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Stereoselective synthesis of (2*S*)-2-hydroxymethylglutamic acid, a potent agonist of metabotropic glutamate receptor mGluR3

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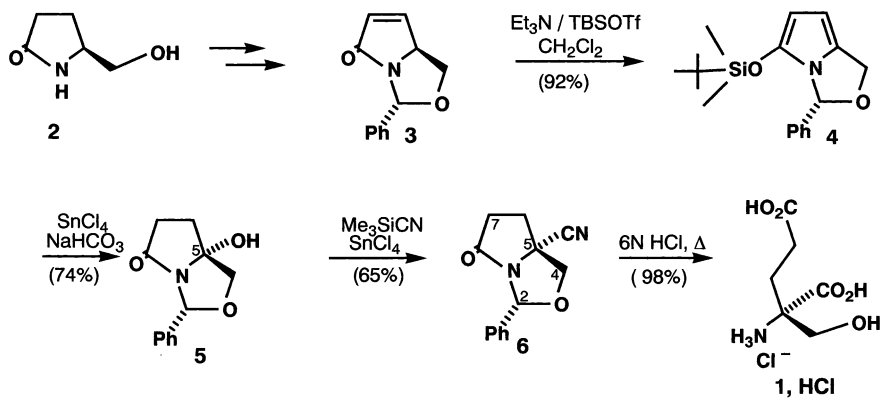
Abstract—Straightforward stereocontrolled synthesis of (2*S*)-2-hydroxymethylglutamic acid was achieved from (*S*)-pyroglutaminol, through a bicyclic silyloxypyrrole derived from the versatile unsaturated lactam **3**.

(*S*)-Glutamic acid (L-Glu) is one of the main excitatory neurotransmitter in the mammalian central nervous system and considerable attention was devoted to the discovery of selective agonists and antagonists of the diverse glutamate receptors. Among them, the metabotropic receptors which can be divided into eight subunits, have been shown to have important functions in neuronal signaling processes.[1] Therefore, numerous substituted glutamates and conformationally constrained analogues have been synthesized in order to better know the roles of these receptors and to modulate the biological activities.[2,3]

A new α-substituted glutamic acid (2*S*)-2-hydroxymethylglutamic acid **1**, was shown to act as a relative potent agonist of mGlu3 and a weak antagonist of mGluR2, both belonging to class II, and the (2*R*) enantiomer was very recently synthesized from serine by Kozikowski et al.[4]

Here we describe a highly diastereoselective synthesis of **1**, from (*S*)-pyroglutaminol **2** as convenient chiral starting material, demonstrating the validity of the route summarized in Scheme 1. This route involved the introduction of a cyano group as the precursor of the carboxylic acid linked to the quaternary stereogenic center.

The rather unstable silyloxypyrrole **4** was easily prepared by treating the α,β-ethylenic bicyclic lactam **3** with a base (2,6-lutidine[5] was advantageously replaced



Scheme 1.

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by triethylamine) and with *tert*-butyldimethylsilyltrifluoromethanesulfonate in dichloromethane. This derivative was already used as donor in vinylogous Mukaiyama-type aldol[6] and in Michael-type[7] reactions. We discovered also that it could lead in acidic medium to a bicyclic C-5 iminium ion of the pyrrolidinone, which could trap a nucleophile. The most efficient substitution at C-5 by this way was obtained with hydroxide anion as the nucleophile and the stable compound **5** was isolated in 74% yield, allowing the further substitution by other nucleophiles in the presence of Lewis acid.[5] The addition of cyanide (with trimethylsilyl cyanide) occurred with the same stereoselectivity as that of hydroxide ion, giving rise to **6** (65%).[8,9]

The *N*,*O*-protective oxazolidine ring of the 5-cyanopyrrolidinone **6** could be selectively cleaved by heating in methanol in the presence of TsOH, keeping intact the nitrile function. The cyano group could be also converted in one pot into carboxylic acid under more drastic conditions by heating in 6N HCl (118°C, 16 h), with concomitant opening of the lactam ring and isolation of the enantiomer (*S*)-**1**, as its hydrochloride in 98% yield.[4]

This work constitutes a straightforward diastereoselective synthesis of (2*S*)-2-hydroxymethylglutamic which could be extended to more substituted and more complex analogues to evaluate their activity on mGluRs.

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9. Selected data of **6**: mp 118°C; $[\alpha]_D^{23}=+131$ (*c* 0.40, $CHCl_3$); IR: 3028, 2220 (weak), 1727, 1460, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, $\delta=0$: TMS): 7.54 (2H, H-Ar), 7.42 (m, 3H, H-Ar), 6.34 (s, 1H, H-2), 4.48 (d, 1H, $J_{4a,4b}=9$ Hz, Ha-4), 3.84 (d, 1H, $J_{4a,4b}=9$ Hz, Hb-4), 3.07 (m, 1H), 2.76 (m, 1H), 2.62 (m, 1H), 2.35 (m, 1H); H_2-7, H_2-6; ^{13}C NMR: 176.5 (CO), 136.1 (qC, Ar), 129.4 (CH, Ar), 128.7 (CH, Ar), 126.5 (CH, Ar), 119.6 (CN), 89.7 (C-2), 75.6 (C-4), 61.9 (C-5), 33.1 (C-7), 30.8 (C-6). Anal. calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.64; H, 5.41; N, 12.24.