SYNTHESIS OF DIHYDROPYRONE CONTAINING NATURAL PRODUCTS

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Abstract. *The dihydropyrone natural products derive from various marine sources and are known for different bioactivities. The 2,6-disubstituted dihydropyrone moiety is present in hepialone, obolactone and dihydroobolactone. The related natural products stegobiol, stegobinone, maurenone, membrenone, vallartanone and auripyrone have highly substituted dihdydropyrone unit. The synthetic community has paid close attention to these marine-derived fungal molecular structures and several intriguing strategies has been reported in the literature for their syntheses.*

Contents

1. Introduction

Marine originated microorganisms are a considerable source of a variety of pharmaceutically active metabolites that have greatly aided in the isolation of various structurally intriguing compounds, some of which have excellent bioactivities. This has therefore stimulated active research in pharmaceutical and drug development programs.[1] Natural products based on γ-pyrones are a broad class of biologically active molecules that can be found in all three kingdoms of life. With the first isolation of structurally simple γ-pyrone poppy acid from *Papaver somniferum* by Sertürner in 1805,[2] several additional γ-pyrone natural products were later isolated. The majority of these came from marine creatures, where they appear to play an important role as allomones or defensive chemicals. Therefore, most biological studies on γ-pyrones have been dedicated toward their function in a marine ecosystem. Siphonaria pulmonates from the sea are a significant source of polyketide-derived natural compounds. Siphonarins A and B, muamvatin, denticulatins A and B, membrenones A–C (dihyropyrone), and vallartanones A and B (dihydropyrone and pyrone) are some examples of polyketide natural compounds.[3] Because of their use as bioactive agents, chiral pyrones are components of many naturally occurring compounds, and the study of their chemistry continues unabated. These molecules exert powerful effects on many cell functions, making them useful tools for understanding life processes and for treating life-threatening diseases.[4] The structural features of these γ-pyrone containing compounds are asymmetric centres at the neighbouring positions of the γ-pyrone part.

A group of compounds bearing the substituted pyrone moiety, named maurenone **5**, membrenones A-C **6a-c**, vallartanones A **7a** and B **7b**, auripyrones A **8a** and B **8b** (Figure 1), have been isolated from various marine-derived sources. All of these compounds have the same core structure (substituted dihydropyrone). Related, hepialone **1**, obolactones **2**, stegobiol **3** and stegobinone **4** were isolated from male moth, trunk bark

and fruits, drugstore beetle, respectively. In this chapter we have reviewed the isolation, bioactivities and various syntheses of the substituted dihydro-γ-pyrone molecules as depicted in Figure 1.

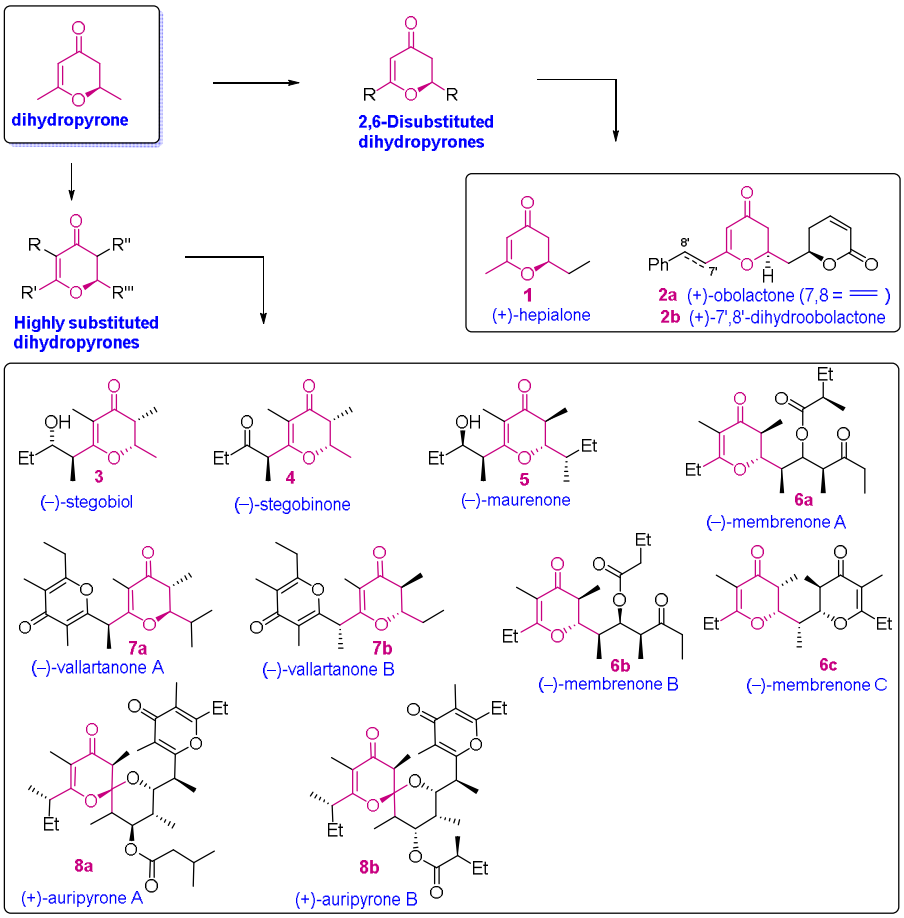


Figure 1. Various dihydropyrone containing natural products.

2. 2,6-Disubstituted dihydropyrone natural products

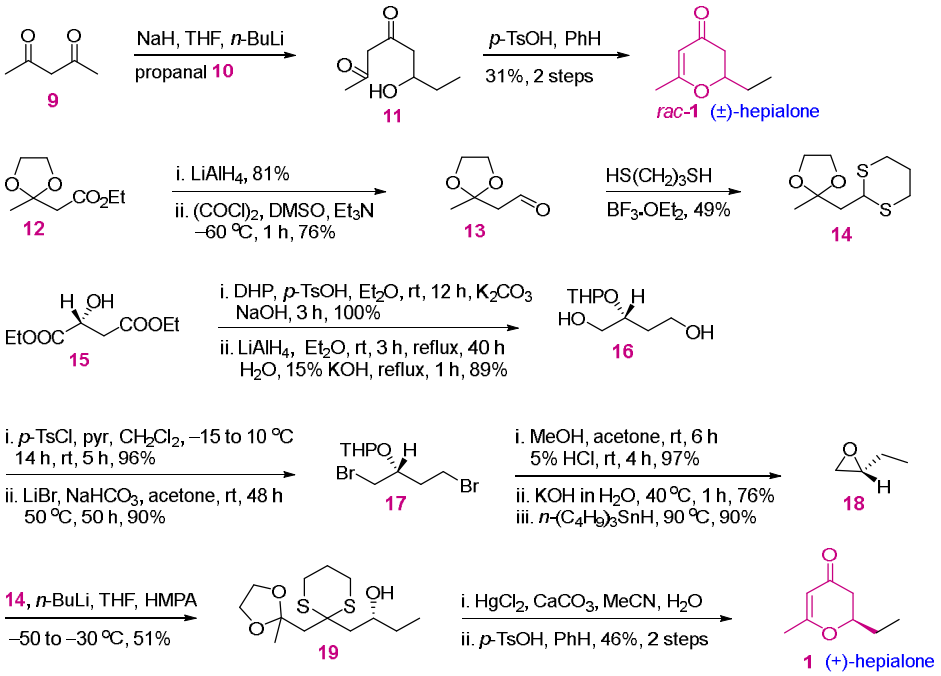
The 2,6-disubstituted dihydropyrone natural products include hepialone, obolactone and 7,8-dihydroobolactone. These are discussed below for their isolation, bioactivity and synthesis.

2.1. Total synthesis of (+)-hepialone

In 1985, Kubo and co-workers[5] isolated a pheromonal component of the male moth named hepialone **1** from *Hepialus Californicus Bvd.,* which is responsible for the strange sexual behaviour of this insect. The structure elucidation of hepialone was completed on the basis of ^{1}H-NMR and CD spectrum with the proposed structure as shown in Figure 1.

The first total synthesis of (+)-hepialone was reported by Kamikawa's group[6] in 1985. The synthesis of racemic and optically active hepialone was beautifully achieved using commercially available starting materials 2,4-pentanedione and *d*-malic acid respectively (Scheme 1). Thus, preparation of (±)-hepialone *rac*-**1** commenced with the formation of dianion of compound **9**. Subsequently, propanal **10** was treated with resultant dianion to give aldol product **11**. Eventually, the latter underwent cyclization upon treatment with

p-TsOH to form (±)-hepialone *rac*-**1**. After the successful synthesis of *rac*-**1**, optically active (*R*)-(+)-hepialone **1** was envisaged. For this purpose, firstly the masked 3-oxobutanal **13** was prepared from compound **12** by reduction-oxidation sequence, which then upon thioacetalization furnished compound **14**. Further, (*R*)-1,2-epoxybutane **18** was prepared from *d*-malic acid according to the method of Seebach.[7,8] Here, compound **15** was THP protected and then hydrolyzed and reduced to get the diol **16**. Furthermore, the diol was tosylated and brominated to dibromo compound **17**. Next, THP was removed and the resultant alcohol underwent cyclization to form epoxide, which upon reductive debromination gave **18**. Later, the regioselective ring opening of **18** with carbanion derived from **14** produced dithianyl alcohol **19**. Finally, mercuric chloride assisted deprotection followed by cyclization gave (+)-hepialone **1**. The synthesis of (±)-hepialone *rac*-**1** and (+)-hepialone **1** was concluded in two and ten steps with 31% and 12% overall yields, respectively.

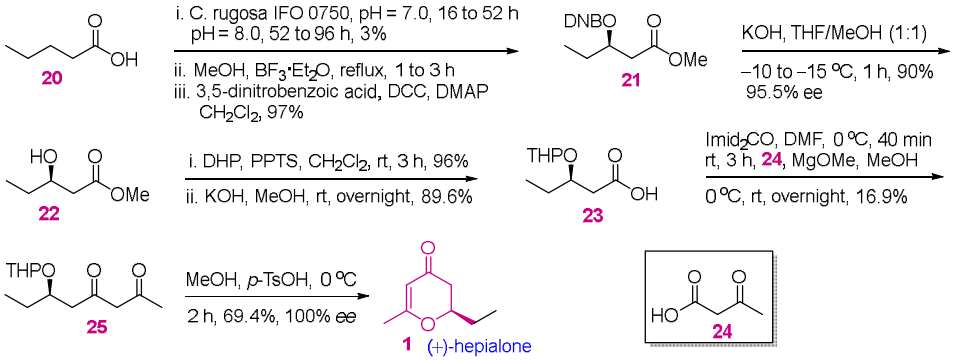


Scheme 1. Kamikawa's synthesis of (±)-hepialone and (+)-hepialone.

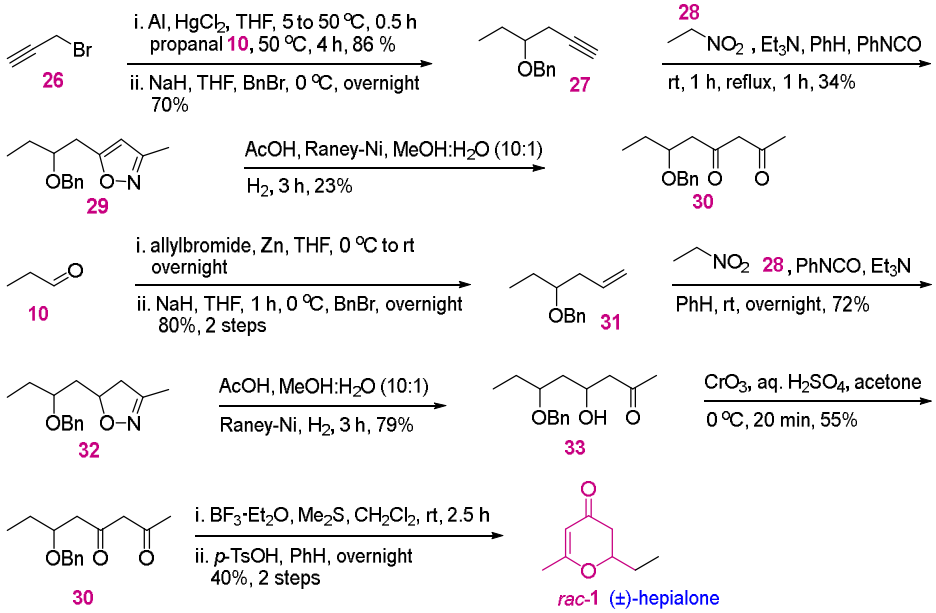
Hayashi and Mori[9] in 1986 disclosed a concise total synthesis of (+)-hepialone **1** starting from methyl (*R*)-3-hydroxypentanoate **22** (Scheme 2). Firstly, compound **22** was prepared using reported procedure where valeric acid **20** underwent β-hydroxylation by microbial transformation[10] using C. rugosa IFO 1542 bacteria followed by esterification. The resultant compound was coupled with 3,5-dinitrobenzoic acid using DCC to give **21**. Next, hydrolysis of purified **21** gave β-hydroxylated ester **22**. Further, protection of OH group as THP ether and saponification furnished **23**. Later, using known protocol,[11] compound **23** was treated with *N,N'*-carbonyldiimidazole and magnesium acetoacetate (from **24**) to get β-diketone **25**. Finally, deprotection of THP group followed by cyclization furnished (+)-hepialone **1**. The total synthesis of latter was completed in eight steps and overall yield of 0.26%. The low yield in the enzymatic conversion rendered this approach less efficient.

Yadav and Rao[12] in 1988 described the total synthesis of (±)-hepialone *rac*-**1** strategizing the 1,3-dipolar cycloaddition reaction as a key step (Scheme 3). The synthesis started with the preparation of diketone **30** from propargyl bromide **26** that was added to propanal **10** as organo-aluminium reagent producing acetylenic alcohol, which was protected as its benzyl ether to get **27**. Further, using Mukaiyama reaction conditions,[13] the 1,3-dipolar cycloaddition reaction gave the isoxazole **29**. This, upon hydrogenolytic O–N bond cleavage

using H_2/Raney-Ni[14] in acetic acid, resulted in β-diketone **30**. Since the sequence in last two steps resulted in lower yields, the scheme was slightly changed. The benzyl ether **31** was prepared from propanal **10** through allylation and benzyl protection. Next, the 1,3-dipolar cycloaddition reaction with nitroethane **28**, phenylisocyanate and triethylamine gave dihydroisoxazole **32**. The latter on hydrogenolysis produced β-hydroxyketone **33**, which upon Jones oxidation delivered the β-diketone **30**. Finally, debenzylation with $BF_3 \cdot Et_2O$/dimethyl sulfide followed by *p*-TsOH-mediated cyclization furnished (±)-hepialone *rac*-**1**. The synthesis of latter involved seven steps and 4.7% overall yield.



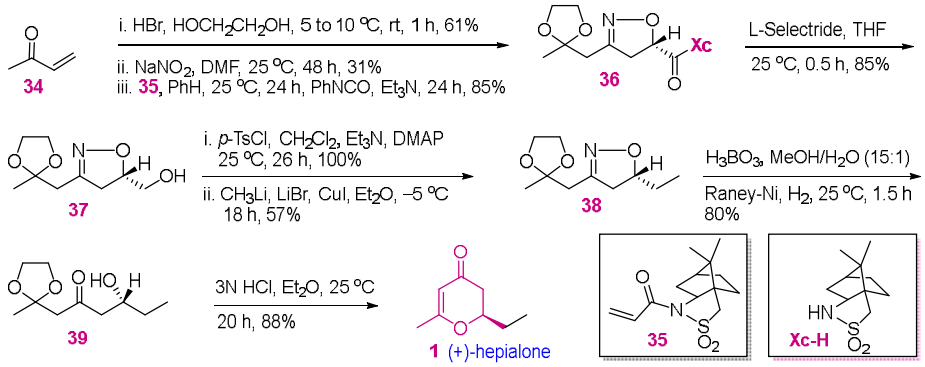
Scheme 2. Mori's synthesis of (+)-hepialone.



Scheme 3. Yadav's synthesis of (±)-hepialone.

