Synopsis
The thesis entitled “Studies towards the total synthesis of Psymberin, Hyptolide and Hypurticin” is divided into three chapters.

**CHAPTER I:**
This chapter is further divided into two sections.

**Section A:**
This section deals with the introduction to 5,6-dihydropyran-2-ones and previous synthetic approaches of Hyptolide.

**Section B:**
This section describes the studies towards the total synthesis of Hyptolide and Hypurticin.

**CHAPTER II:**
This chapter deals with the introduction and earlier synthetic approaches of Psymberin.

**CHAPTER III:**
This chapter describes the studies directed towards the total synthesis of Psymberin.

**CHAPTER I:**
**Section A: Introduction to 5,6-Dihydropyranones (α,β-unsaturated δ-lactones):**

Lactone rings are a structural feature of many natural products. Of the naturally occurring lactones, which display a wide range of pharmacological activities, those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources. Because of their manifold biological properties, these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic. In addition, they inhibit HIV protease, induce apoptosis, and have even proven to be antileukemic along with many other relevant pharmacological properties. At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.
This section describes in brief introduction to 5,6-dihydropyranones (α,β-unsaturated δ-lactones) and their significance in the natural products and also describes the introduction and previous synthetic approaches of hyptolide, a potent cytotoxic agent.

Section B: Studies directed towards the total synthesis of Hyptolide and Hypurticin:
PRESENT WORK AND DISCUSSION:
HYPTOLIDE 1:

Lactone ring constitute a structural feature of a broad range of natural products. Many of these lactones, most particularly those being α,β-unsaturated, display pharmacologically relevant properties (e.g. antitumoral or tumor-promoting activity). Among them the conjugated δ-lactone (+)-hyptolide 1 have been isolated from the leaves of *Hyptis pectinata* species of the family *Lamiaceae*. This compound contains a polyoxygenated chain connected with an α,β-unsaturated six membered δ-lactone and shows cytotoxicity against human tumor cell lines (Figure 1).

![Figure 1. Hyptolide 1](image)

HYPURTICIN 2:

Hypurticin 2 is a highly flexible polyacyloxy-6-heptenyl-5,6-dihydro-2H-pyran-2-one isolated from *Hyptis urticoides* by Romo de Vivar’s group. The structural reassignment, absolute configuration and conformational behavior of highly flexible natural product hypurticin were ascertained by a molecular modeling protocol, which includes extensive conformational searching, geometry optimization ¹H-¹H NMR coupling constants. The structure of hypurticin was found to be 6S-[3’S,5’R,6’S-triacetoxy-1Z-heptenyl]-5S-acetoxy-5,6-dihydro-2H-pyran-2-one (Figure 2).

![Figure 2. Hypurticin 2](image)
Retrosynthetic analysis of Hyptolide 1:

As depicted in Scheme 1, retrosynthetically hyptolide 1 was envisioned to be obtained by the ring closing metathesis of acrylate 3. Intermediate 4 was in turn obtained from the Brown asymmetric allylation of Z-alkenal derived from 5. The alcohol 5 in turn obtained by the series of reactions involving Still-Gennari olefination, Sharpless asymmetric dihydroxylation and Jacobsen kinetic resolution as key reactions starting from benzyl glycidyl ether 6.

Retrosynthetic analysis of Hypurticin 2:

Retrosynthetic analysis revealed that hypurticin 2 can be obtained by the ring closing metathesis of acrylate 19, which in turn obtained by the diastereo and enantioselective hydroxy crotylation of Z-alkenal derived from 5.
The alcohol 5 in turn obtained by the series of reactions involving Still-Gennari olefination, Sharpless asymmetric dihydroxylation and Jacobsen kinetic resolution as key reactions starting from benzyl glycidyl ether 6 (Scheme 2).

RESULTS AND DISCUSSION:

The reaction sequence showed in Scheme 3, describes the synthesis of hyptolide 1 and hypurticin 2. Synthesis commenced from (S)-benzyl glycidyl ether 7. The Jacobsen resolution of benzyl glycidyl ether 6 using (R,R)-(salen)cobalt(II) precatalyst, acetic acid (AcOH) and H₂O (0.55 equiv) for 22 h resulted in (S)-benzyl glycidyl ether 7 in 42% yield. Regioselective opening of the epoxide 7 with propynyllithium, formed on treatment of condensed propyne gas with n-BuLi, in the presence of boron trifluoride diethyl etherate (BF₃·OEt₂) in THF at -78 °C resulted in homopropargyl alcohol 8 in 88% yield, which was protected as TBS ether using TBDMSCl and imidazole in CH₂Cl₂ at 0 °C to room temperature furnished TBS ether 9 in 95% yield. Partial hydrogenation of triple bond under Lindlar’s conditions (H₂-Pd/CaCO₃) in EtOAc afforded the Z-olefin 10 in 93% yield.

