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2,6-Dioxabicyclo[3.3.1]nonan-3-ones: from natural product treasure troves to synthetic triumphs

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2,6-Dioxabicyclo[3.3.1]nonan-3-ones represent a structurally captivating and biologically potent class of natural products. This review comprehensively chronicles the discovery, isolation, and synthetic evolution of 2,6-disubstituted THP containing diverse bridged bicyclic lactone derivatives. Spanning over three decades of research, we present a chronological survey of naturally occurring THP-fused lactones highlighting their origins, structural diversity, and the synthetic ingenuity employed to construct these challenging frameworks. Emphasis is placed on oxa-Michael addition, tandem isomerization followed by C–O and C–C bond forming reaction, Prins reactions, and ring-closing metathesis each offering unique strategic advantages. Particular attention is paid to the stereochemical complexity and regioselectivity challenges inherent in assembling the densely functionalized polyol systems of these compounds. The purpose of this review is to offer a comprehensive introduction for those new to the field, while also spotlighting the latest exciting advancements in the field.

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Dr Pragna Pratic Das obtained his PhD from CSIR-Indian Institute of Chemical Technology and completed postdoctoral research at Wayne State University, focusing on asymmetric synthesis and bioactive molecule construction. With a strong foundation in both academia and industry, he remained committed to advancing organic and medicinal chemistry, bridging fundamental research with real-world applications. With over 15 years of expertise in organic synthesis, he has led pioneering advancements in rational drug design, the total synthesis of natural products, and innovative synthetic methodologies. As a Principal Scientist at CSIR-National Chemical Laboratory (NCL), his research focuses on molecular complexity, late-stage functionalization, and drug discovery. During his industrial tenure, he has developed PFAS-free protective coatings, advanced adhesion promoters, NCE discovery targeting PDE-4/7, TOPO-IV, and antibiotic-resistant pathogens.

1. Introduction

The chemistry of bicyclic lactones represents a significant and evolving area of research, owing to their presence in numerous natural products and biologically active molecules. These structures are considered privileged scaffolds in pharmaceutical chemistry due to their pronounced bioactivity, high structural rigidity, and well-defined stereochemical architecture. Among them, the 2,6-disubstituted tetrahydropyran (THP) scaffold and its bridged bicyclic lactone derivatives (2,6-dioxabicyclo[3.3.1]nonan-3-ones) have garnered substantial interest from both natural product and synthetic organic chemists. This attention is driven by their complex molecular frameworks and diverse biological activities, which render them attractive targets for both natural product discovery and synthetic development (Fig. 1). In this comprehensive review, we explore the multifaceted roles of THP-based bicyclic lactones, with particular focus on their isolation from natural sources and their total synthesis. We provide a systematic account of natural products featuring this core motif, followed by a critical examination of the synthetic methodologies employed to access these architecturally complex and biologically significant compounds. The review includes the discoveries of key natural product, their biosynthetic origins, alongside insights into the synthetic strategies devised to construct them. Through this detailed analysis, we aim to offer a valuable resource for the scientific community, highlighting the interplay between natural product chemistry, synthetic innovation, and biological relevance.

Debendra Kumar Mohapatra

Prof. Debendra K. Mohapatra completed his PhD in Organic Chemistry at CSIR-IICT in 1999 and obtained his degree from Osmania University. He pursued postdoctoral research in USA, and served as a visiting scientist at both the University of Cambridge and the University of Oxford. After his postdoctoral work, he joined the National Chemical Laboratory (NCL), Pune, where he served as a Scientist from 2002 to 2008. In 2008, he returned to CSIR-IICT, Hyderabad, where he held successive roles from Principal Scientist to Chief Scientist (2008–2025). His research focuses on organic chemistry, particularly the asymmetric total synthesis of complex natural products with medicinal relevance. Prof. Mohapatra has been recognized with numerous awards, including the CRSI Bronze Medal, NASI-Reliance Industries Platinum Jubilee Award, CSIR Technology Award, CDRI award, UDCT young scientist award, AVRA Young Scientist Award, and INSA Young Scientist Award. He is currently serving as a Professor of Organic Chemistry at the Indian Institute of Science Education and Research (IISER) Berhampur, Odisha.

2. Biosynthetic pathway

In *Goniothalamus* and *Polyalthia* species, styryllactones are proposed to arise from a shikimate-derived phenylpropanoid precursor that is extended through polyketide-like condensations and then sculpted by oxidative tailoring and stereocontrolled cyclizations. Through this cascade, a broad repertoire of lactone frameworks goniothalamin, goniodiols, parvistones, and pyranopyrone-type styryllactones emerges, as shown below and outlined in the subsequent steps (Scheme 1).[1]

2.1 Biosynthesis of the phenylpropanoid starter unit through the shikimate pathway

The shikimate pathway furnishes L-phenylalanine, which undergoes PAL-mediated deamination to generate *trans*-cinnamic acid. Subsequent activation through CoA ligation produces cinnamoyl-CoA **31**, the principal starter unit for downstream polyketide chain assembly.

2.2 Polyketide extension to a triketide intermediate

Cinnamoyl-CoA condenses sequentially with two malonyl-CoA **32** units to generate a linear triketide thioester **33**, following the well-established logic of type III PKSs. A chalcone synthase like enzyme, likely tailored to styryllactone formation, is presumed to catalyze this step. The nascent triketide then undergoes reduction, intramolecular lactonization, and dehydration to produce the α,β-unsaturated δ-lactone **34** that serves as the core precursor for the styryllactone family. In some cases, premature thioester cleavage, dehydration, or *O*-methylation diverts this intermediate toward metabolites such as methyl-5-hydroxy-7-phenylhepta-2,6-dienoate and structurally related linear phenylalkenoates.

2.3 Biosynthesis of goniothalamin from lactone

Reduction of the C7/C8 olefin within the δ-lactone yields goniothalamin **35**, a well-characterized styryl-δ-lactone. This compound represents a central branching node in styryllactone biosynthesis, serving as the precursor to the majority of known derivatives.

2.4 Enzymatic epoxidation to goniothalamin oxides

Oxidation at the C7–C8 olefinic bond of goniothalamin generates the goniothalamin oxides **36**, most likely through monooxygenase- or haloperoxidase-driven epoxidation. From these intermediates, biosynthetic pathways can diverge to yield a broad array of stereochemically elaborate styryllactone scaffolds.

2.5 Hydrolytic ring opening

Hydrolytic opening of the epoxide furnishes goniodiol-type diols, such as (6*S*,7*S*,8*S*)-goniodiol, with high stereoselectivity. These diols act as pivotal intermediates along biosynthetic pathways leading to more extensively oxidized or cyclized styryllactone structures.

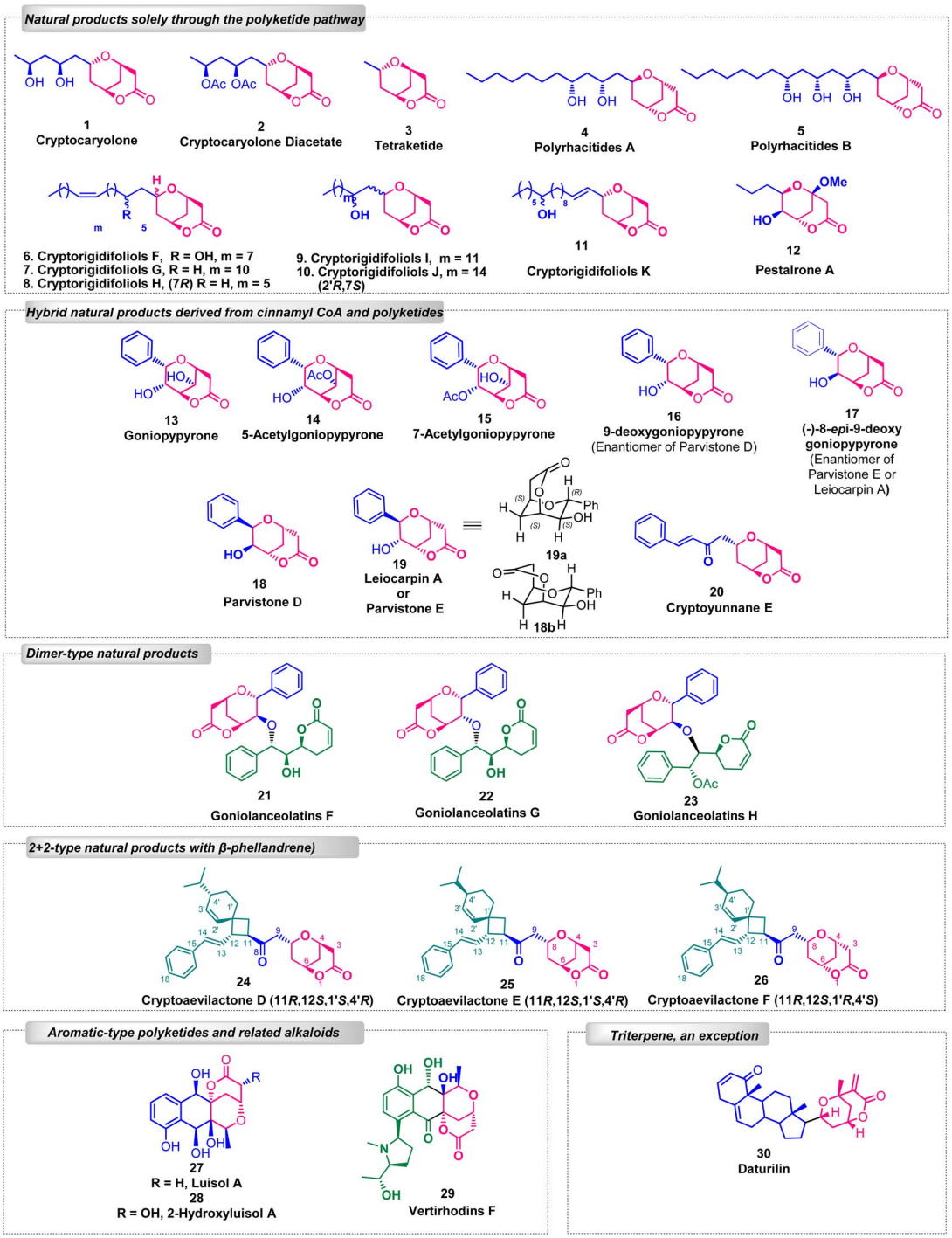


Fig. 1 Natural product structures of THP containing bicyclic lactones.

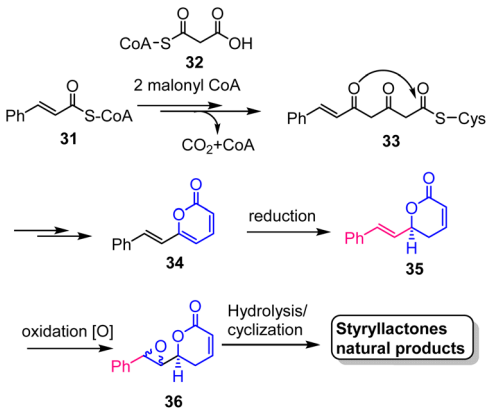
2.6 Intramolecular 1,4-Michael addition

An ensuing intramolecular attack by a hydroxyl group on the lactone ring gives rise to pyranopyrone-type architectures. In particular, for substrates with the (6*S*,7*S*,8*S*) configuration, the hydroxyl produced during epoxide opening can trigger a spontaneous intramolecular 1,4-oxa-Michael addition, forming bicyclic frameworks such as parvistone D and related styryllactones. This step provides the biosynthetic origin of both the pyranopyrone and 9-deoxygoniopyrone skeletons.

Overall, the interplay of oxidation, reduction, and both non-enzymatic and enzyme-mediated rearrangement steps helps to explain the broad structural diversity characteristic of styryllactones.

3. Synthetic strategies

Over the past two decades, significant efforts within the synthetic chemistry community have focused on addressing the



Scheme 1 Biosynthetic pathway.

challenges of constructing the complex and distinctive tetrahydropyran (THP)-containing bridged bicyclic core structures. This pursuit has driven the development and refinement of numerous innovative synthetic strategies. Although, a variety of strategies have been developed for the construction of dihydropyran frameworks, such as electrophile-initiated alkylation of glycals,[2] hetero-Diels–Alder cycloadditions,[3] ring-closing metathesis,[4] Prins cyclizations,[5] metal halide-induced cyclizations, and vinylsilane cyclization of oxocarbenium ions,[6] or the intramolecular silyl-modified Sakurai reaction (ISMS),[7] many of these methods suffer from drawbacks such as prolonged reaction times, the requirement for stoichiometric amounts of expensive reagents, harsh conditions, and occasionally low yields or poor stereoselectivity.

Among these, the late-stage oxa-Michael reaction on unsaturated ester moieties has emerged as a key methodology due to its efficiency, versatility, and broad applicability. In addition to the oxa-Michael reaction, several other strategies have demonstrated notable success, including iodine-mediated tandem isomerization followed by C–O and C–C bond forming reaction and Prins cyclization, each offering unique advantages in specific synthetic contexts. These approaches are further enriched by a range of alternative methodologies that highlight the ingenuity and adaptability of synthetic chemists in tackling such structurally intricate targets. These bicyclic frameworks majorly have been constructed using four principal synthetic approaches, which include:

(1) Oxa-Michael reaction.

(2) Iodine-catalyzed tandem isomerization followed by C–O and C–C bond formation.

(3) Lactonization.

(4) Prins cyclization.

3.1 Oxa-Michael approach

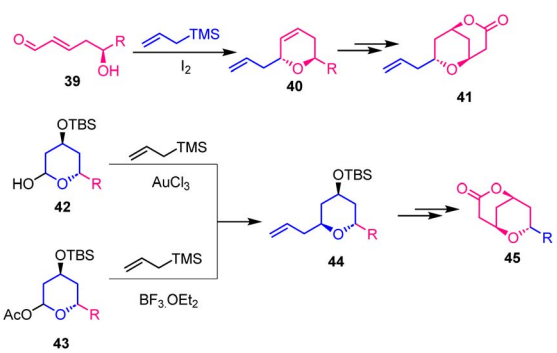
Oxa-Michael reaction is a nucleophilic conjugate addition in which an oxygen-based nucleophile typically an alcohol or phenol (compound **37**) adds to an activated α,β-unsaturated carbonyl or related Michael acceptor (compound **38**). This transformation efficiently forms C–O bonds, enabling the construction of ethers and cyclic oxygen-containing

Scheme 2 Oxa-Michael.

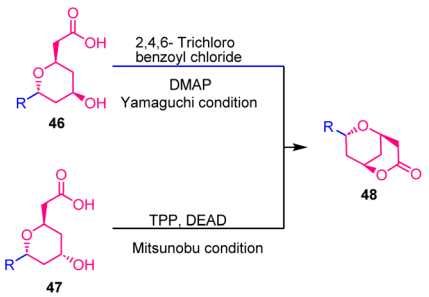
frameworks. Because of its mild conditions, broad substrate scope, and stereoselective variants, the oxa-Michael reaction is widely applied in the synthesis of natural products, polymers, and complex bioactive molecules (Scheme 2). The stereoselective synthesis of 2,6-disubstituted tetrahydropyrans continues to pose a significant challenge in synthetic organic chemistry, largely due to the structural complexity these molecules exhibit, including multiple functional groups and stereogenic centers. The versatility and efficiency of oxa-Michael reaction have established it as a foundational method in synthesizing complex natural products with bicyclic lactone cores. This intramolecular oxa-Michael provides an easy acess to bicyclic lactone framework as depicted in Scheme 2.

3.2 Tandem isomerization followed by C–O and C–C bond forming reaction

There is a continued search for catalytic systems that combine high efficiency with operational simplicity, environmental compatibility, and mild reaction conditions. In this context, molecular iodine has garnered increasing interest. Its advantages include low cost, low toxicity, ready availability, and demonstrated catalytic efficiency in a variety of organic transformations (Scheme 3).[8] As a mild Lewis acid,[9] iodine has shown particular promise in activating carbonyl compounds, notably in acetalization and related reactions. Motivated by this reactivity, an iodine-mediated protocol was developed involving the reaction of δ-hydroxy α,β-unsaturated aldehydes **39** with allyltrimethylsilane, which proceeds under mild conditions in a highly regio- and stereoselective fashion to afford 2,6-disubstituted-3,4-dihydropyrans **40**. This method offers an efficient route to the *trans*-2,6-disubstituted-3,4-dihydropyran core, a key structural motif found in a wide range of biologically active natural products. Additional reactions using other Lewis acids (*e.g.*, $AuCl_3$, $BF_3.OEt_2$) have likewise been developed starting from compound **42** and **43**.



