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The total synthesis of 5-methoxy-3,4-dehydroxanthomegnin, dehydroherbarin lactone and 6-ferrocenyl-3,4-dihydroisochromene

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Response to the examiners comments on my PhD thesis

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Title of thesis: The total synthesis of 5-methoxy-3,4-dehydroxanthomegnin, dehydroherbarin lactone and 6-ferrocenyl-3,4-dihydroisochromene.

Reports from the 1st examiner as per the order the reports were arranged

Summary

The report was comprehensive and most of the suggested comments were acted upon. Some of the comments dealt with the grammar/typographical errors and were very helpful in improving the readability of the thesis. In general, we corrected ml, cm^3 to mL and this was done throughout the thesis. The description of the proposed mechanisms which were generally given in past tense was changed to present tense throughout the thesis. In cases where the examiner had differed with the other two examiners we opted to use the suggestions of the examiners which we felt was in conformity with the flow of the thesis and effort was made to avoid making too many changes to avoid introducing errors in the course of making the suggested changes.

The examiner also highlighted the differences between the expected mass and the reported mass. We found that the calculations of the expected mass were erroneous. This was the case because we did not include the proton in the calculations and when that was done most of the values were within the required range. The MS data for compound ***trans*-425** has been removed because we were unable to correlate the two reported values. However, this does not take away the fact that the ^{1}H and ^{13}C NMR spectra clearly showed loss of one aromatic proton which was available in the starting material. Furthermore, the crystal structure of compound **JS-X10** confirmed the availability of the bromine atom. In some cases the values were misquoted probably because we were working under limited time. For example, the mass of compound **242** was reported as 391.1708 amu instead of the correct mass of 391.1748 amu. This project is ongoing in our laboratory and more data will be generated by the students who are continuing with this project. Selected corrections from the first examiner are given the table below:

	Comment	Action/response
1.	Page vii Line 16...fell	Corrected to…fall
2.	Page xii header…leader	Corrected to…reader
3.	Page 8 Line 7…via not italicized	'via' italicized (throughout the thesis)
4.	Page 16 Line 6…has been done	Corrected to…have been carried out
5.	Page 21 Line 1...homochiral	Corrected to…enantiomerically pure (throughout the thesis)
6.	Page 23 Line 16…done	Corrected to…carried out (throughout the thesis)
7.	Page 37 last Line…carcinogenic	Corrected to…carcinogen
8	Page 47 Line 10…lipopolysaccharides stimulated	Corrected to…lipopolysaccharides stimulated macrophages
9	Page 58 Line 4…key	Corrected to…major as suggested
10.	Page 63 Line 5…refluxed	Corrected to…heated to reflux (throughout the thesis)
11	Page 209 Line 3...procedure	Corrected to…synthetic pathway
12.	Page 231 Line 7…clear	Corrected to…colourless (throughout the thesis)
13.	Page 235 Line 9…washed off	Corrected to…purges as suggested
14.	Page 241…delete the whole of the second paragraph	The other two examiners did not recommend deleting this paragraph and therefore the paragraph was maintained, however, the suggested comments by the other examiners were dealt with.
15.	Page 242..addition of more reference	Reference to the work done by Harwood was included. **Reference 252**: (b) Harwood L. M., *J. Chem. Soc.*, **1982**, 1120; (c) Harwood L. M., *Chem. Commun.*, **1983**, 530; (d) Harwood L. M., *J. Chem. Soc., Perkin Trans. 1*,**1984**, 2577.

16.	Page 282 last Lines…corroboration	Corrected to…correlation (throughout the thesis)
17.	Page 336 Line 2…celite	Corrected to…Celite® (throughout the thesis)
18.	Page 343 Line 23…light	Corrected to…pale
19.	Page 359 Line 6…columned	Corrected to…purified
20.	Reference 35…capitalize throughout title	Corrected as suggested
21.	Reference 243/244…removed space	Corrected as suggested

Reports from the 2nd examiner as per the order the reports were arranged

Summary

The report was comprehensive and most of the suggested comments were acted upon. The examiner recommended that all the schemes and figures must be referenced in the text and this was corrected as suggested. In most cases, the reference to the schemes or figures was done as soon as they were discussed. The examiner also suggested that the numbering of the compounds should appear sequentially and this was acted upon. Cases in point were Compounds **70**, ***R*-97**, **100** and ***R*-109** and these were corrected accordingly.

