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Studies in Lipase Catalyzed Transesterifications: Synthesis of (+)-Albicanol, (+)-Albicanyl Acetate and Chiral Intermediates Useful in the Synthesis of Drimanes and Labdanes

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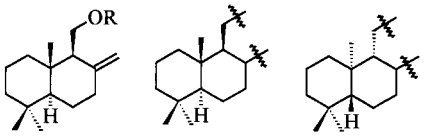
Abstract—Chiral intermediates [(−)-**8**, (+)-**9**, (−)-**9**, (+)-**10**, (−)-**10**, (+)-**11**] useful in the synthesis of drimanes and labdanes, as well as optically active albicanol **1** and albicanyl acetate **2**, have been synthesized using enzymatic transesterification as the key step.

Introduction

Synthetic efforts towards naturally occurring drimane sesquiterpenes have been continuing for a while due to the interesting biological activity profile of many of these compounds.[1] Asymmetric syntheses of drimanes and labdanes have mostly commenced from higher terpenes such as sclareol, abietic acid, manool, etc. However, owing to their simpler structures, the two fish antifeedant compounds (+)-albicanol **1**, first isolated from the liverwort *Diplophyllum albicans*,[2] and (+)-albicanyl acetate **2**, isolated from the dorid nudibranch *Cadlina luteomarginata*,[3] have been synthesized by Fukumoto[4] starting from enantiomerically pure Wieland–Miescher ketone.

Since any synthetic efforts towards **1** and **2** would also provide chiral synthons, which have wide potential for the synthesis of other drimanes, labdanes, etc., such a program was initiated in our laboratory a few years ago. Accordingly, we set out with the aim of obtaining chiral units **3** and **4** containing the bicyclo [4.4.0] ring system with three pendant methyl groups and necessary functionalities for further elaboration.

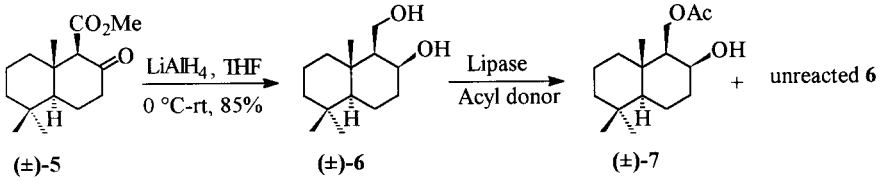


1 R=H
2 R=OAc
3
4

Results and Discussion

Ready availability of β-ionone and the ease with which it could be converted to the β-ketoester **5** prompted us to investigate various enzymatic approaches for its conversion to optically pure intermediates.[5] Compound **5** has been found to be recalcitrant towards reduction using baker's yeast.[6] Since it could be readily converted to the diol **6**, enzymatic resolution of **6** using various lipases was first studied (Scheme 1).

Treatment of (±)-**6** with *Porcine Pancreatic* Lipase (PPL) and *Candida cylindracea* Lipase (CCL) led to selective



(±)-**5** (±)-**6** (±)-**7**

Scheme 1.

Keywords: lipase; albicanol; albicanyl acetate; chiral intermediates; drimanes; labdanes.

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Table 1.

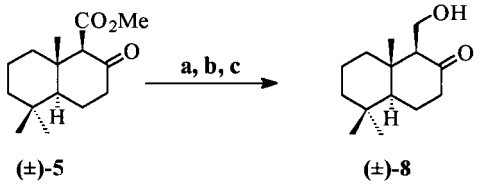
Entry[a]	Lipase	Acyl donor/solvent	Time (h)	Ester **7** % y[b] (% ee)[c]	Diol **6** % y[b]
1	PPL	Vinyl acetate	22	38 (4)	50
2	CCL (700–1500 U/mg)	Vinyl acetate	3	97 (0)	–
3	CCL (24.2 U/mg)	Vinyl acetate	14	75 (0)	20
4	CCL (700–1500 U/mg)	Vinyl acetate/ethyl acetate	18	47 (5)	34
5	CCL (700–1500 U/mg)	Vinyl acetate/Et_2O-THF	20	40 (5)	50
6	CCL (24.2 U/mg)	Isopropenyl acetate	96	40 (10)	58
7	CCL (700–1500 U/mg)	Isopropenyl acetate	72	42 (0)	53
8	WGL	Vinyl acetate	48	No reaction	–
9	SAM 2	Vinyl acetate	7 days	34 (0)	50

