CHAPTER 2

Asymmetric Synthesis of Antifungal Agents via Hydrolytic Kinetic Resolution of Epoxides
2.1 Introduction

During the past two decades, infections caused by opportunistic fungal pathogens have increased substantially *in vivo* compromised patients. Amphotericin B, discovered in 1956, was the drug of choice for the treatment of most severe systemic infections. However, more recently, there has been an expansion in the number of antifungal drugs available. Five major classes of antifungal compounds are currently in clinical use: polyenes, azole derivatives, allylamines, thiocarbamates, and fluoropyrimidines. Numerous studies on the SAR (structure-activity relationships) of antifungal azoles have been developed since the discovery of the first imidazoles, and these studies have led to new compounds endowed with better biological and/or pharmacological properties. Although today’s antifungal research is mainly focused on systemic fungal infections, dermatomycoses are among the most widespread and common human superficial and cutaneous fungal infections.

Triazole antifungal agents demonstrate potential drug to treat these infectious diseases because of their broad antifungal spectrum and low toxicity. Azoles such as ketoconazole (1), econazole (2), miconazole (3), itraconazole (4) and fluconazole (5) (Fig. 1), act as 14-a-demethylase inhibitors. These are potent broad-spectrum antimycotics, which show high *in vitro* activity against almost all fungi of clinical interest. They have also been successfully applied for topical use in many clinical trials, particularly in mucocutaneous candidosis of the vagina and in dermatophytosis. The major disadvantage of miconazole, econazole, and clotrimazole is that serum, urine, and body fluid levels after oral doses are disappointingly low, at best hardly sufficient to inhibit fungal growths.
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Unlike miconazole and clotrimazole, ketoconazole (1), is a potent, orally active, broad-spectrum antifungal agent, well absorbed in the bloodstream. It has been found to be highly effective against crop candidosis in turkeys, vaginal candidosis in rats, systemic candidosis in chickens, systemic and skin candidosis, as well as dermatophytosis, in guinea pigs and mice. The basis of the antifungal activity of ketoconazole (1) and related azoles are blockade of the conversion of lanosterol to ergosterol, which is necessary for maintaining the integrity of the organism's cell membrane. Ketoconazole (1) has shown a similar inhibitory effect on the corresponding enzyme responsible for conversion of lanosterol to cholesterol in mammals and has been demonstrated to lower cholesterol in humans.

Fig. 1: Structures of antifungal agents
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Fluconazole (5) is used to treat fungal infections, including yeast infections of the vagina, mouth, throat, esophagus, abdomen, lungs, blood, and other organs. It is also used to treat meningitis caused by fungus. Further, fluconazole, itraconazole, and voriconazole are clinically used representative antifungal drugs of this family. Therefore, the development of an efficient and convergent synthetic route that can be applied to large-scale synthesis of these antifungals is an important goal.

2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis antifungal agents namely ketoconazole (1), miconazole (3) and fluconazole (5). However, most of the reports deal with the racemic synthesis of these antifungal agents, while some methods are known to obtain enantiomerically pure material mostly with chiral pool approaches, which are enumerated below.

Heeres’s approach (1979)\(^{10}\).

Heeres et al. have synthesized ketoconazole (1) starting from 2,4-dichloroacetophenone (Scheme 1). The ketal 7, obtained from 6 was brominated at 30 °C to give bromo ketal 8, followed by its benzoylation afforded the corresponding ester as a cis/trans mixture, from which the cis form 9 was isolated by crystallization from EtOH. Coupling of bromo ketal 9 in dry dimethylacetamide (DMA) with imidazole gave the imidazole derivative 10, which on saponification gave alcohol 11. Alcohol 11 was converted to methanesulfonate 12, which was coupled with the sodium salt of phenol 13 furnishing ketoconazole (1).
Rotstein’s approach (1992)\textsuperscript{11}.

Rotstein et al have synthesized ketoconazole (1) starting from 2,4-dichloroacetophenone (6) (Scheme 2). Bromination of 6 with copper(II) bromide in 1:1 CH\textsubscript{2}Cl\textsubscript{2}-EtOAc gave 2-bromo-2’\textprime,4’-dichloroacetophenone (14), which on ketalization using (S)-solketal tosylate in the presence of p-TsOH and n-BuOH in refluxing toluene, accompanied by azeotropic removal of water, afforded a 1.2:1 mixture of the cis and trans bromotosylates 15 and 16, which were separated by chromatography. Displacement of bromide with excess imidazole in dimethylacetamide under reflux condition led to ketoconazole (1) after 4-16 h in 40-50% yields.
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Scheme 2: (i) CuBr₂, EtOAc:CH₂Cl₂, reflux, 85%; (ii) (R)-solketal tosylte, p-TsOH, n-BuOH, toluene, reflux, 43%; (iii) NaH 50%, Me₂SO, 80 °C, 78%; (v) K₂CO₃, imidazole, DMF, reflux, 53%.


Lennon et al. have synthesized alcohol 20, the key intermediate for myconazole, by carrying out the asymmetric transfer hydrogenation of amino ketone (19) with [(R,R)-TsDPEN]Ru(p-cymene)Cl (21) as catalyst and formic acid in triethylamine as hydrogen source which resulted in the formation of 20 in 91% ee (Scheme 3).

