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A new asymmetric route to synthetically useful γ-substituted γ-butyrolactones

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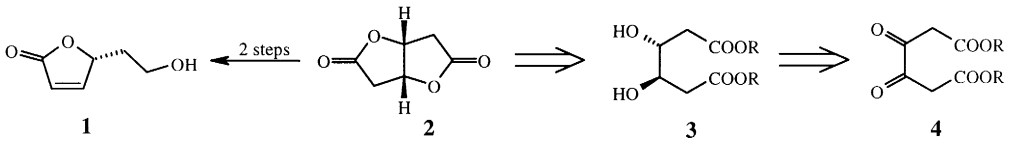
Abstract

The results of asymmetric hydrogenation of diethyl 3,4-dioxohexanedioate are presented. (*R*,*R*)-1,5-Dioxa-2,6-dioxobicyclo[3.3.0]octane, the product of hydrogenation and subsequent cyclization, was obtained in high enantiomeric excess. This compound was transformed into synthetically useful (*R*)-4-hydroxyethyl-2-buten-4-olide. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: γ-butyrolactones; asymmetric hydrogenation; diethyl 3,4-dioxohexanedioate.

Searching for a new synthetic approach to enantiomerically pure butenolides we considered compound **1** as a versatile synthon (Scheme 1). Its synthetic utility has recently been shown by the syntheses of eldanolide,[1] Geissman–Waiss lactone[2] and 11-deoxyprostaglandines.[3] Known procedures enabled a preparation of **1** in optically pure form starting from (*R*)-malic acid[4] or employing enzymatic procedures[5] and asymmetric synthesis.[6] One of the simplest methods to produce racemic **1** was a two-step transformation of dilactone **2** as shown by Sakai et al.[1] Potential application of this approach to the asymmetric synthesis of **1**, prompted us to elaborate a synthesis of optically active dilactone **2**.[7] Its logical retrosynthetic precursor was diol **3** which could be considered as a product of asymmetric reduction of 3,4-dioxohexanedioates **4**.



1 **2** **3** **4**

Scheme 1.

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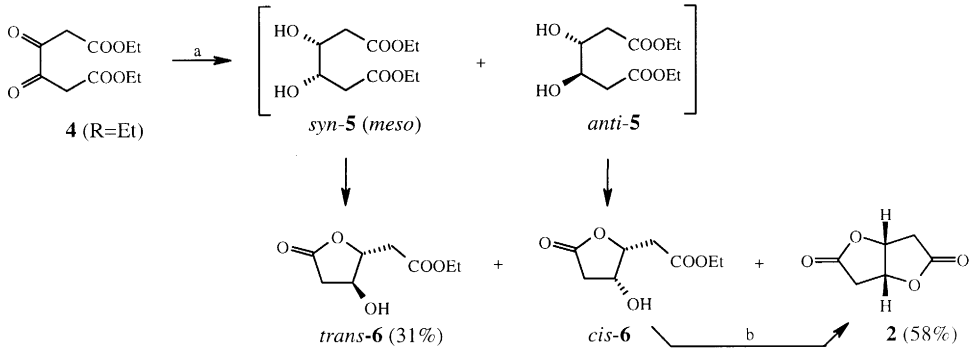
Asymmetric hydrogenation of functionalized ketones in the presence of chiral Ru(II) catalysts is already a well established method in organic synthesis.[8] However, little is known about this method when applied to functionalized diketones.[9] In this communication we present the results of the asymmetric hydrogenation of diethyl 3,4-dioxohexanedioate (**4**, R=Et)[10] as a representative of this class of compounds.

Under hydrogenation conditions using $RuCl_2$[(*S*)-BINAP](*p*-cymene) as the catalyst, diketone **4** (R=Et) gave three products: an inseparable mixture of hydroxylactones *trans*-**6** and *cis*-**6**, and dilactone **2** (Scheme 2). In order to complete the cyclization reaction, we heated the crude post-hydrogenation mixture in toluene, in the presence of *p*-toluenesulfonic acid. As expected, lactone *trans*-**6** did not change under these conditions, and finally only two separable products remained: *trans*-**6** and **2** (89% overall yield, ratio 35:65, respectively). Hydroxylactone *trans*-**6** showed no optical activity and obviously represented a product of cyclization of the *meso*-diol. This result suggested that the first step was the formation of both diols **5**, followed by cyclization leading to hydroxylactones **6**. Unlike *trans*-**6**, hydroxylactone *cis*-**6** underwent further cyclization to dilactone **2**.

