# SYNTHETIC APPROACHES TO SPIRO BIS-THF NATURAL PRODUCTS: CEPHALOSPOROLIDES, PENISPOROLIDES, ASCOSPIROKETALS AND PYRENOLIDES

DOI: http://dx.medra.org/10.17374/targets.2022.25.113

**Rodney A. Fernandes,* Ashvin J. Gangani,[#] Naveen Chandra[#]**
*Department of Chemistry, Indian Institute of Technology Bombay,*
*Powai, Mumbai 400076, Maharastra, India*
*(e-mail: rfernand@chem.iitb.ac.in) [#]These authors contributed equally*

***Abstract.*** *The γ-lactone fused bis-THF natural products are derived from various marine sources and are known for different bioactivities. The rigid tetrahydro-spirofurofuranone moiety is present in cephalosporolides E, F, H and I, penisporolides A and B and ascospiroketal B. The related ascospiroketal A and pyrenolides have THF ring instead of the furanone, while the latter has the butenolide moiety as well. These marine-derived fungus molecular architectures have attracted much attention of the synthetic community with various interesting approaches being documented in the literature. The total synthesis of some of them have clarified the need of structure revision and all these synthetic attempts are compiled in this chapter.*

**Contents**

1. Introduction
2. Total syntheses of cephalosporolides E and F
3. Total synthesis of cephalosporolides H, I and penisporolides A and B
4. Total synthesis of ascospiroketals A and B
5. Total synthesis of pyrenolide D
6. Conclusion
Acknowledgement
References

## 1. Introduction

Marine originated microorganisms are an important source of various pharmacologically active metabolites that have contributed largely toward isolation of various structurally intriguing molecules, some of them having interesting bioactivities. This has therefore stimulated active research in pharmaceutical and drug development programs. Marine species, particularly algae, sponges and coelenterates are fertile grounds for prominent biologically and pharmacologically potent molecules.[1] Fungi and their associated metabolites since long have influenced many aspects of human culture and development. Antibiotic production by fungal sources has immensely influenced the drug discovery and development research endeavors. The first report indicating the antibacterial potential of fungi was by Tyndall, in which he described the antagonistic effect of a *Penicillium* sp. on bacteria.[2] Later, Gosio reported the isolation of mycophenolic acid, a crystalline compound possessing excellent antibacterial properties. Effects of *Penicillium notatum* and penicillin on bacteria was first described by Sir Alexander Fleming. A group from Oxford University started investigating penicillin for use as an antibiotic in humans, while the importance of such natural products was not fully understood until the early 1940s. Later, the Brotzu group investigated seawater samples for antibiotic producing microorganisms[3] and *Siccayne* was the first antibiotic isolated from a marine fungus.[4] Natural products isolation from various marine-derived species has led to the discovery of many new molecules out of which some have effective pharmacological properties, thus providing evidence that marine-derived fungi have the potential to be a rich source of lead compounds in drug discovery.[5] This has also provided the impetus for development of elegant strategies for synthesis of complex natural products. Using various new synthetic strategies, chemists have been able to synthesize thousands of natural products and natural product-like molecules with interesting biological properties. Isolation of natural products from natural sources such as marine species, plants, animals and microorganisms in larger quantities is not feasible as it disturbs the environmental balance. Hence, the laboratory synthesis of natural products has a great significance. This also enables process development and many molecules are produced on larger scale enabling their studies for bioactivity and clinical trials.

A class of compounds bearing the tetrahydro-spirofurofuranone moiety, named cephalosporolides E, F, H and I, penisporolides A and B and ascospiroketals A and B (Figure 1), have been isolated from various marine-derived sources. All these molecules have the common core structure and differ in having different alkyl substituents. Related pyrenolide D was isolated from a plant fungus and differ in having the fused THF-rings and the spiro-butenolide moiety. While suitably placed hydroxy functions and a keto group for intended spiro-ketalization is a well-recognised strategy for synthesis of such molecules, many new routes have been developed to access spiroketals.[6,7] In this chapter we have reviewed the isolation, bioactivities and various syntheses of the tetrahydro-spirofurofuranone molecules shown in Figure 1.

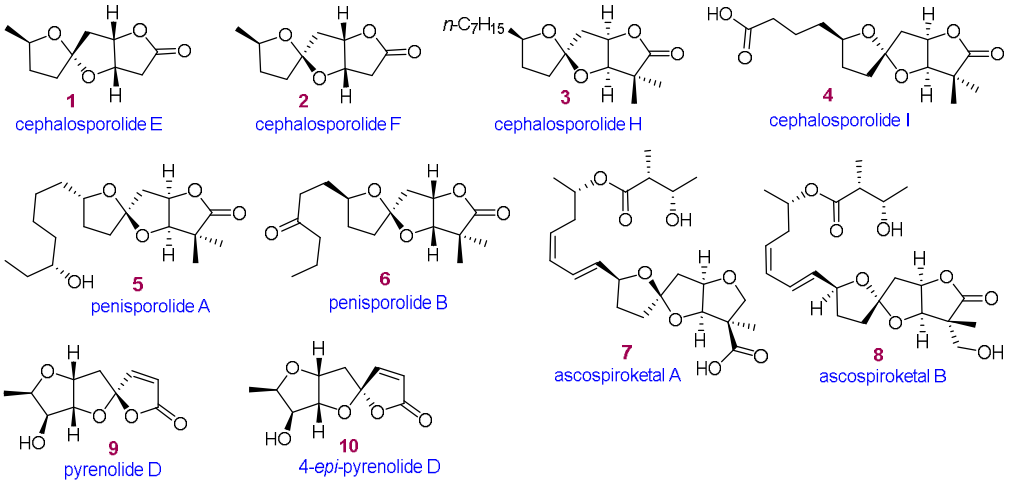


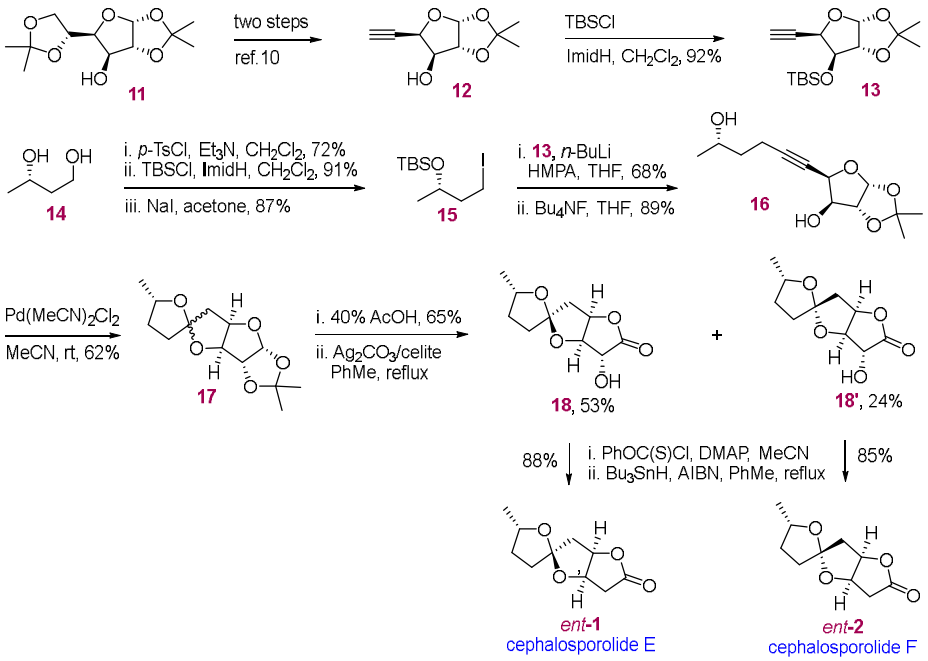

**Figure 1.** Spiro-bis-THF natural products cephalosporolides, penisporolides, ascospiroketals and pyrenolides.

## 2. Total synthesis of cephalosporolides E and F

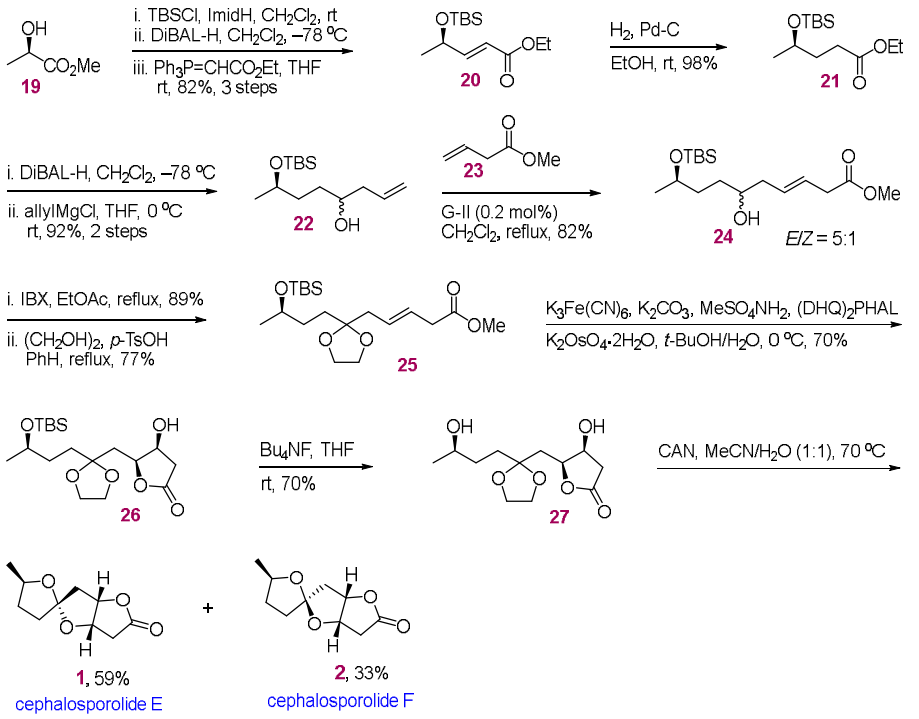
In 1985, Hanson and co-workers[8a] isolated the rare metabolites named cephalosporolides E and F from the fungus *Cephalosporium aphidicola*. Later in 2005, Oltra and co-workers[8b] established the chemical structure of (+)-bassianolone (the keto form) derived from the entomopathogenic fungus *Beauveria bassiana*. When bassianolone was passed through silica gel, a mixture of cephalosporolides E and F were obtained, which indicated that it is the actual precursor of cephalosporolides E and F. Further, *in vitro* antimicrobial activity of cephalosporolides E and F and bassianolone (100 μg $mL^{-1}$) against gram-positive (*Bacillus megaterium* and *Staphylococcus aureus*), gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal (*Candida albicans*) species was tested. Cephalosporolides E and F showed no antimicrobial activity while (+)-bassianolone completely inhibited the visible growth of *S. aureus* and *C. albicans*.

The first synthesis of the antipodes of cephalosporolides E and F was reported by Ramana and co-workers from chiral pool material (Scheme 1).[9] Glucose diacetonide **11** was converted into alkynol **12** in 2 steps,[10] which upon TBS protection gave **13**. The other coupling partner **15** was prepared from (*S*)-butane-1,3-diol **14** in 3 steps and coupled with fragment **13** followed by desilylation to afford **16**. Next, the Pd-mediated alkynediol cycloisomerization of **16** gave an inseparable diastereomeric mixture (1:1) of **17** which upon acetonide deprotection followed by treatment with Fetizon's reagent gave lactones **18** and **18′** that were separated by column chromatography. Removal of the free hydroxyl group furnished the unnatural (−)-cephalosporolide E (*ent*-**1**) and (+)-cephalosporolide F (*ent*-**2**). The full synthesis required 8 steps from **12** with an overall yield of 10.5% and 4.6% for *ent*-**1** and *ent*-**2**, respectively.

The first generation synthesis of natural cephalosporolides E and F by the Fernandes group involved the late stage spiroketalization strategy.[11] TBS protection followed by DiBAL-H reduction of (*R*)-methyl lactate **19** gave an aldehyde intermediate, which upon Wittig olefination furnished **20** (Scheme 2).



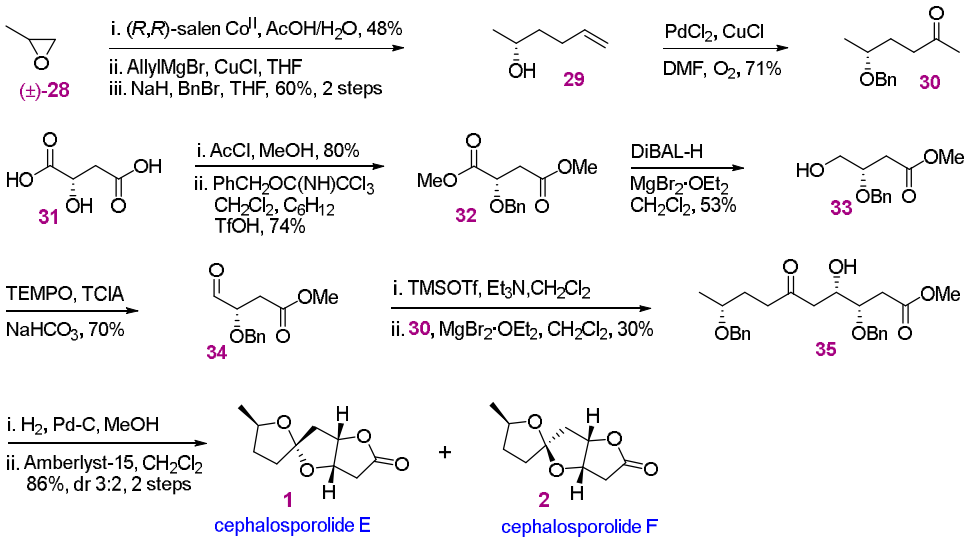

**Scheme 1.** Ramana's synthesis of unnatural cephalosporolides E and F.




**Scheme 2.** Fernandes' first generation synthesis of cephalosporolides E and F.

The double bond reduction of **20** to **21** followed by ester reduction to aldehyde and allyl Grignard addition provided **22**. Cross-metathesis[12] of the latter with **23** gave compound **24** with good *E:Z* selectivity (5:1). This upon IBX oxidation resulted in ketone which on dihydroxylation gave a mixture of inseparable products. Hence, ketalization with ethylene glycol furnished **25**. Next, asymmetric dihydroxylation[13] on **25** afforded the lactone **26** as a single diastereomer. A convergent removal of all protections and trans-ketalization gave poor yields. Hence, a stepwise removal of TBS group to **27**, followed by the ketal moiety gave the mixture of **1** and **2** that were separated by column chromatography in good yeilds. The synthesis involved 12 linear steps and had an overall yield of 12% for **1** and 6.7% for **2**. Here the first synthesis of natural cephalosporolides E and F was achieved (Scheme 2).

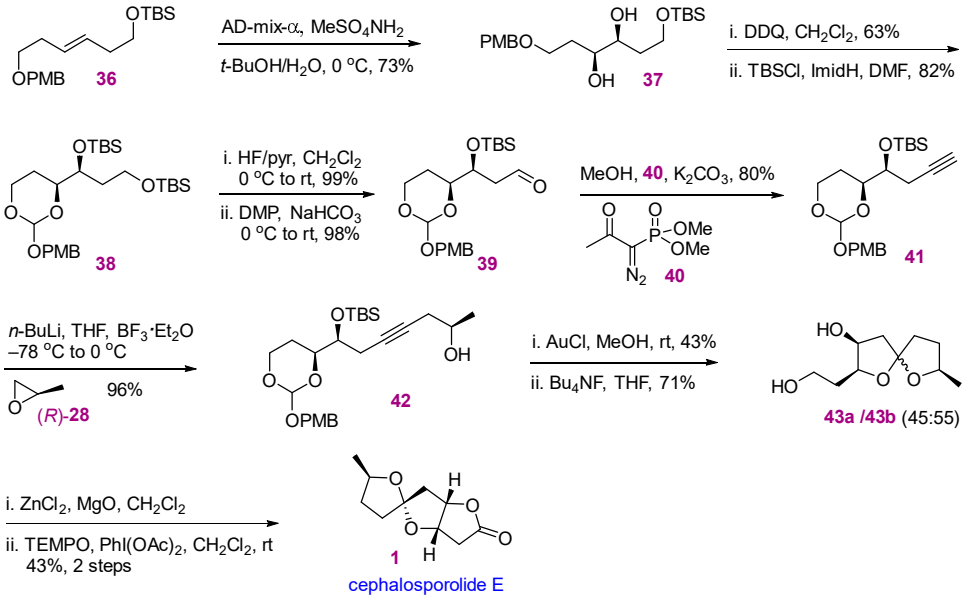
Brimble and coworkers[14] used chelation-controlled Mukaiyama aldol reaction to achieve the synthesis of cephalosporolide E **1** and cephalosporolide F **2** (Scheme 3). Chiral pool material (*S*)-malic acid **31** was converted into methyl ester followed by benzyl protection to give **32**. Controlled ester reduction to mono ester **33** and TEMPO/trichloroisocyanuric acid (TCIA)-oxidation gave aldehyde **34**. The hydrolytic kinetic resolution of propylene oxide (±) **28** using Jacobsen catalyst resulted in enantiopure (*R*)-propylene oxide **28**, which upon allyl Grignard addition and benzyl protection gave benzyl protected olefin **29**. The latter was subjected to Wacker oxidation to furnish methyl ketone **30**. Next, the chelation-controlled Mukaiyama aldol reaction[15] on aldehyde **34** with ketone **30** provided the coupled product **35** as a single *syn*-diastereomer. Removal of benzyl group and subsequent treatment with Amberlyst-15 catalyst delivered cephalosporolide E **1** and cephalosporolide F **2** in 3:2 diastereomeric ratio. The synthesis of both **1** and **2** was completed in 8 steps with 3.4% and 2.3% overall yields, respectively based on dr 3:2.




