CHAPTER 3

ENANTIOSELECTIVE SYNTHESSES OF (-)-α-CONHYDRINE AND (-)-ACATERIN VIA ASYMMETRIC DIHYDROXYLATION
3.1 SECTION A: ENANTIOSELECTIVE SYNTHESIS OF
(-)-α-CONHYDRINE

3.1.1 Introduction

Alkaloid mimics with a nitrogen in the ring, including naturally occurring and synthetic monocyclic and bicyclic derivatives, constitute a realm of important functional molecules which have drawn considerable attention by virtue of their potent and varied biological activities. A search of the chemical and patent literatures reveal thousands of references concerning this simple ring system, both in clinical and pre-clinical states. Due to the extension of life expectancy in industrial countries, neurological disorders, like Alzheimer’s or Parkinson’s disease pose an important public health problem. Thus, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future.

Biologically active alkaloids containing a 2-(1-hydroxyalkyl) piperidine unit 1 are abundant in nature. Conhydrine 2 and 3, is one such compound which falls into hydroxyalkyl piperidine category (Fig. 1), conhydrine was isolated from seeds and leaves of the poisonous plant Conium maculatum L in 1856 and elucidation of its structure was made in 1933, whose extracts were used in the ancient Greece for the execution of criminals. The indolizidine alkaloids castanospermine 4, slaframine 5 and swainsonine 6 also fall into this category and have attracted considerable attention from the synthetic community due to their antiviral and antitumor activities. (Fig. 1) It is believed that Socrates was a stone mason by trade and was also a hoplite in the Athenian military and was accused of impiety and of neglect of the Gods whom the city worships and the practice of religious novelties
and of the corruption of young. In the trial which followed Socrates was condemned to
death. At that time it was considered a humane method of execution for the condemned
person to drink a potent solution from the hemlock plant. Socrates was thus expected to
take his own life in this way, which being a man of honour, he did.

3.1.2 Review of Literature

Many synthetic approaches have been documented in the literature for (+)-α-conhydrine,\(^5\)
and (+)-β-conhydrine based on either resolution method or auxiliary supported procedure,\(^6\)
or chiral pool approaches,\(^7\) but less attention has been paid to (-)-α-conhydrine 2. The first
asymmetric synthesis of (-)-α-conhydrine 2 and its structural assignment has been reported by Enders et al.\(^8\) using his RAMP/SAMP hydrazone methodology. Some of the interesting syntheses of α and β-conhydrine are described below.

**Enders et al. (2002)\(^8\)**

The first asymmetric synthesis of the conium alkaloid (-)-α-conhydrine 2 has been achieved by Enders et al. based on his RAMP/SAMP methodology.\(^8\) Towards this end, iodo acetal 11 was first prepared from 4-bromo-butyric acid ester 7 by DIBAL-H reduction to the aldehyde 8 followed by acetalization to 9 and subsequent Finkelstein reaction with lithium iodide led to the desired iodide 10. The required acetal containing organolithium reagent was prepared by halogen-metal exchange reaction from the corresponding iodoacetal 11 following the procedure of Negishi and Bailey\(^9\) (Scheme 1). The enantiopure TBS-protected glycol aldehyde SAMP hydrazone 12 which was prepared from (Z)-butenediol was alkylated at low temperature to give 13. Diastereoselective 1,2 addition of 11 to this compound gave 12. Removal of the remaining part of the auxiliary was facilitated by a reductive nitrogen-nitrogen bond cleavage followed by reduction with NaBH\(_4\) to give (-)-α-conhydrine 2 (Scheme 2).

![Scheme 1](image)
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 1: Reaction conditions: (a) DIBAL-H, Et_2O, -78 °C, 99%; (b) 1,2-ethane diol, toluene, p-TSA, reflux, 90%; (c) LiI, THF, reflux, 68%; (d) t-BuLi, Et_2O, -78 °C-0 °C.

![Scheme 1 Diagram]

Scheme 2: Reaction conditions: (a) LDA, THF, -78 °C, then EtI, -78 °C; (b) compound 11, THF, then, NaHCO_3 (aq); (c) BH_3·THF, THF, reflux, then 3M HCl (aq), CH_2Cl_2, rt; (d) NaBH_4, EtOH, rt.

Comins et al. (2000)  
Comins and co-workers have developed an iodocyclocarbamation procedure for the stereoselective preparation of (+)-α-conhydrine ent-2. Cis-propenyl magnesium bromide was added to a mixture of 4-methoxy-3-(triisopropyl)pyridine and chloroformate of (-)-TCC to give 16. One-pot removal of the chiral auxiliary and TIPS groups gave enantiopure dihydropyridone 17. Treatment of 17 with benzyl chloroformate provided the intermediate 18. Conjugate addition of 18 with L-selectride followed by addition of N-(5-chloro-2-pyridyl)triflimide afforded vinyl triflate 19 which was subjected to the
iodocyclocarbamation reaction to give 20. Dehydrohalogenation of 20 was carried out to afford an enol carbamate 21. Catalytic hydrogenation of 21 from the convex face gave the desired oxazolidinone 22 which was hydrolyzed to afford ent-2.

**Scheme 3**: Reaction conditions: (a) (-)-TCCOCOCl, C\textsubscript{3}H\textsubscript{5}Cl, H\textsubscript{3}O\textsuperscript{+}, 78%; (b) (i) NaOMe, MeOH, reflux, (ii) 10% HCl, 80%; (c) n-BuLi, BnOCOCl, 85%; (d) L-selectride, N-(5-chloro-2-pyridyl)triflimide, 80%; (e) Li\textsubscript{2}CO\textsubscript{3}, I\textsubscript{2}, CH\textsubscript{3}CN, 70%; (f) BDU, THF, rt, 2 h, 99%; (g) H\textsubscript{2}, PtO\textsubscript{2}, Li\textsubscript{2}CO\textsubscript{3}, iodine, EtOAc, 78%; (h) KOH, EtOH\textsubscript{2} reflux, 79%.

**Masaki et al. (1989)**

Enantiospecific synthesis of (+)-β-conhydrine 3, was achieved via partial ring opening of 6,8-dioxabicyclo[3.2.1]-octane skeleton 25 prepared from (S,S)-tartaric acid 23. Compound
25 was converted into epoxide 27 through mesylate and subsequently homologated with Gillman's reagent on the terminal position of the epoxide 27 followed by protection of the free alcohol as benzyl ether and oxidation of acetal portion to afford the lactone 29. Methanolysis of 29 followed by the Mitsunobu type reaction of the ester-alcohol using hydrazoic acid gave the azide ester 31. Reduction of azido group and subsequent cyclization of the intermediate amino ester 31 gave lactam 32. Reduction of the lactam 32 with LiAlH₄ afforded O-benzyl conhydrine which was deprotected by hydrogenolysis to give (+)-β-conhydrine 3. (Scheme 4)

Scheme 4: Reaction conditions: Na (10 equiv)/EtOH (10 equiv)/THF/-20 °C/2 h, 78%; (b) PhCH₂OH, BF₃·Et₂O (2eq), rt, 15 h, 74%; (c) K₂CO₃, MeOH, 0 °C, 0.5 h, 92%; (d) (i)
Couty et al. (2001)\textsuperscript{7c}

Couty and group developed a synthetic route based on N-Boc-2-acyloxazolidine chemistry combined with ring closing metathesis for a 2-(1-hydroxyalkyl) side chain which is commonly found in natural alkaloids. Weinreb amide 35 derived from (S)-phenyl 33.
Scheme 5: Reaction conditions: (a) (i) Ethyl oxalate (ii) (Boc)$_2$O (iii) LiOH, 77% overall; (b) Isobutyl chloroformate, NHMe(OMe), HCl, 79%; (c) Ethyl magnesium bromide, Et$_2$O, rt, 75%; (d) NaBH$_4$, EtOH, -78 °C, 72%; (e) NaBH$_4$, EtOH, CeCl$_3$, -78 °C, 54%; (f) Na, EtOH, THF, NH$_3$, 93%; (g) NaH, DMF, C$_3$H$_5$Br, 74%; (h) Grubb’s catalyst, CH$_2$Cl$_2$, reflux, 79%.

Alaninol was stereoselectively reduced. Treatment of isomeric alcohol 37 with NaH led to transcarbamation product 39 which was subjected to $N$-alkylation with corresponding olefin chain followed by ring closing metathesis to give bicyclic oxazolidinone 41 which is a common structural pattern for conhydrine and its analogue.

Husson et al. (1985) 6a

Husson et al. described the enantiospecific synthesis of (+)-β-conhydrine 3 using 2-cyano-6-oxazolo-piperidine 42. Preparation of the anion using LDA and its reaction with propan-1-ol led to the formation of a single product 43. The complete reduction of 43 using NaBH$_4$ was stereospecific giving the amino alcohol 44, which was cleanly debenzylated to (+)-β-conhydrine 3. An alternative route to 3 was the chemospecific decynation of aminonitrile 43. Reaction of 43 with Zn(BH$_4$)$_2$ at -60 °C in THF after complexation of the cyano group with AgBF$_4$ afforded 45. The same product was also obtained using liq Na/NH$_3$. Finally, hydrogenolytic cleavage of the $N$-benzyl and aminoether groups gave (+)-β-conhydrine 3.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 6: Reaction conditions: (a) LDA, THF, -78 °C, 30 min; (b) C₂H₅CHO, THF, -78 °C, 5 min; (c) NaBH₄, EtOH, reflux, 5 h; (d) H₂, Pd/C 5 %; MeOH, 15 h; (e) AgBF₄, THF, rt, 10 min'; (f) Zn(BH₄)₂, THF, -60 °C, 1 h; (g) Na, liq. NH₃, -78 °C, 1 h; (h) H₂, Pd(OH)₂, MeOH, 4 days.

Kumar et al. (2005)⁵️

Very recently, Kumar et al. described a general strategy for all the isomers of conhydrine by diastereoselective alkylation of an amino aldehyde derivative 47 with ethylmagnesium bromide and diethylzinc.
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 7: Reaction conditions: (a) EtMgBr, dry Et₂O, 0 °C, 2 h, 73%; (b) Et₂Zn, toluene, 0 °C, 8 h, 76%.

