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TETRAHEDRON: *ASYMMETRY*

An efficient and general enantioselective synthesis of some isoxazole-containing analogues of the neuroexcitant glutamic acid

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Abstract

Isoxazole amino acids are an important class of neuroexcitant which are difficult to prepare in enantiopure form. Diastereoselective alkylation of the enantiomerically pure glycine derivative, tert-butoxycarbonyl-2-(tert-butyl)-3-methyl-4-oxo-1-imidazolidinecarboxylate (Boc-BMI) with 4-bromomethyl-2-methoxymethyl-5-methylisoxazolin-5-one **5** or 5-bromomethyl-4-bromo-3-methoxyisoxazole, gives intermediates which under mild hydrolysis conditions produce the amino acids (*S*)- and (*R*)-bromohomoibotenic acid and (*S*)- and (*R*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid with e.e. >99%.

1. Introduction

(*S*)-Glutamic acid [(*S*)-Glu] is well known to be the major excitatory neurotransmitter in the mammalian central nervous system. The actions of (*S*)-Glu are mediated through a diverse set of receptor sub-populations, each defined pharmacologically by the archetypal chemical which selectively activates them. 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid (AMPA) and 2-amino-4-bromo-3-hydroxy-5-isoxazolpropionic acid (Br-homo IBO) are functional bioisosteres of (*S*)-Glu which activate the AMPA glutamate sub-receptor, potently and selectively. As a part of our ongoing program to develop new and efficient routes for the synthesis of α-amino acids and related compounds, we have developed a methodology utilizing Seebach's chiral gycinate imidazolidines[1] for the synthesis of isoxazole-containing amino acids in e.e.s of greater than 99% and overall yields of greater than 55%.

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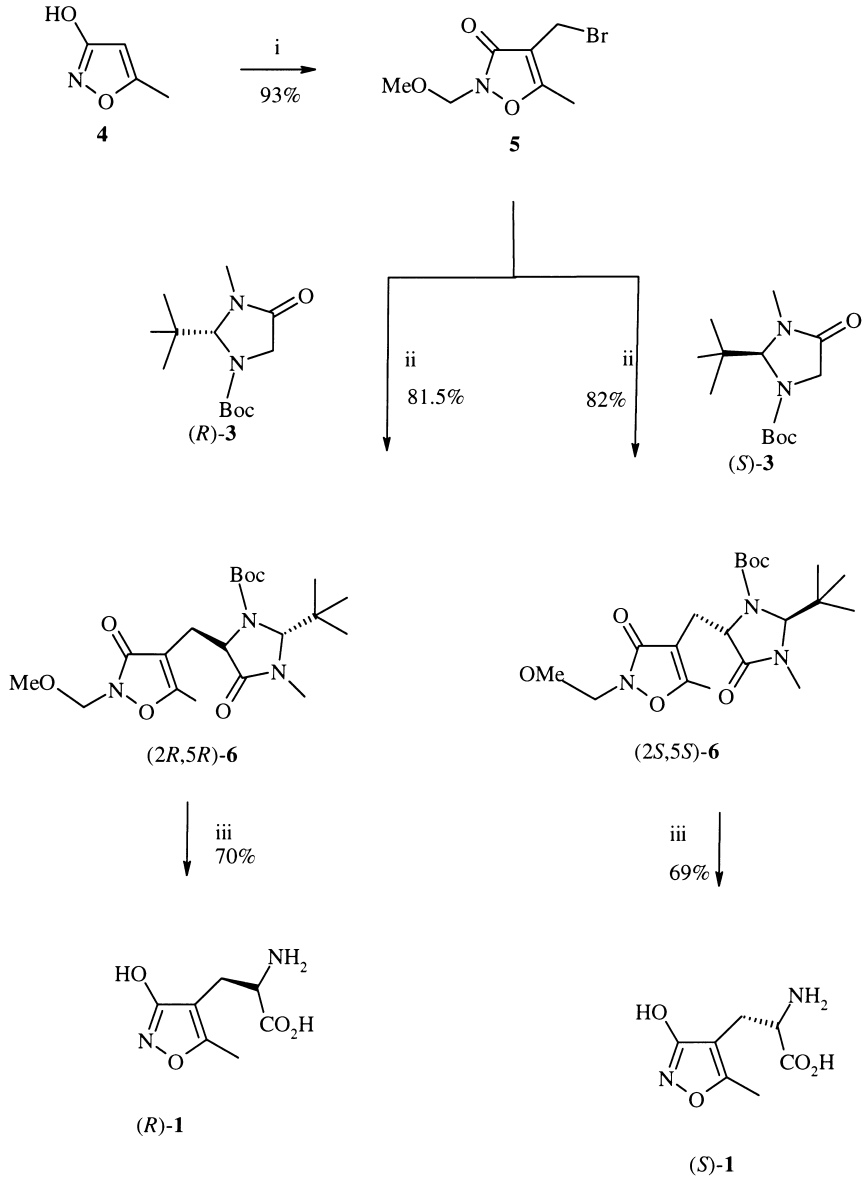
2. Synthesis

