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REVIEW

Recent advances in the applications of Wittig reaction in the total synthesis of natural products containing lactone, pyrone, and lactam as a scaffold

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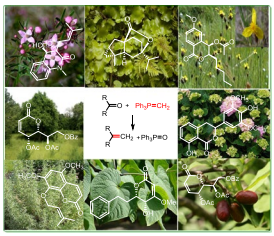
Abstract

The Wittig reaction enables the synthesis of an alkene from the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. Undoubtedly, its usefulness in the synthesis of alkenes in an anticipated manner has resulted in the introduction of an attractive principle in synthetic organic chemistry, particularly in the total synthesis of natural products. In this review, we try to highlight the applications of Wittig reaction in total synthesis of natural products. Worthy to mention that due to the vast numbers of related achievements, described in chemical literature, we had to limit ourselves to the applications of Wittig reaction to the total synthesis of natural products that contain lactone, pyrone, or lactam as scaffold in their complex structures.

Graphic abstract



Keywords Wittig reaction · Carbon–carbon bond · Lactone · Lactam · Pyrone · Natural products

Introduction

Natural products obtained from oceans are the gorgeous source of biologically active compounds [1], for example, alkaloids [2], cyclic peptides [3], and cyclic depsipeptides [4]. Marine fungi and cyanobacteria, mainly with structural scaffolds such as modified peptides, depsipeptides, polyketides, and peptide–polyketide hybrids, have developed as an appreciated and precious source of naturally occurring molecules having extraordinary bioactivities [5, 6]. They are found to be auspicious and gifted molecules in drug discovery, several of them are secondary metabolites exhibiting a wide range of pharmacological potencies, comprising cytotoxic antimicrobial, antimalarial, and neurotoxic potencies [7]. Moreover, some of them have been discovered for use in impending cancer therapeutics [4]. Most of these secondary metabolites have not been well investigated, thus necessitating further studies on both structural modifications and manners of activities [8].

Natural products are an ironic source of latent medications and painkillers. Nowadays, they are playing an important role in drug design and discovery. Worthwhile to mention is that drugs (roughly 40%) were publicized from natural products or their modified derivatives [9, 10]. Thus,

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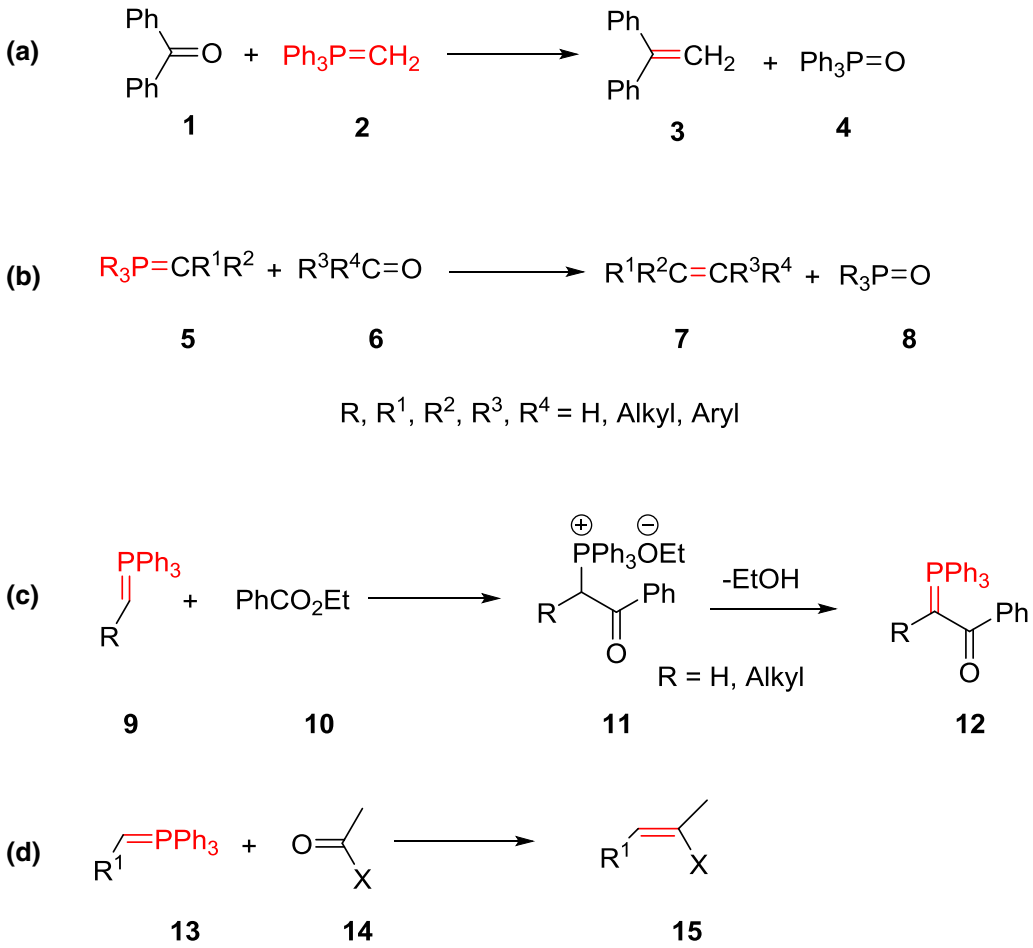
Scheme 1



natural products and their molecular constructions have a long folklore as appreciated models for the screening of biological activity and further drug discovery [11–13]. Natural products have since long been renowned as precious lead structures in the anticancer drug discovery area [14]. Large percentage (approximately 75%) of anticancer drugs in clinical screening for the treatment of cancer are either natural products or pharmacophores derived by the modification of their structures. Nowadays, natural products, particularly marine natural products exhibiting anticancer property, have attracted much attention of synthetic organic chemists, stirred up their interest and inspired them to achieve more operational and scalable total syntheses of these valuable targets as well as their new analogs that may show improved property [14]. After the innovative scrutiny by Wittig and Geissler [15] in which methylene triphenylphosphorane (**2**) reacted with benzophenone (**1**) to provide diphenylethylene (**3**) (Scheme 1a), the Wittig reaction was employed innumerable times as a remarkable methodology in synthetic organic chemistry [16, 17]. Basically, the Wittig reaction involves the condensation of an aldehyde or ketone and **6**, with a phosphorus ylide **5** resulting in the production of an olefin **7** along with phosphine oxide **8** (Scheme 1b). A number of papers and reviews on the application of Wittig reaction in organic synthesis can be found in the chemical literature [18, 19]. They cover different issues and aspects of this reaction reflecting its significance, describing it from the synthetic and mechanistic points of view.

Lactone rings as building blocks are extensively found in complex molecules and several natural products. Examples are anticancer drugs (vernolepin, epothilones), phytoestrogens (resorcylic acid lactones, cardiac glycosides), enzymes (lactonase), neurotransmitters (butyrolactone, avermectins), antibiotics, ascorbic acid, kavain, nepetalactone, gluconolactone, hormones (spironolactone, mevalonolactone), macrolides such as erythromycin, amphotericin B, anticancer drugs (vernolepin, epothilones), phytoestrogens (resorcylic acid lactones, cardiac glycosides).

Pyrones and pyranones are common heterocyclic compounds both containing an unsaturated six-membered ring comprising an oxygen atom as well as a carbonyl group of a ketone [20]. They exist in two isomeric forms designated as 2-pyrone and 4-pyrone. The 2-pyrone (α-pyrone) is found as a fragment of the coumarin ring system which is a scaffold in the natural product. In 2013, α-pyrones were recognized as a new group of molecule for bacterial communication, something comparable to quorum sensing [21]. 4-Pyrone (γ-pyrone) is also found in several naturally occurring molecules such as chromone, maltol, and kojic acid.

Basically, a lactam is a cyclic amide. The tenancy is a combination of the two words lactone and amide. They are cyclic amides of different ring sizes, designated as alpha, beta, and gamma lactams. β-Lactams are prominent antibiotics; nonetheless, lactam ring derivatives show some additional pharmacological effects. β-Lactams demonstrated biological activities as inhibitors of a wide range of enzymes, including HFAAH inhibitors, HDAC inhibitors, anti-inflammatory drugs (tryptase inhibitors), cathepsin K inhibitors, and vasopressin inhibitors, as well as anticancer and antitubercular activities.

β-Lactam antibiotics are a family of wide-spectrum antibiotics, comprising of all antibiotic agents that cover a β-lactam moiety in their complicated molecular structures that involves penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems [22]. Most β-lactam antibiotics act by inhibiting cell wall biosynthesis in the bacterial organism and are the most broadly utilized among antibiotics. Until 2003, more than half of all prescribed antibiotics have β-lactam in their structures [23]. However, it has been found that bacteria habitually develop resistance to β-lactam antibiotics via synthesizing a β-lactamase, an enzyme that spasms the β-lactam ring. To overcome this resistance, β-lactam antibiotics are frequently prearranged with β-lactamase inhibitors, for example, clavulanic acid.

In continuation of our interest in the applications of name reactions [24–35] in the total synthesis of natural products and due to the importance of Wittig reaction in total synthesis of natural products leading to publication of large number of related papers, herein, we try to underscore the applications of the Wittig reaction in the total synthesis of natural products showing diverse biological properties focusing on their structures bearing lactone, pyrone, and lactam scaffold. It is worthwhile to mention that because of the importance of this reaction and a plethora of published papers, this review is limited to the application of Wittig reaction in the total synthesis of lactone, pyrone, and lactam as a scaffold. The application of Wittig reaction in the total synthesis of alkaloids is under preparation for submission.