The Z-olefin 10 was subjected to Sharpless asymmetric dihydroxylation protocol by using the combination ADmix-α and methane sulfonamide in ³BuOH:H₂O (1:1) afforded the diol 11a and 11b as a inseparable diastereomeric mixture in 4:1 ratio. The diol 11a and 11b upon treating with 2,2-dimethoxy propane in CH₂Cl₂ using catalytic PPTS at 0 °C afforded the acetonide protected compound 12a and 12b as a separable diastereomeric mixture in 4:1 ratio in 92% yield, cleavage of the benzyl ether 12a using Pd(OH)₂ afforded the primary alcohol 13 in 89% yield. The primary alcohol 13 was oxidized under Swern oxidation conditions at -78 °C to afford the corresponding aldehyde, which was subjected
to a Still-Gennari reaction in presence of NaH in THF to provide the α,β-unsaturated ester compound 14 in 90% yield. The chemoselective reduction of α,β-unsaturated ester 14 with DIBAL-H at -78 °C in CH₂Cl₂ afforded the allyl alcohol 5 in 95% yield. The allyl alcohol 5 was oxidized to its corresponding aldehyde 15 by treating with Dess-Martin Periodinane in dry CH₂Cl₂, which was used for next reaction without further purification (Scheme 4).

As depicted in Scheme 5, aldehyde 15 was subjected to asymmetric allylation following Brown’s protocol by using (+)-β-allyldiisopinocampheylborane solution (1 M in Pentane) to afford the secondary alcohol 4. Acylation of 4 with acryloyl chloride in the presence of Hünig’s base furnished acrylate 3.

Acrylate 3 was subjected to ring closing metathesis using Grubbs’ 1st generation catalyst to afford the α,β-unsaturated δ-lactone 17 in 80% yield, which was converted to...
hyptolide 1 in two steps-global deprotection by using PPTS in MeOH at room temperature, followed by acetylation of the resulting triol with acetic anhydride, triethylamine and catalytic DMAP in CH₂Cl₂ at 0 °C afforded hyptolide 1 in 80% yield (Scheme 5). The spectral and analytical data of 1 were in good agreement with those reported in the literature.

The treatment of aldehyde 15 with in situ generated [(Z)-γ-(methoxymethoxy)allyl]-diisopinocampheyloborane, [prepared from methoxy-methyl allyl ether, s-BuLi, Ipc₂-BOMe (derived from (+)-α-pinene) and BF₃OEt₂] in THF at -78 °C to 25 °C in a regioselective and stereoselective manner yielded the corresponding threo-β-methoxymethyl homoallyl alcohol 18 with ≥ 99% diastereoselectivity and > 95% enantioselectivity in 62% yield (Scheme 6).

The protection of the secondary alcohol was achieved with acryloyl chloride in the presence of Hünić’s base to afford compound 19 in 82% yields. The crucial ring closing metathesis of the compound 19 was achieved with Grubbs’ 2nd generation catalyst in CH₂Cl₂ at reflux condition to afford the required 5,6-dihydro-2H-pyran-2-one 20 in 90% yield. Unfortunately, the deprotection of acetonide, TBS ether and MOM ether groups of compound 20 gave no desired product on exposure to the various acidic conditions (Scheme 6).

In conclusion, we have synthesized hyptolide 1 by using Jacobsen’s hydrolytic kinetic resolution, Sharpless asymmetric dihydroxylation, Brown’s asymmetric allylation
and Grubbs’ ring closing metathesis as key reactions. Further trails are in progress for the total synthesis of hypurticin 2.

CHAPTER II:

Natural products continue to be excellent sources for new drug molecules, especially in the area of anticancer therapeutics. In several instances, the minute quantities of the material typically isolated from natural source restrict the ability of research groups to investigate the lead compounds. The natural sources like plants, terrestrial microorganism and marine organisms (sponges, tunicates and shell less mollusks) have been in the focus for the search of new drug candidate. Especially those from marine origin are often obtained in minute quantities, which is insufficient for extensive in vitro studies, determination of structure-activity relationship (SAR) and in vivo studies. Organic synthesis can facilitate the preparation of sufficient amounts of such compounds and even create the simplified analogs of the target compound which can be of same or more biological activity.

