MICROBIOLOGICAL ASYMMETRIC INDUCTION OF 4,9-DIMETHYL-3,5-DIOXO-$\Delta^{4(10)}$-OCTALIN[1]

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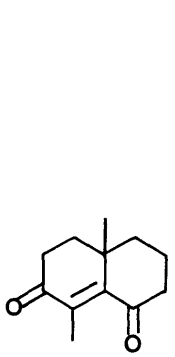
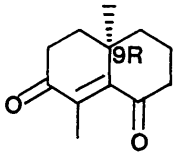
Microbiological asymmetric induction of 4,9-dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin, (±)-1 was accomplished with various yeasts. With properly selected microorganisms, (+)-4,(9*S*)-dimethyl-(5*S*)-hydroxy- (2) and (-)-4,(9*R*)-dimethyl-(5*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (3), (-)-4,(9*R*)-dimethyl-(3*S*)-hydroxy- (6) and (+)-4,(9*S*)-dimethyl-(3*S*)-hydroxy-5-oxo-$\Delta^{4(10)}$-octalin (7) were obtained with high optical purity.

KEYWORDS 3,5-dioxooctalin; (5*S*)-hydroxy-3-oxooctalin; (3*S*)-hydroxy-5-oxooctalin; microbiological reduction; asymmetric induction; yeast; *Kloeckera saturunus*; lipase; *Rhodotorula rubla*

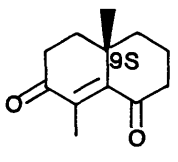
The use of biological systems (enzymes or microorganisms) to prepare chiral alcohols is widespread and very efficient. There are numerous examples[2] of biological reduction of acyclic ketones, but only a few reports[3] of bicyclic ketone reduction using microorganisms such as yeasts. Earlier we reported[4,5] the reduction of bicyclic ketones by microorganisms (yeasts). These optically active bicyclic compounds were useful for the syntheses of the optically active natural products.[4b,5b] The reduction of 4-methoxycarbonyl-9-methyl-3,8-dioxo-$\Delta^{4(10)}$-octalin afforded the optically pure (+)-4-methoxycarbonyl-(8S)-hydroxy-9-methyl-3-oxo-$\Delta^{4(10)}$-octalin by the specialized yeasts.[4] In this case, the unsaturated ketone with an α-ester group was inert, but only the saturated one was reduced in moderate yield. The additional (-)-diketone was obtained in high optical purity by repeated reductions. Both the *normal*-type ketol and the *ent*-type diketone were close-up to be key intermediates for the syntheses of sesquiterpenoids and diterpenoids. The saturated ketone of 4,9-dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin was reduced to afford the *normal*-type and *ent*-type synthons using selected yeast each.[5] On the other hand, the use of a specified lipase for asymmetric hydrolysis is a convenient method, since the reaction is brief and gives a relatively large amount of product with high optical purity. Then asymmetric hydrolysis of only the above acetate afforded the optically pure *trans*-4,(9*S*)-dimethyl-(7*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin among other hydrolysates of low optical purity.[6] In the



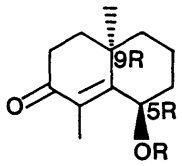
(±)-1



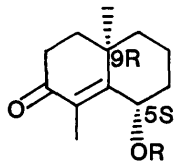
(-)-1(J)



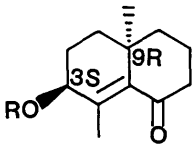
(+)-1(I)



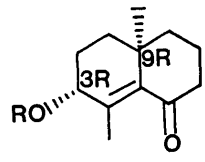
(-)-2 R=H
(-)-4 R=Ac
(-)-11 R=(+)-MTPA



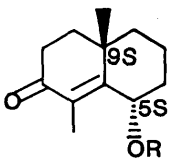
(-)-3 R=H(B)
(-)-5 R=Ac(F)
(-)-10 R=COC_6H_4Br-p
(-)-12 R=(+)-MTPA



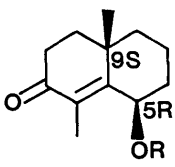
(-)-6 R=H(C)
(-)-8 R=Ac(G)
(-)-13 R=(+)-MTPA



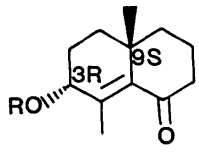
(-)-7 R=H
(-)-9 R=Ac
(-)-14 R=(+)-MTPA



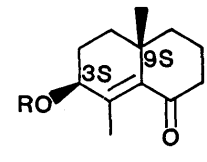
(+)-2 R=H(A)
(+)-4 R=Ac(E)
(+)-11 R=(+)-MTPA