Application of Wittig reaction in the total synthesis of natural products

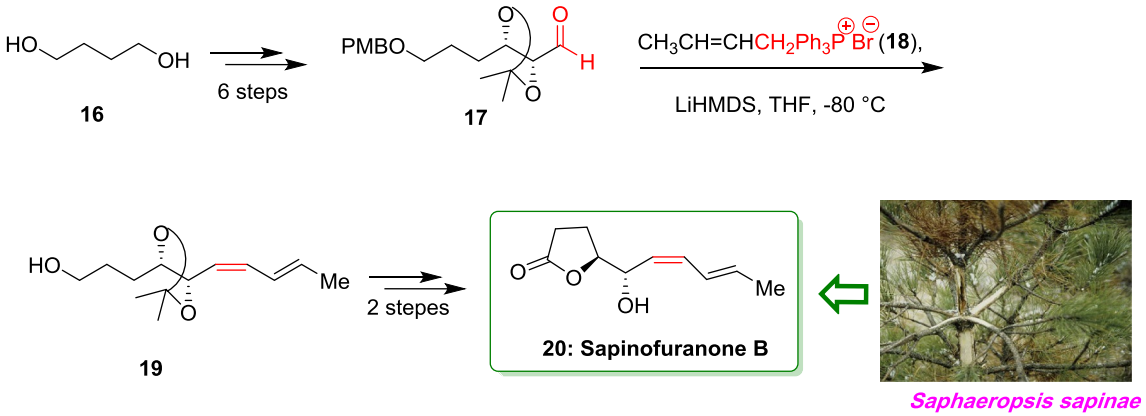
Containing lactone as moiety

Sapinofuranone B, a phytopathogenic fungus making a broad series of disease symptoms on conifers, has been extracted from liquid cultures of *Sphaeropsis sapinea* [36]. Significantly, the *A. strictum* lactone was demonstrated as (4*R*,5*S*)-(+)-sapinofuranone B (**20**). It can be prepared from market purchasable 1,4-butanediol (**16**) as the starting material. A useful and asymmetric total synthesis of sapinofuranone B was achieved through Sharpless enantioselective dihydroxylation, Sonogashira coupling, and Wittig olefination reaction as the main steps. Total synthesis of sapinofuranone B (**20**) was started from 1,4-butanediol (**16**) which upon several steps gave aldehyde **17**. Next, aldehyde **17** was allowed to react with Wittig salt **18** in tetrahydrofuran using lithium bis(trimethylsilyl)amide to provide a mixture of *trans*- and *cis*-Wittig products (*Z:E* 80:20). The corresponding *Z* isomer **19** has been readily separated using silica gel column chromatography. Finally, diene **19** upon several steps gave the desired natural product sapinofuranone B (**20**) (Scheme 2) [37].

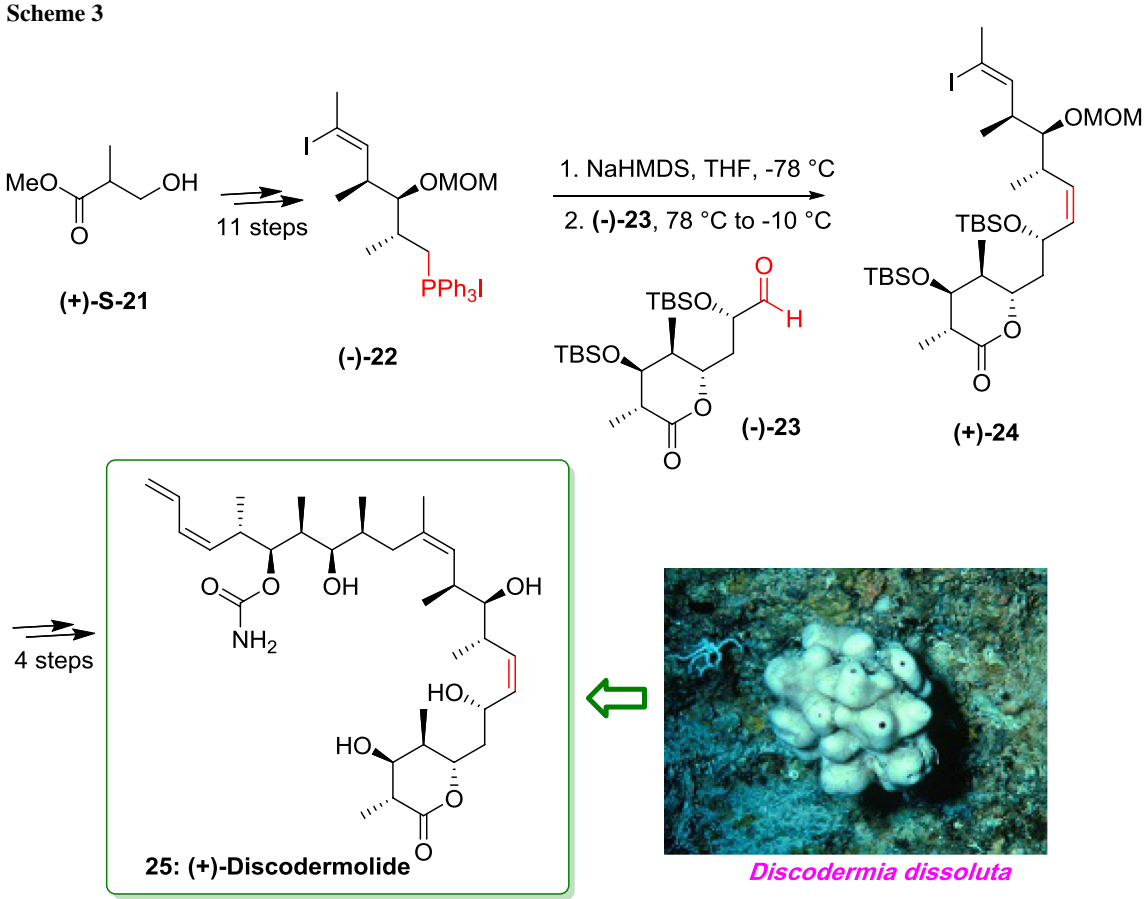
(+)-Discodermolide (**25**) has been isolated from the deep sea marine sponge *Discodermia dissoluta* in 1990 by Gunasekera and co-workers [38]. Later, Ter Haar and co-workers [39] and then Schreiber and co-workers [40] independently demonstrated that (+)-discodermolide shows strong antimitotic property, similar to the clinical anticancer agent taxol. Outstandingly, (+)-discodermolide exhibits important tumor cell growth inhibitory property against a broad series of recognized cancer cell lines. Smith and co-workers in 2005 reported a very convergent, fourth-generation total synthesis of (+)-discodermolide (**25**) in a longest linear sequence of 17 steps with an overall yield of 9.0% [41]. Total synthesis of (+)-discodermolide has been started from (+)-*S*-Roche's ester (+)-**21** that upon several steps afforded compound (−)-**22**. In this route, slow addition of sodium bis(trimethylsilyl) amide (NaHMDS) to a tetrahydrofuran solution of the Wittig salt (−)-**22** improved the construction of the desired phosphonium ylide significantly by reductive β-removal of the vinyl iodide. Subsequently, tetrahydrofuran solution of aldehyde (−)-**23** was added to the obtained ylide to provide vinyl iodide (+)-**24** in 62% yield. Lastly, upon several steps, vinyl iodide (+)-**24** has been converted into (+)-discodermolide (**25**) (Scheme 3) [41].

δ-Lactones, specially β-hydroxy-δ-lactones, are structural constituents of various bioactive naturally occurring compounds. Prelactones [42] isolated from different polyketide macrolide-providing microorganisms are a

Scheme 2



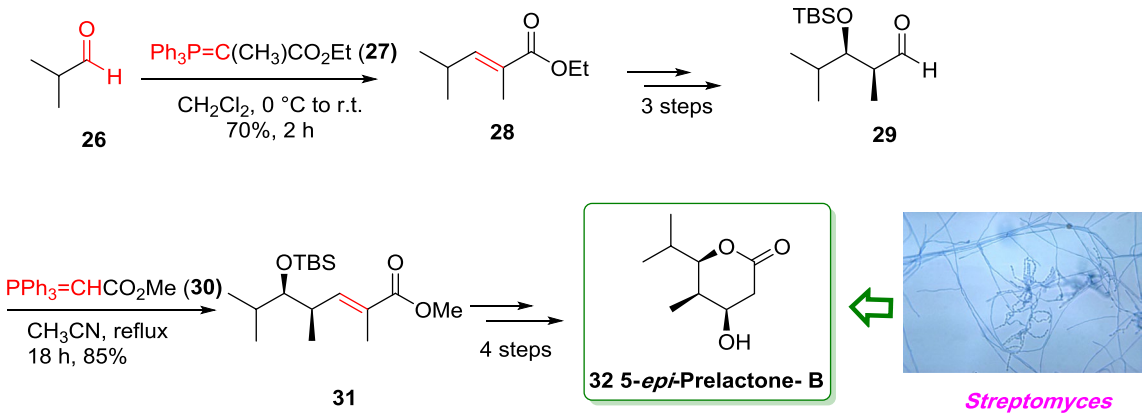
Scheme 3



subgroup of this class of compounds. They have obtained considerable interest due to their structural moieties that are valuable scaffolds for the formation of complex structures including concanomycin [43], bafilomycins [44], hygrolidin [45], and compactin [46]. Prelactone **B** has been isolated from *Streptomyces griseus* [42] and exhibits an early metabolite in the biosynthesis of polyketide antibiotics. It was applied as a standard for examinations relating to the mechanism of polyketide synthase (PKS).

Because of the significance of this group of compounds, several methods for the synthesis of prelactone B [47, 48] and *epi*-prelactones [49, 50] were described. First concise total synthesis of 5-*epi*-prelactone B **32** was accomplished in an overall yield of 21% in nine steps using Sharpless enantioselective epoxidation and intramolecular hydride transfer reaction as the key stages [51]. The formation of 5-*epi*-prelactone **32** started from the market-purchasable isobutyraldehyde (**26**) that has been subjected to the Wittig

Scheme 4



reaction with [1-(ethoxycarbonyl)ethyl]triphenylphosphoniumbromide (**27**) to give only *trans*-ester **28**. Next, *trans*-ester **28** afforded aldehyde **29** in three steps. Then aldehyde **29** was submitted to the Wittig reaction with (methoxycarbonylmethyl)triphenylphosphonium bromide (**30**) to give the *trans*-homologated product **31** in 85% yield. Lastly, compound **31** converted into 5-*epi*-prelactone B **32** after four steps (Scheme 4) [51].

The xanthanolide sesquiterpene lactones, a group of naturally occurring compounds, were extracted from the plants of the genus *Xanthium* (family Composite). They contain a bicyclic 5,7-fused ring scaffold, and show antimalarial [52], antitumor [53, 54], allelopathic [55], and antimicrobial activities [56, 57]. 8-*epi*-Xanthatin (**34**) was found in the extracts of the aerial parts of different species in the genus *Xanthium* [58, 59] showing antitumor property [53] as well as in vitro inhibitory property on insects [59], farnesyl transferase [54], and also auxin-prompted growth of sunflower hypocotyls [55].

Total synthesis of 8-*epi*-xanthatin (**34**) was started from 3-butyn-1-ol (**33**). Next, the reaction between **34** and the Wittig reagent ($Ph_3PC(CH_3)CO_2C_2H_5$) under reflux in xylene afforded the butenolide **36** in 91% yield. Lastly, butenolide **36** was converted into the desired natural products 8-*epi*-xanthatin (**37**), sundiversifolide (**38**), (−)-dihydroxanthatin (**39**), and (−)-xanthatin (**40**) in good yields, after several steps (through different pathways) (Scheme 5) [60].

Tetryhydroxanthones, a quick growing group of mycotoxins, contain remarkable biological properties. The secalonic acids that are symmetric or unsymmetric dimers of blennolides exhibit antibacterial, anti-HIV, and cytostatic activities [61, 62]. Diversonol (**50**), a secondary metabolite, was isolated by Turner from *P. diversum*. Lachnones are a member of chromone lactones extracted from the filamentous fungus *Lachnum* sp [63]. Manuel and co-workers developed the first asymmetric syntheses of diversonol (**50**), lachnone C (**45**), and *epi*-lachnone C (*epi*-**45**). Remarkably, this method is appropriate for the synthesis of various members of the tetrahydroxanthone and chromone lactones [64].