**Scheme 3.** Brimble's synthesis of cephalosporolides E and F.

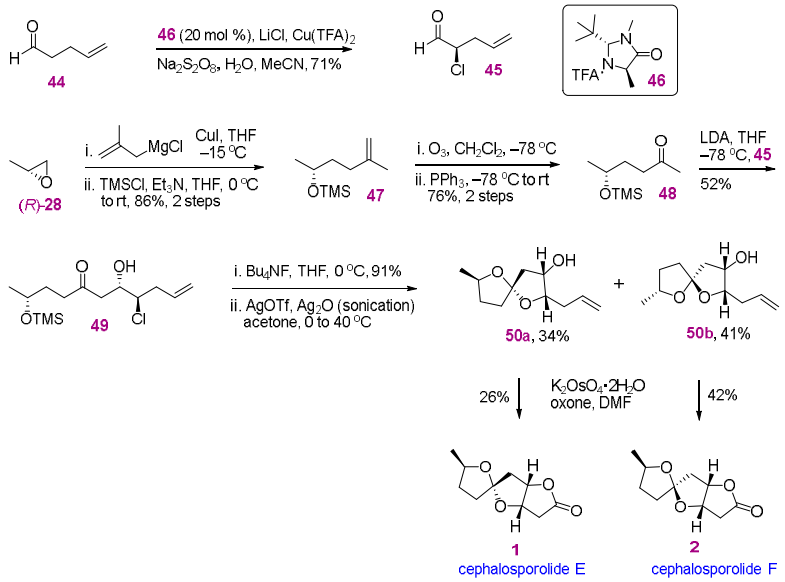
Using gold-catalyzed cyclodimerization reaction, Dudley's group[16] achieved the first diastereoselective synthesis of cephalosporolide E **1**. They started their synthesis with olefin **36** which was obtained from (*E*)-dimethyl hex-3-enedioate (Scheme 4). Compound **36**, on Sharpless asymmetric dihydroxylation furnished diol **37** which upon treatment with DDQ followed by TBS protection gave 1,3-dioxane **38**. Regioselective deprotection to primary alcohol and oxidation furnished aldehyde **39**, which upon treatment with Ohira-Bestmann reagent **40** delivered homopropargylsilyl ether **41**. Reaction of **41** with the (*R*)-propylene oxide **28** in presence of *n*-BuLi delivered the internal alkyne **42**. Next, the gold(I) chloride-catalyzed cycloismerization and deprotection of TBS ether gave diastereomeric mixture of **43a** and **43b** (55:45). Treatment of this mixture with zinc chloride (for isomerization) followed by TEMPO oxidation

delivered desired product cephalosporolide E **1**. Synthesis of cephalosporolide E by this method was completed in 11 steps from **36** and 3.7% overall yield.




**Scheme 4.** Dudley's synthesis of cephalosporolide E.

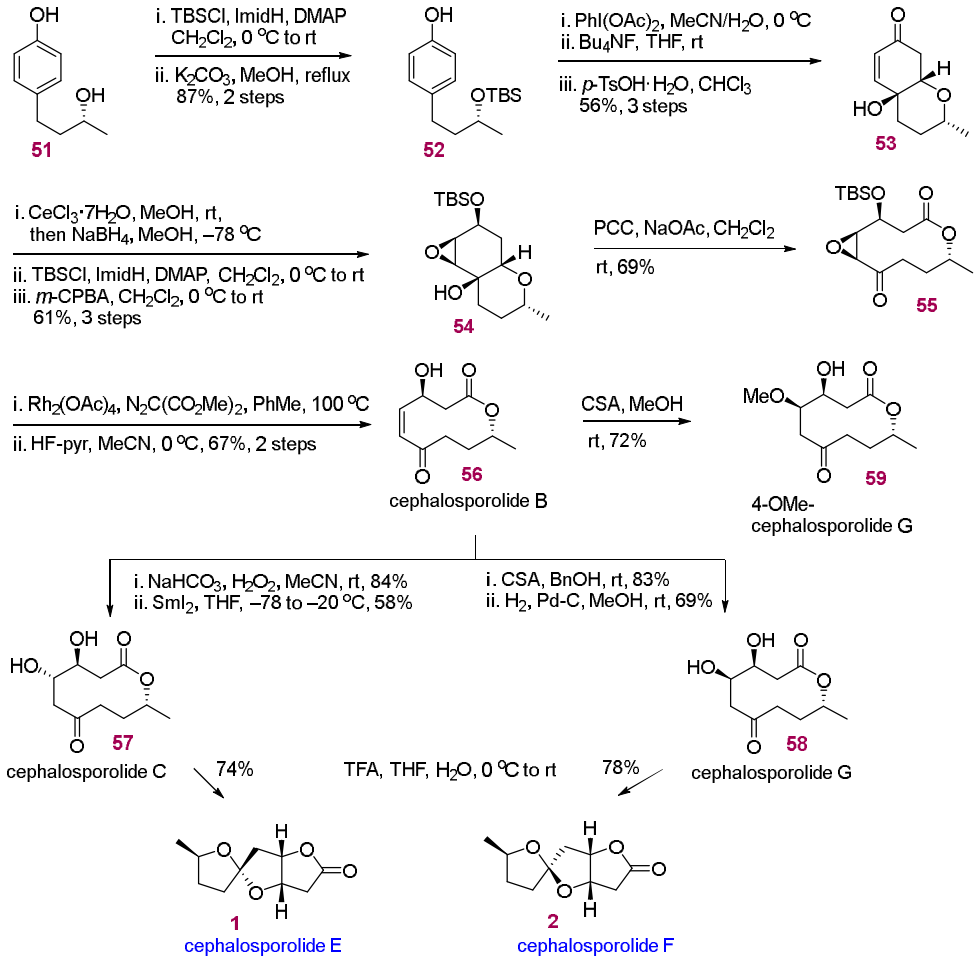
Britton and co-workers[17] synthesized both cephalosporolides E and F by utilizing spirocyclization of ketochlorohydrins using silver(I) reagent. Enantioselective (*R*)-chlorination[18] of 4-pentenal **44** with 20 mol% of catalyst **46** gave chiral α-chloroaldehyde **45** (Scheme 5).




**Scheme 5.** Britton's synthesis of cephalosporolides E and F.

The synthesis of methyl ketone **48** started from epoxide (*R*)-**28** which on copper-mediated 2-methylallylmagnesium chloride addition provided the alcohol. This was TMS ether-protected and then ozonolysis of double bond furnished methyl ketone **48**. The enolate of latter generated using LDA was allowed to react with aldehyde **45** to give the key intermediate ketochlorohydrin **49** in good diastereoselectivity (dr>13:1). Next, deprotection of TMS ether and reaction with Ag(I)-salt delivered spiroacetals **50a** (34%) and **50b** (41%), which upon terminal double bond cleavage using potassium osmate and cyclization-oxidation furnished final products cephalosporolides E **1** (26%) and F **2** (42%). The spiroketalization was achieved by cheaper Ag(I)-salt with the correctly placed keto and chloride groups. The synthesis of cephalosporolides E and F was completed in 8 steps with 2.7% and 5.3% overall yields, respectively (Scheme 5).

Tong and co-workers[19] demonstrated the total synthesis of cephalosporolides E and F *via* oxidative ring expansion of β-hydroxyethers[20] as a key step to deliver the 10-membered lactone and subsequent ring-contraction rearrangement (Scheme 6).

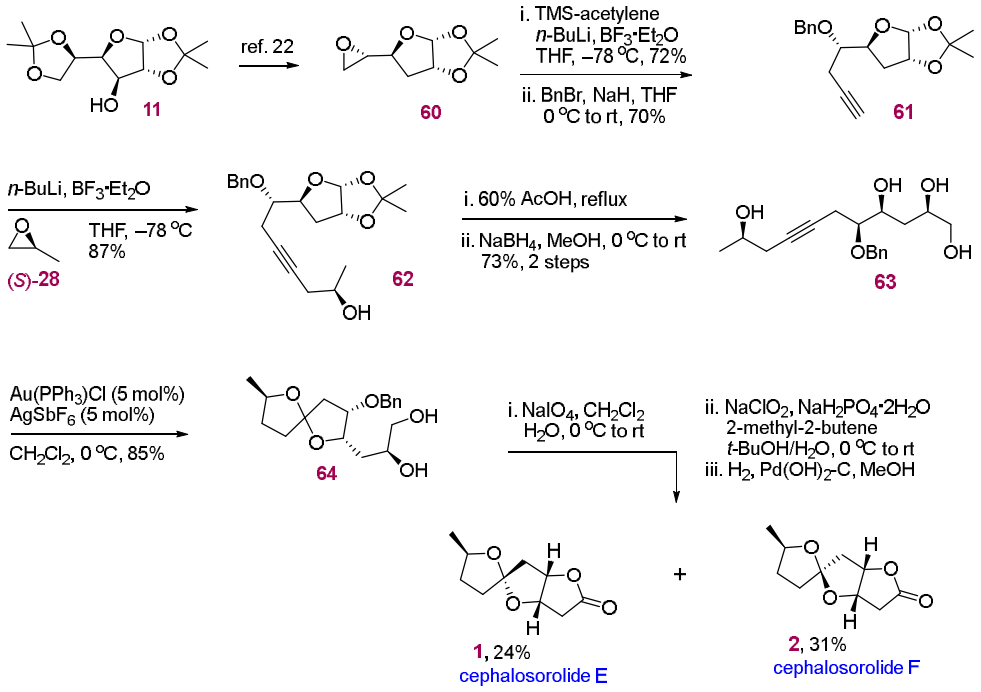



**Scheme 6.** Tong's synthesis of cephalosporolides E and F

The rhododendrol **51** was selectively sillyl ether-protected to give **52**, which on phenol dearomatization, removal of silyl group and intramolecular oxa-Michael cyclization delivered bicyclic ether

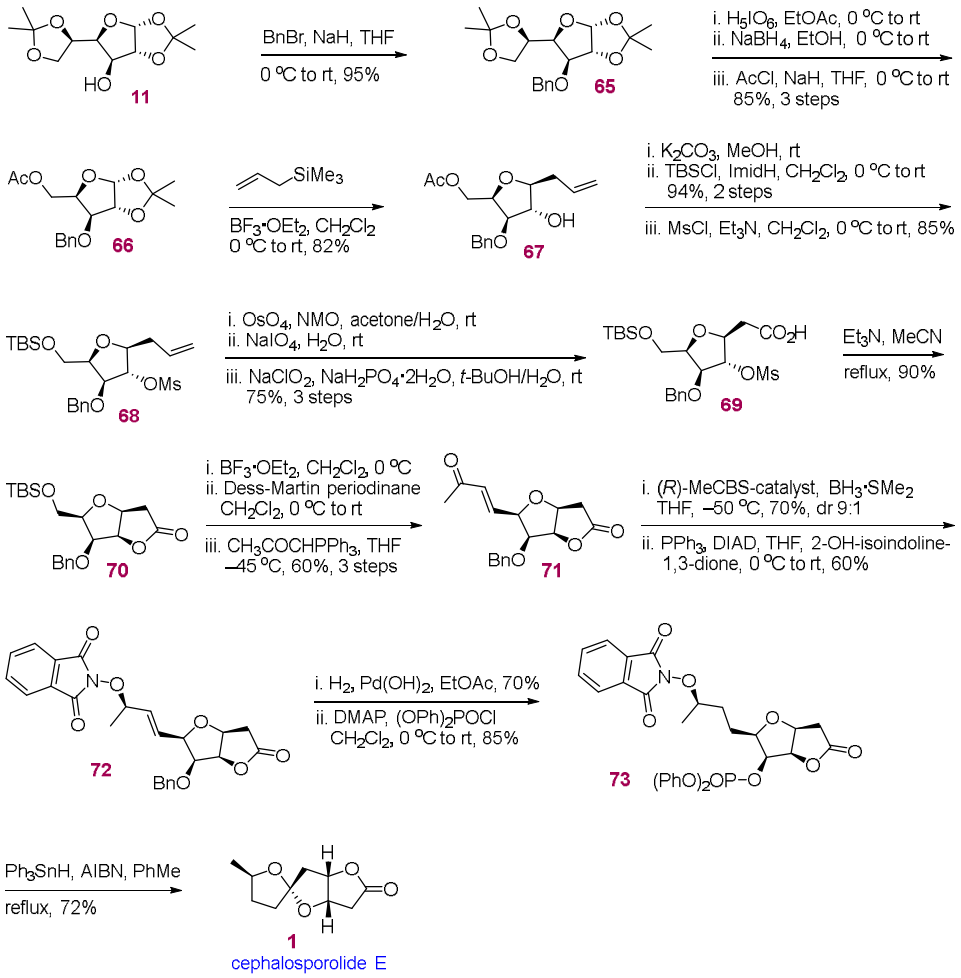
**53**. Next, the Luche reduction, selective TBS protection and subsequent hydroxyl-directed epoxidation furnished epoxide **54**. The oxidative ring expansion in presence of PCC provided 10-membered lactone **55**. The latter on Rh-catalyzed deoxygenation with dimethyl diazomalonate and then removal of TBS with HF-pyridine complex resulted in cephalosporolide B **56**. Compound **56** provided epoxide in presence of hydrogen peroxide and $SmI_2$-mediated reductive epoxide ring-opening delivered cephalosporolide C **57**. Further, compound **56** in presence of CSA and BnOH followed by debenzylation formed cephalosporolide G **58**, however CSA and MeOH yielded 4-OMe-cephalosporolide G **59**. Finally, compounds **57** and **58** were separately subjected to TFA-mediated ring-contraction rearrangement reaction to deliver 5,5-spiroketal-*cis*-fused-γ-lactones cephalosporolides E **1** and F **2**. The strategy was quite unique as it started from aromatics with only one chiral center in **51** that could set the other required chirality in the final products. The synthesis involved 14 linear steps and had an overall yield of 5% for cephalosporolide E **1** and 6% for cephalosporolide F **2** (Scheme 6).

Ramana and co-workers[21] in 2014 reported the total synthesis of natural cephalosporolides E and F by epoxide-alkyne coupling and gold-catalyzed alkynolcycloisomerization strategy to construct the central spiroketal core as key steps. The synthesis began with the opening of known epoxide[22] **60** with TMS-acetylene in presence of *n*-BuLi and $BF_3{\cdot}Et_2O$ (Scheme 7). The resultant hydroxyl compound on benzyl protection furnished **61**. Commercially available (2*S*)-propylene oxide (*S*)-**28** was coupled with alkyne **61** to give alkynol **62**, which on reaction with acetic acid followed by $NaBH_4$ reduction afforded alkyne-tetrol **63**. The latter, upon gold-catalyzed alkynediol spiroketalization, delivered **64**. Since the epimeric mixture was not separable, this was further subjected to diol cleavage, Pinnick oxidation and subsequent debenzylation to afford separable cephalosporolides E **1** and F **2**. This strategy is similar to the previously developed route for the synthesis of unnatural cephalosporolides E and F (Scheme 1).[9] The synthesis required 9 linear steps from **60** and had an overall yield of 6.5% for **1** and 8.4% for **2**.