Scheme 8: Reaction conditions: (a) H₂/Pd(OH)₂, Boc₂O, EtOAc, 12 h, 83%; (b) 2,2-DMP, p-TsOH, CH₂Cl₂, 0 °C-rt, 1 h, 87%; (c) (i) (COCl)₂, DMSO, dry CH₂Cl₂, -78 °C, Et₃N, -60 °C, 1 h (ii) Ph₃P=CHCOOEt, dry THF, rt, 24 h, 96%; (d) LiAlH₄, dry THF, rt, 4 h, 78%; (e) MsCl, Et₂N, -78 °C, 1 h; (f) CF₃COOH, dry DCM, 88%. 
3.1.3 Present work

Objective

The advent of Sharpless asymmetric dihydroxylation (AD) greatly facilitated the synthesis of optically active dihydroxy compounds that serve as important synthons to a vast array of natural products. This section discloses a new approach from chiral dihydroxy compounds to poisonous alkaloid (-)-α-conhydrine 2. We have employed two different synthetic strategies towards the target molecule depending on the olefinic substrates chosen. The key steps are asymmetric dihydroxylation, regioselective opening of cyclic sulfate and Wittig olefination.

The retrosynthetic analysis of (-)-α-conhydrine 2 is shown in Scheme 9. Compound 55 is the ultimate precursor to obtain the target molecule and it can be derived from two different fragments 56 and 58, prepared by two different synthetic strategies. The Boc protected amino alcohol ester 56 could be obtained from regioselective opening of cyclic sulfate 59 which in turn could be obtained from the Sharpless asymmetric dihydroxylation of α, β-unsaturated ester 63 which can be derived from propionaldehyde 64. In the second synthetic route, compound 58 could be derived from azido benzylidene 61 which in turn would be obtained from Sharpless asymmetric dihydroxylation of allylic alcohol 67.

The common fragment, salt 57 could be prepared from bromo propanol which in turn would be obtained from 1,3-propanediol 60.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 9: Retrosynthetic analysis of (-)-α-conhydrine
3.1.4 Results and Discussion

The detailed synthetic strategy involving AD and regiospecific opening of cyclic sulfate by nucleophile as key steps is illustrated in Scheme 10.

Scheme 10. Reaction conditions: (a) Ph₃P=CHCOOMe, benzene, reflux, 2 h, 85%; (b) (DHQ)₂PHAL, OsO₄, CH₃SO₂NH₂, K₂Fe(CN)₆, K₂CO₃, t-BuOH:H₂O (1:1), 24 h, 0 °C, 88%; (c) (i) SOCl₂, Et₃N, 15 min. (ii) RuCl₃/NaIO₄, 1 h, 88%; (d) NaN₃, acetone, 1 h, 20% aq. H₂SO₄, ether, 10 h, 78%; (e) Boc₂O, Pd/C, H₂, EtOAc, 6 h, 98%; (f) DIBAL-H, -78 °C, 1 h.

The synthesis of (-)-α-conhydrine 2 commenced from propionaldehyde 64, a readily available starting material. Compound 64 was treated in benzene under reflux conditions with (methoxycarbonylmethylene)triphenyl phosphorane to give the Wittig product in 85% yield. The IR spectrum of 63 showed C=O stretching at 1648 cm⁻¹ and C=O stretching at 1712 cm⁻¹. ¹H NMR spectrum showed the presence of olefinic peaks at δ 5.74 (d, J = 16
Hz), 6.87-6.98 (m). The methoxy signal appeared at δ 3.64 (s). The dihydroxylation of 63 with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of (DHQ)\textsubscript{2}PHAL as chiral ligand under the Sharpless asymmetric dihydroxylation conditions gave the diol in 88% yield with 95% ee, [α]\textsubscript{D}\textsuperscript{25} : -5.5 (c 1.0, CHCl\textsubscript{3}) [lit.\textsuperscript{13} [α]\textsubscript{D}\textsuperscript{25} : -5.9 (c 0.35, CHCl\textsubscript{3})]. The enantiomeric excess was determined using chiral HPLC. The presence of strong hydroxyl absorption stretching at 3450 cm\textsuperscript{-1} and absence of C=C stretching in the IR spectrum clearly indicated the formation of product 62. \textsuperscript{1}H NMR spectrum showed absence of the olefinic peaks, and presence of broad singlets for hydroxyl protons at δ 2.05. The diol 62 was then treated with thionyl chloride and triethyl amine to give the cyclic sulfite which was further oxidized using NaIO\textsubscript{4} and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate 59 in excellent yield. The IR spectrum of 59 showed the absence of hydroxyl absorption. A downfield shift in the \textsuperscript{1}H NMR spectrum, of –CH\textsubscript{2}OSO\textsubscript{2}– protons to δ 4.89-4.93 as multiplet was observed in comparison to the same protons (δ 3.73-4.14) of diol 62. The essential feature of our synthetic strategy shown in Scheme 10 was based on the presumption that the nucleophilic opening of cyclic sulfate would occur in a regiospecific manner at the α-carbon atom.\textsuperscript{14} Indeed, the cyclic sulfate reacted with NaN\textsubscript{3} with apparent complete selectivity for attack at the C-2, giving azide 68 in 78% yield. The carbonyl group must be responsible for the increased reactivity of the α-position. The IR spectrum of 68 showed hydroxyl absorption at 3378 cm\textsuperscript{-1} and strong azide absorption at 2112 cm\textsuperscript{-1}. Reduction of the azide 68 under hydrogenation conditions in the presence of Boc\textsubscript{2}O gave the Boc protected amino alcohol 56. The absence of azide stretching in the IR spectrum and the presence of 9 protons for Boc group at δ 1.44 as singlet in the \textsuperscript{1}H NMR spectrum showed the formation of 56. The
CHAPTER 3 Enantioselective syntheses of (*-*)-a-conhydrine and
(-*)-acaterin via asymmetric dihydroxylation

Ester group of 56 was reduced to aldehyde 69 using DIBAL-H at -78 °C. The 1H NMR spectrum showed doublet at δ 9.38 for aldehyde.

The other fragment to reach the target molecule (-*)-a-conhydrine has been synthesized as shown in Scheme 11. The synthesis of salt 57 was carried out from commercially available 1,3-propanediol 60. Mono bromination of 1,3-propanediol using 48% aqueous HBr under Dean-Stark apparatus in benzene solvent gave 70 which was treated with triphenyl phosphine in acetonitrile under reflux conditions to give salt 57.

Scheme 11 : Reaction conditions : (a) 48% aq. HBr, benzene, 28 h, 79% ; (b) PPh3, K2CO3, dry acetonitrile, reflux, 7 h, 26%.

As shown in Scheme 12 the coupling between the aldehyde 69 and salt 57 through Wittig olefination using n-BuLi gave the olefin 71 in 40% yield. The IR spectrum of 71 showed the olefin stretching at 1602 cm⁻¹. In the 1H NMR spectrum, olefinic peaks appeared at δ 5.99 and 6.53. The reduction of the double bond in 71 was achieved using Pd/C in ethyl acetate. The IR and 1H NMR spectrum revealed absence of olefinic peaks. The compound 55 was subjected to cyclization using methanesulfonyl chloride and triethyl amine at -78 °C to give the piperidine. Finally, the Boc group was deprotected using trifluoroacetic acid in dichloromethane to furnish the target molecule (-*)-α-conhydrine 2 in 74% yield.
Scheme 10: Reaction conditions: (a) n-BuLi, -78 °C, 40%; (b) Pd/C, H₂, MeOH, 4 h, 95%; (c) (i) MsCl, Et₃N, -78 °C, 1 h; (ii) CF₃COOH, CH₂Cl₂, 74%.

Though we successfully achieved the synthesis of target molecule 2 in high ee, the yield obtained at the Wittig step was not very satisfactory. Therefore, we looked into the alternative synthetic strategy with an aim to synthesize the target molecule in high yield and good enantiomeric excess. An alternative sequence of reactions to arrive at the target molecule is depicted in Scheme 13. In this case the required amino alcohol functionality is arrived through selective 1,3-benzylidene formation. As shown in Scheme 13, the Sharpless asymmetric dihydroxylation of allylic alcohol trans-pent-2-ene-1-ol 67 with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis(9-O-dihydroquinine)phthalazine [(DHQ)₂PHAL] ligand gave (2S,3S)-triol 66 in good yield, [α]D²⁵ : -6.7 (c 1.0, CHCl₃). The IR spectrum of 66 showed hydroxyl absorption at 3400-3200 cm⁻¹ and absence of olefin C=C stretching. In the ¹H NMR spectrum the olefinic proton disappeared and corresponding protons related to stereogenic centres appeared at δ 3.67-3.73 as multiplets. In order to achieve the amino alcohol functionality from triol 66,
we required the transformation of C-2 hydroxyl group to azido with concomitant reversal of stereochemistry. Towards this end, the benzylidene protection of triol 66 was effected with benzaldehyde dimethyl acetal in the presence of catalytic amount of p-TsOH to afford a mixture of 1,3- and 1,2-benzylidene compounds in 9:1 ratio. The desired major 1,3-benzylidene compound 65 was separated by flash silica gel column chromatography and obtained in 74% yield. The $^1$H NMR spectrum of 65 showed acetal proton at $\delta$ 5.58 as
singlet and aromatic protons appeared at δ 7.37-7.58 (m). Compound 65 was then converted into 5-O-mesylate with methanesulfonyl chloride using Et$_3$N and catalytic amount of DMAP. The crude mesylate was treated with sodium azide in DMF to give the azido compound 61 with desired stereochemistry at 5-position. The IR spectrum of compound 61 showed absence of hydroxyl absorption and presence of strong azide absorption at 2122 cm$^{-1}$. The opening of benzylidene compound 61 was achieved using DIBAL-H at -78 °C.$^{15}$ The $^1$H NMR and $^{13}$C NMR spectra showed absence of acetal proton and carbon respectively. Compound 58 was oxidised under PCC conditions to afford the aldehyde which was subsequently treated with salt 57 using n-BuLi as a base to give the olefin 72 as a cis-trans mixture. The IR spectrum of 72 showed olefin absorption at 1616 cm$^{-1}$ and in the $^1$H and $^{13}$C NMR spectra olefin peaks appeared at δ 5.48-5.55 and δ 127.9 and 28.4 respectively. Our next objective was to prepare compound 55 in one step, which was achieved, by reducing double bond and azide under hydrogenation conditions using 10% Pd/C and subsequent protection of free amine with Boc$_2$O. Compound 55 showed similar physical and chemical properties, as obtained by synthetic strategy described in Scheme 12. Subsequent conversion into the target compound 2 was carried out following the same reaction as described in Scheme 12.

### 3.1.5 Conclusion

In conclusion, we have accomplished enantioselective synthesis of (-)-α-conhydrine by two different synthetic strategies employing Sharpless asymmetric dihydroxylation, regioselective opening of a cyclic sulfate and Wittig olefination as the key steps. The merits of this synthesis are high enantioselectivity and various possibilities available for
structural modifications. The other enantiomer can be synthesized by β-dihydroxylation of olefin 64 and 67 and following the reaction sequence as shown above.

