Synthetic efforts on the road to marine natural products bearing 4-O-2,3,4,6-tetrasubstituted THPs: an update

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Scientific literature is inundated with secondary metabolites from marine sources. In this ocean of natural products, the presence of recurring patterns has traditionally led scientists to unravel the biosynthetic mechanisms that naturally yield these products, as well as to imitate Nature to prepare them in the laboratory, especially when promising bioactivities and stimulating molecular architectures are involucrated. For instance, natural products containing multisubstituted oxygenated rings and macrocyclic lactones are recurrently selected as targets for developing total syntheses. Thus, in the last decades a noteworthy number of synthetic works regarding miyakolide, madeirolide A and representative compounds of polycavernosides, lasonolides and clavosolides have come to fruition. Up to now, these families of macrolides are the only marine natural products bearing a tetrasubstituted tetrahydropyran ring with carbon substituents at positions 2, 3 and 6, as well as an oxygen at position 4. Their splendid structures have received the attention of the synthetic community, up to the point of starring in dozens of articles, and even some reviews. This work covers all the synthetic studies towards miyakolide and madeirolide A, as well as the synthetic efforts performed after the previous specialised reviews about lasonolide A, polycavernoside A and clavosolides, published in 2006, 2007 and 2016, respectively. In total, this review summarises 22 articles in which these marine natural products with 4-O-2,3,4,6-tetrasubstituted tetrahydropyrans have the leading role.

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1. Introduction

Mother Nature has been an endless source of inspiration for drug discovery throughout history.1 Over the past decades, natural products (NPs) from marine sources have been progressively catching the attention and interest of the scientific community due to their biological potential.2 Marine NPs show a panoply of molecular scaffolds,3 as a consequence of the biosynthetic pathways implied in their formation.4 Tetrahydropyrans (THPs) and macrocyclic lactones (macrolides) are interesting examples of this structural diversity. On the one hand, macrolides constitute an important subgroup of polyketides, formed in nature from acyl-CoA precursors by polyketide synthases.5 Artificial pathways have also been developed in laboratories worldwide to access these secondary metabolites.6 Pharmacological activities of macrolides are wide-ranging, including antimicrobial, anti-inflammatory, antitumour, antimalarial, and so on.7 On the other hand, THPs are also structural motifs recurrently found in NPs,8 likewise display numerous bioactivities.9 The synthesis of THPs in the laboratory is generally challenging, specially when they are highly substituted. Thus, reviews focusing on the building of THPs in the context of NPs syntheses are recurrently issued.8 Moreover, in last years, several methodological studies concretely targeting 2,3,4,6-tetrasubstituted THPs have also been published.10 For this work, we have directed our attention to marine NPs owning these 2,3,4,6-tetrasubstituted THPs, and besides, restricting our search to those in which the substituent at C4 is an oxygen, either ester, ether or hydroxy group. To the best of our knowledge, only 5 families of compounds come to terms with our baseline, i.e., miyakolide (1), polycavernosides (2), lasonolides (3), clavosolides (4) and madeirolide A (5a) (Fig. 1).

NPs 1–5 have in common a core formed by a macrolactone of, respectively, 16, 13 (or 14 in the case of 2f and 2g), 20, 16 and 21 members. The presence of oxygenated rings such as tetrahydrofurans (THFs) (2a–e and 5a), methylated deoxy sugars (2 and 4) and cyclohexanones (1 and 5a) is also widespread, being our target 2,3,4,6-tetrasubstituted THPs the leitmotif of all of them. These densely substituted THPs also display the C–O bond at the position 4 of the ring, being part of an ether linkage (2, 4 and 5a), the ester group of the macrolide (1) or a hydroxy group (3). Table 1 shows that the molecular weight of representative compounds of these families of macrolides ranges from 676 to 857 g mol$^{−1}$.

Table 1 also illustrates the noteworthy bioactivities exhibited by most of these marine NPs, highlighting the importance of the development of new synthetic pathways to access them in an efficient fashion. Indeed, the irrefutable importance of these metabolites is laid bare by the previously published reviews focusing on syntheses of lasonolide A (3a), polycavernoside A (2a) and clavosolides (4). After their respective releases in 2006, 2007 and 2016, more approaches to these NPs have appeared in the literature, highlighting the everlasting interest of the synthetic community in them. Thus, we compile herein all the new synthetic efforts towards the obtaining of marine macrolides 2–4. Additionally, we gather for the first time all the approaches which tackle the synthesis of 1 and 5a, updating in this way the existing information about syntheses of marine NPs owning 2,3,4,6-tetrasubstituted THPs.

2. Miyakolide

Miyakolide (1) was isolated in 1992 from a sponge of the genus *Polyfibrospongia*, collected in Miyako island (Okinawa Prefecture, Japan).11 NMR and X-ray analyses allowed the characterization of the molecule. It was initially proposed as its enantiomer until absolute configuration was corrected after the total synthesis performed by Evans’ group (vide infra).12 Fig. 1 shows the real miyakolide structure: a 16-membered macrolide bearing three THP rings (A, B and D) in chair conformations, being THP D trans-fused to the cyclohexanone ring C. The tetrasubstituted THP (ring A) is separated from

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THP D via a methylene bridge at C2, and also owns a methyl group at C3, the oxygen of the ester of the macrocyclic structure at C4 and a 2-methylprop-1-en-1-yl group at C6 (Fig. 1). Despite its structural similarity to anti-cancer bryostatins, 16 miyakolide exhibited a weaker in vitro (IC50 17.5 mg mL⁻¹ against P388 mouse leukemia, IC50 17.1 mg mL⁻¹ against A-549 human lung carcinoma cells, and >20 mg mL⁻¹ against HT-29 human colon adenocarcinoma cells) and in vivo (T/C 127% at 800 mg kg⁻¹ against P388 mouse leukemia, and T/C 123% at 400 mg kg⁻¹ against B-16 melanoma) antitumor activities. 11 Curiously, the authors speculate that these differences in bioactivity may be indeed related, among other reasons, with the structure of the tetrasubstituted THP presented by miyakolide. Herein, the ethereal oxygen of this THP is not oriented to the inner of the macrocycle, as occurs with the three THPs of bryostatin-1. 16 This difference may affect the ability of miyakolide to bind cations and, consequently, disrupt its bioactivity. With respect to synthetic works towards 1, the three up-to-date approaches are summarised below, maintaining the original nomenclature of the rings above described (A–D) for clarity.

2.1 Masamune’s contribution (1997) 17

In 1997, Masamune and co-workers presented a synthetic approach to the rings A and D of ent-miyakolide, 17 as an application of the enantioselective anti-aldol tactic previously developed by the same research group. 18 The synthesis of the ring A began with the preparation of the known aldehyde 6, 19 which was submitted to a stereoselective aldol reaction with the enol borinate 7 to provide the anti-aldol 8 (Scheme 1). Cleavage of the chiral auxiliary with LAH provided diol 9, which was transformed into the O-benzylated alcohol 10 in excellent yield. Swern oxidation 20 and subsequent hydrolysis of the acetonide in acidic conditions, followed by an in situ cyclisation, provided the hemiacetal 11 in excellent yield. The selective silylation and PCC oxidation of 11 gave the lactone 12, which was then converted into the aldol adduct 13 by treatment with LiHMDS and EtOAc. The stereoselective reduction of 13 using triethyl silane in the presence of boron trifluoride diethyl etherate (i.e., through the formation of an oxocarbenium ion), furnished the THP 14, which was finally transformed into desired THP 15 via the tandem PDC oxidation/Wittig olefination. Thus, THP A was obtained from 6 after 13 steps with an overall yield of 19%.

| NP | Formula | g mol⁻¹ | Relevant bioactivity |
|----|---------|---------|---------------------|
| 1  | C36H54O12 | 678.36  | Antitumour: IC50 17.5 mg mL⁻¹ (P388 mouse leukaemia), 17.1 mg mL⁻¹ (A549 human lung carcinoma cells)¹¹ |
| 2a | C43H68O15 | 824.46  | Toxin: LC₅₀ 0.2–0.4 mg kg⁻¹ in mice¹² |
| 3a | C41H60O9  | 696.42  | Antitumour: IC₅₀ 2.0 mg mL⁻¹ (P388 mouse leukaemia), 40 ng mL⁻¹ (A549 human lung carcinoma cells)¹³ |
| 4a | C44H72O16 | 856.48  | No cytotoxic or antiproliferative activities described |
| 5a | C37H56O11 | 676.38  | Antifungal: MIC 12.5 µg mL⁻¹ (Candida albicans)¹⁴ |
Regarding the synthesis of the precursor of the ring D, it commenced with the stereoselective formation of the anti-aldol 18, treating the aldehyde 16 with the borinate 17 (Scheme 2).