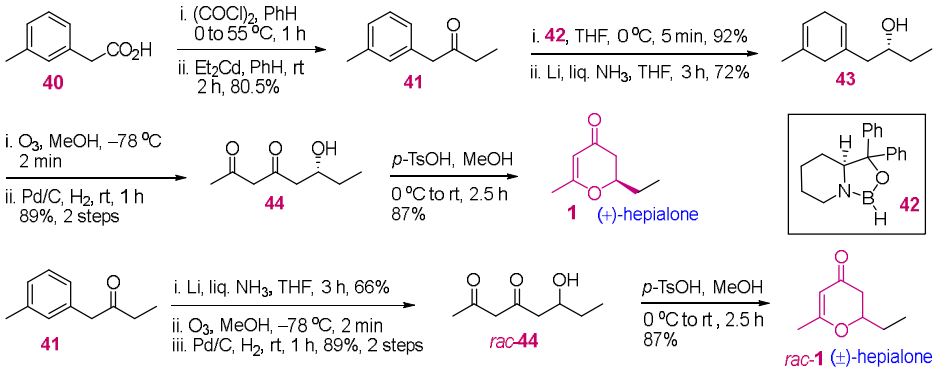
In 1990, Curran and Heffner[15] reported the total synthesis of (+)-hepialone **1** using asymmetric nitrile oxide cycloaddition with Oppolzer's chiral sultam as a key step (Scheme 4). The synthesis commenced with condensation of methyl vinylketone **34** with ethylene glycol in presence of HBr followed by nitration to get nitro ketal, which on cycloaddition by Mukaiyama method[13] with Opplozer's chiral sultam **35** as a chiral auxiliary (derived from acrylamide using reported protocol)[16] gave compound **36** as a major diastereomer. The

latter was selectively reduced with L-Selectride to get alcohol **37** and also Opplozer's chiral sultam **Xc-H** recovered. Further, tosylation of alcohol **37** followed by methylation delivered **38**. Next, the β-hydroxyketone **39** was unveiled by isooxazoline cleavage using standard Raney-Ni reduction.[17] Finally, **39** was exposed to HCl-mediated cyclization to give (+)-hepialone **1**. The synthesis was concluded in eight steps with 5.5% overall yield.



Scheme 4. Curran's synthesis of (+)-hepialone.

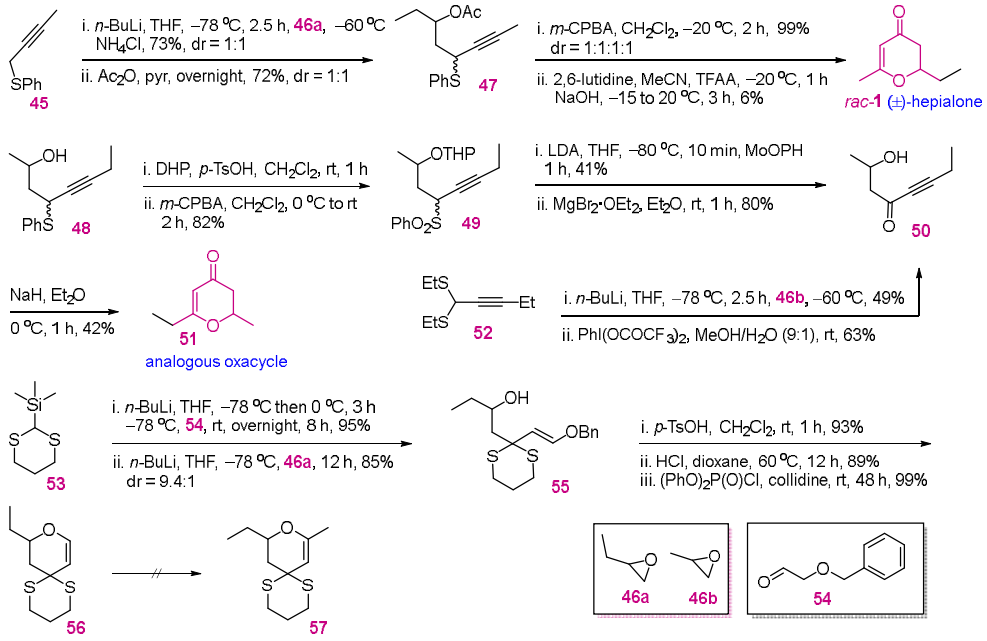
Rao and Rao[18] in 1995 demonstrated the total synthesis of (+)-hepialone **1** using enantioselective reduction of ketone with oxazaborolidine as key step (Scheme 5). The key intermediate ketone **41** was prepared from acid **40** upon treatment with oxalyl chloride and reaction with diethyl cadmium in benzene. Next, the ketone **41** was enantioselectively reduced using (*S*)-oxazaborolidine **42**[19] as a chiral catalyst and then Birch reduction produced optically active compound **43**. Later, ozonolysis of **43** and intermediate reduction with H_2/Pd-C furnished **44**. Eventually, compound **44** underwent cyclisation upon treatment with *p*-TsOH in methanol to give (+)-hepialone **1**. Using same approach, (±)-hepialone *rac*-**1** was also synthesized from ketone **41** by direct Birch reduction. The synthesis of (+)-hepialone was accomplished in seven linear steps with 41% overall yield.



Scheme 5. Rao's synthesis of (+)-hepialone and (±)-hepialone.

Schaumann and co-workers[20] in 2001 investigated four different routes toward the synthesis of (±)-hepialone *rac*-**1** and the analogous oxacycle **51** from chiral oxiranes **46** (Scheme 6). The synthesis of (±)-*rac*-**1** was successfully achieved using Pummerer route from propargyl sulfide **45**. Oxirane **46a** underwent ring opening with lithiated propargyl sulfide **45** and the subsequent alcohol was acetylated to give **47**. The latter underwent mono-oxidation of the sulfide unit and then reaction with trifluoroacetic anhydride promoted the Pummerer reaction followed by basic hydrolysis allowing Michael-type addition to give hepialone *rac*-**1**.

Unfortunately, low yield was obtained in this route as a result the sulfone hydroxylation route was next investigated. Analogous oxacycle **51** was achieved from compound **48** which was prepared by ring opening of oxirane **46b** with lithiated propargyl sulfide **45**. Further, compound **48** was first protected as THP ether and subsequently oxidised to give sulfone **49**. Moreover, sulfone hydroxylation by deprotonation with LDA and addition of MoOPH reagent[21] followed by THP removal gave α,β-unsaturated alkynone **50**. Alternatively, **50** was also prepared from thioacetal **52** by lithiation and ring opening of oxirane **46b** regioselectively followed by hydrolysis using Stork's hypervalent iodine reagent.[22] Finally, **50** underwent cyclization to the six-membered oxacycle **51**. Later, another synthetic route was considered, which started from compound **53**. Lithiated **53** was added to aldehyde **54** and second lithiation and ring opening of oxirane **46a** gave **55**. Later, regioselective acid-catalyzed cyclization of **55** followed by removal of benzyl group and resultant hemiacetal dehydration furnished dihydropyran **56**. However, several reaction conditions explored for deprotonation of **56** for methylation to get **57** were unsuccessful. The synthesis of hepialone *rac*-**1** and the oxacycle **51** was completed in four and six steps with 3.1% and 11.3% overall yields, respectively.

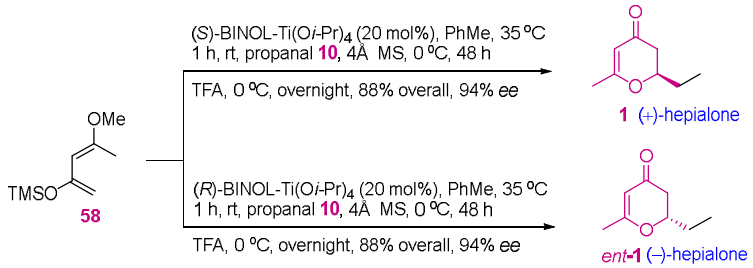


Scheme 6. Schaumann's synthesis of (±)-hepialone.

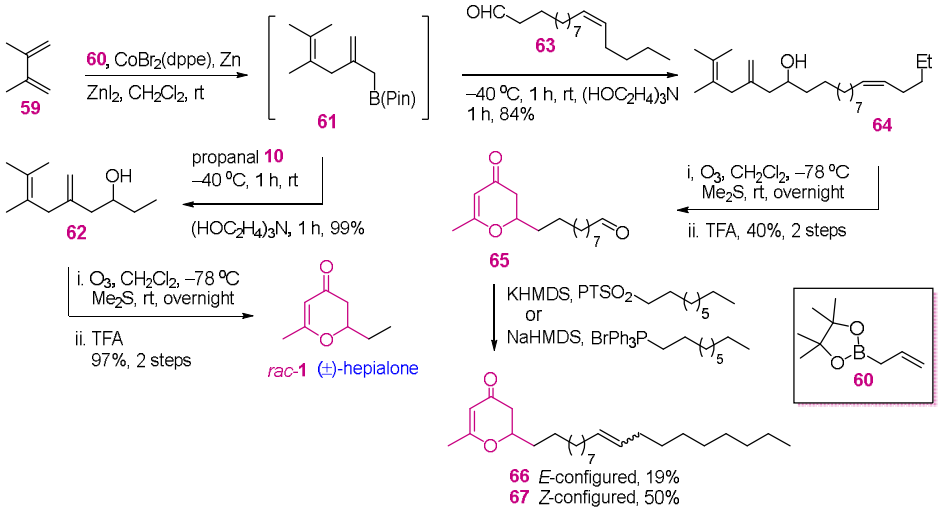
In 2005, Feng and co-workers[23] disclosed highly enantioselective one step synthesis of (+)-hepialone **1** by hetero-Diels-Alder (HDA) reaction. The synthesis of **1** was achieved from diene **58** and propanal **10** (Scheme 7**)** using (*S*)-BINOL-Ti(O*i*-Pr)$_4$ complex for the reaction. After several investigations, it was found that asymmetric HDA reaction proceeded in a Mukaiyama aldol pathway from the isolated intermediate. Using similar reaction conditions, (–)-hepialone was also achieved from **58** using (*R*)-BINOL-Ti(O*i*-Pr)$_4$ complex. The synthesis of (+)-hepialone **1** and (–)-hepialone *ent*-**1** was concluded in one step with 88% overall yield in each case and 94% *ee*.

In 2009, Hilt and co-workers[24] reported the synthesis of (±)-hepialone *rac*-**1** as an application of cobalt-catalyzed 1,4-hydrovinylation of alkenes with 1,3-dienes (Scheme 8). Intermediate **62** was beautifully executed when pinacolallyl-boronate **60** was treated with substituted butadiene **59** using cobalt-catalysed 1,4-hydrovinylation approach. Subsequently, propanal **10** was added *in situ* to get corresponding alcohol **62**. Eventually, ozonolysis was carried out on **62** followed by acid-catalysed cyclization of the 1,3-dicarbonyl functionality to get hepialone *rac*-**1** in a one-pot sequence. A similar approach was adopted for the synthesis

of lipids **66** and **67**, which were isolated from Vanilla beans.[25] In this case, intermediate **61** was submitted for allylation with commercially available aldehyde **63** to furnish alcohol **64**. This on ozonolysis to 1,3-diketone and acid-mediated cyclization produced pyrone aldehyde **65**. At the end, the side chain of the natural products **66** and **67** was introduced by Wittig reaction for *Z*-configuration and Julia-Kocienski reaction for *E*-configuration using corresponding salts. The synthesis of *rac*-**1** was achieved in four steps with 96% overall yield and that of lipids **66** and **67** in five steps with 6.4% and 17% overall yields, respectively.



Scheme 7. Feng's synthesis of (+)- and (–)-hepialones.



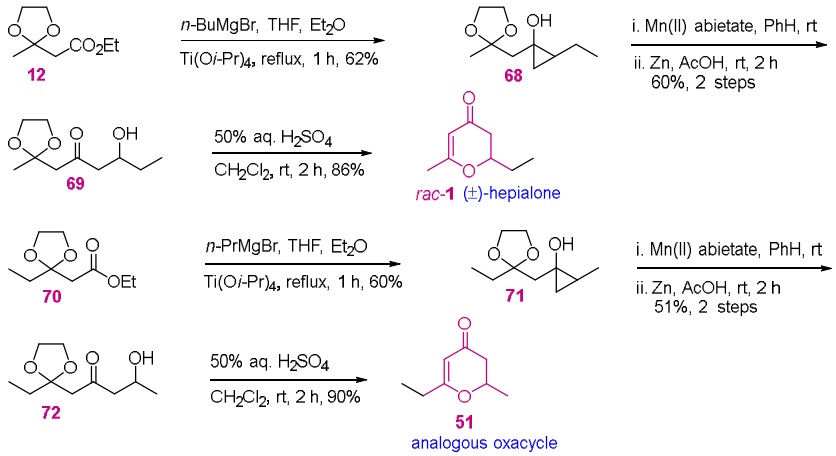
Scheme 8. Hilt's synthesis of (±)-hepialone.

In 2011, Astashko and Tyvorskii[26] developed the efficient total synthesis of (±)-hepialone *rac*-**1** and its analog **51** involving Kulinkovich cyclopropanation reaction[27] and oxidative cleavage of the three-membered ring as key steps (Scheme 9). The synthesis of *rac*-**1** commenced with preparation of cyclopropanol **68** by the Kulinkovich cyclopropanation of a protected 3-ketocarboxylic acid ester **12** using suitable Grignard reagent. Next, **68** was subjected to oxidative cleavage of the three-membered ring using unique oxidant Mn(II)-abietate[28] followed by reduction to give β-hydroxyketone **69**. Finally, **69** underwent acid-promoted cyclisation to furnish (±)-hepialone *rac*-**1**. Using similar protocol, compound **51** was also prepared from ester **70** *via* the intermediates **71** and **72**. The total synthesis of (±)-hepialone *rac*-**1** and its analog **51** was successfully achieved in four steps with 32% and 27.5% overall yields, respectively.

2.2. Total synthesis of (+)-obolactone

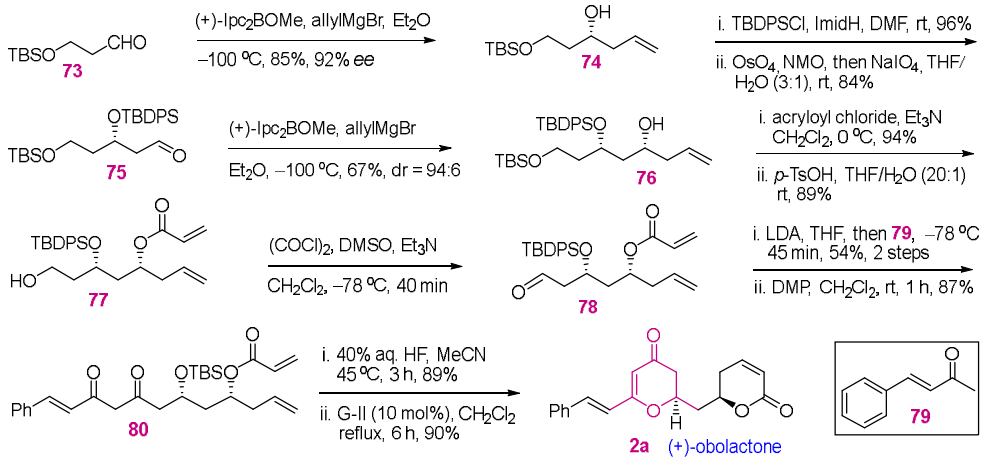
(+)-Obolactone **2a** was isolated from the trunk bark of *Cryptocrya obovate*, a tropical plant of Yen Chau, Son La Province in north Vietnam.[29] It is active against *nasopharyngeal* carcinoma with an IC_{50} of 3 μM and

against *Trypanosoma brucei*, with IC_{50} 5.3 μM. It also shows impressive effects on many cell functions and activities against life-threatening diseases, for example, the antifungal and antimicrobial properties, insect growth inhibition, and cytotoxicity against a broad spectrum of cancer cells.



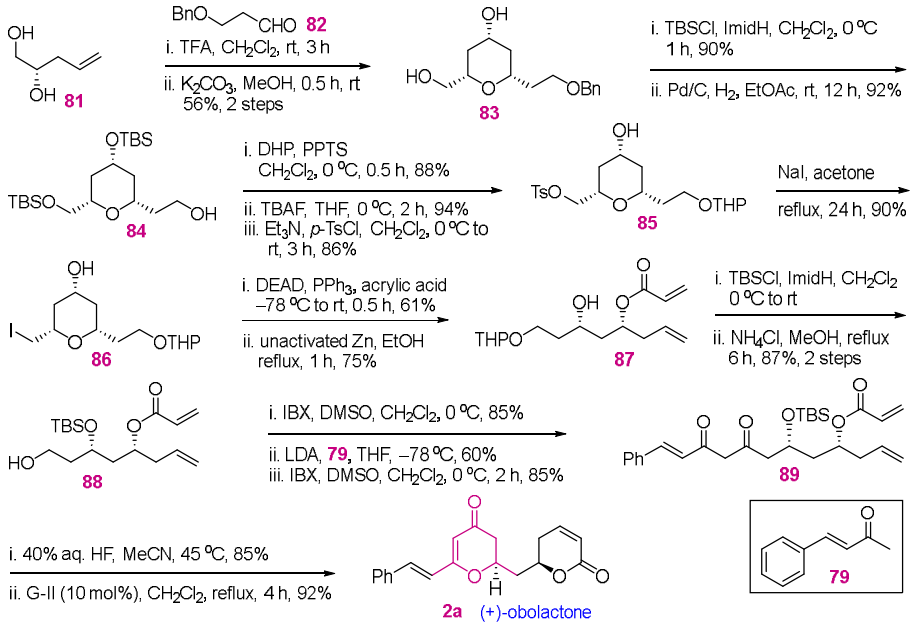
Scheme 9. Astashko's synthesis of (±)-hepialone.

