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Synthetic Approaches to Diospongins: A Two Decade Journey

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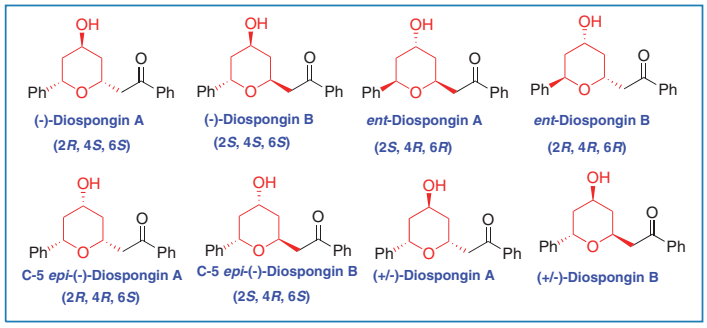

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Abstract Tetrahydropyran units having multiple stereogenic centers serve as excellent building blocks for various active pharmaceutical ingredients (APIs). In particular, the presence of the unique molecular architecture of the trisubstituted tetrahydropyran (THP) unit in diospongins enhances their biological activity due to multiple stereogenic centers and has attracted attention from the synthetic community over the last two decades. In this review, we discuss synthetic approaches to chiral and racemic forms of diospongins during the period 2006–2020 in chronological order.

Key words diospongins, diarylheptanoids, tetrahydropyran, cross-metathesis, hetero-Diels–Alder reaction, asymmetric allylation, enzyme resolution, oxa-Michael addition, Prins cyclization

Introduction

Oxygen-containing heterocyclic compounds, especially tetrahydrofurans and tetrahydropyrans, are important scaffolds in many biologically active compounds.[1–4] Diospongins belong to a family of cyclic 1,7-diarylheptanoids isolated from rhizomes of *Dioscorea spongiosa* in 2004 by Kadota et al. Diospongins have 2,6-*cis*- and 2,6-*trans*-tetrahydro-2*H*-pyran rings, as a core, constructed by intramolecular cyclization of 5,7-dihydroxy-1,7-diphenyl-2-hepten-1-one, in their biosynthesis. Moreover, these compounds possess a trisubstituted tetrahydropyran unit with different stereochemistries at C-3.

Diospongins A and B exhibit inhibitory activity against bone resorption induced by parathyroid hormone in a bone organ culture, with diospongin B showing more potent anti-osteoporotic activity than diospongin A, presumably due to the different configurations of their tetrahydropyran rings.[5–8]

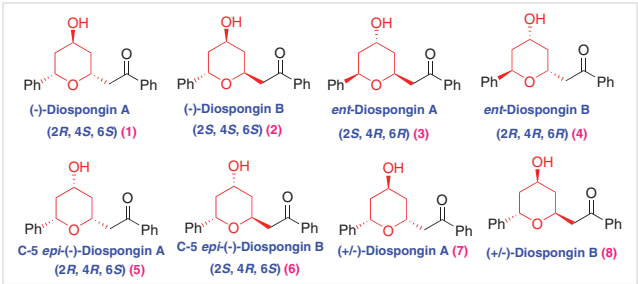


Figure 1 Various structures of diospongins

In a continuation of our efforts towards the synthesis of various biologically active molecules,[3d,9,10] we present the synthetic efforts that have been made toward the synthesis of various diospongins from 2006 to date in the form of a review in chronological order (Figure 1). Moreover, this review should help the synthetic community to explore further the synthesis of various trisubstituted tetrahydropyran-containing natural products (Figure 2). Most of the synthetic approaches reported so far have been asymmetric syntheses, but enantioselective approaches involving chiral auxiliaries, chiral pool precursors, or resolution have also been reported. In summary, the key steps involved in the racemic and chiral synthetic approaches, including the total number of steps and overall yields, are collected and compared in Table 1.

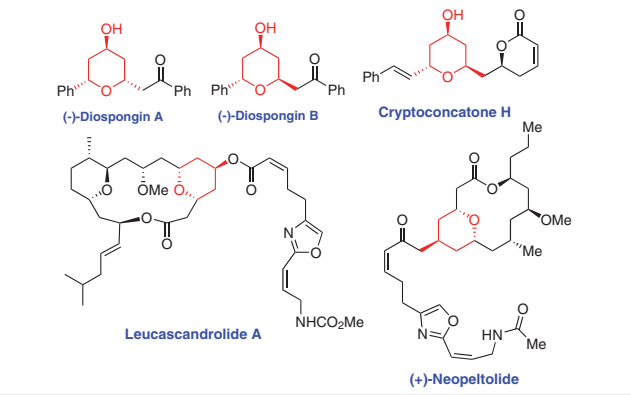


Figure 2 Natural products containing a trisubstituted tetrahydropyran (THP) as a core unit

Synthesis of Chiral Diospongins

Chandrasekhar's Approach (2005)

In 2005, Chandrasekhar et al. reported the synthesis of (–)-diospongin A (**1**) using a Keck asymmetric allylation, a base-catalysed conjugate addition of an α,β-unsaturated ester, and an intramolecular oxy-Michael reaction as the key steps.[11] Initially, the optically pure allyl phenyl carbinol **9**, was subjected to one-pot ozonolysis followed by Wittig olefination to provide the α,β-unsaturated ester **10** in 79% yield. Next, the protected *syn*-1,3-diol derivative **11** was obtained by base-catalysed intramolecular conjugate addition of PhCHO with **10** in the presence of ^{t}BuOK in 61% yield. The ester group in **11** was then reduced with $LiAlH_4$ to furnish compound **12** in 77% yield. The (*E*)-enone **13** was obtained from **12** by one-pot IBX-mediated oxidation followed by Wittig olefination in 77% yield over two steps. Finally, (–)-diospongin A (**1**) was obtained from **13** by hydrolysis of the benzylidene acetal group and intramolecular oxy-Michael addition in 69% overall yield (Scheme 1).

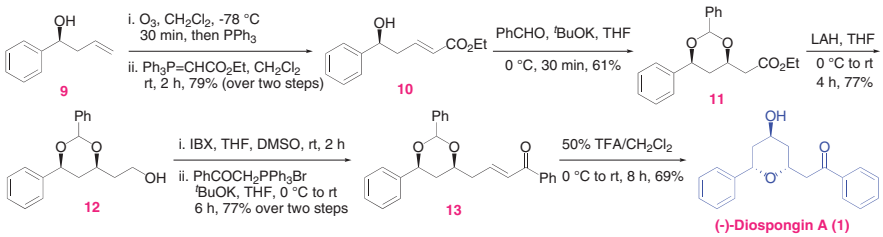
Cossy's Approach (2006)

In 2006, Bressy and Cossy reported the synthesis of (–)-diospongin A (**1**) using two enantioselective allyl titanations, cross-metathesis, and an intramolecular oxy-Michael reaction as key steps.[12] Initially, optically pure allylic alcohol **9** (ee > 98%) was prepared from benzaldehyde **14** by reaction with allyl titanium complex (*R*,*R*)-Ti. The hydroxyl group was protected as its TBS ether **15** in 75% yield. Next, the terminal olefin in **15** was subjected to oxidative cleavage to obtain the corresponding aldehyde, which was then treated in situ with the highly face-selective complex (*R*,*R*)-Ti to obtain the 1,3-*syn*-diol **16** (dr 95:5, 87% yield for two steps). Next, 1,3-diol **16** was subjected to cross-metathesis with phenyl vinyl ketone using Grubbs' catalyst (**G-II**) to afford the 1,7-diarylheptenone **17** (75%, *E*/*Z*95:5). Finally, (–)-diospongin A (**1**) was obtained in 60% yield from **17** by intramolecular oxy-Michael addition using TBAF (Scheme 2).

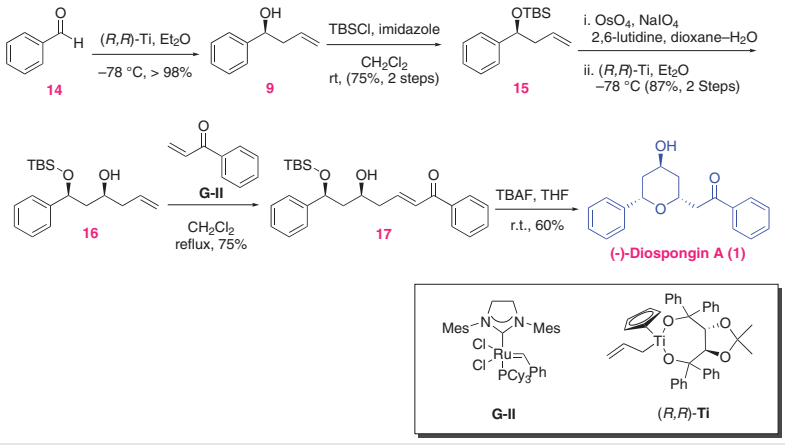
Biographical Sketch

Dr. Krishnaji Tadiparthi was born in Eluru, Andhra Pradesh, India, and obtained his Ph.D. in 2008 from the Indian Institute of Chemical Technology (IICT), Hyderabad with Dr. Ahmed Kamal. He carried out postdoctoral studies at the Freie University Berlin, Germany (with Prof. Hans-Ulrich Reissig) and Versailles Saint-Quentin-en-Yvelines University, France (with Prof. Gwilherm Evano). He has held positions as Senior Scientist at AstraZeneca, Bangalore, and Senior Manager at Dr. Reddy's Laboratory, Hyderabad. Currently, he is an Assistant Professor in the department of chemistry, CHRIST (Deemed to be University), Bangalore, India. His research interests are in the areas of organic synthesis, including the development of novel synthetic transformations and total synthesis of biologically active molecules using biocatalytic principles.

