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# ENANTIOSPECIFIC SYNTHESIS OF QUISQUALIC ACID

C. GUIBOURDENCHE, M.L. ROUMESTANT*, Ph. VIALLEFONT

**Laboratoire Aminoacides et Peptides URA 468 Universite MONTPELLIER II**
**34095 MONTPELLIER Cedex 5**

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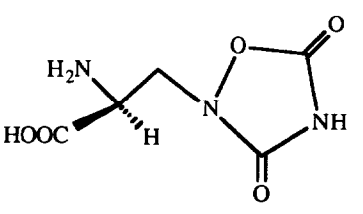
**Abstract :** A new enantiospecific route to (R)- or (S)-Quisqualic acid is established starting from (R)- or (S)-serine.

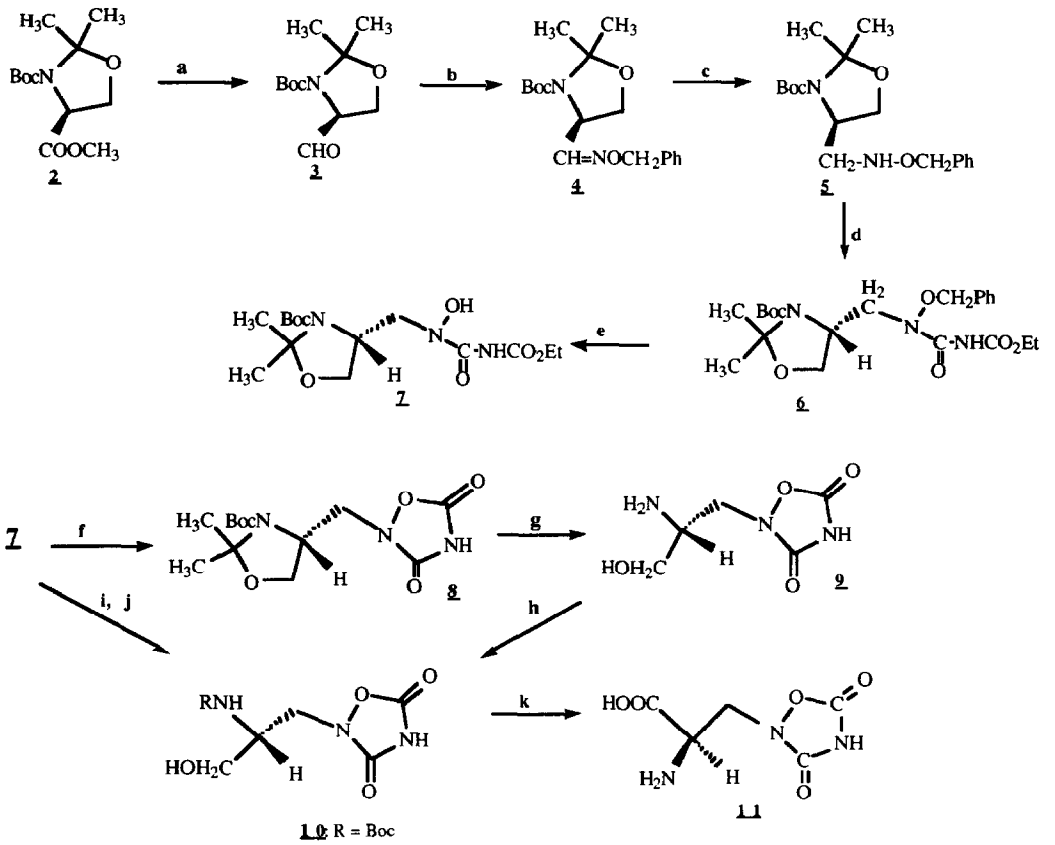
**Introduction :** L-Glutamic acid is one of the major neurotransmitters in the mammalian central nervous system (CNS) and peripheral neurons of invertebrates. The development of selective agonists and antagonists has permitted the classification[1] of excitatory amino acid (EEA) receptors into four ionotropic receptors : NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or Quisqualate, Kaïnate, L-AP4 (L-2-amino-4-phosphonobutanoate) and metabotropic receptors. One of these last receptors coupled to the generation of inositol 1,4,5 triphosphite (IP3) and the mobilization of intracellular $Ca^{2+}$ is activated by quisqualate and not by AMPA. This classification is not definitive and will probably need to be revised in the future in response to the ever-growing interest and the consequent rapid increase in knowledge in this field. Recent studies demonstrated that the receptors of L-Glu took part in the acquirement of memory and learning. Neurodegeneration sickness, HUNTINGTON's and ALZHEIMER's diseases could arise from the abnormal function of the glutamatergic systems[2].