In 2006 She and co-workers[30] reported the first asymmetric total synthesis of obolactone **2a** using asymmetric Brown's allylation as a key step (Scheme 10). The synthesis started with 3-(*O*-TBS)-propionaldehyde **73**, which on Brown and Racherla's asymmetric allylation[31] provided **74**. Next, hydroxyl protection and oxidative cleavage of the vinyl group delivered aldehyde **75**. Then the second asymmetric allylation gave **76**. The latter on esterification with acryloyl chloride, followed by selective deprotection of silyl ether produced alcohol **77**. Then, the sequence of Swern oxidation to aldehyde **78**, aldol reaction with **79** followed by Dess-Martin periodinane (DMP) oxidation gave compound **80**. The latter on treatment with HF underwent TBS deprotection and cyclization to dihydropyrone, which on ring-closing metathesis (RCM)[32] resulted in (+)-obolactone **2a**. The synthesis of **2a** was completed in eleven steps with 14.5% overall yield. Thus, the double allylation strategy worked well to set both the stereogenic centers of the natural product.



Scheme 10. She's synthesis of (+)-obolactone.

In 2010, Sabitha and co-workers[33] achieved the synthesis of (+)-obolactone **2a** using Prins cyclization as a key step (Scheme 11). The synthesis started with the known chiral homoallylic alcohol **81**, which on Prins cyclization with aldehyde **82** in presence of trifluoroacetic acid (TFA) gave trisubstituted pyran **83**. Then, protection of two hydroxy groups as silyl ethers followed by benzyl deprotection afforded alcohol **84**. Next, the sequence of THP protection, desilylation and selective tosylation of primary alcohol gave **85**. The latter was converted to iodide **86** and esterified with acrylic acid using Mitsunobu[34] conditions followed by ring opening with Zn to furnish the diene **87**. Protection of alcohol as silyl ether followed by deprotection of THP group gave corresponding alcohol **88**. Now, IBX oxidation of alcohol and subsequent aldol reaction with **79** and oxidation afforded **89**. The latter underwent cyclization to pyrone and RCM provided the target molecule (+)-obolactone **2a**. The synthesis of **2a** was completed in seventeen steps with a 4% overall yield.

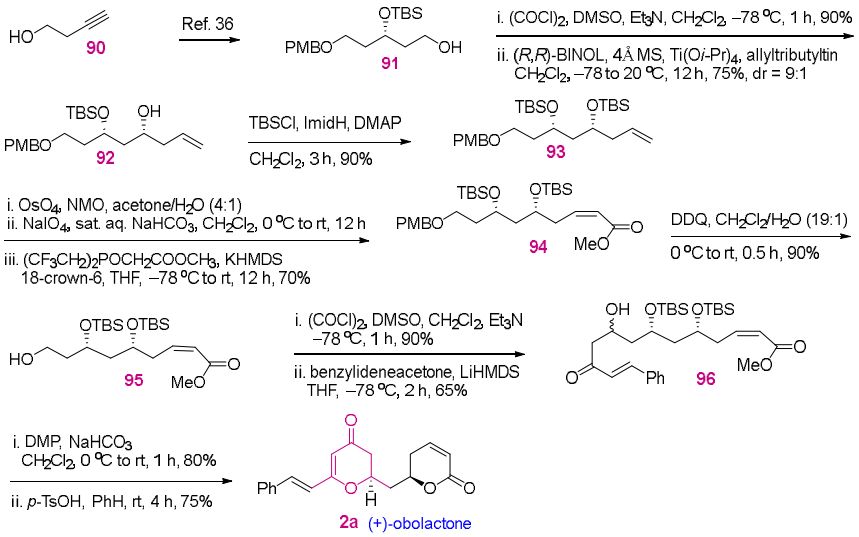


Scheme 11. Sabitha's synthesis of (+)-obolactone.

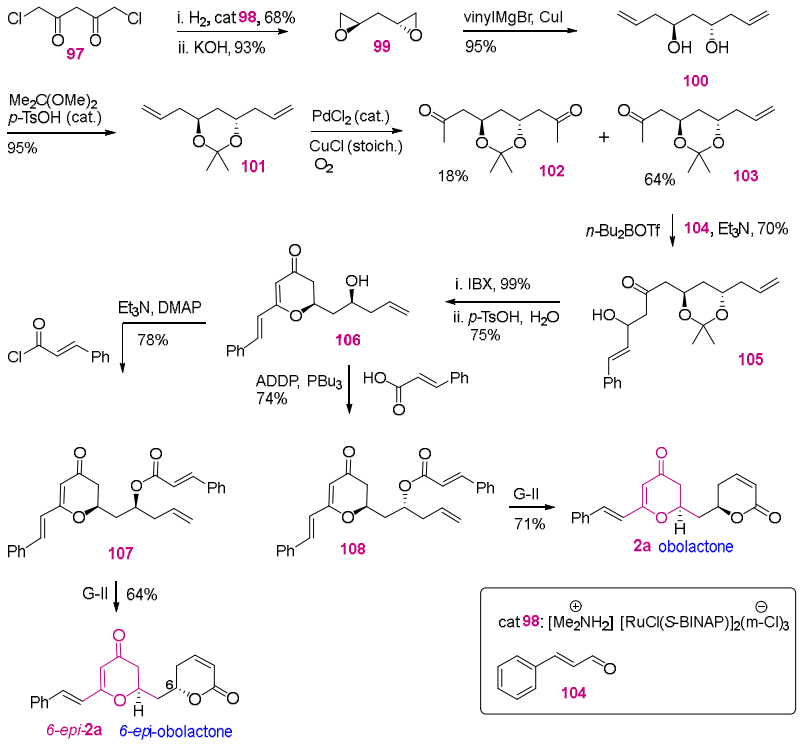
In 2010, Krishna and Srinivas[35] synthesized (+)-obolactone **2a** using Keck allylation and *p*-TsOH-mediated cyclization as key steps (Scheme 12). The synthesis started with commercially available homopropargyl alcohol **90** that was transformed into **91** as reported earlier.[36] Next, the free alcohol oxidation and Keck allylation[37] gave **92** with diastereoselectivity, dr=9:1. The protection of hydroxy group as TBS ether afforded compound **93**. Then the terminal olefin bond cleavage through diol to the aldehyde and Wittig olefination furnished **94**. This on PMB deprotection gave alcohol **95**, which upon, oxidation and aldol reaction with benzylideneacetone delivered **96**. DMP oxidation of **96** followed by *p*-TsOH-mediated cyclization furnished (+)-obolactone **2a**. The synthesis of **2a** was completed in eleven steps with 13.4% overall yield from **91**.

In 2013, Walleser and Brückner[38] synthesized (+)-obolactone **2a** using Wacker mono-oxidation and Mitsunobu reactions as key steps (Scheme 13). The synthesis started with the preparation of 1,3-diol **100** from 1,3-diketone **97** following a three-step sequence *via* intermediate bis-epoxide **99** (obtained by keto reduction in **97** using catalyst **98**).[39] Then acetonoide protection of the hydroxy groups gave **101** followed by Wacker mono-oxidation afforded monoketone **103** with undesired minor product **102**. The former was subjected to aldol reaction with cinnamaldehyde **104** to give β-hydroxy ketone **105**. Then oxidation followed by cyclization furnished pyrone **106**. Using Mitsunobu[40] esterification conditions **106** afforded two diastereomers. The inversion yielded **108** and direct esterification gave **107**. Finally, RCM provided (+)-obolactone **2a** and its

diastereomer *6-epi*-**2a**. The synthesis of (+)-obolactone and *epi*-isomer was completed in ten steps with 10% and 9.5% overall yields, respectively. Thus, the hidden symmetry in the target molecule was beautifully visualized and traced back to the symmetric diene compound **101**.

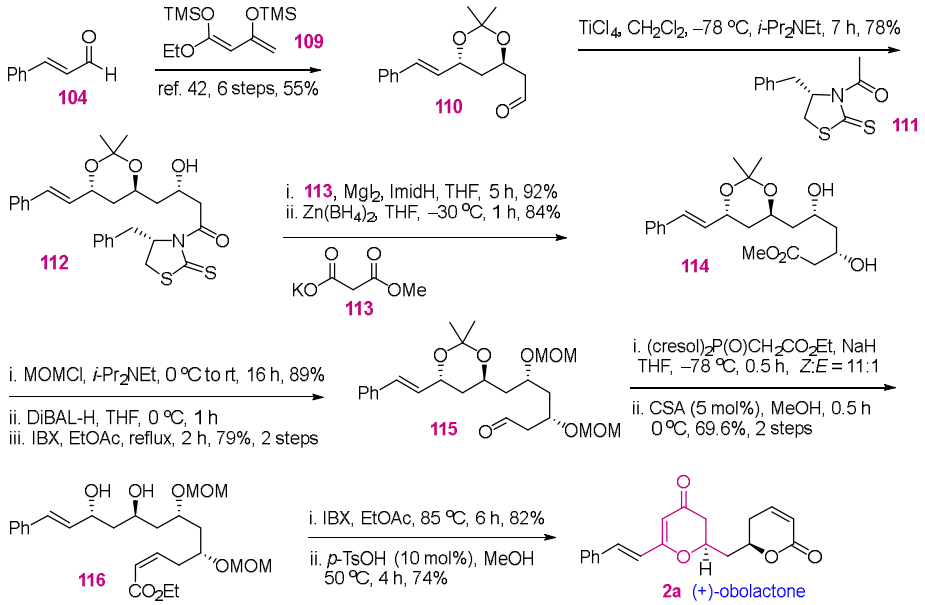


Scheme 12. Krishna's synthesis of (+)-obolactone.



Scheme 13. Brückner's synthesis of (+)-obolactone.

In 2017, Kumar and Meshram[41] synthesized (+)-obolactone **2a** using Keck allylation and *p*-TsOH-mediated cyclization as key steps (Scheme 14). The synthesis began with Chan's diene **109** and aldehyde **104** to give compound **110** using reported protocol.[42] This on reaction with **111** under Crimmins' modified Evans' aldol reaction conditions[43] delivered **112**. Then the chiral auxiliary was removed using **113** in presence of MgI_2 to yield β-keto ester, which was reduced diastereoselectively to get **114**. MOM protection of free hydroxy groups followed by DiBAL reduction and subsequent oxidation of resulting alcohol furnished aldehyde **115**. Later, the highly stereoselective Ando's modified Horner-Wadsworth-Emmons (HWE)[44] olefination followed by acetonide deprotection provided diol **116**. Eventually, IBX oxidation followed by *p*-TsOH cyclization delivered (+)-obolactone **2a**. The synthesis was accomplished in sixteen steps with a 10% overall yield.

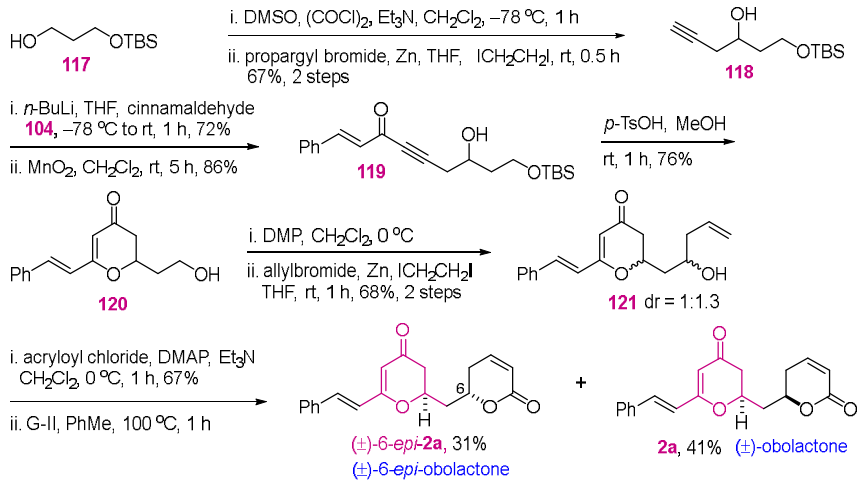


Scheme 14. Kumar's synthesis of (+)-obolactone.

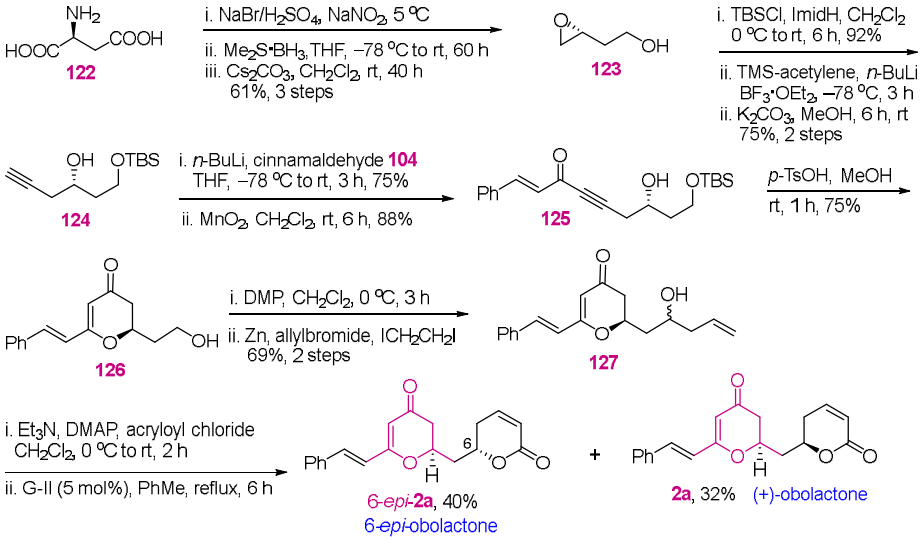
In 2019, Fernandes and co-workers[45] synthesized (±)-obolactone *rac*-**2a** using δ-hydroxyalkynone rearrangement catalyzed by *p*-TsOH as a key step (Scheme 15). The synthesis started with Swern oxidation of **117** followed by propargylation to give **118**. This was added to cinnamaldehyde **104** and next allylic oxidation provided the δ-hydroxyalkynone **119**. Further, the *p*-TsOH-catalyzed rearrangement gave the dihydropyrone **120** with concomitant TBS removal. The latter was oxidized to aldehyde and Barbier allylation delivered **121**. Finally, (±)-6-*epi*-**2a** and (±)-obolactone **2a** were synthesized by esterification followed by RCM. The diastereomeric synthesis of these was accomplished in nine steps with 4.4% and 5.8% overall yields, respectively.

Fernandes and co-workers[46] recently disclosed the stereoselective total synthesis of (+)-obolactone **2a** through chiral pool approach to an epoxide and utilizing *p*-TsOH-catalyzed rearrangement as key steps (Scheme 16). The synthesis started with commercially available *l*-aspartic acid **122**, which by Volkmann's[47] procedure was converted to epoxy alcohol **123**. Then, TBS protection and epoxide opening using TMS-acetylene and desilylation gave alkyne intermediate **124**. This was added to cinnamaldehyde **104** followed by allylic oxidation afforded **125**. The latter on, *p*-TsOH-mediated rearrangement[45] gave **126** with TBS deprotection in the same reaction. Further, DMP oxidation, Barbier-type allylation furnished compound **127**. Finally, esterification with acryloyl chloride and RCM provided (+)-obolactone **2a** and its diastereomer

6-*epi*-obolactone *epi*-**2a**. The synthesis of these was completed in thirteen steps with 4.6% and 5.8% overall yields, respectively.



Scheme 15. Fernandes' synthesis of (±)-obolactone.

