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# Enzymatic resolution of albicanol and its application to the synthesis of (−)-copalic acid

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ABSTRACT

The optical resolution of racemic albicanol (*rac*-**1**) based on the lipase-catalyzed transesterification by using vinyl myristate as an acyl donor afforded (8a*R*)-**1** (99% ee) in 43% yield and (8a*S*)-**1** (99% ee) in 37%. *E* value of the enzymatic reaction was 56.7 which was superior to that of the reported value (*E* = 25) by using isopropenyl acetate as an acyl donor. As the synthetic application of obtained (8a*R*)-**1**, (−)-copalic acid ((8a*R*)-**3**) and (−)-copalol ((8a*R*)-**4**) were synthesized from (8a*R*)-**1** in 35% and 34% total yield, respectively.


## 1. Introduction

Optically active albicanol (**1**) is an important chiral building block for synthesis of natural terpenoids [1–7]. Due to the antimicrobial and antitumor activity of the derivable natural products from optically active **1**, such as yahazuol [1] and coronarin A [4], much attention has been paid to their synthesis. There are several reports to synthesize optically active **1**. For example, Poigny and his co-workers reported preparation of (8a*S*)-**1** from commercially available sclareolide [5]. Furuichi and his co-workers reported optical resolution of *rac*-**1** by using 1,4-di-*O*-benzyl-L-threitol as a chiral auxiliary and obtained both enantiomers of **1** [8]. On the other hand, we reported lipase-catalyzed optical resolution of *rac*-**1** (Scheme 1) [9]. When *rac*-**1** was treated with isopropenyl acetate and lipase QL (lipase PL-266) in diisopropyl ether for 1 day, the corresponding acetate ((8a*S*)-**2a**) was obtained in 56% with 67% ee and (8a*R*)-**1** was recovered in 38% yield with >99% ee. The *E* value of this enzymatic acetylation was estimated to be 25 [10]. Furthermore, (8a*S*)-**2a** with 67% ee was converted to (8a*S*)-**1** by LAH reduction, and was subjected the lipase-catalyzed reaction again to afford highly optically active (8a*S*)-**2a**. (8a*S*)-**2a** was converted to (8a*S*)-**1** (>99% ee) and (8a*S*)-**1** was obtained in 27% from *rac*-**1**. However the efficiency of the optical resolution, such as low isolated yield of both enantiomers of **1** and high enzyme/substrate ratio (2.0 g/2.3 g), was still unsatisfied.

In this study, we improved the reaction conditions of the lipase-catalyzed optical resolution to obtain both enantiomers of **1** in high yield and applied (8a*R*)-**1** with high optical purity to the synthesis of (−)-copalic acid ((8a*R*)-**3**) and (−)-copalol ((8a*R*)-**4**) (Fig. 1).

## 2. Materials and methods

### 2.1. General

The NMR spectra were recorded in $CDCl_3$ on JEOL AL-400 spectrometer. Mass spectra were measured by JEOL JMS-AM II 50. IR spectra were carried out on JASCO FT/IR 4100. Specific rotation was measured on JASCO P-2200. HPLC analysis was performed on SSC-3210 pump equipped with chiral column, SSC-5200 UV detector and SIR Chromatocordor 21.

Chemicals were purchased from Tokyo Kasei Industry Co. Ltd., Wako Chemicals or Aldrich Inc. otherwise indicated. *rac*-Albicanol (*rac*-**1**) was synthesized by previously reported procedure [9]. Lipase QL from *Alcaligenes* sp. was equally lipase PL-266 [9] in previous papers and was purchased from Meito Co. Ltd. Isopropenyl butyrate was synthesized by the reported procedure [11].

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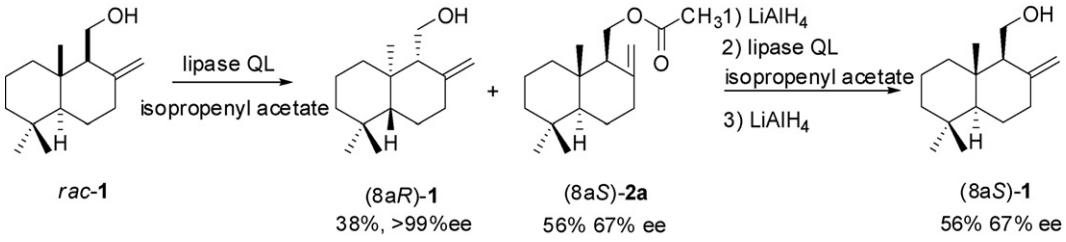



**Scheme 1.**

### 2.2. General procedure for enzymatic kinetic resolution of albicanol

To a solution of *rac*-**1** (100 mg, 0.45 mmol) and acyl donor (0.9 mmol) in diisopropyl ether (50 mL) was added lipase QL (100 mg) and the resulting mixture was stirred at 40 °C or the temperature indicated in Table 2. The reaction course was monitored by TLC, and the reaction was stopped by filtration through a pad of Celite 545. The residue was washed with ether and then the filtrate and ether solution were combined, evaporated under reduced pressure and afforded the mixture of the substrate and the corresponding product. The conversions were determined by the measurement of $^1$H NMR of the reaction mixture. The residue was purified by silica gel column chromatography to afford **1** and **2** and the ee of **1** was determined by HPLC analysis equipped with CHIRALPAK AD-H. *E* value of the reaction was calculated based on ee of recovered (8a*R*)-**1** and the extent of conversion. HPLC analysis: *n*-hexane/*i*-PrOH = 100/1; flow rate, 1.0 mL/min; detection, 220 nm. (8a*S*)-**1**: $t_R$ = 11.8 min; (8a*R*)-**1**: $t_R$ = 13.2 min. The results are summarized in Tables 1 and 2.

#### 2.2.1. Albicanyl propanoate (**2b**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.69 (3H, s), 0.75 (3H, s), 0.81 (3H, s), 1.05 (3H, t, $J$ = 7.6 Hz), 1.02–1.11 (1H, m), 1.12–1.21 (2H, m), 1.27 (1H, dd, $J$ = 4.4, 12.8 Hz), 1.31–1.35 (1H, m), 1.43–1.55 (2H, m), 1.63–1.68 (2H, m), 1.92–2.01 (2H, m), 2.23 (2H, q, $J$ = 7.6 Hz), 2.33 (1H, ddd, $J$ = 2.4, 4.4, 13.2 Hz), 4.12 (1H, dd, $J$ = 9.2, 11.2 Hz), 4.28 (1H, dd, $J$ = 3.6, 11.2 Hz), 4.44 (1H, dd, $J$ = 1.6, 2.8 Hz), 4.77 (1H, dd, $J$ = 1.6, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 9.1, 15.1, 19.2, 21.7, 23.9, 27.7, 33.5, 33.6, 37.6, 39.0, 39.1, 41.9, 54.8, 55.0, 61.4, 107.1, 146.8, 174.8. HR-EI-Mass—calcd. for $C_{18}H_{30}O_2$: 278.2246; found: 278.2247.