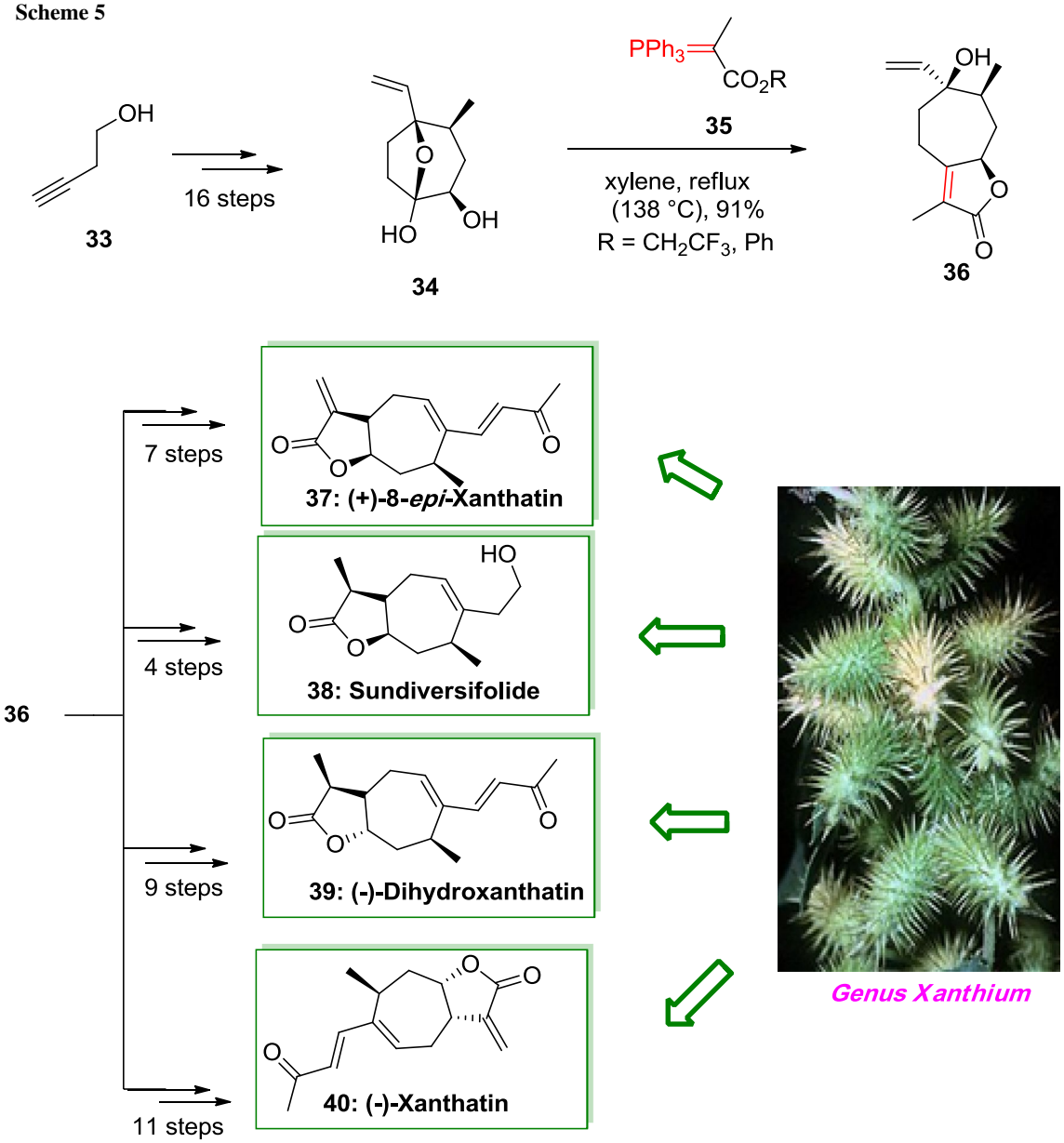
A unified synthetic approach for the enantioselective syntheses of the natural products diversonol and lachnone C has been established through the domino vinylogous aldol-oxa-Michael reaction as the asymmetric main stage. In this route, other main reactions are Wittig reaction and lactonization. The chromone lactones, a group of mycotoxins, were transformed to tetrahydroxanthones via a Dieckmann condensation reaction. *Epi*-lachnone C (*epi*-**45**) was provided in 39% yield from salicylaldehydes as precursors [64]. Total synthesis of *epi*-lachnone C has been achieved from the reaction of salicylaldehyde **41a** and prenal (**42**) with Jørgensen's catalysts [65]. After several steps, diol **43a** has been opened using a Wittig reaction. Fascinatingly, the result of the reaction has been powerfully reliant on temperature and the phosphonate applied. Once obtained in hot toluene, the reaction of diol **43a** and the stabilized ylide A afforded a mixture of the corresponding alkene **44**. Lastly, compound **44** gave lachnone C (**45**) after three steps (Scheme 6) [64].

A similar reaction sequence has also been applied to the formation of lachnone C (**45**) commenced from salicylaldehyde **41a**. Based on this method, salicylaldehyde **41a** afforded diol **46a**, after several steps. In the following, Wittig reaction, hydrogenation and reaction with *p*-toluenesulfonic acid afforded a mixture of lactone **47** and ether **48** in 18% and 64% yields, respectively. Lastly, both of them have been transformed to **45** in 39% yield, after two steps (Scheme 7) [65].

In the following, total synthesis of diversonol (**50**) was started from salicylaldehyde **41b** that produced lactol **43b** after several steps. Next, lactol **43b** using Wittig reaction gave unsaturated ester **49** in 83% yields. Lastly, after several steps, ester **49** was transformed to diversonol (**50**) (Scheme 8) [65].

Natural products obtained from polydeoxypropionates show different biological properties [66–68].

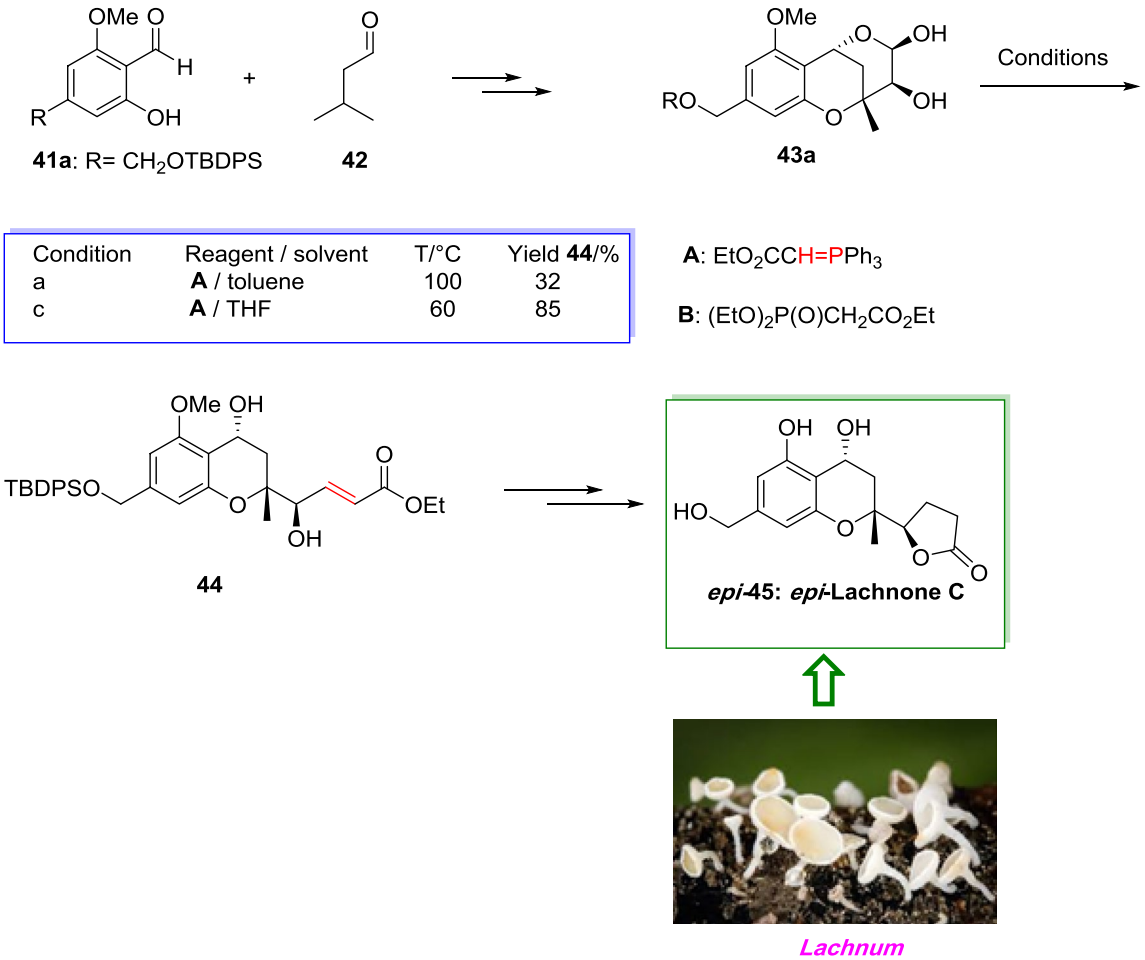
Scheme 5



(+)-Vittatalactone (**58**), a structurally unique pheromone, contains five stereogenic centers. For the first time, (+)-vittatalactone (**58**) was recognized by Morris and Francke and co-workers in 2005 from the pheromone mixture secreted, *Acalymma vittatum* [69]. An asymmetric enantioselective total synthesis of (+)-vittatalactone was achieved through enzymatic desymmetrization method to generate two methyl chiral centers. In this route, main stages are Wittig reaction, Evan's asymmetric alkylation, hydroboration, and TEMPO–BAIB-catalyzed selective oxidation of 1,3-diol and lactonization. The total synthesis was achieved via a linear synthetic sequence with an overall yield of 11.8%. This synthesis of (+)-vittatalactone **58** was started from butan-2-one (**51**) that created alcohol **6**, after several steps.

