Microbiologically Modified Chiral Synthon. III. 4,9-Dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin for Formal Total Syntheses of Certain Sesquiterpenoids[1)]

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

These compounds have now become available for the total syntheses of sesquiterpenoids such as tuberiferine and temisin.

Keywords 3,5-dioxooctalin; 5*S*-hydroxy-3-oxooctalin; 3*S*-hydroxy-5-oxooctalin; microbiological transformation; enantioselective reduction; yeast; *Kloeckera saturnus*; lipase; *Rhodotorula rubra*

In recent years, the most significant development in the field of synthetic organic chemistry of natural products has been made in stereospecific, stereoselective and chemospecific functional group transformations. Most natural products with many chiral centers in their molecules are known to be optically active. Generally, these biological and pharmacological activities are indeed quite different from those of enantiomers. We require optically active products rather than racemates, in the case of total syntheses of natural products and medical supplies with many chiral carbones.

Two spproaches including chemical and biological methods are commonly used in enantioselective syntheses. Biological syntheses using microorganisms and enzymes are useful from the viewpoints of ease and efficiency of reaction and their self-multiplying ability. The most striking differences between enzymes and chemical catalysts lie in their substrate specificities. They catalyze specific reactions for one or just a few structurally related compounds, and distinguish almost absolutely some specific structural feature among various stereoisomers or regioisomers. However, it is possible to screen for various synthetic non-natural products and substrates by the use of microorganisms and/or enzymes. The results and scope of this biological strategy for organic syntheses have been extensively evaluated. The substrate has been used in a higher concentration, from below one percent to several percent. Therefore, the biological reactions performed by microorganisms or catalyzed by enzymes have been regarded as essentially equivalent to those carried out in conventional organic chemistry. The high optical purity must be made possible by microorganisms and enzymes with a high stereoselective ability and chemospecific reactivities, which cannot be obtained by using conventional chemical reagents. The kinetic resolution by biological reactions produced the optically active products as well as the recovered optically active substrate, which can also be useful. Numerous reviews[3)] are available for the hydrolysis using lipases and the reduction or oxidation by microorganisms.

We now intend to study the above chiral syntheses of biologically and pharmacologically active natural and non-natural products. These optically active natural products such as eudesmanolide-type sesquiterpenolids bearing α-methylene-γ-lactones[4-11)] as well as non-natural related compounds may be expected to exhibit antitumor activities.[12)] However, in order to investigate the biological activities of these compounds, it appears important that fairly large samples should be obtained by use of the biological approaches. Instead of many conventional racemic sesquiterpenoids syntheses, we examined the synthesis of the optically active synthons by biological enantioselective reactions such as reduction with microorganisms and hydrolysis with enzymes. The use of these biological methods to prepare chiral alcohols has been widespread and very efficient. There are numerous examples[13)] of biological reduction of acyclic ketones, but only a few reports[14)] of bicyclic ketone reduction.

We communicated earlier the reduction of bicyclic ketones by microorganisms (yeasts).[15,16)] These optically active bicyclic compounds were useful for the syntheses of the optically active natural products.[15b,16b)] The reduction of 4-methoxycarbonyl-9-methyl-3,8-dioxo-$\Delta^{4(10)}$-octalin afforded the optically pure (+)-8*S*-hydroxy-4-methoxycarbonyl-9-methyl-3-oxo-$\Delta^{4(10)}$-octalin by the specialized yeasts.[15)] Both the normal-type ketol and the ent-type diketone were 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 yeasts.[16)] On the other hand, the use of a specified lipase for enantioselective hydrolysis is an appealingly a convenient method, since the reaction is quick and yields a relatively large amount of product with high optical purity. Then through a single enantioselective hydrolysis, *trans*-7-acetoxy-4,9-dimethyl-3-oxo-$\Delta^{4(10)}$-octalin afforded the corresponding optically pure ketol.[17)] In the hydrolysis of a simpler monocyclic acetate, only one yielded the pure optical product.[17)] In general, it was considered that biological reduction of α,β-unsaturated ketones was difficult because the resonance stability occurs in its carbon–oxygen double bond. However, the α,β-unsaturated ketone of the C(15)-position and the ω-chain of the building block of prostaglandin (PG)[18)] and 4-methoxycarbonyl-3,8-dioxo-$\Delta^{4(10)}$-octalin[15)] were biologically reduced to afford the corresponding allyl alcohol.

We examined the enantioselective hydrolysis of the *trans*-(**4**)[19)] and *cis*-5-acetoxy-4,9-dimethyl-3-oxo-$\Delta^{4(10)}$-

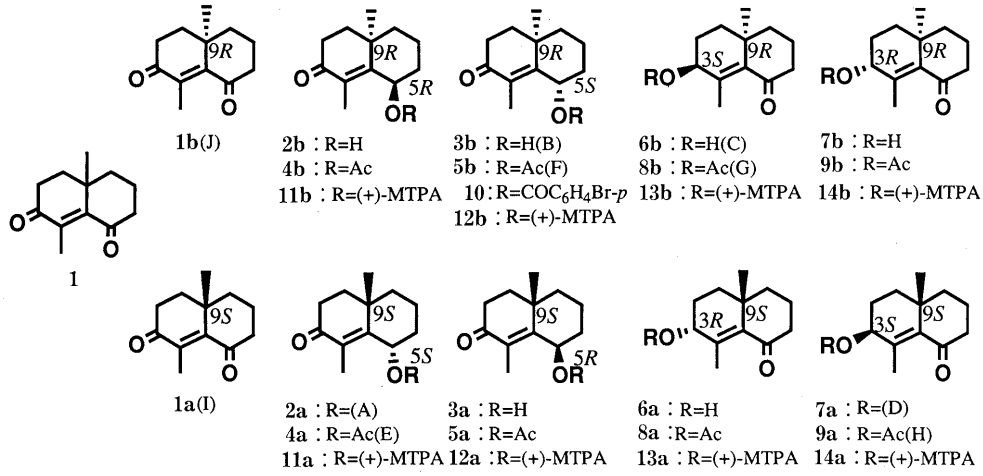

Chart 1

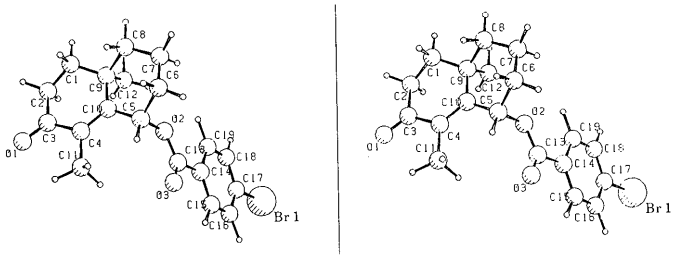

Fig. 1. Stereoscopic Drawing of *p*-Bromobenzoate (**10**) of (−)-4,9*R*-Dimethyl-5*S*-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (**3b**)