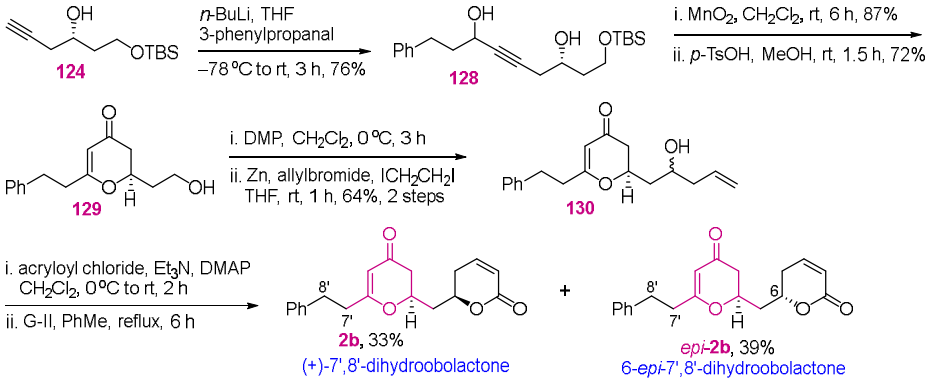


Scheme 16. Fernandes' synthesis of (+)-obolactone and 6-*epi*-obolactone.

2.3. Total synthesis of (+)-7′,8′-dihydroobolactone

In 2010, Quinn and co-workers[48] isolated the dihydro-α-pyrone, (+)-7′,8′-dihydroobolactone **2b** along with obolactone **2a** from the leaves of *Cryptocarya obovata*. It was isolated form the organic extracts of the plant leaves in CH_2Cl_2/MeOH followed by the mass-directed fractionation and purification. By following CD data analysis, they also assigned the absolute *R*-configuration at both chiral centres. It exhibits *anti*-trypanosomal activity towards *T. b. brueci* (IC_{50}=2.8 μM) and cytotoxicity against two cancer cell lines, *i.e.* A549 (IC_{50}=78.0 μM), HeLa cells (IC_{50}=43 μM) and also one non-cancer cell line HEK293 (selectivity index of 7.4). [48]

Fernandes and co-workers[46] recently disclosed the first stereoselective total synthesis of dihydroobolactone **2b** by utilizing the same strategy of *p*-TsOH-catalyzed rearrangement as the key step (Scheme 17). The alkyne intermediate **124** was added to 3-phenylpropanal to afford **128** that upon allylic oxidation and metal-free *p*-TsOH-catalyzed rearrangement[45] gave **129**. This was subjected to DMP oxidation and Barbier-type allylation to furnish **130**. Finally, esterification with acryloyl chloride and RCM provided dihydroobolactone **2b** and its diastereomer 6-*epi*-dihydroobolactone 6-*epi*-**2b**. The synthesis of these was completed in thirteen steps with 4.2% and 5% overall yields, respectively.



Scheme 17. Fernandes' synthesis of (+)-7′,8′-dihydroobolactone and 6-*epi*-7′,8′-dihydroobolactone.

3. Highly substituted dihydropyrone natural products

Apart from the 2,6-disubstituted pyrone molecules discussed above, there are many highly substituted dihydropyrone molecules like the stegobiol, stegobinone, maurenone, membranones, vallartanones and auripyrones indicating the highly represented γ-pyrone class of natural products. These natural products having different biological activity are described below along with their syntheses.

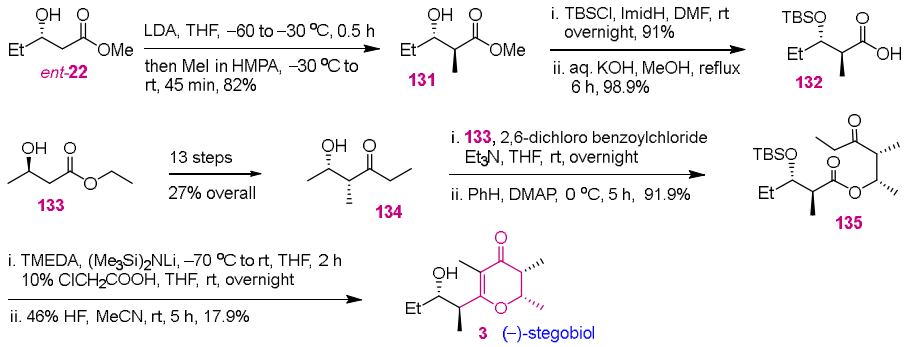
3.1. Total synthesis of (–)-stegobiol and (–)-stegobinone

In 1975, Kuwahara and co-workers[49] isolated and proposed the structure of stegobinone **4**, as major component of female-produced sex pheromone of drugstore beetle *Stegobium paniceum*. Later on, the minor component of the beetle known as stegobiol **3** was isolated by Kodama and co-workers[50] in 1987. Stegobinone has also been reported to be an attractant of the furniture beetle, *Anobium pounctatum*.[51] Drugstore beetle can cause economic loss and damage to post-harvesting and stored grains and food products.[52]

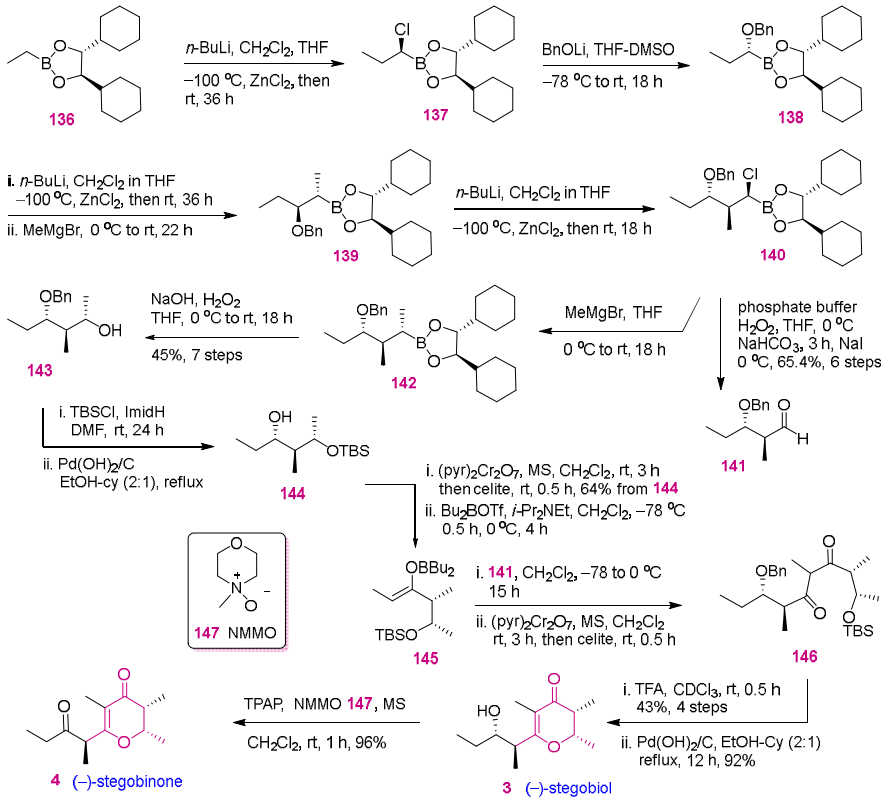
The first asymmetric synthesis of (–)-stegobiol **3** was reported by Mori and Ebata[53] using intramolecular acylation as key step (Scheme 18). Alkylation of hydroxyl ester *ent*-**22**[54] gave **131** along with its minor isomer. This mixture was subjected to acylation and saponification to give optically and chemically pure isomer **131**. Silylation of **131** with TBSCl followed by saponification afforded acid **133** in 98.9% yield. Conversion of **133** to a hydroxyl ketone **134** was reported in thirteen steps with 27% overall yield.[55] Later on, **134** was subjected to esterification with **132** using Yamaguchi conditions[56] to deliver ester **135**. Now, treatment of resulting ester with $(Me_3Si)_2NLi$ for cyclization and TBS-deprotection produced stegobiol **3**. The synthesis required seventeen steps from **133** with 4.4% overall yield.

In 1993, Matteson and Man[57] achieved the synthesis of (–)-stegobiol **3** and (–)-stegobinone **4** using highly stereoselective boronic ester chemistry (Scheme 19). The key intermediate **140** was synthesized in 5 steps using chiral boronic ester **136**. The latter was prepared in 3 steps using *trans*-stilbene.[58] This reacted with (dichloromethyl)Li to produce chain-extended chloro boronic ester **137** and further reaction with lithium benzyl oxide afforded **138**. A repeat of the earlier reaction using (dichloromethyl)Li, followed by reaction of resultant chloro boronic ester with MeMgBr delivered **139**. Another chain extension using same conditions produced key intermediate **140**. Then the deboronation using H_2O_2 provided aldehyde **141**. Intermediate **140** was also investigated with Me-Grignard reagent to give **142**, which upon deboronation resulted in **143**. The

latter was silyl protected and debenzylated to **144**. After oxidation of alcohol to resultant ketone, it was converted to dibutyl boron enolate **145**. The aldol reaction[59] of aldehyde **141** with enolate **145**, followed by oxidation of resultant alcohol gave diketone **146**, which quickly ring closed with trifluoroacetic acid and next debenzylation produced (–)-stegobiol **3**. (–)-Stegobinone **4** was synthesized by oxidation of stegobiol with *N*-methylmorpholine *N*-oxide **147**. This synthesis of stegobiol **3** and stegobinone **4** was completed in fifteen and sixteen steps with 11.3% and 10.9% overall yields from **136**, respectively.

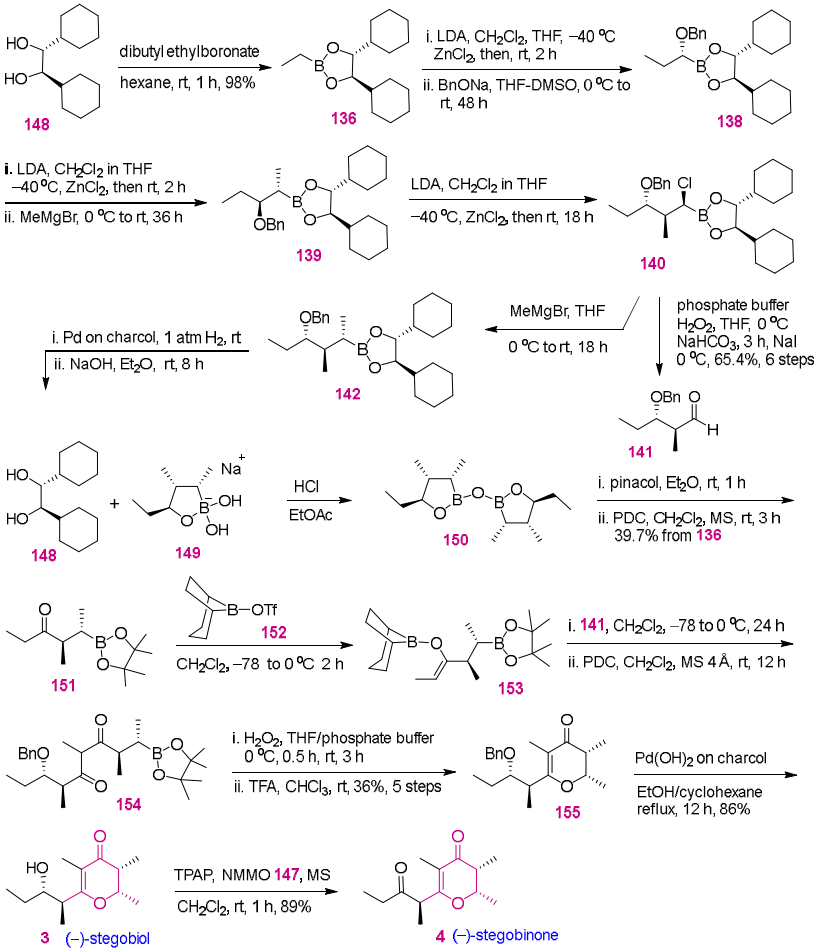


Scheme 18. Mori's synthesis of (–)-stegobiol.



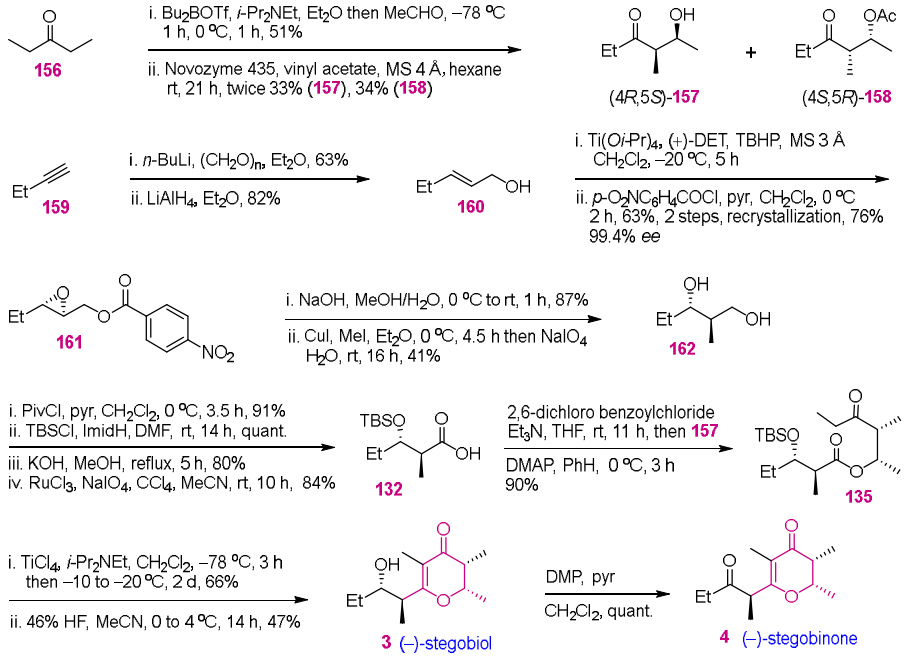
Scheme 19. Matteson's synthesis of (–)-stegobiol and (–)-stegobinone.

Three years later (1996), Matteson and co-workers[60] reported the synthesis of (–)-stegobiol and (–)-stegobinone (Scheme 20) using stereoselective asymmetric boronic ester chemistry for installation of all chiral centres with a few modification to the chemistry discussed above. They started the synthesis *via* the preparation of key intermediate **140** by using ethylboronate **136**, that was synthesized from **148** and dibutyl ethylboronate. The former reacted with (dichloromethyl)Li to afford chain-extended chloro boronic ester and then reaction with lithium benzyl oxide afforded **138**. Using similar reaction with (dichloromethyl)Li, followed by MeMgBr addition delivered **139**. A repeat chain extension produced key intermediate **140**. Later on, deboronation using H_2O_2 gave aldehyde **141**. Intermediate **140** was subjected to Grignard reagent to give **142**, which upon debenzylation and hydrolysis delivered separated compounds **148** and oxaborolane salt **149**. Acidification of **149** afforded oxaborolane in its dimer form **150**. This was treated with pinacol to give the mixture of compounds, which on PDC oxidation yielded stable keto boronic ester **151**. For the coupling of aldehyde **141**, several boron enolates were tested and **153** obtained from **151** using **152** underwent aldol reaction to afford ketone **154**. Peroxidic deboronation of ketone **154** followed by acidification delivered *O*-benzyl stegobiol **155**. Benzyl deprotection yielded desired product (–)-stegobiol **3**, which on oxidation with NMMO **147** furnished (–)-stegobinone **4**. The synthesis of these required nineteen and twenty steps and completed with 11.8 and 10.5% overall yields, respectively.



Scheme 20. Matteson's synthesis of (–)-stegobiol and (–)-stegobinone.

