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HIGHLY ENANTIOSELECTIVE REDUCTION OF ACETOACETYLATED MELDRUM'S ACID WITH FERMENTING BAKER'S YEAST

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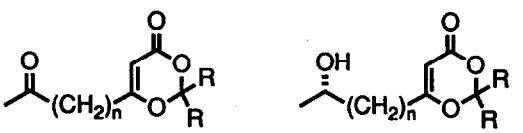
Summary: *Acetoacetylated Meldrum's acid was enantioselectiviely reduced with fermenting baker's yeast to afford the corresponding chiral (S)-alcohol, which could be easily converted to δ-lactone derivatives.*

Asymmetric microbial reduction of prochiral ketones with baker's yeast (*Saccharomyces cerevisiae*) is an effective method for the preparation of chiral secondary alcohols. The enantioselectivity of the reduction has been well recognized to be dependent much upon the difference between bulkiness of two groups attached to the carbonyl.[1] Therefore it is desirable to explore new functional groups which not only display the marked steric requirement but also accept a variety of following manipulations. Previously, we have demonstrated that alkyl ketones having 4-oxo-1,3-dioxin-6-yl group (**1**: n=0~2) are reduced with the yeast to give the alcohol (**2**) in satisfactory enantiomeric excesses (90~100% e.e.), whose dioxinone moiety serves as acylketene as well as β-ketoester equivalents.[2] In this paper we report successful use of Meldrum's acid (1,3-dioxan-4,6-dione) as the alternative functional group for the yeast reduction and completely enantioselective synthesis of hexanolides by the manipulation of the dioxane ring.

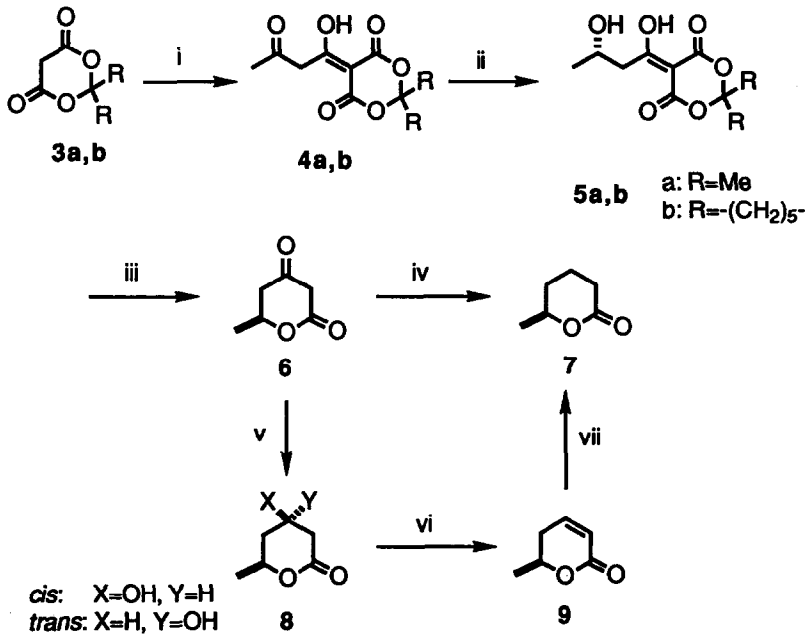


1 **2**

Scheme 1

Meldrum's acid (**3a**) and its acylated analogues have been well known as versatile synthons.[3] When acetoacetylated Meldrum's acid (**4a**)[4] readily prepared from **3a** and diketene was reduced with fermenting yeast,[5] the alcohol (**5a**) having *S*-configuration was obtained in *ca.* 60% yield. On refluxing in methanol or benzene, **5a** was quantitatively converted to the keto hexanolide (**6**). Though one recrystallization of the product (**6**) from ethanol affords enantiomerically pure **6** [mp 142-143 °C, $[\alpha]_D^{29}$ +153.4° (*c* 2.1, EtOH)], the crude (**6**) was directly subjected to the hydrogenation using PtO_2[6] to give the known *S*-hexanolide [**7**: $[\alpha]_D^{27}$ -40.4° (*c* 1.0, EtOH), lit.[7] $[\alpha]_D^{20}$ -34.3° (*c* 2.0,

EtOH). The precise e.e. of **6** was determined to be more than 99% by HPLC using ChiraSpher (Merck) column. The spiro analogue (**4b**) was also reduced under the same condition to give the alcohol (**5b**) in 55% yield. The e.e. of **7** derived from **5b** in the same manner as above was 98%.

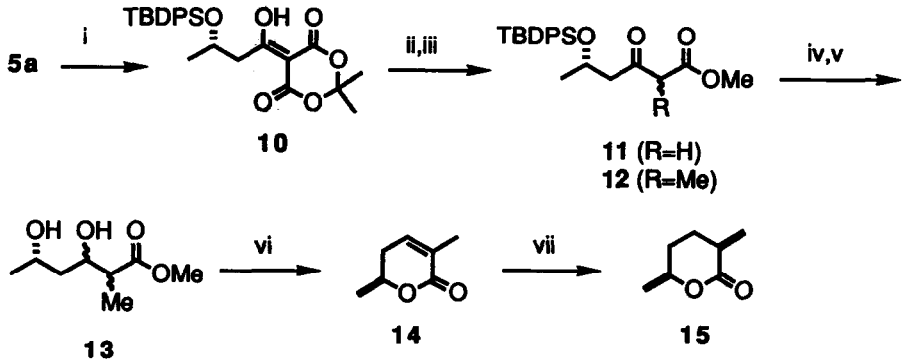


Scheme 2

Conditions: i) diketene, Et_3N, ii) baker's yeast, 30-32 °C, iii) MeOH or toluene, Δ, 80%, iv) H_2/ PtO_2, AcOEt, 56%, v) H_2, Raney Ni, EtOH, 41%, vi) TsOH, benzene, Δ, 90%, vii) H_2/ Pd-C, 65%

