Synthetic Approaches to Diospongins: A Two Decade Journey

Krishnaji Tadiparthi* 0000-0003-1727-6305
Sourav Chatterjee

Department of Chemistry, CHRIST (Deemed to be University), Hosur Road, Bangalore – 560029, India
krishnaji.tadiparthi@christuniversity.in

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-2H-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,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.

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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
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 allylic 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 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).
In 2006, Sawant and Jennings demonstrated the synthesis of (−)-diospongin A and B using stereoselective reduction of an oxocarbenium cation as a key step. 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 Ac₂O to provide 23. Finally, (−)-diospongin B (2) was obtained by reaction of 23 with BF₃·OEt₂ to form the corresponding oxocarbenium cation, followed by concomitant removal of the TES group in 81% yield (Scheme 3).
This approach was also modified to allow the preparation of diospongin A. 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 Et3SiH to furnish TES ether. 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 (-)-diospongin A (1) and B (2) using CBS reduction, Brown allylation, and Wacker oxidation as key steps. The synthesis started from compound 25, which was subjected to Brown allylation using (+)-Ipc 2B-allyl, to furnish 26a in 62% yield along with diastereisomer 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 tril 29a in 94% yield. Next, compound 29a was subjected to cyclization using PdCl2(CH3CN)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. 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-
cine pancreatic lipase (PPL) to produce acetate 33 and alcohol 32a. Next, acetate 33 was hydrolysed using K$_2$CO$_3$ 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. Initially, (S)-phenylbutanol 9 was converted into tert-butyl carbonate 35. Next, compound 35 was converted into epoxy alcohol 37 by iodo-cyclization, followed by methanalysis 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).

**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. 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(OiPr)$_4$ (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 δ-keto ester 40 in 80% yield. The syn-selective reduction of δ-hydroxy-β-keto ester 40 was performed with catecholborane to afford the 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 (–)-diosponge A and B by Sabitha’s approach

Xian’s approach (2008)

In 2008, Xian et al. demonstrated syntheses of diospongins A and B by using Linchpin coupling, Luchi reduction, and Mitsunobu inversion as key steps.\textsuperscript{15} Initially, the Linchpin coupling of TBS dithiane \textsuperscript{43} with epoxides (+)\textsuperscript{44} and (+)\textsuperscript{45} provided the alcohol (–)\textsuperscript{46} in 74\% yield. Next, compound (+)\textsuperscript{46} was subjected to dithiane deprotection, Dess-Martin oxidation, and acidic cyclization to furnish the dihydropyranone (+)\textsuperscript{47a}. Subsequently, compound (+)\textsuperscript{47a} was subjected to Luche reduction followed by hydrogenation, and benzyl group deprotection to afford the diol (–)\textsuperscript{48a}, either in one pot or stepwise. Next, the primary hydroxyl group in (–)\textsuperscript{48a} was oxidized with TEMPO/NaClO\textsubscript{2}, followed by reaction with PhMgBr to give \textsuperscript{49a}. Then, selective oxidation of the benzylic hydroxyl of \textsuperscript{49a} using Dess-Martin periodinane followed by Mitsunobu inversion completed the synthesis of (–)-diospongin A (\textsuperscript{1}) (Scheme 9).

Synthesis of (–)-diospongin B (\textsuperscript{2}) was initiated by switching the order of epoxide addition with \textsuperscript{43} under the same protocol to afford (–)\textsuperscript{50} in a similar yield to that of the earlier approach. Next, Luche reduction of (+)\textsuperscript{47b} provided alcohol (+)\textsuperscript{50} in high yield. Hydroxyl group-directed hydrogenation of (+)\textsuperscript{50} was performed in the presence of chlorotris{triphenylphosphine}rhodium \{[\textsuperscript{3}P\textsubscript{3}]\textsubscript{3}RhCl\} to give (+)-\textsuperscript{51a} in modest yield along with stereoisomer (+)-\textsuperscript{51b} as by-product. Finally, the synthesis of (–)-diospongin B (\textsuperscript{2}) was completed in four steps from (+)-\textsuperscript{51a} (Scheme 10).

Kumaraswamy’s Approach (2009)

In 2009, Kumaraswamy et al. demonstrated the enantioselective synthesis of (–)-diospongin A (\textsuperscript{1}) and \textit{ent}-diospongin A (\textsuperscript{3}) from achiral starting materials.\textsuperscript{19} The synthesis commenced with the asymmetric hetero-Diels–Alder reaction between Danishefsky’s diene \textsuperscript{50} and furfuraldehyde \textsuperscript{51} in the presence of (\textit{S})-BINOL/Ti(OiPr)\textsubscript{4} to furnish dihydropyranone \textsuperscript{52} (60\%, 99.9\% ee). Next, compound \textsuperscript{52} was treated with phenylboronic acid in the presence of Rh(cod)\textsubscript{2}BF\textsubscript{4} to obtain the 1,4-addition product \textsuperscript{53} in a 95\% yield. Reduction of the ketone in \textsuperscript{53} was performed with Noyori’s catalyst, (\textit{R}, \textit{R}-diamine-Ru catalyst A) to afford alcohol \textsuperscript{54} (96\%, >99.9\% de). The hydroxyl group in \textsuperscript{54} was protected as its PMB ether \textsuperscript{55} in 98\% yield. Next, the furyl group of \textsuperscript{55} was subjected to oxidative cleavage followed by esterification and DIBAL-H reduction to provide \textsuperscript{56} in 88\% yield over three steps. Aldehyde \textsuperscript{56} was subjected to Horner–
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(OiPr)4 followed by a similar sequence of reactions (Scheme 12).
Hashimoto’s Approach (2010)

