CHARLES UNIVERSITY
Faculty of science

Doctoral Thesis Review Report

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Doctoral Thesis	"Exploring the Unconventional Reactivity of Electron-Deficient Dendralenes Towards Nucleophiles."
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The submitted doctoral thesis deals with the study of the unconventional reactivity of electron-deficient dendralenes towards nucleophiles, with a particular focus on understanding their behavior under reductive conditions and in carbon–carbon and carbon–heteroatom bond-forming processes. At the beginning the work explores the preparation of a variety of dendralene derivatives, including acyclic and cyclic systems with a variety of electron-withdrawing groups. The main part of the work is focused on their transformations, revealing unexpected reaction pathways such as cyclizations and rearrangements instead of simple nucleophilic additions. These findings provide valuable insights into the reactivity patterns of cross-conjugated systems and expand their potential applications in organic synthesis as versatile and unique building blocks.

The thesis is traditionally structured and consists of standard chapters (Introduction, Aims of the Work, Results and Discussion, Conclusion and Outlook, Experimental Part, and References). It is written in clear and generally good English, with an acceptable number of typographical and stylistic inaccuracies. The text is logically organized and supported by an appropriate amount of graphical material (schemes, figures, and tables). *Note 1: Unfortunately, the sizes and the formats of the schemes are inconsistent. Uniform formatting would improve readability.* The Introduction provides a comprehensive overview of dendralene chemistry, cross-conjugation, nucleophilic reactivity, and Michael and *anti*-Michael additions, placing the work into a broader scientific context. The aims of the thesis are clearly formulated. The Results and Discussion section is well structured and describes the experimental work and obtained results in a systematic manner. The author demonstrates a solid understanding of the studied topic, knowledge of advanced NMR techniques and experiments and presents a significant amount of original experimental data. *Note 2: Personally, I highly appreciate discussions over NMR studies in a context of structure elucidation*. The Conclusion and Outlook summarize the key findings and outline possible future directions. *Note 3: I would recommend using a narrative format instead of a bulleted list to improve the flow.* The Experimental section is detailed and provides sufficient information for reprodu-

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cibility. The thesis is supported by an extensive list of 128 references presented mostly in an appropriate format.

The thesis originates from recent research in the field of dendralene chemistry and focuses on an emerging area dealing with their application as versatile building blocks in organic synthesis. The stated aims of the work were successfully achieved. The author prepared a series of novel electron-deficient dendralenes and demonstrated their diverse and often unexpected reactivity towards nucleophiles, including the formation of complex cyclic and polycyclic structures. These results represent a valuable contribution to the field and open new perspectives for further research. I highly appreciate this work, and it was a pleasure for me to be a referee.

Selected errors and inaccuracies appearing in the text:

1) Abbreviations: a) several abbreviations are missing, such as hx, LSB, etc. , b) some of the abbreviations are with capitals, others without, c) AcO, Ac2O, MeCN should not be listed when Ac and Me are already explained.
2) Schemes are not uniform; various fonts are used (Ariel, Times New Roman, etc.), different representations for the same molecules and sizes of bonds are not acceptable, the numbering of substituents is denoted using superscripts rather than subscripts, and the quality of reprinted figures is low.
3) Some chemical structures utilize a combination of skeletal formulas and condensed abbreviations for specific groups, such as COOMe.
4) Several references are written with abbreviations of journals, for example, ref. 6, 15, 16, 29; others are written with the full name of the journal.
5) Intermediate **Ia** (Scheme 35) is not zwitterionic as stated at p. 36, all compounds (Fig. 8) are not drugs as stated at p. 37, the scheme caption (Scheme 77) does not adequately describe the content, mentioned wrong Chapter 3.4 and Scheme 94 on p. 74, etc.
(The above list of errors is only indicative and not exhaustive, and minor typographical errors are not listed here.)

Questions and notes:

1) L-Proline and iodine were tested in the catalytic thia-Michael addition between dendralene **40e** and ethanethiol. Could you please describe what is the role of L-proline?
2) Could you please comment on the use of wedge bonds at the double bonds in dendralenes? For instance, compounds **40e, 40g, 40h** and **215c** are depicted both with and without wedge bonds. It would be helpful to clarify the rationale for this representation.

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3) Compound **215c** was used as a mixture of E/Z isomers. Do you expect different reactivity in the reactions with nuclephiles, for example reaction with sulfanylethanol (Scheme 89)?
4) The sulfonyl group significantly influences the reactivity of the dendralene compared to esters (e.g., Scheme 88). Have you considered to study cyclic (α,β-unsaturated) sulfones? Promising results were obtained with malonate-types nucleophiles and nitromethane (Chapter 3.7). Do you think that "C-acidic" heterocycles, of this type, such as oxindoles, pyrazolones, etc. could undergo similar Michael/cyclization cascades?
5) Characterization of compound **222** is not clearly described in the experimental part. 13C NMR presented contains 15 carbons, on the other hand there should be only 13 carbons. In Figure 16 it seems that compound **222** contains only two deuteriums. Could you please comment on that?

In conclusion, I would like to note that the results of the thesis are original and with high scientific value. The aims stated in the thesis were achieved, and the main results of the work were published in a peer-reviewed journal *J. Org. Chem.* In my opinion, the thesis fulfills the requirements posed on the thesis aimed at obtaining the academic degree Ph.D. I recommend the submitted work as a basis for the defense.

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