Scheme 3 C–O and C–C bond forming reaction sequence.



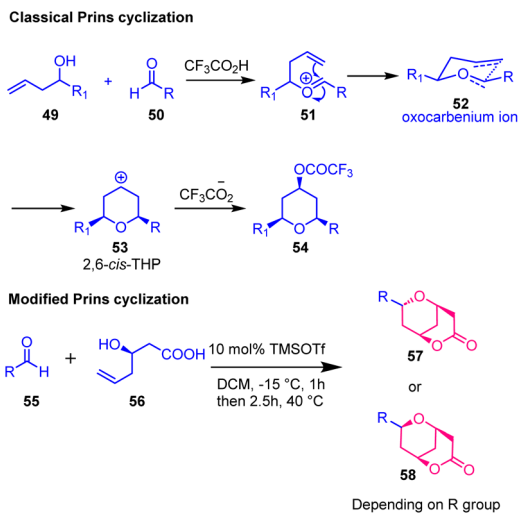
Scheme 4 Lactonization reaction.

3.3 Lactonization

Lactonization is widely used in natural product synthesis, enabling the construction of five- and six-membered oxygen heterocycles with good efficiency and stereocontrol. Yamaguchi lactonization is a high-yielding method for forming medium- and large-sized lactones using 2,4,6-trichlorobenzoyl chloride (TCBC) and DMAP under mild conditions (**46**), whereas lactonization under Mitsunobu conditions involves the intramolecular formation of lactones using alcohols and carboxylic acids activated by the Mitsunobu reagent system (commonly PPh_3 and DEAD/DIAD) (**47**). This approach allows esterification with inversion of configuration at the alcoholic stereocenter, enabling stereoselective lactone construction (Scheme 4).

3.4 Prins cyclization

Prins cyclization is a classical reaction in organic chemistry involving the condensation of an alkene with an aldehyde or ketone in the presence of a Lewis or Brønsted acid. This process generates key carbocation intermediates that undergo intramolecular capture, leading to the formation of oxygen-containing cyclic structures such as tetrahydropyrans and tetrahydrofurans. Owing to its ability to construct complex rings with high stereocontrol, Prins cyclization has become a valuable tool in the synthesis of natural products and other structurally intricate molecules (Scheme 5).



Scheme 5 Prins cyclization.

4. Cryptocaryolone and cryptocaryolone diacetate

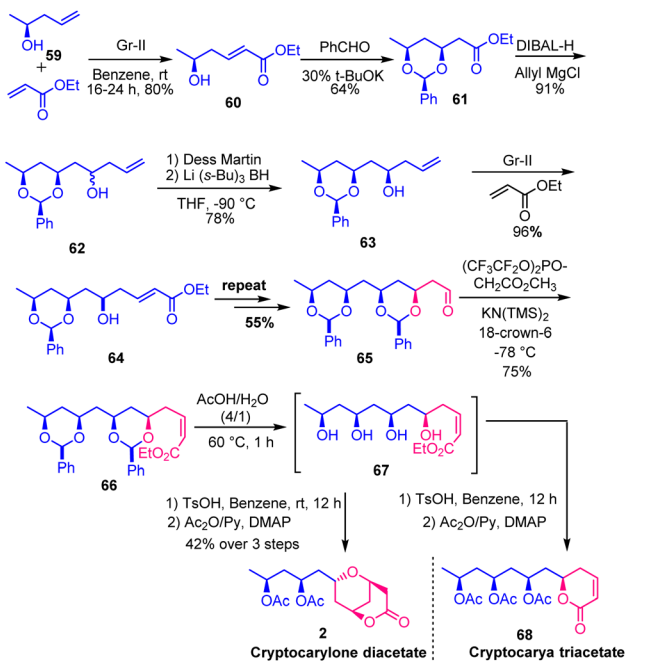
4.1 Isolation and biological activity

In 1995, Horn *et al.*[10a] uncovered an array of structurally similar 6-substituted 5,6-dihydropyran-2-ones, among which were compounds such as cryptocarya diacetate and cryptocarya triacetate. Additionally, two complex bicyclic pyranone/polyol structures of cryptocaryolone **2** and cryptocaryolone diacetate **3** were identified. These entities were isolated from the biologically potent hexane and acetone extracts derived from the leaves and bark of *Cryptocarya latifolia*, a plant indigenous to South Africa, historically esteemed for its purported therapeutic and mystical attributes (Fig. 1).[10b]

4.2 Synthesis of cryptocaryolone and cryptocaryolone diacetate

In their 2003 work, O'Doherty and colleagues[11] meticulously detailed an enantioselective total synthesis of cryptocarya triacetate, cryptocaryolone, and cryptocaryolone diacetate. Their approach hinged on a sophisticated two-step sequence involving consecutive Evans acetal-forming reactions to establish 1,3-*syn* polyol frameworks, accompanied by a strategic cross-metathesis, followed by an oxa-Michael reaction to forge the intricate bicyclic ring system (Scheme 6).

To accomplish this, they efficiently synthesized the pivotal *trans*-α-hydroxy-1-enoates **60** *via* cross-metathesis between ethyl acrylate and a chiral homoallyl alcohol **59**, catalyzed by Grubbs' second-generation catalyst. Subsequently, treatment of δ-hydroxy enoate **60** with an excess of benzaldehyde (4 equivalents) and a catalytic quantity of KO*t*-Bu afforded a 55% yield of



Scheme 6 Synthesis of cryptocarylone diacetate by O'Doherty and colleagues (2003).[11]

the bis-benzylidene-protected ester **61**. It was then transformed to homoallylic alcohol **62** by DIBAL-H reduction and treatment with allylmagnesium chloride. It was further oxidized to keto and then stereoselective reduction was performed by Li(*s*-Bu_3)BH to get *syn*-homoallyl alcohol **63**. They performed cross metathesis to get δ-hydroxy enoate which was then subjected to Evans acetal-forming reaction to get **64** and replicated similar reaction sequences to finally embark on the intermediate **65**. Subsequent treatment of compound **65** with the potassium salt of compound $(CF_3CH_2O)_2POCH_2CO_2Me$ in the presence of 18-crown-6 resulted product **66** with a desirable 4 : 1 *cis* double-bond stereoselectivity. O'Doherty *et al.* then explored a deprotection and lactonization sequence to transform enoate **67** into pyranone **68** rather than the targeted bicyclic lactone. Refluxing with 80% aqueous acetic acid successfully removed the benzylidene protecting group, predominantly yielding tetraol **68** with minor lactone formation. However, under alternative conditions (1% TsOH in benzene), triol lactone was obtained more effectively with minimal formation of the bicyclic lactone and rapid peracylation using an excess of Ac_2O in pyridine with catalytic DMAP, produced cryptocarya triacetate **68**.

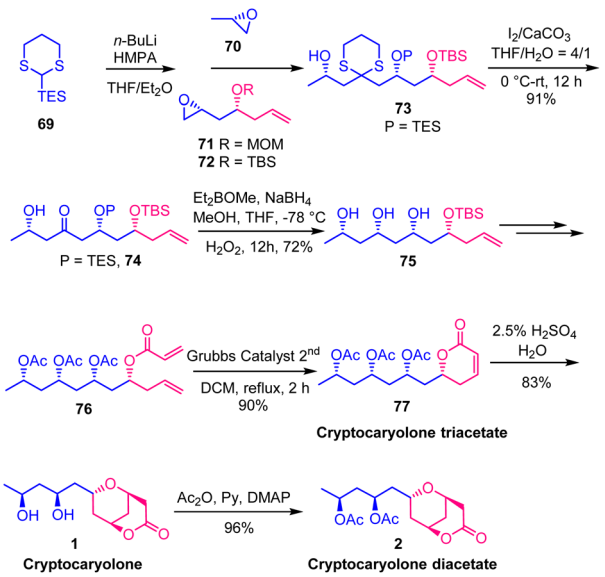
Further, they refined the acid-catalyzed deprotection strategy, employing prolonged TsOH treatment in benzene to efficiently convert substrates to the bicyclic natural products, specifically cryptocaryolone **1**, achieving high conversion rates. Peracylation with Ac_2O/pyridine in these cases furnished cryptocaryolone diacetate **2** with exceptional yields.

4.3 Synthesis of cryptocaryolone and cryptocaryolone diacetate

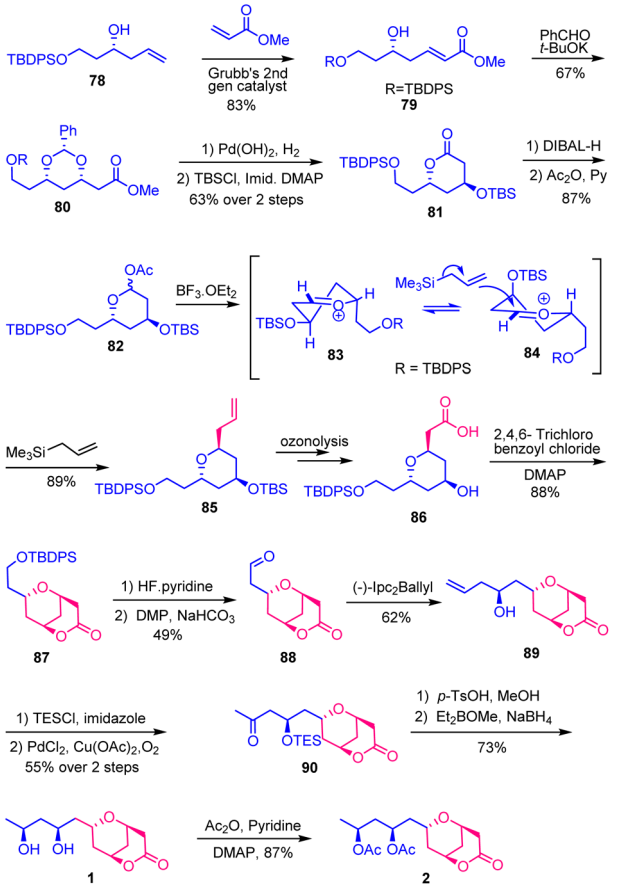
In 2009, X. She and colleagues delineated an asymmetric total synthesis of cryptocaryolone triacetate **77**, cryptocaryolone **1**, and cryptocaryolone diacetate **2**.[12] Their approach leveraged the Tietze–Smith linchpin convergence strategy to assemble polyols from a chiral epoxide scaffold, employed ring-closing metathesis to yield an unsaturated lactone moiety, and utilized a tandem sequence of deacetylation and intramolecular oxa-Michael addition as pivotal steps in constructing the dioxabicyclo[3.3.1]nonan-2-one unit (Scheme 7).

The synthesis commenced with a tri-component linchpin coupling, utilizing 2-triethylsilyl-1,3-dithiane **69** with two distinct epoxide electrophiles to afford the unsymmetrical adducts **73**. Among various solvent systems, a THF/Et_2O mixture was identified as optimal, and TBS-protected epoxide **72** proved to be the superior electrophile compared to the MOM-protected variant **71**, delivering the target product **73** in a commendable 74% yield.

Subsequently, dithiane deprotection was executed, followed by a stereoselective, hydroxyl-directed reduction of the resultant ketone **74**, yielding the all-syn triol **75** in 72% yield. This triol derivative was then transformed into a di-acrylate intermediate **76** through standard modifications, and ring-closing metathesis, facilitated by the second-generation Grubbs catalyst, led to the formation of cryptocarya triacetate **77** with a yield of 90%. A critical tandem process of deacylation followed by 1,4-oxa-Michael addition was evaluated under both acidic and basic conditions. Ultimately, when cryptocarya triacetate **77** was exposed to H_2O in the presence of a catalytic quantity of H_2SO_4, it underwent comprehensive deacylation succeeded by spontaneous oxa-Michael addition, yielding cryptocaryolone **1**. Finally, cryptocaryolone **2** was



Scheme 7 Synthesis of cryptocaryolone and cryptocaryolone diacetate by X. She *et al.* (2009).[12]



Scheme 8 Synthesis of the cryptocarya diacetate by M. P. Jennings *et al.* (2012).[13]

subjected to Ac_2O in pyridine, resulting in cryptocaryolone diacetate **2** with an impressive 96% yield.

4.4 Synthesis of cryptocarya triacetate, cryptocaryolone and cryptocaryolone diacetate

In 2012, M. P. Jennings[13] and colleagues synthesized (−)-cryptocaryolone and cryptocaryolone diacetate through a sequence of sophisticated transformations. Initiating from a TBDPS-protected homoallylic alcohol **78**, synthesized *via* an enantioselective allylboration of 3-((tertbutyldiphenylsilyl)-oxy) propanal (Scheme 8). Their approach proceeded with olefin cross-metathesis using methyl acrylate which furnished the δ-hydroxy-(*E*)-α,β-unsaturated methyl ester **79** in high diastereoselective form. Subsequently, employing the Evans-acetal protocol, the δ-hydroxy enoate was transformed into the *syn*-benzylidene acetal **80** upon the addition of PhCHO and KO*t*Bu.

This compound underwent hydrogenolytic cleavage with H_2 and Pearlman's catalyst [$Pd(OH)_2$], prompting an intramolecular cyclization/transesterification to yield hydroxy lactone **81**. Following TBS protection, DIBAL-H reduction at −78 °C afforded a diastereomeric mixture (4 : 1 ratio) of lactol **82**. This lactol mixture was then acylated with acetic anhydride to form a pivotal intermediate, primed for oxocarbenium ion-mediated allylation. The allylation employed $BF_3{\cdot}OEt_2$ and allyltrimethylsilane at −78 °C, forming the desired α-C-glycoside subunit **85**. Their stereochemical predictions, aligned with Woerpel's work,[14] suggested that the "matched" conformer, **84**, would favour axial addition *via* a chair-like transition state, selectively producing **85**. Oxidative cleavage of the terminal olefin, followed by Pinnick oxidation and deprotection, yielded the *seco*-acid **86**. Subjected to Yamaguchi lactonization, this provided the 2,6-dioxabicyclo [3.3.1]nonan-3-one **87** with the TBDPS protecting group intact. Desilylation and subsequent Dess–Martin periodinane oxidation generated an aldehyde, poised for an asymmetric allylboration utilizing Brown's (−)-Ipc_2Ballyl.

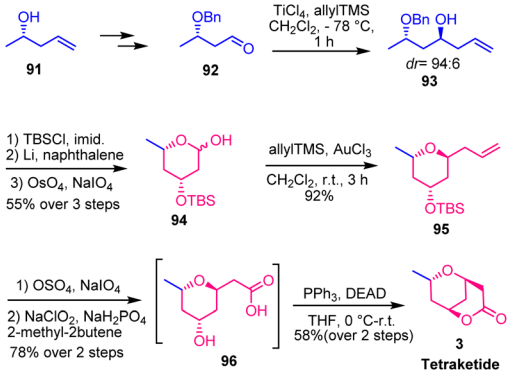
This reaction achieved a homoallylic alcohol **89** with a moderate diastereoselectivity ratio of 6 : 1. After protecting the resulting alcohol, Wacker oxidation of the terminal alkene introduced a β-hydroxy keto intermediate **90**, setting the stage for a hydroxy-directed *syn*-reduction. This selective reduction with Et_2BOMe afforded the 1,3-*syn* diol, culminating in a near-quantitative yield (92%) of cryptocaryolone **1**. The final step entailed acetylation with Ac_2O and pyridine, delivering cryptocaryolone diacetate **2**.

Further, they refined the acid-catalyzed deprotection strategy, employing prolonged TsOH treatment in benzene to efficiently convert substrates to the bicyclic natural products, specifically cryptocaryolones **1**, achieving high conversion rates. Peracylation with Ac_2O/pyridine in these cases furnished cryptocaryolone diacetate **2** with exceptional yields.

5. Tetraketide

5.1 Isolation and biological activity

The new tetraketide was isolated from the leaves of *Euscaphis japonica* in 2000 by Y. Takeda *et al.*[15] The compound tetraketide



Scheme 9 Total synthesis of the tetraketide by Mohapatra *et al.* (2016).[16]

3 was obtained from the *n*-BuOH-soluble fraction of a methanol extract through repeated column chromatography using highly porous synthetic resin (Fig. 1).