Scheme 3: (i) 21, formic acid: triethylamine, CH₂Cl₂, 91% ee.
Richardson approach (1983)\(^{13}\).

In this approach, fluconazole (5) was synthesized in 2 steps; (i) addition of 1-bromo-2, 4-difluoro-phenyllithium onto 1,3-dichloroacetone to afford 1,3-dichloro alcohol 23; (ii) Nucleophilic displacement of the chloro derivative 23 with triazole furnished fluconazole (5) in 26% yield (Scheme 4).

Veinberg approach (1996)\(^{14}\).

In this approach, the first step involves the Friedel-Crafts’ acylation of 1,3-difluorobenzene (22) with chloroacetyl chloride to give α-chloro-2,4-difluoro-acetophenone (24). Nucleophilic displacement of the chloro compound 24 with triazole, gave ketone 25, which was epoxidized using sulfur ylide to give the epoxide 26 in 27% yield. Regiospecific ring opening of epoxide 26 with imidazole afforded fluconazole (5) (Scheme 5).
2.3 Present Work

2.3.1 Objective

All the reported methods described above for the synthesis of these antifungal agents suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, etc. In order to develop a new general route for the asymmetric synthesis of these compounds, we have decided to make use of cobalt-catalyzed kinetic resolution of racemic epoxides. This chapter describes the new synthetic routes for the asymmetric synthesis of ketoconazole (1), econazole (2) and myconazole (3) using cobalt-catalyzed kinetic resolution of epoxides 29 and 32 respectively. (A brief account of Co-catalyzed asymmetric kinetic resolution of terminal epoxides is given in Chapter I).
2.4 Results and Discussion

2.4.1 Ketoconazole

For the synthesis of ketoconazole (1), chiral 1,2-diol 28 was visualized as the key intermediate, which could be prepared by the Os-catalyzed asymmetric dihydroxylation (ADH) of the corresponding allyl ether 27 (Scheme 6).

\[
\text{Scheme 6: (i) allyl bromide, } K_2CO_3, \text{ acetone, } 75 \degree C, 96\%; (ii) } K_2Fe(CN)_6, K_2CO_3, OsO_4, (DHQ)_2-PHAL, \text{ tert-BuOH:H}_2O (1:1), 92\% \text{ yield, } 83\% \text{ ee.}
\]

Thus, the O-allylation of 4-bromophenol was carried out in the presence of \( K_2CO_3 \) to give allyl ether 27 in 96\% yield. The \(^1\text{H NMR} \) spectrum of allyl ether 27 showed typical a doublet at \( \delta 4.49 \) for -O-CH \(_2\) protons; other multiplets at \( \delta 5.34 \) (2H) and 6.01 (1H) are due to olefinic protons. Its \(^{13}\text{C NMR} \) spectrum showed characteristic signals at \( \delta 117.6 \) and 132.7 due to olefinic carbons. Allylic ether 27 was then subjected to Os-catalyzed ADH using (DHQ)_2-PHAL as chiral ligand in tert-BuOH: \( H_2O \) mixture at 0 \( \degree C \) to produce the corresponding chiral diol 28 in 92\% yield and 83\% ee. The \(^1\text{H NMR} \) spectrum of diol 28 showed a multiplet at \( \delta 3.95 \) due to methine (-OCH \(_2\)CHOH) and methylene (-CH \(_2\)OH) protons. Its \(^{13}\text{C NMR} \) showed typical signals at \( \delta 62.4 \) and 96.4 corresponding to methine (-OCH \(_2\)CHOH) and methylene (-CH \(_2\)OH) carbons respectively (Fig. 2).
Fig. 2: $^1$H and $^{13}$C NMR spectra of (R)-3-(4-Bromophenoxy)propane-1, 2-diol (28)

Although the ADH route to diol 28 was facile and high yielding, it suffers from low enantioselectivity (83% ee). Hence, it was of interest to provide an alternate synthesis for 1 in which we have employed cobalt-catalyzed hydrolytic kinetic resolution (HKR) of racemic epoxide 29 as the key reaction (Scheme 7). The racemic epoxide, 29, was subjected to hydrolytic kinetic resolution\textsuperscript{15} [(R,R)-salen-Co(III).OAc (0.5 mol %), THF, distilled H$_2$O (0.45 equiv), 0 °C, 24 h] to afford the chiral epoxide 30 in 48% yield and 93% ee (chiral HPLC (Fig. 3)) along with its diol 28 in 42% yield. The chiral diol 28 was readily separated from its epoxide 30 by column chromatographic purification.
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Scheme 7: (i) (R,R)-Co(salen)OAc, H2O (0.45 equiv.), 0 °C, 24 h, 48%, 93% ee for 30 and 42%, 96% ee for 28; (ii) p-TSA, benzene, 110 °C, 82%; (iii) N-acylpiperazine, Cul, Cs2CO3, DMF, 150 °C, 78%.

