SYNOPSIS

The thesis entitled **"Synthesis of Cryptopyranmoscatones A2, A3, B4, Cryptoconcatone H and Tetrahydropyran ring containing Macrolactin"** is divided into three chapters.

CHAPTER I: This chapter is divided into two sections.

Section A: This section deals with the introduction and the stereoselective total synthesis of Cryptopyranmoscatone A2.

Section B: This section deals with the introduction and the stereoselective total synthesis of Cryptopyranmoscatone A3 and B4.

CHAPTER II: This chapter deals with the introduction, earlier synthetic approaches and the stereoselective synthesis of C1-C9, C11-C19 and C18-C24 fragments of Macrolactin 3.

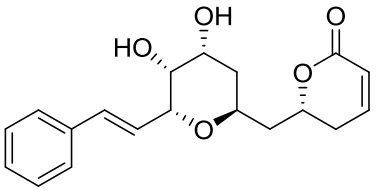
CHAPTER III: This chapter deals with the introduction and studies towards the synthesis of Cryptoconcatone H.

Chapter I: It is divided into two sections

Section A: This section deals with the introduction and the stereoselective total synthesis of Cryptopyranmoscatone A2.

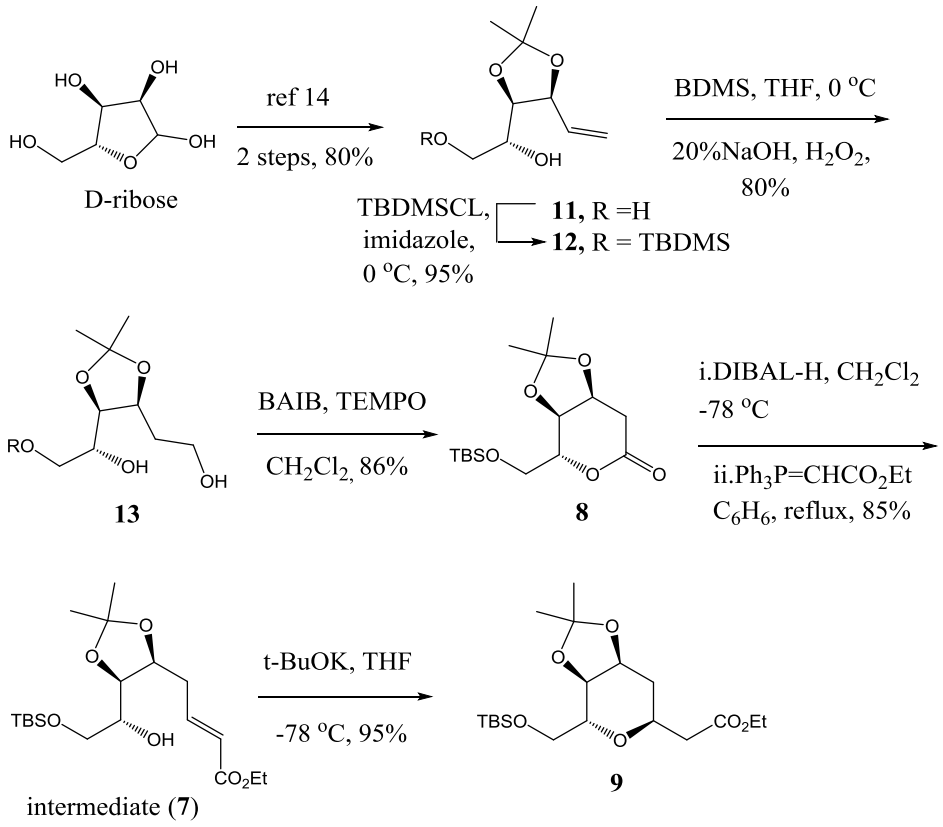
Cryptopyranmoscatones A1, A2, A3, B1, B2 and B4 (**1-6**) (Figure 16) were isolated from the branch and stem bark of *Cryptocarya moschata*, Lauraceae, a tree growing up to 30-40m high, found in the Atlantic Forest, mainly in the Southeastern Region of Brazil. The structures were established by spectroscopic studies and these 5,6-dihydro-α-pyrones contain a styryl group attached to the C6 side chain. Styryllactones in general are reported to possess significant cytotoxicity toward several human tumor lines. Some of the *Cryptocarya* pyrones have been identified as highly efficacious inhibitors of the G2 check point, which can enhance killing of cancer cells by ionizing radiation and DNA-damaging chemotherapeutic agents, particularly in cells lacking p53 function. *Cryptocarya* species showed outstanding equipotent activity towards COX-1 and COX-2.

The highly unique structures and the impressive levels of biological activities makes them as attractive targets for total synthesis. The common feature of these pyrones is that they all contain a styryl group; however they have varying carbon skeletons.



Cryptopyranmoscatone A2 (**2**)

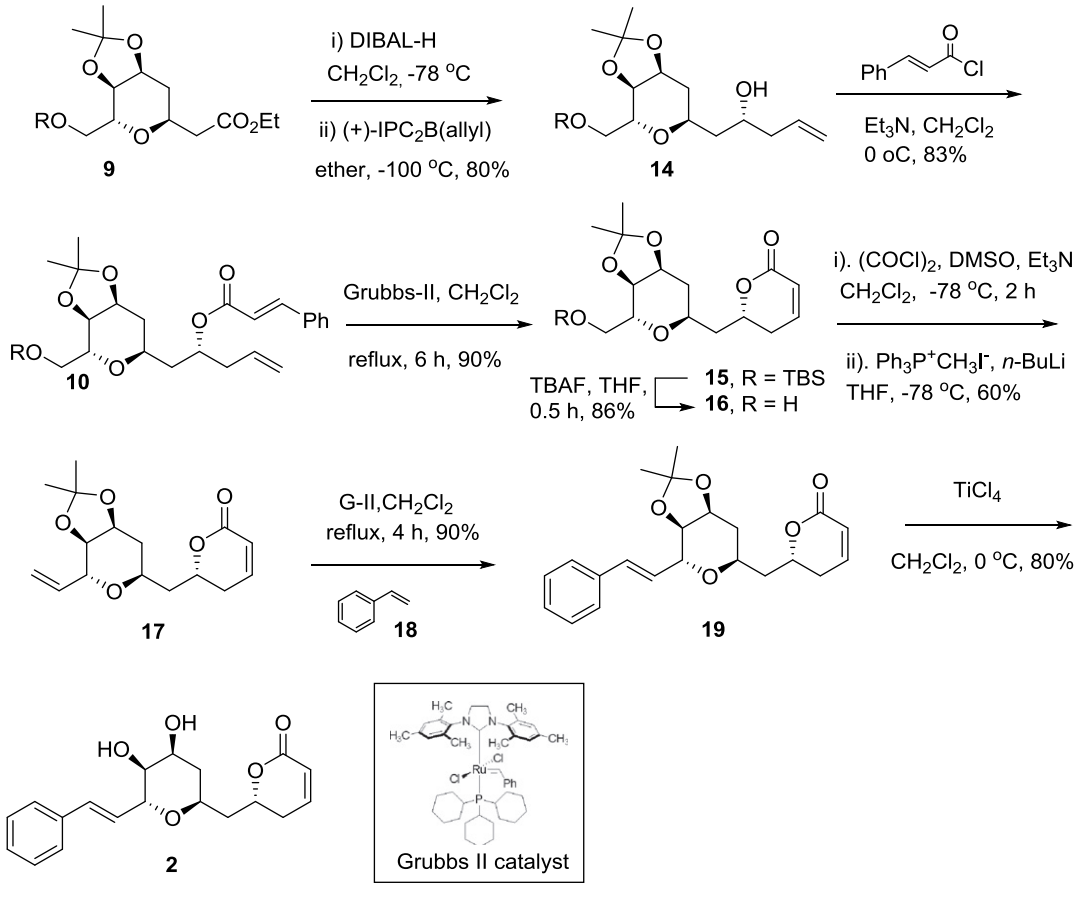
The synthesis of 2,6-*trans*-tetrahydropyran core (*trans*-**9**) of Cryptopyranmoscatone A2 is illustrated in Scheme 2. It was initiated from compound **11**, which was synthesized in two steps from commercially available D-ribose following a known protocol. The primary alcohol **11** was protected with TBSCl/imidazole to give silyl ether **12** in 95% yield. Hydroboration of **12** with $BH_3 \cdot Me_2S$ followed by oxidative workup afforded 1,5-diol **13** in 80% yield. Oxidative cyclization of diol **13** with 2,2,6,6-tetramethyl-1-piperidinyloxy