**Scheme 7.** Ramana's synthesis of cephalosporolides E and F.

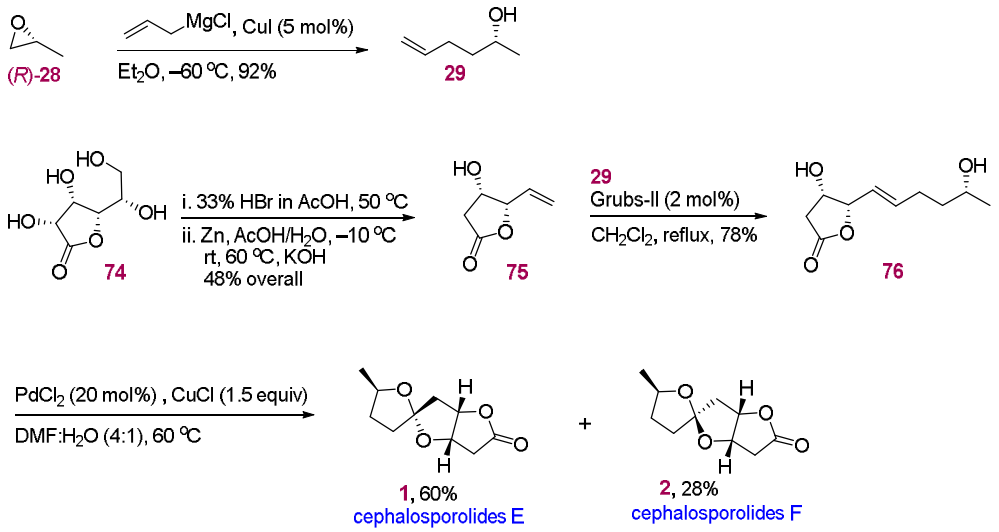
Sartillo-Piscil and co-workers[23] in 2015 for first time utilized the chemistry of radical cations under non-oxidative conditions involving a late-stage tandem radical-polar crossover reaction toward the stereoselective synthesis of cephalosporolide E **1**. Diacetonide **11** upon benzyl protection gave **65**, which was further converted to **66** *via* Robins's dehomologation protocol[24] and acylation (Scheme 8). Allylation of **66** to **67**, then de-acylation, silyl protection and mesylation yielded **68**. Next, the olefinic bond was oxidatively converted to carboxylic acid **69** and subsequent intramolecular $S_N2$ OMs-substitution resulted in bicyclic furan-γ-lactone **70**. Further, the removal of TBS group, oxidation and subsequent Wittig olefination delivered α,β-unsaturated ketone **71**. The stereoselective reduction of ketone using Corey-Bakshi-Shibata (CBS) catalyst afforded allylic alcohol in good diastereoselectivity (dr=9:1) which upon Mitsunobu reaction[25] with *N*-hydroxyphthalimide furnished *N*-phthalimido derivative **72**. Next, the double bond reduction, debenzylation and subsequent phosphorylation with phenyldichlorophosphate and DMAP delivered radical precursor **73**. This by the reaction with triphenyltin radical in refluxing toluene formed radical cation that led in the first instance to cephalosporolide F, which was transformed into cephalosporolide E **1** *via* a stereocontrolled spiroketal isomerization promoted by the diphenylphosphate acid that is formed during the transformation.




**Scheme 8.** Sartillo-Piscil's synthesis of cephalosporolide E.

The total synthesis of cephalosporolide E was completed in total 20 steps and 4% overall yield from **11**. The strategy was based on a new chemistry, however, the synthetic route was quite long due to involvement of several protecting group manipulations (Scheme 8).

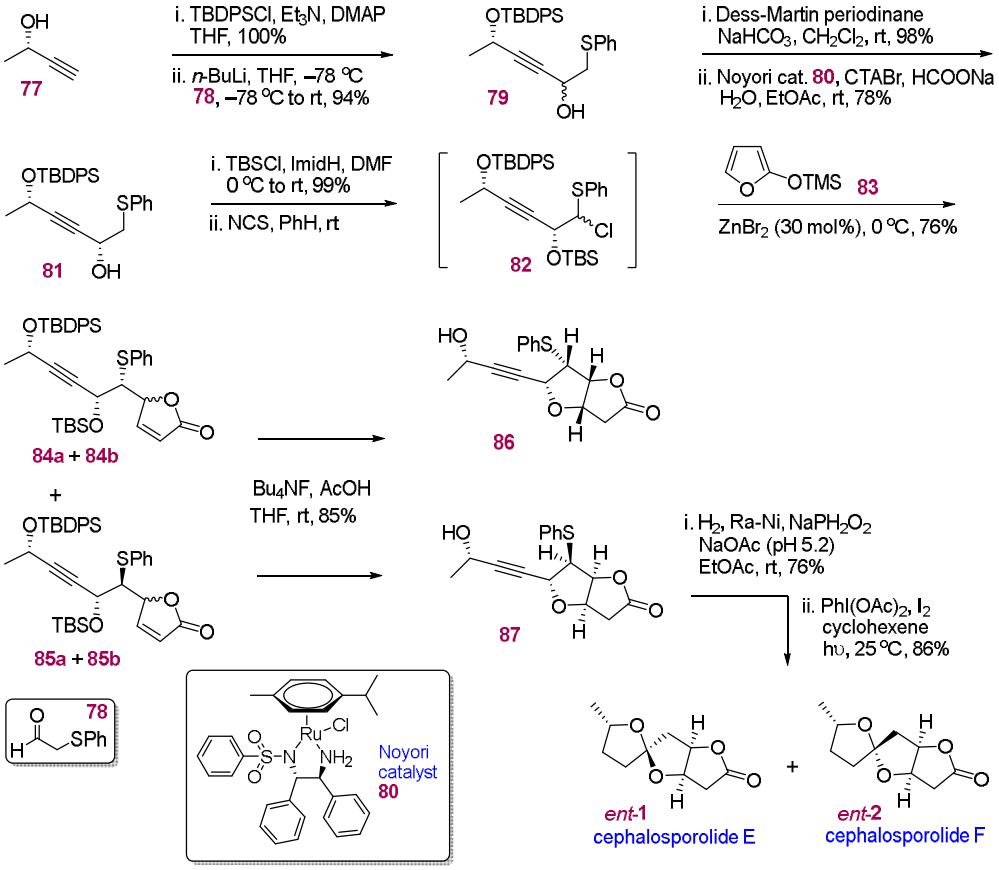
In 2016, Fernandes and co-workers[26] disclosed the protecting-group-free second-generation synthesis of cephalosporolides E and F involving a one-pot conversion of L-mannonic-γ-lactone to β-hydroxy-γ-lactone, cross-metathesis and Wacker-type oxidative spiroketalization as key steps. The one-pot 2 step conversion of L-mannonic-γ-lactone **74** delivered the β-hydroxy-γ-lactone **75** (Scheme 9). The chiral propylene oxide (*R*)-**28** through epoxide opening with allyl magnesium chloride furnished terminal olefin **29**. Cross-metathesis of **29** and **75** using 2 mol% of Grubbs-II catalyst gave **76**, which on Wacker-type oxidative spiroketalization resulted in cephalosporolides E **1** and F **2**. The heteroatom-directed Wacker oxidation occurred at the desired position on the olefin group in **76** functioning as a latent keto functionality without need for any protecting groups. The synthesis of cephalosporolides E **1** and F **2** involved 4 linear steps having an overall yield of 22.5% for **1** and 10.5% for **2**. This represents the shortest synthesis for these molecules.




**Scheme 9.** Fernandes' second generation synthesis of cephalosporolides E and F.

In 2016, Raghavan and co-workers[27] described the total synthesis of cephalosporolides E and F involving the diastereoselective reduction of a propargylic ketone using Noyori catalyst, vinylogous Mukaiyama-type reaction with chloro sulphide, and oxidative cyclization as key steps. The synthesis started with silyl protection of commercially available alcohol **77**, then reaction of the lithium acetylide with phenylthio acetaldehyde **78** to afford inseparable equimolar mixture of diastereomeric alcohols **79** (Scheme 10). Next, the alcohol oxidation to keto and reduction with (*S*,*S*)-Noyori catalyst **80** gave the chiral alcohol **81** (dr 98:2). TBS protection of free hydroxy group and then treatment with *N*-chlorosuccinimide furnished an epimeric mixture of α-chloro sulfides **82**, which was directly used for next step.

Compound **82** reacted with siloxyfuran **83** in presence of $ZnBr_2$ to deliver a mixture of all possible diastereomers **84a**, **84b**, **85a** and **85b** in 1:1:10:2 ratio, respectively. The mixture of **85a** and **85b** was eluted first due to its lower polarity, followed by **84a** and **84b**, in 86:14 ratio and with a 76% total yield. The treatment of the mixture of **84a** and **84b** with TBAF gave single lactone product **86**. Similarly, the mixture of **85a** and **85b** furnished lactone **87** as single product. Finally, reduction of alkyne and sulfanyl in lactone **87** followed by key oxidative radical cyclization[28] in presence of iodobenzene diacetate and iodine provided a 1:1 mixture of cephalosporolides E **1** and F **2**. The synthesis was completed in 10 linear steps and 13% overall yield in each case for cephalosporolides E **1** and F **2** (Scheme 10).



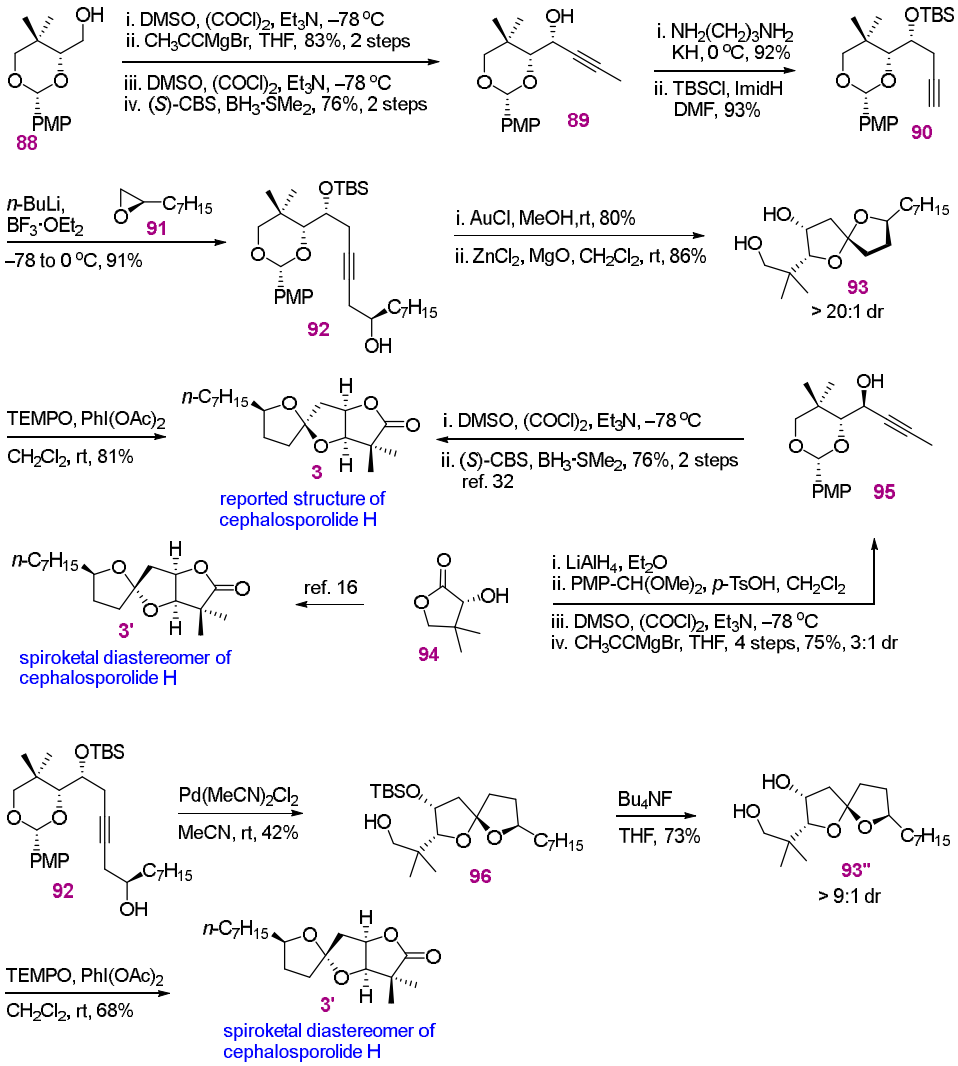

**Scheme 10.** Raghavan's synthesis of antipodal cephalosporolides E and F.

### 3. Total synthesis of cepholosporolides H, I and penisporolides A and B

Cephalosporolides H and I were isolated from the lyophilized culture broth of the marine derived fungus, *Penicillium* sp.[29] (Figure 1). These have been shown to possess potent anti-inflammatory activity as they inhibit the enzyme 3α-hydroxysteroid dehydrogenase (3α-HSD) and xanthin oxidase at concentrations under 290 μM.[29] In 2007, Li and co-workers[30] isolated other spirolactones penisporolides A and B from marine-derived fungus *penicillium* sp. These show moderate inhibition to xanthine oxidase.

The first total synthesis of two spiroketal epimers of cephalosporolide H was reported by Dudley's group.[16,31,32] The synthesis started with Swern oxidation of **88** followed by propynyl Grignard addition to give the alcohol intermediate that was further oxidized and stereoselectively reduced using (*S*)-CBS catalyst to furnish alcohol **89** (Scheme 11). Next, the alkyne zipper reaction[33] and TBS ether protection gave terminal alkyne **90**. The coupling between (*R*)-1,2-epoxynonane **91** and alkyne **90** furnished the key intermediate internal alkyne **92**. This upon gold(I) chloride-catalyzed[32] cycloisomerization furnished 5,5-spiroketal **93** as 1:1 mixture with spiroketal epimer **93′** (not shown). When this diastereomeric mixture was reacted with zinc chloride, it produced under chelation-controlled isomerization the spiroketal **93** (dr>20:1) as a single diastereomer in good yield. Further, the TEMPO-mediated oxidation of diol **93** and lactonization provided the reported structure of cephalosporolide H **3**. The spectral data and optical rotation of this synthesized isomer was not identical with that of reported natural product and these results suggested the desired structural revision. When alkyne **92** was subjected to bis-acetonitrile palladium(II) chloride-mediated cycloisomerization, it gave the 5,5-spiroketal **96** as 9:1 mixture with opposite spiroketal stereochemistry.

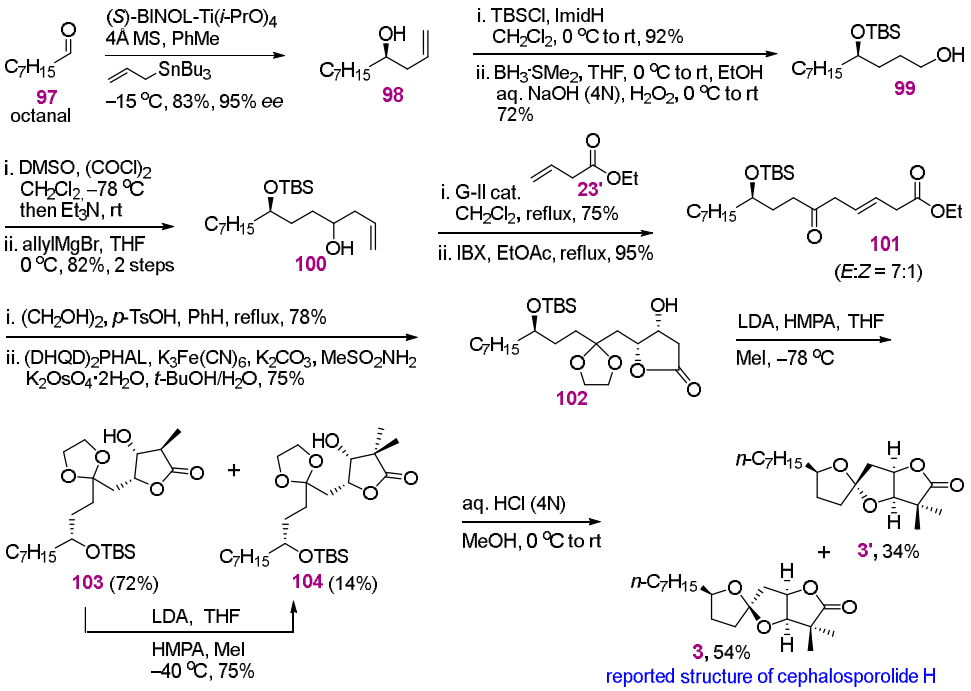
Removal of TBS group to **93″** followed by TEMPO-catalyzed oxidation furnished **3′** with spectroscopic data well in agreement with that reported for cephalosporolide H. This represented the first diastereoselective synthesis of either spiroketal stereoisomer from the common intermediate **92**. The synthesis was completed in 10 steps for both isomers **3** and **3′** from **88** in 27.4% and 10.2% overall yields, respectively. The synthesis of both isomers was also achieved by the same group[16,32] starting from **94** using similar protocol.