octalin (**5**)[19] with seventeen kinds of commercially available lipases, but recovered solely the starting material. Steric interference occurs between the C(4)-methyl and the C(5)-acetoxyl in (±)-**4**, and a 1,3-diaxial interaction also occurs between the angular methyl and the C(5)-acetoxyl in (±)-**5**. After the screening of various microoganisms, the reduction of (±)-diketone (**1**)[19] with *Rhodotorula rubra* produced the four possible ketols (A+B+C+D), which were sensitive to air, to afford the diketones. The corresponding four ketol acetates (E+F+G+H) were subjected to a silica gel chromatography; they were separated into the less polar fraction yielding E, the more polar fraction containing (F+G+H) and the (+)-diketone (27% yield), $[\alpha]_D$ +84.0°. The acetate (E) and the acetate mixture (F+G+H) were each treated with potassium carbonate to afford the optically active ketol (A) (7.5% yield), $[\alpha]_D$ +126.7°, and a mixture of the ketols (B+C+D), respectively. The ketols were successively separated by repeated chromatography into the ketol (B), $[\alpha]_D$ −43.5°, the ketol (C), $[\alpha]_D$ −156.4° and the ketol (D), $[\alpha]_D$ +88.1° 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=**3b**) (Fig. 1). The final atomic coordinates and equivalent isotropic temperature factors are given in Table IV. The structure of the molecule is illustrated in Fig. 1 by the stereoscopic drawing plotted by the PLUTO program.[20] Figure 2 is another view of the molecule showing the planarity of the C(2), C(3), O(1), C(4), C(11), C(10), C(5) and C(9) atoms and the orientation of the C(9)–C(12) bond and the *p*-bromobenzoate group with respect to the molecular plane. The above mentioned

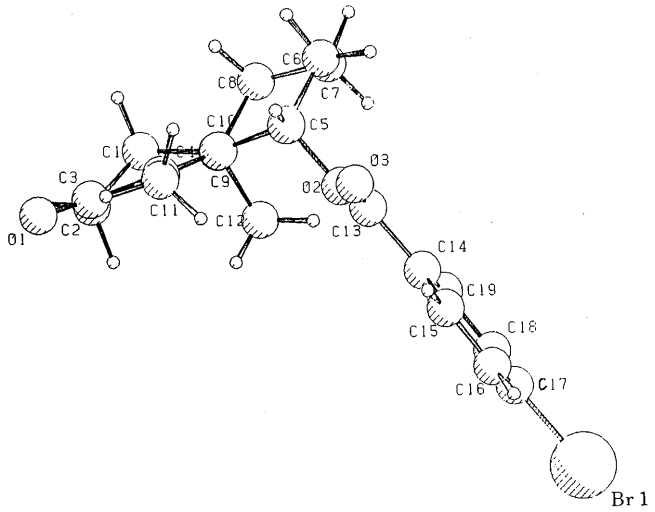

Fig. 2. Another View of the Molecule (**10**)

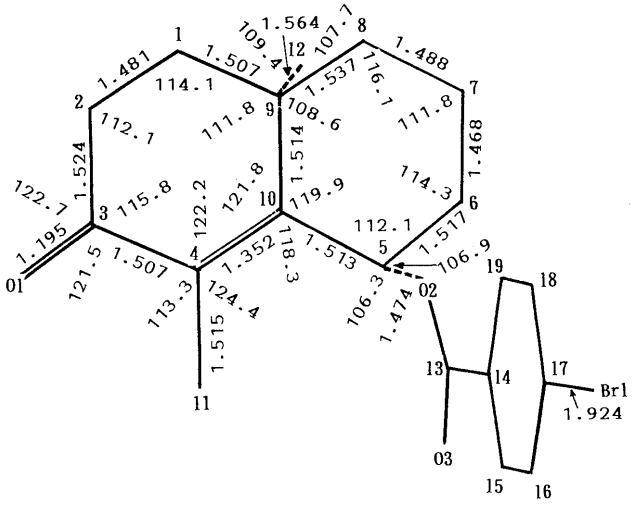

Fig. 3. Bond Lengths (Å) and Valency Angles (°)

molecular plane is planar within the root mean square displacement of the atoms from the least-squares plane of 0.059 Å. As is clear from Fig. 2, C(1), C(5), and C(8) are puckered from the plane so that rings A and B adopt an

envelope and a chair form, respectively. In Tables VI and VII, the bond lengths and valency angles are listed, and Fig. 3 illustrates some important values found the skeleton of the molecule. The values show general agreement with the chemical structure. The ketol (A) was oxidized with Jones reagent to provide the diketone (I), $[\alpha]_D$ +166.8°, which was identical except for the sign of the rotation with 9*R*-diketone (**1b**) (J), $[\alpha]_D$ −168.4° obtained by Jones oxidation of the aforegoing ketol (B). Since the sign of the optical rotation in I was opposite to that in **1b**, the absolute configuration of I and the above recovered diketone was found to be 9*S* (hence I=**1a**), respectively. The stereochemistry of the C(5)-hydroxy group in A was found to be equatorial because the C(5)-hydroxy group of **3b** was just as axial as in **10**. Therefore, the absolute configuration of A was determined to be 5*S*,9*S* (hence A=**2a**). Ketols (C) and (D) were oxidized to provide the corresponding diketones (J), $[\alpha]_D$ −169.0° and (I), $[\alpha]_D$ +153.6°, respectively. The absolute configuration of their angular methyl groups were determined in the same way as for the ketol (A). The stereochemistry of the C(3)-hydrogen atom in C was found to be equatorial; the signal of the proton nuclear magnetic resonance spectrum (^{1}H-NMR) appeared at δ 4.00 as dd with coupling constants of 2.6 and 2.9 Hz. Thus the absolute configuration of C was determined to be 3*S*,9*R* (hence C=**6b**). The stereochemistry of the C(3)-hydrogen atom in D was found to be axial; the ^{1}H-NMR signal due to the C(3)-hydrogen atom appeared at δ 4.07 as dd with *J* values of 5.5 and 8.4 Hz. Therefore, the absolute configuration of D was determined to be 3*S*,9*S* (hence D=**7a**).

