Butyl), 1.98 (1H,td,H-4, J_{gem}= 13.1 Hz, $J_{4,3cis}$= 7.7 Hz, $J_{4,5trans}$= 7.7 Hz), 2.34 (1H,m,H-4, J_{gem}= 13.1 Hz, $J_{4,3trans}$= 8.2 Hz, $J_{4,5cis}$= 3.9 Hz), 2.69 (1H,m,H-3, $J_{3,Me}$= 7.3 Hz, $J_{3,4trans}$= 8.2 Hz,

(1H,ddd,H-6, J_{gem} = 14.6 Hz, $J_{6,NH}$ = 7.1 Hz, $J_{6,5}$ = 3.7 Hz), 4.62 (1H,m,H-5, $J_{5,6}$ = 5.9,3.7 Hz, $J_{5,4cis}$ = 3.9 Hz, $J_{5,4trans}$ = 7.7 Hz), 4.94 (1H,m,NH).- ^{13}C-NMR ($CDCl_3$): δ(ppm) = 16.1 CH_3, 28.3 C($\underline{C}H_3$), 32.5 C-4, 34.1 C-3, 44.2 C-6, 77.3 C-5, 79.8 $\underline{C}(CH_3)$, 156.1 C=O-Boc, 179.7 C-2. $C_{11}H_{19}O_4N$ (229.28) Calcd.: C 57.63 H 8.35 N 6.11 found: C 57.76 H 8.21 N 6.43.

3S,5R-5-(N-t-Butoxycarbonyl)aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 7a)

From **ent 6a** as described for **7a**. Yield: 532 mg (72%).- $[\alpha]_D^{20}$: -32.7 (c=0.8, $CHCl_3$).- $C_{11}H_{19}O_4N$ (229.28) Calcd. C 57.63 H 8.35 N 6.11 found: C 57.59 H 8.43 N 6.12.

3R,5S-5-Aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone-hydrochloride (8a)

7a (450 mg 1.96 mmol) was stirred for 4h at r.t. in methanolic HCl (30 ml). The solvent was evaporated and the waxy residue was triturated with acetonitrile. Recrystallisation from CH_3CN/EtOH furnished **8a** as colorless plates. Yield: 243mg (75%).- mp.: 187°C (CH_3CN/EtOH).- $[\alpha]_D^{20}$: +81.0 (c=0.4, MeOH).- IR (KBr): 3000-2900, 1770, 1170 cm^{-1}.- ^{1}H-NMR (MeOD): δ(ppm) = 1.27 (3H,d,CH_3, $J_{Me,3}$ = 7.3 Hz), 2.15 (1H,td,H-4, J_{gem} = 13.2 Hz, $J_{4,3cis}$ = 8.2 Hz, $J_{4,5trans}$ = 8.2 Hz), 2.31 (1H,m,H-4, J_{gem} = 13.2 Hz, $J_{4,3trans}$ = 9.1 Hz, $J_{4,5cis}$ = 4.5 Hz), 2.86 (1H,m,H-3, $J_{3,Me}$ = 7.3 Hz, $J_{3,4trans}$ = 9.1 Hz, $J_{3,4cis}$ = 8.2 Hz), 3.22 (1H,dd,H-6, J_{gem} = 11.5 Hz, $J_{6,5}$ = 2.7 Hz), 3.31 (1H,H-6, in CH_3-MeOD), 4.86 (1H,m,H-5, in OH-MeOD).- ^{1}H-NMR (DMSO-d_6): δ(ppm) = 1.14 (3H,d,CH_3, $J_{Me,3}$ = 7.2 Hz), 2.04 (1H,td,H-4, J_{gem} = 13.1 Hz, $J_{4,3cis}$ = 8.5 Hz, $J_{4,5trans}$ = 8.5 Hz), 2.26 (1H,m,H-4, J_{gem} = 13.1 Hz, $J_{4,3trans}$ = 9.2 Hz, $J_{4,5cis}$ = 3.9 Hz), 2.79 (1H,m,H-3, $J_{3,Me}$ = 7.2 Hz, $J_{3,4trans}$ = 9.2 Hz, $J_{3,4cis}$ = 8.5 Hz), 3.05 (1H,d,H-6, $J_{6,5}$ = 1.4 Hz), 3.08 (1H,s,H-6), 4.76 (1H,m,H-5,$J_{5,4trans}$ = 8.5 Hz, $J_{5,4cis}$ = 3.9 Hz, $J_{5,6}$ = 1.4 Hz). ^{13}C-NMR (MeOD): δ(ppm) = 15.9 CH_3, 33.2 C-4, 34.8 C-3, 44.0 C-6, 76.2 C-5, 182.7 C-2.- ^{13}C-NMR (DMSO-d_6): δ(ppm) = 15.2 CH_3, 31.8 C-4, 32.6 C-3, 42.0 C-6, 74.0 C-5, 179.0 C-2.- $C_6H_{12}O_2NCl$ (165.62) Calcd.: C 43.51 H 7.30 N 8.46 found: C 43.32 H 7.58 N 8.34.

