Stereoselective Synthesis of the Conformationally Constrained Glutamate Analogue, (–)-(2*R*,3*S*)-*cis*-2-Carboxyazetidine-3-acetic Acid, from (*S*)-*N*-Tosyl-2-phenylglycine

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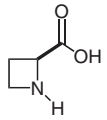
Abstract: The stereoselective synthesis of a novel *cis* conformationally constrained glutamate analogue containing an azetidine framework was accomplished from (*S*)-*N*-tosyl-2-phenylglycine in moderate overall yield. The key steps in the synthesis involved a N–H carbenoid insertion promoted by $Cu(acac)_2$, a very efficient Wittig olefination of an azetidin-3-one, followed by a highly stereoselective rhodium-catalyzed hydrogenation. Epimerization of the *cis* to the *trans* analogue was performed using DBU as base in toluene at reflux.

Key words: azetidin-3-ones, glutamate analogues, N–H insertion, conformationally constrained amino acids, Wittig reaction

Glutamate and aspartate are the predominant excitatory amino acid (EAAs) neurotransmitters in the mammalian brain.[1a,b] These excitatory amino acids activate a family of ligand-gated ion channels, called ionotropic receptors (AMPA, KA and NMDA), and a family of receptors coupled through GTP-binding proteins, called metabotropic receptors, implicated in a variety of intracellular signaling molecules.[2a–2d] EAA receptors participate in fast excitatory transmission as well as in more complex signaling processes, such as those required for synaptic plasticity and higher cognitive functions.[3a–3c] In contrast to these normal signaling pathways, excessive activation of the ionotropic EAA receptors can trigger a cascade of events that eventually leads to neuronal death. This process, referred to as excitotoxicity, is thought to be an underlying pathological mechanism in a wide variety of neurological insults and degenerative disorders, such as ischemia, trauma, hypoglycemia, epilepsy, Huntington's and Parkinson's diseases.[4a–4d]

In the last decades many research groups have been involved with the synthesis of conformationally restricted glutamate and aspartate analogues and the majority of the glutamate analogues synthesized so far display a pyrrolidine ring as their rigid element.[5] Four-membered rings as conformational constraining elements are less common and have been attracting considerable attention lately, especially for their increased rigidity and interesting physiological activities exhibited by four-membered ring containing amino acids.[6] Regarding four-membered amino acids, the naturally occurring (*S*)-azetidine-2-carboxylic acid (Figure 1) represents the prototype of an α-amino acid containing an azetidine motif.



(*S*)-azetidine-2-carboxylic acid

Figure 1

Two illustrative examples of azetidine containing amino acids displaying important biological activities are the chiral glutamate analogues **1** and **2** (Figure 2).[6a–6c] Glutamate **1** has been shown to act as an activator of the metabotropic receptors, whereas analogue **2** appears to be a potent agonist of the kainate receptor, as well as a potent inhibitor of sodium-dependent glutamate uptake.

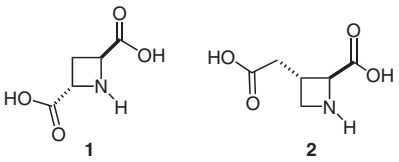


Figure 2 Chiral glutamate analogues displaying biological activity

In spite of several examples of the synthesis of azetidinic amino acids available in the literature,[6] the synthesis of chiral glutamate analogues has been accomplished with rather low stereoselectivity or has been restricted to the synthesis of the *trans*-glutamate analogues.[6a–6c,6i]

Our research group has been involved in the application of azetidin-3-ones as key building blocks for the synthesis of azetidines and azetidine alkaloids. As illustrated in Scheme 1, chiral azetidin-3-ones can be readily prepared from commercially available amino acids, which make them potential intermediates for the synthesis of the *cis*- and *trans*-glutamate analogues. Herein, we report a short stereoselective synthesis of the (2*R*,3*S*) *cis* isomer of glutamate **2** from (*S*)-*N*-tosyl-2-phenylazetidin-3-one (**4**, Scheme 2), and a successful epimerization of the *cis*-glutamate analogue to the *trans* analogue using DBU. This approach extends the applicability of the metal-cata-

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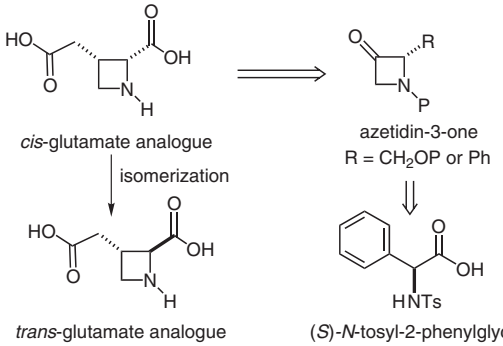