Then, the aldol 18 was converted into acetonide 19, after removal of the chiral auxiliary and protection as acetonide of the resulting diol. Selective deprotection of 19 followed by an Appel reaction gave the chlorinated compound 20, which then underwent to an asymmetric Sharpless dihydroxylation to afford the chlorohydrin 21. Finally, the epoxidation of 21 followed by TBS protection gave the targeted compound 22 with an overall yield of 24% (8 steps from 16).

2.2 Evans’ synthesis (1999)15
The first total synthesis of the originally proposed structure of miyakolide (ent-1) was reported by Evans and co-workers in 1999. They envisioned the construction of the NP in a convergent fashion by means of the assembly of three different fragments (Scheme 3). Astonishingly, the three synthons (with minimal structural differences indicated as R1 and R2, see Scheme 3) were successfully assembled via the same three reactions in different order: aldol addition, [3 + 2] dipolar cycloaddition and esterification.

The synthetic route towards THPs 31a and 31b (future ring B) started with the keto alcohol 24, previously obtained from the epoxide 23 in five steps via addition of allyl magnesium bromide, protection of the resulting secondary alcohol as PMB ether, trityl deprotection, Swern oxidation and Chan’s diene addition (Scheme 4). Then, the stereoselective reduction of the keto group of 24 afforded a syn diol which was protected as acetonide prior to the DIBAL-H reduction of the ester group to yield aldehyde 25. Addition of chiral auxiliary 26 to aldehyde 25 via Evans aldol protocol yielded diastereoselectively the aldol adduct, which was subsequently oxidised to give the β-ketoimide 27. THP 28 was furnished from 27 via acidic deprotection, in situ cyclisation and Swern oxidation. Peterson–Yamamoto olefination of 28 conducted quantitatively to the exocyclic olefin 30, which was finally transformed to 31a (R = TIPS) through auxiliary hydrolysis, osmium-catalysed dihydroxylation of the terminal olefin, periodate cleavage and O-silylation (15% overall yield after 17 steps from 23). Alternatively, 31b (R = Bn) was synthesised from 30 via hydrolysis, benzylation, hydroxylation and treatment with periodate (24% overall yield after 17 steps from 23).

The approach to the region of future rings C and D started with the preparation of the fragments 35a and 35b via the cleavage of the chiral auxiliary in 32 to give a primary alcohol which was oxidised to the corresponding aldehyde and submitted to olefination to yield dibromoalkene 33 (Scheme 4). Then, secondary alcohol 34 was obtained via successive ester cleavage, elimination of the dibromoalkene, N-acylation of the
acyl chloride using lithiated (4S)-benzyl-oxazolidin-2-one, and aldol addition. Subsequent oxidation of 34 delivered compound 35a (32% after 9 steps), whereas O-silylation yielded 35b (31% after 9 steps). Synthesis of the tetrasubstituted THP 39 (future ring A) was achieved in 13 steps starting from commercially available (R)-4-(benzyloxy)-3-methylbutan-2-one and 3-methylbut-2-enal (Scheme 4). Aldol addition involving these reagents quantitatively yielded aldol 36. It was transformed into the key intermediate compound 37 after six steps: anti reduction, di-silylation of the diol, deprotection and oxidation of the primary alcohol, Horner–Wadsworth–Emmons (HWE) homologation26 and removal of the protecting silyl groups. Cyclisation under basic condition of 37 gave THP 38 in excellent yield though with low diastereoselectivity (dr 60 : 40).

This setback was resolved protecting the epimeric mixture as silyl ethers and submitting them again to the base-mediated cyclisation (dr > 95 : 5). Then, desired THP 39 was obtained via reduction, bromination and nitration27 (33%, 13 steps from commercial starting materials).

Evans’ group designed fragments 31, 35 and 39 to be interconnected through any of these three reaction sequences: aldol addition, [3 + 2] dipolar cycloaddition and esterification; cycloaddition, aldol addition and esterification; and aldol addition, esterification and cycloaddition. In all of the cases, compound 40 was the final key intermediate (Scheme 5). Finally, it was submitted to N–O bond reduction using Mo(CO)6 (Nitta’s procedure),28 followed by the subsequent treatment with TsOH and DDQ. Thus, they achieved the first total synthesis of ent-1 after 29 linear steps and in 6.8% overall yield in the shortest and most efficient pathway.

2.3 Trost’s contribution (2008)29

In 2008, Trost’s group displayed the synthesis of the miyakolide THPs A and B (according to the original nomenclature).29 As key
reactions for the rings formation, their approach involved the Pd-catalysed alkyne–alkyne coupling\(^{30}\) and the Ru-catalysed alkyne–alkyne coupling\(^{31}\) previously developed by them. The route towards THP B began with the preparation of the compound 42 from bisepoxide 41 through a TMS-acetylide addition followed by TBS protection of the resulting secondary alcohol (Scheme 6). A subsequent addition of lithiated methyl propiolate to epoxide 42 yielded diyne 43. Later, the alkyne–alkyne coupling between 43 and 44 in the presence of Pd(OAc)\(_2\) afforded product 45. Its treatment with PdCl\(_2\)(MeCN)\(_2\) followed by removal of the TMS group yielded 46, a precursor of the ring B of 1 (19% after 6 steps). The synthesis of tetrastubstituted THP A started with the preparation of 49 by Ru-catalysed alkyne–alkyne coupling between 47 and 48 (Scheme 6). Then, treatment of epoxide 49 with Et\(_2\)AlCN provided the allylic alkylation precursor 50, which was submitted to a Pd-catalysed allylic alkylation in the presence of DIPEA and S,S-L to obtain the desired cis isomer 51. Chemoselective epoxidation of 51\(^{32}\) followed by cleavage with HIO\(_4\) afforded the pyranone 52. It was transformed into ketone 53 after reduction with NaBH\(_4\), TBS protection and treatment with MeLi/CeCl\(_3\). Finally, cross metathesis using Grubbs II catalyst (54)\(^{33}\) yielded the THP A (55) with an overall yield of 20% after 9 steps.