3S,5R-5-Aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone-hydrochloride (ent 8a)

From **ent 7a** as described for **8a**. Yield: 227 mg (70%) mp.: 189°C (CH_3CN/EtOH).- $[\alpha]_D^{20}$: -81.1 (c=0.9, MeOH) $C_6H_{12}O_2NCl$ (165.62) Calcd.: C 43.51 H 7.30 N 8.46 found: C 43.56 H 7.33 N 8.41.

2R,4S-5-Amino-4-hydroxy-2-methyl-pentanoic acid (9a)

8a (280 mg, 1.69 mmol) was dissolved in 0.5M-KOH (50 ml) at r.t. and stirred for 24h. The mixture was diluted with water (80 ml) and brought to a chromatographic column filled with 100 ml Dowex 50Wx2 (111 mval), which was thoroughly washed with water prior to use. The raisin was rinsed with water (300 ml) and the amino acid was eluated with 0.5M-NH_4OH (250 ml). After evaporation of the solvent the residue was freeze-dried. Trituration and recrystallisation with acetonitrile/ethanol furnished a colorless powder. Yield: 120 mg (49%).- mp.: 171°C (CH_3CN/EtOH).- $[\alpha]_D^{20}$: -13.5 (c=0.3, H_2O).- IR (KBr): 3060, 2960-2880, 1640, 1590, 1540, 1400 cm^{-1}.- ^{1}H-NMR (MeOD/D_2O): δ(ppm) = 1.22 (3H,d,CH_3, $J_{Me,2}$ = 7.0 Hz), 1.47 (1H,ddd,H-3, J_{gem} = 13.9 Hz, $J_{3,2}$ = 3.9 Hz, $J_{3,4}$ = 9.1 Hz), 1.78

(1H,ddd,H-3, J_{gem}= 13.9 Hz, $J_{3,2}$=10.2 Hz, $J_{3,4}$= 4.0 Hz), 2.62 (1H,m,H-2, $J_{2,Me}$= 7.0 Hz, $J_{2,3}$= 3.9,10.2 Hz), 2.76 (1H,dd,H-5, J_{gem}= 12.8 Hz, $J_{5,4}$= 9.1 Hz), 3.00 (1H,dd,H-5,J_{gem}= 12.8 Hz, $J_{5,4}$= 3.3 Hz), 3.81 (1H,m,H-4, $J_{4,3}$= 4.0,9.1 Hz, $J_{4,5}$= 3.3,9.1 Hz).- ^{13}C-NMR (MeOD/D_2O): δ(ppm)= 19.2 CH_3, 39.0 C-3, 40.1 C-2, 46.2 C-5, 67.3 C-4, 182.8 C-1.- MS (CI): m/z= 148 [M+H$^+$, 6.6%], 130 [M+H$^+$ -H_2O, 100%], 112 [M+H$^+$ -2H_2O, 50.4%].- $C_6H_{13}O_3N$ (147.17) Calcd.: C 48.97 H 8.84 N 9.45 found: C 47.79 H 8.88 N 9.34.

2S,4R-5-Amino-4-hydroxy-2-methyl-pentanoic acid (ent 9a)

From **ent 8a** as described for **9a**. Yield: 68 mg (47%).- mp.: 173°C (CH_3CN/EtOH).- $[\alpha]_D^{20}$: +12.8 (c=0.2, H_2O).- $C_6H_{13}O_3N$ (147.17) Calcd.: C 48.97 H 8.84 N 9.45 found: C 47.00 H 8.26 N 8.70.

