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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 involucrate. 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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Celina García received her PhD degree in Organic Chemistry at the University of La Laguna (ULL) in 2001, working on the enantioselective total synthesis of polyfunctionalized oxacyclic compounds, with Prof. Víctor S. Martín. The same year, she joined the laboratories of Prof. Patrick J. Walsh at the University of Pennsylvania as a postdoctoral researcher, working in the area of organocatalysis. In 2005 she came back as a researcher from a Ramón y Cajal Program of the Spanish Government to the ULL, where she is currently Associate Professor.

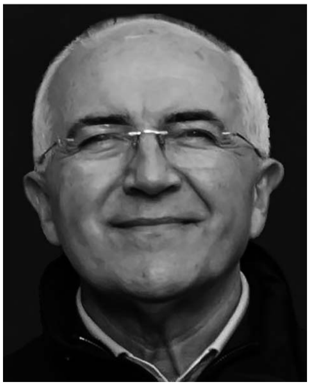
1. Introduction

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 theses 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*).[15] 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



Víctor S. Martín was born in La Palma (Canary Islands), and received his PhD at the University of La Laguna (ULL) in 1978. From 1980–82 he was a postdoctoral fellow with Prof. K. Barry Sharpless in Stanford University and the Massachusetts Institute of Technology. He moved to the ULL as Associate Professor in 1984 and since 1992 he holds a Full Professor position. His research interests include asymmetric synthesis, methodology and total synthesis of bioactive natural products. He is the director of the Institute of Bio-Organic Antonio González and recipient of the 2016 Felix Serratosa Medal awarded by the Spanish Royal Society of Chemistry.

Sergio J. Álvarez-Méndez was born in 1987 in La Palma (Canary Islands). He received his BSc degree in Chemistry in 2010 at the Universidad de La Laguna (ULL), with honours "Extraordinary Award to the Best Student's Academic Record". At the same university, he obtained his MSc in Research in Organic Chemistry (2011) and his PhD in Chemistry and Chemical Engineering (2016), under the supervision of Prof. Víctor S. Martín and Dra. Celina García. After that, he has been working at the Technical College of Agricultural Engineering (ULL), with research interests in the application of organic chemistry to plant physiology and anaerobic digestion.

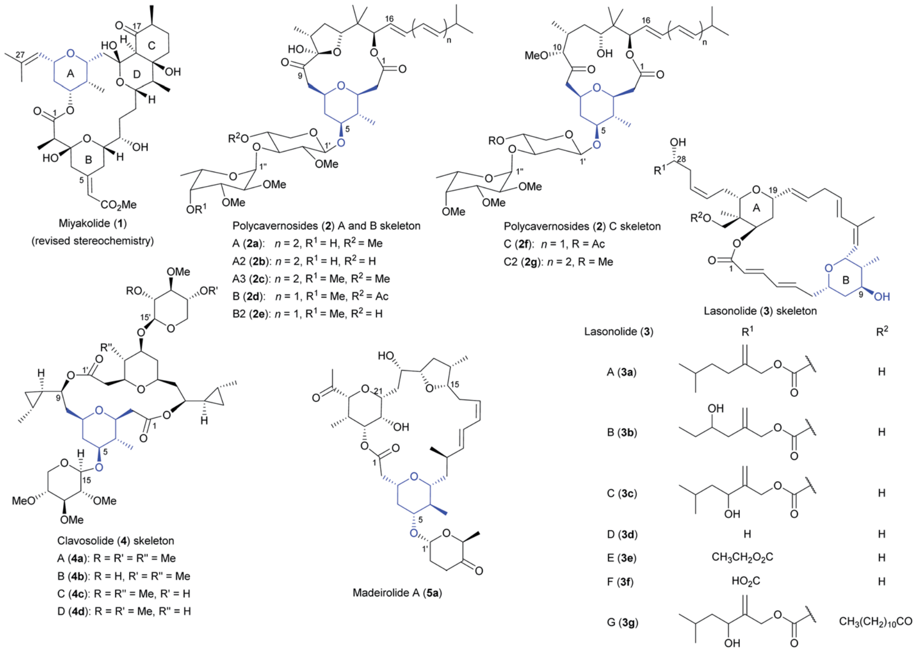


Fig. 1 NPs bearing a 4-*O*-2,3,4,6-tetrasubstituted THP. This figure has been adapted from ref. 15, 36, 41, 87, 132 and 162 with permission from ACS PUBLICATIONS, copyright 1999; ELSEVIER, copyright 2007; WILEY, copyright 2007; SPRINGER, copyright 2006; ACS PUBLICATIONS, copyright 2002; and ACS PUBLICATIONS, copyright 2016.

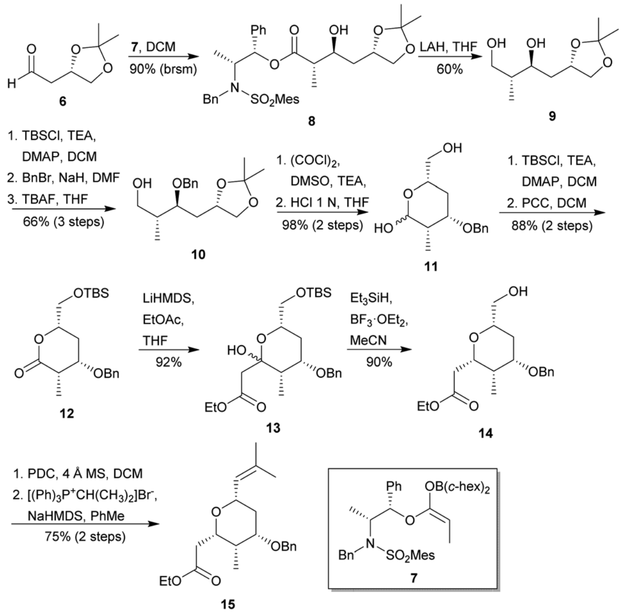
THP D *via* a methylene bridge at C2, and also owns a methyl group at C3, the oxygen of the ester of the macrocyclic structure at C4 and a 2-methylprop-1-en-1-yl group at C6 (Fig. 1). Despite its structural similarity to anti-cancer bryostatins,[16] miyakolide exhibited a weaker *in vitro* (IC_{50} 17.5 μg mL^{-1} against P388 mouse leukemia, IC_{50} 17.1 μg mL^{-1} against A-549 human lung carcinoma cells, and >20 μg mL^{-1} against HT-29 human colon adenocarcinoma cells) and *in vivo* (T/C 127% at 800 μg kg^{-1} against P388 mouse leukemia, and T/C 123% at 400 μg 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%.

Table 1 Molecular formulas, molecular weights and most relevant bioactivities for characteristic macrolides **1–5**

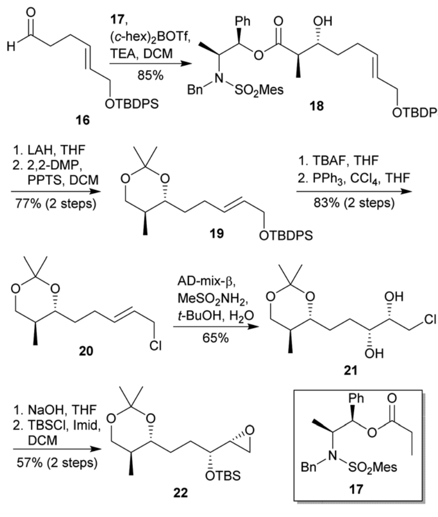
NP	Formula	g mol^{-1}	Relevant bioactivity
1	$C_{36}H_{54}O_{12}$	678.36	Antitumour: IC_{50} 17.5 mg mL^{-1} (P388 mouse leukaemia), 17.1 mg mL^{-1} (A549 human lung carcinoma cells)[11]
2a	$C_{43}H_{68}O_{15}$	824.46	Toxin: LC_{Lo} 0.2–0.4 mg kg^{-1} in mice[12]
3a	$C_{41}H_{60}O_{9}$	696.42	Antitumour: IC_{50} 2 ng mL^{-1} (P388 mouse leukaemia), 40 ng mL^{-1} (A549 human lung carcinoma cells)[13]
4a	$C_{44}H_{72}O_{16}$	856.48	No cytotoxic or antiproliferative activities described
5a	$C_{37}H_{56}O_{11}$	676.38	Antifungal: MIC 12.5 μg mL^{-1} (*Candida albicans*)[14]



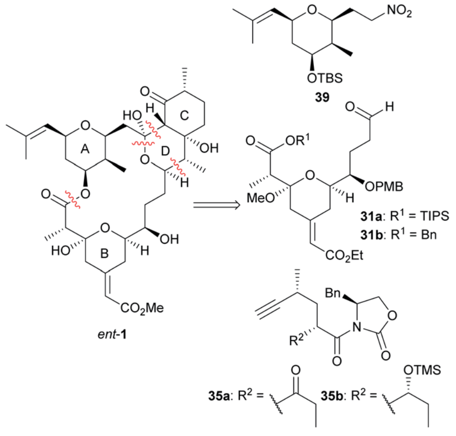
Scheme 1 Masamune's approach to ring A of miyakolide (**1**). This figure has been adapted from ref. 17 with permission from ACS PUBLICATIONS, copyright 1997.

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[21] gave the chlorinated compound **20**, which then underwent to an asymmetric Sharpless dihydroxylation to afford the chlorohydrin **21**.[22] Finally, the epoxidation of **21**[22] followed by *T*BS protection gave the targeted compound **22** with an overall yield of 24% (8 steps from **16**).



Scheme 2 Masamune's approach to ring D of miyakolide (**1**). This figure has been adapted from ref. 17 with permission from ACS PUBLICATIONS, copyright 1997.



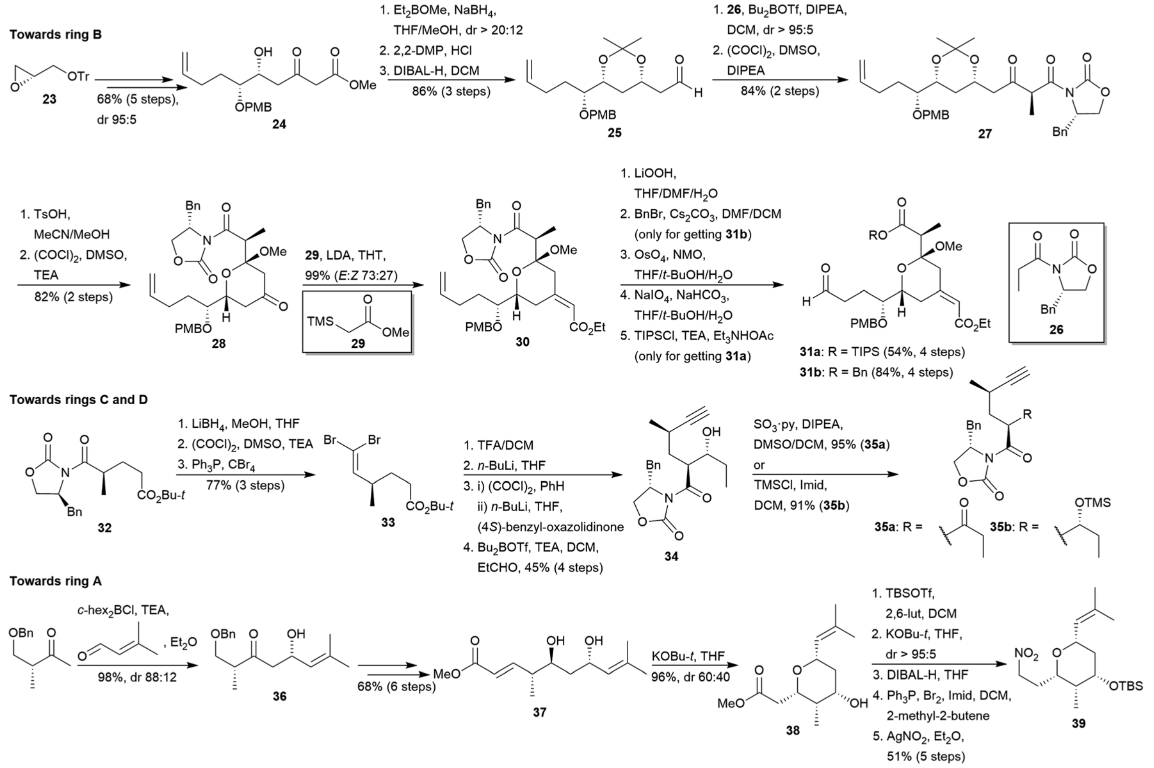
Scheme 3 Evans' retrosynthesis of miyakolide (**1**). This figure has been adapted from ref. 15 with permission from ACS PUBLICATIONS, copyright 1999.

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.[15] 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 R^1 and R^2, 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 *P*MB ether, trityl deprotection, Swern oxidation[20] and Chan's diene addition (Scheme 4).[23] 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[24] yielded diastereoselectively the aldol adduct, which was subsequently oxidised[20] to give the β-ketoimide **27**. THP **28** was furnished from **27** *via* acidic deprotection, *in situ* cyclisation and Swern oxidation.[20] Peterson–Yamamoto olefination[25] of **28** conduced 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[20] 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



Scheme 4 Evans' preparation of miyakolide (**1**) fragments. This figure has been adapted from ref. 15 with permission from ACS PUBLICATIONS, copyright 1999.

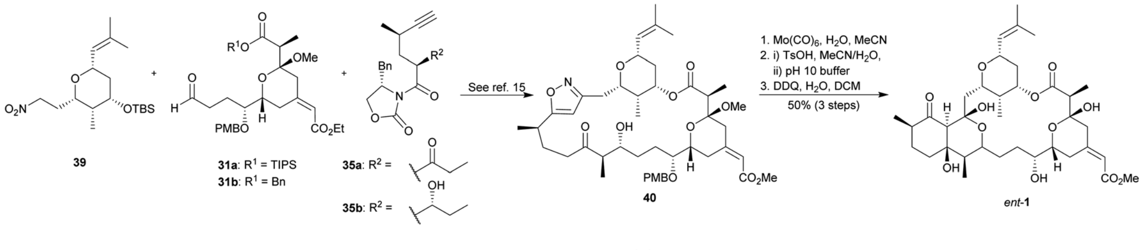
acyl chloride using lithiated (4*S*)-benzyl-oxazolidin-2-one, and aldol addition. Subsequent oxidation of **34** delivered compound **35a** (32% after 9 steps), whereas *O*-silylation yielded **35b** (31% after 9 steps). Synthesis of the tetrasubstituted THP **39** (future ring A) was achieved in 13 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) homologation[26] 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 nitration[27] (33%, 13 steps from commercial starting materials).