3. Polycavernosides

*Gracilaria edulis* (also known as *Polycavernosa tsudai*) is an edible red alga of the *Gracilaria* genus, widely used in the gastronomy of the Pacific area. It was the cause of a grave human intoxication suffered in Guam by 13 people in April 1991, of which 3 died after consumption. For the purpose of isolating the involved toxins, Yasumoto’s group collected 2.6 kg of the alga in June 1991, and its extract was purified by mice bioassays guided column chromatography.\(^{34}\) Thus, they isolated 400 µg and 200 µg of two compounds which were named polycavernoside A (2a) and B (2d), respectively (Fig. 1). It was observed that both presented high toxicity on mice, causing less intense but identical symptoms that those previously registered in sick patients (diarrhea, hypersalivation, lachrymation, muscle spasms, and cyanosis).\(^{34}\) The incident rose again the next year in the same season, though at lower levels. Thus, the same group published the isolation and structural determination of polycavernosides A2 (2b), A3 (2c) and B2 (2e) (Fig. 1) from *P. tsudai* collected in 1991 and 1992.\(^{35}\) Further studies about the same extract led to the description of analogues polycavernosides C (2f) and C2 (2g) (Fig. 1).\(^{36}\) The seasonal nature of this phenomenon was laid bare by the identification of 2a as the causative agent of new fatal food poisoning incidents (8 deaths of 36 patients) in the Philippines.\(^{37}\) All these polycavernosides...
differ mainly in the substituents carried by the disaccharide fragment (a fucosyl-xylose), as well as in the hemiacetal THF owned by 2a–e (Fig. 1). However, as part of the same family, they have in common several structural characteristics, such as a conjugated lateral chain contiguous to the macrolide ester and the presence of an all-trans tetrasubstituted THP with the following substituents: at C2 a methylene unit is joined to the carbonyl of the macrocyclic ester, a methyl group at C3, a glycosidic bond at C4 and a keto group connected to C6 via a methylene bridge. It should be now remarked that a new analogue of this family (polycavernoside D) was isolated in 2015 from the marine cyanobacterium Okeania sp.38 Besides some structural changes regarding the other polycavernosides, its THP is pentasubstituted due to an extra methyl group at C3, hence further details exceeds the scope of this review. Nevertheless, it is worth mentioning that this isolation was the first evidence that these macrocyclic toxins are actually cyanobacterial secondary metabolites, what explains the difficulty for reisolating them from algae. Whatever the biosynthetic origin is, it is clear that the toxicity of these products deserves a careful attention. Both polycavernosides A (2a) and B (2d) exhibit a minimal lethal dose in mice of 0.2–0.4 mg kg\(^{-1}\), higher values than some synthetic analogues prepared.32 Pharmacological studies developed with a synthetic derivative of 2a (in which the middle double bond of the lateral triene moiety was replaced by an alkyne group), gave a hint about the mechanism of action of this neurotoxin, suggesting that polycavernosides evokes a cytosolic calcium influx and a membrane potential depolarization.40 Keeping in mind the aforementioned stimulant molecular architecture and potent toxic bioactivities, it was reasonable that synthetic strategies were developed to attain polycavernosides in the laboratory. The first total synthesis of 2a performed by Muraï’s group in 1998 allowed the unambiguous establishment of its absolute stereochemistry.40 After that pioneering work, other synthetic efforts were performed, as reviewed by Paquette and Yotsu-Yamashita in 2007.41 Due to the considerable time interval that has elapsed since then, our intention herein is bringing polycavernosides syntheses up to date.

### 3.1 Markó’s contribution (2009)

Following their previous synthesis of the THP fragment of polycavernoside A (2a) via an intramolecular Sakurai cyclisation,43 Markó and co-workers reported the synthesis of the fragment containing both the 5-membered ring and the triene side chain (Scheme 7).42 At first, starting compound 56 was lithiated and treated with isobutyraldehyde to yield sulphoxide 57 after a double sigmatropic rearrangement. Secondly, chemoselective oxidation of 57 gave sulphone 58. Then, it was treated with n-BuLi and aldehyde 59 to provide the corresponding diol-sulphone, which was selectively protected as benzoyl ester to afford compound 60. A Julia-type 1,6-reductive elimination in the presence of SmI\(_2\) and HMPA furnished the desired triene 61 with an overall yield of 60% after 5 steps.

### 3.2 Lee’s synthesis (2010)

The key feature of the total synthesis of polycavernoside A (2a) published in 2010 by Lee and co-workers is the use of an intramolecular Prins bicyclisation to simultaneously construct the macro lactone and the tetrasubstituted THP.44 As illustrated in Scheme 8, the synthesis began with an enantioselective allyl-transfer using Nokami alcohol over aldehyde 6245 to yield the homoallylic alcohol 63. Basic treatment of 63 followed by opening of the epoxide with lithiated alkyne 6446 provided secondary alcohol 65, which was submitted to a sequence of desilylation, regioselective tosylation, silylation of the secondary alcohol and iodide substitution to afford compound 66. A Julia-type 1,6-reductive elimination in the presence of SmI\(_2\) and HMPA furnished the desired triene 61 with an overall yield of 60% after 5 steps.

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**Scheme 8** Lee’s total synthesis of polycavernoside A (2a). This figure has been adapted from ref. 44 with permission from ACS PUBLICATIONS, copyright 2010.
67 gave a mixture of secondary alcohols, which were transformed into the corresponding ketone by treatment with Dess-Martin Periodinane (DMP). After PMB deprotection, the desired anti-relationship was accomplished by means of reduction mediated by Me₃NBH(OAc)₃. Condensation of the resulting anti-diol with appropriate activated carboxylic acid provided the compound 68. Acidic cleavage of THBS group in 68 provided the key homoallylic alcohol, which was submitted to a stereoselective intramolecular Prins cyclisation to furnish the desired 2,6-cis-THP 69. The intramolecular alkyne hydration of 69 proceed in the 6-endo mode to give 70 in the presence of PtCl₂ as catalyst.⁴⁹ Oxidation of 70 with DMDO followed by MeOH addition delivered the corresponding hydroxyl ketal intermediate, which was submitted to Ley oxidation conditions⁵⁰ to yield 71. The 5-membered ring hemiacetal 72 was procured via ozonolysis of the terminal olefin, iodoolefination and rearrangement by prolonged exposition to Takai conditions, and basic hydrolysis to release the hydroxy group at C4 position of the THP. NBS-mediated glycosylation of 72 was carried out by using the thioglycoside 73.⁵¹ Posterior debenzylation and Stille-type coupling reaction employing dienylstannane 74 finally provided (−)-polycavernoside A (2a) with an overall yield of 1.5% after 22 linear steps.

### 3.3 Sasaki’s synthesis (2012)⁵⁵

Sasaki and co-workers reported the total synthesis of polycavernoside A (2a) in 2012 (Scheme 9).⁵⁵ They proposed a convergent approach starting from two fragments and employing as key reactions Suzuki–Miyaura coupling⁶⁶ and Keck macrolactonization.⁶⁷ As shown in Scheme 9, the construction of the THP fragment started with a catalytic asymmetric hetero Diels–Alder reaction between diene 76 (derived from 75)⁶⁸ and aldehyde 77 by using Jacobsen tridentate chromium(III) catalyst (78)⁶⁹ to yield dihydropyran 79. Then, treatment of 79 with K₂CO₃ in MeOH afforded a separable mixture of ketones 80a and 80b. Full conversion of minor 80b into desired isomer 80a was possible after two cycles of isomerization by means of DBU in toluene. Then, alcohol 81 was diastereoselectively obtained from 80a by Luche reduction.⁶⁴ Subsequently, compound 81 was sequentially submitted to a silylation, deprotection of primary alcohol and iodination to deliver iodide 82, whose treatment with t-BuOK allowed the obtaining of desired fragment 83. Thereafter, they embarked on the future THF fragment synthesis (Scheme 9). (R)-(−)-citronellal (84) was transformed into enol 85,⁶⁴ which was submitted to an ozonolysis to yield aldehyde 86. Then, 86 was submitted to a catalytic asymmetric alylation with bromide 87 and using sulphonamide 88 as chiral ligand,⁶² affording 89 (31%) together with the corresponding diol (69%), which was selectively resilylated to give 90. Asymmetric dihydroxylation of alkenne 89 using (DHQ)₂PYR as chiral ligand⁷² provided triol 90. Later, it was transformed into lactone 91 by selective protection of the primary alcohol as TBDPS ether, cleavage of the THS group, oxidative lactonisation⁷³ and protection of the secondary alcohol as TES ether. Treatment of 91 with KHMDS and PhN(Tf)₂ afforded desired triflate 92. The Suzuki–Miyaura coupling of fragments 83 and 92 allowed the obtaining of desired 2,6-cis-THP 93 (Scheme 10).⁶⁴ Oxidation of the enol 93 using m-CPBA provided a mixture of two epimeric alcohols which were individually oxidised to the same tetrahydropyranone 94. After that,
Scheme 10  Sasaki’s fragments assembly and final steps in the direction of polycavernoside A (2a). This figure has been adapted from ref. 55 with permission from ACS PUBLICATIONS, copyright 2012.