This chapter describes in brief the marine natural products and their significance as anticancer primary leads and also describes the introduction and previous synthetic approaches to psymberin, which is a highly potent cytotoxic agent.

CHAPTER III:

This chapter describes our studies directed towards the total synthesis of psymberin a potent cytotoxic agent.

In 2004, two groups led by Pettit and Crews independently disclosed the isolation of constitutionally identical cytotoxins, irciniastatin A and psymberin from the marine sponges Irinia ramose and Psammocinia sp., respectively. From the outset, irciniastatin A and psymberin appeared to be constitutionally equivalent based on high resolution mass spectrometry, in conjunction with the 1D and 2D NMR data. The absolute configuration of psymberin was assigned by the Crews group based on combination of CD and other spectroscopic studies. Importantly, both isolates displayed significant cancer cell growth inhibitory activity against a wide variety of human cancer cell lines. The DeBrabander group announced the first total synthesis of (+)-psymberin, which not only established the
structural assignment, including absolute configuration, but also confirmed that (+)-irciniastatin A and (+)-psymberin 21 were in fact one and the same (Figure 3).

![Figure 3. Psymberin 21](image)

Structurally psymberin 21 consists of an aromatic part i.e., dihydroisocoumarin unit, dimethyl tetrahydropyran ring, N-acyl aminal group and acyclic psymberic acid side chain.

Because of the scarcity from natural source and high importance in terms of its cytotoxicity, psymberin attracted the attention of several synthetic organic chemists towards its synthesis which resulted in its total syntheses, some analogues and its intermediates syntheses. Our efforts en route to the synthesis of psymberin, we report herein the studies directed towards its total synthesis.

**RETROSYNTHETIC ANALYSIS OF PSYMBERIN (21):**

![Scheme 7. Retrosynthetic analysis of psymberin 21](image)
Retrosynthetically, psymberin 21 was envisioned to be obtained by the late stage attachment of psymberic acid side chain by coupling of acid chloride derived from the 23 with the hemiaminal derived from 22. Compound 22 was synthesized by Lewis acid mediated Mukaiyama aldol reaction of enolsilane 24 with dimethyl tetrahydropyran acetate 25 (Scheme 7).

Structurally psymberin 21 consists of three major units i.e., dihydroisocoumarin unit 24, dimethyl tetrahydropyran ring 25 and acyclic psymberic acid side chain 23.

**Synthesis of dihydroisocoumarin unit 24:**

Retrosynthetic strategy for dihydroisocoumarin fragment 24 of psymberin 21 was depicted in Scheme 8. It has been envisaged that fragment 24 can be prepared by the Diels Alder reaction of diene 26 with the dienophile 27. The dienophile 27 is obtained by the reductive opening of chloromethyl tetrahydropyran 28 by some functional group modifications. Compound 28 in turn is obtained from the Prins cyclization of homoallylalcohol 29 with acetaldehyde. The homoallylic alcohol 29 with its single stereogenic center could be easily synthesized from (R)-benzyl glycidyl ether 30.

As depicted in Scheme 9, synthesis commenced from (R)-benzyl glycidyl ether 30. The Jacobsen resolution of benzyl glycidyl ether 6 using (S,S)-(salen)cobalt(II) precatalyst, acetic acid (AcOH) and H₂O (0.55 equiv) for 22 hours resulted in (R)-benzyl glycidyl ether 30 in 44% yield. Regioselective opening of the epoxide 30 with propynyllithium, formed on treatment of condensed propyne gas with n-BuLi, in the presence of boron trifluoride diethyl etherate (BF₃ OEt₂) in THF at -78 °C resulted in homopropargyl alcohol 31 in 88% yield. Birch reduction of 31 using Na in liquid NH₃ furnished dihydroxy trans olefin 32 in
70% yield. Then, selective protection of the primary hydroxyl group as benzyl ether in presence of Bu₂Sn(O), TBAI and BnBr in toluene reflux for 15 hours afforded homoallylic alcohol 29 in 85% yield.