Scheme 2

(TEMPO) and [bis(acetoxy)iodo]benzene [($PhI(OAc)_2$) (BAIB)] produced the desired δ-lactone **8** in 86% yield. The intermediate **7** could be made from **8** by lactone opening. Thus, lactone **8** was reduced to lactol using DIBAL-H and subjected to Wittig olefination using stabilized ylide to furnish α,β-unsaturated ester **7** in 85% overall yield.

Since, we need a *trans*-tetrahydropyran unit, the hydroxy ester **7** was subjected to Intramolecular oxa-conjugate cyclization (oxa-Michael reaction) by exposure to KO^t-Bu in THF at -78 ^oC for 30 min, which gave rise to 2,6-*trans*-tetrahydropyran (*trans*-9) in 95% yield with high diastereoselectivity (dr = 20:1). This *trans*-stereochemistry of the newly generated ring-junction of tetrahydropyran **9** was assigned based on ^1H NMR (600 MHz, $CDCl_3$) data and assignments were made with the aid of TOCSY and NOESY experiments.

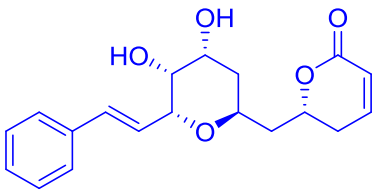


Scheme 3. Total Synthesis of Cryptopyranmoscatone A2 (**2**)

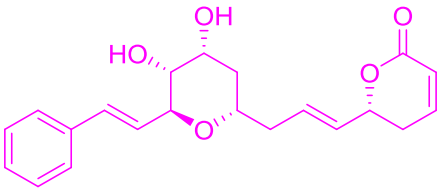
Diisobutylaluminium hydride (DIBAL-H) Reduction of ester in *trans*-9 furnished an aldehyde, which was subjected to Brown asymmetric allylation with (+)-Ipc_2B-allyl at -100 ^oC to give homoallyl alcohol **14** in 80% yield. Acylation of **14** with cinnamic acid under DCC−DMAP conditions provided compound **10** in 83% yield with dr 99:1 (by HPLC). Treatment of **10** with second-generation Grubbs' catalyst (10 mol%) in CH_2Cl_2 at reflux temperatures afforded lactone **15** in 90% yield. The ^1H NMR spectral data confirmed the presence of *cis* olefin.

Removal of the TBS group with TBAF in THF gave primary alcohol **16**. Alcohol **16** was oxidized under Swern reaction conditions to give an aldehyde, which was subjected to Wittig olefination with methyltriphenylphosphonium iodide to give an olefinic lactone **17** in 60% yield over two steps. The cross-metathesis reaction of olefin **17** with styrene **18** using Grubbs' second generation carbene catalyst in CH_2Cl_2 under reflux conditions for 4 h afforded **19** in 90% yield. Finally deprotection of the acetonide group in compound **19** using conc $TiCl_4$ completed the first total synthesis of cryptopyranmoscatone A2 (**2**) in 80% yield.

Section B: This section deals with the introduction and the stereoselective total synthesis of Cryptopyranmoscatone A3 and B4.



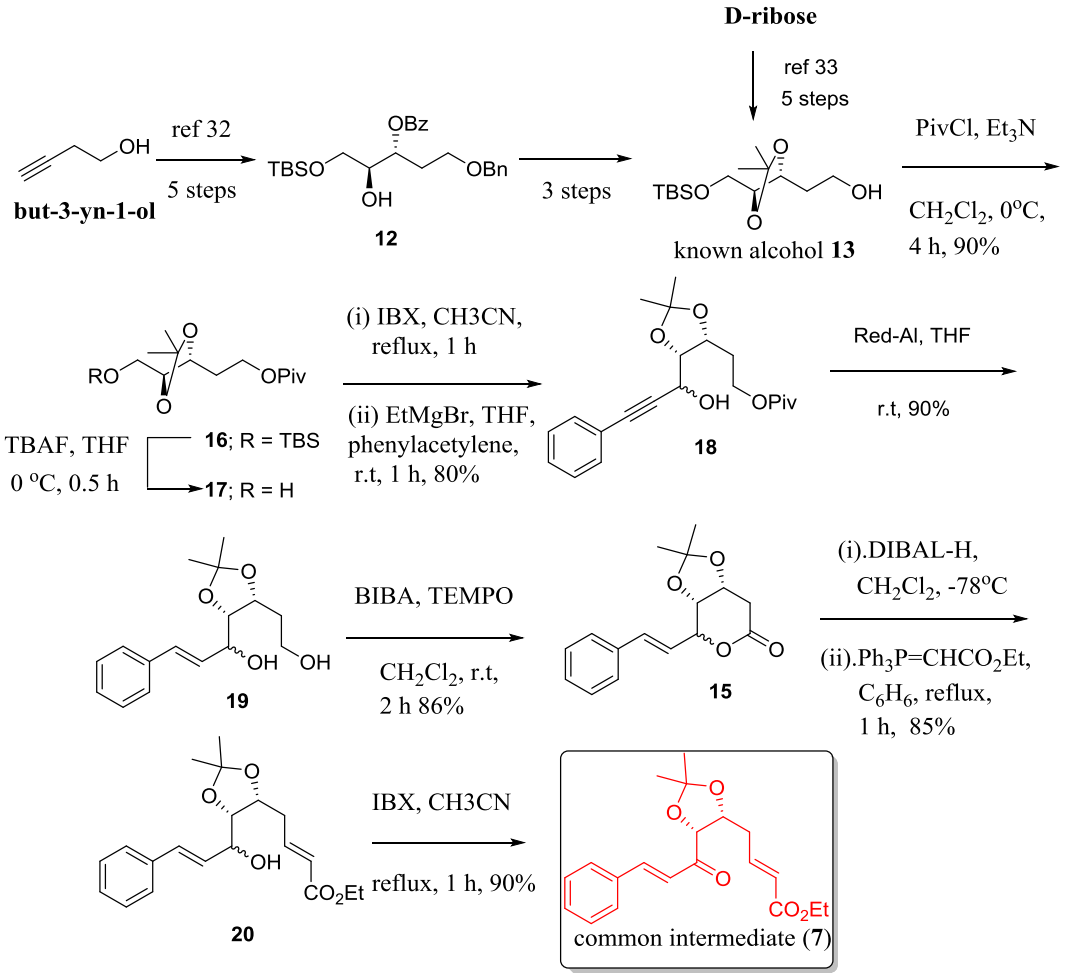
cryptopyranmoscatone A3 (**3**)



cryptopyranmoscatone B4 (**6**)

