$InCl_3$ Catalyzed Regioselective Opening of Epoxide with Indole; Enantioselective Approach towards the Synthesis of Sattazolin

Thesis submitted in partial fulfillment of the requirements

For the award of the degree of

Masters of Science

In

Chemistry

Submitted By:

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Under the guidance of

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to the

School of Chemistry and Biochemistry

Thapar University

Patiala-147004 (Punjab)

INDIA

July 2015

Certificate

This is to certify that the project entitled "$InCl_3$ Catalyzed Regioselective Opening of Epoxide with Indole; Enantioselective Approach towards the Synthesis of Sattazolin" being submitted by Ms. Anamika Garg in the partial fulfillment of requirement for the award of the degree of Masters of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonified work carried under the supervision of Dr. Satyendra Kumar Pandey and no part of this project has been submitted for award of any other degree by me.

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Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled "$InCl_3$ Catalyzed Regioselective Opening of Epoxide with Indole; Enantioselective Approach towards the Synthesis of Sattazolin" in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of January to July 2015, under the supervision of Dr. Satyendra Kumar Pandey. My thesis has not previously formed the basis for award of any degree, or other similar title or recognition.

Patiala **Anamika Garg**

Date: 15-07-2015

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

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To make a project successful, there are many helping hands. I would like to express my heartiest appreciation to all those who support me and encourage me to complete my project.

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Anamika Garg

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$InCl_3$ Catalyzed Regioselective Opening of Epoxide with Indole; Enantioselective Approach towards the Synthesis of Sattazolin

1. Introduction:

Natural product chemistry has experienced explosive and diversified growth, making natural products the subject of much interest and promise in the present day research directed towards drug design and discovery. Recently, there has been a renewed interest in natural products research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as immune-suppression, anti-infective, and metabolic diseases.

Natural products have provided considerable value to the pharmaceutical industry over the past half century. Approximately 2,00,000 natural compounds derived from natural sources such as plants, animals or microorganisms are currently known, this figure is with small variety regards to the widen of natural resources; only about 5–15% of nearly 2,50,000 higher plants and less than 1% of the microbial world have been explored so far chemically, the vast majority of these sources remains untapped.[1-3] The World Health Organization (WHO) estimates that approximately 80% of the world's population relies mainly on traditional medicine, predominantly originated from plants, for their primary health care.[4-5]

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to varied applications in drug and pharmaceutical industries. A large number of enantiomerically pure compounds have been obtained from nature, but again a few of them is either not easily isolated or not available in useful amounts. However, an organic chemist can provide multi-gram biologically active compounds. The ultimate goal of an organic chemist is, how to assemble a given target molecule from readily available starting materials and reagents in highly efficient way. It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes.

In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to

their economical use of asymmetric inducing agents.[6] Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Despite the considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched terminal epoxides, arguably the most valuable class of epoxides for organic synthesis.[7] Notably, this reaction exhibits high levels of enantioselectivity, this reaction also proceeds under mild conditions with good chemical yield and with high regio- and chemoselectivity.

3-Substituted indoles are potential intermediates for many alkaloids and pharmacologically important substances. Sattazolin **1**,[8] indolactam V **2**,[9] epiindolactam **3**,[10] tryptostatins A **4**[11] and Claviciptic acid **5**,[12] are few examples of natural products containing 3-substituted indoles (Figure1). Accordingly the synthetic elaboration of the indole side chain at the 3-position has been employed as a key step in the synthesis of related alkaloids. Various synthetic approaches to 3-substituted indoles are documented in the literature, among which, the methods *via*3-(dimethylaminomethyl)indole and 3-bromomethyl indole are the most important for introducing and extending functionalized carbon chains at C-3. However, both of these methods are limited to the preparation of compounds in which an unsubstituted methylene group links the indole ring and the nucleophile.