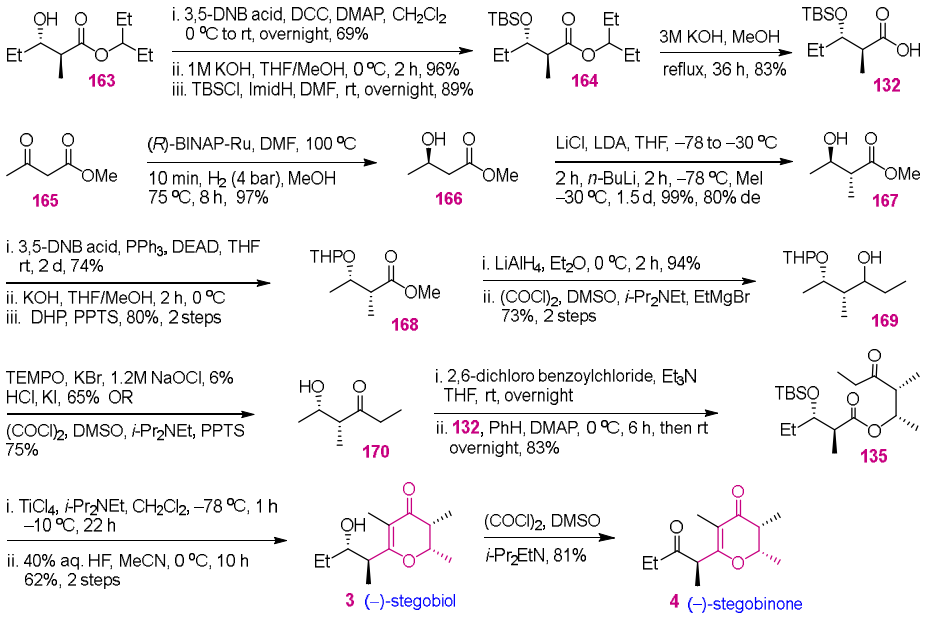
Mori and co-workers[61] in 1998 described the total synthesis of (–)-stegobiol **3** and (–)-stegobinone **4** using lipase-catalyzed resolution and Sharpless epoxidation as keys steps (Scheme 21). Preparation of **157** started with boron enolate of **156** addition to acetaldehyde followed by enzymatic acetylation using Novazyme 435 as suitable enzyme (good reactivity at room temp), followed by chromatographic separation of afforded (–)-**157** and (+)-**158**. A repeat reaction of (–)-**157** produced enantioenriched (4*R*,5*S*)-**157** and its diastereomer (dr=88.8:11.2) with 97.2% *ee*. 2-Pentene-1-ol **160** was synthesized by known procedure[62] using 1-butyne **159** and then subjected to Sharpless asymmetric epoxidation followed by esterification with *p*-nitrobenzoyl chloride and recrystallization to yield **161** with 99.4% *ee*. Alkaline hydrolysis of **161**, followed by treatment with lithium dimethylcuprate afforded methylated 1,3-glycol **162** with undesired product 1,2-glycol, which was removed by using sodium periodate. Next, the orthogonal protection of primary hydroxy as pivalate and secondary as TBS, then selective deprotection of pivaloyl group and further alcohol oxidation using *in situ* formed ruthenium tetroxide[63] gave desired acid **132**. By the known procedure,[53,64] both fragments **132** and **157** were taken for esterification to produced **135**. Next, cyclization followed by deprotection of silyl ether afforded (–)-stegobiol **3**. The latter was oxidized to give crystalline (–)-stegobinone **4**. The synthesis of these was completed in thirteen and fourteen steps with 1.5% overall yields in each case.



Scheme 21. Mori's synthesis of (–)-stegobiol and (–)-stegobinone.

Gil and co-workers[65] in 1998 reported the synthesis of (–)-stegobiol **3** and (–)-stegobinone **4** by catalytic hydrogenation of carbonyl group and asymmetric alkylation as key steps (Scheme 22). The synthesis began with hydroxyester **163**, which was transformed into 3,5-dinitrobenzoate (for column purification) followed by deprotection to obtain 100% *de* and *O*-silylation of hydroxyester to afford **164**. Hydrolysis of ester group furnished acid **132**. The second intermediate **170** was obtained from 3-oxo-butanoate **165**, which was converted into hydroxyester **166** by catalytic hydrogenation followed by asymmetric alkylation to afford **167**. Mitsunobu inversion[34,66] and DHP protection of resulting hydroxy group delivered **168**. The latter was chain extended through reduction/oxidation and addition of EtMgBr to furnish **169**. Oxidation of secondary alcohol followed by THP deprotection afforded **170**. Now, acid **132** was esterified with **170** to deliver oxo ester **135**, which on intramolecular Ti-mediated cyclization and TBS deprotection afforded (–)-stegobiol **3**. Swern

oxidation of this furnished (–)-stegobinone **4**. The synthesis of these involved twelve and thirteen steps with 15% and 12.2% overall yields, respectively.



Scheme 22. Gil's synthesis of (–)-stegobiol and (–)-stegobinone.

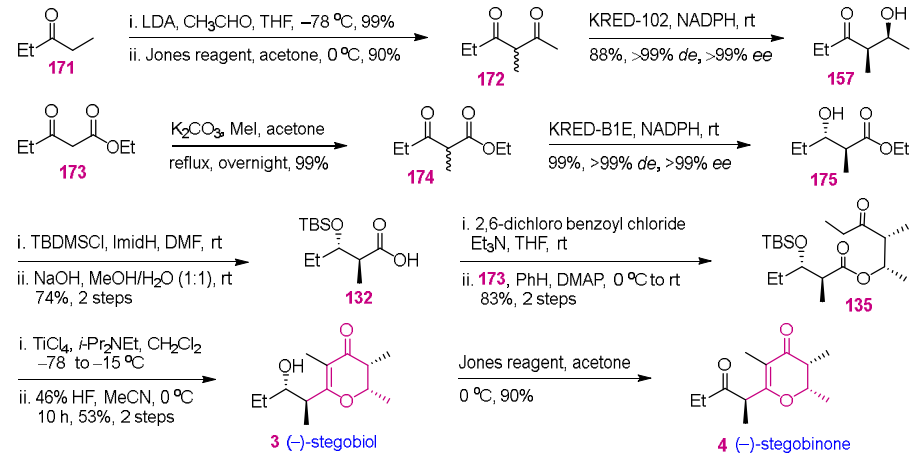
In 2012, Kalaitzakis and Smonou[67] developed a new strategy for (–)-stegobiol **3** and (–)-stegobinone **4** synthesis using enzymatic reduction for asymmetric synthesis of key precursor (Scheme 23). Preparation of hydroxy ketone **157** started with commercially available 3-pentanone **171**. The simple conversion of ketone **171** into diketone **172** followed by enzymatic reduction catalyzed by KRED-102 afforded keto alcohol **157**. Now, for the synthesis of intermediate **132**, 3-oxopentanoate **173** was alkylated to ketoester **174** in the presence of MeI. This was similarly reduced with KRED-BIE to result in **175**. Next, the TBS protection of hydroxy group and ester hydrolysis gave acid **132** that was esterified with **157** to deliver **135**. The well-established intramolecular cyclization and TBS removal gave (–)-stegobiol **3** and after oxidation furnished (–)-stegobinone **4**. The synthesis of these was completed in eight and nine steps with 32% and 28.7% yields, respectively.

3.2. Total synthesis of (–)-maurenone

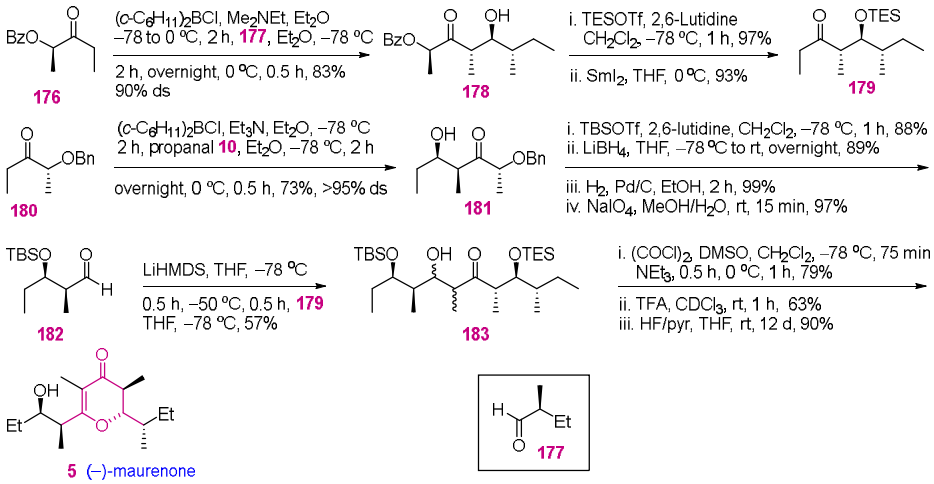
In 1986, (–)-maurenone **5** was first isolated by Faulkner and co-workers[68] from specimens of the pulmonate molluscs *Siphonaria maura*, which were collected from Jaco Beach, Costa Rica. The structural elucidation of maurenone was completed on the basis of ^{1}H and ^{13}C NMR data and it contains the relatively uncommon, tetra-substituted dihydropyrone moiety with the proposed structure as shown in Figure 1.

The first total synthesis of (–)-maurenone **5** was reported by Perkins'[69] group in 2006 (Scheme 24). The synthesis started with commercially available (*S*)-2-methylbutan-1-ol as a starting material and involved highly diastereoselective *syn*- and *anti*-boron aldol reactions to prepare key fragments. These were coupled using a lithium-mediated aldol reaction followed by acid-promoted cyclization/dehydration to get γ-dihydropyrone ring. All the key steps were commonly used to prepare eight isomers of one enantiomeric series of maurenone **5**. The synthesis of *anti-anti* ketone **179** commenced with coupling of dicyclohexylboron enolate of α-chiral ketone **176** with α-chiral aldehyde **177** (obtained by Swern oxidation of (*S*)-2-methylbutan-1-ol) to give compound **178**. This on silyl protection and debenzoylation with SmI_2 produced ketone **179**. The aldehyde **182** preparation started by coupling of dicyclohexylboron enolate of

α-chiral ketones **180** with propanal **10** to produce **181**. This on sequential TBS protection, $LiBH_4$ reduction of ketone, debenzylation and oxidative cleavage of resulting diol gave aldehyde **182**. Finally, ketone **179** was coupled with aldehyde **182** using lithium bis(trimethylsilyl)-amide to provide **183** in moderate yield. This was next oxidised using Swern protocol followed by selective deprotection of TES group and spontaneous cyclization/dehydration and TBS removal using buffered HF-pyridine to afford (–)-maurenone **5**. The synthesis was accomplished in nine linear steps with 14% overall yield.



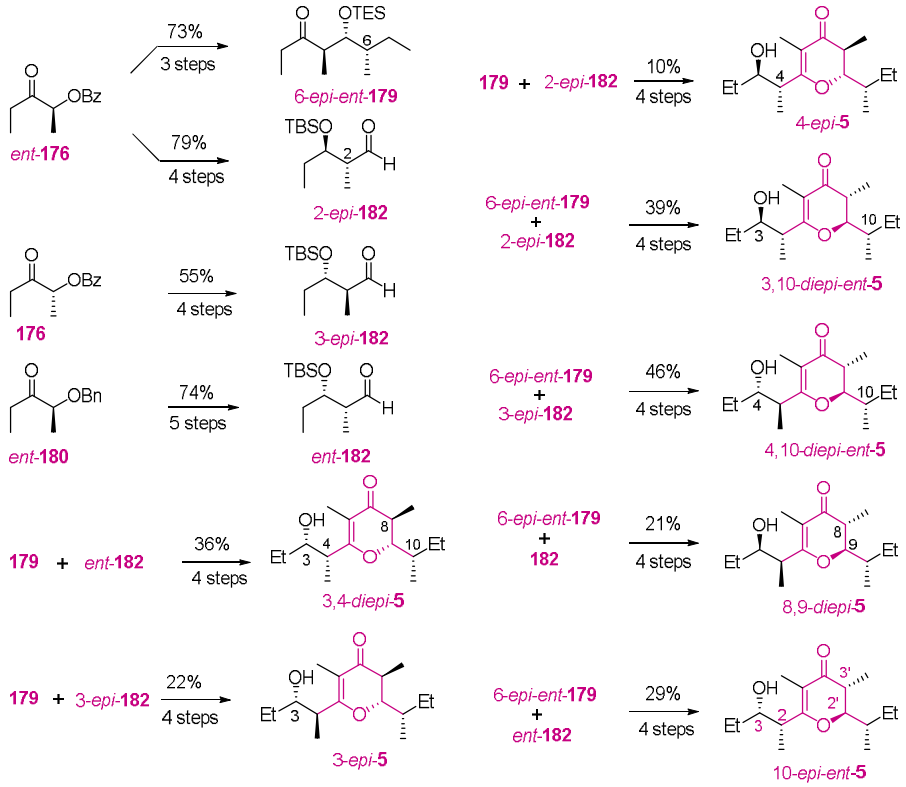
Scheme 23. Kalaitzakis's synthesis of (–)-stegobiol and (–)-stegobinone.



Scheme 24. Perkins' synthesis of (–)-maurenone.

Once (–)-maurenone **5** was synthesized, using a similar approach seven more stereoisomers of one enantiomeric series of maurenone were prepared. For this *anti-syn*-ketone 6-*epi*-*ent*-**179** was synthesised from *ent*-**176** in three steps with 73% yield by following same pathway as used for ketone **179**. Later, synthesis of aldehydes 2-*epi*-**182** and 3-*epi*-**182** were completed in four steps from *ent*-**176** and **176** with 79% and 55% yields, respectively. The aldehyde *ent*-**182** was prepared in five steps from *ent*-**180** with 74% yield using similar protocol as used for aldehyde **182**. Finally, the series of enantiomers of maurenone were achieved each

in four steps by coupling of ketones **179** and 6-*epi*-*ent*-**179** with each of aldehydes *ent*-**182**, 3-*epi*-**182**, 2-*epi*-**182**, and **182** in moderate to low yields as shown in Scheme 25.



Scheme 25. Perkins' synthesis of (–)-maurenone stereoisomers.

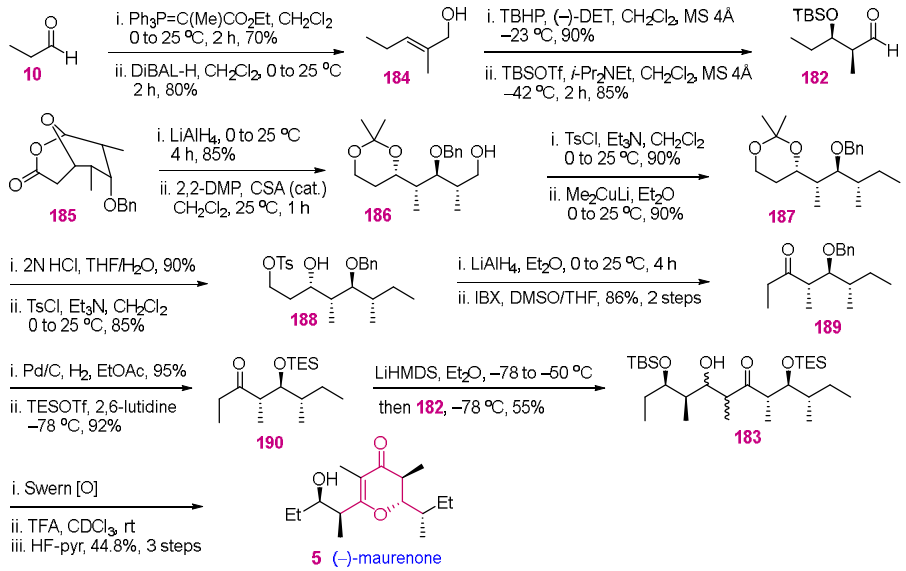
Yadav and co-workers[70] in 2007 described a formal stereoselective synthesis of (–)-maurenone **5** (Scheme 26). The synthesis of key fragment **182** started from *n*-propanal **10** with three-carbon Wittig olefination followed by DiBAL-H reduction to give allylic alcohol **184**. Next, the Sharpless asymmetric epoxidation of **184** and epoxide rearrangement with TBSOTf afforded the formal *syn*-aldol **182**. The other key fragment **190** was prepared starting from bicyclic compound **185** (obtained by desymmetrisation of *meso*-bicyclic dihydrofuran)[71] that was reduced and acetonide protection gave **186**. Chain extension *via* a tosylate provided **187**. Next, acetonide deprotection and tosylation gave **188** that on tosyl removal and oxidation furnished **189**. Further, debenzylation and silyl protection provided **190**. The latter on aldol reaction with **182** gave **183** that on oxidation, cylization and desilylation furnished (–)-maurenone **5**.[69] Thus the synthesis of (–)-maurenone **5** was completed in fourteen steps from **4** with 9.8% overall yield.