Sourav Chatterjee was born in Burnpur, West Bengal, India and received his B.Sc. (hons) (Chemistry) from Kazi Nazrul University, West Bengal. Currently he is pursuing his M.Sc. (Organic Chemistry) from CHRIST (Deemed to be University), Bangalore and is carrying out research on the development of novel synthetic transformations in the group of Dr. Krishnaji Tadiparthi.



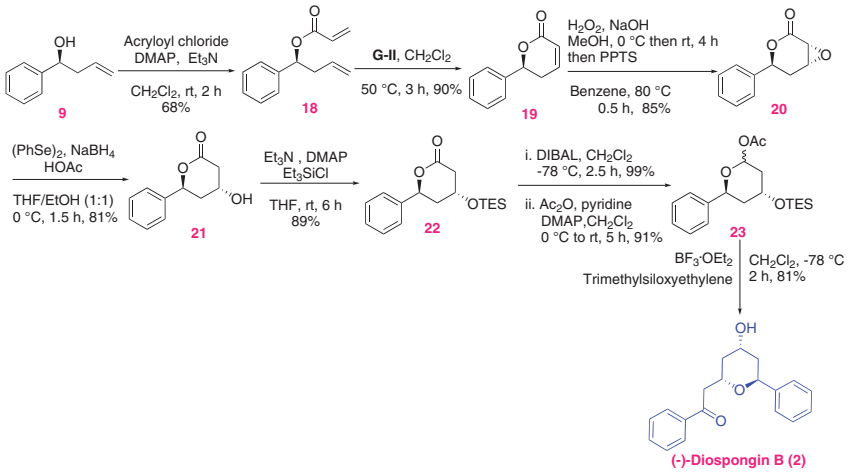
Scheme 1 Synthesis of (–)-diospongin A (**1**) by Chandrasekhar's approach



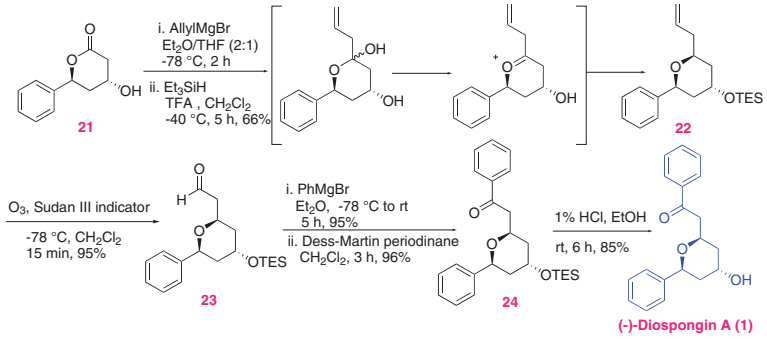
Scheme 2 Synthesis of (–)-diospongin A (**1**) by Cossy's approach

Jennings' Approach (2006)

In 2006, Sawant and Jennings demonstrated the synthesis of (–)-diospongins A **1** and B **2** using stereoselective reduction of an oxocarbenium cation as a key step.[13] Initially, alcohol **9** was subjected to esterification to furnish the dienic ester **18** in 68% yield. Next, compound **18**, upon ring-closing olefin metathesis using Grubbs' catalyst (**G-II**), provided the unsaturated lactone **19** in 90% yield. Subsequently, **19**, upon epoxidation in the presence of hydroperoxide, afforded the epoxy lactone **20** stereoselectively in 85% yield. The oxirane was converted into TES ether **22** by regioselective reduction followed by hydroxyl group protection in 89% overall yield. Next, the lactone **22** was reduced to the corresponding lactol using DIBAL-H, followed by acetylation with Ac_2O to provide **23**. Finally, (–)-diospongin B (**2**) was obtained by reaction of **23** with $BF_3{\cdot}OEt_2$ to form the corresponding oxocarbenium cation, followed by concomitant removal of the TES group in 81% yield (Scheme 3).



Scheme 3 Synthesis of (–)-diospongin B (**2**) by Jennings' approach



Scheme 4 Synthesis of (–)-diospongin A (**1**) by Jennings' approach

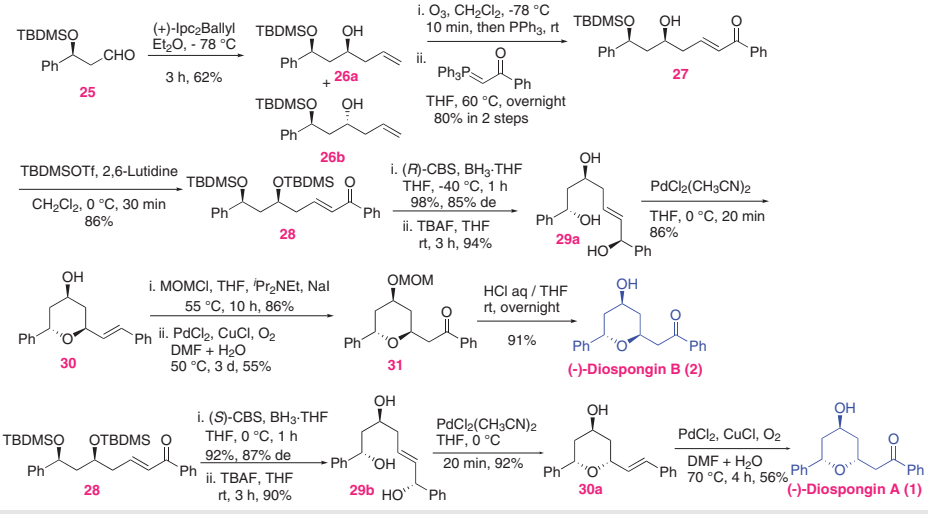
This approach was also modified to allow the preparation of diospongin A.[14] Lactone **21** was reacted with allyl magnesium bromide to obtain the corresponding lactol, which was treated with TFA in situ to afford the oxocarbenium species followed by reduction with Et_3SiH to furnish TES ether **22**.[15] Subsequently, compound **22** was transformed into aldehyde **23** by reductive ozonolysis in 95% yield. Next, Grignard addition to the aldehyde provided the secondary alcohol, followed by Dess–Martin periodinane oxidation to give ketone **24** in 91% yield for two steps. Finally, (–)-diospongin A (**1**) was obtained in 85% yield by deprotection of the TES ether **24** with 5% HCl (Scheme 4).

Uenishi's Approach (2007)

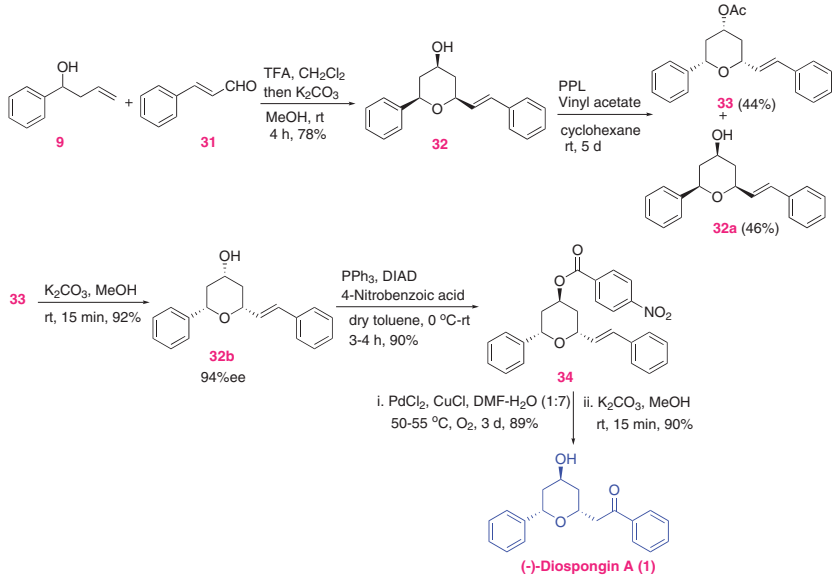
In 2011, Uenishi's group executed the synthesis of (–)-diospongins A (**1**) and B (**2**) using CBS reduction, Brown allylation, and Wacker oxidation as key steps.[14] The synthesis started from compound **25**, which was subjected to Brown allylation using (+)-Ipc_2B-allyl, to furnish **26a** in 62% yield along with diastereoisomer **26b** in 14% yield. Next, compound **26a** was converted into **27** by ozonolysis, followed by Wittig olefination in 80% yield over two steps. Subsequently, the hydroxyl group in **27** was protected as a TBS ether **28** in 86% yield. The reduction of the keto-group in **28** with (*R*)-CBS (98%, 85% de), followed by deprotection of the silyl ether, provided triol **29a** in 94% yield. Next, compound **29a** was subjected to cyclization using $PdCl_2(CH_3CN)_2$, to furnish *cis*-(*E*)-tetrahydropyran **30** in 92% yield. Finally, (–)-diospongin B (**2**) was obtained from **30** by MOM protection, Wacker oxidation, followed by removal of the MOM group with aq. HCl in 91% yield. Similarly, (–)-diospongin A (**1**) was obtained from **28** by reduction of the keto-group with (*S*)-CBS, TBS deprotection followed by cyclization and Wacker oxidation in moderate overall yield (Scheme 5).