3.1.6 Experimental section

General Information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60-80 °C was used. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer model 683 grating infrared spectrometer. \(^{1}H\) (200 MHz) and \(^{13}C\) (50 MHz) NMR spectra were recorded in CDCl\(_3\) solution with residual CHCl\(_3\) as internal standard.

Preparation of Methyl-trans-pent-2-enoate

To a solution of (methoxycarbonylmethylene)triphenylphosphorane (63.46 g, 0.19 mol) in benzene (200 mL) was added propionaldehyde 64 (10 g, 0.172 mol). The reaction mixture was refluxed for 2 h and solvent concentrated to near dryness. Column chromatography on silica gel using EtOAC/pet ether (0.2:9.8) as eluent gave the Wittig product 63 (16.72 g) as a colorless oil.

Yield : 85%

IR (neat, cm\(^{-1}\)) : \(\nu_{\text{max}}\) 1617, 1722

\(^{1}H\) NMR (200 MHz, CDCl\(_3\)) : \(\delta\) 0.98 (t, \(J = 8\) Hz, 3H), 2.08-2.18 (m, 2H), 3.64 (s, 3H), 5.74 (d, \(J = 16\) Hz, 1H), 6.87-6.98 (m, 1H)

\(^{13}C\) NMR (50 MHz, CDCl\(_3\)) : \(\delta\) 9.8, 25.1, 53.8, 122.2, 135.5, 174.2
Preparation of Methyl (2S,3S)-2,3-dihydroxypentanoate

To a mixture of K$_3$Fe(CN)$_6$ (42.80 g, 0.13 mol), K$_2$CO$_3$ (17.96 g, 0.13 mol), (DHQ)$_2$PHAL (341 mg, 1 mol%) in t-BuOH:H$_2$O (1:1) was added osmium tetroxide (1.75 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methane sulfonamide (4.16 g, 43.80 mol). After stirring for 5 min at 0 °C, the olefin 63 (5 g, 43.80 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2.5 g). The stirring was continued for an additional 45 min and then the solution extracted with ethyl acetate (5x100 mL). The combined organic phases were washed with 10% aq. KOH, brine, dried (Na$_2$SO$_4$) and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (4:6) as eluent gave 62 (5.71 g) as a viscous liquid.

Yield : 88%

[α]$^{25}_{D}$ : -5.5 (c 1.0, CHCl$_3$)

IR (neat, cm$^{-1}$) : v$_{max}$ 3562, 1722

$^1$H NMR (200 MHz, CDCl$_3$):  δ 1.0 (t, J = 6 Hz, 3H), 1.57-1.72 (m, 2H), 2.05 (brs, 2H), 3.73-3.78 (m, 1H), 3.83 (s, 3H), 4.14 (d, J = 4 Hz, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$):  δ 9.8, 26.0, 53.3, 72.8, 73.8, 173.4

Analysis : C$_6$H$_{12}$O$_4$ (148.16) requires C, 48.64 ; H, 8.16. Found. C, 48.52 ; H, 8.09.
Preparation of (2S,3S)-5-ethyl-2,2-dioxo-[1,3,2]dioxathiolane-4-carboxylic acid methyl ester

To a solution of diol 62 (2 g, 13.49 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (12 mL) was added Et\textsubscript{3}N (5.46 g, 7.52 mL, 53.99 mmol). The mixture was cooled in an ice bath and thionyl chloride (2.4 g, 1.47 mL, 20.17 mmol) was added dropwise. The reaction mixture was stirred for 20 min. and then quenched by adding water (10 mL). The phases were separated and aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x20 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. Then the solution was cooled with an ice-water bath and diluted with CH\textsubscript{3}CN (32 mL) and CCl\textsubscript{4} (32 mL). RuCl\textsubscript{3}.H\textsubscript{2}O (15 mg, 0.072 mmol) and NaIO\textsubscript{4} (6.16 g, 28.83 mmol) were added followed by water (47 mL). The resulting orange mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether (50 mL), and the two phases were separated. The organic layer was washed with water (40 mL), saturated aq. NaHCO\textsubscript{3} (30 mL), brine and dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet.ether (2:8) as eluent gave 59 (2.5 g) as a colorless liquid.

Yield: 88%

[α]\textsuperscript{25}\textsubscript{D} : -15.6 (c 1, CHCl\textsubscript{3})

IR (neat, cm\textsuperscript{-1}) : \nu_max 3142, 3022, 2914, 1722
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.12 (t, $J = 7.4$ Hz, 3H), 1.97-2.09 (m, 2H), 3.89 (s, 3H), 4.89-4.93 (m, 1H), 5.30-5.32 (m, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 8.5, 25.8, 52.7, 79.3, 85.2, 164.4.

Analysis: C$_6$H$_{10}$O$_6$ (210.21) requires C, 34.28; H, 4.80. Found. C, 34.16; H, 4.72.

Preparation of Methyl (2R,3S)-2-azido-3-hydroxypentanoate

![Chemical Structure](image)

To a solution of cyclic sulfate 59 (2.5 g, 11.89 mmol) in acetone (15 mL) cooled to 0 °C was added NaN$_3$ (3.86 g, 59.46 mmol) and the resulting mixture was stirred for 1 h at room temperature until no cyclic sulfate remained as indicated by TLC. The solution was then concentrated, and the residue was stirred with 20% aq. H$_2$SO$_4$ and ether (5 mL of each phase/mmol substrate) for 12 h. The resultant solution was then extracted with ether. The combined organic phases were washed with water, brine and dried (Na$_2$SO$_4$), and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (1:9) as eluent furnished 68 (1.60 g) as a colorless liquid.

Yield: 78%

[$\alpha$]$_D^{25}$: -4.68 (c 1, CHCl$_3$)

IR (neat, cm$^{-1}$): $\nu_{max}$ 3429, 2112, 1744

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.0 (t, $J = 7.43$ Hz, 3H), 1.50-1.69 (m, 2H), 2.33 (brs, 1H, OH), 3.83 (s, 3H), 3.87-3.91 (m, 1H), 3.97 (d, $J = 5.87$ Hz, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 9.5, 25.6, 51.7, 61.0, 73.0, 168.9

Preparation of Methyl (2R,3S)-2-tert-butoxycarbonylamino-3-hydroxypentanoate

To a solution of azide 68 (2.0 g, 11.54 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (75 mg) and Boc₂O (3.97 mL, 17.32 mmol). The resulting solution was stirred under hydrogen atmosphere at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave 56 (2.8 g) as a liquid.

Yield : 98%

[α]²⁵ᵣ : -6.9 (c 2, CHCl₃)

IR (neat, cm⁻¹) : νₘₐₓ 3522, 3342, 1719

¹H NMR (200 MHz, CDCl₃): δ 0.99 (t, J = 8 Hz, 3H), 1.44 (s, 9H), 1.52-1.63 (m, 2H), 2.54 (brs, OH, 1H), 3.62 (s, 3H), 3.83-3.86 (m, 1H), 4.38-4.40 (m, 1H), 5.54 (brs, 1H)

¹³C NMR (50 MHz, CDCl₃): δ 10.1, 26.3, 28.1, 52.3, 58.0, 74.3, 80.3, 155.8, 171.2

Analysis : C₁₁H₂₁NO₅ (247.27) requires C, 53.43 ; H, 8.56 ; N 5.66. Found. C, 53.40 ; H, 8.52.

Synthesis of salt (3-hydroxypropyl)triphenylphosphoniumbromide 57

3-bromopropanol
To a stirred solution of 1,3-propanediol 60 (5 g, 65.70 mmol) in benzene (100 mL) was added 48% aq. HBr (12.7 mL, 78.84 mmol) and the mixture stirred under reflux for 28 h while trapping the water formed using a Dean-stark water separator. The mixture was washed with 6N NaOH solution (50 mL), 10% HCl (50 mL), water (2x100mL) and brine (75 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to near dryness. The crude product was purified by silica gel column chromatography using EtOAc/pet ether (1:9) to give 70 (7.2 g) as a colorless oil.

**¹H NMR (200 MHz, CDCl₃)**: δ 2.05-2.25 (m, 3H), 2.55 (brs, 1H), 3.54 (t, $J = 6$ Hz, 2H), 3.78 (t, $J = 8$ Hz, 2H)

**¹³C NMR (50 MHz, CDCl₃)**: δ 30.1, 34.6, 59.5

**Preparation of (3-hydroxypropyl)-triphenylphosphoniumbromide**

\[
\begin{align*}
\text{Br} & \quad \text{Ph₃P} \\
\text{OH} & \quad \text{57}
\end{align*}
\]

A solution of 3-bromopropanol 70 (5 g, 35.97 mmol), triphenylphosphine (9.43 g, 35.97 mmol), and K₂CO₃ (4.97 g, 35.97 mmol) in dry CH₃CN (50 mL) was heated at reflux under nitrogen for 7 h. K₂CO₃ was filtered off and the filtrate was diluted with ether and the solution allowed to stand, during which the product 57 was precipitated out as white crystals (3.8 g, 26%).

**¹H NMR (200 MHz, CDCl₃)**: δ 1.88-1.92 (m, 2H), 3.70-3.85 (m, 3H), 4.60-4.66 (m, 2H), 7.71-7.79 (m, 15H)
[5-hydroxy-1-(1-hydroxypropyl)-pent-2-enyl]-carbamic acid tert-butyl ester

To a solution of 56 (0.3 g, 1.21 mmol) dissolved in dry DCM (5 mL) was added DIBAL-H (0.48 mL, 1.21 mmol, 2.5 M solution of DIBAL-H in toluene) dropwise at -78 °C. The reaction mixture was stirred for 1 h until disappearance of the starting material as indicated by TLC and then quenched with saturated sodium potassium tartrate. The precipitate obtained was filtered off and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated to near dryness which was used as such in the next step without further purification.

To a suspension of Wittig salt 57 (0.4 g, 1.01 mmol) in dry THF (5 mL) was added n-BuLi (1.1 mL, 2.3 mmol) at 0 °C and stirred for 30 min. To this solution the above crude aldehyde was added and stirred at rt for 12 h, and then quenched with sat. aq. NH$_4$Cl. The aqueous layer was extracted with EtOAc (4x50 mL). The combined organic extracts were washed with brine and dried over Na$_2$SO$_4$ and concentrated. Purification of the residue by silica gel column chromatography using EtOAc/pet ether (6:4) as eluent gave 71 (0.127 g) as a colorless oil.