3.3. Total synthesis of (–)-membrenones A, B and C

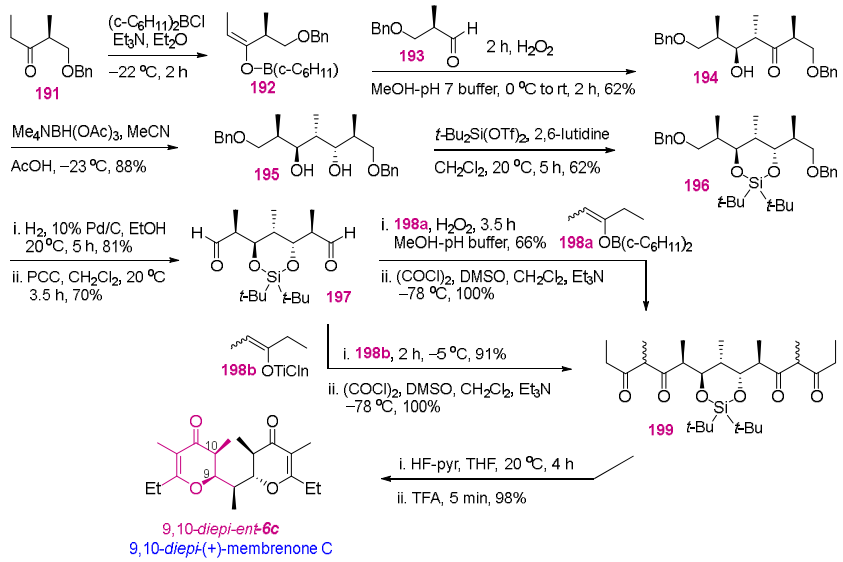
In 1993, Ciavatta and co-workers[72] isolated three new polypropionates from the skin of a Mediterranean mollusc and were named as (–)-membrenone-A **6a**, (–)-membrenone-B **6b**, and (–)-membrenone-C **6c**. Due to paucity of material isolated the bioactivity investigation could not be completed.

In 1998, Perkins and Sampson[73] reported the first stereoselective total synthesis of an isomer of membrenone-C using a novel two-directional chain extending double titanium aldol coupling as a key step (Scheme 27). The synthesis started with enolization of compound **191** to obtain dicyclohexyl borinate **192** that was subjected to addition with chiral aldehyde **193** resulting in *anti*-*anti* aldol isomer **194**. After Evan's

reduction[74] to **195** and protection of 1,3-diol produced the key intermediate **196**. Then debenzylation and oxidation provided di-aldehyde compound **197**. Later, the two-directional chain extending double aldol was performed using two different reagents with different outcome. In the first case, dicyclohexyl borinate **198a** after oxidative removal of borinate added to **197** to furnish one major product (66%) and a mixture of compounds (17%), while in the second case the Ti(IV) enolate **198b**[75] added to **197** giving high-yielding product though less stereoselective. Subsequent Swern oxidation provided **199**. Finally, deprotection and double cyclization/dehydration gave the desired molecule 9,10-*diepi-ent*-**6c**. The synthesis of this was completed in ten steps and 17% overall yield.

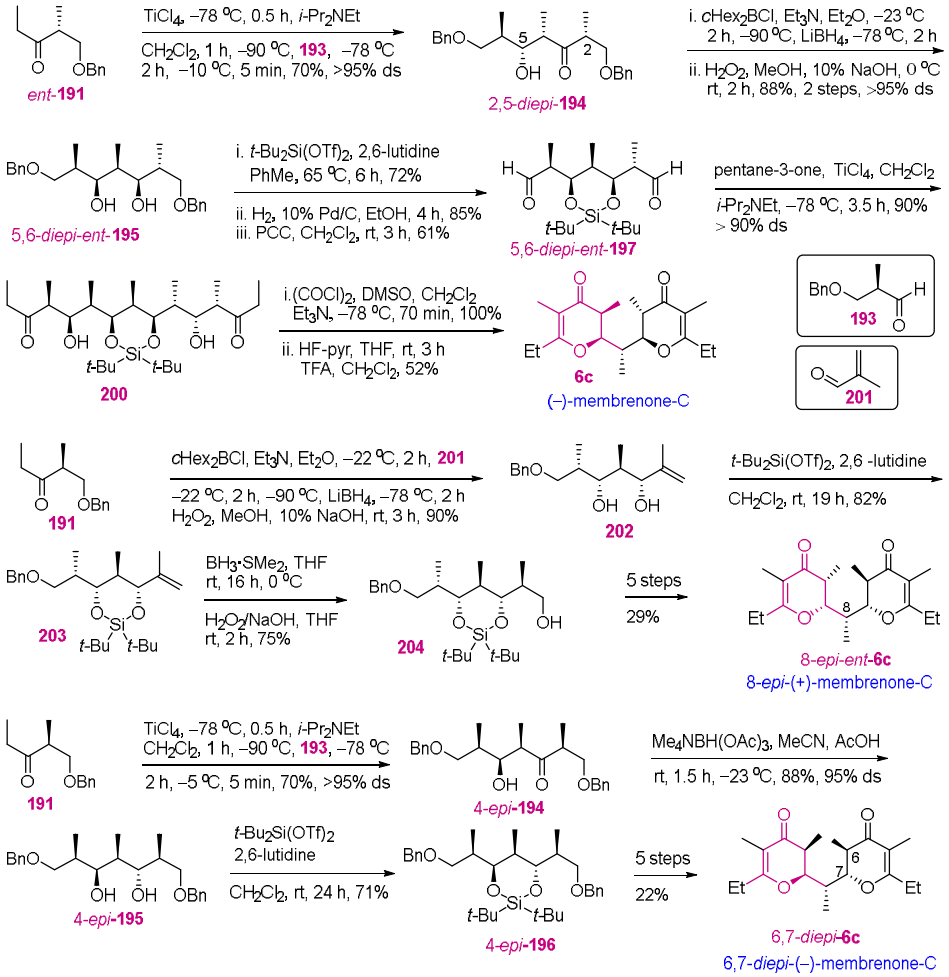


Scheme 26. Yadav's synthesis of (–)-maurenone.



Scheme 27. Perkin's synthesis of an isomer of (–)-membrenone.

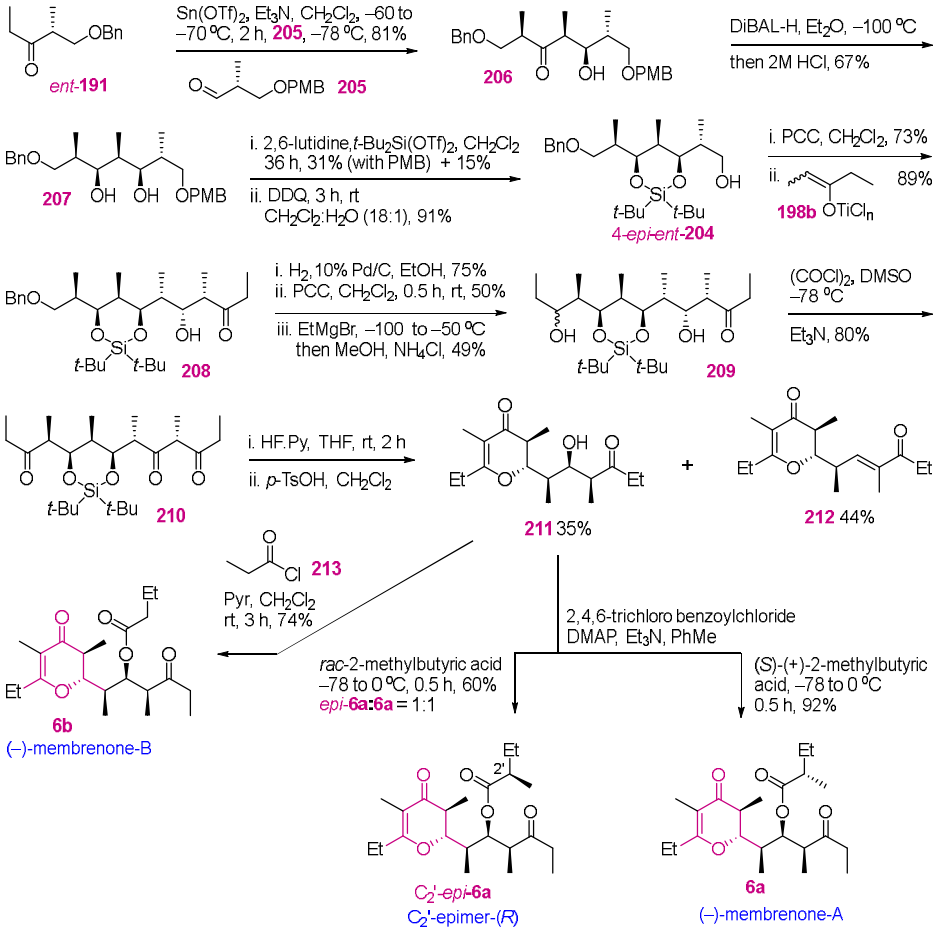
In 2001, Perkins and Sampson[76] disclosed a shorter and enantioselective synthesis of (−)-membrenone-C **6c** together with two diastereomers and confirmed its absolute structure. They adopted the same two directional chain extending double titanium aldol coupling strategy (Scheme 28). The synthesis started with the treatment of *ent*-**191** with aldehyde **193** to give *syn,syn*-aldol product 2,5-*diepi*-**194**. Then ketone reduction to 5,6-*diepi*-*ent*-**195** followed by silyl protection of 1,3-diol and subsequent debenzylation/oxidation gave 1,7-di-aldehyde product 5,6-*diepi*-*ent*-**197**. The next two-directional chain extending aldol reaction furnished compound **200**. Finally, the synthesis of (−)-membrenone-C **6c** was completed by Swern oxidation followed by acidic cyclization. The synthesis of (−)-membrenone was completed in eight steps and 10.8% overall yield. Similarly, the synthesis of two other diastereomers 8-*epi*-*ent*-**6c** (from **191** *via* intermediates **202**, **203** and **204**) and 6,7-*diepi*-**6c** was completed in eight steps and 16% and 9.6% overall yields, respectively.



Scheme 28. Perkins' synthesis of (−)-membrenone-C and other stereoisomers.

In 2002, Sampson and Perkins[77] synthesized membrenone-B **6b**, membrenone-A **6a** and its C_2-epimer using tin(II)-mediated aldol followed by *syn* selective reduction as key steps (Scheme 29). The synthesis of

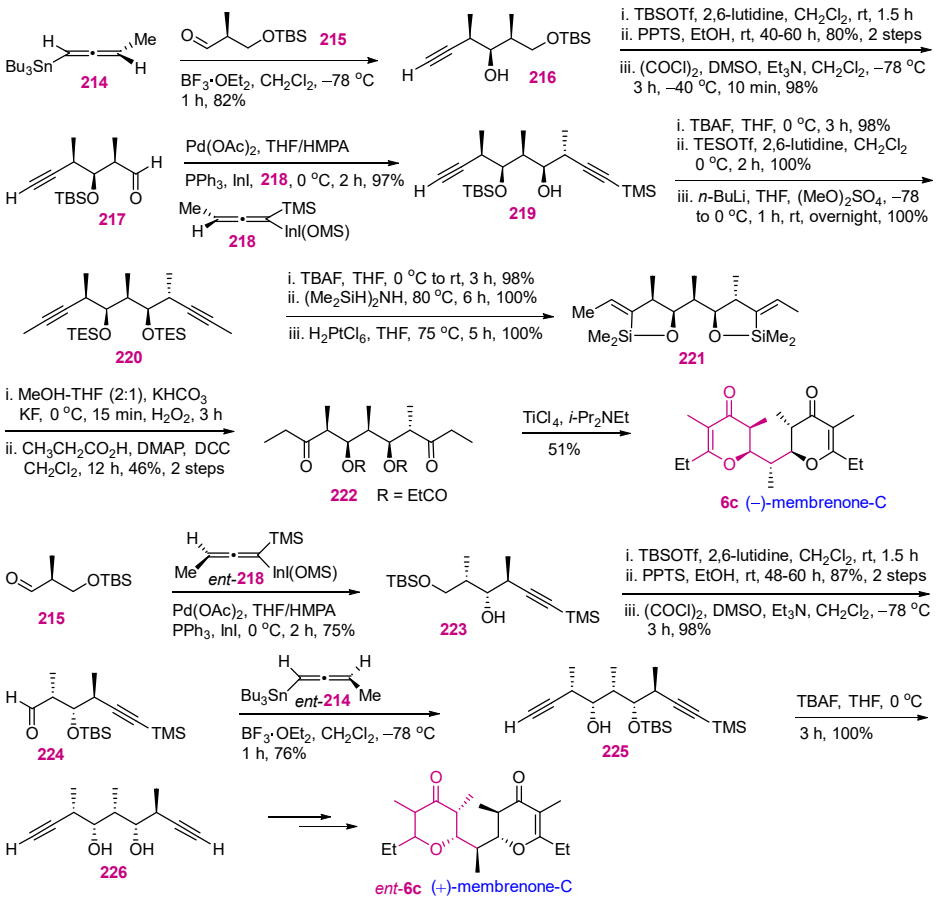
membrenones started with the preparation of tin enolate[78] of *ent*-**191** that reacted with chiral aldehyde **205** and gave *syn-syn*-aldol product **206**. The latter on reduction afforded 1,3-diol **207**. Next, protection of 1,3-diol and PMB removal furnished 4-*epi*-*ent*-**204**, which on oxidation to aldehyde and subsequent aldol reaction with **198b** gave **208**. Then, benzyl deprotection, oxidation to aldehyde and Grignard reaction produced a single diastereomer alcohol **209**. Further, Swern oxidation furnished trione **210**. Finally, silyl deprotection followed by cyclo-dehydration afforded compounds **211** and **212** (arising from β-hydroxy elimination). The former was reacted with propionylchloride **213** to give (–)-membrenone-B **6b**. Next, (–)-membrenone-A **6a** and its epimer C2′-*epi*-**6a** were also synthesized using Yonemitsu-Yamaguchi esterification with (*S*)-2-methylbutyric acid and *rac*-2-methylbutyric acid, respectively. The synthesis of (–)-membrenone-B **6b** and (–)-membrenone-A **6a** was accomplished in thirteen steps each and 0.6% and 0.7% overall yields, respectively.



Scheme 29. Perkins' synthesis of (–)-membrenones-A and -B.

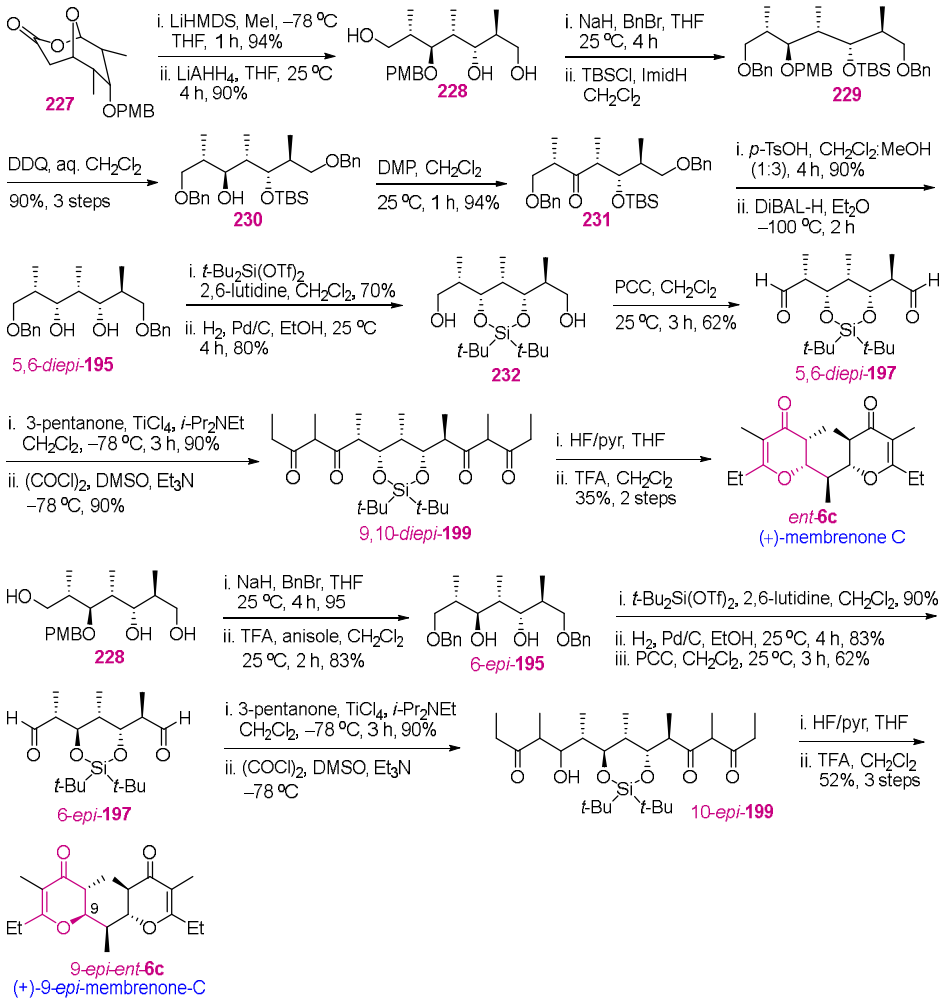
In 2003, Marshall and Ellis[79] synthesized (–)-membrenone-C **6c** and its enantiomer *ent*-**6c** by intramolecular hydrosilylation-oxidation, and bis-intramolecular aldol reaction (Scheme 30). The synthesis started with the addition of allenylstannane **214** to aldehyde **215** to give *syn-syn* product **216**. Next, the orthogonal protection/deprotection of alcohols and oxidation produced the aldehyde **217**. This on addition of allenylindium reagent **218** gave **219**. The latter on desilylation and hydroxy silylation followed by alkyne

methylation produced the internal diyne **220**. Again, desilylation and treatment with tetramethyldisilazane furnished the cyclic vinyl silanes **221**. Later, Tamao oxidation[80] was performed to provide diketo compound that was esterified with propionic acid to **222**. This was subjected to intramolecular double aldol cyclization resulting in (–)-membrenone-C **6c**. The synthesis was completed in fourteen steps with a 14% overall yield. They also synthesized the enantiomer (+)-membrenone-C. Here, the addition of allenylindium reagent *ent*-**218** to aldehyde **215** gave *anti*-adduct **223** in 99:1 dr. Then, selective manipulation of hydroxy functions and oxidation delivered aldehyde **224**, which was reacted with allenylstannane *ent*-**214** to afford alcohol **225**. Desilylation provided diol **226**, which is enantiomeric to the diol from **220**. Hence, further similar steps resulted in (+)-membrenone-C completed from **215** in fourteen steps and overall yield of 11.2%.