#### 2.2.2. Albicanyl butyrate (**2c**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.68 (3H, s), 0.74 (3H, s), 0.80 (3H, s), 0.85 (3H, t, $J$ = 7.4 Hz), 1.06 (1H, dd, $J$ = 2.8, 12.8 Hz), 1.07–1.28 (3H, m), 1.30–1.35 (1H, m), 1.38–1.60 (4H, m), 1.63–1.67 (2H, m), 1.92–1.99 (2H, m), 2.17 (2H, t, $J$ = 7.4 Hz), 2.33 (1H, ddd, $J$ = 2.4, 4.0, 11.0 Hz), 4.11 (1H, dd, $J$ = 8.8, 11.3 Hz), 4.27 (1H, dd, $J$ = 3.8, 11.3 Hz), 4.44 (1H, dd, $J$ = 1.6, 2.8 Hz), 4.77 (1H, dd, $J$ = 1.6, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 13.6, 15.1, 18.4, 19.1, 21.7, 23.9, 33.5, 33.6, 36.3, 37.6, 38.9, 39.0, 41.9, 54.8, 55.0, 61.3, 107.1, 146.8, 174.0. HR-EI-Mass—calcd. for $C_{19}H_{32}O_2$: 292.2402; found: 292.2405.

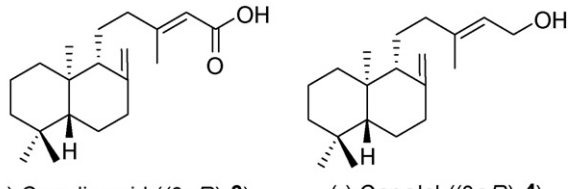



**Fig. 1.** Structures of (−)-copalic acid ((8a*R*)-**3**) and (−)-copalol ((8a*R*)-**4**).

#### 2.2.3. Albicanyl hexanoate (**2d**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.86 (3H, t, $J$ = 6.9 Hz), 1.11 (1H, dd, $J$ = 2.4, 12.6 Hz), 1.13–1.33 (7H, m), 1.37–1.40 (1H, m), 1.42–1.65 (4H, m), 1.67–1.73 (2H, m), 1.97–2.04 (2H, m), 2.23 (2H, t, $J$ = 7.5 Hz), 2.37 (1H, ddd, $J$ = 2.4, 4.3, 13.1 Hz), 4.15 (1H, dd, $J$ = 9.2, 11.2 Hz), 4.31 (1H, dd, $J$ = 4.2, 11.2 Hz), 4.48 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.82 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 13.9, 15.1, 19.1, 21.7, 22.3, 23.9, 24.6, 31.3, 33.5, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.7, 55.0, 61.3, 107.1, 146.8, 174.1. HR-EI-Mass—calcd. for $C_{21}H_{36}O_2$: 320.2715; found: 320.2714.

#### 2.2.4. Albicanyl octanoate (**2e**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, t, $J$ = 7.0 Hz), 0.85 (3H, s), 1.10 (1H, dd, $J$ = 2.8, 12.6 Hz), 1.13–1.33 (11H, m), 1.35–1.39 (1H, m), 1.42–1.62 (4H, m), 1.67–1.73 (2H, m), 1.96–2.05 (2H, m), 2.23 (2H, t, $J$ = 7.5 Hz), 2.37 (1H, ddd, $J$ = 2.4, 4.3, 13.1 Hz), 4.15 (1H, dd, $J$ = 9.0, 11.2 Hz), 4.32 (1H, dd, $J$ = 3.8, 11.2 Hz), 4.48 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.82 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.0, 15.1, 19.1, 21.7, 22.6, 23.9, 25.0, 28.9, 29.1, 31.6, 33.5, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.8, 55.0, 61.3, 107.1, 146.8, 174.2. HR-EI-Mass—calcd. for $C_{23}H_{40}O_2$: 348.3028; found: 348.3027.

#### 2.2.5. Albicanyl decanoate (**2f**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.78 (3H, s), 0.85 (3H, s), 0.85 (3H, t, $J$ = 6.7 Hz), 1.10 (1H, dd, $J$ = 1.2, 12.6 Hz), 1.13–1.35 (15H, m), 1.35–1.43 (1H, m), 1.43–1.64 (4H, m), 1.65–1.73 (2H, m), 1.95–2.05 (2H, m), 2.22 (2H, t, $J$ = 7.5 Hz), 2.36–2.42 (2H, m), 4.17 (1H, dd, $J$ = 9.0, 11.3 Hz), 4.33 (1H, dd, $J$ = 3.8, 11.3 Hz), 4.50 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.83 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 15.1, 19.1, 21.7, 22.6, 23.9, 25.0, 29.1, 29.2, 29.2, 29.4, 31.8, 33.4, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.7, 55.0, 61.3, 107.1, 146.7, 174.1. HR-EI-Mass—calcd. for $C_{25}H_{44}O_2$: 376.3341; found: 376.3335.

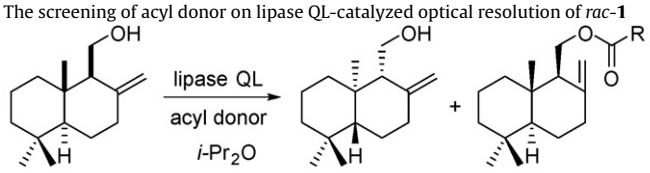
#### 2.2.6. Albicanyl laurate (**2g**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.85 (3H, t, $J$ = 6.8 Hz), 1.10 (1H, dd, $J$ = 12.6, 2.6 Hz), 1.13–1.34 (19H, s), 1.35–1.41 (1H, m), 1.42–1.59 (4H, m), 1.65–1.72 (2H, m), 1.96–2.06 (2H, m), 2.23 (2H, t, $J$ = 7.6 Hz), 2.35–2.40 (1H, m), 4.15 (1H, dd, $J$ = 8.8, 11.2 Hz), 4.31 (1H, dd, $J$ = 3.8, 11.2 Hz), 4.48 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.81 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 15.1, 19.2, 21.7, 22.7, 23.9, 25.0, 29.1, 29.2, 29.3, 29.4, 29.6, 29.6, 31.9, 33.5, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.8, 55.0, 61.3, 107.1, 146.8, 174.1. HR-EI-Mass—calcd. for $C_{27}H_{48}O_2$: 404.3654; found: 404.3652.

#### 2.2.7. Albicanyl myristate (**2h**)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.85 (3H, t, $J$ = 6.7 Hz), 1.11 (1H, dd, $J$ = 2.8, 12.6 Hz), 1.17–1.33 (23H, m), 1.34–1.41 (1H, m), 1.42–1.60 (4H, m), 1.67–1.73 (2H, m), 1.95–2.05 (2H, m), 2.23 (2H, t, $J$ = 7.5 Hz), 2.37 (1H, ddd, $J$ = 2.2, 4.2, 13.2 Hz), 4.15 (1H, dd, $J$ = 8.8, 11.2 Hz), 4.32 (1H, dd, $J$ = 3.9, 11.2 Hz), 4.49 (1H, brs), 4.82 (1H, dd, brs). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 15.1, 19.2, 21.7, 22.7, 23.9, 25.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6,

**Table 1**
The screening of acyl donor on lipase QL-catalyzed optical resolution of *rac*-**1**




*rac*-**1** (8a*R*)-**1** (8a*S*)-**2**

**2a**: R = $CH_3$, **2b**: R = $C_2H_5$, **2c**: R = $C_3H_7$, **2d**: R = $C_5H_{11}$, **2e**: R = $C_7H_{15}$, **2f**: R = $C_9H_{19}$, **2g**: R = $C_{11}H_{23}$, **2h**: R = $C_{13}H_{27}$, **2i**: R = $C_{15}H_{31}$, **2j**: R = $C_{17}H_{34}$, **2k**: R = Ph, **2l**: R = CH=CHCH$_3$, **2m**: R = $CH_2Cl$.