5.2 Synthesis of tetraketide

In 2016, Mohapatra[16] and colleagues documented the total synthesis of tetraketide and cryptorigidifoliol I, advancing the field of complex natural product synthesis. Both target molecules exhibit a bicyclic lactone core, achievable through an intramolecular Mitsunobu lactonization of a *seco* acid precursor. This *seco* acid, in turn, originates from lactols, accessed through a gold-catalyzed, highly diastereoselective allylation—an innovation pioneered by research team.[17]

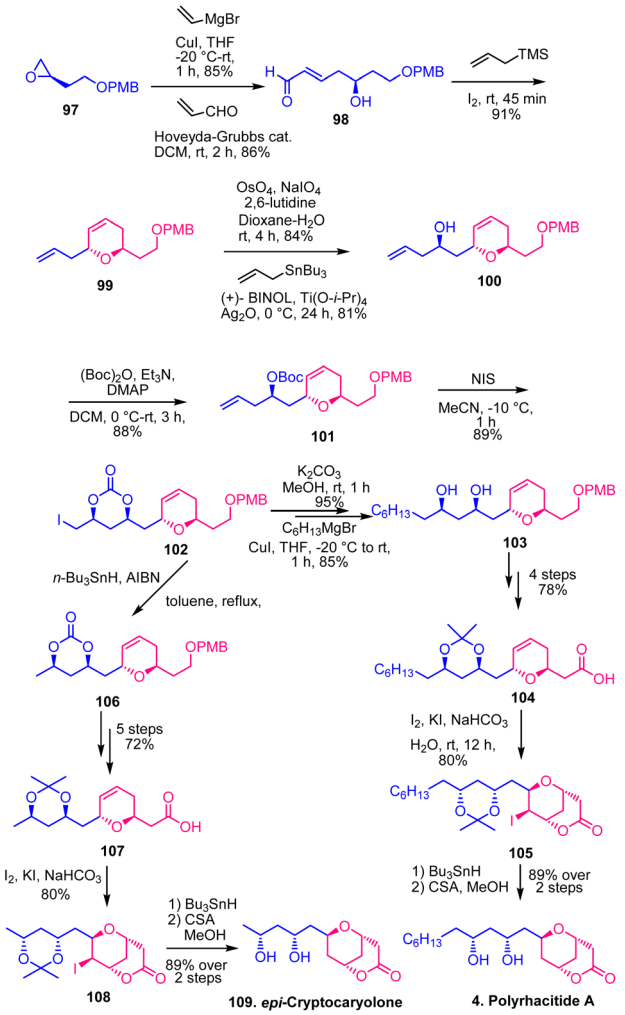
The synthetic pathway for tetraketide **3** initiated with commercially available (*S*)-pent-4-en-2-ol **91** which was transformed into aldehyde intermediate **92** by literature method (Scheme 9). A subsequent Reetz allylation afforded the homoallylic alcohol **93**, demonstrating high diastereoselectivity (dr = 93 : 7). Progressing from **93**, a sequence of protection–deprotection steps, followed by oxidative cleavage of the terminal olefin, yielded the lactol intermediate **94**. Here, author used their proprietary diastereoselective allylation technique[27] at the anomeric position, utilizing $AuCl_3$ and allyltrimethylsilane.

This reaction proceeded through an oxocarbenium ion intermediate, culminating in the formation of the desired 2,6-*trans*-tetrahydropyran **95** with impressive yield and excellent diastereoselectivity (dr > 95 : 5). Transformation of **95** to *seco* acid derivative **96**, followed by an intramolecular Mitsunobu lactonization, yielded the target bicyclic structure, tetraketide **3**. Analytical and spectroscopic comparisons confirmed the structural fidelity the natural product.

6. Polyrhacitides A and B

6.1 Isolation and biological activity

Another noteworthy series includes two newly identified bicyclic polyketide lactones, polyrhacitides A **4** and B **5**, which were isolated by Z. H. Jiang and colleagues in 2008 from the ether fraction of methanol extracts of the Chinese medicinal ant *Polyrhacis lamellidens*. These species have traditionally been used in China to treat conditions such as rheumatoid arthritis



Scheme 10 Synthesis of *epi*-cryptocaryolone and polyrhacitide A by Mohapatra *et al.* (2010).[19]

and hepatitis.[18] Based on the ^{13}C NMR data of the acetal and isopropylidene methyl carbons in both compounds, a *syn* relationship was established between C-9 and C-11, as well as between C-11 and C-13. Additionally, the absolute configuration at C-9 was determined to be *R* using the modified Mosher's method (Fig. 1).

6.2 Synthesis of polyrhacitide A and *epi*-cryptocaryolone

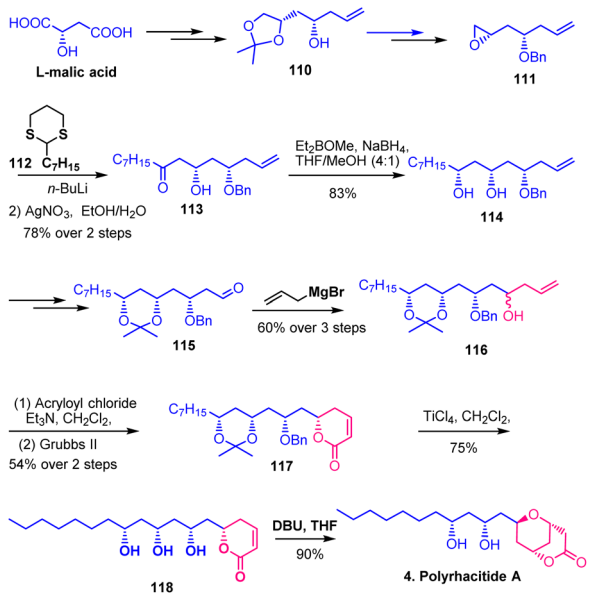
In 2010, Mohapatra and colleagues meticulously reported the total synthesis of polyrhacitide A and *epi*-cryptocaryolone.[19] Here, they elucidated an intricate iodine-catalyzed cyclization approach to establish the tetrahydropyran (THP) ring, complemented by sequential iodo-lactonization to secure the *syn*-1,3 polyol array as well as the requisite bicyclic ring system (Scheme 10). The synthesis commenced from the established chiral epoxide **97**. This intermediate underwent ring-opening with vinylmagnesium bromide to yield the corresponding homoallylic alcohol, which then engaged in cross-metathesis with acrolein, catalyzed by Hoveyda–Grubbs catalyst, producing δ-hydroxy α,β-unsaturated aldehyde **98** pivotal intermediate. This aldehyde was transformed into a *trans*-2,6-disubstituted dihydropyran ring system **99** *via* a highly stereoselective, iodine-catalyzed allylation protocol.[20] Specifically, treatment with 10 mol% molecular iodine afforded the desired *trans*-2,6-disubstituted-3,4-dihydropyran **100**. Subsequent dihydroxylation–oxidation, utilizing Jin's protocol,[21] selectively oxidized the terminal olefin to furnish aldehyde which then underwent Maruoka's asymmetric allylation with (*R*)-BINOL, delivering the homoallylic alcohol **101** as a single isomer. Protection of this intermediate as the *tert*-butyl carbonate, followed by treatment with *N*-iodosuccinimide (NIS), yielded the critical iodo-carbonate derivative **102** in a single diastereomeric form. This compound served as a cornerstone for both synthetic routes. The iodo-carbonate **102** was then subjected to treatment with K_2CO_3 in MeOH, facilitating rapid hydrolysis and *in situ* epoxidation to generate the 1,3-*syn*-epoxy alcohol which was reacted with hexylmagnesium bromide to led the formation of the 1,3-*syn* diol **103**, which, following additional transformations, culminated in the production of an acid intermediate **104**. At this pivotal stage, a second iodo-lactonization event constructed the bicyclic iodo-lactone **105** with complete diastereoselectivity. The final steps included the selective removal of the iodine using tri-*n*-butyl tin hydride, followed by straightforward deprotection to achieve polyrhacitide A **4**. The aforementioned iodo-carbonate derivative **102** also facilitated the synthesis of *epi*-cryptocaryolone. Here, terminal iodo functionality was reduced to a methyl group *via* tri-*n*-butyl tin hydride in the presence of a catalytic quantity of AIBN to get intermediate **106**. Subsequent transformations yielded the acid intermediate **107**, which, upon treatment with I_2, furnished the bicyclic iodo-lactone intermediate **108**. The concluding deiodination and final deprotection afforded the target compound, *epi*-cryptocaryolone **109**.

This methodology underscores the strategic utility of iodine catalysis and stereocontrolled allylation and provides an efficient route for constructing complex polycyclic frameworks with high diastereoselectivity.

6.3 Synthesis of polyrhacitide A

In 2010, S. Ghosh and colleagues detailed a stereoselective synthesis of polyrhacitide A (Scheme 11).[22] The synthetic strategy commenced from L-malic acid, which was transformed into homoallylic alcohol **110** through established methodologies. Following this, the terminal acetonide protected diol moiety was converted into a terminal epoxide intermediate **111**, subsequently opened by the nucleophilic attack of dithiane derivative **112**. Subsequent deprotection of the dithioacetal functional group yielded keto compound **113**. The keto intermediate **113** then underwent a hydroxyl-directed stereoselective reduction utilizing sodium borohydride ($NaBH_4$) and diethylboromethoxide (Et_2BOMe), facilitating the formation of the 1,3-syn diol **114**. Through several standard transformations, this intermediate was further advanced to aldehyde **115**. At this stage, asymmetric allylation was attempted through the Brown and Keck allylation protocol.

Although these approaches disappointingly furnished low yields, a straightforward substrate-directed allylation using



Scheme 11 Synthesis of polyrhacitide A by S. Ghosh *et al.* (2010).[22]

allylmagnesium bromide was conducted, producing compound **116** as an inseparable mixture of diastereomers. Then, a pivotal transformation involved acylation with acryloyl chloride, afforded the separable diastereomer. This bis-olefinic intermediate subsequently underwent a ring-closing metathesis (RCM) reaction in the presence of Grubbs' second-generation catalyst in CH_2Cl_2, yielding compound **117**. The synthetic sequence was finalized by globally deprotecting compound **117** with titanium tetrachloride ($TiCl_4$) in CH_2Cl_2 at 0 °C to afford compound **118**. Finally, treatment of compound **118** with DBU in tetrahydrofuran (THF) at 0 °C successfully completed the synthesis, yielding polyrhacitide A **4** with a 72% yield over the final two steps.

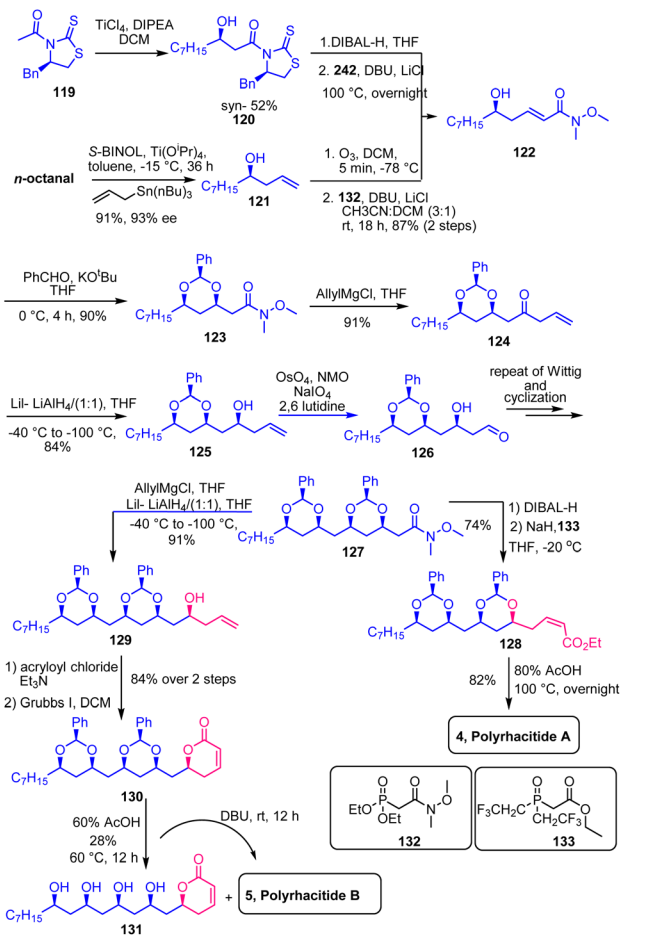
6.4 Synthesis of polyrhacitide A and B

In a seminal 2011 report, J. S. Yadav and colleagues[23] described an intricate, stereoselective total synthesis of polyrhacitides A and B, employing an innovative approach to construct the challenging skipped polyol structure with exceptional selectivity. Their methodology encompasses a precise, iterative five-step synthesis comprising olefinic oxidation, a modified Wittig–Horner transformation, the Evans mixed acetal oxa-Michael reaction, allylation, and a highly selective chelation-controlled *syn*-reduction (Scheme 12).

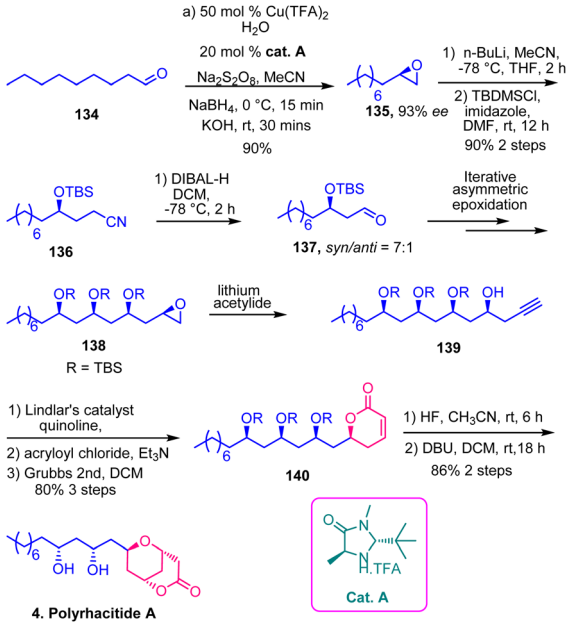
At the outset, the authors attempted to induce chirality *via* an auxiliary-based asymmetric acetate aldol reaction with (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (compound **119**). However, this approach yielded suboptimal outcomes with poor yield of **120** and unanticipated impurities. This initial setback prompted them to pivot to an alternative asymmetric pathway—namely, Keck allylation—applied to *n*-octanal, yielding the homoallylic alcohol **121** in favourable yield with an enantiomeric excess of 93%. Subsequent ozonolysis of the terminal olefin, followed by a Horner–Wittig reaction generated the δ-hydroxy-α,β-unsaturated amide **122** with the requisite stereochemistry. This intermediate served as a scaffold to establish three consecutive hydroxyl groups.

Employing Evans' mixed acetal oxa-Michael reaction, intermediate **122** was treated with benzaldehyde in the presence of catalytic potassium *tert*-butoxide at 0 °C, resulting in compound **123**. Allylation with allylmagnesium chloride introduced a ketone functionality, which was then selectively reduced under the chelation-controlled conditions outlined by Mori *et al.*,[24,25] yielding the major *syn*-polyol **124** and its separable anti isomer. Then Wittig olefination and cyclization was repeated to afford the Weinreb amide intermediate **127**. To finalize polyrhacitide A, this amide was reduced to aldehyde and subsequently subjected to the Horner–Wittig reaction with ethyl 2-[bis(2,2,2-trifluoro-ethyloxy)phosphoryl]acetate **133**, producing the *Z*-configured olefinic intermediate with an all-*syn* dibenzylidene-protected tetrol with an α,β-unsaturated ester **128**. Exposure of this precursor to 80% acetic acid at 100 °C for 18 hours afforded the bicyclic target molecule polyrhacitide A **4** in an impressive yield of 82%.

