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Stereospecific Synthesis of the Enantiomers of Nicotinylalanine, a Neuroprotecting Agent

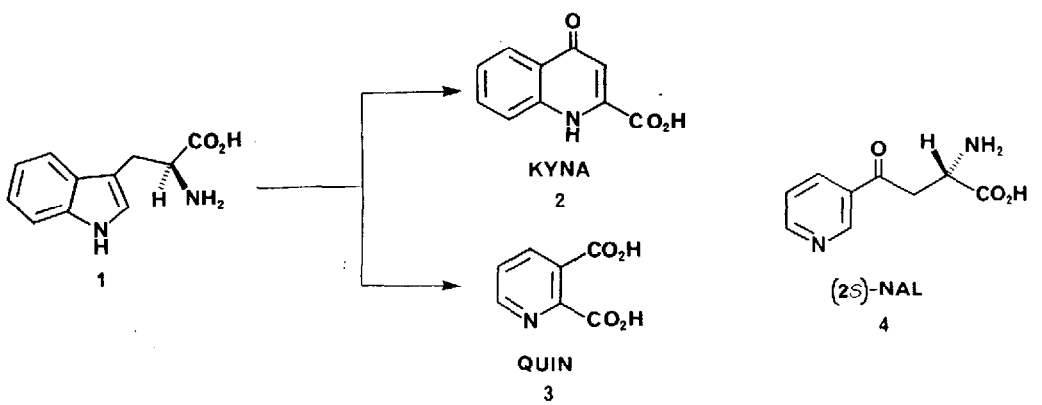
Roberto Pellicciari,* Miguel Angel Gallo-Mezo,+ Benedetto Natalini and Atef M. Amer.++

Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università degli Studi, Perugia, Italy.

Key Words: Stereospecific synthesis, enantiomer, neurodegenerative disorders, neuroprotective, enzyme inhibitor.

Abstract: *Stereospecific synthesis of the title compounds has been achieved in >95% ee by use of palladium-catalyzed cross-coupling of S- and R-(3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)-acetyl chloride, respectively, with 3-trimethylstannyl pyridine at room temperature.*

Kynurenic acid (2, KYNA) and quinolinic acid (3, QUIN), two metabolites on the route from L-tryptophan (1) to nicotinic acid ribonucleotide (kynurenine pathway), exhibit opposite modulatory effects on the N-methyl-D-aspartate (NMDA) receptor-ion channel complex: QUIN is an agonist at the NMDA site and a potent excitotoxin [1] whose abnormal accumulation in brain has been implicated in an array of neurodegenerative disorders such as Huntington's disease, hepatic encephalopathy, acquired immune deficiency syndrome (AIDS)-related disorders and epileptiform activity. KYNA, on the other hand, is a neuroprotective agent which prevents the action of QUIN by interacting as a competitive antagonist with the glycine site of the NMDA receptor.[2]

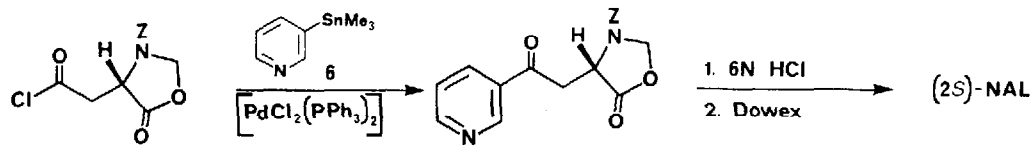


We have previously reported that nicotinylalanine (NAL), an effective inhibitor of the two enzymes kynurenine hydroxylase and kynureninase [3] en route from (1) to (3), prevents the accumulation of QUIN while inducing an increase in KYNA concentration.[4] More recently, the anticonvulsant activity of NAL has also been discovered.[5] In the biological experiments carried out so far, NAL has always been used as a racemate arising from the condensation of acetamidomalonic ester with bromomethyl-3-pyridyl ketone followed by decarboalkoxylation and acid hydrolysis.[6] We herein report the first efficient, stereospecific

+ On leave from Departamento de Quimica Organica, Facultad de Farmacia, 18071 Granada (Spain).

++ On leave from Faculty of Science, Zagazig University, Zagazig (Egypt).

synthesis of both 2*S*- and 2*R*-enantiomers of NAL, achieved by using the organotin/acid chloride coupling methodology first developed by Stille.[7] Thus, a mixture of 3-trimethylstannyl pyridine (**6**)[7b] and *S*-(3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)-acetyl chloride (**5**),[7c] prepared from *S*-aspartic acid, was refluxed for 12 h in dry benzene in the presence of 0.7% mol of dichlorobis(triphenyl-phosphine)palladium (II) [$PdCl_2(PPh_3)_2$] to give the corresponding pyridyl-ketone (**7**) (48% yield) which was converted into the 2*S*-(+)-enantiomer of nicotinylalanine (**4**) (44.6% overall),[8] $[\alpha]_D^{25}$= +18.3 (c = 0.6, H_2O) by hydrolysis with 6N hydrochloric acid followed by Dowex ion exchange resin chromatography.



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Analogously, treatment of (**6**) with *R*-(3-benzyloxycarbonyl-5-oxo-4-oxazolidinyl)-acetyl chloride in the presence of [$PdCl_2(PPh_3)_2$] followed by deprotection gave 2*R*-(-)-nicotinylalanine, $[\alpha]_D^{25}$= -21 (c= 1, H_2O). Optical purity of the final products was assessed by ^{31}P-NMR spectroscopy of the corresponding diastereoisomeric methylphosphonic diamides [9] and was found to be 95-98% ee for each NAL enantiomer.

In summary, the synthetic route described affords the enantiomers of nicotinylalanine in good overall yield and optical purity, thus facilitating more advanced studies of the pharmacological and metabolic properties of this new neuroprotecting agent.

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8. ^1H-NMR (D_2O) δ 3.45 (2H, dd, J= 5 Hz and J= 1 Hz, CH_2); 4.02 1H, dt, J= 5 Hz and J= 1 Hz, CH); 7.33 (1H, dd, J= 7.4 Hz and J= 4 Hz, H-5 Py); 8.19 (1H, dt, J= 7.4 Hz and J= 1.5 Hz, H-4 Py); 8.45 (1H, dd, J= 4 Hz and J= 1.5 Hz, H-6 Py); 8.78 (1H, d, J= 1.5 Hz, H-2 Py); ^{13}C-NMR (D_2O) δ 39.0, 50.4, 124.6, 131.6, 136.9, 148.5, 153.3, 173.1, 198.6.
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