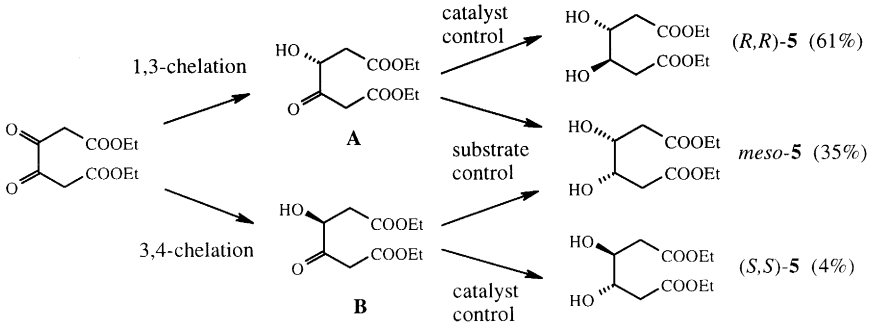


Scheme 2. (a) H_2, 100 atm, $RuCl_2$[(*S*)-BINAP](*p*-cymene), EtOH, 65°C, 16 h; (b) *p*-TsOH, toluene, reflux, 30 min

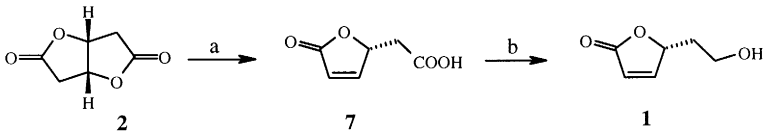
Dilactone **2** was optically active {$[\alpha]_D^{23}$ +125 (*c* 1.0, H_2O); lit.[7] $[\alpha]_D^{19}$ +143 (*c* 1.0, H_2O)} and its enantiomeric excess (89% ee) was confirmed using ^1H NMR by addition of chiral shift reagent [Eu(hfc)$_3$]. After recrystallization from 2-propanol, the enantiomeric purity reached 96% ee. The absolute configuration of dilactone **2** was established to be (*R*,*R*) on the basis of the sign of the specific rotation. (+)-Dilactone **2** had originally been correlated to (+)-malic acid.[7]

Considering the stereochemistry and the ratio of the reaction products, a preliminary conclusion about the competition between 1,3- and 3,4-chelation of the catalyst could be made. Disregarding other factors, two extreme possibilities may be imagined: either the substrate is reduced as a typical 3-oxoester (ethyl 3-oxobutanoate) and then, by using Ru-(*S*)-BINAP catalyst, the product with the (*R*,*R*) configuration (>99% ee) should predominate;[11] or the substrate is reduced as a 1,2-diketone (diacetyl), and then the *meso* compound (74%) is expected together with the minor product with the (*S*,*S*) configuration (26%, >99% ee).[11] Since we obtained 65% (89% ee) of the *anti*-(*R*,*R*)-product and 35% of the *meso* product, we might calculate that both ways of chelation had unequal impact on the stereochemical outcome (ca. 84:16 ratio of the products of 1,3- and 3,4-chelation, respectively). The reaction could be considered stepwise, but this does not bring too much complexity, since the intermediates **A** and **B** should follow the indicated pathways (Scheme 3). On the basis of the ratio of *meso*-**5** and (*S*,*S*)-**5** one may also calculate that both intermediates **A** and **B** follow a substrate controlled transformation into *meso*-**5** to an approximately equal extent.

Finally, having dilactone **2** in high enantiomeric excess we transformed it into the target **1**[12] via muconolactone **7**[12] as described by Sakai et al.[1] for racemic material (Scheme 4).



Scheme 3. Possible pathways of the asymmetric catalytic hydrogenation of diethyl 3,4-dioxohexanedioate



Scheme 4. (a) K_2CO_3, acetone, MeOH, rt, 16 h; (b) $BH_3 \cdot Me_2S$, THF, rt, 6 h

In conclusion, we have developed a short synthetic route to butenolides **7** and **1**, based on a highly enantioselective hydrogenation. These lactones could be very attractive chirons if one considers the possibility of stereoselective functionalization in positions 2 and 3, based on 1,4-addition of nucleophilic reagents and subsequent trapping with electrophiles. Such a sequence has recently been applied to similar 4-substituted 2-buten-4-olides, offering an attractive route to natural compounds.[3,13]

Acknowledgements

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12. Both compounds **1** and **7** have spectroscopic data consistent with the literature (see Refs. 1 and 5). Compound **1**: $[\alpha]_D^{23}$ −45.7 (*c* 1.0, $CHCl_3$) {lit.[5a] $[\alpha]_D^{21}$ −46.4 (*c* 0.91, $CHCl_3$)}; **7**: $[\alpha]_D^{23}$ −78.2 (*c* 0.5, AcOEt) {lit.[7] $[\alpha]_D^{20}$ −80.9 (*c* 0.865, AcOEt)}.
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