Microbiologically Modified Chiral Synthon. II. 4,9-Dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin for Formal Total Syntheses of Certain C(8) Oxygenated Sesquiterpenoids[1)]

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4,(9*S*)- (2a) and 4,(9*R*)-dimethyl-(7*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (4a) were prepared in high optical purity (>99% ee) and in moderate yield by asymmetric reduction of the corresponding racemic diketone (±)-1 using yeasts. These compounds were used for formal total syntheses of C(8) oxygenated sesquiterpenoids such as (−)-artemisin, (−)-yomogin, (−)-3-oxodiplophyllin, β-elemenone, (+)-isotelekin, (+)-cuauhtemone and 4-*epi*-aubergenon.

Keywords asymmetric induction; microbiological reduction; 3,7-dioxo-octalin; (7*S*)-hydroxy-3-oxo-octalin; yeast; *Rhodotorula rubla*; chiral synthon; C(8)-oxygenated sesquiterpenoid; (−)-artemisin; (+)-isotelekin

One of the most fundamental processes in natural products syntheses is the stereoselective construction of a new chiral center. Recently there have been many reports on asymmetric syntheses. These are represented by asymmetric epoxidation,[2)] hydroboration,[3)] aldol condensation,[4)] reduction[5)] and Diels–Alder reaction.[6)] These organic asymmetric syntheses are not always adequate because the chiral reagents required are often not generally available, and also most of the methods do not offer sufficiently high optical yields. Microbiological asymmetric inductions have been employed for a variety of purposes: *e.g.*, reduction,[7)] oxidation[8)] and hydrolysis.[9)] Since such biological methods are specific with respect to the substrates and the reactions are stereoselective, regioselective and enantioselective under moderate conditions, efficient asymmetric inductions can often be achieved with minimal side reactions.

We reported earlier the enantioselective reduction of 4-carbomethoxy-3,8-dioxo-9-methyl-$\Delta^{4(10)}$-octalin with certain yeasts, especially *Hansenula anomala*, to yield the optically pure ketol (>99% ee) along with the highly optically pure diketone (>99% ee) corresponding to the starting racemate.[10a)] Our results indicate that a kinetic resolution of the bicyclic diketoester was effected by microorganisms. One of the features of microbiological asymmetric induction is naturally the specificity of microorganisms for substrates.[10)] Among forty yeasts, only three specialized yeasts including *H. anomala* were suitable for the reaction mentioned above.

Attempted preparations of C(8) oxygenated sesquiterpenoids by microbiological oxidation of the corresponding desoxy congeners have not always been successful. Many-step chemical modifications for this purpose are of almost no practical usefulness, as in the transformation from *l*-α-santonin to artemisin.[11)] The chiral octalin derivatives with an oxygen functional group at C(7) (equivalent to C(8) in sesquiterpenoids) are some of the most important optically active synthons to be used in syntheses of various naturally occurring sesquiterpenoids. Some examples are (−)-artemisin,[12a)] (−)-yomogin,[12b)] (−)-3-oxodiplophyllin,[12c)] β-elemenone,[12d)] (+)-isotelekin,[12e)] (+)-cuauhtemone[12f)] and aubergenon.[12g)] Nevertheless, the chiral diketones have not yet been synthesized by conventional asymmetric cyclization.

Here we describe the enantioselective reduction of (±)-4,9-dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin[10b,13)] using yeasts. As

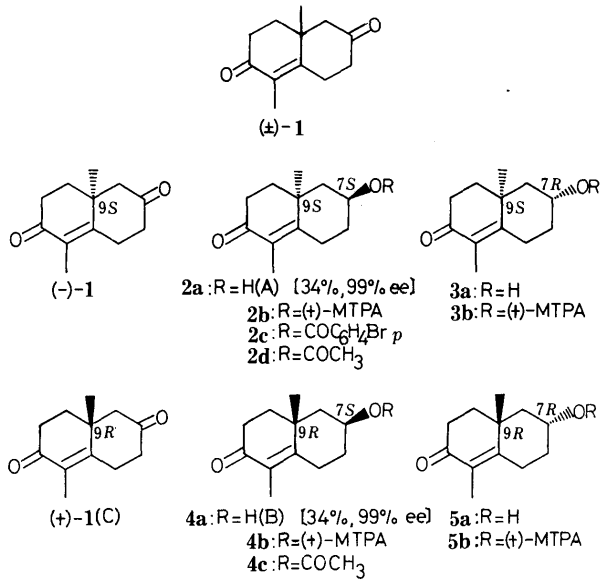

Chart 1

reported before,[10b)] the microbial transformation of (±)-**1** with some selected yeasts, especially *Rhodotorula rubla*[14)] CCY 20-7-1, produced the ketol A, $[\alpha]_D^{19}$ −147.9° (c=1.0, $CHCl_3$), mp 69-75 °C, and another ketol B, $[\alpha]_D^{20}$ +157.2° (c=1.0, $CHCl_3$), mp 98—101 °C, along with optically active starting diketone, $[\alpha]_D^{20}$ +9.4° (c=1.0, $CHCl_3$), mp 86—89 °C, in 34%, 25% and 24% yields, respectively. As shown in Fig. 1, the absolute configuration of the main product A was determined by X-ray analysis of its *p*-bromobenzoate (**2c**) to be 7*S*, 9*S* (hence A=**2a**). The X-ray analysis of **2c** clearly defined the presence of two configurational isomers of the *p*-bromobenzoyl group. The unit cell contains two kinds of crystallographically independent molecules (a) and (b) which are shown in Fig. 1 (a) and (b). The two structures are very similar to each other. The only significant differences are seen in the twisting of the *p*-bromobenzoate group with respect to the molecular skelton. Thus, the torsional angles C6–C7–O2–C13 and C6′–C7′–O2′–C13′ are 88.6(9)° and 149.7(8)°, respectively, for (a) and (b).