Scheme 1 Strategy to construct the *cis*- and *trans*-glutamate analogues

lyzed N–H insertion methodology commonly used for the preparation of azetidin-3-ones.[7]

We started our synthesis with the preparation of chiral azetidin-3-one **4**[8] (Scheme 2). Based on a previous protocol[9] compound **4** was readily prepared in two steps from (*S*)-*N*-tosyl-2-phenyl glycine in good overall yields. The protocol involved the conversion of N-protected phenyl glycine to the diazoketone **3** in 64% (Scheme 2), followed by the reaction of **3** with $Cu(acac)_2$ in reflux benzene for just one minute to promote the N–H insertion reaction in 50–55% yield.[10]

The azetidin-3-one **4** was then converted to the enoate **5** in quantitative yield by a Wittig olefination reaction[11] using the stabilized ylide carboethoxyethylidene-triphenylphosphorane. Catalytic hydrogenation of enoate **5** was carried out under a variety of conditions aiming at optimization of the stereoselectivity and yield of this key reduction step (Table 1). Hydrogenation using palladium on carbon as catalyst gave only 19% of the desired ester **6** in a diastereomeric ratio of 95:05 for the *cis*:*trans* stereoisomers, together with 81% of some unidentified material.[12]

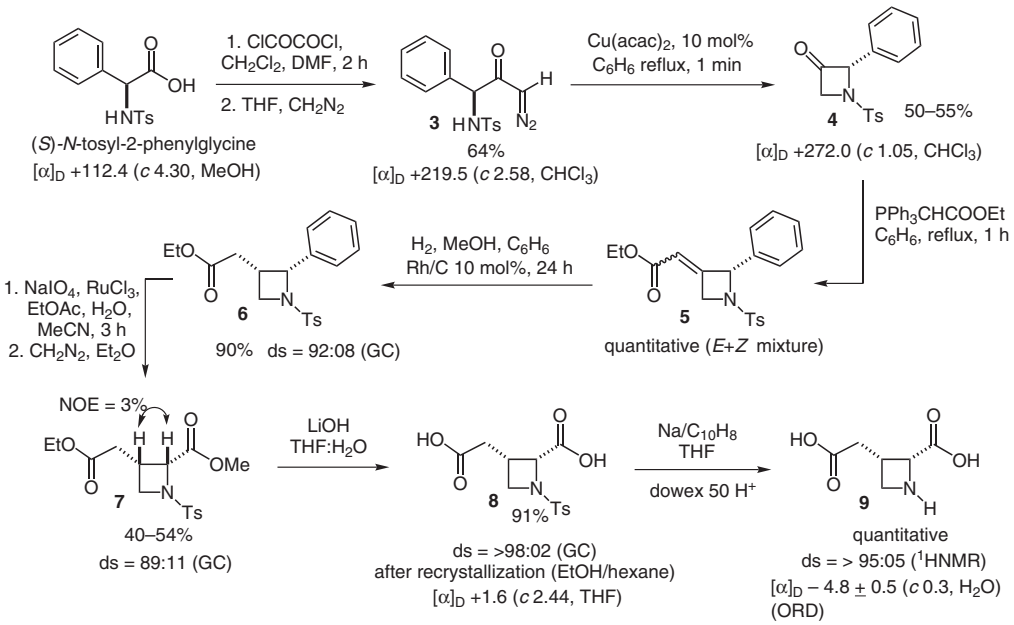
Table 1 Conditions Employed for the Reduction of Enoate **5**

Condition[a]	Yield of diester **6** (%)	*cis*:*trans*
H_2, Pd/C	19[b]	95:05
H_2, Pt/C	0	
Et_3SiH/ Wilkinson cat.	80[b]	88:12
H_2, Rh/C	90[c]	92:08

[a] Reductions were carried out at atmospheric pressure using a balloon filled with hydrogen.
[b] Average of two experiments.
[c] Average of three experiments.

Hydrogenation using platinum over carbon failed to provide the diester **6**. Better results were obtained using rhodium on carbon or Et_3SiH in the presence of the Wilkinson catalyst.[13] Under these conditions the *cis*-ester **6**[14] was obtained in good yields (90% and 80%, Table 1) and in good diastereoselectivities (92:8 and 88:12, *cis*:*trans* ratio, respectively).