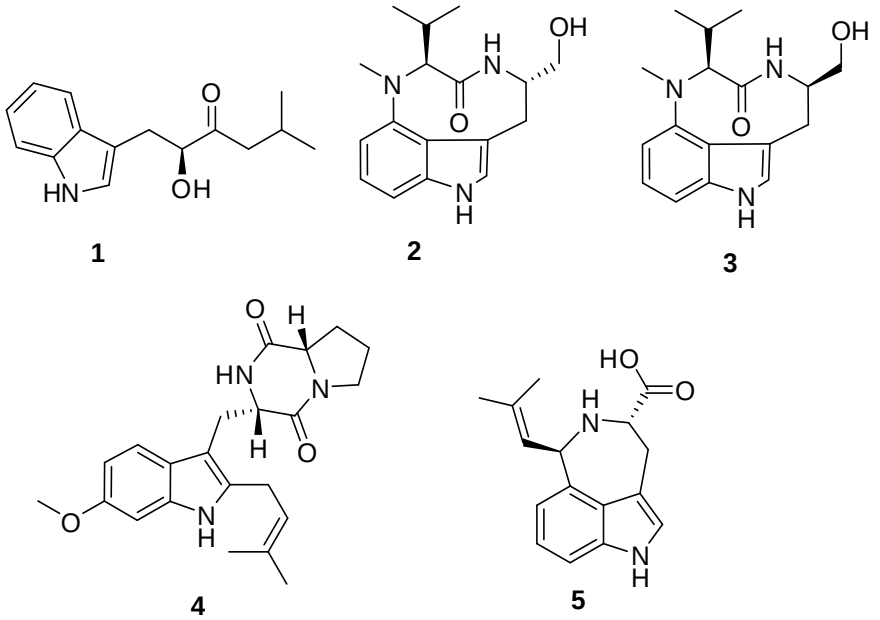


Figure 1. Structure of some bioactive natural products containing 3-substituted indoles.

Epoxides are well known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regeoselective ring opening reaction contributes largely to their synthetic value. The epoxide ring opening with certain nucleophiles is generally carried out with acid or base catalysis to produce ring opened products. In recent years, indium reagents have emerged as mild and tolerantlewis acids imparting high regio- and chemoselectivityin various chemical transformation. Since 3-position of indole is the prefferedsite for electrophile substitution reactions, 3-alkyl indole derivatives were obtained exclusively in all reactions.

Sattazolin **1** is produced by the soil bacteria *Bacillus sp*. along with other structurally related acyloinssattabacin **6** and 4-hydroxysattabacin **7** (Figure 2). Sattazolin **1** is an indole acyloin natural product reported to exhibit potent antiviral activity, with an ID_{50} of 1.5 μg/mL against herpes simplex virus type 1 (HSV1) and type 2 (HSV2).[13] New treatments for HSV infections are critical considering that much of the world population is infected with some member of the human herpesvirus family.[14] In particular, HSV infections can be life threatening for immune compromised patients, pregnant women, and newborns.[14] Acyclovir and related nucleoside analogs are currently prescribed for HSV infections,[15-17] but nucleoside-resistant HSV infections have become more common.[18] Herein, we wish to develop a new enatioselectivesynthetic strategy for sattazolin **1** employing Jacobsen hydrolytic kinetic resolution of terminal epoxide followed by $InCl_3$ catalyzed regioselective opening with indole as key steps.

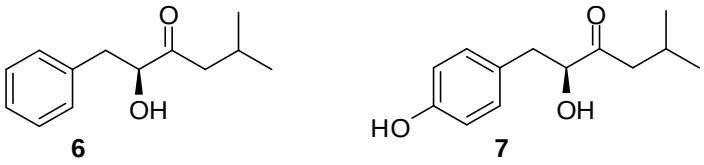
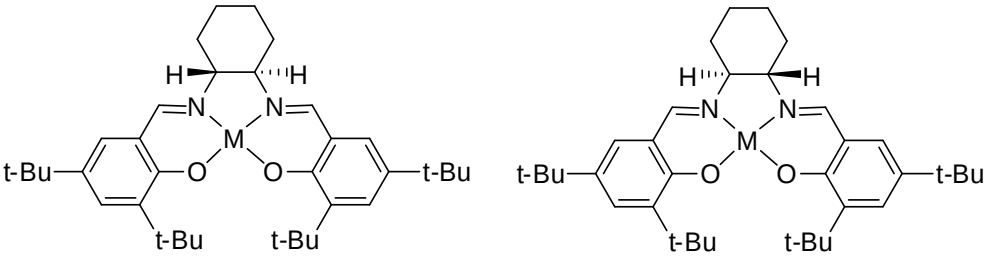


Figure 2. Structure of some related acyloins.