Scheme 11  Fürstner’s formal synthesis of polycavernoside A (2a). This figure has been adapted from ref. 66 with permission from WILEY, copyright 2013.
was submitted to TES and PMB deprotection followed by selective oxidation of the primary alcohol,\textsuperscript{47} providing carboxylic acid \textsuperscript{95}. Macrolactonisation under Keck conditions led to \textsuperscript{96}, which was converted into iodoolefin \textsuperscript{97} after cleavage of the TBDPS, oxidation with DMP\textsuperscript{48} and Takai reaction.\textsuperscript{31} Afterwards, TFA-mediated removal of the TIPS and concomitant rearrangement to 5-membered hemiacetal yielded the intermediate \textsuperscript{72}. Finally, NBS-mediated glycosylation\textsuperscript{73} of \textsuperscript{72} with the known glycosyl sulphide \textsuperscript{73},\textsuperscript{51} followed by the oxidative cyclisation of the benzyl ether group using DDQ and a Stille-type coupling\textsuperscript{44} with \textsuperscript{74}, consummated the total synthesis of \textsuperscript{2a} with an overall yield of 2.4\% from \textsuperscript{84} after 29 steps in the longest linear sequence.

\subsection*{3.4 Fürstner’s formal synthesis (2013)\textsuperscript{66}}

The key feature of the formal synthesis of \textsuperscript{2a} proposed by Fürstner and co-workers is the ring-closing alkyne metathesis (RCAM) to form the alkyne-macrolactone \textsuperscript{69},\textsuperscript{66} the late-stage intermediate obtained by Lee and co-workers (vide supra).\textsuperscript{44} Scheme 11 shows the preparation of the three required fragments and the subsequent assembly. They started with an aldol addition of \textsuperscript{98} with acrolein to yield racemic aldol \textsuperscript{99}, immediately converted into chiral acetalated \textsuperscript{100} through a lipase-catalysed kinetic resolution. Subsequently, \textsuperscript{101} was achieved after basic hydrolysis, silylation and again basic treatment to hydrolyse undesired bis-silylated precursor. Parallely, the Sonogashira coupling\textsuperscript{67} of propyne with \textsuperscript{102} afforded alkyne \textsuperscript{103}, which was submitted to a Mn-salen (\textsuperscript{104a}) catalysed epoxidation followed by a Co-salen (\textsuperscript{104b}) catalysed hydrolytic kinetic resolution to provide chiral epoxide \textsuperscript{105}.\textsuperscript{66} Epoxide opening with \textsuperscript{MeLi} and subsequent O-tosylation yielded \textsuperscript{106}. Treatment of \textsuperscript{106} with \textsuperscript{LiBr} supplied the volatile bromide derivate, which was exposed to Zn dust to provide the organozinc compound \textsuperscript{107}. In third place, asymmetric hydrogenation of \textsuperscript{108} followed by PMB protection of the resulting secondary alcohol and DIBAL-H reduction of the ester allowed the obtaining of \textsuperscript{109}. Treatment of this aldehyde with organosilicon compound \textsuperscript{110} yielded $\beta,\gamma$-unsaturated alcohol \textsuperscript{111}, consecutively submitted to $O$-silylation, DDQ-based deprotection, epoxidation and cross metathesis with methyl acrylate to give epoxide \textsuperscript{113}. Epoxide opening with the propynyl borane obtained \textit{in situ} from lithiated proprune and BF\textsubscript{3}-OEt\textsubscript{3} yielded \textsuperscript{114},\textsuperscript{69} the proper precursor for a DBU/LiCl-promoted \textit{cis}-selective oxy-Michael addition that led to the desired THP ring, subsequently reduced with DIBAL-H to yield \textsuperscript{115}.

Once synthesized the three fragments \textsuperscript{101}, \textsuperscript{107} and \textsuperscript{115}, their assembly started with the CuCN–2LiCl-mediated\textsuperscript{70} acylation of organozinc \textsuperscript{107} with the acid chloride of \textsuperscript{101} to furnish ketone \textsuperscript{116} after desilylation (Scheme 11). Then, \textsuperscript{116} was employed in an Evans–Tischenko reaction\textsuperscript{71} with TPH \textsuperscript{115} to yield diyne \textsuperscript{117}, which was protected as dichloroacetate and submitted to a RCAM catalysed by Mo-complex \textsuperscript{118}.\textsuperscript{72} The removal of the dichloroacetate and the change of the protective group in the THP afforded Lee’s cycloalkyne \textsuperscript{69}.\textsuperscript{74} Transannular hydroalkoxysylation of \textsuperscript{69} using the complex \textsuperscript{119} yielded enol ether \textsuperscript{70}, thus ending the formal synthesis of \textsuperscript{2a}.

\subsection*{3.5 Sasaki’s synthesis (2017)\textsuperscript{73}}

In 2017, Sasaki and co-workers reported an improved version of their previously reported synthesis of polycavernoside A (\textsuperscript{2a}) (vide supra),\textsuperscript{75} as well as the application of this protocol to the synthesis of polycavernoside B (\textsuperscript{2d}).\textsuperscript{73} Fragment \textsuperscript{83} was again prepared as shown in Scheme 9 without any modifications, albeit synthesis of fragment \textsuperscript{92} was modified. The new strategy towards \textsuperscript{92} began with the Kiyoka aldol reaction\textsuperscript{74} between acetal \textsuperscript{120} and known aldehyde \textsuperscript{121},\textsuperscript{75} affording enantioselectively $\beta$-hydroxy ester \textsuperscript{122} which was, in turn, converted into Weinreb amide \textsuperscript{123} (Scheme 12). Alkylation of Weinreb amide \textsuperscript{123} was achieved by using 2-methylallylmagnesium chloride to afford the $\beta$-hydroxy ketone \textsuperscript{124}, subsequently protected with TESCl and diastereoselectively reduced to give \textit{anti} compound \textsuperscript{125}. Diene \textsuperscript{126} was accessed by $O$-acylation of alcohol \textsuperscript{125}, and submitted to ring-closing metathesis (RCM) conditions\textsuperscript{76} to

![Scheme 12](image-url)  
Sasaki’s syntheses of polycavernosides A (\textsuperscript{2a}) and B (\textsuperscript{2d}). This figure has been adapted from ref. 73 with permission from ACS PUBLICATIONS, copyright 2017.
prepare lactone 127. Its hydrogenation allowed 91, which was transformed after 12 steps in the late intermediate 72, as reported in their previous work (see Schemes 9 and 10). This is the common precursor to complete both synthesis of 2a and 2d, based on the employment of sugar moieties 73 and 128 for the glycosylation and stannous polyene 74 and 129 for stilbetype coupling, respectively. Thus, Sasaki and co-workers achieved the synthesis of 2a and 2d in 0.96% and 2.0% overall yield after 23 and 22 steps, respectively.

3.6 Kadari & Yerrabelly’s contribution (2018)77

In 2018, Kadari et al. reported the synthesis of the \( \gamma \)-butyrolactone ring of polycavernoside A (2a).77 The starting sequence implied a mono-benzylation of diol 130 followed by a Swern oxidation68 to access aldehyde 131 (Scheme 13). Its HWE homologation26 afforded \( (E) \)-\( \alpha, \beta \)-unsaturated ester 132. Ensuing ester reduction and Sharpless asymmetric epoxidation78 yielded epoxide 133, which was transformed into iodo derivative 134. Treatment with Zn and Na in MeOH allowed the obtaining of allylic alcohol 135, whose \( O \)-acylation with 136 gave the bis-olefine 137. Subsequently, 137 was submitted to RCM employing Grubbs II [54] as catalyst84 and providing thus \( \gamma \)-butyrolactone 138. Diastereofacial reduction of 138 with concomitant debenzylation and subsequent \( O \)-silylation finally yielded target 139.