To obtain polyrhacitide B, the common amide intermediate **127** was treated with allylmagnesium chloride to form a ketone intermediate, subsequently reduced with excess $LiAlH_4$/LiI under high-dilution conditions to yield the *syn*-isomer **129** as a singular



Scheme 12 Synthesis of polyrhacitide A and B by J. S. Yadav *et al.* (2011).[23]



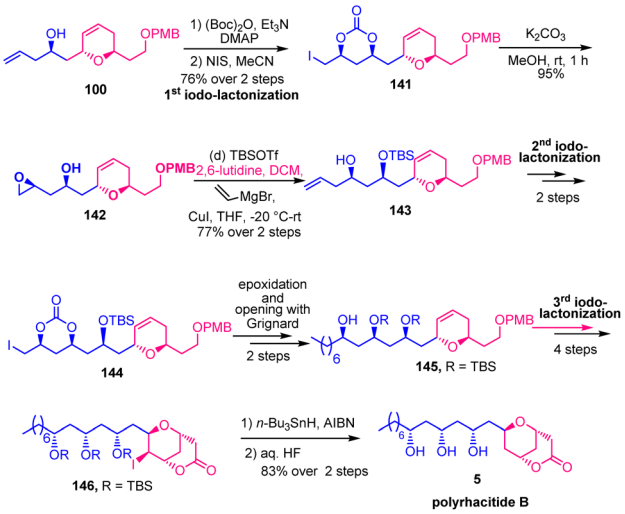
Scheme 13 Synthesis of polyrhacitide A by G. Kumaraswamy *et al.* (2012).[26]

diastereomer. Acylation of the free hydroxy group with acryloyl followed by exposure to Grubbs' 1st generation catalyst provided unsaturated lactone **130**. Finally, polyrhacitide B was achieved by a one pot sequential deprotection, oxa-Michael reaction using 60% acetic acid at 60 °C, affording **5** as a white solid in 65% yield along with the simple deprotected lactone **131** in 28% yield which was further treated with DBU in dichloromethane for 12 h to afford the targeted polyrhacitide B **5**.

6.5 Synthesis of polyrhacitide A

In 2012, G. Kumaraswamy *et al.*[26] pioneered a meticulously refined enantioselective approach to synthesize polyrhacitide A *via* organocatalysis. The researchers developed a sophisticated pathway to produce stereochemically precise 1,3,5-polyols, harnessing enantioselective catalysis to construct chiral centers with precision (Scheme 13). By employing the MacMillan asymmetric epoxidation protocol, the team generated enantiomerically pure terminal epoxides with selective *syn*-configuration. The process began by subjecting nonanal **134** to organocatalytic asymmetric epoxidation using **cat. A**, yielding terminal epoxide **135**. The ensuing epoxide was then strategically opened with an acetonitrile-derived carbanion, forming a γ-hydroxynitrile derivative **136**. This intermediate was subsequently converted into aldehyde **137**, enabling the initiation of a series of iterative, stereocontrolled epoxidations to furnish intermediate **138**.

A targeted ring-opening reaction with lithium acetylide advanced the synthesis to intermediate **139**, ensuring precise configuration control. The sequence proceeded with the partial reduction of terminal acetylene to an olefin, achieved under Lindlar hydrogenation conditions. This olefin was then functionalized by treatment with acryloyl chloride, producing a precursor for ring-closing metathesis (RCM). Utilizing Grubbs' second-generation catalyst, the precursor underwent cyclization, yielding an α,β-unsaturated lactone **140** with high stereochemical fidelity. In the final steps, global deprotection of silyl groups was induced by fluoride ions, followed by an oxa-Michael reaction in the presence of DBU to get the target molecule, polyrhacitide A, showcasing a powerful approach to constructing complex architectures with high selectivity.



Scheme 14 Synthesis polyrhacitide B by Mohapatra *et al.* (2014).[27]

6.6 Synthesis of polyrhacitide B

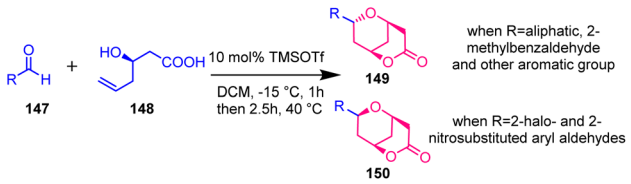
In 2014, Mohapatra[27] and colleagues advanced the aforementioned synthetic protocol (Scheme 14), culminating in the comprehensive synthesis of polyrhacitide B. They leveraged an iodine-catalyzed cyclization, complemented by sequential iodo-lactonization steps, to achieve the stereocontrolled formation of *syn*-1,3-polyols and the intricate polycyclic framework essential to the molecule. Initially, the synthesis began with the preparation of a key intermediate, derived from a well-characterized known intermediate **100**.

Employing two iterative iodo-lactonizations, they efficiently orchestrated the formation of contiguous *syn*-1,3-polyols intermediate **145**. Subsequently, a third iodo-lactonization step facilitated the construction of the bicyclic core intermediate **146**, crucial for the compound's structural integrity. The process was then completed through strategic de-iodination and deprotection steps, yielding the final structure of polyrhacitide B **5**.

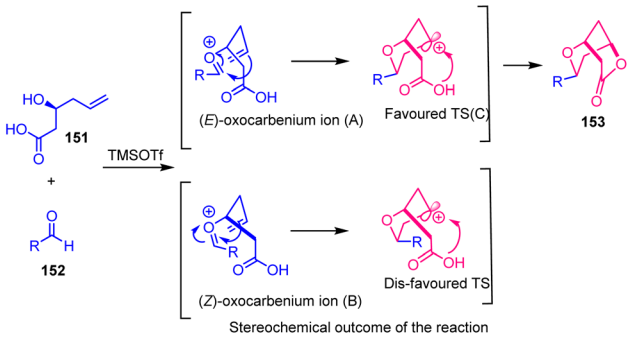
6.7 Synthesis of polyrhacitide A

In 2016, B. V. S. Reddy[28] and colleagues published a meticulous exploration of the stereoselective total synthesis of polyrhacitide A. Their work pioneered an innovative cascade strategy based on Prins cyclization for synthesizing the dioxabicyclo[3.3.1] nonan-3-one framework.

Initially, the authors explored the reaction between benzaldehyde and (*R*)-3-hydroxyhex-5-enoic acid (**148**), catalyzed by 10 mol% trimethylsilyl triflate (TMSOTf) within a temperature range of −15 °C to 40 °C in a dichloromethane solvent system (Scheme 15). This reaction efficiently yielded the anticipated



Scheme 15 Cascade strategy based on Prins cyclization by B. V. S. Reddy *et al.* (2016).[28]

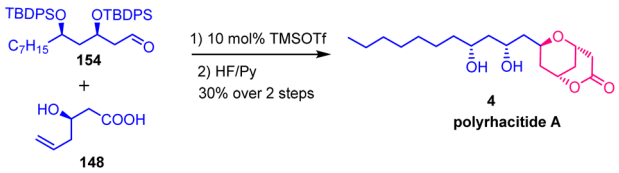


Scheme 16 Mechanistic aspect of Prins cyclization.

bicyclic lactone **149**/**150**. The versatility of this methodology was further substantiated through trials with a variety of aliphatic and aromatic aldehydes. Notably, products derived from 2-halo- and 2-nitro-substituted aryl aldehydes exhibited stereochemical variation at the C8 position, an outcome likely influenced by the electronic characteristics of the substituents on the aromatic ring. Interestingly, reactions involving 2-methylbenzaldehyde and other aliphatic aldehydes resulted in the *trans*-isomer rather than the anticipated *cis*-isomer, as confirmed by nOe analyses. This finding underscored the pivotal influence of the 2-position substituent on the stereochemical course of the reaction. Mechanistically, this transformation proceeds through an acid-catalyzed Prins reaction that generates an (*E*)-oxocarbenium ion (A), assuming a chair-like transition state and culminating in the formation of a tetrahydropyranyl cation (Scheme 16). Here, the hydrogen atom at C-4 adopts a pseudo-axial orientation, facilitating equatorial nucleophilic attack by an appended moiety to circumvent unfavorable 1,3-diaxial interactions, thus driving the formation of the bicyclic lactone. Subsequently, the authors adeptly applied this synthetic protocol to the total synthesis of polyrhacitide A (Scheme 17). The requisite (*S*)-3-hydroxyhex-5-enoic acid (**154**) was synthesized from L-aspartic acid following a documented procedure,[29] while the chiral aldehyde coupling partner **148** was prepared *via* a known multi-step sequence.[30]

Upon treatment of these two reactants with 10% TMSOTf, the target bicyclic lactone emerged in 50% yield. A final, comprehensive deprotection step then afforded the desired polyrhacitide A in an overall yield of 60%.

This work showcases a methodologically robust approach, delineating the profound influence of substituents on stereochemical outcomes, and represents a significant advancement in the stereoselective synthesis of complex bicyclic cores.



Scheme 17 Synthesis of polyrhacitide A by B. V. S. Reddy *et al.* (2016).[28]

7. Cryptorigidifoliols F–K

7.1 Isolation and biological activity

In 2015, six bicyclic tetrahydro-α-pyrone derivatives cryptorigidifoliols F–K (**17**–**22**) were isolated form antimalarial bioassay-guided fractionation of an EtOH extract of the root wood of *Cryptocarya rigidifolia* (Lauraceae) by D. G. I. Kingston *et al.*[31] An EtOH extract of the root wood of *Cryptocarya rigidifolia* (Lauraceae) was selected for bioassay-directed fractionation because of its reproducible activity against *Plasmodium falciparum* Dd2 ($IC_{50} \sim 5$ μg mL^{-1}). All the compounds were also evaluated for their antiproliferative activity against A2780 human ovarian cancer cells (Fig. 1).

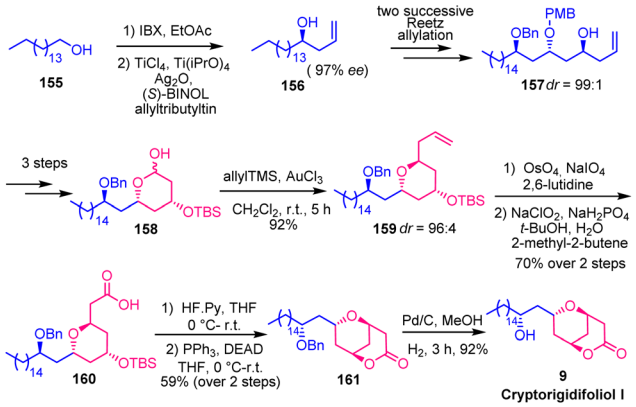
7.2 Synthesis of cryptorigidifoliol I

Following the successful synthesis of tetraketide, in 2016, Mohapatra[16] and colleagues documented, the group sought to explore their methodology's applicability in the total synthesis of cryptorigidifoliol I **9** through successive allylation reactions. Beginning with commercially sourced cetyl alcohol **155**, we applied asymmetric Maruoka allylation, producing homoallyl alcohol **156** (Scheme 18). Chelation-controlled successive Reetz allylation then precisely configured two stereocenters with exceptional diastereoselectivity and produced **157**. Further modifications alongside terminal olefin oxidation *via* Jin's dihydroxylation–oxidation methodology, furnished the lactol intermediate **158**.

The stereogenic center at the anomeric position of **159** was installed analogously to previous steps, employing $AuCl_3$ and allyltrimethylsilane to have **159** with excellent diastereoselectivity. Subsequent terminal olefin oxidation to the carboxylic acid and TBS deprotection provided the *seco* acid **160**, which, upon intramolecular Mitsunobu lactonization, yielded the target bicyclic framework **161**. Final debenzylation using H_2/Pd/C successfully completed the synthesis, delivering cryptorigidifoliol I **9**. Their work demonstrates both precision in chemical methodology and the utility of accessible chiral starting materials in the synthesis of complex bioactive molecules.

7.3 Synthesis of cryptorigidifoliol K

In 2017, Mohapatra[32] and colleagues unveiled the synthesis of four stereoisomers attributed to the hypothesized structures of cryptorigidifoliol K. Herein, the authors again implemented the pioneering sequence of consecutive iodo-cyclizations to architect the core bicyclic framework. Initially, they employed a self-devised iodine-catalyzed allylation coupled with cyclization, facilitating the construction of a *trans*-2,6-disubstituted dihydropyran ring. This system was subsequently subjected to an iodo-lactonization, orchestrating the assembly of the intricate



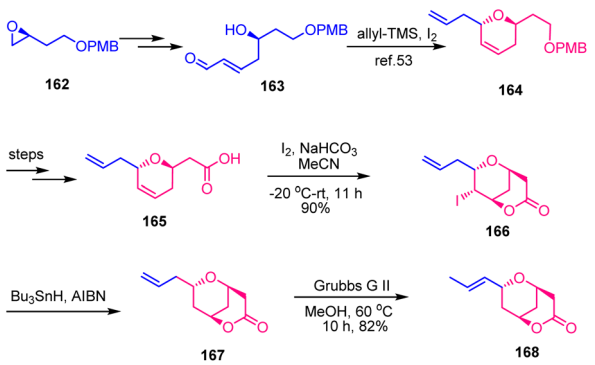
Scheme 18 Total synthesis of the tetraketide by Mohapatra *et al.* (2016).[16]

bicyclo-lactone motif. The final stages involved integrating the bicyclic scaffold with the side-chain moiety *via* a cross-metathesis strategy.

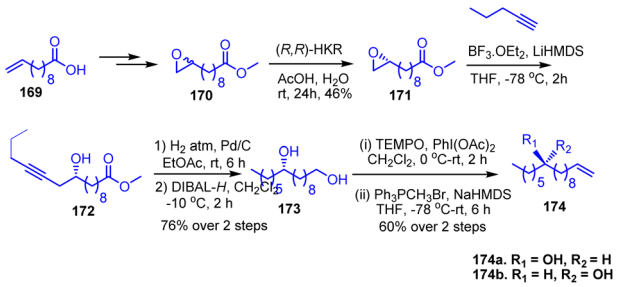
The synthesis of novel bicyclic core was commenced from optically pure epoxides **162** which was converted to δ-hydroxy α,β-unsaturated aldehyde **163** by known literature method (Scheme 19). At this juncture, author has utilized their iodine catalyzed cyclization strategy to build *trans*-2,6-disubstituted dihydropyran ring system **164**.[21] Later, it was converted to acid by simple and known transformation. When acid **165** was treated with iodine, it underwent a facile intramolecular iodo lactonization to furnish intermediate **166**.

Deiodination was achieved smoothly under Barton–McCombie conditions. Then isomerization of the terminal double bond was carried out using Grubbs' second-generation catalyst to produce intermediate **168**, a key coupling partner.

Synthesis of the side-chain segment initiated from commercially available undecanoic acid **169** which was converted to racemic epoxide **170**, and subjected to hydrolytic kinetic resolution in the presence of Jacobsen's (*R*,*R*)-(salen) Co(III) catalyst, obtaining **171** in 46% yield (Scheme 20). The resultant terminal epoxide (*R*)-**171** was treated with lithiated-1-pentyne, producing alkynol **172**. Subsequent reduction with H_2–Pd/C, followed by DIBAL-H treatment, furnished diol intermediate **173**, which underwent TEMPO/BAIB-mediated



Scheme 19 Synthesis of the bicyclic fragment **215**.



Scheme 20 Synthesis of the side-chain fragment **221**.

selective oxidation of the primary hydroxyl group, followed by Wittig olefination, to afford compound **174**.

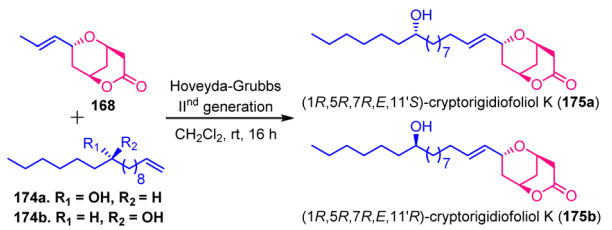
The coupling between bicyclic lactone **168** and enantiomers **174a**/**174b** (bearing a hydroxyl group on C7), was achieved through cross-metathesis by the second-generation Hoveyda–Grubbs' catalyst, yielding compounds **175a** and **175b** in yields of 72% and 74%, respectively (Scheme 21). The synthesis of another olefin-coupling partners (bearing a hydroxyl group at C8) began with commercially accessible decen-1-ol **176**, converted into PMB-protected racemic epoxide (±)-**177**, and subsequently resolved hydrolytically in the presence of Jacobsen's (*R*,*R*)-(salen)Co(III) catalyst, resulting in epoxide **178** with a 46% yield (Scheme 22). Employing reactions analogous to those in Scheme 20, coupling partners **179a** and **179b** were synthesized (Scheme 21).

With both C8-hydroxyl-bearing coupling partners prepared, the authors performed the concluding cross-metathesis reaction with bicyclic lactone, again using the Hoveyda–Grubbs' second-generation catalyst (Scheme 23).

