ABSTRACT
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The thesis entitled “Total synthesis of Microcarpalide, Aspinolide B and synthetic studies towards the top half of the Phorbaside A” has been divided into three chapters.

CHAPTER I: Deals with the total synthesis of (−)-Microcarpalide.

CHAPTER II: Describes the total synthesis of Aspinolide B.

CHAPTER III: Describes the synthetic studies on Phorbaside A.

CHAPTER I: Deals with the total synthesis of (−)-Microcarpalide.

Microcarpalide 1 (Figure 1) has been recently characterized as a new secondary metabolite produced by an endophytic fungus isolated from the bark of the tropical tree Ficus microcarpa L. by Thomas Hemscheidt et al. in 2001. Bioassay-guided purification of the fermentation broth using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of a new substance displaying remarkable disrupting action on actin microfilaments, to which the structure of 1 was assigned. Microcarpalide was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle). Moreover, it displayed weak cytotoxicity towards mammalian cells, thus providing an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs. We developed a convergent total synthesis of (−)-microcarpalide from chiral pool starting material D-mannitol.

Retrosynthetic strategy of Microcarpalide:

The retrosynthetic scheme for 1 was based on coupling of two partners, 3 and 4, via esterification (Scheme 1) and subsequent ring closing metathesis (RCM). D-mannitol was used as the chiral pool source for the construction of both the coupling partners.
Synthesis of olefinic alcohol 3:

Synthesis of olefinic alcohol fragment 3 was commenced from 7, which was prepared as an inseparable 9:1 diastereomeric mixture in favour of required isomer according to the reported procedure from D-mannitol. Protection of the secondary hydroxy group of 7 with TBDPS-Cl, imidazole and DMAP in DMF gave compound 8, which on treatment with 60% acetic acid at room temperature for 12 hours afforded diol 9 in 98% yield. Chemoselective acetylation of the primary hydroxy group of 9 with acetyl chloride in the presence of 2,4,6-collidine in CH$_2$Cl$_2$ at –78 °C furnished compound 10 in 80% yield as a pure diastereomer after the minor isomer had been easily separated by standard silica gel column chromatography. The mono acetylated compound was then treated with Ms-Cl, Et$_3$N and DMAP in CH$_2$Cl$_2$ to give the mesylated compound, which on treatment with K$_2$CO$_3$ in MeOH provided the epoxide 11 in 70% yield over two steps (Scheme 2).
Now epoxide 11 was treated with \( n \)-pentyl cuprate at \(-20\) °C to produce the secondary alcohol 12 in 70% yield, which was treated with MEMCl and DIPEA in \( \text{CH}_2\text{Cl}_2 \) at rt for 3 days to furnish the compound 13 in 80% yield. Finally TBDPS deprotection with TBAF in THF furnished the olefinic alcohol fragment 3 in 90% yield.

**Synthesis of Olefinic acid 4:**

Synthesis of olefinic acid 4 was started from compound 15, which was synthesized from D-mannitol 6 according to the reported procedure. Oxidative cleavage of the diol 15 followed by two-carbon Wittig olefination gave 16 (\( E:Z = 7:3 \)) in 80% overall yield (Scheme 3). Double bond reduction of both the isomers under hydrogenation conditions furnished compound 17 in 90% yield. Acid mediated deisopropylidination of 17 gave the diol 18, which on treatment with TPP, imidazole and I\(_2\) in toluene afforded the olefinic ester 19 in 80% yield. The saponification of ester 19 with LiOH gave the olefinic acid 4.
The union of the two fragments 3 and 4 was achieved by using DCC to furnish the diene ester 2 (Scheme 4).

Treatment of 2 with the Grubbs’ first generation catalyst under high dilution conditions (0.001 M in degassed CH₂Cl₂) furnished a E: Z (10:1) mixture of macrocyclic lactones, from which the (E)-isomer 20 was isolated by silica gel column chromatography. Global deprotection of E-20 gave microcarpalide 1 (Scheme 4). The spectroscopic and analytical data of compound 1 and other compounds were in good agreement with the literature data.
In conclusion, we have achieved a convergent total synthesis of (−)-microcarpalide from the commercially available, cheap starting material D-mannitol.

CHAPTER II: This part describes the Total synthesis of Aspinolide B.