4. Lasonolide A

Lasonolide A (3a) was isolated from a Caribbean species of sponges of the genus *Forcepia*, collected close to Guana Island, British Virgin Islands. Its originally proposed structure (3a’) was published in 1994 by McConnell and co-workers (Fig. 2),13 and the same group published the initial elucidation of lasonolide B (3b’) in 1997.74 Some years later, Lee’s group published a series of works regarding the first synthesis of proposed 3a’, highlighting certain inconsistencies in spectroscopic data, optical rotation and bioactivity compared to those originally reported.80 As consequence, structure of 3a was unambiguously established (Fig. 2). Lasonolides possess a 2,3,3,4,6-pentasubstituted THP (ring A) and a 2,3,4,6-tetrasubstituted THP (ring B). Their 20-membered macrolide core own a polyene linkage (4 \( E \) double bonds and a Z double bond between C12–C13). The initially proposed \( Z \) geometry of C17–C18 double bond was corrected to \( E \), as well as the C25–C26 \( E \) geometry was re-assigned as \( Z \) after Lee’s work.80 In 2004, 3a was again isolated from *Forcepia* sponges collected in the Gulf of Mexico, together with other new metabolites called lasonolides C–G (3c–3g, Fig. 2). All these lasonolides share the lasonopyran skeleton, and they differ in the nature of the \( R^1 \) and \( R^2 \) side chains.

The interest in lasonolides lie in the potent in vitro anti-proliferative activity exhibited by 3a against A549 human lung adenocarcinomatous epithelial cells (IC50 40 ng mL\(^{-1}\), i.e., 0.057 \( \mu \)M) and P388 murine leukemia cell lines (IC50 2 ng mL\(^{-1}\), i.e., 0.003 \( \mu \)M).14 In addition, it was found that 3a inhibits cell adhesion in the EL-4 cell line (IC50 19 ng mL\(^{-1}\), i.e., 0.027 \( \mu \)M), that correlates with signal transduction activity, although toxicity against this line is greater than 25 \( \mu \)g mL\(^{-1}\).13 Indeed, the term lasonolide derives from the word *lason*, which means poison or toxin in Philippine. 3c–3g showed cytotoxicity against A549, human pancreatic carcinoma PANC-1 and the resistant human breast NCI/ADR-RES cell lines, although 3a showed the lowest values in all the cases.81 In 2004, four synthetic analogues (3h–3k, Fig. 2) were prepared and biologically evaluated against A549, human colon carcinoma HCT116 and human non-small cell lung carcinoma NCI-H460 cell lines, showing cytotoxicity but greater values than 3a.82 Once established the biopotential of 3a, further studies digging into its unique mechanism of action were developed. Thus, it was found that 3a acts as activator of protein kinase C in Panc-1 pancreatic carcinoma cells, inducing the formation of blebs and contraction of the cells shortly after the exposure and the final loss of adherence.83 3a also incites rapid, massive and reversible protein hyperphosphorylation and premature chromosome condensation at all phases of the cell-division cycle independently of cyclin-dependent kinases,84 in a process mediated by RAF1 gene.85 Very recently, it has also been reported the connection between 3a and lipid droplets, where it becomes a toxic metabolite by a lipid droplet-associated hydrolase.86

In the light of its stimulating structure, and mainly to respond to the request of more amount of product to explore the promising anticancer activity, it is evident that scientific community has directed considerable efforts towards the synthesis of 3a. Herein we discuss all the synthetic contributions published after the previous review, issued in 2006.87

4.1 Jennings’ contribution (2006)88

Jenning and co-workers presented in 2006 the asymmetric synthesis of the C1–C14 fragment of lasonolide A (3a),88 using a SmI2-mediated Molander–Reformatsky intramolecular aldol

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**Scheme 13** Kadari & Yerrabelly’s approach to the THF segment of polycavernoside A (2a). This figure has been adapted from ref. 77 with permission from WILEY, copyright 2018.
addition as key reaction to form the oxygenated 6-membered ring. Their approach started with carbocupration under Corey conditions of the known ester providing an α,β-unsaturated ester which yielded aldehyde after a reduction/oxidation sequence (Scheme 14). Evans aldol condensation between aldehyde and pre-formed (Z)-enolate of diastereoselectively gave syn-aldol. The chiral auxiliary was then cleavage by treatment with , providing a diol whose primary alcohol was protected as TBS ether providing a terminal alcohol which was then oxidised with DMP to give aldehyde. The SmI2-mediated intramolecular Reformatsky reaction of under Molander conditions provided a samarium(III) intermediate, which underwent an intramolecular cyclisation to yield β-hydroxy lactone. Alkylation of with allyl magnesium bromide followed by the treatment with TFA allowed the formation of an oxocarbenium ion which was reduced using TES to a THP with the desired configuration. Subsequently, the terminal olefin in was

Scheme 14  Jennings’ approach to the 2,3,4,6-tetrasubstituted THP ring of lasonolide A (3a). This figure has been adapted from ref. 88 with permission from ELSEVIER, copyright 2006. 

Fig. 2  Lasonolides (3). This figure has been adapted from ref. 82 and 87 with permission from ELSEVIER, copyright 2004 and SPRINGER, copyright 2006.
subjected to a chemo and diastereoselective cross-metathesis
using Grubbs II catalyst (54) to afford an \(\alpha,\beta\)-unsaturated
aldehyde which was, in turn, homologated with appropriate
phosphonium ylide to deliver target compound 149 in 3%
overall yield after 14 steps.

4.2 Jennings’ contribution (2007)95
Shortly after, Jenning and co-workers acceded to the C17–C25
fragment of lasonolide A (3a). This approach involves
a Tsuchihashi–Yamamoto rearrangement,96 and again a SmI2-
mediated aldol reaction97 to achieve the oxygenated 6-
membered ring (Scheme 15). Thus, Wittig olefination of known
aldehyde 15097 yielded ester 151, whose reduction and Sharpless
asymmetric epoxidation78 led to the epoxy alcohol 152. The
alcohol to aldehyde oxidation followed by nucleophilic addition
of vinyl magnesium bromide and subsequent protection of the
resulting alcohol as its TMS ether gave compound 153. As re-
ported by Tsuchihashi–Yamamoto,96 the addition of TiCl4

Scheme 15 Jennings’ approach to the 2,3,3,4,6-pentasubstituted THP ring of lasonolide A (3a). This figure has been adapted from ref. 95 with permission from ELSEVIER, copyright 2007.
triggered the 1,2-vinyl migration to deliver 154. Esterification of 154 with 2-bromoacetyl bromide gave 155, whose treatment with SmI$_2$ provided the corresponding Sm(III) enolate which undergo a cyclisation via a 6-membered transition state to yield δ-lactone 156 as a single diastereoisomer.$^{14}$ Nucleophilic addition of allyl magnesium bromide to 156 afforded lactol 157, whose treatment with TFA and TES provided, via formation of an oxocarbonium ion, the THP 158. Finally, simultaneous ozonolysis of both terminal alkenes followed by NaBH$_4$-mediated reduction and subsequent treatment with PPTS yielded desired acetone 159, completing thus the synthesis of 3a fragment C17–C25 with an overall yield of 0.51% after 14 steps from 151.

4.3 Ghosh’s synthesis (2007)$^{98}$

The total synthesis of lasonolide A (3a) published by Ghosh and co-workers employ as key steps an intramolecular [3 + 2] dipolar cycloaddition and a hetero-Diels–Alder reaction to construct the penta- and tetrasubstituted THPs, respectively (Scheme 16).$^{100}$ The pathway towards the tetrasubstituted THP B fragment started from commercial alkynol 160, which was O-benzylated, lithiated and treated with $n$-propanal to yield alkylnol 161. It underwent alkyne reduction, alcohol oxidation and treatment with TESOTf to afford desired silylated dienol 162. After that, it was submitted to a hetero-Diels–Alder reaction with TBSOCH$_2$CHO in the presence of the chiral Schiff base chromium(ii) complex 78 (Scheme 9) developed by Jacobsen,$^{101}$ providing the 2,6-cis-tetrahydropyranone 163. Reduction of ketone 163 with DIBAL-H gave a 1/2 mixture of axial/equatorial alcohols, albeit an extra amount of desired axial alcohol 164 was achieved after tedious separation of equatorial alcohol, Swern oxidation and again DIBAL-H reduction. O-Silylation of secondary alcohol in 164, followed by hydrocyanogenative removal of benzyl group provided primary alcohol 165. Then, olefin 166 was accomplished through the sequence Dess–Martin oxidation,$^{102}$ Wittig reaction and acidic deprotection of the primary alcohol. Cross-metathesis between olefins 166 and 167 by means of Grubbs II catalyst (54)$^{94}$ led mainly to the (Z)-olefin 168. Successful oxidation of its primary alcohol followed by HWE olefination under Ando conditions$^{103}$ afforded the (Z)-$\alpha$-$\beta$-unsaturated ester 170. Finally, a tandem reduction/oxidation yielded aldehyde 171.