5S,3R-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-3-phenylseleno-4,5-dihydro-2(3H)-furanone (10)

To a solution of LDA (18.26 mmol) in THF (70 ml) at -78°C was added **3a** (4.50 g, 12.21 mmol). After 45 min the enolate was treated with a solution of phenylselenenyl chloride (2.57 g, 13.43 mmol) in THF (30 ml). After 90 min the reaction was quenched with sat. NH_4Cl-solution. Extractive isolation and column chromatography (petroleum ether/EtOAc 9:1) afforded a yellow viscous oil. Yield: 4.41 g (69%).- $[\alpha]_D^{20}$: +17.6 (c=0.3, $CHCl_3$).- IR (KBr): 3070, 2960-2860, 1770, 1430, 1115 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.03 (9H,s,t-Butyl), 1.64 (3H,s,CH_3), 2.34 (1H,d,H-4, $J_{4,5cis}$= 2.5 Hz), 2.37 (1H,m,H-4, $J_{4,5trans}$= 4.8 Hz), 3.65 (1H,dd,H-6, J_{gem}= 11.5 Hz, $J_{6,5}$= 3.8 Hz), 3.84 (1H,dd,H-6, J_{gem}= 11.5 Hz, $J_{6,5}$= 3.4 Hz), 4.38 (1H,m,H-5, $J_{5,6}$= 3.8,3.4 Hz, $J_{5,4cis}$= 2.5 Hz, $J_{5,4trans}$= 4.8 Hz), 7.41 (9H,m,H-arom.), 7.65 (6H,m,H-arom.).- $C_{28}H_{32}O_3SiSe$ (523.61) Calcd.: C 64.23 H 6.16 found: C 63.99 H 6.25.

5R,3S-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-3-phenylseleno-4,5-dihydro-2(3H)-furanone (ent 10)

From **ent 3a** as described for **10**. Yield: 4.92 g (77%).- $[\alpha]_D^{20}$: -16.6 (c=2.0, $CHCl_3$).- $C_{28}H_{32}O_3SiSe$ (523.61) Calcd.: C 64.23 H 6.16 found: C 64.43 H 6.42.

5S-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-2(5H)-furanone (11)

To a stirred solution of **10** (3.10 g, 5.92 mmol) in CH_2Cl_2 (50 ml) and pyridine (0.4 ml) at 0°C was added a mixture of H_2O_2 (2.1 ml) and H_2O (2.1 ml). After 1h at r.t. sat. Na_2CO_3-solution was added and the organic layer was extracted with 2M-HCl and H_2O. Drying and evaporation of the organic phase afforded a colorless powder, which was pure enough for the next reaction step. Analytical pure material was isolated by column chromatography (petroleum ether/EtOAc 8:2). Yield: 1.65 g (76%).- mp.: 63°C.- $[\alpha]_D^{20}$: +68.8 (c=0.5, $CHCl_3$).-IR (KBr): 3080-3040, 2960-2860, 1760, 1470, 1430, 1115 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.06 (9H,s,t-Butyl), 1.92 (3H,t,CH_3, $J_{Me,4}$= 1.7 Hz, $J_{Me,5}$= 1.7 Hz), 3.84 (2H,d,H-6, $J_{6,5}$= 4.6 Hz), 4.92 (1H,m,H-5, $J_{5,Me}$= 1.7 Hz, $J_{5,6}$= 4.6 Hz, $J_{5,4}$= 3.1 Hz), 6.95 (1H,m,H-4, $J_{4,Me}$= 1.7 Hz, $J_{4,5}$= 3.1 Hz), 7.42 (6H,m,H-arom.), 7.63 (4H,m,H-arom.).- $C_{22}H_{26}O_3Si$ (366.53) Calcd.: C 72.09 H 7.15 found: C 72.37 H 7.04.

5R-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-2(5H)-furanone (ent 11)

From **ent 10** as described for **11**. Yield: 1.76 g (81%).- mp.: 64°C.- $[\alpha]_D^{20}$: -71.2 (c=0.1, $CHCl_3$).- $C_{22}H_{26}O_3Si$ (366.53) Calcd.: C 72.09 H 7.15 found: C 72.16 H 7.29.

