Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[C0025]

Different Ways to Lardolure Precursors: Application of Enzymatic Methods

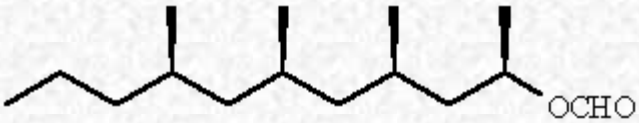
Marina Vogel, Andreas Krödel, Alexander Schulze

University of Leipzig, Institute of Organic Chemistry, Johannisallee 29, D-04103 Leipzig, Germany
E-mail: vogel@organik.chemie.uni-leipzig.de

Received: 7 August 2000 / Uploaded: 10 August

Introduction

Seven-membered lactones which possess alkyl or substituted alkyl groups in different positions are interesting pheromone precursors.[1] Such a compound is (-)-lardolure (**1**), the aggregation

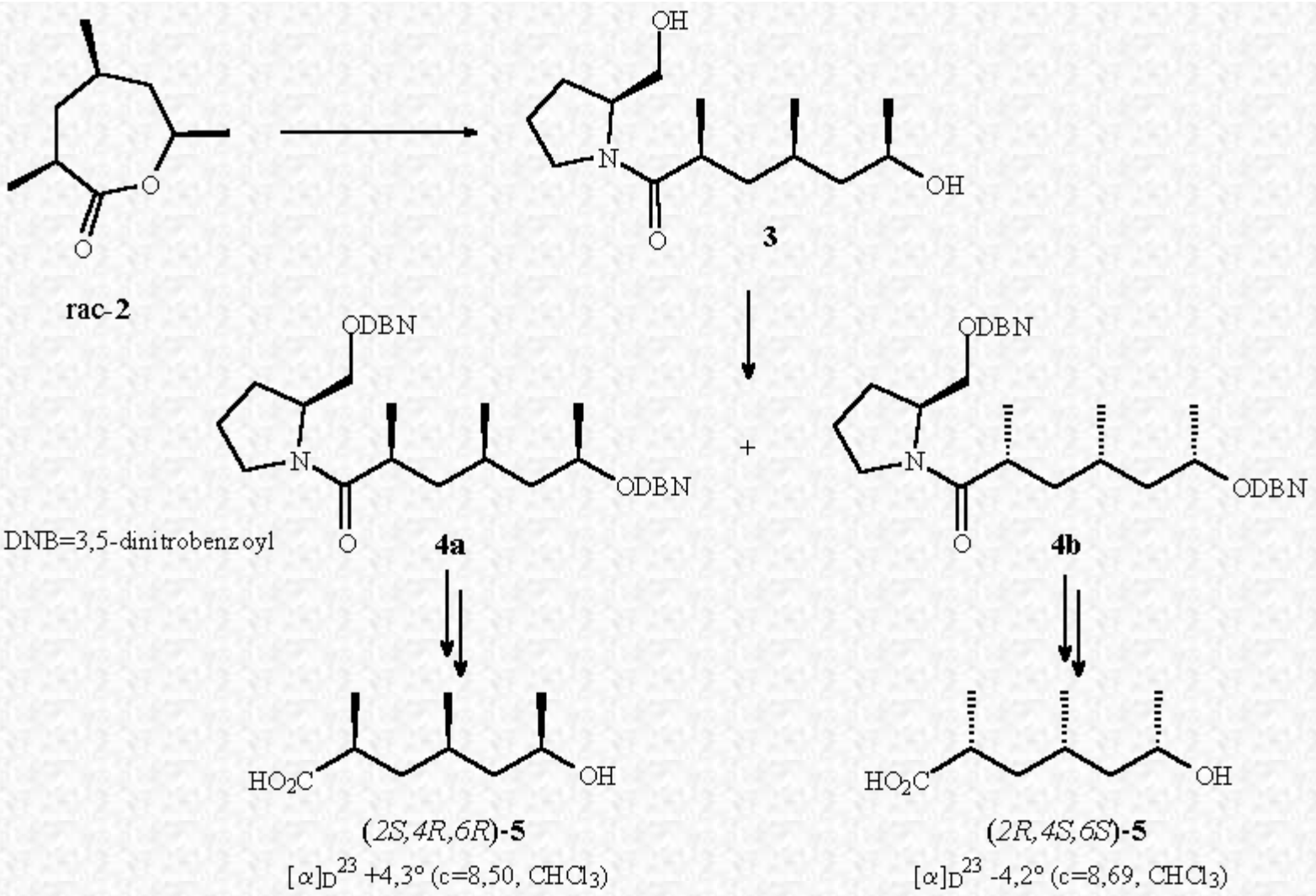


(-)-1

pheromone of the acarid mite, *Lardoglyphus konoi*,[2] which was prepared in a thirteen-step synthesis starting from the racemic lactone **2** by Mori et al.[3] The resolution of the hydroxycarboxylic acids (+)-**5** and (–)-**5** via the diastereomeric precursors **4a** and **4b** was the key reaction of this synthesis (scheme 1).