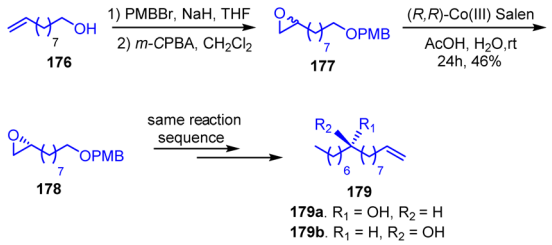
This reaction afforded two isomers, **180** and **181**, proposed by Kingston and coworkers as alternate structures of cryptorigidifoliol K, with yields of 70% and 74%, respectively.

7.4 Total synthesis and determination of absolute configuration of cryptorigidifoliol G

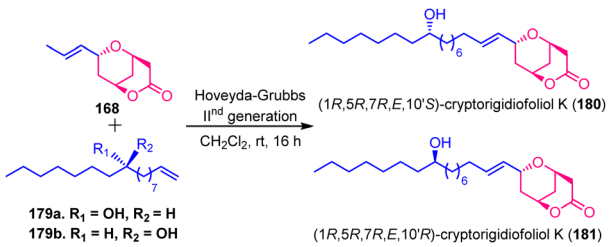
In 2024, Mohapatra and co-workers accomplished the first asymmetric total synthesis of both (1*S*,5*R*,7*S*)- and (1*S*,5*R*,7*R*)-cryptorigidifoliol G, the proposed structures of the natural product.[32] Their approach employed Keck–Maruoka allylation to access a key homoallyl alcohol intermediate, followed by iodolactonization, cross-metathesis, and their previously developed protocol for the stereoselective construction of



Scheme 21 Synthesis of the first proposed structure of cryptorigidifoliol K.



Scheme 22 Synthesis of the side-chain fragment **226a** and **226b**.

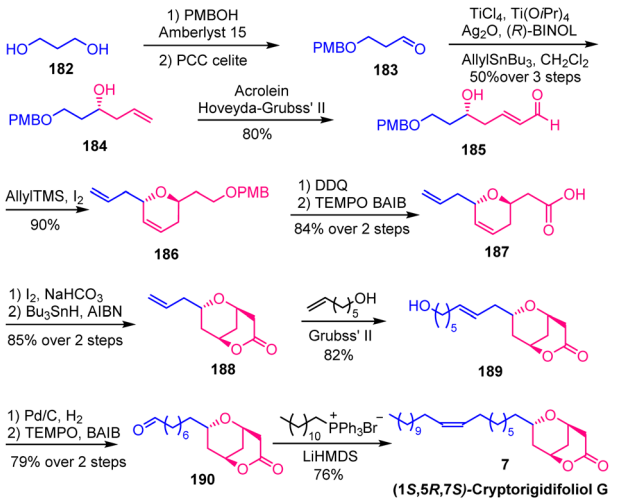


Scheme 23 Synthesis of the second proposed structure of cryptorigidifofoliol K.

a *trans*-2,6-disubstituted dihydropyran (Scheme 24). The synthesis commenced from 1,3-propane diol **182**, which was converted to aldehyde **183** after protection. Treatment of this aldehyde with allyltributyltin in the presence of $Ti(OiPr)_4$ and (*R*)-BINOL in CH_2Cl_2 at −20 °C furnished the homoallyl alcohol **184** in 98% ee. Cross-metathesis with acrolein using Hoveyda–Grubbs' catalyst provided the δ-hydroxy-α,β-unsaturated aldehyde **185** in 80% yield. Subsequent reaction with molecular iodine (10 mol%) and allyl-TMS delivered the *trans*-2,6-disubstituted-3,4-dihydropyran **186** in 90% yield with excellent diastereoselectivity (dr = 99 : 1).

Oxidative debenzylation and conversion of the alcohol to the corresponding carboxylic acid proceeded in 90% yield. Iodolactonization with iodine/$NaHCO_3$ in acetonitrile afforded the bicyclic iodolactone with high stereocontrol (dr = 98 : 2), and deiodination under Barton–McCombie conditions furnished compound **188** in 96% yield. Cross-metathesis with 6-hepten-1-ol using Grubbs' second-generation catalyst yielded alcohol **189** in 82% yield, which was subsequently converted to aldehyde **190** *via* hydrogenation and oxidation. A final Wittig olefination (LHMDS, $PPh_3{}^+C_{12}H_{25}Br^-$) afforded (1*S*,5*R*,7*S*)-cryptorigidifofoliol G **7** in 76% yield.

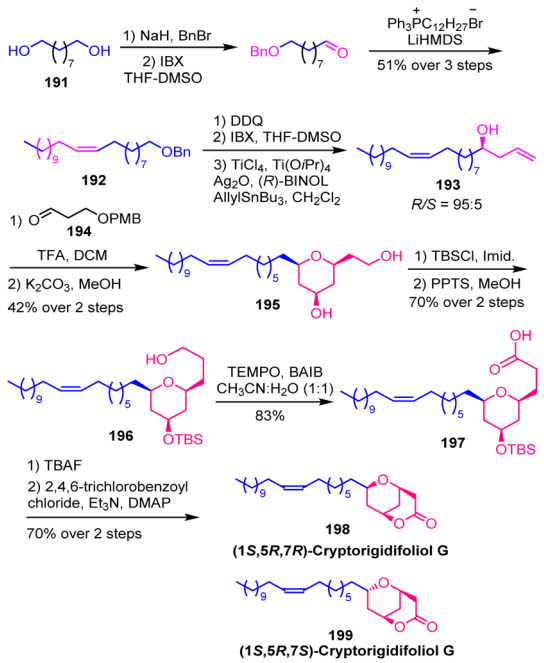
The spectroscopic and analytical data of this synthetic isomer were in close agreement with those reported for the natural product, with only a minor deviation in one ^{13}C NMR resonance. Importantly, the observed optical rotation $\{[\alpha]_D{}^{21}$ −3.8 (*c* 0.6, MeOH)} matched that of the natural isolate $\{[\alpha]_D{}^{21}$ −4.0 (*c* 0.5, MeOH)}, thereby supporting its assignment as the natural product. Nonetheless, to unequivocally establish the absolute configuration at C7, the authors also pursued the synthesis of the alternative isomer, (1*S*,5*R*,7*R*)-cryptorigidifofoliol G, which is discussed in the following section.



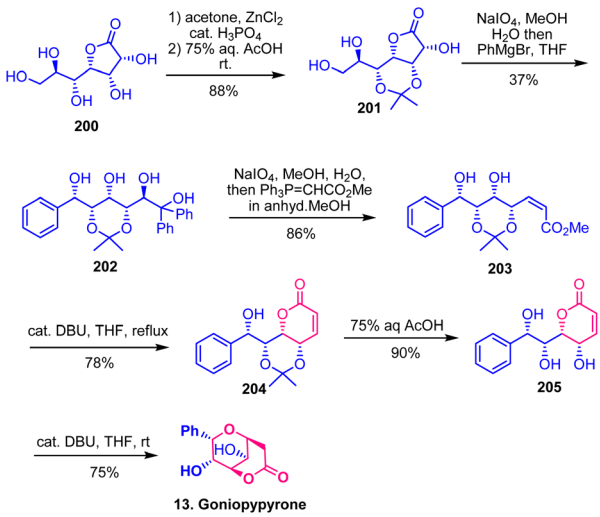
Scheme 24 Synthesis of the (1*S*,5*R*,7*S*) cryptorigidifofoliol G (2024).[32]

7.5 Total synthesis and determination of absolute configuration of cryptorigidifofoliol G

In 2024, Mohapatra and co-workers reported a novel synthetic route to (1*S*,5*R*,7*R*)-cryptorigidifofoliol G, the stereoisomer of (1*S*,5*R*,7*S*)-cryptorigidifofoliol G.[33] Their strategy was designed to install the side chain at an early stage, with construction of the bicyclic core deferred to the final steps of the synthesis. The sequence relied on Yamaguchi lactonization, Prins cyclization, and Keck asymmetric allylation as key transformations. Starting from 1,9-nonanediol **191** (Scheme 25), the primary hydroxyl groups were protected as benzyl ethers, followed by oxidation to the corresponding aldehyde. Subsequent *cis*-Wittig olefination with the phosphonium ylide ($PPh_3{}^+C_{12}H_{27}Br^-$) in the presence of LHMDS in THF at −78 °C afforded the *Z*-olefin **192** exclusively. Oxidative debenzylation and subsequent IBX oxidation furnished an aldehyde intermediate, which underwent Keck allylation[34] with allyltributyltin in the presence of (*S*)-BINOL and $Ti(OiPr)_4$ to give the homoallylic alcohol **193**. Prins cyclization with the aldehyde **194** in presence of TFA in CH_2Cl_2, followed by hydrolysis with K_2CO_3 in methanol, delivered diol intermediate **195**. Direct oxidation of this diol using TEMPO/BAIB provided the lactone (1*S*,5*R*,7*R*)-cryptorigidifofoliol G, albeit in low yield. To overcome this limitation, the authors employed a sequence of silyl protection, selective deprotection, and oxidation, which generated the corresponding *seco*-acid intermediate **197**. Final intramolecular lactonization under Yamaguchi conditions furnished (1*S*,5*R*,7*R*)-cryptorigidifofoliol G **198**. However, comparison of the ^1H and ^{13}C NMR data, along with the specific rotation values $\{[\alpha]_D{}^{21}$ +12.7 (*c* 0.4, MeOH)}; lit. $\{[\alpha]_D{}^{21}$ −4.0 (*c* 0.5, MeOH)}, revealed significant discrepancies from those reported for the natural product. The authors achieved the first asymmetric total synthesis of (1*S*,5*R*,7*S*)-cryptorigidifofoliol G of the proposed natural product following Keck–Maruoka allylation, own developed tandem isomerization followed by C–O and C–C bond forming protocol for the construction of the *trans*-2,6-disubstituted dihydropyran, iodolactonization, cross-metathesis and Wittig olefination reaction. Notably, the ^1H



Scheme 25 Synthesis of the (1*S*,5*R*,7*R*) cryptorigidifoliol G (2024).[33]



Scheme 26 First total synthesis of potent antitumor agent (+)-goniopyrone by T. K. M. Shing (1993).[40]

NMR and ^{13}C NMR data of the synthetic one closely matched the data reported for the natural product. The magnitude of specific rotation of the synthetic isomer **199**; {$[\alpha]_D^{21}$ −3.8 (*c* 0.6, MeOH)} matched with the natural product {$[\alpha]_D^{21}$ −4.0 (*c* 0.5, MeOH)} suggested that the absolute stereochemistry of the proposed natural product is (1*S*,5*R*,7*S*)-cryptorigidifoliol G.

8. Goniopypyrone

8.1 Isolation and biological activity

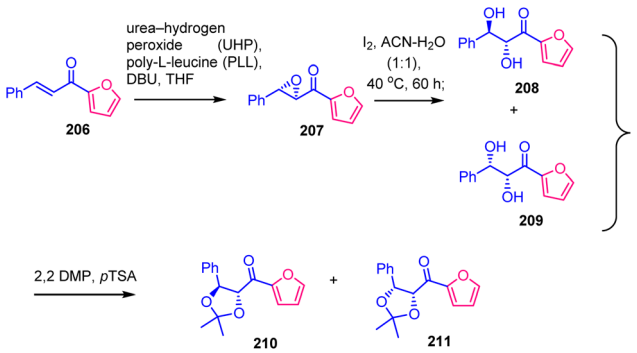
McLaughlin *et al.* first reported the isolation of goniopypyrone **13** in 1990, along with other styryllactones from *Goniothalamus giganteus* (Annonaceae).[35] These compounds exhibited cytotoxic activity against human tumor cell lines, with goniopypyrone emerging as the most potent, displaying non-selective ED_{50} values of approximately 0.67 μg mL^{-1} across several cancer cell lines. In 1999, Quan Yu *et al.* isolated goniopypyrone **13**, 5-acetylgoniopypyrone **14**, and 7-acetylgoniopypyrone **15** from *Goniothalamus griffithii*.[36] These compounds showed cytotoxic activity against multiple human cancer cell lines, including A2780 (ovarian), HCT-8 (colon), KB (oral epidermoid), and MCF-7 (breast). Among them, 7-acetylgoniopypyrone **15** (ref. 37) was the most active against A2780, HCT-8, and KB cell lines, while 5-acetylgoniopypyrone **14** demonstrated weak antiproliferative activity against MCF-7 (IC_{50} = 13.4 μM). Goniopypyrone **13** showed marginal activity, with an IC_{50} of approximately 20 μM against mouse leukemia P-388 cells.[38] Subsequently, in 2006, Tuchinda *et al.* reported the isolation of goniopypyrone **13** from the cytotoxic ethyl acetate extract of leaves and twigs of *P. crassa*.[39] More recently, in 2015, Moosophon *et al.* again isolated goniopypyrone **13**, along with 14 known compounds, from chromatographic separation of crude EtOAc and MeOH extracts of *G. elegants* bark. Structural elucidation of these compounds was accomplished using spectroscopic methods (Fig. 1).[38]

8.2 First asymmetric total synthesis of potent antitumor agent (+)-goniopypyrone

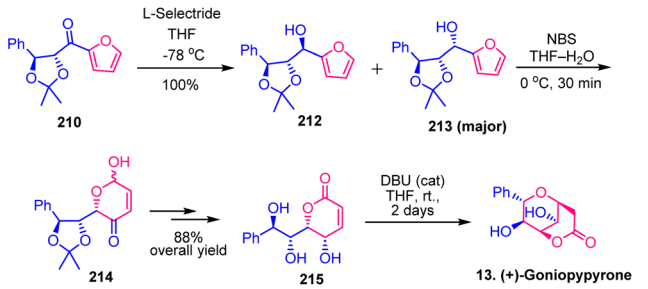
In 1993, T. K. M. Shing *et al.* reported the first total synthesis of goniopypyrone **12**, employing a chiral pool approach to establish both the compound's constitution and absolute configuration (Scheme 26).[40] The synthesis was initiated from D-glycero-D-gluco-heptono-γ-lactone **200** which was transformed into the tritol intermediate **201**. The first key step involved glycol cleavage oxidation using sodium metaperiodate, followed by reaction of the resulting aldehyde with excess phenylmagnesium bromide. This generated a mixture of the alcohol and its 6-epimer in a ratio of approximately 2.5 : 1.5, which were subsequently separated by flash chromatography to isolate tetraol **202**. A second glycol cleavage oxidation was then conducted, immediately followed by Wittig olefination in anhydrous methanol, yielding the *Z*-alkene **203** with high stereoselectivity (>95% *Z*). This intermediate underwent lactonization, catalyzed by DBU, to form pyrone **204**, acetonide cleavage *via* acid hydrolysis exposed the tritol **205**, which, under DBU catalysis in THF, formed the target pyran **13** as long, needle-like crystals. This intramolecular Michael-type cyclization involved the 7-OH group, thereby confirming the structure and absolute stereochemistry of natural goniopypyrone **13**. The overall synthetic route was accomplished in nine steps, affording a stereoselective synthesis with an overall yield of 9.7%.

8.3 Julia–Colonna asymmetric epoxidation of furyl styryl ketone as a route to intermediates to naturally-occurring styryl lactones

In 1999, Wei-ping Chen, Stanley M. Roberts, and co-workers reported the synthesis of (+)-goniopypyrone.[41] The authors employed the Julia–Colonna asymmetric epoxidation of furyl



Scheme 27 Keto intermediate synthesis.



Scheme 28 Goniopyrone synthesis by Wei-ping Chen *et al.* (1999).[41]

styryl ketone, utilizing a chiral phase-transfer catalyst to generate a pivotal intermediate for further synthetic elaboration, culminating in the formation of a bicyclic moiety *via* an oxa-Michael reaction.

The critical asymmetric epoxidation of furyl styryl ketone **206** to yield epoxide **207** (Scheme 27) was executed through a biphasic polyleucine-catalyzed method. This reaction exhibited a high rate of transformation, enabling a minimal catalyst loading of 2.5 mol% (Scheme 27). The catalyst was efficiently recovered and demonstrated reusability for at least six cycles without compromising the reaction rate or stereoselectivity. The resultant chiral epoxide **207** proved instrumental as a precursor in the syntheses of other styryl lactones *e.g.* goniotriol, goniofufurone, 8-acetylgoniotriol, and goniopypyrone.