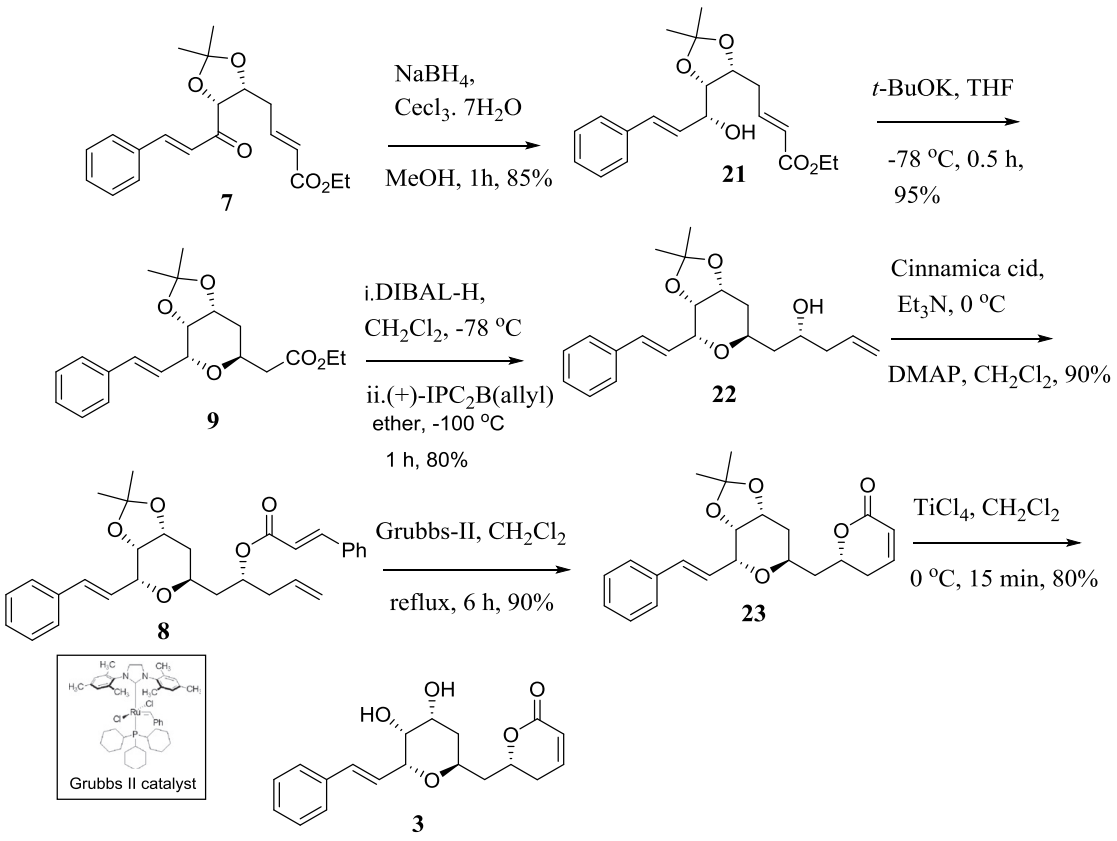
The synthesis of the key intermediate **7** was started with the known alcohol **13** (Scheme 2). Initially, it was planned to get **13** from benzoate diol **12** in a three step sequence by protecting group manipulations, *i.e.*, TBS protection to obtain silyl ether followed by removal of benzoyl and benzyl groups to give **13** in 50% overall yield. The known benzoate diol **12** could be prepared in five steps following literature procedures. Keeping in mind that the number of steps involved and overall yield in obtaining alcohol **13**, it was alternatively prepared from D-ribose in 5 steps in an overall yield of 70%. After

protecting the free hydroxyl group in **13** was protected with pivaloyl ether gave pivaloyl protected ether **16**. The TBS group of compound **16** was removed with TBAF to yield the corresponding alcohol **17**. Oxidation of alcohol **17** with IBX gave an



Scheme 2. Synthesis of key intermediate **7**

aldehyde, which was subjected to Grignard addition reaction with phenyl acetylene led to propargyl alcohol **18** as a mixture of diastereomers in 88:12 ratio (determined by chiral HPLC). This compound (**18**) was carried further (inseparable) for the preparation of an intermediate keto compound **7**. Therefore, in practice, the mixture of diastereomers from the Grignard reaction was carried on to the keto stage. Thus, partial reduction of triple bond in **18** with Red-Al furnished diol **19**. The Oxidative cyclization of 1,5-diol **19** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB) produced the desired δ-lactone **15** in 86% yield.



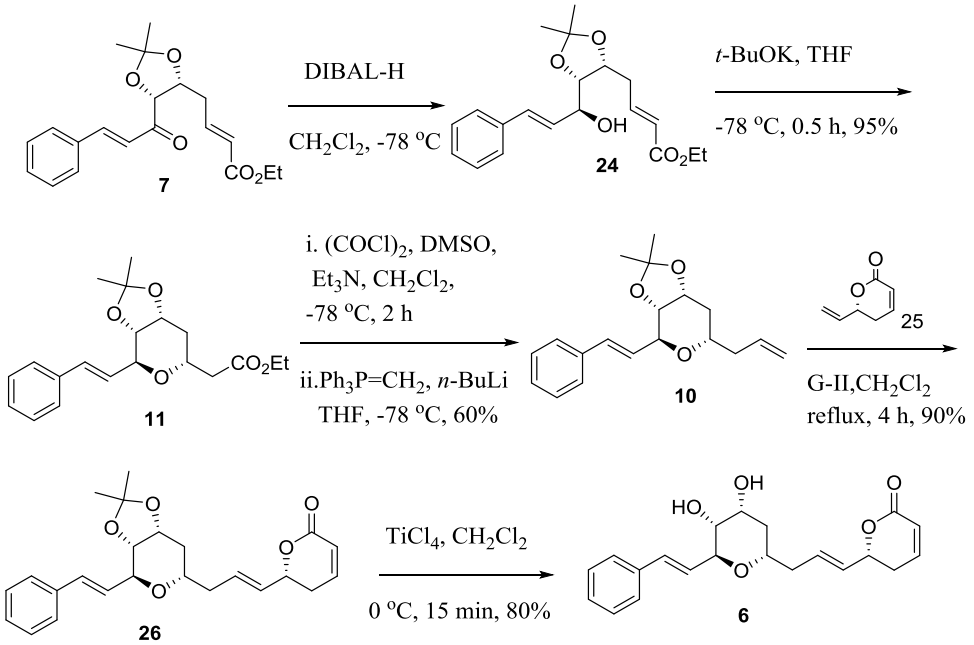
Scheme 3

The lactone **15** was reduced to lactol using DIBAL-H and subjected to Wittig olefination using two carbon stabilized ylide to furnished α,β-unsaturated ester **20** in 78% overall yield (Scheme 2). IBX oxidation of **20** furnished the key intermediate **7**, from which the two target molecules, **A3** and **B4** could be synthesized by adopting a chemoselective reduction of keto group.