The enzymatic Baeyer-Villiger oxidation of the ketone **6** (scheme 2) and the kinetic resolution of the racemic lactone **2** with an esterase (scheme 3) could be alternative ways for a shorter synthesis of the hydroxyacids (+)-**5** and (–)-**5**, respectively.

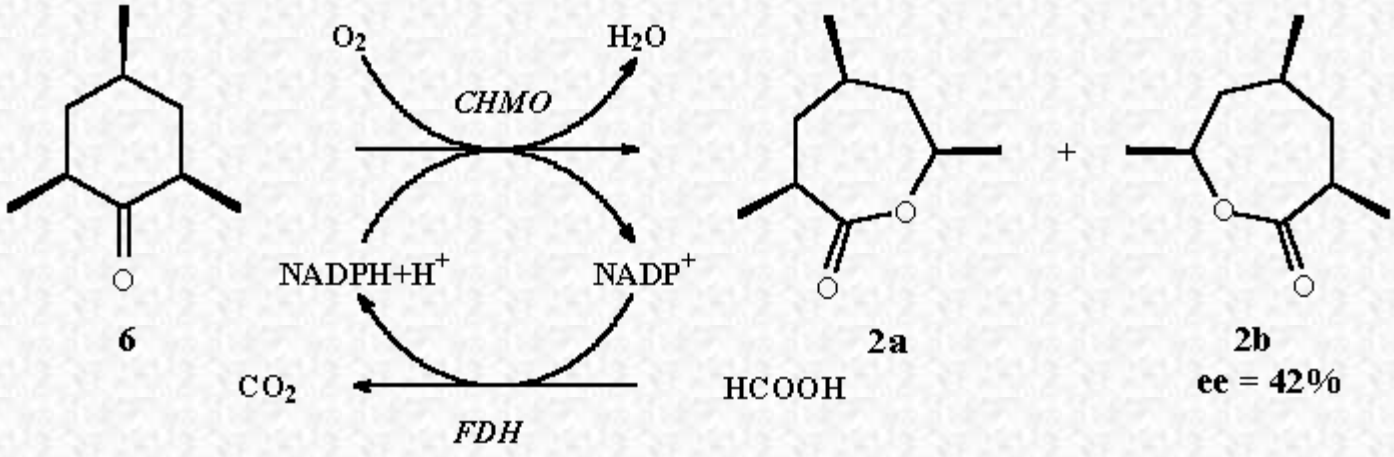
Mori´s Synthesis



Scheme 1. Synthesis of the enantiomeric hydroxycarboxylic acids (+)- and (-)-**5**, respectively.[3]

Application of Enzymatic Methods

A. Baeyer-Villiger Oxidation with Cyclohexanone Monooxygenase from *Acinetobacter* NCIMB 9871



Scheme 2. Baeyer-Villiger oxidation of ketone **6** with cyclohexanone monooxygenase (CHMO) under cofactor regeneration with formate dehydrogenase (FDH)[4].