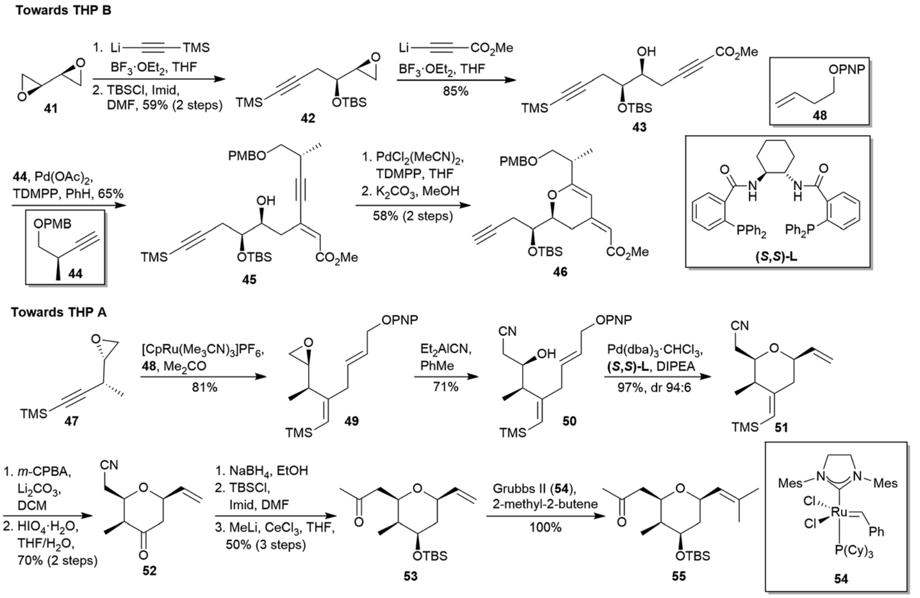
Evans' group designed fragments **31**, **35** and **39** to be interconnected through any of these three reaction sequences: aldol addition, [3 + 2] dipolar cycloaddition and esterification; cycloaddition, aldol addition and esterification; and aldol addition, esterification and cycloaddition. In all 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



Scheme 5 Evans' fragments coupling and final steps on the way to miyakolide (**1**). This figure has been adapted from ref. 15 with permission from ACS PUBLICATIONS, copyright 1999.

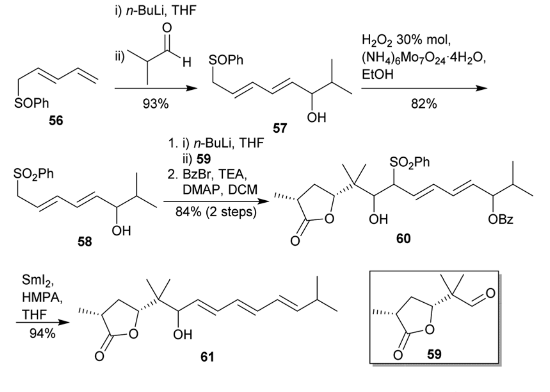


Scheme 6 Trost's approach to THPs A and B of miyakolide (**1**). This figure has been adapted from ref. 29 with permission from ACS PUBLICATIONS, copyright 2008.

reactions for the rings formation, their approach involved the Pd-catalysed alkyne–alkyne coupling[30] and the Ru-catalysed alkene–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 *T*BS 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**.[30] 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 tetrasubstituted THP A started with the preparation of **49** by Ru-catalysed alkene–alkyne coupling between **47** and **48** (Scheme 6).[31] 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$_4$, *T*BS 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



Scheme 7 Markó's approach to polycavernoside A (**2a**). This figure has been adapted from ref. 42 with permission from ELSEVIER, copyright 2009.

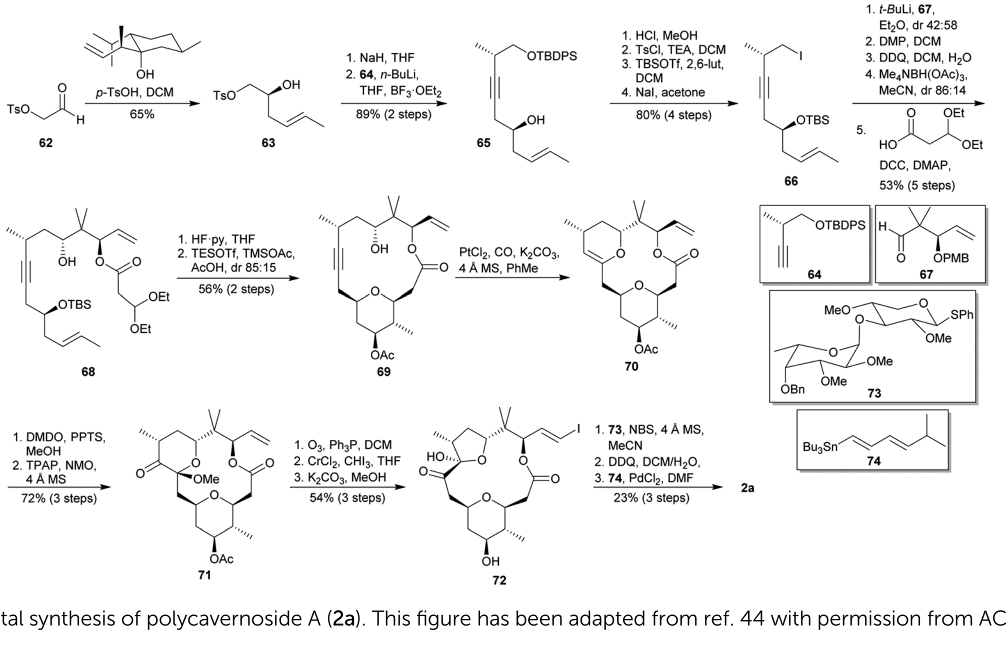
differ mainly in the substituents carried by the disaccharide fragment (a fucosyl-xylose), as well as in the hemiacetal THF owned by **2a–e** (Fig. 1). However, as part of the same family, they have in common several structural characteristics, such as a conjugated lateral chain contiguous to the macrolide 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 its isolation was the first evidence that these macrocyclic toxins are actually cyanobacterial secondary metabolites, what explains the difficulty for re-isolating 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.[12] 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.[39] 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 Murai'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)[42]

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)[44]

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 macrolactone and the tetrasubstituted THP.[44] As illustrated in Scheme 8, the synthesis began with an enantioselective allyl-transfer using Nokami alcohol over aldehyde **62**[45] to yield the homoallylic alcohol **63**. Basic treatment of **63** followed by opening of the epoxide with lithiated alkyne **64**[46] provided secondary alcohol **65**, which was submitted to a sequence of desilylation, regioselective tosylation, silylation of the secondary alcohol and iodide substitution to afford the iodide **66**. Lithium-iodide exchange followed by reaction with aldehyde

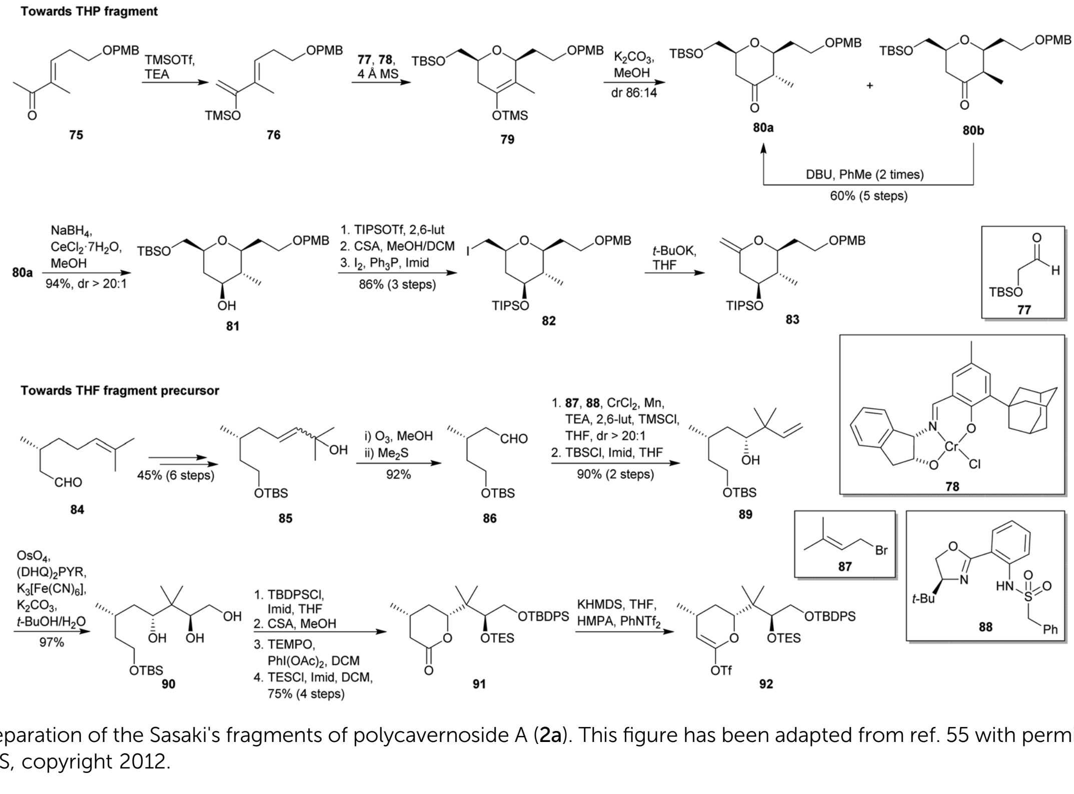


Scheme 8 Lee's total synthesis of polycavernoside A (2a). This figure has been adapted from ref. 44 with permission from ACS PUBLICATIONS, copyright 2010.

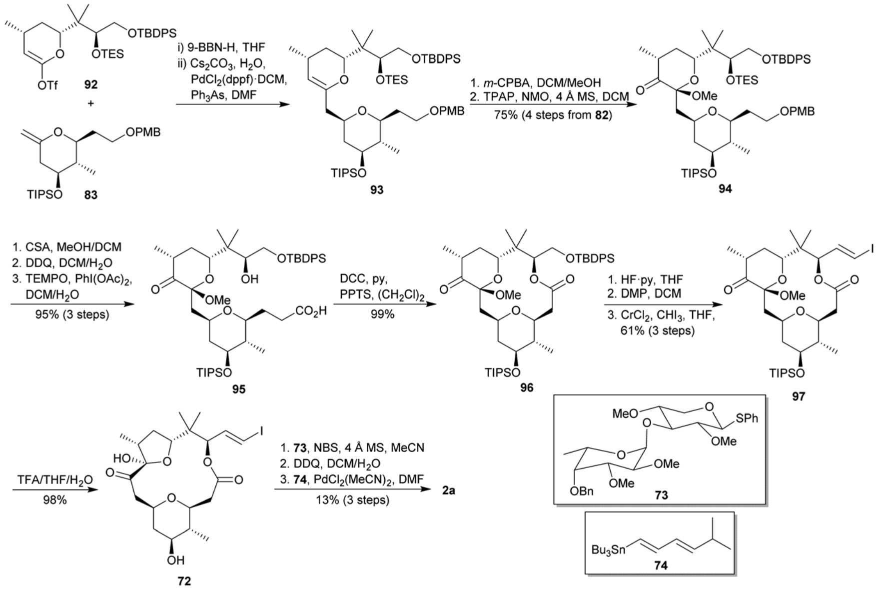
67[47] gave a mixture of secondary alcohols, which were transformed into the corresponding ketone by treatment with Dess–Martin Periodinane (DMP).[48] After *P*MB deprotection, the desired *anti*-relationship was accomplished by means of reduction mediated by $Me_4NBH(OAc)_3$. Condensation of the resulting *anti*-diol with appropriate activated carboxylic acid provided the compound **68**. Acidic cleavage of *T*BS 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 $PtCl_2$ as catalyst.[49] Oxidation of **70** with DMDO followed by MeOH addition delivered the corresponding hydroxyl ketal intermediate, which was submitted to Ley oxidation conditions[50] 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,[51] and basic hydrolysis to release the hydroxy group at C4 position of the THP. *N*BS-mediated glycosylation[52] of **72** was carried out by using the thioglycoside **73**.[53] Posterior debenzylation and Stille-type coupling reaction employing dienylstannane **74**[54] finally provided (−)-polycavernoside A (**2a**) with an overall yield of 1.5% after 22 linear steps.

3.3 Sasaki's synthesis (2012)[55]

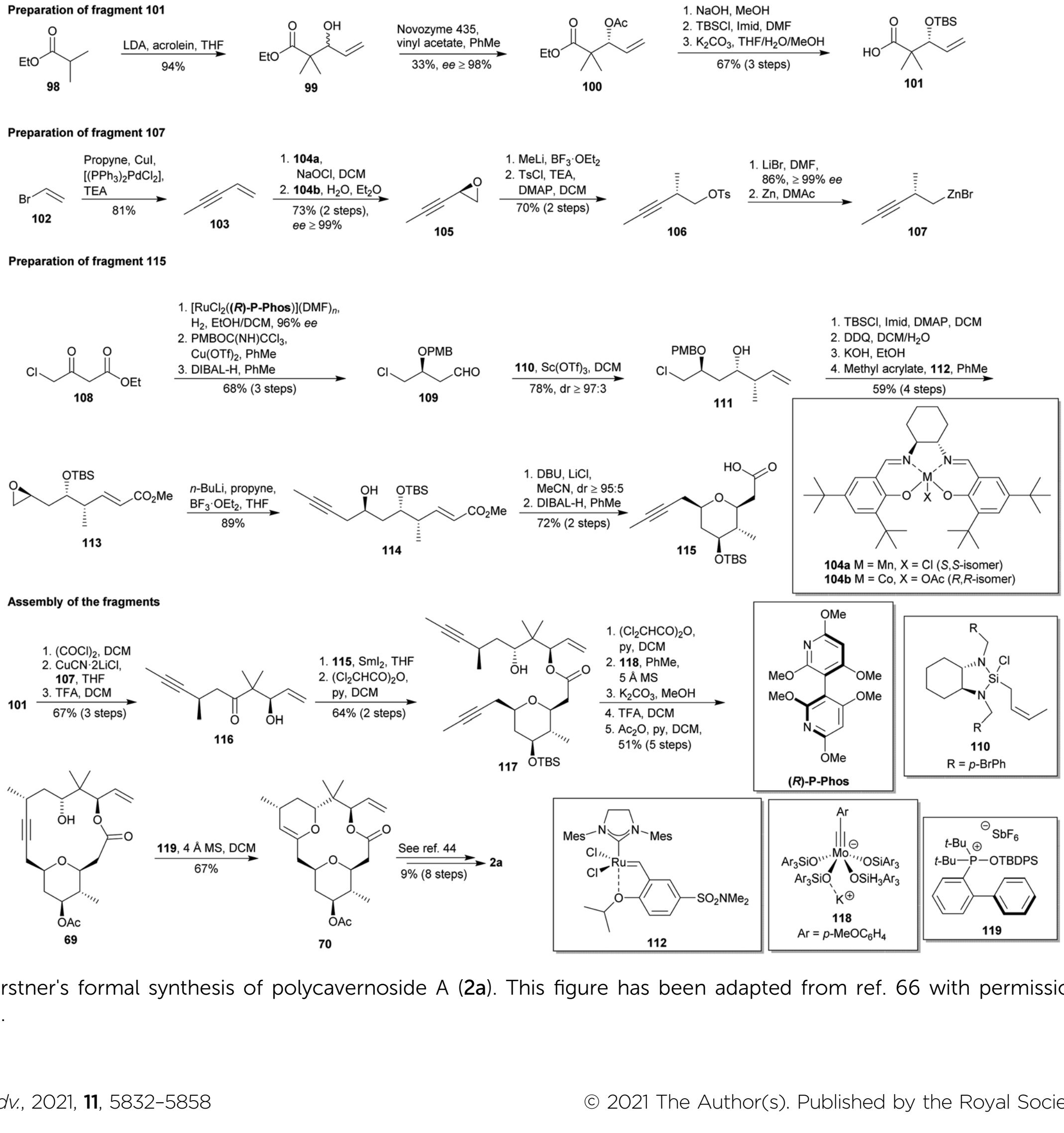
Sasaki and co-workers reported the total synthesis of polycavenroside A (**2a**) in 2012 (Scheme 9).[55] They proposed a convergent approach starting from two fragments and employing as key reactions Suzuki–Miyaura coupling[56] and Keck macrolactonization.[57] As shown in Scheme 9, the construction of the THP fragment started with a catalytic asymmetric hetero Diels–Alder reaction between diene **76** (derived from **75**)[58] and aldehyde **77** by using Jacobsen tridentate chromium(III) catalyst (**78**)[59] to yield dihydropyran **79**. Then, treatment of **79** with K_2CO_3 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.[60] 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**,[61] which was submitted to an ozonolysis to yield aldehyde **86**. Then, **86** was submitted to a catalytic asymmetric allylation with bromide **87** and using sulphonamide **88** as chiral ligand,[62] affording **89** (31%) together with the corresponding diol (69%), which was selectively re-silylated to give **89**. Asymmetric dihydroxylation of alkene **89** using $(DHQ)_2PYR$ as chiral ligand[22] provided triol **90**. Later, it was transformed into lactone **91** by selective protection of the primary alcohol as *T*BDPS ether, cleavage of the *T*BS group, oxidative lactonisation[63] and protection of the secondary alcohol as TES ether. Treatment of **91** with KHMDS and $PhNTf_2$ 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 9 Preparation of the Sasaki's fragments of polycavernoside A (**2a**). This figure has been adapted from ref. 55 with permission from ACS PUBLICATIONS, copyright 2012.