Yield : 40 %

$[\alpha]_{D}^{25} : -10.3$ (c 1, CHCl$_3$)

IR (neat, cm$^{-1}$) : $\nu_{max}$ 3511, 3328, 1609
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.98 (t, $J$ = 10 Hz, 3H), 1.25-1.36 (m, 2H), 1.47 (s, 9H), 2.1 (brs, 2H), 2.15-2.30 (m, 2H), 2.89-2.97 (m, 2H), 4.20 (q, $J$ = 6 Hz, 1H), 4.30 (t, $J$ = 6 Hz, 1H), 5.42 (brs, 1H), 5.98-5.99 (m, 1H), 6.53 (t, $J$ = 6 Hz, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 12.6, 21.6, 28.0, 30.5, 61.0, 64.9, 71.2, 80.1, 128.5, 132.0, 153.2.

Analysis: C$_{13}$H$_{25}$NO$_4$ (259.34) requires C, 60.21; H, 9.79; N, 5.40. Found. C, 60.18; H, 9.73; N, 5.38.

Preparation of [5-Hydroxy-1-(1-hydroxypropyl)-pentyl]-carbamic acid tert-butyl ester

![Chemical Structure](image)

To a solution of 71 (0.50 g, 1.93 mmol) in methanol (10 mL) was added Pd/C (50 mg) under hydrogen atmosphere and mixture stirred for 4 h. After completion of the reaction, the mixture was filtered through celite pad and concentrated to near dryness. The crude product was purified by silica gel column chromatography using EtOAc/pet ether (6:4) as eluent to give 55 (0.478 g) as a liquid.

Yield: 95%

$[\alpha]^{25}_D$ : -9.8 (c 1, CHCl$_3$)

IR (neat, cm$^{-1}$) : $\nu_{\text{max}}$ 3520, 3318

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.98 (t, $J$ = 10 Hz, 3H), 1.23-1.25 (m, 2H), 1.43 (s, 9H), 1.46-1.49 (m, 4H), 1.55-1.62 (m, 2H), 2.01 (brs, 2H), 3.52 (t, $J$ = 8 Hz, 2H), 3.66-3.83 (m, 2H), 5.56 (brs, 1H)
\[ \text{NMR} \ (50 \text{ MHz, CDCl}_3): \ \delta \ 8.2, 19.0, 22.7, 25.6, 28.0, 31.7, 56.2, 62.2, 64.9, 77.8, 153.2. \]

**Analysis**: C\textsubscript{13}H\textsubscript{27}NO\textsubscript{4} (261.36) requires C, 59.74 ; H, 10.41 ; N, 5.36. Found. C, 59.72 ; H, 10.38 ; N, 5.32.

**Preparation of 2-(1-Hydroxypropyl)-piperidine-1-carboxylic acid-\textit{tert}-butyl ester**

![Structural formula](image)

To a stirred solution of compound 55 (0.4 g, 1.53 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (6 mL) was added methanesulfonyl chloride (0.14 mL, 1.83 mmol) at -78 °C and then triethyl amine (0.25 mL, 1.83 mmol) was added dropwise. After the mixture was stirred at -78 °C for 1 h, aqueous ammonium chloride (3 mL) was added. The mixture was warmed to room temperature and diluted with CH\textsubscript{2}Cl\textsubscript{2} (5 mL), washed with brine, and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed, and the residue was purified by flash chromatography using EtOAC/pet ether (4:6) to give 73 (0.31 g) as a colorless liquid.

**Yield**: 84%

\([\alpha]^{25}_D\) : -12.2 (c 1, CHCl\textsubscript{3})

**IR (neat, cm\textsuperscript{-1})**: \( \nu_{\text{max}} \) 3422, 1688

\[ \text{H NMR} \ (200 \text{ MHz, CDCl}_3): \ \delta \ 0.96 \ (t, J = 6 \text{ Hz, 3H}), 1.32-1.45 \ (m, 6H), 1.45 \ (s, 9H), 1.52-1.63 \ (m, 2H), 2.02' \ (t, J = 8 \text{ Hz, 2H}), 2.96 \ (\text{bri, 1H}), 3.32-3.42 \ (m, 2H) \]

\[ \text{C NMR} \ (50 \text{ MHz, CDCl}_3): \ \delta \ 9.8, 23.3, 24.4, 25.3, 26.2, 27.3, 53.2, 60.2, 70.9, 75.5, 164.9 \]
Analysis: C_{13}H_{25}NO_3 (243.18) requires C, 64.16; H, 10.36; N, 5.76. Found. C, 64.12; H, 10.33; N, 5.72.

Synthesis of (-)-α-conhydrine

To an ice-bath solution of 73 (23 mg, 0.095 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added trifluoroacetic acid (0.2 mL, 0.095 mmol). The reaction mixture was stirred at room temperature for 12 h and then saturated aq. NaHCO\textsubscript{3} added and mixture extracted with dichloromethane (3x5 mL). The combined organic layers were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography using CH\textsubscript{3}OH/CH\textsubscript{2}Cl\textsubscript{2} (4:6) as eluent to give 2 (12 mg) as a solid. [α]\textsubscript{D}\textsuperscript{25} : -8.9 (c 1.0, ethanol). The physical and spectroscopic data of 2 were in full agreement with the literature data.*

Yield: 74%

M.p.: 116-118 °C [lit.*118 °C]

[α]\textsubscript{D}\textsuperscript{25} : -8.9 (c 1, ethanol) [lit.\textsuperscript{8} [α]\textsubscript{D}\textsuperscript{25} : -8.6 ; ethanol].

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): δ 0.96 (t, J = 6 Hz, 3H), 1.32-1.55 (m, 5H), 1.55 (m, 2H), 1.88 (m, 1H), 2.52 (t, J = 8 Hz, 1 H), 2.72 (t, J = 10 Hz, 1H), 3.11-3.16 (m, 1H), 3.22 (brs, 2 H), 3.42-3.44 (m, 1H)

\textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}): δ 7.8, 24.0, 25.9, 26.3, 28.1, 46.0, 58.1, 78.1
Preparation of (2S,3S)-Pent-1, 2, 3-triol

To a mixture of K$_3$Fe(CN)$_6$ (55.97 g, 0.17 mmol), K$_2$CO$_3$ (23.49 g, 0.17 mmol) and (DHQ)$_2$PHAL (452 mg, 1 mol%) in t-BuOH-H$_2$O (1:1) cooled at 0 °C was added osmium tetroxide (2.3 mL, 0.1 M solution in toluene, 0.4 M mol%) followed by methanesulfonamide (5.5 g, 58.09 mmol). After stirring for 5 min. at 0 °C, the olefin 67 (5 g, 58.09 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite. The stirring was continued for an additional 45 min. and then the solution was extracted with ethyl acetate (5x100 mL). The combined organic phases were washed with 10% aq. KOH, brine, dried (Na$_2$SO$_4$) and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (6:4) as eluent gave 66 (5.21 g) as a viscous liquid.

Yield : 75%

[α]$^D_{25}$ : -6.7 (c 1, CHCl$_3$)

IR (neat, cm$^{-1}$) : ν$_{max}$ 3400-3200, 2919, 2851, 1455, 1375, 1074

$^1$H NMR (200 MHz, CDCl$_3$): δ 0.9 (t, $J$ = 6 Hz, 3H), 1.42-1.56 (m, 2H), 2.11 (brs, 2H), 3.51-3.59 (m, 2H), 3.67-3.73 (m, 3H)

Analysis : C$_5$H$_{12}$O$_3$ (261.36) requires C, 49.98 ; H, 10.07 . Found. C, 49.96 ; H, 10.02.
Preparation of (2S,3S)-1,3-O-Benzylidenepentane-1,2,3-triol

To a solution of 66 (3 g, 24.96 mmol) in dry CH₂Cl₂ (40 mL) were added p-TsOH (80 mg) and benzaldehyde dimethyl acetal (4.56 g, 4.49 mL, 29.96 mmol). The reaction mixture was stirred at room temperature for 12 h. Subsequently, it was neutralized with saturated aq. NaHCO₃. The organic phase was separated and the aqueous phase extracted with CH₂Cl₂. The combined organic extracts were washed with aq. NaHCO₃, brine, dried (Na₂SO₄) and concentrated. Column chromatography over silica gel using EtOAc/pet ether (1:9) as eluent furnished the major product 65 (3.82 g) as a colorless liquid.

Yield : 74%

[α]²⁵D : -11.5 (c 0.48, CHCl₃)

IR (neat, cm⁻¹) : νₘₐₓ 3512, 2922, 2849, 1451, 1377, 1276, 1215

¹H NMR (200 MHz, CDCl₃): δ 1.0 (t, J = 7.4 Hz, 3H), 1.69-1.87 (m, 2H), 2.52 (brs, 1H, OH), 3.45-3.74 (m, 1H), 3.63-3.72 (m, 1H), 3.93 (dd, J = 2, 12 Hz, 2H ), 5.58 (s, 1H), 7.37-7.58 (m, 5H)

¹³C NMR (50 MHz, CDCl₃): δ 9.2, 24.0, 72.7, 79.8, 81.5, 101.3, 125.8, 128.1, 134.3, 137.9.

Preparation of (2R,3S)-2 azido-1,3-O-benzylidenepentane-1,3-diol

To a solution of 65 (2 g, 9.6 mmol) in dry CH$_2$Cl$_2$ (20 mL) at 0 °C was added methanesulfonyl chloride (1.65 g, 1.1 mL, 14.40 mmol), Et$_3$N (2.27 mL, 16.32 mmol) and DMAP (cat). The reaction mixture was stirred at room temperature for 6 h and then poured into Et$_2$O-H$_2$O mixture. The organic phase was separated and the aqueous phase extracted with Et$_2$O. The combined organic phases were washed with water, brine, dried (Na$_2$SO$_4$) and concentrated to a white solid which was dissolved in dry DMF (20 mL). Sodium azide (3.4 g, 48.01 mmol) was added and the reaction mixture stirred at 80 °C for 24 h. It was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine and dried (Na$_2$SO$_4$) and concentrated. Column chromatography on silica gel using EtOAc/pet ether (0.7:9.3) as eluent gave 61 (1.92 g) as a colorless liquid.