Scheme 30. Marshall's synthesis of both enantiomers of membrenone-C.

In 2006, Yadav and co-workers[81] synthesized (+)-membrenone-C *ent*-**6c** using earlier prepared lactone **227** (Scheme 31). The sequence started with the alkylation of **227** followed by reduction to furnish the triol **228**. Then protection of the primary alcohol groups and silylation of secondary alcohol led to **229**. Next, PMB removal to **230** and oxidation gave **231**. Later, the sequence of desilylation, keto reduction to 5,6-*diepi*-**195** and protection of 1,3-diol and subsequent debenzylation gave **232**. Then, oxidation to 5,6-*diepi*-**197**, double aldol chain extension, and further Swern oxidation provided 9,10-*diepi*-**199**. Finally, deprotection and cyclization/dehydration furnished (+)-membrenone-C *ent*-**6c**. Similarly, they also synthesized (+)-7-*epi*-membrenone-C from **228** in nine steps.

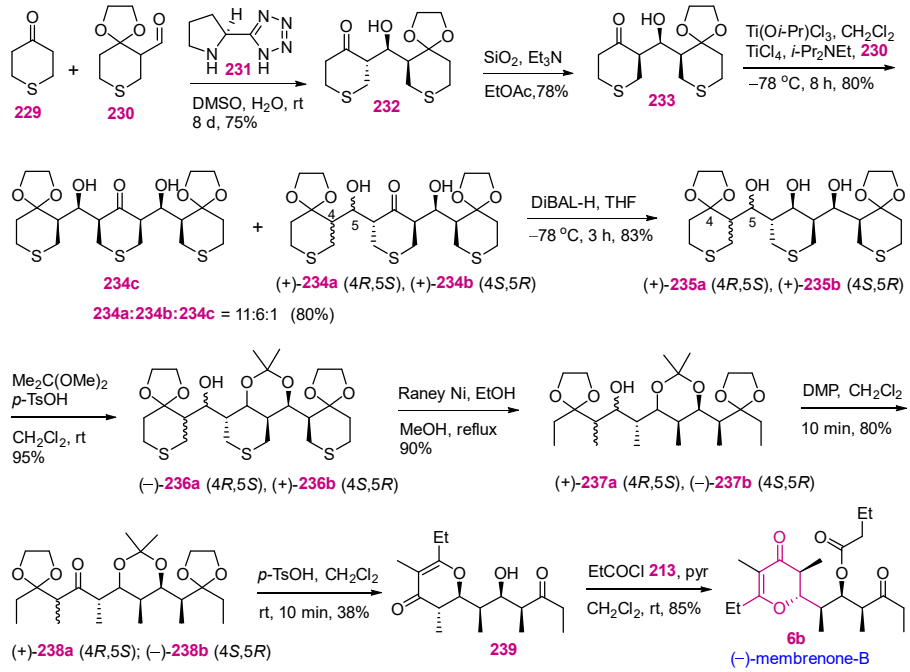


Scheme 31. Yadav's synthesis of (+)-membrenone-C.

In 2007, Jheengut and Ward[82] synthesized (–)-membrenone-B **6b** using two directional aldol reaction as key step (Scheme 32). The synthesis started with organocatalyzed aldol reaction of **229** and **230** in presence of **231** to give **232** followed by isomerization resulting in **233**. A repeat aldol in presence of Ti-salt between **233** and **230** provided a 11:6:1 mixture of (±)-**234a**, (±)-**234b**, and **234c**. Then reduction to **235a**/**235b** followed by protection of 1,3 diol furnished 2.8:1 mixture of (–)-**236a** and (+)-**236b**. This mixture on desulfurization to **237a**/**237b** and oxidation gave a 2.8:1 mixture of (+)-**238a** and (–)-**238b**. Further, deprotection and cyclization resulted in **239**. Finally, acylation gave (–)-membrenone-B **6b**. The synthesis was completed in nine steps and 8.6% overall yield. The 6-membered thiopyran was beautifully used as masked surrogate for 1,3-dimethyl functionality in the target compounds.

In 2014, Alagiri and co-workers[83] synthesized (–)-membrenone-A **6a** and (–)-membrenone-B **6b** using direct aldol reaction (Scheme 33). The synthesis started with treatment of thiopropionamide **240** with propanal **10** in the presence of mesitylcopper and (*R,R*)-Ph-BPE and **241**, which exclusively delivered the *syn*-aldol product **242**. The latter on silyl protection to **243** and thioamide reduction after *S*-methylation[84] gave aldehyde *ent*-**182**, which was taken for second aldol reaction with **240** to **244** followed by silyl protection and

S-methylation/reduction to the aldehyde **245**. Next, the chain extension by aldol reaction with 3-pentanone to **246** and protection of secondary alcohol with **247** afforded **248**. The latter on cyclization and TBS removal gave **249**. This was oxidized and TBDPS deprotection furnished **211**. Finally, the synthesis of (−)-membrenone-A **6a** and (−)-membrenone-B **6b** were completed by acylation of **211**. The synthesis of these was completed in thirteen steps each with 6.5% and 6% overall yields, respectively.



Scheme 32. Ward's synthesis of (−)-membrenone-B.

3.4. Total synthesis of (−)-vallartanone B

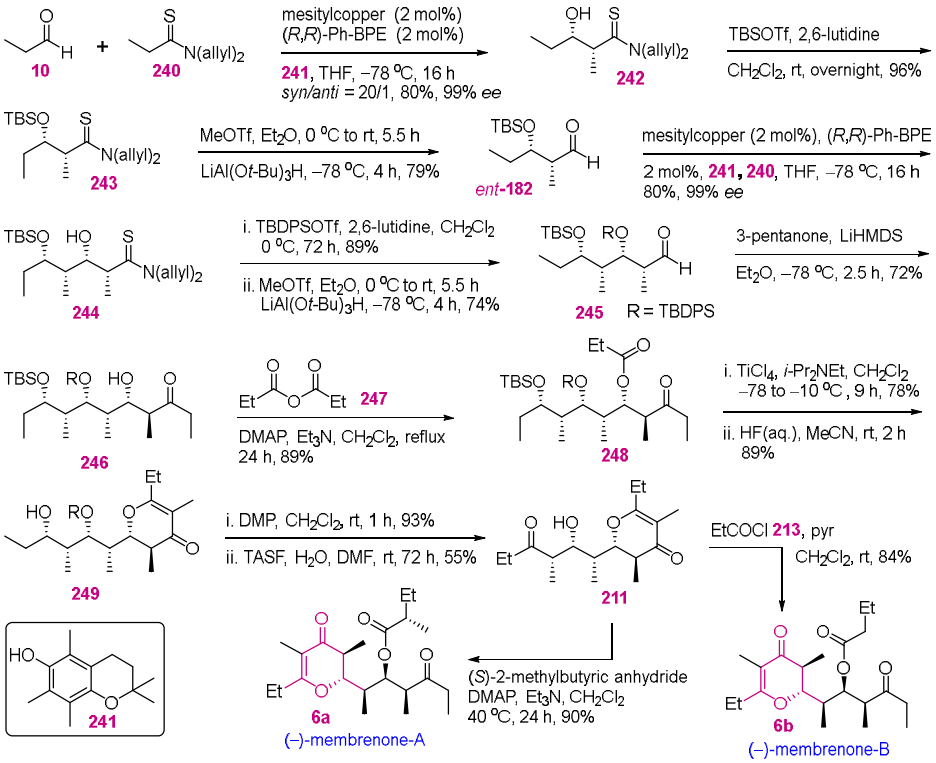
In 1989, Manker and Faulkner[85] isolated vallartanone B **7b** from *Siphonaria maura*, that deters feeding by the fish *Thallasoma lunate*, which was collected from Costa Rica. The structural elucidation of vallartanone B was interpreted on the basis of spectral data and it contains tetraalkylsubstituted γ-pyrone moiety and the proposed structure is as shown in Figure **1**.

In 1996, Arimoto and co-workers[86,87] with their initial communication and later with a full account reported the total synthesis of proposed (8*R*)-vallartanone B (8*R*)-**7b** and the revised natural product structure (−)-vallartanone B **7b** from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate **250** and methyl (*S*)-3-hydroxy-2-methylpropionate *ent*-**250**, respectively (Scheme 34). The synthesis of proposed vallartanone B commenced with the preparation of β-triketone **252** from compound **250** by TBDPS protection followed by alkylation with **251**. Next, pyrone **253** was achieved from β-triketone **252** by PPh_3-CCl_4 cyclization and silyl deprotection. Later, compound **253** was oxidised and directly submitted to aldol reaction with ketone **254** to give **255**. This was further oxidised to give β-diketone and then cyclized to furnish the epimer of vallartanone B, *i.e.* (8*R*)-**7b**. Similarly, (−)-vallartanone **7b** was also synthesised using same reaction sequence from *ent*-**250**. The synthesis of **7b** and its C8-epimer was completed each in eight steps with 16.2% and 13% overall yields, respectively.

3.5. Total synthesis of (+)-auripyrones A and B

In 1996, Yamada and co-workers[88] isolated auripyrones A and B from methanol extract of specimens *Dolabella auricularia* accumulated near Mie Prefecture, Japan. For more than 40 years, *D. auricularia*, a sea

hare belonging to the aplysiidae family of marine opisthobranchs, has been a reliable source of bioactive metabolites ranging from peptides and depsipetides to polyketides.[89]

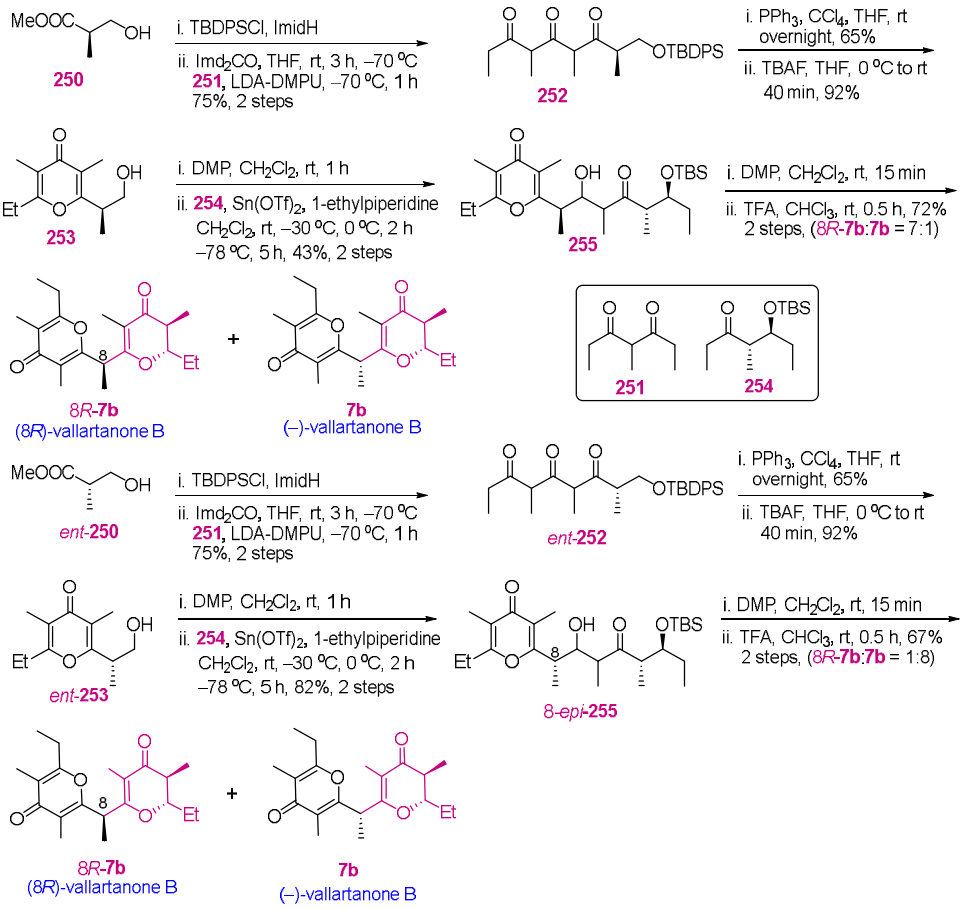


Scheme 33. Alagiri's synthesis of (–)-membrenones-A and -B.

In 2006, Lister and Perkins[90] described the first total synthesis of (+)-auripyrone A **8a** and also identified the absolute stereochemistry of the natural product (Scheme 35). They began their synthesis with dipropionate equivalent **256**.[91] Enolate of β-ketoimide **256** on highly stereoselective aldol addition with aldehyde **205** delivered **257**. The latter on DiBAL-H reduction of ketone, then diol protection with DDQ-mediated *p*-methoxybenzylidene acetal formation and treatment with isovaleric acid under Yamaguchi conditions[56] furnished **258**. This was subjected to auxiliary removal to give primary alcohol **260** along with minor amount of diol **259** that could be recycled to **260**. Oxidation of **260** gave aldehyde **261** that was taken for aldol reaction with the enolate of silyl protected **262** to deliver the major isomer **263** (*de*=85%) along with other isomers. TMS removal and oxidation gave mixture of keto and enol forms of triketone **264**. The latter on hydrogenolysis of acetal and cyclization furnished **265** with high diastereoselectivity (94% *de*). This on DMP oxidation to aldehyde **266** and aldol addition with enolate of ketone **267** (to give aldolate in 88% *de*) followed by desilylation and oxidation furnished **268**. Finally, the cyclization of triketone with amberlyst-15 led to (+)-auripyrone A **8a** in 39% yield. The synthesis of latter was completed in sixteen steps with 5.6% overall yield from **256**.