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.

94 was submitted to TES and *P*MB deprotection followed by selective oxidation of the primary alcohol,[65] providing carboxylic acid **95.** Macrolactonisation under Keck conditions led to **96,** which was converted into iodoolefin **97** after cleavage of the *T*BDPS, oxidation with DMP[48] and Takai reaction.[51] Afterwards, TFA-mediated removal of the TIPS and concomitant rearrangement to 5-membered hemiacetal yielded the intermediate **72.** Finally, *N*BS-mediated glycosylation[52] of **72** with the known glycosyl sulphide **73,**[53] followed by the oxidative cleavage of the benzyl ether group using DDQ and a Stille-type coupling[54] with **74**, consummated the total synthesis of **2a** with an overall yield of 2.4% from **84** after 29 steps in the longest linear sequence.

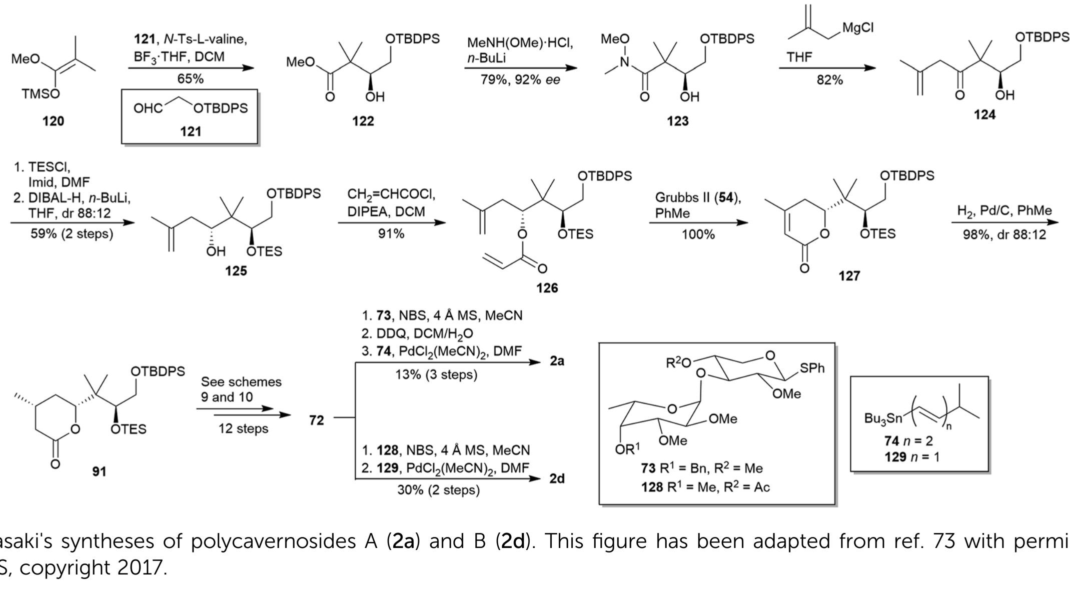
3.4 Fürstner's formal synthesis (2013)[66]

The key feature of the formal synthesis of **2a** proposed by Fürstner and co-workers is the ring-closing alkyne metathesis (RCAM) to form the alkyne-macrolactone **69,**[66] the late-stage intermediate obtained by Lee and co-workers (*vide supra*).[44] Scheme 11 shows the preparation of the three required fragments and the subsequent assembly. They started with an aldol addition of **98** with acrolein to yield racemic aldol **99**, immediately converted into chiral acetated **100** through a lipase-catalysed kinetic resolution. Subsequently, **101** was achieved after basic hydrolysis, silylation and again basic treatment to hydrolyse undesired bis-silylated precursor. Parallelly, the Sonogashira coupling[67] of propyne with **102** afforded alkyne **103**, which was submitted to a Mn-salen (**104a**) catalysed epoxidation followed by a Co-salen (**104b**) catalysed hydrolytic kinetic resolution to provide chiral epoxide **105.**[68] Epoxide opening with MeLi and subsequent *O*-tosylation yielded **106.** Treatment of **106** with LiBr supplied the volatile bromide derivate, which was exposed to Zn dust to provide the organozinc compound **107**. In third place, asymmetric hydrogenation of **108** followed by *P*MB protection of the resulting secondary alcohol and DIBAL-H reduction of the ester allowed the obtaining of **109.** Treatment of this aldehyde with organosilicon compound **110** yielded β,γ-unsaturated alcohol **111**, consecutively submitted to *O*-silylation, DDQ-based deprotection, epoxidation and cross metathesis with methyl acrylate to give epoxide **113**. Epoxide opening with the propynyl borane obtained *in situ* from lithiated propyne and $BF_3 \cdot OEt_2$ yielded **114,**[69] the proper precursor for a DBU/LiCl-promoted *cis*-selective oxy-Michael addition that led to the desired THP ring, subsequently reduced with DIBAL-H to yield **115.**

Once synthesized the three fragments **101, 107** and **115**, their assembly started with the CuCN·2LiCl-mediated[70] acylation of organozinc **107** with the acid chloride of **101** to furnish ketone **116** after desilylation (Scheme 11). Then, **116** was employed in an Evans–Tischenko reaction[71] with THP **115** to yield diyne **117**, which was protected as dichloroacetate and submitted to a RCAM catalysed by Mo-complex **118.**[72] The removal of the dichloroacetate and the change of the protective group in the THP afforded Lee's cycloalkyne **69.**[44] Transannular hydroalkoxylation of **69** using the complex **119** yielded enol ether **70**, thus ending the formal synthesis of **2a.**

3.5 Sasaki's synthesis (2017)[73]

In 2017, Sasaki and co-workers reported an improved version of their previously reported synthesis of polycavernoside A (**2a**) (*vide supra*),[55] as well as the application of this protocol to the synthesis of polycavernoside B (**2d**).[73] Fragment **83** was again prepared as shown in Scheme 9 without any modifications, albeit synthesis of fragment **92** was modified. The new strategy towards **92** began with the Kiyooka aldol reaction[74] between acetal **120** and known aldehyde **121,**[75] affording enantioselectively β-hydroxy ester **122** which was, in turn, converted into Weinreb amide **123** (Scheme 12). Alkylation of Weinreb amide **123** was achieved by using 2-methylallylmagnesium chloride to afford the β-hydroxy ketone **124**, subsequently protected with TESCl and diastereoselectively reduced to give *anti* compound **125.** Diene **126** was accessed by *O*-acylation of alcohol **125**, and submitted to ring-closing metathesis (RCM) conditions[76] to



Scheme 12 Sasaki's syntheses of polycavernosides A (**2a**) and B (**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).[55] 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[52] and stannous polyene **74** and **129** for Stille-type coupling,[54] 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 γ-butyrolactone ring of polycavernoside A (**2a**).[77] The starting sequence implied a mono-benzylation of diol **130** followed by a Swern oxidation[20] to access aldehyde **131** (Scheme 13). Its HWE homologation[26] afforded (*E*)-α,β-unsaturated ester **132**. Ensuing ester reduction and Sharpless asymmetric epoxidation[78] yielded epoxide **133**, which was transformed into iodide derivate **134**. Treatment with Zn and NaI in MeOH allowed the obtaining of allylic alcohol **135**, whose *O*-acylation with **136** gave the bis-olefin **137**. Subsequently, **137** was submitted to RCM employing Grubbs II (**54**) as catalyst[33] and providing thus γ-butyrolactone **138**. Diastereofacial reduction of **138** with concomitant debenzylation and subsequent *O*-silylation finally yielded target **139**.

4. Lasonolide A

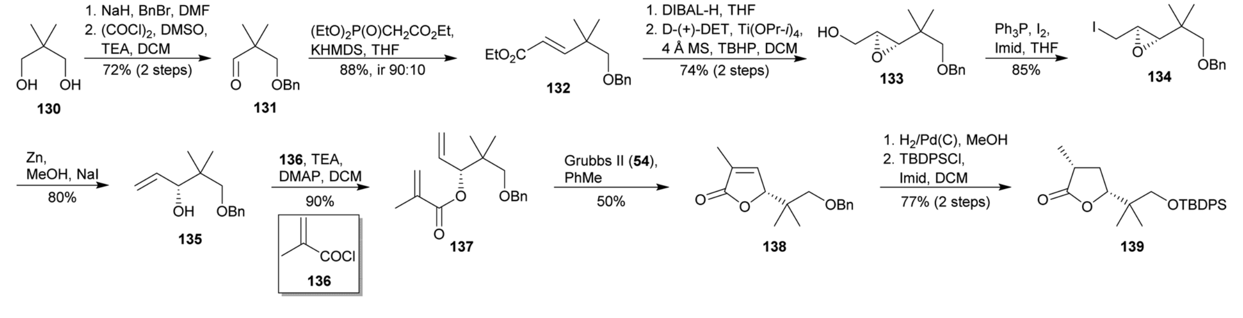
Lasonolide A (**3a**) was isolated from a Caribbean species of sponges of the genus *Forcepia*, collected close to Guana Island, British Virgin Islands. Its originally proposed structure (**3a′**) was published in 1994 by McConnell and co-workers (Fig. 2),[13] and the same group published the initial elucidation of lasonolide B (**3b′**) in 1997.[79] 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).[81] 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* antiproliferative activity exhibited by **3a** against A549 human lung adenocarcinomatous epithelial cells (IC_{50} 40 ng mL^{-1}, *i.e.*, 0.057 μM) and P388 murine leukaemia cell lines (IC_{50} 2 ng mL^{-1}, *i.e.*, 0.003 μM).[13] In addition, it was found that **3a** inhibits cell adhesion in the EL-4.IL2 cell line (IC_{50} 19 ng mL^{-1}, *i.e.*, 0.027 μM), that correlates with signal transduction activity, although toxicity against this line is greater than 25 μg 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 SmI_2-mediated Molander–Reformatsky intramolecular aldol



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.

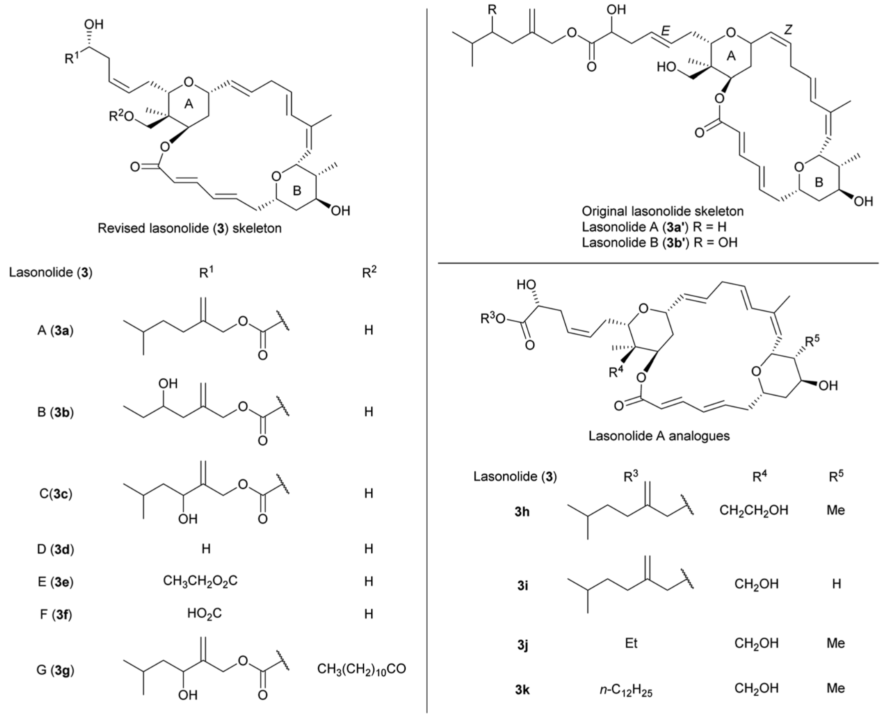
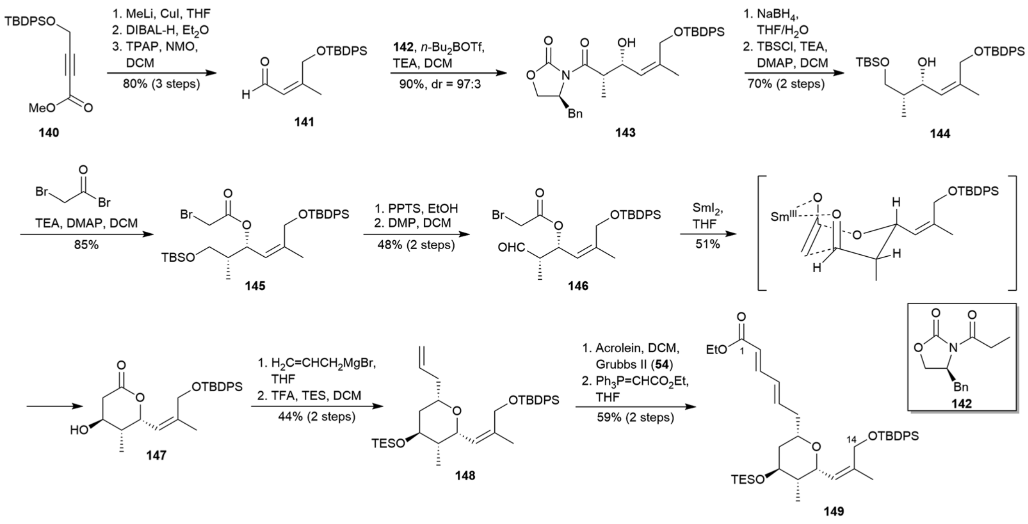
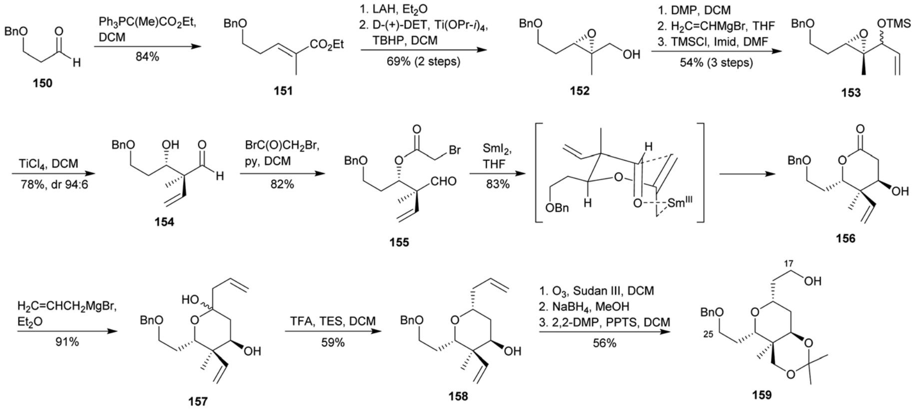