| Entry | Acyl donor | Time (h) | ee (%) of **1**[a] (yield)[b] | ee (%)[c] (yield)[b] | Conv. (%)[d] | *E*[e] |
|---|---|---|---|---|---|---|
| 1 | Vinyl acetate | 23 | 38.8 (58) | **2a**: 69.0 (31) | 36.0 | 7.9 |
| 2 | Vinyl propionate | 120 | 37.9 (63) | **2b**: 81.3 (29) | 31.8 | 14.0 |
| 3 | Vinyl butyrate | 8 | 46.9 (60) | **2c**: 90.6 (31) | 34.1 | 32.4 |
| 4 | Vinyl hexanoate | 8 | 51.9 (60) | **2d**: 89.9 (33) | 36.6 | 28.8 |
| 5 | Vinyl octanoate | 6 | 79.6 (49) | **2e**: 81.9 (46) | 49.3 | 24.2 |
| 6 | Vinyl decanoate | 6 | 64.3 (52) | **2f**: 76.4 (43) | 45.7 | 14.4 |
| 7 | Vinyl laurylate | 9 | 38.0 (68) | **2g**: 88.2 (30) | 30.1 | 23.2 |
| 8 | Vinyl myristate | 23 | 62.0 (57) | **2h**: 90.0 (39) | 40.8 | 35.7 |
| 9 | Vinyl palmitate | 6 | 52.0 (51) | **2i**: 59.3 (42) | 46.7 | 6.5 |
| 10 | Vinyl stearate | 6 | 36.6 (55) | **2j**: 48.9 (41) | 42.8 | 4.1 |
| 11 | Vinyl benzoate | 168 | 33.0 (68) | **2k**: 79.6 (29) | 29.3 | 12.1 |
| 12 | Vinyl crotonate | 120 | 24.3 (69) | **2l**: 80.9 (20) | 23.1 | 12.0 |
| 13 | Vinyl chlroroacetate | 72 | 14.4 (68) | **2m**: 33.9 (27) | 29.8 | 2.3 |
| 14 | Isopropenyl acetate | 44 | 37.5 (65) | **2a**: 60.4 (31) | 38.3 | 5.8 |
| 15 | Isopropenyl butyrate | 44 | 37.5 (59) | **2c**: 60.4 (38) | 38.3 | 33.8 |

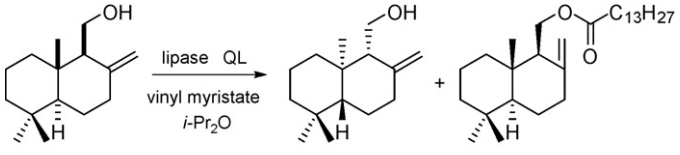
[a] ee of **1** was determined by chiral HPLC analysis equipped with CHIRALPAK AD-H.
[b] Isolated yield (%) in the parenthesis.
[c] The ee of **2** was calculated based on the ee of **1** and the extent of conversion.
[d] The extent of conversion was determined by $^1$H NMR spectra of the reaction mixture.
[e] *E* value of the reaction was calculated based on ee of recovered (8a*R*)-**1** and the extent of conversion.

29.7, 31.9, 33.5, 33.6, 34.5, 37.6, 38.9, 39.0, 41.9, 54.8, 55.1, 61.3, 107.1, 146.8, 174.1. HR-EI-Mass—calcd. for $C_{29}H_{52}O_2$: 432.3967; found: 432.3955.

### 2.2.8. Albicanyl palmitate (*2i*)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.85 (3H, t, $J$ = 7.0 Hz), 1.10 (1H, dd, $J$ = 2.7, 12.6 Hz), 1.15–1.33 (27H, m), 1.34–1.40 (1H, m), 1.42–1.65 (4H, m), 1.65–1.74 (2H, m), 1.95–2.05 (2H, m), 2.22 (2H, t, $J$ = 8.0 Hz), 2.32–2.39 (1H, m), 4.15 (1H, dd, $J$ = 8.9, 11.2 Hz), 4.31 (1H, dd, $J$ = 3.9, 11.2 Hz), 4.48 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.80 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 15.1, 19.1, 21.7, 22.7, 23.9, 25.0, 29.1, 29.2, 29.3, 29.4, 29.6, 29.6 (2C), 29.6, 29.7, 29.7, 31.9, 33.4, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.8, 55.0, 61.3, 107.1, 146.7, 174.0. HR-EI-Mass—calcd. for $C_{31}H_{56}O_2$: 460.4280; found: 460.4286.

**Table 2**
Effect of reaction temperature to *E* value on the transesterification of *rac*-**1**




*rac*-**1** (8a*R*)-**1** (8a*S*)-**2h**

| Entry | Temperature (°C) | Time (h) | ee (%) of (8a*R*)-**1**[a] (yield)[b] | ee (%) of **2h**[c] (yield)[b] | Conversion (%)[d] | *E*[e] |
|---|---|---|---|---|---|---|
| 1 | 45 | 17 | 77.2 (48) | 73.6 (50) | 50.3 | 15.1 |
| 2 | 40 | 23 | 82.8 (48) | 83.5 (49) | 49.1 | 28.5 |
| 3 | 35 | 25 | 86.5 (47) | 84.8 (50) | 50.6 | 33.8 |
| 4 | 30 | 22.5 | 72.4 (54) | 91.4 (40) | 50.7 | 48.2 |
| 5 | 25 | 23 | 79.6 (47) | 78.3 (50) | 50.4 | 19.8 |
| 6 | 20 | 24 | 77.1 (47) | 75.0 (46) | 44.2 | 16.1 |
| 7 | 15 | 26 | 72.4 (47) | 70.7 (47) | 50.5 | 12.4 |
| 8 | 10 | 25 | 51.6 (49) | 53.5 (48) | 49.8 | 5.4 |
| 9 | 6 | 27 | 47.3 (45) | 46.9 (48) | 51.2 | 4.3 |

[a] ee of **1** was determined by chiral HPLC analysis equipped with CHIRALPAK AD-H.
[b] Isolated yield (%) in the parenthesis.
[c] The ee of **2** was calculated based on the ee of **1** and the extent of conversion.
[d] The extent of conversion was determined by $^1$H NMR spectra of the reaction mixture.
[e] *E* value of the reaction was calculated based on ee of recovered (8a*R*)-**1** and the extent of conversion.

*2.2.9. Albicanyl stearate (**2j**)*

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 0.85 (3H, t, $J$ = 7.0 Hz), 1.10 (1H, dd, $J$ = 2.7, 12.6 Hz), 1.15–1.33 (27H, m), 1.34–1.40 (1H, m), 1.42–1.65 (4H, m), 1.66–1.73 (2H, m), 1.95–2.05 (2H, m), 2.22 (2H, t, $J$ = 7.4 Hz), 2.34–2.40 (1H, m), 4.15 (1H, dd, $J$ = 8.8, 11.2 Hz), 4.32 (1H, dd, $J$ = 4.0, 11.2 Hz), 4.49 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.81 (1H, dd, $J$ = 1.2, 2.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 15.1, 19.1, 21.7, 22.7, 23.9, 25.0, 29.1, 29.2, 29.3, 29.4, 29.6, 29.6, 29.6, 29.7, 29.7 (4C), 31.9, 33.4, 33.6, 34.4, 37.6, 38.9, 39.0, 41.9, 54.8, 55.0, 61.3, 107.1, 146.7, 174.0. HR-EI-Mass—calcd. for $C_{33}H_{60}O_2$: 488.4593; found: 488.4599.

