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A short synthesis of both enantiomers of 2-aminobicyclo[3.2.0]heptane-2,7-dicarboxylic acid

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ABSTRACT

A concise method is reported for the synthesis of 2-aminobicyclo[3.2.0]heptane-2,7-dicarboxylic acid, a close analogue of the glutamate receptor ligand LY354740, in both enantiomeric forms. The strategy features the creation of the core structure at the start of the synthesis *via* a photochemical [2 + 2] cycloaddition reaction, an efficient resolution procedure using a chiral oxazolidinone, and requires only minimal purification of the synthetic intermediates. The title compounds showed little or no affinity for the mGlu2 and mGlu3 receptors.

Introduction

Glutamic acid is the most abundant mammalian excitatory amino acid and is involved in many aspects of brain function and in the regulation of numerous neuropathological conditions [1]. It interacts with both fast-acting ionotropic (iGlu) receptors and slow-acting G protein-coupled metabotropic (mGlu) receptors. Eight mGlu receptor subtypes have been identified and classified into three groups, and have been targeted over several decades in the search for treatment of anxiety and stress disorders, including schizophrenia, Alzheimer's disease and Parkinson's disease [2]. The search for analogues of glutamic acid that behave as selective ligands for the group II receptors, mGlu2 and mGlu3, led to the discovery of the potent agonist LY354740 (Eglumegad)[3] (Fig. 1), which entered clinical trials as a potential anti-psychotic agent [4] and has recently been shown to alleviate dyskinesia [5] and to counter retinal cell apoptosis in glaucoma [6].

While the bicyclo[3.1.0]hexane core of LY354740 has featured in other group II mGlu receptor ligands [7], numerous cyclic glutamic acid derivatives have been investigated over the years [8]. One such compound is (1S,2S,5S,7S)-2-aminobicyclo[3.2.0]heptane-2,7-dicarboxylic acid (**1**) whose molecular structure is very similar to that of LY354740, having just one extra carbon atom in the smaller of the two rings (Fig. 1). Pharmacological evaluation of **1** revealed a weak agonist activity for mGlu1, mGlu2, mGlu4 and mGlu6 receptor subtypes, although the activity towards the mGlu3 receptor subtype was not reported [9]. There is still a need for glutamate analogs that differentiate between mGlu2 and mGlu3 receptors [10], so we felt that the mGlu3 activity should also be assessed. Furthermore, in a more general context there is considerable current interest in polyfunctional compounds with a bicyclo[3.2.0]heptane core for drug discovery [11] and as rigid molecular scaffolds for multiple functional group displays [12].

The published synthesis [9] of **1** adopted a "chiral pool" strategy, starting from L-serine. It involved a lengthy sequence (10 steps; undisclosed yield) featuring a late-stage intramolecular photochemical [2 + 2]-cycloaddition reaction to construct the bicyclic core, which took place with low diastereoselectivity. We report here our own investigation focusing on an alternative synthesis of **1**, which we reasoned should be more expedient. The pivot of this simplified strategy is to conduct an early-stage intermolecular photochemical [2 + 2]-cycloaddition reaction, which is followed by a resolution protocol. As we will show, it has the advantage of providing both (1S,2S,5S,7S)-2-aminobicyclo[3.2.0]heptane-2,7-dicarboxylic acid (**1**) and its enantiomer (*ent*-**1**).

The photochemical [2 + 2]-cycloaddition reaction between cyclopent-2-enone and methyl acrylate was previously reported to give a roughly 1:1 mixture of head-to-head and head-to-tail regioisomers, in which the former was a 86:14 mixture of *exo:endo* stereoisomers, respectively [13]. We reexamined this

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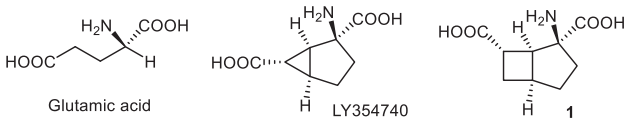


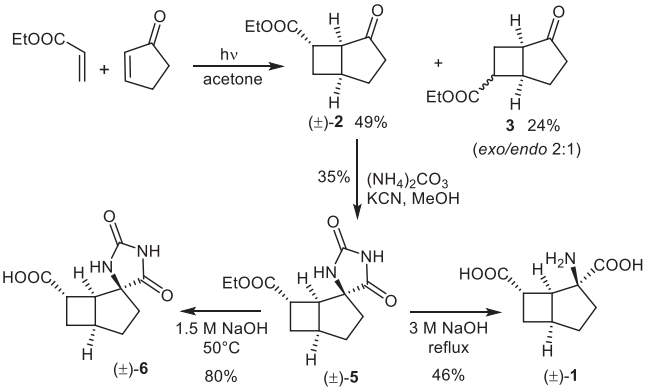
Fig. 1. Structures of glutamic acid and two restricted analogs.