Fig. 2 Lasonolides (3). This figure has been adapted from ref. 82 and 87 with permission from ELSEVIER, copyright 2004 and SPRINGER, copyright 2006.

addition[89] as key reaction to form the oxygenated 6-membered ring. Their approach started with carbocupration under Corey conditions[90] of the known ester **140**,[91] providing an α,β-unsaturated ester which yielded aldehyde **141** after a reduction/oxidation sequence (Scheme 14). Evans aldol condensation[92] between aldehyde **141** and pre-formed (*Z*)-enolate of **142** diastereoselectively gave *syn*-aldol **143**. The chiral auxiliary was then cleavage by treatment with $NaBH_4$,[93] providing a diol whose primary alcohol was protected as *T*BS ether (**144**) prior to be submitted to an esterification of its secondary alcohol to yield **145**. Selective desilylation of **145** by using P*P*TS supplied a terminal alcohol which was then oxidised with DMP[48] to give aldehyde **146**. The SmI_2-mediated intramolecular Reformatsky reaction of **146** under Molander conditions[89] provided a samarium(III) intermediate, which underwent an intramolecular cyclisation to yield β-hydroxy lactone **147**. Alkylation of **147** with allyl magnesium bromide followed by the treatment with TFA allowed the formation of an oxocarbenium ion which was reduced using TES to afford the 2,6-*cis*-THP **148** with the desired configuration.[94] Subsequently, the terminal olefin in **148** 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.

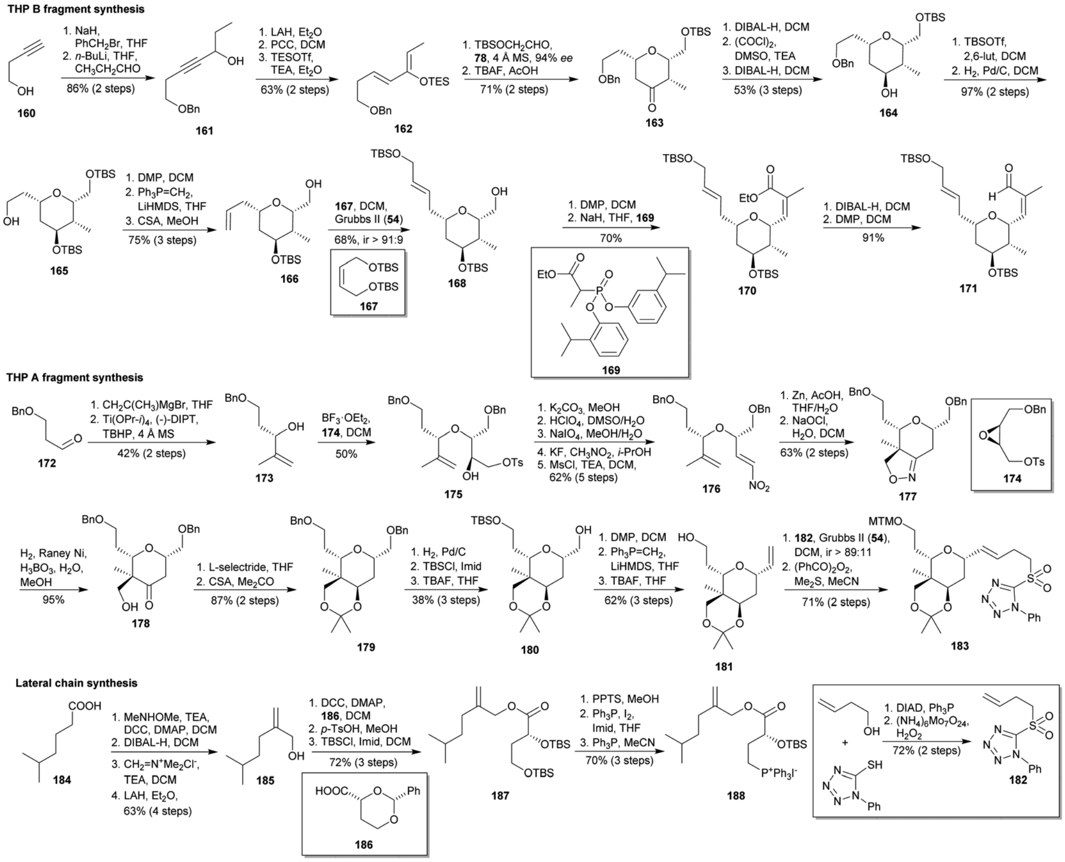


Scheme 15 Jennings' approach to the 2,3,3,4,6-pentasubstituted THP ring of lasonolide A (**3a**). This figure has been adapted from ref. 95 with permission from ELSEVIER, copyright 2007.

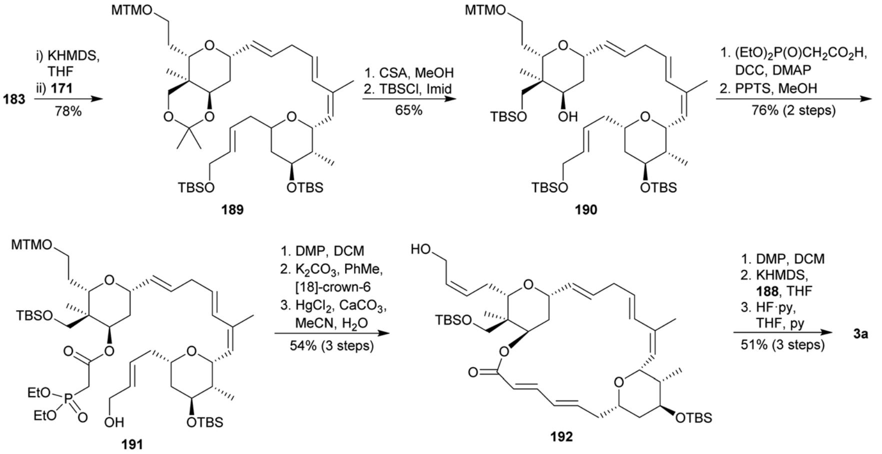
subjected to a chemo and diastereoselective cross-metathesis using Grubbs II catalyst (**54**)[33] to afford an α,β-unsaturated aldehyde which was, in turn, homologated with appropriate phosphonium ylide to deliver target compound **149** in 3% overall yield after 14 steps.

4.2 Jennings' contribution (2007)[95]

Shortly after, Jenning and co-workers acceded to the C17–C25 fragment of lasonolide A (**3a**).[95] This approach involves a Tsuchihashi–Yamamoto rearrangement,[96] and again a SmI$_2$-mediated aldol reaction[89] to achieve the oxygenated 6-membered ring (Scheme 15). Thus, Wittig olefination of known aldehyde **150**[97] yielded ester **151**, whose reduction and Sharpless asymmetric epoxidation[78] 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 reported by Tsuchihashi–Yamamoto,[96] the addition of TiCl$_4$



Scheme 16 Ghosh's syntheses of the fragments of lasonolide A (**3a**). This figure has been adapted from ref. 98*b* with permission from ACS PUBLICATIONS, copyright 2007.



Scheme 17 Ghosh's fragments assembly and final steps on the way to lasonolide A (**3a**). This figure has been adapted from ref. 98*b* with permission from ACS PUBLICATIONS, 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.[94] Nucleophilic addition of allyl magnesium bromide to **156** afforded lactol **157**, whose treatment with TFA and TES provided, *via* formation of an oxocarbenium ion, the THP **158**. Finally, simultaneous ozonolysis of both terminal alkenes followed by $NaBH_4$-mediated reduction and subsequent treatment with P*P*TS yielded desired acetonide **159**, completing thus the synthesis of **3a** fragment C17–C25 with an overall yield of 0.51% after 14 steps from **151**.

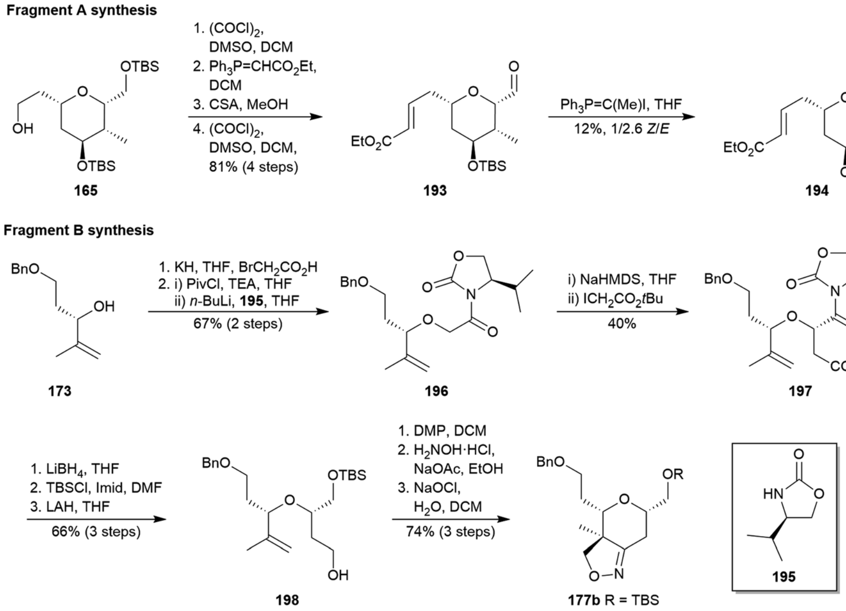
4.3 Ghosh's synthesis (2007)[98]

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).[98] 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 alkynol **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 *T*BSOCH$_2$CHO in the presence of the chiral Schiff base chromium(III) complex **78** (Scheme 9) developed by Jacobsen,[59] 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 hydrogenative removal of benzyl group provided primary alcohol **165**. Then, olefin **166** was accomplished through the sequence Dess–Martin oxidation,[48] Wittig reaction and acidic deprotection of the primary alcohol. Cross-metathesis between olefins **166** and **167** by means of Grubbs II catalyst (**54**)[33] led mainly to the (*E*)-olefin **168**. Successive oxidation of its primary alcohol followed by HWE olefination under Ando conditions[99] afforded the (*Z*)-α,β-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[100] to access alcohol **173**. This alcohol allowed the opening of the epoxide of tosylate **174** to yield **175**.[100] 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-*T*BS 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,[48] Wittig olefination and desilylation. Finally, cross-metathesis[33] between **181** and the sulphone **182**, followed by protection of the alcohol as MTM ether[101] 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**,[103] 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[104] to provide the tetraene **189** (Scheme 17). Acetonide and *T*BS protecting groups cleavage followed by bis-silylation of both primary alcohols yielded tris-*T*BS ether **190**. Its secondary free alcohol was treated with activated phosphonoacetic acid, and



Scheme 18 Ghosh's original approaches to the THP rings of lasonolide A (**3a**). This figure has been adapted from ref. 98*a* with permission from WILEY, copyright 2008.

the allylic *T*BS-ether was selectively deprotected to afford alcohol **191**. After oxidation to aldehyde, the macrolactonization was carried out *via* an intramolecular HWE olefination,[26] followed by MTM removal to yield macrolide **192**. Lasonolide A (**3a**) was finally obtained *via* oxidation, Wittig olefination with phosphonium salt **188** and *T*BS bis-deprotection, with an overall yield of 0.12% after 32 steps in the longest sequence.

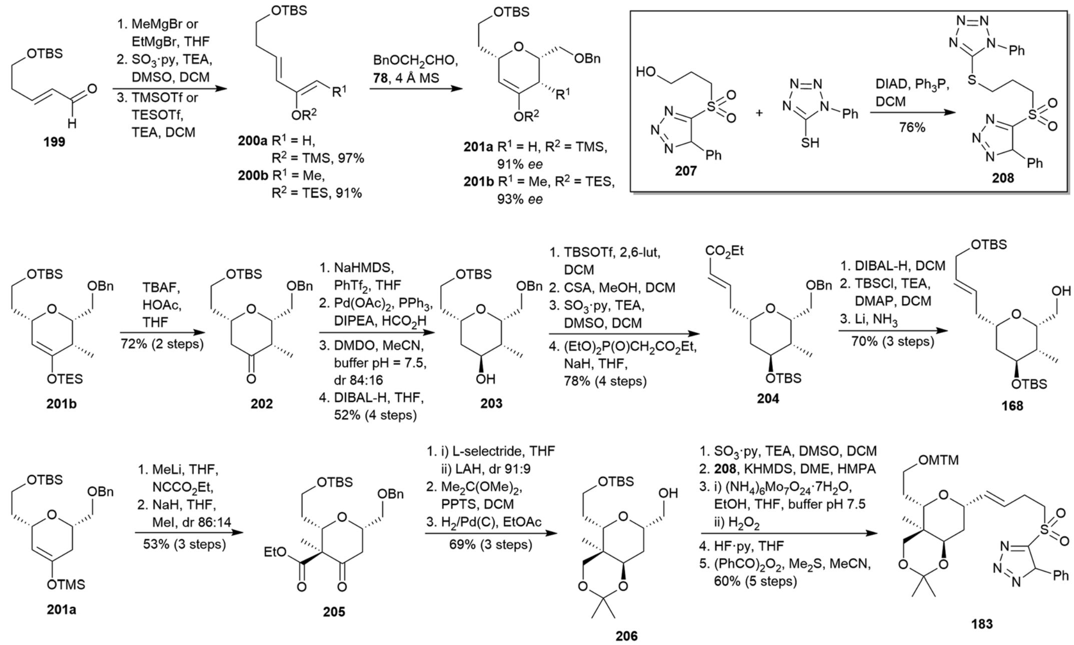
4.4 Ghosh's contribution (2008)[98a]

One year later, Ghosh and co-workers published a comprehensive explanation of their previous reported synthesis of **3a** (*vide supra*).[98a] 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**,[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[105] were infructuous. On the other hand, the pathway to the fragment B began with allylic alcohol **173** (Scheme 16),[98] 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 alkylation[106] 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 isooxazoline **177b**.