(+)-3 R=H
(+)-5 R=Ac
(+)-12 R=(+)-MTPA



(+)-6 R=H
(+)-8 R=Ac
(+)-13 R=(+)-MTPA



(+)-7 R=H(D)
(+)-9 R=Ac(H)
(+)-14 R=(+)-MTPA

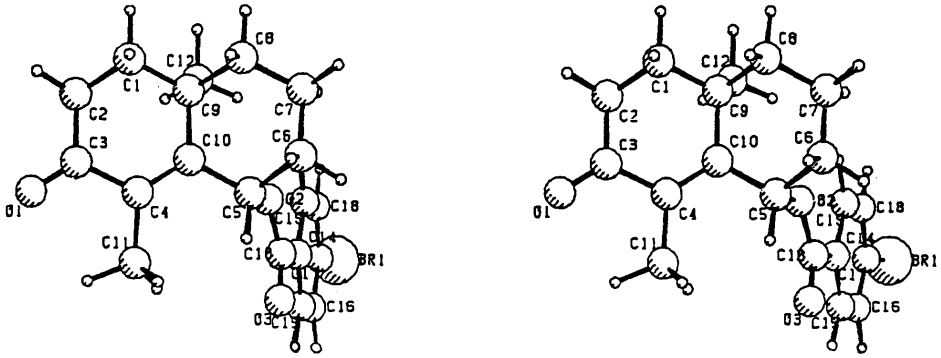


Fig. 1. Stereoview of (-)-*p*-Bromobenzoate (10) of (-)-4,(9*R*)-Dimethyl-(5*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (3)

hydrolysis of a simpler monocyclic acetate, only one yielded the pure optical product.[6]

Initially, we examined the asymmetric hydrolysis of the *trans*-5- (±)-4[7] and *cis*-5-acetoxyl-4,9-dimethyl-3-oxo-$\Delta^{4(10)}$-octalin, (±)-5[7] with seventeen kinds of commercially available lipases but recovered only the starting material. There are the steric interference between the C(4)-methyl and the C(5)-acetoxyl in (±)-4 and the 1,3-diaxial interaction between the angular methyl and the C(5)-acetoxyl in (±)-5. After the screening of various microorganisms, the reduction of diketone (±)-1[7] with *Rhodotorula rubla* produced the four possible ketols (A+B+C+D), which were sensitive to air to afford the diketone. The corresponding four ketol acetates (E+F+G+H) were subjected to a silica gel chromatography to be separated into the less polar fraction yielding E, the more polar fraction containing (F+G+H) and the (+)-diketone (27% yield), $[\alpha]_D^{24}$ +84.0° (*c* = 2.5, $CHCl_3$). The acetate (E) and the acetate mixture (F+G+H) were treated with potassium carbonate to afford the optically active ketol (A) (7.5% yield), $[\alpha]_D^{29}$ +126.7° (*c* = 3.0, $CHCl_3$), and a mixture of the ketols (B+C+D), respectively. The ketols were successively separated by repeated chromatography into the ketol (B), $[\alpha]_D^{27}$ -43.5° (*c* = 1.7, $CHCl_3$), the ketol (C), $[\alpha]_D^{27}$ -156.4° (*c* = 2.2, $CHCl_3$) and the ketol (D), $[\alpha]_D^{25}$ +88.1° (*c* = 2.6, $CHCl_3$) in 24%, 5.4% and 9.4% yield, respectively. The absolute configuration of the main product (B) was determined by X-ray analysis of its *p*-bromobenzoate (-)-10 to be 5*S*,9*R* [hence B = (-)-3] (Fig. 1).[8] The ketol (A) was oxidized with Jones reagent to provide the diketone (I), $[\alpha]_D^{27}$ +166.8° (*c* = 3.0, $CHCl_3$), which was identical except for the sign of the rotation with (9*R*)-diketone (-)-1 (J), $[\alpha]_D^{29}$ -168.4° (*c* = 2.5, $CHCl_3$) obtained by Jones oxidation of the foregoing ketol (B). Since the sign of $[\alpha]_D$ in I was opposite to that in (-)-1, the absolute configuration of I and the above recovered diketone was found to be 9*S* [hence I = (+)-1], respectively. The stereochemistry of C(5)-OH in A was found to be equatorial because the C(5)-OH of (-)-3 (B) was equally as axial as in (-)-10. Therefore, the absolute configuration of A was determined to be 5*S*,9*S* [henceA = (+)-2)]. Ketol (C) and (D) were oxidized to provide the corresponding diketone (J), $[\alpha]_D^{32}$ -169.0° (*c* = 1.1, $CHCl_3$) and (I), $[\alpha]_D^{32}$ +153.6° (*c* = 1.4, $CHCl_3$), respectively, and the absolute configuration of their angular methyl groups were determined by the same way as for the ketol (A). The stereochemistry of C(3)-H in C was found to be equatorial because this ^{1}H-NMR signal appeared at δ 4.00 (dd, J = 2.6, 2.9 Hz). Thus the absolute configuration of C was determined to be 3*S*,9*R* [hence C = (-)-6]. The stereochemistry of C(3)-H in D was found to be axial because the ^{1}H-NMR signal due to C(3)-H appeared in δ 4.07 (dd, J = 5.5, 8.4 Hz). Therefore, the absolute configuration of D was determined to be 3*S*,9*S* [hence D = (+)-7].