1.1. Hydrolytic Kinetic Resolution (HKR):

The Sharpless epoxidation reaction has the most profound impact for asymmetric catalytic reaction, providing general access to highly enantio-enriched epoxy alcohols.[19] The Sharpless asymmetric epoxidation is limited for only allylic alcohol systems. Despite the considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched terminal epoxides, arguably the most valuable class of epoxides for organic synthesis.[7]

Recently Eric N. Jacobsen discovered the (salen) Co (III) complex **8a** & **8b** (Figure3) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 1).[20-23] Since its discovery in the year 1997, HKR has got tremendous application for the synthesis of variety of compounds of biological interest.[24-31] Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes.

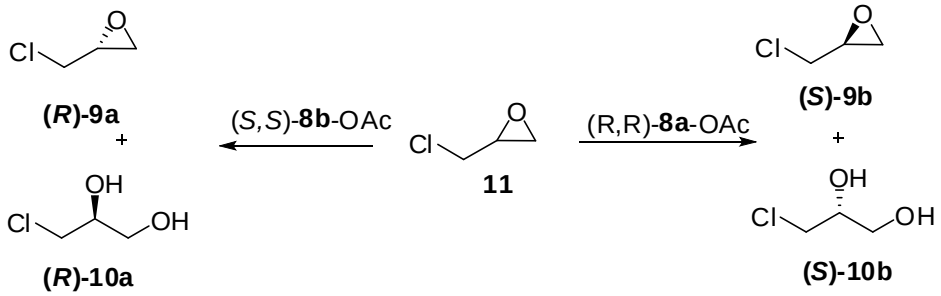


M = Co: (*R*,*R*)-**8a**
M = Co-O Ac: (*R*,*R*)-**8a**-O Ac

M = Co: (*S*,*S*)-**8b**
M = Co-O Ac: (*S*,*S*)-**8b**-O Ac

Figure 3. Structure of Jacobsen HKR catalysts **8a** & **8b.**

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantioenriched form. The commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks. Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.[32]

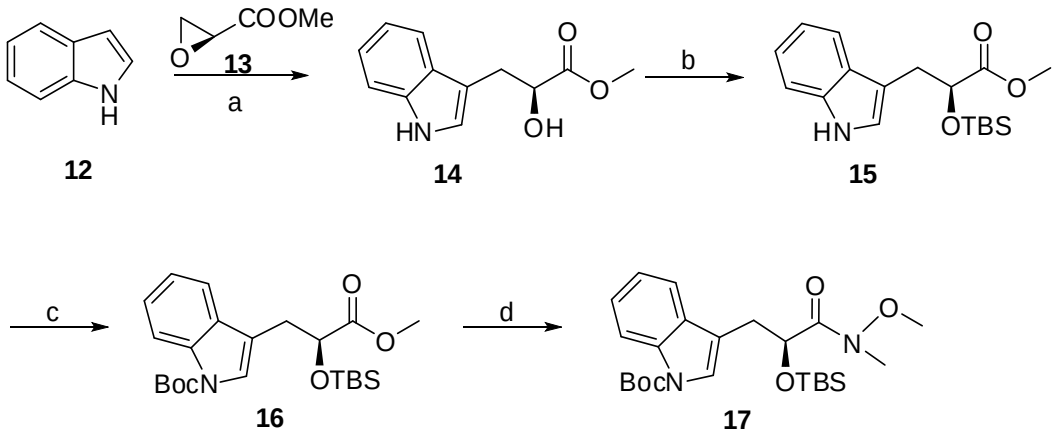


Scheme 1. Hydrolytic kinetic resolution reaction.

2. Review of literature:

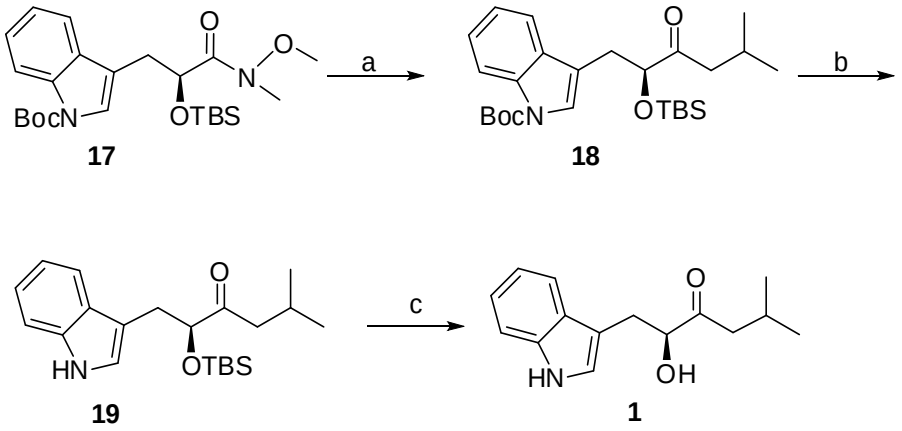
Snyder, K. M. *et. al*. (2013)[33]

