CHAPTER 4
ENZYME MEDIATED TRANSESTERIFICATION OF (±)-ALBICANOL

4.1 Introduction

Labdanes and drimanes are natural products of considerable biological interest as many of these have shown antifeedant, antitumor, and antifungal activities. A key feature of these natural products is the presence of a functionalized bicyclo[4,4,0] ring system with three pendant methyl groups. The interesting biological activities combined with natural scarcity prompted the chiral synthesis of these compounds. Asymmetric synthesis of these compounds has mainly been achieved through chiral intermediates obtained by the degradation of higher terpenes such as sclareol, abietic acid, manool, etc. which possess structures with established stereochemistry. Few asymmetric syntheses have also been reported starting from optically pure starting materials.

Albicanol 1 and albicanyl acetate 2 are two of the simplest sesquiterpenes with bicyclo[4,4,0] ring system. Interestingly they possess potent fish antifeedant activity.

![Figure 1](image1.png)

Figure 1

Owing to the simple and promising structure of these compounds, they also serve as chiral synthons for the synthesis of many more complex biologically active drimane sesquiterpenes as illustrated in Figure 2.
4.2 Isolation and synthesis of albicanol and albicanyl acetate

Albicanol was first isolated from the liverwort *Diplophyllum albicans* and albicanyl acetate from the dorid nudibranch *Cadlina leuteomarginata*. Fukumoto *et al.* synthesized (+)-albicanol and (+)-albicanyl acetate starting from optically pure Wieland-Miesher ketone. Barrero *et al.* later synthesized (+)-albicanyl acetate along with other drimanes starting from the natural product sclareol. (+)-Albicanol and (+)-albicanyl acetate were also synthesized starting from sclareolide and were converted to Hyatellaquinone. Very recently Katsumara *et al.* have reported a resolution based on acetal formation strategy for the synthesis of (-)-albicanol, the
unnatural isomer. The resolution was accomplished using a chiral auxiliary. As shown in Scheme 1, the \( \beta \)-ketoester (\( \pm \))-3 was resolved to get (+)-3 and (-)-3 separated. (+)-3 was then converted to (-)-albicanol.

Seifert et al. synthesized (-)-albicanol starting from \( \beta \)-ionone and used it as an intermediate for the synthesis of sesquiterpene quinones and hydroquinone like zonarone, isozenaronone, cyclozonarone etc. Here the resolution of albicanic acid was achieved with chiral (+)- or (-)-\( \alpha \)-phenylethylamine and the resulting salt was purified by recrystallization (Scheme 2).

### Scheme 1

Seifert et al. synthesized (-)-albicanol starting from \( \beta \)-ionone and used it as an intermediate for the synthesis of sesquiterpene quinones and hydroquinone like zonarone, isozenaronone, cyclozonarone etc. Here the resolution of albicanic acid was achieved with chiral (+)- or (-)-\( \alpha \)-phenylethylamine and the resulting salt was purified by recrystallization (Scheme 2).

### Scheme 2

**4.3 Synthesis of drimane sesquiterpenes involving enzymatic resolution**

Asymmetric synthesis of organic compounds with multiple chiral centers is one among the most challenging tasks in modern organic synthesis. Among the methods to achieve asymmetric induction, use of biocatalysts has become an area of
high extemporary interest. Use of enzymes as catalysts for the synthesis of optically active labdanes and drimanes is particularly attractive. In this direction, an interesting approach involves the use of optically active functionalized decalin derivatives. However, there are not many examples of the synthesis of optically active compounds with decahydro-5,5,8a-trimethylnaphthalene skeleton based on enzymatic resolution. The available examples are illustrated in the following schemes.

Enzymatic resolution of the drimane diol (±)-6 was carried out using lipase PS-30 and (-)-6a was converted to enantiopure Ambrox® by Oritani et al.\textsuperscript{13} They have also carried out the hydrolysis of the racemic acetate (±)-6a using the same lipase which gave alcohol (±)-6.

![](image.png)

**Scheme 3**

Same authors have studied kinetic resolution of the one carbon elongated substrate (±)-7. Enzymatic hydrolysis proceeded satisfactorily as depicted in Scheme 4.\textsuperscript{13} However, enzymatic acetylation of the alcohol (±)-7a under transesterification condition was proved unsuccessful.