Yadav's Approach (2007)

In 2007, our group reported the synthesis of (–)-diospongin A (**1**) by using Prins cyclization and enzymatic kinetic resolution as key steps.[16] Initially, the homoallylic alcohol **9** was subjected to Prins cyclization with cinnamaldehyde **31** to form **32** in 78% yield as a single diastereomer. Next, **32** was subjected to enzymatic resolution using por-



Scheme 5 Synthesis of (–)-diospongin A (**1**) and B (**2**) by Uenishi's approach

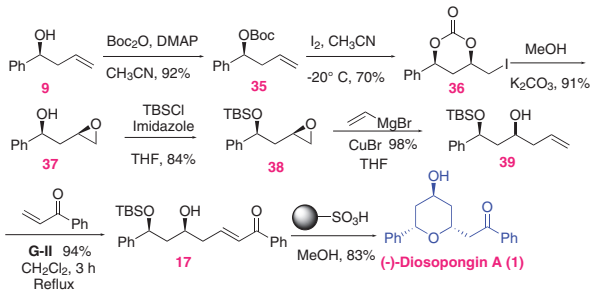


Scheme 6 Synthesis of (–)-diospongin A (**1**) by Yadav's approach

cine pancreatic lipase (PPL) to produce acetate **33** and alcohol **32a**. Next, acetate **33** was hydrolysed using K_2CO_3 to provide alcohol **32b** in 92% yield (94% ee). Inversion of the alcohol **32b** was achieved under Mitsunobu conditions to lead to **34** in 90% yield. Finally, (–)-diospongin A (**1**) was obtained by Wacker oxidation followed by hydrolysis of **34** in 90% overall yield (Scheme 6).

Bates' Approach (2007)

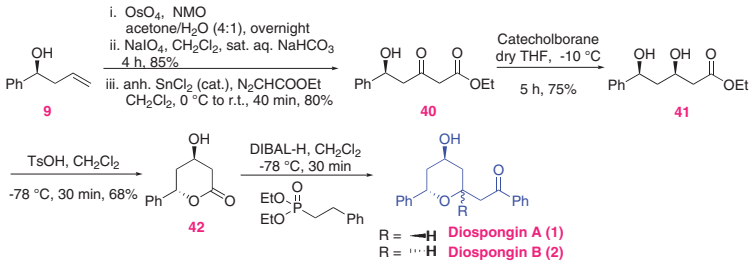
In 2007, Bates and Song executed the synthesis of (–)-diospongin A (**1**) using cross-metathesis, and intramolecular Michael addition as key steps.[17] Initially, (*S*)-phenylbutenol **9** was converted into *tert*-butyl carbonate **35**. Next, compound **35** was converted into epoxy alcohol **37** by iodocyclization, followed by methanolysis using potassium carbonate. The hydroxyl group in **37** was protected as its TBS ether **38** and subsequent ring-opening of the epoxide with vinyl magnesium bromide and CuBr to provide homoallylic alcohol **39**. Finally, (–)-diospongin A (**1**) was obtained by cross-metathesis of **39** with phenyl vinyl ketone in the presence of Grubbs' catalyst (**G-II**), followed by one-pot TBS deprotection and cyclization using Amberlyst 15 in 83% yield (Scheme 7).



Scheme 7 Synthesis of (–)-diospongin A (**1**) by Bates' approach

Sabitha's approach (2008)

In 2008, our group demonstrated the synthesis of (–)-diospongins A **1** and B **2** using Keck allylation, stereoselective reduction, Horner–Wadsworth–Emmons olefination, and intramolecular oxy-Michael reaction as key steps.[18] The synthesis commenced with the chiral 1-phenyl but-3-en-1-ol **9**, prepared from benzaldehyde by Keck allylation with allyl tributyltin in the presence of (*S*)-BINOL and $Ti(O^iPr)_4$ (73%, 97% ee). Oxidative cleavage of the terminal olefin moiety of **9** produced the corresponding aldehyde, which, without isolation, was treated with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride to afford the β-keto ester **40** in 80% yield. The *syn*-selective reduction of δ-hydroxy-β-keto ester **40** was performed with catecholborane to afford the *syn*-1,3-diol **41** in 75% yield. Cyclization of ester **41** was accomplished with *p*-TsOH to afford δ-lactone **42** in 68% yield. Next, reduction of lactone **42** with DIBAL-H followed by Horner–Wittig olefination provided (–)-diospongin A (**1**) and (–)-diospongin B (**2**) (4:6 ratio) in 60% yield over two steps (Scheme 8).



Scheme 8 Synthesis of (–)-diospongins A and B by Sabitha's approach

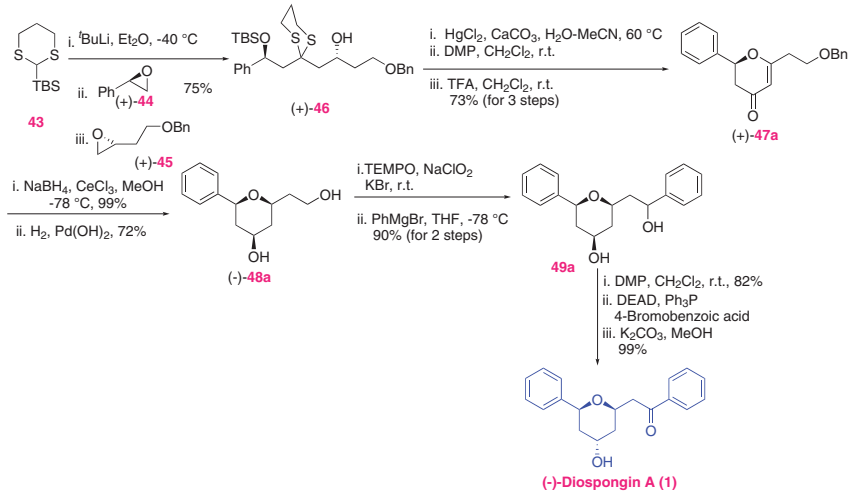
Xian's approach (2008)

In 2008, Xian et al. demonstrated syntheses of diospongin A and B by using Linchpin coupling, Luchi reduction, and Mitsunobu inversion as key steps.[15] Initially, the Linchpin coupling of TBS dithiane **43** with epoxides (+)-**44** and (+)-**45** provided the alcohol (–)-**46** in 74% yield. Next, compound (+)-**46**was subjected to dithiane deprotection, Dess–Martin oxidation, and acidic cyclization to furnish the dihydropyranone (+)-**47a**. Subsequently, compound (+)-**47a**was subjected to Luche reduction followed by hydrogenation, and benzyl group deprotection to afford the diol (–)-**48a**, either in one pot or stepwise. Next, the primary hydroxyl group in (–)-**48a** was oxidized with TEMPO/$NaClO_2$, followed by reaction with PhMgBr to give **49a**. Then, selective oxidation of the benzylic hydroxyl of **49a** using Dess–Martin periodinane followed by Mitsunobu inversion completed the synthesis of (–)-diospongin A (**1**) (Scheme 9).

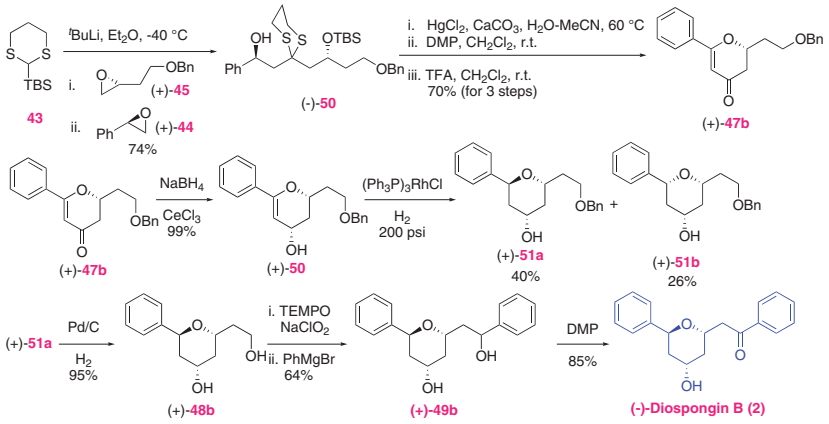
Synthesis of (–)-diospongin B (**2**) was initiated by switching the order of epoxide addition with **43** under the same protocol to afford (–)-**50** in a similar yield to that of the earlier approach. Next, Luche reduction of (+)-**47b** provided alcohol (+)-**50** in high yield. Hydroxyl group-directed hydrogenation of (+)-**50** was performed in the presence of chlorotris(triphenylphosphine)rhodium [$(Ph_3P)_3RhCl$] to give (+)-**51a** in modest yield along with stereoisomer (+)-**51b** as by-product. Finally, the synthesis of (–)-diospongin B (**2**) was completed in four steps from (+)-**51a** (Scheme 10).