In the following, oxidation reaction of alcohol **52** followed by two-carbon atom extension using Wittig reaction gave the α,β-unsaturated ester **53** in 86% yield after two steps. Next, the α,β-unsaturated ester **53** was transformed to the primary alcohol **54** containing a novel additional chiral center in 92% yield. Then alcohol **54** was subjected to oxidation reaction using 2-iodoxybenzoic acid (IBX) in dimethyl sulfoxide and C3-Wittig reaction to give the α,β-unsaturated ester **55** (*E* isomer) as the only product in 86% over two steps [46]. Next, the α,β-unsaturated ester **55** afforded alcohol **56** in 93% yield in two steps. In the following, oxidation reaction of alcohol **56** with 2-iodoxybenzoic acid in dimethyl sulfoxide generated the corresponding aldehyde for the designed Wittig reaction with $Ph_3P{=}CH(CH_3)CO_2Et$ to provide

Scheme 6



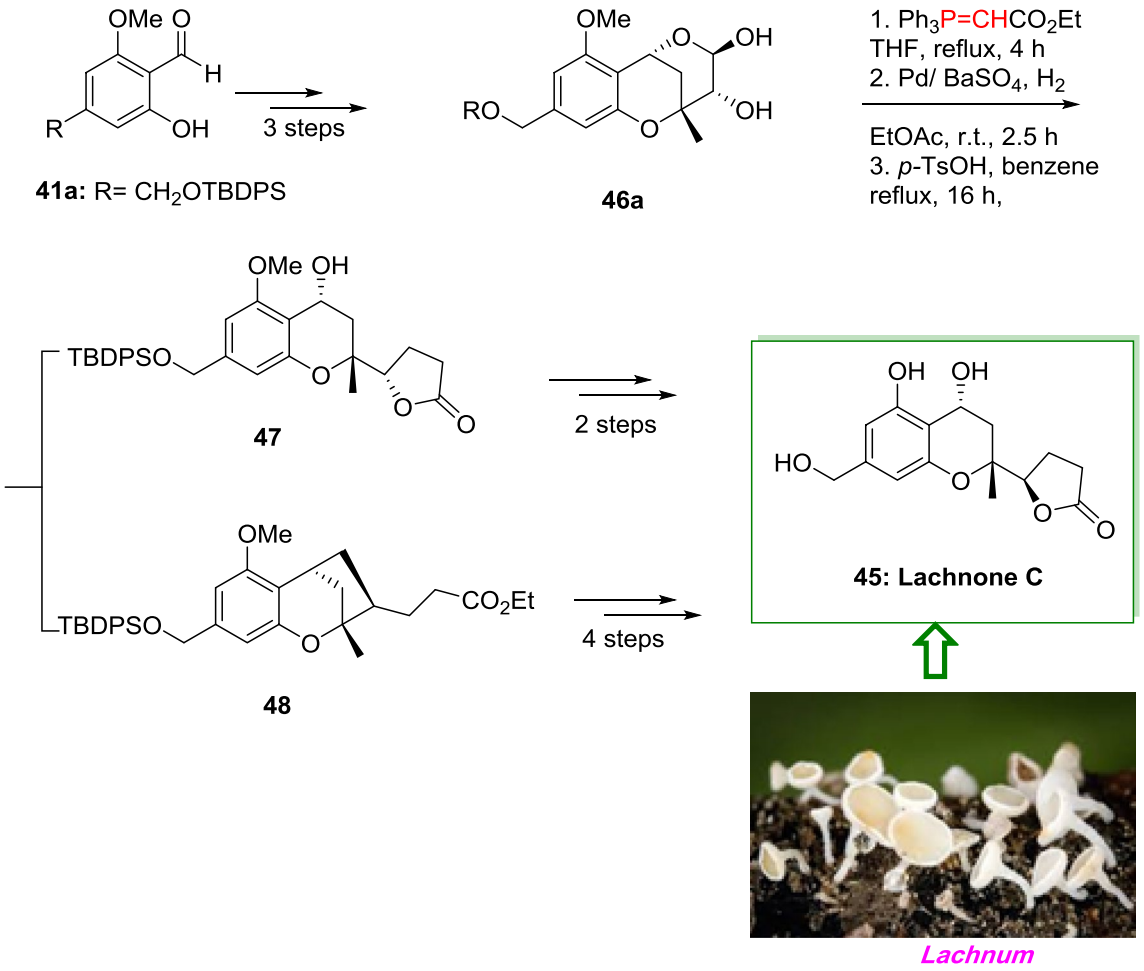
α,β-unsaturated ester **57** in > 85% yield from alcohol **56** [70]. Finally, the α,β-unsaturated ester **57** was transformed into the desired natural product, (+)-vittatalactone (**58**) in 78% yield (Scheme 9) [71].

Acetogenins, natural products isolated from tropical plants *Annonaceae*, show potential biological properties including antimicrobial, antitumor, pesticidal, and immunosuppressive properties [72]. Muricatacin (**62**), an acetogenin [73] isolated from the seeds of *Annona muricata* (Annonaceae) and correlated to γ-butyrolactone, exhibits antiproliferative property against certain cell lines. A significant asymmetric total synthesis of (+)-(4*S*,5*S*)-muricatacin was achieved in 93% total yields in nine steps from inexpensive, market-purchasable (+)-diethyl tartrate (DET) and undecan-1-ol. Mitsunobu and Julia–Kocienski reactions, Wittig homologation reaction, Swern oxidation, and lactonization were considered as the key steps.

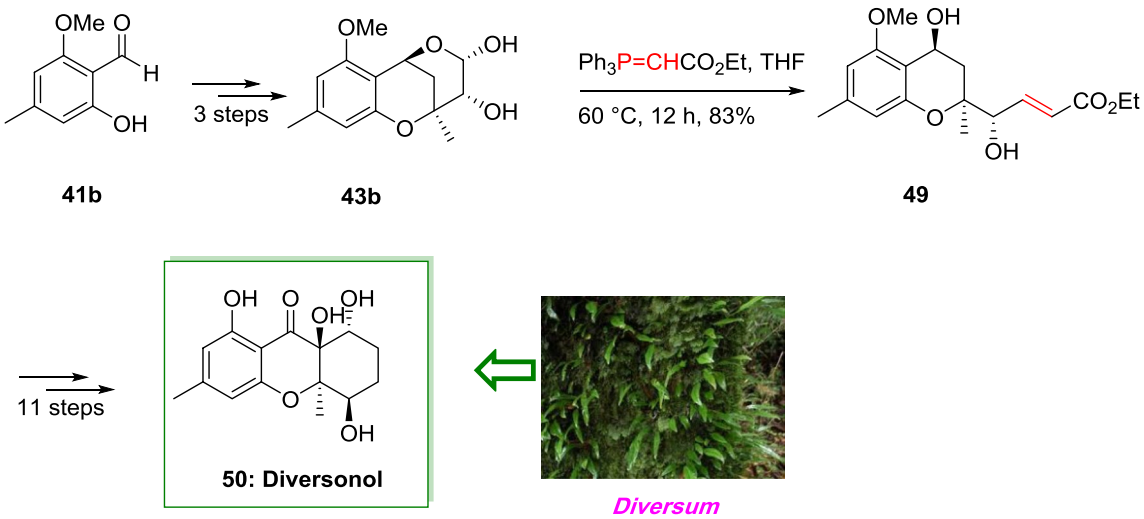
Total synthesis of muricatacin (**62**) was commenced from diethyl L-tartrate (**59**) that transformed into aldehyde **60** after several steps. Next, aldehyde **60** using C2-Wittig olefination reaction afforded the unsaturated ester **61** in 97% yields. In the following, this ester **61** gave (+)-(4*S*,5*S*)-muricatacin (**62**) in 98% yield, after two steps (Scheme 10) [74, 75].

δ-Lactones and γ-butyrolactones that are significant structural scaffolds are found in various biologically active natural products [76]. These lactone-derived compounds are significantly known as pheromones and aroma compounds of various flowers, fruits, and other naturally occurring compounds [77]. (−)-*cis*-Aerangis lactone ((4*S*,5*S*)-4-methyl-5-decanolide, **68**) was identified in 1993 by Kaiser as the main odor constituent of the African moth orchids *Aerangis confusa* and *Aerangis kirkii* as a 1:1 mixture along with its *trans*-diastereomer [78]. (−)-*cis*-Cognac lactone ((4*S*,5*S*)-*cis*-4-methyl-5-pentyldihydrofuran-2(3*H*)-one, **66**), one of the *Quercus* lactones, is found in different kinds of wood. (−)-*cis*-Aerangis lactone was provided in 29% overall yield in seven steps starting from *n*-hexanal (**63**). Moreover, (−)-*cis*-cognac lactone was produced in 34% overall yield in eight stages. A short and significant asymmetric total synthesis of natural products (−)-*cis*-aerangis lactone and (−)-*cis*-cognac lactone has been demonstrated in 2011 by Yadav and co-workers. The Sharpless enantioselective

