Communications to the Editor

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MICROBIOLOGICAL ASYMMETRIC REDUCTION OF 4-CARBOMETHOXY-3,8-DIOXO-9-METHYL-$\Delta^{4(10)}$-OCTALIN

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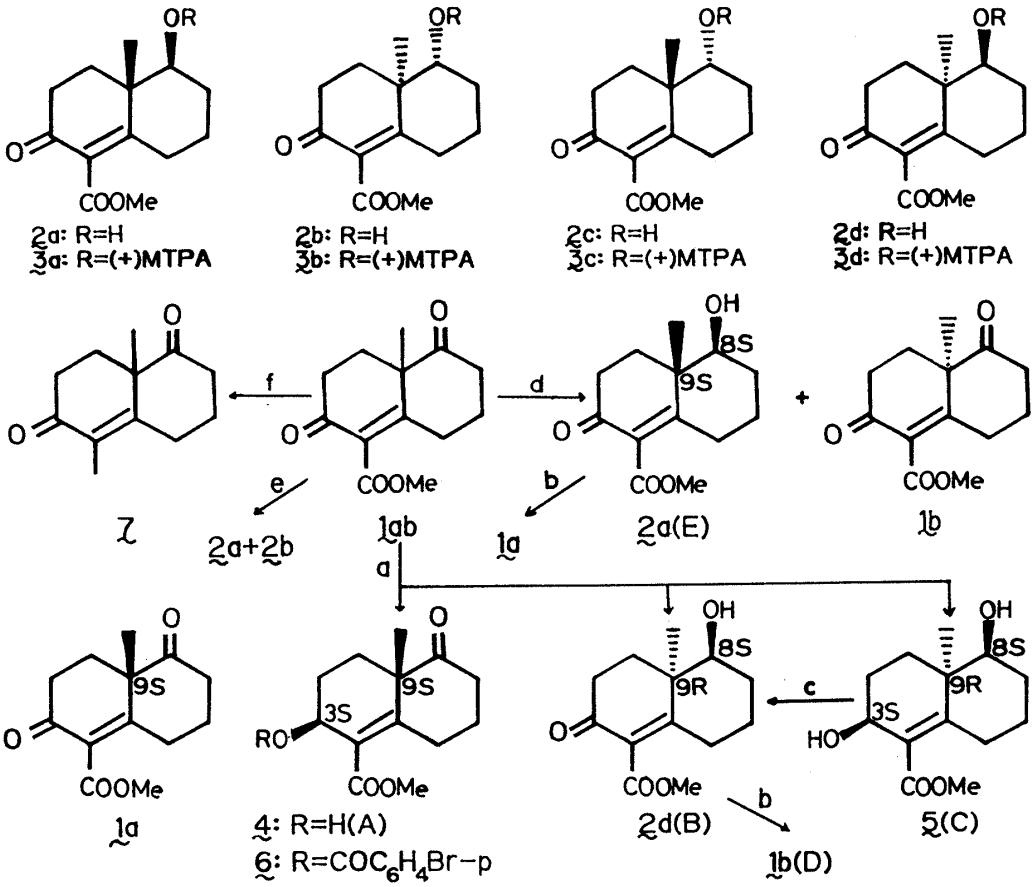
Microbiological asymmetric reduction of 4-carbomethoxy-3,8-dioxo-9-methyl-$\Delta^{4(10)}$-octalin (1ab) with various yeasts was carried out. With properly selected microorganisms, the desired (+)-4-carbomethoxy-(8S)-hydroxy-3-oxo-(9S)-methyl-$\Delta^{4(10)}$-octalin (2a) was obtained with high optical purity (>99% ee).

KEYWORDS — 3,8-dioxooctalin; 8-hydroxyoctal-3-one; microbiological induction; asymmetric reduction; yeast; Schizosaccharomyces; Kloeckera

Microbiological asymmetric reduction of synthetic substrates is a useful method for preparing chiral intermediates in synthesis chemistry. Although there are numerous examples[1] of the biological reduction of acyclic ketones using microorganisms such as yeast and a few reports[2] of bicyclic ketones, no optically active bicyclic diketoester (1a) has been synthesized using biological reduction as the key intermediate,[3a] not even by the conventional asymmetric cyclization using amino acid derivatives.[3b] Furthermore the optically active ketol (2a), to be derived from the corresponding octalindione (1ab), is considered to be an essential chiral intermediate for the synthesis of optically active diterpenoids such as andrographolide.[4] Here we describe the synthesis of the optically active hydroxyoctalone (2a) based on the asymmetric reduction of 1ab by a variety of yeasts.[5]