Chemistry has played a very prominent role in the development of the excitatory amino acid field and as part of a program aimed to the synthesis of compounds for better knowledge of metabotropic receptors, we planned to prepare quisqualic acid and several analogues[3]. L-Quisqualic acid 1 , a natural α-amino acid, first isolated from seeds of "Quisqualis indica" is able to function as an agonist at mutiple EAA receptor subtypes in the CNS ; it has a high affinity for kaïnate[4], AMPA[5] and the metabotropic receptors[6]. To our knowledge, two syntheses [7] of chiral Quisqualic acid have been published and in this letter we report our results on this topic.




1

The synthesis of 1 is summarized in the following scheme :



a) Diisobutyl aluminium Hydride, Toluene, -90°C, 86% ;b) $HCl.H_2NOBn$, $C_5H_5N$, 95% ; c) $NaBH_3CN$, $CH_3CO_2H$, 76% d)$OCNCO_2CH_2CH_3$, THF, 100% ;e) $H_2$, PdC 10%, MeOH, 95% ;f) 3.5N NaOH, Dioxane, 78% ;g )a) HCl/Dioxane 4N ; b) Propylene oxide, MeOH, 100% ; h) $Boc_2O$, $H_2O$/THF/Dioxane, $NaHCO_3$, 92% ; i ) Amberlyst, MeOH, 36h ; j) 3.5N NaOH, Dioxane, 46% ;k) a) $RuCl_3$, $NaIO_4$, $CH_3CN/H_2O/CCl_4$ , 95%; b) $CF_3COOH$, Dowex 50 X8, 54%

**RESULTS :** Starting from commercially available Boc-L-serine and according to GARNER's method[8] the acetonide **2** was obtained in 82% yield which after reduction with DIBAL led to the aldehyde **3** in 86% yield. The oxime **4** (95%), easily prepared by reaction of *O*-benzylhydroxylamine in pyridine, was reduced by sodium cyanoborohydride in acetic acid at room temperature to give **5** in 76% yield. Ethoxycarbonylisocyanate reacted quantitatively with **5** to give **6** ; after cleavage of the benzyl goup by hydrogenolysis, **7** was obtained in 90% yield. From **7** two routes have been explored : the first one consists in cleavage of the acetonide by amberlyst resin without affecting the BOC group and cyclisation to the heterocycle : 1,2,4-oxazolidine-3,5-dione. In the second strategy, cyclisation was performed before cleavage of the acetonide ; **7** under basic

conditions (3,5 N NaOH) afforded **8** in 78% yield. For the cleavage of the acetonide several experimental conditions have been checked (for example : Dowex 50 WX8 in MeOH, 1N HCl in THF at room temperature or at 40°C, pTsOH in Acetone or MeOH) without success ; the starting product was recovered or degraded ; **8** treated by Amberlyst in MeOH at room temperature during 24 h led to **9** in 51% yield. Oxidation of the Boc amino alcohol **10** was achieved using $RuCl_3$ / $NaIO_4$[9] in $H_2O$ / $CH_3CN$ / $CCl_4$ in 95% yield ; Jone's reagent, Pyridinium dichromate or $KMnO_4$ in $H_2O$[10] didn't work. Deprotection of Boc amino acid with $CF_3COOH$ gave D-quisqualic acid in 54% yield. D-quisqualic acid was obtained from Boc-L-serine with a 17% overall yield ; from Boc-D-serine, L-quisqualic acid can be obtained.

