

Pardubice, February 12, 2020

Evaluation of MSc. Sara Eunice Agostinho Monteiro's Ph.D. Thesis

In thesis of the doctoral dissertation titled „Synthesis of Advanced Prostaglandin Intermediates“ MSc. Sara Eunice Agostinho Monteiro presents original research results in the area of preparation of several valuable intermediates for the synthesis of prostaglandins.

The general informations in Chapter 1 describe theoretical introduction in prostaglandins nomenclature, biosynthesis and biological activity and stability of natural prostaglandins and their synthetic analogues.

In Chapters 2 and 3, MSc. Monteiro describes published synthetic methods applicable for preparation of target active pharmaceutical ingredients based on prostaglandins. The chapter is broad and sufficiently deep. On the other hand, this chapter is difficultly readable because of quantity of abbreviations and oversimplifications of some described published synthetic protocols. This is furthermore complicated with occurrence of typing errors and usage of more types of labeling for some discussed compounds. For example:

- the explanation of abbreviation TES used in Scheme 9 is missing;
- two types of labelling for mentioned target molecule in Scheme 11 are used;
- ZnCl and CHCl₄ in description of Scheme 12 are used;

Due to above mentioned reasons I have some questions dealing with this chapter:

1. Could you explain mechanism of reactions depicted in Scheme 1, namely formation of product III from II and product VI from intermediate V?
2. Could you describe in more details formation of XXX from XXIX in Scheme 10? (page 26)
3. Which type of reagents mean abbreviations C₇H₇ used in Scheme 12 and C₄H₁₀BF₃O in Scheme 16?
4. Could you explain role of toluene in preparation of compound LV in Scheme 18? Could you describe formation of LV from LVI in Scheme 18 using toluene /bromine/sulfuric acid/heating in ethanol in more details?
5. I have not found any Reference dealing with Figure 12 – Schematic reactor for PG synthesis. Is this reactor design your own idea?

In Chapter 4, MSc. Monteiro discusses results obtained from experiments based on aims of her doctoral work described on page 50, particularly preparation of alfaprostol intermediates from cheap and available raw materials according to the Scheme 32. Unfortunately, the description of performed

experimental work suffers with application of different labeling of molecules in comparison with Chapters 2 and 3.

For example, synthetic route to intermediate **18** from **11** depicted in Scheme 38 is described in text on page 57, however, the same route is mentioned in Scheme 23 using another labeling of compounds **11** and **18** (**LXXX** and **LXXXI** in Scheme 23 on page 40).

The crucial intermediate labeled **4** on page 51, Scheme 32, is labeled as **8** in Scheme 33 on page 52 and as **LXV** in Chapter 3, page 40, similarly another in both Chapter 4 and Chapters 2 or 3 described compounds.

On the other hand, it must be stated that MSc. Monteiro verified very labourious reactions based on ideas mentioned in "Aims" chapter on page 50.

MSc. Monteiro proved that synthetic strategy based on direct metal-catalyzed reaction of acetylene derivative **2** (or **LXXIX**) with aldehydes is not applicable for preparation of intermediate **10**.

Using activation of **2** with SnBu₃ group enables subsequent preparation of key propargyl ketone **19** by Pd catalyzed reaction. Another successfully proved approach to the target molecule **1** (mentioned in text even as **13** in Scheme 34) is based on preparation of metalated acetylene and subsequent reaction with appropriate aldehyde. For this purpose effective preparation of corresponding bromoacetylene derivative **11** using two different synthetic routes was evaluated. Prepared compounds were fully characterized using available NMR, MS and/or X-ray techniques.

In addition, Corey alcohol **43** was prepared successfully using modified route based on cyclopentadiene.

Despite above mentioned drawbacks, the PhD thesis of MSc. Monteiro presents applicable synthetic approaches to produce desired intermediates for the synthesis of active pharmaceutical ingredient alfaprostol from available starting materials. MSc. Sara Eunice Agostinho Monteiro authored and co-authored three publications related with her dissertation thesis and presented her research results on many international conferences.

In summary, my conclusion is that the PhD thesis of MSc. Monteiro presents original research results of large importance and

I recommend MSc. Monteiro to be awarded the doctoral degree.

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