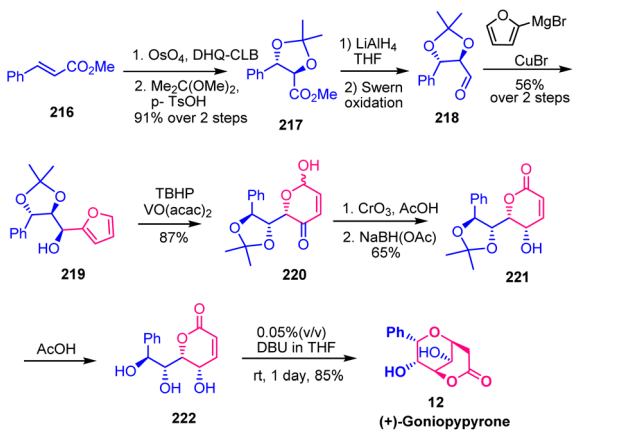
Subsequent hydrolysis of the oxirane ring yielded **208** and **209** in approximately equal amounts, which were protected as acetonides with 2,2-dimethoxypropane and separated *via* silica chromatography, achieving yields of 46% and 38%, respectively (**210** and **211,** Scheme 27). Initial reduction of ketone **210** with sodium borohydride resulted in poor diastereoselectivity (**212** and **213** in a 1 : 2.6 ratio); however, L-Selectride improved the selectivity, favoring diastereomer **213** as the major product (*ca.* 2 : 1) (Scheme 28). This mixture was treated with NBS in aqueous acetone, yielding lactol **214** in 61% yield, which was isolated by chromatography. Further oxidation with CrO_3, followed by $NaBH_4$ reduction, afforded keto-lactone intermediate **215**, which upon treatment with DBU underwent an intramolecular oxa-Michael reaction to furnish (+)-goniopypyrone **13.**

8.4 Asymmetric total synthesis of (+)-goniopypyrone

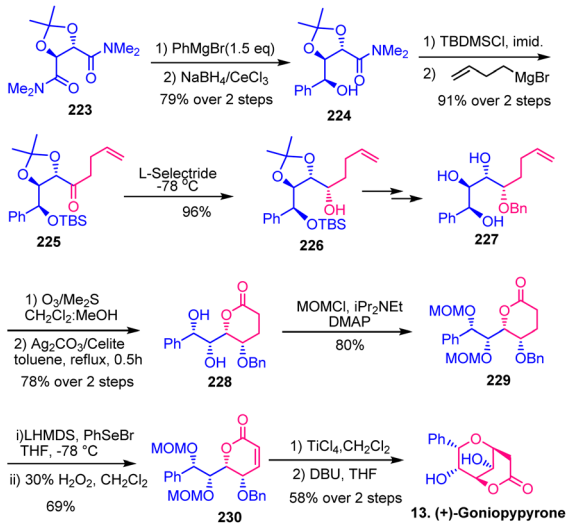
The synthesis by Wei-Shan[42] commenced with the asymmetric dihydroxylation of methyl cinnamate **216**, facilitated by dihydroquinine-4-chlorobenzoate (DHQ-CLB) as a chiral ligand, yielding a chiral diol intermediate (Scheme 29). This intermediate was subsequently protected as an acetonide using 2,2-dimethoxypropane to produce intermediate **217**. Reduction with lithium aluminum hydride ($LiAlH_4$) afforded an alcohol, which was then oxidized using Swern conditions to give the aldehyde **218**. The resulting aldehyde intermediate was treated with 2-furylcopper, synthesized *in situ* from a furyl Grignard reagent and CuBr, to yield the *syn*-adduct **219** with high selectivity. Notably, the use of 2-furyllithium alone resulted in reduced selectivity, yielding only a 2.5 : 1 *syn*-to-*anti* ratio. The furan ring was oxidized using *tert*-butyl hydroperoxide (TBHP) in the presence of catalytic $VO(acac)_2$, smoothly providing hydropyranone **220** as a mixture of α- and β-anomers in a 3 : 1 ratio. Further oxidation of this anomeric mixture with CrO_3 in acetic acid, followed by stereoselective reduction of the α,β-unsaturated lactone using $NaBH(OAc)_3$ in a 1 : 1 mixture of isopropyl alcohol and acetic acid at −10 °C, yielded an inseparable diastereomeric mixture of hydropyranone **221** and the ratio of the two isomers (α-OH and β-OH) was 9 : 1. Acidic hydrolysis of the acetonide group liberated the previously known triol **222**, which subsequently underwent a facile Michael reaction catalyzed by DBU in THF, affording goniopypyrone **13** as colorless needles.

8.5 Stereoselective total synthesis of bioactive goniopypyrone

In 2008, K. R. Prasad and colleagues presented an alternate synthetic pathway for the complex molecule (+)-goniopypyrone **13** starting from same intermediate **223.**[43] Through the sequential application of Grignard addition and stereoselective reduction, Prasad's team adeptly constructed an all-*syn* tetraol intermediate (Scheme 30). Phenylselenation followed by elimination of the phenylselenyl moiety subsequently enabled the formation of an unsaturated lactone. The synthesis commenced with the addition of a 1.5 equivalent molar ratio of phenylmagnesium bromide to a diamide substrate **223** obtained from



Scheme 29 Asymmetric total synthesis of (+)-goniopypyrone by Wei-Shan *et al.* (1993).[42]



Scheme 30 Synthesis of (+)-9-deoxygoniopypyrone and (+) goniopyrone by Kavirayani R. Prasad *et al.* (2008).[43]

D-(−)-tartaric acid. This reaction generated a γ-oxo butyramide structure, which was reduced using $NaBH_4$ in conjunction with $CeCl_3$. This reduction yielded a diastereomeric alcohol mixture with an impressive 94 : 6 ratio. The newly formed alcohol **224** was protected as a silyl ether and subsequently reacted with 3-butenylmagnesium bromide, producing ketone **225**. A reduction using L-Selectride selectively afforded the all-*syn* isomer **226**. At this juncture, the secondary alcohol was further protected as a benzyl ether. Following these steps, both the acetonide and TBDMS groups were cleaved to reveal the triol **227**, while ozonolysis of the terminal olefin furnished the corresponding lactol, which was oxidized with silver carbonate supported on Celite10, resulting in the formation of the δ-lactone **228**. The secondary hydroxyl groups were protected as methoxymethyl (MOM) ethers **229**, which were later subjected to phenylselenation followed by deselenation, yielding the unsaturated lactone **230**.

A final global deprotection of the MOM and benzyl groups was achieved using $TiCl_4$ in dichloromethane, which uncovered the triol structure of 8-*epi*-goniotriol. Subsequently, treatment with a catalytic quantity of DBU in THF provided the target molecule, (+)-goniopypyrone, **13** in an efficient 12-step sequence.

9. 9-Deoxygoniopypyrone

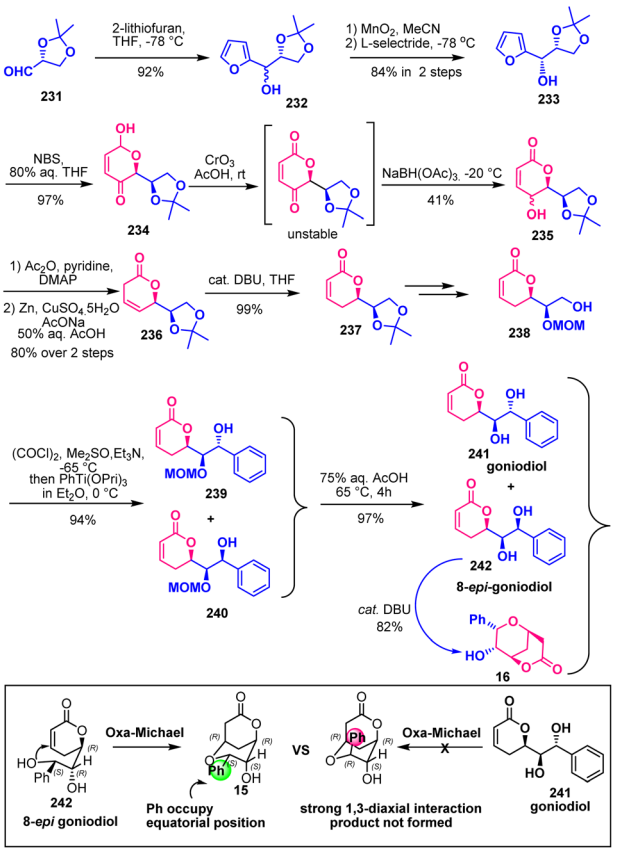
9.1 Isolation and biological activity

In 2004, Yang Wu *et al.* reported 9-deoxygoniopypyrone A **16**, along with 10 known compounds were isolated from the aerial parts of *Goniothalamus amuyon* in 2004.[44] In 2013, Khalijah *et al.* also reported 9-deoxygoniopypyrone isolated from the stem bark of *Gonioyhalamus tapisolides* (Fig. 1).[45]

9.2 Goniodiol and 9-deoxygoniopypyrone: syntheses and absolute configuration

In 1992, Toshio Honda and colleagues reported the inaugural synthesis of 9-deoxygoniopypyrone **16**, establishing its absolute configuration.[46] The synthesis involved constructing the α,β-unsaturated lactone from chiral furylmethanol *via* an NBS-mediated oxidative ring transformation, employing the Achmatowicz reaction.[47] Subsequently, the bicyclic lactone moiety was formed through an intramolecular oxa-Michael reaction (Scheme 31). The synthetic route commenced with 2,3-*O*-isopropylidene-glyceraldehyde **231** which was treated with lithiated furan as per Jurczak's protocol[26] to yield diastereoisomeric furylmethanols **232**. Oxidation with MnO_2 converted this intermediate to a ketone, followed by reduction with L-Selectride to afford the *syn*-diol **233** which was treated with NBS to undergo oxidative ring transformation and produced intermediate **234**. This intermediate, upon treatment with chromic oxides in acetic acid (AcOH), formed an unstable lactone, which was subsequently reduced *in situ* with sodium triacetoxyborohydride, yielding allyl alcohols **235** in a 1 : 7 ratio.

Further steps included acetylation of compound **235** and reductive deacetoxylation of the allyl acetate with Zn and $CuSO_4$ to produce a β,γ-unsaturated lactone intermediate **236**, which was then isomerized using DBU to obtain the α,β-unsaturated lactone **237**. Sequential protection and deprotection steps generated the primary alcohol intermediate **238**, which was subjected to Swern oxidation to yield the aldehyde intermediate. A chemoselective phenylation of aldehyde intermediate using triisopropoxyphenyltitanium provided a mixture of

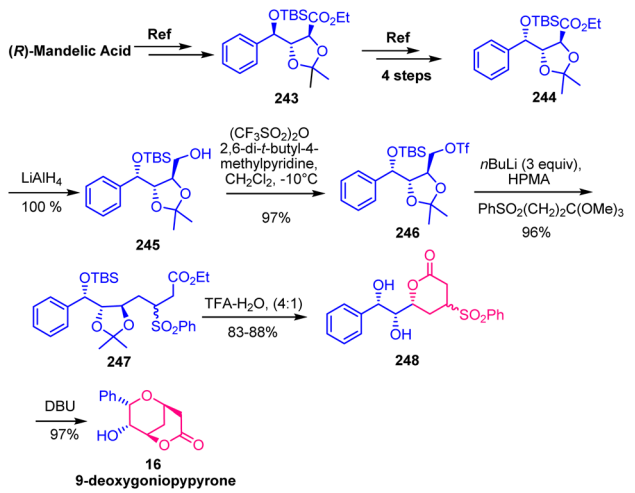


Scheme 31 Goniodiol and 9-deoxygoniopypyrone by Toshio Honda *et al.* (1992).[46]

diastereoisomers **239** and **240** in a 1 : 1 ratio. Deprotection of the methoxymethyl group of this mixture with aqueous AcOH afforded goniodiol **241** and 8-*epi*-goniodiol **242** as a colorless oil, alongside 9-deoxygoniopypyrone **15**. Lastly, catalytic DBU treatment of 8-*epi*-goniodiol **242** facilitated an intramolecular oxa-Michael addition, yielding 9-deoxygoniopypyrone **15**. It is important to note that goniodiol **241** does not undergo the oxa-Michael reaction because the bulky phenyl group creates a strong 1,3-diaxial interaction. In contrast, in 8-*epi*-goniodiol **242**, the phenyl group resides in the energetically favourable equatorial position, enabling formation of the desired oxa-Michael product. Therefore, the absolute configuration of the diol dictates the feasibility of the oxa-Michael reaction.

9.3 A short and efficient total synthesis of (+)-goniodiol and (+)-9-deoxygoniopypyrone

In 1998, a concise and efficient total synthesis of the cytotoxic compounds (+)-goniodiol and (+)-9-deoxygoniopypyrone **16** was reported by Jean-Philippe Surivet and Jean-Michel Vatele *et al.*[48a] Their synthetic approach commenced from the known intermediate **243**, which was derived from (*R*)-mandelic acid following a documented procedure (Scheme 32).[48b] The ester moiety was selectively reduced to the corresponding alcohol *via* lithium aluminum hydride (LAH) and subsequently converted into the triflate derivative **246**. At this critical juncture, Ghosez' methodology[49] was employed to introduce the *Z*-acrylate surrogate with high specificity. The triflate intermediate 59 was smoothly displaced at −78 °C by the lithium salt of methyl 3-phenylsulfonylorthopropionate in the presence of HMPA, yielding the sulfone **247** as an inseparable diastereomeric mixture. Acidic treatment facilitated the cleavage of both silyl and acetal protecting groups, generating a lactone intermediate **248** containing the sulfone functionality. Subsequent exposure to DBU induced the elimination of $PhSO_2H$ and triggered a concomitant intramolecular oxa-Michael addition yielding the crystalline final product, (+)-9-deoxygoniopypyrone **16**.



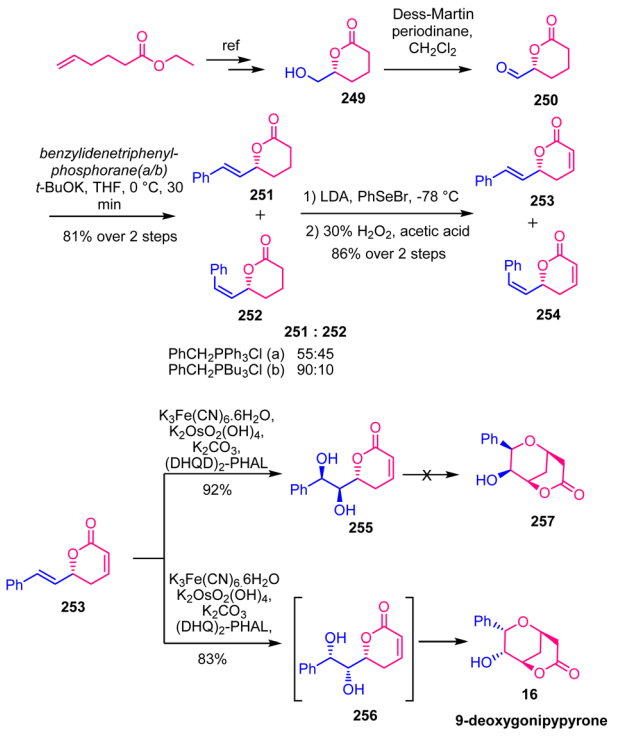
Scheme 32 Total synthesis of (+)-goniodiol and (+)-9-deoxygoniopypyrone by J.-P. Surivet and J.-M. Vatele (1998).[48a]

9.4 Efficient synthesis of the styryllactones, (+)-goniothalamin, (+)-7-*epi*-goniodiol and (+)-9-deoxygoniopypyrone

Zhi-Yu Liu *et al.* have published a comprehensive synthesis of the styryllactones, including (+)-goniothalamin, (+)-7-*epi*-goniodiol, and (+)-9-deoxygoniopypyrone.[50] Their research focused on developing an efficient synthetic route for (+)-goniothalamin **249**, a pivotal intermediate that enables the synthesis of multiple styryllactone analogues through straightforward transformations. Here, authors successfully prepared four possible diastereomers and illustrated the synthesis of potential bicyclic lactones *via* an oxa-Michael addition reaction (Scheme 33).