Homoallylic alcohol 29 subjected to crucial Prins cyclization with acetaldehyde using trifluoroacetic acid (TFA) in CH₂Cl₂ followed by hydrolysis of resulting trifluoroacetate 33a using potassium carbonate (K₂CO₃) in methanol afforded tetra substituted pyran 33 in 35% yield. The secondary alcohol of tetrahydropyran 33 was protected as methoxymethylether (MOM ether) using MOMCl in presence of diisopropylethylamine and a catalytic DMAP in CH₂Cl₂ at 0 °C to room temperature to provide MOM ether 34 in 94% yield. Compound 34 on benzyl ether deprotection with Li in liquid ammonia in THF resulted in primary alcohol 35 in 90% yields.
The primary alcohol 35 was treated with TPP, CCl₄ and NaHCO₃ under reflux conditions to furnish corresponding chloromethyl tetrahydropyran 28 in 78% yield. Reductive-elimination of chloromethyl pyran system 28 with LiNH₂ in liquid NH₃ following our group well established protocol, resulted in 1,3-anti diol motif 36 in 70% yield. Protection of secondary hydroxyl group as TBS ether by using TBS chloride and imidazole in CH₂Cl₂ furnished TBS protected alcohol 37 in 90% yield. The alkyne 37 was lithiated with n-BuLi in THF and then treated with methylchloroformate at -78 °C to afford substituted propargylic ester 27 in 86% yield (Scheme 10).

As depicted in Scheme 11, the diene 26 was prepared from 4,6-Dimethyl-1,3-cyclohexadienone 79, which in turn prepared from methylmethacrylate 80 and 2-butanone 81 in presence of sodium ethoxide in xylene. 4,6-Dimethyl-1,3-cyclohexadienone 79 converted to diene 26 upon treatment with Et₃N and TBSOTf or TMSOTf in Et₂O at 0 °C, which was used directly for the Diels Alder reaction without further purification.

As our initial efforts to standardize the Diels Alder reaction between different dienes 26 and dienophile 27 under various conditions were unsuccessful (Scheme 12). We were forced to revise the synthetic strategy for the synthesis of fragment 24.
Revised retrosynthetic strategy for fragment 54:

Revised retrosynthetic strategy for dihydroisocoumarin unit 54 of psymberin 21 is depicted in Scheme 13. It has been envisaged that regioselective opening of epoxide 40 with an amide 39 followed by subsequent reactions will provide dihydroisocoumarin unit 24. The epoxide 40 in turn obtained from cis-2-butane-1,4-diol 41. Amide 39 obtained from resorcinol 42 by involving a series of reactions.

The synthesis of aromatic fragment began with the Vilsmeier formylation of resorcinol 42 with POCl₃ and DMF in acetonitrile yielded 2,4-dihydroxy benzaldehyde 43 in 70% yield, which on subsequent reduction with sodium cyanoborohydride in THF gave dihydroxy toluene 44 in 83% yield. Protection of hydroxyl groups as methyl ethers using potassium carbonate and methyl iodide in acetone afforded 2,4-dimethoxy toluene 45 in 88% yield.

![Scheme 13.](image)

![Scheme 14.](image)
Synopsis

Vilsmeier formylation of 45 gave aldehyde 46, which on subsequent oxidation with NaH2PO4 and NaClO2 in DMSO gave acid 47 in 80% yield. Amidation of acid 47 by treating with thionyl chloride in benzene followed by addition of diethyl amine yielded \(N,N'\)-diethyl-2,4-dimethoxy-5-methylbenzamide 39 in 85% yield. Lithiation of amide 39 with sec-BuLi and TMEDA in THF at -78 °C followed by addition of methyl iodide afforded methylated amide 48 in 78% yield (Scheme 14).

Synthesis of epoxide 40 begun with commercially available \(cis\)-butene-1,4-diol 41, which was protected as its mono benzyl ether in THF at room temperature to yield 49 in 73% yield. The allylic alcohol 49 was subjected to Sharpless asymmetric epoxidation using L-(+)-DET, Ti(O’Pr)4 and TBHP at -20 °C in CH2Cl2 to furnish the chiral epoxy alcohol 50 in 80% isolated yield. The regioselective opening of chiral epoxy alcohol 50 with \(n\)-BuLi and trimethyl aluminium (Me3Al) in CH2Cl2 at 0 °C to room temperature afforded a mixture of 1,3-diol 51a and 1,2-diol 51b in 92:8 ratio in 90% yield. Selective protection of primary alcohol 51a with TBDPSCI and imidazole in CH2Cl2 gave TBDPS ether 52 in 88% yield. Deprotection of benzyl ether using Li-naphthalenide in THF at -20 °C afforded diol 53 in 85% yield. The 1,2-diol was converted to oxirane by treatment with NaH and tosylimidazole in THF at 0 °C to room temperature to yield epoxide 40 in 82% yield (Scheme 15).
Initially we thought that lithiation of tertiary amide 39 with sec-BuLi or t-BuLi followed by the addition of epoxide 40 in presence of boron trifluoride diethyl etherate (BF₃OEt₂) or TMEDA in THF at -78 °C under various conditions will provide aromatic core 54a, but efforts were unsuccessful (Scheme 16).