Reducing diketone (1ab) with the usual fermenting Baker's yeast (Saccharomyces cerevisiae) resulted in the formation of an inseparable mixture of the products. However, the reduction using some selected yeasts, especially Kloeckera saturnus[6] produced three alcohols: A ($[\alpha]_D$ +92.3°), B ($[\alpha]_D$ -77.4°) and C ($[\alpha]_D$ -168.3°) in 44%, 18% and 12% yield, respectively. The absolute structure of the main product A was determined by X-ray analysis of its p-bromobenzoate (6) as shown in Fig. 1 and the absolute configuration of alcohol A was established as 3S,9S (A = 4).[7] The second alcohol, B, was oxidized with Jones reagent to provide the diketone D ($[\alpha]_D$ -85.0°), which was identical with (9S)-diketone (1a) ($[\alpha]_D$ +62.3°) obtained by Jones oxidation of (3S,9S)-A (= 4). Since the sign of $[\alpha]_D$ in D was opposite to that of 1a, the absolute configuration of D was found to be 9R (hence D = 1b). The stereochemistry of C(8)-H in the alcohol B was found to be equatorial because the ^{1}H-NMR signal due to C(8)-H appeared in δ 3.679 (br s $W_{\frac{1}{2}}$ = 7.1 Hz).



a; Kloeckera saturnus b; Jones reagent c; MnO_2 d; Schizosaccharomyces octosporus
e; $NaBH_4$ f; 1) $(CH_2OH)_2/TsOH$ 2) $LiAlH_4$ 3) CCl_4/Ph_3P 4) Bu_3SnH

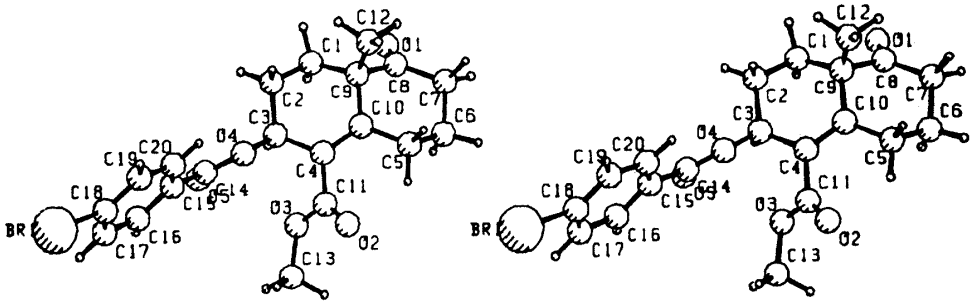


Fig. 1. Stereoview of p-Bromobenzoate (6) of 4-Carbomethoxy-(9S)-methyl-8-oxo-$\Delta^{4(10)}$-octal-(3S)-ol (4)

Therefore the absolute configuration of B was determined to be 8S,9R (hence B = 2d). The MnO_2 oxidation product ($[\alpha]_D$ -105.0°) of the third alcohol, C, was identical with B and the α-configuration of C(3)-H was determined by NMR. Thus the absolute structure of C was determined to be (9S)-octalin-(3S,8S)-diol (5). To determine the optical purity of B, it was treated with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(+)-MTPACl],[8] to give the corresponding (+)-MTPA ester (3d) (δ 3.512), which was found to be 88% ee by taking account of the small peak (δ 3.480) due to an isomer (3c) in the 400 MHz ^{1}H-NMR spectrum without any shift reagent.