**Scheme 11.** Dudley's synthesis of reported cephalosporolides H and its epimer.

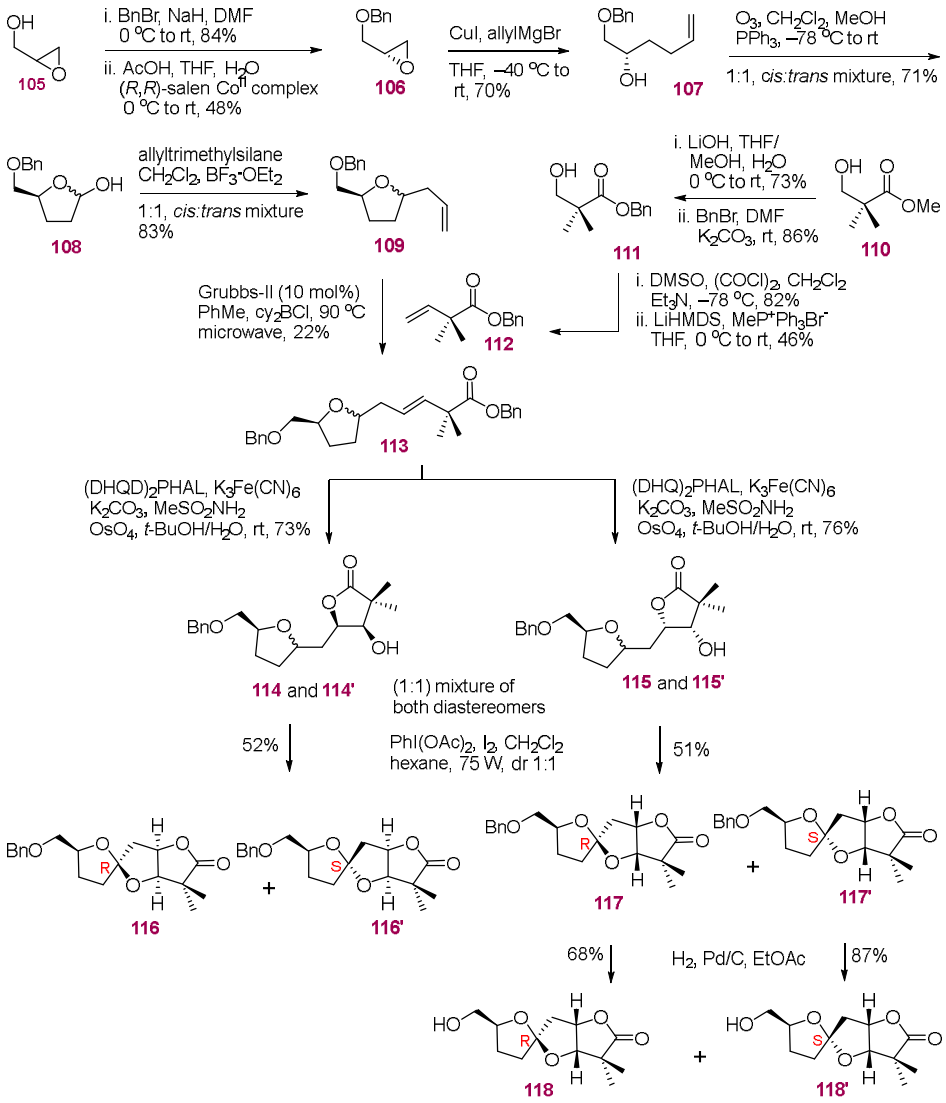
Fernandes and Halle[34] achieved the synthesis of two spiroketal epimers of **3** based on spiroketalization approach. Octanal **97** under Keck allylation[35] gave homoallyl alcohol **98** in 95% ee (Scheme 12). This on TBS protection and hydroboration oxidation furnished primary alcohol **99**. The latter on Swern oxidation followed by treatment with allyl Grignard led to formation of homoallyl alcohol **100**, which on cross-metathesis with **23′** using G-II catalyst gave the β,γ-unsaturated ester as 7:1 (*E*/*Z*) mixture that was

further oxidized to ketone **101**. Protection of ketone **101** as acetal followed by asymmetric dihydroxylation gave the γ-lactone **102** as a single diastereomer. Methylation of lactone **102** using excees LDA and MeI led to formation of methylated compound **103** as major product along with *gem*-dimethylated compound **104** as minor product. Repeating the methylation reaction on isolated **103** then afforded the *gem*-dimethylated product **104**. Next, the removal of TBS group along with ketal resulted in trans-ketalization affording the chromatographically separable spiroketal diastereomers of cephalosporolide H **3** and **3'** in 1:1.6 ratio. The spectral and optical data of synthesized compound **3** showed a mismatch with that of natural isomer concluding the need of structure revision as suggested earlier by Dudley (Scheme 11).[31] The synthesis of **3** and **3'** was completed in 11 steps with 5.5% and 3.5% overall yields, respectively.




**Scheme 12.** Fernandes' synthesis of cephalosporolide H epimers.

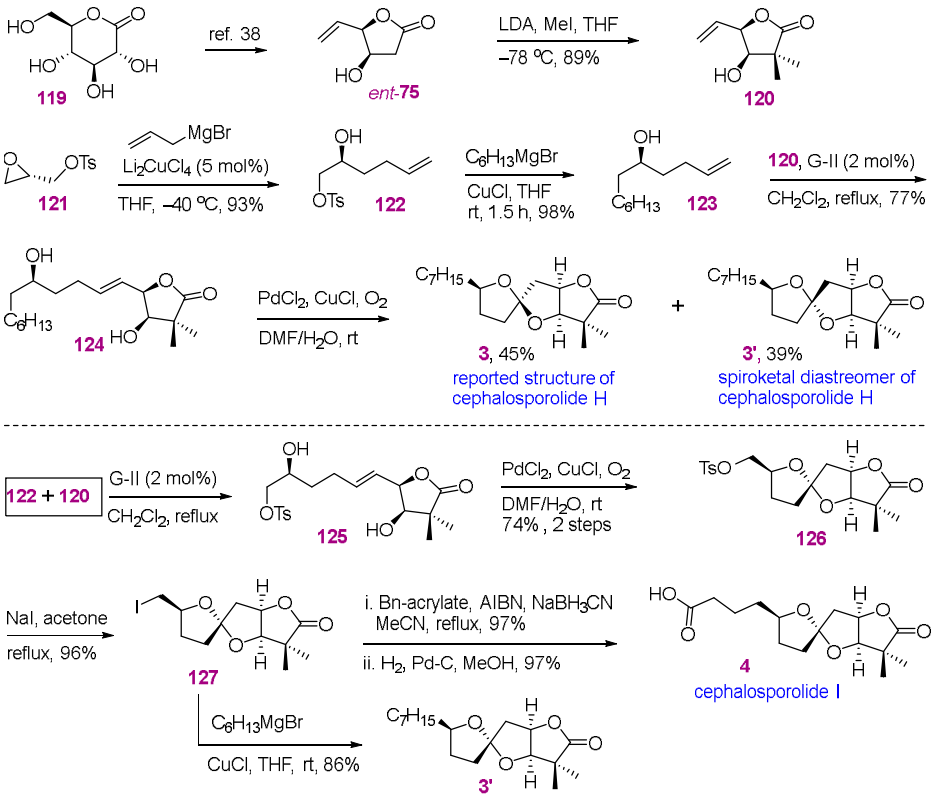
In 2014, Brimble and coworkers[36] disclosed the synthesis of four possible stereoisomers of spiroketal core structures of cephalopsorolides H and I and penisporolides A and B involving Sharpless asymmetric dihydroxylation and radical cyclization to form spiroketal ring system as key steps (Scheme 13). Commercially available glycidol **105** after benzyl protection was subjected to chiral resolution using (*R,R*)-salen Co(II) complex to furnish enantiopure (*R*)-epoxide **106**. Epoxide ring opening with allyl cuprate delivered secondary alcohol **107**. Next, the olefinic bond cleavage gave lactol **108** obtained as 1:1 diastereomer mixture. This was treated with allyltrimethylsilane-$BF_3{\cdot}OEt_2$ to afford olefin **109** as 1:1 diastereomer mixture. Transesterification of **110** yielded **111** which on oxidation followed by Wittig olefination resulted in **112**. Further, the cross-metathesis of **109** and **112** using G-II catalyst afforded **113** in only 22% yield. This on Sharpless asymmetric dihydroxylation using AD-mix-α and AD-mix-β gave lactones **114-114'** and **115-115'** as separable 1:1 mixture of diastereomers in each case. The oxidative radical cyclization was performed independently on **114-114'** to give separable 1:1 mixture of **116** and **116′**. Similarly, **117** and **117′** were obtained from **115** and **115′**. The hydrogenation of **117** and **117′** delivered primary alcohols **118** and **118′** separately. All these can be further elaborated to cephalosporolides H, I and penisporolides A and B.




**Scheme 13.** Brimble's synthesis of cephalosporolide and penisporolide spiroketal core structures.

An efficient total synthesis of spiroketal diastereomers of cephalosporolides H **3** and I **4** was reported by Du and co-workers.[37] This synthesis involved a similar strategy as that used by the Fernandes group (Scheme 9). The synthesis started with conversion of **119** to *ent*-**75** in a one-pot, two-step procedure (Scheme 14).[38] The α-*gem*-dimethylation with LDA and MeI resulted in **120**. The fragment **123** was synthesised from chiral epoxide **121** which upon allyl Grignard addition to **122** and subsequent tosyl substitution with hexyl Grignard furnished the olefin compound **123**. Lactone **120** and olefin **123** upon cross-metathesis using G-II catalyst provided **124**. The domino Wacker-type oxidative spiroketalization of compound **124** delivered cephalosporolide H diastereomers **3** and **3′**. Lactone **120** and olefin **122** upon similar cross-metathesis to **125** followed by Wacker-type spiroketalization furnished spiroketal **126** as a

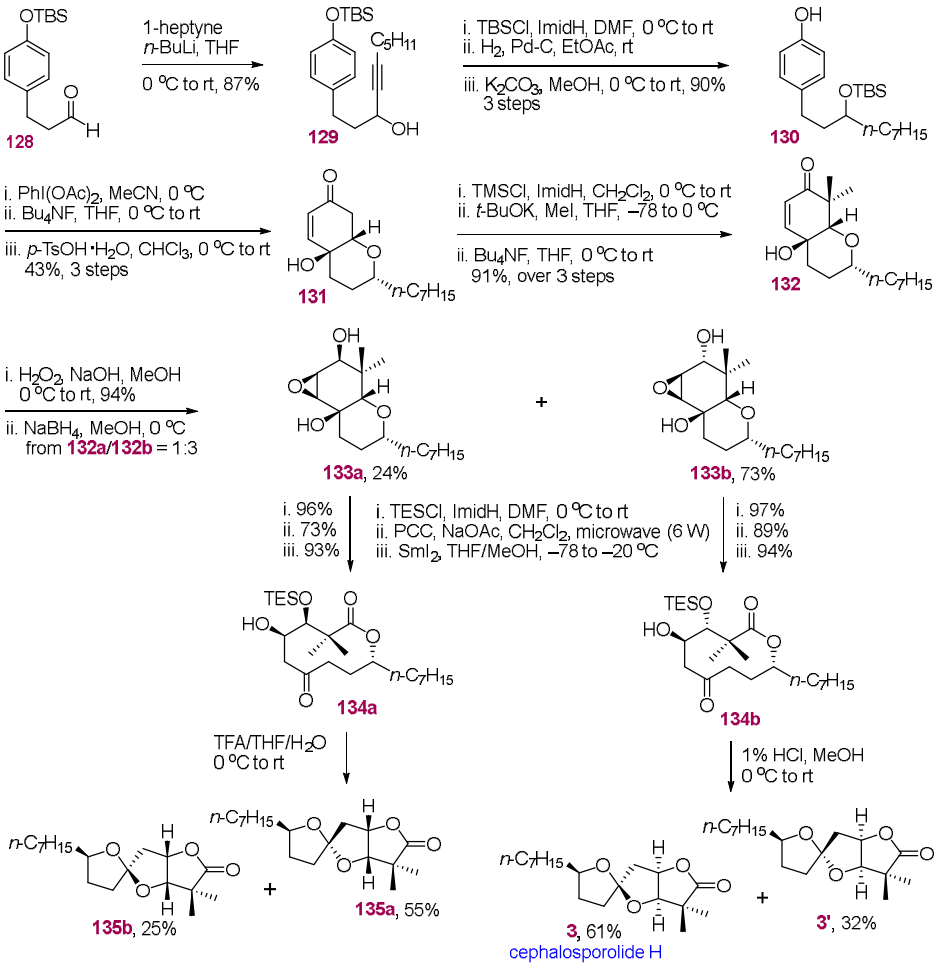
single diastereomer. Compound **126** using Finkelstein-type reaction was converted into iodo compound **127**, which on radical reaction with benzoyl acrylate followed by hydrogenation produced final compound cephalosporolide I **4**. Displacement of iodide in **127** with hexyl-Grignard reagent produced cephalosporolide H isomer **3′**. The synthesis of cephalosporolides H isomers **3** and **3′** was completed in 4 steps from **121** with 31.6% and 27.4% overall yields, respectively. Similarly, the synthesis of cephalosporolide I **4** was achieved in 6 steps with 62% overall yield. The isomer **3′** was completed in 5 steps with 57% overall yield *via* **127**.




**Scheme 14.** Du's synthesis of cephalosporolides H and I isomers.

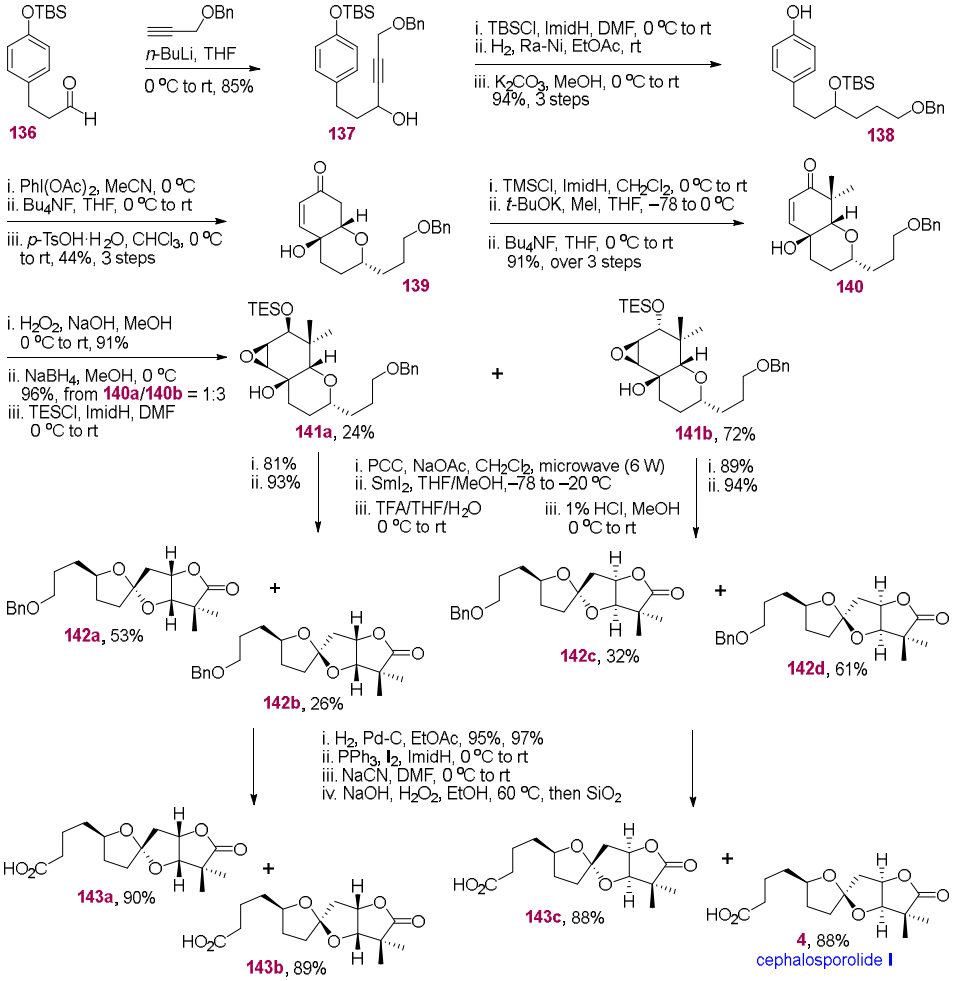
Tong and co-workers[39] in 2016 described the total synthesis of cephalosporolides H, I and penisporolide B and their possible diastereomers *via* PCC-promoted oxidative ring expansion of β-hydroxy cyclic ethers and dehydrative ring-contraction rearrangement of 10-membered lactones. The synthesis of cephalosporolide H and its diastereomers began with nucleophilic addition of lithiated 1-heptyne to aldehyde **128** to afford propargylic alcohol **129** (Scheme 15). Silyl protection, then hydrogenation and selective desilylation delivered phenol **130**. Next, the oxidative dearomatization, followed by TBS removal and subsequent oxa-Michael cyclization furnished bicyclic ether **131**, which after selective methylation at α-position of unsaturated ketone gave **132**. Epoxidation of olefinic bond and reduction of ketone resulted in separable diastereomeric mixture of epoxy alcohols **133a** and **133b** (1:3 dr). The free hydroxy in **133a** and **133b** was protected as TES ether separately and subjected to PCC-mediated oxidative ring expansion[40] followed by $SmI_2$-promoted reductive epoxide opening[41] to furnish decanolides **134a** and **134b**, respectively. Finally, the ring-contraction rearrangement was carried out with TFA-THF-$H_2O$ for **134a** and 1% HCl, MeOH for **134b** to afford separable mixture of **135a** and **135b** from **134a** and **3** and **3′** from **134b**,

respectively. The total synthesis of cephalosporolide H **3** was completed in 16 steps and had an overall yield of 11%.