*2.2.10. Albicanyl benzoate (**2k**)*

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.83 (3H, s), 0.83 (3H, s), 0.90 (3H, s), 1.16–1.46 (5H, m), 1.48–1.65 (2H, m), 1.72–1.90 (2H, m), 2.08 (1H, td, $J$ = 5.2, 13.0 Hz), 2.20–2.23 (1H, m), 2.43 (1H, ddd, $J$ = 2.3, 4.4, 13.2 Hz), 4.42 (1H, dd, $J$ = 8.6, 11.0 Hz), 4.62–4.67 (2H, m), 4.90 (1H, dd, $J$ = 1.2, 2.8 Hz), 7.41 (2H, t, $J$ = 7.2 Hz), 7.47 (1H, t, $J$ = 7.2 Hz), 8.01 (2H, d, $J$ = 7.2 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 15.2, 19.2, 21.8, 23.9, 33.5, 33.6, 37.6, 39.0, 39.2, 41.9, 54.9, 55.1, 62.1, 107.3, 128.3 (2C), 129.5 (2C), 130.5, 132.7, 146.8, 166.7. HR-EI-Mass—calcd. for $C_{22}H_{30}O_2$: 326.2246; found: 326.2240.

*2.2.11. Albicanyl crotonate (**2l**)*

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.70 (3H, s), 0.75 (3H, s), 0.81 (3H, s), 1.07 (1H, dd, $J$ = 2.6, 12.6 Hz), 1.07–1.23 (2H, m), 1.27 (1H, dd, $J$ = 4.4, 13.2 Hz), 1.31–1.35 (1H, m), 1.43–1.56 (2H, m), 1.66 (2H, m), 1.78 (3H, dd, $J$ = 1.8, 6.8 Hz), 1.93–2.03 (2H, m), 2.33 (1H, ddd, $J$ = 2.4, 4.2, 13.0 Hz), 4.16 (1H, dd, $J$ = 8.8, 11.2 Hz), 4.34 (1H, dd, $J$ = 4.0, 11.2 Hz), 4.47 (1H, dd, $J$ = 1.2, 2.8 Hz), 4.78 (1H, dd, $J$ = 1.2, 2.8 Hz), 5.75 (1H, dq, $J$ = 1.8, 14.8 Hz), 6.86 (1H, qd, $J$ = 6.8, 14.8 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 15.1, 17.9, 19.2, 21.7, 23.9, 33.5, 33.6, 37.6, 39.0, 39.0, 41.9, 54.8, 55.0, 61.3, 107.2, 122.9, 144.4, 146.9, 166.8. HR-EI-Mass—calcd. for $C_{19}H_{30}O_2$: 290.2246; found: 290.2241.

*2.2.12. Albicanyl chloroacetate (**2m**)*

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.70 (3H, s), 0.75 (3H, s), 0.81 (3H, s), 1.07 (1H, dd, $J$ = 2.8, 12.8 Hz), 1.08–1.23 (2H, m), 1.27 (1H, dd, $J$ = 4.4, 12.8 Hz), 1.31–1.37 (1H, m), 1.40–1.57 (2H, m), 1.62–1.69 (2H, m), 1.92–2.05 (2H, m), 2.34 (1H, ddd, $J$ = 2.4, 4.4, 13.2 Hz), 3.95 (2H, s), 4.24 (1H, dd, $J$ = 9.2, 11.2 Hz), 4.41 (1H, dd, $J$ = 4.0, 11.2 Hz), 4.43 (1H, d, $J$ = 1.2 Hz), 4.78 (1H, d, $J$ = 1.2 Hz). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 15.1, 19.1, 21.7, 23.8, 33.5, 33.6, 37.5, 39.0, 39.0, 41.0, 41.8, 54.6, 55.0, 63.4, 107.2, 146.4, 167.5. HR-EI-Mass—calcd. for $C_{17}H_{27}O_2Cl$: 298.1700; found: 298.1698.

*2.3. Lipase-catalyzed optical resolution*

(i) To a solution of *rac*-**1** (10.0 g, 45 mmol) and vinyl myristate (11.4 g, 45 mmol) in diisopropyl ether (100 mL) was added lipase QL (2.0 g) and the resulting mixture was stirred at 30 °C for 15 h. The reaction was stopped by filtration using Celite 545. The residue was washed with ether and then the filtrate and the etheral solution were combined, evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (100 g), hexane:ethyl acetate (100:1)] to afford (8a*R*)-**1** (4.30 g, 19.4 mmol, 43% yield) and (8a*S*)-**2h** (11.2 g, 25.5 mmol, 57%).

(ii) To the solution of (8a*S*)-**2h** (11.2 g) in methanol (200 mL) containing water (10 mL) was added $K_2CO_3$ (12 g, 34 mmol), the mixture was stirred at r.t. for 10 h. The mixture was evaporated and the residue was added to water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (100 g), hexane/ethyl acetate (20/1)] to afford (8a*S*)-**1** (5.51 g, 24.8 mmol, 97% yield, 82% ee). The obtained (8a*S*)-**1** (5.11 g, 82% ee) was subjected to the enzymatic reaction described above to afford (8a*S*)-**1** (1.25 g, 5.6 mmol, 23% yield, 30% ee) and (8a*S*)-**2h** (7.40 g, 17.1 mmol, 74% yield). Then (8a*S*)-**2h** (7.40 g) was subjected hydrolysis to afford (8a*S*)-**1** (3.71 g, 16.8 mmol, 98% yield, 99% ee). (8a*R*)-**1**: $\alpha_D^{23}$ − 12.8 (c 0.50, $CHCl_3$), lit. [9] (8a*R*)-**1**: $\alpha_D^{26}$ − 12.7 (c 0.74, $CHCl_3$, >99% ee). Colorless needles. mp: 71.1–73.9 °C. (8a*S*)-**1**: $[\alpha]_D^{23}$ +12.7 (c 0.98, $CHCl_3$). Colorless needles. mp: 72.0–73.0 °C. (8a*S*)-**2h**: $[\alpha]_D^{23}$ +18.6 (c 1.04, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 2923, 1736, 1646, 1173.

*2.3.1. (−)-Albicanylphenylsulfide ((8aR)-**5**)*

To a solution of (8a*R*)-**1** (2.22 g, 10.0 mmol) in pyridine (5 mL) was added mesyl chloride (1 mL, 12 mmol) at 0 °C. The mixture was stirred at r.t. for 2 h, poured into water, extracted with a mixture of hexane and ethyl acetate (3/1). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was added to a mixture of sodium hydride (40% in mineral oil, 1.2 g) and thiophenol (3.3 g, 30 mmol) in DMF (100 mL) and stirred at 90 °C for 6 h. The mixture was cooled to r.t. and poured into water and extracted with a mixture of hexane and ethyl acetate (3/1). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (50 g), hexane/ethyl acetate (50/1)] to afford (8a*R*)-**5** (2.85 g, 9.08 mmol, 91% yield).