The 1H NMR spectrum of epoxide 30 showed typical signals at δ 2.74 (dd) and 2.90 (dd) for methylene -CH-CH2-O protons of epoxide. Its 13C NMR spectrum showed characteristic signals at δ 44.2 and 68.7 corresponding to methylene carbons and a signal at δ 49.7 is due to the methine carbon of the epoxide 30.
The diol 28 was converted into its ketal derivative 31 by condensing with ketone 19 (p-TSA, benzene, 100 °C). Finally, copper-catalyzed amination of bromoderivative 31 with \( N \)-acetylpenicillazine in the presence of Cs\(_{2}\)CO\(_{3}\) afforded ketoconazole (1) in 78% yield and 96% ee. The spectral data obtained for ketoconazole (1) were in complete agreement with the values reported in the literature\(^{11}\) (Fig. 4).
2.4.2 Myconazole (2) and Econazole (3)

Synthetic route for (S)-econazole (2) and (S)-myconazole (3) is shown in Scheme 8, wherein HKR constitutes the key chiral inducing reaction.

Thus, the racemic epoxide 32 was subjected to hydrolytic kinetic resolution\(^1\) [(S,S)-salen-Co(III).OAc (0.5 mol %), THF, distilled H\(_2\)O (0.55 equiv), 0 °C, 24 h] to afford chiral epoxide 33 in 46% yield and 96% ee (chiral HPLC) along with its diol 34 in 49% yield and 93% ee. The chiral epoxide 33 was readily separated from the corresponding diol 34 by simple column chromatographic purification.
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\[
\begin{align*}
\text{Antifungal agents} \\
\text{(+) 32} & \overset{\text{i}}{\rightarrow} 33 \quad 46\%; \ 96\% \ ee & + & 34 \quad 49\%; \ 93\% \ ee \\
\text{ii} & \quad 20 \\
\text{iii} & \quad 2, \ R = 4\text{-chlorobenzyl} \ \quad \quad 3, \ R = 2,4\text{-dichlorobenzyl}
\end{align*}
\]

Scheme 8: (i) (S,S)-Co(salen).OAc, H₂O (0.55 equiv.), 0 °C, 24 h, (46%, 96% ee for 33 and 49% yield, 93% ee for 34); (ii) imidazole, reflux, EtOH, 88%, 96% ee; (iii) NaH, DMF, 2,4-dichlorobenzyl bromide, 25 °C, 78%; or NaH, DMF, 4-chlorobenzyl bromide, 25 °C, 73%.

The \(^1\)H NMR spectrum of epoxide 33 showed signals at \(\delta\) 2.60 (dd) and 3.18 (dd) corresponding to methylene protons; other signal at \(\delta\) 4.13 (dd) for methine proton. Its \(^{13}\)C NMR spectrum showed typical signal at \(\delta\) 49.4 and 50.4 due to methylene and methine carbons respectively. The \(^1\)H NMR spectrum of diol 34 showed typical signals at \(\delta\) 3.45 (dd) and 3.79 (dd) corresponding to -CH₂ protons; other signal at 4.45 (dd) due to methine proton. Its \(^{13}\)C NMR showed signal at \(\delta\) 65.9 and 70.9 corresponding to methylene and methine carbons respectively. Regiospecific ring opening of epoxide 33.
with imidazole in ethanol gave amino alcohol 20 in 88% yield and 96% ee. The $^1$H NMR spectrum of amino alcohol 20 showed signals at δ 3.85 (dd) and 4.20 (dd) corresponding to methylene -CH$_2$ protons (Fig. 5).

Finally, O-alkylation of the amino alcohol 20 either with 2,4-dichlorobenzyl bromide or 4-chlorobenzyl bromide under basic conditions in DMF afforded (S)-miconazole (3) and econazole (2) in 78% and 73% yield and 96% ee respectively (chiral HPLC (Fig. 7)). The $^1$H NMR spectrum of miconazole (3) showed typical signals δ 4.07 (dd) and 4.24 (dd) corresponding to -CH$_2$-N protons; other signal at δ 4.42 (dd) due to Ar-CH$_2$ protons. Its $^{13}$C NMR showed typical benzylic carbon signals at δ 51.2 and 68.1 corresponding to -CH$_2$-N and Ar-CH$_2$ respectively (Fig. 6).
Fig. 7: HPLC Chromatogram of Miconazole (3)

### Table 1: HPLC Analysis of Miconazole (3)

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<th>Peak No.</th>
<th>Ret. Time (mins)</th>
<th>Area (mAU*s)</th>
<th>Area (%)</th>
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<tr>
<td>2</td>
<td>14.45</td>
<td>2065809</td>
<td>1.96</td>
</tr>
</tbody>
</table>

Fig. 6a: $^1$H NMR spectrum of miconazole (3)

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2.4.3 Fluconazole

The synthetic route for fluconazole (5), a class of antifungals, is shown in Scheme 9.

![Scheme 9: (i) 1,2,4-triazole, K₂CO₃, CH₃CN, 65 °C, 88%; (ii) 35, THF, -40 °C, 85%.

We have begun our synthesis with the preparation of ketone 25, which was readily achieved in 96% yield by the condensation of 1,2,4-triazole with 2-chloro-1-(2,4-difluorophenyl)ethanone (24) in refluxing CH₃CN. The ¹H NMR spectrum of ketone 25 showed a doublet at δ 5.60 for -CH₂ protons. Its ¹³C NMR showed characteristic signals at δ 58.1 and 187.5 corresponding to -CH₂ and C=O carbons respectively. Its IR spectrum
has exhibited a characteristic strong band at 1702 cm\(^{-1}\) indicating the presence of a carbonyl group.

