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HIGHLY ENANTIOSELECTIVE REDUCTION OF δ-KETO ACIDS WITH FERMENTING BAKER'S YEAST. A FACILE SYNTHESIS OF OPTICALLY PURE (R)-(+)-5-HEXADECANOLIDE

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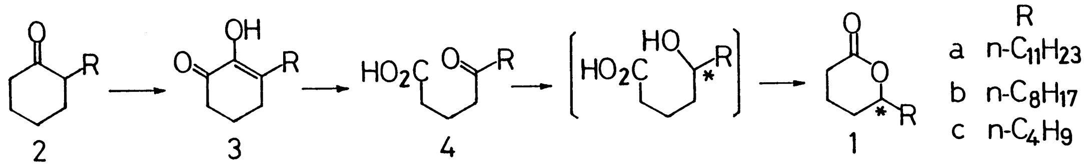
Optically pure (R)-(+)-hexadecanolide, (+)-5-tridecanolide, and (+)-5-nonanolide were prepared from the corresponding δ-keto acids by reduction with fermenting baker's yeast.

5-Hexadecanolide (**1a**), a pheromone isolated from the oriental hornet (*vespa orientalis*) in 1969,[1] has induced ten attempts to synthesize the optically active form.[2] Here we wish to report the eleventh synthesis of **1a** that involves the most effective method of obtaining the optically pure (R)-(+)-enantiomer of **1a** by using fermenting baker's yeast as shown in Scheme 1. Use of baker's yeast in the reduction of δ-keto acid **4a** was once reported to be unsatisfactory because the optical yield was only 39%.[2d,h] We have not yet clarified why our reduction was highly enantioselective.

2-Undecylcyclohexanone (**2a**)[3] was converted via its 2,6-dibromo derivative to 3-undecyl-1,2-cyclohexanedione (**3a**) in 57% yield.[4] The dione **3a** reacted readily with oxygen by catalysis of $CuCl_2$ to afford δ-keto acid **4a** in 81% yield.[5] A suspension of baker's yeast (2.76 g, Nisshin Seihun Co.), glucose (3.10 g), KH_2PO_4 (7 mg), $MgSO_4$ (4 mg) in boiled water (9 ml) was stirred for 30 min at 25 °C. To the fermenting mixture was added **4a** (135 mg, 0.50 mmol) dissolved in water by addition of 1 M KOH and the resulting mixture was adjusted to pH 7 with 1 M KOH.[6] After stirring for 5 h at 25 °C, the glucose added initially was consumed as checked by a test paper (Diastix–II, Miles-Sankyo Co.). Then 6.2 g of glucose was added to the mixture. After 17 h, when the vigorous fermentation appeared to cease, the equal amount of the initially used yeast-glucose suspension was added and stirring was continued at 25 °C until the total elapse of fermentation reached 48 h. The mixture was stirred with Celite (8.2 g) for 30 min and filtered. The Celite was washed with water and then with ether three times. The filtrate and washings were combined, acidified to pH 2 with 10% HCl, and extracted with ether five times. The combined ethereal solution, after drying ($MgSO_4$) and evaporation,



Scheme 1.

gave a crude oil (305 mg) which was refluxed in benzene for 1 h with *p*-TsOH. The crude product (293 mg) was purified by passing through a silica gel column (hexane–acetone 30:1) to give 129 mg of a semisolid. This was further purified by HPLC (silica gel, hexane–AcOEt 5:1) to afford 51 mg (40%) of (R)-(+)-**1a** as colorless crystals, mp 37.5–38 °C (lit.2h) 37 °C), $[\alpha]_D^{23}$ +39.5° (c 1.74, THF) (lit.2h) $[\alpha]_D^{21.5}$ +40.2° (c 1.76, THF). In order to determine the optical purity accurately, **1a** was converted to the diol with MeLi,7) followed by ^1H FT NMR examination of the diol in the presence of $Eu(hfc)_3$. The two methyl groups attached to the quaternary carbon atom appeared as two singlets without any trace of paired signals,8) indicating that the optical purity was >98% ee.

In similar ways, the use of fermenting baker's yeast in the reduction of 5-oxotridecanoic and 5-oxononanoic acids (**4b**,**c**) afforded the corresponding (+)-5-tridecanolide (**1b**) and (+)-5-nonanolide (**1c**) in 54% yield (>98% ee, $[\alpha]_D^{26}$ +45.2° (c 1.58. THF)) and 67% yield (>98% ee, $[\alpha]_D^{27}$ +58.1° (c 3.66, THF)) (lit.9) $[\alpha]_D^{20}$ +58.2° (MeOH)), respectively.

In conclusion, we have found that the δ-keto group can be reduced by fermenting baker's yeast with high enantioselectivity. This methodology can be applied to the synthesis of optically pure δ-lactones effectively.

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