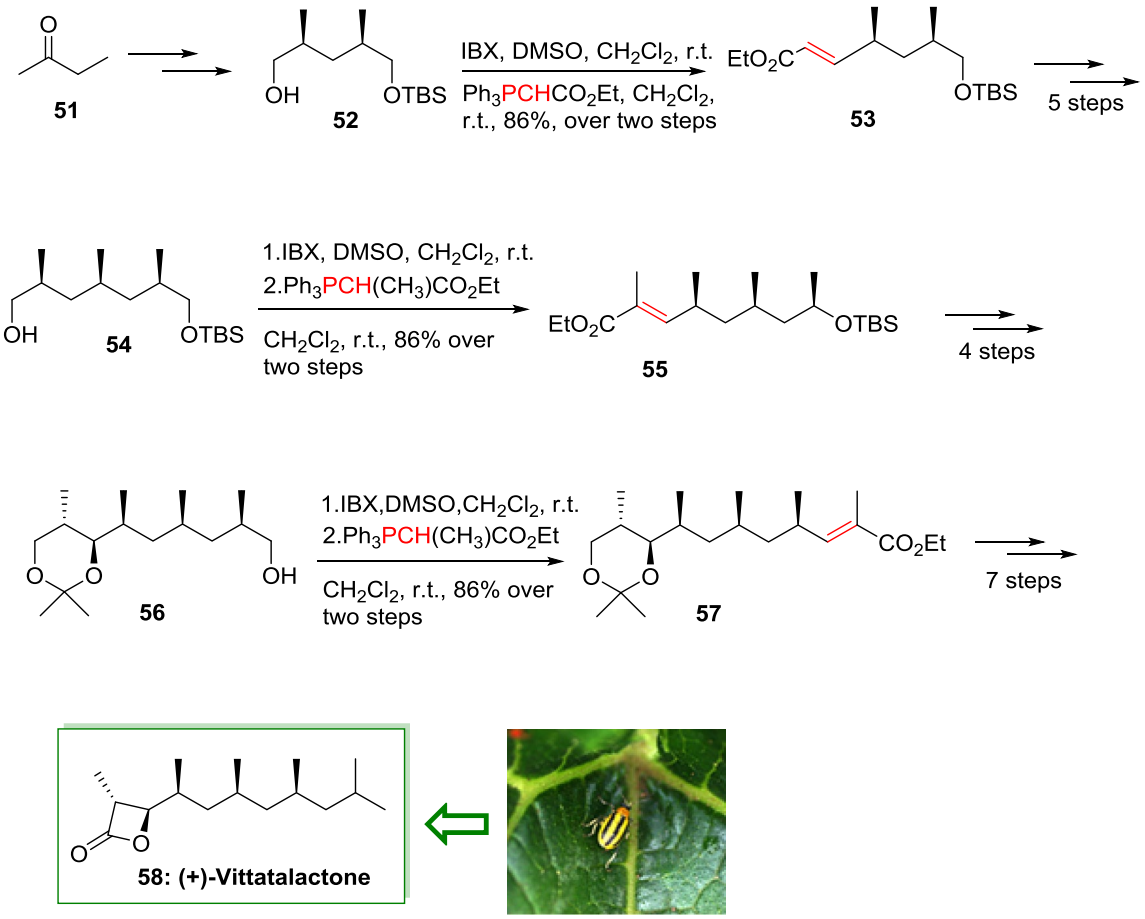
Scheme 7



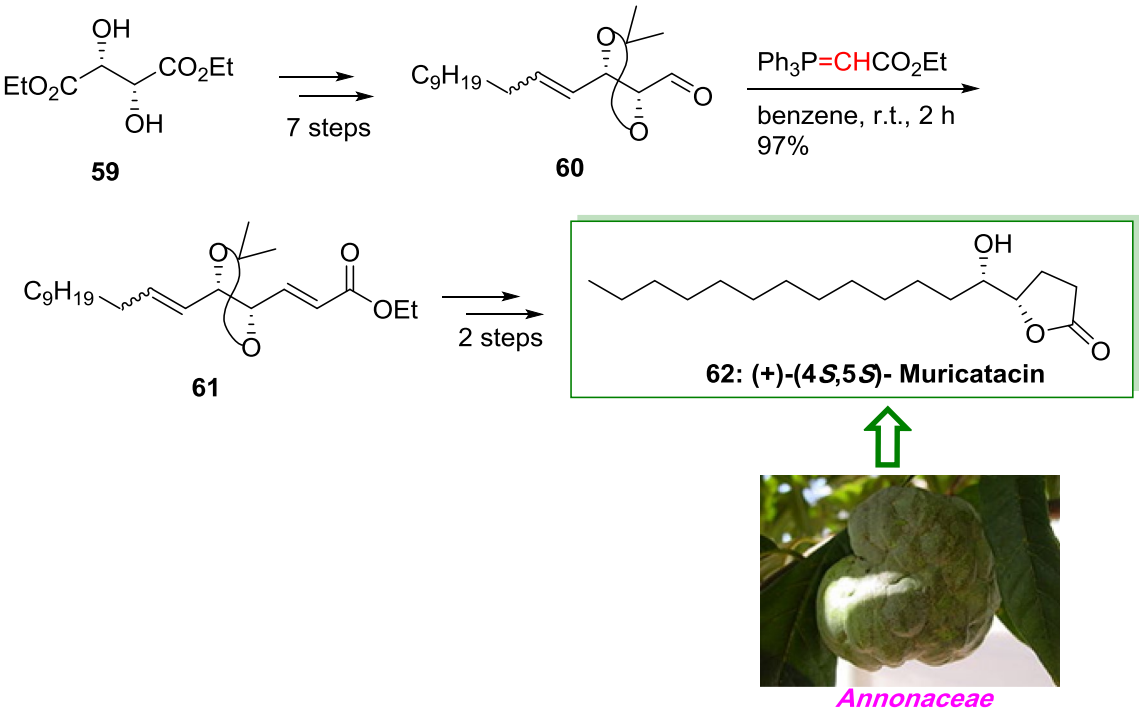
Scheme 8



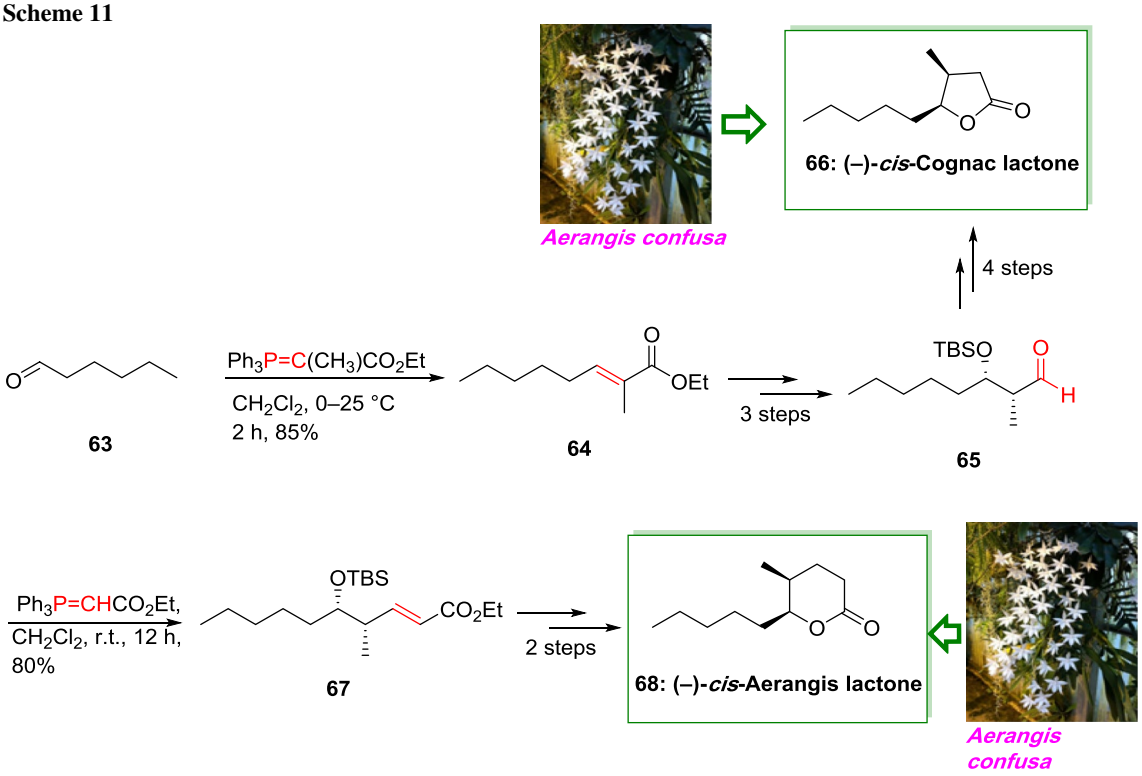
Scheme 9



Scheme 10



Scheme 11

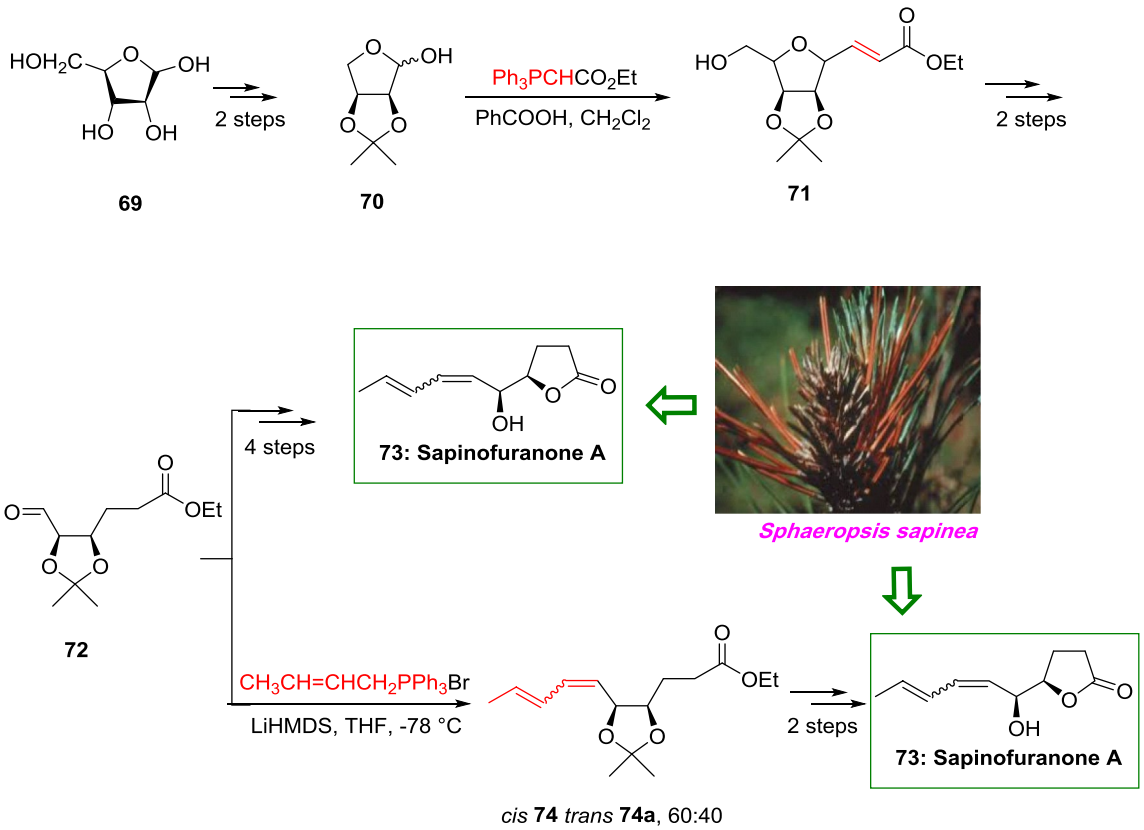


epoxidation reaction of a primary allylic alcohol and TBSOTf-catalyzed intramolecular hydride transfer of a chiral epoxy alcohol were effectively used for the construction of a main material with *syn*-aldol stereochemistry using a non-aldol approach. Total synthesis of *cis*-aerangis lactone (**68**) has been positively started from *n*-hexanal (**63**) that has been transformed to the corresponding α,β-unsaturated ester **64** utilizing a stabilized Wittig ylide [$Ph_3P{=}C(CH_3)CO_2Et$] in 85% yield [79]. Selective reduction of α,β-unsaturated ester **64** afforded TBS-protected *syn*-aldol product **65** in 85% yield [80] upon three steps. Next, aldehyde **65** was made to react more with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 to provide α,β-unsaturated ester **67** as a mixture of *trans*- and *cis*-isomers in 80% yield. Lastly, α,β-unsaturated ester **67** produced the (−)-*cis*-aerangis lactone (**68**) in 65% yield after two steps.

On the other hand, in an analogous pathway, the synthesis of (−)-*cis*-cognac lactone (**66**) was started from *n*-hexanal (**63**) that has been transformed to α,β-unsaturated ester **64** using a stabilized Wittig ylide [$Ph_3P{=}C(CH_3)CO_2Et$] in 85% yield [79]. Selective reduction of α,β-unsaturated ester **64** afforded TBS-protected *syn*-aldol product **65** in 85% yield [80] after three steps. Finally, aldehyde **65** gave the target molecule (−)-*cis*-cognac lactone (**66**) in 70% yield after four steps (Scheme 11) [81].

