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Tomáš Svoboda: Toward Asymmetric Total Synthesis of Podophyllotoxin Derivatives

Bachelor Thesis Review

Tomáš Svoboda's Bachelor Thesis is focused on the synthesis of natural products. Its aim is to develop a synthetic approach to selected podophyllotoxin derivatives, which are not only challenging targets but may exhibit a range of biological effects, including antiviral and anticancer activities.
The theoretical part (19 pages) provides a detailed literature overview of the class of podophyllotoxin compounds. It is very well written and provides the reader with all necessary information. I cannot help thinking that this part of the Bachelor Thesis could be a good basis for a future review article. I have only a minor comment on this part, that the text and Figures/Schemes could be better linked; for example, by numbering the structures of the substances presented and specific positions discussed. A brief description of the key synthetic methodologies later used by Tomáš Svoboda is included.
The objectives (1 page) of the Thesis are stated, but they are too detailed and not well formulated. This short but important section of the Thesis deserves to be rewritten.
The Experimental Part (10 pages) describes the key experiments of Tomáš Svoboda. They are presented in a standard way with all the necessary details with respect to the characterisation of the synthesised compounds. Sometimes laboratory jargon appears in the text.
The Results and Discussion section (12 pages) is the most important part of the Thesis, where the author describes his own experimental results. The most outstanding results include the enantioselective addition of vinylsilane to the carbonyl group of 2-bromopiperonal, determination of the absolute configuration of the addition product by XRD, the highly diastereoselective 1,4-conjugated addition of lithiated substance **2** to cinnamate-like ester **3**, determination of the relative configuration of the addition product by NMR, and RCM metathesis of substance **7** to an advanced intermediate **8** in the synthesis of podophyllotoxin **1**.
In the Conclusion section (1 page), the author concisely summarises his accomplishments, but the lack of any graphical items makes it difficult to follow.

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The Thesis contains adequate 33 references.

Some technical comments:
(1) Page 6, line 8: Correct "... *adice organolithiu k α,β-nenasycenému esteru.*" to "... *adice organolithia na α,β-nenasycený ester*."
(2) Page 26, Scheme 5, first reaction: H2SO4 correct to H_2SO_4
(3) Page 27, line 6: Rephrase the sentence "*The reaction is catalyzed by metal carbenes, which are generated in situ from metal alkylidenes*" to "*The reaction is catalyzed by carbene metal complexes, which are generated in situ from a precatalyst*."
(4) Page 27, line 9: Rephrase the sentence "*Alkene inserts itself to the carbon-metal double bond, ...*" to "*Alkene undergoes a formal [2+2] cycloaddition with carbon-metal double bond of the catalyst ...*"
(5) Page 28, Scheme 7 and the discussion on 1,4-conjugate addition: Organocuprates typically undergo 1,4-conjugate addition but the mechanism is completely different from the classical Michael addition.
(6) Page 32, first line: Correct "*To degas reaction solvent ...*" to "*To degassed reaction solvent ...*"
(7) Page 33, part 3.4, first line: Correct "... *Cinnamate ...*" to "... cinnamate ..."
(8) Page 33, last two lines: It should be said that the reaction gave **4** as a 5.5:1 mixture of diastereomers when the major diastereomer was obtained diastereopure after flash chromatography, otherwise it is confusing as stated in the Thesis.
(9) Page 35, part 3.6: Stereochemistry of the starting **3** and final **6** should be clarified (as well as *R**, *S** prefixes which are used for the unspecified absolute configuration). Did the author use *rac*-**3** of (*S*)-**3** in the experiment?
(10) Page 36, line 8: Correct "... *diastereomeric mix*." to "... *diastereomeric mixture*."
(11) Page 40, second to last line: Instead of "TBAI is an iodide salt ..." use "TBAI containd iodide anions ..." (iodide is salt itself).
(12) Page 40, last line: "Finkelstein reaction to interchange bromine for iodide ..." correct to "Finkelstein reaction of replacement of a bromine atom by an iodine atom ..."
(13) Page 41, first line: "... specie." correct to "... species."
(14) Page 41, line 4: "*This reaction proceeded one-pot in a racemic manner.*" change to "*This one-pot reaction provided a racemic product*."
(15) Page 42, first line: "... 2-br-piperonal ..." change to "... 2-Br-piperonal ..."
(16) Page 42, line 5: Isn't "... *the residue of the silyl polymer ...*" actually polysiloxane?
(17) Page 43, line 4: "*This olefination reaction is an approach leading preferentially to trans isomer*." rephrase as "*This olefination reaction leads preferentially to trans-isomers*."
(18) Page 44 and around: The term "*humidity*" is not appropriately used for residual water in solvents or substrates.
(19) Page 44, line 9: Correct "*Levis base ...*" to "*Lewis base ...*"
(20) Page 44, lines 3-4 from bottom: The sentence "*The proposed 5-membered metallacycle is formed by two ether oxygens of the MOM group and the carbonyl oxygen from cinnamate 3.*" is unclear and should be reworded.
(21) Page 44, Scheme 12: In the transition state (bottom right structure), the vinyl group configuration should be reversed.
(22) Page 51, line 5: Correct "... *THF or Toluene ...*" to "... *THF or toluene ...*"
(23) There are no experimental data on XRD analysis.

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Questions:
(1) How were the *ee* values determined?
(2) Would RCM metathesis of **7** be helped by the presence of molecular sieves absorbing the ethylene produced?

Although there have been rather critical words so far, the Bachelor Thesis deserves high appreciation for its quality and a large number of challenging experiments including enantioselective catalysis, work with organometallics or transition metal complexes. This synthetic study provides a valuable basis for the development of an efficient synthesis of target podophyllotoxin and its derivatives. The reviewer has no choice but to congratulate the author for his excellent mastery of the principles of total asymmetric synthesis in the field of natural compounds.

In conclusion, I find that the Bachelor Thesis of Tomáš Svoboda "*Toward Asymmetric Total Synthesis of Podophyllotoxin Derivatives*" meets the standard requirements for bachelor theses in the field of organic chemistry, and therefore I unequivocally recommend this scientific work for defence.

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