The other ketol B was oxidized with Jones reagent to provide the diketone C, $[\alpha]_D^{21}$ +7.8 (c=1.0, $CHCl_3$), which was identical, except for the sign of the optical rotation, with the (9*S*)-diketone (−)-**1**, $[\alpha]_D^{21}$ −11.5° (c=1.0, $CHCl_3$), obtained by Jones oxidation of the foregoing ketol

TABLE I. Fractional Atomic Coordinates (x, y and z) and Equivalent Isotropic Temperature Factors (B_{eq} in Å^2)

No.	Atom	x 10^5	y 10^5	z 10^5	B_{eq} Å^2
1	Br1	96210 (0)	67564 (0)	78123 (0.)	5.85 (0.03)

No.	Atom	x 10^4	y 10^4	z 10^4	B_{eq} Å^2
2	C1	4239 (10)	−2639 (12)	13248 (14)	4.9 (0.2)
3	C2	3739 (11)	−3768 (13)	14264 (16)	5.9 (0.3)
4	C3	4783 (12)	−3551 (12)	15278 (15)	5.2 (0.3)
5	C4	6185 (11)	−2818 (11)	14713 (13)	4.5 (0.2)
6	C5	8050 (10)	−1715 (11)	12571 (14)	4.5 (0.2)
7	C6	8412 (9)	−361 (11)	11919 (14)	4.6 (0.2)
8	C7	7510 (9)	−682 (10)	10655 (13)	4.1 (0.2)
9	C8	6084 (9)	−1147 (10)	11460 (14)	4.1 (0.2)
10	C9	5642 (8)	−2468 (9)	12194 (11)	3.4 (0.2)
11	C10	6614 (9)	−2308 (9)	13250 (12)	3.8 (0.2)
12	C11	7149 (14)	−2747 (16)	15752 (16)	7.1 (0.4)
13	C12	5606 (11)	−3719 (10)	10767 (13)	4.8 (0.2)
14	C13	8715 (9)	999 (10)	8874 (12)	4.0 (0.2)
15	C14	8904 (9)	2390 (9)	8614 (12)	3.6 (0.2)
16	C15	8204 (9)	3199 (9)	9770 (12)	3.5 (0.2)
17	C16	8415 (10)	4520 (11)	9547 (12)	4.2 (0.2)
18	C17	9329 (10)	4988 (10)	8156 (13)	4.3 (0.2)
19	C18	10016 (11)	4193 (12)	7002 (13)	4.7 (0.2)
20	C19	9794 (10)	2853 (11)	7226 (13)	4.6 (0.2)
21	O1	4419 (10)	−4094 (10)	16517 (11)	7.5 (0.2)
22	O2	7758 (7)	634 (7)	10158 (9)	4.5 (0.1)
23	O3	9376 (8)	323 (8)	8047 (10)	5.5 (0.2)

No.	Atom	x 10^5	y 10^5	z 10^5	B_{eq} Å^2
24	Br1′	6307 (15)	−67939 (13)	23411 (18)	5.76 (0.02)

No.	Atom	x 10^4	y 10^4	z 10^4	B_{eq} Å^2
25	C1′	2815 (11)	1063 (11)	−4980 (13)	4.6 (0.2)
26	C2′	3392 (11)	2266 (12)	−5963 (14)	5.0 (0.2)
27	C3′	4846 (12)	2744 (12)	−6329 (14)	5.2 (0.3)
28	C4′	5598 (11)	2649 (11)	−5165 (13)	4.7 (0.2)
29	C5′	5671 (11)	2081 (13)	−2552 (15)	5.5 (0.3)
30	C6′	5090 (11)	733 (13)	−1824 (16)	5.6 (0.3)
31	C7′	3648 (11)	400 (10)	−1236 (14)	4.6 (0.2)
32	C8′	2892 (10)	162 (10)	−2632 (13)	4.1 (0.2)
33	C9′	3429 (9)	1476 (9)	−3406 (11)	3.6 (0.2)
34	C10′	4919 (9)	2042 (10)	−3819 (12)	3.8 (0.2)
35	C11′	7094 (11)	3282 (15)	−5526 (16)	6.5 (0.3)
36	C12′	2960 (12)	2608 (10)	−2119 (14)	4.9 (0.2)
37	C13′	2102 (10)	−1141 (10)	615 (12)	4.1 (0.2)
38	C14′	1746 (9)	−2523 (9)	1011 (11)	3.5 (0.2)
39	C15′	897 (10)	−2812 (10)	2536 (13)	4.2 (0.2)
40	C16′	557 (10)	−4115 (11)	2957 (12)	4.4 (0.2)
41	C17′	1037 (9)	−5044 (9)	1848 (12)	3.8 (0.2)
42	C18′	1903 (11)	−4778 (10)	318 (13)	4.5 (0.2)
43	C19′	2230 (11)	−3496 (11)	−105 (12)	4.6 (0.2)
44	O1′	5479 (11)	3325 (13)	−7514 (13)	8.4 (0.3)
45	O2′	3161 (7)	−909 (7)	−639 (9)	4.9 (0.2)
46	O3′	1591 (7)	−315 (7)	1344 (10)	5.0 (0.2)