[a] All the reactions were carried out in triplicate.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$.

acylation of the primary hydroxyl group leading to (±)-**7**, albeit without enantioselectivity.[7] Enzymatic transesterification of (±)-**6** was studied in detail and some of the salient results are given in Table 1.

Next, we turned our attention to the enzymatic resolution of the ketoalcohol (±)-**8**, which could be readily obtained in three steps from (±)-**5** as shown in Scheme 2.[8]

When the ketoalcohol (±)-**8** was treated with CCL (Aldrich) which had high activity (700–1500 U/mg) in vinyl acetate at 28°C, transacylation proceeded rapidly and produced 56% of the acetate **9** in 45 min. However, ^{1}H NMR studies using Eu(hfc)$_3$ as chiral shift reagent indicated that no enantiodifferentiation has occurred. After much experimentation, we found that treatment of (±)-**8** with CCL (Fluka, 24.2 U/mg) in vinyl acetate at 30°C for 24 h resulted in the formation of ketoacetate (+)-**9** in 47% yield and 68% ee (E=6.5). First crystallization of the above acetate using pentane as solvent readily yielded material of 92% ee, while a second crystallization delivered (+)-**9** of 100% ee (Scheme 3). Subsequently, the ketoalcohol recovered with 53% ee was subjected to lipase catalyzed acylation once more, which resulted in ketoacetate of poor ee but provided (−)-**8** with 82% ee. On crystallization from hexane, (−)-**8** of 97% ee was obtained. The ee at each stage was ascertained by ^{1}H NMR using Eu(hfc)$_3$ as shift reagent. Details of our studies on the effect of different solvent and enzymes are given in Table 2.

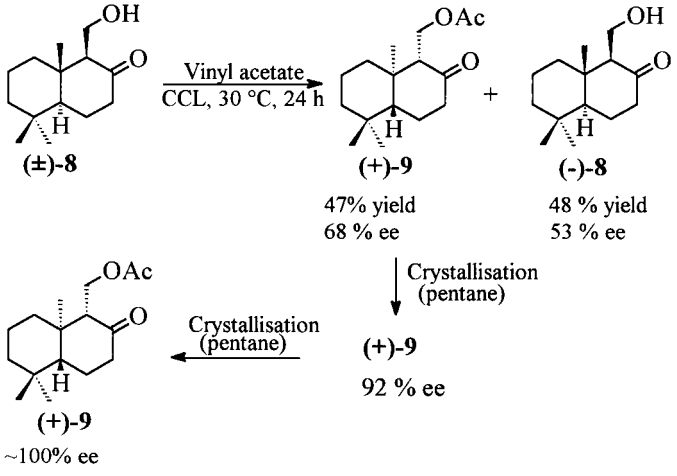


(±)-5 (±)-8

Scheme 2. Reagents and conditions: (a) Ethylene glycol, PTS, benzene, reflux, 96%; (b) $LiAlH_4$, Et_2O, 0°C–rt, 86%; (c) PTS, acetone (wet), rt, 99%.

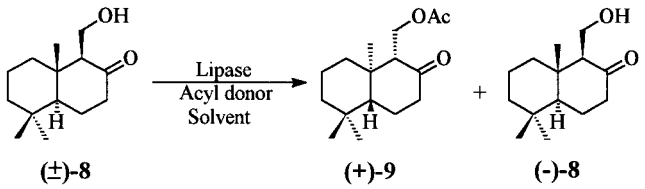
(+)-**9** was rapidly converted to the chiral intermediate (+)-**10** in 95% yield and 98% ee through elimination on an alumina column as reported by us earlier.[9] Conversion of (+)-**10** to the marine natural product zonarol has been reported by Mori et al.[6] Furthermore, a much more versatile chiral intermediate (+)-**11** especially useful in the synthesis of *ent*-labdanes has been synthesized in 92% yield, through the addition of nitromethane to (+)-**10** as shown in Scheme 4.

