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Enantioselective synthesis of both enantiomers of the neuroexcitant 2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl) propanoic acid (ATPA)

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Abstract

The preparation of both enantiomers of 2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl) propanoic acid (ATPA), **1**, an analogue of the neuroexcitant 2-amino-3-(3-hydroxy-5-methyl-4-yl) propanoic acid (AMPA) is described. The enantiomerically pure glycine derivative *tert*-butoxycarbonyl-2-(*tert*-butyl)-3-methyl-4-oxo-1-imidazolidinecarboxylate (BOC-BMI) was coupled with 4-bromomethyl-2-methoxy-methyl-5-*tert*-butylisoxazolin-3-one **6** to give the intermediates (2*R*,5*R*)-**8** and (2*S*,5*S*)-**8**. These alkylated products were hydrolyzed under mild conditions to give enantiopure (*R*)-**1** and (*S*)-**1** with e.e.'s in excess of 99% in 33% overall yield.

1. Introduction

(*S*)-Glutamic acid (*S*-Glu) is now well understood to be the major excitatory neurotransmitter in the mammalian central nervous system. These excitatory responses are mediated through a family of receptor sub-populations, each defined pharmacologically by agonists and antagonists, which selectively activate or block them.

Racemic **1** has been known for many years and was first synthesized in an attempt to obtain structure activity relationship data for AMPA analogues.[1] The racemate itself is not very potent as a neuroexcitant and only recently was it discovered that it was very specific in its interaction with the GluR5 sub-receptor.[2] Since receptor/drug interaction is highly dependent on a number of physico chemical parameters, including stereochemistry, we felt that the enantioselective synthesis of **1** was a priority in order to determine the biological activity. Recently, a separation

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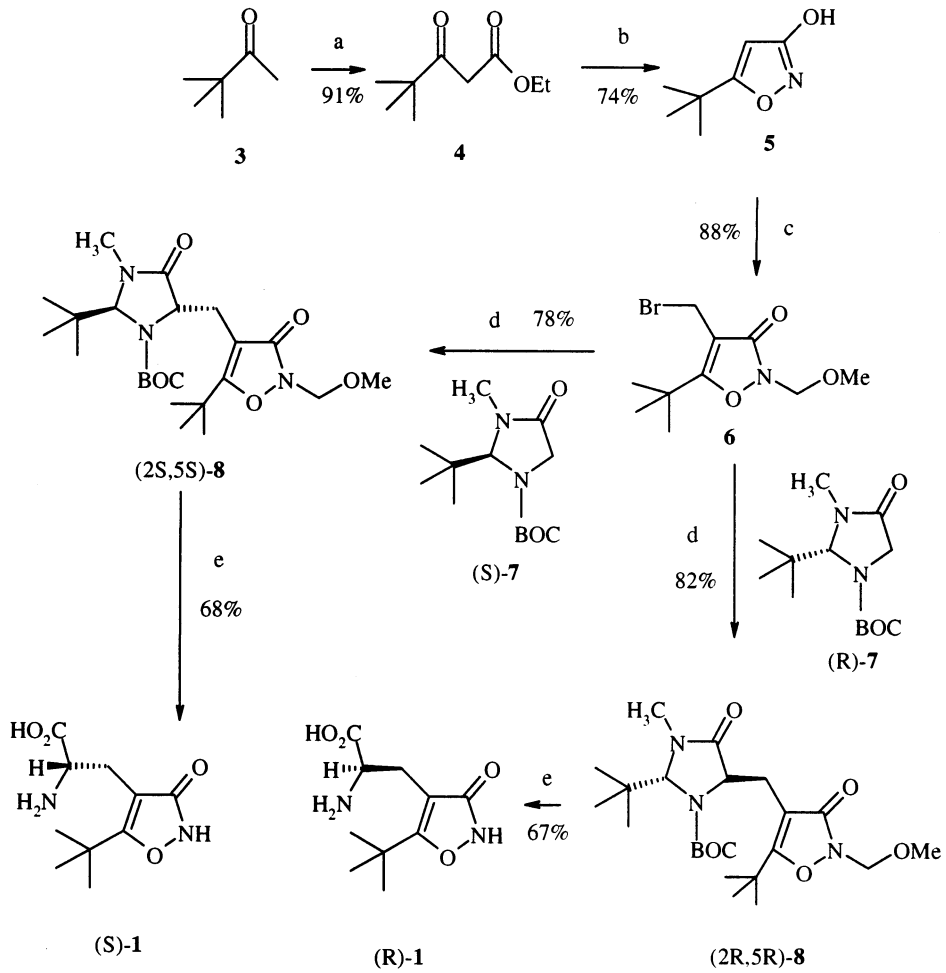
of the enantiomers of **1** and their electrophysiological characterization has been reported.[3] As a part of our ongoing program to develop new and efficient routes for the synthesis of isoxazole containing α-amino acids,[4] herein we describe the enantiospecific synthesis of (*S*)-**1** and (*R*)-**1** in high e.e. and good yield using chiral glycinate imidazolidines.[5]