Aspinolide B 1 (Figure 2) was isolated from the cultures of *Aspergillus ochraceus*, whose relative stereochemistry was established by X-ray analysis. The absolute stereochemistry was established on the basis of Helmchen’s method, followed by total synthesis. As a part of our constant interest on stereoselective syntheses of natural products from the chiralpool, herein we report a convergent approach for the total synthesis of aspinolide B (1) started from the cheap and easily available chiralpool starting material, D-mannitol.

![Figure 2](image)

**Aspinolide B (1)**

**Retrosynthetic Strategy for Aspinolide B:**

Retrosynthetically (Scheme 5), aspinolide B could be obtained *via* esterification of crotonic acid with alcohol 2, which could be synthesized from bis-alkene 3 *via* ring closing metathesis, a key reaction, which has been widely used for the synthesis of natural products having similar skeletal. Again *bis*-alkene 3 could be obtained from two synths, olefinic alcohol 4 and olefinic acid 5, *via* Yamaguchi esterification. Both of them in turn could be synthesized from D-mannitol 6.

![Scheme 5](image)
Synthesis of olefinic alcohol 4:

The synthesis of olefinic alcohol 4, (Scheme 6) commenced from 7, which was prepared from D-mannitol according to the reported procedure. Oxidative cleavage of the diol 7 with NaIO₄, followed by in situ reduction of the resulting aldehyde with NaBH₄ gave primary alcohol 8.

Compound 8 was converted to allylic alcohol 10 in two steps, involving formation of iodide 9 with TPP, I₂ and imidazole in toluene followed by Zn-mediated elimination to furnish allylic alcohol 10 in 75% yield over two steps. PMB protection of the resulting alcohol, followed by acetonide deprotection with AcOH:THF:H₂O (2:1:1) afforded diol 12. Selective tosylation of the primary hydroxyl group gave the corresponding tosylate, which on treatment with K₂CO₃ in anhydrous methanol gave epoxide 13 with 75% yield over two steps. Finally epoxide opening with DIBAL-H in CH₂Cl₂ afforded alcohol fragment 4 in 88% yield.

Synthesis of Olefinic Acid 5:

The synthesis of fragment 5 (Scheme 7) commenced from allylic alcohol 10. Acetonide deprotection followed by selective protection of the primary hydroxyl group as its TBDPS ether gave 14. Benzylation of 14 with NaH, BnBr and TBAI in THF gave 15. Dihydroxylation of 15 with OsO₄ gave a diol, which on oxidative cleavage with NaIO₄, followed by Wittig olefination with Ph₃P=CHCOOEt in CH₂Cl₂ at rt gave 16 (E:Z = 70:30) in 70% yield over three steps. Selective hydrogenation of double bond in presence of benzylos of compound 16 with H₂ over Pd-C, and cat. n-BuNH₂ in methanol gave 17,
which on treatment with TBAF in THF afforded primary alcohol 18. Compound 18 was transformed into alkene ester 19 in two steps. Swern oxidation of 18 gave an aldehyde, which on Wittig olefination with Ph$_3$P=CH$_2$ in ether gave alkene ester 19 in 75% yield over two steps. Finally, saponification of ester 19 with LiOH provided the desired olefinic acid fragment 5.

Condensation of fragments 4 and 5 was achieved under Yamaguchi conditions to furnish the bis-olefinic ester 3 (Scheme 8).
The crucial ring closing metathesis of 3 using Grubbs’ 1st generation catalyst failed under various conditions. Gratifyingly, use of the Grubbs’ 2nd generation catalyst (20 mol%) in toluene under argon at 90 °C for 20 h, resulted in ring-closing metathesis of 3 to afford \( E-20 \) as the only isolable product in 35% yield. Selective deprotection of the PMB group with TFA in \( CH_2Cl_2 \) furnished alcohol 2. Finally, acylation of 2 with crotonic acid gave ester 21, which on debenzylation with TiCl₄ in \( CH_2Cl_2 \) afforded Aspinolide B (1). The spectroscopic and analytical data of compound 1 and other compounds were in good agreement with the literature data.

In conclusion, we have achieved the highly convergent stereoselective total synthesis of aspinolide B from the commercially available, cheap starting material D-mannitol, using ring-closing metathesis as a key step.