$[\alpha]_D^{20} = -170.2$ (c 1.20, $CHCl_3$). $^1$H NMR: 0.73 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 1.06–1.19 (3H, m), 1.24–1.39 (2H, m), 1.43–1.61 (2H, m), 1.67–1.78 (2H, m), 1.98–2.07 (2H, m), 2.41 (1H, brd, $J$ = 12.0 Hz), 2.95 (1H, t, $J$ = 11.6 Hz), 3.15 (1H, dd, $J$ = 1.0, 11.6 Hz), 4.64 (1H, s), 4.94 (1H, s), 7.12 (1H, t, $J$ = 6.4 Hz), 7.22–7.30 (4H, m). $^{13}$C NMR ($CDCl_3$): 14.5, 19.2, 21.7, 24.1, 29.9, 33.5, 33.6, 37.8, 39.1, 40.2, 41.9, 55.1, 56.9, 107.8, 125.5, 128.5 (2C), 128.7 (2C), 138.4, 147.2. HR-EI-MS calcd. for $C_{21}H_{30}S$: 314.2068; found: 314.2052.

*2.3.2. (−)-Albicanylphenylsulfone ((8aR)-**6**)*

To a mixture of (8a*R*)-**5** (1.57 g, 5.00 mmol) and $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (120 mg, 0.1 mol) in ethanol (20 mL) was added aq. 30% hydrogen peroxide (30%, 8 mL) at 0 °C, the mixture was stirred at r.t. for 8 h and added ice-cold aq. sodium sulfite. The mixture was extracted with ethyl acetate, the organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [silica gel (100 g), hexane/ethyl acetate (10/1)] to afford (8a*R*)-**6** (1.71 g, 4.94 mmol, 99% yield).

$[\alpha]_D^{19} = -26.3$ (c 1.21, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 2953, 1742, 1436, 1370, 1232. $^1$H NMR: 0.58 (3H, s), 0.75 (3H, s), 0.85 (3H, s), 1.01 (1H, dt, $J$ = 5.2, 12.0 Hz), 1.10–1.38 (4H, m), 1.43–1.57 (3H, m), 1.67–1.72 (1H, m), 1.98 (1H, dt, 4.7, 12.6 Hz), 2.29–2.37 (2H, m), 3.20 (1H, dd, $J$ = 1.8, 13.5 Hz), 3.34 (1H, dd, $J$ = 9.2, 13.5 Hz), 4.44 (1H, s), 4.73 (1H, s), 7.51 (2H, t, $J$ = 8.0 Hz), 7.60 (1H, t, $J$ = 8.0 Hz), 7.86 (2H, d, $J$ = 8.0 Hz). $^{13}$C NMR ($CDCl_3$): 14.9, 19.0, 21.5, 23.8, 33.3, 33.6, 37.5, 38.5, 39.8, 41.7, 50.6, 52.2, 55.1, 107.7, 128.1 (2C), 129.1 (2C), 133.4, 140.1, 145.6. HR-EI-MS calcd. for $C_{21}H_{30}O_2S$: 346.1967; found: 346.1964.

*2.3.3. 4-((1R,4aR,8aR)-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl)butan-2-ol ((8aR)-**7**)*

To a solution of (8a*R*)-**6** (1.22 g, 3.53 mmol) in THF (20 mL) were added *n*-butyl lithium in hexane (2.6 M, 1.5 mL) at 0 °C and then propylene oxide (1.0 mL, 16 mmol). The mixture was stirred at r.t. for 2 h, then poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated

under reduced pressure. The residue was chromatographed by silica gel [silica gel (50 g), hexane/AcOEt (10/1)] to afford crude product (1.2 g). To the mixture of the crude product, sodium hydrogen phosphate (1.50 g) and ethanol (2 mL) in THF (50 mL) was added Na (1.0 g) and the mixture was stirred at r.t. for 12 h. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography [silica gel (30 g), hexane/AcOEt (10/1)] to afford a diastereomeric mixture of (8a*R*)-**7** (680 mg, 2.58 mmol, 73%). $^1$H NMR: 0.68 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 1.00–1.81 (18H, m), 1.93–2.01 (1H, m), 2.36–2.41 (1H, m), 3.73–3.80 (1H, m), 4.47 (0.7H, s), 4.53 (0.3H, s), 4.82 (1H, s). $^{13}$C NMR ($CDCl_3$): 14.4, 19.4, 19.5, 19.8, 21.7, 23.4, 23.6, 24.4, 24.4, 33.6, 33.6, 38.3, 38.6, 39.1, 39.1, 39.7, 39.7, 42.2, 55.5, 55.6, 56.7, 67.0, 68.4, 68.8, 106.2, 106.5, 148.6, 148.8. HR-EI-MS calcd. for $C_{18}H_{32}O$: 246.2453; found: 246.2441.

### 2.3.4. 4-((1R,4aR,8aR)-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl)butan-2-one ((8aR)-*8*)

To a solution of (8a*R*)-**7** (386 mg, 1.46 mmol) in $CH_2Cl_2$ (10 mL) was added Dess-Martin periodinane (800 mg, 1.88 mol), stirred at r.t. for 2 h, poured into water and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel chromatography [silica gel (10 g), hexane/AcOEt (15 /1)] to afford (8a*R*)-**8** (371 mg, 1.42 mmol, 97%).

$[\alpha]_D^{27} = -36.00$ (c 0.21, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 2953, 1742, 1436, 1370, 1232. $^1$H NMR: 0.64 (3H, s), 0.76 (3H, s), 0.82 (3H, s), 0.98–1.30 (3H, m), 1.21–1.39 (3H, m), 1.40–1.60 (3H, m), 1.65–1.95 (4H, m), 2.06 (3H, s), 2.22–2.36 (2H, m), 2.54 (1H, ddd, $J$ = 3.6, 8.8, 13.6 Hz), 4.39 (1H, s), 4.78 (1H, d, $J$ = 1.0 Hz). $^{13}$C NMR ($CDCl_3$): 14.2, 17.4, 19.3, 21.6, 24.4, 29.9, 33.5, 33.6, 38.2, 38.9, 39.7, 42.1, 42.8, 55.4, 56.2, 106.2, 148.3, 209.3. HR-EI-MS calcd. for $C_{18}H_{30}O$: 262.2297; found: 262.2297.