2. Synthesis

Our synthesis of the (*R*)- and (*S*)-enantiomers of **1** is outlined in Scheme 1. The β-ketoester **4** was prepared from the addition of diethylcarbonate to the pinacolone **3** in the presence of sodium hydride.[6] Treatment of **4** with hydroxylamine under Jacobsen's conditions[7] afforded 3-hydroxy-5-*tert*-butylisoxazole **5** in 74% yield. The isoxazole **5** was subsequently converted to 4-bromomethyl-2-methoxymethyl-5-*tert*-butylisoxazolin-3-one **6** using 62% aqueous HBr and 1,3,5-trioxane by a known procedure.[8]



Scheme 1. *Reagents and conditions*: (a) (i) NaH, diethyl carbonate, HMPA, 50°C, 1 h; (ii) EtOH, H_2O, 6N HCl; (b) (i) $NH_2OH{\cdot}HCl$, H_2O, 2N NaOH, 0°C, −5°C, 2 h; (ii) conc. HCl; (c) (i) 1,3,5-trioxane, 62% HBr, 60°C, 20 h; (ii) CH_2Cl_2, CH_3OH, 2 h, rt; (d) (i) (*R*)-**7** or (*S*)-**7**, LDA, THF, −78°C; (ii) **6**, THF, 2.5 h; (iii) NH_4Cl; (e) (i) TFA, CH_2Cl_2, N_2, rt, 15 h; (ii) 0.75 M HCl, Dowex 50 WX8-100, 48 h, reflux

In separate experiments, each of the (*R*)- and (*S*)-imidazolidinones **7** was treated with LDA, and the resulting enolate added to **6**. The desired alkylated products (2*R*,5*R*)-**8** and (2*S*,5*S*)-**8** were obtained with very high diastereoselectivity (>98%) as determined by ^{1}H NMR (Scheme 1). The adducts (2*R*,5*R*)-**8** and (2*S*,5*S*)-**8** were purified by flash chromatography to afford the pure derivatives in 82 and 84% yield, respectively. Removal of the BOC protecting group using TFA under anhydrous conditions, followed by mildly acidic hydrolysis gave the free (*R*)- and (*S*)-enantiomers in 67 and 68% yield, respectively, and with e.e. greater than 99% by chiral HPLC analysis (Scheme 1). Thus, (*R*)-**1** and (*S*)-**1** were obtained in 33% overall yield from pinacolone over five steps.

In conclusion, we have achieved a simple and high yielding synthesis of both enantiomers of **1**. The methodology described is amenable to scale-up, and we have typically prepared **1** in 2–4.0 g quantities. This general synthetic methodology also allows for the synthesis of other analogues of isoxazole-containing amino acids.

3. Experimental

3.1. General procedures

Melting points are uncorrected. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Bruker AC-200 spectrometer. Optical rotations were obtained on an Optical Activity AA-1000 polarimeter. Isomers were evaluated by chiral HPLC on a Chirex D-Penicilamine column stationary phase and eluting with 1 mM $CuSO_4$ aqueous solution containing 5% methanol. Detection was at 254 nm. Column chromatography was performed using silica gel 60 of 70–230 mesh. THF was dried over benzophenone ketyl under an argon atmosphere and distilled before use. BOC-BMI was synthesized[5] following the procedure of Fitzi and Seebach.

3.2. Synthesis of 3-hydroxy-5-tert-butylisoxazole **5**

To an ice-cold solution of hydroxylamine and hydrochloride (2.4 g 34.7 mmol) in water (10 mL) was added 2 M NaOH (35 ml). Ethyl-4,4-dimethyl-3-oxopentanoate **4** (6.0 g 34.7 mmol) was added slowly and the mixture stirred for 2 h at 0°C. The reaction was quenched by the addition of ice-cold concentrated HCl (10.5 mL) and the mixture placed in the fridge overnight to precipitate crystals of **5**; mp 95–97°C; ^{1}H NMR ($CDCl_3$): 1.20 (s, 9H), 5.45 (s, 1H), 10.70 (br, 1H).