Yield: 85%

[$\alpha$]$^\text{D}_{25}$: -8.8 (c 1, CHCl$_3$)

IR (neat, cm$^{-1}$): \( \nu_{\text{max}} \) 2122, 2752, 1432, 1327, 1256, 1225

$^1$H NMR (200 MHz, CDCl$_3$): \( \delta \) 1.09 (t, \( J = 4 \) Hz, 3H), 1.62-1.76 (m, 2H), 3.50-3.62 (m, 2H), 3.99-4.01 (m, 2H), 5.97 (s, 1H), 7.39-7.53 (m, 5H)

$^{13}$C NMR (50 MHz, CDCl$_3$): \( \delta \) 9.8, 25.4, 51.7, 69.0, 80.0, 103.2, 126.4, 128.4, 129.2, 137.3
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

**Analysis**: \( C_{12}H_{15}N_3O_2 \) (261.36) requires C, 61.79; H, 6.48; N 18.01. Found. C, 61.76; H, 6.44; N, 17.98.

**Preparation of \((2R,3S)-2\text{-azido}-3\text{-benzyloxy}\text{pentan-1-ol}\)**

To a solution of 61 (0.4 g, 1.71 mmol), in dry \( CH_2Cl_2 \) (10 mL) was added dropwise DIBAL-H (2.57 mL, 2 M solution in toluene, 5.14 mmol) at \(-78 \, ^\circ C\) under argon atmosphere. The mixture was gradually allowed to warm to room temperature and the stirring was continued overnight. The reaction mixture was cooled to 0 \, ^\circ C\) and to this was added successively saturated \( NH_4Cl \) (3 mL) and ethyl acetate (5 mL). After being stirred for 1 h at room temperature the mixture was filtered through a celite pad. The filtrate was dried over anhydrous \( Na_2SO_4 \) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/pet ether (1:9) as eluent to give 58 (0.36 g) as a colorless oil.

**Yield**: 90%

\[ [\alpha]^{25}_D = -12.2 \quad (c 1, \text{CHCl}_3) \]

**IR (neat, cm\(^{-1}\))**: \( \nu_{\text{max}} 3433, 2126, 1322, 1216, 1156, 1025 \)

\(^1\text{H NMR (200 MHz, CDCl}_3\)): \( \delta 0.96 \,(t, \, J = 6.8 \, Hz, \, 3H), \, 1.29-1.41 \,(m, \, 2H), \, 2.08 \,(brs, \, 1H), \, 2.11-2.14 \,(m, \, 1H), \, 3.37-3.43 \,(m, \, 1H), \, 3.60 \,(d, \, J = 5.9 \, Hz, \, 2H), \, 4.69 \,(s, \, 2H), \, 7.33- \, 7.40 \,(m, \, 5H) \)

\(^{13}\text{C NMR (50 MHz, CDCl}_3\)): \( \delta 9.3, \, 24.4, \, 59.6, \, 61.2, \, 74.2, \, 76.3, \, 127.6, \, 128.3, \, 129.6, \, 137.4 \)
CHAPTER 3 Enantioselective syntheses of (-)-c-conhydrine and (-)-acaterin via asymmetric dihydroxylation


Preparation of (5R,6S)-5-azido-6-benzyloxy-Oct-3-ene-1-ol

To a stirred solution of PCC (0.68 g, 3.19 mmol), anhydrous sodium acetate (0.26 g, 3.19 mmol) and celite in dry CH₂Cl₂ (5 mL) at 0 °C was added alcohol 58 (0.5 g, 2.12 mmol) in dry CH₂Cl₂ (3 mL) under argon atmosphere and the stirring was continued for 4 h at room temperature until the completion of reaction as indicated by TLC. The reaction mixture was washed thoroughly with diethyl ether and concentrated to give aldehyde which was used immediately in the next step without further purification.

To a stirred solution of salt 57 (1.70 g, 4.25 mmol) in dry THF (20 mL) was added n-BuLi (2.12 mL, 2 M solution in hexane, 4.25 mmol) at 0 °C and stirring was continued for further 30 min. The above aldehyde was added to the reaction mixture and stirred for 12 h at ambient temperature and quenched with saturated ammonium chloride solution. The organic layer was separated and aqueous layer extracted with ethyl acetate (3x20 mL) and dried over Na₂SO₄ and concentrated to near dryness. Purification by silica gel column chromatography using EtOAc/pet ether (7:3) as eluent gave 72 (0.35 g) as a viscous liquid.

Yield: 78%

[α]ᵣₒD : -19.3 (c 0.52, CHCl₃)

IR (neat, cm⁻¹): νmax 3429, 2133, 1616, 1221, 1156, 1025
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.96 (t, $J = 6.0$ Hz, 3H), 1.32-1.46 (m, 2H), 2.02 (s, 1H), 2.15-2.23 (m, 2H), 2.62-2.66 (m, 1H), 3.01 (q, $J = 8.2$ Hz, 1H), 3.62 (t, $J = 10.5$ Hz, 2H), 4.69 (s, 2H), 5.48 (t, $J = 12.6$ Hz, 1H), 5.55 (q, $J = 12.6$ Hz, 1H), 7.15-7.28 (m, 5H)

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 9.4, 24.6, 36.5, 62.2, 64.6, 73.9, 81.2, 126.4, 127.6, 128.4, 129.3, 132.6, 137.5

Analysis: C$_{15}$H$_{21}$N$_3$O$_2$ (275.35) requires C, 65.43; H, 7.69; N, 15.26 Found. C, 65.40; H, 7.63; N, 15.21.

Preparation of [5-Hydroxy-1-(1-hydroxypropyl)-pentyl]-carbamic acid tert-butyl ester

To a solution of azide 72 (0.3 g, 1.09 mmol) in ethyl acetate was added 10% Pd/C (75 mg) and Boc$_2$O (0.3 mL, 1.3 mmol). The resulting solution was stirred under hydrogen atmosphere for 24 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave 55 (0.24 g) as a colorless liquid. yield: 86%; $[\alpha]_{D}^{25}$: -8.9 (c 0.86, CHCl$_3$). The physical and spectroscopic data were in accord with those described in Scheme 12. The transformation of 55 to the target compound 2 is already described in Scheme 12.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

3.1.7 Spectra

1. $^1$H & $^{13}$C NMR spectra of 62
2. $^1$H & $^{13}$C NMR spectra of 59
3. $^1$H & $^{13}$C NMR spectra of 68
4. $^1$H & $^{13}$C NMR spectra of 56
5. $^1$H & $^{13}$C NMR spectra of 71
6. $^1$H & $^{13}$C NMR spectra of 55
7. $^1$H & $^{13}$C NMR spectra of 65
8. $^1$H & $^{13}$C NMR spectra of 61
9. $^1$H & $^{13}$C NMR spectra of 58
10. $^1$H & $^{13}$C NMR spectra of 2
CHAPTER 3 Enantioselective syntheses of (-)-α-camphorhydrine and (-)-acaterin via asymmetric dihydroxylation

\[ \text{NMR Spectrum of compound 62 in CDCI}_3 \]

\[ ^1\text{H NMR Spectrum of compound 62 in CDCl}_3 \]

\[ ^{13}\text{C NMR Spectrum of compound 62 in CDCl}_3 \]
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR Spectrum of compound 59 in CDCl$_3$

$^{13}$C NMR Spectrum of compound 59 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

1H NMR Spectrum of compound 68 in CDCl₃

13C NMR Spectrum of compound 68 in CDCl₃
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

\[ \text{NMR Spectrum of compound 56 in CDCl}_3 \]

\[ \text{\[^1H\] NMR Spectrum of compound 56 in CDCl}_3 \]

\[ \text{\[^{13}C\] NMR Spectrum of compound 56 in CDCl}_3 \]
CHAPTER 3 Enantioselective syntheses of (−)-α-conhydrine and (−)-acaterin via asymmetric dihydroxylation

$^1$H NMR Spectrum of compound 71 in CDCl$_3$

$^{13}$C NMR Spectrum of compound 71 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR Spectrum of compound 55 in CDCl$_3$

$^{13}$C NMR Spectrum of compound 55 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR Spectrum of compound 65 in CDCl$_3$

$^{13}$C NMR Spectrum of compound 65 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR Spectrum of compound 61 in CDCl$_3$

$^{13}$C NMR Spectrum of compound 61 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

\[ ^{1}H \text{NMR Spectrum of compound 58 in CDCl}_3 \]

\[ ^{13}C \text{NMR Spectrum of compound 58 in CDCl}_3 \]

163
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

1H NMR Spectrum of compound 2 in CDCl₃

13C NMR Spectrum of compound 2 in CDCl₃
3.2 SECTION B: ASYMMETRIC SYNTHESIS OF (-)-ACATERIN

3.2.1 Introduction

Acyl-CoA cholesterol acyltransferase (ACAT), a microsomal enzyme catalyzes the synthesis of cholesteryl esters from acyl-CoA and cholesterol\textsuperscript{16} and cholesteryl accumulation in macrophages incubated with modified low density lipoprotein (LDL), such as acetylated LDL.\textsuperscript{17} It plays important role in the control of intracellular cholesterol content via its cholesterol esterifying.\textsuperscript{18} ACAT inhibitors play an essential role both in intestinal absorption of cholesterol and cholesteryl ester formation in a variety of tissues and cells.\textsuperscript{19} Since elevated plasma of cholesterol is related to an increased risk of coronary heart disease and massive accumulation of cholesteryl esters in macrophage-derived foam cells, is a hallmark of the atherosclerotic plaques. Inhibitors of acyl-CoA : cholesterol acyltransferase (ACAT) activity are expected to be effective for treatment of atherosclerosis and hypercholesterolemia.\textsuperscript{20} Although, several synthetic ACAT inhibitors are known,\textsuperscript{21} those of natural origin have rarely been reported.\textsuperscript{22} (Fig. 2)

Acaterin\textsuperscript{22} (Fig. 3), a novel inhibitor of acylCoA : cholesterol acyltransferase (ACAT), was isolated from a culture broth of pseudomonas sp. A 92 by Dianion HP-20 column chromatography, solvent extraction and reverse phase HPLC. Spectroscopic analyses of the compound yielded 3-(1-hydroxyoctyl)-5-methyl-2(5H)-furanone as the proposed structure. In the presence of oxidised low density lipoprotein, acaterin inhibited the synthesis of cholesteryl ester in macrophage J774 by 50% at a concentration of 45 micro M.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Acaterin also inhibited ACAT activity in the rat liver microsomes by 50% at a concentration of 120 micro M. Kinetic studies showed that inhibition of ACAT by acaterin was noncompetitive with respect to Oleoyl-CoA. Acaterin contains butenolide skeleton with alkyl chain at C-2 position, which is related to annonaceous acetogenins,\textsuperscript{24} such as Uvaricin,\textsuperscript{25} with remarkable antitumor activity.

