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New synthesis of 2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid-I (ABHxD-I), a potent metabotropic receptor agonist

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Abstract

A new versatile synthesis of racemic ABHxD-I, a potent mGluR agonist, is presented. The synthesis was achieved by means of a Wolff rearrangement, which converted a 3-diazobicyclo[2.2.1]heptan-2-one into a bicyclo[2.1.1]hexane derivative.

The excitatory amino acid, glutamate (Glu), plays a pivotal role in many biological processes such as neuronal plasticity, memory and learning as well as in neuronal degeneration.[1] Glutamate interacts with two families of receptors, the ionotropic glutamate receptors and the metabotropic glutamate receptors, each of which is composed of several subtypes.[2,3] In recent years, research has been focusing on the design and synthesis of new ligands that selectively interact with different receptor subtypes, in order to better characterize the physiological and pathophysiological role of the different GluRs and to identify molecules of potential use in therapy.

As a step towards this goal, we previously reported the synthesis of ABHxD-I,[4,5] a potent mGluR agonist which selectively activates metabotropic receptors without any activity at the ionotropic receptors.

In this paper we report a new versatile synthesis of racemic ABHxD-I by means of a Wolff rearrangement, which converts a 3-diazobicyclo[2.2.1]heptan-2-one into a bicyclo[2.1.1]hexane derivative.[6–10] This new synthesis was designed to take advantage of the key intermediate **8a** (Scheme 1) in which the carbon in α position to the carbonyl group can be suitably functionalized in order to develop the structure–activity relationships of this series of compounds. Based upon results from modeling studies, we hypothesized that functionalization at this site might lead to improved metabotropic receptor subtype selectivity.

The synthesis of **8a** together with its diastereoisomer **8b** starting from bicyclo[2.2.1]heptadiene has been described by Meinwald and Crandall.[9] We developed an alternative approach (Scheme 1) using 5-norbornen-2-ol (**1**) as starting material, which was converted into the required α-diazoketone in six steps. Thus, commercially available 5-norbornen-2-ol was oxidized under Swern conditions, and the

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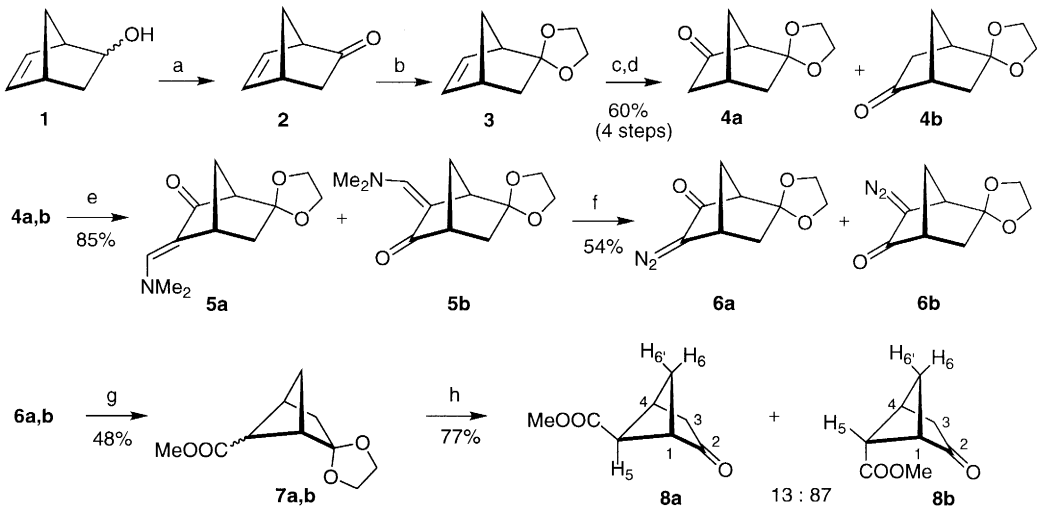


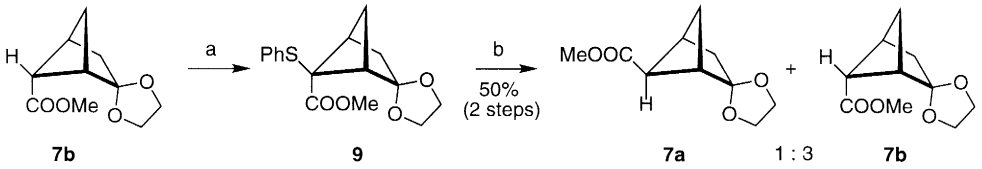
Scheme 1. (a) Swern oxidation; (b) $HOCH_2CH_2OH$, TsOH, toluene, reflux; (c) BH_3–THF, THF; (d) PCC, CH_2Cl_2, reflux; (e) $(Me_2N)_2CHO$*t*-Bu, 80°C; (f) TsN_3, Et_2O; (g) hν, MeOH; (h) 2N HCl, acetone

ketone function was protected as ethylene ketal to give **3**. A second carbonyl group was introduced via hydroboration of the double bond, followed by oxidation with PCC. A mixture of the ketones **4a**,**b** was obtained, which was then converted into a mixture of the corresponding α-diazoketones by alkylation with Bredereck's reagent followed by treatment with *p*-toluenesulfonyl azide.[11] It was not necessary to separate the two diazoketone regioisomers as they both underwent ring contraction by irradiation with UV light in MeOH,[12] leading to the bicyclo[2.1.1]hexane derivatives **7a**,**b** in an *exo*:*endo* ratio of 13:87. The *exo*:*endo* ratio reflects the preferred attack of MeOH from the less hindered face of the ketene intermediate and is consistent with the literature.[9,10] The two diastereoisomers, **7a** and **7b**, can be separated by silica gel chromatography at this stage and then hydrolyzed in turn with 2N HCl and acetone. However, we found it more convenient to hydrolyze **7a**,**b** as a mixture. The obtained ketones **8a** and **8b** were chromatographically separated and characterized.