Equivalent positions
x y z

TABLE II. Anisotropic Thermal Parameters

No.	Atom	$U11$	$U22$	$U33$	$U12$	$U13$	$U23$
		$U(ij)$'s are multiplied by 10^4					
1	Br1	958 (8)	606 (6)	716 (7)	230 (6)	−187 (6)	249 (5)
		$U(ij)$'s are multiplied by 10^3					
2	C1	44 (6)	71 (7)	70 (7)	11 (5)	−2 (5)	34 (6)
3	C2	58 (7)	86 (9)	78 (8)	6 (6)	−5 (6)	46 (7)
4	C3	76 (8)	60 (7)	63 (7)	27 (6)	0 (6)	19 (5)
5	C4	62 (6)	55 (6)	56 (6)	20 (5)	−18 (5)	9 (5)
6	C5	42 (5)	58 (6)	78 (7)	13 (5)	−13 (5)	32 (5)
7	C6	37 (5)	57 (6)	81 (7)	5 (4)	−14 (5)	32 (5)
8	C7	47 (5)	45 (5)	71 (7)	12 (4)	−2 (5)	34 (5)
9	C8	42 (5)	49 (5)	72 (7)	13 (4)	−15 (5)	26 (5)
10	C9	34 (4)	45 (5)	51 (5)	10 (4)	−6 (4)	19 (4)
11	C10	47 (5)	38 (5)	63 (6)	11 (4)	−25 (5)	7 (4)
12	C11	84 (9)	128 (12)	74 (9)	27 (9)	−34 (7)	42 (8)
13	C12	77 (7)	47 (6)	53 (6)	11 (5)	−18 (5)	8 (5)
14	C13	46 (5)	49 (5)	50 (5)	3 (4)	−3 (4)	25 (4)
15	C14	42 (5)	44 (5)	50 (5)	11 (4)	−9 (4)	13 (4)
16	C15	41 (5)	44 (5)	51 (5)	10 (4)	−5 (4)	22 (4)
17	C16	47 (6)	66 (6)	50 (6)	25 (5)	−3 (4)	14 (5)
18	C17	59 (6)	51 (6)	59 (6)	7 (5)	−24 (5)	23 (5)
19	C18	55 (6)	67 (7)	56 (6)	22 (5)	−13 (5)	10 (5)
20	C19	58 (6)	69 (7)	49 (6)	16 (5)	−2 (5)	30 (5)
21	O1	123 (8)	103 (7)	62 (5)	40 (6)	8 (5)	46 (5)
22	O2	53 (4)	54 (4)	65 (4)	20 (3)	9 (3)	30 (3)
23	O3	77 (5)	60 (5)	74 (5)	36 (4)	17 (4)	24 (4)
		$U(ij)$'s are multiplied by 10^4					
24	Br1′	863 (8)	538 (6)	748 (7)	144 (5)	−166 (6)	194 (5)
		$U(ij)$'s are multiplied by 10^3					
25	C1′	62 (6)	58 (6)	60 (6)	20 (5)	−22 (5)	11 (5)
26	C2′	56 (6)	70 (7)	62 (7)	18 (5)	−9 (5)	19 (6)
27	C3′	84 (8)	62 (7)	57 (7)	32 (6)	−4 (6)	15 (5)
28	C4′	57 (6)	60 (6)	57 (6)	19 (5)	−3 (5)	13 (5)
29	C5′	48 (6)	79 (8)	80 (8)	0 (5)	−20 (6)	39 (6)
30	C6′	60 (7)	79 (8)	92 (9)	17 (6)	−20 (6)	47 (7)
31	C7′	68 (7)	47 (5)	63 (6)	17 (5)	−16 (5)	17 (5)
32	C8′	50 (6)	45 (5)	63 (6)	16 (4)	−7 (5)	17 (5)
33	C9′	49 (5)	40 (5)	45 (5)	18 (4)	−9 (4)	1 (4)
34	C10′	45 (5)	46 (5)	50 (5)	16 (4)	−4 (4)	11 (4)
35	C11′	47 (6)	100 (10)	77 (8)	4 (6)	8 (6)	37 (7)
36	C12′	78 (8)	46 (6)	63 (7)	36 (5)	3 (6)	6 (5)
37	C13′	49 (5)	58 (6)	48 (5)	13 (5)	−8 (4)	18 (5)
38	C14′	43 (5)	47 (5)	46 (5)	15 (4)	−10 (4)	14 (4)
39	C15′	54 (6)	53 (6)	53 (6)	24 (5)	−8 (5)	8 (5)
40	C16′	49 (6)	69 (7)	49 (6)	17 (5)	0 (4)	27 (5)
41	C17′	49 (5)	42 (5)	56 (6)	14 (4)	−16 (4)	12 (4)
42	C18′	66 (7)	47 (5)	56 (6)	14 (5)	−12 (5)	14 (5)
43	C19′	68 (7)	62 (6)	48 (6)	35 (6)	−12 (5)	−2 (5)
44	O1′	98 (7)	156 (9)	81 (6)	53 (7)	16 (5)	68 (6)
45	O2′	69 (5)	58 (4)	61 (4)	25 (4)	6 (4)	28 (4)
46	O3′	66 (5)	55 (4)	75 (5)	28 (4)	−1 (4)	18 (4)

Temperature factor T is the form of $T=\exp\{-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12hka^*b^*+2U13hla^*c^*+2U23klb^*c^*)\}$.