**Scheme 15.** Tong's synthesis of cephalosporolide H and its diastereomers.

Similarly, the synthesis of cephalosporolide I and its diastereomers (Scheme 16) started with addition of protected alkyne to aldehyde **136** to afford alkynol **137**. Next, the TBS protection, alkyne reduction and selective TBS removal gave phenol **138**. Further, the sequential oxidative dearomatization, desilylation and oxa-Michael cyclization furnished the bicyclic ether **139**. The latter on methylation at α-position of unsaturated ketone gave **140**. Epoxidation of compound **140**, then $NaBH_4$ reduction and TES protection resulted in a separable diastereomeric mixture of **141a** and **141b** (1:3 dr). These were separately subjected to PCC-mediated oxidative ring expansion followed by $SmI_2$-promoted reductive epoxide opening and sequential ring-contraction rearrangement with TFA-THF-$H_2O$ and 1% HCl/MeOH to furnish separable diastereomeric mixture of **142a-142b** from **141a** and **142c-142d** from **141b**, respectively. Individually, benzyl deprotection of **142a**, **142b**, **142c** and **142d** formed primary alcohol that was converted to acid *via* sequential Apple reaction, $S_N2$ nitrile substitution and hydrolysis giving all diastereomers of cephalosporolide I, *i.e.* **143a**, **143b** and **143c, 4**. The synthesis of cephalosporolide I **4** involved 20 steps and had 8.8% overall yield.



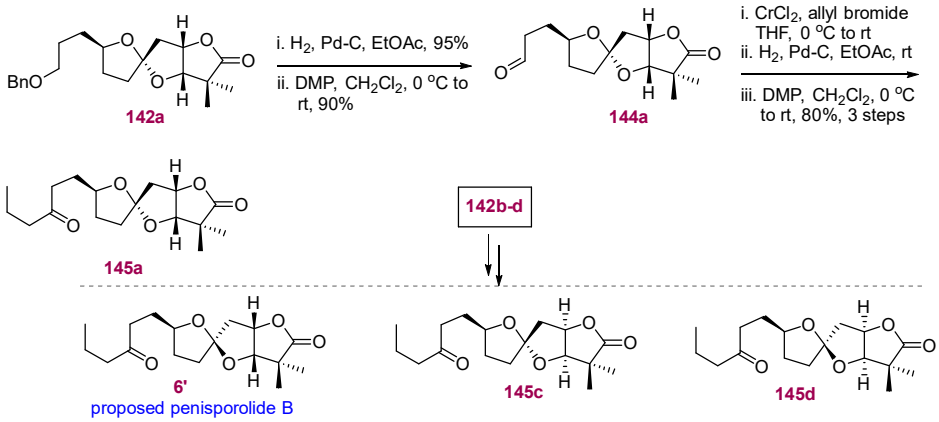

**Scheme 16.** Tong's synthesis of cephalosporolide I and its diastereomers.

For the synthesis of penisporolide B and its stereoisomers, **142a** was debenzylated and oxidized by DMP to deliver **144a** and then the sequential Nozaki-Hiyama-Kishi (NHK) allylation,[42] hydrogenation followed by DMP oxidation afforded **145a** as one of the diastereomer of penisporolide B (Scheme 17). Similarly, other stereoisomers of penisporolide **6′**, **145c**,**d** were achieved from **142b-d** *via* similar transformations and yields. Since the spectral data of penisporolide B diastereomers (**145a, 6′**, **145c,d**) did not match those of the natural isolate, it was concluded that natural penisporolide B structure needed revision. The synthesis of proposed penisporolide B **6′** required total 21 steps and had 1.8% overall yield.

**4. Total synthesis of ascospiroketals A and B**

Ascospiroketals A **7** and B **8** were isolated from marine-derived fungus *Ascochyta salicorniae* by König's group.[43] The relative configuration of the tricyclic part of ascospiroketals A and B was determined using NOE, COSY, HMBC and HSQC NMR spectral studies, but no stereochemical information about the side chain was obtained after unsuccessful attempts using degradation and *J*-based approaches.[43] Britton and co-workers[44] in 2015 synthesized the possible four isomers and assigned the relative and absolute

stereochemistry of ascospiroketal A by comparison of NMR data and optical rotation to that of natural isolate. The bioactivities of these molecule are yet to be studied.

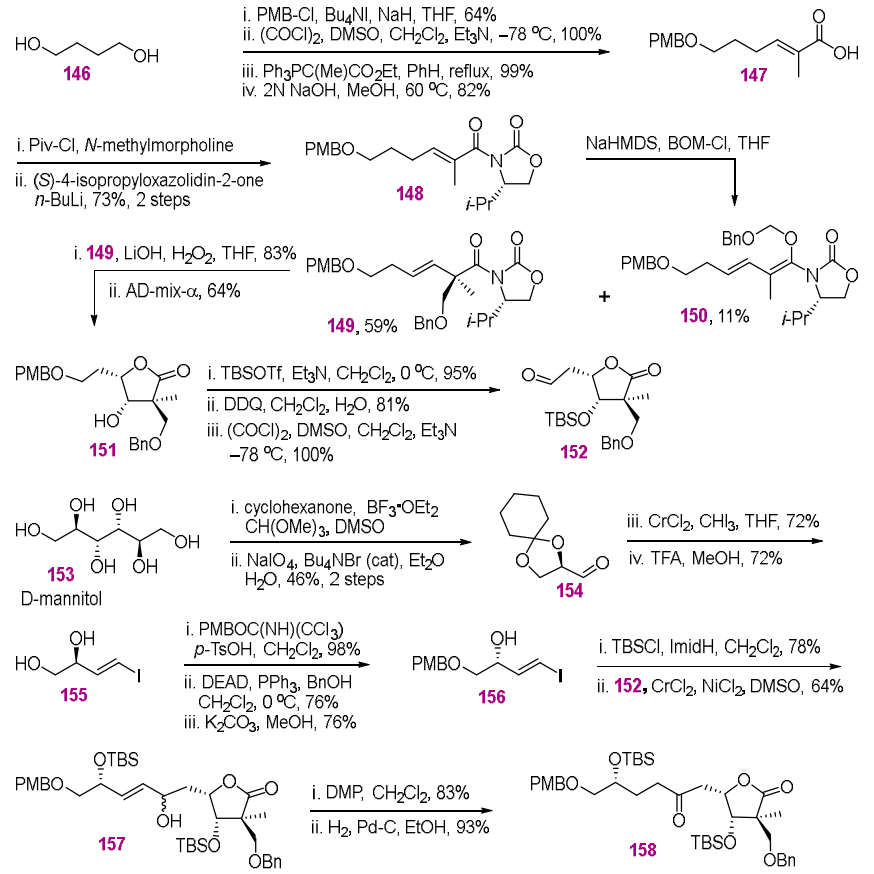



**Scheme 17.** Tong's synthesis of proposed penisporolide B and its diastereomers.

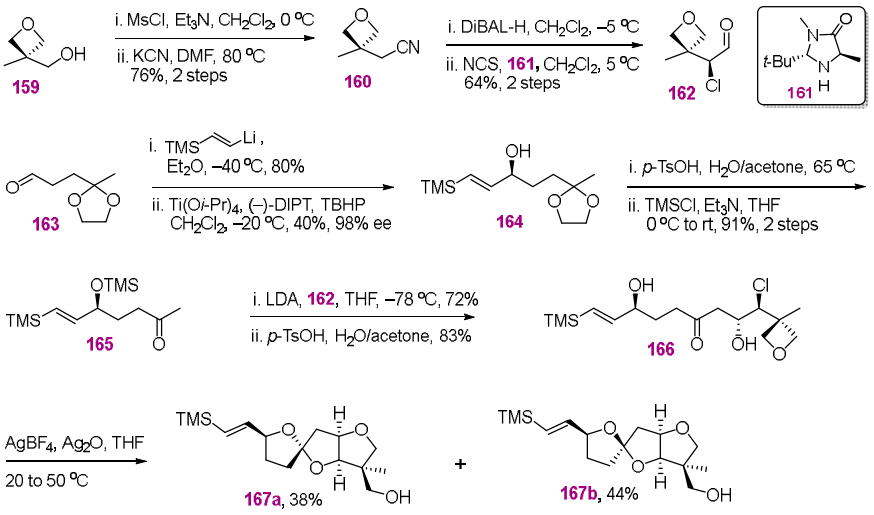
Lee and co-workers[45] in 2011 synthesized an important fragment of ascospiroketal B. The synthesis started with commercially available butanediol **146** which on PMB mono protection followed by two carbon homologation *via* Wittig olefination and subsequent ester hydrolysis resulted in acid **147** (Scheme 18). Next, the chiral auxiliary (*S*)-4-isopropyloxazolidin-2-one was attached to give **148** that on stereoselective α-alkylation with BOM-Cl *via* the extended enolate gave products **149** and **150**. Removal of chiral auxiliary in **149** and Sharpless asymmetric dihydroxylation resulted in the hydroxy lactone **151**. Then, the free hydroxy group was silyl protected followed by PMB deprotection and subsequent Swern oxidation led to the intermediate aldehyde **152**. Another coupling intermediate **156** was synthesised from D-mannitol **153** by protection using cyclohexanone and oxidative cleavage to aldehyde **154**. Next, using the Takai[46] protocol the aldehyde **154** was converted to (*E*)-vinyl iodide followed by deprotection to give diol **155**. Protection of primary hydroxy group as PMB group and secondary hydroxy inversion using Mitsunobu conditions resulted in iodide **156**. TBS protection of **156** followed by reaction with intermediate **152** using Nozaki-Hiyama-Kishi reaction[42] led to the lactone **157**. This was further oxidized with DMP and catalytic hydrogenation furnished the fragment ketone **158**. This fragment could be used for construction of the tricyclic core of ascospiroketal B. The synthesis of advanced fragment **13** was completed in 15 steps (from diol **146**) with 4.5% overall yield.

In 2015, Britton and co-workers[44] achieved the first total synthesis of ascospiroketal A **7** along with assignment of its relative and absolute configuration. The alcohol **159** underwent mesylation followed by mesyl displacment with KCN to give **160**, which further on DiBAL-H reduction resulted into aldehyde and α-chlorination of this aldehyde in presence of MacMillan's catalyst[18] **161** and NCS[47] as chlorine source provided chloro aldehyde **162** with 85% ee (Scheme 19). Next, the ketal aldehyde **163** reacted with 2-TMS-vinyl lithium to give allyl alcohol, which upon Sharpless asymmetric epoxidation conditions led to unreacted recovered chiral allylic alcohol **164** (98% ee). Then, the ketal deprotection and allylic hydroxy protection as TMS ether provided methyl ketone **165**. The latter on aldol reaction with aldehyde **162** followed by selective TMS deprotection resulted in important intermediate **166** (dr=12:1),[48] which was subjected to Ag(I)-promoted cascade cyclization[17] to furnish the separable tricyclic products **167a** and **167b**. Since, these were in equilibrium with each other the undesired epimer **167a** was equilibrated with $ZnCl_2$ to 2:1 mixture of **167a** and **167b**. The latter is used in the total synthesis discussed below.

The Mitsunobu inversion followed by TBS protection and ester hydrolysis of **168** provided acid **169** (Scheme 20). Similarly, acid **169'** was synthesized from **170**. Epoxide (*S*)-**28** or (*R*)-**28** upon ring opening with TMS-acetylene followed by coupling with either acid **169** or **169'** and subsequent removal of TMS group provided alkynes **170a**-**170d**.

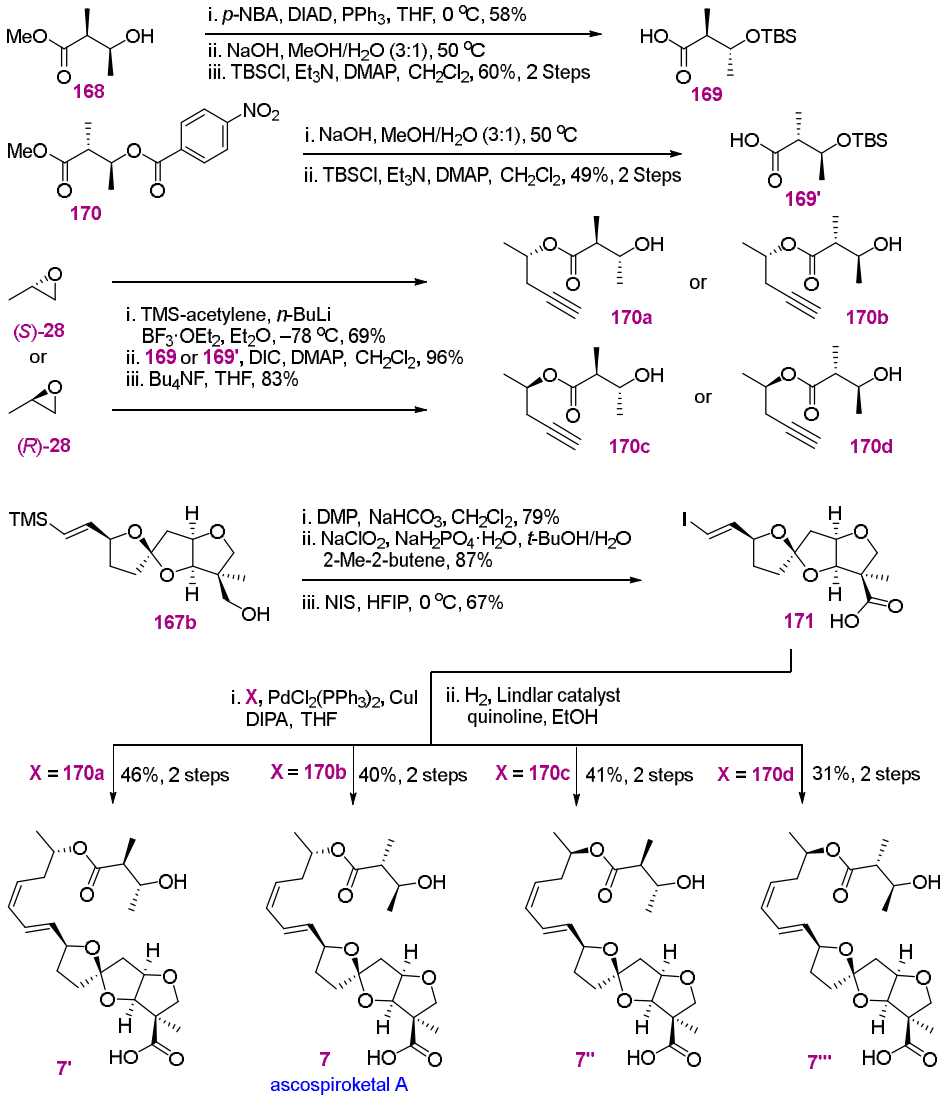



**Scheme 18.** Lee's synthetic studies toward ascospiroketal B.




**Scheme 19.** Britton's synthesis of ascospiroketal A fragment **167b**.

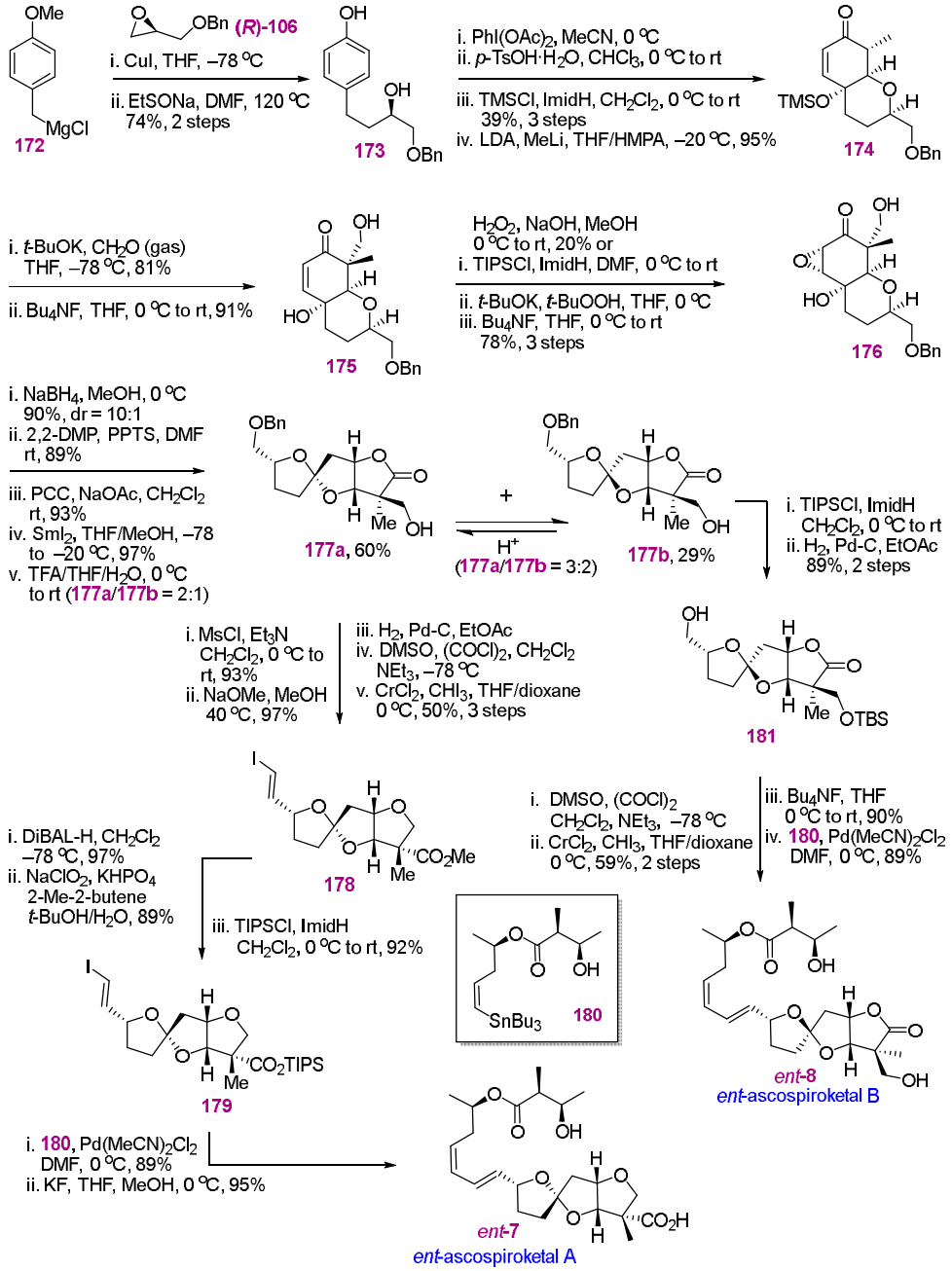
Out of the two epimers, **167b** upon oxidation and silicon to iodide exchange led to formation of acid **171** (Scheme 20). The Sonogashira coupling of acid **171** with fragments **170a-170d** and subsequent Lindlar reduction provided four diastereomers of ascospiroketal A. Comparision of NMR spectral data and value of optical rotation of all four diastereomers with that of the natural isolate suggested that data of compound **7** was a closer match with natural one. Synthesis of **7′**, **7** (ascospiroketal A), **7″** and **7‴** was completed in 12 steps from **153** with 1.6, 1.4, 1.4 and 1.1% overall yields, respectively (Scheme 20).




