Review on Mgr. Robert Betik's PhD thesis:

"Total Synthesis of (–)-Methoxyestrone"

The total synthesis of natural products is of ever increasing importance in organic chemistry, since on one hand synthetic methodology can be probed and on the other hand the natural product and its analogs may be of importance with respect to a desired biological activity. Mgr. Robert Betik took the challenge to a new synthetic access to (–)-methoxyestrone, from which the enantiomer to naturally occurring estrone can be produced. *ent*-Steroids have recently gained importance as biochemical tools in a number of applications.

The thesis is typically organized. In the introduction, significant synthetic approaches to naturally occurring estrone and methoxyestrone are outlined with respect to the keysteps involved. To put the described total syntheses in a desired more general context the information would be useful, how many total syntheses of estrone and methoxyestrone overall exist. Another question remains, why the groundbreaking work by Johnson on biomimetic cationic cyclizations, which clarified much of the biosynthetic work on steroids and was inspiring to much other chemistry, is not mentioned among the total syntheses. The presentation contains unfortunately a number of mistakes. In Scheme 3.2.1 ethyl succinyl chloride is shown instead of ethyl glutaryl chloride. The chiral imine **XIV** was generated from phenylalanine and not as stated in the text from "L-proline". Grieco's total synthesis (Scheme 3.4.1) is not correctly presented, as **XXIX** must contain a double bond in the cyclopentane ring, while **XXX** should not, and the configuration of the alcohol is β-fixed in **XXXI**. Pattenden's radical cascade approach (Scheme 3.5.1) depicts the initial macrocyclization correctly, but the depicted 5-exo cyclization intermediate (second line right structure) has kinetically not the trace of a chance to occur in competition to cyclopropylcarbinyl radical ring opening, which leads then to a zipper process, which closes the B ring via a 6-exo cyclization first, only then followed by the formation of the CD ring. The alcohol in **XXXV** (Scheme 3.6.1) is not oxidized to a ketone but to an aldehyde. On page 13, it is stated that the "conjugated addition proceeded highly diastereoselectively". This is, however, not true, since during the conjugate no creation of a stereocenter is involved. The establishment of the new stereocenter happens only on subsequent protonation. Kocovsky's synthesis is strategically not correctly placed in chapter 3.8, since it does not contain a transition metal-mediated step. Structure **LXV** is wrong. Some names such as Reformatsky, Bakshi, Grubbs, or Danishefsky are misspelled.

The aims are very briefly presented next. It would have been appreciated, if the motivation of the work had been outlined more detailed.

The major results are summarized in chapter 5. In the first part a racemic formal synthesis of 3-methoxyestrone is described. The AB ring was constructed first by a zirconium-mediated cycloisomerization. Several other cycloisomerization methods were also studied, but did not lead to better results. In the course of these investigations an interesting intramolecular carbolithiation was discovered. The CD rings were subsequently assembled by a Pauson-Khand reaction. A Zr-mediated cyclocarbonylation was also investigated and complements the PK reaction for the silicon-substituted substrate. It should be mentioned that 3-C_3H_5N (Scheme 5.1.7) does not correspond to a pyridyl group.

In the second part, a diastereoselective chiral auxiliary-promoted conjugate addition was applied to introduce the chirality into the AB tetraline ring. Other methods such as catalytic Rh- or Cu-catalyzed conjugate additions did not provide good results. The CD ring was formed similarly as before. A final epoxide rearrangement gave rise to the target molecule.

In the experimental part the procedures of most compounds described in the text are summarized. In the general methods section, the measurement of IR spectra was stated to be

in THF solution. Throughout the data presentation KBr is stated as the medium no matter what the physical state of the compound was. However, KBr is normally used for preparing pellets for measurements of crystalline solids. The ions in the low-resolution mass spectra are provided with decimals (for example **15-17**, **23**, **26**, **27**, **45**), does that make physical sense? A number of major products were only partly (**9**, **19**, **37**) or not at all characterized (**35**, **46**, **47**, **57**, **62**).

Formally the thesis has some shortcomings like the extensive use of "I", which is strictly forbidden in scientific writing in English. Moreover judging words, such as the often used "nice" or "sadly" should not have a place in a scientific work, which should be written using the common scientific terms and without personal attributes.

Several questions should be addressed:

1.) After generation of the allylic Grignard reagent **8a** an equilibrium with cyclic alkyl Grignard intermediate is shown. Is such a reversible interconversion of intermediates **8a** and **8b** relevant, especially in light of the experimental outcome at 60 and 100 °C, respectively? (p. 28) How can the preferred formation of the *cis*-isomer explained in comparison to the Zr-mediated reactions, which proceed trans-selective?

2.) On page 31 cyclization product **19** is depicted as a single diastereomer. However, no evidence was found in the thesis, how its stereochemistry was established and no rationalization for the formation of this diastereomer was presented. Provide an explanation!

3.) How was the relative configuration of compounds **22-27** established?

4.) The diastereoselectivity of the cuprate conjugate addition, which proceeds under substrate control, is not surprising. How could you in principal reverse the outcome of the conjugate addition (especially in the enantiomerically enriched series)?

5.) How was the structure of compound **62** established, what is the configuration at C13 and how can its formation be explained?

6.) Several contradictions of reagent amounts and yields between the Results and discussion versus the Experimental section exist: On the bottom of p.31 and Scheme 5.1.10 a lithiation with 0.95 equiv. BuLi at –10 °C was recommended based on the unexpected cyclization, while the experimental procedures for the preparation of **17** and **18** clearly state that the lithiation was performed with 1.1 equiv. BuLi between –78 and –30 °C. Clarification is here very important. The yield of **21** is 27% in Scheme 5.1.11, but to 24% in the experimental part. Furthermore, it is stated that the product was further purified by distillation under reduced pressure. Is this true given that the compound has a boiling point of ca. 40 °C as stated in the text on p.33? In the text on p.34 1.1 equiv. of $Co_2(CO)_8$ is recommended, while 1.3 equiv. are used in the procedure. On p.51 in the text and Scheme 5.2.13 the application of 10 mol% Et_2Zn is mentioned, while 5 mol% are stated in the experimental procedure. By the way, how was the 86% of **59** assayed or is this a copy-paste error? Further on p.51 the "CuCl catalyzed (10 mol%) reaction between **59** and 1,2-dibromopropene…" is mentioned. According to the experimental part this reaction was performed with overstoichiometric amounts of CuCl (3 equiv.). The presentation of the values in Schemes 5.1.4 and 5.1.5 are differing from those presented in the experimental part. Although they are not wrong they are at first glance misleading. A unified value system should be used throughout.

Overall Mgr. Betik fulfilled the aims of his work and provided a thesis, which fulfills the requirements. The experimental results were published in two papers. Therefore, I recommend the acceptance of the thesis and further proceeding to the defense to earn the degree of a PhD.

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