The examiner suggested that **Section 4.1.16.1** should be deleted but this was not acted upon because the other two examiners did not recommend deleting this Chapter. However, the corrections that were suggested to this section by the examiner were acted upon.

The examiner noted the different coding system used for compounds **JS-D**, **JS-QCl** and **JS-X10**. This was not changed but the reader is alerted of the change in the coding system at the beginning of the thesis. This coding was used for bioactivity testing and it was decided that for the continuity of this project it was better that the coding used for bioactivity testing be maintained.

The examiner suggested changing the format of the thesis to A4 and this was acted upon.

The examiner highlighted the issue of inconsistencies in the HRMS data and this was corrected by re-calculating the expected masses to including the masses of the proton.

Lastly, the examiner pointed out that the word corroboration should be changed to correlation and this was done accordingly. Selected major corrections from this examiner are given in the table below:

	Comment	**Action/response**
1.	Page 4 Line 15...carbons	Corrected to…carbon atoms (throughout the thesis)
2.	Page 11…**Scheme 1.2**	Corrected to…**Scheme 1.1** and the rest of the Schemes were changed accordingly
3.	Page 52…paragraph not necessary	The paragraph was not deleted because

		the information served completely different purposes such that deleting this paragraph would have left the subsequent paragraphs hanging. The other two examiners did not recommend deleting this paragraph.
4.	Page 60 Line 8…As part of the model study, we envisaged that…	Corrected to…We envisaged that..
5.	Page 63 Change page formatting from Letter to A4…	Acted as suggested
6.	Page 67 Too much experimental detail for the results section (made a couple of times)	Noted but it was not changed because the examiner did not indicate that it was wrong to include the information that was included. The other two examiners did not recommend modifying this section.
7.	Page 176 **Scheme 2.91**…red arrow to indicate that the reaction was not successful	Corrected to as suggested
8	Page 226 The multiplicity of the signal did not match the nature of the structure. Commented a couple of times	The multiplicity was given as observed on the spectrum and this particular compound (**370**) was published by Mmutlane with similar analysis of NMR data, reference 119.
9	Page 293 No need to include compound **429**	The section was not deleted because it was meant to highlight the complexity of analyzing NMR data for complex molecules. The other two examiners did not recommend deleting this section.

Reports from the 3rd examiner as per the order the reports were arranged

Summary

Just like the first two reports, this report was comprehensive and most of the suggested comments were acted upon. Most of the comments were similar to the first two reports and were dealt in a similar manner. Of note was the suggestion on the mechanism which were acted upon accordingly. All typographical errors which were different from the other reports were included as suggested.

The examiner suggested the inclusion of the percentage yield in the schemes used in the introduction section of the thesis. This suggestion was noted but it was not acted upon because the percentage yields were included in the schemes carried out in our project. This difference gave a clear distinction about what we carried out against what was done before us.

The examiner suggested the proton exchange reaction between the protonated hydroxy group and the methoxy group adjacent to the protonated alcohol in one of the schemes which was very notable. Selected major corrections from this examiner are given in the table below:

	Comment	**Action/response**
1.	Page 34 **Scheme 1.18** (changed to **Scheme 1.17**)	The stereochemistry of the hydrogen atom which is the smallest group is the same i.e. pointing towards the observer and it is therefore expected that the stereochemistry of the two compounds is the same considering that the position of the largest group did not change position. However, the comment was acted upon and necessary changes were made.
2.	Page 54…**Scheme 1.29** (changed to **Scheme 1.28**)	The 2-iodo-1,3-dimethoxybenzene is included under reagents and conditions
3.	Page 67/68…reference for compound **170**	The reference is given under experimental and therefore it was not included at this point.
4.	Page 111 comparison of NMR	To the best of our knowledge this is the

	spectroscopic data for compound **208** with the literature data.	first time this compound has been synthesized, however, the NMR data for 10-*O*-methylpaepalantine is available.
5.	Page 116 **Scheme 2.40**	Brilliant suggestion and it was incorporated accordingly
6.	Page 149 **Scheme 2.66** destruction of the aromaticity in the process of nucleophilic substitution	Noted but the aromaticity is regenerated which means the overall reaction may be energetically viable. Molecular modelling would shed more light in this regard.
7.	Page 169 lactone carbonyl group ignored	It was maintained from the reactant and would, therefore, not offer new information.
8	Page 209 The structure of compound **341** wrong	Corrected accordingly
9	Page 261 The spectra in **Figure 4.10** not superimposed.	Superimposed deleted