Similarly, the bicyclic enone (−)-**10** was synthesized from the ketoalcohol (−)-**8** through conversion to the acetate (−)-**9** and subsequent elimination on alumina as shown in Scheme 5.



Scheme 3.

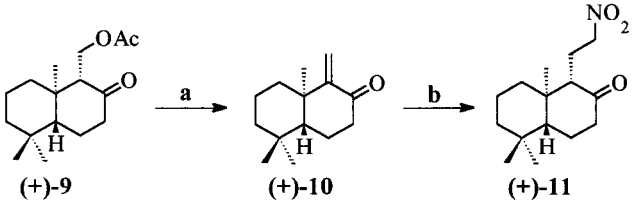
Table 2.



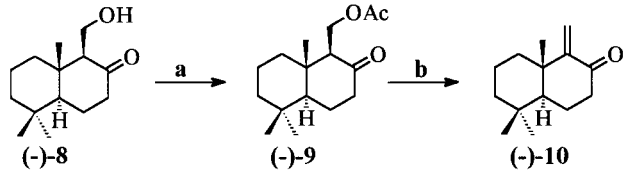
Entry	Lipase	Acyl donor/solvent	Time (h)	Temperature (°C)	Ester **9** % y[a] (% ee)[b]	Alcohol **8** % y[a] (% ee)[c]
1	PPL	Vinyl acetate	70	28–30	No reaction	[d]
2	CCL (700–1500 U/mg)	Vinyl acetate	0.75	28	56 (0)	38 (n.d.)[e]
3	CCL (24.2 U/mg)	Vinyl acetate	17	28	33.6 (70)	64 (n.d.)
4	CCL (24.2 U/mg)	Vinyl acetate	21	28	41.6 (68)	47 (n.d.)
5	CCL (24.2 U/mg)	Vinyl acetate	20	30	43.5 (70)	54 (n.d.)
6	CCL (24.2 U/mg)	Vinyl acetate	24	30	47 (68)	48 (53)
7	CCL (24.2 U/mg)	Vinyl acetate/diisopropyl ether	76	28	55.8 (4)	43 (n.d.)
8	CCL (24.2 U/mg)	Isopropenyl acetate/benzene	76	30	47 (10)	51 (n.d.)
9	CCL (24.2 U/mg)	Vinyl acetate/pet. ether	3.5	31	31 (18)	64 (n.d.)
10	Lipase PS Amano	Vinyl acetate	7 days	28–31	20.5 (10)	62 (n.d.)

[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$.
[c] Determined by comparison of the optical rotation with literature value.
[d] Almost complete recovery of alcohol (±)-**8**.
[e] n.d.=ee not determined.

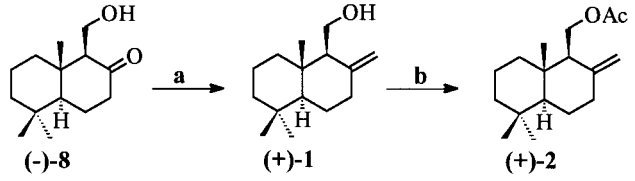
The natural product (+)-albicanol **1** was synthesized from (−)-**8** in a modest yield of 30% through a Wittig type methylenation using the Takai modification of adding PbI_2 to the Nozaki–Lombardo methylenation reagent viz. $TiCl_4$–Zn–CH_2I_2.[10] This was converted to (+)-albicanyl acetate **2** through routine acetylation (Scheme 6).



Scheme 4. Reagents and conditions: (a) Al_2O_3, 95%; (b) CH_3NO_2, TMG, 0°C, 92%.



Scheme 5. Reagents and conditions: (a) Ac_2O, Py, 0°C, 91%; (b) Al_2O_3, 94%.