3S,5S-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-4,5-dihydro-2(3H)-furanone (3b)

11 (1.20 g, 3.27 mmol) was dissolved in EtOAc (20 ml) and hydrogenated over Pd/C 20% (120 mg) at r.t.and 10 bar for 5h. After "filtration" over silica gel and evaporation of the solvent **3b** was isolated as colorless crystals. Yield: 1.18 g (98%).- mp.: 84°C (MeOH).- $[\alpha]_D^{20}$: +13.9 (c=0.6, $CHCl_3$).- IR (KBr) : 3080-3040, 2980-2860, 1770, 1430, 1130-1110 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.06 (9H,s,t-Butyl), 1.29 (3H,d,CH_3, $J_{Me,3}$= 7.0 Hz), 1.85 (1H,td,H-4, J_{gem}= 12.3 Hz, $J_{4,3trans}$= 11.9 Hz, $J_{4,5trans}$= 11.9 Hz), 2.39 (1H,m,H-4, J_{gem}= 12.3 Hz, $J_{4,3cis}$= 6.3 Hz, $J_{4,5cis}$= 3.4 Hz), 2.71 (1H,m,H-3, $J_{3,Me}$= 7.0 Hz, $J_{3,4trans}$= 11.9 Hz, $J_{3,4cis}$= 6.3 Hz), 3.69 (1H,dd,H-6, J_{gem}= 11.4 Hz, $J_{6,5}$= 4.3 Hz), 3.86 (1H,dd,H-6, J_{gem}= 11.4 Hz, $J_{6,5}$= 3.6 Hz), 4.54 (1H,m,H-5, $J_{5,6}$= 4.3,3.6 Hz, $J_{5,4cis}$= 3.4 Hz, $J_{5,4trans}$= 11.9 Hz), 7.40 (6H,m,H-arom.), 7.65 (4H,m,H-arom.).- ^{13}C-NMR ($CDCl_3$): δ(ppm)= 15.4 CH_3, 19.2 $\underline{C}(CH_3)$, 26.7 $C(\underline{C}H_3)$, 32.1 C-4, 35.4 C-3, 64.6 C-6, 78.1 C-5, 127.8, 129.8, 132.5, 132.9, 135.5 C-arom., 179.3 C-2.- $C_{22}H_{28}O_3Si$ (368.55) Calcd.: C 71.70 H 7.66 found: C 71.97 H 7.76.

3R,5R-5-(t-Butyldiphenylsiloxymethyl)-3-methyl-4,5-dihydro-2(3H)-furanone (ent 3b)

From **ent 11** as described for **3b**. Yield: 1.19 g (99%).- mp.: 85°C (MeOH).- $[\alpha]_D^{20}$: -13.8 (c=0.4, $CHCl_3$).- $C_{22}H_{28}O_3Si$ (368.55) Calcd.: C 71.70 H 7.66 found: C 71.93 H 7.73.

3S,5S-5-Hydroxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (4b)

3b (1.26 g, 3.42 mmol) was treated in the same manner as described for **3a**. Yield: 400 mg (90%).- $[\alpha]_D^{20}$: +22.5 (c=0.3, EtOH).- IR (neat): 3440, 2980-2880, 1760, 1455, 1200-1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.28 (3H,d,CH_3, $J_{Me,3}$= 7.1 Hz), 1.78 (1H,td,H-4, J_{gem}= 12.3 Hz, $J_{4,3trans}$= 11.8 Hz, $J_{4,5trans}$= 11.8 Hz), 2.38 (1H,ddd,H-4, J_{gem}= 12.3 Hz, $J_{4,3cis}$= 6.4 Hz, $J_{4,5cis}$= 3.5 Hz), 2.74 (1H,m,H-3, $J_{3,Me}$= 7.1 Hz, $J_{3,4trans}$= 11.8 Hz, $J_{3,4cis}$= 6.4 Hz), 3.63 (1H,dd,H-6, J_{gem}= 12.7 Hz, $J_{6,5}$= 5.0 Hz), 3.91 (1H,dd,H-6, J_{gem}= 12.7 Hz, $J_{6,5}$= 2.6 Hz), 3.75 (1H,s,OH), 4.51 (1H,m,H-5, $J_{5,6}$= 5.0,2.6 Hz, $J_{5,4cis}$= 3.5 Hz, $J_{5,4trans}$= 11.8 Hz).- $C_6H_{10}O_3$ (368.55) Calcd.: C 55.37 H 7.24 found: C 55.30 H 7.55.

