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An efficient approach to D-*threo*-3-hydroxyaspartic acid for the synthesis of novel L-*threo*-oxazolines as selective blockers of glutamate reversed uptake

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Abstract—An efficient, stereoselective synthetic strategy to D-*threo*-3-hydroxyaspartic acid was developed. Starting from L-(2*S*,3*S*)-*N*-benzoyl-3-hydroxyaspartic acid dimethyl ester by a Deoxo-fluor-catalyzed cyclization reaction, an inversion of configuration at the β-center (*erythro* isomer), was observed. A base-induced epimerization reaction led to the D-*trans*-isomer, which was hydrolyzed to give D-*threo*-3-hydroxyaspartic acid with excellent stereoselectivity and overall yield. Starting from D-*threo*-3-hydroxyaspartic acid, L-*threo*-oxazolines can be stereoselectively synthesized.
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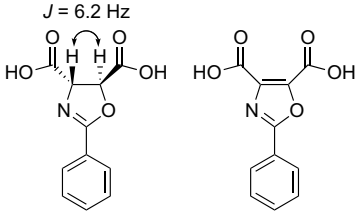
L-Glutamate (Glu) is an important nutrient involved in several biochemical pathways such as gluconeogenesis and ammonia detoxification. In the mammalian central nervous system (CNS) Glu plays an even more important role as an excitatory neurotransmitter modulating the function of most neuronal circuits. Clearance of Glu from the synaptic cleft and from the extracellular space is mediated by high affinity sodium-dependent excitatory amino acid transporters (EAAT) subdivided into five different subtypes. Their dysfunction may contribute to neurological disorders and neurodegenerative diseases. EAATs may be the major source of extracellular Glu by acting as a site of efflux from the intracellular compartment. This latter mechanism has been supposedly implicated during acute brain ischemia. We recently developed a 3D-model for EAAT2/3 for the successful design of the first, potent and highly selective EAAT blockers based on an oxazoline/oxazole structure (**1**,**2**) as novel neuroprotective agents to reduce the acute damage of specific regions of the brain during the ischemic insult.[1]



(4*S*,5*S*)-1 **2**

The stereoselective synthesis of L-β-hydroxyamino acids is a topic of interest since they represent key structural component of a variety of natural products, including antibiotics, and other biologically active compounds.[2]

Among them, L-*threo*-3-hydroxyaspartic acid (L-*t*-3OHAsp) is a potent transported substrate of EAAT2 while its *erythro* counterpart is less potent. On the contrary, much less is available on the synthesis of D-β-hydroxyamino acids such as D-*t*-3OHAsp.[3] L-β-hydroxyamino acids can be synthesized from chiral oxazolines, and enantioselective synthesis of these heterocycles and their ring opening reactions are well documented. Oxazolines are important intermediates in organic chemistry,[4–7] and in our case, potent pharmacological tools. Recently several authors[8,9] reported that *cis* oxazolines, bearing a phenyl ring at position 5 and a methoxycarbonyl function at C-4, could be converted into their *trans* epimers using catalytic amounts of bases.

Keywords: D-*threo*-3-Hydroxyaspartic acid; Glutamate; L-*threo*-Oxazolines; L-*t*-3OHAsp.
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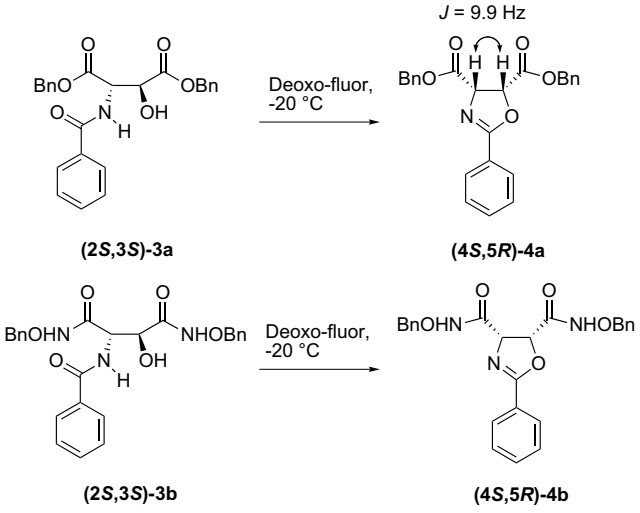
According to our pharmacophoric model we designed several blockers based on an oxazole/oxazoline skeleton. The acidic nature and the relative position of the two carboxylic functions is crucial for activity, and to deeply investigate their role, it was necessary to modify the pK_a of these acidic functions by their replacement with two hydroxamic acid groups. Furthermore, we decided to investigate also the role of alkyl functions in place of the aromatic ring at C-2. Structural manipulations of oxazolines such as transformation of the carboxylic groups of **1** to hydroxamic acid functions may be difficult due to the high instability of the oxazoline ring system. Consequently, to synthesize analogues of compound **1**, we decided to use L-*t*-3OHAsp, an easy synthesis of which was recently developed,[10] as starting core system to generate a versatile synthetic approach to these heterocyclic compounds. The chiral 3-hydroxyaspartic acid was converted into the *N*-benzoyl derivative leading to **3a**,**b**, after protection and transformation of the carboxylic functions. Cyclization to oxazolines was attempted by using the Deoxo-fluor reagent (Scheme 1).[7]