To find more selective microorganisms, we next tried reductions with a variety of yeasts and found that several yeasts have the desired reducing ability. Schizosaccharomyces octosporus catalysed asymmetric reduction of lab provided predominantly the forth alcohol E ($[\alpha]_D$ +105.2°, δ 1.242 s, 9-CH_3) in 12% yield together with an antipodal diketone (1b) ($[\alpha]_D$ -42.0°) in 50% yield. The absolute structure and the optical purity of E were determined as follows: $NaBH_4$ reduction of lab gave a racemic cis-alcohol (2ab)[4] which accorded with the present reduction product E regardless of rotations. Since the Jones oxidation product ($[\alpha]_D$ +119.0°) of E was identified as (9S)-diketone (1a) including the sign of $[\alpha]_D$, the absolute structure of E was determined to be 8S,9S (hence E = 2a). To determine the optical purity of E, E and racemate (2ab) were also converted in the usual way to the corresponding (+)-MTPA ester (3a) (δ 1.257) and 3ab, respectively. In the case of racemate (+)-MTPA ester (3a and 3b), two peaks due to each angular methyl group appeared in distinctly different fields (δ 1.257 and δ 1.249), and one of the peaks was coincident with that of 3a. Consequently, the optical purity of E was found to be more than 99% ee and the remaining signal (δ 1.249) was ascribed to (8R,9R)-3b.

Since we established a relationship between the absolute structure and the chemical shift, the result of the asymmetric reduction of lab using various yeasts is shown in Table I.

The particular features of the present asymmetric reduction are as follows: 1) The asymmetric reduction mediated by Schizosaccharomyces octosporus, Hansenula anomala, Hansenula anomala NI-7572, Saccharomyces acidifaciens afforded cis ketol having more than 99% ee in every case. 2) On the other hand, the asymmetric reduction catalysed by Kloeckera saturnus and Candida albicans gave the trans ketol (2c or 2d) in moderate optical purity. In this case, the absolute structure of each reduction product showed the enantio relationship. 3) In the biological asymmetric reduction with Baker's yeast, Pichia membranaefaciens and Candida guilliermondii, an inseparable mixture of cis-ketol (2a) and trans isomer (2d) was obtained, but the optical purity of the former was considerably higher in every case. 4) In all cases, the recovered diketone (1b) corresponding to the starting substrate was found to be optically active and to have a (9R)-configuration.

The asymmetric reduction of lab catalysed by Hansenula anomala and Saccharomyces acidifaciens gave diketone (1b) in 50% and 58% chemical yield with 9.3% and 20.0% optical purity, respectively. Continuing the same biological reduction of 1b favored the production of cis-ketol (2a) (>99% ee) and highly optically pure diketone (1b) (>99% ee)[9] in 64% and 58% yield, respectively. Since the conversion of the racemic diketoester (lab) to the 4-methyl diketone (7) was successfully achieved by the sequential reactions of ketalization and lithium aluminium hydride reduction followed by treatment with triphenyl phosphine and tributyltin hydride, the synthesis of optically active 7 has been found to be transformed from the aforesaid optically active precursors (2a or 1b). Now the optically active key intermediates (1a or 1b) can be available for the synthesis of optically active natural products such as sesquiterpenoids or diterpenoids.

Table I. Microbiological Reduction of 4-Carbomethoxy-3,8-dioxo-9-methyl-$\Delta^{4(10)}$-octalin (lab)[a)]

Entry	Yeast	Chemical yield (%)	recovery (%) as 1b	cis/trans[b)]	Optical purity (% ee)
1	Schizosaccharomyces octosporus	12	50	100/0	2a >99
2	Hansenula anomala	20	58	100/0	2a >99
3	Hansenula anomala NI-7572	11	78	100/0	2a >99
4	Saccharomyces acidifaciens	10	75	100/0	2a >99
5	Kloeckera saturnus	18	Trace	0/100	2d 88
6	Candida albicans	12	87	0/100	2c 44
7	Saccharomyces cerevisiae[c)]	40	--	77/23	2a >99; 2d 6
8	Pichia membranaefaciens	7	78	17/83	2a >99; 2d >99
9	Candida guilliermondii	12	--	22/78	2a >99; 2d 25
cf	$NaBH_4$	70	--	100/0	0

a) 400 mg of substrate (lab) in 800 ml of the culture.[5)]
b) Ratio determined by ^{1}H-NMR spectrum. c) Baker's yeast.

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7) Crystal data of 6: $C_{20}H_{21}O_5Br$, MW 421.3, orthorhombic, space group $P2_12_12_1$, Z = 4, Dc = 1.446 gcm^{-3}, a = 10.525(5), b = 19.267(10), c = 9.548(5) Å, U = 1936 Å^3, R_{final} = 0.087.

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9) Optical purity of the diketone (1b) was confirmed by ^{1}H-NMR analysis of the (+)-MTPA ester (3b), which was derived from $NaBH_4$ reduction product (2b) of the optically active 1b (cf. ref. 8).

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