(7*S*, 9*S*)-A (**2a**). Since the sign of $[\alpha]_D$ in C was opposite to that in (−)-**1**, the absolute configuration of C and of the recovered diketone was found to be 9*R* (hence C=(+)-**1**). There was a downfield shift of the angular methyl signal of B in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (δ +0.198 ppm) in comparison with that of A (**2a**) and an upfield shift of the corresponding methyl signal of the acetate of B (δ −0.090 ppm) in comparison with that of B. This accords with the earlier report[15] of the 1,3-diaxial

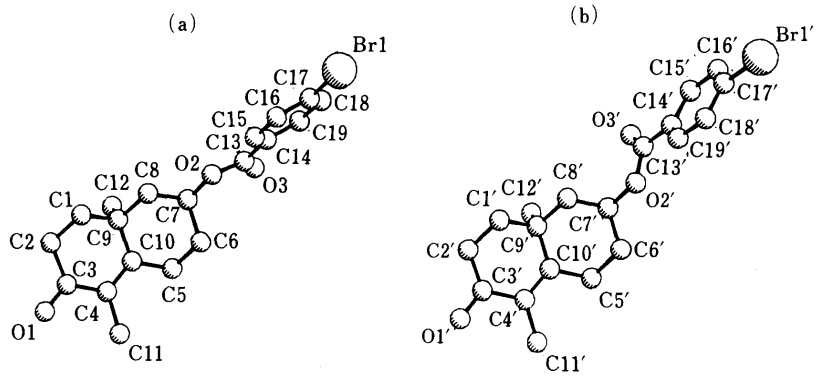

Fig. 1. Perspective View of Molecules (a) and (b) of the *p*-Bromobenzoate (**2c**) of 4,(9*S*)-Dimethyl-(7*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (**2a**)

TABLE III. Bond Lengths in Å

Atom 1	Atom 2	Length (STD)	Atom 1	Atom 2	Length (STD)
Br1	C17	1.893 (12)	Br1′	C17′	1.894 (11)
C1	C2	1.519 (20)	C1′	C2′	1.558 (18)
C1	C9	1.557 (13)	C1′	C9′	1.539 (16)
C2	C3	1.540 (21)	C2′	C3′	1.473 (17)
C3	C4	1.464 (15)	C3′	C4′	1.503 (21)
C3	O1	1.235 (17)	C3′	O1′	1.230 (16)
C4	C10	1.383 (16)	C4′	C10′	1.362 (15)
C4	C11	1.534 (23)	C4′	C11′	1.518 (15)
C5	C6	1.564 (18)	C5′	C6′	1.561 (20)
C5	C10	1.491 (13)	C5′	C10′	1.514 (19)
C6	C7	1.544 (18)	C6′	C7′	1.483 (16)
C7	C8	1.499 (13)	C7′	C8′	1.541 (18)
C7	O2	1.489 (14)	C7′	O2′	1.474 (14)
C8	C9	1.554 (16)	C8′	C9′	1.554 (15)
C9	C10	1.517 (16)	C9′	C10′	1.511 (13)
C9	C12	1.543 (13)	C9′	C12′	1.563 (15)
C13	C14	1.498 (16)	C13′	C14′	1.490 (16)
C13	O2	1.330 (11)	C13′	O2′	1.358 (11)
C13	O3	1.206 (14)	C13′	O3′	1.196 (14)
C14	C15	1.419 (14)	C14′	C15′	1.415 (13)
C14	C19	1.389 (13)	C14′	C19′	1.390 (15)
C15	C16	1.405 (17)	C15′	C16′	1.422 (17)
C16	C17	1.402 (13)	C16′	C17′	1.352 (15)
C17	C18	1.400 (16)	C17′	C18′	1.420 (14)
C18	C19	1.423 (19)	C18′	C19′	1.404 (17)

TABLE IV. Bond Angles (°)