### 2.3.5. (E)-Methyl copalate ((8aR)-(E)-*9*) [12]

To a mixture of trimethyl acetoxyphosphate (360 mg, 2.0 mmol) and sodium hydride (40% in mineral oil, 80 mg, 2.0 mmol) in DMF (20 mL) was added (8a*R*)-**8** (346 mg, 1.32 mmol), and the reaction mixture was stirred at 0 °C for 6 h. The mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed by silica gel (10 g, hexane/benzene = 1/1) to afford (8a*R*)-(*E*)-**9** (264 mg, 63%) and (8a*R*)-(*Z*)-**9** (95.9 mg, 22.8%). (8a*R*)-(*E*)-**9**: $[\alpha]_D^{25} = -46.3$ (c 1.46, $CHCl_3$), lit. [12] $[\alpha]_D^{24} = -47.4$ (c 1.08, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 2946, 2844, 1719, 1644, 1435, 1386, 1145. $^1$H NMR: 0.68 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 0.97–1.04 (1H, m), 1.08 (1H, dd, $J$ = 4.4, 13.2 Hz), 1.13–1.22 (1H, m), 1.32 (1H, dd, $J$ = 4.4, 13.2 Hz), 1.35–1.42 (1H, m), 1.44–1.76 (7H, m), 1.92–2.00 (2H, m), 2.16 (3H, d, $J$ = 1.0 Hz), 2.29 (1H, ddd, $J$ = 4.0, 6.8, 12.8 Hz), 2.39 (1H, ddd, $J$ = 2.4, 4.0, 12.8 Hz), 3.69 (3H, s), 4.49 (1H, brs), 4.84 (1H, brs), 5.65 (1H, brs). $^{13}$C NMR ($CDCl_3$): 14.4, 18.3, 19.4, 21.4, 21.6, 24.4, 31.4, 33.5, 38.3, 39.0, 39.7, 39.8, 42.1, 50.7, 55.5, 56.1, 106.3, 114.8, 148.3, 161.2, 167.3. HR-EI-MS calcd. for $C_{21}H_{34}O_2$: 318.2559; found: 318.2568. (8a*R*)-(*Z*)-**9**: $[\alpha]_D^{25} = -2.1$ (c 1.17, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 2946, 2844, 1719, 1644, 1435, 1386, 1144. $^1$H NMR: 0.67 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 1.02–1.22 (3H, m), 1.32 (1H, dd, $J$ = 4.4, 12.8 Hz), 1.35–1.41 (1H, m), 1.44–1.77 (8H, m), 1.89 (3H, d, $J$ = 1.2 Hz), 2.40 (1H, ddd, $J$ = 2.4, 4.0, 12.8 Hz), 2.50–2.59 (2H, m), 3.67 (3H, s), 4.66 (1H, brs), 4.87 (1H, d, $J$ = 1.2 Hz), 5.64 (1H, brs). $^{13}$C NMR ($CDCl_3$): 14.4, 19.4, 21.7, 22.3, 24.4, 25.3, 32.7, 33.6, 38.3, 38.9, 39.7, 42.1, 50.7, 55.5, 57.1, 106.3, 115.5, 148.4, 161.0, 166.6. HR-EI-MS calcd. for $C_{21}H_{34}O_2$: 318.2559; found: 318.2556.

### 2.3.6. (−)-Copalic acid ((8aR)-*3*)

To a solution of methyl copalate ((8a*R*)-(*E*)-**9**) (69.7 mg, 0.219 mmol) in ethanol (10 mL) was added 2 M aq. sodium hydroxide (10 mL). The mixture was stirred at r.t. for 6 h, acidified by 2 M hydrochloric acid, extracted with ether twice. The organic layers were combined, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel chromatography [silica gel (10 g), hexane/AcOEt (5/1)] to afford (−)-copalic acid ((8a*R*)-**3**) (58.9 mg, 0.210 mmol, 95%).

$[\alpha]_D^{27} = -41.4$ (c 1.28, $CHCl_3$), lit. [13] $[\alpha]_D^{25} = -33.7$ (c 0.40, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 3500–2400 (br), 2926, 2844, 1688, 1638, 1442, 1389, 1254, 1173. $^1$H NMR: $\delta$ 0.69 (3H, s), 0.80 (3H, s), 0.88 (3H, s), 0.96–1.05 (1H, m), 1.08 (1H, dd, $J$ = 4.4, 13.2 Hz), 1.13–1.22 (1H, m), 1.25–1.32 (1H, dd, $J$ = 4.4, 13.2 Hz), 1.35–1.42 (1H, m), 1.44–1.77 (7H, m), 1.92–2.05 (2H, m), 2.17 (3H, d, $J$ = 1.0 Hz), 2.32 (1H, ddd, $J$ = 2.4, 4.0, 12.1 Hz), 2.38 (1H, ddd, $J$ = 2.4, 4.0, 12.1 Hz), 4.50 (1H, s), 4.85 (1H, d, $J$ = 1.0 Hz), 5.67 (1H, d, $J$ = 1.0 Hz). $^{13}$C NMR ($CDCl_3$): 14.4, 19.1, 19.3, 21.4, 21.6, 22.6, 24.4, 33.5, 38.2, 39.0, 39.6, 40.0, 42.0, 55.4, 56.1, 106.3, 114.8, 148.2, 163.8, 172.0. HR-EI-MS calcd. for $C_{20}H_{32}O_2$: 304.2402; found: 304.2400.

### 2.3.7. Copalol ((8aR)-*4*) [12]

A solution of (8a*R*)-(*E*)-**9** (65.7 mg, 0.208 mmol) in THF (3 mL) was added Dibal in $CH_2Cl_2$ (1 M, 1 mL, 1.0 mol) at 0 °C and stirred for 1 h. The mixture was diluted by water and extracted with ether and the organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography [silica gel (10 g), hexane/AcOEt (4/1)] to afford (*E*)-copalol (**4**) (56.4 mg, 0.194 mmol, 93%).

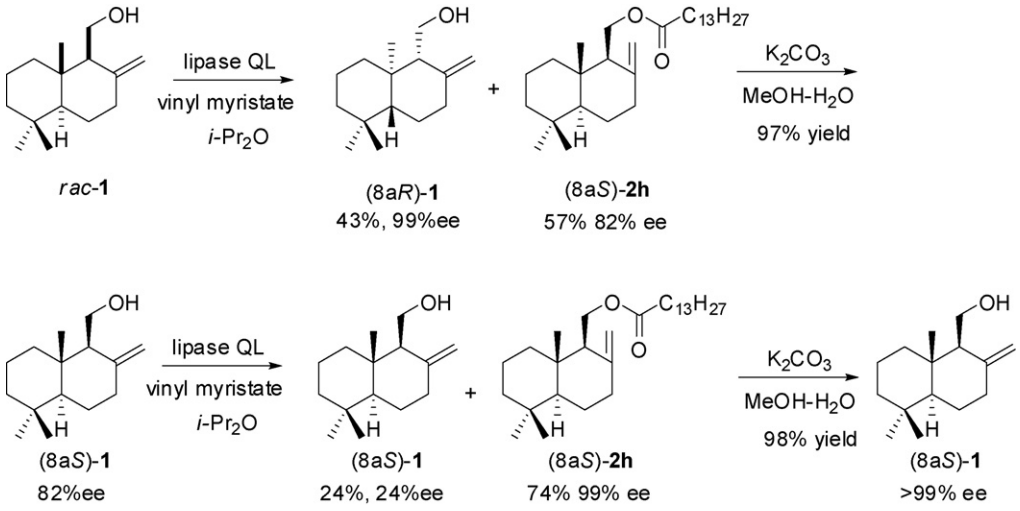
$[\alpha]_D^{26} = -33.6$ (c 2.00, $CHCl_3$), lit. [12] $[\alpha]_D = -35.5$ (c 1.02, $CHCl_3$). IR ($cm^{-1}$): $\nu$ 3299 (br), 2925, 2843, 1642, 1442, 1386. $^1$H NMR: 0.65 (3H, s), 0.77 (3H, s), 0.84 (3H, s), 0.91–1.02 (1H, m), 1.06 (1H, dd, $J$ = 2.4, 12.8 Hz), 1.10–1.19 (1H, m), 1.20–1.82 (11H, m), 1.65 (3H, s), 1.90–1.98 (1H, m), 2.08–2.18 (1H, m), 2.36 (1H, ddd, $J$ = 2.4, 4.4, 12.1 Hz), 4.12 (2H, d, $J$ = 7.0 Hz), 4.48 (1H, s), 4.80 (1H, brs), 5.36 (1H, t, $J$ = 7.0 Hz). $^{13}$C NMR ($CDCl_3$): 14.5, 16.3, 19.4, 21.7, 21.8, 24.4, 33.5, 33.5, 38.3, 38.4, 39.0, 39.6, 42.1, 55.5, 56.3, 59.4, 106.2, 122.9, 140.6, 148.2. HR-EI-MS calcd. for $C_{20}H_{34}O$: 290.2610; found: 290.2597.

