SYNTHESES OF (2S, 4S)- AND (2S, 4R)-4-SUBSTITUTED GLUTAMIC ACID ANALOGUES FOR NEUROEXCITATORY ACTIVITY STUDIES

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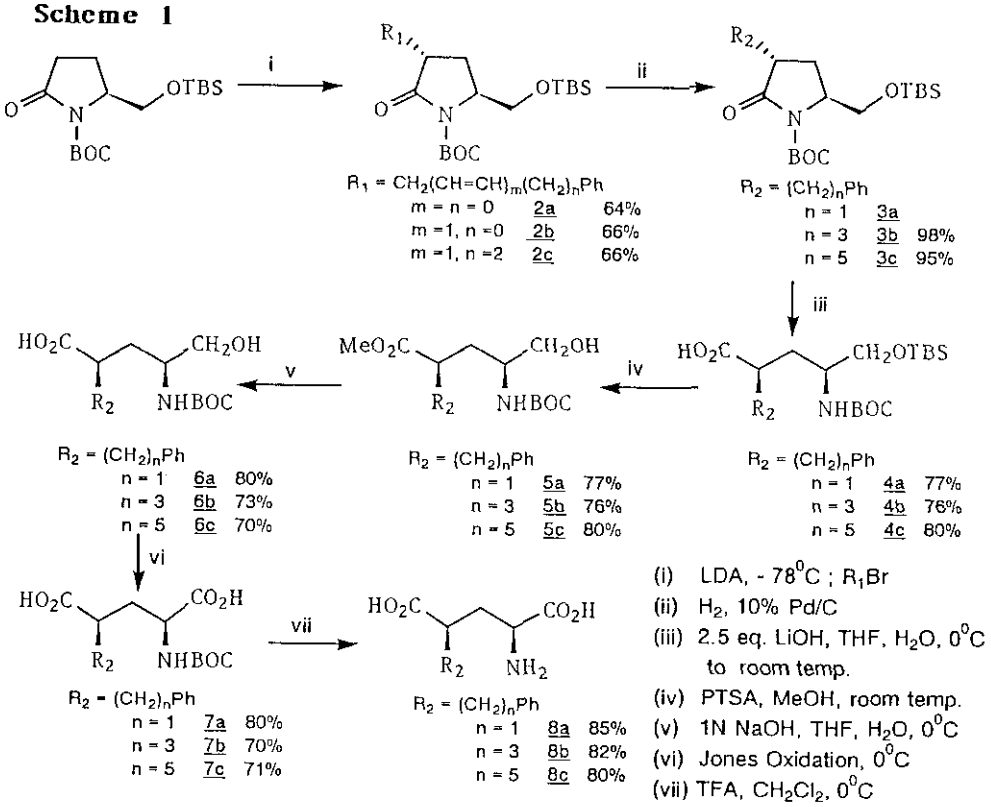
Abstract - The stereospecific syntheses of various length of 4(R)- and 4(S)-substituted 2(S)-glutamic acid were described.

It is widely recognized that glutamic acid (Glu) acts as one of the major neurotransmitters at excitatory synapses in the mammalian central nervous system (CNS).[1,2] This amino acid transmitter and its receptors have also been implicated in the pathogenesis of many CNS disorders,[3] in the genesis of learning and memory processes[4,5] and in the synaptic reorganization that occurs in the CNS as part of the postnatal development.[6,7] Potent and selective Glu analogues that both displace the binding of Glu and reduce its excitatory actions on central neurons are invaluable to extensive studies of the Glu transmission system. Recently Yamanoi and Ohfune synthesized four diastereomers of α-(carboxycylcopropyl)glycines and indicated clear conformation-activity relationship among these synthetic L- glutamate analogues.[8,9] Shirahama et al. also synthesized four configurational isomers of 3-benzylglutamic acid and examined their structure-activity relationships.[10] In this communication, we describe our independent work in synthesizing (2S,4S)- and (2S,4R)-substituted glutamic acids. The advantage of this synthesis is that various length of the substituents can be introduced into the glutamic acid backbone in a general and stereospecific way. Therefore, we can study the importance of both the stereochemistry and chain length at 4-position of glutamic acid in its excitatory effects on the nervous system.

The starting material (S)-(+)-N-t-BOC-5-(tert-butyldimethylsiloxymethyl)-2-pyrrolidinone 1 was readily prepared from (S)-(+)-glutamic acid.[11,13](Scheme 1) Compound 1 was treated with 1.05 molar equivalent LDA in tetrahydrofuran at -78 °C for 30 min and then quenched by benzyl or allyl bromide at the same temperature. This alkylation was highly stereoselective (ca. 15:1). Not only the selectivity will drop to ca. 4:1, but also the dialkylation product will form if the reaction temperature is raised to -25 °C. The substituents on compound (2a-2c) were assigned to be trans to each other since the electrophiles prefer to attack the resulted enoates anti to the bulky tert-