The synthetic pathway commenced with racemic terminal olefin, which was converted to δ-lactones **249** using the hydrolytic kinetic resolution (HKR) developed by Jacobsen, achieving an overall yield of 77% with 96% enantiomeric excess. Oxidation of alcohol to aldehyde **250** was effectively achieved using Dess–Martin periodinane and the crude aldehyde was directly applied in the Wittig reaction. Employing benzylidenetriphenylphosphorane in the Wittig reaction afforded a mixture of *E*- and *Z*-olefins (**251** and **252**) in an 81% yield over two steps, with a ratio of 55 : 45.

Further stereoselectivity was improved by condensing tributylphosphonium salt (**b**) with aldehyde **250** in the presence of potassium *tert*-butoxide, resulting in lactones **251** and **252** at



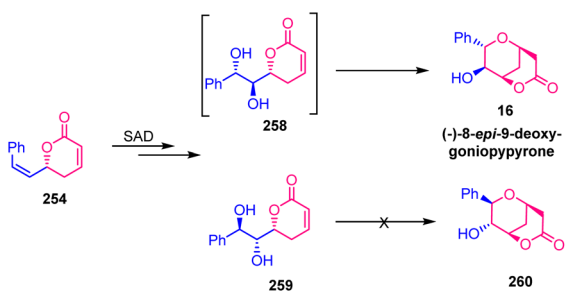
Scheme 33 Synthesis of (+)-9-deoxygoniopypyrone by Zhi-Yu Liu *et al.* (2004).[50]

a 90 : 10 ratio. The desired α,β-unsaturated-δ-lactone, (+)-goniothalamin **253** and **254**, was then obtained *via* phenylselenation of lactone **251** and/or **252**, followed by oxidative elimination. Next, Sharpless dihydroxylation was carried out and since OsO_4 is an electrophilic reagent, the rate of osmylation on electro-deficient olefins, such as α,β-unsaturated ketones could be very slow and external electron rich olefin will only participate. Thus, Sharpless AD reaction of **253** using $(DHQD)_2$-PHAL as ligand furnished **255** as almost a single product. However, this diol did not undergo intramolecular Michael addition even at elevated temperature due the bulky phenyl group at the high-energy axial position of the chair form which will make it unstable molecules. On the contrary, Sharpless AD reaction of **253** using $(DHQ)_2$-PHAL as ligand at 0 °C is predicted to give diol **256**, which was directly converted into a cyclisation product, 9-deoxygoniopypyrone **16** due to the presence of the hydroxy with *S*-configuration at C8 of **256**.

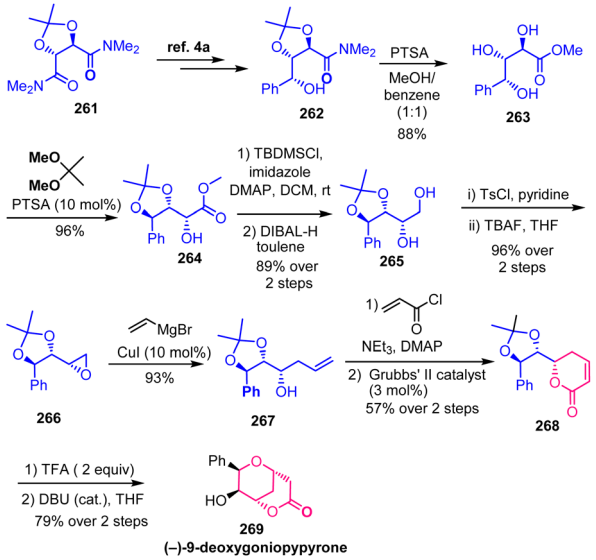
Here, the phenyl group will be at the low-energy equatorial position to afford stable molecules and therefore it is the absolute configuration of C8 that determines whether diols or Michael addition products are formed. Other two possible diastereomers could also be prepared from *cis*-olefin **151** (Scheme 34). It is also important to note that there has been no previous report of the isolation of **256**, **257**, **258**, and **260** from nature which corroborates well with their studies (Schemes 33 and 34).

9.5 Stereoselective total synthesis of (−)-9-deoxygoniopypyrone

In 2007, Kavirayani R. Prasad and Madhuri G. Dhaware reported the total synthesis of (−)-9-deoxygoniopypyrone *via* chiral pool synthesis.[51] Their synthetic strategy involved the cyclization of a diol derived from L-(+)-tartaric acid and a subsequent ring-closing metathesis (RCM) reaction to construct the lactone ring. The synthesis (Scheme 35) commenced with the preparation of bisdimethylamide **261** from L-(+)-tartaric acid, following the method previously described by Prasad and Gholap.[52] This bisdimethylamide intermediate was transformed into a benzylic alcohol derivative **262** using established protocols. Deprotection of the acetonide, accompanied by hydrolysis of the amide to yield the methyl ester **263** was effectively achieved through acid hydrolysis. Following this, the alcohol was protected, and subsequent reduction of the ester generated the key alcohol intermediate **265**.



Scheme 34 Synthesis of (−)-8-*epi*-9-deoxygoniopypyrone by Zhi-Yu Liu *et al.* (2004).[50]



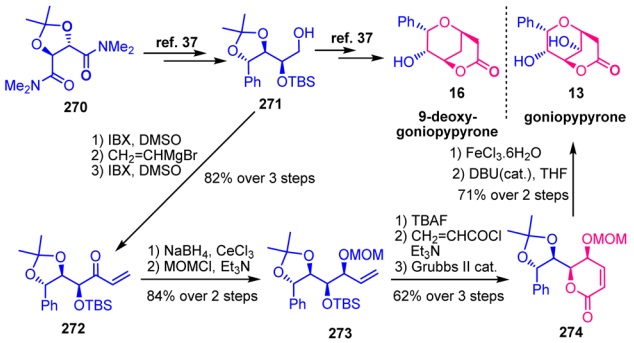
Scheme 35 Synthesis of (−)-9-deoxygoniopypyrone by Kavirayani R. Prasad *et al.* (2007).[51]

This intermediate was then converted to a terminal epoxide **266** *via* tosylation and subsequent treatment with TBAF. Reaction with vinylmagnesium bromide in the presence of CuI furnished homoallylic alcohol **267**, which upon treatment with acryloyl chloride provided the diene precursor necessary for RCM. Subjecting this precursor to Grubbs' second-generation catalyst yielded the desired lactone **268** in a 76% yield. Finally, treatment with DBU completed the synthesis, affording *ent*-9-deoxygoniopypyrone **269** in an impressive 91% yield.

9.6 Stereoselective total synthesis of 9-deoxygoniopypyrone, goniopypyrone

Later in the same calendar year, Kavirayani R. Prasad and Madhuri G. Dhaware reported the total synthesis of 9-deoxygoniopypyrone **16** and goniopypyrone **13** by employing a comparable synthetic methodology.[53] The sequence initiated with the generation of bis(dimethylamide) derived from L-(−)-tartaric acid. Subsequent transformations mirrored a previously established sequence to yield 9-deoxygoniopypyrone **16**. Here, author synthesized 9-deoxygoniopypyrone from Bisdimethylamide **270** from D-(−)-tartaric acid using same protocol mentioned in earlier report (Scheme 36).[51] For goniopypyrone **13**, the synthesis proceeded from a recognized intermediate **271**, which underwent oxidation *via* IBX to yield aldehyde intermediate. A vinylmagnesium bromide addition, followed by further oxidation with IBX, afforded the keto intermediate **272**, which was subsequently reduced using sodium borohydride and cerium(III) chloride, producing alcohol as a single diastereomer. This alcohol was then protected as a methoxymethyl (MOM) ether using chloromethyl methyl ether, yielding compound **273**.

Deprotection of the silyl group was achieved with tetrabutylammonium fluoride (TBAF), and subsequent acylation with acryloyl chloride produced the RCM precursor, the acrylate

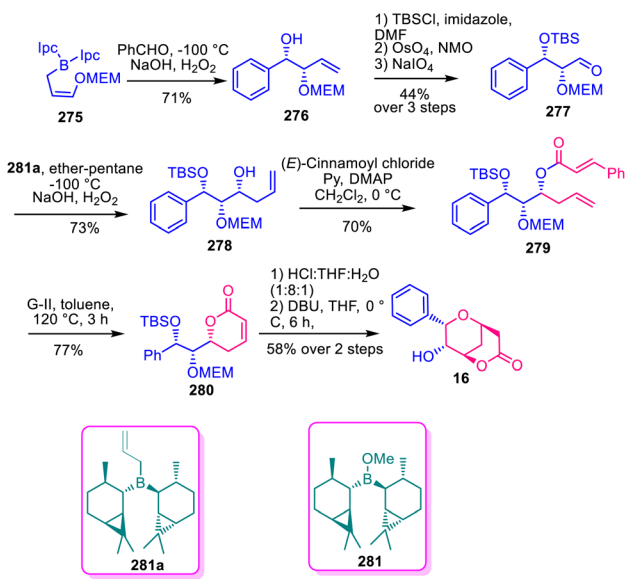


Scheme 36 Synthesis of (+)-9-deoxygoniopypyrone and goniopyrone by Kavirayani R. Prasad *et al.* (2007).[53]

ester. Ring-closing metathesis (RCM) of ester, facilitated by Grubbs' second-generation catalyst, delivered lactone **274**. At this juncture, both the acetonide and MOM protecting groups were meticulously removed using iron(III) chloride, furnishing the known triol intermediate and finally, exposure of this to DBU led to the formation of goniopypyrone **13** in an 83% yield.

9.7 Stereoselective syntheses of (+)-goniodiol, (−)-8-*epi*-goniodiol, and (+)-9-deoxygoniopypyrone *via* alkoxyallylboration and ring-closing metathesis

In this work, P. Veeraraghavan Ramachandran *et al.*[54] employed an *R*-pinene-derived chiral auxiliary to achieve asymmetric alkoxyallylboration, resulting in *syn*-diol units with remarkable diastereo- and enantioselectivity (Scheme 37). The synthetic route began from preparation of **275** by reacting (+)-*B*-methoxydiisopinocampheylborane **281** and lithiated allyl *p*-methoxyphenyl ether in THF at −78 °C, followed by oxidation.[40] Next, aryloxyallylboration was performed by the reaction of



Scheme 37 Syntheses of (+)-goniodiol, (−)-8-*epi*-goniodiol, and (+)-9-deoxygoniopypyrone by Ramachandran *et al.* (2002).[54]

benzaldehyde and (+)-*B*-γ-methoxyethoxymethoxyallyldiisopinocampheylborane **275**, yielding a monoprotected diol **276** with an impressive 98% ee.[55,56]

Subsequent steps involved protection of the alcohol **276**, followed by oxidation of the terminal olefin to produce an aldehyde **277**, which underwent asymmetric allylation with B-allyldiiso-2-caran-ylborane **281a.** This transformation afforded a homoallylic intermediate **278**, which was subsequently converted to cinnamate ester **279.** Ring-closing metathesis was then performed using Grubbs' second-generation imidazolyl ruthenium catalyst, yielding the pyrone derivative **280.** Final deprotection of the TBS and MEM groups with HCl in THF, followed by DBU treatment, led to (+)-9-deoxygoniopypyrone **16** *via* an intramolecular oxa-Michael addition.

10. (−)-8-*Epi*-9-deoxygoniopypyrone

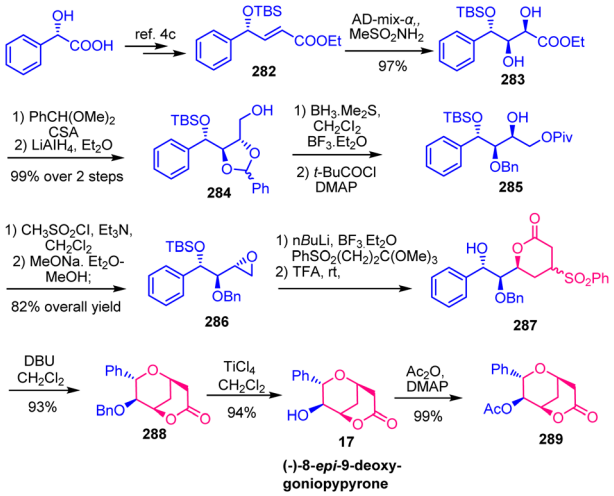
10.1 Isolation and biological activity

In 2010, Young H. Kim and colleagues isolated a new pyranopyrone compound, (+)-8-*epi*-9-deoxygoniopypyrone **17**, from a chloroform extract of *Goniothalamus tamirensis* leaves. This compound is an epimer of the previously reported 9-deoxygoniopypyrone. At a concentration of 2.67 μM, it was found to stimulate both the growth and differentiation of osteoblastic MC3T3-E1 cells, suggesting its potential to enhance osteoblastic activity and promote bone formation (Fig. 1).[57]

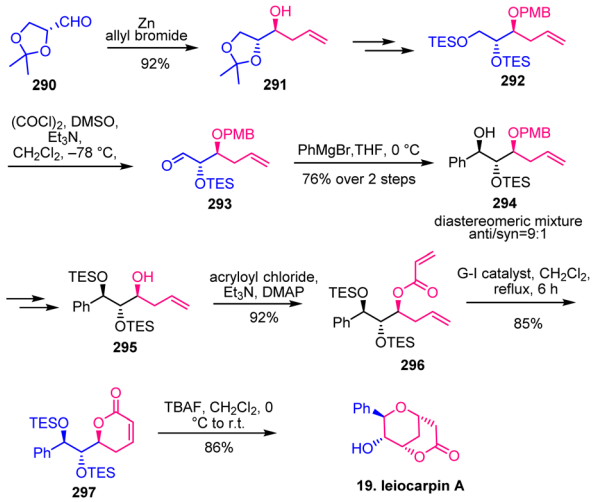
10.2 First total synthesis of (−)-8-*epi*-9-deoxygoniopypyrone

In the same year, J.-M. Vatèle *et al.* reported the first total synthesis of (−)-8-*epi*-9-deoxygoniopypyrone, utilizing a synthetic approach akin to the strategy previously outlined.[58] A pivotal aspect of their methodology involved coupling a sulfone with an epoxide to yield a β-hydroxy sulfone intermediate, which subsequently served as a precursor for constructing the lactone moiety (Scheme 38). The epoxide was efficiently synthesized from (*S*)-mandelic acid, a readily available starting material. Following established protocols (*S*)-mandelic acid was transformed into the enantiopure (*E*)-α,β-unsaturated ester **282.** The critical 1,2-*syn* diol stereocenters were introduced *via* Sharpless asymmetric dihydroxylation (AD), utilizing AD-mix-α. This dihydroxylation of compound **282** proceeded with exceptional double stereoselectivity, yielding the desired diol **283** with high enantioselectivity. The diol was then protected as a benzylidene acetal, and subsequent reduction of the ester with lithium aluminum hydride at 0 °C yielded the corresponding alcohol **284.**

A hydroxy directed regioselective reductive cleavage of the benzylidene with $BH_3 \cdot Me_2S$ and $BF_3 \cdot Et_2O$ afforded the benzyl ether and primary hydroxyl group of the resulting terminal diol was selectively protected as a pivalate **285.** The secondary hydroxyl was converted to a mesylate and treatment with sodium methoxide then generated the terminal oxirane ring **286.** At this stage, oxirane ring was opened and Ghosez's methodology[50] was employed to incorporate the lactone-bearing fragment. Finally, oxa-Michael by DBU followed by $TiCl_4$ mediated debenzylation furnished (−)-8-*epi*-9-



Scheme 38 First total synthesis of (−)-8-*epi*-9-deoxygoniopypyrone by J.-M. Vatèle *et al.* (1998).[58]



Scheme 39 Synthesis of leiocarpin A by K. Nagaiah *et al.* (2009).[59]

deoxygoniopypyrone **17** and they accomplished first total synthesis in a highly stereocontrolled manner.