In order to determine the opticalpurity of the reduction products, the racemic *trans*-5-hydroxy-3-ketone (**2**)[21] and *cis*-5-hydroxy-3-ketone (**3**)[21] were treated with (+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride [(+)-MTPACl][22] to give the corresponding (+)-MTPA esters (**11**) and (**12**). The two NMR signals due to the C(4)-methyl group 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 each different field. The racemic *cis*-3,9-hydroxy-5-ketone (**7**)[23] 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*-(**2a**) (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 signal (δ 1.75) due to its enantiomer (**11b**). The second ketol 5*S*,9*R*-(**3b**) (B) was converted to the corresponding (+)-MTPA ester (**12b**) (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*- (**6b**) (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*-(**13a**). The optical purity of the fourth ketol 3*S*,9*S*-(**7a**) (D) was found to be 96% ee [(+)-MTPA ester (**14b**) (δ 1.03) and its enantiomer (**14a**) (δ 0.99)], as usual. Thus the relation ship between the absolute configuration and the chemical shift was established. The result of the enantioselective reduction of (±)-diketone (**1**), using the specified yeast, is shown in Table I.

In conclusion, with the properly selected microorganism, the enantioselective 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 (**3b**) was obtained as the main product in reasonable yield by reduction of *Rhodotorula rubra*, and another normal-type, 9*S*-ketol (**7a**) was acquired in a good yield by reduction of *Kloeckera saturnus*. Since the two racemic sesquiterpenoids, tuberiferine[24] and temsin,[25] have been synthesized starting from (±)-(**1**), the synthesis of the optically active compound, *i.e.* (+)-3*S*-hydroxy-4,9*S*-dimethyl-5-oxo-$\Delta^{4(10)}$-octalin (**7a**), may be regarded as implicating the formal total syntheses of the two optically active sesquiterpenoids starting from the normal-type chiral synthon. The ent-type chiral key intermediate (**3b**) will be available for the syntheses of various optically active natural products, such as (−)-frullanolide[5] and (+)-*cis*-β-cyclocostunolide.[5]

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

Yeasts	Products		Recovery
	5-OH	3-OH	
Rhodotorula rubra	**2a** (7.5%, 97% ee)	**6b** (5.4%, 91% ee)	**1a**
	3b (24%, >99% ee)	**7a** (9.4%, 96% ee)	(27%, 50% ee)
Kloekera saturnus	**2a** (1.6%, 94% ee)	**6b** (8.5%, 88% ee)	**1b**
	3b (15%, 98% ee)	**7a** (16.3%, 95% ee)	(34.4%, 8% ee)

Experimental

Melting points were measured with a Kofler micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were measured in a chloroform ($CHCl_3$) solution on a JASCO A-3 spectrophotometer. All the 400 MHz ^{1}H-NMR spectra were determined on a JEOL FX 400 instrument in 5—10% (w/v) solutions of deuterochloroform ($CDCl_3$) with tetramethylsilane (Me_4Si) as an internal reference. Both gas chromatography-mass (GC-MS) and high resolution mass (MS) spectrometries were carried out on a JEOL JMS-D-300 (JMA-200 data analysis system) mass spectrometer. Optical rotations were measured on a JASCO polarimeter in the $CHCl_3$ solution otherwise stated.

Enantioselective Reduction of 4,9-Dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin (1) with *Rhotorula rubra* i) A test tube (200×25 i.d. mm) contained 10 ml of a culture medium comprising 5% glucose, 0.1% potassium dihydrogen phosphate (KH_2PO_4), 0.1% ammonium sulfate ($(NH_4)_2SO_4$), 0.05% urea, 0.05% magnesium sulfate ($MgSO_4\cdot 7H_2O$), 0.05% calcium chloride ($CaCl_2\cdot 2H_2O$), 0.1% manganese chloride ($MnCl_2\cdot 4H_2O$), and 0.1% zinc sulfate ($ZnSO_4\cdot 7H_2O$), and tap water (pH 6.5). It was incubated with *Rhodotorula rubra*. The yeast was cultured at 30 °C for 3 d with continuous shaking. Then 1 ml of the seed culture was transferred to 1 l each of the same medium. After cultivation for 3 d, two 325 mg of the substrate (**1**) were added and cultivation was continued for an additional 3 d under the same conditions. ii) These reaction mixtures were filtered with the aid of celite, and the filtrate was extracted with ethyl acetate (EtOAc). The EtOAc extract was dried over anhydrous $MgSO_4$. Removal of the solvent gave an oily product (711.7 mg). Pyridine (10 ml) was added to a mixture of the reaction product, acetic anhydride (Ac_2O) (1.83 g) and dimethylaminopyridine (DMAP) (10 mg). Then the reaction mixture was stirred for 17.5 h at room temperature. After the addition of water (H_2O), the reaction mixture was extracted with ether. The ether extract was washed with saturated aqueous sodium chloride (NaCl), dried over anhydrous $MgSO_4$ and concentrated to give an oily product (E+F+G+H), which was chromatographed on silica gel (70 g) to give the less polar fraction (E, 61 mg, 7.5%), the more polar fraction (F+G+H, 320 mg) and diketone (176 mg, 27%) from hexane–EtOAc (1:1) elute. Diketone (**1a**): mp 35—36 °C. MS Calcd for $C_{12}H_{16}O_2$ (M^+, *m/z*): 192.115, Found: 192.114. $[\alpha]_D^{27}$ +84° (*c*=2.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1694, 1685. ^{1}H-NMR ($CDCl_3$) δ: 1.148 (3H, s, 9-CH_3), 1.741 (3H, s, 4-CH_3), iii) Metanol (MeOH) (0.3 ml) was added to a mixture of acetate (E) (40 mg) and potassium carbonate (K_2CO_3) (5 mg). Then the reaction mixture was stirred for 5.5 h at room temperature. After the addition of H_2O, the

reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give compound (A), (30 mg, 92% yield). A: MS Calcd for $C_{12}H_{18}O_2$ (M^+, m/z): 194.130, Found: 194.130. $[\alpha]_D^{27}$ +126.67° (c=3.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3400, 3330, 1660, 1646, 1616, 1593. ^{1}H-NMR ($CDCl_3$) δ: 1.217 (3H, s, 9-CH_3), 1.933 (3H, s, 4-CH_3), 4.729 (1H, dd, J=4 Hz, 5-H). iv) MeOH (0.5 ml) was added to the acetate mixture (F+G+H) (320 mg) and K_2CO_3 (10 mg). The reaction mixture was stirred for 6 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product, which was subjected to preparative thin layer chromatography (TLC) (silica gel, 20×20 cm; solvent, hexane–EtOAc (1:1)] and was chromatographed on silica gel (hexane–EtOAc (4:1)] to provide the ketol (B) (157 mg, 24.2% yield), (C) (36 mg, 5.4% yield) and (D) (62 mg, 9.4% yield). B: mp 67—70 °C. MS Calcd for $C_{12}H_{18}O_2$ (M^+, m/z): 194.131, Found: 194.131. $[\alpha]_D^{27}$ −43.5° (c=1.7, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3425, 1673, 1661, 1608. ^{1}H-NMR ($CDCl_3$) δ: 1.406 (3H, s, 9-CH_3), 1.850 (3H, s, 4-CH_3), 4.946 (1H, t, J=3 Hz, 5-H). C: mp 92—99 °C. MS Calcd for $C_{12}H_{18}O_2$ (M^+, m/z): 194.131, Found: 194.126. $[\alpha]_D^{27}$ −156.4° (c=2.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3420, 1678, 1632. ^{1}H-NMR ($CDCl_3$) δ: 0.973 (3H, s, 9-CH_3), 1.862 (3H, s, 4-CH_3), 3.989 (1H, br s, 3-H). D: mp 100—102 °C. MS Calcd for $C_{12}H_{18}O_2$ (M^+, m/z): 194.131, Found: 194.127. $[\alpha]_D^{27}$ +88.1° (c=2.6, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3425, 1673, 1618. ^{1}H-NMR ($CDCl_3$) δ: 1.039 (3H, s, 9-CH_3), 1.814 (3H, d, J=1 Hz, 4-CH_3), 4.063 (1H, dd, J=6, 14 Hz, 3-H).

Preparation of 5*S*,9*S*-Benzoate (10) from 5*S*-Hydroxy-4,9*S*-dimethyl-3-oxo-$\Delta^{4(10)}$-octalin (2) Pyridine (0.5 ml) was added to a mixture of the ketol (B) (22 mg), *p*-bromobenzoyl chloride (50 mg) and DAMP (10 mg); then the reaction mixture was stirred for 2 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with ether. The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give the oily product, which was subjected to preparative TLC (silica gel, 20×20 cm; solvent, hexane–EtOAc (1:1)) to provide *p*-bromobenzoate (**10**) (26 mg, 61% yield) which was crystallized from hexane, $[\alpha]_D^{27}$ +77.7° (c=1.09, $CHCl_3$). MS Calcd for $C_{19}H_{21}O_3Br$, (M^+, m/z): 378.063, Found: 378.063. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1716, 1678, 1616, 1594.

Collection of the Crystal Data and Intensity Data The crystals of *p*-bromobenzoate (**10**) were grown in a hexane solution as colorless plates. An X-ray specimen of the approximate dimensions 0.15×0.30×0.04 mm was chosen and set on a Philips PW1100 diffractometer. The lattice constants and intensity data were obtained by measurement using graphite monochromated CuK_α radiation. The crystal data is summarized in Table II. Intensities were measured using a $\theta-2\theta$ scan method with the scan speed θ=4°/min. Scans were repeated twice if the total counts in the first scan were less than 3000. The background was measured at each end of half the scan time. A total of 2239 reflections were measured in the 2θ range of 6° through 120° of which 180 were symmetry eqivalent reflections and 788 were Friedel reflections. The R_F[26] values were 0.047 for the former and 0.077 for the latter kind of reflections.

The number of independent observed structure factors was 1267 taking the averages of equivalent reflections, which corresponds to about 80% of the number theoretically possible.

Crystal Structure Analysis The crystal structure was solved by the heavy

Table II. Crystal Data of the Molecule of **10**

(−)-5-*p*-Bromebenzoyl-4,9*R*-dimethyl-5*S*-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin: $C_{19}H_{21}O_3Br$, M.W. 377.3
Crystal system : orthorhombic
Space group : $P2_12_12_1$, Z=4
Lattice constants: a=9.953 (5), b=20.408 (11), c=8.979 (5) Å, U=1824 Å^3, D_x=1.374 g cm^{-3}, μ for CuK_α=31.7 cm^{-1}

Table III. Determination of the Absolute Configuration by Comparison of the Calculated and Observed Values of $\{F(hkl)/F(\bar{h}\bar{k}\bar{l})\}^2$

$\{F(hkl)/F(\bar{h}\bar{k}\bar{l})\}^2$						$\{F(hkl)/F(\bar{h}\bar{k}\bar{l})\}^2$					
h	k	l	Cal.	Obs.	(S.T.D.)	h	k	l	Cal.	Obs.	(S.T.D.)
1	1	1	0.85	0.77	(0.04)	2	8	3	0.82	0.53	(0.28)
4	10	1	0.84	0.65	(0.30)	7	9	3	1.23	1.29	(0.10)
1	2	2	0.84	0.71	(0.12)	1	15	3	0.85	0.73	(0.07)
8	2	2	0.85	0.82	(0.08)	5	15	3	0.82	0.77	(0.13)
3	6	2	1.35	1.46	(0.19)	2	1	4	1.23	1.24	(0.09)
1	8	2	1.30	1.76	(0.22)	8	1	4	0.84	0.66	(0.17)
4	9	2	1.19	1.61	(0.17)	1	6	4	1.55	1.54	(0.19)
7	12	2	1.15	2.49	(0.17)	4	3	5	0.85	0.56	(0.12)
6	14	2	1.19	3.69	(0.32)	7	4	5	1.35	1.79	(0.14)
3	17	2	1.22	1.78	(0.23)	1	6	6	1.17	1.85	(0.12)
4	5	3	0.81	0.69	(0.11)	4	8	8	0.85	0.46	(0.42)
1	8	3	1.22	1.79	(0.16)						

Table IV. Fractional Atomic Coordinates (x, y and z) and Equivalent Isotropic Temperature Factors (B_{eq} in Å)