The synthesis of the pentasubstituted A-ring THP began with the addition of isopropenyl magnesium bromide to aldehyde 172 and subsequent Sharpless kinetic resolution$^{104}$ to access alcohol 173. This alcohol allowed the opening of the epoxide of tosylate 174 to yield 175.$^{105}$ This compound underwent successive epoxidation to remove the O-tosyl moiety, acid epoxide opening to get a diol, oxidative cleavage of the diol to install an aldehyde, condensation with nitromethane and mesylation followed by an in situ elimination to finally obtain nitroalkene 176. Its reduction afforded the corresponding oxime, which was subsequently subjected to an intramolecular [3 + 2] cycloaddition to diastereoselectively provide the isoxazoline 177. Hydrogenolysis of isoxazoline ring yielded the hydroxy ketone 178, which was submitted to a L-selectride reduction followed by the diol protection to afford acetonide 179. Then, it was transformed into alcohol 180 by cleavage of benzyl groups, bis-protection as bis-TBS ether and treatment with TBAF (the also obtained diol was again bis-silylated and treated with TBAF). Alcohol 180 was transformed into olefin 181 via DMP oxidation,$^{106}$ Wittig olefination and desilylation. Finally, cross-metathesis$^{11}$ between 181 and the sulphone 182, followed by protection of the alcohol as MTM ether$^{11}$ yielded target compound 183.

The approach to the lateral chain fragment employed commercial acid 184 as starting material. It was converted into a Weinreb amide, reduced to aldehyde, methylenated with Eschenmoser’s salt,$^{102}$ and reduced to allylic alcohol 185. Next it was submitted to esterification with known acid 186,$^{107}$ removal of benzylidene group and bis-silylation to access 187. Later, primary alcohol was deprotected, converted into iodide and finally into the required phosphonium salt 188.

The final steps of this synthesis started with the fragment A (183) and B (171) coupling under Julia–Kocienski conditions$^{108}$ to provide the tetraene 189 (Scheme 17). Acetonide and TBS protecting groups cleavage followed by bis-silylation of both primary alcohols yielded tris-TBS ether 190. Its secondary free alcohol was treated with activated phosphonoacetic acid, and

Scheme 17 Ghosh’s fragments assembly and final steps on the way to lasonolide A (3a). This figure has been adapted from ref. 98b with permission from ACS PUBLICATIONS, copyright 2007.
the allylic TBS-ether was selectively deprotected to afford alcohol 191. After oxidation to aldehyde, the macroactonization was carried out via an intramolecular HWE olefination,\textsuperscript{26} followed by MTM removal to yield macrolide 192. Lasonolide A (3a) was finally obtained via oxidation, Wittig olefination with phosphonium salt 188 and TBS de-protect, with an overall yield of 0.12% after 32 steps in the longest sequence.

4.4 Ghosh’s contribution (2008)\textsuperscript{\textsuperscript{99,100}}

One year later, Ghosh and co-workers published a comprehensive explanation of their previous reported synthesis of 3a (vide supra).\textsuperscript{98} Additionally, in that work they related preliminary strategies through the obtaining of the THP fragments, which were finally replaced by the above described pathways. Nevertheless, within the context of this review, it is adequate to highlight the most relevant points of the original approaches. On the one hand, effort towards fragment A started from THP 165,\textsuperscript{98} which was successively submitted to Swern oxidation, Wittig reaction, selective desilylation and again to Swern oxidation to yield aldehyde 193 (Scheme 18). However, the attempts to exclusively transform 193 into desired Z-194 via a Stork–Zhao–Wittig reaction\textsuperscript{98} were fruitless. On the other hand, the pathway to the fragment B began with allylic alcohol 173 (Scheme 16),\textsuperscript{163} which was alkylated with bromoacetic acid, and the resulting acid was activated and treated with lithiated oxazolidin-2-one 195 to yield 196. Key Evans allylation\textsuperscript{183} of N-acyl oxazolidin-2-one 196 was not as diastereoselective as expected, and undesired diastereoisomer was always the main product even when different chiral auxiliaries were employed (dr 48 : 52 in the shown best conditions). Even so, alkylated product 197 was isolated and transformed into 198 after reductive cleavage of the auxiliary, silylation and reduction of the ester group. After that, alcohol 198 was oxidized to aldehyde and transformed into an oxime, which underwent an intramolecular 1,3-dipolar cycloaddition via nitrile oxide to yield desired isoxazoline 177b.

4.5 Ghosh’s contribution (2012)\textsuperscript{107}

Four years later, Ghosh et al. envisioned the syntheses of 168 and 183 (the lasonolide A THP fragments previously prepared, see Scheme 16)\textsuperscript{98} from two similar precursors: dihydropyrans 201a and 201b (Scheme 19).\textsuperscript{107} At first, known aldehyde 199\textsuperscript{108} was submitted to a nucleophilic addition with both methyl and ethyl magnesium bromide, Parikh–Doering oxidation\textsuperscript{109} and silylation with both TMS and TES to yield silyl enol ethers 200a and 200b, respectively. An asymmetric hetero-Diels–Alder reaction was carried out using 2-(benzyloxy)acetaldehyde\textsuperscript{110} in the presence of Jacobsen catalyst 78\textsuperscript{26} in order to obtain 201a and 201b from 200a and 200b, respectively. On the one hand, 201b was transformed into ketone 202. Its DIBAL-H reduction to get alcohol 203 was inefficient since a diastereoselectivity standpoint, as previously occurred in the conversion of 163 to 164 (Scheme 16). Thus, it was replaced by conversion of 202 to 203 via formation of an enol triflate, Pd-catalysed reduction to alkene, diastereoselective DMDO-based epoxidation and diaxial epoxide opening by DIBAL-H. Protection of secondary alcohol in 203 as its TBS ether followed by selective primary TBS acidic deprotection, Parikh–Doering oxidation\textsuperscript{109} and HWE olefination\textsuperscript{26} yielded the α,β-unsaturated ester 204. Finally, DIBAL-H reduction, protection of the resulting alcohol as TBS ether and selective cleavage of the benzyl group afforded target 168.

On the other hand, 201a was lithiated and treated with ethyl cyanoformate to yield a β-keto ester, straightaway methylated to give tetrahydropryanone 205. It underwent a double reduction protocol: L-selectride provided the axial alcohol and then LAH reduced the ester moiety. The corresponding diol was protected as acetonide, and benzyl hydrogenation supplied alcohol 206.
Finally, it was submitted to Parikh–Doering oxidation,\textsuperscript{109} Julia–Kocienski olefination\textsuperscript{104} with sulphone 208 (previously obtained from known alcohol 207\textsuperscript{111} via a Mitsunobu reaction), oxidation of sulphide to sulphone using ammonium heptamolybdate and hydrogen peroxide,\textsuperscript{112} desilylation and protection as MTM ether\textsuperscript{111} to yield target 183.

### 4.6 Trost's synthesis (2014)\textsuperscript{113}

Trost and co-workers disclosed the enantioselective total synthesis of lasonolide A (3a) in 2014.\textsuperscript{113} The highlighted feature of this route is the Ru-catalysed alkene–alkyne coupling\textsuperscript{111} to assemble the two THPs moieties. Initially, β-hydroxy-ynone 209 was obtained via a Zn/prophenol-catalysed aldol addition\textsuperscript{114} between appropriate aldehyde and ynone (Scheme 20). The new stereocentre orientated the subsequent Dibal-H reduction of 209 to afford the corresponding 1,3-syn-alcohol, which was selectively protected to yield silyl ether 210. Transacetalization of 210 and subsequent oxidation provided aldehyde 211. Then, cleavage of silyl groups in 211 led to an in situ cyclisation affording lactol 212, immediately submitted to an HWE olefination\textsuperscript{106} and Dibal-H reduction to aldehyde 213. Finally, the alkynyl 215 was achieved by Wittig olefination of 213 with the phosphonium salt 214 (obtained from isopentylmagnesium bromide via carbocuration, transesterification, silylation and nucleophilic substitution, see Scheme 20), followed by removal of the benzylidene acetal.