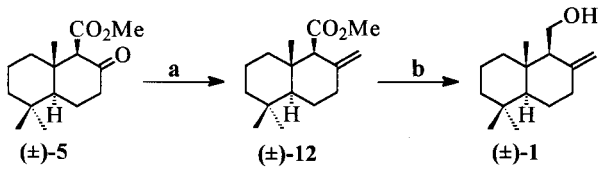


Scheme 6. Reagents and conditions: (a) CH_2I_2–Zn–(PbI_2)–$TiCl_4$, THF, CH_2Cl_2, 0°C–rt, 30%; (b) Ac_2O, Py, 0°C, 90%.

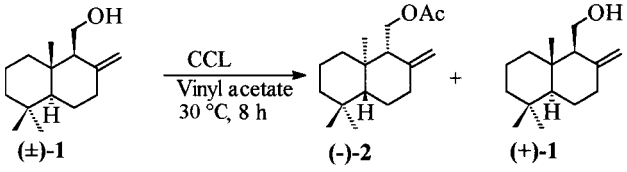
Since the yield of the above methylenation reaction was poor, it was decided to synthesize (±)-albicanol and carry out the enzymatic acetylation as the last step. Accordingly, the β-ketoester (±)-**5** was converted to the methylene ester **12** through a Wittig reaction as reported by Liapis et al.[11] and further reduced to (±)-albicanol with $LiAlH_4$ at 0°C in THF as shown in Scheme 7.[12]

Most interestingly, treatment of (±)-**1** with CCL in vinyl acetate at 28°C for 8 h gave (−)-albicanyl acetate in 57% yield and 73% ee and (+)-albicanol in 37% yield and 77% ee (Scheme 8). The ee in these cases were determined by comparison of their optical rotations with reported values.

In conclusion, we have shown that enzymatic transesterification can be utilized to obtain (+)-albicanol, both enantiomers of albicanyl acetate, as well as various versatile chiral intermediates.



Scheme 7. Reagents and conditions: (a) $Ph_3P^+MeBr^-$, $NaNH_2$, toluene, reflux; (b) $LiAlH_4$, 0°C–r.t, THF (45% for two steps).



Scheme 8.

Experimental

Anhydrous reactions were carried out in oven dried glassware under an atmosphere of argon or nitrogen using distilled or dry solvents as required. PPL, Type II with activity 110–220 U/mg and CCL, Type VIII with activity 700–1500 U/mg were purchased from Aldrich. CCL with activity 24.2 U/mg and SAM 2 (*Pseudomonas fluorescens* lipase) with activity 31.5 U/mg were purchased from Fluka. WGL (Wheat germ lipase) with activity 9.5 U/mg was purchased from Sigma. Lipase PS 'Amano' (from *Pseudomonas cepacia*) with activity 30 U/mg was gifted by Amano Pharmaceutical Co., Japan. β-ionone obtained from M/s Kelkar & Co., Bombay, was purified by flash column chromatography before use.

All melting points are uncorrected and were determined on a Buchi-530 melting point apparatus. IR spectra were recorded on a Perkin–Elmer Model 882 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Bruker-200 and Bruker-300 NMR spectrometers and ^{13}C NMR on JEOL EX-90 spectrometer using tetramethylsilane as internal standard. The mass spectra were recorded on a Hewlett Packard 5890 Series II GC connected to a 5890 mass selective detector. Elemental analyses were obtained using Perkin–Elmer Model 240C-CHN analyzer. Optical rotations were recorded on JASCO DIP-370 digital polarimeter in $CHCl_3$. Column chromatography was performed using 100–200 mesh silica gel.