Kumaraswamy's Approach (2009)

In 2009, Kumaraswamy et al. demonstrated the enantioselective synthesis of (–)-diospongin A (**1**) and *ent*-diospongin A (**3**) from achiral starting materials.[19] The synthesis commenced with the asymmetric hetero-Diels–Alder reaction between Danishefsky's diene **50** and furfuraldehyde **51** in the presence of (*S*)-BINOL/$Ti(O^iPr)_4$ to furnish dihydropyranone **52** (60%, 99.9% ee). Next, compound **52** was treated with phenylboronic acid in the presence of $Rh(cod)_2BF_4$ to obtain the 1,4-addition product **53** in a 95% yield. Reduction of the ketone in **53** was performed with Noyori's catalyst, (*R*,*R*-diamine-Ru catalyst A) to afford alcohol **54** (96%, >99.9% de). The hydroxyl group in **54** was protected as its PMB ether **55** in 98% yield. Next, the furyl group of **55** was subjected to oxidative cleavage followed by esterification and DIBAL-H reduction to provide **56** in 88% yield over three steps. Aldehyde **56** was subjected to Horner–

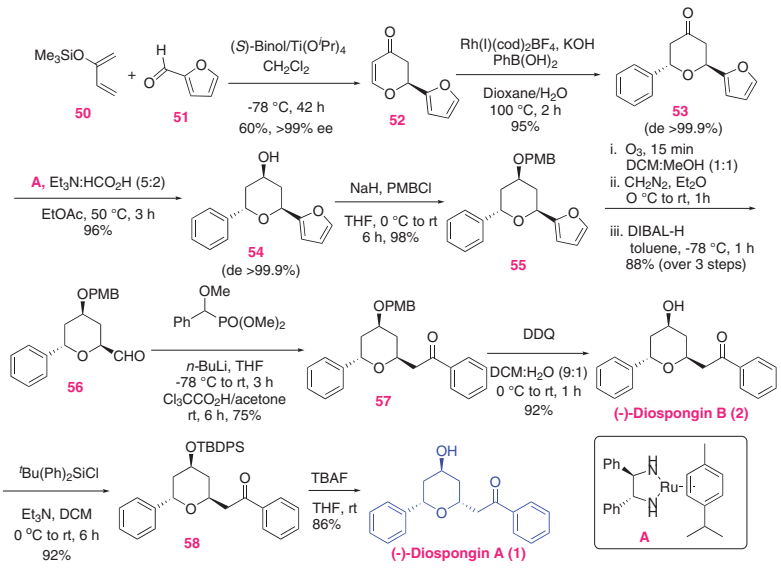


Scheme 9 Synthesis of (–)-diospongin A (**1**) by Xian's approach

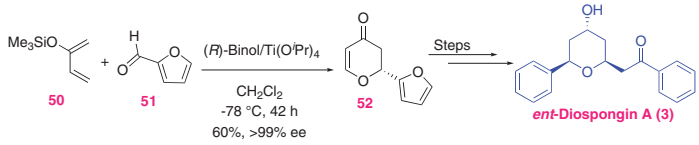


Scheme 10 Synthesis of (–)-diospongin B (**2**) by Xian's approach

Emmons olefination and subsequent hydrolysis of the intermediate enol ether to provide **57** in 75% yield. Finally, **57** was converted into (–)-diospongin B (**2**) using DDQ in 92% yield. Furthermore, the C-5 hydroxyl group of (–)-diospongin B (**2**) was protected as its TBDPS ether to furnish **58**. Unexpectedly, deprotection of the TBDPS group of **58** with excess TBAF furnished (–)-diospongin A (**1**) in 86% yield (Scheme 11). Similarly, *ent*-diospongin A (**3**) was obtained from the hetero-Diels–Alder reaction between Danishefsky's diene **50** and furfuraldehyde **51** in the presence of (*R*)-BINOL/Ti(O^iPr)$_4$ followed by a similar sequence of reactions (Scheme 12).



Scheme 11 Synthesis of (–)-diospongin A (**1**) by Kumaraswamy's approach



Scheme 12 Synthesis of *ent*-(–)-diospongin A (**3**) by Kumaraswamy's approach

Hashimoto's Approach (2010)

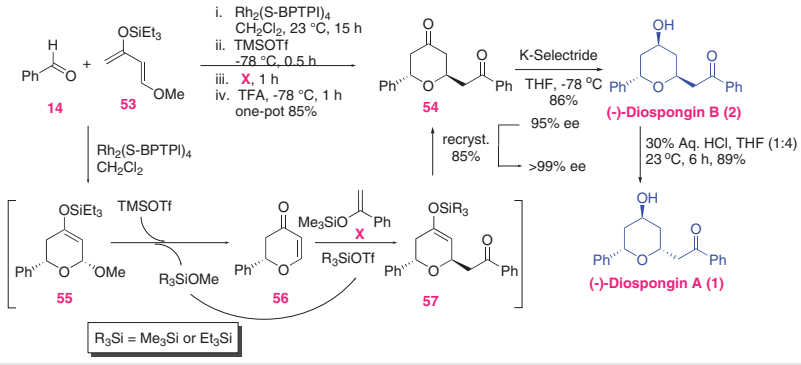
In 2010, Hashimoto et al. demonstrated the preparation of (–)-diospongin A **1** and B **2** using sequential enantioselective hetero-Diels–Alder and TMSOTf-catalysed Mukaiyama–Michael reactions as a key steps.[20] Initially the HDA reaction between Danishefsky's diene (**53**) and benzaldehyde (**14**) was performed in the presence of [Rh_2(S-BPTPI)$_4$] and subsequently the reaction mixture was treated with TMSOTf at –78 °C to obtain the dihydropyranone **56**. Next, the reaction mixture was treated with silyl enol ether **X** to provide **54** (85%, 95% *ee*). Finally, (–)-diospongin B (**2**) was obtained by chemo- and stereoselective reduction of **54** with K-Selectride as a single diastereomer in 86% yield. Furthermore, (–)-diospongin A (**1**) was obtained from (–)-diospongin B (**2**) in 89% yield by using 30% hydrochloric acid (Scheme 13).

Meshram's Approach (2011)

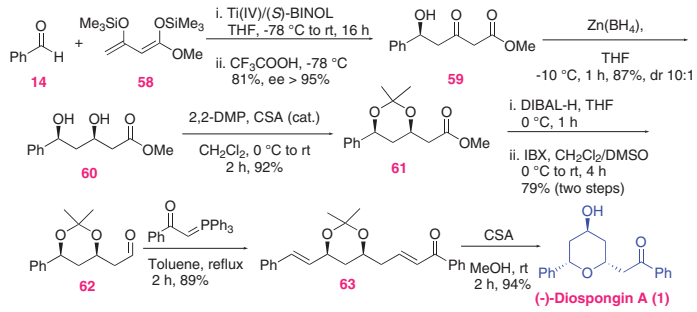
In 2011, Kumar and Meshram executed the synthesis of (–)-diospongin A (**1**) using the enantioselective Mukaiyama aldol reaction, diastereoselective reduction of δ-hydroxy-β-keto ester, and intramolecular oxa-Michael reaction as key steps.[21] The synthesis started with stereoselective Mukaiyama aldol reaction between Chan's diene **58** and PhCHO **14** in the presence of Ti(O^{i}Pr)$_4$/(*S*)-BINOL (1:1) to obtain the aldol product **59** (81%, >95% ee). Next, δ-hydroxy-β-keto ester **59** was reduced selectively using Zn(BH$_4$)$_2$ to obtain the *syn*-1,3-diol **60** (87%, *syn*/*anti* 10:1). Subsequently, 1,3-*syn*-diol **60** was protected as its acetonide followed by DIBAL-H reduction and *ortho*-iodoxybenzoic acid (IBX) oxidation to provide aldehyde **62** in 79% yield over two steps. Finally, (–)-diospongin A (**1**) was obtained from aldehyde **62** by Wittig olefination and one-pot deprotection–cyclization in the presence of CSA in good overall yield (Scheme 14).