As planned, the phenyl ring of **6** was then converted to the carboxylic acid by oxidation with $RuCl_3$ hydrate and $NaIO_4$[15] followed by addition of diazomethane to furnish the *cis*-diester **7**[16] in moderate yields ranging from 40% to 54%. A small 3% epimerization was observed at this step, as the *cis*:*trans* ratio dropped from 92:08 to 89:11 as observed by GC (average of three experiments). Next, hydrolysis of the diester **7** with LiOH[17] gave the N-protected glutamate acid derivative **8** as a white solid (91% yield, *cis*:*trans* = 89:11). The major *cis*-compounds **6**, **7** and even **8** could not be separated from their respective *trans* isomers by column chromatography along the synthetic pathway. Fortunately, after a careful recrystallization (ethanol–hexane) of diacid **8** (*cis*:*trans* = 89:11) we were

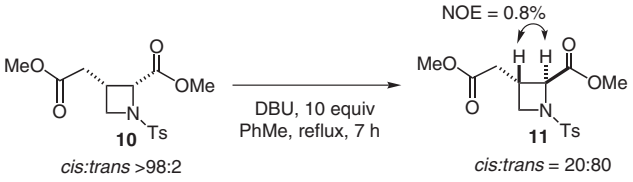


Scheme 2 Synthesis of glutamate analogue **9**

able to obtain this key compound in almost pure form (ds > 98:02 after a single recrystallization).[18]

Finally, completion of the synthesis of the novel conformational restricted *cis*-azetidine glutamate **9** was carried out by N-deprotection of diacid **8** with Na/naphthalene in quantitative yield, after purification on ion exchange resin (Dowex 50 H^+).[19]

After completion of the synthesis of the *cis*-glutamate analogue **9**, we have also examined the conversion of the *cis*-diester **10** (prepared from diacid **8** with diazomethane) to its *trans* stereoisomer. The use of bases such as LHMDS, KHMDS, *t*-BuOK, proton sponge, Me_2NH[20] and pyridine led to no epimerization[21] at C2 or led to decomposition of the diester **10**. However, reaction of diester **10** with DBU (10 equiv) in toluene at reflux for seven hours provided a diastereomeric mixture of diester **10** and **11** in a 20:80 (GC) ratio as described in Scheme 3. Attempts to carry out this epimerization step beyond the *cis*:*trans* ratio of 20:80 were fruitless.



Scheme 3 Epimerization of **10** with DBU

In summary, we have accomplished for the first time the stereoselective synthesis of the novel *cis*-glutamate analogue **9** containing an azetidine nucleus in seven steps in 15% yield from the chiral (*S*)-*N*-tosyl-phenylglycine. Epimerization of the *cis*-glutamate analogue **10** with DBU allowed the synthesis of the *trans*-glutamate analogue **11** with good diastereoselectivity. The synthesis of other constrained azetidine glutamates and aspartates will be reported in due course.

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(18) Mp 201–202 °C (dec). IR: 3300–2500, 1698, 1437, 1346, 1229, 1161, 943 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ = 7.79 (d, *J* = 8.8 Hz, 2 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 4.62 (d, *J* = 9.5 Hz, 1 H), 3.90 (t, *J* = 8.1 Hz, 1 H), 3.50 (dd, *J* = 8.1, 4.4 Hz, 1 H), 2.97 (m, 1 H), 2.67 (d, *J* = 8.1 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (75 MHz, acetone-d_6): δ = 172.5, 169.6, 145.1, 134.1, 130.8, 129.0, 63.8, 54.2, 34.5, 28.4, 21.6.

(19) IR: 3077, 1679, 1625, 1574, 1421, 1184, 1129, 974, 801, 723 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 4.90 (d, *J* = 9.5 Hz, 1 H), 4.30 (dd, *J* = 10.9, 8.8 Hz, 1 H), 3.77 (dd, *J* = 10.9, 6.6 Hz, 1 H), 3.40 (m, 1 H), 2.60 (dd, *J* = 16.1, 5.1 Hz, 1 H), 2.44 (dd, *J* = 16.1, 11.7 Hz, 1 H). ^{13}C NMR (75 MHz, D_2O): δ = 176.0, 170.6, 61.8, 48.5, 34.5, 30.5. ESI-MS: *m/z* = 160 [M + 1], 114, 97, 96, 84, 78, 68. HRMS: *m/z* calcd for $C_6H_9NO_4$: 159.05316; found: 159.06178.

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