

Supporting Information File 2
for
**Stereocontrolled synthesis of 5-azaspiro[2.3]hexane
derivatives as conformationally “frozen” analogues
of L-glutamic acid**

Beatrice Bechi^{1,2}, David Amantini^{3,4}, Cristina Tintori¹, Maurizio Botta*¹ and Romano di Fabio*^{3,5}

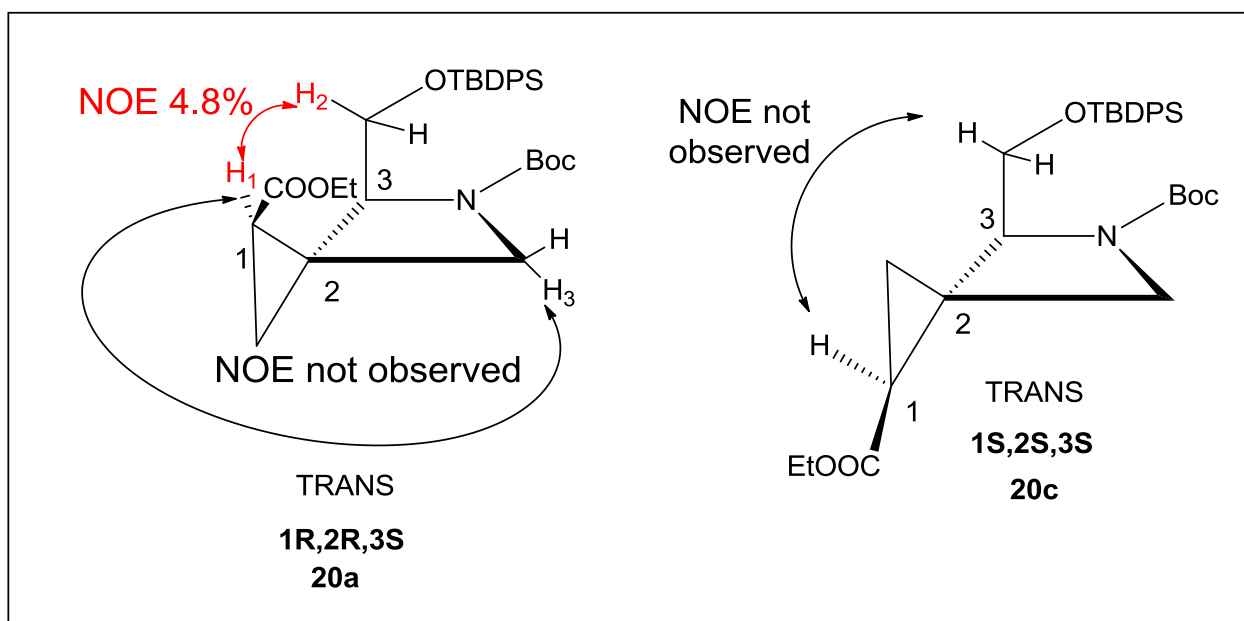
Address: ¹Università degli Studi di Siena, Dipartimento Farmaco Chimico Tecnologico, Via A. Moro 2, 53100, Siena, Italy; ²Present address: Manchester Institute of Biotechnology, School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK, ³Neurosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline Medicines Research Centre, Via A. Fleming 4, 37135, Verona, Italy, ⁴Present address: Galapagos SASU, 102 avenue Gaston Roussel, 93230 Romainville, France and ⁵Present address: Drug Design and Discovery, Aptuit S.r.l., Via A. Fleming 4, 37135 Verona, Italy

Email: Maurizio Botta - botta.maurizio@gmail.com, Romano di Fabio - romano.difabio@aptuit.com

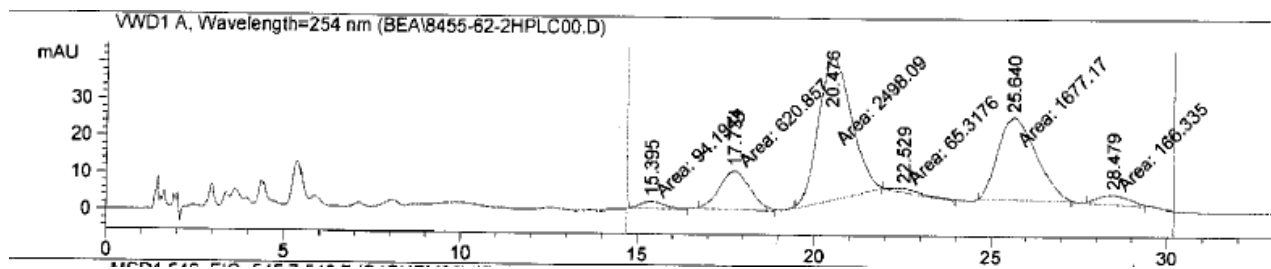
* Corresponding author

NOE studies on compounds 20a and 20c

When H1 proton of the diastereoisomer obtained in 49% yield (major diastereoisomer) was irradiated, 4.8% NOE effect was observed on H2 proton (see figure below). This is possible only for the trans isomer **20a** and cis diastereoisomer **20b**, while in the other 2 diastereoisomers **20c** and **20d** this protons are too far away to afford a NOE effect. Since this reaction proceeded with trans diastereoselectivity, the major product was identified as **20a**. This was confirmed also through irradiation of the proton H3: in this case, no NOE effect was observed both at the H2 and H3 protons, while in the case of the **20b**, it should be observed. Accordingly, when NOE experiments were performed on the second most abundant diastereoisomer obtained in 32% yield, no NOE effect was observed. Therefore, this compound was identified as the *trans*-cyclopropane derivative **20c**.



HPLC analysis on compound 20



Determined by analytical HPLC–MS using an (S,S)-WheIk-O1 column

(methanol/water 85:15, flow rate: 1.0 mL/min, UV-254 nm).