![NMR spectra of Huconazole (5)](image)

**Fig. 8: \(^1\)H and \(^{13}\)C NMR spectra of fluconazole (5)**

Finally, the Grignard reagent 35, prepared by a modified procedure from the corresponding 1-(bromomethyl)-1\(H\)-1,2,4-triazole,\(^{16}\) with Mg, was added to ketone 25 to afford fluconazole (5) in 85% yield. The \(^1\)H NMR spectrum of fluconazole (5) showed characteristic two doublets at \(\delta 4.47(d)\) and \(4.76(d)\) corresponding to \(-\text{CH}_2\text{-N}\) protons. Its \(^{13}\)C NMR showed typical signals at \(\delta 72.3\) and 53.4 due to \(-\text{CH}_2\text{-N}\) and \(-\text{C-\ OH}\) carbons.
respectively (Fig. 8). A broad band at 2900-3200 cm⁻¹ in its IR spectrum confirms the presence of OH group in the molecule.

2.5 Conclusion

In conclusion, we have successfully applied cobalt-catalyzed kinetic resolution of terminal epoxides (29 and 32) for obtaining ketoconazole (1), (S)-econazole (3) and (S)-myconazole (3) respectively in high optical purities. The reactions are rapid, and require only catalytic amount of cobalt chiral catalyst. The high yields and less number of steps associated with our approach render our method a good alternative to the known procedures.

2.6 Experimental Section

1-(Allyloxy)-4-bromobenzene (27):

To a stirred mixture of 4-bromophenol (8.65 g, 50 mmol), allyl bromide (12.1 g, 100 mmol) and anhyd. K₂CO₃ (13.8 g, 100 mmol) in dry acetone (100 mL) was refluxed under nitrogen atmosphere for 12 h. The reaction mixture was then cooled to 25 °C, filtered through sintered funnel to remove solid crude product and the filtrate was evaporated to dryness. The crude product was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to obtain pure allyl ether 27 in 96% yield.

Yield: 10.2 g (96%); viscous liquid; IR (CHCl₃, cm⁻¹): 823, 914, 1031, 1072, 1242, 1286, 1488, 1577, 1589, 2925, 3001, 3058; H NMR (200 MHz, CDCl₃): δ 4.47-4.50 (m, 2H), 5.25-5.43 (m, 2H), 5.92-6.11 (m, 1H), 6.77 (d, J= 9.0 Hz, 2H), 7.35 (d, J= 9.0 Hz, 2H); C NMR (50 MHz, CDCl₃): δ 68.8, 112.8, 116.3, 117.6, 132.0, 132.7, 157.5; MS (m/z,
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% relative intensity): 212 (M+, 8), 143 (9), 133 (16), 105 (12), 63 (19), 41 (100, base peak); Analysis: C₉H₉BrO requires C, 50.73; H, 4.26; found C, 50.90; H, 4.51%.

**(R)-3-(4-Bromophenoxy)propane-1, 2-diol (28):**

To a solution of K₃Fe(CN)₆ (8.93 g, 27.1 mmol), K₂CO₃ (3.74 g, 27.1 mmol), (DHQ)₂-PHAL (0.140 g, 0.18 mmol) in t-BuOH: H₂O (1:1, 80 mL) was added a solution of OsO₄ (229 µL, 0.09 mmol, 0.5 M solution in toluene) at 0 °C. The resulting reaction mixture was stirred at the same temperature for 5 minutes and then allyl ether 27 (1.917 g, 9 mmol) was added. The reaction mixture was stirred at 0 °C for 20-24 h (monitored by TLC). It was quenched with sodium sulfite (5.0 g) and extracted with ethyl acetate (4 x 30 mL). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (7:3) as eluent to give pure diol 28.

**Yield:** 2.04 g (92%); **mp:** 82 °C; [α]D -10.52 (c 1, EtOH) 83% ee; {[lit. 17] [α]D -12.3 (c 1, EtOH) 97% ee}; IR (CHCl₃, cm⁻¹): 669, 756, 823, 1043, 1215, 1242, 1488, 1591, 2879, 2931, 3018; **¹H NMR** (200 MHz, CDCl₃): δ 2.10 (brs, 1H), 2.67 (s, 1H), 3.17-3.84 (m, 2H), 3.99-4.12 (m, 3H), 6.80 (d, J= 9.1 Hz, 2H), 7.39 (d, J= 9.0 Hz, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 62.4, 68.5, 69.4, 111.7, 115.6, 131.2, 157.1; MS (m/z, % relative intensity): 246 (M+, 10), 172 (100, base peak), 157 (7), 136 (7), 93 (17), 75 (19), 65 (36), 43 (48); Analysis: C₉H₇BrO requires C, 43.75; H, 4.49; found C, 43.59; H, 4.58%.