Parasorbic acid **9** is a potential chiral intermediate for a variety of natural products, since it accepts conjugate addition with high stereoselectivity.[8] We have found a facile method for preparation of enantiomerically pure **9**. The recrystallized keto lactone (**6**) was converted to the hydroxy lactone (*cis*- and *trans*-**8**, 4:1), which was dehydrated to give enantiomerically pure **9** [$[\alpha]_D^{26}$ +182.6° (*c* 2.04, EtOH), lit[9] $[\alpha]_D$ +180-200° (EtOH)]. The e.e. of this sample was determined to be 100% by HPLC analysis using Chiralcell OB (Daicel) column. The enantiomerically pure **7** [$[\alpha]_D^{24}$ -40° (*c* 1.0, EtOH)] was obtained by hydrogenation of either **6** or **9**.

cis-3,6-Dimethyltetrahydropyran-2-one (**15**) is the major component of the pheromonal secretion of the male carpenter bee (*Xylocopa hirutissima*).[10] Thus our attention has been focused on the enantionselective synthesis of this pheromone by using **5a** as a chiral synthon. Although synthesis of **15** *via* the β-ketolactone (**6**) has been reported in racemic series, *C*-methylation of **6** at the 3-position is accompanied with undesired *O*-methylation at the 4-position.[6] Another synthetic method *via* direct methylation of δ-lactone (**7**) at the 3-position gave 3,6-dimethyl derivative as a mixture of *cis* and *trans* isomers (*ca.* 1:1).[8] Our synthetic route to **15** overcoming these shortcomings is shown in Scheme 3. Optically pure alcohol **5a** was protected with silyl group and the silyl ether (**10**) was ring-opened by methanol to give the β-ketoester (**11**), which could be methylated selectively at the α-position. Compound **12** thus obtained was converted to the α,β-unsaturated δ-lactone [**14**: $[\alpha]_D^{23}$ +184.4° (*c* 1.14, $CHCl_3$)] *via* reduction of carbonyl group by $NaBH_4$, fluoride-mediated deprotection of the silyl group, and lactonization followed by dehydration by reflux in benzene containing catalytic amount of TsOH. According to the reported procedure,[6,11] the lactone (**14**) was reduced by catalytic hydrogenation[12] to give 3,6-dimethyl δ-lactone (*cis*:*trans*=96:4),[13] which was easily separated by preparative HPLC to afford enantiomerically pure (3*R*, 6*S*)-dimethyl-pyran-2-one [**15**: mp 49-50 °C, $[\alpha]_D^{21}$ -98.0° (*c* 0.39, $CHCl_3$), lit[11] mp 49-50 °C, $[\alpha]_D^{20}$ -97.6° (*c* 0.7, $CHCl_3$)].



Scheme 3

Conditions: i) TBDPS-Cl, imidazole, 91%, ii) MeOH, Δ, 90%, iii) MeI, NaH, 81%, iv) $NaBH_4$, 91%, v) $Bu_4N^+F^-$, 70%, vi) TsOH, benzene, Δ, 87%, vii) H_2/ Pd-C, AcOEt, 99%

In summary, acetoacetylated Meldrum's acid (**4**) was found to be reduced enantioselectively (>99% e.e.) by baker's yeast to the corresponding (*S*)-alcohol (**5**). Since yeast reduction of 6-(2-oxopropyl)-1,3-dioxin-4-one (**1**: n=1) gave the corresponding (*S*)-alcohol in 90% e.e.,[2] use of **5** in

the same reduction is obviously much superior. It should also be noted that, while the 6-(2-oxobutyl)dioxinone was reduced in poor e.e. (43%), the same reduction of the corresponding homologue (**4**: EtCO instead of MeCO) was again found to give the corresponding (*S*)-alcohol in >99% e.e. [yield, 63%; $[\alpha]_D^{23}$ +40.4° (*c* 2.03, EtOH)]. Baker's yeast reduction of a variety of prochiral ketones having Meldrum's acid as one terminal unit is now under active investigation and the result will be reported in due course.

References and Notes

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5. Typical procedure for the preparation of **5a**: A mixture of baker's yeast (Oriental Yeast Co., 150 g), sucrose (75 g), and water (300 ml) was shaken at 32 °C for 30 min. Compound **4a** (10 mmol) was added to the mixture and the whole was shaken at the same temperature for 12 h. Most of water was evaporated *in vacuo* at below 35 °C. Salt (*ca.* 50 g) and Celite (50-100 g) were added to the mixture and the resulting paste was extracted repeatedly with dichloromethane by means of mechanical stirring followed by decantation. The combined extract was dried over $MgSO_4$ and then evaporated. The oily residue was purified by silica gel column chromatography (CH_2Cl_2-MeOH= 20:1 V/V) to give oily **5a** (1.23 g, 62%) $[\alpha]_D^{25}$ +50.6° (*c* 2.05, EtOH).
6. Conversion of **6** to **7** in racemic form: R. Bacardit and M. Moreno-Manas, *Tetrahedron Lett.*, **21**, 551 (1980).
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12. The hydrogenation was examined by changing solvent, catalyst, and temperature (-20~25 °C) and the highest *cis*/*trans* ratio was obtained using 10% Pd-C in AcOEt at room temperature.
13. Determined by 500 MHz ^{1}H-NMR.

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