Accordingly, the synthesis of A3 (**3**) commenced (Scheme 3) by stereo selective reduction of keto group in **7** using $NaBH_4$ in the presence of $CeCl_3.7H_2O$ at -78 ^oC in MeOH to furnish the *syn* alcohol **21**. The hydroxyl ester **21** on exposure to *t*-BuOK in THF at -78 ^oC readily underwent intramolecular oxa-Michael reaction to afford 2,6-*trans* tetrahydropyran **9** as a single diastereomer (> 20:1) in 92% yield. This *trans*-stereochemistry of the newly generated ring-junction of tetrahydropyran **9** was assigned based on ^1H NMR (600 MHz, $CDCl_3$) data and assignments were made with the aid of TOCSY and NOESY experiments**.**

After confirming the structure, ester group in **9** was reduced with DIBAL-H and the resulting aldehyde was subjected to Brown's asymmetric allylation using (+)-Ipc_2B-allyl to furnish the homoallyl alcohol **22** in 80% overall yield over the two step-sequence. Subsequent coupling of alcohol **22** with cinnamic acid under DCC-DMAP conditions provided diene **8** in 85% yield. Ring closing metathesis (RCM) of diene **8** using the second-generation Grubbs' catalyst in DCM under refluxing conditions yielded lactone **23** exclusively. Finally, removal of acetonide group using TFA in DCM at 0 ^{o}C- r.t. for 0.5 h furnished the target lactone, cryptopyranmoscatone A3 (**3**) in 80% yield.

Next, we focused on the synthesis of cryptopyranmoscatone B4 (**6**) from a common intermediate **7**, which on DIBAL-H reduction produced *anti* alcohol **24** and correlated the stereochemistry with the literature precedence. The hydroxyl ester **24** on exposure to *t*-BuOK in THF at -78 ^{o}C readily underwent intramolecular oxa-Michael reaction to afford 2,6-*trans* tetrahydropyran **11** as a single diastereomer (> 20:1) in 90% yield.



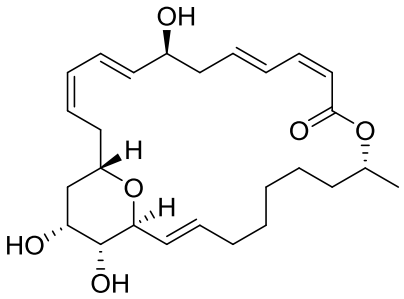
Scheme 4

This *trans*-stereochemistry of the newly generated ring-junction of tetrahydropyran **11** was assigned based on ^{1}H NMR (600 MHz, $CDCl_3$) data and assignments were made with the aid of TOCSY and NOESY experiments.

After confirming the structure, ester group in **11** was converted into terminal alkene by subsequent reduction using DIBAL-H in CH_2Cl_2 followed by one-carbon Wittig reaction to afford **10**. The cross-metathesis (CM) reaction of terminal alkene with the known vinyl lactone **25** using Grubbs' second generation catalyst in DCM under refluxing conditions for 4 h afforded the required lactone **26**. Finally, the deprotection of acetonide group was achieved by treatment with TFA in DCM at 0 ^{o}C-r.t for 0.5 h to give the target lactone, cryptopyranmoscatone B4 (**6**) in 80% yield.

Chapter II: This chapter deals with the introduction, literature approaches and the present work related to the synthesis of C1-C9, C11-C19 and C18-C24 fragments of Macrolactin **3**

Isolation and biological studies macrolactin3: Marine microorganisms are rich sources of novel, bioactive secondary metabolites, and have attracted much attention of chemists, pharmacologists, and molecular biologists. Three novel bioactive 24-membered macrolactines **1-3** (Figure 18) were isolated by Shin and co-workers from fermentation of a marine microorganism *Bacillus sp*. 09ID194 and subsequent bio-assay-guided fractionation and showed antimicrobial activities against both Gram-positive and Gram-negative pathogens. The structures and absolute stereochemistry of macrolactins **1-3** were established by a combination of coupling constants, ROESY data analysis, and application of the modified Mosher's method. Compounds **1−3** each showed a minimum inhibitory concentration (MIC) of 0.16μM against *Bacillus subtilis* and *Escherichia coli* in a standard *in vitro* broth dilution assay. Their MICs against *Saccharomyces cerevisiae* were 0.16, 0.02, and 0.16μM, respectively.

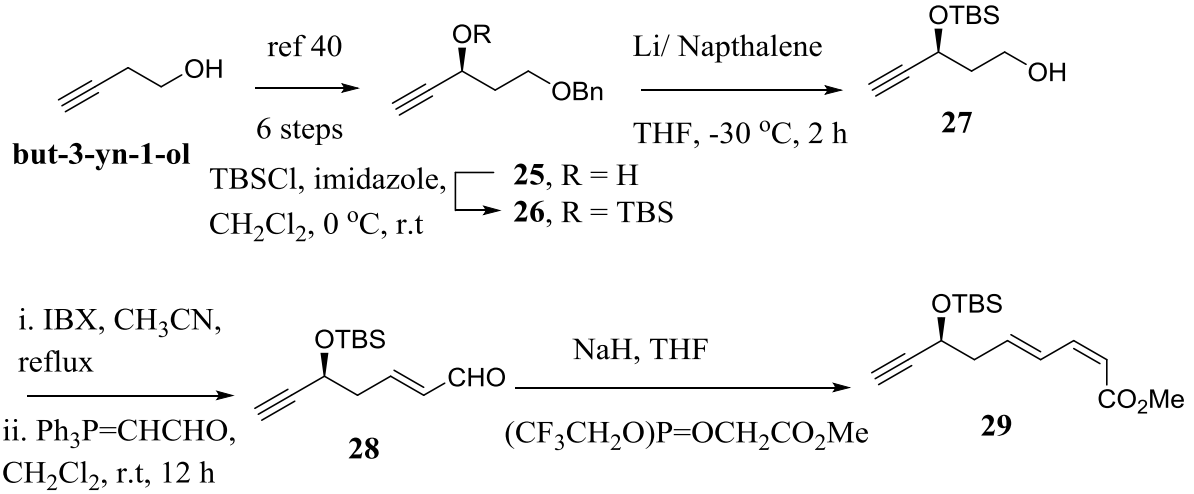


Macrolactin 3

Macrotactin **3** (Figure 18) is a 24 membered cyclic ester containing ene diene, tetrahydropyran ring moieties and conatining three -OH groups attached to C7, C15 and C16. It shows antimicrobial activities against both Gram-positive and Gram-negative pathogens.

Synthesis of C1-C9 fragment (**29**)

The key building block C1-C9 fragment (**29**) of macrolactin **3** also present in macrolactins **1** and **2**, derived from commercially available 3-butyn-1-ol (homopropargylic alcohol). The known benzyl protected (*S*)-alcohol (**25**) was prepared following the similar procedure used for the PMB and THP protected alcohols. The free secondary hydroxyl group was protected as a silyl ether **26**. The removal of benzyl group in compound **26** using Li/Naphthalene in THF at -30 ^{o}C furnished alcohol **27**. Oxidation of alcohol **27** with IBX furnished the corresponding aldehyde, which was subjected to a two-carbon extension using triphenylphosphoranylideneacetaldehyde (Ph_3P=CHCHO) to afford **28**.