**Experimental :**

Reagents and solvents were purified in the usual way. Spectra were recorded with the following instruments : 1H NMR : Varian EM 360 and Brucker 250, 13C NMR : Brucker 250 ; Mass Spectra : Jeol JMS D X 100 and D X 300. Optical rotations were determined with a Perkin Elmer model 141 polarimeter.

According to GARNER's[8] method, the acetonide **2** was obtained in 82% yield. S configuration $[\alpha]_D$= -54 ( c 2.59 , $CHCl_3$ ). lit. 70% , $[\alpha]_D$ = -46.7 (c 1.30, $CHCl_3$).This product was also prepared by an other method : To Boc serine methyl ester (22.6 mmol, 4.95 g) dissolved in dichloromethane (45.4 ml) was added p.toluenesulfonic acid (22 mg). The solution was refluxed during 4 h, MeOH being trapped by 4 Å molecular sieves . The solvent was evaporated, the residue dissolved in ether, washed by saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated. The oily residue was chromatographed over silicagel ( ether / hexane 1 / 1 ). Yield = 78% : $^1$H NMR ($CDCl_3$): 1.34 (s, 9H) ; 1.55 (s, 3H) ; 1.67 (s, 3H) ; 3.8 (s, 3H) ; 4.12 (m, 2H) ; 4.42 (m, 1H).

The aldehyde **3** was obtained following GARNER's[8] method : Yield = 86% .S configuration $[\alpha]_D$ = -89.4 (c 1.04, $CHCl_3$). lit. 76%, $[\alpha]_D$ = -91.7 (c 1.34, $CHCl_3$). $^1$H NMR ( $CDCl_3$) : 1.51 (s, 9H) ; 1.55 (s, 3H) ; 1.69 (s, 3H) ; 4.12 (m, 3H) ; 9.5 (s, 1H). MS : $[M+H]^+$ = 230

Synthesis of **4** :

The aldehyde **3** (3.47 mmol, 0.9 g) was dissolved in anhydrous pyridine (4 ml) and *O*-benzylhydroxylamine (1.05 mmol, 0.17 g) was added in small portions. The mixture was stirred 5h at room temperature, pyridine was evaporated under vacuum, the residue taken in water and extracted three times with ether. The organic layers were dried ($MgSO_4$) concentrated and the precipitate chromatographed over silicagel (ether/hexane : 1/1). Yield = 95% ; m.p. = 48°C (ether / hexane). R configuration $[\alpha]_D$ = -29.06 (c 0.86, $CHCl_3$). $^1$H NMR ($CDCl_3$) : 1.43 (s, 9H) ; 1.51 (s, 3H) ; 1.58 (s, 3H) ; 4.04 (m, 3H) ; 4.49 (m, 1H) ; 5.1 (s, 2H) ; 7.28 (s, 5H) MS : $[M+H^+]$ = 335

Synthesis of **5** :

Under $N_2$, to the oxime **4** (5.08 mmol, 1.7 g) dissolved in acetic acid (55 ml) was added $NaBH_3CN$ (8.37 mmol, 0.55 g) in small portions and the mixture was stirred 4h at room temperature. Water was added to obtain a cloudy solution which was basified to pH = 9 by addition of NaOH pellets. After extraction with ether, the organic layers were dried ($MgSO_4$) concentrated and the residue chromatographed over silicagel (ether / hexane

1 / 1). Yield = 76%. R configuration [ α ]$_D$ = -6.92 (c 1.156, $CHCl_3$). $^1$H NMR ($CDCl_3$) : 1.49 (s, 12H) ; 1.55 (s, 3H) ; 3.06 (m, 2H) ; 3.94 (m, 3H) ; 4.68 (s, 2H) ; 7.4 (s, 5H). MS : $[M+H]^+$ = 337

Synthesis of **6** :