CCL catalyzed transesterification of diol-(±)-6

A mixture of diol **6** (100 mg, 0.44 mmol) and CCL (700–1500 U/mg, 200 mg) in vinyl acetate (15 mL) was stirred at 30°C for 3 h. Lipase was then removed by filtration through a small layer of silica gel. Solvent was removed under reduced pressure and the residue purified by rapid chromatography on a silica gel column using 15% EtOAc in petroleum ether as eluent which furnished acetate **7**, which was crystallized from dichloromethane as white crystals (115 mg, 97%). mp 70–71°C; IR (KBr): 3553, 2925, 1745, 1462, 1267 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 0.85 (3H, s), 0.88 (3H, s), 1.05 (3H, s), 1.05–1.95 (13H, m), 2.06 (3H, s), 3.90–3.91 (1H, m), 4.17 (1H, dd, J=10.9, 3.8 Hz) 4.45 (1H, dd seen as apparent triplet J=10.7 Hz, J=10.6 Hz); ^{13}C NMR (22.4 MHz, $CDCl_3$): 16.4, 16.9, 18.2, 21.0, 21.7, 33.2, 33.6, 34.6, 37.0, 39.5, 41.8, 53.0, 55.7, 62.0, 66.3, 171.8; GC–MS *m/z*: 208 (M^+-60, 15), 193 (25), 190 (20), 178 (27), 174 (25), 163 (30), 149 (30), 136 (40), 124 (68), 123 (58), 109 (100), 95 (72). Anal. Calcd for $C_{16}H_{28}O_3$: C 71.59, H 10.52; Found: C 71.68, H 10.54.

CCL catalyzed transesterification of ketoalcohol-(±)-8

To a solution of (±)-**8** (520 mg, 2.32 mmol) in vinyl acetate (45 mL) was added CCL (24.2 U/mg, 490 mg and stirred at 30°C for 12 h, following which an additional amount of lipase (490 mg) was added. The reaction mixture was stirred for a total period of 24 h. Lipase was then filtered off and washed with ethyl acetate. Combined filtrate was concentrated under reduced pressure and the residue chromatographed over silica gel using 10% EtOAc in petroleum ether as eluent to furnish the ketoacetate as white crystals (+)-**9** (290 mg, 47%, 68% ee) and ketoalcohol (−)-**8** as white crystals (250 mg, 48%, 53% ee). (+)-**9** (100% ee); mp: 57–58.2°C; $[\alpha]_D^{24}$=+35.1 (*c* 0.96, $CHCl_3$); IR (KBr): 2979, 2931, 1744, 1723, 1464, 1374, 1249, 1045 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 0.77 (3H, s), 0.86 (3H, s), 0.98 (3H, s), 1.20–1.80 (9H, m), 2.00 (3H, s), 2.05–2.60 (3H, m), 4.20 (2H, m); ^{13}C NMR (22.4 MHz, $CDCl_3$): 15.1, 18.6, 20.7, 21.4, 23.5, 33.3, 33.4, 38.9, 41.5, 41.7, 41.8, 53.6, 58.6, 62.1, 170.7, 209.1; Anal. Calcd for $C_{16}H_{26}O_3$: C 72.14, H 9.84; Found: C 72.38, H 9.85.

(−)-**8**. $[\alpha]_D^{25}$=−37.6 (*c* 0.46, $CHCl_3$) (97% ee) {lit[4b] $[\alpha]_D^{26}$=−38.9 (*c* 1.24, $CHCl_3$)}. The spectral data were in accordance with those reported in literature.[4b]

(4aR, 8aR)-(+)-1-Methylene-5,5,8a-trimethyl-2-oxodecahydronaphthalene-(+)-10

The ketoacetate (+)-**9** (100 mg, 0.38 mmol) of ~100% ee was adsorbed on a short column of neutral alumina (Brockmann grade 1, 5 g) and on elution with 10% ethyl acetate in petroleum ether after 1 h readily furnished optically pure enone (+)-**10** as an oil (73 mg, 95%, 98% ee) $[\alpha]_D^{24}$=+73.6 (*c* 1.00, $CHCl_3$) {lit[6] $[\alpha]_D^{23}$=+71.9 (*c* 0.695, $CHCl_3$)}. All spectral data matched with those reported in the literature.[6]