Scheme 1



$R_1 = CH_2(CH=CH)_m(CH_2)_nPh$

m = n = 0	2a	64%
m = 1, n = 0	2b	66%
m = 1, n = 2	2c	66%

$R_2 = (CH_2)_nPh$

n = 1	3a	
n = 3	3b	98%
n = 5	3c	95%

$R_2 = (CH_2)_nPh$

n = 1	4a	77%
n = 3	4b	76%
n = 5	4c	80%

$R_2 = (CH_2)_nPh$

n = 1	5a	77%
n = 3	5b	76%
n = 5	5c	80%

$R_2 = (CH_2)_nPh$

n = 1	6a	80%
n = 3	6b	73%
n = 5	6c	70%

$R_2 = (CH_2)_nPh$

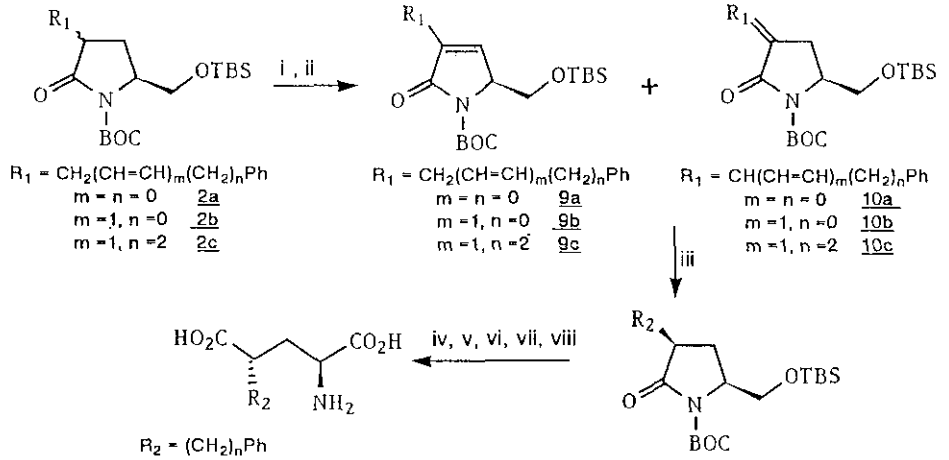
n = 1	7a	80%
n = 3	7b	70%
n = 5	7c	71%

$R_2 = (CH_2)_nPh$

n = 1	8a	85%
n = 3	8b	82%
n = 5	8c	80%

(i) LDA, - 78°C ; R_1Br
(ii) H_2, 10% Pd/C
(iii) 2.5 eq. LiOH, THF, H_2O, 0°C to room temp.
(iv) PTSA, MeOH, room temp.
(v) 1N NaOH, THF, H_2O, 0°C
(vi) Jones Oxidation, 0°C
(vii) TFA, CH_2Cl_2, 0°C

Scheme 2



$R_1 = CH_2(CH=CH)_m(CH_2)_nPh$

m = n = 0	2a
m = 1, n = 0	2b
m = 1, n = 2	2c

$R_1 = CH_2(CH=CH)_m(CH_2)_nPh$

m = n = 0	9a
m = 1, n = 0	9b
m = 1, n = 2	9c

$R_1 = CH(CH=CH)_m(CH_2)_nPh$

m = n = 0	10a
m = 1, n = 0	10b
m = 1, n = 2	10c

$R_2 = (CH_2)_nPh$

n = 1	11a	67% from 2a
n = 3	11b	51% from 2b
n = 5	11c	54% from 2c

$R_2 = (CH_2)_nPh$

n = 1	12a	31% from 11a
n = 3	12b	30% from 11b
n = 5	12c	33% from 11c

(i) LDA, -78°C, PhSeCl (ii) 30% H_2O_2 , 0°C (iii) H_2 , 10% Pd/C (iv) 2.5 eq. LiOH, THF, H_2O 0°C to room temp. (v) PTSA, MeOH, room temp. (vi) 1N NaOH, THF, H_2O, 0°C (vii) Jones Oxidation, 0°C (viii) TFA, CH_2Cl_2, 0°C

butyldimethylsiloxymethyl group.[12-15] The double bonds on compound 2b and 2c were saturated by catalytic hydrogenation in excellent yield. The lactam ring was opened by basic hydrolysis conditions to give compound 4a-4c.[16] The BOC group was removed instead of ring opening if methanolic sodium methoxide was used. The hydroxy ester (5a-5c) was formed when we tried to deprotect the tert-butyldimethylsilyl protecting group in acidic methanolic solution. Therefore, these hydroxy ester needed to be hydrolyzed by aqueous sodium hydroxide solution. The hydroxy acid (6a-6c) was then oxidized to dicarboxylic acid by Jones oxidation.[17a,18] Finally, the BOC group was removed by trifluoroacetic acid.

In order to synthesize (2S,4S)-4-substituted L-glutamic acid (12a-12c), the inversion of the chiral center at 3 position of compound 2a-2c is needed. The standard deprotonation-reprotonation processes were found to be unsuitable for achieving this goal. Therefore, the α,β-unsaturated lactams (9a-9c and 10a-10c) were prepared by the selenenylation-deselenenylation processes[19] (Scheme 2). These compounds were treated with catalytic hydrogenation condition to give compounds 11a-11c as the sole product. The rest steps on Scheme 2 are the same as the one described in Scheme 1.[17b, 20] Effects of these synthetic Glu analogues on the neuromuscular junctions of insects and on mammalian central neurons are under investigation and will be reported later.

