**Response to Reviewers JSCS 6866**

We have revised our manuscript meticulously following the reviewers’ recommendations. Their comments allowed us to make several improvements to the manuscript which we believe is now acceptable for publishing. Please see the detailed answer below. Our responses are in blue. In the manuscript the changes are highlighted in red.

**Referee report JSCS 6866**

**Title:** Anti-inflammatory activity of synthetic and natural glucoraphanin

**Authors:** Quan V. Vo, Pham C. Nam, Thuc N. Dinh, And Thi T. V. Tran

Authors described synthesis of the natural product glycoside glucoraphanin **4b** and compared anti-inflammatory activity of synthetic and natural product. Besides that, they described synthesis of **2a** and **3a** the α-epimers of corresponding precursors **2b** and **3b** for glucoraphanin. However, they did not success in their plans to obtained product **4a** which present α-epimers of glucoraphanin.

Presented investigations offers opportunity for direct comparison of anti- inflammatory activity of synthetic and natural product, which is contribution to medicinal chemistry. Since glucoraphanin shows very good activity it is very important to enable trusted methods for its reliable production. For that reason, results that shows identical activity at 15.00 μM and 10.00 μM concentration and almost identical at lower concentrations are very valuable. Also, stabile production of glucoraphanin enables detailed ADMET investigation which are hardly possible with limited amounts of compund that belongs only from natural sources.

Although that the same synthesis of the products **2b** – **4b** was already published (with corresponding spectra and identical copies) in Vo et al., *Tetrahedron* **69** (2013) 8731, obtaining of corresponding α-epimers is also valuable.

However, authors omitted to investigate anti-inflammatory activity for precursors **2** and **3** and in that way they did not provide valuable SAR informations about this group of products. Also, they did not provide any discussion about efforts for synthesis of product **4a**. They just said that they did not obtained **4a**, but without any comments of description of outcomes of corresponding attempting.

We thank the reviewer for understanding our difficulties. The α-isomer of glucoraphanin is decomposed in the last step of the synthetic progress that is confirmed by mass spectrometry analysis. We have tried by other de-O-acetylation conditions following the Ref [17] but we could not obtain it. That is explained in the line 66-71.

Minor corrections are necessary:

- Authors should clarified did reactions described in Discussion and illustrated on the Scheme 1 were performed with α/β-epimer mixtures, or with single stereoisomers. It could be concluded, intuitively, that epimers **2** were obtained from reaction of starting compound **1**, separated, and that singe isomers were put into next reaction step, for synthesis of compounds **3**. Also, did authors performed last reaction **3** 🠖 **4** with mixture of isomers **3a** and **3b**, or with single isomers. Since, on the Scheme 1 it is presented like reaction were done with mixtures of isomers.

The α/β-glucoraphanin were synthesized separately. In which, the α-epimer was synthesized from oxime **1** and **2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl thiol** following the Ref [15], while β-epimer was created from oxime **1** with **2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl thiol** following the literate [14]. However, we used a similar methodology to synthesize both the α/β-epimers, so the **Scheme 1** was used for two separate processes. Thus the synthesis of **2a**, **3a** and **4a** separated from that of **2b**, **3b**, **4b**.

The synthetic paragraph has been rewritten.

- Some NMR spectra were recorded in CDCl3, not all. Some were recorded in CD3OD (1H and 13C for **3a** and **3b**), and NMR spectra of **4a** were recorded in D2O. That should be corrected in Experimental part.

It has been corrected.

- Several mistakes of compounds labelling should be corrected:

Line 62 The resulting potassium salts **3a,b** (73% and 40% yields) were isolated by flash column chromatography on silica gel. 73% + 40% is more than 100%? Please clarify that!

As above explanations, the synthesis of **3a** separated from **3b**, so the yield was calculated on their own reaction. Thus a total yield is able to be more than 100%.

Line 153 … ***(2a,b)*** should be ***(3a,b)***

Line 174 **7b** should be **3b.**

It has been corrected.

This manuscript should be accepted for publication as Communication after minor corrections without my additional reading.