CHAPTER III: This chapter describes the synthetic studies on Phorbaside A.

Phorbasides A (1) and B (2) (Figure 3) were isolated from the sponge Phorbas sp. from Western Australia. From the major fractions of Phorbas extracts phorbaxozoles A
and B, two highly cytostatic macrolides, were isolated. Minor fractions of Phorbas extracts using a highly sensitive $^1$H NMR cryoprobe (600 MHz) showed the presence of macrolides in only micromole amounts and led to the isolation of the new compounds (+)-phorbasides A (1) and B (2). The later are unrelated to phorboxazoles but closely resemble the rare callipeltosides (e.g., (−)-callipeltoside A) from a different sponge, Callipelta sp. The low natural abundance and fascinating architecture of phorbaside A attracted our attention for its synthetic studies. Herein we report the synthesis of C$_1$-C$_9$ fragment of phorbaside A (3).

Retrosynthesis:

The top half of the molecule (3) could be devided into two fragments 4 and 5 which could be obtained via glycosidation of pyran core 5 with glycoside 4, which could be synthesized from L-rhamnose 6. The pyran core 5 could be achieved from methyl (S)-3-hydroxy 2-methyl propionate 7 (Scheme 9).
**Synthesis of pyran core 5:**

Synthesis of pyran core 5 started from commercially available 7. Protection of the primary hydroxyl group with TBDPSCl and TEA in CH$_2$Cl$_2$ afforded compound 8, which on reduction with LiBH$_4$ followed by oxidation under Swern conditions gave the aldehyde 9 in 75% yield over two steps. Now the addition of the enolate, generated from 10 under Crimmins conditions, to the aldehyde 9 furnished compound 11 in 90% yield. Reductive removal of the chiral auxiliary followed by $p$-methoxybenzylidene protection of the resultant diol gave compound 12 in 80% yield over two steps. TBDPS deprotection of 12 gave primary alcohol which on Swern oxidation furnished the aldehyde 13 in 75% yield over two steps. Aldol reaction between the aldehyde 13 and 15 under Crimmins conditions afforded the compound 16 (Scheme 10) in 85% yield.
Compound 16 was then treated with LiBH₄ in ether to give the diol 17, which was protected with 2,2-dimethoxypropane in CH₂Cl₂ in presence of catalytic amount of CSA to furnish the compound 18. Reductive opening of the benzylidene ring in 18 from the less hindered side with DIBAL-H furnished the primary alcohol 19, which on Swern oxidation gave aldehyde 20. (−)-Spartine mediated aldol reaction between 20 and 15 gave compound 21, which on treatment with LiBH₄ afforded the diol compound 22 in 70% yield over two steps. Chemoselective protection of the primary alcohol with pivoloyl chloride in pyridine afforded compound 23, which on oxidation with Dess-Martin periodinane gave the keto compound 24 in 95% yield. Acetonide deprotection followed by hemiketal formation under acidic conditions furnished the compound 25, which on treatment with TBSOTf and 2,6-lutidine furnished the compound 5 (Scheme 11).
Glycosidic part was synthesized from L-rhamnose 6. Treatment of L-rhamnose with MeOH and TMSCl at reflux conditions gave the β-O-methyl rhamnopyranoside 26. Compound 26 was treated with PMP acetal in CH₂Cl₂ in presence of catalytic amount of CSA to afford the compound 27 in 80% yield. Compound 27 was treated with TBSOTf and 2,6-lutidine to give the compound 28, which on treatment with DIBAL-H gave compound 29 as major product in 70% yield. Compound 29 was treated with Dess-Martin periodinane to give the keto compound 30 in 90% yield, which was treated with CH₃MgI and MgBr₂Et₂O ether at −78 °C to furnish the compound 31 in 80% yield. Compound 31 was treated with TFA in CH₂Cl₂ at 0 °C to give the compound 32. Selective protection of the secondary hydroxy group in presence of tertiary hydroxy with CH₃I and NaH afforded compound 4 (Scheme 12).
In conclusion, we developed a short and efficient synthesis for the C₁-C₉ fragment 5 and glycosidic moiety 4. Synthetic studies are under progress towards the ‘Total synthesis of Phorbaside A’ in our laboratory.