Snyder, K. M. and co-workers reported first to synthesize sattazolin **1**. In scheme 2, the synthesis of sattazolin **1** has been started from (*S*)-methyl glycidate **13** which on treatment with excess indole **12** in the presence of 10 mol % $Yb(OTf)_3$ afforded 3-substituted indolehydroxy ester **14**.[34] Further treatment of hydroxyl ester **14** with TBS-Cl and imidazole led to a protection of the hydroxyl group as the silyl ether which gave TBS protected indole **15**. Then the indole nitrogen was protected as the corresponding *tert*-butyl carbamate. Then the treatment of this doubly protected ester with the anion of *N*,*O*-dimethylhydroxylamine provided the Weinreb amide **17** as a white crystalline solid.[34]



Scheme 2: *Reagents and conditions*: (a) $Yb(OTf)_3$, DCE, 80 ^oC, 99%; (b) TBSCl, Imidazole, DMF, 0 ^oC to rt, 89%; (c) $(Boc)_2O$, DMAP, CH_3CN, 99%; (d) HNMe(OMe).HCl, *n*-BuLi, THF, -78 ^oC, 88%.

Then addition of isobutyllithium and deprotection was required to complete sattazolin **1** Scheme 3.[35] Thus, the treatment of amide **17** with a slight excess of isobutyllithium led to the corresponding ketone **18**, a protected version of the natural product.To avoid the unwanted α-ketol rearrangement, the Boc-group was removed first by gently heating **18** in the presence of silica gel under vacuum. Finally, treatment of the silyl ether **19** with excess TBAF smoothly produced sattazolin **1** as a colorless solid.



Scheme 3: *Reagents and conditions*: (a) Isobutyllithium, THF, -78 ^{o}C, 82%; (b) silica gel, 80 ^{o}C, 0.1 mm Hg, 83%; (c) TBAF, THF, 86%.

3. Present work:

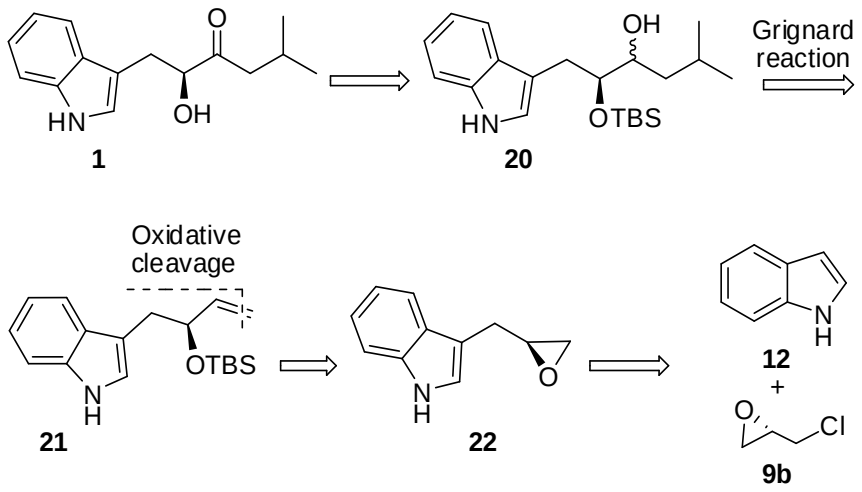
3.1. Objective:

To the best of our knowledge so far only one method for the synthesis of sattazolin **1** using chiral starting material has been known in the literature. As part of our continuing research program aimed at developing enantioselective synthesis bioactive natural products, we became interested in developing an efficient synthetic approach for the total synthesis of sattazolin **1** using achiral starting material. Herein, we wish to report a new synthetic approach for sattazolin **1** using $InCl_3$ catalyzed regioselective opening of epoxide with indole as a key step.