Butanolide and the related γ-lactone scaffolds comprising naturally occurring products have obtained important attention because of their effective biological activities [82]. 5-Functionalized dihydrofuranones, named sapinofuranone A (**73**) isolated from liquid cultures of *Sphaeropsis sapinea*, a phytopathogenic fungus, provide an extensive variety of disease symptoms on conifers. This natural butanolide, sapinofuranone A, was isolated from liquid cultures of a phytopathogenic fungus, *S. sapinea* in 1999 by Antonio Evidente and co-workers [36]. In 2012, Nagarapu and co-workers successfully achieved total synthesis of sapinofuranone A via a concise (eight steps), excellent yielding pathway (18% overall yield). The main reactions included in this strategy were Sonogashira coupling reaction, one-pot tandem acetonide deprotection and subsequent dihydrofuranone ring construction [81]. Total synthesis of sapinofuranone A (**73**) was started from D-ribose (**69**) that upon two steps afforded aldehyde **70**. Next, aldehyde was exposed to Wittig olefination reaction using ylide to afford segment **71** with a yield of 89%. Next, after two steps, main intermediate **72** was produced. Finally, aldehyde **72** after several steps provided sapinofuranone A (**73**) [83]. Based on another method, Nagarapu and co-workers provided the following diastereomeric mixture. In this route, compound **72** has been exposed to Wittig olefination reaction to provide **74** that was non-stereoselective and resulted in a mixture of approximately 7/3 of diastereomers *cis*-**74**:*trans*-**74a**. Whereas the two diastereomers were inseparable, the obtained mixture was reacted with catalytic amount of hydrochloric acid that afforded inseparable diastereomeric mixture of sapinofuranone A (**73**) (Scheme 12) [83].

Scheme 12



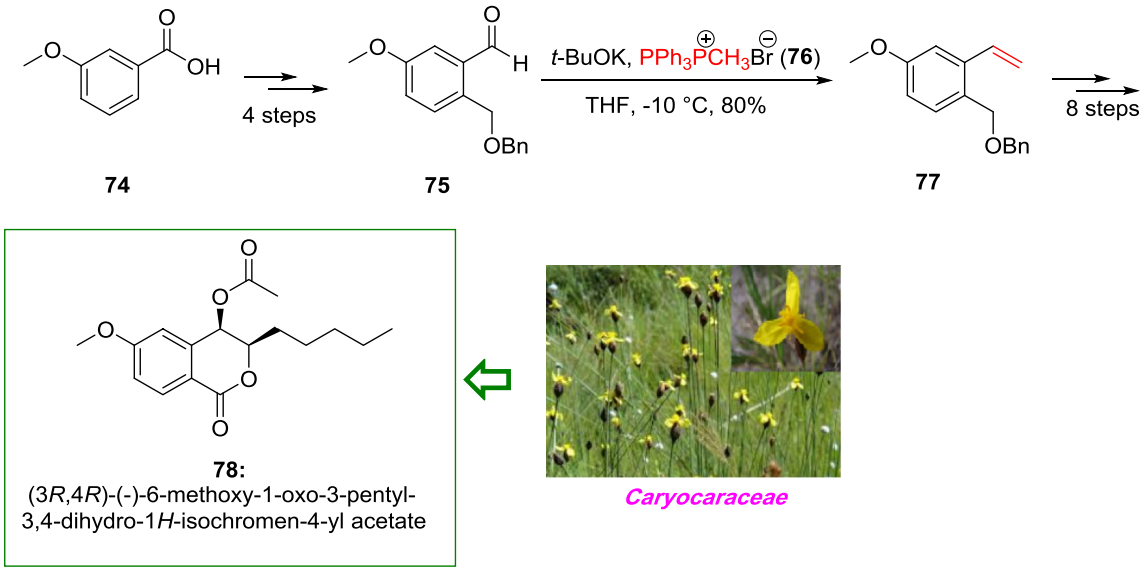
cis **74** *trans* **74a**, 60:40

Dihydroisocoumarin derivatives are phenolic compounds correlating to isocoumarin. Dihydroisocoumarin glucosides were found in *Caryocar glabrum* that is a species of tree in the family *Caryocaraceae* [84]. Asymmetric total synthesis of a dihydroisocoumarin, (3*R*,4*R*)-(−)-6-methoxy-1-oxo-3-pentyl-3,4-dihydro-1*H*-isochromen-4-yl acetate (**78**) was started with market-purchasable *meta*-anisic acid. Venkateswarlu and co-workers described the application of protective opening of lactones and successful construction of δ-lactone. In this line, Wittig reaction, Grubbs cross metathesis, and Sharpless dihydroxylation reactions were considered as main steps [84]. This group demonstrated total synthesis of the biologically active dihydroisocoumarin **78** with 92.4% *ee* and 16% overall yield. Noticeably, very excellent selectivity has been identified in the formation of the six-membered lactone derivate [84]. Total synthesis of (3*R*,4*R*)-(−)-6-methoxy-1-oxo-3-pentyl-3,4-dihydro-1*H*-isochromen-4-yl acetate (**78**) was started from *meta*-methoxybenzoic acid **74** that has been transformed into the corresponding aldehyde **75**. The latter has been transformed into the terminal alkene **77** via Wittig reaction with methyltriphenylphosphonium bromide salt (**76**) using potassium *tert*-butoxide. Lastly, compound **77** after several steps gave (3*R*,4*R*)-(−)-6-methoxy-1-oxo-3-pentyl-3,4-dihydro-1*H*-isochromen-4-yl acetate (**78**) (Scheme 13) [84].

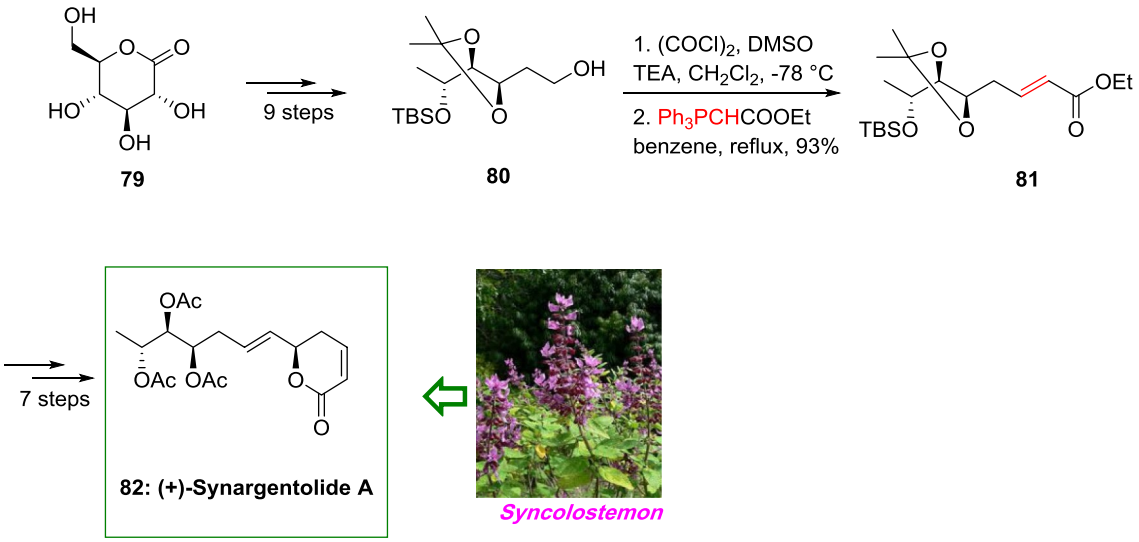
Natural products having polyacetate α,β-unsaturated δ-lactone ring display a wide range of biological properties such as cytotoxicity against human tumor cells, as well as antimicrobial and antifungal properties [85]. Among these, (+)-synargentolide A (**82**) [86], spicigerolide [87], hyptolide [88], synrotolide [89], and anamarine [90] were isolated from *Syncolostemon* and *Hyptis* species [91]. Yadav and co-workers demonstrated a significant and direct method for the total synthesis of (+)-synargentolide A (**82**) in an efficiently asymmetric approach. Based on hydroboration, C_2-Wittig olefination reaction, Brown's enantioselective allylation, and ring-closing metathesis were considered as main steps [92]. Total synthesis of (+)-synargentolide A (**82**) commenced from cheap and easily accessible D-1,5-gluconolactone (**79**) that has been transformed into the corresponding primary alcohol **80**. Next, oxidation reaction of **80** under Swern oxidation reaction afforded the desired aldehyde that has been exposed to C_2-Wittig olefination to yield α,β-unsaturated ester **81** in 93% yield. Upon several steps, α,β-unsaturated ester **81** gave (+)-synargentolide A (**82**) in 61% yield (Scheme 14) [92].

Marine fungi are a rich source of biologically potent secondary metabolites containing antibacterial, antitumor, antiviral antifungal activities [93, 94]. Marine bacilli are found for their ability to make different cyclic acylpeptides,

Scheme 13



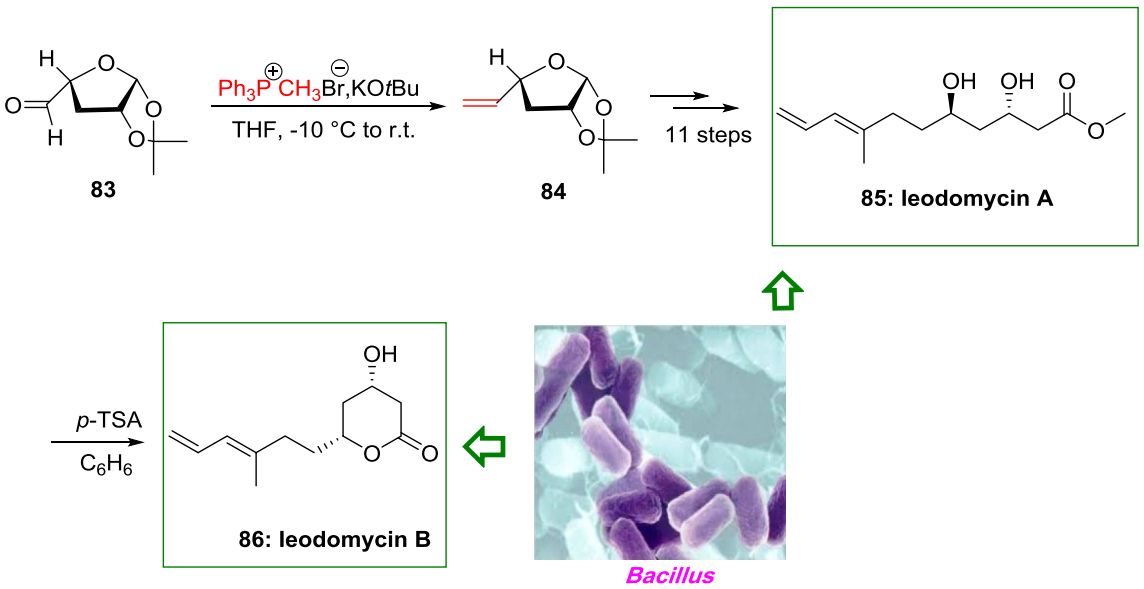
Scheme 14



glucanases, and antibiotics [95]. Two antimicrobial compounds ieodomycins A (**85**) and B (**86**), isolated from marine bacterial *Bacillus* species, exhibit antimicrobial property against *Bacillus subtilis* and *Escherichia coli* [96]. The initial asymmetric syntheses of ieodomycins A and B were achieved in 15 steps using the chiral pool method initiating from D-glucose. The main reactions involved in this synthetic approach are Wittig olefination, Barbier reaction, and dehydration which resulted in preferential construction of the corresponding *E* isomer. In this route, the total synthesis of ieodomycins A and B was commenced from aldehyde **83**. Wittig olefination reaction of aldehyde **83** with methyltriphenylphosphonium bromide afforded alkene **84** [97] in 81% yield. Next, alkene **84** gave ieodomycin A (**85**) in 42% yield after several steps. In the following, compound **85** was lactonized in the presence of *p*-toluenesulfonic acid (*p*-TSA) [98] to provide the corresponding ieodomycins B (**86**) in 87% yield (Scheme 15) [99].