Atom 1	Atom 2	Atom 3	Angle (STD)	Atom 1	Atom 2	Atom 3	Angle (STD)
C2	C1	C9	112.7 (10)	C2′	C1′	C9′	110.8 (9)
C3	C2	C1	109.7 (11)	C3′	C2′	C1′	110.8 (10)
C4	C3	C2	120.9 (11)	C4′	C3′	C2′	120.4 (11)
C4	C3	O1	120.7 (12)	C4′	C3′	O1′	118.1 (12)
C2	C3	O1	118.2 (12)	C2′	C3′	O1′	121.2 (12)
C10	C4	C3	121.1 (10)	C10′	C4′	C3′	119.3 (10)
C10	C4	C11	122.2 (11)	C10′	C4′	C11′	122.9 (11)
C3	C4	C11	116.5 (11)	C3′	C4′	C11′	117.8 (10)
C6	C5	C10	112.4 (9)	C6′	C5′	C10′	113.0 (10)
C7	C6	C5	107.6 (9)	C7′	C6′	C5′	109.1 (11)
C8	C7	C6	111.0 (9)	C8′	C7′	C6′	113.3 (10)
C8	C7	O2	104.8 (8)	C8′	C7′	O2′	107.1 (9)
C6	C7	O2	107.7 (8)	C6′	C7′	O2′	106.0 (9)
C9	C8	C7	113.1 (9)	C9′	C8′	C7′	109.8 (9)
C10	C9	C1	111.8 (8)	C10′	C9′	C1′	111.2 (8)
C10	C9	C8	110.0 (8)	C10′	C9′	C8′	112.6 (8)
C10	C9	C12	108.4 (8)	C10′	C9′	C12′	108.2 (8)
C1	C9	C8	105.9 (8)	C1′	C9′	C8′	106.2 (8)
C1	C9	C12	110.9 (9)	C1′	C9′	C12′	110.2 (9)
C8	C9	C12	109.8 (8)	C8′	C9′	C12′	108.4 (8)
C14	C13	O2	111.3 (9)	C14′	C13′	O2′	110.0 (9)
C14	C13	O3	123.9 (10)	C14′	C13′	O3′	125.8 (10)
O2	C13	O3	124.8 (10)	O2′	C13′	O3′	124.2 (10)
C15	C14	C13	120.5 (9)	C15′	C14′	C13′	118.0 (9)
C15	C14	C19	122.0 (9)	C15′	C14′	C19′	121.7 (10)
C13	C14	C19	117.6 (9)	C13′	C14′	C19′	120.3 (9)
C16	C15	C14	120.2 (9)	C16′	C15′	C14′	119.1 (10)
C17	C16	C15	117.5 (10)	C17′	C16′	C15′	118.0 (10)
C18	C17	Br1	118.9 (8)	C18′	C17′	Br1′	115.8 (8)
C18	C17	C16	122.7 (10)	C18′	C17′	C16′	124.0 (10)
Br1	C17	C16	118.4 (8)	Br1′	C17′	C16′	120.0 (8)
C19	C18	C17	119.7 (11)	C19′	C18′	C17′	118.0 (10)
C4	C10	C5	121.0 (10)	C4′	C10′	C5′	119.1 (10)
C4	C10	C9	121.0 (9)	C4′	C10′	C9′	123.1 (9)
C5	C10	C9	117.7 (9)	C5′	C10′	C9′	117.3 (9)
C7	O2	C13	117.9 (8)	C7′	O2′	C13′	118.1 (8)
C14	C19	C18	118.0 (10)	C14′	C19′	C18′	119.1 (10)

relationship between the hydroxyl group and the methyl group, showing that C(7)-OH in B is axially oriented. This is also supported by the C(7) equatorial OH of **2a** found in the X-ray analysis of **2c**. Therefore the absolute configuration of B was determined to be 7*S*, 9*R* (hence B=**4a**).

In order to determine the optical purity of the reduction products, the four possible steroisomers (**2a**, **3a**, **4a** and **5a**) were synthesized from the (±)-diketone (**1**) as follows. Reduction of **1** with diisobutylaluminum hydride, followed by manganese dioxide oxidation, afforded a racemic *cis*-ketol (**3a**+**4a**) and a racemic *trans*-ketol (**2a**+**5a**) in 35% and 26% overall yields, respectively. These two racemic ketols were treated directly with (+)-α-methoxy-α-trifluromethylphenylacetic acid chloride [(+)-MTPACl][16] to give the corresponding (+)-MTPA esters, (**2b**+**5b**) and (**3b**+**4b**). The nuclear magnetic resonance (NMR) signals due to each angular methyl group appeared at distinctly different fields, at δ 1.318 and 1.326 for (**2b**+**5b**) and at δ 0.978 and 1.128 for (**3b**+**4b**). Thus, the (+)-MTPA ester **2b** (δ 1.318) corresponding to the main reduction product (7*S*, 9*S*)-**2a** (A) mentioned above was found to be more than 99% ee. Therefore, the remaining NMR signal (δ 1.326) of (**2b**+**5b**) should be ascribed to (7*R*, 9*R*)-**5b**. The second product (7*S*, 9*R*)-**4a** was also converted to the corresponding (+)-MTPA ester **4b** (δ 0.978). This was found to be 67% ee by taking account of the small signal (δ 1.128) due to the enantiomer (7*R*, 9*S*)-**3b**. The optical purity of the recovered diketone (+)-**1** was determined to be 60—61% ee.

Since the relationship between the absolute structure and the chemical shift of the four possible (+)-MTPA esters (**2b**, **3b**, **4b** and **5b**) was thus established, we began the following microbial screening experiments. To find more effective reducing microorganisms to produce (7*S*, 9*R*)-**4a**

selectively, a series of reductions with a variety of yeasts was undertaken.