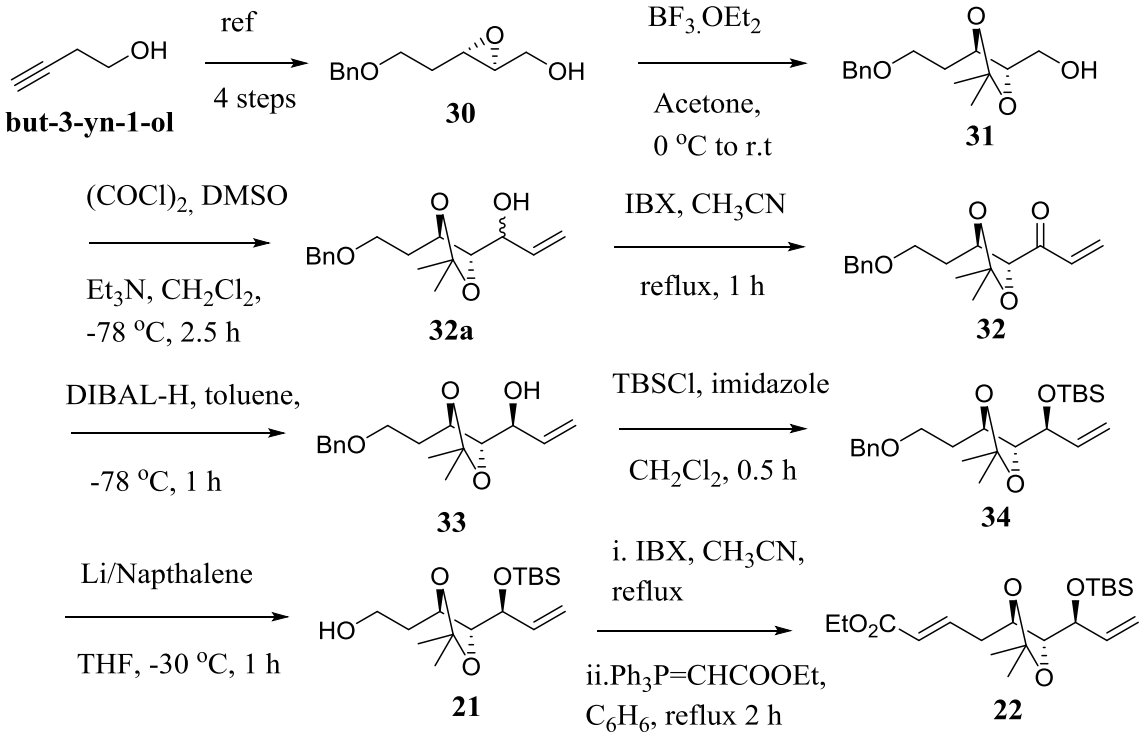


Scheme 2

Applying the Stille–Gennari reaction to compound **28** provided (*E*),(*Z*)-yn-ol ester **29** (C1-C9 fragment) using methyl *P*,*P*'-bis(2,2,2-trifluoroethyl)phosphonoacetate in the presence of NaH in THF at -78 ^{o}C with excellent stereoselectivity (*Z*,*E*/*E*,*E* 95:5) in 80% yield.

Synthesis of C11-C19 fragment (**24**)

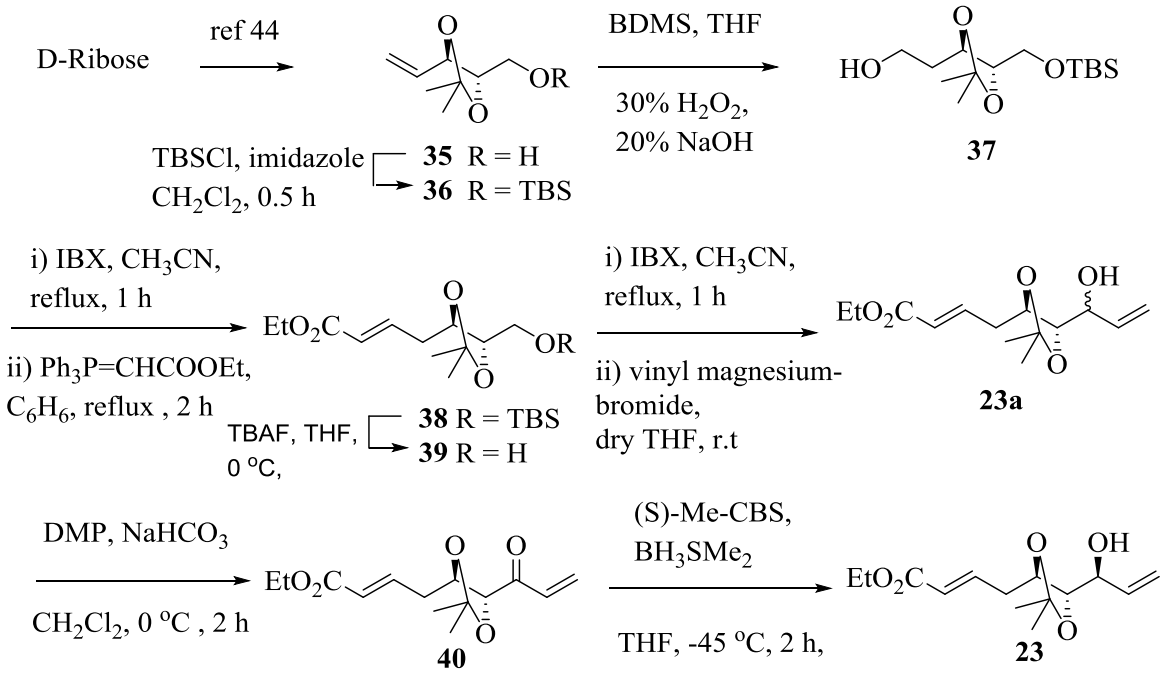
To allow flexibility in our synthetic plan, we envisaged two pathways to access an intermediate **22**. Pathway A (Scheme 3) was based on epoxide opening with $BF_3.OEt_2$. Accordingly, 3-butyn-1-ol (homopropargyl alcohol) was converted into known benzyl protected 2,3-epoxy alcohol **30** in 4 steps as reported. Epoxy compound **30** was treated with anhydrous acetone in the presence of $BF_3.OEt_2$ at 0 ^oC to furnish acetonide **31** in 85% yield. The alcohol **31** was converted into the corresponding aldehyde by Swern oxidation, which was used for further reaction without isolation and characterization. To create a third stereogenic center, a vinyl Grignard reaction was performed using in situ generated vinyl magnesium bromide which provided allyl alcohol **32a**. It is converted into a keto compound **32**. The Stereoselective reduction of keto group in compound **32** with DIBAL-H in dry toluene at -78 ^oC affording the required alcohol **33** in 85% yield. The free hydroxyl group in **33** is protected as silyl ether with TBSCl/imidazole to give compound **34**.



Scheme 3

Debenzylation of **34** with Li/naphthalene in THF at -30 ^{o}C gave alcohol **21**. Oxidation of primary alcohol in **21** with IBX (2-iodoxybenzoic acid) produced the desired aldehyde, which was then subjected to Wittig olefination for the homologation of the chain using a stabilized ylide, Ph_3P=CHCOOEt to give α,β-unsaturated ester **22**.