3.2.2 Review of Literature

Kitahara \textit{et al.}\textsuperscript{26} first synthesized all stereoisomers of cholesterol inhibitor acaterin through determination of its absolute configuration. Since then very few synthetic approaches have appeared in the literature. Biosynthesis of acaterin was described by Fujimoto \textit{et al.}\textsuperscript{27} using labelling studies. Very recently, two similar synthetic routes have been presented using Baylis-Hillman reaction as key step. Singh\textsuperscript{28} and co-workers have used direct Baylis-Hillman reaction followed by ring-closing metathesis as key steps, whereas the first
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

The synthetic sequence of Kitahara group was based on the construction of α-alkyl thio-γ-lactones from readily available chiral source, ethyl 3-hydroxybutanoate, (S)- and (R) 83. In order to establish the synthetic scheme and relative stereochemistry, (R)- and (S)-γ-valero lactones were prepared from corresponding 3-hydroxybutanoates. (R)-γ-Valerolactone was treated with LDA and methyl methanethiosulfonate and resultant separable product was treated with LDA and octanoyl chloride to afford single β-keto lactone 87. Reduction of 87 with NaBH₄ in aqueous THF followed by MCPBA oxidation and pyrolysis gave natural acaterin 78.

Kitahara et al. (Scheme 14)

The synthetic sequence of Kitahara group was based on the construction of α-alkyl thio-γ-lactones from readily available chiral source, ethyl 3-hydroxybutanoate, (S)- and (R) 83. In order to establish the synthetic scheme and relative stereochemistry, (R)- and (S)-γ-valero lactones were prepared from corresponding 3-hydroxybutanoates. (R)-γ-Valerolactone was treated with LDA and methyl methanethiosulfonate and resultant separable product was treated with LDA and octanoyl chloride to afford single β-keto lactone 87. Reduction of 87 with NaBH₄ in aqueous THF followed by MCPBA oxidation and pyrolysis gave natural acaterin 78.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 14

Scheme 14: Reaction conditions: (a) LDA, MeSSO₂, THF, -78 °C to -20 °C, 2.5 h, 69%; (b) LDA, n-C₇H₁₅COCl, THF, -78 °C to -10 °C, 2.5 h, 73%; (c) NaBH₄, THF-H₂O (10:1), -5 °C, 1 h, 44%; (d) MCPBA, CH₂Cl₂, -78 °C, 15 min; (e) CaCO₃, toluene, reflux, 3 h, 64% in two steps.

**Fujimoto et al.**²⁷ (Scheme 15)

Fujimoto’s approach explains the biosynthesis of acaterin through feeding experiments with ²H-and ¹³C labelled decanoic acid which suggested that acaterin is biosynthesized via coupling of a C₅ unit with octanoate, rather than via introduction of a C₃ unit at the
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

α-position of a decanoate derivative. Further feeding study of [2,3\(^{13}\)C\(_2\)] decanoic acid concluded that the former route is operating in the biosynthesis of acaterin.

\[ X \text{ = H, OH, or O} \]

\[ \text{SCoA} \]

Scheme 15: Two possible modes in the biosynthesis of acaterin

Singh et al. \(^{28}\) (Scheme 16)

Singh and co-workers reported the asymmetric synthesis of (-)-acaterin 78 and its diastereomer through ring closing metathesis. The Baylis-Hillman reaction of caprylic aldehyde 94 with methyl acrylate in the presence of a catalytic amount of quiniclidine gave 95 followed by protection of free hydroxy group using 2-methoxy ethoxymethyl chloride. Hydrolysis of ester 96 and subsequent DCC coupling with \(R\)-\((-\)-3-buten-2-ol furnished 98. Finally, the butenolide skeleton was achieved using RCM which gave a 1:1 diastereomeric mixture of cyclized products 99 and 100 which were separated by radial chromatography. The absolute configurations were assigned after conversion to natural acaterin and its diastereomer using TiCl\(_4\).
Scheme 16: Reaction conditions: (a) Methyl acrylate, quinclidine, 48 h, 72%; (b) 2-methoxyethoxy chloride, N-ethyldiisopropyl amine, DCM, 6 h, 83%; (c) 1 N aq. LiOH, THF/water (2:1), 24 h; (d) $R$-(-)-3-buten-2-ol, DCC, DMAP, DCM, 24 h; (e) Grubb's catalyst (30 mol%), DCM, reflux, 48 h; (f) TiCl$_4$, DCM, 8 h.

Figadere et al. $^{29}$ (Scheme 17)

The first application of the Baylis-Hillman reaction to $\alpha,\beta$-unsaturated lactones was used for the synthesis of acaterin as shown in Scheme 17. In this report, Baylis-Hillman conditions were employed for the synthesis of racemic acaterin via the coupling of $\delta$-butyrolactone with octanal. However, their attempts to employ this strategy for obtaining enantiopure acaterin starting from 101 which was prepared by asymmetric reduction of the
required α-chlorinated ketone with Baker’s yeast\textsuperscript{30} were unsuccessful due to the possible racemization as shown in Scheme 18.

\begin{center}
\textbf{Scheme 17}
\end{center}

\begin{center}
\textbf{Scheme 18}
\end{center}
3.2.3 Present work

Objective

A very few syntheses of (-)-acaterin were documented in the literature mainly using Baylis-Hillman reaction and ring closing metathesis as key steps. Hence, a general strategy with limited steps and higher optical purity to achieve the synthesis of all the stereoisomers of acaterin is still desirable. The Sharpless asymmetric dihydroxylation of α,β-unsaturated esters is an excellent method to prepare chiral diols in a highly enantiomeric purity. Thus, the objective of present work is to devise a new synthesis of (-)-acaterin employing AD as the key step and source of chirality.

3.2.4 Results and Discussion

The retrosynthetic analysis for the asymmetric synthesis of (-)-acaterin 78 is shown in Scheme 19. The left half of (-)-acaterin is represented by the fragment 105, which could be derived from regioselective conversion of diol 107 which in turn would be obtained from the Sharpless asymmetric dihydroxylation of α,β-unsaturated olefin 109. The olefin 109 in turn could be easily derived from octanol 110. The right half fragment 106 of (-)-acaterin would be easily obtained from commercially available methyl-(R)-lactate 108. Thus, the hydroxyl center in (-)-acaterin 78 would be obtained from AD and the butenolide ring can be constructed using Wittig olefination and subsequent cyclization.
The detailed synthetic route and reaction conditions are given in Scheme 20. The synthesis of (-)-acaterin 78 started from commercially available octan-1-ol 110 which was oxidised using P₂O₅, dry dimethyl sulfoxide and triethylamine in dry dichloromethane at 0 °C to afford aldehyde which was used in the next step without further purification. The crude ¹H NMR of aldehyde showed singlet at δ 9.2 indicating the presence of product aldehyde. The aldehyde was subsequently treated in dry THF under reflux conditions with (methoxycarbonylmethylene)triphenylphosphorane to give the trans-olefin 109 in excellent yield. The IR spectrum of 109 showed strong absorption peaks for olefin and carbonyl at δ 1610, 1720 cm⁻¹ respectively. Olefin peaks were confirmed by ¹H and ¹³C NMR which showed 5.77 (doublet, J = 14 Hz), 6.88-6.99 (multiplet) and 121.1, 148.8
respectively. The Sharpless asymmetric dihydroxylation of olefin 109 using (DHQD)$_2$PHAL as chiral ligand and catalytic OsO$_4$ as oxidant and potassium ferricyanide as co-oxidant in t-butanol/water gave the diol 107 in 98% yield with excellent enantiomeric purity $[\alpha]_D^{25} : + 10.1$ (c 1.42, CHCl$_3$), [lit.$^{31}$]$[\alpha]_D^{25} : + 11.23$ (c 1, CHCl$_3$)]. The IR spectrum of 107 showed hydroxyl absorption at 3452 cm$^{-1}$. In the $^1$H NMR spectrum, the olefinic protons disappeared and in the $^{13}$C NMR spectrum, the hydroxyl carbons appeared at $\delta$ 72.4 and 73.2. Regioselective conversion of dihydroxy compound 107 to bromohydrin 111 was achieved employing the protocol developed by Sharpless.$^{32}$ Thus, treatment of 107 with hydrogen bromide in acetic acid and methanol at 50 °C gave 111 in 83% yield. The $^1$H NMR spectrum of 107 showed a downfield shift of -CH-Br proton as observed at $\delta$ 4.26 (doublet) and 4.09 (multiplet) in comparison to the same protons of dihydroxy compound. Finally, the mass spectrum clearly showed presence of bromine with indication of peak at 279 (M$^+$.2). The preparation of salt 113 carried out in following manner completed the synthesis of left fragment. Thus, the free hydroxyl group of 111 was protected as silyl ether 112 using tert-butyldimethylsilyl chloride, imidazole and catalytic amount of DMAP. The IR spectrum of 112 showed absence of hydroxyl absorption and in the $^1$H NMR spectrum three singlets appeared at $\delta$ 0.03, 0.07 and 1.26 showing the presence of TBS group. Consequently, bromo silyl compound 112 was treated with triphenyl phosphine in dry acetonitrile under reflux conditions to furnish the salt 113 in moderate yield. The presence of three phenyl groups in the form of 15 protons at $\delta$ 7.73 and down field shifting of -CH-P to $\delta$ 5.26 in $^1$H NMR spectrum clearly confirmed the formation of salt.
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

Scheme 20 : Reagents and conditions : (a) (i) P₂O₅, DMSO, CH₂Cl₂, Et₃N, 0 °C, 4 h, 96%; (ii) Ph₃P=CHCOOME, THF, reflux, 12 h, 93%; (b) (DHQD)₂PHAL, OsO₄, CH₃SO₂NH₂, K₃Fe(CN)₆, K₂CO₃, t-BuOH:HO (1:1), 24 h, 0 °C , 98%; (c) HBr/AcOH, dry MeOH, 45 °C, 24 h, 83%; (d) TBDMSCl, imidazole, DMAP(cat.), CH₂Cl₂, 36 h, 92%; (e) PPh₃, CH₃CN, reflux, 12 h, 66%.