3R,5R-5-Hydroxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 4b)

From **ent 3b** as described for **4b**. Yield: 404 mg (91%).- $[\alpha]_D^{20}$: -25.2 (c=0.3, EtOH).- $C_6H_{10}O_3$ (368.55) Calcd.: C 55.37 H 7.24 found: C 54.89 H 6.98.

3S,5S-5-Mesyloxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (5b)

4b (350 mg, 2.69 mmol) was treated with Et_3N (0.41 ml, 2.96 mmol) and mesyl chloride (0.23 ml, 2.96 mmol) in CH_2Cl_2 (30 ml) as described for 5a. Yield: 381 mg (68%).- mp.: 84°C (EtOAc).- $[\alpha]_D^{20}$: +29.4 (c=0.2, EtOH).- IR (KBr): 3030-2880, 1760, 1350, 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.32 (3H,d,CH_3, $J_{Me,3}$= 7.0 Hz), 1.75 (1H,td,H-4, J_{gem}= 12.6 Hz, $J_{4,3trans}$= 11.5 Hz,

$J_{4,5trans}$= 11.5 Hz), 2.53 (1H,ddd,H-4, J_{gem}= 12.6 Hz, $J_{4,3cis}$= 6.4 Hz, $J_{4,5cis}$= 3.6 Hz), 2.74 (1H,m,H-3, $J_{3,Me}$= 7.0 Hz, $J_{3,4trans}$= 11.5 Hz, $J_{3,4cis}$= 6.4 Hz), 3.09 (3H,s,CH_3-Mesyl), 4.28 (1H,dd,H-6, J_{gem}= 11.7 Hz, $J_{6,5}$= 5.5 Hz), 4.46 (1H,dd,H-6, J_{gem}= 11.7 Hz, $J_{6,5}$= 2.9 Hz), 4.65 (1H,m,H-5, $J_{5,6}$= 5.5,2.9 Hz, $J_{5,4cis}$= 3.6 Hz, $J_{5,4trans}$= 11.5 Hz).- $C_7H_{12}O_5S$ (208.18) Calcd.: C 40.38 H 5.81found: C 40.65 H 5.86.

3R,5R-5-Mesyloxymethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 5b)

From **ent 4b** as decribed for **5b**. Yield: 398 mg (71%).- mp.: 84°C (EtOAc).- $[\alpha]_D^{20}$: -29.9 (c=0.3, EtOH).- $C_7H_{12}O_5S$ (208.18) Calcd.: C 40.38 H 5.81 found: C 40.30 H 5.91.

3S,5S-5-Azidomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (6b)

5b (200 mg, 0.96 mmol) was treated in acetonitrile (20 ml) with sodium azide (95 mg, 1.46 mmol) and 15-Crown-5 (20 mg) as described for **6a**. Yield: 139 mg (93%).- $[\alpha]_D^{20}$: +98.4 (c=0.3, EtOH).- IR (KBr): 2980-2880, 2100, 1770, 1450 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.30 (3H,d,CH_3, $J_{Me,3}$= 7.0 Hz), 1.72 (1H,td,H-4, J_{gem}= 12.3 Hz, $J_{4,3trans}$= 11.9 Hz, $J_{4,5trans}$= 11.9 Hz), 2.48 (1H,ddd,H-4, J_{gem}= 12.3 Hz, $J_{4,3cis}$= 6.6 Hz, $J_{4,5cis}$= 3.6 Hz), 2.72 (1H,m,H-3, $J_{3,Me}$= 7.0 Hz, $J_{3,4trans}$= 11.9 Hz, $J_{3,4cis}$= 6.6 Hz), 3.44 (1H,dd,H-6, J_{gem}= 13.4 Hz, $J_{6,5}$= 5.5 Hz), 3.61 (1H,dd,H-6, J_{gem}= 13.4 Hz, $J_{6,5}$= 3.6 Hz), 4.54 (1H,m,H-5, $J_{5,6}$= 5.5,3.6 Hz, $J_{5,4cis}$= 3.6 Hz, $J_{5,4trans}$= 11.9 Hz).- ^{13}C-NMR ($CDCl_3$): δ(ppm)= 15.1 CH_3, 34.9 C-4, 36.5 C-3, 44.3 C-6, 75.8 C-5, 180.5 C-2.- $C_6H_9O_3N_3$ (155.16) Calcd.: C 46.45 H 5.85 N 27.08 found: C 46.51 H 5.65 N 27.09.