Reduction of (±)-**1** with *Trichosporon fermentans* IFO-1199 provided the *cis*-ketol (7*S*, 9*R*)-**4a**, $[\alpha]_D^{19}$ +198.8° (c=1.0, $CHCl_3$) corresponding to >99% ee in 34% yield and a small amount of the *trans*-ketol (7*S*, 9*S*)-**2a** (>99% ee, 6%), along with recovered diketone (9*S*)-**1**, $[\alpha]_D^{19}$ −4.5° (c=1.0, $CHCl_3$), corresponding to 39% ee based on $[\alpha]_D^{21}$ −11.5° (c=1.0, $CHCl_3$), in 44% yield. Another asymmetric reduction with *Torulopsis famata* gave a complex mixture, in which the optical purity of the product **4a** (14% yield) was very high (>99% ee).

In conclusion, the used of properly selected microorganisms in microbial asymmetric reduction of (±)-4,9-dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin (**1**) afforded 4, (9*S*)- (**2a**) and/or 4, (9*R*)-dimethyl-(7*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (**4a**) with high optical purity (>99% ee) in moderate yields.

Since the six racemic sesquiterpenoids corresponding to the respective natural products mentioned above have been synthesized,[17] the aforementioned preparation of the optically active key intermediates, *i.e.* (−)-4, (9*S*)- (**1**) and (+)-4, (9*R*)-dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin (**1**) constitutes formal total syntheses of the sesquiterpenoids, *i.e.* (−)-artemisin,[17a] (−)-yomogin,[13] (−)-3-oxodiplophyllin,[13] β-elemenone,[17b] (+)-isotelekin,[17c] (+)-cuauhtemone[17a] and 4-*epi*-augergenon.[17e]

Experimental

Melting points were measured with a Kofler micro melting point apparatus and are uncorrected. Infrared (IR) spectra ($CHCl_3$) were measured on a JASCO A-3 spectrophotometer, and 400 MHz ^{1}H-NMR spectra were measured on a JEOL FX 400 instrument. Spectra were taken as 5—10% w/v solutions in $CDCl_3$ with Me_4Si as an internal reference. Gas chromatography-mass spectroscopy (GC-MS) and high-resolution mass spectra (MS) were carried out on a JEOL JMS D-300 (JMA-200 data analysis system) mass spectrometer. $[\alpha]_D$ measured on a Perkin–Elmer model 241MC polarimeter in $CHCl_3$ solution unless otherwise stated.

Asymmetric Reduction of (±)-4,9-Dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin (1) with *Rhodotorula rubla* i) A test tube (25 mm i.d. × 200 mm) containing 10 ml of culture medium comprising 5% glucose, 0.1% KH_2PO_4, 0.1% $(NH_4)_2SO_4$, 0.05% Urea, 0.05% $MgSO_4 \cdot 7H_2O$, 0.05% $CaCl_2 \cdot 2H_2O$, 0.1% yeast extract, a trace of mineral solution (0.1% $FeSO_4 \cdot 7H_2O$, 0.1% $MnCl_2 \cdot 4H_2O$, 0.1% $ZnSO_4 \cdot 7H_2O$; 0.2 ml per 100 ml of culture medium) and tap water (pH 6.5) was incubated with *Rhodotorula rubla* and the yeast was cultured at 30 C for 3 d with continuous shaking. Then 1 ml of the above seed culture was transferred to 800 ml of the same medium. After cultivation for 3 d, 400 mg of the substrate (±)-**1** was added and cultivation was continued for an additional 3 d under the same conditions.

ii) The reaction mixture was filtered with the aid of celite and the filtrate was extracted with ethyl acetate. The ethyl acetate extract was dried over $MgSO_4$. Removal of the solvent gave an oily product, which was chromatographed on silica gel (45 g) to give the reduction products (A, 135.2 mg, 34% yield; B, 98.6 mg, 24% yield) along with some starting material C (97 mg, 25% recovery) from the *n*-hexane–ethyl acetate (9 : 1) eluate. A: mp 69—75 °C. MS Calcd for $C_{12}H_{18}O_2$ (M^+, m/z): 194.130. Found. 194.128. $[\alpha]_D^{19}$ −147.9° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3445, 1658, 1610. ^{1}H-NMR δ: 1.245 (3H, s, 9-CH_3), 1.782 (3H, s, 4-CH_3), 4.030—4.107 (1H, m, 7-H). B: mp 98—101 °C. MS Calcd. for $C_{12}H_{18}O_2$ (M^+, m/z); 194.130. Found: 194.132. $[\alpha]_D^{19}$ +157.2° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1650, 1610. ^{1}H-NMR δ: 1.439 (3H, s, 9-CH_3), 1.792 (3H, s, 4-CH_3), 4.220—4.224 (1H, m, 7-H).

Preparation of the (7*S*,9*S*)-*p*-Bromobenzoate (2c) from 4, (9*S*)-Dimethyl-(7*S*)-hydroxy-3-oxo-$\Delta^{4(10)}$-octalin (2a) Pyridine (0.3 ml) was added to a mixture of the ketol A (19.1 mg), *p*-bromobenzoyl chloride (25.8 mg) and 4-dimethylaminopyridine (DAMP) (10 mg), and the reaction mixture was stirred for 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 $MgSO_4$ and concentrated to give crude **2c**; this was subjected to preparative thin layer chromatography (TLC) with *n*-hexane–ethyl acetate (1 : 1) to provide the *p*-bromobenzoate (**2c**) (26.5 mg, 82% yield), which was crystallized from pentane, $[\alpha]_D^{22}$ +150.3° (c=0.34, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1717, 1664, 1620, 1600.