4.5 Ghosh's contribution (2012)[107]

Four years later, Ghosh *et al.* envisioned the syntheses of **168** and **183** (the lasonolide A THP fragments previously prepared, see Scheme 16)[98] from two similar precursors: dihydropyrans **201a** and **201b** (Scheme 19).[107] At first, known aldehyde **199**[108] was submitted to a nucleophilic addition with both methyl and ethyl magnesium bromide, Parikh–Doering oxidation[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[110] in the presence of Jacobsen catalyst **78**[59] 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 *T*BS ether followed by selective primary *T*BS acidic deprotection, Parikh–Doering oxidation[109] and HWE olefination[26] yielded the α,β-unsaturated ester **204**. Finally, DIBAL-H reduction, protection of the resulting alcohol as *T*BS 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 tetrahydropyranone **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**.



Scheme 19 Ghosh's preparation of lasonolide A (**3a**) THPs from a quasi-common dihydropyran precursor. This figure has been adapted from ref. 107 with permission from ACS PUBLICATIONS, copyright 2012.

Finally, it was submitted to Parikh–Doering oxidation,[109] Julia–Kocienski olefination[104] with sulphone **208** (previously obtained from known alcohol **207**[111] *via* a Mitsunobu reaction), oxidation of sulphide to sulphone using ammonium heptamolybdate and hydrogen peroxide,[112] desilylation and protection as MTM ether[101] to yield target **183**.

4.6 Trost's synthesis (2014)[113]

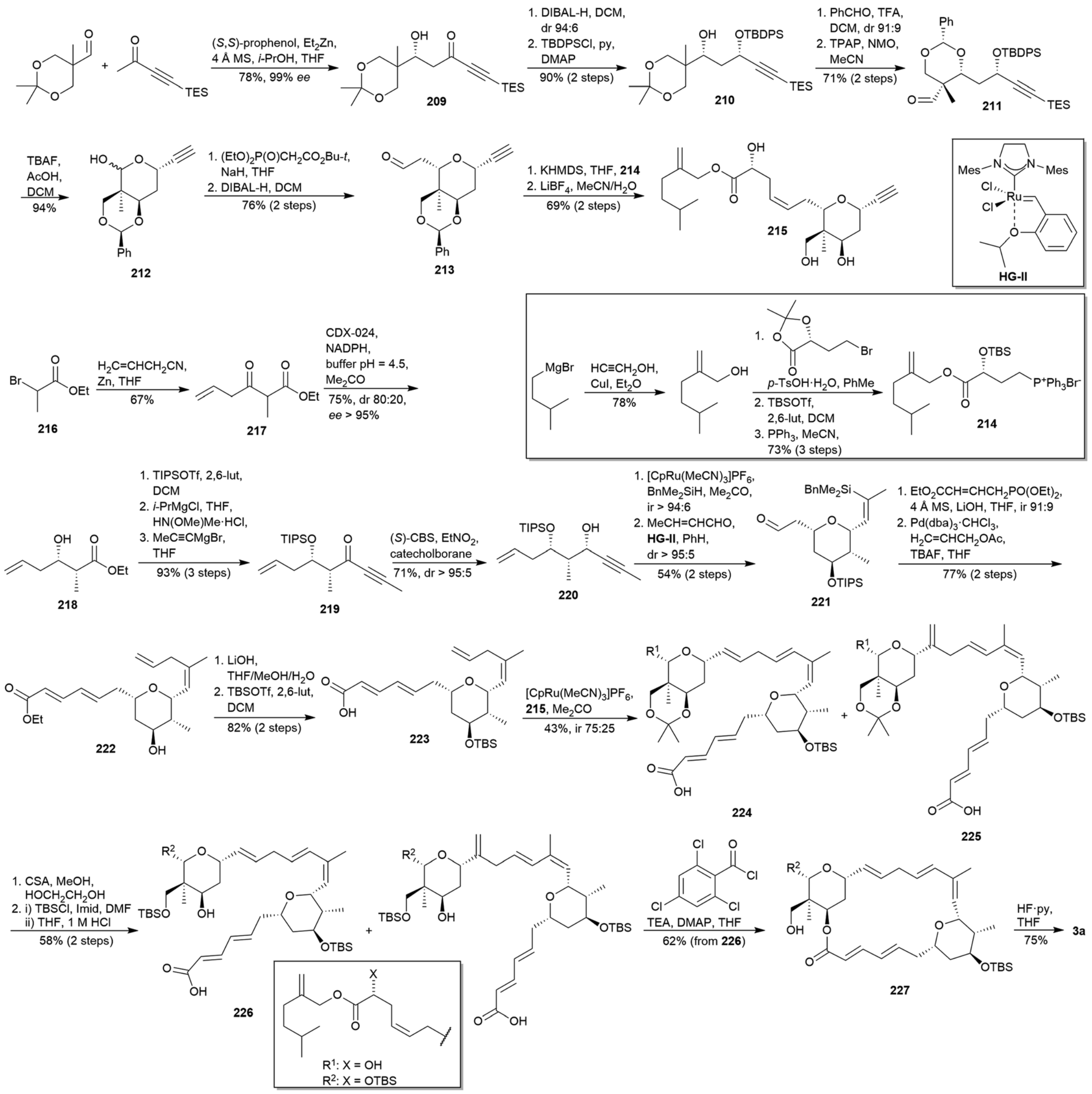
Trost and co-workers disclosed the enantioselective total synthesis of lasonolide A (**3a**) in 2014.[113] The highlighted feature of this route is the Ru-catalysed alkene–alkyne coupling[31] to assemble the two THPs moieties. Initially, β-hydroxy-ynone **209** was obtained *via* a Zn/prophenol-catalysed aldol addition[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[26] and DIBAL-H reduction to aldehyde **213**. Finally, the alkyne **215** was achieved by Wittig olefination of **213** with the phosphonium salt **214** (obtained from isopentylmagnesium bromide *via* carbocupration, 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[115] with allyl cyanide to supply the β-ketoester **217**. An enzymatic kinetic asymmetric reduction[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.[117] (*S*)-Corey–Bakshi–Shibata (CBS) catalysed reduction diastereoselectively afforded **220**.[118] Afterwards, its Ru-catalysed hydrosilylation[119] gave a (*Z*)-vinylsilane, which was underwent Hoveyda–Grubbs[120] cross metathesis with crotonaldehyde and simultaneous oxa-Michael conjugated addition to provide **221**.[121] Terminal aldehyde of the 2,6-*cis*-THP **221** was submitted to an HWE olefination,[26] and then the vinyl silyl group was involved in a Pd-catalysed Hiyama coupling[122] with allyl acetate to furnish desilylated **222**. Ester saponification followed by secondary alcohol protection as its *T*BS ether yielded **223**.

Fragments **223** and **215** were joined *via* an alkene–alkyne coupling employing $[CpRu(MeCN)_3]PF_6$ as catalyst in acetone,[31] 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 *T*BSCl to yield required tris-silyl ether **226** together with its undesired branched isomer. Both were submitted to Yamaguchi macrolactonization to provide, after separation by chromatography, macrolide **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)[123]

Two years later, Trost's group reported a detailed description of their previously published synthesis of **3a**.[113,123] 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, alkynol **220** was transformed into target THP **221** through the following sequence: Ru-catalyzed hydrosilylation,[119] cross-metathesis with ethyl acrylate employing



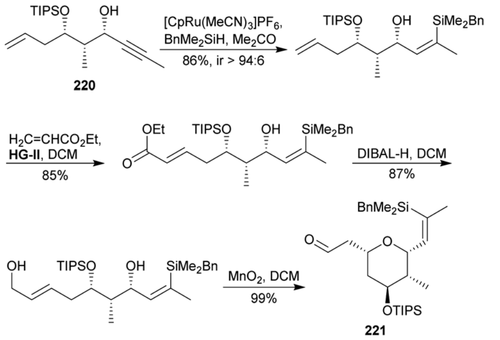
Scheme 20 Trost's synthesis of lasonolide A (**3a**). This figure has been adapted from ref. 113 with permission from ACS PUBLICATIONS, copyright 2014.

Hoveyda–Grubbs catalyst,[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)[124]

In 2018, Hong and co-workers published an enantioconvergent total synthesis of lasonolide A (**3a**).[124] The modular approach employed an iterative Julia olefination to link the THP-containing fragments A and B, previously accessed from both enantiomers of α-allenic alcohol *rac*-**228** after an enzymatic kinetic resolution (Scheme 22).[125] The ring A synthesis began with the direct hydroboration of (*R*)-**228** followed by allylation of the 3-(benzyloxy)propanal[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 *P*TSA triggered a cascade process involving removal of the acetal, oxa-Michael addition, Nef reaction and acetalisation to yield 2,6-*cis*-tetradropyran **231**. Subsequent ozonolysis of the terminal alkene in **231** followed by reduction and silylation afforded **232**. Compound **233** was achieved by deprotection of benzyl group (after an *in situ* BBN protection of secondary alcohol), TEMPO/BAIB oxidation and Wittig olefination with **214** (Scheme 20).[111] Then, **233** was deacetylated and submitted to a selective Julia olefination[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

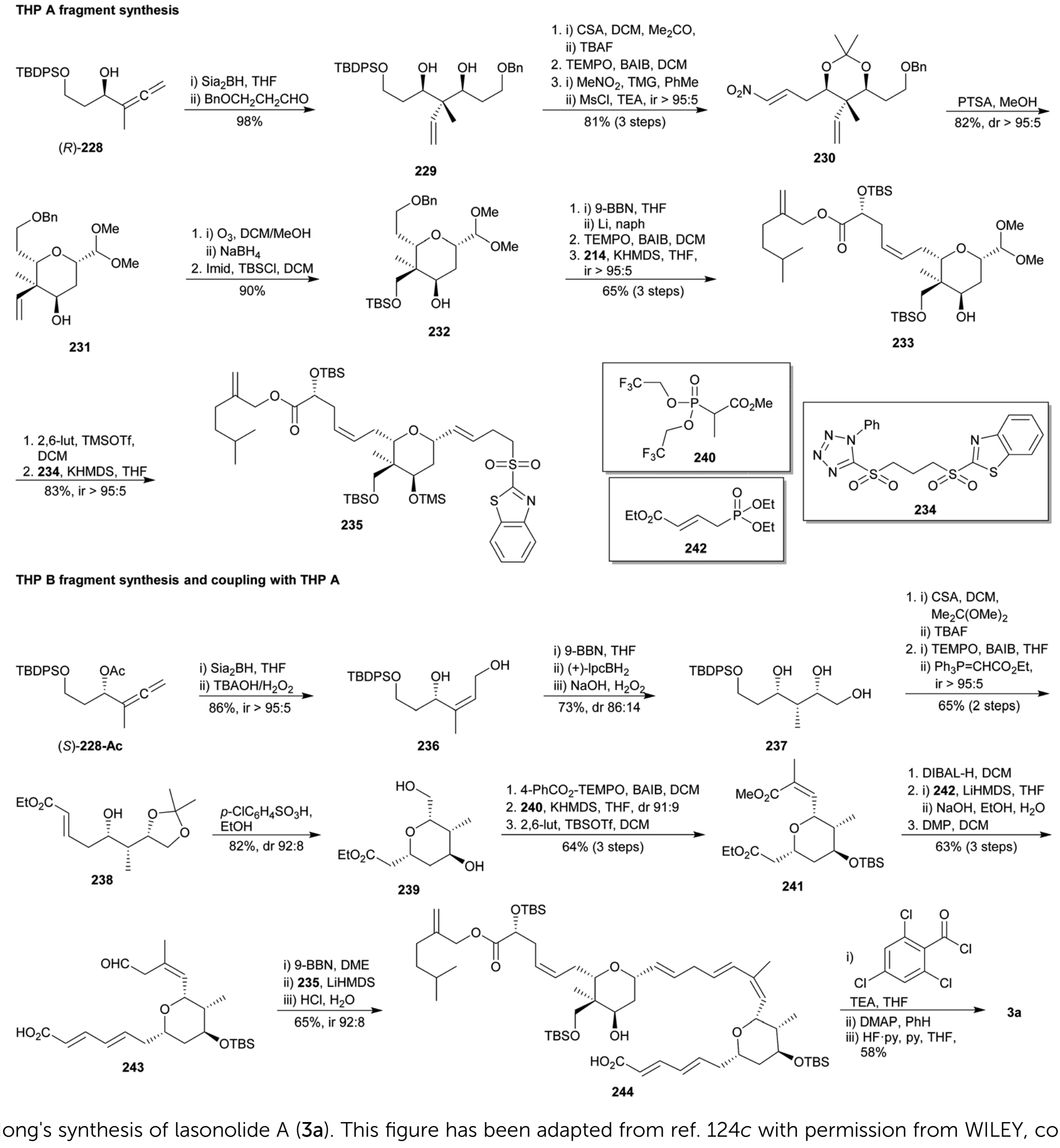


Scheme 21 Trost's alternative approach to the tetrasubstituted THP of lasonolide A (**3a**). This figure has been adapted from ref. 123 with permission from ACS PUBLICATIONS, copyright 2016.