3.2. Retrosynthetic Approach:

Our retrosynthetic strategy for the enantioselective synthesis of sattazolin **1** is outlined in Scheme 4. We envisioned that the TBS protected indole **20** from which target compound **1** could be synthesized *via*oxidation of alcohol followed by TBS deprotection. The TBS protected alcohol derivative **20** could be obtained from TBS protected allyl alcohol substituted indole **21** by oxidative cleavage of terminal double bond followed by Grignardreaction. The protected allyl alcohol substituted indole derivative **21** could be easily obtained from terminal epoxide substituted indole **22** through opening with dimethylsulfoniummethylide with subsequent TBS protection of allyl alcohol. Finally, terminal epoxide substituted indole **22** could be obtained by

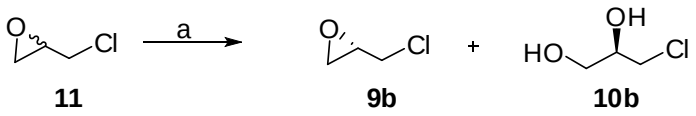
regioselective opening of chiral epichlorohydrin **9b** in the presence of $InCl_3$ with indole **12** followed by base catalysed oxirane formation.



Scheme 4: Retrosynthesis of Sattazolin **1**.

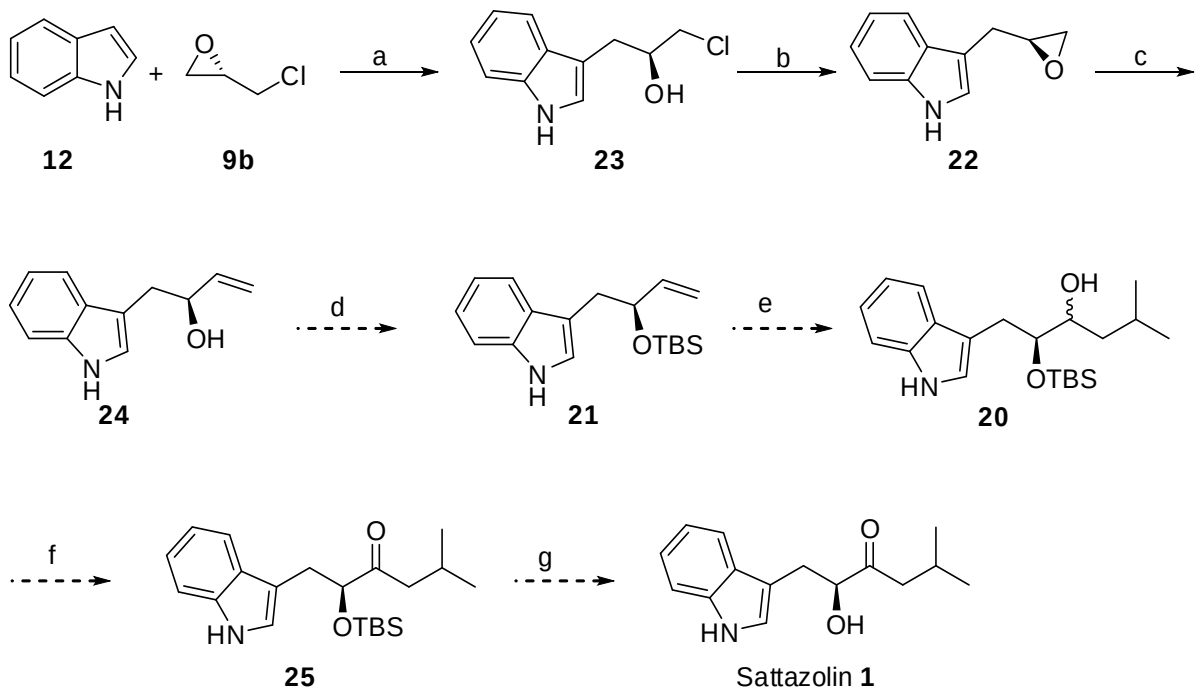
3.3. Results and Discussions:

The synthesis of sattazolin **1** started from the commercially availableepichlorohydrin **11** as shown in Scheme 5. Epichlorohydrin **11** was subjected to Jacobsen's HKR using (*R,R*)-Salen-Co-(OAc) **8a** catalyst to give (*S*)-epichlorohydrin **9b** as a single isomer $[\alpha]_D^{25}$ +30.8(*c* 1, MeOH); {lit.[36] $[\alpha]_D^{25}$+28.1(*c* 2.47, MeOH)}, which was easily isolated from the more polar diol **10b** by distillation.