Piva's Approach (2011)

In 2011, Piva's group demonstrated the synthesis of diospongin A homologues using Prins cyclization, Mitsunobu inversion, cross-metathesis, and Wacker oxidation as key steps.[22] Initially, hepta-1,6-dien-4-ol (**64**), was subjected to Prins cyclization with benzaldehyde in the presence of trifluoroacetic acid, followed by methanolysis to furnish the *syn*,*syn*-diastereomer **65** in high yield. Next, cross-metathesis was performed with **65** and styrene in the presence of Grubbs' catalyst (G-II) to prepare **66** in 68% yield, and **66** was subjected to Wacker oxidation to produce **67a** and **68a** (Scheme 15). Similarly, diospongin A homologues were prepared from **70** by Mitsunobu reaction to prepare **71** in 88% yield. A similar set of reactions was performed on unsatu-

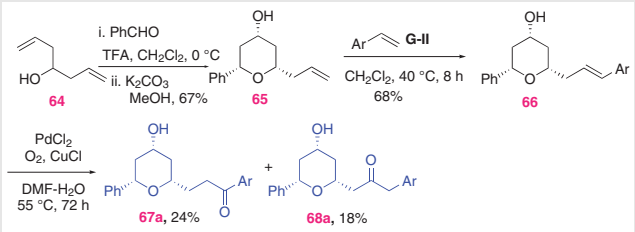


Scheme 13 Synthesis of (–)-diospongins A and B by Hashimoto's approach



Scheme 14 Synthesis of (–)-diospongin A (**1**) by Meshram's approach

rated tetrahydropyranol **71** with styrene cross-metathesis, followed by Wacker oxidation to provide both homologues **67a** and **67b** (Scheme 16).



Scheme 15 Synthesis of THP homologues by Piva's approach

Reddy's Approach (2011)

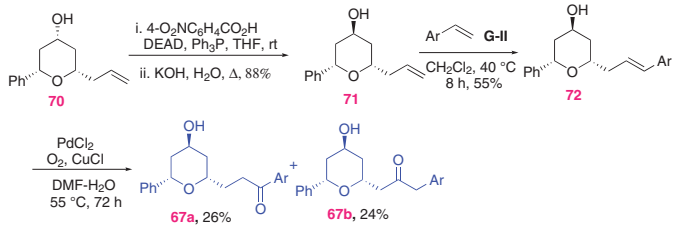
In 2011, Reddy et al. synthesized *ent*-diospongin A (**3**) by intramolecular oxa-Michael addition, Mitsunobu reaction, and hydrogenation as key steps.[23] The synthesis commenced with the hydroxy-Weinreb amide **74**, which could be prepared from L-malic acid in three steps.[24] Weinreb amide **74** was then treated with phenylacetylene in the presence of *n*-BuLi to form β-hydroxyalkynone **75**. Next, compound **75** was converted into dihydropyranone **76** in 85% yield by treating with AgOTf. Compound **76** was subjected to hydrogenation in the presence of palladium on charcoal to form *cis*-tetrahydropyranol **77**, which was subjected to Mitsunobu esterification followed by TBDPS deprotection to give benzoate **79** in 80% yield. Oxidation of the alcohol group in **79** with Dess–Martin periodinane gave the corresponding aldehyde, followed by Wittig reaction to provide tetrahydropyranol **30b** (1:9 *E*/*Z*). However, hydrolysis of the benzoate ester also occurred during Wittig reaction under the basic conditions. Finally, *ent*-diospongin A (**3**) was obtained by Wacker oxidation of **30b** in 52% yield (Scheme 17).

Taylor's Approach (2013)

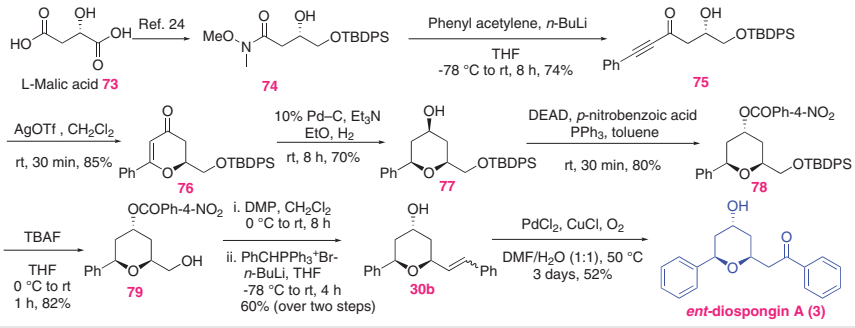
In 2013, Taylor's group demonstrated the synthesis of (–)-diospongins A (**1**) and B (**2**) by using second-generation activation conditions for ether transfer as a key step.[25] Accordingly, 2-bromoethoxymethyl ether **80** was converted into *syn*-1,3-diol mono ether **81** by activating with NIS/1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidative cleavage with *m*-CPBA. Next, conjugate addition of **81** to phenyl ketone afforded the vinylogous ester **82** in 85% yield. Finally, (–)-diospongin A (**1**) was obtained by reductive deprotection of the 2-bromoethyl ether in 75% yield. For the synthesis of (–)-diospongin B (**2**), compound **83** was prepared from **81** through alkylation with diazomethylsulfonyltoluene in a 66% yield. Next, the sulfonyl pyran was treated with lithium bis(trimethylsilyl)amide followed by treatment with aluminum chloride, in the presence of TBS-enol ether, and zinc-mediated deprotection to obtain (–)-diospongin B (**2**; Scheme 18).

Meruva's Approach (2014)

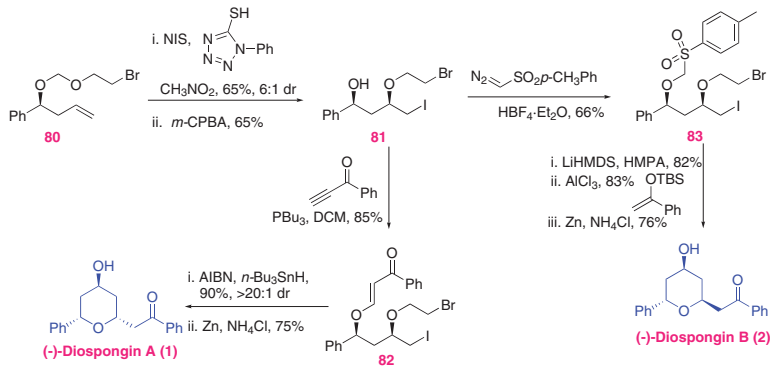
In 2014, Meruva et al. accomplished the synthesis of *ent*-diospongin A (**3**) and *epi*-diospongin B (**6**) with Julia–Kocienski olefination, Weinreb amide formation, and



Scheme 16 Synthesis of diospongin A homologues by Piva's approach



Scheme 17 Synthesis of *ent*-diospongin A (**3**) by Reddy's approach

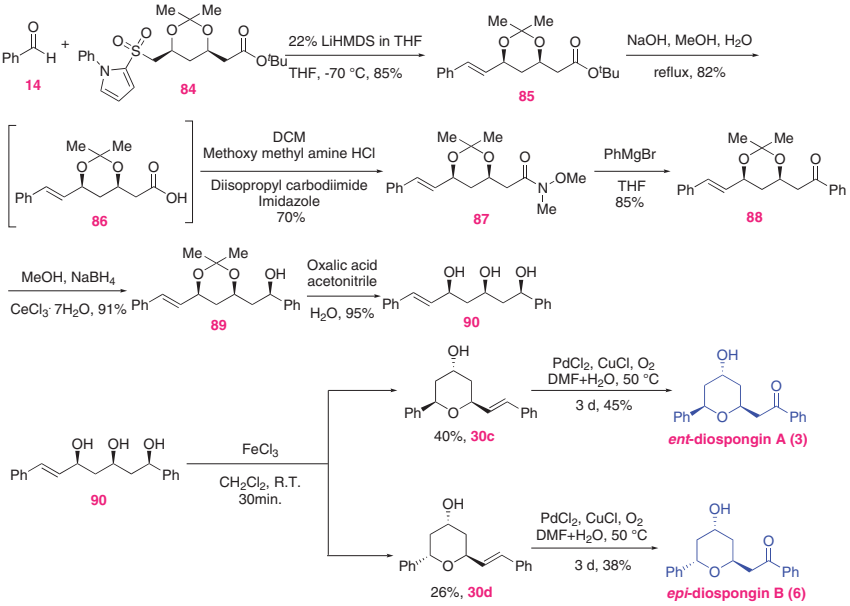


Scheme 18 Synthesis of (–)-diospongin A (**1**) and B (**2**) by Taylor's approach

Wacker oxidation as key steps.[26] The synthesis commenced from sulfone **84** with Julia–Kocienski olefination with benzaldehyde **14** to obtain olefin ester **85** as a 92:8 mixture of *E*/*Z*diastereomers. This diastereomeric mixture **85** was subjected to ester hydrolysis, followed by formation of Weinreb amide **87**. Next, compound **87** was treated with phenyl Grignard reagent to obtain benzoyl derivative **88** in an 85% yield. Reduction of **88** was performed under Luche conditions to provide alcohol **89**, followed by acetonide deprotection to give triol **90**, which was treated with $FeCl_3$ to furnish cyclized products **30c** (40%) and **30d** (26%), which were separated by column chromatography. Finally, *ent*-diospongin A (**3**) and *epi*-diospongin B (**4**) were obtained from **30c** and **30d**, respectively, by Wacker oxidation (Scheme 19).