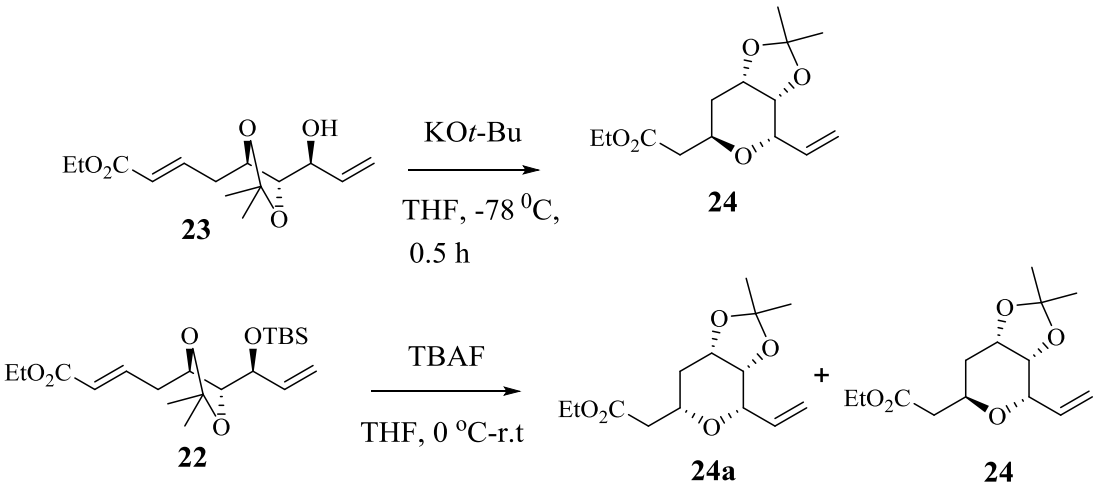
While our manuscript under preparation, a report appeared, in which a relatively close synthetic scheme was discussed for accessing pyran core. Therefore, we adopted another pathway from D-ribose to access an intermediate compound **23**. The synthesis of **23** began with the known alcohol **35**, obtained from D-ribose as reported. Protection of the hydroxyl group in **35** as its silyl ether furnished **36**. The terminal alkene in **36** on hydroboration/oxidation with and alkaline hydrogen peroxide furnished the corresponding alcohol **37** in 80% yield (over two steps). Oxidation of the primary alcohol **37** in to the corresponding aldehyde followed by Wittig olefination with Ph_3P=CHCOOEt gave α,β-unsaturated ester **38**. The silyl group in **38**, on deprotection with TBAF gave the alcohol **39**.



Scheme 4

Oxidation of alcohol **39** with IBX followed by addition with vinyl magnesium bromide gave the racemic mixture of vinyl alcohols **23a**. The compound **23a** on oxidation with DMP (Dess–Martin periodinate) and $NaHCO_3$ provided the keto compound **40**. This on treatment with (*S*)-Me-CBS, BH_3SMe_2 provided the compound **23**.

Now, Intramolecular Oxa-Michael addition reactions were studied. To access the tetrahydropyran core of the macrolactin3, we envisaged several bases. Intramolecular oxa-Michael cyclization of **23** by exposure to KO*t*-Bu (0.05 or 1 equiv) in THF at -78 °C for 30 min gave rise to 2,6-*trans*-tetrahydropyran (**24**) in 90% yield with excellent diastereoselectivity (dr 19:1) (Scheme 5). In contrast, treatment of **22** with TBAF in THF at 0^oC-r.t. afforded 2,6-*cis*-tetrahydropyran (*cis*-**24a**) and 2,6-*trans*-tetrahydropyran (*trans*-**24**) in 81% yield in a ratio of 7.5:2.5. Thus, either *syn*-**24a** or *anti*-**24** could be synthesized from **22** in a stereo selective manner simply by switching the reaction conditions.

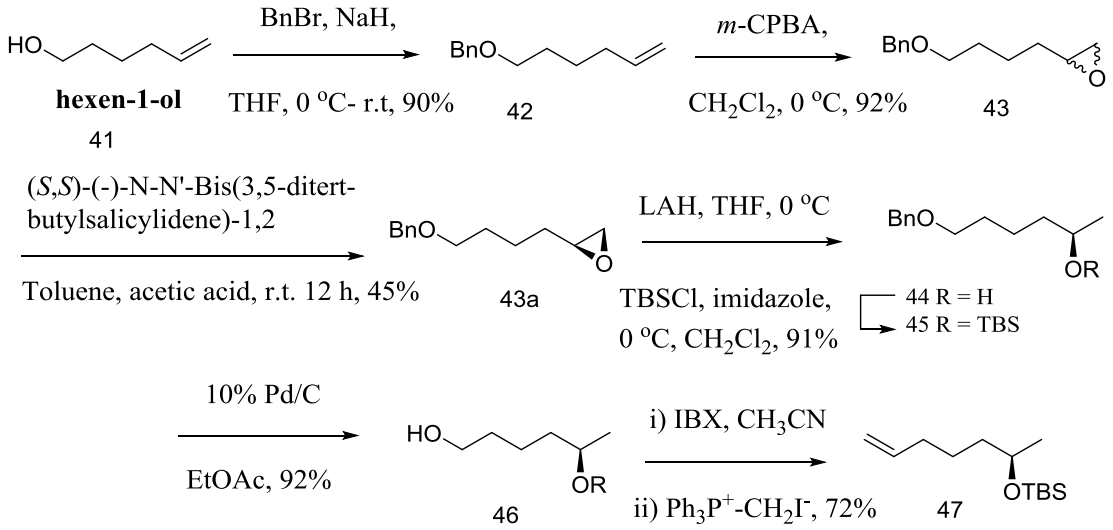


Scheme 5

Synthesis of C19-C24 fragment (**47**)

Synthesis of C18-C24 fragment began with commercially available hexen-1-ol. Accordingly, hexen-1-ol was converted to its corresponding racemic epoxide **43** by reacting with *m*-CPBA after protecting it as benzyl ether (Scheme 6).

The chiral *S*-epoxide **43a** was obtained from **43** by Jacobsen resolution with *S,S*-Jacobsen catalyst. Epoxide **43a** on reduction with LAH furnished **44**, which on silylation with TBSCl and imidazole in CH_2Cl_2 gave **45**.



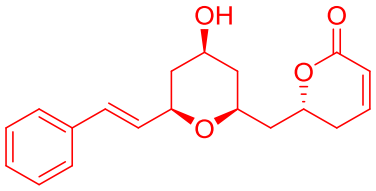
Scheme 6

Debenzylation of **45** provided the alcohol **46**. Compound **46** on oxidation followed by one-carbon Wittig reaction produced C19-C24 fragment (**47**). In conclusion we have accomplished the asymmetric synthesis of the C1-C9, C11-C19 and C18-C24 fragments of macrolatin **3**.

Chapter III: This chapter deals with the introduction and the stereoselective total synthesis of Cryptoconcatone H.