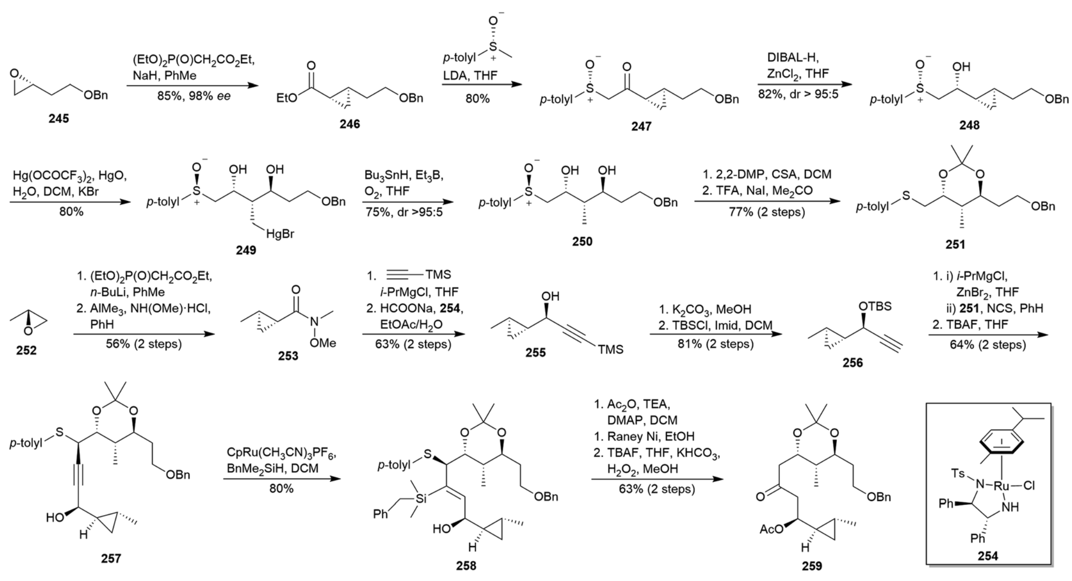
reaction to supply the *E*-α,β-unsaturated ester **238.** Exposure of ester **238** to acidic conditions gave rise to a cascade acetal cleavage and 6-*exo* oxa-Michael addition,[128] affording the corresponding 2,6-*cis*-THP **239.** It was selectively oxidized,[129] treated with the Still–Gennani phosphonate **240**,[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[26] with phosphonate **242** and then to a saponification. Lastly, a DMP-based oxidation[48] of the allylic alcohol provided aldehyde **243.** *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 *via* a macrolactonisation/desilylation protocol.[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 *Myriastra clavosa* in 2002.[131] A short while after, Gustafson group reported the



Scheme 22 Hong's synthesis of lasonolide A (**3a**). This figure has been adapted from ref. 124c with permission from WILEY, copyright 2018.



Scheme 23 Raghavan's approach to clavosolide A (**4a**). This figure has been adapted from ref. 134 with permission from ELSEVIER, copyright 2017.

isolation of clavosolides A–D (**4a–d**) from the same source, as well as the absence of cytotoxic or antiproliferative activities regarding these compounds.[132] 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.[133] Herein, we summarise the two synthetic works regarding clavosolide A (**4a**) subsequent to that date.

5.1 Raghavan's contribution (2017)[134]

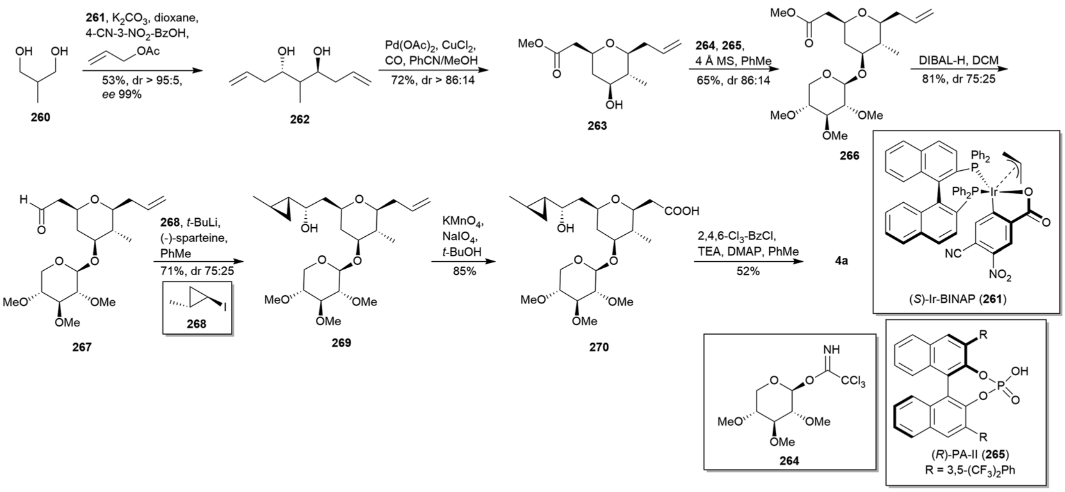
In 2017, Raghavan and co-workers reported a convergent approach to clavosolide A (**4a**),[134] employing as key feature two HWE cyclopropanations[26] over the starting epoxides **245** and **252** (Scheme 23). On the one hand, the HWE cyclopropanation of the epoxide **245**[135] was carried out in order to access ester **246**. Its treatment with lithiated commercial (*R*)-methyl *p*-tolyl sulphoxide afforded the keto sulphoxide **247**. The diastereoselective reduction[136] of ketone in **247** yielded alcohol **248** with the required stereochemistry. Then, the sulphinyl moiety was employed as an internal nucleophile to open the Hg(II)-activated cyclopropane ring,[137] providing thus mercuric bromide **249**, whose subsequent demercuration[138] led to diol **250**. Protection of **250** as acetonide followed by sulphoxide reduction[139] 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**)[140] 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 $ZnBr_2$ and added to previously chlorinated **251** to furnish **257** after *T*BS deprotection. Trost regioselective hydrosilylation[141] afforded the silyl alkene **258**. Finally, acetylation, RANEY® Ni desulphurisation and Tamao–Fleming oxidation[142] of **258**, yielded ketone **259**, an advanced intermediate of clavosolide A (**4a**).

5.2 Krische's synthesis (2019)[143]

The absence of protecting groups and chiral auxiliaries are the distinctive features of Krische's total synthesis of clavosolide A (**4a**).[143] Firstly, a bidirectional asymmetric allylation[144] 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–Semmelhack alkoxypalladation/carbonylation[145] of **262** provided the 2,6-*cis*-THP **263**. A Schmidt-type glycosylation[146] of **263** using trichloroacetimidate **264** and (*R*)-PA-II (**265**)[147] 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,[148] the use of (−)-sparteine[149] 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*)

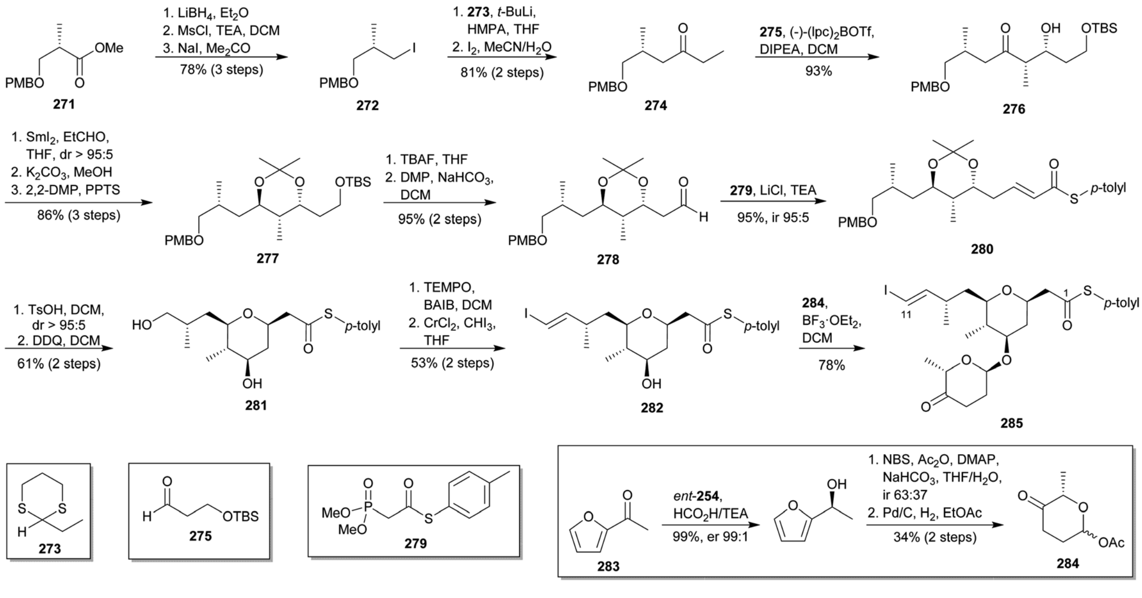


Scheme 24 Krische's total synthesis of clavosolide A (**4a**). This figure has been adapted from ref. 143 with permission from WILEY, copyright 2019.

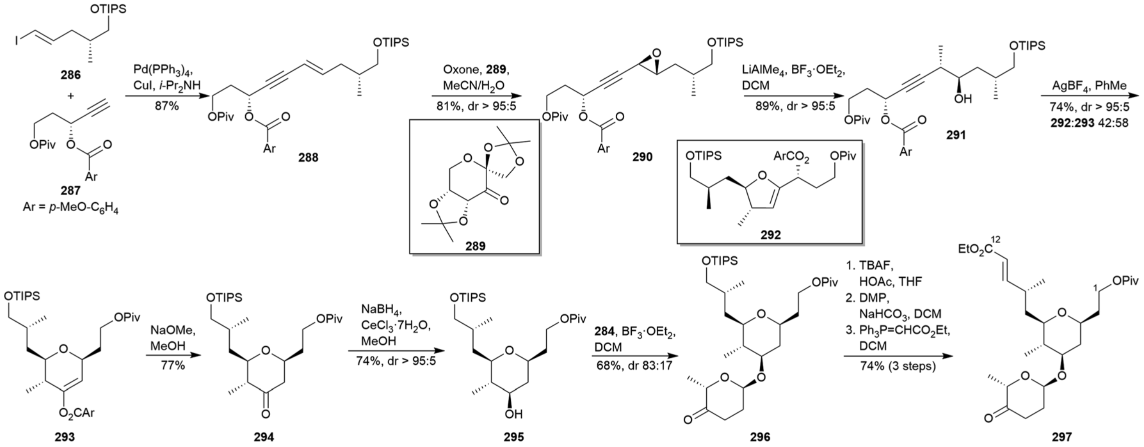
harvested from the deep sea off the coast of Madeira (Portugal).[14] Madeirolide A (**5a**) consists of a 21-membered macrolide with a 2,3,4,6-tetra and a 2,3,4,5,6-pentasubstituted THP, as well as a 2,3,5-trisubstituted THF, all of them with a *cis* ring closure (Fig. 1). A *trans* ring closure is also 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}).[14] 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)[150]

In 2013, Paterson and co-workers, reported the C1–C11 fragment synthesis of madeirolide A (**5a**).[150] 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* methanolysis into the corresponding diol which was, in turn, protected as acetonide **277**. *T*BS-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



Scheme 25 Paterson's approach to madeirolide A (**5a**). This figure has been adapted from ref. 150 with permission from ACS PUBLICATIONS, copyright 2013.

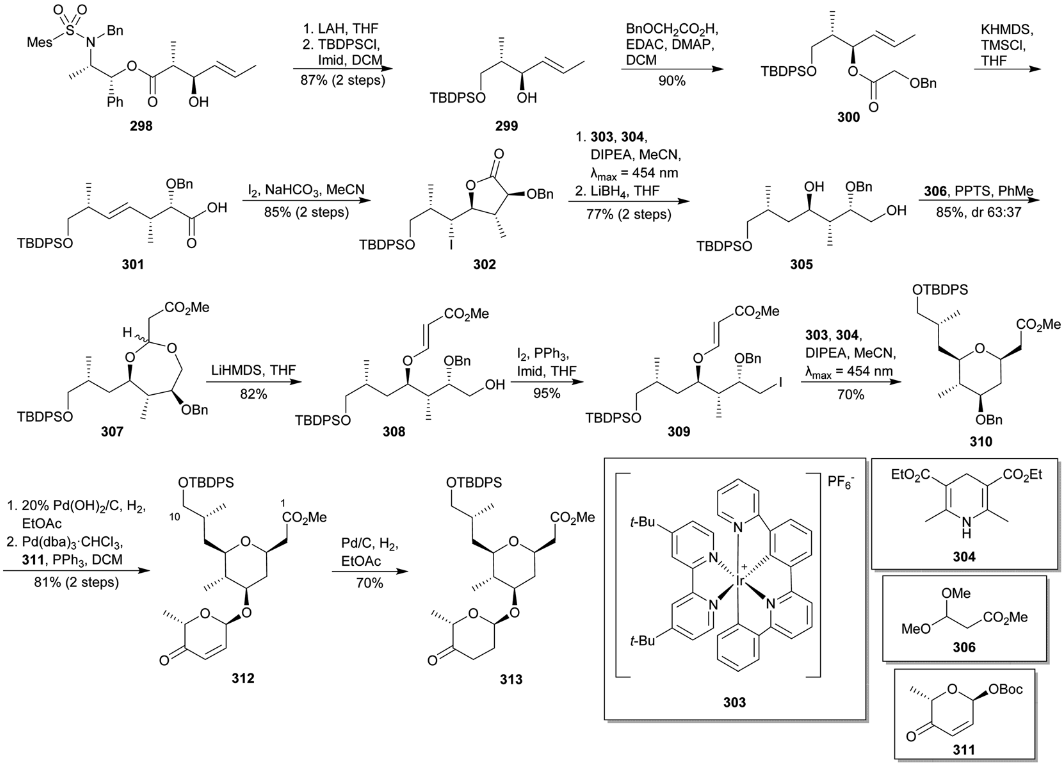


Scheme 26 Carter's approach to madeirolide A (**5a**). This figure has been adapted from ref. 158 with permission from ACS PUBLICATIONS, copyright 2016.

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,[156] then converted into compound **281** after *P*MBO cleavage. Selective oxidation of the primary alcohol in **281,** followed by Takai olefination[51] supplied vinyl iodide **282.** Finally, $BF_3 \cdot OEt_2$-mediated glycosylation of **282** with **284** (previously synthesised in 3 steps from **283** *via* Noyori reduction,[140] Achmatowicz rearrangement followed by *in situ* acetylation of the lactol[157] and hydrogenation) provided the C1–C11 fragment (**285**) of **5a** in 11% overall yield after 17 steps.

6.2 Carter's contribution (2016)[158]

In 2016, Carter and co-workers prepared the C1–C12 fragment of madeirolide A (**5a**) as a showcase of their silver catalyzed cyclisations to obtain THP.[158] The approach began with the Sonogashira coupling[67] between both known iodide **286**[159] and alkyne **287**[160] to provide the propargylic alkene **288** (Scheme 26). Then, it was submitted to a Shi epoxidation[161] to afford epoxide **290**, whose opening by utilizing $LiAlMe_4$ supplied homopropargylic alcohol **291.** Treatment of **291** with $AgBF_4$ delivered a 58 : 42 mixture of the desired dihydropyran **293** together



Scheme 27 Lee's approach to madeirolide A (**5a**). This figure has been adapted from ref. 162 with permission from ACS PUBLICATIONS, copyright 2016.