Fall's Approach (2015)

The synthesis of (–)-diospogin A (**1**) and *ent*-diospongin A (**3**) was demonstrated by Fall et al. from *tri*-*O*-acetyl-D-glucal, by using copper-catalysed Michael addition of phenyllitium.[27] Initially, compound **92** was synthesized from **91** in two steps. Next, **92** was subjected to PDC-mediated oxidation to form α,β-unsaturated ketone **93** followed by copper-catalysed Michael addition of PhLi, to give diastereomeric ketones **94a** and **94b**. The ketone group of **94a** was reduced selectively using L-Selectride to give alcohol **95a** followed by subsequent protection to give MOM ether **96** in 90% yield. Next, compound **96** was converted into **101a** by protection and deprotection steps. Alcohol **101a** was converted into nitrile **102a** by tosylation followed by tosylate displacement with sodium cyanide in quantitative yield. Nitrile **102a** was reduced with DIBAL-H followed by

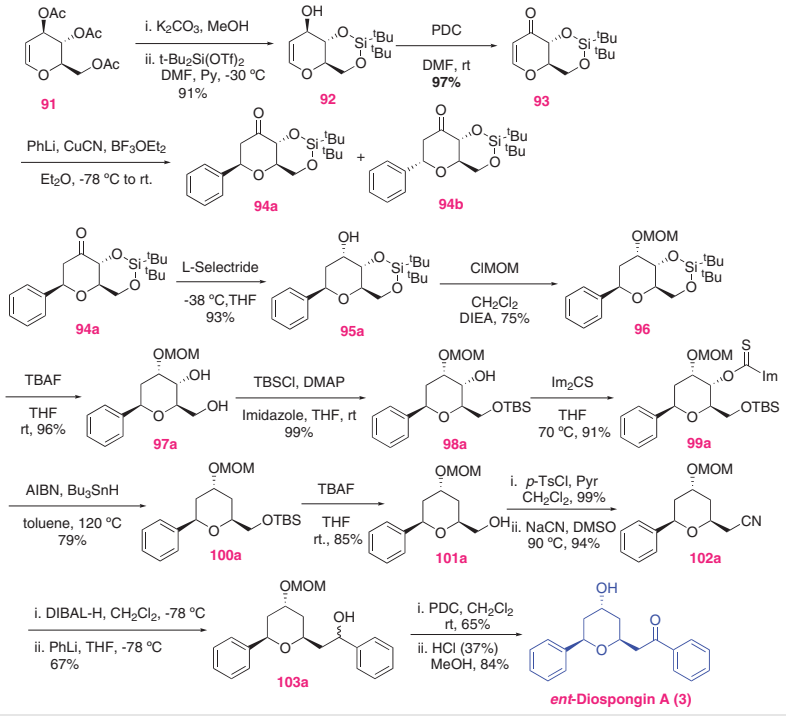


Scheme 19 Synthesis of *ent*-diospongin A (**3**) and *epi*-diospongin B (**6**) by Meruva's approach

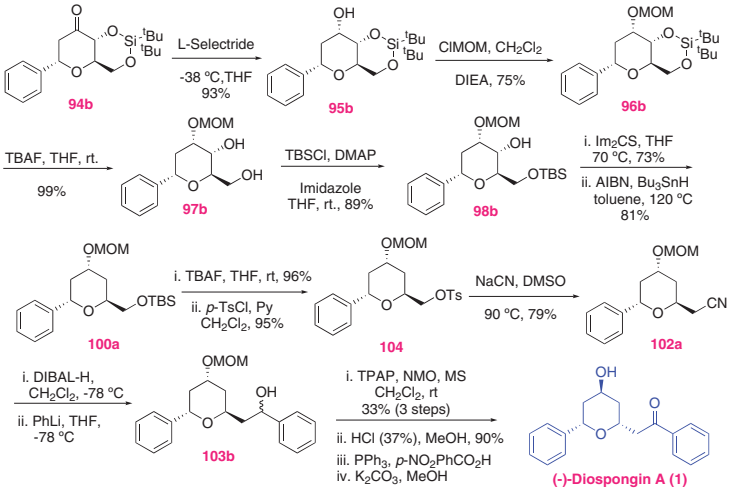
PhLi addition to furnish alcohol **103a** in 67% yield over the two steps. Finally, *ent*-diospongin A (**3**) was obtained from alcohol **103a** by PDC-mediated oxidation followed by MOM deprotection (Scheme 20). Similarly, (–)-diospongin A (**1**) was also prepared by using a similar sequence of reactions from ketone **94b** (Scheme 21).

Hall's Approach (2015)

In 2015, Hall's group demonstrated the synthesis of (–)-diospongin B using Suzuki–Miyaura cross-coupling and inverse-electron demand oxa [4+2] cycloaddition as key steps.[28] The synthesis started with the preparation of **107** using inverse-electron demand oxa [4+2] cycloaddition in 77% yield (96% ee). Next, selective epoxidation of **108** was performed in the presence of *m*-CPBA, to form **109** in a 70% yield (13:1). The epoxide ring was opened with DIBAL-H



Scheme 20 Synthesis of *ent*-diospongin A (**3**) by Fall's approach



Scheme 21 Synthesis of (–)-diospongin A (**1**) by Fall's approach

followed by hydroxyl group protection as its TES ether **111** in 72% yield for two steps. Finally, synthesis of (–)-diospongin B (**2**) was completed by Mukaiyama-type addition of **112** with **111** followed by TES group removal in 66% yield over two steps (Scheme 22).

Clarke's Approach (2016)

In 2016, Clarke et al. demonstrated the synthesis of (–)-diospongin B (**2**) using the Maitland–Japp reaction as a key step.[29] Accordingly, the synthesis commenced with dihydropyran formation **114** using the Maitland–Japp reaction in the presence of the dimethylacetal of *N,N*-dimethyl formamide (97%), followed by conjugate addition of Ph_2CuLi to give **115** in 91% yield. Next, decarboxylation was performed under microwave conditions to provide the required tetrahydropyran-4-one, which was further reduced with L-Selectride to form THP **30c** as the major diastereomer (9:1). Finally, (–)-diospongin B (**2**) was obtained from **116** by MOM protection and Wacker oxidation followed by MOM deprotection (Scheme 23).

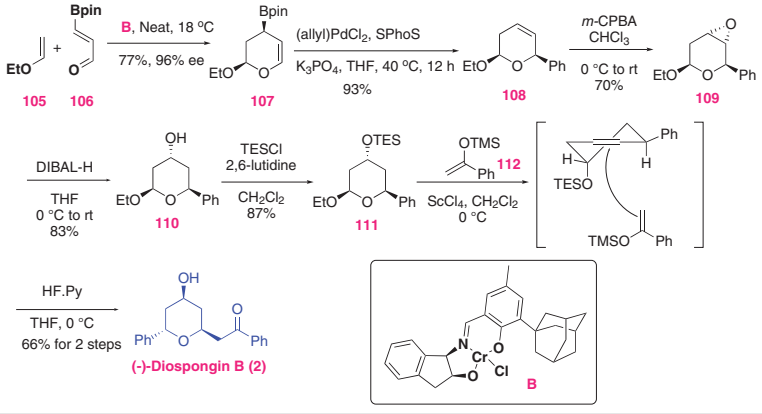
Prasad's Approach (2020)

In 2020, Vaithegi and Prasad executed the synthesis of (–)-diospongin A isomers using vinylogous a Mukaiyama aldol reaction and *oxa*-Michael addition reaction as key steps.[30] The synthetic sequence commenced with the Nagao acetate aldol reaction of benzaldehyde with **117** to give aldol products (**118a** and **118b**). Next the β-alkoxy aldehyde **120** was prepared from the aldol product **118a** by hydroxyl protection followed by DIBAL-H reduction. Subsequently, Mukaiyama aldol reaction of the aldehyde **120** with the silyl enol ether of allyl phenyl ketone afforded the mono silyloxy protected diol **121** in 71% yield, as an inseparable mixture of diastereomers (77:23) and the diol **122** in 14% yield (79:21). Reaction of the alcohol **121** with camphor sulfonic acid resulted in smooth deprotection of the TES group and this was followed by oxa-Michael reaction, affording (–)-diospongin A (*ent*-**3**) in 18% yield and 5-*epi*-diospongin A (5-*epi*-*ent*-**5**) in 66% yield. Similarly, the same products were obtained from **122** in the presence of TFA. Furthermore, Mitsunobu inversion of 5-*epi*-*ent*-**5** afforded *ent*-diospongin A (*ent*-**3**) in 67% yield (Scheme 24).