11. (1*S*)-Phenylpyranopyrones (leiocarpin A or parvistone D and parvistone E)

11.1 Isolation and biological activity

In 2014, Yang Wu and colleagues carried out chromatographic purification of the methanolic extract from *Polyalthia parviflora* leaves, leading to the isolation of several (1*S*)-phenylpyranopyrones, which exhibited moderate anti-cancer and cytotoxic activities.[44] Among these, the absolute configuration of parvistone D **18** was determined to be (1*S*,5*S*,7*R*,8*R*), as depicted in Fig. 1. This configuration was confirmed through analysis of its circular dichroism (CD) spectrum and X-ray crystallographic data. Notably, compound **18** was identified as having the reversed stereochemistry of (+)-9-deoxygoniopypyrone **17**, and was thus assigned as (1*S*,5*S*,7*R*,8*R*)-3-*endo*,7-*endo*-(−)-9-deoxygoniopypyrone. This marked the first report of its natural occurrence. Two additional diastereomers were also isolated: compound **19a** (also known as leiocarpin A or parvistone E), assigned as (1*S*,5*S*,7*R*,8*S*)-3-endo,7-*endo*-(−)-8-*epi*-9-deoxygoniopypyrone, and compound **19b**, assigned as (1*S*,5*S*,7*R*,8*S*)-3-*exo*,7-*endo*-(+)-8-*epi*-9-deoxygoniopypyrone (Fig. 1).

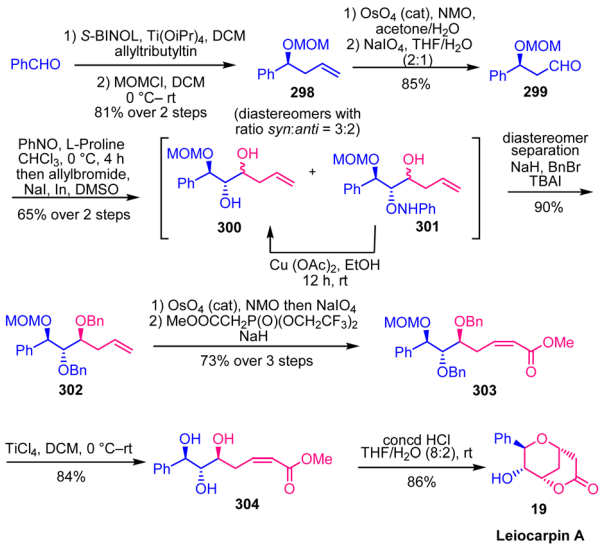
11.2 Stereoselective total synthesis of leiocarpin A and (−)-galantinic acid starting from D-mannitol

In 2009, K. Nagaiah *et al.*[59] meticulously detail the stereoselective synthesis of leiocarpin A **19** and (−)-galantinic acid employing D-mannitol-derived (*R*)-2,3-*O*-isopropylidene glyceraldehyde [(4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde] **290** as the foundational chiral synthon (Scheme 39). Notably, this compound serves as an accessible and economical starting material, facilitating advanced synthetic applications. Their process initiates with a zinc-mediated, stereoselective allylation of (*R*)-2,3-*O*-isopropylidene glyceraldehyde **290**, a derivative of D-mannitol. This reaction yields a mixture of homoallylic alcohol diastereomers with a high selectivity ratio (*anti*/*syn* = 95 : 5). The predominant isomer **291** subsequently underwent methodical transformation into the terminal alcohol *via* conventional protection and deprotection steps. Further, the team oxidized the primary alcohol to the corresponding aldehyde **293** utilizing Swern oxidation conditions which then subjected to a Grignard reaction with phenylmagnesium bromide, producing benzylic alcohol as a diastereomeric mixture (*anti*/*syn* = 9 : 1). The *anti*-diastereomer **294** was subjected a sequential protective and deprotective scheme to prepare the intermediate alcohol **295**, which was then acryloylated with acryloyl chloride, yielding the Grubbs precursor **296**. Upon exposure to Grubbs' first-generation catalyst, this precursor undergoes efficient cyclization, generating bis(triethylsilyl)-protected 6-*epi*-goniodiol **297**. The final deprotection was achieved using tetrabutylammonium fluoride which induced an intramolecular Michael addition, culminating in the synthesis of leiocarpin A **19** with an impressive yield of 86%.

11.3 Tandem α-aminoxylation–allylation reaction based approach for the synthesis of goniothalesdiol A, leiocarpin A and (+)-goniodiol

In 2011, Gowravaram Sabitha *et al.* pioneered an innovative route for synthesizing goniothalesdiol A, leiocarpin A, and (+)-goniodiol through a tandem α-aminoxylation–allylation approach (Scheme 40).[60] Central to the construction of key 1,2-anti diols, the researchers employed a proline-catalyzed tandem α-aminoxylation and allylation of an aldehyde intermediate, subsequently followed by an acid-catalyzed oxo-Michael reaction to furnish the bicyclic lactone framework.

The synthesis commenced from commercially available benzaldehyde which was initially converted into homoallylic alcohol with an exceptional enantioselectivity of 98% *ee*, as confirmed *via* chiral HPLC, using the Keck allylation protocol.

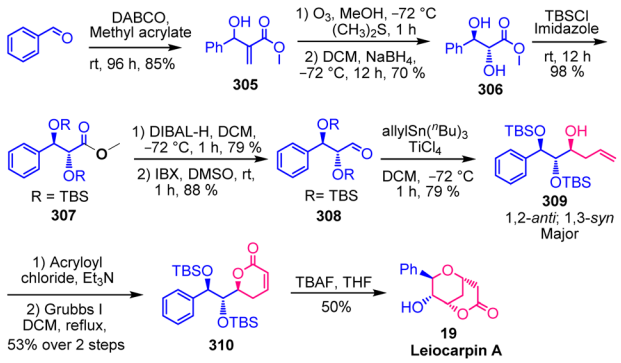


Scheme 40 Synthesis of leiocarpin A by Gowravaram Sabitha *et al.* (2011).[60]

Following this, the hydroxyl group was protected with a methoxymethyl (MOM) group to get **298** and the terminal olefin was then subjected to oxidative cleavage using OsO_4 and NMO, yielding an aldehyde **299**. In the pivotal α-aminoxylation step, the team reacted the aldehyde with nitrosobenzene (1 equivalent) in the presence of L-proline (20 mol%) as the catalyst. This reaction was immediately followed by an *in situ* indium-mediated allylation with allyl bromide in the presence of NaI at ambient temperature, producing a mixture of isomers (**300** & **301**). The crude mixture was subsequently treated with $Cu(OAc)_2$ in ethanol to achieve N–O bond cleavage, resulting in the isolation of the diol intermediate as a mixture of anti/syn isomers in a 4 : 6 ratio (confirmed *via* chiral HPLC) and a yield of 65%. Next, the *anti*-isomer alcohol was protected as OBn ether **302** and the terminal double bond of underwent dihydroxylation with OsO_4 and $NaIO_4$ to generate an aldehyde. This was followed by a (*Z*)-selective Wittig olefination to afford the corresponding α,β-unsaturated ester **303**. Finally, a global deprotection using $TiCl_4$ liberated the tetrol **304**, which, under acidic conditions with HCl, yielded leiocarpin A **19**.

11.4 A Morita–Baylis–Hillman adduct allows the diastereoselective synthesis of styryl lactones

In 2011, Coelho *et al.* delineated a diastereoselective pathway for the synthesis of (±)-leiocarpin A, utilizing a highly functionalized aldehyde as the pivotal precursor.[61] This aldehyde was efficiently derived from a Morita–Baylis–Hillman (MBH) adduct, which subsequently enabled the construction of an α,β-unsaturated lactone *via* ring-closing metathesis (RCM). Upon the removal of the protecting group under basic conditions, this lactone underwent a spontaneous cyclization, forming leiocarpin A (Scheme 41). Fernando Coelho and colleagues initiated this synthesis by crafting the MBH adduct **305** from benzaldehyde and methyl acrylate. Following ozonolysis, they obtained the corresponding carbonyl intermediate, which was then



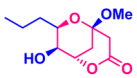
Scheme 41 Synthesis of leiocarpin A by Coelho *et al.* (2011).[61]

reduced using sodium borohydride to yield the *anti*-dihydroxylated ester **306**. Remarkably, this product exhibited a high diastereoisomeric purity, exceeding 95% *de*. The pronounced diastereoselectivity was plausibly attributed to the Cram-chelate model, a stereoelectronic framework that rationalizes the observed 1,2-asymmetric induction within acyloin systems. The diol substrate was initially protected using TBSCl, followed by a reduction with diisobutylaluminum hydride (DIBAL-H), yielding the primary alcohol. This intermediate was subsequently oxidized with IBX to furnish the desired aldehyde **308**. To establish the requisite stereocenter and finalize the molecular framework, the authors explored allylation using allylmagnesium bromide and allyltributylstannane, both with and without various Lewis acid catalysts such as boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) and titanium tetrachloride ($TiCl_4$). The optimal diastereoselectivity emerged in the reaction with allyltributylstannane in the presence of $TiCl_4$, affording the product with a 1,2-*anti*-1,3-*syn* stereochemical configuration **309**. This outcome aligns with the Felkin–Ahn stereochemical model, providing a rational basis for the observed selectivity.[62] Subsequently, this homoallylic alcohol **309** underwent acylation with acryloyl chloride to yield the corresponding ester, which was subjected to ring-closing metathesis, forming the α,β-unsaturated lactone **310**. The final deprotection with tetra-*n*-butylammonium fluoride (TBAF) delivered (±)-leiocarpin A **19** *via* oxa-Michael in 50% yield, maintaining high diastereomeric purity and achieving an overall yield of 8.5%.

12. Pestalrone A

12.1 Isolation and biological activity

In 2012, D. Q. Luo *et al.* isolated the new oxysporone derivative, pestalrone A **12**. It was from the fermentation broth of the endophytic plant fungus *Pestalotiopsis karstenii*



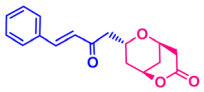
isolated from stems of *Camellia sasanqua* (Fig. 1).[63] Currently,

there are no reported methods for the chemical synthesis of this molecule.

13. Cryptoyunnane E

13.1 Isolation and biological activity

In 2022, Q. He *et al.* reported the isolation of five new α-pyrone derivatives, including cryptoyunnane E **20**, along with four known analogues, from the twigs of *Cryptocarya yunnanensis*.



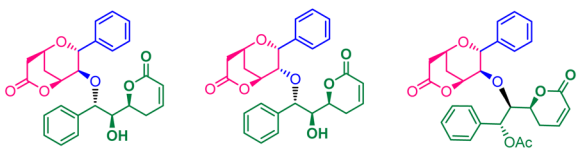
20
Cryptoyunnane E

The air-dried and powdered leaves and twigs (7.2 kg) were extracted with 95% ethanol at room temperature. Cryptoyunnane E exhibited mild cytotoxic activity against A549, HCT-116, MDA-MB-231, PC-3, and HeLa cell lines (Fig. 1).[64] Currently, there are no reported methods for the chemical synthesis of this molecule.

14. Goniolanceolatins F, G and H

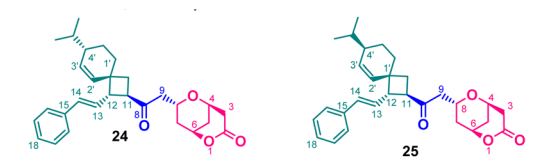
14.1 Isolation and biological activity

N. H. Ismail *et al.* in 2019 isolated new bis-styryllactones, goniolanceolatins F **21**, G **22**, and H **23** from the CH_2Cl_2 extract of the stembark and roots of *Goniothalamus lanceolatus* Miq., a plant

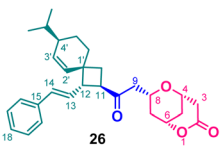


21 Goniolanceolatins F
22 Goniolanceolatins G
23 Goniolanceolatins H

These compound possess a rare α,β-unsaturated δ-lactone moiety with a (6*S*)-configuration. Goniolanceolatins H exhibited moderate to weak cytotoxicity against human lung and colorectal cancer cell lines.[65] No viable or documented synthetic strategy has been described to date.



24 Cryptoaevilactone D (11*R*,12*S*,1'*S*,4'*R*)
25 Cryptoaevilactone E (11*R*,12*S*,1'*S*,4'*R*)



26
Cryptoaevilactone F (11*R*,12*S*,1'*R*,4'*S*)

15. Cryptoaevilactone D–F

15.1 Isolation and biological activity

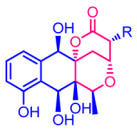
In 2018, Kyoko Nakagawa-Goto *et al.* cryptoaevilactone D–F (**24**, **25**, **26**) were isolated from *Cryptocarya laevigata*, which is called the glossy laurel or red-fruited laurel, are distributed in rainforest areas, mainly in eastern Australia.[66]

They performed a phytochemical study on a 50% MeOH/CH_2Cl_2 extract (N025439) of the leaves and twigs of *C. laevigata*. In this study, six new δ-lactone derivatives, named cryptolaevilactones A–F (**24–26**), were isolated from the EtOAc-soluble portion of the extract. At present, the synthesis of this compound remains unreported.

16. Luisol A and 2-hydroxyluisol A

16.1 Isolation and biological activity

In 2011, the marine actinomycete strain B7617, isolated from sediment at a littoral site near Punta Arenas, Tierra del Fuego (Chile), was identified as being closely related to *Streptomyces rectiviolaceus*. The strain was cultured in M2 medium supplemented with 50% sea water, and the metabolites were extracted using ethyl acetate followed by solid-phase extraction.



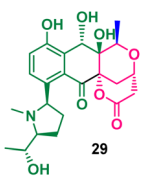
27. R = H, Luisol A
28. R = OH, 2-Hydroxyluisol A

Chemical screening-guided chromatographic separation of the crude extract led to the discovery of a new metabolite, 2-hydroxyluisol A **28**, along with the previously reported compounds luisol A **27**, and aloesaponarin II.[67] No total synthesis of this framework has been disclosed in the literature.

17. Vertirhodins F

17.1 Isolation and biological activity

In 2021, six novel pyranonaphthoquinones, named vertirhodins A–F, were discovered by Carole A. Bewley and colleagues from a soil-derived *Streptomyces* sp. B15-008, isolated from soil in Arizona. 16s rRNA sequencing identified the strain as closely related to *Streptomyces rectiverticillatus*.



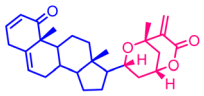
29
Vertirhodins F

Antimicrobial screening using an agar overlay assay revealed activity against *Staphylococcus aureus* (ATCC 25913). The strain was cultured in ISP2 liquid medium at 28 °C for 7 days, after which the broth was extracted with ethyl acetate. Antimicrobial activity-guided fractionation using an LH-20 column (eluted

with methanol), followed by semipreparative C18 reversed-phase HPLC, led to the isolation of compound **29**.[68] To date, no synthetic route to this scaffold has been documented.

18. Daturilin

18.1 Isolation and biological activity



30
Daturilin

To the best of our knowledge, daturilin **30** was one of the first complex bicyclic lactone to be isolated from nature, with its discovery and subsequent reporting in the scientific literature. This novel compound was isolated from the alcohol-soluble extract of the fresh leaves of Datura metel in 1987 by S. Siddiqui and colleagues.[69] To date, no synthetic route to this scaffold has been documented.

19. Conclusion and future perspective

The 2,6-disubstituted tetrahydropyran (THP) core and its bicyclic lactone derivatives represent a remarkable class of natural products distinguished by their structural intricacy, stereochemical richness, and diverse biological activities. Over the past decades, significant advances in isolation techniques, spectroscopic characterization, and stereochemical elucidation have enabled the identification of numerous members of this family from varied terrestrial and marine sources. These discoveries have not only expanded the chemical space of naturally occurring THP-based bicyclic lactones but have also revealed their potent pharmacological potential, including anticancer, antimicrobial, and anti-inflammatory activities.

Synthetic chemists have devised a wide array of strategies ranging from oxa-Michael additions and Prins cyclization to ring-closing metathesis and tandem transformations to construct these challenging architectures with high stereocontrol and efficiency. The evolution of these methodologies underscores the synergistic relationship between natural product chemistry and synthetic innovation, wherein isolation studies inspire new synthetic designs, and synthetic accessibility facilitates biological evaluation and analogue development.

This review will serve as a comprehensive reference for researchers interested in the chemistry of 2,6-disubstituted THP-based bicyclic lactones, providing both a chronological account of their natural occurrence and a critical overview of synthetic methodologies. This will enable readers to appreciate methodological innovations in this field and will aid chemists in designing new synthetic strategies, inspire exploration of novel biological activities, and facilitate the development of structurally related analogues for medicinal chemistry applications.

Author contributions

Utkal Mani Choudhury – writing original draft and editing. Dr Pragna Pratic Das – writing-review and editing. Prof. Debendra Kumar Mohapatra – writing-review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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