In 2009, Jung and Salehi-Rad[92] synthesized (+)-auripyrone A **8a** using tandem non-aldol aldol/Patterson-lactate-derived aldol reaction to generate stereopentad backbone (Scheme 36). The synthesis commenced with the preparation of **272** using the key aldol reaction. Epoxidation of alcohol **269**[93] under reagent controlled Sharpless conditions or substrate controlled *m*CPBA conditions delivered epoxide **270** in 85% and 90% yields, respectively. Silyl protection and epoxide rearrangement gave the formal *syn*-aldol product **271**. Now, *anti*-aldol reaction of aldehyde **271** with *E*-boron enolate of Peterson's lactate derived

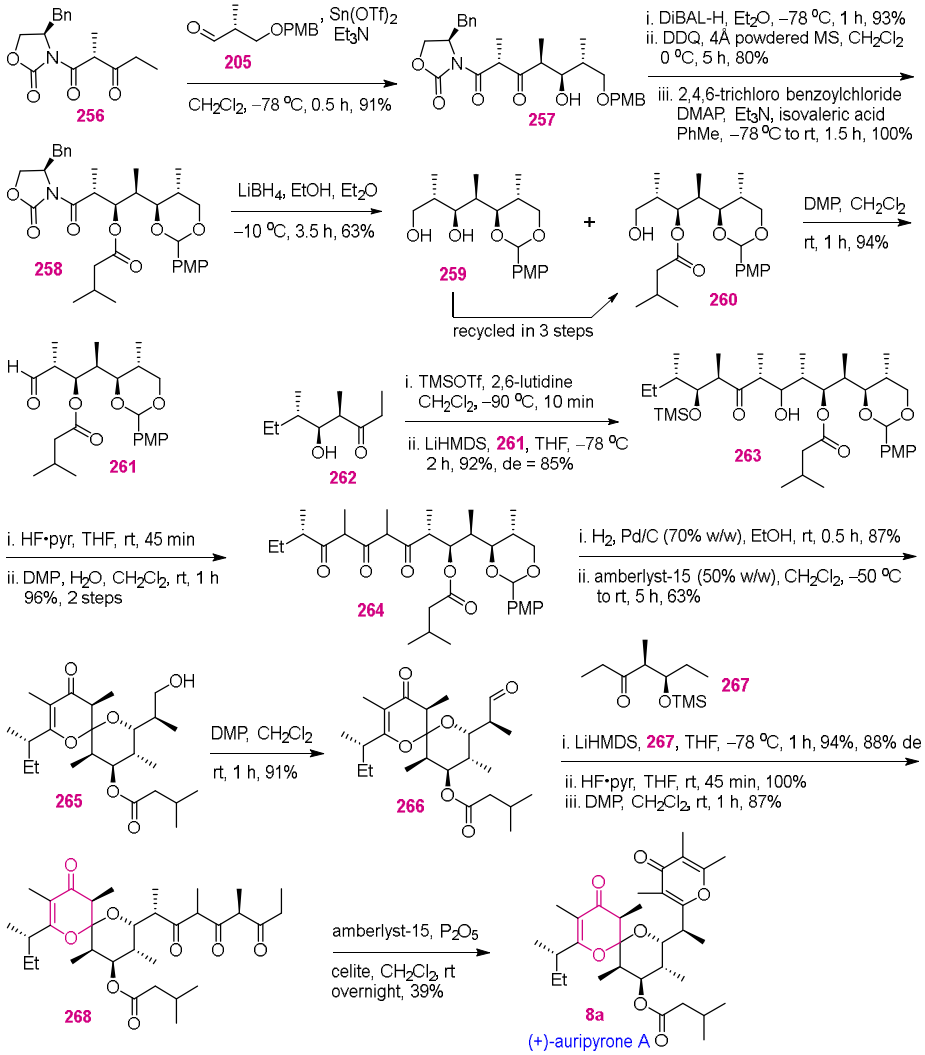
ketone[94] **176** delivered the desired *anti*-aldolate **272** as a single diastereomer. PMB protection of alcohol **272**, followed by removal of benzoate with $LiBH_4$ and periodate cleavage of the resultant diol furnished desired aldehyde **273**. Later on, the aldol reaction of lithium enolate of silyloxy enone **274** with aldehyde **273** gave **275** as a mixture of olefin isomers. Next, the DMP oxidation to diketone and cyclization yielded γ-pyrone **276**. Then removal of TES ether followed by Yamaguchi esterification of resulting alcohol gave the ester, which on desilylation and DMP oxidation delivered aldol precursor **277**. The latter was taken for aldol reaction with the enolate of ketone 3-*epi*-**179** (prepared from known **262**) to diaseteroselectively deliver the *anti*-aldol Felkin-Ahn product **278**. Further, oxidation of alcohol and removal of PMB and TES ethers invoked the cyclization giving hemiketal **279**. Now, oxidation of alcohol and spiroketalization afforded the natural product (+)-auripyrone A **8a**. The latter was synthesized in nineteen steps and 15.6% overall yield.



Scheme 34. Arimoto's synthesis of (8*R*)-vallartanone B and (–)-vallartanone B.

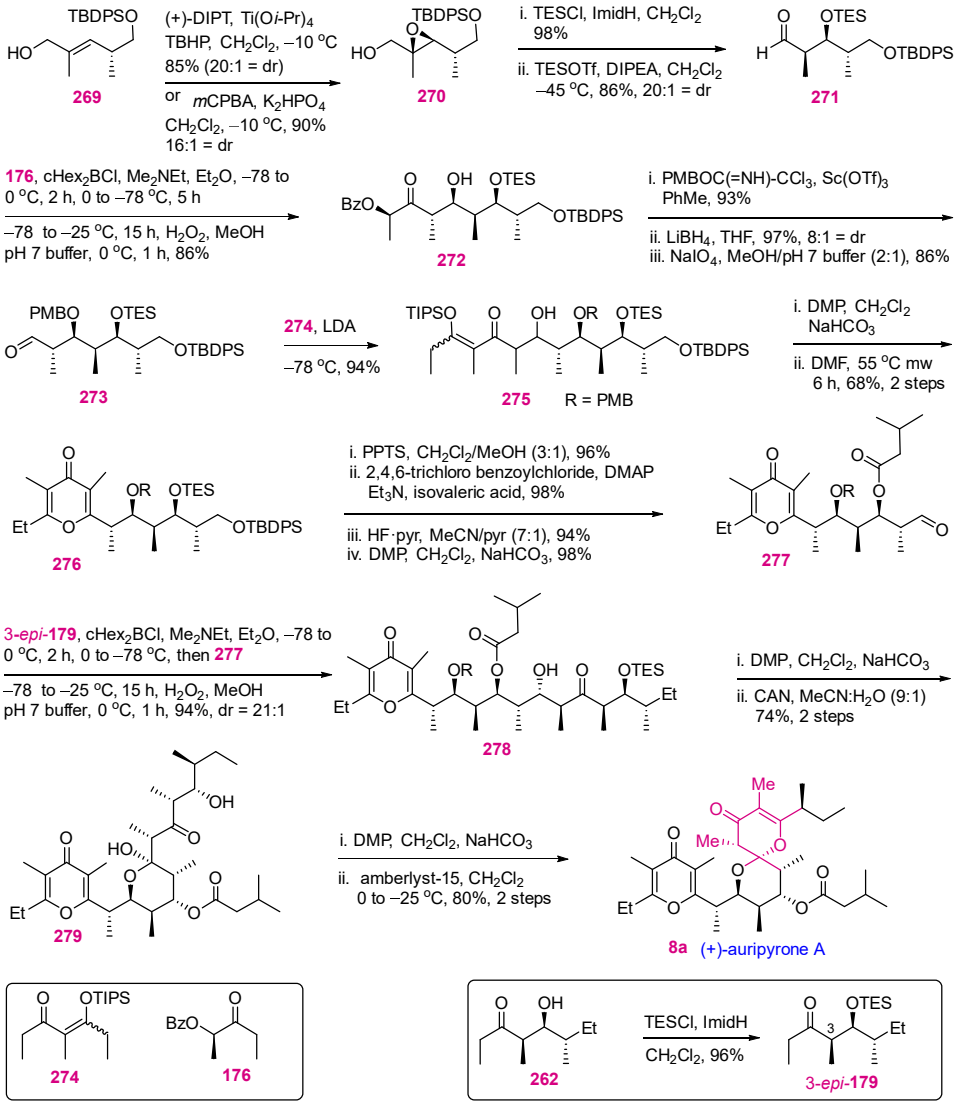
Kigoshi and co-workers[95] in 2010 reported the total synthesis of (+)-auripyrones A **8a** and B **8b** by using diastereoselective aldol-type reaction as key step (Schemes 37 and 38) and also studied their bioactivity.[96] The synthesis commenced with preparation of C1-C13 segment **286** (Scheme 37). Aldehyde **281** and pyrone **280** were subjected to diastereoselective aldol-type reaction to deliver compound **282**. TBS protection of secondary alcohol followed by removal of trityl group and oxidation of resulting alcohol afforded aldehyde **283**. Now, **283** was subjected to Brown crotylboronation[97] reaction with boronate **284** to give homoallylic alcohol **285** as single diastereomer. Acylation of secondary alcohol followed by dihydroxylation and oxidative cleavage of

resulting diol afforded aldehyde **286**. The latter was taken for aldol reaction with ketone **287** and then TES removal and oxidation delivered triketone **288**. Next, removal of TBS ether followed by spiroacetalization by HF.pyr furnished desired natural product (+)-auripyrone A **8a**.



Scheme 35. Perkins's total synthesis of (+)-auripyrone A.

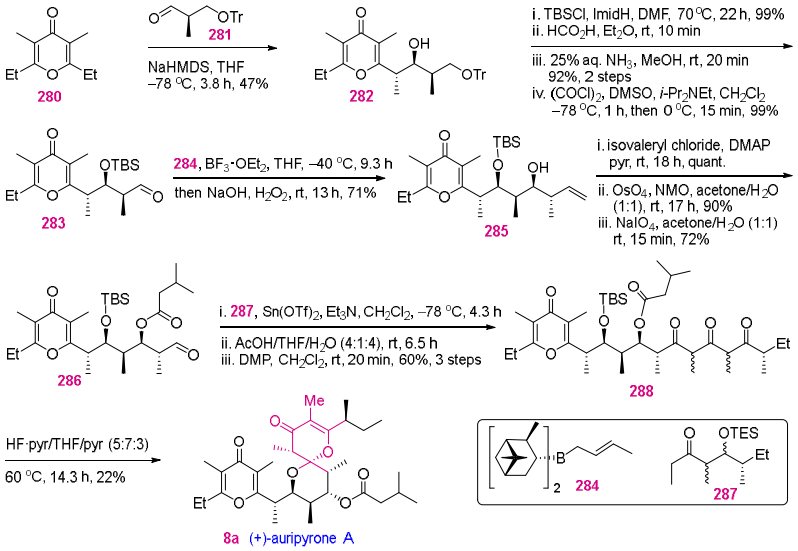
For the synthesis of (+)-auripyrone B, compound **285** and acid **289** underwent the Yamaguchi esterification to afford ester **290** (Scheme 38). Dihydroxylation of terminal alkene **290** followed by oxidative cleavage of resulting diol delivered aldehyde **291**. The latter was subjected to Paterson's aldol reaction with **287** to yield the coupling product, which on TES deprotection followed by oxidation afforded triketone **292** as a mixture of keto and enol forms. Removal of TBS ether by HF.pyr and spontaneous spiroacetalization delivered (+)-auripyrone B **8b**. They also synthesized the (2′*R*)-auripyrone B by using *ent*-**289**. The total synthesis of (+)-auripyrones A **8a** and B **8b** was completed in thirteen steps with 2.6 and 3.1% overall yields, respectively.



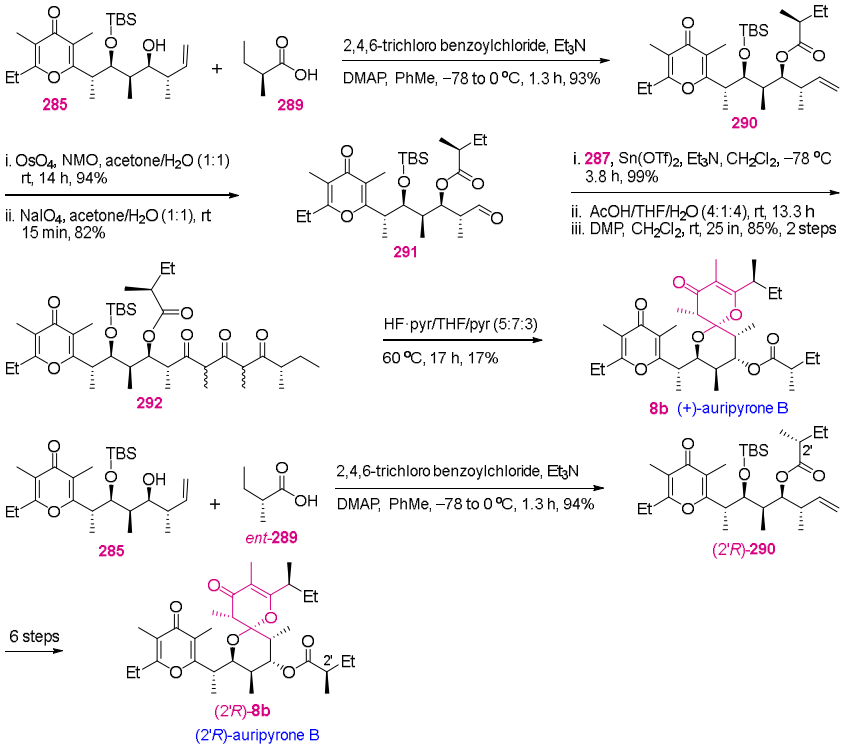
Scheme 36. Jung's synthesis of (+)-auripyrone A.

In 2010, Jung and co-workers[98] reported the synthesis of (+)-auripyrone B **8b** using a late stage spiroketalization onto a stable hemiketal as key step (Scheme 39). The aldehyde **271** was used from their previous work as in Scheme 36. Wittig olefination of intermediate aldehyde **271** gave **293**. Reduction of ester and stereoselective epoxidation under Sharpless conditions furnished epoxide **294**, which was opened with lithium dimethyl cuprate followed by protection of resulting diol to deliver *p*-methoxybenzlidene acetal **295**. Selective reduction of acetal and oxidation gave the stereopentad **273**. Alcohol **296** was obtained from **273** in four steps as reported in Scheme 36. This was subjected to Yamaguchi esterification with **289** and then removal of silyl ether and DMP oxidation furnished **297**. The latter on *anti*-aldol reaction with boron enolate of the ketone 3-*epi*-**179** gave aldolate **298** with 20:1 diastereomeric ratio. Further oxidation to diketone, followed by removal of PMB and TES ether induced cyclization to deliver hemiketal **299**. Oxidation of **299** followed by

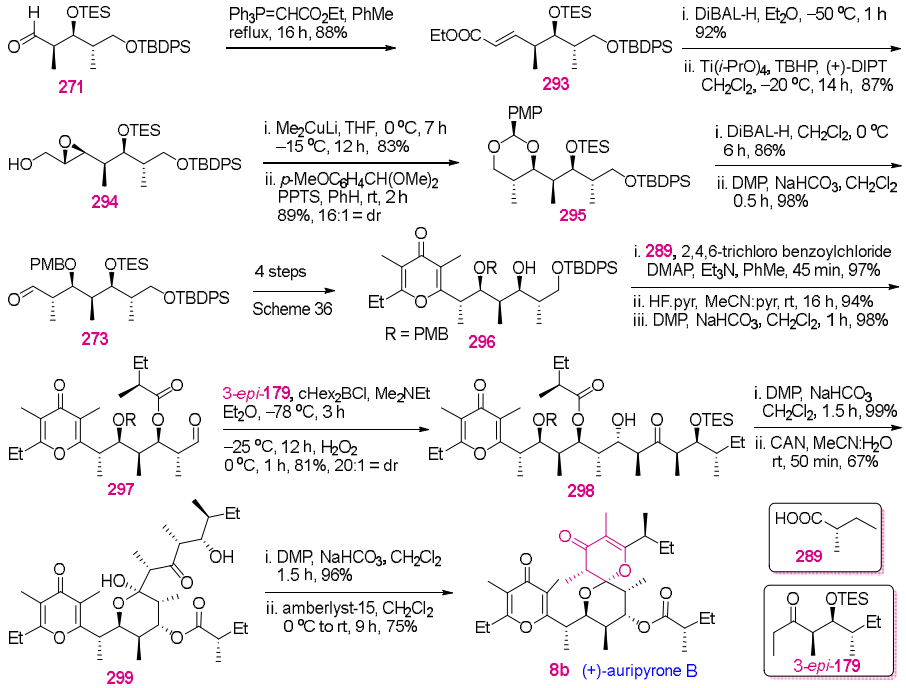
treatment of resulting diketone with amberlyst-15 yielded (+)-auripyrone B **8b** as a single diastereomer. The latter was synthesized in nineteen steps and 9.3% overall yield from **271**.



Scheme 37. Kigoshi's synthesis of (+)-auripyrone A.



Scheme 38. Kigoshi's synthesis of (+)-auripyrone B.



Scheme 39. Jung's synthesis of (+)-auripyrone B.

4. Conclusions

The dihydropyrone natural products represented by hepialone, obolactone, dihydroobolactone, stegobiol, stegobinone, maurenone, membrenones, vallartanones and auripyrones have been synthesized by using various intriguing strategies. While the chiral pool based approach is quite common, other methods like catalytic allylation, asymmetric catalytic reductions, Sharpless epoxidation, enzymatic methods and chiral auxiliary based aldol reactions have also been employed. Besides this the unique use of boronic ester chemistry, alkynone rearrangements and Wacker-based desymmetrization are also elegantly executed. Future directions could be the use of photocatalytic, protecting group-free and atom-economic strategies for synthesis of such an important class of heterocyclic γ-pyrone natural products.

Acknowledgements

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