No.	Atom	x 10^5	y 10^5	z 10^5	B_{eq} Å^2
1	Br1	76529 (14)	−24574 (9)	−26070 (21)	6.65 (0.03)
No.	Atom	x 10^4	y 10^4	z 10^4	B_{eq} Å^2
2	C1	−103 (18)	759 (8)	−88 (23)	7.4 (0.3)
3	C2	58 (19)	1044 (8)	−1594 (26)	8.8 (0.4)
4	C3	−525 (17)	603 (8)	−2801 (22)	7.6 (0.3)
5	C4	−434 (12)	−123 (7)	−2511 (20)	5.3 (0.2)
6	C5	2 (14)	−1104 (6)	−990 (16)	4.5 (0.2)
7	C6	−456 (18)	−1309 (8)	551 (19)	6.4 (0.3)
8	C7	137 (20)	−926 (8)	1769 (18)	7.3 (0.3)
9	C8	−60 (18)	−209 (7)	1549 (18)	6.5 (0.3)
10	C9	446 (15)	73 (7)	64 (18)	5.4 (0.3)
11	C10	−25 (14)	−368 (7)	−1187 (16)	4.7 (0.2)
12	C11	−840 (21)	−537 (11)	−3837 (21)	9.1 (0.4)
13	C12	2015 (15)	101 (9)	138 (22)	7.1 (0.3)
14	C13	1646 (14)	−1774 (7)	−2108 (17)	5.2 (0.2)
15	C14	3138 (12)	−1949 (6)	−2187 (16)	4.3 (0.2)
16	C15	3571 (14)	−2333 (7)	−3317 (16)	5.2 (0.2)
17	C16	4901 (13)	−2482 (7)	−3472 (14)	4.9 (0.2)
18	C17	5779 (12)	−2234 (6)	−2462 (18)	4.8 (0.2)
19	C18	5414 (14)	−1834 (6)	−1301 (16)	4.6 (0.2)
20	C19	4054 (14)	−1674 (7)	−1138 (17)	4.9 (0.2)
21	O1	−978 (17)	813 (7)	−3938 (18)	12.1 (0.4)
22	O2	1420 (9)	−1303 (5)	−1133 (11)	5.2 (0.2)
23	O3	830 (10)	−2047 (6)	−2868 (15)	9.1 (0.3)
No.	Atom	x 10^3	y 10^3	z 10^3	B_{eq} Å^2
24	HC1	−116 (15)	74 (7)	14 (17)	8.0 (4.0)
25	H′C1	33 (18)	105 (8)	78 (20)	12.0 (6.0)
26	HC2	115 (15)	110 (7)	−182 (16)	9.0 (4.0)
27	H′C2	−37 (12)	152 (5)	−166 (13)	5.0 (3.0)
28	HC5	−63 (10)	−135 (5)	−178 (11)	4.0 (3.0)
29	HC6	−24 (11)	−180 (5)	61 (13)	5.0 (3.0)
30	H′C6	−151 (14)	−126 (7)	51 (16)	8.0 (4.0)
31	HC7	115 (12)	−106 (5)	178 (13)	5.0 (3.0)
32	H′C7	−30 (13)	−109 (6)	280 (17)	8.0 (4.0)
33	HC8	−109 (16)	−13 (8)	126 (19)	11.0 (5.0)
34	H′C8	9 (16)	4 (7)	255 (23)	9.0 (4.0)
35	HC11	−2 (16)	−84 (7)	−425 (18)	11.0 (5.0)
36	H′C11	−160 (15)	−87 (7)	−357 (17)	9.0 (4.0)
37	H″C11	−121 (13)	−22 (6)	−473 (14)	6.0 (3.0)
38	HC12	242 (16)	−35 (6)	28 (16)	9.0 (4.0)
39	H′C12	237 (14)	43 (6)	113 (14)	7.0 (3.0)
40	H″C12	233 (18)	29 (7)	−75 (18)	11.0 (5.0)
41	HC15	286 (10)	−252 (6)	−405 (11)	5.0 (3.0)
42	HC16	523 (11)	−283 (5)	−436 (12)	4.0 (3.0)
43	HC18	615 (11)	−161 (5)	−56 (13)	4.0 (3.0)
44	HC19	372 (12)	−133 (5)	−19 (14)	6.0 (3.0)

Equivalent positions

x	y	z
1/2−x	−y	1/2+z
1/2+x	1/2−y	−z
−x	1/2+y	1/2−z

TABLE V. Anisotropic Thermal Parameter for Each Atom

No.	Atom	U11	U22	U33	U12	U13	U23
		U(ij)'s are multiplied by 10^4					
1	Br1	595 (8)	981 (11)	951 (11)	97 (10)	96 (11)	−175 (13)
		U(ij)'s are multiplied by 10^3					
2	C1	92 (13)	66 (10)	124 (16)	7 (10)	−6 (13)	−10 (12)
3	C2	95 (13)	58 (10)	182 (21)	5 (10)	17 (16)	30 (13)
4	C3	83 (11)	98 (12)	106 (15)	4 (10)	18 (13)	46 (12)
5	C4	52 (8)	73 (9)	77 (10)	−3 (7)	0 (13)	14 (10)
6	C5	62 (9)	48 (8)	59 (9)	10 (7)	−3 (8)	−1 (7)
7	C6	95 (12)	70 (10)	77 (11)	−2 (10)	7 (11)	10 (10)
8	C7	127 (15)	83 (11)	70 (11)	18 (12)	3 (12)	3 (10)
9	C8	108 (14)	60 (9)	82 (11)	16 (10)	−5 (12)	−16 (9)
10	C9	57 (9)	59 (9)	89 (12)	5 (8)	2 (9)	3 (9)
11	C10	50 (8)	65 (9)	65 (9)	0 (7)	−7 (8)	3 (8)
12	C11	119 (17)	148 (18)	79 (13)	11 (16)	−1 (14)	41 (14)
13	C12	55 (10)	95 (12)	118 (15)	−1 (10)	−15 (11)	−23 (12)
14	C13	69 (9)	61 (8)	66 (10)	5 (8)	−2 (9)	−1 (8)
15	C14	55 (7)	50 (7)	58 (9)	13 (6)	−4 (8)	−12 (7)
16	C15	64 (9)	66 (10)	66 (9)	10 (8)	−2 (8)	−3 (8)
17	C16	70 (8)	65 (9)	50 (7)	28 (9)	8 (7)	−7 (8)
18	C17	48 (7)	63 (8)	71 (9)	9 (6)	8 (9)	37 (9)
19	C18	68 (9)	47 (8)	59 (9)	3 (7)	−2 (8)	−24 (7)
20	C19	53 (8)	64 (9)	68 (10)	7 (7)	−6 (8)	−17 (8)
21	O1	173 (15)	141 (12)	148 (13)	−1 (12)	−30 (13)	79 (11)
22	O2	53 (6)	73 (6)	73 (7)	14 (5)	0 (6)	−17 (6)
23	O3	62 (6)	143 (10)	142 (12)	8 (7)	−16 (8)	−93 (10)