As shown in Scheme 21, the synthesis of right fragment 106 of (-)-acaterin commenced from (R)-methyl lactate. The protection of free hydroxyl group of 108 was achieved using dihydropyran and p-TSA in dry DCM. The IR spectrum of 114 showed the absence of hydroxyl group. In the ¹H NMR spectrum, presence of tert-proton at δ 4.80 and in the ¹³C NMR tert-carbon at δ 98.69 confirmed the formation of compound 114. The ester group of 114 was reduced using LiAlH₄ in dry THF, to afford 115 in excellent yield. The presence of strong absorption at 3560 cm⁻¹ in IR spectrum and the absence of methyl protons in the ¹H NMR and carbonyl group in the ¹³C NMR spectrum confirmed the reduction of ester to alcohol 115. The PCC oxidation of alcohol 115 using PCC, anhydrous CH₃COONa and
celite gave the aldehyde 106. The crude $^1$H NMR spectrum of 106 showed the doublet at δ 9.23, indicating the presence of aldehyde functionality (Scheme 21).

![Scheme 21: Reaction conditions](image)

**Scheme 21:** Reaction conditions: (a) DHP, p-TsOH (cat), dry CH$_2$Cl$_2$, 96%; (b) LiAlH$_4$, dry THF, 0 °C-rt, 12 h, 92%; (c) PCC, anhydrous CH$_3$COONa, celite, 4 h.

The final step and one of the key reaction involved the construction of butenolide skeleton through Wittig olefination by coupling of phosphonium salt 113 with aldehyde 106 and subsequent cyclization. Towards this end, the Wittig olefination between 113 and 106 was carried out in the presence of LiHMDS at −78 °C to give the olefin 116 in 73% yield.

The IR spectrum of 116 showed peak at 1666 cm$^{-1}$ indicating the presence of olefin and in the $^1$H NMR spectrum, olefin peaks appered at δ 6.83 with coupling constant (J) 8.74 Hz which showed the presence of cis olefin. Presence of olefin peak at δ 128.1 in $^{13}$C NMR also suggested the formation of 116. With olefin 116 in hand we proceeded for cyclization using catalytic amount of p-TSA in methanol and successfully achieved the target molecule (-)-acaterin 78 in good yield and in high optical purity [$\alpha$]$_D^{25}$ : −21.33 (c 0.3, CHCl$_3$) [lit. $^{25}$[$\alpha$]$_D^{25}$ : −19.7 (c 0.61, CHCl$_3$)]. The physical and spectroscopic data exactly matched with the literature values.$^{26}
3.2.5 Conclusion

In conclusion, a short and high yielding asymmetric synthesis of (-)-acaterin has been achieved through the Sharpless asymmetric dihydroxylation and Wittig olefination as key steps for the first time. A short reaction sequence and high yielding steps to (-)-acaterin renders our strategy a good alternative to the known methods. The pseudo of acaterin could also be synthesized via α-dihydroxylation using (DHQ)_2PHAL instead of (DHQD)_2PHAL as the chiral ligand. The protocol is amenable to the synthesis of other isomers of (-)-acaterin i.e (+)-acaterin and its pseudo isomer could also be synthesized via α- and β-dihydroxylations and using (S)-methyl lactate as starting material.
3.2.6 Experimental section

General Information

Solvents were purified and dried by standard procedures before use; petroleum ether of
boiling range 60-80 °C was used. Melting points are uncorrected. Optical rotations were
measured using the sodium D line of a JASCO-181 digital polarimeter. Infrared spectra
were recorded with an ATI MATT-SION RS-1 FT-IR spectrometer. \(^1\)H NMR spectra were
recorded on Brucker AC-200 and DRX-500 NMR spectrometers. Mass spectra were
obtained with GC-MS. Elemental analysis were carried out on Carlo Erbo CHNSO-
analyzer.

Preparation of Methyl trans-dec-2-enoate

![Methyl trans-dec-2-enoate](image)

To a solution of 1-octanol 110 (10 g, 76.78 mmol) in dry CH\(_2\)Cl\(_2\) (100 mL) was added dry
DMSO (11.99 g, 10.64 mL, 0.15 mmol) under nitrogen atmosphere and cooled to 0 °C. To
this solution P\(_2\)O\(_5\) (21.29 g, 0.15 mol) was added in portion wise. The reaction mixture was
stirred and allowed to warm to room temperature until the TLC diagnosis showed complete
disappearance of the starting material (45 min). The round bottom flask was cooled to 0 °C
and triethyl amine (36.23 mL, 0.26 mol) was added dropwise over one minute and stirring
was continued for further 45 min. in ice bath and another 45 min. at room temperature. The
reaction mixture was quenched with 150 ml of 10% aq. HCl and the solution extracted
with CH\(_2\)Cl\(_2\) (3x100 mL). The combined organic extracts were washed with brine, dried
(Na$_2$SO$_4$), filtered and concentrated in vacuo to give the octanal, which was used as such in the next Wittig olefination.

To a solution of (methoxycarbonylmythelene)triphenylphosphorane (25.78 g, 77.22 mmol) in dry THF (60 mL) was added dropwise a solution of aldehyde (9 g, 70.2 mmol) in THF (20 mL) at room temperature. The reaction mixture was refluxed for 12 h and concentrated to near dryness. Silica gel column chromatography of the crude product using pet. ether:ethyl acetate (9.5:0.5) as eluent gave the olefin 109 (12.0 g).

Yield: 93%

IR (neat, cm$^{-1}$): $v_{\text{max}}$ 1616, 1724

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.83 (t, $J = 4$ Hz, 3H), 1.24-1.26 (m, 10H), 2.11-2.18 (m, 2H), 3.70 (s, 3H), 5.79 (d, $J = 14$ Hz, 1H), 6.88-6.99 (m, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 13.9, 22.3, 27.8, 28.8, 31.4, 31.9, 59.9, 121.1, 148.2, 166.2

Analysis: C$_{11}$H$_{20}$O$_2$ (184.28) requires C, 71.70; H, 10.94. Found. C, 71.68; H, 10.91.

Preparation of Methyl (2R,3S)-2,3-dihydroxydecanoate

To a mixture of K$_3$Fe(CN)$_6$ (5.36 g, 16.27 mmol), K$_2$CO$_3$ (2.25 g, 16.27 mmol) and (DHQD)$_2$PHAL (42 mg, 1 mol%) in t-BuOH-H$_2$O (1:1) cooled at 0 °C was added osmium tetroxide (0.22 mL, 0.1 M solution in toluene, 0.4 M mol%) followed by methanesulfonamide (0.52 g, 5.42 mmol). After stirring for 5 min. at 0 °C, olefin 109 (1 g, 5.42 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and
then quenched with solid sodium sulfite (2.5 g). The stirring was continued for an additional 45 min. and then the solution was extracted with ethyl acetate (5x50 mL). The combined organic phases were washed with 10% aq. KOH, brine, dried (Na$_2$SO$_4$) and concentrated. Silica gel column chromatography of the crude product using pet. ether:EtOAc (7:3) as eluent gave the diol 107 (1.5 g) as a low melting solid.

**Yield**: 98%

**M.p.**: 42 °C

[α]$^\circ$D : +11.23 (c 1, CHCl$_3$)

**IR** (CHCl$_3$, cm$^{-1}$) : $\nu_{\text{max}}$ 3506, 1723

**$^1$H NMR** (200 MHz, CDCl$_3$) : $\delta$ 0.87 (t, $J$ = 6 Hz, 3H), 1.31-1.34 (m, 10H), 1.35-1.59 (m, 2H), 3.82 (s, 3H), 4.10-4.20 (m, 2H)

**$^{13}$C NMR** (50 MHz, CDCl$_3$) : $\delta$ 13.8, 22.4, 25.5, 29.0, 28.9, 31.6, 33.2, 52.3, 72.4, 73.2, 174.0

**Analysis**: C$_{11}$H$_{22}$O$_4$ (218.29) requires C, 60.52; H, 10.16. Found. C, 60.48; H, 10.13.

**Preparation of Methyl (2R,3R)-2-bromo-3-hydroxydecanoate**

![Methyl (2R,3R)-2-bromo-3-hydroxydecanoate](image)

Methyl-2,3-dihydroxydecanoate 107 (2 g, 9.16 mmol) was placed in a one neck round bottom flask followed by addition of hydrogen bromide (14 mL, 33% HBr in AcOH, 45.80 mmol) at room temperature, and the reaction mixture was heated at 45 °C. After 1 h of stirring, MeOH (28 mL) was added dropwise. The mixture was stirred overnight at 45 °C, and then allowed to cool to rt over 1 h. The mixture was quenched by slowly pouring into
ice-water, diluted with ether and neutralized by addition of saturated NaHCO₃. The precipitate sodium acetate was filtered off and the filtrate extracted with ether. The extract was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate:pet. ether (1:9) to give 111 (2.14 g) as a low melting white solid.

**Yield**: 83%

[α]D25 : +36.14

**M. p.** : 41-41.5 °C

**IR (CHCl₃, cm⁻¹)**: v_max 3604, 3019, 2928, 2400, 1735, 1658, 1215, 756, 669

**¹H NMR (200 MHz, CDCl₃)**: δ 0.85 (t, J = 6.3 Hz, 3H), 1.26-1.42 (m, 10H), 1.81-1.92 (m, 2H), 3.01 (bs, 1H), 3.77 (s, 3H), 4.11 (d, J = 8 Hz, 1H), 3.97-3.99 (m, 1 H)

**¹³C NMR (50 MHz, CDCl₃)**: δ 13.8, 22.4, 25.0, 28.9, 29.1, 31.5, 33.2, 47.8, 52.7, 72.1, 169.7

**MS**: m/z 279 (M⁺-2), 263, 197, 183, 168, 152, 140, 123, 111, 95, 81.

**Analysis**: C₁₁H₁₃BrO₃ (281.19) requires C, 46.98 ; H, 7.52 ; Br, 28.41. Found. C, 47.07 ; H, 7.65 ; Br, 28.14.

**Preparation of Methyl (2R,3R)-2-bromo-3-tert-butyldimethylsilanyloxydecanoate**

![Compound 112](image)

To a solution of 111 (1 g, 3.55 mmol) in dry CH₂Cl₂ (15 mL) was added imidazole (0.26 g, 4.27 mmol), catalytic amount of DMAP (100 mg), TBDMSCl (0.64 g, 4.27 mmol)
sequentially. The reaction mixture was diagnosed using TLC. To the reaction mixture was added water and extracted with dichloromethane and combined organic layers were washed with brine solution, dried (Na$_2$SO$_4$). The residue was purified by silica gel column chromatography using ethylacetate:pet. ether (0.5:9.5) to give 112 (1.29 g) as a colorless oil.