**Hydrolytic kinetic resolution of 2-[(4-Bromophenoxy)methyl]oxirane (29):**

**Preparation of Co-salen.OAc complex:** To a solution of (R,R)-Co(salen) (0.06 g, 0.1 mmol) in toluene (0.5 mL) was added AcOH (0.126 g, 21 mmol) at 25 °C. The solution
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was allowed to stir at 25 °C open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under vacuo to leave a crude solid.

Thus prepared, Co-salen complex (0.031 g, 0.5 mol%), was dissolved in THF and epoxide 29 (4.58 g, 20 mmol) was added at 25 °C, the solution was cooled to 0 °C and H2O (0.162 g, 9 mmol) was added dropwise over 5 min. The reaction was allowed to 25 °C and stirred for 48 h. Mixture containing epoxide and diol was purified by column chromatography to obtain epoxide 30 in 48% yield and diol 28 in 42% yield respectively.

(5)-2-[(4-Bromophenoxy)methyl]oxirane (30):

Yield: 1.09 g (48%); \([\alpha]^{25}_D +5.02 \ (c \ 2.1, \ CHCl_3)\); HPLC: 93% ee, Chiracel OD-H, \(\lambda = 254 \text{ nm}, \ 2\)-propanol/hexane (10:90), 1 mL/min, retention time: (S)-enantiomer 6.96 min, (R)-enantiomer 9.18 min; IR (CHCl3, cm\(^{-1}\)): 823, 1031, 1072, 1174, 1242, 1286, 1488, 1577, 1589, 2925, 3001, 3058; \(^1\text{H NMR} \ (200 \text{ MHz, CHCl}_3): \delta 2.74 \ (dd, \ J = 2.7, 4.8 \text{ Hz, } 1\text{H}), \ 2.90 \ (dd, \ J = 2.6, 4.3 \text{ Hz, } 1\text{H}), \ 3.30-3.37 \ (m, \ 1\text{H}), \ 3.89 \ (dd, \ J = 5.8, 11.1 \text{ Hz, } 1\text{H}), \ 4.21 \ (dd, \ J = 2.9, 11.0 \text{ Hz, } 1\text{H}), \ 6.80 \ (d, \ J = 9.1 \text{ Hz, } 2\text{H}), \ 7.37 \ (d, \ J = 9.1 \text{ Hz, } 2\text{H}); \ ^{13}\text{C NMR} \ (50 \text{ MHz, CHCl}_3): \delta 44.2, \ 49.7, \ 68.7, \ 113.1, \ 116.2, \ 132.0, \ 157.3; \ Analysis:\ C_9\text{H}_9\text{BrO}_2 \text{ requires } C, 47.19; H, 3.96, \ Br, 34.88; \text{found } C, 47.28; H, 3.88; \ Br, 35.02%.

(R)-3-(4-Bromophenoxy)propane-1, 2-diol (28):

Yield: 1.04 g (42%); mp: 82 °C; \([\alpha]^{25}_D -12.1 \ (c \ 1, \ EtOH) \ 96\% \ ee; \{\text{lit.}^{17} \ [\alpha]^{25}_D -12.3 \ (c \ 1, \ EtOH), \ 97\% \ ee\}.

1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone (19):

A mixture of 2-chloro-1-(2,4-dichlorophenyl)ethanone (2.23 g, 10 mmol), imidazole (1.02 g, 25 mmol), and anhydrous K_2CO_3 (2.07 g, 15 mmol) in dry CH_3CN (20 mL) was
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refluxed under nitrogen atmosphere for 12 h (reaction monitored by TLC). The reaction mixture was then cooled to 25 °C, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to get amino ketone (19) in 96% yield.

**Yield:** 1.83 g (82%

**¹H NMR** (200 MHz, CDCl₃): δ 5.72 (s, 2H), 7.07 (s, 1H), 7.35 (m, 1H), 7.67 (dd, J = 2.1, 6.3 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.97-8.06 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 55.5, 120.0, 127.9, 129.8, 130.8, 131.1, 132.5, 134.1, 138.1, 139.2, 193.7; **Analysis:** C₁₁H₈Cl₂N₂O requires C, 51.79; H, 3.16; N, 10.98; found C, 51.92; H, 3.32; N, 10.75%.

1-[[((25,4'i;)-4-[(4-Bromophenoxy)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl)methyl]-1H-imidazole (31):

To a stirred suspension of ketone 19 (2.55 g, 10 mmol), (R)-1,2-diol 28 (2.47 g, 10 mmol), and n-butanol (2.5 mL) in toluene (50 mL) was added p-toluenesulfonic acid (3.44 g, 20 mmol) at 25 °C. The resulting reaction mixture was heated at reflux through a Dean-Stark trap. After 12 h, the reaction mixture was cooled to 25 °C and evaporated to dryness. The residue was extracted with EtOAc (3 x 50 mL), organic layers were washed with saturated sodium bicarbonate, brine and dried over anhyd. Na₂SO₄, evaporated under reduced pressure and purified by column chromatography.