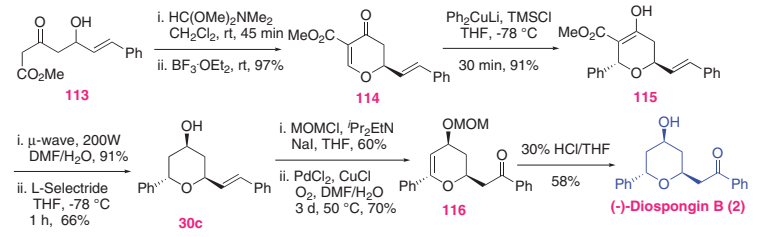
Synthesis of Racemic Diospongins

Piva's Approach (2007)

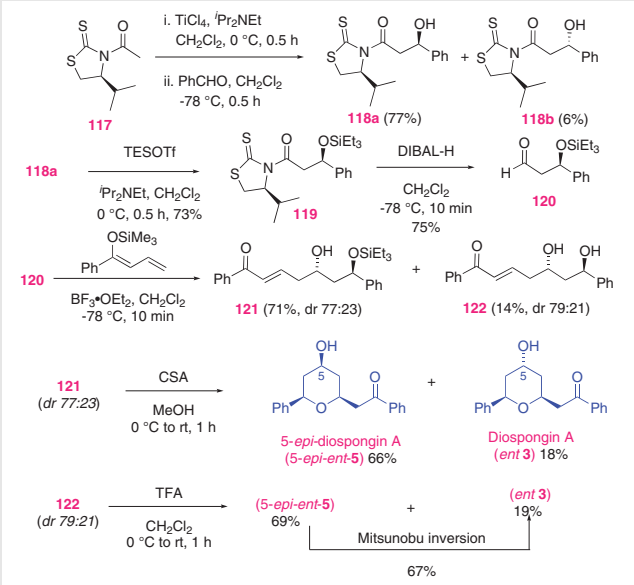
In 2007, the Piva group demonstrated the synthesis of (±)-diospongin A (**7**) using a Prins cyclization and Mitsunobu reaction as key steps.[31] The key intermediate homoallylic alcohol **125** was prepared from benzaldehyde **14** using two allylation reactions, followed by selective oxidation of the benzylic alcohol **124**. Next, the homoallylic alcohol **125** was



Scheme 22 Synthesis of (–)-diospongin B (**2**) by Hall's approach

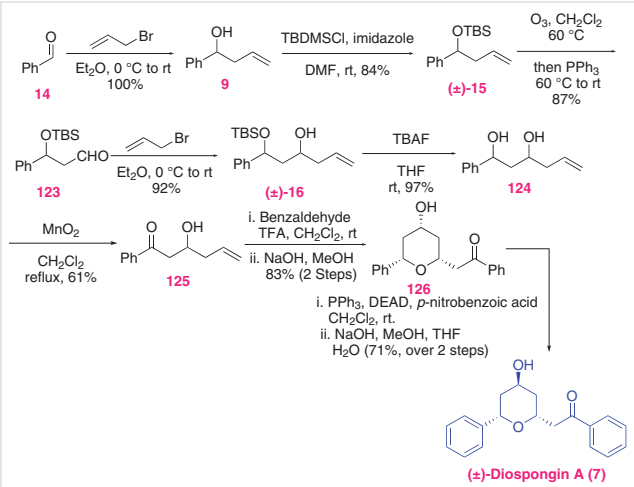


Scheme 23 Synthesis of (–)-diospongin B (**2**) by Clarke's approach



Scheme 24 Synthesis of diospongin isomers by Prasad's approach

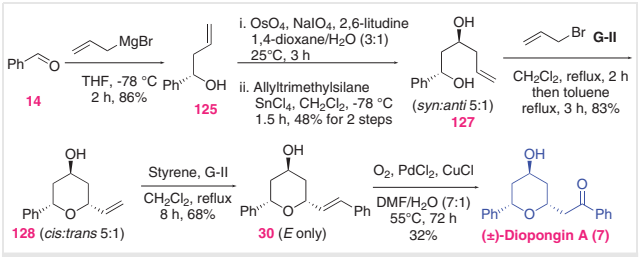
subjected to Prins reaction with benzaldehyde in the presence of TFA to give the tetrahydropyran, which was subjected to hydrolysis to furnish alcohol **126**, an epimer of diospongin A, in 83% yield over the two steps. Next, (±)-diospongin A (**7**) was obtained from **126** using a Mitsunobu inversion in 71% yield over two steps (Scheme 25).



Scheme 25 Synthesis of (±)-diospongin A (**7**) by Piva's approach

Hong's Approach (2009)

In 2009, Hong's group explored a tandem cross-metathesis and thermal S_N2' approach to prepare (−)-diospongin A (**7**) without using protecting groups in the synthetic sequence.[32] Initially allyl Grignard reagent was added to benzaldehyde to give the corresponding homoallylic alcohol **125** in 86% yield. Next, alkene **125** was subjected to oxidative cleavage to give the aldehyde and subsequent treatment with allyltrimethylsilane provided 1,3-diols **127** (*syn*/*anti* 5:1) that were separated by column chromatography. The tandem cross-metathesis and S_N2' sequence was performed with 1,3-*syn*-diol **127** and allylbromide using Grubbs' catalyst (**G-II**) to afford the 4-hydroxy-2,6-*cis*-tetrahydropyran **128** (5:1 dr, 83%). Finally, (±)-diospongin A (**7**) was obtained by a cross-metathesis reaction of **128** with styrene followed by carbonyl group introduction by a Wacker reaction (Scheme 26).



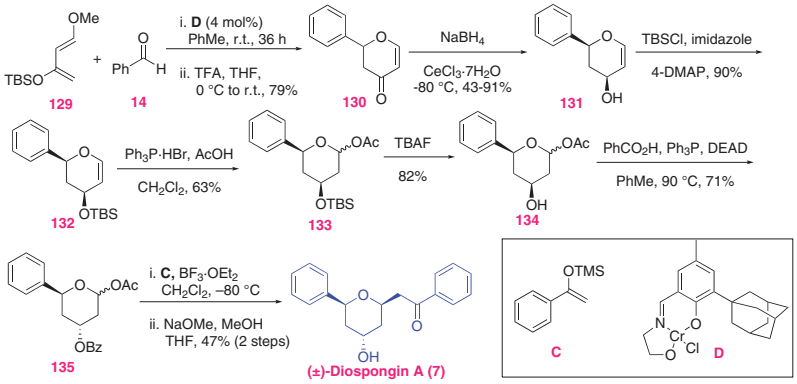
Scheme 26 Synthesis of (±)-diospongin A (**7**) by Hong's approach

More's Approach (2010)

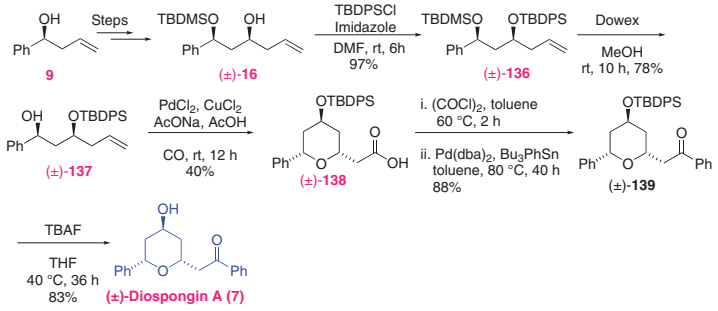
In 2010, More demonstrated the synthesis of (±)-diospongin A (**7**) using hetero-Diels–Alder reaction and an anchimeric assistance-controlled *C*-glycosylation as key steps.[33] Accordingly, the [4+2] cycloaddition of diene **129** and benzaldehyde **14** was performed in the presence of achiral chromium catalyst **D** to provide **130** in 79% yield. Next, **130** was subjected to Luche reduction to furnish alcohol **131** as a single isomer. The C-5 hydroxyl group was protected as its TBS ether **132**, followed by acetoxylation gave **133** as a mixture of anomers (13:1). The TBS group in **133** was removed, followed by esterification under Mitsunobu conditions to give the epimeric benzoate **135**. Finally, (±)-diospongin A (**7**) was obtained from **135** by treating with enol silane **C** and $BF_3{\cdot}OEt_2$ followed by deacylation in 47% yield over two steps (Scheme 27).

Gracza's Approach (2011)

In 2011, Gracza and co-workers explored an approach using palladium (II)-catalysed intramolecular hydroxycarbonylation and Stille coupling as key steps.[34] The key *syn*-diol **136** was prepared from the homoallylic alcohol **16** by a series of simple protection and deprotection steps. Next, the allylic alcohol was protected as its TBDPS ether, followed by selective cleavage of the TBDMS group with acidic Dowex to afford **137** in 76% yield over two steps. Compound **137** was subjected to hydroxycarbonylation using carbon monoxide in acetic acid, providing exclusively the 2,6-*cis*-diastereomer **138** in 40% yield. Subsequently, carboxylic acid **138** was converted into (±)-diospongin A (**7**) in a three-step sequence (Scheme 28).