No.	Atom	U11
		U(ij)'s are multiplied by 10^2
24	HC1	11 (6)
25	H'C1	15 (7)
26	HC2	12 (5)
27	H'C2	6 (4)
28	HC5	5 (3)
29	HC6	6 (4)
30	H'C6	10 (5)
31	HC7	7 (4)
32	H'C7	10 (5)
33	HC8	14 (7)
34	H'C8	12 (5)
35	HC11	14 (6)
36	H'C11	12 (6)
37	H''C11	8 (4)
38	HC12	12 (6)
39	H'C12	8 (4)
40	H''C12	14 (7)
41	HC15	6 (3)
42	HC16	5 (3)
43	HC18	6 (4)
44	HC19	7 (4)

Temperature factor T is the form of

$$T=\exp\{-2\pi^2(U11h^2\boldsymbol{a}^{*2}+U22k^2\boldsymbol{b}^{*2}+U33l^2\boldsymbol{c}^{*2}+2U12hk\boldsymbol{a}^*\boldsymbol{b}^*+2U13hl\boldsymbol{a}^*\boldsymbol{c}^*+2U23kl\boldsymbol{b}^*\boldsymbol{c}^*)\}.$$

atom method and refined by the method of least-squares with block diagonal matrix approximations. The final R value was 0.075 including 21 hydrogen atoms, found on the difference electron-density map, which were assumed to have isotropic temperature factors. The absolute configuration was determined by taking into account the anomalous dispersion effects of bromine, oxygen and carbon atoms for CuK_α radiation. Pairs of Friedel reflections were selected for cases, where the calculated and observed values of $|F(hkl)|/|F(\bar{h}\bar{k}\bar{l})|$ differed more than 5% from unity and where the difference between the observed $|F(hkl)|$ and $|F(\bar{h}\bar{k}\bar{l})|$ is greater than 2σ of $F(hkl)$. Comparison of the calculated and observed values of $\{|F(hkl)|/|F(\bar{h}\bar{k}\bar{l})|\}^2$ for these pairs listed in Table III indicated

TABLE VI. Bond Lengths (Å) (a) and Bond Lengths Including Hydrogen Atoms (Å) (b)

(a) Atom 1 Atom 2	Length (S.T.D.)	(b) Atom 1 Atom 2	Length (S.T.D.)
Br1–C17	1.924 (12)	C1 –HC1	1.07 (15)
C1 –C2	1.481 (30)	C1 –H'C1	1.07 (17)
C1 –C9	1.507 (21)	C2 –HC2	1.11 (15)
C2 –C3	1.524 (27)	C2 –H'C2	1.06 (11)
C3 –C4	1.507 (22)	C5 –HC5	1.07 (10)
C3 –O1	1.195 (25)	C6 –HC6	1.03 (11)
C4 –C10	1.352 (22)	C6 –H'C6	1.05 (15)
C4 –C11	1.515 (26)	C7 –HC7	1.05 (12)
C5 –C6	1.517 (22)	C7 –H'C7	1.08 (14)
C5 –C10	1.513 (19)	C8 –HC8	1.07 (16)
C5 –O2	1.474 (17)	C8 –H'C8	1.04 (19)
C6 –C7	1.468 (24)	C11–HC11	1.09 (16)
C7 –C8	1.488 (22)	C11–H'C11	1.05 (15)
C8 –C9	1.537 (23)	C11–H''C11	1.09 (13)
C9 –C10	1.514 (21)	C12–HC12	1.02 (14)
C9 –C12	1.564 (21)	C12–H'C12	1.17 (12)
C13–C14	1.529 (19)	C12–H''C12	0.93 (16)
C13–O2	1.319 (17)	C15–HC15	1.04 (10)
C13–O3	1.198 (19)	C16–HC16	1.11 (10)
C14–C15	1.354 (19)	C18–HC18	1.09 (11)
C14–C19	1.426 (20)	C19–HC19	1.15 (12)
C15–C16	1.365 (19)		
C16–C17	1.357 (19)		
C17–C18	1.373 (20)		
C18–C19	1.400 (20)		

TABLE VII. Valency Angles in Degrees (Not Including Hydrogen Atoms)

Atom 1 Atom 2 Atom 3	Angle (S.T.D.)	Atom 1 Atom 2 Atom 3	Angle (S.T.D.)
C2 –C1 –C9	114.1 (15)	C8 –C9 –C12	107.7 (13)
C3 –C2 –C1	112.1 (16)	C14–C13–O2	111.5 (11)
C4 –C3 –C2	115.8 (15)	C14–C13–O3	121.6 (13)
C4 –C3 –O1	121.5 (16)	O2 –C13–O3	126.9 (14)
C2 –C3 –O1	122.7 (17)	C15–C14–C13	118.7 (12)
C10–C4 –C3	122.2 (14)	C15–C14–C19	121.3 (12)
C10–C4 –C11	124.4 (14)	C13–C14–C19	119.9 (12)
C3 –C4 –C11	113.3 (14)	C16–C15–C14	120.9 (13)
C6 –C5 –C10	112.1 (12)	C17–C16–C15	118.3 (13)
C6 –C5 –O2	106.9 (11)	C18–C17–Br1	116.7 (10)
C10–C5 –O2	106.3 (11)	C18–C17–C16	123.9 (13)
C7 –C6 –C5	114.3 (14)	Br1 –C17–C16	119.4 (10)
C8 –C7 –C6	111.8 (15)	C19–C18–C17	118.3 (13)
C9 –C8 –C7	116.1 (14)	C4 –C10–C5	118.3 (13)
C10–C9 –C1	111.8 (13)	C4 –C10–C9	121.8 (13)
C10–C9 –C8	108.6 (12)	C5 –C10–C9	119.9 (12)
C10–C9 –C12	111.2 (12)	C5 –O2 –C13	115.0 (10)
C1 –C9 –C8	107.9 (13)	C14–C19–C18	117.2 (13)
C1 –C9 –C12	109.4 (13)		

the absolute configuration as shown in Fig. 1.

