



CHARLES UNIVERSITY  
Faculty of Pharmacy  
in Hradec Králové

## Evaluation Report of the Ph.D. Thesis

by MSc. Sara Eunice Agostinho Monteiro

Title: **Synthesis of Advanced Prostaglandin Intermediates**

Mentor: Assoc. Prof. Aleš Imramovský, Ph.D.; Year of defense: 2020

Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice

Reviewer: Prof. PharmDr. Martin Doležal, Ph.D.; Faculty of Pharmacy in Hradec Králové, Charles University

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I have no conflict of interest in the evaluation process of MSc. Sara Eunice Agostinho Monteiro Ph.D. thesis. In fact, I am not an expert in prostaglandins chemistry, I am only able to evaluate the submitted thesis from the point of pharmaceutical/medicinal chemistry view.

Sara Eunice Agostinho Monteiro prepared her Doctoral Dissertation in Study Program: Organic Technology as monography. The thesis contents 166 pages, 10 chapters, and the abbreviation index. The list of references includes 189 citations. The last part of thesis is the list of published articles (4, *Tetrahedron Lett.*, *Chemistry Select*, *Org. Prep. Proced. Int.*, *BMC*), posters (9) and oral presentation (1) from the years 2016-2019.

Thesis brings the interesting results of the scientific collaboration between the two institutions, Institute of Organic Chemistry and Technology in Pardubice, and Cayman Pharma Ltd. in Neratovice, one of the worldwide leaders in prostaglandins production. Physiologically active lipid compounds called prostaglandins are powerful locally acting vasodilators and inhibit the aggregation of blood platelets. Through their role in vasodilation, prostaglandins are also involved in inflammation. The structural differences between prostaglandins account for their different biological activities. The synthesis of prostaglandins has been a challenge over than 50 years. The complex structure, including a cyclopentane with two lateral chains, associated with the presence of several chiral centers contributes for the difficulty of their preparation process. Although all efforts, their synthesis still follows old multistep protocols, contributing for high time-consumptions and low global yields. New approach is therefore needed.

The dissertation describes a new strategy for the synthesis of alfaprostol, which is a luteolytic agent used injectably for scheduling of estrus in mares for purposes of planned breeding. It is also used for treating of postweaning anestrus in economically important farm animals.

In the first chapter, the author provides a background for the prostaglandin application in medicine (pulmonary hypertension, gastroduodenal ulcer and glaucoma treatment), and the biological, veterinary applications of alfaprostol.

The submitted thesis presents a very deep and rich view on the synthesis of prostaglandins in Chapter 2. The chapter deals in depth with Corey lactone diol synthesis, which is a key intermediate for synthesis of prostaglandins. Author outlines the industrial perspectives of prostaglandins preparation from Corey lactone diol and other, or alternative synthetic approaches.

The chapter 3 describes the synthesis of 13,14-dehydroprostaglandin derivatives, alfaprostol synthesis, resp. 13,14-dehydroprostacyclin derivatives. Such compounds include a propargyl alcohol moiety and current efforts are being targeted in the development of a new methodology for the synthesis of the C-C bond in intermediates, starting from a Corey lactone derivative and 3-cyclohexylpropanal. The new methodology should have in consideration the stereoselectivity of hydroxyl group, as well as the lability of Corey lactone moiety. In this context the use of chiral ligands or other suitable approach are being considerate.

The experimental aims of dissertation are described on the page 50. The submitted thesis deals with preparation of adequate intermediates useful in alfaprostol synthesis, one-pot synthesis of propargyl alcohol moiety, enantioselective alkynylation of an alkyne and aldehyde, and their industrial and technological applications.

Other parts of Ph.D. thesis deal with the **Results and Discussion** of experimental work. Besides the unsatisfying results (Chapter 4, attempts to obtain the propargyl alcohol from terminal alkyne, Sonogashira coupling) author describes some successful methods (Chapter 5, Stille coupling, Pd-catalist; Chapter 6, from Corey lactone bromoalkyne; racemic propargyl alcohol synthesis; ... stereoselectivity studies). Chapter 7 brings new results from the author internship in Cayman Pharma – synthesis of Corey diol from cyclopentadiene and identification of impurities related with prostaglandins synthesis. Chapter 9 deals with alternative approaches.

**Conclusions** on 4 pages (pp. 101-104) describes the main results. The key and final products are chiral, mostly instable compounds, but all products have been fully characterized (NMR, Maldi-TOF, elemental analysis, HPLC, m.p., and X-ray analysis). The results of the submitted Ph.D. thesis were published in respected international journals (one review and 2 experimental works), where the results have been reviewed by other foreign specialists.

Chapter 10 deals with general experimental procedures and all obtained data of prepared compounds (pp. 105-150).

Review of literature (pp. 151-164) is relevant to the theme of research, it is prepared correctly, but more attention to the correct citation of the literature sources is needed.

#### **Questions, notes to the author:**

- An interesting synthetic prostaglandin analogue selexipag is more stable analogue than natural prostaglandins. Do you know other /semi/synthetic prostaglandins analogues in clinical praxis? Which chemical modifications are preffered?
- I have found only one inaccuracy in schemes on pages 14 and 16 ( $R_1$ ,  $R_2$ ,  $R_3$ ), the index means not the number of R, therefore upper index ( $R^1$ ) is necessary to use, it is the most common typographical error in general in some textbooks and journals.
- Which other methods we have for the optical purity of chiral products estimation (which other methods besides the chiral column HPLC are useful?).
- What is the reason for the instability of aldehydes 8a-c and other final products?
- What health protection during of laboratory work was used, prostaglandins are very active in very low concentrations.
- Citation of journal articles includes the full title of the article and the name of the journal in the abbreviated form in italic (see Chemical Abstract Service Source Index). After separation with a comma, the year (bold), volume (italic), pages range, reference always ends with a dot. The year in bold was many times not present in the list of citations.

- The title of a book is always written in italic. At the end of the citation, the publisher's name, place, and year of publication are mentioned. If the book does not have an editor and is cited as a whole, the following form is used: Surname, Name. Title. Edition, Publisher, Place of Publication Year, citation always ends with a dot, ISBN (International Standard Book Number) - ISBN is several times missing in Ph.D. thesis.
- Citation of patents and patent applications should include the names of the originators, the title of the patent, the abbreviation of the country and the patent number or application number. If the applicant is a company, its name must follow in parentheses by the names of the authors. The citation must be (should be) completed by reference to Chemical Abstracts.
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### Overall evaluation

The dissertation of MSc. Sara Eunice Agostinho Monteiro constitutes an interesting collection of results. I have evaluated the thesis for no evidence of plagiarism. The submitted thesis presents more than sufficient number of complex and high-quality original results of large practical importance. Based on my evaluation of the manuscript I conclude that this Ph.D. thesis is carefully written and satisfies all the requirements for a Ph.D. thesis in the field of Organic Technology.

**I recommend the dissertation for a defense and to award the Ph.D. degree to the candidate after the successful defense.**

Sincerely,

*January 24<sup>th</sup>, 2020*

Prof. PharmDr. Martin Doležal, Ph.D.

Faculty of Pharmacy, Charles University, Akademika Heyrovského 1203/8, 500 05 Hradec Králové, Czech Republic  
tel. (+420) 495 067 389  
e-mail: martin.dolezal@faf.cuni.cz  
[www.faf.cuni.cz](http://www.faf.cuni.cz)    <https://portal.faf.cuni.cz/Profile/Dolezal-Martin/>