Scheme 27 Synthesis of (±)-diospongin A (**7**) by More's approach



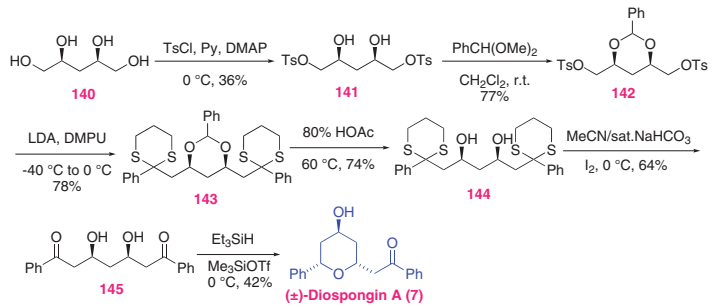
Scheme 28 Synthesis of (±)-diospongin A (**7**) by Gracza's approach

Ho's approach (2012)

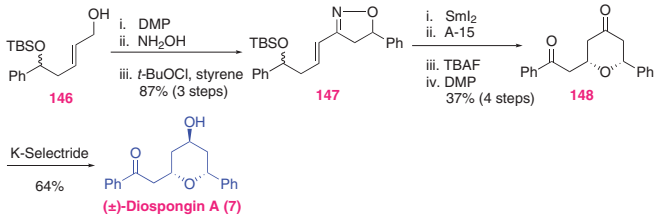
In 2012, the group of Ho synthesized (±)-diospongin A (**7**) by desymmetric cyclization and reduction of a *meso*-1,7-diarylheptanoid as key steps.[35] Initially, ditosylate **141** was prepared from **140** in 36% yield. Next, the two hydroxyl groups were protected as the benzaldehyde dimethyl acetal to give **142** in a 77% yield. After this, compound **142** was treated with 2-lithio-2-phenyl-1,3-dithiane to give **143** in 78% yield. Finally, (±)-diospongin A (**7**) was obtained from **143** by debenzylidenation, desulfurization, and cyclization (Scheme 29).

Tong's Approach (2013)

In 2013, Tong's group demonstrated the synthesis of (±)-diospongin A (**7**) using an efficient 4-step [3+2+1] strategy.[36] Initially allylic alcohol **146** was converted into α,β-unsaturated isoxazoline **147** through a three-step sequence of Dess–Martin oxidation, oxime formation, and [3+2]-cycloaddition with styrene. Next, isoxazoline **147** was subjected to chemoselective ring-opening with SmI_2, followed by intramolecular 6-*endo*-*trig*-oxa-Michael cyclization to obtain tetrahydropyran-4-one **148**. Finally, (±)-diospongin A (**7**) was obtained from **148** by desilylation, Dess–Martin oxidation and chemoselective reduction with K-selectride in 20% overall yield (Scheme 30).



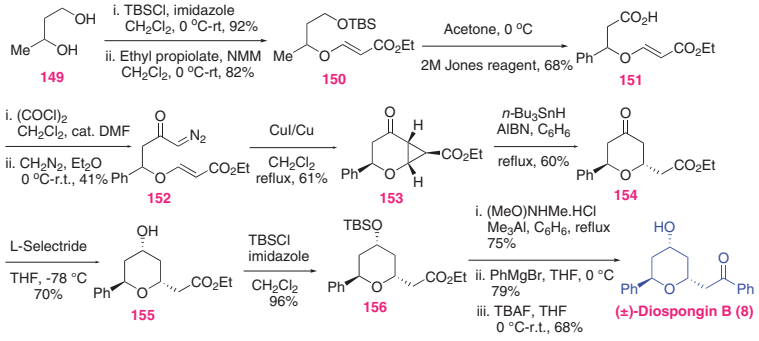
Scheme 29 Synthesis of (±)-diospongin A (**7**) by Ho's approach



Scheme 30 Synthesis of (±)-diospongin A (**7**) by Tong's approach

Gharpure's Approach (2015)

In 2015, the Gharpure group executed the synthesis of (±)-diospongin B using a stereoselective intramolecular cyclopropanation of a vinylogous carbonate with carbene using a copper catalyst as the key step.[37] The approach commenced with selective protection of the primary alcohol of butane-1,3-diol (**149**), as its TBS ether, followed by addition of the secondary alcohol to ethyl propiolate using *N*-methyl morpholine (NMM), to provide the vinylogous carbonate **150**. Next **150** was converted into acid **151** using Jones' reagent by simultaneous protodesilylation, followed by oxidation, in 68% overall yield. Subsequently, acid **151** was converted into diazo ketone **152** by reaction with oxalyl chloride, followed by reaction with diazomethane, in 41% yield over two steps. Compound **152** was then converted into donor-acceptor cyclopropane **153**, the regioselective ring-opening reaction of which was performed in the presence of n-Bu_3SnH and AIBN to give pyranone **154**. The keto group in **154** was selectively reduced with L-Selectride to obtain the alcohol **155** (d.r. 19:1), followed by TBS protection to afford ester **156**. Finally, (±)-diospongin B (**8**) was obtained by converting the ester into the Weinreb amide, phenyl Grignard addition, and deprotection of TBS (Scheme 31).



Scheme 31 Synthesis of (±)-diospongin B (**8**) by Gharpure's approach

Table 1 Comparison of the Total Syntheses of Diospongin

Year	Molecule	Research Group	Key steps	No of steps	Overall Yield (%)
Chiral Approaches					
2005	(–)-Diospongin B	Chandrasekhar	Keck asymmetric allylation, intramolecular oxy-Michael reaction	7	20
2006	(–)-Diospongin A	Cossy	enantioselective allyltitanation, cross-metathesis, intramolecular oxy-Michael reaction	6	29
2006	(–)-Diospongin A (–)-Diospongin B	Jennings	stereoselective reduction of the oxocarbenium cation	8 8	49 27
2007	(–)-Diospongin A (–)-Diospongin B	Uenishi	CBS reduction, Brown allylation, Wacker oxidation	12 13	13 11
2007	(–)-Diospongin A	Yadav	Prins cyclization, enzymatic kinetic resolution	7	22

Year	Molecule	Research Group	Key steps	No of steps	Overall Yield (%)
2007	(–)-Diospongin A	Bates	cross-metathesis, intramolecular Michael addition	8	34
2008	(–)-Diospongin A (–)-Diospongin B	Sabitha	Keck allylation, stereoselective reduction, intramolecular oxy-Michael reaction, Wittig olefination	7 7	26 26
2008	(–)-Diospongin A (–)-Diospongin B	Xian	Linchpin coupling, Luchi reduction, Mitsunobu inversion	12 10	29 10
2009	(–)-Diospongin A *ent*-Diospongin A	Kumaraswamy	hetero-Diels–Alder reaction, asymmetric reduction	11 11	26 26
2010	(–)-Diospongin A (–)-Diospongin B	Hashimoto	hetero-Diels–Alder and Mukaiyama–Michael reaction	6 5	65 73
2011	(–)-Diospongin A	Meshram	Mukaiyama aldol reaction, intramolecular oxa-Michael reaction	8	43
2011	Diospongin A analogues	Piva	Prins cyclization, cross-metathesis, Wacker oxidation	4 6	16 8
2011	*ent*-Diospongin A	Reddy	intramolecular oxa-Michael addition, Mitsunobu reaction, hydrogenation	12	4
2013	(–)-Diospongin A (–)-Diospongin B	Taylor	second-generation activation conditions for ether transfer	8 8	18 12
2014	*ent*-Diospongin A *epi*-Diospongin B	Meruva	Julia–Kocienski olefination, Weinreb amide formation, Wacker oxidation	8 8	7 4
2015	*ent*-Diospogin A Diospongin A	Fall	copper-catalyzed Michael addition of phenyllitium	17 17	12 5
2015	(–)-Diospongin B	Hall	Suzuki–Miyaura cross-coupling, inverse-electron demand oxa[4+2] cycloaddition	7	24
2016	(–)-Diospongin B	Clarke	Maitland–Japp reaction	8	13
2020	(+)-Diospongin A 5-*epi*-Diospongin A	Prasad	vinylogous Mukaiyama aldol reaction, oxa-Michael addition	6 7	20 14
Racemic Approaches					
2007	(±)-Diospongin A	Piva	Prins cyclization, Mitsunobu reaction	10	23
2009	(±)-Diospongin A	Hong	cross-metathesis, thermal S_N2' reaction	6	7.4
2010	(±)-Diospongin A	More	hetero-Diels–Alder reaction, anchimeric assistance-controlled C-glycosylation	9	11
2011	(±)-Diospongin A	Gracza	intramolecular hydroxycarbonylation, Stille coupling	7	20
2012	(±)-Diospongin A	Ho	desymmetric cyclization, reduction of a *meso*-1,7-diarylheptanoid	6	4
2012	(±)-Diospongin A	Tong	oxa-Michael cyclization, chemoselective reduction	8	20
2015	(±)-Diospongin B	Gharpure	intramolecular stereoselective cyclopropanation of vinylogous carbonates with carbenes using copper catalyst	12	2

Conclusions and Outlook

In conclusion, we have compiled and presented all the synthetic approaches to optically active and racemic diospongins from 2006 to date. All the 26 synthetic approaches have been described in chronological order. Having compared the synthetic routes, we conclude that the routes of Hashimoto (2010)[20] and Jennings (2006)[13] are most efficient in terms of yields and number of steps to furnish chiral diospongin derivatives. However, Piva's approach (2007)[31] seems to be best as a racemic approach.

Conflict of Interest

The author declares no conflict of interest.

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