**Scheme 20.** Britton's synthesis of probable ascospiroketal A and its diastereomers.

Tong and Wang[49] in 2016 achieved the total synthesis of *ent*-ascospiroketal A and *ent*-ascospiroketal B, using ring contraction rearrangement of the 10-membered lactone to the tricyclic spiroketal *cis*-fused γ-lactone strategy (Scheme 21). Opening of epoxide (*R*)-**106** with Grignard reagent **172** and demethylation resulted in enantiopure phenol **173**. Next, the phenolic oxidative dearomatization and oxa-Michael addition

followed by silyl protection and α-methylation afforded **174**. The latter on aldol condensation with gaseous formaldehyde and TMS deprotection gave **175**.



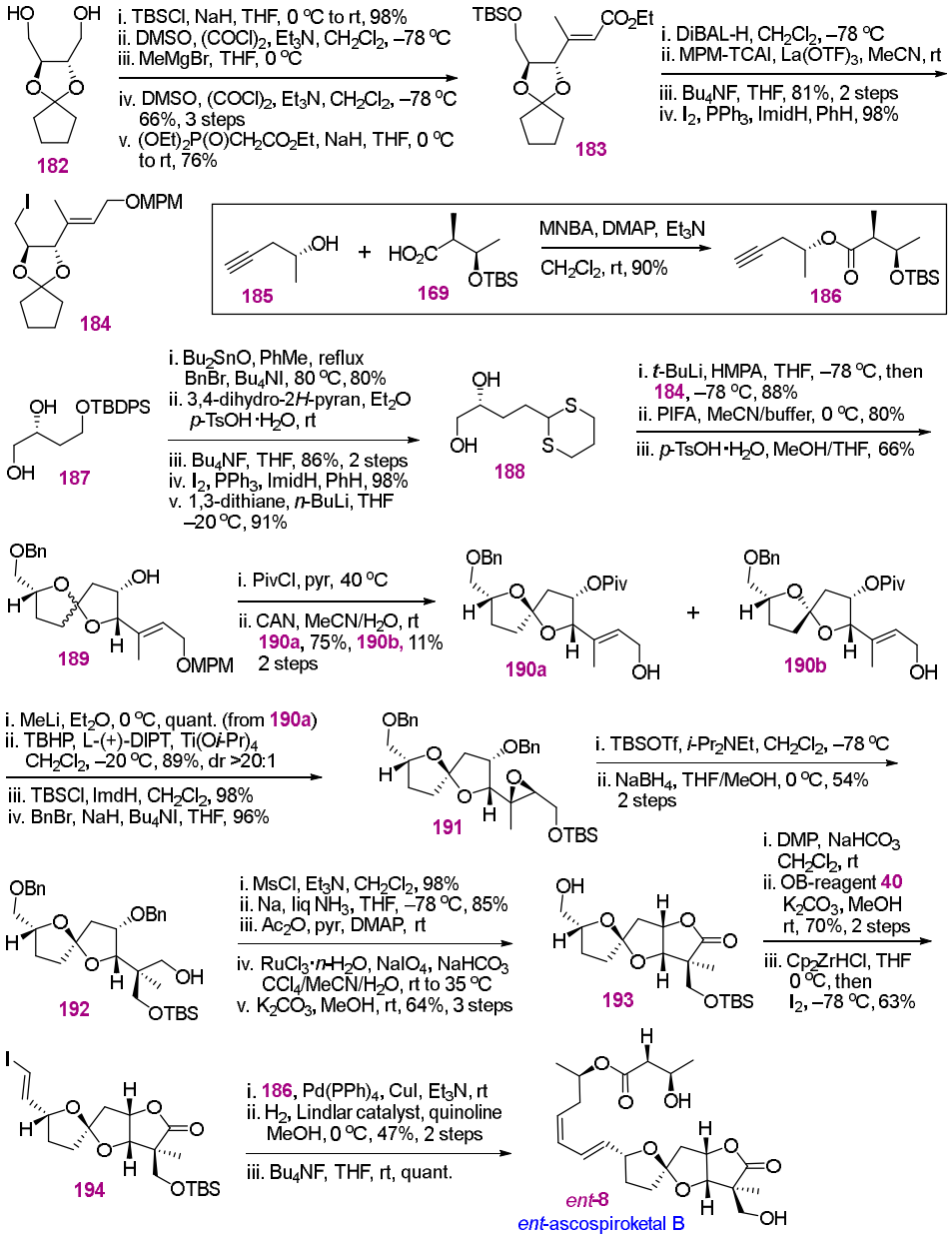

**Scheme 21.** Tong's synthesis of *ent*-ascospiroketal A and *ent*-ascospiroketal B.

This was epoxidized with $H_2O_2$ (low yield 20%) or by a sequential 3 step process involving TIPS protection, epoxidation with *t*-BuOOH and then desilylation to afford **176** (78%, 3 steps). Next, the HO-directed $NaBH_4$ reduction of ketone **176**, and diol protection followed by PCC-mediated oxidative ring expansion provided the 10-membered lactone, which on epoxide ring opening with $SmI_2$ and ring-contraction rearrangement of 10-membered lactone resulted in separable diastereomers **177a** and **177b** (2:1 dr). It was found that spiroisomers **177a** and **177b** were in equilibrium at room temperature in 5% HCl in MeOH (3:2 dr). Further the free hydroxy of **177a** was mesylated and then treatment with NaOMe generated the tricyclic 5,5-spiroacetal *cis*-fused furan, which on debenzylation, oxidation and Takai olefination[46] resulted in vinyl iodide **178**. The latter on DiBAL ester reduction, Pinnick oxidation and then TIPS protection of acid delivered **179**. Finally, Stille coupling of **179** with vinylstannane **180** followed by desilylation furnished *ent*-ascospiroketal A (*ent*-7). To synthesize *ent*-ascospiroketal B, the intermediate **177b** on TBS protection and hydrogenation gave **181**. The latter on sequential Swern oxidation, Takai olefination provided the vinyl iodide, which on desilylation and coupling with vinylstannane **180** resulted in *ent*-ascospiroketal B *ent*-**8**. Further, changing the vinyl stannane **180** to other diastereomers, seven additional diastereomers of *ent*-ascospiroketal B (*ent*-**8**) were obtained to ensure the synthesis of actual enantiomer of ascospiroketal B. The synthesis of *ent*-ascospiroketal A was completed in total 26 steps having 2.1% overall yield, while the first stereoselective synthesis of *ent*-ascospiroketal B involved 22 linear steps and 1.4% overall yield (Scheme 21).

Miyoka and co-workers[50] in 2018 described the total synthesis of *ent*-ascospiroketal B including stereoselective construction of 5,5-spiroketal for ascospiroketal B with stereocontrolled construction of a quaternary asymmetric carbon by rearrangement of a trisubstituted epoxide as a key transformation (Scheme 22). Diol **182** was prepared by known procedure[51] from L-(+)-tartaric acid and then selectively monoprotected as TBS ether. The two carbon homologation *via* Grignard addition and Wittig olefination resulted in α,β-unsaturated ester **183**. DiBAL-H reduction of ester **183** to alcohol, protection as *p*-methoxyphenylmethyl (MPM) ether, then TBS deprotection and subsequent iodination gave **184**. Condensation of known alcohol **185**[52] and carboxylic acid **169**[44] according to Shiina's method[53] delivered desired ester **186**. The diol **187** was prepared by known procedure[54] using D-(+)-malic acid. Next, the selective protection of primary hydroxy as Bn-ether and secondary as THP, then selective deprotection of silyl ether and conversion to iodide followed by treatment of lithiated 1,3-dithiane delivered thioacetal **188**. The latter was alkylated with iodide **184** and the thioketal removal and ketal formation gave the 5,5-spiroketal **189** as diastereomeric mixture (dr 3:1 at C6). The free secondary hydroxy was protected as pivaloate and then CAN-mediated MPM removal delivered spiroketals **190a** and **190b** which were easily separated. The pivaloyl group in spiroketal **190a** was removed and then Sharpless asymmetric epoxidation of allylic alcohol using (+)-DIPT gave epoxide. Further, orthogonal protection as TBS and benzyl ethers led to trisubstituted α-epoxide **191**. Lewis acid-mediated rearrangement of epoxide by migration of siloxymethyl group to the carbocation resulted in aldehyde, which on $NaBH_4$ reduction delivered alcohol **192**. The latter on mesylation and debenzylation resulted in tetrahydrofuran ring formation. Further, the hydroxy group was converted to acetate and $RuCl_3/NaIO_4$-mediated oxidation of tetrahydrofuran to γ-lactone and acetate hydrolysis gave hydroxy γ-lactone **193**. Next, DMP oxidation followed by treatment with Ohira-Bestmann reagent furnished alkyne, which was treated with Schwartz's reagent[55] and iodine to give (*E*)-iodoalkene **194**. The Sonogashira coupling of alkyne **186** with vinyl iodide **194** followed by Lindlar reduction and desilylation furnished *ent*-ascospiroketal B *ent*-**8**. The total synthesis of *ent*-ascospiroketal B was completed in 27 linear steps starting from **187** in 1.1% overall yield. The synthesis involved multiple protection-deprotection steps resulting in low overall yield.

Miyoka and co-workers[56] in 2020 accomplished the total synthesis of ascospiroketal B by stereoselective construction of 5,5-spiroketal through rearrangement of an epoxide in conjunction with an acid-mediated spiroketalization (Scheme 23). α,β-Unsaturated ketone **195** on Sharpless asymmetric dihydroxylation delivered diol having >95% ee, which was acetonide-protected to give **196**. Next, the Wittig olefination, ester reduction to alcohol **197** and Sharpless asymmetric epoxidation with L-(+)-DIPT to β-epoxide (dr 15:1) and silylation of free hydroxy group yielded **198**. The sequential removal of Bn group, acylation as OBz and epoxide rearrangement (with methylaluminum bis-(4-bromo-2,6-di-*tert*-butylphenoxide, MABR) to aldehyde and further oxidation gave the acid. Removal

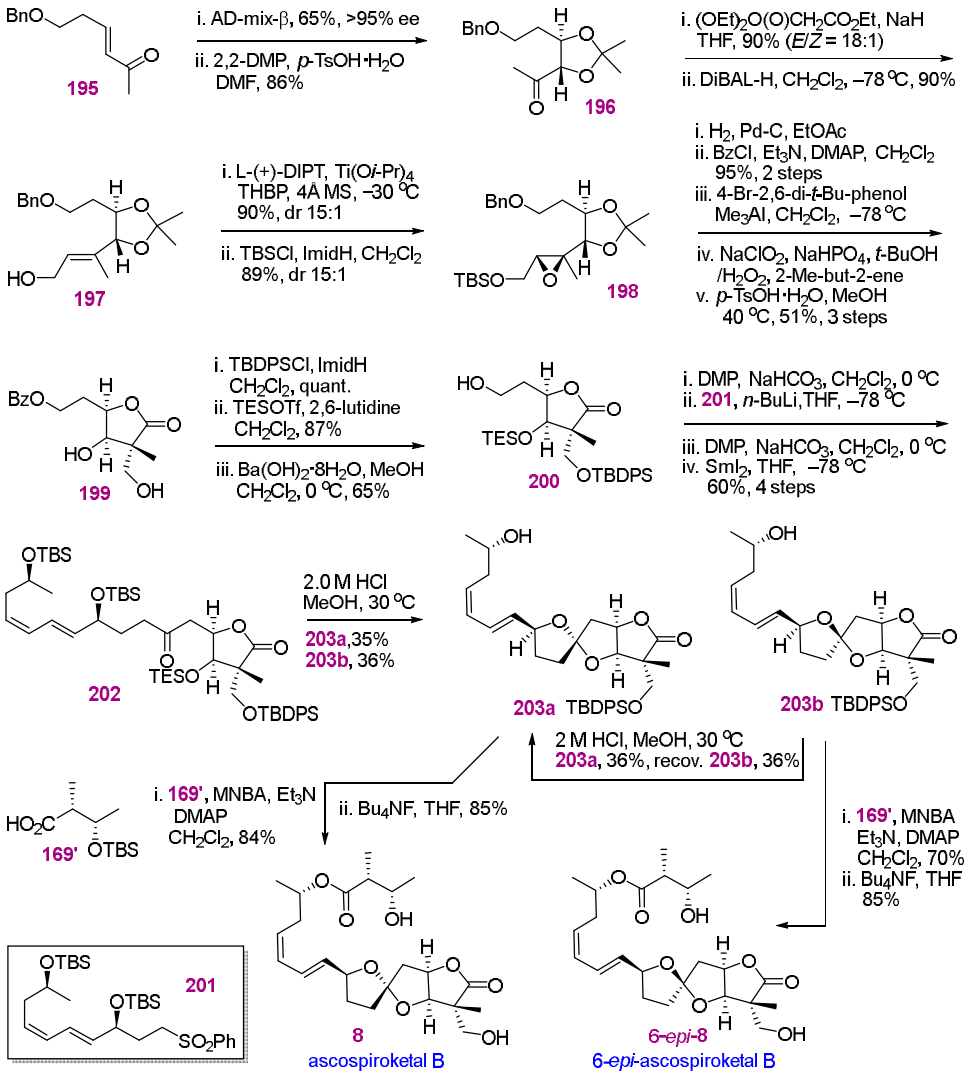
of TBS, acetonide group and lactonization resulted in lactone **199**. Orthogonal processing of hydroxy groups led to alcohol **200**. The latter was oxidised to aldehyde and treated with α-sulfonyl carbanion derived from the (*E*,*Z*)-diene **201** to the alcohol.




**Scheme 22.** Miyoka's synthesis of *ent*-ascospiroketal B.

Further oxidation of secondary alcohol and $SmI_2$-mediated reductive desulfonylation furnished ketone **202**. Acid-mediated desilylation and ketal formation afforded separable diastereomeric mixture of **203a** and

**203b** in 35% and 36% yield, respectively. Further, acid treatment generated a 1:1 mixture of **203a** and **203b** from **203b**. Condensation of **203a** with (2*R*,3*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylbutanoic acid **169'**[49] and global deprotection furnished ascospiroketal B **8**. Similarly, **203b** and acid **169'** were condensed and further desilyation delivered 6-*epi*-ascospiroketal B (6-*epi*-**8**). The synthesis of ascospiroketal B and 6-*epi*-ascospiroketal B was completed in 21 steps with 1.5% and 1.3% overall yields, respectively (Scheme 23).