Table 2 Summary of the strategies employed to the building of the 4-*O*-2,3,4,5-tetrasubstituted THPs

NP	Group	Strategy
1	Masamune's (1997)[17]	Intramolecular nucleophilic addition
1	Evans' (1999)[15]	Intramolecular heteroconjugate addition
1	Trost's (2008)[29]	(1) Ru-catalyzed alkene–alkyne coupling, (2) Pd-catalyzed allylic alkylation
2a	Markó's (2009)[42]	—
2a	Lee's (2010)[44]	Intramolecular Prins cyclisation
2a	Sasaki's (2012)[55]	Catalytic asymmetric hetero Diels–Alder reaction
2a	Fürstner's (2013)[66]	Intramolecular oxy-Michael reaction
2a/ 2b	Sasaki's (2017)[73]	Catalytic asymmetric hetero Diels–Alder reaction
2a	Kadari & Yerrabelly's (2018)[77]	—
3a	Jennings' (2006)[88]	(1) Molander–Reformatsky intramolecular aldol addition, (2) alkylation, (3) reduction
3a	Jennings' (2007)[95]	—
3a	Ghosh's (2007)[98]	Jacobsen catalytic asymmetric hetero-Diels–Alder
3a	Ghosh's (2008)[98a]	—
3a	Ghosh's (2012)[107]	Jacobsen catalytic asymmetric hetero-Diels–Alder
3a	Trost's (2014)[113]	Simultaneous Hoveyda–Grubbs 2nd generation catalyzed cross metathesis/intramolecular oxa-Michael addition
3a	Trost's (2018)[123]	Intramolecular oxa-Michael addition
3a	Hong's (2018)[124]	Intramolecular oxa-Michael addition
4a	Raghavan's (2017)[134]	—
4a	Krische's (2019)[143]	Intramolecular alkoxypalladation/carbonylation of alkenes
5a	Paterson's (2013)[150]	Intramolecular Michael cyclisation
5a	Carter's (2016)[158]	Silver catalysed cyclisation of propargyl benzoate
5a	Lee's (2016)[162]	Ir-catalysed visible light induced radical cyclisation

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 $BF_3\cdot OEt_2$ and glycoside **284**[150] (see preparation in Scheme 25) to furnish compound **296**. Finally, they acceded 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**).[162] 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 assembly 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 ($\lambda_{max} = 454$ 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 led to a radical mediated cyclisation[165] to obtain the 2,6-*cis*-THP **310.** After benzyl hydrogenolysis, a subsequent Pd-catalysed glycosylation of **310** with pyranone **311**[166] gave glycoside **312**[167] 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 macrolides. 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 macrolides.

Abbreviations

2,2-DMP	2,2-Dimethoxypropane
2,6-lut	2,6-Lutidine
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetate
BAIB	Bis(acetoxy)iodobenzene
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl

brsm	Based on recovered starting material
Bz	Benzoyl
c-hex	Cyclohexyl
Cp	Pentamethylcyclopentadienyl
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	Diethyl tartrate
(DHQ)$_2$PYR	Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DIPT	*N*,*N*-Diisopropyltryptamine
DMAc	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMD	Dimethyldioxirane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulphoxide
dppf	1,1′-Bis(diphenylphosphino) ferrocene
dr	Diastereomeric ratio
EDAC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	Enantiomeric excess
Et	Ethyl
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HWE	Horner–Wadsworth–Emmons
IC$_{50}$Half maximal inhibitory concentrationImid	Half maximal inhibitory concentrationImidImidazole
Ipc	Isopinocampheyl
ir	Isomeric ratio
LAH	Lithium aluminium hydride
LC$_{\mathrm{Lo}}$	Lethal concentration low
LDA	Lithium diisopropylamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
Ms	Mesyl
MS	Molecular sieves
MTM	Methylthiomethyl
NADP	Nicotinamide adenine dinucleotide phosphate
naph	Naphthalene
*N*BS	*N*-Bromosuccinimide
*N*CS	*N*-Chlorosuccinimide
*N*MO	*N*-Methylmorpholine *N*-oxide
NP	Natural product
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Piv	Pivaloyl
*P*MB	*p*-Methoxybenzyl
*P*NP	*p*-Nitrophenol
P*P*TS	Pyridinium *p*-toluenesulfonate
*P*TSA	*p*-Toluenesulfonic acid
py	Pyridine
RCAM	Ring closing alkyne metathesis
RCM	Ring-closing metathesis
sia	*sec*-Isoamyl
TBA	Tetra-*n*-butylammonium
*T*BDPS	*tert*-Butyldiphenylsilyl
*T*BHP	*tert*-Butyl hydroperoxide
*T*BS	*tert*-Butyldimethylsilyl
TDMPP	Tris(2,6-dimethoxyphenyl) phosphine
TEA	Triethyl amine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethyl silane
Tf	Triflate
TFA	Trifluoroacetic acid
THP	Tetrahydropyran
THT	Tetrahydrothiophene
TIPS	Triisopropylsilyl
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) G. M. Cragg and D. J. Newman, *Biochim. Biophys. Acta*, 2013, **1830**, 3670–3695; (*b*) A. L. Harvey, *Drug Discovery Today*, 2008, **13**, 894–901; (*c*) A. Ganesan, *Curr. Opin. Chem. Biol.*, 2008, **12**, 306–317.

2 R. Montaser and H. Luesch, *Future Med. Chem.*, 2011, **3**, 1475–1489.

3 D.-X. Kong, Y.-Y. Jiang and H.-Y. Zhang, *Drug Discovery Today*, 2010, **15**, 884–886.

4 A. L. Lane and B. S. Moore, *Nat. Prod. Rep.*, 2011, **28**, 411–428.

5 S. R. Park, A. R. Han, Y.-H. Ban, Y. J. Yoo, E. J. Kim and Y. J. Yoon, *Appl. Microbiol. Biotechnol.*, 2010, **85**, 1227–1239.

6 K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237–4313.

7 (*a*) X. Song, G. Yuan, P. Li and S. Cao, *Molecules*, 2019, **24**, 3913; (*b*) M. Wang, J. Zhang, S. He and X. Yan, *Mar. Drugs*, 2017, **15**, 126; (*c*) D. J. Newman and G. M. Cragg, in *Macrocycles in Drug Discovery*, ed. J. Levin, The Royal Society of Chemistry, Cambridge, 2014, ch. 1, pp. 1–36.

8 (*a*) H. Fuwa, *Mar. Drugs*, 2016, **14**, 65; (*b*) N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323–3335; (*c*) P. A. Clarke and S. Santos, *Eur. J. Org. Chem.*, 2006, 2045–2053.

9 Q. Lu, D. S. Harmalkar, Y. Choi and K. Lee, *Molecules*, 2019, **24**, 3778.

10 (*a*) S. J. Álvarez-Méndez, M. Fariña-Ramos, M. L. Villalba, M. D. Perretti, C. García, L. M. Moujir, M. A. Ramírez and V. S. Martín, *J. Org. Chem.*, 2018, **83**, 9039–9066; (*b*) N. M. Raju, J. M. Babu and B. V. Rao, *Asian J. Chem.*, 2017, **29**, 2771–2775; (*c*) A. Millán, J. R. Smith, J. L.-Y. Chen and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2016, **55**, 2498–2502; (*d*) A. Mahmood, J. R. Suárez, S. P. Thomas and V. K. Aggarwal, *Tetrahedron Lett.*, 2013, **54**, 49–51; (*e*) C. E. Bennett, R. Figueroa, D. J. Hart and D. Yang, *Heterocycles*, 2006, **70**, 119–128; (*f*) C. St, J. Barry, S. R. Crosby, J. R. Harding, R. A. Hughes, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett.*, 2003, **5**, 2429–2432.

11 T. Higa, J. Tanaka, M. Komesu, D. G. Gravalos, J. L. Fernandez Puentes, G. Bernardinelli and C. W. Jefford, *J. Am. Chem. Soc.*, 1992, **114**, 7587–7588.

12 L. Barriault, S. L. Boulet, K. Fujiwara, A. Murai, L. A. Paquette and M. Yotsu-Yamashita, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2069–2072.

13 P. A. Horton, F. E. Koehn, R. E. Longley and O. J. McConnell, *J. Am. Chem. Soc.*, 1994, **116**, 6015–6016.

14 P. L. Winder, PhD thesis, Florida Atlantic University, 2009.

15 D. A. Evans, D. H. B. Ripin, D. P. Halstead and K. R. Campos, *J. Am. Chem. Soc.*, 1999, **121**, 6816–6826.

16 P. Kollár, J. Rajchard, Z. Balounová and J. Pazourek, *Pharm. Biol.*, 2014, **52**, 237–242.

17 T. Yoshimitsu, J. J. Song, G.-Q. Wang and S. Masamune, *J. Org. Chem.*, 1997, **62**, 8978–8979.

18 A. Abiko, J.-F. Liu and S. Masamune, *J. Am. Chem. Soc.*, 1997, **119**, 2586–2587.

19 (*a*) S. Saito, T. Ishikawa, A. Kuroda, K. Koga and T. Moriwake, *Tetrahedron*, 1992, **48**, 4067–4086; (*b*) A. Meyers and J. P. Lawson, *Tetrahedron Lett.*, 1982, **23**, 4883–4886.

20 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165–185.

21 R. Appel, *Angew. Chem., Int. Ed.*, 1975, **14**, 801–811.

22 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.

23 P. Brownbridge, T. H. Chan, M. A. Brook and G. J. Kang, *Can. J. Chem.*, 1983, **61**, 688–693.

24 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127–2129.

25 K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 1620–1621.

26 (*a*) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733–1738; (*b*) L. Horner, H. M. R. Hoffmann, H. G. Wippel and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499–2505.

27 N. Kornblum, B. Taub and H. E. Ungnade, *J. Am. Chem. Soc.*, 1954, **76**, 3209–3211.

28 M. Nitta and T. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1982, 877–878.

29 B. M. Trost and B. L. Ashfeld, *Org. Lett.*, 2008, **10**, 1893–1896.

30 B. M. Trost and A. J. Frontier, *J. Am. Chem. Soc.*, 2000, **122**, 11727–11728.

31 B. M. Trost and M. Machacek, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4693–4697.

32 B. M. Trost, H. Yang and G. Wuitschik, *Org. Lett.*, 2005, **7**, 4761–4764.

33 (*a*) A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370; (*b*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.

34 M. Yotsu-Yamashita, R. L. Haddock and T. Yasumoto, *J. Am. Chem. Soc.*, 1993, **115**, 1147–1148.

35 M. Yotsu-Yamashita, T. Seki, V. J. Paul, H. Naoki and T. Yasumoto, *Tetrahedron Lett.*, 1995, **36**, 5563–5566.

36 M. Yotsu-Yamashita, K. Abe, T. Seki, K. Fujiwara and T. Yasumoto, *Tetrahedron Lett.*, 2007, **48**, 2255–2259.

37 M. Yotsu-Yamashita, T. Yasumoto, S. Yamada, F. F. A. Bajarias, M. A. Formeloza, M. L. Romero and Y. Fukuyo, *Chem. Res. Toxicol.*, 2004, **17**, 1265–1271.

38 G. Navarro, S. Cummings, J. Lee, N. Moss, E. Glukhov, F. A. Valeriote, L. Gerwick and W. H. Gerwick, *Environ. Sci. Technol. Lett.*, 2015, **2**, 166–170.

39 E. Cagide, M. C. Louzao, I. R. Ares, M. R. Vieytes, M. Yotsu-Yamashita, L. A. Paquette and T. Yasumoto, *Cell. Physiol. Biochem.*, 2007, **19**, 185–194.

40 K. Fujiwara, A. Murai, M. Yotsu-Yamashita and T. Yasumoto, *J. Am. Chem. Soc.*, 1998, **120**, 10770–10771.

41 L. A. Paquette and M. Yotsu-Yamashita, in *Phycotoxins: Chemistry and Biochemistry*, ed. L. M. Botana, Blackwell Publishing, Iowa, 2007, ch. 15, pp. 275–296.

42 P. Jourdain, F. Philippart, R. Dumeunier and I. E. Markó, *Tetrahedron Lett.*, 2009, **50**, 3366–3370.

43 C. Pérez-Balado and I. E. Markó, *Tetrahedron*, 2006, **62**, 2331–2349.

44 S. K. Woo and E. Lee, *J. Am. Chem. Soc.*, 2010, **132**, 4564–4565.

45 J. Nokami, M. Ohga, H. Nakamoto, T. Matsubara, I. Hussain and K. Kataoka, *J. Am. Chem. Soc.*, 2001, **123**, 9168–9169.

46 C. H. Kim, H. J. An, W. K. Shin, W. Yu, S. K. Woo, S. K. Jung and E. Lee, *Angew. Chem., Int. Ed.*, 2006, **45**, 8019–8021.

47 P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop and J. D. White, *J. Org. Chem.*, 2005, **70**, 5449–5460.

48 (*a*) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277–7287; (*b*) D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156.

49 S. Bhunia, K.-C. Wang and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2008, **47**, 5063–5066.

50 W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625–1627.

51 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408–7410.

52 K. C. Nicolaou, S. P. Seitz and D. P. Papahatjis, *J. Am. Chem. Soc.*, 1983, **105**, 2430–2434.

53 K. Fujiwara, S. Amano and A. Murai, *Chem. Lett.*, 1995, **24**, 855–856.

54 L. A. Paquette, L. Barriault, D. Pissarnitski and J. N. Johnston, *J. Am. Chem. Soc.*, 2000, **122**, 619–631.

55 Y. Kasai, T. Ito and M. Sasaki, *Org. Lett.*, 2012, **14**, 3186–3189.

56 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.

57 E. P. Boden and G. E. Keck, *J. Org. Chem.*, 1985, **50**, 2394–2395.

58 J. Robertson, J. W. P. Dallimore and P. Meo, *Org. Lett.*, 2004, **6**, 3857–3859.

59 A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 1999, **38**, 2398–2400.

60 (*a*) A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454–5459; (*b*) J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226–2227.

61 E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim and J. K. J. Yun, *J. Org. Chem.*, 1994, **59**, 1444–1456.

62 M. Kurosu, M.-H. Lin and Y. Kishi, *J. Am. Chem. Soc.*, 2004, **126**, 12248–12249.

63 T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams and C. J. Forsyth, *Tetrahedron Lett.*, 2003, **44**, 57–59.

64 M. Sasaki and H. Fuwa, *Nat. Prod. Rep.*, 2008, **25**, 401–426.

65 (*a*) L. J. van den Bos, J. D. C. Codée, J. C. van der Toorn, T. Boltje, J. H. van Boom, H. Overkleeft and G. A. van der Marel, *Org. Lett.*, 2004, **6**, 2165–2168; (*b*) J. B. Epp and T. S. Widlanski, *Org. Chem.*, 1999, **64**, 293–295.

66 L. Brewitz, J. Llaveria, A. Yada and A. Fürstner, *Chem.–Eur. J.*, 2013, **19**, 4532–4537.

67 R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922.

68 M. A. McGowan, C. P. Stevenson, M. A. Schiffler and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2010, **49**, 6147–6150.

69 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391–394.

70 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390–2392.

71 (*a*) K. J. Ralston and A. N. Hulme, *Synthesis*, 2012, **44**, 2310–2324; (*b*) D. A. Evans and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1990, **112**, 6447–6449.

72 (*a*) J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard and A. Fürstner, *Chem.–Eur. J.*, 2012, **18**, 10281–10299; (*b*) J. Heppekausen, R. Stade, R. Goddard and A. Fürstner, *J. Am. Chem. Soc.*, 2010, **132**, 11045–11057.

73 K. Iwasaki, S. Sasaki, Y. Kasai, Y. Kawashima, S. Sasaki, T. Ito, M. Yotsu-Yamashita and M. Sasaki, *J. Org. Chem.*, 2017, **82**, 13204–13219.