On the other hand, α-bromo keto ester 216 was subjected to a Blaise reaction\textsuperscript{115} with allyl cyanide to supply the β-ketoester 217. An enzymatic kinetic asymmetric reduction\textsuperscript{116} upon 217 by an enzyme called CDX-024 allowed the obtaining of β-hydroxyester 218. It was transformed into alkyne 219 following the sequence silylation, conversion into Weinreb amide and nucleophilic addition.\textsuperscript{137} (S)-Corey–Bakshi–Shibata (CBS) catalysed reduction diastereoselectively afforded 220.\textsuperscript{138} Afterwards, its Ru-catalysed hydroisilylation\textsuperscript{139} gave a (Z)-vinylsilane, which was underwent Hoveyda-Grubbs\textsuperscript{26} cross metathesis with crotonaldehyde and simultaneous oxa-Michael conjugated addition to provide 221.\textsuperscript{141} Terminal aldehyde of the 2,6-cis’-THP 221 was submitted to an HWE olefination,\textsuperscript{106} and then the vinyl silyl group was involved in a Pd-catalysed Hiyama coupling\textsuperscript{132} with allyl acetate to furnish desilylated 222. Ester saponification followed by secondary alcohol protection as its TBS ether yielded 223.

Fragments 223 and 215 were joined via an alkene–alkyne coupling employing [CPRu(MeCN)\textsubscript{3}]\textsubscript{2}PF\textsubscript{6} as catalyst in acetonitrile,\textsuperscript{33} providing thus a 3 : 1 inseparable mixture of linear-branched acetonides 224 and 225, respectively. The mixture was treated with CSA to remove the acetonides and then with TBSCl to yield required tri-silyl ether 226 together with its undesired branched isomer. Both were submitted to Yamaguchi macrolactonization to provide, after separation by chromatography, macroclide 227 (9% yield from 223 after 4 steps). Removal of silyl group finally led to lasonolide A (3a), obtained in 1.6% overall yield after 16 linear steps from 216.

### 4.7 Trost's contribution (2016)\textsuperscript{133}

Two years later, Trost’s group reported a detailed description of their previously published synthesis of 3a.\textsuperscript{114,122} In the context of this review, it is interesting to show briefly an alternative pathway that they tried on the road to the tetrasubstituted THP. As shown in Scheme 21, alkyol 220 was transformed into target THP 221 through the following sequence: Ru-catalyzed hydroisilylation,\textsuperscript{119} cross-metathesis with ethyl acrylate employing
Hoveyda–Grubbs catalyst,\textsuperscript{120} reduction of the ester to alcohol, and eventually allylic oxidation of the alcohol to aldehyde with MnO$_2$, which triggered a diastereoselective intramolecular addition to access 221 in $63\%$ overall yield after 4 steps.

4.8 Hong’s synthesis (2018)\textsuperscript{124}

In 2018, Hong and co-workers published an enantioconvergent total synthesis of lasonolide A (3a).\textsuperscript{124} The modular approach employed an iterative Julia olefination to link the THP-containing fragments A and B, previously accessed from both enantiomers of $\alpha$-allenic alcohol rac-228 after an enzymatic kinetic resolution (Scheme 22).\textsuperscript{125} The ring A synthesis began with the direct hydroboration of (R)-228 followed by allylation of the 3-(benzoxyl)propanol\textsuperscript{126} to provide the anti–anti diol 229 as a single diastereoisomer. Thereafter, nitroalkene 230 was prepared through sequential acetalisation of the diol, desilylation, oxidation of the resulting primary alcohol, Henry reaction and elimination. Treatment of 230 with PTSA triggered a cascade process involving removal of the acetal, oxa-Michael addition, Nef reaction and acetalisation to yield 2,6-cis-tetrahydropryan 231. Subsequent ozonolysis of the terminal alkene in 231 followed by reduction and silylation afforded 232. Compound 233 was achieved by deprotection of benzylic group (after an \textit{in situ} BBN protection of secondary alcohol), TEMPO/BAIB oxidation and Wittig olefination with 214 (Scheme 20).\textsuperscript{111} Then, 233 was deacetylated and submitted to a selective Julia olefination\textsuperscript{127} with disulphone 234 to furnish sulphone 235 in good yield.

After that, Hong’s group embarked on the ring B synthesis starting from the acetylated S-enantiomer of 228 ((S)-228-Ac). A novel iterative hydroboration/oxidation protocol allowed them to transform the allene into the Z-alkene 236 first, and then into the syn: syn-triol 237. Compound 237 was subjected to acetalisation, desilylation, oxidation of the primary alcohol and Wittig
reaction to supply the $E$-z,$\beta$-unsaturated ester 238. Exposure of ester 238 to acidic conditions gave rise to a cascade acetal cleavage and 6-exo oxa-Michael addition,\textsuperscript{128} affording the corresponding 2,6-cis-THP 239. It was selectively oxidized,\textsuperscript{129} treated with the Still–Gennani phosphonate 240,\textsuperscript{130} and silylated to yield 241. DIBAL-H reduction led to an allylic alcohol but also to an aldehyde, which immediately submitted to an HWE olefination\textsuperscript{132} with phosphonate 242 and then to a saponification. Lastly, a DMP-based oxidation\textsuperscript{48} of the allylic alcohol provided aldehyde 243. \textit{In situ} BBN-protection of the carboxylic acid in 243 followed by the Julia olefination with sulphone 235 yielded intermediate 244, which was transformed into the final natural product \textit{via} a macrolactonisation/desilylation protocol.\textsuperscript{113} Thus, lasonolide A (3a) was synthesized in 12% overall yield after 15 steps from rac-228.

5. Clavosolide A

Clavosolides A and B (4a,b) were first isolated by Faulkner’s group from the Philippine marine sponge \textit{Myriastra clavosa} in 2002.\textsuperscript{131} A short while after, Gustafson group reported the
isolation of clavosolides A–D (4a–d) from the same source, as well as the absence of cytotoxic or antiproliferative activities regarding these compounds. Clavosolides are 16-membered macrolides with a heterodimeric structure (Fig. 1). All the clavosolides have in common the monomer owning a 2,3,4,6-tetrasubstituted THP, a cyclopropane moiety and a totally methylated D-xylose. Clavosolides B (4b) and C (4c) differ from A in the presence of a free hydroxy group in one of the glycoside units, whereas clavosolide D (4d) exhibit a 2,4,6-trisubstituted THP instead the tetrasubstituted one found in A (Fig. 1). The absence of exhaustive biostudies concerning these metabolites, their unique biosynthetic origin, and specially their stimulating molecular architectures, encouraged the scientific community to dedicate enormous synthetic efforts to access these natural products. Thus, from 2005 to 2016, 16 syntheses towards clavosolides have been described. Herein, we summarise the two synthetic works regarding clavosolide A (4a) subsequent to that date.

5.1 Raghavan’s contribution (2017)

In 2017, Raghavan and co-workers reported a convergent approach to clavosolide A (4a), employing as key feature two HWE cyclopropanations over the starting epoxides 245 and 252 (Scheme 23). On the one hand, the HWE cyclopropanation of the epoxide 245 was carried out in order to access ester 246. Its treatment with lithiated commercial (R)-methyl p-tolyl sulfoxide afforded the keto sulfoxide 247. The diastereoselective reduction of ketone in 247 yielded alcohol 248 with the required stereochemistry. Then, the sulfinyl moiety was employed as an internal nucleophile to open the Hg(II)-activated cyclopropane ring, providing thus mercucric bromide 249, whose subsequent demercuration led to diol 250. Protection of 250 as acetonide followed by sulfoxide reduction yielded sulphide 251. On the other hand, the HWE cyclopropanation of the epoxide 252 allowed the obtaining of an ester which was transformed into Weinreb amide 253. Addition of the corresponding alkynylmagnesium chloride followed by a stereoselective transfer hydrogenation employing (R,R)-Noyori catalyst (254) led to propargylic alcohol 255. Removal of the TMS and silylation yielded terminal alkyne 256. It was treated with isopropyl magnesium chloride, trans-metalated with ZnBr2 and added to previously chlorinated 251 to furnish 257 after TBS deprotection. Trost regioselective hydroxilylation afforded the silyl alkene 258. Finally, acetylation, RANEY® Ni desulphurisation and Tamao–Fleming oxidation of 258, yielded ketone 259, an advanced intermediate of clavosolide A (4a).