3R,5R-5-Azidomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 6b)

From **ent 5b** as described for **6a**. Yield: 87%.- $[\alpha]_D^{20}$: -97.8 (c=0.4/EtOH).- $C_6H_9O_3N_3$ (155.16) Calcd.: C 46.45 H 5.85 N 27.08 found: C 47.12 H 5.78 N 27.95.

3S,5S-5-(N-t-Butoxycarbonyl)aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (7b)

From **6b** (300 mg, 1.93 mmol), Boc_2O (465 mg, 2.13 mmol) and Pd/C 10% (40 mg) as described for **7a**. Yield: 332 mg (75%).- $[\alpha]_D^{20}$: +20.1 (c=0.3, $CHCl_3$).- IR (KBr) : 3380, 2980-2880, 1760, 1710, 1510, 1170 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ(ppm)= 1.28 (3H,d,CH_3, $J_{Me,3}$= 7.2 Hz), 1.46 (9H,s,t-Butyl), 1.58 (1H,td,H-4, J_{gem}= 12.5 Hz, $J_{4,3trans}$= 12.0 Hz, $J_{4,5trans}$= 12.0 Hz), 2.46 (1H,ddd,H-4, J_{gem}= 12.5 Hz, $J_{4,3cis}$= 8.8 Hz, $J_{4,5cis}$= 5.7 Hz), 2.69 (1H,m,H-3, $J_{3,Me}$= 7.2 Hz, $J_{3,4trans}$= 12.0 Hz, $J_{3,4cis}$= 8.8 Hz), 3.23 (1H,td,H-6, J_{gem}= 14.7 Hz, $J_{6,5}$= 6.2 Hz, $J_{6,NH}$= 6.2 Hz), 3.56 (1H,ddd,H-6, J_{gem}= 14.7 Hz, $J_{6,NH}$= 6.3, $J_{6,5}$= 2.8 Hz), 4.48 (1H,m,H-5, $J_{5,6}$= 6.2,6.2 Hz, $J_{5,4cis}$= 5.7 Hz, $J_{5,4trans}$= 12.0 Hz), 4.93 (1H,s,NH).- $C_{11}H_{19}O_4N$ (229.28) Calcd.: C 57.63 H 8.35 N 6.11 found: C 57.72 H 8.51 N 5.95.

3R,5R-5-(N-t-Butoxycarbonyl)aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone (ent 7b)

From **ent 6b** as described for **7a**. Yield: 434 mg (98%).- $[\alpha]_D^{20}$: -19.7 (c=0.4, $CHCl_3$).- $C_{11}H_{19}O_4N$ (229.28) Calcd.: C 57.63 H 8.35 N 6.11found: C 57.34 H 8.62 N 5.92.

3S,5S-5-Aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone-hydrochloride (8b)

From **7b** as described for **8a**. Yield: 234 mg (72%).- mp.: 202°C (CH_3CN/EtOH).- $[\alpha]_D^{20}$: +54.4 (c=0.4, MeOH).- IR (KBr): 3160, 2700, 2030, 1760, 1610, 1200 cm^{-1}.- ^{1}H-NMR (MeOD): δ(ppm)= 1.25 (3H,d,CH_3, $J_{Me,3}$= 7.0 Hz), 1.65 (1H,td,H-4, J_{gem}= 12.4 Hz, $J_{4,3trans}$= 12.1 Hz, $J_{4,5trans}$= 12.1 Hz), 2.61 (1H,ddd,H-4, J_{gem}= 12.4 Hz, $J_{4,3cis}$= 6.7 Hz, $J_{4,5cis}$= 3.7 Hz), 2.90 (1H,m,H-3, $J_{3,Me}$= 7.0 Hz, $J_{3,4trans}$= 12.1Hz, $J_{3,4cis}$= 6.7 Hz), 3.13 (1H,dd,H-6, J_{gem}= 13.7 Hz, $J_{6,5}$= 8.8 Hz), 3.35 (1H,dd,H-6, J_{gem}= 13.7 Hz, $J_{6,5}$= 2.9 Hz), 4.69 (1H,m,H-5, $J_{5,6}$= 2.9,8.8 Hz, $J_{5,4cis}$= 3.7 Hz, $J_{5,4trans}$= 12.1 Hz).- ^{13}C-NMR (MeOD): δ(ppm)= 15.1 CH3, 34.9 C-4, 36.5 C-3, 44.3 C-6, 75.8 C-5, 180.5 C-2..- $C_6H_{12}O_2NCl$ (165.62) Calcd.: C 43.51 H 7.30 N 8.46 found: C 43.20 H 7.25 N 8.61.