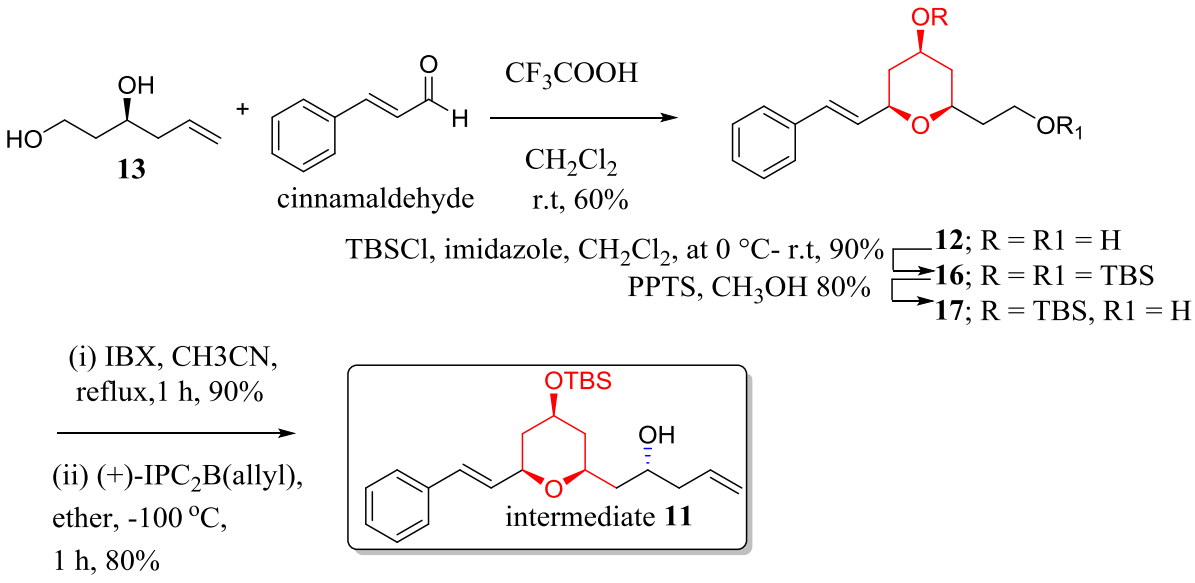
Isolation and biological studies of Cryptoconcatone H: The genus *Cryptocarya* (Lauraceae) comprises more than 220 species that are widely distributed in the subtropics. Phytochemical investigations of this genus have led to the isolation of various secondary metabolites, such as α-pyrone derivatives, flavonoids, and alkaloids.[38,39] *Cryptocarya concinna* Hance is a typical monsoon evergreen broad-leaved tree distributed in lower subtropical mainland China. Recently, a chemical investigation of C. *concinna* was performed on its stems, resulting in the discovery of a series of cytotoxic and antimicrobial flavonoids. The extract of the leaves and branches of C. *concinna* was

reported to exhibit potent anti-inflammatory activity; however, studies are lacking on its chemical constituents, which may pose an obstacle to further developing and utilizing this medicinal plant. During an ongoing search for new anti-inflammatory agents from medicinal plants in China, Kong and Luo investigated the leaves and twigs of C. *concinna* and isolated 10 new arylalkenyl α,β-unsaturated δ/γ-lactones, Cryptoconcatones A-J (**1**-**10**).



Cryptoconcatone H

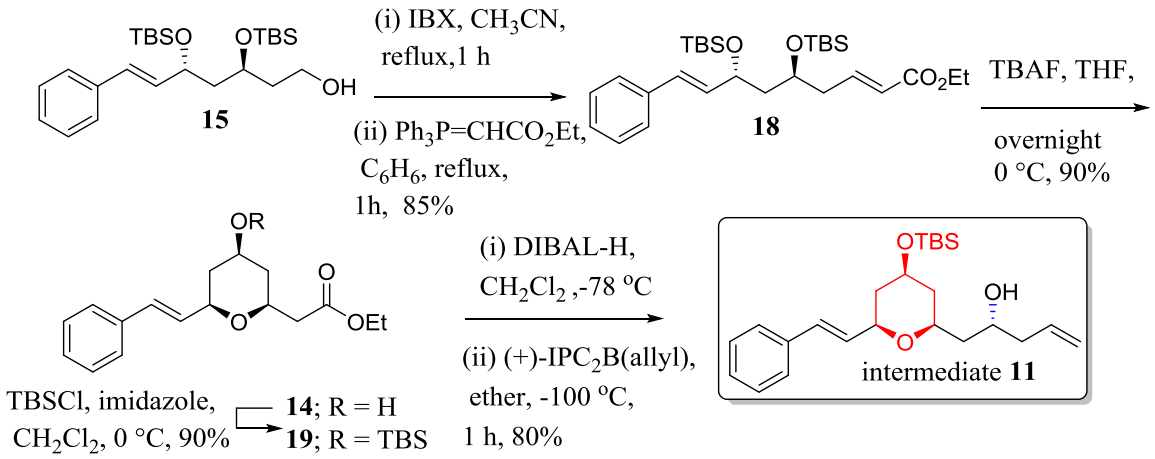
The synthesis of cryptoconcatone H was started with the Prins cyclization (Scheme 2). Accordingly, Prins cyclization was performed between cinnamaldehyde and a known (S)-homoallylic alcohol **13** using TFA (20 equiv, DCM, 12 h, rt) to produce tetrahydropyranyl alcohol **12** (2,4,6-*cis*,*cis* isomer) after hydrolysis of the trifluoroacetate. In the isomer **12**, the two bulky groups and the hydroxy group are in



Scheme 2: Synthesis of intermediate **11** (route a)

equatorial environment. The predominant formation of this particular stereoisomer **12** with the bulky groups and hydroxy in the equatorial positions is most likely due to a thermodynamic effect. The two hydroxyl groups in **12** were protected using 2 eq of TBDMSCl to yield a di-TBS ether **16**. Which on selective removal of primary TBS group using PPTS/MeOH gave an alcohol **17**. IBX oxidation of alcohol **17** in CH_2Cl_2 at 0 ^oC resulted in aldehyde, which was subjected to Brown's asymmetric allylation[52] using (+)-Ipc_2B-allyl to furnish homoallyl alcohol (**11**) with the required stereocentre as a key intermediate in 80% overall yield over the two step-sequence.

Alternatively, the key intermediate **11** could also be prepared in 4 steps from a known alcohol **15** (route b). Oxidation of alcohol **15** by *ortho*-iodoxybenzoic acid (IBX) in CH_2Cl_2/DMSO at 0 °C furnished the corresponding aldehyde, which on Wittig homologation with Ph_3P=CHCOOEt in refluxing benzene afforded α,β-unsaturated ester **18** favouring the desired *E*-isomer in 85% yield. Treatment of compound **18** with TBAF effected a silyl group removal and intramolecular oxa-Michael cyclization under thermodynamic conditions in one-pot provided exclusively the 2,6-*cis*-tetrahyropyran compound (*cis*-**14**).