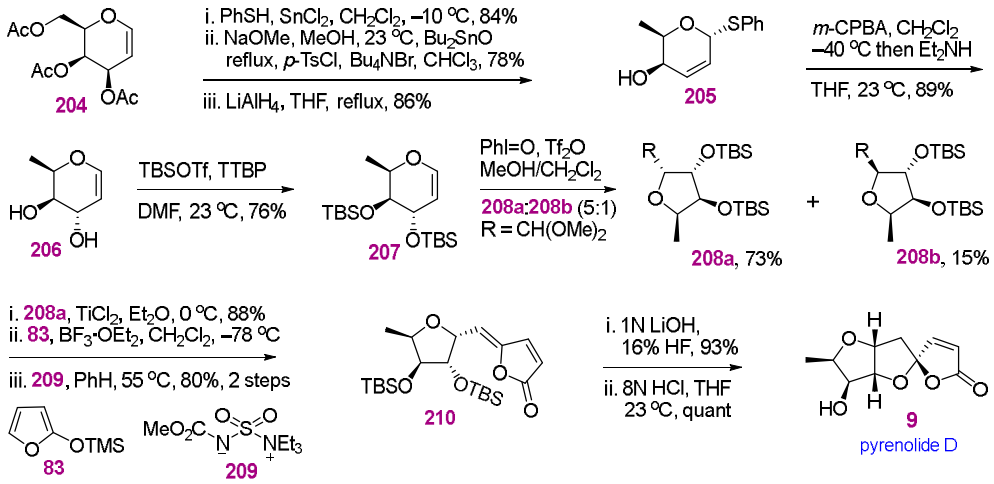

**Scheme 23.** Miyoka's synthesis of *ent*-ascospiroketal B and 6-*epi*-ascospiroketal B.

## 5. Total synthesis of pyrenolide D

Pyrenolide D **9**, a spiro bis-THF molecule was isolated by Hirota and coworkers[57] in 1992 from phytopathogenic fungus *Pyrenophora teres* from which other pyrenolides A, B and C were also isolated. It shows cytotoxic activities to HL-60 cells at $IC_{50}$ of 4 μg/mL. The relative stereochemistry was determined by various spectroscopic studies like COSY, NOSY, HRMS and IR, but the absolute stereochemistry was

confirmed in 2001 by its total synthesis and comparison of spectral data of synthetic compound with natural isolate.[58] Since then, several syntheses have been reported using various strategies for this molecule.

Gin and co-workers[58] reported the first total synthesis of pyrenolide D by chiral pool strategy. The synthesis commenced from commercially available galactal **204** which underwent Ferrier-type glycosylation[59] with thiophenol followed by ester hydrolysis and subsequent selective tosylation of primary hydroxy group that was displaced by hydride to deliver compound **205** (Scheme 24). The sulfide **205** was oxidized with *m*-CPBA to give corresponding sulfoxide which underwent an Evans-Mislow [2,3]-sigmatropic rearrangement[60] and subsequent aminolysis to give the dihydroxy compound **206**. Protection of both the hydroxy groups as TBS ethers to **207** followed by oxidative ring contraction furnished furanoside **208**. The major isomer **208a** upon hydrolysis with $TiCl_4$ followed by reaction with compound **83** produced secondary alcohol. This was dehydrated using Burgess reagent **209** to produce **210**. The latter on hydrolysis using LiOH and acid-mediated deprotection of TBS ether followed by spiro-lactonization gave diastereomeric mixture of pyrenolide D, which on further isomerization with 8N HCl furnished the final molecule pyrenolide D **9**. The spectral data and optical rotation of this synthetic compound well matched with that of natural isolate establishing the absolute stereochemistry. The synthesis was completed in 11 steps and 18% overall yield.

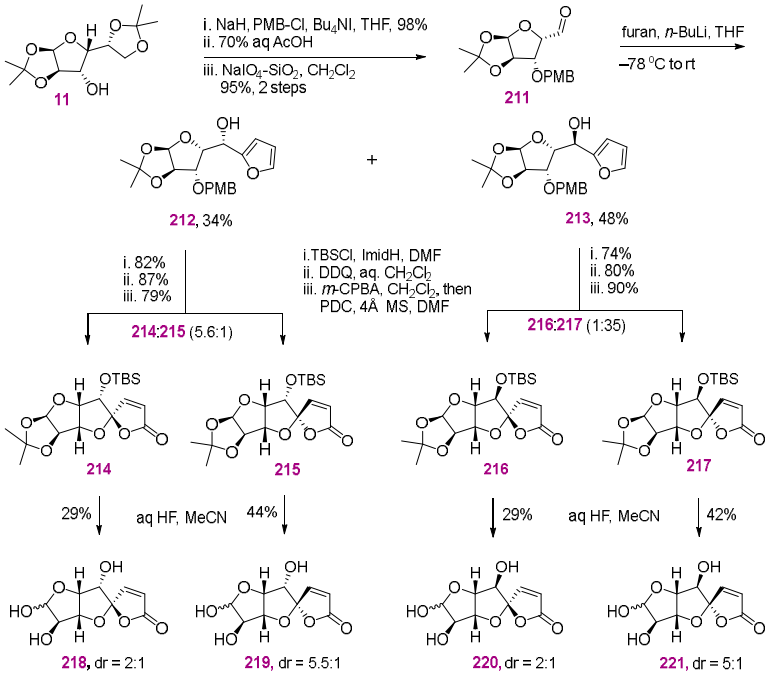



**Scheme 24.** Gin's first total synthesis of pyrenolide D.

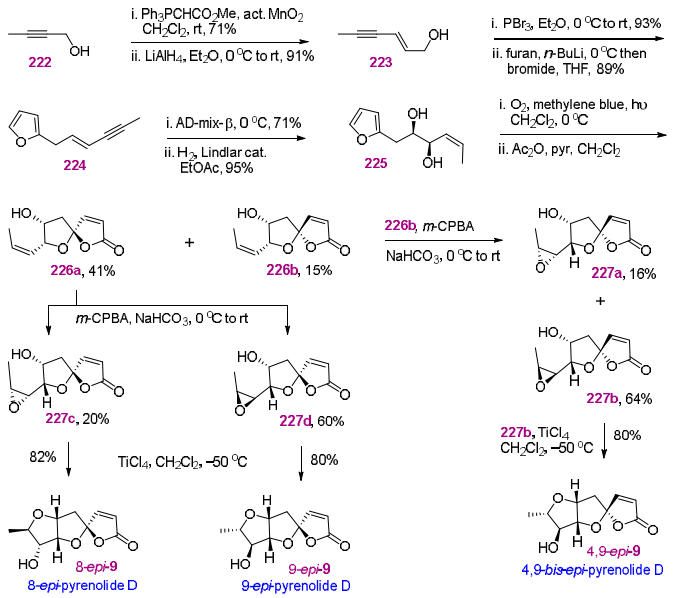
In 2008, the Robertson group[61] synthesized analogues of pyrenolide D using chiral pool material. The synthesis started from diacetonide glucose **11** which upon PMB protection of hydroxyl group followed by selective acetonide deprotection using aqueous AcOH and oxidative cleavage of diol produced aldehyde **211** (Scheme 25). Reaction of lithiated furan with **211** gave the diastereomeric mixture of separable **212** and **213** (dr 1:1.4). Next, the hydroxy protection as TBS ether and subsequent PMB deprotection followed by oxidation with *m*-CPBA and PDC led to spiro-lactonized products **214-215** from **212** and **216-217** from **213**, respectively. The removal of TBS group finally furnished analogues of pyrenolide D **218-221** starting from **214-217**, respectively.

Various diastereomers of pyrenolide D **9** were synthesized by Vassilikogiannakis and co-workers[62] by photooxygenation of furan. 2-Butyn-1-ol **222** upon oxidation, in-situ Wittig olefination and then ester reduction gave the corresponding alcohol **223** (Scheme 26). This was converted to bromide and subsequent displacement with lithiated furan led to formation of **224**. Next, the Sharpless asymmetric dihydroxylation followed by Lindlar reduction of triple bond gave the diol **225** which upon photooxygenation followed by treatment with acetic anhydride provided spiro-lactone diastereomers **226a** and **226b** (2.7:1). In turn, **226a** and **226b** on epoxidation produced possible four epoxides **227a-227b** from **226b** and **227c-227d** from **226a**, respectively. Epoxides **227b**, **227c** and **227d** were treated with $TiCl_4$ to furnish 4,9-bis-*epi*-pyrenolide D

(4,9-*epi*-**9**), 8-*epi*-pyrenolide D (8-*epi*-**9**) and 9-*epi*-pyrenolide D (9-*epi*-**9**), respectively. The synthesis of these epimers 4,9-*epi*-**9**, 8-*epi*-**9** and 9-*epi*-**9** was completed in 10 steps with 3, 2.4 and 7.1% overall yields, respectively.

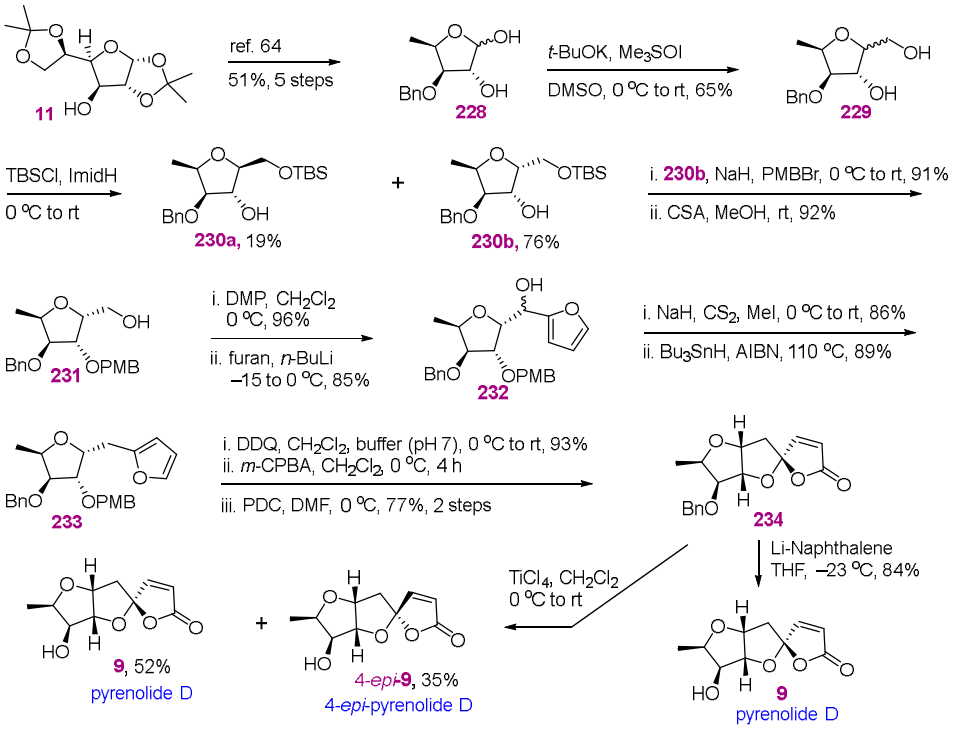



**Scheme 25.** Robertson's synthesis of pyrenolide D analogues.




**Scheme 26.** Vassilikogiannakis' synthesis of pyrenolide D diastereomers.

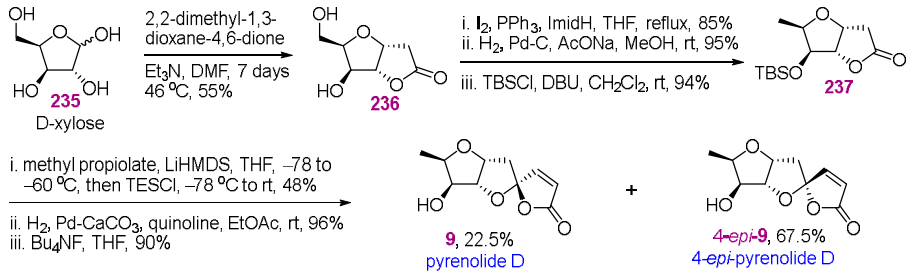
Mohapatra and co-workers[63] used diacetonide glucose **11** to achieve the synthesis of pyrenolide D and its C-4 epimer. Diol **228** was prepared according to reported procedure[64] in 5 steps and 51% overall yield from **11** (Scheme 27). Reaction of diol **228** with Corey-Chaykovsky reagent[65] ($Me_3SOI$) led to the formation of unseparable diastereomer diols **229** which on selective TBS protection of primary hydroxy resulted in separable diastereomers **230a** (minor) and **230b** (major). Next, the PMB protection and TBS removal from **230b** gave alcohol **231** which further on DMP oxidation followed by reaction with lithiated furan led to mono substituted furan alcohol **232**. Reductive deoxygenation of **232** using Barton-McCombie protocol[66] gave **233** and then PMB deprotection with DDQ followed by oxidative spiroketalization furnished spiroketal lactone **234**. Finally, the deprotection of benzyl group in **234** using lithiated naphthalene resulted in pyrenolide D **9** as major product. However, deprotection of benzyl group in **234** with excees $TiCl_4$ led to pyrenolide D **9** as major product along with 4-*epi*-pyrenolide D (4-*epi*-**9**) as minor isomer due to epimerization at spiro carbon. The synthesis of pyrenolide D and 4-*epi*-pyrenolide D was completed in 17 steps (starting from **11**) with 5% and 3.3% overall yields, respectively when $TiCl_4$ was used for deprotection. The overall yield was 8% for pyrenolide D with the use of lithiated naphthalene for benzyl deprotection in final step.




**Scheme 27.** Mohapatra's synthesis of pyrenolide D and 4-*epi*-pyrenolide D.

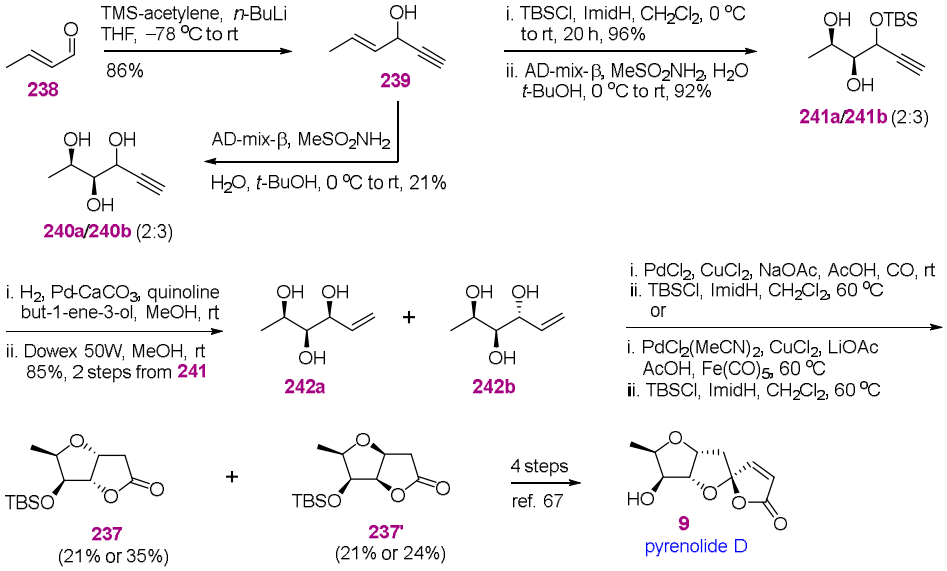
Du and co-workers[67] in 2013 disclosed a concise total synthesis of pyrenolide D and 4-*epi*-pyrenolide D from commercially available D-xylose **235** (Scheme 28). Lactone **236** was synthesized from **235** in one step *via* literature known procedure.[68] Selective iodination followed by Pd/C-catalyzed dehalogenation and subsequent silyl ether protection of secondary hydroxyl group provided lactone **237**. The latter was treated with lithiated methyl propiolate at low temperature followed by conversion of hemiketal intermediate to the corresponding triethylsilyl ether. Next, the reduction of alkyne to *cis*-olefin, desilylation-lactonization delivered diastereomeric mixture of pyrenolide D **9** and 4-*epi*-pyrenolide D (4-*epi*-**9**) as 3:1 mixture that was

further seperated by flash column chromatography. The concise synthesis of pyrenolide D **9** and its isomer 4-*epi*-**9** was completed in 7 steps and 4.3% and 13% overall yields, respectively.