Under $N_2$, to the compound **5** (3.9 mmol, 1.31 g) dissolved in anhydrous THF (75 ml) was added dropwise ethoxycarbonylisocyanate (4.3 mmol, 0.43 ml). The mixture was stirred 24h at room temperature and the solvent evaporated to furnish **6** in quantitative yield. R configuration [ α ]$_D$ = +6.42 (c 1.245, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$) : 1.28 (t, 3H, J = 14 Hz) ; 1.53 (s, 12H) ; 1.6 ( s, 3H) ; 3.95 (m, 5H) ; 4.21 (q, 2H, J = 8 Hz) ; 4.91 (s, 2H) ; 7.48 (s, 5H) ; 7.46 (s, 1H). MS : $[M+H]^+$ = 452.

Synthesis of **7** :

To compound **6** (2.08 mmol, 0.98 g) dissolved in MeOH (30 ml) was added Pd/C 10% (0.14 g), the solution was stirred under $H_2$ (atm. pressure) until absorption of the requisite quantity (47 ml). After filtration through celite, the catalyst was washed with MeOH and the solvent evaporated. Yield = 95% m.p. = 120°C (Ether). R configuration. [α]$_D$ = -6.06 ( c 0.99, $CHCl_3$). MS : $[M+H]^+$ = 362. $^1$H NMR ($CDCl_3$) : 1.3 (t, 3H, J = 14 Hz) ; 1.37 (s, 12H,) ; 1.62 (s, 3H) ; 4.2 (m, 7H) ; 8.2 (s, 1H). Anal. Calcd for $C_{15}H_{27}N_3O_7$ : C, 49.86 ; H, 7.48 ; N, 11,63 Found : C, 49.87 ; H, 7.74 ; N, 11.41

Synthesis of **8** :

To a solution of **7** (0.27 mmol, 0.1 g) in dioxane (5 ml) at 0°C was added slowly under stirring 3.5 N NaOH (0.55 mmol, 0.16 ml). The mixture was stirred at 0°C during 15 min. and 7h at room temperature. The solvent was evaporated, the residue taken up in water and the aqueous solution acidified to pH = 5 with 1N HCl. The solution was extracted with ethyl acetate, the organic layers dried ($MgSO_4$) and the solvent evaporated to yield a white solid (78%). m.p. = 179-181°C ( EtOAc / Hexane). R configuration [ α ]$_D$ = -16.54 (c 1.028, $CH_2Cl_2$). MS : $[M+H]^+$ = 316. $^1$H NMR ($CDCl_3$) : 1.52 (s, 12H) ; 1.61 (s, 3H) ; 4.03 (m, 5H). Anal. Calcd for $C_{13}H_{21}N_3O_6$ : C, 49.52 ; H, 6.66 ; N, 13.33 ; Found : C, 49.34 ; H, 6.85 ; N, 13.10.

Synthesis of **10** :

a) From **7** : To a suspension of Amberlyst resin (10.2 mmol, 2.22 g) in MeOH (32 ml) was added **7** (5.09 ml, 1.84 g). The mixture was stirred 36h at room temperature and the resin subsequently filtered off and washed with MeOH. The solvent was concentrated to give an oily product which was used without purification. Yield = 51%. This product (2.58 mmol, 0.83 g) was dissolved in dioxane, cooled to 0°C and to this was added dropwise (7.74 mmol,2.21 ml) 3.5N NaOH solution. The mixture was stirred 8h at room temperature, the solvent was evaporated and the residue taken in water ; the aqueous solution was acidified (pH=5) with 1N HCl and extracted with ethyl acetate. The organic layers were dried ($MgSO_4$) and concentrated to give a white solid in 46% yield. m.p. = 136-138°C (Acetone / ether). R configuration [ α ]$_D$ = -7.93 (c 1.26, MeOH) ; MS : $[M+H]^+$ = 276. $^1$H NMR ($CD_3COCD_3$) : 1.35 (s, 9H) ; 2.87 (s, 1H) ; 3.69 (m, 2H) ; 3.89 (m, 2H) ; 4 (m, 1H) ; 5.81 (d, 1H, J= 7.03 Hz). $^{13}$C NMR ($CD_3COCD_3$) : 51.05 ($CH_2$) ; 51.32 (CH) ; 63.08 ($CH_2$) ; 79.62 (C-O) ; 152.70 (N-CO-O) ; 156.55 (N-CO-O) ; 157.83 (N-CO-N). Anal. Calcd for $C_{10}H_{17}N_3O_6$ : C, 43.63 ; H, 6.18 ; N, 15.27 ; Found : C, 43.67 ; H, 6.28 ; N, 15.28.