![](image.png)

**Scheme 4**

Enzymatic resolution of (±)-drimenol, 8 was achieved with lipase PL-266 from *Alcaligenes sp* using isopropenyl acetate as acyl donor (Scheme 5).\textsuperscript{7}
Enzymatic hydrolysis of the racemic β-acyloxyester (±)-9 was carried out using lipase OF-360 from *Candida rugosa* in water-saturated organic solvent (Scheme 6). Enantioselective acetylation was also carried out using lipase OF-360 and vinyl acetate.

Enzymatic acetylation of the *anti*-diol (±)-10 was accomplished in the presence of lipase Godo E-4 from *Pseudomonas sp.* This provided 42% yield of recovered diol with 89% ee along with diacetate and monoacetates (Scheme 7). Other enzymes were found to be unsuitable for this resolution.
Acylase from *Aspergillus melleus* selectively hydrolyzed the (-)-isomer of the phenolic acetal (±)-11 (Scheme 8). The ee of both the products were improved by crystallization. The diol was further converted to the marine natural product (+)-zonarol and the perfumary compound (-)-ambrox.

![Diagram of (±)-11 and products](image)

Scheme 8

Previous studies from our laboratory revealed that while regioselective acylation of (±)-12 was possible with PPL, CCL, WGL, SAM-2, etc., enantioselectivity was very poor. The monoacetate was found to undergo 1,3-transacylation on keeping in silica gel column for long periods. However, enzymatic diacetylation was not observed even after long exposure (Scheme 9).

![Diagram of (±)-12 and (±)-12a](image)

Scheme 9

Very recently a related study was reported which used chiral auxiliary mediated resolution strategy for the synthesis of optically pure (+)-12 and (-)-12. Here Toshima et al. have used Boc-L-Proline as chiral catalyst to resolve the diol (±)-12. The diastereomeric monoesters could be easily separated by column chromatography. The optically pure diols were further converted to other chiral building blocks and the synthesis of (+)- and (-)-copalol was also achieved.
Earlier studies from our laboratory revealed that the ketoalcohol (+)-13 could be readily resolved using CCL(Fluka) giving the acetate (+)-13a in 47% yield and 68% ee.\(^{18}\) This optically enriched compound on further crystallization led to optically pure (+)-13a in \(~100\)% ee. (+)-13a is a very useful synthon for the synthesis of terpenoids like albicanol,\(^{19}\) albicanyl acetate,\(^{19}\) and acuminolide.\(^{20}\)

An attempt by our group to synthesize albicanol and albicanyl acetate from chiral intermediates (-)-13 or (+)-13a as shown below in Scheme 12 resulted in modest chemical yield. The olefination of the ketoacetate using the well established Nozaki method resulted in the formation of diastereomers.\(^{21}\) With a slight modification of the olefination procedure which involved addition of PbI\(_2\) to the Nozaki-Lombardo reagent resulted in the synthesis of (+)-1 \textit{albeit} in low yield.
This clearly indicated that in order to obtain albicyanl acetate in good yield, another approach had to be followed. Thus the present work was initiated. Since the yield of the above mentioned methylenation reaction was poor, the reaction strategy was changed to one where introduction of the double bond was carried out earlier and the chirality ensured through enzymatic resolution as the last step as shown below (Scheme 13).

4.4 Results and discussion

The required advanced intermediate (±)-3 was synthesized starting from the readily available β-ionone using a modification of the literature procedure as detailed below. The β-ketoester (±)-3 was obtained in three steps from β-ionone viz. (i) transfer hydrogenation using ammonium formate and 10% palladium on charcoal, (ii) carbomethylation using sodium hydride and dimethyl carbonate and (iii) final cyclization using SnCl₄ (Scheme 14).
Next step was to introduce the required methylene group. Liapis et al.\textsuperscript{23} have studied earlier the Wittig reaction of the $\beta$-ketoester 3 under salt free conditions (by refluxing methyl triphenyl phosphonium bromide and sodamide in toluene followed by decantation) at ambient temperature. When the reaction was carried out without decantation or by using other bases, it resulted in the formation of epimers which could not be separated by conventional chromatographic techniques. We too carried out the olefination reaction under essentially salt free conditions by refluxing the phosphonium bromide and NaNH\textsubscript{2} in toluene and by syringing out the supernatant yellow solution to a solution of the ketoester 3 in toluene and further stirring the resulting solution under an atmosphere of argon for 7 h at room temperature.