photochemical reaction using ethyl acrylate as the alkene component (Scheme 1). When the gram scale reaction was carried out in acetone (25 °C, 4 h, 10 equiv. ethyl acrylate, 400 W Hg vapor lamp) we obtained a 2:1 mixture of regioisomers which were separated by simple column chromatography in good overall yield. The major compound was the head-to-head regioisomer (±)-**2**, isolated in 49% yield as a single diastereomer. By analogy with the literature [13], the *exo* configuration was expected and was subsequently confirmed by transformation into compound **5** (*vide infra*). The minor head-to-tail regioisomer **3** was isolated in 24% yield as a 2:1 mixture of *exo* and *endo* diastereomeric forms. To confirm the identity of **3** we took advantage of compound **4** [14], available from previous studies.[12b] A four-step procedure involving hydrogenation, ester hydrolysis, oxidation then esterification gave an authentic sample of *endo*-**3** in 65% overall yield (Scheme 2). Comparison of the spectroscopic data indicated that this was the minor diastereomer present in the *endo*/*exo*-**3** mixture obtained in Scheme 1.

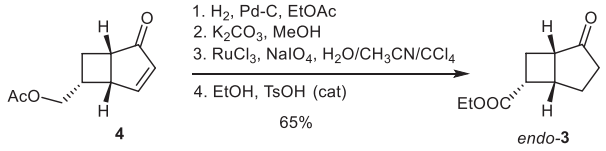
To validate the photochemical strategy for accessing the target amino acid, (±)-**2** was transformed into a hydantoin using a Bucherer-Bergs reaction to provide derivative (±)-**5** as a single diastereomer, albeit in modest yield, after crystallization from water [15]. The molecular structure and the relative stereochemistry of (±)-**5** were confirmed by X-ray diffraction analysis (Fig. 2) [16]; the requisite *endo* orientation of the ring-bound nitrogen is in agreement with the attack of cyanide on the least hindered face of the bicyclic core during the Bucherer-Bergs reaction. Rapid transformation of (±)-**5** into the target compound now seemed clearly feasible. Treatment with moderately strong aqueous base resulted in the efficient selective hydrolysis of the ester to provide (±)-**6**, while slightly stronger basic conditions achieved the desired complete hydrolysis to give (±)-**1** in 46% isolated yield. In this way, a very short and simple synthesis (3 steps) of (1S*,2S*,5S*,7S*)-2-aminobicyclo[3.2.0]heptane-2,7-dicarboxylic acid (±)-**1** was validated (Scheme 1).

In order to adapt this strategy to allow access to enantiomerically pure samples, our initial plan was to incorporate a resolution step implicating fractional crystallization of a diastereomeric salt mixture obtained by treatment of (±)-**6** with readily available (*S*)-α-methylbenzylamine. Indeed, this approach had proven successful for the resolution of the corresponding hydantoin-acid precursor of LY354740 [3]. Despite considerable efforts, however, we were unable to crystallize salt samples with any significant diastereoselectivity.

We then turned our attention to a resolution strategy based on diastereomeric derivatization by covalent attachment of a chiral resolving agent. Previously, our group has employed non-racemic oxazolidinones in this way to resolve a number of cyclic amino acids [17]. Derivatization of (±)-**6** seemed likely to be problematic due to the reactivity of the hydantoin so we focused on the simpler keto derivative. Saponification of (±)-**2** in aqueous base gave the corresponding carboxylic acid which was activated as a mixed anhydride by reaction with pivaloyl chloride, then treated with the lithium salt of (*R*)-4-phenyloxazolidine-2-one (Scheme 3). The two diastereomers **7a** and **7b** obtained from this three-step procedure were separated easily by column chromatography and were isolated as single compounds in gratifying overall yields of 33% and 24% respectively from (±)-**2**. Single crystal X-ray diffraction analysis of **7b** provided the absolute configuration assignment (Fig. 3) [16].



Scheme 1. Synthesis of (±)-**1**.



Scheme 2. Independent preparation of *endo*-**3**.