3R,5R-5-Aminomethyl-3-methyl-4,5-dihydro-2(3H)-furanone-hydrochloride (ent 8b)

From **ent 7b** as described **8a**. Yield: 244 mg (75%).- mp.: 201°C (CH_3CN/Aceton).- $[\alpha]_D^{20}$: -58.7 (c=0.2, MeOH).- $C_6H_{12}O_2NCl$ (165.62) Calcd.: C 43.51 H 7.30 N 8.46 found: C 43.40 H 7.40 N 8.72.

2S,4S-5-Amino-4-hydroxy-2-methyl-pentanoic acid (9b)

8b (150 mg, 0.91 mmol) was treated in the same manner as described for **9a**. Yield: 65 mg (49%).- mp.: 162°C (CH_3CN/MeOH).- $[\alpha]_D^{20}$: +19.4 (c=0.3, H_2O).- IR (KBr): 3120, 2960, 1570, 1460, 1390, 1080 cm^{-1}.- ^{1}H-NMR (MeOD/D_2O): δ(ppm)= 1.11 (3H,d,CH_3, $J_{Me,2}$= 6.9 Hz), 1.50 (1H,td,H-3, J_{gem}= 14.0 Hz, $J_{3,2}$= 5.7 Hz, $J_{3,4}$= 5.7 Hz), 1.82 (1H,td,H-3, J_{gem}= 14.0 Hz, $J_{3,2}$= 7.8 Hz, $J_{3,4}$= 7.8 Hz), 2.39 (1H,m,H-2, $J_{2,Me}$= 6.9 Hz, $J_{2,3}$= 5.7, 7.8 Hz), 2.84 (1H,dd,H-5, J_{gem}= 13.0 Hz, $J_{5,4}$= 9.3 Hz), 3.12 (1H,dd,H-5,J_{gem}= 13.0 Hz, $J_{5,4}$= 3.1 Hz), 3.65 (1H,m,H-4, $J_{4,3}$= 5.7,7.8 Hz, $J_{4,5}$= 3.1,9.8 Hz).- ^{13}C-NMR (MeOD/D_2O): δ(ppm)= 18.6 CH_3, 39.9 C-3, 40.0 C-2, 45.7 C-5, 67.3 C-4, 185.5 C-1.- MS (FAB): m/z= 148 [M+H^+, 47.4%], 240 [M+H^++Glycerin, 5.1%].- $C_6H_{13}O_3N$ (147.17) Calcd.: C 48.97 H 8.84 N 9.45 found: C 48.72 H 8.55 N 9.38.

2R,4R-5-Amino-4-hydroxy-2-methyl-pentanoic acid (ent 9b)

From **ent 8b** as described **9b**. Yield: 92 mg (69%).- mp.: 158-162°C (CH_3CN/MeOH).- $[\alpha]_D^{20}$: -16.8 (c=0.4, H_2O).- $C_6H_{13}O_3N$ (147.17) Calcd.: C 48.97 H 8.84 N 9.45 found: C 46.85 H 8.45 N 9.30.

Acknowledgement: We thank the DFG (Deutsche Forschungsgemeinschaft) for financial support (He 1513/2-3), the Fonds der Chemischen Industrie for generous grant and Degussa AG Hanau for D-glutamic acid. Dr. O. Seligmann, Institut für Pharmazeutische Biologie der Universität München provided valuable mass spectroscopic measurments. Mrs. A. Betz, University of Würzburg, is thanked for preparation of starting materials.