74 (*a*) S.-I. Kiyooka and M. A. Hena, *J. Org. Chem.*, 1999, **64**, 5511–5523; (*b*) S.-I. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo and M. Nakano, *J. Org. Chem.*, 1991, **56**, 2276–2278.

75 K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada and P. G. Nantermet, *J. Am. Chem. Soc.*, 1995, **117**, 634–644.

76 (*a*) A. H. Hoveyda and A. R. Zhugralin, *Nature*, 2007, **450**, 243–251; (*b*) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442–4489.

77 S. Kadari, H. Yerrabelly, T. Gogula, Y. G. Erukala, J. R. Yerrabelly and P. K. Begari, *J. Heterocycl. Chem.*, 2018, **55**, 1986–1990.

78 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976.

79 P. A. Horton, F. E. Koehn, R. E. Longley, O. J. McConnell and S. A. Pomponi, *US Pat.*, 5684036, 1997.

80 (*a*) H. Y. Song, J. M. Joo, J. W. Kang, D.-S. Kim, C.-K. Jung, H. S. Kwak, J. H. Park, E. Lee, C. Y. Hong, S. Jeong, K. Jeon and J. H. Park, *J. Org. Chem.*, 2003, **68**, 8080–8087; (*ab*) E. Lee, H. Y. Song, J. M. Joo, J. W. Kang, D. Kim, C. K. Jung, C. Y. Hong, S. Jeong and K. Jeon, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3519–3520; (*ac*) E. Lee, H. Y. Song, J. W. Kang, D. Kim, C. Jung and J. M. Joo, *J. Am. Chem. Soc.*, 2002, **124**, 384–385.

81 A. E. Wright, Y. Chen, P. L. Winder, T. P. Pitts, S. A. Pomponi and R. E. Longley, *J. Nat. Prod.*, 2004, **67**, 1351–1355.

82 J. M. Joo, H. S. Kwak, J. H. Park, H. Y. Song and E. Lee, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1905–1908.

83 R. A. Isbrucker, E. A. Guzmán, T. P. Pitts and A. E. Wright, *J. Pharmacol. Exp. Ther.*, 2009, **331**, 733–739.

84 Y.-W. Zhang, A. K. Ghosh and Y. Pommier, *Cell Cycle*, 2012, **11**, 4424–4435.

85 R. Jossé, Y.-W. Zhang, V. Giroux, A. K. Ghosh, J. Luo and Y. Pommier, *Mar. Drugs*, 2015, **13**, 3625–3639.

86 (*a*) R. Dubey, C. E. Stivala, H. Q. Nguyen, Y.-H. Goo, A. Paul, J. E. Carette, B. M. Trost and R. Rohatgi, *Nat. Chem. Biol.*, 2020, **16**, 206–213; (*b*) Z. Li, S. N. S. Morris and J. A. Olzmann, *Nat. Chem. Biol.*, 2020, **16**, 111–112.

87 M. Shindo, in *Marine Natural Products. Topics in Heterocyclic Chemistry*, ed. H. Kiyota, Springer, Berlin, 2006, vol. 5, pp. 179–254.

88 K. B. Sawant, F. Ding and M. P. Jennings, *Tetrahedron Lett.*, 2006, **47**, 939–942.

89 G. A. Molander, J. B. Etter, L. S. Harring and P. J. Thorel, *J. Am. Chem. Soc.*, 1991, **113**, 8036–8045.

90 E. J. Corey and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, 1969, **91**, 1851–1852.

91 M. Nakada, E. Kojima and H. Ichinose, *Synth. Commun.*, 2000, **30**, 863–868.

92 D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre and J. Bartroli, *Pure Appl. Chem.*, 1981, **53**, 1109–1127.

93 M. Prashad, D. Har, H.-Y. Kim and O. Repic, *Tetrahedron Lett.*, 1998, **39**, 7067–7070.

94 F. Ding and M. P. Jennings, *Org. Lett.*, 2005, **7**, 2321–2324.

95 K. B. Sawant, F. Ding and M. P. Jennings, *Tetrahedron Lett.*, 2007, **48**, 5177–5180.

96 K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki and G. Tsuchihashi, *J. Am. Chem. Soc.*, 1986, **108**, 3827–3829.

97 L. Coppi, A. Ricci and M. Taddei, *J. Org. Chem.*, 1988, **53**, 911–913.

98 (*a*) A. K. Ghosh and G. Gong, *Chem.–Asian J.*, 2008, **3**, 1811–1823; (*b*) A. K. Ghosh and G. Gong, *Org. Lett.*, 2007, **9**, 1437–1440.

99 K. Ando, *J. Org. Chem.*, 1998, **63**, 8411–8416.

100 Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780.

101 J. C. Medina, M. Salomon and K. S. Kyler, *Tetrahedron Lett.*, 1988, **29**, 3773–3776.

102 J. Schreiber, H. Maag, N. Hashimoto and A. Eschenmoser, *Angew. Chem., Int. Ed.*, 1971, **10**, 330–331.

103 X. Ma, R. Saksena, A. Chernyak and P. Kovac, *Org. Biomol. Chem.*, 2003, **1**, 775–784.

104 (*a*) P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett*, 1998, 26–28; (*b*) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175–1178.

105 J. Chen, T. Wang and K. Zhao, *Tetrahedron Lett.*, 1994, **35**, 2827–2828.

106 D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737–1739.

107 A. K. Ghosh and G.-B. Ren, *J. Org. Chem.*, 2012, **77**, 2559–2565.

108 P.-Y. Caron and P. Deslongchamps, *Org. Lett.*, 2010, **12**, 508–511.

109 J. R. Parikh and W. v. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505–5507.

110 S. E. Denmark and B. J. Herbert, *J. Org. Chem.*, 2000, **65**, 2887–2896.

111 S. H. Kang, S. Y. Kang, H. Choi, C. M. Kim, H. Jun and J. Youn, *Synthesis*, 2004, 1102–1114.

112 D. R. Williams, D. A. Brooks and M. A. Berliner, *J. Am. Chem. Soc.*, 1999, **121**, 4924–4925.

113 B. M. Trost, C. E. Stivala, K. L. Hull, A. Huang and D. R. Fandrick, *J. Am. Chem. Soc.*, 2014, **136**, 88–91.

114 B. Trost, A. Fettes and B. T. Shireman, *J. Am. Chem. Soc.*, 2004, **126**, 2660–2661.

115 H. S. P. Rao, S. Rafi and K. Padmavathy, *Tetrahedron*, 2008, **64**, 8037–8043.

116 Y. Kawai, K. Takanobe and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 285–288.

117 J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling and E. J. J. Grabowski, *Tetrahedron Lett.*, 1995, **36**, 5461–5464.

118 C.-M. Yu, C. Kim and J. H. Kweon, *Chem. Commun.*, 2004, 2494–2495.

119 B. M. Trost, Z. T. Ball and T. Joge, *Angew. Chem., Int. Ed.*, 2003, **42**, 3415–3418.

120 S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168–8179.

121 H. Fuwa, K. Noto and M. Sasaki, *Org. Lett.*, 2010, **12**, 1636–1639.

122 T. Hiyama and Y. Hatanaka, *Pure Appl. Chem.*, 1994, **66**, 1471–1478.

123 B. M. Trost, C. E. Stivala, D. R. Fandrick, K. L. Hull, A. Huang, C. Pook and R. Kalkofen, *J. Am. Chem. Soc.*, 2016, **138**, 11690–11701.

124 (*a*) L. Yang, Z. Lin, K. Zheng, L. Kong and R. Hong, *Chin. J. Chem.*, 2020, **38**, 725–736; (*b*) L. Yang and R. Hong, in *Strategies and Tactics in Organic Synthesis*, ed. M. Harmata, Academic Press, London, 2019, ch. 4, pp. 107–138; (*c*) L. Yang, Z. Lin, S. Shao, Q. Zhao and R. Hong, *Angew. Chem., Int. Ed.*, 2018, **57**, 16200–16204, *Angew. Chem., Int. Ed.*, 2019, **58**, 4431.

125 W. Li, L. Chen, Z. Lin, X. Tian, Y. Wang, S.-H. Huang and R. Hong, *Tetrahedron Lett.*, 2016, **57**, 603–606.

126 L. Yang, G. He, R. Yin, L. Zhu, X. Wang and R. Hong, *Angew. Chem., Int. Ed.*, 2014, **53**, 11600–11604.

127 S. H. Kang, S. Y. Kang, C. M. Kim, H.-W. Choi, H. S. Jun, B. M. Lee, C. M. Park and J. W. Jeong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4779–4782.

128 (*a*) J. Hu, M. Bian and H. Ding, *Tetrahedron Lett.*, 2016, **57**, 5519–5539; (*b*) H. Fuwa, *Heterocycles*, 2012, **85**, 1255–1298.

129 M. Rafiee, K. C. Miles and S. S. Stahl, *J. Am. Chem. Soc.*, 2015, **137**, 14751–14757.

130 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405–4408.

131 M. R. Rao and D. J. Faulkner, *J. Nat. Prod.*, 2002, **65**, 386–388.

132 K. L. Erickson, K. R. Gustafson, L. K. Pannell, J. A. Beutlerand and M. R. Boyd, *J. Nat. Prod.*, 2002, **65**, 1303–1306.

133 K. Lee, M. L. Lanier, J.-H. Kwak, H. Kim and J. Hong, *Nat. Prod. Rep.*, 2016, **33**, 1393–1424.

134 S. Raghavan and R. K. Chiluveru, *Tetrahedron Lett.*, 2017, **58**, 2465–2467.

135 B. Reddy and H. M. Meshram, *Tetrahedron Lett.*, 2010, **51**, 4020–4022.

136 G. Solladie, G. Demailly and C. Greck, *Tetrahedron Lett.*, 1985, **26**, 435–438.

137 S. Raghavan, V. S. Babu and B. Sridhar, *J. Org. Chem.*, 2011, **76**, 557–565.

138 D. A. Evans, S. L. Bender and J. Morris, *J. Am. Chem. Soc.*, 1988, **110**, 2506–2526.

139 J. Drabowicz and S. Oae, *Synthesis*, 1977, 404–405.

140 K. Matsumara, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738–8739.

141 B. M. Trost, Z. T. Ball and K. M. Laemmerhold, *J. Am. Chem. Soc.*, 2005, **127**, 10028–10038.

142 (*a*) K. Tamao and K. Maeda, *Tetrahedron Lett.*, 1986, **27**, 65–68; (*b*) K. Tamao, K. Maeda, T. Tanaka and Y. Ito, *Tetrahedron Lett.*, 1988, **29**, 6955–6956.

143 J. M. Cabrera and M. J. Krische, *Angew. Chem., Int. Ed.*, 2019, **58**, 10718–10722.

144 Y. Lu, I. S. Kim, A. Hassan, D. J. Del Valle and M. J. Krische, *Angew. Chem., Int. Ed.*, 2009, **48**, 5018–5021.

145 (*a*) M. F. Semmelhack and C. Bodurow, *J. Am. Chem. Soc.*, 1984, **106**, 1496–1498; (*b*) D. M. Fenton and P. J. Steinwand, *J. Org. Chem.*, 1972, **37**, 2034–2035.

146 (*a*) T. Kimura, M. Sekine, D. Takahashi and K. Toshima, *Angew. Chem., Int. Ed.*, 2013, **52**, 12131–12134; (*b*) D. J. Cox, M. D. Smith and A. J. Fairbanks, *Org. Lett.*, 2010, **12**, 1452–1455.

147 J. B. Son, S. N. Kim, N. Y. Kim and D. H. Lee, *Org. Lett.*, 2006, **8**, 661–664.

148 D. A. Evans, B. D. Allison, M. G. Yang and C. E. Masse, *J. Am. Chem. Soc.*, 2001, **123**, 10840–10852.

149 H. Nozaki, T. Aratani and T. Toraya, *Tetrahedron Lett.*, 1968, **38**, 4097–4098.

150 I. Paterson and G. W. Haslett, *Org. Lett.*, 2013, **15**, 1338–1341.

151 I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott and N. Sereinig, *J. Am. Chem. Soc.*, 2001, **123**, 9535–9544.

152 (*a*) J. S. Dickschat, S. Wickel, C. J. Bolten, T. Nawrath, S. Schulz and C. Wittmann, *Eur. J. Org. Chem.*, 2010, 2687–2695; (*b*) A. B. Smith III, C. M. Adams, S. A. Lodise Barbosa and A. P. Degnan, *J. Am. Chem. Soc.*, 2003, **125**, 350–351.

153 H. Kim and J. Hong, *Org. Lett.*, 2010, **12**, 2880–2883.

154 M. C. Pirrung and N. J. G. Webste, *J. Org. Chem.*, 1987, **52**, 3603–3613.

155 (*a*) M. W. Rathke and M. Nowak, *J. Org. Chem.*, 1985, **50**, 2624–2626; (*b*) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183–2186.

156 H. Fuwa, N. Ichinokawa, K. Noto and M. Sasaki, *J. Org. Chem.*, 2012, **77**, 2588–2607.

157 (*a*) J. P. M. Nunes, L. Veiros, P. D. Vaz, C. A. M. Afonso and S. Caddick, *Tetrahedron*, 2011, **67**, 2779–2787; (*b*) O. Achmatowicz and R. Bielski, *Carbohydr. Res.*, 1977, **55**, 165–176.

158 K. Watanabe, J. Li, N. Veerasamy, A. Ghosh and R. G. Carter, *Org. Lett.*, 2016, **18**, 1744–1747.

159 (*a*) Y. Ni, R. Kassab, M. Chevliakov and J. Montgomery, *J. Am. Chem. Soc.*, 2009, **131**, 17714–17718; (*b*) Z. Huang and E. Negishi, *Org. Lett.*, 2006, **8**, 3675–3678.

160 S. Mahapatra and R. G. Carter, *J. Am. Chem. Soc.*, 2013, **135**, 10792–10803.

161 Y. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 9806–9807.

162 S. Hwang, I. Baek and C. Lee, *Org. Lett.*, 2016, **18**, 2154–2157.

163 (*a*) T. Inoue, J. F. Liu, D. C. Buske and A. J. Abiko, *J. Org. Chem.*, 2002, **67**, 5250–5256; (*b*) A. Abiko, J. F. Liu and S. Masamune, *J. Am. Chem. Soc.*, 1997, **119**, 2586–2587.

164 M. Caballero, M. Garcia-Valverde, R. Pedrosa and M. Vicente, *Tetrahedron: Asymmetry*, 1996, **7**, 219–226.

165 E. Lee, J. S. Tae, C. Lee and C. M. Park, *Tetrahedron Lett.*, 1993, **34**, 4831–4834.

166 B. Wu, M. Li and G. A. O'Doherty, *Org. Lett.*, 2010, **12**, 5466–5469.

167 (*a*) R. S. Babu, M. Zhou and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2004, **126**, 3428–3429; (*b*) A. C. Comely, E. Eelkema, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 8714–8715; (*c*) R. S. Babu and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2003, **125**, 12406–12407.