The structure of the product 15 was followed from spectroscopic data. In the $^1$H NMR spectrum the singlet at 3.64 ppm for three protons clearly indicated that the methoxycarbonyl ester is $\beta$ (for $\alpha$-isomer this peak is seen at 3.42 ppm). The protons of the double bond were seen as two singlets at 4.66 ppm and 4.83 ppm. In $^{13}$C NMR spectrum the ester carbonyl was observed at 172.04 ppm. All other spectral data matched with that reported earlier.

To our surprise, contrary to that reported earlier, reduction of 15 using a large excess of lithium aluminum hydride (LAH) in dry THF resulted in the formation of two products as indicated by tlc. This led to the surmise that probably two
diastereomers are formed due to some epimerisation in the reaction medium prior to LAH reduction. Chromatographic purification of the crude product gave the required isomer (±)-albicanol, 1 in 58% yield. This was also fully characterized by spectroscopic techniques. In the $^1$H NMR spectrum the olefinic protons resonated at 4.64 ppm and 4.94 ppm as broad singlets. The methylene protons adjacent to OH group were seen at 3.79 ppm as a multiplet. In $^{13}$C NMR spectrum the carbons of the exocyclic double bond were seen at 147.75 ppm and 106.15 ppm. The carbon attached to hydroxyl group resonated at 59.07 ppm.

![Image of chemical structures](image)

**Scheme 16**

Having obtained (±)-1 in sufficient amount, the next step was its enzymatic resolution. For this (±)-1 was dissolved in vinyl acetate and stirred with CCL (Fluka) for 8 h. This gave albicanyl acetate viz., (-)-2 (57%, 73% ee) and albicanol viz., (+)-1 (37%, 77% ee) after work up and chromatographic separation. The enantiomeric purity of the products of the enzymatic reaction was determined by direct comparison of specific rotation values reported for the natural product as determination using $^1$H NMR spectra with chiral shift reagents proved unsuitable.

**Scheme 17**

Similar studies were described by Akita et al. They could resolve (±)-1 using a lipase PL-266 from *Alcaligenes sp.* to get (-)-1 in >99% ee and by applying a sequential enzymatic resolution they were able to synthesize (+)-2 with > 99% ee.
Thus we have shown that enzymatic transesterification methodology can be applied for the synthesis of (+)-albicanol and (-)-albicanyl acetate using readily available enzymes.

4.5 Experimental

General experimental procedure is the same as given in Chapter 2. The enzyme Candida cylindracea lipase used for this study was purchased from Fluka and has an activity of 24.2 U/mg. β-Ionone was obtained as a gift from M/s Kelkar & Co., Bombay.

Methyl (1β,4α,8α,8β)-decahydro-5,5,8a-trimethyl-2-oxonaphthalene-1-carboxylate (+)-3 was prepared from β-ionone in three steps by a reported procedure.21,22 (+)-3 thus obtained showed all characteristics of the reported compound.

\[
\text{mp } 105-107 ^\circ C; \text{ lit } 23 \ 106-108 ^\circ C.
\]

\[\text{Methyl (1β,4α,8α,8β)-decahydro-5,5,8a-trimethyl-2-methylenenaphthalene-1-carboxylate (±)-15}\]

A solution of methyltriphenyl phosphonium bromide (626 mg, 1.75 mmol) and sodamide (92 mg, 2.36 mmol) in toluene (8 mL) was heated under reflux for 3 h under argon. After cooling, the suspension was allowed to settle, the clear yellow solution was syringed out and added to a solution of (±)-3 (117 mg, 0.47 mmol) in toluene (1 mL). The reaction mixture was stirred at room temperature for 7 h. Then the reaction mixture was diluted with more toluene, washed with water, dried and the toluene was removed under reduced pressure. The residue was washed with warm petroleum ether to remove most of the triphenylphosphonium oxide. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (petroleum ether-ethyl acetate 95:5) to afford the title compound in 85% yield (99 mg).

\[\text{Appearance } \text{colorless oily liquid.}\]

\[\text{IR (thin film, } \nu_{\text{max}} \text{, cm}^{-1}) : 2935, 1742, 1647, 1431, 1371, 1263, 1162, 899.\]

\[\text{^1H NMR (CDCl}_3, \delta \text{) : 4.82 (s, 1H, } =\text{CHH}, 4.66 (s, 1H, } =\text{CHH}, 3.64 (s, 3H, CO}_2\text{CH}_3, 2.80 (s, 1H, CHCO}_2\text{CH}_3, 2.45-2.39 (m, 1H, CHH near the exocyclic double bond), 2.07-2.05 (m, 1H, CHH).}\]
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$^{13}$C NMR (CDCl$_3$, $\delta$) : 172.04, 143.77, 108.31, 63.06, 54.56, 50.83, 42.05, 39.24, 39.07, 36.25, 33.44, 33.34, 23.24, 21.69, 18.88, 14.14 ppm.