**Yield :** 92%

**IR (neat, cm$^{-1}$):** $\nu_{\text{max}}$ 3019, 2929, 2857, 1746, 1463, 759, 594

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ 0.03 (s, 3H), 0.07 (s, 3H), 0.83 (t, $J$ = 5.6 Hz, 3H), 1.26 (s, 9H), 1.28-1.32 (m, 10H), 1.61-1.69 (m, 2H), 3.76 (s, 3H), 4.11-4.24 (m, 2H)

$^{13}$C NMR (50 MHz, CDCl$_3$) : $\delta$ -5.1, -4.4, 14.0, 18.0, 22.4, 25.6, 29.1, 29.6, 31.7, 33.2, 47.4, 52.6, 72.8, 169.5

**Analysis :** C$_{17}$H$_{35}$BrO$_3$Si (395.45) requires C, 51.63 ; H, 8.92 ; Br, 20.21 Found. C, 51.60 ; H, 8.89 ; Br, 20.19.

**Preparation of salt 113**

To a solution of 112 (0.5 g, 1.26 mmol) in dry acetonitrile (5 mL) was added triphenyl phosphine (0.33 g, 1.26 mmol). The reaction mixture was refluxed till the disappearance of the starting material. Then, the solvent was concentrated under reduced pressure and residue thus obtained was thoroughly washed with petroleum ether to remove the unreacted triphenyl phosphine. The crude salt was used as such in the next reaction.

**Yield :** 66%
**CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation**

$^1$H NMR (200 MHz, CDCl$_3$) : δ -0.03 (s, 3H), 0.00 (s, 3H), 0.89-0.92 (m, 13 H), 1.22 (s, 9H), 1.42-1.53 (m, 2H), 3.76 (s, 3H), 4.12-4.34 (m, 1H), 5.34 (d, $J = 16$ Hz, 1H), 7.35-7.49 (m, 15H)

**Preparation of Methyl (2R)-2-(Tetrahydropyran-2-yloxy)-propionate**

![image]

To a solution of methyl-(R)-lactate $^{108}$ (5 g, 48.03 mmol) in dry CH$_2$Cl$_2$ (30 mL) was added 3,4-dihydro-2H-pyran (4.38 mL, 48.03 mmol) and cat. p-TSA (100 mg) sequentially. The reaction mixture was stirred overnight and neutralized with solid NaHCO$_3$. The crude product was purified over silica gel column chromatography using ethyl acetate:pet. ether (0.5:9.5) as eluent to give $^{114}$ (8.7 g) as a colorless liquid.

**Yield :** 96%

**IR (neat, cm$^{-1}$) :** $\nu_{\text{max}}$ 1723, 1329, 1222, 765

$^1$H NMR (200 MHz, CDCl$_3$) : δ 1.25 (d, $J = 6.06$ Hz, 3H), 1.55-1.69 (m, 4H), 1.74-1.78 (m, 2H), 3.60 (t, $J = 8.2$ Hz, 2H), 3.67 (s, 3H), 3.85 (d, $J = 7.5$ Hz, 1H), 4.95 (t, $J = 6.3$ Hz, 1H)

$^{13}$C NMR (50 MHz, CDCl$_3$) : δ 15.9, 19.2, 28.0, 35.6, 52.7, 63.6, 72.8, 98.4, 171.6

**Analysis :** C$_9$H$_{16}$O$_4$ (188.22) requires C, 57.43 ; H, 8.57. Found. C, 57.41 ; H, 8.53.

**Preparation of (2R)-2-(Tetrahydropyran-2-yloxy)-propan-1-ol**

![image]
To a stirred solution of LAH (0.6 g, 15.94 mmol) in dry THF (60 mL) was added ester 114 (3 g, 15.94 mmol) in dry THF (10 mL) at 0 °C dropwise. The reaction mixture was stirred at ambient temperature till disappearance of starting material and it was cooled to 0 °C. The excess of LAH was quenched with 2N NaOH and filtered. The white precipitate was washed repeatedly and the combined layers were concentrated to near dryness. The residue was purified on silica gel column chromatography using ethyl acetate:pet. ether (1:9) to furnish the alcohol 115 (2.3 g) as a colorless liquid.

Yield: 92%

IR (neat, cm⁻¹): νmax 3466, 1226, 852, 788

¹H NMR (200 MHz, CDCl₃) : δ 1.23 (d, J = 6.1 Hz, 3H), 1.49-1.78 (m, 6H), 2.12 (brs, 1H), 3.17-3.20 (m, 1H), 3.33 (t, J = 6.8 Hz, 2H), 3.66 (dd, J = 10.3, 3.1 Hz, 2H), 4.93 (td, J = 4.4 Hz, 1H)

¹³C NMR (50 MHz, CDCl₃) : δ 18.4, 20.3, 30.2, 33.6, 61.7, 66.1, 70.4, 98.4

Analysis: C₈H₁₆O₃ (160.21) requires C, 59.97 ; H, 10.07. Found. C, 59.96 ; H, 10.04

Preparation of 2-[1-tert-Butyldimethylsilyloxy)-octyl]-4-(tetrahydropyran-2-yloxy)-pent-2-enoic acid methyl ester

To a stirred solution of PCC (1.0 g, 4.68 mmol), anhydrous CH₃COONa (0.38 g, 4.68 mmol) and celite was added alcohol 115 (0.5 g, 3.12 mmol) at 0 °C. The reaction mixture was stirred for 4 h. After removal of dichloromethane the crude was extracted with ether
several times. The combined ether extracts were concentrated to afford the desired aldehyde which was used as such in the next step.

To a suspension of the Wittig salt 113 (1.12 g, 1.77 mmol) in dry THF (20 mL) was added LiHMDS (2.13 mL, 2.13 mmol, 1 M solution in THF) dropwise at -78 °C. The reaction mixture was stirred till all solids dissolved (30 min). To the dark red solution was added the above aldehyde (0.28 g, 1.77 mmol) in dry THF (5 mL) dropwise at -78 °C. The reaction mixture was stirred for 10 h at -78 °C. It was quenched with sat. aq. ammonium chloride and extracted with EtOAc (3x30 mL). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petroleum ether : ethyl acetate (9:1) as eluent gave 116 (0.53) as a colorless liquid.

Yield : 73%

[α]D²⁵ : -12.67

IR (neat, cm⁻¹) : νmax 1723, 1666

¹H NMR (500 MHz, CDCl₃) : δ 0.03 (s, 3H), 0.08 (s, 3H), 0.86-0.89 (t, J = 6.3 Hz, 3H), 1.28-1.31 (m, 10H), 1.27 (s, 9H), 1.41-1.46 (dd, J = 17.7, 7.90 Hz, 3H), 1.52-1.56 (m, 2H), 1.59-1.87 (m, 6H), 3.74 (s, 3H), 4.24-4.26 (t, J = 11.2 Hz, 2H), 4.32-4.44 (m, 1H), 4.70-4.71, (m, 1H), 4.95-4.97 (m, 1H), 6.83-6.84 (d, J = 8.7 Hz, 1H)

¹³C NMR (125 MHz, CDCl₃) : δ -3.79, -4.72, 13.80, 17.94, 18.91, 22.40, 25.26, 28.95, 28.93, 29.25, 30.15, 31.57, 36.42, 41.09, 60.73, 62.14, 97.39, 115.19, 128.19, 173.19, 156.37

GC-MS : m/z 456 (M⁺)

Analysis : C₂₅H₄₈O₇Si (456.73) requires C, 65.74 ; H, 10.59 ; Found. C, 65.52 ; H, 10.21.
Synthesis of (-)-acaterin

To a stirred solution of 116 (0.36 g) in methanol (5 mL) was added catalytic amount of p-toluene sulfonic acid (50 mg) and the reaction mixture stirred overnight. After TLC diagnosis, saturated NaHCO₃ (5 mL) was added and the reaction mixture was extracted with dichloromethane. The combined organic layers were dried over Na₂SO₄ and concentrated to near dryness. Purification of the crude product on silica gel column chromatography using ethyl acetate:pet. ether (8:2) gave (-)-acaterin 78 in 68% yield. The physical and spectroscopic data of compound 78 were in full agreement with natural acaterin.

Yield: 68%

[α]₀^2⁵ : [α]₀^2⁵ = −21.33 (c 0.3, CHCl₃) [lit. 28 −19.7 (c 0.61, CHCl₃)]

¹H NMR (500 MHz, CDCl₃) : δ 0.88 (t, J = 7 Hz, 3H), 1.26-1.32 (m, 10H), 1.43-1.53 (m, 3H), 1.82-2.04 (m, 2H), 3.33 (s, 1H), 4.12-4.15 (m, 1H), 5.11-5.24 (m, 1H), 6.84 (dd, J = 6, 2 Hz, 1H)

¹³C NMR (125 MHz, CDCl₃) : δ 14.3, 19.4, 23.1, 24.2, 30.0, 30.7, 32.5, 72.1, 75.3, 135.6, 137.7, 165.0
3.2.7 Spectra

1. $^1\text{H}$ & $^{13}\text{C}$ NMR spectra of 107
2. $^1\text{H}$ & $^{13}\text{C}$ NMR spectra of 111
3. $^1\text{H}$ & $^{13}\text{C}$ NMR spectra of 112
4. $^1\text{H}$ & $^{13}\text{C}$ NMR spectra of 116
5. $^1\text{H}$ & $^{13}\text{C}$ NMR spectra of 78
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

\[\text{\begin{align*}
\text{\textsuperscript{1}H NMR spectrum of compound 107 in CDCl}_3
\end{align*}}\]

\[\text{\textsuperscript{13}C NMR spectrum of compound 107 in CDCl}_3\]
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

\[ \text{NMR spectrum of compound 111 in CDCl}_3 \]

\[ \text{\textsuperscript{1}H NMR spectrum of compound 111 in CDCl}_3 \]

\[ \text{\textsuperscript{13}C NMR spectrum of compound 111 in CDCl}_3 \]
CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^{1}H$ NMR spectrum of compound 112 in CDCl$_3$

$^{13}C$ NMR spectrum of compound 112 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and
(-)-acaterin via asymmetric dihydroxylation

\[ \text{\(^1H\) NMR spectrum of compound 116 in CDCl}_3 \]

\[ \text{\(^13C\) NMR spectrum of compound 116 in CDCl}_3 \]
CHAPTER 3 Enantioselective syntheses of (-)-α-conhydrine and (-)-acaterin via asymmetric dihydroxylation

$^1$H NMR spectrum of compound 78 in CDCl$_3$

$^{13}$C NMR spectrum of compound 78 in CDCl$_3$
CHAPTER 3 Enantioselective syntheses of (-)-aconhydrine and (-)-acaterin via asymmetric dihydroxylation

3.3 References


CHAPTER 3 Enantioselective syntheses of (-)-a-conhydrine and (-)-acaterin via asymmetric dihydroxylation