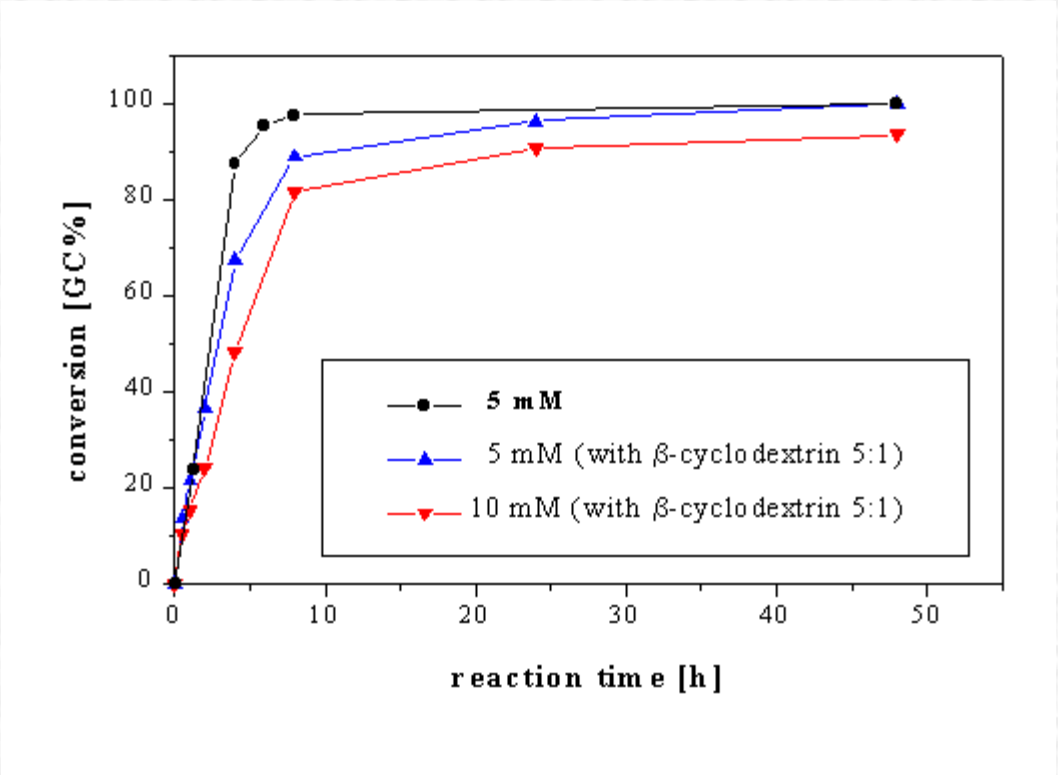
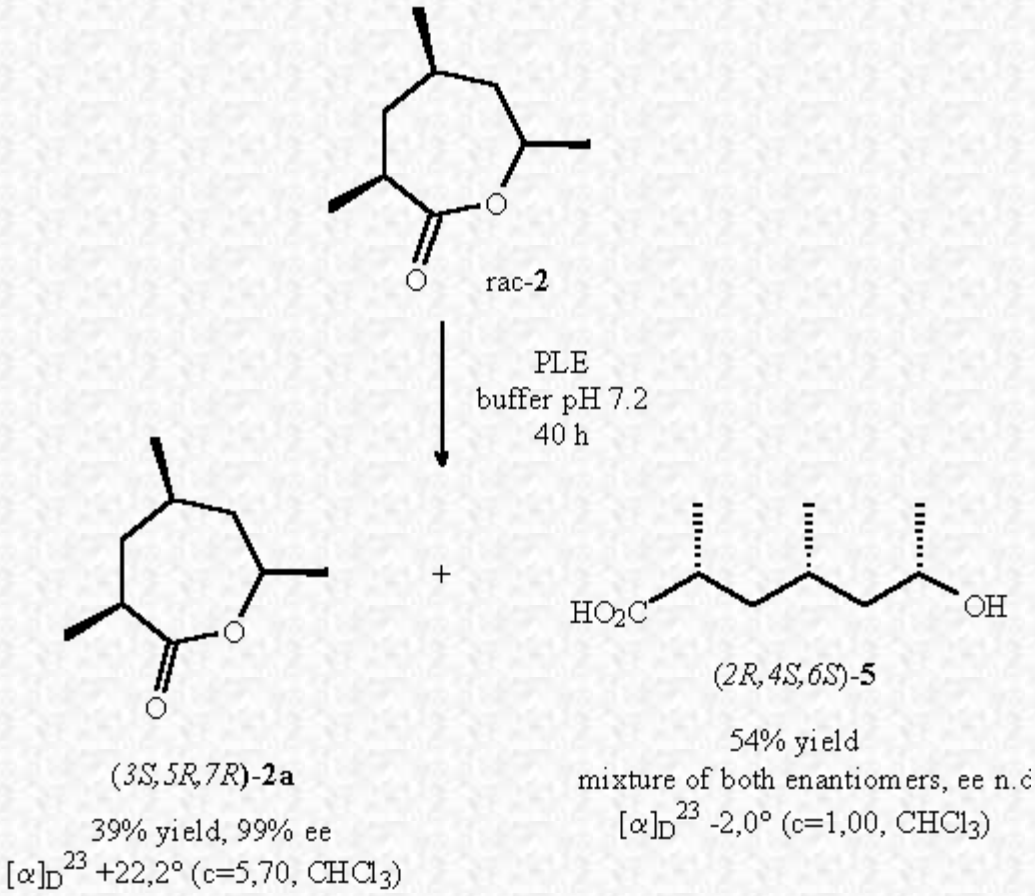


Figure 1. Formation of the lactones **2a**+**2b** under variation of the substrate concentration on analytical scale (5 m mol and 10 m mol of **6**, respectively).