Marine microorganisms having various chemical structures contain a wealth of novel secondary metabolites. Marine *Bacillus* species that are widespread and distinct in similar marine ecosystems exhibit antimicrobial [100] and anticancer properties [101]. Also, some of the naturally occurring compounds from marine microorganisms show antimicrobial properties such as anti-inflammatory, antifungal, and antiviral properties [102]. Shin [96] and co-workers extracted four bioactive secondary metabolites, ieodomycin A and B from the marine bacterium strain Bacillus species

Scheme 15

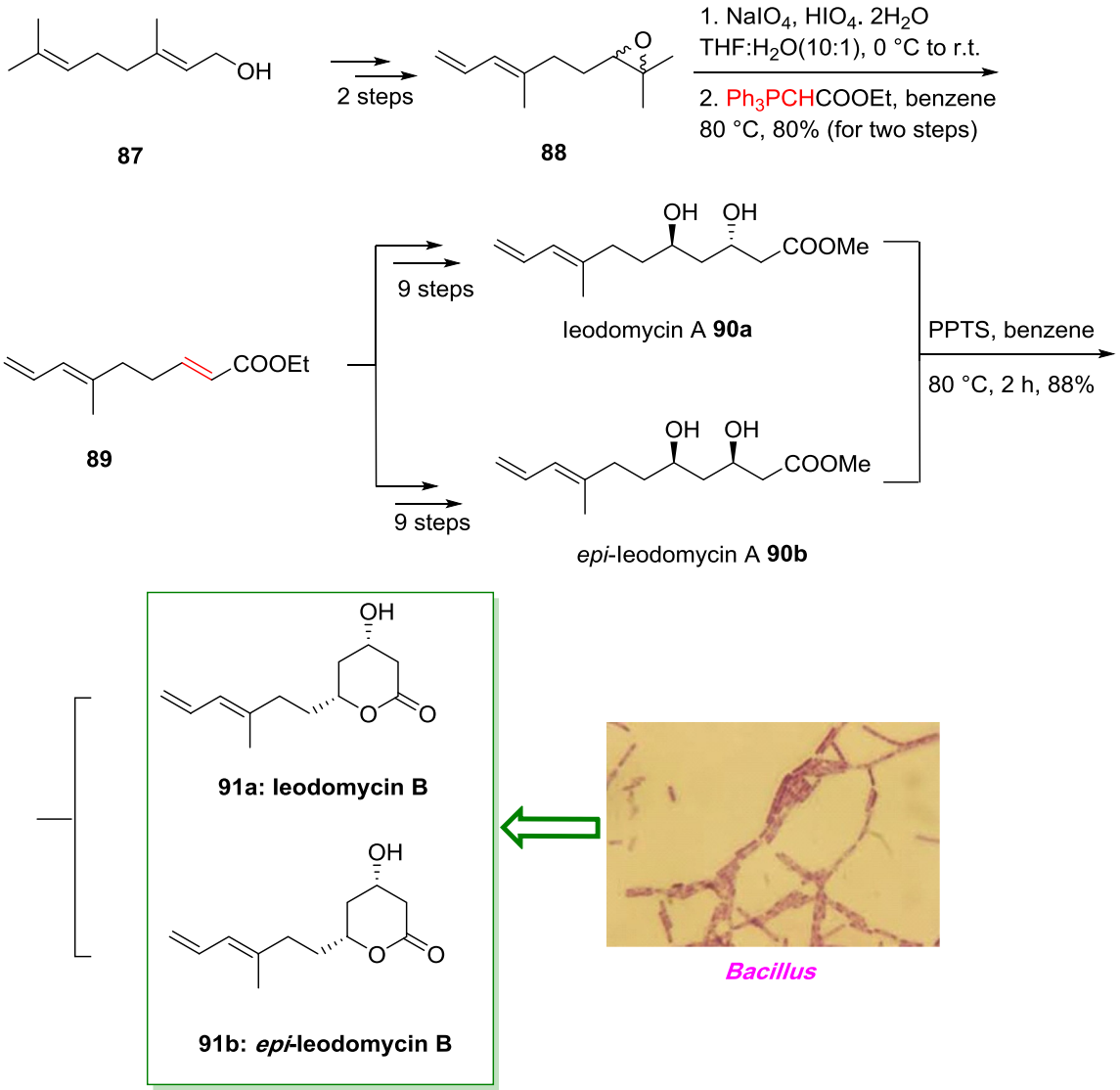


that have exhibited active antimicrobial property against *B. subtilis* and *E. coli*. Koul and co-workers [99] successfully achieved the total synthesis of ieodomycin A and B starting from D-glucose in 15 steps. Krishnaiah and co-workers reported total synthesis of ieodomycins A and B and their C-3 epimer via a facile and concise pathway, starting from market purchasable geraniol. Remarkably, a Wittig reaction, Sharpless enantioselective epoxidation, and intramolecular lactonization of ieodomycin A to ieodomycin B were considered as key steps. Based on this method, the formation of ieodomycins A (**91**) was begun from geranial. After two steps, geranial produced compound **88** in 75% yields. In the next step, the epoxy group of compound **88** has been opened using $NaIO_4/HIO_4$ [103, 104] to provide the corresponding aldehyde, which was subjected to a Wittig reaction with (ethoxycarbonyl)methylenetriphenyl phosphorane in benzene to afford conjugated ester **89** in 80% yield. Upon several steps, compound **89** gave compounds **90a** and **90b**. Compound **90b** was refluxed in benzene in the presence of pyridinium *p*-toluenesulfonate to afford the C-3 epimer of ieodomycin B (**91b**) in 87% yield, after one step [105]. Compound **90a** was refluxed in benzene in the presence of pyridinium *p*-toluenesulfonate to afford ieodomycin B (**91a**) in 88% yield, after one step (Scheme 16) [105].

Crispatanolide (**96**) has a unique structure comprising of three-, five-, and six-membered rings and a lactone. Furthermore, it has five chiral centers in a compact molecule. Noticeably, this compound belongs to a cycloeudesmane kind of sesquiterpenoid. Remarkably, compounds having eudesmane-type scaffold are very complicated, but their diastereoisomers can be extracted [106, 107]. Crispatanolide (**96**) was extracted by Asakawa and co-workers in 1980 from *Makinoa crispate* (liverwort) [108]. Crispatanolide was provided in its chiral form starting from 3-functionalized-2-bromocyclohex-2-en-1-one. (+)-Crispatanolide (**96**) was provided using CBS reduction, Eschenmoser rearrangement, alkylation reaction, lactonization, RCM reaction, and cyclopropanation [109]. Total synthesis of (+)-crispatanolide (**96**) was commenced from enone **92** [110], which produced the corresponding aldehyde (+)-**93** after several steps. Next, the Wittig reaction gave allyl bromide (+)-**94** in 76% yield upon two steps. After several steps, the desired target product (+)-crispatanolide (**96**) and its diastereoisomer (+)-**95** were synthesized in 39% and 9% yield (Scheme 17) [109].

McLaughlin and co-workers in 1991 isolated the γ-lactone natural product muricatacin **100** from the seeds of *Annona muricata* L. [73, 111]. Fernandes and co-workers in 2016 developed a short and significant seven-step synthesis of (4*R*,5*R*)-(−)-muricatacin (**100**) and (4*R*,5*R*)-L-(−)-factor (**101**) from the market-purchasable D-glucono-δ-lactone. Noticeably, the one-pot transformations of the latter to γ-vinyl-γ-lactone, cross metathesis and Wittig olefination reaction were the main steps in this synthesis. The formation of **100** and **101** was accomplished in 18.4% and 19.1% overall yields, respectively, from compound **97**. Remarkably, this method can be expanded for the formation of different analogs by varying the alkyl chain length of the Wittig ylide utilized. Total synthesis of **100** and **101** was commenced from D-glucono-δ-lactone **97** that produced ester **98** as the *E* isomer in 88% yield [112, 113]. Then compound **98** produced compound **99a**. In this route, IBX oxidation of the primary alcohol to the aldehyde and olefination with C10-Wittig ylide ($Ph_3P^+C_{10}H_{21}Br^-$ *n*-BuLi) afforded **99a** as the major *Z* isomer in 72% overall yield from **98**. In the

Scheme 16



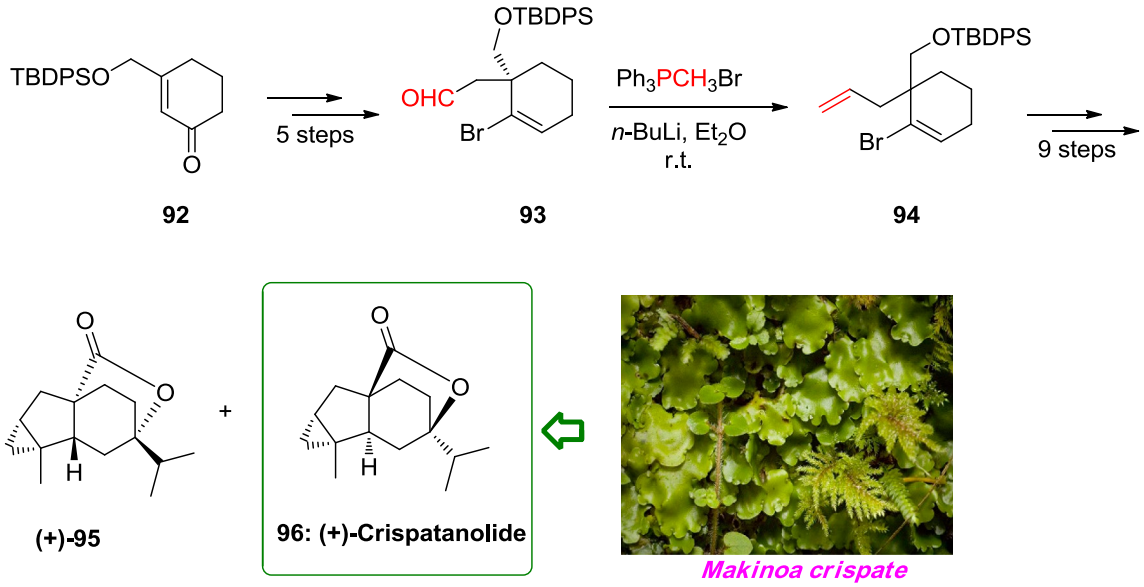
following, reduction of the double bonds in **99a** via catalytic hydrogenation in a one-pot manner leading to deprotection of the acetonide substituent which upon spontaneous lactonization afforded (4*R*,5*R*)-(−)-muricatacin (**100**) in 80% yield. Remarkably, the spectroscopic data of provided **100** were in agreement to those reported previously [114].