Crystal Data of 2c $C_{19}H_{21}BrO_3$, M_r=377.3, triclinic, space group $P\bar{1}$, a=11.230 (6), b=10.788 (7), c=8.470 (5) Å, α=105.79 (6), β=74.63 (4), γ=113.61 (6)°, U=890.5 Å^3, Z=2, D_c=1.407 g·cm^{-3}, CuK_α=32.5 cm^{-1}.

Crystallographic Measurements of 2c A small crystal of **2c** (approximately 0.2 × 0.15 × 0.1 mm) grown in pentane solution was used for the present X-ray study. Cell dimensions and intensity data were measured on a Phillips PW1100 diffractometer using CuK_α radiation monochromated by a graphite plate. Intensities of 3626 reflections were measured in the 2θ range of 6° through 156°. Among these, 3201 were above the 2σ (I) level and these were used for structure determination. An additional 748 hkl and $\bar{h}k\bar{l}$ reflections (2θ=20—80°) were measured in pairs, and these were used for the determination of absolute configuration. No absorption corrections were applied. The disagreement factor R for 392 Friedel pair of $|F|$'s observed for $hk0$ through $hk2$ reflections was 3.45%.

Structure Analysis of 2c Structure was determined by the heavy atom method and refined by the block-diagonal least-squares method. The absolute configuration was determined by the anomalous dispersion method of the 118 Friedel pairs having a significant difference[18] between observed $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$; 115 pairs yielded the absolute configuration shown in Fig. 1. Final refinement, allowing for the dispersion corrections of atomic scattering factors of C, O and Br for CuK_α, gave the R value of 0.063 without hydrogen atoms.

Preparation of (+)-MTPA Esters (2a and 4b) i) Pyridine (0.3 ml) was added to A (**2a**) (23.8 mg), (+)-MTPACl (30 mg) and DAMP (10 mg) and the reaction mixture was stirred for 17 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 $MgSO_4$ and concentrated to give an oil, which was subjected to preparative TLC (silica gel, 20 × 20 cm; solvent, *n*-hexane–ethyl acetate (1 : 1)) to provide the (+)-MTPA ester **2b** (39.0 mg, 77% yiled). ^{1}H-NMR δ: 1.318 (3H, s, 9-CH_3), 1.780 (3H, s, 4-CH_3), 3.550 (3H, d, O-CH_3), 5.344—5.424 (1H, m, 7H). The optical purity of **2b** and hence that of **2a** was found to be more than 99% ee. ii) Pyridine (0.3 ml) was added to a mixture of B (**4a**) (16.4 mg), (+)-MTPACl (30 mg) and DAMP (10 mg). The reaction mixture was stirred for 17 h at room temperature, then worked up and purified in the same way as in the case of A to afford the (+)-MTPA ester **4b** (24.3 mg, 70% yield). ^{1}H-NMR δ: 0.979 (3H, s, 9-CH_3), 1.128 (each 3H, s, 9-CH_3), 1.742, 1.764 (each 3H, s and d, each J=1.22 Hz, O-CH_3), 5.400—5.416 (each 1H, m, 7-H).

Conversion A into (−)-4,(9*S*)-Dimethyl-3,7-dioxo-$\Delta^{4,(10)}$-octalin (1) Jones reagent (2 drops) was added to a stirred solution of A (21.1 mg) in acetone (5 ml), and this mixture was cooled in an ice-salt bath for 30 min. After the addition of isopropyl alcohol and $NaHCO_3$, the reaction mixture was filtered and the filtrate was concentrated to give an oil, which was subjected to preparative TLC (silica gel, 20 × 20 cm; solvent *n*-hexane–ethyl acetate (1 : 1)) to provide the dione (−)-**1**; $[\alpha]_D^{21}$ −10° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1710, 1658, 1615. ^{1}H-NMR δ: 1.253 (3H, s, 9-CH_3), 1.832 (3H, s, 4-CH_3).

Asymmetric Reduction of (±)-1 with *Trichosporon fermentans* After cultivation, the crude reaction mixture was chromatographed on silica gel (45 g) to give the reaction products (**2a**: 137 mg, 34% yield) and (**4a**: 25.3 mg, 6% yield) along with some starting material ((−)-**1**: 178 mg, 44% recovery) from the *n*-hexane–ethyl acetate (9 : 1) eluate. The NMR spectra of the reduction products were identical with those of the authentic enantiomers **2a** and **4a** described above. **2a**: $[\alpha]_D^{19}$ +198.8° (c=1.0; $CHCl_3$). (−)-**1**: $[\alpha]_D^{19}$ −4.5° (c=1.0, $CHCl_3$). The optical purities of **2a** and **4a** were determined by the (+)-MTPA ester method described above and were both found to be >99% ee.

Asymmetric Reduction of (±)-1 with *Torulopsis famata* After cultivation, the crude reaction mixture was chromatographed on silica gel (45 g) to afford the reduction product (**2a**) along with an inseparable mixture. The NMR spectra of the reduction product was identical with that of the authentic **2a** described above. **2a**: $[\alpha]_D^{20}$ −209.4° (c=1.0, $CHCl_3$). The optical purity of **2a** was determined by the (+)-MTPA ester method described above and found to be >99% ee.