Scheme 5. *Reagents and conditions*: (a) (*R,R*)-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 14 h, (46% for **9b**, 45% for **10b**).

With enantiomerically pure epichlorohydrin **9b** in hand, we then subjected it to $InCl_3$ catalyzed regioselective ring-opening with indole **12** followed by treatment with base to give epoxide **22**.[37] Subsequent treatment of resulting epoxide **22** with trimethylsulfoniumiodide affords one-carbon homologated allylic alcohols **24** in excellent yield.[38]



Scheme 5: *Reagents and conditions*: (a) $InCl_3$, DCM, rt, 12 h, 89%; (b) KOH, Et_2O, rt, 6 h, 90%; (c) Trimethylsulfonium iodide, THF, *n*-BuLi, 0 °C to rt, 4 h, 85%. (d) TBSCl, Imidazole, DCM (e) OsO_4, $NaIO_4$, 2,6-Lutidine, dioxane: water (1:1) (f) Isobutyl magnesiumbromide, dry THF (g) i) Swern oxidation ii) TBAF, THF.

The ^{1}H NMR spectrum of (*S*)-epichlorohydrin **9b** showedmethylene protons in oxiranering at 2.69 (dd, *J* = 2.76, 5.04 Hz, 1H), 2.90 (t, *J* = 4.60 Hz, 1H), methine proton at 3.23-3.26 (m, 1H), and methylene protons adjacent to chlorine atom appeared at 3.55 (dd, *J* = 5.96, 11.92 Hz, 1H), 3.62 (dd, *J* = 4.60, 11.92 Hz, 1H) ppm. The ^{13}C NMR spectrum of (*S*)-epichlorohydrin **9b** showed methylene carbon in oxirane ring at 46.7, chiral carbon at 51.1, and carbon adjacent to chlorine atom appeared at 44.9 ppm. The ^{1}H NMR spectrum of (*S*)-1-chloro-3-(1*H*-indol-3-yl)propan-2-ol **23** showed amine proton at 8.11 (bs, 1H), aromatic protons of indole ring at 7.63 (d, *J* = 8.7, 1H), 7.38 (d, *J* = 9.16, 1H) and 7.24-7.11 (m, 3H), methine proton of chiral carbon at 4.19-4.11 (m, 1H), methylene protons attached to chlorine at 3.66-3.62 (m, 1H) and 3.58-3.53 (m, 1H), methylene protons attached to indole ring at 3.08-3.06 (m, 2H), hydroxyl proton at 2.27 (bs, 1H) ppm. The^{13}C NMR spectrum of (*S*)-1-chloro-3-(1*H*-indol-3-yl)propan-2-ol **23** showed aromatic carbons at 136.1, 127.2, 123.1, 122.1, 119.4, 118.6, 111.3, 110.4, carbon attached to