**Yield:** 3.97 g (82%); **mp:** 150-151 °C; [α]²⁵D -10.9 (c 1.0, CHCl₃); **¹H NMR** (200 MHz, CDCl₃): δ 3.27 (dd, J = 6.8, 9.4 Hz, 1H), 3.59-3.64 (m, 2H), 3.83-3.91 (m, 1H), 4.29-4.55 (m, 3H), 6.77 (d, J = 9.0 Hz, 2H), 6.89 (d, J =9.0 Hz, 2H), 6.97 (br, 1H), 6.99 (br, 1H), 7.28 (br, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.52-7.61 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃):
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δ 41.1, 50.7, 50.9, 67.2, 67.3, 74.4, 77.2, 107.7, 113.4, 116.3, 120.9, 126.9, 128.2, 129.2, 131.0, 132.2, 132.7, 134.3, 135.5, 145.4, 152.5; Analysis: C_{10}H_{17}BrCl_{2}N_{4}O_{3} requires C, 49.61; H, 3.54; N, 5.79; found C, 49.52; H, 3.72; N, 5.85%.

1-(4-(4-((2S,4R)-2-((1R-imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)ethanone {Ketoconazole} (1):
To a stirred mixture of copper(I) iodide (0.019 g, 0.1 mmol), aryl bromide 31 (0.968 g, 2 mmol) and Cs_{2}CO_{3} (1.3 g, 4.0 mmol) in DMF (5 mL) was added 1-acylpiperazine (0.248 g, 2.2 mmol) at 25 °C and heated to 150 °C. After 12 h, the reaction mixture was cooled to 25 °C, diluted with dichloromethane and filtered to remove inorganic salts. Solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to obtain ketoconazole.

Yield: 0.83 g (78%); mp: 157-158 °C; [α]^{25}_{D} -10.16 (c 0.5, CHCl_{3}) 96% ee {lit.}^{11} [α]^{25}_{D} -10.58 (c 0.4, CHCl_{3}); ^{1}H NMR (200 MHz, CDCl_{3}): δ 2.14 (s, 3H), 3.00-3.08 (m, 4H), 3.27 (dd, J = 6.8, 9.4 Hz, 1H), 3.59-3.64 (m, 2H), 3.67-3.79 (m, 4H), 3.83-3.91 (m, 1H), 4.29-4.55 (m, 3H), 6.77 (d, J = 9.0 Hz, 2H), 6.89 (d, J =9.0 Hz, 2H), 6.97 (br, 1H), 6.99 (br, 1H), 7.28 (br, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.52-7.61 (m, 2H); ^{13}C NMR (50 MHz, CDCl_{3}): δ 21.1, 41.1, 46.0, 50.3, 50.7, 50.9, 67.2, 67.3, 74.4, 77.2, 107.7, 114.9, 118.4, 120.9, 126.9, 128.2, 129.2, 131.0, 132.7, 134.3, 135.5, 138.5, 145.4, 152.5, 168.6; Analysis: C_{26}H_{28}Cl_{2}N_{4}O_{4} requires C, 58.76; H, 5.31; Cl, 13.34; N, 10.54; found C, 58.59; H, 5.52; Cl, 13.45; N, 10.47%.

Hydrolytic kinetic resolution of 2-(2, 4-dichlorophenyl)oxirane (32):
Preparation of Co-salen.OAc complex:
To a solution of (S,S)-Co(salen) (0.06 g, 0.1 mmol) in toluene (0.5 mL) was added AcOH (0.126 g, 21 mmol) at 25 °C. The solution

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was allowed to stir at 25 °C open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under vacuo to leave a crude solid.

Thus prepared, Co-salen complex (0.031 g, 0.5 mol%), was dissolved in THF and epoxide 32 (3.78 g, 20 mmol) was added at 25 °C, the solution was cooled to 0 °C and H₂O (0.198 g, 11 mmol) was added dropwise over 5 min. The reaction was allowed to 25 °C and stirred for 48 h. Mixture containing epoxide and diol was purified by column chromatography to obtain epoxide 33 in 46% yield and diol 34 in 49% yield respectively.

(S)-2-(2,4-Dichlorophenyl)oxirane (33):
Yield: 1.739 g (46%); viscous liquid; [α]²⁵_D +62.36 (c 1.2, CHCl₃); HPLC: 96% ee, (R,R)-Whelk-O 1, λ = 220 nm, 2-propanol/hexane (0.1:99.9), 1 mL/min, retention time: (S)-enantiomer 4.53 min; IR: (CHCl₃, cm⁻¹): 817, 952, 1130, 1162, 1380, 1467, 1648, 2933, 3297, 3370; ¹H NMR (200 MHz, CDCl₃): δ 2.60 (dd, J= 2.5, 3.1 Hz, 1H), 3.18 (dd, J=4.1, 1.6 Hz, 1H), 4.13 (dd, J= 2.5, 1.6 Hz, 1H), 7.14-7.26 (m, 2H), 7.36-7.37 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 49.4, 50.4, 126.5, 127.3, 128.8, 133.7, 133.9, 134.3;
Analysis: C₅H₄Cl₂O requires C, 50.83; H, 3.20; Cl, 37.51; found C, 50.72; H, 3.45; Cl, 37.62%.