b)From **8** : To a solution of **8** (0.617 mmol, 0.194 g) in dioxane (8.24 ml) at 0°C under stirring was added dropwise a solution of 12N HCl (4.11 ml). The mixture was stirred 30 min. at 0°C and 24h at room

temperature. The solvent was evaporated, the residue taken up in water and extracted with dichloromethane. After evaporation in the presence of toluene the hydrochloride **9** was obtained in quantitative yield. m.p. = 165-167°C (MeOH). R configuration. $[\alpha]_D$= +20.24 (c 1.235, MeOH) ; MS : $[M+H]^+$=176.

Under $N_2$, to a solution of **9** (8.22 mmol, 1.73 g) in MeOH (24 ml) was added propylene oxide (41.1 mmol, 3 ml). The mixture was stirred at room temperature and a precipitate was formed. After filtration, the filtrate was concentrated, taken up in anhydrous ether and stirred for 19h at room temperature to give a precipitate. Yield = 97%

To the aminoalcohol (2 mmol, 0.35 g) dissolved in THF / $H_2O$ / Dioxane (1.15 / 3.15 / 2) was added $NaHCO_3$ (2.6 mmol, 0.35 g) and $Boc_2O$ (2.57 mmol, 0.56 g). The mixture was stirred for 72h at room temperature, the solution concentrated, and the residue taken up in water. This was extracted three times with ethyl acetate (3 x 15 ml), one time with dichloromethane (15 ml) and three times with THF (3 x 15 ml), after saturation of the aqueous layer with NaCl. The organic layers were dried and concentrated. The aqueous layer was acidified (pH=4) with 10% citric acid and extracted with THF (3 x 15 ml). The organic layers were dried and concentrated. Yield = 92%. m.p. = 136-138°C (Acetone / ether) ; MS : $[M+H]^+$ = 276.

Synthesis of **11** :

To a solution of **10** (0.72 mmol, 0.2 g) in $H_2O$ / $CH_3CN$ / $CCl_4$ (2.17 ml / 1.46 ml / 1.46 ml) was added $NaIO_4$ (O.635g) and $RuCl_3$ (0.0037 g). The mixture was stirred for 3 days at room temperature, $CH_3CN$ (1 ml) was added and the solution stirred for a further 11 days. After filtration and washing with $CH_3CN$, the solid was taken up in water and washed with ethyl acetate (5 x 15 ml). The organic layers were dried ($MgSO_4$) and concentrated to give the Boc amino acid without purification in 95% yield. $^1$H NMR ($CD_3COCD_3$) : 1.32 (s, 9H) ; 4.02 (m, 2H) ; 4.45 (m, 1H) ; 6.2 (d, 1H, J= 8.19 Hz).

The Boc amino acid (0.346 mmol, 0.1 g) was dissolved in TFA / $CH_2Cl_2$ (1.73 ml / 1.73 ml). This mixture was stirred 1h30' at room temperature. The solvent was removed under vacuum. This residue was dissolved in water (20 ml) and subjected to ion-exchange chromatography [ Dowex 50W-X8(H)]. The quisqualic acid **11** was obtained in 54% yield. m.p.= 188-189° C ( from $H_2O$ / EtOH) (lit.[11], 187-188°C) [ M+H] $^+$= 190. R configuration $[\alpha]_D$ = -16.5 (c 2.0, 6M HCl ), $[\alpha]_D$ = -16.7 (c 0.6, 6M HCl) [ lit.[11], -17.3 (c 2.0, 6M HCl).

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