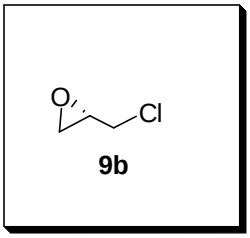
hydroxyl at 71.1, carbon attached to chlorine at 49.1, carbon attached to indole ring at 29.9 ppm. The IR strechings of (*S*)-1-chloro-3-(1*H*-indol-3-yl)propan-2-ol **23** are: O-H stretching at 3440, N-H stretching at 2981, C-O stretching of alcohol at 1244, C-Cl stretching at 742 cm^{-1}. The ^{1}H NMR spectrum of (*S*)-3-(oxiran-2-ylmethyl)-1*H*-indole **22** amine proton at 8.07 (bs, 1H), aromatic protons of indole ring at 7.63 (d, *J* = 7.8, 1H), 7.36 (d, *J* = 8.24, 1H), 7.23-7.09 (m, 3H), methine proton of oxirane ring at 3.27-3.22 (m, 1H), methylene protons attached to indole ring at 3.11-3.05 (m, 1H) and 3.01-2.96 (m, 1H), methylene protons of oxirane ring at 2.82-2.80 (m, 1H) and 2.62-2.60 (m, 1H) ppm. The ^{13}C NMR spectrum of (*S*)-3-(oxiran-2-ylmethyl)-1*H*-indole **22** showed aromatic carbons at 136.1, 127.5, 122.3, 122.1, 119.4, 118.8, 111.3, 111.2, methine carbon of oxirane ring at 52.3, methylene carbon of oxirane ring at 47.3, methylene carbon attached to indole ring at 28.4 ppm. The IR strechings of (*S*)-3-(oxiran-2-ylmethyl)-1*H*-indole **22** : C-O stretching of epoxide at 1455, O-H stretching at 3410, N-H stretching at 3003 cm^{-1}. The ^{1}H NMR spectrum of (*S*)-1-(1*H*-indol-3-yl)but-3-en-2-ol **24** showed amine proton at 8.09 (bs, 1H), aromatic protons of indole ring at 7.64 (d, *J* = 7.32, 1H), 7.38 (d, *J* = 7.8, 1H), 7.23-7.09 (m, 3H), proton on the inner carbon of the terminal double bond at 6.04-5.96 (m, 1H), protons on the terminal carbon of the double bond at 5.39-5.28 (m, 1H) and 5.17-5.13 (m, 1H), methine attached to hydroxyl at 4.47-4.42 (m, 1H), methylene protons attached to indole ring at 3.11-3.06 (m, 1H) and 2.95-2.89 (m, 1H), hydroxyl proton at 1.82 (bs, 1H) ppm. The IR strechings of (*S*)-1-(1*H*-indol-3-yl)but-3-en-2-ol **24** are: O-H stretching at 3407, N-H stretching at 2913, terminal C=C stretching at 1720 cm^{-1}.

4. Conclusions:

In conclusion, an enantioselective synthetic approach towards total synthesis of sattazolin**1**has been attempted employing Jacobsen's HKR and $InCl_3$ catalyzed alkylation of indoleas the key steps. The merit of this synthesis is high yielding reaction steps with high enantioselectivity. The synthetic strategy described has significant potential for further extension to optimize the different reaction conditions to achieve the target compound.The work is under progress in further direction to achieve the target compound.

5. Experimental Section:

5.1. (*S*)-2-(Chloromethyl)oxirane, 9b



9b

A solution of the catalyst (*R*,*R*)-Salen-Co-(OAc) (484 mg, 800 μmol, 0.005 equiv) in 10 mL DCM was treated with 500 μL AcOH. The crude catalyst residue obtained after concentration was treated with (±)-epichlorohydrin (12.52 mL, 14.80 g, 160 mmol) and 1.6 mL THF. The solution was cooled to 0 ^{0}C and treated with H_2O (1600 μL, 88 mmol, 1.10 equiv) and the reaction was maintained at 0 –4 ^{o}C for 16 h. (*S*)-Epichlorohydrin **9b** (5.96 g, 64.4 mmol, 43%) was isolated by vacuum transfer (25 ^{o}C & 0.25 torr) from reaction mixture into a cooled receiving flask. The recovered epoxide was determined to be > 99% ee by chiral GC analysis.

Yield: 7.40 g, 45%.

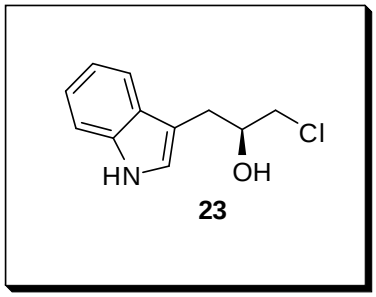
Mol. Formula: C_3H_5OCl.

$[\alpha]_D^{25}$ = +30.8 (*c* 1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, *J* = 2.76, 5.04 Hz, 1H), 2.90 (t, *J* = 4.60 Hz, 1H), 3.23-3.26 (m, 1H), 3.55 (dd, *J* = 5.96, 11.92 Hz, 1H), 3.62 (dd, *J* = 4.60, 11.92 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.9, 46.7, 51.1 ppm.

5.2. (*S*)-1-Chloro-3-(1*H*-indol-3-yl)propan-2-ol, 23



23

A mixture of epichlorohydrin (3.15 g, 34.14 mmol), indole (2 g, 17.07 mmol) and indium trichloride (377 mg, 1.70 mmol) in dichloromethane (40 mL) was stirred at ambient temperature

for an appropriate time. After completion of the reaction, as indicated by the TLC, the reaction mixture was diluted with water (2 x 10mL) and extracted with dichloromethane (2 x 15mL). The combined organic layers were dried over anhydrous sodium sulphate, concentrated *in vacuo* and purified by column chromatography on silica gel (ethyl acetate/hexane 2:8 v/v) to afford pure product **23**.