(R)-1-(2,4-Dichlorophenyl)ethane-1,2-diol (34):
Yield: 2.028 g (49%); viscous liquid; [α]²⁵_D -52.4 (c 1, CHCl₃); IR: (CHCl₃, cm⁻¹): 759, 1046, 1216, 1472, 1563, 1670, 3020, 3390; ¹H NMR (200 MHz, CDCl₃): δ 3.45 (dd, J = 8.1, 11.5 Hz, 1H), 3.79 (dd, J = 2.8, 11.6 Hz, 1H), 4.04 (brs, 2H), 4.45 (dd, J = 2.7, 8.1 Hz, 1H), 7.18-7.24 (m, 1H), 7.30-7.31 (m, 1H), 7.41-7.45 (m, 1H); ¹³C NMR (50 MHz,
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\[ \text{Analysis: } C_8H_5Cl_2O_2 \]
requires C, 46.41; H, 3.89; Cl, 34.25; found C, 46.48; H, 3.75; Cl, 34.41%.

\((S)-1-(2,4\text{-Dichlorophenyl})-2-(1H\text{-imidazol-1-yl})\text{ethanol (20):}\)

To a stirred solution of epoxide 33 (0.945 g, 5 mmol) in ethanol (15 mL) was added imidazole (0.340 g, 5 mmol) at 25 °C. The reaction mixture was refluxed under N\(_2\) for 12 h (reaction monitored by TLC). The reaction mixture was then cooled and the solvent was removed under reduced pressure. The residue was purified by column chromatography using pet. ether: EtOAc (3:7) as eluent to get amino alcohol 20 in 88% yield.

Yield: 1.13 g (88%); mp: 129-130 °C; \([\alpha]^{25}_D +85.5\ (c\ 1,\ MeOH)\ 96\%\ ee; \) {lit.\(^{12}\) \([\alpha]^{25}_D +88\ (c\ 1.06,\ MeOH)\ 98.8\%\ ee}; \[\text{IR (CHCl}_3,\ cm^-1):\ 669,\ 759,\ 1081,\ 1216,\ 1512,\ 1590,\ 2400,\ 3020,\ 3351; \text{H NMR (200 MHz, CDCl}_3):\ \delta\ 3.85\ (dd,\ J=8.2,\ 14.2\ Hz,\ 1H),\ 4.20\ (dd,\ J=2.4,\ 14.2\ Hz,\ 1H),\ 5.22\ (dd,\ J=2.3,\ 8.2\ Hz,\ 1H),\ 6.02\ (bs,\ 1H),\ 6.79\ (br,\ 1H),\ 6.88\ (br,\ 1H),\ 7.28\ (dd,\ J=2.0,\ 8.3\ Hz,\ 1H),\ 7.34\ (br,\ 1H),\ 7.39\ (d,\ J=2.0,\ 1H),\ 7.57\ (d,\ J=8.5,\ 1H); \text{C NMR (50 MHz, CDCl}_3):\ \delta\ 58.4,\ 69.7,\ 120.4,\ 128.0,\ 129.1,\ 129.9,\ 132.3,\ 133.4,\ 137.9; \text{Analysis: } C_{11}H_{10}Cl_2N_2O \]
requires C, 51.38; H, 3.92; N, 10.90; found C, 51.54; H, 3.72; N, 10.75%.

\(1-((S)-2-(4\text{-Chlorobenzyloxy})-2-(2,4\text{-dichlorophenyl})\text{ethyl})-1H\text{-imidazole}\)

{Econazole} (2):

To a stirred mixture of NaH (88 mg, 2.2 mmol) in dry DMF (5 mL) was added 4-chlorobenzyl bromide (0.452 g, 2.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 25 °C followed by addition of amino alcohol 20 (0.514 g, 2 mmol). After completion of reaction (TLC), the reaction mixture was extracted with EtOAc (3 x 50
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mL). The combined organic layer was dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography to afford 2.

**Yield:** 0.557 g (73%); [α]²⁵D +40.29 (c 2, acetone) 96% ee; IR (CHCl₃, cm⁻¹): 758, 819, 1044, 1094, 1216, 1382, 1472, 1506, 1590, 1695, 2953, 3018, 3390; ¹H NMR (200 MHz, CDCl₃): δ 4.03 (dd, J = 7.6, 14.5 Hz, 1H), 4.15-4.24 (m, 2H), 4.40-4.16 (m, 1H), 4.96 (dd, J = 2.9, 7.6 Hz, 1H), 6.90 (bs, 1H), 7.04-7.08 (m, 3H), 7.26-7.32 (m, 4H), 7.44 (d, J = 1.3, 2H); **Analysis:** C₁₉H₁₅Cl₃N₂O requires C, 56.64; H, 3.96; N, 7.34; found C, 56.54; H, 3.72; N, 7.15%.

*1-((S)-2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole (Miconazole)* (3):

To a stirred mixture of NaH (88 mg, 2.2 mmol) in dry DMF (5 mL) was added 2,4-chlorobenzylbromide (0.48 g, 2 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 25 °C followed by addition of amino alcohol 20 (0.514 g, 2 mmol). After completion of reaction (TLC), the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography to afford 2.