Scheme 16.

Then we thought that aromatic core can be achieved by the ortho-metallation of tertiary amide 39, followed by the regioselective opening of epoxide 40 with lithium exchange of ortho-metallated tertiary amide 55 but the ortho-metallation of tertiary amide under various experimental conditions were unsuccessful (Scheme 17).

Scheme 17.

Regioselective opening of epoxide 40 with ethylpropiolate in presence of n-BuLi and boron trifluoride diethyl etherate (BF₃OEt₂) in THF at -78 °C afforded substituted propargylic ester 56 in 86% yield. Protection of secondary alcohol 56 as methoxymethylether (MOM ether) using MOMCl in presence of diisopropylethylamine in CH₂Cl₂ at 0 °C to room temperature provided MOM ether 57 in 92% yield (Scheme 18).
The diene 58 was prepared from 1,3-cyclohexadienone 83. The 1,3-cyclohexadienone 83 was converted into 3-methoxy-2-cyclohexenone 84 upon treatment with catalytic amount of H$_2$SO$_4$ in anhydrous methanol, which was further alkylated at 6$^{th}$ position using lithium diisopropylamide and iodomethane, yielding 3-methoxy-6-methyl-2-cyclohexenone 85. Methylated enone 85 was converted to diene 58 upon treatment with LDA and TMSCl/TESCl or Et$_3$N and TBSOTf in THF, which was used directly for the Diels Alder reaction without further purification (Scheme 19).

Efforts to standardize the Diels Alder reaction between different dienes 58 and dienophile 57 under various conditions were unsuccessful (Scheme 20).

Above results forced us to re-revise the synthetic strategy for the synthesis of aromatic fragment.
Revised retrosynthetic strategy for fragment 61:

Revised retrosynthetic strategy for dihydroisocoumarin unit 61 of psymberin 21 is depicted in Scheme 21. It has been envisaged that the anion derived from amide 48 will be added smoothly onto the aldehyde 60, which on further sequence of reactions will afford dihydroisocoumarin unit. The aldehyde 60 in turn obtained from cis-2-butane-1,4-diol 41. Amide 48 obtained from resorcinol 42 by involving a series of reactions.

As depicted in Scheme 22, synthesis of aldehyde 60 began with the mono protected benzyl ether 49, which was subjected to Sharpless asymmetric epoxidation by using D(-)-DET, Ti(OiPr)4 and TBHP at -20 °C in CH2Cl2 to furnish the chiral epoxy alcohol 62 in 80% isolated yield. The regioselective opening of chiral epoxy alcohol 62 with n-BuLi and trimethyl aluminium (Me3Al) in CH2Cl2 at 0 °C to room temperature afforded a mixture of 1,3-diol 63a and 1,2-diol 63b in 92:8 ratio in 90% yield. Selective oxidation of primary alcohol 63a with TEMPO and BAIB in CH2Cl2 at 0 °C to room temperature afforded corresponding aldehyde, which was protected as TBS ether using TBSOTf and 2,6-lutidine in CH2Cl2 at 0 °C to give the TBS protected aldehyde 60.

Scheme 21.

Scheme 22.
Initially we thought that the anion derived from amide 48 with LDA in THF at -78 °C, followed by the addition of aldehyde 60 will afford the adduct 61 (Scheme 23), but the efforts were unsuccessful.

![Scheme 23.](image)

**Synthesis of dimethyl tetrahydropyran ring 25:**

As depicted in Scheme 24, retrosynthetically dimethyl tetrahydropyran ring 25 was envisioned to be obtained by the ozonolytic cleavage of terminal alkene of 64, followed by trapping as acetate 25, which in turn obtained by the sequence of reaction involving Barbier type allylation, oxidation and syn-stereoselective reduction starting from known alcohol 65 derived from L-malic acid 66.