The synthesis of (*R*)- and (*S*)-AMPA is shown in Scheme 1. Commercially available 3-hydroxy-3-methylisoxazole **4**, was converted to 4-bromoethyl-2-methoxymethyl-5-methylisoxazolin-3-one **5** by known procedures.[2] The (*R*)- and (*S*)-imidazolidinones **3** were then treated with LDA at −78°C and the resulting enolates were added to **5**. The alkylated products (2*S*,5*S*)-**6** and (2*R*,5*R*)-**6** were purified by flash chromatography to afford the pure derivatives in 82% and 81.5% yields respectively.

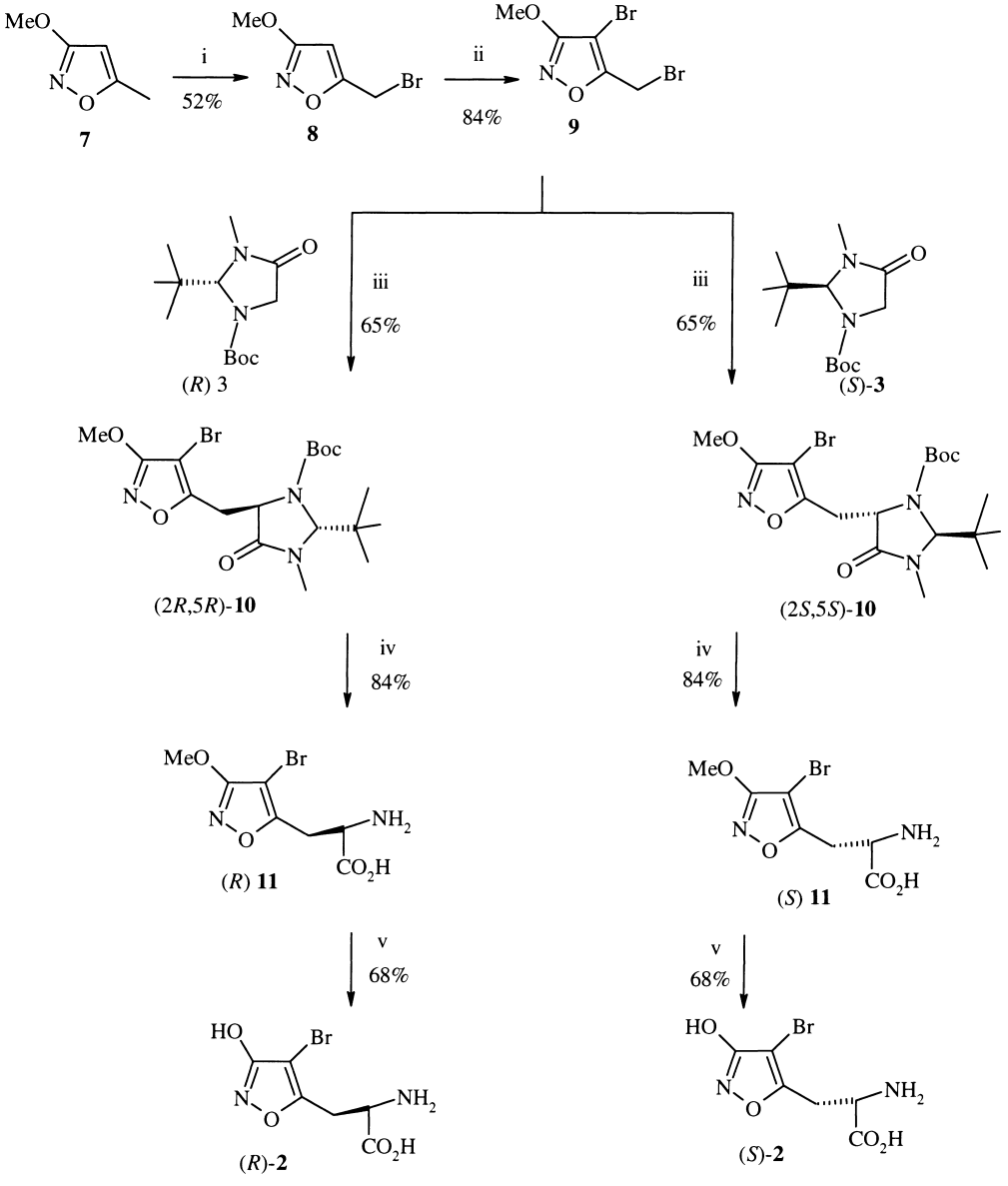


Scheme 1. *Reagents and conditions*: (i) 1,3,5-trioxane, 62% HBr, 60°C 20 h, CH_3OH 2 h, rt; (ii) LDA/THF, −78°C 3 h, NH_4Cl; (iii) TFA, CH_2Cl_2, N_2 rt 15 h, 0.75 M HCl, Dowex 50 WX8-100 ion exchange resin, 48 h reflux

Removal of Boc under anhydrous conditions, followed by mild hydrolysis gave the free (*R*)- and (*S*)-amino acids in 70% and 69% yields respectively with e.e. greater than 99% by chiral HPLC. Specific

rotations: (*R*)-AMPA $[\alpha]_D^{20}$=+23.0 (H_2O, c=0.19) [lit.[3] $[\alpha]_D^{28}$=+19.2 (H_2O, c=0.18)]. Mp 212°C (dec.) [lit.[3] >200°C]. (*S*)-AMPA $[\alpha]_D^{20}$=−25.5 (H_2O, c=0.19) [lit.[3] $[\alpha]_D^{28}$=−21.0 (H_2O, c=0.19)]. Mp 212°C (dec.) [lit.[3] >200°C].

A similar procedure was employed for the synthesis of (*R*)- and (*S*)-Br-homo IBO (Scheme 2). Thus, treatment of 3-methoxy-5-methylisoxazole **7** with N-bromosuccinimide (NBS)[4] produced 5-bromomethyl-3-methoxyisoxazole **8** which on reaction with neat bromine gave 5-bromomethyl-4-bromo-3-methoxyisoxazole **9** in good yield.