In order to determine the optical purity of the reduction products, the racemic *trans*-5-hydroxy-3-ketone (±)-2[9] and *cis*-5-hydroxy-3-ketone (±)-3[9] were treated with (+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride [(+)-MTPACl][10] to give the corresponding (+)-MTPA esters (±)-11 and (±)-12, respectively. The two NMR signals due to the C(4)-methyl at δ 1.75 and δ 1.65 for 11 and those due to each angular methyl group at δ 0.96 and δ 1.10 for 12 appeared in different fields. The racemic *cis*-3-hydroxy-5-ketone (±)-7 gave the (+)-MTPA ester 14 as usual. The NMR signal due to the angular methyl appeared in distinctly different fields at δ 0.99 and δ 1.03 for 14. The first ketol (5*S*,9*S*)-(+)-2 (A) was converted to the corresponding (+)-MTPA ester (±)-11 (δ 1.65), which was found to be 97% ee by taking account of the small

Table I. Microbiological Reduction of 4,9-Dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin, (±)-1

Entry	Yeast	Product	Recovery
1	*Rhodotorula rubla*	(+)-2 (7.5%, 97% ee) (-)-6 (5.4%, 91% ee) (-)-3 (24%, >99% ee) (+)-7 (9.7%, 96% ee)	(+)-1 (27%, 50% ee*)
2	*Kloeckera saturnus*	(+)-2 (1.6%, 94% ee) (-)-6 (8.5%, 86% ee) (-)-3 (15%, 95% ee) (+)-7 (16.3%, 95% ee)	(-)-1 (34.4%, 8% ee*)

*) calculation based on $[\alpha]_D$

signal (δ 1.75) due to its enantiomer (-)-11. The second ketol (5*S*,9*R*)-(-)-3 (B) was converted to the corresponding (+)-MTPA ester (-)-12 (δ 0.96), whose optical purity was found to be more than 99% ee. Although the racemic sample of the third ketol (±)-6 was not obtained, the optical purity of the (+)-MTPA ester of the microbial reduction product (3*S*,9*R*)-(-)-6 (C) (δ 0.97 for C(9)-methyl) was found to be 91% ee by taking account of the small signal for the C(9)-methyl due to its enantiomer (3*R*,9*S*)-(+)-13. The optical purity of the fourth ketol (3*S*,9*S*) (+)-7 (D) was found to be 96% ee [(+)-MTPA ester (-)-14 (δ 1.03) and its enantiomer (+)-14 (δ 0.99)], as usual.

Thus the relationship between the absolute configuration and the chemical shift was established, and the result of the asymmetric reduction of diketone (±)-1, using the specified yeast, is shown in Table I.

In conclusion, with the properly selected microorganism, the asymmetric reduction of 4,9-dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin (±)-1 afforded the four optically pure ketols in both cases. The *ent*-type (9*R*)-ketol (-)-3 was obtained as the main product in reasonable yield by reduction of *Rhodotorura rubla*, and another *nomal*-type (9*S*)-ketol (+)-7 was acquired in a good yield by reduction of *Kloeckera saturnus*. Since the two racemic sesquiterpenoids, tuberiferine[12] and temsin,[13] have been synthesized via (±)-1, the synthesis of the optically active compound, *i.e.* (+)-4,(9*S*)-dimethyl-(3*S*)-hydroxy-5-oxo-$\Delta^{4(10)}$-octalin (7), constitutes the formal total syntheses of the two optically active sesquiterpenoids starting from the *nomal*-type chiral synthon. The *ent*-type chiral key intermediate (-)-3 will be available for the syntheses of various optically active natural products, such as (-)-frullanolide[14] and (+)-*cis*-β-cyclocostunolide.[14]

ACKNOWLEDGEMENT This work was supported in part by a Grant-in-Aid (62430027) for Scientific Research from the Ministry of Education, Science and Culture of Japan, for which one of the authors (S.I.) is grateful.

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7) The substrate (±)-4 and (±)-5 were obtained by treatment of the ketols[9] with acetic anhydride/pyridine followed by separation with column chromatography. The other substrate (±)-1 was obtained by Jones oxidation of the above ketol mixture.
8) Crystal data of (-)-10: $C_{19}H_{21}O_3Br$, MW 377.3, Orthorhombic, Space group $P2_12_12_1$, Z = 4, a = 9.953(5), b = 20.408(11), c = 8.879(5) Å, U = 1824 Å^3, D_X = 1.374 gcm^{-3}, R_{final} = 0.075.
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(Received July 13, 1989)