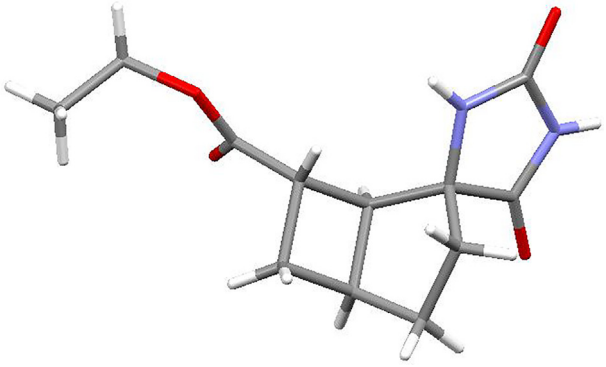
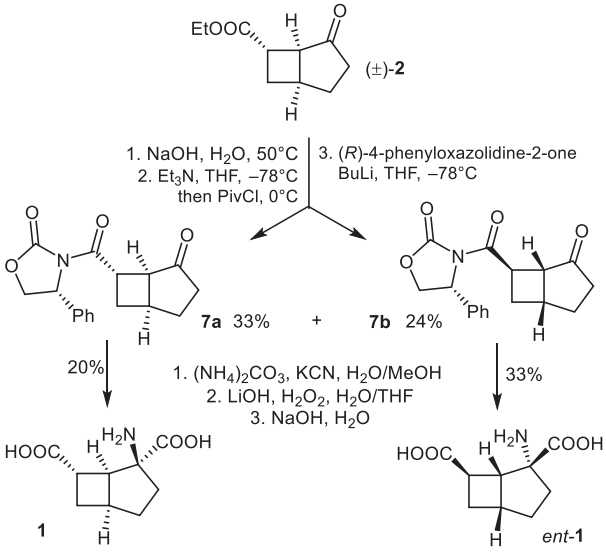


Fig. 2. X-ray structure of compound (±)-**5**.



Scheme 3. Resolution procedure and synthesis of **1** and *ent*-**1**.

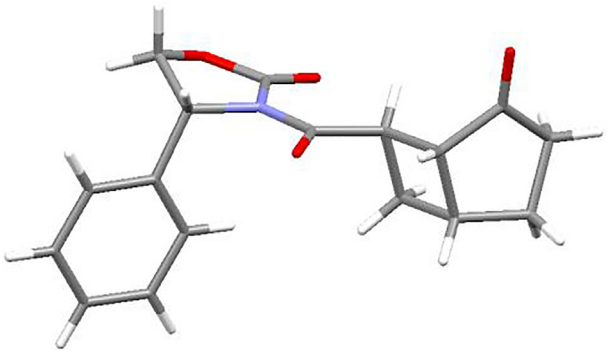


Fig. 3. X-ray structure of compound **7b**.

The expedient synthesis of both enantiomers of the title compound was then completed in three steps, requiring minimal work-up of intermediates. A Bucherer-Bergs reaction was carried out on compounds **7a** and **7b** to provide the corresponding hydantoin as a single stereoisomer with roughly the same efficiency as had been observed in the racemic route. Each hydantoin was treated, in a one-pot protocol, with lithium hydroperoxide to cleavage the oxazolidine-2-one then with stronger base to hydrolyze the hydantoin, to furnish the free amino acids **1** and *ent*-**1** in overall yields of 20% and 33%, respectively, for the three steps (Scheme 3). Spectroscopic data of these compounds were in full agreement with the proposed structures and the specific rotation values, which had not been previously reported, were $[\alpha]_D^{23}$ = −26.3 (*c* = 0.99, H_2O) for **1** and $[\alpha]_D^{23}$ = +26.4 (*c* = 1.00, H_2O) for *ent*-**1**.

Compounds **1** and *ent*-**1** were tested as ligands for the mGlu2 and mGlu3 receptors using a HTRF (Homogeneous Time-Resolved FRET) immuno-assay with LY354740 as the control ligand. Response curves indicated little or no affinity of the test compounds for either the mGlu2 or the mGlu3 receptor. These observations confirm and complete the previous findings regarding **1** [9].

Conclusion

In summary, we have established a short and simple synthesis of the title compound in single enantiomer form. The key initial photochemical step allowed facile access to the core bicyclic skeleton on near-gram-scale and although the Bucherer-Bergs reactions gave moderate yields they had the advantage of being entirely stereoselective. The resolution protocol confirms the synthetic value of oxazolidinones as chiral resolving agents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152912.

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[14] The sample of compound 4 used here was obtained from the work described in ref. 12b and was non racemic, with the 1S,5R,6R configuration shown in Scheme 2.
[15] NMR analysis of the crude reaction mixture (before crystallization) showed only one set of signals (see ESI document), suggesting the reaction to be highly stereoselective.
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