Scheme 2. *Reagents and conditions*: (i) NBS, benzoyl peroxide, CCl_4, reflux 24 h; (ii) neat Br_2 rt 6 h; (iii) LDA, THF −78°C, 2 h then r.t 3 h NH_4Cl; (iv) TFA, CH_2Cl_2, N_2, rt 15 h, 0.75 M HCl, Dowex 50 WX8-100 resin, 48 h reflux; (v) 33% HBr/AcOH, rt overnight, then cation exchange column chromatography

Reaction of the imidazolidinones (*R*)- and (*S*)-**3** with **9** produced the alkylated adducts (2*S*,3*S*-**10** and 2*R*,3*R*-**10**) in good yield and with excellent diastereofacial selection.

Analogous deprotection and hydrolysis conditions as employed in the synthesis of (*R*)- and (*S*)-**1**, gave the free amino acids (*R*)- and (*S*)-**11**. Further treatment with 33% AcOH/HBr at room temperature provided (*R*)- and (*S*)-**2** in enantiomerically pure form. Specific rotations: (*R*)-Br-homo IBO $[\alpha]_D^{20}=-11.4$ (50 mM HCl, c=0.40) [lit.[5] $[\alpha]_D^{27}=-10.8$ (50 mM HCl, c=0.40)]. Mp 204°C [lit.[5] 202°C]. (*S*)-Br-homo IBO $[\alpha]_D^{20}=+11.2$ (50 mM HCl, c=0.40) [lit.[5] $[\alpha]_D^{27}=-11.4$ (50 mM HCl, c=0.40)]. Mp 204°C [lit.[5] 202°C].

Structures of all intermediates were confirmed by ^{1}H NMR and the final products were consistent with the spectral data from **3** and **5**, respectively. Chiral HPLC on a Chirex D-penicillamin column showed single peaks for each isomer.

Previous syntheses of the isoxazole amino acids have led to efficient syntheses of racemic mixtures,[2] or inefficient enzymic resolution.[3,5] This general synthetic methodology allows for the synthesis of a wide variety of isoxazole-containing amino acids in multi-gram batches. The yields and stereochemical purities make this the most convenient currently available procedure for production of these important biologically active compounds.

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