**Scheme 28.** Du's synthesis of pyrenolide D and 4-*epi*-pyrenolide D.

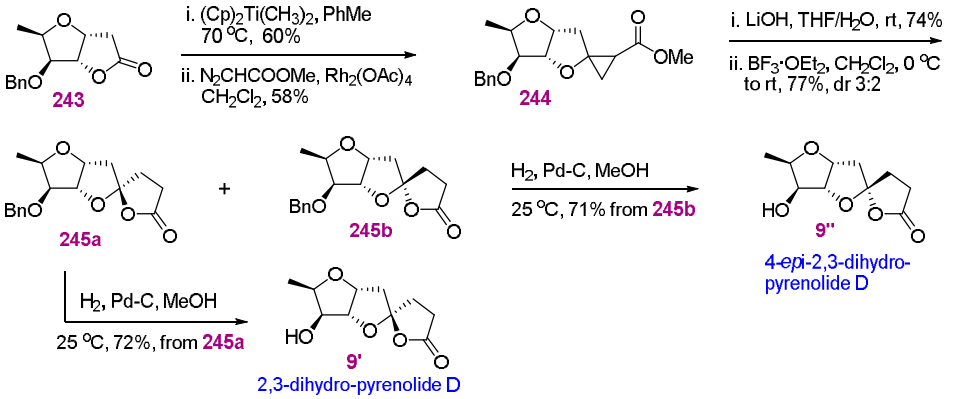
In 2015, Gracza and co-workers[69] reported the asymmetric formal synthesis of (+)-pyrenolide D from (*E*)-crotonaldehyde involving Sharpless asymmetric dihydroxylation and highly diastereoselective palladium-catalyzed oxy-carbonylation as key steps (Scheme 29). TMS-acetylene was added to (*E*)-crotonaldehyde **238** to furnish alkynol **239** that on asymmetric dihydroxylation with AD-mix-β resulted in very poor yield (21%) of **240a** and **240b** (dr 2:3). However, with silyl ether protection of compound **239** and then asymmetric dihydroxylation worked excellently with 92% yield of **241** having diastereomeric ratio of 2:3. Next, the Lindlar reduction of alkyne **241** followed by desilylation afforded mixture of **242a** and **242b**. These on Pd-catalyzed carbonylative cyclization and silyl protection gave separable lactones **237** and **237'**. Alternatively, Pd-catalyzed oxidative carbonylation using $PdCl_2(MeCN)_2$ and $Fe(CO)_5$[70] as a CO source, followed by silyl protection of free hydroxy group furnished lactones **237** and **237'** in better yields. The synthesis of pyrenolide D from intermediate **237** is known in literature,[67] completing the formal synthesis.




**Scheme 29.** Gracza's formal synthesis of pyrenolide D.

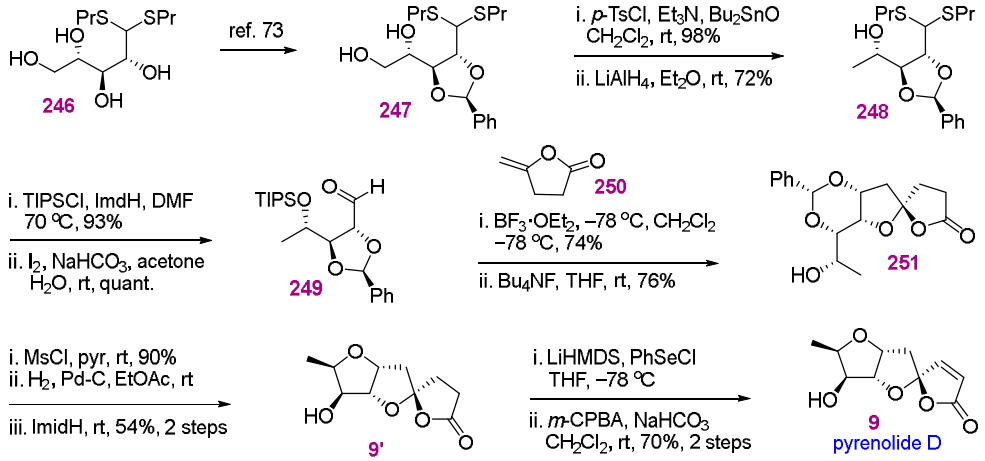
In 2016, Ramakrishna and Sridhar[71] developed an efficient and new method to construct 1,6-dioxaspiro[4.n]decan-2-one systems from sugar derived spiro-cyclopropane carboxylic acids *via* a

one-pot ring-opening-cyclization reaction (Scheme 30). This methodology was further applied to the total synthesis of dihydro-pyrenolide D and 4-*epi*-dihydro-pyrenolide D. Literature known lactone **243**[67] (prepared from D-xylose) on treatment with dimethyl titanocene formed exo-cyclic olefin which on $Rh_2(OAc)_4$-catalyzed cyclopropanation delivered the spiro-cyclopropanecarboxylate **244** as an inseparable anomeric mixture. Next, the ester **244** was hydrolyzed to acid which on reaction with $BF_3{\cdot}OEt_2$ underwent a facile one-pot ring-opening-cyclization reaction resulting in spirolactones **245a** and **245b** as a separable diastereomeric mixture (dr 3:2). These were individually debenzylated to furnish 2,3-dihydro-pyrenolide D **9'** and 4-*epi*-2,3-dihydro-pyrenolide D **9''**, respectively. The synthesis of **9'** and its epimer **9''** was completed in total 5 steps starting from compound **243** in 8.6% and 5.7% overall yields, respectively.




**Scheme 30.** Sridhar's synthesis of 2,3-dihydro-pyrenolide D and 4-*epi*-2,3-dihydro-pyrenolide D.

In 2018, Sugimura and co-workers[72] described the total synthesis of pyrenolide D *via* $BF_3$-promoted formal [3+2] annulation of formyl-aldose derivatives with γ-methylene-γ-butyrolactone. L-Arabinose dipropyl dithioacetal **246** was converted to 2,3-O-benzylidene derivative **247** using literature procedure (Scheme 31).[73] Tosylation of primary hydroxy group followed by reductive detosylation[74] afforded alcohol **248**. Next, the silyl protection of secondary alcohol and dithioacetal hydrolysis delivered aldehyde **249**.




**Scheme 31.** Sugimura's synthesis of pyrenolide D.

The latter was reacted with γ-methylene-γ-butyrolactone **250** in presence of $BF_3 \cdot OEt_2$ to generate the desired spiro-γ-lactone core and then desilylation gave alcohol **251**. Next, the sequential mesylation of free hydroxy group of **251**, removal of benzylidene and imidazole induced cyclization yielded dihydro-pyrenolide D **9'**. Finally, α-phenylselenation followed by oxidative β-elimination (without protection of the C8 hydroxy group) furnished pyrenolide D **9**. The total synthesis of pyrenolide D was completed in 11 linear steps starting from **247** and 12.6% overall yield (Scheme 31).

## 7. Conclusions

The tetrahydro-spirofurofuranone containing natural products cephalosporolides E, F, H and I, penisporolides A and B and ascospiroketal B along with the related ascospiroketal A and pyrenolide D have been synthesized using various strategies. While the use of chiral pool approaches are quite common, the oxidative dearomatization and ring-expansion/ring-contraction chemistry developed by Tong has been quite unique for the spiro-furofuranone molecules. Some of the protecting-group-free synthesis developed by Fernandes and Du with olefin as latent keto functionality were quite short and efficient. Other catalytic approaches based on Sharples dihydroxylation and epoxidation were also useful in the synthesis of these molecules. The oxy-carbonylative cyclization and the cyclopropane ring expansion chemistry developed by Sridhar added new dimension to the strategies involved in spiro-lactone synthesis. Future direction could be photo-catalytic and atom-economic strategies for synthesis of such important tetrahydro-spirofurofuranone natural products.

## Acknowledgements

This work was financially supported by the Department of Science and Technology, SERB, New Delhi (Grant No. EMR/2017/000499). A.J.G. and N.C. thank IIT Bombay and the Council of Scientific and Industrial Research (CSIR) New Delhi, India, respectively for research fellowships.

## References

1. Halle, M. B.; Fernandes, R. A. *Asian J. Org. Chem.* **2016**, *5*, 839-854; b) Yao, H.; Wang, J.; Tong, R. *Chem. Rec.* **2017**, *17*, 1109-1123.
2. Florey, H. W.; Chain, E.; Heatley, N. G.; Jennings, M. A.; Sanders, A. G.; Abraham, E. P.; Florey, E. M. *Antibiotics*, Oxford University Press: Oxford, **1949**.
3. Abraham, E. P.; Loder, P. B. Cephalosporin C, in *Cephalosporins and Penicillins: Chemistry and Biology, ed*. E. H. Flynn, Academic Press: New York, **1972**.
4. Kupka, J.; Anke, T.; Steglich, W.; Zechlin, J. *J. Antibiot.* **1981**, *34*, 298-304.
5. Bugni, T. S.; Ireland, M. S. *Nat. Prod. Rep.* **2004**, *21*, 143-163.
6. a) Quach, R.; Chorley, D. F.; Brimble, M. A. *Org. Biomol. Chem.* **2014**, *12*, 7423-7432. b) Song, L.; Yao, H.; Dai, Y.; Wu, M.; Tong, R. *Tetrahedron Lett*. **2016**, *57*, 4257-4263. c) Green, J. C.; Burnett IV, G. L.; Pettus, T. R. R. *Pure Appl*. *Chem*. **2012**, *84*, 1621-1631. d) Paterson, I.; Dalby, S. M.; Maltas, P. *Isr*. *J. Chem.* **2011**, *51*, 406-419.
7. Zhang, F.-M.; Zhang, S.-Y.; Tu, Y.-Q. *Nat. Prod. Rep.* **2018**, *35*, 75-104.
8. a) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc. Perkin Trans. 1* **1985**, 843-847. b) Oller-López, J. L.; Iranzo, M.; Mormeneo, S.; Oliver, E.; Cuervaa, J. M.; Oltra, J. E. *Org. Biomol. Chem.* **2005**, *3*, 1172-1173.
9. Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem*. **2009**, *74*, 2842-2845.
10. a) Hanessian, S.; Plessas, N. R. *J. Org. Chem*. **1969**, *34*, 2163-2170. b) Hanessian, S. *Methods Carbohydr. Chem*. **1972**, *6*, 190-193. c) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett*. **1989**, *30*, 5455-5458.
11. Fernandes, R. A.; Ingle, A. B. *Synlett* **2010**, *2010*, 158-160.
12. For olefin cross metathesis see: a) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923. b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc*. **2003**, *125*, 11360-11370. c) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett*. **2008**, *10*, 1325-1328.

13. For Sharpless dihydroxylation see: a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogiito, Y.; Shibata, T.; Ukita, T. *J. Org. Chem*. **1991**, *56*, 4585-4590. b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu. D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771. c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
14. Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P; O'Connor, P. D. *Tetrahedron* **2011**, *67*, 995-1001.
15. Fujisawa, H.; Sasaki, Y.; Mukaiyama, T. *Chem. Lett*. **2001**, 190-191.
16. Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem*. **2012**, *8*, 1287-1292.
17. Chang, S.; Britton, R. *Org. Lett*. **2012**, *14*, 5844-5847.
18. Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem. Int. Ed*. **2009**, *48*, 5121-5124.
19. Song, L.; Liu, Y.; Tong, R. *Org. Lett.* **2013**, *15*, 5850-5853.
20. a) Ferraz, H. M. C.; Longo Jr., L. S. *Org. Lett*. **2003**, *5*, 1337-1339. b) Ferraz, H. M. C.; Longo Jr., L. S. *J. Org. Chem*. **2007**, *72*, 2945-2950.
21. Kona, C. N.; Ramana, C. V. *Tetrahedron* **2014**, *70*, 3653-3656.
22. a) Rondot, B.; Durand, T.; Rossi, J. C.; Rollin, P. *Carbohydr. Res.* **1994**, *261*, 149-156. b) Falck, J. R.; Reddy, L. M.; Byun, K.; Campbell, W. B.; Yi, X.-Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2634-2638.
23. Cortezano-Arellano, O.; Quintero, L.; Sartillo-Piscil, F. *J. Org. Chem*. **2015**, *80*, 2601-2608.
24. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem*. **1996**, *61*, 5178-5179.
25. Mitsunobu, O. *Synthesis* **1981**, *1981*, 1-28.
26. Chaudhari, D. A.; Kattanguru, P.; Fernandes, R. A. *RSC Adv*. **2015**, *5*, 42131-42134.
27. Raghavan, S.; Patel, J. S.; Ramakrishna, K. V. S. *RSC Adv.* **2016**, *6*, 72877-72884.
28. a) Concepcion, J. J.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett*. **1984**, *25*, 1953-1956. b) Martin, A., Salazar, J. A.; Suarez, E. *Tetrahedron* **1995**, *36*, 4489-4492.
29. Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res*. **2007**, *30*, 812-815.
30. Li, X.; Sattler, I.; Lin, W. *J. Antibiot.* **2007**, *60*, 191-195.
31. Tlais, S. F.; Dudley, G. B. *Org. Lett*. **2010**, *12*, 4698−4701
32. Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem*. **2011**, *17*, 570-577
33. Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc*. **2007**, *129*, 8968-8969.
34. Fernandes, R. A.; Halle, M. B. *Asian J. Org. Chem*. **2013**, *2*, 593-599.
35. a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467-8468. b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett*. **1993**, *34*, 7827-7828. c) Kurosu, M. Lorca, M. *Synlett* **2005**, 1109-1112.
36. Finch, O. C.; Furkert, D. P.; Brimble, M. A. *Tetrahedron* **2014**, *70*, 590-596.
37. Li, J.; Zhao, C.; Liu, J.; Du, Y. *Tetrahedron* **2015**, *71*, 3885-3889.
38. Fernandes, R. A.; Kattanguru, P. *J. Org. Chem*. **2012**, *77*, 9357-9360.
39. Wang, J.; Tong, R. *J. Org. Chem.* **2016**, *81*, 4325-4339.
40. For the related oxidative ring expansion, see: a) ref. 20. b) Barradas, S.; Urbano, A.; Carreño, M. C. *Chem. Eur. J.* **2009**, *15*, 9286-9294.
41. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596-2599.
42. a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179-3181. b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc*. **1986**, *108*, 5644-5646.
43. Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; König, G. M. *Org. Lett.* **2007**, *7*, 239-242.
44. a) Chang, S.; Hur, S.; Britton, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 211-214. b) Chang, S.; Hur, S.; Britton, R. *Chem. Eur. J.* **2015**, *21*, 16646–16653.
45. Kim, J. W.; Lee, H. W.; Lee, D-H. *Bull. Korean Chem. Soc.* **2011**, *32*, 2877-2878.
46. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.
47. Winter, P.; Swatschek, J.; Willot, M.; Radtke, L.; Olbrisch, T.; Schäfer, A.; Christmann, M. *Chem. Commun.* **2011**, *47*, 12200-12202.
48. Britton, R.; Kang, B. *Nat. Prod. Rep.* **2013**, *30*, 227-236
49. Wang, J.; Tong, R. *Org. Lett.* **2016**, *18*, 1936-1939.

50. Hara, Y.; Honda, T.; Arakawa, K.; Ota, K.; Kamaike, K.; Miyaoka H. *J. Org. Chem.* **2018**, *83*, 1976-1987.
51. Rzepecki, P. W.; Prestwich, G. D. *J. Org. Chem.* **2002**, *67*, 5454-5460.
52. Dimitriadis, C.; Gill, M.; Harte, M. F. *Tetrahedron: Asymmetry* **1997**, *8*, 2153-2158.
53. Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, *31*, 286-287.
54. Glebocka, A.; Sicinski, R. R.; Plum, L. A.; DeLuca, H. L. J. *Steroid Biochem. Mol. Biol.* **2013**, *136*, 39-43.
55. a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115-8116. b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853-12910.
56. Hara, Y.; Kamaike, K.; Ota, K.; Miyaoka, H. *Synlett* **2020**, *31*, 1730-1734.
57. Nukina, M.; Hirota, H. *Biosci. Biotechnol. Biochem*. **1992**, *56*, 1158-1159.
58. Engstrom, K. M.; Mendoza, M. R; Navarro-Villalobos, M.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1128-1130.
59. Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720-5749.
60. a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc*. **1968**, *90*, 4869-4876. b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147-154.
61. Robertson, J.; Stevens, K.; Naud, S. *Synlett* **2008**, 2083–2086.
62. Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 4556-4559.
63. Thirupathi, B.; Reddy, P. P.; Mohapatra, D. K. *J. Org. Chem*. **2011**, 76, 9835-9840.
64. Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903-2905.
65. a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc*. **1962**, *84*, 867-868. b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc*. **1965**, *87*, 1353-1364.
66. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans.* 1 **1975**, *16*, 1574-1585. b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413-1432.
67. Zhang, C.; Liu, J.; Du, Y. *Tetrahedron Lett.* **2013**, *54*, 3278-3280.
68. Mata, F. Z.; Martinez, M. B.; Perez, J. A. G. *Carbohydr. Res*. **1990**, *201*, 223-231
69. Markovic, M.; Lopatka, P.; Koós, P.; Gracza, T. *Synthesis* **2014**, *46*, 817-821.
70. Babjak, M.; Markovič, M.; Kandríková, B.; Gracza, T. *Synthesis* **2014**, *46*, 809-816.
71. Ramakrishna, B.; Sridhar, P. R. *RSC Adv.* **2015**, *5*, 8142-8145.
72. Ogawa, Y.; Kato, M.; Sasaki, M.; Sugimura, H. *J. Org. Chem.* **2018**, *83*, 12315-12319.
73. Kuszmann, J.; Gács-Baitz, E. *Aust. J. Chem.* **1996**, *49*, 273-280.
74. Zinner, H.; Wessely, K.; Kristen, H. *Chem. Ber.* **1959**, *92*, 1618-1623.