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15. The relative stereochemistry of the C-3 and C-5 substituent on compounds 2a-2c was determined on the transition state model described by professor Nozoe in reference 12. The steric repulsion of the tert-butyldimethylsiloxymethyl group and the enolate nitrogen lone pair electrons present on the si-face to the electrophiles may contribute to form the 2a-2c as the predominant products. In the same article, professor Nozoe concluded that the chemical shift of 3-hydrogen on the pyroglutamate ring system will be a little bit downfield (0.2 ppm) for the 3,5-trans-substituent isomer compared to those of the cis-epimer. In our system, the chemical shift of 3-hydrogen of compounds 2a-2c was always 0.1-0.2ppm downfield shift compared to those of compounds 11a-11c. This phenomenon was consistent with Nozoe's observations. Two typical examples showing this chemical shift difference are listed as following:

Compound 2a: nmr ($CDCl_3$) δ 7.15-7.35 (m, 5H), 4.04-4.12 (m, 5H), 3.88 (dd, J=10.4 and 3.9 Hz, 1H), 3.65(dd, J=10.4 and 2.2 Hz,1H), 3.40 (dd, J= 3.1 and 9.8 Hz, 1H), 3.1 (m, 1H), 2.52(dd, J=13.1 and 9.2 Hz, 1H), 1.7-2.1 (m, 2H), 1.54 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H).

Compound 11a: nmr ($CDCl_3$) δ 7.15-7.35 (m, 5H), 4.0-4.13 (m, 1H), 3.89 (dd, J=10.2 and 4.4 Hz, 1H), 3.62 (dd, J=10.2 and 2.2 Hz, 1H), 3.27 (br d, J=10 Hz, 1H), 2.73 (m, 2H*), 1.6-2.1(m,2H),1.52 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H).

*: H-3 and one of the benzylic proton chemical shift were overlapped.

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17. (a) Compounds 7a -7c were treated with CH_2N_2 to give coresponding diesters (13a-13c). It was estimated by hplc (column: Zorbax Sil, 4.6 mm ID x 25 cm, hexane : ethyl acetate = 10:1) that 5-8% epimerization occurred during the oxidation stage.

(b) Compounds 12a-12c were treated with CH_2N_2 to give coresponding diesters (14a-14c). It was estimated by hplc (column: Zorbax Sil, 4.6 mm ID x 25 cm, hexane : ethyl acetate = 10:1) that 5-8% epimerization occurred during the oxidation stage.

18. Compound 13a: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 4.8-5.0(br d, J=7.4 Hz, 1H), 4.2-4.4(m, 1H), 3.61(s, 3H), 3.58(s, 3H), 2.6-2.8(m, 2H), 2.1-2.25(m, 1H), 1.6-1.75(m, 2H), 1.35

(s, 9H).

Compound 13b: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 5.0(br d, J=8.6 Hz, 1H), 4.2-4.4(m, 1H), 3.7(s, 3H), 3.68(s, 3H), 2.5-2.65(t, J=7.4 Hz, 2H), 2.2-2.3(m, 1H),1.4-1.8(m, 15H).

Compound 13c: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 5.0(br d, J=7.3 Hz, 1H), 4.2-4.4(m, 1H), 3.73(s, 3H), 3.69(s, 3H), 2.55-2.65(t, J=7.2 Hz, 2H), 2.2-2.3(m, 1H), 1.2-1.8(m, 19H).

Compound 7b: $[\alpha]_D$ -13.45° (c 0.45, $CHCl_3$).

Compound 7c: $[\alpha]_D$ -14.37° (c 0.70, $CHCl_3$)

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20. Compound 14a: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 4.9-5.0(br d, J=8.3 Hz, 1H), 3.71(s, 3H), 3.57(s, 3H), 2.7-3.0 (m, 3H), 1.9-2.1(t, J= 6.9 Hz, 2H), 1.5(s, 9H).

Compound 14b: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 4.9-5.0(br d, J=6.8 Hz, 1H), 4.2-4.4(m, 1H), 3.71(s, 3H), 3.66(s, 3H), 2.4-2.7(m, 3H), 1.9-2.1(m, 2H), 1.4-1.7(m, 14H).

Compound 14c: nmr ($CDCl_3$) δ 7.1-7.3(m, 5H), 4.9-5.0(br d, J=7.1 Hz, 1H), 4.2-4.4(m, 1H), 3.73(s, 3H), 3.66(s, 3H), 2.4-2.7(m, 3H), 1.9-2.0(m, 2H), 1.2-1.7(m, 17H).

Compound 12a: $[\alpha]_D$ +2.23° (c 1.80, $CHCl_3$).

Compound 12b: $[\alpha]_D$ +7.43° (c 0.54, $CHCl_3$).

Compound 12c: $[\alpha]_D$ +12.30° (c 0.98, $CHCl_3$).

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