Conversion of Ketols (A—D) into 4,9*S* or 4,9*R*-Dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin (I or J) (General Procedure) Jones reagent (2—5 drops) was added to a stirred solution of A—D in acetone (1—2.5 ml); this mixture was cooled in an ice-salt bath for 30 min. After the addition of isopropyl alcohol and sodium hydrogen carbonate ($NaHCO_3$), the reaction mixture was filtered and concentrated to an oil; this was subjected to TLC (silica gel, 20 × 20 cm; solvent, hexane–EtOAc (1 : 1)) to provide the diketone.

The diketone (I) (25 mg, 89% yield from A (28 mg)). I: $[\alpha]_D^{25}$ +166.8° (c=3.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1694, 1685, 1610.

The diketone (J) [(−)-**1b**] [25 mg, 70% yield from B (35 mg)] **1b**: $[\alpha]_D^{26}$ −168.4° (c=2.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1694, 1685, 1610.

The diketone (J) (11 mg, 85% yield from C (13 mg)]. J: $[\alpha]_D^{32}$ −169° (c=1.1, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1694, 1685, 1610.

The diketone (I) (14 mg, 78% yield from D (18 mg)]. I: $[\alpha]_D^{32}$ +154°

($c=1.4$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1694, 1685, 1610.

Preparation of (+)-MTPA Ester (11 and 12) from Racemic 5,9-*trans*- and *cis*-Ketol (2 and 3) (General Procedure) Pyridine (0.3 ml) was added to a mixture of 5-hydroxy (**2** and **3**), (+)-MTPACl (20 mg) and DMAP (10 mg). Then the reaction mixture was stirred for 16 h at room temperature. After the addition of H_2O, the reaction mixture was extracted withs ether. The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give (+)-MTPA ester which was subjected to preparative TLC (silica gel, 20 × 20 cm; solvent, hexane–EtOAc (2 : 1)) to provide the MTPA ester. The MTPA ester (**11**) (22 mg, 95% yield from **2** (11 mg)]. **11**: ^{1}H-NMR ($CDCl_3$) δ: 1.225 (3H, s, 9-CH_3), 1.649, 1.746 (each 3H, s, 4-CH_3), 3.509 (1H, d, $J=1.2$ Hz, –OCH_3), 3.533 (3H, d, $J=1.2$ Hz, –OCH_3), 6.108 (1H, m, 5-H). The MTPA ester (**12**) (14 mg, 48% yield from **3** (14 mg)). **12**: ^{1}H-NMR ($CDCl_3$) δ: 0.956, 1.105 (each 3H, s, 9-CH_3), 1.866, 1.879 (each 3H, s, 4-CH_3), 3.489 (1H, d, $J=1.2$ Hz, –OCH_3), 3.556 (3H, d, $J=0.98$ Hz, –OCH_3), 6.294 (each 1H, br s, 5-H).

Preparation of (+)-MTPA Ester (14) from Racemic 3,9-*cis*-Ketol (7) i) Pyridine (2 ml) was added to mixture of racemic ketols (**2**) and (**3**) (1.077 g), Ac_2O (1.698 g) and DMAP (10 mg). Then the reaction mixture was stirred for 6.5 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give crude acetate (1.195 g, 92% yield). ii) Abs. MeOH (10 ml) was added to a mixture of the above acetate (793 mg), sodium borohydride ($NaBH_4$) (63.5 mg) and cerium chloride ($CeCl_3 \cdot 7H_2O$) (1.252 g). Then the reaction mixture was stirred for 6.5 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with ether. The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product which was subjected to chromatography (silica gel (20 g), solvent, hexane–EtOAc (19 : 1)) to provide a mixture of 3,9-ketol (593 mg, 74% yield). 3,9-Ketol: ^{1}H-NMR ($CDCl_3$) δ: 1.166, 1.219 (each 3H, s, 9-CH_3), 1.778 (3H, s, 4-CH_3), 1.847 (3H, d, $J=0.97$ Hz, 4-CH_3), 2.021, 2.059 (each 3H, s, –OCH_3), 5.139, 5.605, 5.881, 6.014 (each 1H, m, 5-H). iii) *N*,*N*-dimethylformamide (DMF) (3 ml) was added to a mixture of 3,9-ketol (533 mg) and imidazol (374 mg). To the mixture was added *tert*-butyldimethylsilyl chloride (TBDMSCl) (374 mg) in an ice bath, then the reaction mixture was stirred at room temperature for 1 h and 40 min. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product which was subjected to chromatography [silica gel (20 g), solvent, and hexane–EtOAc (99 : 1)] to provide the coresponding sillilated ketone (574 mg, 72% yield). iv) MeOH (1 ml) was added to a mixture of the sillilated ketone (472 mg) and K_2CO_3 (10 mg). Then the reaction mixture was stirred for 4.5 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product, which was subjected to chromatography [silica gel (80 g), solvent, hexane–EtOAc (19 : 1)] to provide the sillilated ketol (220 mg, 53% yield) and the starting material (212 mg, 45% yield). v) MeOH (0.5 ml) was added to a mixture of the sillilated ketol (50 mg) and *p*-toluenesulfonic acid (*p*-TsOH) (10 mg). Then the reaction mixture was stirred for 30 min at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product which was subjected to preparative TLC [solvent, hexane–EtOAc (2 : 1)] to provide 3,9-*cis*-ketol (**6**) (14 mg, 45% yield). vi) The MTPA ester (**13**) was obtained in the same manner as described for the MTPA esters (**11** or **12**). The MTPA ester (**13**) [3 mg, 48% yield from 3,9-*cis*-ketol (**6**) (3 mg)]. **13**: ^{1}H-NMR ($CDCl_3$) δ: 0.990, 1.035 (each 3H, s, 9-CH_3), 1.477 (each 3H, d, $J=0.92$ Hz, 4-CH_3), 1.669 (3H, s, 4-CH_3), 3.548, 3.565 (each 1H, d, $J=1.2$ Hz, –OCH_3), 5.501 (each 1H, m, 3H).