Scheme 1.

This reaction did not provide the desired (4*S*,5*S*)-oxazolines, but the amides underwent epimerization, leading to the epimers (4*S*,5*R*)-**4**, with high diastereomeric purity, by a clean inversion of configuration at the β-center. The configuration of compounds **4a** and **4b** was determined by NMR and by comparing the analytical data of these compounds with those of L-*threo*-analogues obtained using *N*-benzoylaspartic acid derivatives as starting materials. The NMR spectra of the *cis*-isomer **4a** and its *trans*-epimer showed a distinct difference in the coupling constants. To bypass the inversion of configuration induced by the SN_2 cyclization reaction, and to obtain L-*threo*-oxazolines, we investigated a new synthetic strategy based upon the use of D-*t*-3OHAsp as a key intermediate. Low cost and commercially available L-aspartic acid was the starting point of our synthesis. Consequently, the first step of our strategy was the development of an efficient method to synthesize D-*t*-3OHAsp. Following our retrosynthetic analysis, L-(2*S*,3*S*)-*N*-benzoyl-3-hydroxyaspartic acid dimethyl ester, in turn obtained from L-aspartic acid, could be initially transformed into the corresponding *cis*-oxazoline by a SN_2 ring closure (epimerization at the β-center) which, after treatment with a catalytic amount of DBU, could be epimerized to the D-*trans*-oxazoline. Finally, deprotection might provide D-*t*-3OHAsp (Fig. 1).

Successively by the same set of stereoselective reactions, D-*t*-3OHAsp may provide L-*threo*-oxazolines. As shown in Scheme 2, diester **6** was cyclized to the oxazoline by using the Deoxo-fluor reagent. In this step the epimerization of the β-center occurred and the *cis* oxazoline was obtained in 75% yield. Subsequently, by the addition of a catalytic amount of DBU the *erythro* (*cis*) intermediate was converted into its D-*threo* (*trans*) counterpart **7**, by epimerization of the α-center, with a *trans cis* ratio of 95:5*dr*. After separation of the two diasteroisomers by flash chromatography, the optical purity of the D-enantiomer **7** was verified by an optical rotation analysis, compared to the value reported in lit. for the L-enantiomer ($[\alpha]_D$ −42.6° (*c* 1, $CHCl_3$); lit.[10] $[\alpha]_D$ +42.2° (*c* 1.2, $CHCl_3$)). Oxazoline **7** was obtained with a

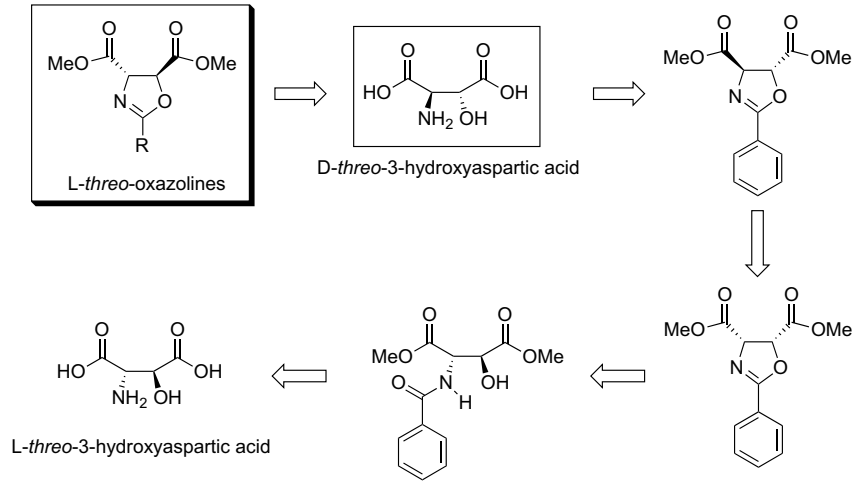
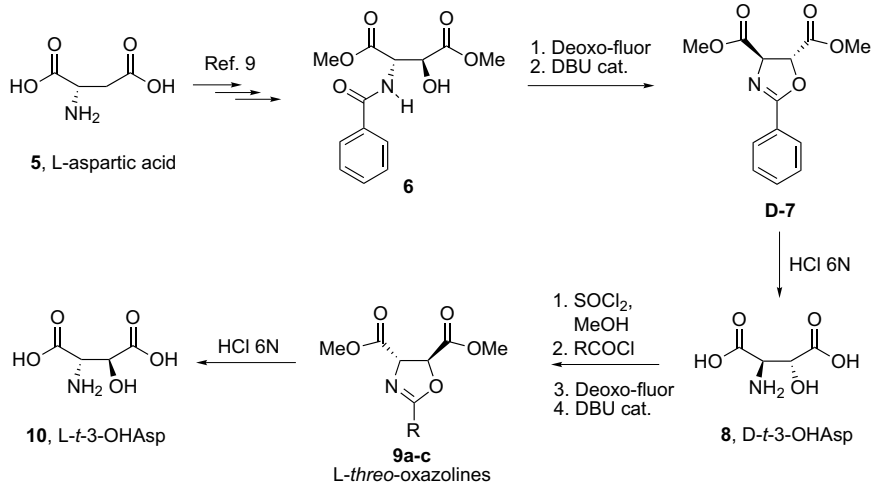