## 3. Results and discussion

### 3.1. The lipase-catalyzed transesterification of rac-*1*

#### 3.1.1. Screening of acyl donors

Firstly, various acyl donors on the lipase-catalyzed transesterification of *rac*-**1** were tested to increase the stereoselectivity of the reaction [14–16], and the results and *E* values of the reaction were listed in Table 1. When the vinyl acetate was used as an acyl donor, *E* value of the reaction was 7.9 (entry 1, Table 1). Several acyl donors with various length of alkyl chain were tested to the reaction (entries 2–10, Table 1) and the use of vinyl butyrate and vinyl myristate exhibited higher *E* value (32.4 and 35.7, respectively) than the others. Then, vinyl benzoate, vinyl crotonate and vinyl chloroacetate were tested and the *E* values of the reaction were low (*E* = 2.3–12.1). In this case, the reaction rate was slow (entries 11–13). The use of isopropenyl acetate was slightly increased the *E* value compare to the reaction with vinyl acetate. The *E* value of the reaction by using isopropenyl butyrate exhibited 33.5, showing the same level as using vinyl butyrate (*E* = 32.4) (entry 15). As the use of vinyl myristate on the transesterification of *rac*-**1** exhibited the best result (*E* = 35.7), vinyl myristate was used for the following enzymatic reaction.



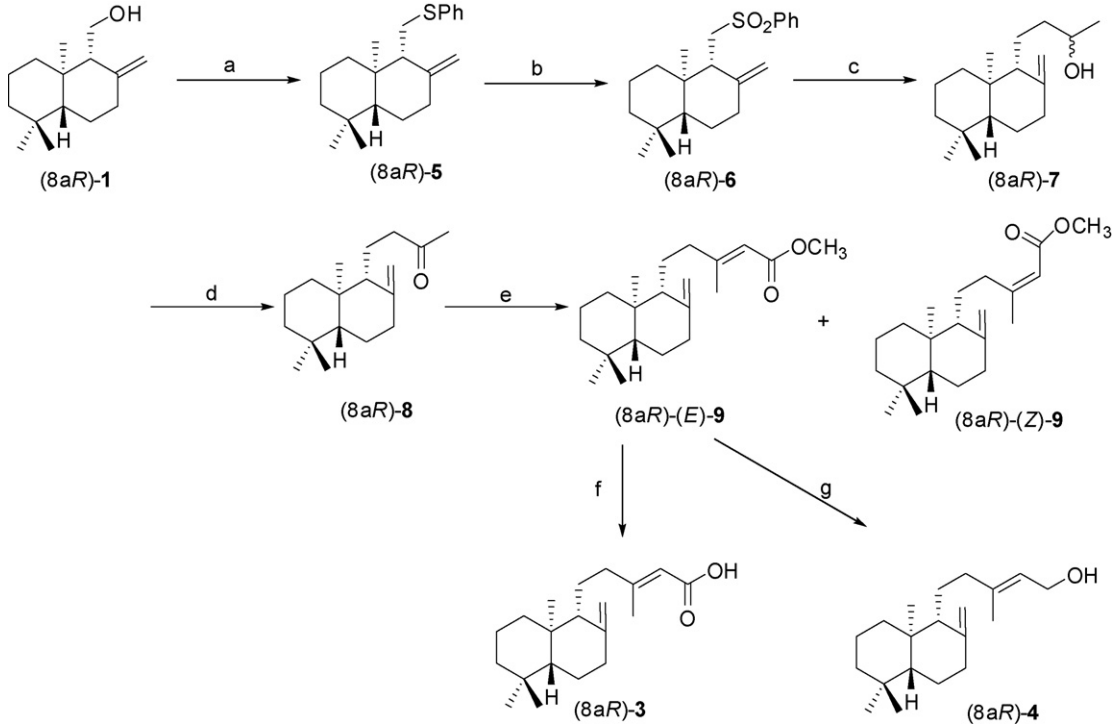

**Scheme 2.**

*3.1.2. Effect of reaction temperature and solvent volume to the stereoselectivity of the optical resolution of rac-**1***

As it was known that the stereoselectivity of the lipase-catalyzed kinetic optical resolution increased at low temperature [17], the reaction was performed at lower temperature and the *E* values of the reactions at 6 and 20 °C were 4 and 16, respectively. It was found the stereoselectivity of the reaction at 6 °C was worse than that at 40 °C. Thus, the effects of reaction temperature to the *E* value of the reaction were investigated and the results were shown in Table 2. The *E* value of the reaction was affected by the temperature and found to give the maximum *E* value (48.2) at 30 °C (entry 4). Next, the effect of the solvent volume to *E* value of the reaction was investigated. When 1 mL of diisopropyl ether was used to 100 mg of substrate and the *E* value was increased to 58.5 and the degree of conversion reached to 50% at 8 h and the ee of the remaining (8a*R*)-**1** and (8a*S*)-**2h** were 90% and 89%, respectively. On the other hand, *E* value of the reaction without solvent gave 28.5. The reason of the effect of the reaction temperature and solvent volume to the stereoselectivity is unclear, further mechanistic study is underway.

*3.1.3. Optical resolution of rac-**1** on preparative scale*

Lipase-catalyzed optical resolution of 10 g of *rac*-**1** using 11.4 g of vinyl myristate and 2 g of lipase QL in 100 mL of diisopropyl ether was performed and (8a*R*)-**1** was recovered in 43% yield in 99% ee and **2h** was obtained in 53% yield with 82% ee (*E* = 56.7) (Scheme 2). The obtained (8a*S*)-**2h** (82% ee) was converted to (8a*S*)-**1** by hydrolysis, then applied to the enzymatic reaction again to gave (8a*S*)-**2h**




**Scheme 3.** (a) (i) MsCl, Pyr; (ii) PhSNa, DMF, two steps, 91%. (b) $H_2O_2$, $Mo_7O_{24}(NH_4)\cdot 4H_2O$, 99%. (c) (i) *n*-BuLi, propylene oxide, 73%; (ii) Na, $Na_2HPO_4$, EtOH, THF, 92%. (d) Dess-Martin periodinane, $CH_2Cl_2$, 97%. (e) $PO(OCH_3)CH_2CO_2CH_3$, (8a*R*)-(*E*)-**9**, 63%; (8a*R*)-(*Z*)-**9**; 23%. (f) NaOH, EtOH, 95%. (g) Dibal, $Et_2O$, 93%.

in 74% yield. Hydrolysis of (8a*S*)-**2h** afforded (8a*S*)-**1** with 99% ee in 98% yield. (8a*S*)-**1** with 99% ee was obtained in 37% yield from *rac*-**1** in three steps. Whereas lipase QL was used 2 g against 2.33 g of *rac*-**1** and it took 1 day to obtain (8a*R*)-**1** (>99% ee) in previously reported method [9], this present lipase-catalyzed reaction took only 15 h to reach 57% conversion using 2.0 g of lipase QL against 10 g of *rac*-**1**.