The assignment of the stereochemistry of **8a** and **8b** was based on their ^{1}H NMR spectra; highly diagnostic is the W-coupling between 5-H and the bridgehead proton 6-H which is observed only in the *exo* isomer **8a** (typically J=7–8 Hz).[13] Thus, the proton observed at highest field which, according to the literature,[9,13] is 6-H, appears as a doublet ($J_{6-6'}$=7.5 Hz) in the *endo* isomer **8b**, and as a triplet ($J_{6-6'}=J_{6-5}$=7.8 Hz) in the *exo* isomer **8a**.

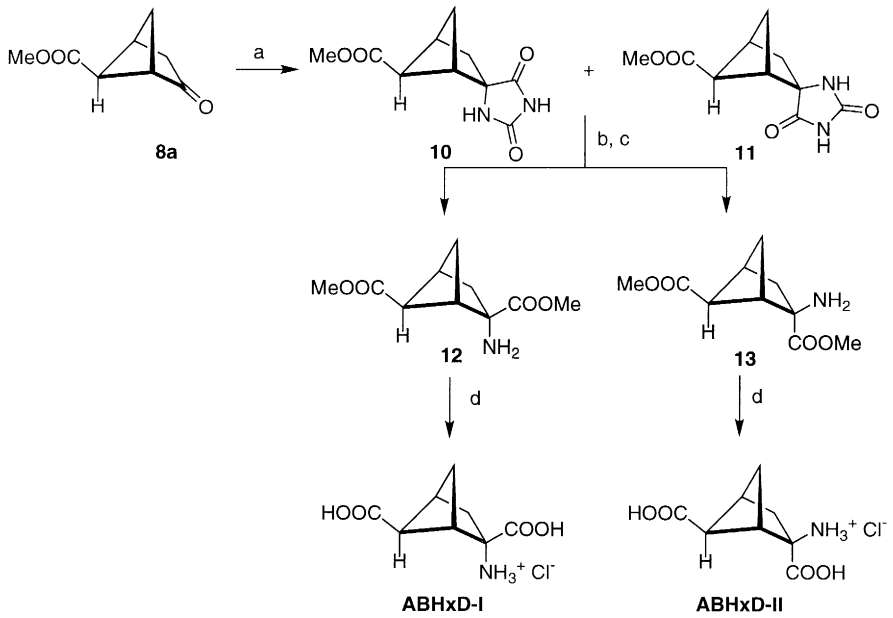
In order to increase the percentage of the stereoisomer **8a**, which is the direct precursor of the target compound ABHxD-I, we first treated the undesired *endo* isomer **7b** with base both under thermodynamic (DBU, toluene, reflux) and kinetic (LDA, THF, −78°C) conditions. However, in both cases, the unmodified *endo* isomer **7b** was recovered. We then operated under radical conditions by converting **7b** into the corresponding phenylthio derivative **9**, which was subsequently desulfurized with Raney-nickel; in this case a mixture of **7a** and **7b**, in a 1:3 ratio, was obtained. After chromatographic separation on silica gel, **7b** could be recycled (Scheme 2).

The keto group of **8a** was converted into a spirohydantoin under Bucherer–Bergs[14] reaction conditions, giving rise to a mixture of stereoisomers **10** and **11** with identical chromatographic mobility. Without separation, the mixture of spirohydantoins was hydrolyzed by alkali, and the two carboxyl groups were subsequently protected as methyl esters. The resulting free amines **12** and **13** were easily separated by



Scheme 2. (a) LDA, PhSSPh, −78°C; (b) H_2/Raney-nickel, EtOH

column chromatography, and the ester groups were hydrolyzed with 6N HCl to give the amino acid ABHxD-I and its isomer ABHxD-II,[15] respectively (Scheme 3).



Scheme 3. (a) KCN, $(NH_4)_2CO_3$, MeOH:H_2O 1:1, 55°C, 18 h; (b) 2N NaOH reflux; (c) MeOH, $SOCl_2$; (d) 6N HCl, reflux

In conclusion, we have developed a new, shortened synthesis of ketone **8a** and a method for the partial conversion of the major *endo* isomer into the desired *exo* isomer. This ketone is not only the key intermediate for the synthesis of ABHxD-I, but is also a useful starting material for the synthesis of functionalized derivatives. Trapping of the ketene intermediate with an optically pure alcohol should also permit access to non-racemic products.

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15. 100 mg of **8a**, 86 mg of KCN (2 equiv.) and 312 mg of $(NH_4)_2CO_3$ (5 equiv.) in 2 mL of MeOH:H_2O 1:1 were heated at 55–60°C for 18 h. The solution was evaporated, the residue was taken up in MeOH, and the solution was filtered and concentrated. The crude material was dissolved in 4 mL 2N NaOH and heated at 120°C in a resealable Pyrex vial for 8 h. The solution was acidified to pH 2 and evaporated to dryness. To the crude material, in 6 mL of MeOH, was added at 0°C 0.5 mL of $SOCl_2$, and the mixture was stirred at rt overnight. After evaporation of the solvent, the residue was dissolved in water, and the solution was basified with $NaHCO_3$ and extracted with EtOAc. Flash chromatography on silica gel (hexanes:AcOEt 1:4) gave 26 mg of **12** and 38 mg of **13** (overall yield: 46%). The aminoesters **12** and **13** were treated with 6N HCl at reflux for 4 h to afford the final products ABHxD-I and ABHxD-II, respectively, as hydrochloric acid salts. The spectroscopic data for the final compounds are identical to those previously reported (see Ref. 4).