Figure 1. Retrosynthetic analysis to D-*threo*-3-hydroxyaspartic acid and L-*threo*-oxazolines.



Scheme 2.

high optical purity. Compound **7** was hydrolyzed to provide D-*t*-3OHAsp **8** in good overall yield (38%) and high optical purity ($[\alpha]_D$ −7.4° (*c* 0.9, 5 N HCl); lit.[3] $[\alpha]_D$ −7.5° (*c* 1, 5 N HCl)). Subsequently, D-*t*-3OHAsp was converted to the *N*-acyl intermediates by using acetyl chloride, benzoyl chloride, and 2,2-dimethylpropionyl chloride, respectively. These compounds were then treated with Deoxo-fluor reagent followed by catalytic DBU to give the desired L-*threo* oxazolines (**9a**–**c**) after double epimerization at β- and α-centers.[11] (4*S*,5*S*)-2-Phenyloxazoline-4,5-dicarboxylic acid dimenthyl ester **9b** showed spectroscopic data comparable to the compound reported in lit. ($[\alpha]_D$ +41.8° (*c* 0.8, $CHCl_3$); lit.[10] $[\alpha]_D$ +42.2° (*c* 1.2 $CHCl_3$)). Furthermore, ring-opening reaction under acidic conditions of compounds **9a**–**c** provided L-*t*-3OHAsp (**10**) as a pure enantiomer ($[\alpha]_D$ +7.6° (*c* 1.1, 5 N HCl); lit.[10] $[\alpha]_D$ +7.5° (*c* 1, 5 N HCl)).

In conclusion we have shown an efficient stereoselective synthesis of D-*threo*-3-hydroxyaspartic acid starting from L-*threo*-3-hydroxyaspartic acid. D-*t*-3OHAsp was used as a key structural intermediate for a general and versatile synthesis of L-*threo*-oxazolines.

Acknowledgement

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11. D-*threo*-3-Hydroxyaspartic acid dimethyl ester hydrochloride. ^{1}H NMR (MeOH-d_4) δ 3.85 (s 3H), 3.90 (s, 3H), 4.45 (br s, 1H).
(4*R*,5*R*)-*N*-Pivaloyl-3-hydroxyaspartic acid dimethyl ester. 73% yield as colorless prisms (mp: 94–95 °C): $[\alpha]_D$ −69.2° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.78 (s, 3H), 3.79 (s, 3H), 4.69 (d, 1H, $J = 1.8$ Hz), 5.09 (dd, 1H, $J = 1.8$, 8.8 Hz), 6.35 (br s, 1H).
(4*S*,5*S*)-2-(*tert*-Butyl)oxazoline-4,5-dicarboxylic acid dimethyl ester (**9c**). Deoxo-fluor-catalyzed cyclization: *erythro*-isomer (4*R*,5*S*): $[\alpha]_D$ −115.8° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 3.71 (s 3H), 3.73 (s, 3H), 4.97 (d, 1H, $J = 10.3$ Hz), 5.06 (d, 1H, $J = 10.8$ Hz). DBU-catalyzed epimerization of α-center (4*S*,5*S*)-**9c**: $[\alpha]_D$ +147.1° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 3.78 (s, 3H), 3.80 (s, 3H), 4.72 (d, 1H, $J = 6.0$ Hz), 5.16 (d, 1H, $J = 6.0$ Hz).