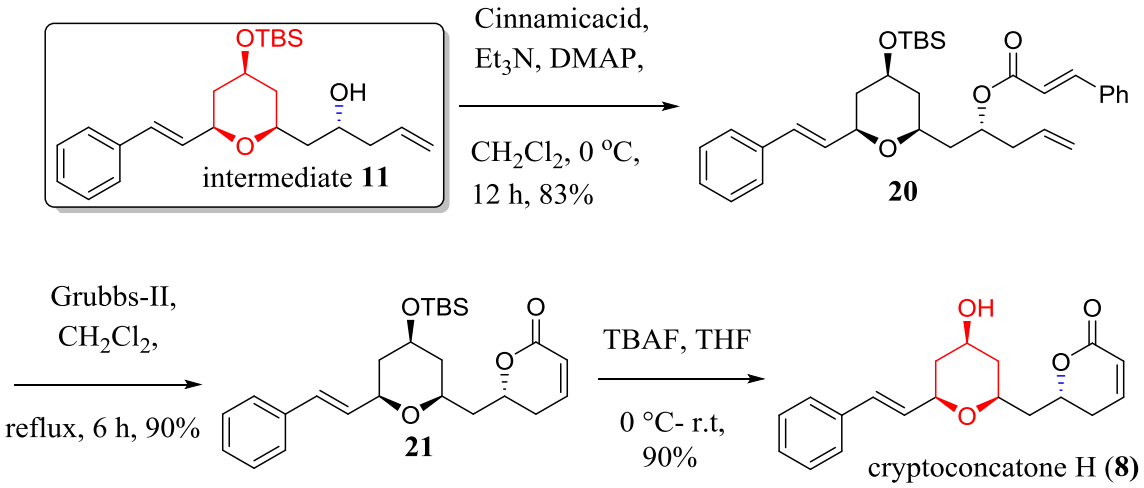


Scheme 3 Synthesis of intermediate **11** (route b)

DIBAL-H reduction of the ester **14** at -78 °C afforded aldehyde, which was subjected to Brown's allylation in the presence of (+)-Ipc_2B-allyl to furnish the allylic alcohol **11** in 80% yield. The compound obtained by this route b compared with that of the compound

obtained from route a. Both the compounds are found to be same by their ^{1}H NMR and mass spectral data.

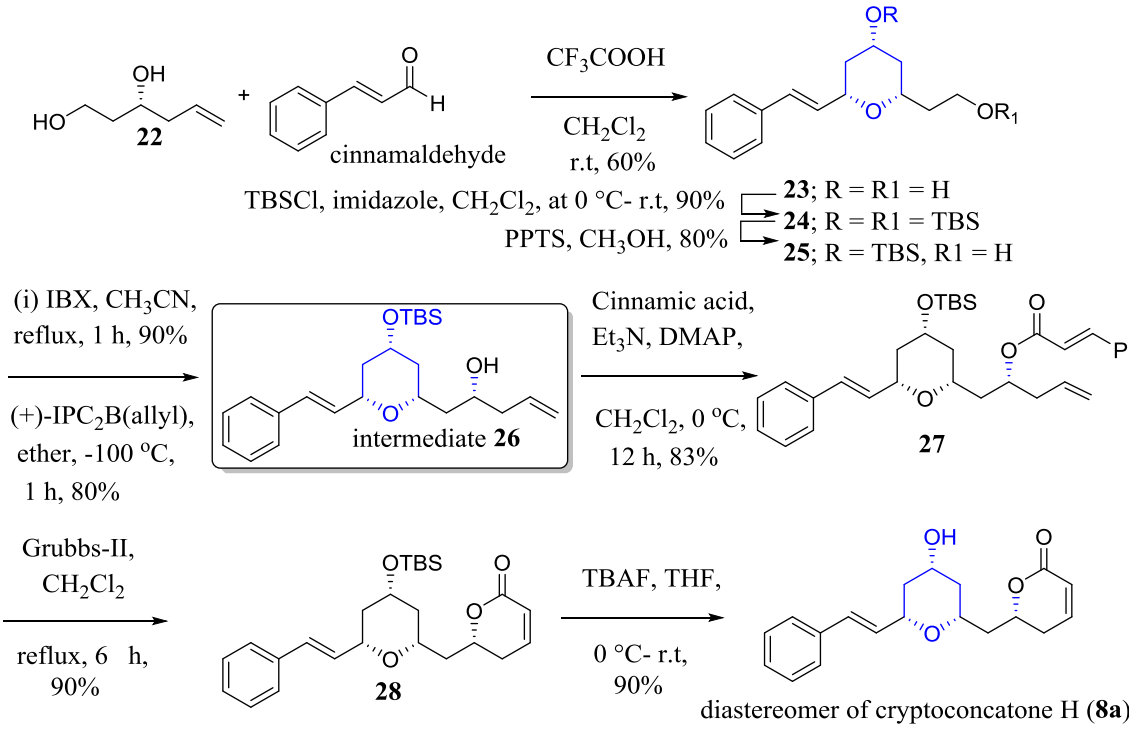
Next, coupling of alcohol **11** with cinnamic acid under DCC-DMAP conditions gave the desired cinnamate **20** in 83% yield. Ring-closing metathesis of the homoallylic cinnamate employing 5 mol% of the Grubbs II catalyst resulted lactone **21** in 90% yield.



Scheme 4. Synthesis of the proposed structure of cryptoconcatone H (**8**)

Finally, removal of TBS group provided the target lactone, cryptoconcatone H. Unfortunately, the NMR spectra of synthetic sample **8** was not identical with the reported natural product. Thus, the total synthesis of the proposed structure of **8** was achieved.

Thus, we next focused on the synthesis of the diastereomer of **8**, 2',4',6'-*cis*-cryptoconcatone H (**8a**). The synthesis of 2',4',6'-*cis*-cryptoconcatone H (**8a**) was also accomplished in an identical manner from **22** (Scheme 5). Prins cyclization between **22** and cinnamaldehyde gave trisubstituted tetrahydropyran **23**, and further functional group transformations by the use of the same reagents and conditions as those described for the conversion of **12** into **8** via **11** (Scheme 2 & 4) gave rise to **8a**.



Scheme 5. Synthesis of diastereomer of proposed structure of cryptoconcatone H(**8a**).

Unfortunately, on comparison of the spectroscopic data of synthetic **8a** with those of the natural product revealed that the structure **8a** also did not represent the true structure of cryptoconcatone H. On the basis of these results, it was concluded that the structures of synthetic compounds **8** and **8a** and the natural product are very similar, but not completely identical.

NMR analysis of the synthetic products **8** and **8a** showed some differences from the reported NMR data. In particular, differences in the ^{1}H NMR spectra were observed with respect to the chemical shifts of the H-2′, H-4′ and H-6′ protons of the tetrahydropyran ring (see Table 1). The ^{1}H NMR chemical shifts of H-2′, H-4′ and H-6′ of the natural product were reported to occur at δ = 4.13, 4.03 and 4.79 ppm as multiplets, whereas those of H-2′ H-4′ and H-6′ of the synthetic **8** appeared as multiplets at δ = 3.94, 3.82 and 4.05 ppm, respectively, and those of **8a** appeared as multiplets at δ = 3.90, 3.74 and 4.01 ppm, respectively. Likewise, significant differences were noted in the ^{13}C chemical shifts of the chiral carbon atoms C2′, C4′ and C6′. The ^{13}C chemical shifts of C2′, C4′ and C6′ in the natural product occurred at δ = 65.6, 64.6 and 72.7 ppm,

respectively, whereas the resonances of the same carbon atoms appeared at δ = 71.3, 67.7 and 74.9 ppm, respectively, for synthetic **8** and at δ = 70.8, 67.8 and 74.5 ppm respectively, for **8a**. However, chemical shifts in ^{1}H NMR and ^{13}C spectra for remaining protons and carbon atoms respectively showed similar values for the natural and synthetic compounds. The specific rotation for synthetic **8** was $[\alpha]_D^{25}$ (+16.4) and that of **8a** was $[\alpha]_D^{25}$ (+38.5), compared with the reported value of $[\alpha]_D^{20}$ (-24.0) for the natural product. The spectral data for the two synthetic compounds **8** and **8a** did not match the reported data for the natural compound.

In conclusion, we have achieved the synthesis of the proposed structures of cryptoconcatone H (**8**).