Tetrahedron Letters,Vol.26,No.4,pp 451-452,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

PREPARATION OF CHIRAL CYCLOHEXANOL DERIVATIVE WITH HIGH OPTICAL PURITY BY YEAST REDUCTION

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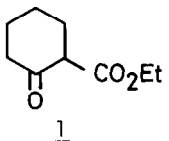
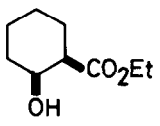
Summary: Reduction of 2-ethoxycarbonyl-4,4-ethylenedioxycyclohexanone (6) with baker's yeast provided cis-hydroxy ester 7 in 74% yield as a sole product. Optical purity of 7 was determined as its MTPA ester to be 98.4% e.e. 10 g of the chiral 7 could be produced in one lot.

Since Ridley and co-workers first reported the reduction of β-keto esters by baker's yeast (Saccharomyces cerevisiae) affording β-hydroxy esters with high optical purity,[1] it has been known that many types of β-keto esters including ethyl acetoacetate[1,2] could be a substrate for this biochemical asymmetric reduction. Only a few cyclic β-keto esters, however, were employed for this reduction and optical purities of the products did not exceed 90% e.e. For example, according to Ridley[1] and Fráter,[3] 2-ethoxycarbonylcyclohexanone (1) gave cis-(1R,2S)-hydroxy ester 2 in 69% yield (86% e.e.), while Hoffmann and co-workers reported that optical purities of five- and six-membered thia analogues, 3 and 4, were ca. 85% e.e.[4]

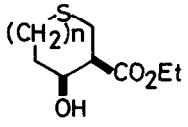
We wish to report an efficient preparation of a chiral cyclohexanol derivative 7 with extremely high optical purity (98.4% e.e.). The substrate, 4,4-ethylenedioxy-2-ethoxycarbonylcyclohexanone (6) was prepared from β-2-furylacrylic acid (5) in a similar manner as reported[5] with several modifications. Overall yield was improved from 31%[5] to 61% in our modified procedure.[6] Asymmetric reduction of 6 with baker's yeast gave a single product in 74% yield based on the unrecovered 6 (67% efficiency), which was identified as ethyl (1R,2S)-4,4-ethylenedioxy-2-hydroxycyclohexanecarboxylate (7).[7] In a preparative scale, ca. 10 g of 7 could be isolated from 15 g of the substrate 6 in one batch.



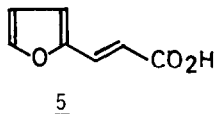
1



2 (86% e.e.)



3: n= 0
4: n= 1
(85% e.e.)



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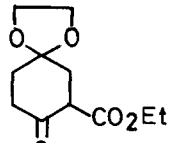
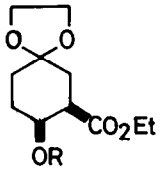
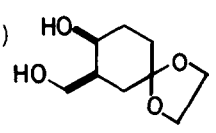


6



7: R= H (98.4% e.e.)
8: R= Ac
9: R= (S)- and (R)-MTPA



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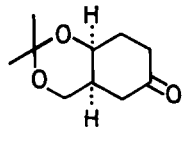

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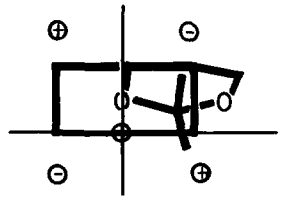

Relative stereochemistry of 7 was determined by ^{1}H-NMR spectrum of its crystalline acetate 8. Observed half-hights-width (hhw) of C-2 H, acetoxy methine proton, was 7.0 Hz and this concludes

that 8 (therefore 7) has cis-configuration. Optical purity was determined by HPLC analysis of its (R)-and (S)-MTPA esters 9[8] and shown to be 98.4% e.e.[9] This extremely high optical purity was probably resulted bacause the presence of ethylenedioxy substituent forced the flexible cyclohexane ring to fix more tightly than the unsubstituted cyclohexanones.

Finally absolute configuration was determined as follows: Reduction of 7 with $LiAlH_4$ gave a diol 10, which was treated with refluxing acetone in the presence of p-TsOH to give a cis-dioxadecalone 11, showing negative Cotton effect in CD spectrum.[10] Absolute configuration of 11, therefore, was determined as (4aR,8aS).

In conclusion, asymmetric reduction of the keto ester 6 with baker's yeast gave ethyl (1R, 2S)-2-hydroxycyclohexanecarboxylate (7) in 98.4% e.e. Both 7 and 11 should be very useful intermediate for the synthesis of chiral natural products and applications are in progress.

Acknowledgment: We thank Japan spectroscopic Co. Ltd. for CD measurement.

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6. After the acetalization of diethyl 4-oxopimerate with ethylene glycol, crude product was treated with 0.5% EtONa in EtOH under reflux for 40 min. During this treatment, substantial amount of ethylene glycol esters in crude mixture were converted to diethyl ester and the yield of diethyl 4,4-ethylenedioxypimerate was remarkably improved.
7. 200 g of dry yeast (Supplier: Oriental yeast Co. Ltd.) was used for the reduction of 6 (15 g). SiO_2 chromatography followed by distillation gave the recovered 6 (1.55 g) and 7 (10.1 g; 67%, 74% based on the recovery). Detailed procedure will be published in a full account. 7: bp 117--8 °C / 0.35 mmHg, n_D^{25} 1.4695, R_f = 0.37 (hexane / EtOAc = 1 / 1), $[\alpha]_D^{23}$ +51.1° (c 1.02, $CHCl_3$).
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9. HPLC condition: Column; normal phase, Nucleosil® 50-5, 4.6 mmφ x 25 cm. Solvent; Hexane / THF = 10 / 1. Flow rate; 1.2 ml / min (50 kg / cm^2). Detector; UV, 254 nm. Ratio was calculated by peak areas of two diastereomers at t_R 20.1 min and 23.5 min obtained from both (S)- and (R)-MTPA esters.
10. 11: bp 90--95 °C / 0.2 mmHg, n_D^{25} 1.4656, $[\alpha]_D^{22}$ +26.7° (c 0.30, $CHCl_3$), CD; $[\theta]_{288}$ -3534 (MeOH).

(Received in Japan 20 October 1984)