References and Notes

1. a) Part II: C. Herdeis and D. Waibel, Arch. Pharm. (Weinheim) **1991**, 324, 269-274. b) U. Kristiansen, A. Hedegaard, C. Herdeis, T. M. Lund, B. Nielsen, J. J. Hansen, E. Falch and P. Krogsgaard-Larsen, J. Neurochem. **1992**, 58, 1150-1159.

2. a) W. Ziegelgänsberger and M. Hausser in GABA: Basic Research and Clinic Applications, Ed. G. Nisticò and N. G. Bowery, Pythagora Press, Rome-Milan **1989** 59-101. b) P. Krogsgaard-Larsen, H. Hjelds, E. Falch, F. S. Jørgensen and L. Nielsen, Adv. Drug Res. **1989**, 17, 382-445.

3. Chiral pool synthesis of R(-) Baclofen: C. Herdeis and H. P. Hubmann, Tetrahedron: Asymmetry, **1992**, 3, 1213-1221.

4. R. H. Prager, D. I. B. Kerr, J. Chiefari, S. Galanopoulos and W. K. Janowski, Aust. J. Chem. **1987**, 40, 1511-1518. A. J. Cross, I. N. Robinson, A. R. Green, J. M. Toczek and B. R. Boar, Br. J. Pharmacol. **1989**, 98, 833-840. R. G. Hall, Synthesis **1989**, 6, 442-443. D. I. B. Kerr, J. Ong, R. H. Prager, B. D. Gynther and D. R. Curtis, Brain Research, **1987**, 405, 150-154.

5. D. I. B. Kerr, J. Ong, A. R. Johnston, J. Abbenante and R. H. Prager, Neurosci. Lett. **1988**, 92, 92-96.

6. H. R. Olpe, G. Karlsson, M. F. Pozza, F. Brugger, M. Steinmann, H. van Riezen, G. Fagg, R. G. Hall, W. Froestl and H. Bittiger, Eur. J. Pharmacol. **1990**, 187, 27-38. P. C. Waldmeier, Naunyn-Schmiedeberg's Arch. Pharmacol. **1991**, 343, 173-178.

7. T. Klockgether U. Wüllner, M. Schwarz and K.-H. Sontag, Brain Research, **1987**, 422, 129-139. M. Schwarz, T. Klockgether, U. Wüllner, L. Turski and K.-H. Sontag, Exp. Brain Res. **1988**, 70, 618-626.

8. C. Herdeis, Synthesis **1986**, 3, 232-233.

9. The enantiomeric excess of **S-1** (**R-1**), **4a** (**ent-4a**), **4b** (**ent-4b**) was determined by GC on a Lipodex D (25mx0.25 mm) column (Macherey and Nagel). The e.e. values were greater than 98%. The $[\alpha]_D^{20}$ values of **S-1** (**R-1**) differ considerably in the literature[10]. Accuracy should be applied to the nitrosation of S(R)-glutamic acid[10]. The (S)-5-oxo-tetrahydrofurane-2-carboxylic acid must be crystallized[8] ($[\alpha]_D^{20} = +15.8$-16.0 (c = 2,EtOH). The Organic Synthesis procedure (**1985**, 63, 121-126) is not recommended by us.

10. a) S. Hanessian and P. J. Murray, Tetrahedron, **1987**, 43, 5055-5072. b) see ref. **8**. c) R. M. Silverstein, U. Ravid and L. R. Smith, Tetrahedron, **1978**, 34, 1449-1452.. d) J. C. Harmange, B. Frigadère and R. Hocqumiller, Tetrahedron: Asymmetry, **1991**, 2, 347-350. e) J. P. Vigneron, R. Méric, M. Larchevêque, A. Debal, J. Y. Lallemand, G. Kunesch, P. Zagetti and M. Gallois, Tetrahedron, **1984**, 40, 3521-3529.

11. a) K. Tomioka, Y.-S. Cho, F. Sato,and K. Koga, J. Org. Chem. **1988**, 53, 4094-4098. b) S. Hanessian, P. J. Murray, S. P. Sahoo, Tetrahedron Lett. **1985**, 26, 5623-5626.

12. Private communication from P. Krogsgaard-Larsen.