Preparation of (+)-MTPA Esters (11a, 12b, 13b or 14a) from Ketols (A—D) (General Procedure) The MTPA esters (**11a** or **12b** or **13b** or **14a**) were obtained in the same manner as described for the MTPA esters (**11** or **12**). The MTPA ester (**11a**) [16 mg, 95% yield from ketol (A) (6 mg)]. **11a**: ^{1}H-NMR ($CDCl_3$) δ: 1.225 (3H, s, 9-CH_3), 1.649, 1.745 (each 3H, s, 4-CH_3), 3.509, 3.533 (each 3H, d, $J=1.2$ Hz, –OCH_3), 6.094 (1H, m, 5-H). The optical purity of **11a** (hence A) was found to be 97% ee. The MTPA ester (**12b**) [16 mg, 72% yield from ketol (B) (10 mg)]. **12b**: ^{1}H-NMR ($CDCl_3$) δ: 0.956 (3H, s, 9-CH_3), 1.866 (3H, s, 4-CH_3), 3.556 (3H, d, $J=0.98$ Hz, –OCH_3), 6.294 (1H, br s, 5-H). The optical purity of **12b** (hence B) was found to be more than 99% ee. The MTPA ester (**13b**) [4 mg, 95% yield from ketol (C) (3 mg)]. **13b**: ^{1}H-NMR ($CDCl_3$) δ: 0.990, 0.969 (each 3H, s, 9-CH_3), 1.649, 1.745 (each 3H, s, 4-CH_3), 3.509, 3.533 (each 3H, d, $J=1.2$ Hz, –OCH_3), 6.094 (1H, m, 3-H). The optical purity of **13b** (hence C) was found to be 91% ee. The MTPA ester (**14a**) (16 mg, 85% yield from ketol (D) (9 mg)]. **14a**: ^{1}H-NMR ($CDCl_3$) δ: 0.990, 1.035 (each 3H, s, 9-CH_3), 1.476, 1.669 (each 3H, s, 4-CH_3), 3.548, 3.565 (each 3H, d, $J=1.2$ Hz, –OCH_3), 5.517 (1H, m, 3-H). The optical purity of **14a** (hence D) was found to be 97% ee.

Enantioselective Reduction of 4,9-Dimethyl-3,5-dioxo-$\Delta^{4(10)}$-octalin (1) with *Kloekera saturnus* i) After cultivation, the reaction mixture was worked up in the same way as in the case of *Rhodotorula rubra* to afford the oily product (617.5 mg). After the acetylation, an oily product (**4a**+**5b**+**8b**+**9a**) was obtained. The mixture product was chromatographed on silica gel (75 g) to give the less polar fraction **4a** (13 mg, 1.6%), the more polar fraction (**5b**+**8b**+**9a**, 320 mg) and (–)-diketone (**1**) (224 mg, 34.4%) from hexane–EtOAc (1 : 1) elute. (–)-Diketone (**1**): mp 58—59 °C. $[\alpha]_D^{25}$ –13.6° ($c=1.7$, $CHCl_3$). ii) MeOH (0.5 ml) was added to a mixture of acetate **4a** (13 mg) and K_2CO_3 (5 mg). The reaction mixture was stirred for 24.5 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give crude **2a** (7 mg, 65% yield). **2a**: $[\alpha]_D^{32}$ +75.0° ($c=1.2$, $CHCl_3$). iii) MeOH (0.5 ml) was added to the acetates (**5b**+**8b**+**9a**) (320 mg) and K_2CO_3 (10 mg). Then the reaction mixture was stirred for 16 h at room temperature. After the addition of H_2O, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated to give an oily product, which was subjected to preparative TLC [silicagel, 20 × 20 cm; solvent, hexane–EtOAc (1 : 1)] and was chromatographed on silica gel [hexane–EtOAc (4 : 1)] to provide the ketol **3b** (97 mg, 15% yield), **6b** (55.4 mg, 8.5% yield) and **7a** (106.1 mg, 16.3% yield). **3b**: mp 73—76 °C. $[\alpha]_D^{32}$ –41.1° ($c=1.8$, $CHCl_3$). **6b**: mp 85—88 °C. $[\alpha]_D^{32}$ –156.7° ($c=1.3$, $CHCl_3$). **7a**: mp 94—97 °C. $[\alpha]_D^{32}$ +88.1° ($c=1.2$, $CHCl_3$).

Preparation of (+)-MTPA Esters (11a, 12b, 13b or 14a) from Ketols (2a, 3b, 6b, or 7a) The MTPA esters (**11a** or **12b** or **13b** or **14a**) were obtained in the same manner as described for the MTPA esters (**11** or **12**). The MTPA ester **11a** (7 mg, 48% yield from ketol **2a** (7 mg)]. **11a**: ^{1}H-NMR ($CDCl_3$) δ: 1.225 (3H, s, 9-CH_3), 1.649, 1.745 (each 3H, s, 4-CH_3), 3.509, 3.533 (each 3H, d, $J=1.2$ Hz, –OCH_3), 6.094 (1H, m, 5-H). The optical purity of **11a** (hence **2a**) was found to be 94% ee. The MTPA ester **12b** [12 mg, 57% yield from ketol **3b** (10 mg)]. **12b**: ^{1}H-NMR ($CDCl_3$) δ: 0.956 (3H, s, 9-CH_3), 1.866 (3H, s, 4-CH_3), 3.556 (3H, d, $J=0.98$ Hz, –OCH_3), 6.294 (1H, br s, 5-H). The optical purity of **12b** (hence **3b**) was found to be 98% ee. The MTPA ester **13b** (16 mg, 76% from yield ketol **6b** (10 mg)). **13b**: ^{1}H-NMR ($CDCl_3$) δ: 0.990. 0.969 (each 3H, s, 9-CH_3), 1.649, 1.745 (each 3H, s, 4-CH_3), 3.509, 3.533 (each 3H, d, $J=1.2$ Hz, –OCH_3), 6.094 (1H, m, 3-H). The optical purity of **13b** (hence **6b**) was found to be 91% ee. The MTPA ester **14a** [14 mg, 67% yield from ketol **7a** (10 mg)]. **14a**: ^{1}H-NMR ($CDCl_3$) δ: 0.990, 1.035 (each 3H, s, 9-CH_3), 1.476, 1.669 (each 3H, s, 4-CH_3), 3.548, 3.565 (each 3H, d, $J=1.2$ Hz, –OCH_3), 5.517 (1H, m, 3-H). The optical purity of **14a** (hence **7a**) was found to be 95% ee.

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