5.2 Krische’s synthesis (2019)

The absence of protecting groups and chiral auxiliaries are the distinctive features of Krische’s total synthesis of clavosolide A (4a). Firstly, a bidirectional asymmetric allylation employing (S)-IrBINAP (261), allyl acetate and 4-cyano-3-nitrobenzoic acid allowed the transformation of starting diol 260 into diol 262 (Scheme 24). Then, Fenton–Sennelhack alkoxypalladation/carbonylation of 262 provided the 2,6-cis-THP 263. A Schmidt-type glycosylation of 263 using trichloroacetimidate 264 and (R)-PA-II furnished selectively the β-isomer 266. DIBAL-H reduction of ester group in 266 proceed smoothly to provide aldehyde 267. In contrast to Cram–Reetz model dictate, the use of (−)-sparteine in the carbonyl addition between 267 and Li-treated 268 allowed the access to desired 269. Finally, terminal alkene oxidation gave carboxylic acid 270, whose macrolactonisation led to clavosolide A (4a) in only 7 steps from 260 with an overall yield of 6.3%.

6. Madeirolide A

Madeirolide family (5) was described in 2009 by Winder after its isolation from a species of sponge (genus Leiodermatium).
harvested from the deep sea off the coast of Madeira (Portugal). Madeirolide A (5a) consists of a 21-membered macrolide with a 2,3,4,6-tetra and a 2,3,4,5,6-pentasubstituted THP, as well as a 2,3,5-trisubstituted THF, all of them with a cis ring closure (Fig. 1). A trans ring closure is also found in the peripheral 2- methyl-3-oxo-6-oxy-trisubstituted THP linked to the 4-oxy position of the tetrasubstituted THP. 5a displayed antifungal activity against Candida albicans (fungicidal MIC = 12.5 μg mL\(^{-1}\)). However, further biostudies remain unexplored due to the low amount of isolated 5a. The synthetic efforts performed towards its obtaining are gathered herein.

6.1 Paterson's contribution (2013)

In 2013, Paterson and co-workers, reported the C1–C11 fragment synthesis of madeirolide A (5a). This approach involves a hetero Michael cyclisation, a Takai olefination and glycosylation as key reactions steps (Scheme 25). The synthesis was initiated with reduction of known (S)-ester 271\(^{151}\) to alcohol, mesylation and iodination to access 272. Reaction of lithiated dithiane 273\(^{152}\) with 272, followed by treatment of the resulting dithiane adduct with aqueous iodine, provided ketone 274.\(^{153}\) Aldol reaction between ketone 274 and aldehyde 275,\(^{154}\) mediated by chiral ligand (−)-(lpc)\(_2\)BOTf, led to alcohol 276 as a single diastereoisomer. 1,3-anti reduction of 276 under Evans–Tishchenko conditions\(^{71}\) led to an ester, immediately transformed via methanalysis into the corresponding diol which was, in turn, protected as acetonide 277. TBS-deprotection and Dess–Martin oxidation\(^{48}\) provided the necessary aldehyde 278. Condensation between aldehyde 278 and phosphonate 279 under Masamune–Roush conditions\(^{155}\) delivered unsaturated
ester 280. Acidic removal of the acetal of 280 provided the corresponding diol, which immediately underwent a Michael cyclisation to yield a 2,6-cis-THP, then converted into compound 281 after PMBO cleavage. Selective oxidation of the primary alcohol in 281, followed by Takai olefination supplied vinyl iodide 282. Finally, BF$_3$·OEt$_2$-mediated glycosylation of 282 with 284 (previously synthesised in 3 steps from 283 via Noyori reduction, Achmatowicz rearrangement followed by in situ acetylation of the lactol and hydrogenation) provided the C1–C11 fragment (285) of 5a in 11% overall yield after 17 steps.

6.2 Carter’s contribution (2016) In 2016, Carter and co-workers prepared the C1–C12 fragment of madeirolide A (5a) as a showcase of their silver catalysed cyclisations to obtain THP. The approach began with the Sonogashira coupling between both known iodide 286 and alkyne 287 to provide the propargylic alkene 288 (Scheme 26). Then, it was submitted to a Shi epoxidation to afford epoxide 290, whose opening by utilizing LiAlMe$_4$ supplied homo-propargylic alcohol 291. Treatment of 291 with AgBF$_4$ delivered a 58 : 42 mixture of the desired dihydropyran 293 together
with dihydrofuran 292. Once separated, treatment of 293 with NaOMe afforded ketone 294, which was, in turn, underwent to a stereoselective reduction to yield alcohol 295. The glycosylation step was carried out in the presence of BF3·OEt2 and glycoside 284150 (see preparation in Scheme 25) to furnish compound 296. Finally, they accessed to C1–C12 fragment (297) via TIPS-deprotection, DMP-based oxidation of the resulting primary alcohol,48 and Wittig olefination.

### 6.3 Lee’s contribution (2016)162

Lee and co-workers disclosed their approach towards the C1–C10 fragment of madeirolide A (5a).163 Their approach involved the use of an Ir-catalysed visible light induced radical cyclisation to construct the THP ring and a Pd-catalysed glycosylation to assemble the saccharide fragment. Known anti-aldol 298 was selected as starting material (Scheme 27).163 It was submitted to a reductive removal of the chiral auxiliary and selectively silylated to yield alcohol 299. O-Acylation allowed the access to 300, whose Ireland–Claisen rearrangement yielded acid 301 with excellent stereoselectivity. Stereoselective iodolactonization, reductive deiodination of 302 using iridium catalyst 303, Hantzsch ester (304), DIPEA and visible light ($\lambda_{\text{max}} = 454 \text{ nm}$) as photocatalyst, and subsequent reduction of the lactone provided 305. This diol was then submitted to an acetalisation with dimethyl acetal 306 to furnish the diastereomeric mixture of cyclic acetal 307. Chemo and stereoselective basic elimination induced ring opening to yield acrylate 308,164 whose primary alcohol was transformed into iodide derivate 309. Once again, exposure of 309 to visible light in the presence of 303, 304 and DIPEA lead to a radical mediated cyclisation165 to obtain the 2,6-cis-THP 310. After benzyl hydrogenolysis, a subsequent Pd-catalysed glycosylation of 310 with pyranone 311166 gave glycoside 312. Eventually, hydrogenation of the alkene in 312 furnished the C1–C10 fragment (313) of madeirolide A (5a).

### 7. Conclusions

In this review we have provided a comprehensive study about the synthetic efforts performed towards the preparation of some marine macroolides. Due to the vast amount of these metabolites, we focused our interest in those families containing 4-O-2,3,4,6-tetrasubstituted THPs in their structures. Thus, synthesis directed at miyakolide, polycavernosides A and B, lasonolide A, clavosolide A and madeirolide A were tackled in detail, with a special emphasis on the strategies used for building target THPs (see a summary in Table 2). We hope that this bibliographic update presented herein may become a useful tool for the synthetic community to continue being inspired by the fascinating world of marine macroolides.

### Abbreviations

- 2,2-DMP: 2,2-Dimethoxypropane
- 2,6-Lut: 2,6-Lutidine
- 9-Borabicyclo[3.3.1]nonane: 9-BBN
- Ac: Acetate
- BAIB: Bis(acetoxy)iodobenzene
- BINAP: 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
- Benzyl
- tert-Butyloxy carbonyl
Conflicts of interest

There are no conflicts to declare.

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