B) Kinetic Resolution by Enzymatic Hydrolysis



Scheme 3. Kinetic resolution of racemic lactone **2** (0,64 mmol) with Guinea Pig liver esterase (PLE) analogous to a procedure of Fouque et al.[5]

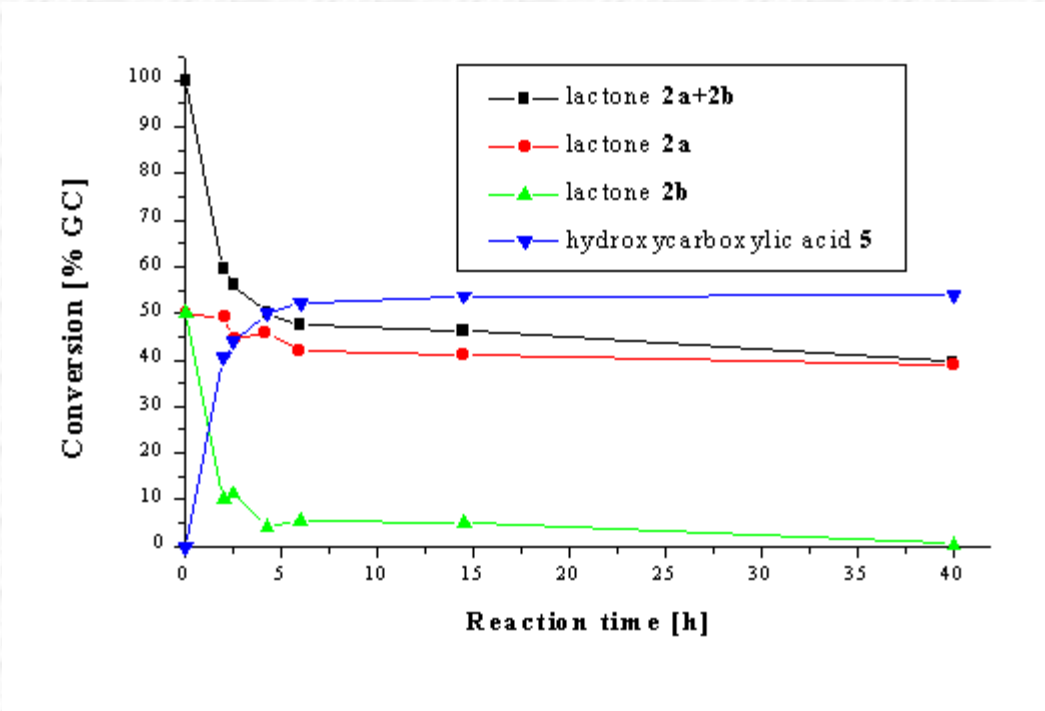


Figure 2. Conversion curves of the hydrolysis of the racemic lactone **2** with PLE.

Conclusion

1. The Baeyer-Villiger oxidation of ketone **6** is the first example of the oxidation of a symmetrically trisubstituted cyclohexanone with the cyclohexanone monooxygenase. However, the reaction proceeded only with medium enantioselectivity. The absolute configurations of the products of the enzymatic Baeyer-Villiger oxidation could be deduced by comparing the gaschromatograms of the Baeyer-Villiger products and of the enzymatic hydrolysis of the racemic lactone **2**. The major product **2b** possesses the *S*-configuration at position 7. Unfortunately, the reaction could be carried out only on analytical scale.

2. PLE hydrolyzed one of the enantiomeric lactones preferentially. The absolute configuration of this major product was deduced by comparing the sign of the optical rotation with the values of Mori et al.[3] to be *2R,4S,6S*. Hence, the absolute configuration of the lactone which belongs to (2R,4S,6S)-**5** was deduced to be *3R,5S,7S* (lactone **2b**). The synthesis of the hydroxyacid (+)-**5** via the enantiomerically pure lactone (+)-**2a** could be carried out in two simple steps starting from the racemic lactone **2** also on larger scale. The enzymatic kinetic resolution of the lactone **2** proves to be an alternative way to Mori´s synthesis.

Acknowledgements

We wish to thank Prof. U. Kragl (University of Rostock) for the fruitful co-operation. Especially, we want to thank Prof. V.I. Tishkov (Moscov State University, Russia) for the generous gift of the formate dehydrogenase. We thank Prof. P.Welzel (University of Leipzig) for the support and useful discussions. This work has been supported in the Graduate College "Mechanisms and Applications of Non-Conventional Oxidation Reactions" by the Deutsche Forschungsgemeinschaft.

References

1. Hoberg, J.O. *Tetrahedron* **1998**, *54*, 12631

2. Kuwahara, Y., Yen, L.T.M., Tominaga, Y., Matsumoto, K., Wada, Y. *Agric. Biol. Chem.* **1982**, *46*, 2283

3. Mori, K., Kuwahara, S. *Tetrahedron* **1986**, *42*, 5539

4. Rissom, S., Schwarz-Linek, U., Vogel, M., Tishkov, V.I., Kragl, U. *Tetrahedron: Asymmetry* **1997**, *8*, 2523

5. Fouque, E., Rousseau, G. *Synthesis* **1989**, 661