In 2010, Hashimoto et al. demonstrated the preparation of (−)-diospongins A and B using sequential enantioselective Mukaiyama–Michael reactions as a key steps. Initially, the HDA reaction between Danishefsky’s diene (53) and benzaldehyde (14) was performed in the presence of [Rh(II)(S-BPTPl)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 (−)-diospongins A and B using the enantioselective Mukaiyama aldol reaction, diastereoselective reduction of δ-hydroxy-β-keto ester, and intramolecular oxa-Michael reaction as key steps. 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)/(-)-BINOL (1:1) to obtain the aldol product 59 (81%, >95% ee). Next, δ-hydroxy-β-keto ester 59 was reduced selectively using Zn(BH4)2 to obtain the syn-1,3-diol 60 (87%, syn/anti 10:1). Subsequently, 1,3-syn-diol 60 was protected as its acetone 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 diosponge A homologues using Prins cyclization, Mitsunobu inversion, cross-metathesis, and Wacker oxidation as key steps. 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, diospongins A homologues were prepared from 70 by Mitsunobu reaction to prepare 71 in 88% yield. A similar set of reactions was performed on unsatu-
rated tetrahydropyranol 71 with styrene cross-metathesis, followed by Wacker oxidation to provide both homologues 67a and 67b (Scheme 16).

**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 dihydroxypropanone 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 (−)-diospongin 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/phenyl-1H-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-ene 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
Wacker oxidation as key steps.\textsuperscript{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 a 85% yield. Reduction of $88$ was performed under Luche conditions to provide alcohol $89$, followed by acetonide deprotection to give triol $90$, which was separated by column chromatography. Finally, ent-diospongin A ($3$) and epi-diospongin B ($6$) were obtained from $30c$ and $30d$, respectively, by Wacker oxidation (Scheme 19).

**Fall’s Approach (2015)**

The synthesis of ($-)$-diospongin 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 phenyllithium.\textsuperscript{27} Initially, compound $92$ was synthesized from $91$ in two steps. Next, $92$ was subjected to PDC-mediated oxidation to form $\alpha,\beta$-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...
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.
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 \(N,N\)-dimethylformamide (97%), followed by conjugate addition of \(\text{Ph}_2\text{CuLi}\) 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 \(\text{L-Selectride}\) to form \(\text{THP} 30\text{c}\) 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 oxo-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 \((118\text{a} \text{ and } 118\text{b})\). Next the \(\beta\)-alkoxy aldehyde \(120\) was prepared from the aldol product \(118\text{a}\) 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 oxo-Michael reaction, affording \((-\)-diospongin A \((\text{ent-3})\) in 18% yield and \(5\text{-epi-diospongin A} (5\text{-epi-ent-5})\) in 66% yield. Similarly, the same products were obtained from \(122\) in the presence of TFA. Furthermore, Mitsunobu inversion of \(5\text{-epi-ent-5}\) afforded \(\text{ent-3}\) in 67% yield (Scheme 24).

**Synthesis of Racemic Diospongins**

**Piva’s Approach (2007)**

In 2007, the Piva group demonstrated the synthesis of \((\pm\)-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
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).

In 2009, Hong’s group explored a tandem cross-metathesis and thermal S<sub>2</sub>’ approach to prepare (-)-diospongin A (7) without using protecting groups in the synthetic sequence. 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<sub>2</sub>’ 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).

More’s Approach (2010)

In 2010, More demonstrated the synthesis of (±)-diospongin A (7) using hetero-Diels–Alder reaction and an achimeric assistance-controlled C-glycosylation as key steps. 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 TBDPS ether, followed by acetoxylation gave 133 as a mixture of anomers (13:1). The TBDPS 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<sub>3</sub>-OEt<sub>2</sub> 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 hydroxy carbonylation and Stille coupling as key steps. 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 hydroxy carbonylation 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).
In 2012, the group of Ho synthesized (±)-diospongin A (7) by desymmetric cyclization and reduction of a meso-1,7-diarylheptanoid as key steps. 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 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).

In 2013, Tong’s group demonstrated the synthesis of (±)-diospongin A (7) using an efficient 4-step [3+2+1] strategy. Initially allylic alcohol 146 was converted into (±)-diospongin A (7) was obtained from 148 by desilylation, Dess–Martin oxidation and chemoselective reduction with K-selectride in 20% overall yield (Scheme 30).
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-Bu3SnH 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).

Table 1  Comparison of the Total Syntheses of Diospongin

<table>
<thead>
<tr>
<th>Year</th>
<th>Molecule</th>
<th>Research Group</th>
<th>Key steps</th>
<th>No of steps</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>(–)-Diospongin B</td>
<td>Chandrasekhar</td>
<td>Keck asymmetric allylation, intramolecular oxy-Michael reaction</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>2006</td>
<td>(–)-Diospongin A</td>
<td>Cossy</td>
<td>enantioselective allyltitanation, cross-metathesis, intramolecular oxy-Michael reaction</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>2006</td>
<td>(–)-Diospongin A (–)-Diospongin B</td>
<td>Jennings</td>
<td>stereoselective reduction of the oxocarbenium cation</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>2007</td>
<td>(–)-Diospongin A</td>
<td>Yadav</td>
<td>Prins cyclization, enzymatic kinetic resolution</td>
<td>7</td>
<td>22</td>
</tr>
</tbody>
</table>
### Conclusions and Outlook

In conclusion, we have compiled and presented all the synthetic approaches to optically active and racemic diosponins 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 diosponin 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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(33) More, J. D. Synthesis 2010, 2419.


