Diastereoselective Lactonization of Optically Active α-Hydroxy-β-oxoesters

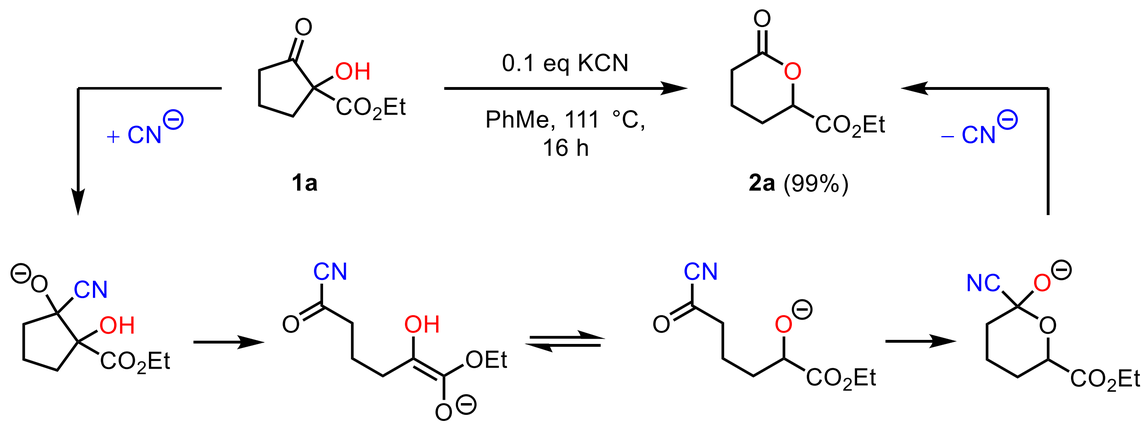
Oliver Groben, David Kieslich, and Jens Christoffers*

Institut für Chemie, Universität Oldenburg, Carl-von-Ossietzky Str. 9-11, 26111 D-Oldenburg

We report on the synthesis of optically active δ-lactones. Subjecting cyclopentenones to asymmetric 1,4-addition and introducing an ester moiety in 2-position provides β-oxoesters, which are smoothly transformed into α-hydroxy-β-oxoesters applying a cerium catalyst and atmospheric oxygen. Finally the α-hydroxy-β-oxoesters undergo a cyanide catalyzed rearrangement forming δ-lactones.

Introduction

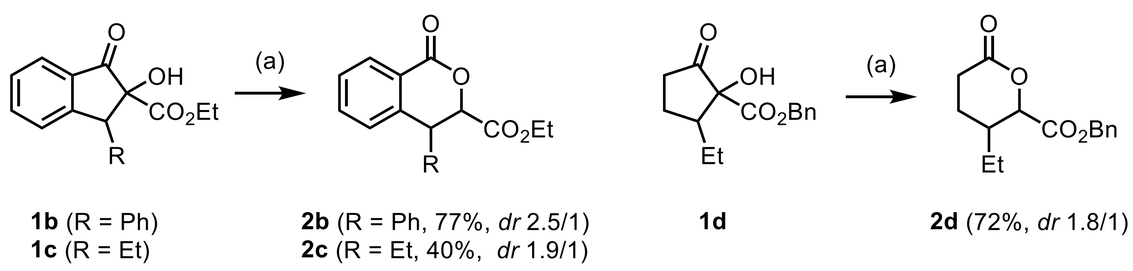
The δ-lactone unit is a widely spread structural motif in natural and synthetic products. They are commonly synthesized by intramolecular esterification or the Baeyer-Villiger Oxidation. We developed a novel approach by reacting an α-hydroxy-β-oxoester **1a** with a nucleophilic cyanide catalyst.[1] This method furnishes a δ-lactone **2a** with up to 99% yield (Scheme 1).



Scheme 1: Conditions and proposed mechanism of the cyanide catalyzed lactonization.