### 3.2. Synthesis of (−)-copalic acid ((8aR)-3) and (−)-copalol ((8aR)-4) from (8aR)-1

(−)-Copalic acid ((8a*R*)-**3**) from *Copaifera* sp. have antimicrobial activity, oil resin from *Copaifera* sp. was used as traditional medicine in Brazil [18,19], and (8a*R*)-**3** could be only a natural source of the (8a*R*)-labdane type diterpenes to be able to use organic synthesis in our knowledge [20]. (−)-Copalol ((8a*R*)-**4**) and its phosphate were considered as important biosynthetic intermediate for the complex terpenes [12]. For the purpose of the synthetic application of (8a*R*)-**1** (99% ee), we tried to synthesize highly optically active (8a*R*)-**3** and (8a*R*)-**4** (Scheme 3).

Three steps conversion of (8a*R*)-**1** to sulfone (8a*R*)-**6** was achieved in 91% yield by the mesylation, followed by the treatment of sodium phenylthiolate at 90 °C, and then oxidation of sulfide (8a*R*)-**5** by hydrogen peroxide and molybdenum complex (Scheme 2). Sulfone (8a*R*)-**6** was treated by *n*-butyl lithium and propylene oxide, and then desulfonated to afford alcohol (8a*R*)-**7** in two steps 73% yield. Dess-Martin oxidation of (8a*R*)-**7** gave ketone (8a*R*)-**8** in 97% yield. Horner-Emmons condensation of (8a*R*)-**8** and methyl dimethoxyphosphonoacetate afforded (8a*R*)-(*E*)-methyl copalate ((8a*R*)-(*E*)-**9**) and (8a*R*)-(*Z*)-methyl copalate ((8a*R*)-(Z)-**9**) in 63% yield and 27% yield, respectively. The specific rotation of (8a*R*)-(*E*)-**9** was −46.3 and was similar with the reported value ($[\alpha]_D = -47.4$) [12]. Alkaline hydrolysis of (8a*R*)-(*E*)-**9** gave (−)-copalic acid ((8a*R*)-**3**) in 93% yield. The specific rotation of −41.4 was similar with those of natural product ($[\alpha]_D = -33.7$) [13]. Dibal reduction of (*E*)-**9** gave (−)-copalol ((8a*R*)-**4**) in 95% yield. The specific rotation of synthesized (8a*R*)-**4** ($[\alpha]_D = -33.6$) was similar with that of reported ($[\alpha]_D = -35.5$) [12].

## 4. Conclusion

The stereoselectivity on the lipase-catalyzed transesterification of *rac*-albicanol (*rac*-**1**) was improved by the use of vinyl myristate as an acyl donor. The *E* value of the reaction was affected by the temperature and the solvent volume and was increased to 58.5 under optimized conditions. In addition, the enzymatic reaction using vinyl myristate was accelerated comparing with the reported reaction used isopropenyl acetate. Both enantiomers, (8a*S*)-**1** and (8a*R*)-**1**, were obtained in 37% yield (99% ee) and 43% yield (99% ee), respectively.

For the purpose of the synthetic application of (8a*R*)-**1** with 99% ee, (−)-copalic acid ((8a*R*)-**3**) and (−)-copalol ((8a*R*)-**4**) were synthesized in 35% and 34% total yield from (8a*R*)-**1** in 7 steps, respectively. First total synthesis of (8a*R*)-**3** was achieved in this study.

## References

[1] T. Laube, J. Schröder, R. Stehle, K. Seifert, Tetrahedron 58 (2002) 4299–4309.
[2] D.H. Hua, X. Huang, Y. Chen, S.K. Battina, M. Tamura, S.K. Noh, S.I. Koo, I. Namatame, H. Tomoda, E.M. Perchellet, J.-P. Perchellet, J. Org. Chem. 69 (2004) 6065–6078.
[3] M. Kinoshita, M. Ohtsuka, D. Nakamura, H. Akita, Chem. Pharm. Bull. 50 (2002) 930–934.
[4] T. Miyake, K. Uda, M. Kinoshita, M. Fujii, H. Akita, Chem. Pharm. Bull. 56 (2008) 398–403.
[5] S. Poigny, T. Huor, M. Guyot, M. Samadi, J. Org. Chem. 64 (1999) 9318–9320.
[6] M. Kolympadi, M. Liapis, V. Ragoussis, Tetrahedron 61 (2005) 2003–2010.
[7] N. Maezawa, N. Furuichi, H. Tsuchikawa, S. Katsumura, Tetrahedron Lett. 48 (2007) 4865–4867.
[8] N. Furuichi, T. Hata, H. Seotjipto, M. Kato, S. Katsumura, Tetrahedron 57 (2001) 8425–8442.
[9] H. Akita, M. Nozawa, A. Mitsuda, H. Ohsawa, Tetrahedron: Asymmetry 11 (2000) 1375–1388.
[10] C.S. Chen, Y. Fujimoto, G. Girdaukas, C.J. Sih, J. Am. Chem. Soc. 104 (1982) 7289–7299.
[11] Y.-F. Wang, J.J. Lalonde, M. Momongan, D.E. Bergbreiter, C.-H. Wong, J. Am. Chem. Soc. 110 (1988) 7200–7205.
[12] H. Toshima, H. Oikawa, T. Toyomatsu, T. Sassa, Tetrahedron 56 (2000) 8443–8450.
[13] G.B. Messiano, L. Vieira, M.B. Machado, L.M.X. Lopes, S.A. de Bortoli, J. Zukerman-Schpector, J. Agric. Food Chem. 56 (2008) 2655–2659.
[14] T. Ema, S. Maeno, Y. Takaya, T. Sakai, M. Utaka, J. Org. Chem. 61 (1996) 8610–8616.
[15] K. Nakamura, K. Takenaka, A. Ohno, Tetrahedron: Asymmetry 11 (2000) 4429–4439.
[16] M. Kawasaki, M. Goto, S. Kawabata, T. Kometani, Tetrahedron: Asymmetry 12 (2001) 585–596.
[17] T. Sakai, I. Kawabata, T. Kishimoto, T. Ema, M. Utaka, J. Org. Chem. 62 (1997) 4906–4907.
[18] T. Nakano, C. Djerassi, J. Org. Chem. 26 (1961) 167–173.
[19] B.M. Tincusi, I.A. Jiménez, I.L. Bazzocchi, L.M. Moujir, Z.A. Mamani, J.P. Barroso, A.G. Ravelo, B.V. Hernández, Planta Med. 68 (2002) 808–812.
[20] N. Ungur, M. Gavagnin, A. Fontana, G. Cimino, Tetrahedron 56 (2000) 2503–2512.