**Yield:** 0.649 g (78%); [α]²⁵D +44.16 (c 2, acetone); **HPLC:** 96% ee, Chiracel OD-H, λ = 220 nm, diethylamine/2-propanol/hexane (0.1:20:80), 1 mL/min, retention time: (S)-enantiomer 11.51 min, (R)-enantiomer 14.45 min; IR (CHCl₃, cm⁻¹): 758, 819, 1044, 1094, 1216, 1382, 1472, 1506, 1590, 1695, 2953, 3018, 3390; ¹H NMR (200 MHz, CDCl₃): δ 4.07 (dd, J = 7.3, 14.5 Hz, 1H), 4.24 (dd, J = 2.8, 14.5 Hz, 1H), 4.42 (dd, J = 12.6, 31.6 Hz, 2H), 5.02 (dd, J = 2.8, 7.3 Hz, 1H), 6.90 (br, 1H), 7.02 (br, 1H), 7.20-7.22 (m, 2H), 7.29-7.34 (m, 3H), 7.44 (d, J = 1.4, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 51.2,
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68.1, 77.5, 119.6, 127.2, 127.8, 128.3, 129.0, 129.1, 129.5, 129.9, 133.1, 133.2, 133.6, 134.2, 134.9, 137.7; Analysis: C₁₈H₁₄Cl₄N₂O requires C, 51.95; H, 3.39; N, 6.73; found C, 52.08; H, 3.54; N, 6.97%.

1-(2, 4-Difluorophenyl)-2-(1H-1, 2, 4-triazol-1-yl)ethanone (25):

A mixture of 2-chloro-1-(2, 4-difluorophenyl)ethanone (24) (2.23 g, 10 mmol), 1,2,4-triazole (1.726 g, 25 mmol), and anhydrous K₂CO₃ (2.07 g, 15 mmol) in dry CH₃CN (20 mL) was refluxed under nitrogen atmosphere for 12 h (reaction monitored by TLC). The reaction mixture was then cooled to 25 °C, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to get amino ketone 25 in 96% yield.

Yield: 1.96 g (88%); mp: 110 °C; IR (CHCl₃, cm⁻¹): 538, 678, 827, 881, 970, 1104, 1147, 1278, 1437, 1515, 1613, 1702, 2967, 3071, 3134; ¹H NMR (200 MHz, CDCl₃): δ 5.60 (d, J = 3.7 Hz, 2H), 6.94-7.10 (m, 2H), 8.00-8.11 (m, 2H), 8.22 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 58.1, 104.6, 112.8, 118.7, 132.7, 144.7, 151.5, 160.3, 163.8, 165.4, 169.1, 187.5; Analysis: C₁₀H₇F₂N₃O requires C, 53.82; H, 3.16; N, 18.83; found C, 53.59; H, 3.32; N, 18.71%.

1-(Bromomethyl)-1H-1, 2, 4-triazole (35):

A mixture of 1,2,4-triazole (0.235 g, 3.4 mmol), paraformaldehyde (0.510 g, 17 mmol), 33 wt% HBr/acetic acid (4 mL) was kept at 70-80 °C for 3 h, cooled and then poured over ice. The aqueous solution was immediately extracted with CH₂Cl₂ (2 x 25 mL), and the organic extracts were washed with 10% NaHCO₃ solution, brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column
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chromatography using pet. ether: EtOAc (9:1) as eluent to give bromomethyl derivative 35.

**Yield:** 0.519 g (82%); IR (CHCl₃, cm⁻¹): 634, 679, 883, 979, 1064, 1157, 1281, 1473, 1518, 1582, 1632; **¹H NMR** (200 MHz, DMSO-d₆): δ 5.46 (s, 2H), 7.98 (s, 1H), 8.58 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 71.4, 144.3, 151.8; **Analysis:** C₃H₄BrN₃ requires C, 22.24; H, 2.49; N, 25.94; found C, 22.45; H, 2.64; N, 26.11%.

2-(2,4-Difluorophenyl)-1-di(1H-1,2,4-triazol-1-yl)propan-2-ol {Fluconazole} (5):

To a stirred mixture of magnesium (1.2 mmol, 28 mg) in THF (10 mL) was added 1-(bromomethyl)-1H-1,2,4-triazole (186 mg, 1 mmol) at 0 °C and was refluxed for 1 h. A solution of ketone 25 (1 mmol, 223 mg) in 10 mL was added dropwise to the above prepared Grignard reagent at 25 °C. The reaction mixture was refluxed for 2 h, cooled to 25 °C, quenched with 2 M HCl (20 mL) and extracted with ether. The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether: EtOAc (7:3) as eluent to give fluconazole.

**Yield:** 0.260 g (85%); IR (KBr, cm⁻¹): 571, 654, 834, 853, 967, 1140, 1276, 1421, 1505, 1516, 1619, 1726, 3107, 3116; **¹H NMR** (200 MHz, CDCl₃): δ 1.99 (brs, 1H), 4.57 (d, J = 14.3 Hz, 2H), 4.76 (d, J = 14.3 Hz, 2H), 6.75-6.86 (m, 2H), 7.37-7.49 (m, 1H), 7.85 (s, 2H), 8.07 (s, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 53.4, 72.3, 102.3, 109.4, 121.5, 128.2, 143.4, 149.2, 155.1, 158.4, 160.0, 163.3; **Analysis:** C₁₂H₁₂F₂N₆O requires C, 50.98; H, 3.95; N, 27.44; found C, 50.83; H, 4.11; N, 27.59%.

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**2.7 References**