![Scheme 24.](image)

As shown in Scheme 25, synthesis began with L-malic acid 66. Malic acid was converted into malic acid dimethyl ester 68 upon treatment with catalytic amount of BF$_3$OEt$_2$ in anhydrous methanol, which was reduced to (S)-1,2,4-butanetriol upon treatment with borane-dimethylsulfide (BH$_3$Me$_2$S) in presence of catalytic amount of NaBH$_4$ at 0 °C to room temperature. The triol was protected as 1,2-O-cyclohexylidene acetal using cyclohexanone and catalytic PTSA in anhydrous CH$_2$Cl$_2$ to yield cyclohexylidene acetal 65 in 78% yield. Alcohol 65 subjected to Swern oxidation conditions to give the corresponding aldehyde, which on further treatment with Zn and 3,3-dimethyl allyl bromide in THF-aqueous NH$_4$Cl at 0 °C to room temperature for 4 h,
under Barbier reaction conditions afforded carbinol 67a and 67b as a separable diastereomeric mixture (3:7 ratio) in 88% yield.

Oxidation of unrequired anti alcohol 67b with IBX in DMSO and CH$_2$Cl$_2$ gave ketone 69, which on highly syn-stereoselective 1,3-asymmetric reduction afforded the desired syn-diol 67a in 94% yield (syn:anti=92:8) by using LiAlH$_4$-LiI in ether at -100 °C.

Protection of hydroxyl group as benzyl ether 70 using NaH and benzyl bromide in THF, followed by acid catalyzed cleavage of cyclohexylidene acetal 70 using catalytic PTSA in methanol at room temperature for 4 h afforded diol 71 in 85% yield (Scheme 26).

Selective protection of the primary hydroxyl group 71 as TBS ether using TBSCl and imidazole in CH$_2$Cl$_2$ at 0 °C provided TBS ether 64. The terminal alkene 64 subjected to ozonolytic cleavage and the resulting lactol was trapped as acetate using pyridine and acetic anhydride to provide dimethyl tetrahydropyran 25 in 80% yield (Scheme 27).
**Synthesis of psymberic acid side chain fragment 23:**

As depicted in Scheme 28, retrosynthetically psymberic acid side chain 23 was envisioned to be obtained by the regioselective opening of epoxide 72 with isopropenyl magnesium bromide followed by subsequent reactions, the epoxide 72 in turn obtainable by the Sharpless asymmetric resolution of allylic alcohol 73.

The reaction sequence shown in Scheme 29, describes the synthesis of psymberic acid side chain 23. Treatment of epichlorohydrin 75 with benzoxide formed by the treatment of benzyl alcohol with NaH in THF yielded benzylglycidyl ether 6 in 88% yield. Opening of epoxide with trimethylsulphonium iodide and n-Butyl lithium in THF at -8 °C furnished homologated allylic alcohol 73 in 80% yield. The allylic alcohol was subjected to Sharpless asymmetric kinetic resolution protocol using D-(-)-diisopropyl tartarate, Ti(OIPr)₄ and TBHP in CH₂Cl₂ at -20 °C for 2 days afforded epoxyalcohol 76 in 40% yield. The secondary alcohol was protected as methoxymethyl ether using MOMCl in presence of diisopropylethylamine in CH₂Cl₂ at 0 °C to room temperature provided MOM ether 72 in 92% yield. Regioselective opening of epoxide 72 with isopropenyl magnesium bromide in presence of CuI at -15 °C in THF afforded the homoallylic alcohol 74 in 76% yield. Protection of hydroxyl group as methyl ether using NaH and MeI in THF at 0 °C to room temperature provided methyl ether 77 in 83% yield. Cleavage of benzyl ether by using Li-naphthalenide in THF at -23 °C afforded primary alcohol 78 in 88% yield. Oxidation of primary alcohol 78 using Dess Martin reagent in CH₂Cl₂ furnished aldehyde.
which was further converted to acid using NaClO₂, NaH₂PO₄ and 2-methyl-2-butene in 
¹BuOH and H₂O afforded acid³ 23 in 85% yields.

In conclusion, we have synthesized three key building blocks i.e., aryl fragment 48, 
dimethyl tetrahydropyran core 25 and psymberic acid side chain 23 for the total synthesis 
of psymberin. Coupling of these fragments to en route to the total synthesis of psymberin 
are in progress.