Yield: 3.17g, 89%.

Chemical Formula: $C_{11}H_{12}ClNO$.

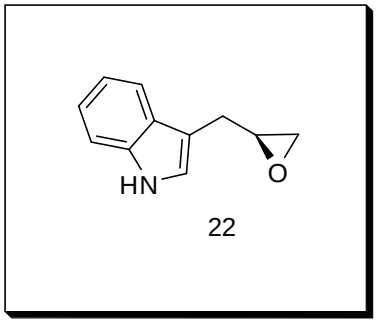
$[\alpha]_D^{25}$ = +21.2 (*c* 1.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (bs, 1H), 7.63 (d, *J* = 8.7, 1H), 7.38 (d, *J* = 9.16, 1H), 7.24-7.11 (m, 3H), 4.19-4.11 (m, 1H), 3.66-3.62 (m, 1H), 3.58-3.53 (m, 1H), 3.08-3.06 (m, 2H), 2.27 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 127.2, 123.1, 122.1, 119.4, 118.6, 111.3, 110.4, 71.1, 49.1, 29.9 ppm.

IR ($CHCl_3$, cm^{-1}): ν 3440, 2981, 1711, 1244, 1042, 742.

5.3. (*S*)-3-(oxiran-2-ylmethyl)-1*H*-indole, 22



22

To a solution of **23** (3.17 g, 15.16 mmol) in Et_2O (25 mL) was added finely powdered KOH (2.54 g, 45.50 mmol). The mixture was stirred vigorously for 6 h and poured into 20mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 50mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and silica gel

column chromatographic purification (EtOAc / hexane 1:49 v/v) of the crude product afforded **22** as a colorless liquid.

Yield: 2.34g, 90%.

Chemical Formula: $C_{11}H_{11}NO$.

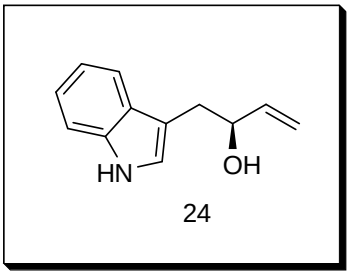
$[\alpha]_D^{25}$ = +19.9 (*c* 1.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (bs, 1H), 7.63 (d, *J* = 7.8, 1H), 7.36 (d, *J* = 8.24, 1H), 7.23-7.09 (m, 3H), 3.27-3.22 (m, 1H), 3.11-3.05 (m, 1H), 3.01-2.96 (m, 1H), 2.82-2.80 (m, 1H), 2.62-2.60 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 127.5, 122.3, 122.1, 119.4, 118.8, 111.3, 111.2, 52.3, 47.3, 28.4 ppm.

IR ($CHCl_3$, cm^{-1}): *v* 3410, 3003, 1455, 1092, 739.

5.4. (*S*)-1-(1*H*-indol-3-yl)but-3-en-2-ol, 24



24

To a −10 °C suspension of trimethylsulfonium iodide (11.07g, 54.24 mmol) in THF (15 mL) was added *n*-BuLi (20.28 mL, 50.17 mmol, 2.5 M in hexane). After 30 min, epoxide (2.34 g, 13.56 mmol) in THF (3 mL) was introduced and the reaction slowly allowed to warm to 0 °C over 1 h, the mixture was then stirred at ambient temperature for 2 h. The reaction was quenched with water and extracted with diethyl ether or ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using (EtOAc / hexane 1:4 v/v) to give the desired allylic alcohol **24**.

Yield: 2.53 g, 85%.

Chemical Formula: $C_{12}H_{13}NO$.

$[\alpha]_D^{25}$ = +10.0 (*c* 1.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (bs, 1H), 7.64 (d, *J* = 7.32, 1H), 7.38 (d, *J* = 7.8, 1H), 7.23-7.09 (m, 3H), 6.04-5.96 (m, 1H), 5.39-5.28 (m, 1H), 5.17-5.13 (m, 1H), 4.47-4.42 (m, 1H), 3.11-3.06 (m, 1H), 2.95-2.89 (m, 1H), 1.82 (bs, 1H) ppm.

IR ($CHCl_3$, cm^{-1}): *v* 3407, 2913, 2360, 1720, 1248, 1042, 740.

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