Preparation of Four Alcohols (2a, 3a, 4a and 5a) and Their (+)-MTPA Esters (2b, 3b, 4b and 5b) i) 2.5 ml of DIBAL (1.0 M solution in *n*-hexane) was added dropwise with stirring to a solution of 192 mg of 4,9-dimethyl-3,7-dioxo-$\Delta^{4(10)}$-octalin in 10 ml of absolute ether under cooling with dry ice and acetone, and the mixture was stirred for 1 h at −20 °C. Then the reaction mixture was extracted with ether after the addition of H_2O, and the extract was filtered with the aid of celite. The filtrate was washed with

saturated aqueous NaCl, dried over $MgSO_4$ and concentrated to give an oil. This was chromatographed on silica gel (16 g) to afford the less polar fraction I (93 mg, 47% yield) and the more polar fraction II (32 mg, 16% yield). ii) A suspension of manganese dioxide (MnO_2) (238.5 mg) and the less polar fraction I (85 mg) in CH_2Cl_2 was stirred at room temperature for 18 h. Then additional MnO_2 (238.5 mg) was added and the mixture was stirred for 18 h again. MnO_2 was filtered off and the filtrate was evaporated to give (**2a**+**5a**) (62.7 mg, 73% yield). A suspension of MnO_2 (33.7 mg) and the more polar fraction II (51 mg) in CH_2Cl_2 (3 ml) was stirred at room temperature for 18 h. More MnO_2 (33.7 mg) was added, and the mixture was stirred for 18 h, then the reaction mixture was worked up in the same way as in the case of the less polar fraction I to afford (**3a**+**4a**) (50.6 mg, 99% yield). iii) Pyridine (0.3 ml) was added to a mixture of (**2a**+**5a**) (15.7 mg), (+)-MTPACl (30 mg) and DAMP (10 mg), and the reaction mixture was stirred for 18 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 $MgSO_4$ and concentrated to give an oil, which was subjected to preparative TLC (silica gel, 20 × 20 cm; solvent, *n*-hexane–ethyl acetate (1 : 1)) to provide the (+)-MTPA ester (**2b**+**5b**)(24.8 mg, 75% yield). ^{1}H-NMR δ: 0.978, 1.127 (each 3H, s, 9-CH_3), 1.740, 1.762 (each 3H, s, 4-CH_3), 3.563, 3.581 (each 3H, s, O-CH_3) 5.412 (1H, d, J=3.17 Hz, 7-H). Pyridine (0.3 ml) was added to a mixture of (**3a**+**4a**) (31 mg), (+)-MTPACl (30 mg) and DAMP (10 mg), and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was worked up and purified in the same way as in the case of the preparation of the (+)-MTPA ester (**2b**+**5b**) to provide the (+)-MTPA ester (**3b**+**4b**), 44.9 mg, 69% yield. ^{1}H-NMR δ: 1.318, 1.326 (each 3H, s, 9-CH_3), 1.771, 1.780 (each 3H, d, J=1.22, 0.98 Hz, 4-CH_3), 3.556 (3H, s, O-CH_3), 5.345—5.425 (1H, m, 7-H).

Conversion of B into (−)-4,(9*S*)-Dimethyl-3,7-dioxo-$\Delta^{4,(10)}$-octalin (1) Jones reagent (2 drops) was added to a stirred solution of B (20.7 mg) in acetone (10 ml), and the mixture was cooled in an ice-salt bath for 10 min. The reaction mixture was worked up and purified in the same way as mentioned above to afford (+)-**1**: $[\alpha]_D$ +7.8° (c=1.0; $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3600, 3450, 1710, 1658, 1615. ^{1}H-NMR δ: 1.253 (3H, s, 9-CH_3), 1.832 (3H, s, 4-CH_3).

Preparation of (7*S*)-Acetyl- and (7*R*)-Acetyl-4,(9*R*)-dimethyl-3-oxo-$\Delta^{4(10)}$-octalin (2d and 4c) i)Pyridine (0.3 ml) was added to a mixture of the ketol (**2a**) (21.1 mg) and acetic anhydride (0.05 ml), and the reaction mixture was stirred for 18 h at room temperature. After the addition of H_2O, the reaction mixture was washed with saturated aqueous NaCl, then dried over $MgSO_4$. Removal of the solvent gave an oil, which was subjected to preparative TLC (silica gel, 20 × 20 cm; solvent, *n*-hexane–ethyl acetate (1 : 1)) to provide the acetate (**2d**) as an oil (9.5 mg, 39% yield) ^{1}H-NMR δ: 1.290 (3H, s, 9-CH_3), 1.785 (3H, d, J=0.98 Hz, 4-CH_3), 2.049 (3H, s, $COCH_3$), 5.109—5.130 (1H, m, 7-H). ii) Pyridine (0.3 ml) was added to a mixture of the ketol (**4a**) (34.5 mg) and acetic anhydride (0.05 ml), and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was worked up and purified in the same way as mentioned above to afford the acetate (**4c**) (15.3 mg, 44% yield). ^{1}H-NMR δ: 1.350 (3H, s, 9-CH_3), 1.794 (3H, d, J=1.46 Hz, 4-CH_3), 2.104 (3H, s, $COCH_3$), 5.110—5.127 (1H, m, 7-H).

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