Stereoselectivity of the rearrangement reaction

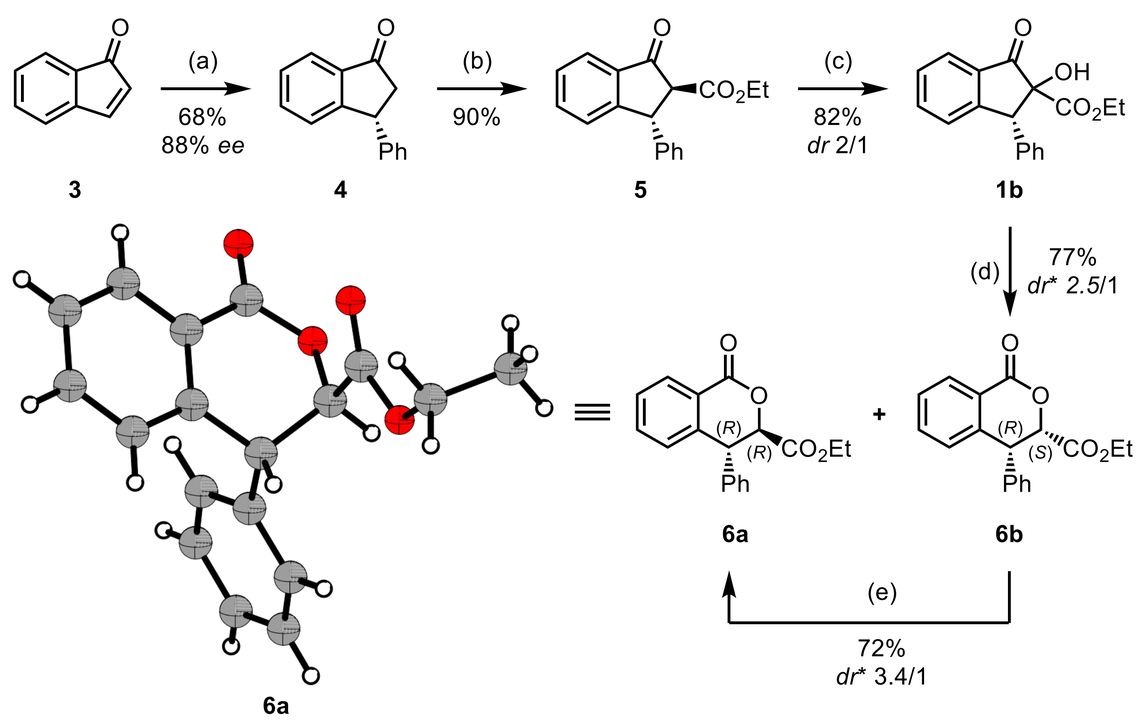
First investigations showed, in agreement with the proposed mechanism (Scheme 1), that the stereoinformation within the α-hydroxy-β-oxoesters is not conserved during the lactonization, when applying optically active starting material. We therefore pursued a strategy utilizing internal stereoinduction by having implemented a second stereogenic center vicinal to the first one on the α-hydroxy-β-oxoesters **1b-d** (Scheme 2). With ethyl and phenyl substituents the lactonization was found to be diastereoselective. The highest diastereomeric ratios were achieved by carrying out the reaction in refluxing toluene with diastereomeric ratios up to 2.5/1. Straightforward NOE-spectroscopy revealed that the favored diastereomer has *trans*-configuration in all cases.



Scheme 2: Diastereoselective lactonization of substituted α-hydroxy-β-oxoesters. Reagents and conditions: (a) 0.2 eq KCN, PhMe, 111°C, 16 h.

Establishing the synthetic route

We started with the conjugate addition to indenone **3** (Scheme 3). Minaard *et al*.[2] developed a procedure for the asymmetric conjugate addition of aryl boronic acids which we modified using (*R*)-DTBM-SEGPHOS in a ethanol/water-mixture resulting in an enantiomeric excess of 88% of phenylindanone **4** with 68% yield. In the following Claisen condensation we applied kinetic conditions for the deprotonation of **4** in order to avoid epimerization of the already established stereocenter. LiHMDS at low temperatures turned out to be the conditions of choice for conserving the enantiomeric excess while achieving a good yield of 90%. Hydroxylation of the α-position was carried out according to prior work of our research group.[3] Oxoester **5** was stirred over night in the presence of a cerium catalyst in *i*-PrOH under aerobic conditions. This reaction gave α-hydroxy-β-oxoester **1b** smoothly with 82% yield. The lactonization furnished lactones **6a** and **6b** in 77% yield with a diastereomeric ratio of 2.5/1, favoring *trans*-configuration. After column chromatographic separation of both diastereomers **6a** and **6b** pure lactone **6b** was epimerized using the bulky triphenyl methanolate base in order to obtain additional lactone **6a**. From indenone **3** we synthesized lactone **6a** in over five steps with 34% yield and an enantiomeric excess of 88%. Furthermore, we were able to elucidate the absolute configuration of lactone **6a** by X-ray structure analysis.



Scheme 3: Synthesis of optically active δ-lactones. Reagents and conditions: (a) 2.0 eq $PhB(OH)_2$, 0.1 eq (*R*)-DTBM-SEGPHOS, 0.2 eq $AgPF_6$, 0.05 eq $Pd(OAc)_2$, EtOH/H_2O (10/1), r.t., 16 h; (b) 1) 2.0 eq LiHMDS, abs. Et_2O, –80°C, 2 h. 2) 4.0 eq $NC(CO)CO_2Et$, r.t., 4 h; (c) 0.05 eq $CeCl_3 \cdot 7\ H_2O$, r.t., 16 h, O_2 (air); (d) 0.2 eq KCN, PhMe, 111°C, 16 h; (e) 0.5 eq TrONa, abs. THF, 50°C, 16 h. **dr* = trans/cis

[1] D. Kieslich, J. Christoffers, *Org. Lett*. **2021**, *23*, 953–957.
[2] F. Gini, B. Hessen, A. J. Minnaard, *Org. Lett*. **2005**, *7*, 5309–5312.
[3] J. Christoffers, T. Werner, *Synlett* **2002**, 119–121.