1-(2′-Nitroethyl)-5,5,8a-trimethyl-2-oxodecahydronaphthalene-(+)-11

A solution of enone (+)-**10** (70 mg, 0.34 mmol) in nitromethane (2 mL) under argon was cooled to 0°C, and 1,1,3,3-tetramethylguanidine (0.04 mL, 0.32 mmol) was added to it. The reaction mixture was stirred at 0°C for 2 h. When the reaction was complete as shown by TLC, it was diluted with ether (10 mL), washed with aqueous 5% HCl, water saturated $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue chromatographed over silica gel using 10% ethyl acetate in petroleum ether as eluent to furnish nitro compound (+)-**11** as a low melting solid (82 mg, 90%) $[\alpha]_D^{24}$=+19.7 (*c* 1.45, $CHCl_3$); IR (film): 2952, 2865, 1708, 1552, 1440, 1372, 1185, 1079 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 0.76 (3H, s), 0.87 (3H, s), 0.98 (3H, s), 1.10–1.80 (9H, m), 2.00–2.55 (5H, m), 4.25–4.53 (2H, m); ^{13}C NMR (22.4 MHz, $CDCl_3$): 14.4, 18.6, 20.3, 21.4, 23.4, 33.2, 33.4, 38.8, 41.5, 41.9, 42.0, 53.6, 60.0, 74.7, 210.7; Anal. Calcd for $C_{15}H_{25}O_3N$: C 67.39; H 9.43, N 5.24; Found C 67.45, H 9.45, N 5.28.

(+)-Albicanol 1

A mixture of Zn (244 mg, 3.73 mmol), catalytic amount of PbI_2 (8 mg), diiodomethane (0.09 mL, 215 mg, 1.24 mmol) and $TiCl_4$ (0.1 mL, 0.91 mmol) in dry THF (4 mL) was stirred at 0°C for 1 h. A solution of (−)-**8** (38 mg, 0.17 mmol, ~97% ee) was added and stirred at 0–28°C for 12 h. Reaction mixture was diluted with hexane (8 mL) and a saturated aqueous $NaHCO_3$ solution was added. The hexane layer was separated and aqueous layer extracted with hexane (3×5 mL). The combined extracts were washed with water, brine and dried over Na_2SO_4/$NaHCO_3$ mixture. Solvent was removed under reduced pressure and the residue purified over silica gel using 6%

EtOAc in petroleum ether as eluent to furnish (+)-albicanol (11.5 mg, 30%). Spectral data matched with those reported in literature.[4b]

(+)-Albicanyl acetate 2

Acetic anhydride (21 mg, 0.20 mmol) was added to a solution of the (+)-albicanol (11.5 mg, 0.05 mmol) in pyridine at 0°C and stirred at rt for 6 h and worked up. The residue was chromatographed over silica gel using 4% ethyl acetate in petroleum ether as eluent to afford (+)-Albicanyl acetate (12 mg, 88%) $[\alpha]_D^{24}=+21.6$ (*c* 0.46, $CHCl_3$) {lit[4b] $[\alpha]_D^{26}=+21.9$ (*c* 0.37, $CHCl_3$)}. All spectral data were identical with those reported in literature.[4b]

CCL catalyzed resolution of (±)-albicanol

To a solution of racemic albicanol (40 mg, 0.18 mmol) in vinyl acetate (4 mL) was added CCL (24.2 U/mg, 23 mg) and stirred at 30°C for 8 h, until TLC showed nearly half completion of the reaction. Lipase was then filtered off and the solvent removed under reduced pressure. The crude product was purified by column chromatography using 4% ethyl acetate in petroleum ether as eluent to afford the (−)-albicanyl acetate (27.2 mg, 57%, 73% ee). $[\alpha]_D^{28}=-17.6$ (*c* 1.08, $CHCl_3$). Further elution of the column with 6% ethyl acetate in petroleum ether gave (+)-albicanol **1** (14.8 mg, 37%, 77% ee) $[\alpha]_D^{28}=+9.98$ (*c* 0.59, $CHCl_3$) {lit[4b] $[\alpha]_D^{20}=+13$ (*c* 0.60, $CHCl_3$)}. The spectral data matched with those reported in literature.[4b] The ee was calculated based on comparison of optical rotation.

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