3.3. Synthesis of 4-bromomethyl-2-methoxymethyl-5-tert-butylisoxazolin-3-one **6**

3-Hydroxy-5-*tert*-butylisoxazole **5** (3.0 g, 21.2 mmol) and 1,3,5-trioxane (2.86 g, 31.8 mmol) were placed in a round bottomed flask and 62% aqueous HBr (25 mL) was added. The flask was sealed and stirred at 60°C for 22 h. The mixture was extracted with CH_2Cl_2 (3×30 mL) followed by the addition of methanol (75 mL) to give the crude product. Further addition of CH_2Cl_2 (75 mL) and extraction with water (3×90 mL) followed by drying of the CH_2Cl_2 solution over $MgSO_4$ and evaporation gave **6** as an oil (5.2 g, 88%); ^{1}H NMR ($CDCl_3$): 1.35 (s, 9H), 3.37 (s, 3H), 4.22 (s, 2H), 5.10 (s, 2H). Anal. calcd for $C_{10}H_{16}BrNO_3$: C, 43.18; H, 5.80; Br, 28.73; N, 5.04. Found: C, 43.22; H, 5.77; Br, 28.61; N, 5.01.

3.4. Synthesis of alkylated adducts (2R,5R)-8

n-Butyllithium (1.6 M, 12.2 mmol) was added dropwise to a stirred solution of diisopropylamine (1.72 mL, 12.2 mmol) in THF (15 mL) at −78°C and stirred for 30 min. Maintaining the temperature at −78°C, a solution of BOC-BMI (3.04 g, 11.86 mmol) in THF (12 mL) was added dropwise and stirred continuously for 45 min. A solution of **6** (3.3 g, 11.9 mmol) in THF (10 mL) was then added in one portion and the resulting solution stirred at −78°C for 2 h. The mixture was allowed to warm to −20°C over 1 h and then quenched with saturated NH_4Cl solution and extracted with ether. The organic layers were combined and dried then evaporated to an oil which was subjected to flash chromatography (hexane:ethyl acetate, 1:2). Evaporation of the product band afforded an oil of (2*R*,5*R*)-**8** (4.4 g, 82%); $[\alpha]_D^{25}$+91.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 0.6 (s, 9H), 1.18 (s, 9H), 2.30 (m, 1H), 2.59 (s, 3H), 2.98 (s, 3H), 3.21 (dd, $J=14$, 3, 1H), 3.98 (dd, $J=14$, 3, 1H), 4.63 (s, 1H); ^{13}C NMR ($CDCl_3$): 18.5, 26.5, 28.5, 32.5, 37, 56.5, 73.5, 75, 107, 165.3, 168, 169.3, 172. HRMS calcd for $C_{23}H_{40}N_3O_6$: 454.2838; found: 454.2836. Anal. calcd for $C_{23}H_{39}N_3O_6$: C, 60.89; H, 8.67; N, 9.27. Found: C, 60.81; H, 8.69; N, 9.30.

3.5. Synthesis of (R)-2-amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl) propionic acid (R)-1

A solution of (2*R*,5*R*)-**8** (4.4 g, 9.7 mmol) in CH_2Cl_2 (8 mL) was stirred overnight with TFA (7.2 mL, 96 mmol). Solvent was removed and the residue dissolved in 0.75 M HCl (100 mL) and Dowex 50WX8 resin (16 g) added and the mixture stirred under reflux for 2 days. The resin was placed in a column and the remaining solution evaporated, taken up in water and also placed on the column. The column was washed with water and then with 1 M NH_4OH. The collected eluents were evaporated and the product crystallized from water at pH 3.0 to give (*R*)-**1** (1.48 g 67%); mp 245–247°C dec. (lit. for racemate 246–247°C dec.[1]); $[\alpha]_D^{25}$ −30.0 (*c* 0.20, 0.1N HCl); ^{1}H NMR (D_2O): 1.35 (s, 9H), 1.82 (d, $J=7.1$ Hz, 2H), 3.01 (t, $J=7.1$ Hz, 1H). Anal. calcd for $C_{10}H_{16}N_2O_4 \cdot H_2O$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.54; H, 7.09; N, 11.98.

3.6. (S)-2-Amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl) propionic acid (S)-1

This compound was synthesized in an analogous manner to (*R*)-**1**. Anal. calcd for $C_{10}H_{16}N_2O_4 \cdot H_2O$. Found: C, 52.49; H, 6.97; N, 11.93. $[\alpha]_D^{25}$ +31.0 (*c* 0.21, 0.1N HCl).

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