MS (m/z) relative : 250 (M$^+$, 31), 235 (29), 176 (28), 137 (100), 123 (48), 114 ppm.

(1β,4αβ,8αβ) Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenemethanol [Albicanol] (±)-1

To a well stirred suspension of lithium aluminium hydride (90 mg, 2.37 mmol) in 4 mL dry THF at 0 °C was added dropwise a solution of the methylene ester (±)-15 (204 mg, 0.82 mmol) in 1 mL dry THF. The reaction mixture was stirred at room temperature for 20 h. Excess LiAlH$_4$ was destroyed by adding THF containing few drops of water to the reaction mixture at 0 °C. The reaction mixture was then filtered to remove the precipitate formed. The filtrate was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether-ethyl acetate 9:1) and the required compound (±)-1 was obtained in 58 % yield (99 mg) after crystallizing from hexane.

Appearance : white solid.

mp : 65-67 °C; lit.$^9$ mp: 68-69 °C.

IR (KBr, $\nu_{\text{max}}$) : 3374 (br), 2943, 1645, 1458, 1021, 964, 877, 671 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, $\delta$) : 4.93 (d, 1H, $J = 1.3$ Hz, =CHH), 4.63 (d, 1H, $J = 1.3$ Hz, =CHH), 3.81-3.71 (m, 2H, CH$_2$OH), 2.43-2.38 (m, 1H, CHH near the exocyclic double bond), 2.01-1.94 (m, 2H, CHH near the exocyclic double bond and CH near the exocyclic double bond), 1.66-1.09 (m, 10H, 4 × ring CH$_2$, CH and OH), 0.87 (s, 3H, CH$_3$), 0.79 (s, 3H, CH$_3$), 0.71 (s, 3H, CH$_3$) ppm.

$^{13}$C NMR (CDCl$_3$, $\delta$) : 147.85, 106.25, 59.16, 58.74, 55.15, 41.95, 38.97, 37.84, 33.60, 33.44, 24.19, 21.71, 19.19, 15.26 ppm.
**Enzymatic resolution of (±)-albicanol**

To a solution of (±)-1 (40 mg, 0.18 mmol) in 4 mL vinyl acetate was added CCL (Fluka) (23 mg) and stirred at room temperature for 8 h. The reaction was stopped by filtering off the lipase and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether-ethyl acetate 25:1-25:2). This afforded (-)-2 (27.2 mg, 57%) and (+)-1 (14.8 mg, 37%).

**(-)-2**

**Appearance**
- colorless oily liquid.

**[α]_D^{25}**
- -17.6 (c 1.08, CHCl₃); 73% ee; lit.¹⁰ [α]_D^{26} +21.9 (c 0.37, CHCl₃).

**IR (thin film, ν_max)**
- 2937, 1739, 1645, 1458, 1370, 1233, 1027, 883 cm⁻¹.

**¹H NMR (CDCl₃, δ)**
- 4.85 (s, 1H, =CHH), 4.51 (s, 1H, =CHH), 4.34 (dd, 1H, J = 3.7 Hz, 11.2 Hz, CHHOCOCH₃), 4.19 (dd, 1H, J = 9.2 Hz, 11.0 Hz, CHHOCOCH₃), 2.38 (m, 1H, CHH near the exocyclic double bond), 2.02 (s and m, 5H, OCOCH₃, CHH near the exocyclic double bond and CH near the exocyclic double bond), 1.74-1.15 (m, 9H, 4 x CH₂, and CH), 0.88 (s, 3H, CH₃), 0.81 (s, 3H, CH₃), 0.76 (s, 3H, CH₃) ppm.

**¹³C NMR (CDCl₃, δ)**
- 171.41, 146.82, 107.12, 61.57, 55.05, 54.73, 41.91, 39.03, 38.96, 37.59, 33.61, 33.47, 23.89, 21.74, 21.10, 19.15, 15.09 ppm.

**(+)-1**

**[α]_D^{28}**
- +9.9 (c 0.59, CHCl₃); 77% ee; lit.⁹ [α]_D^{20} +13.0 (c 0.60, CHCl₃).

Other spectral data matched with that of the racemic 1.
4.6 References