In a similar way, the Wittig olefination of the aldehyde from **98** using a C3-ylide ($Ph_3P^+C_3H_7Br^-$*n*-BuLi) afforded diene **99b** as the major *Z* isomer in 74% yield over two steps. Next was the catalytic hydrogenation of the double bonds in **99b** in acidic media, resulting in the deprotection of the acetonide substituent and spontaneous lactonization to give (4*R*,5*R*)-L-(−)-factor (**101**) in 81% yield in one-pot fashion. Noticeably, the spectroscopic data of the resultant compound **101** were in agreement with those demonstrated formerly (Scheme 18) [114, 115].

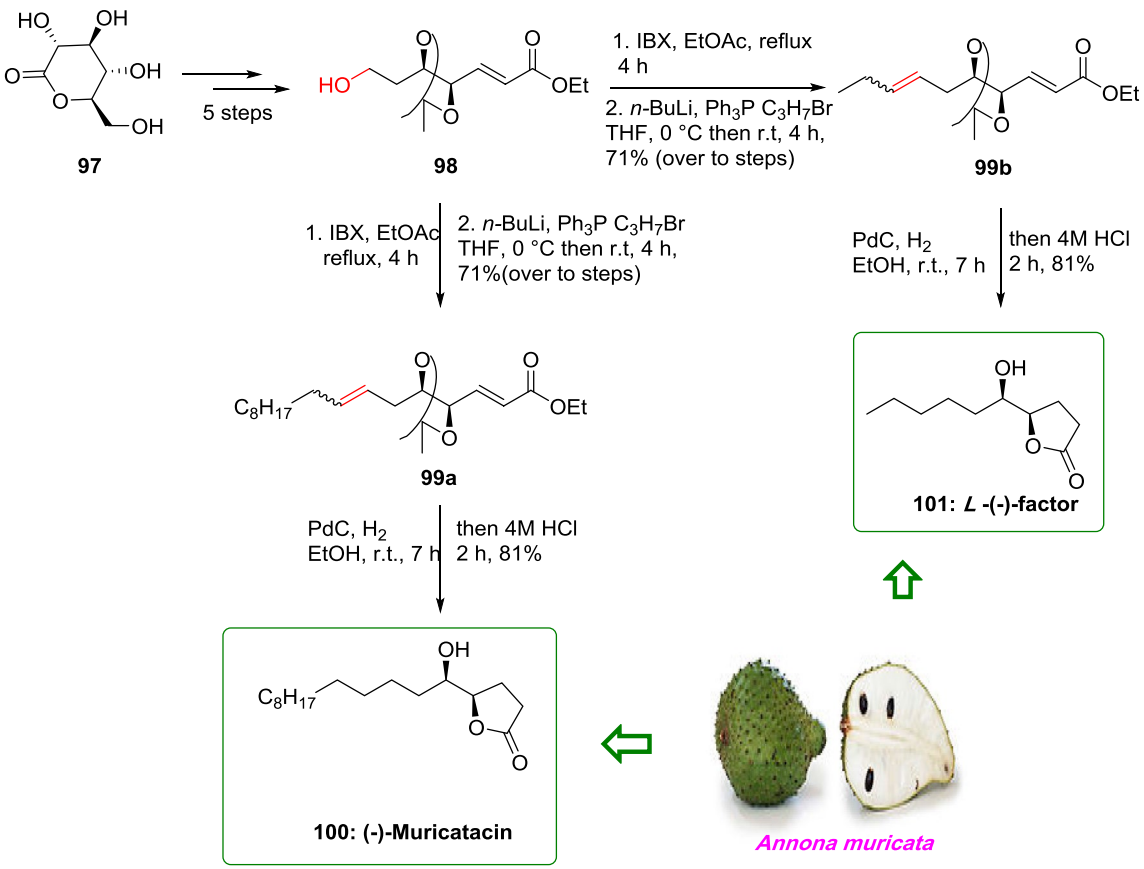
Lingzhilactone B, isolated from *Ganoderma lingzhi*, exhibits in vivo and in vitro effects to protect against renal injuries by increasing the properties of antioxidants and preventing inflammation [115]. Total synthesis of (±)-lingzhilactone B was achieved in 13 steps. Total synthesis of (±)-lingzhilactone B (**106**) was commenced with alkylation of ethyl 2-oxocyclopentanecarboxylate (**102**) with 2-bromomethyl-1,3-dioxolane (**103**). Next, the Wittig reaction of ketone **104** and potassium *tert*-butoxide in toluene afforded *exo*-alkene smoothly [116] that was converted into **105**. The latter has been transformed into (±)-lingzhilactone B (in 95% yield) upon several steps (Scheme 19) [117].

Phostriecin, a structurally unique phosphate ester provided by *Streptomyces roseiscleroticus* no. L827-7, was isolated from a soil sample of Gujarat state in India [118]. Natural products structurally related [119] to phostriecin were

Scheme 17

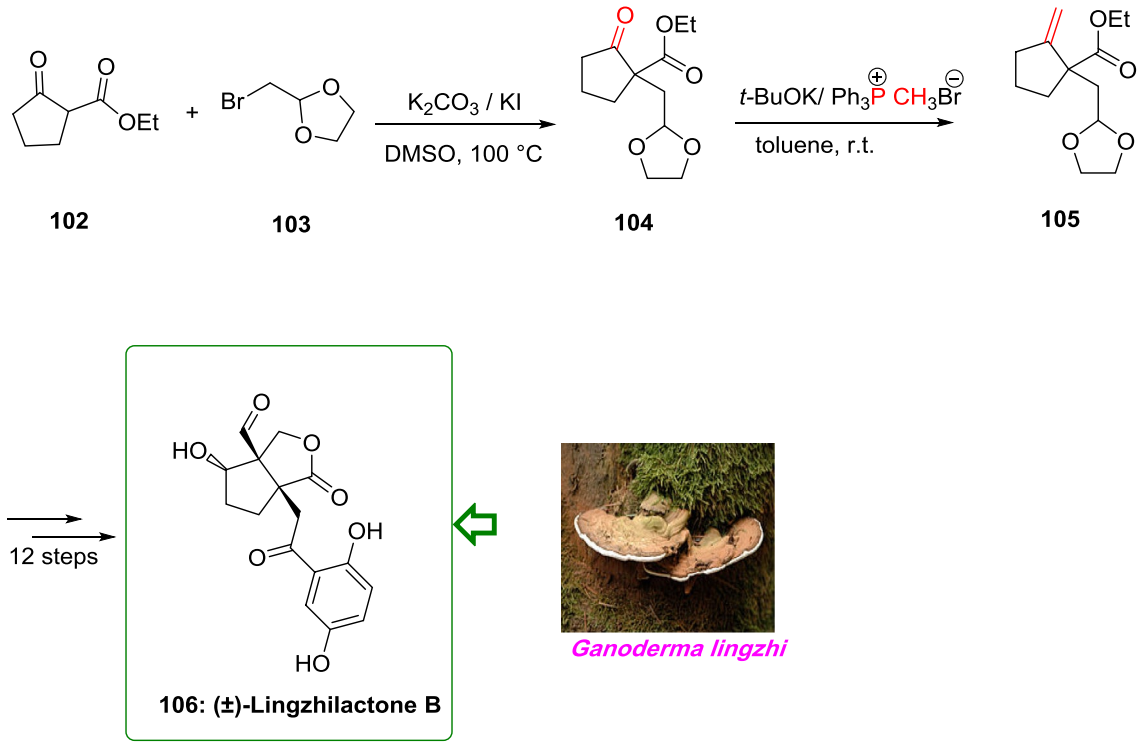


Scheme 18

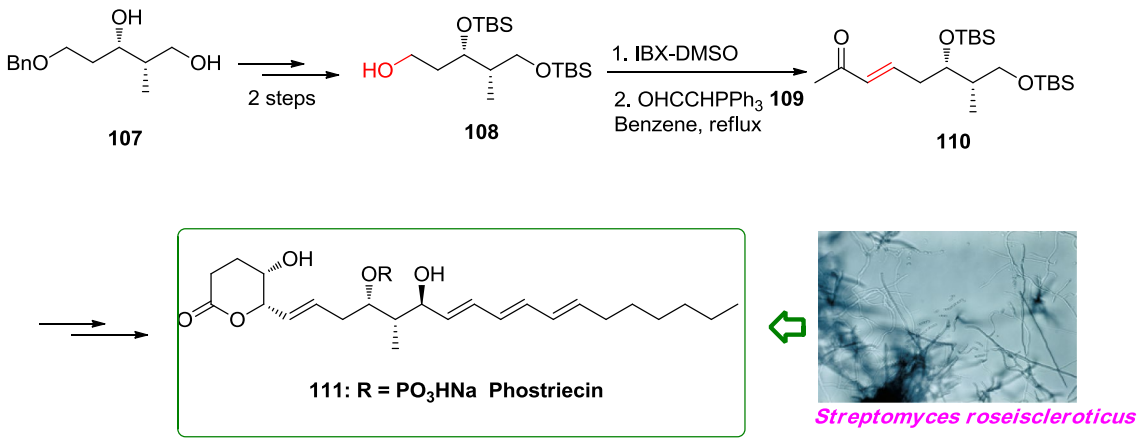


cytostatin, fostriecin, phoslactomycin, and leustroducsin. From structural viewpoint, phostriecin includes an electrophilic unsaturated lactone, the hydrophobic *Z,Z,E*-triene tail and also a central-substituted 1,3-diol. Boger and co-workers [120] demonstrated the initial total synthesis of phostriecin (aka sultriecin) [121]. Yadav and co-workers have achieved

Scheme 19



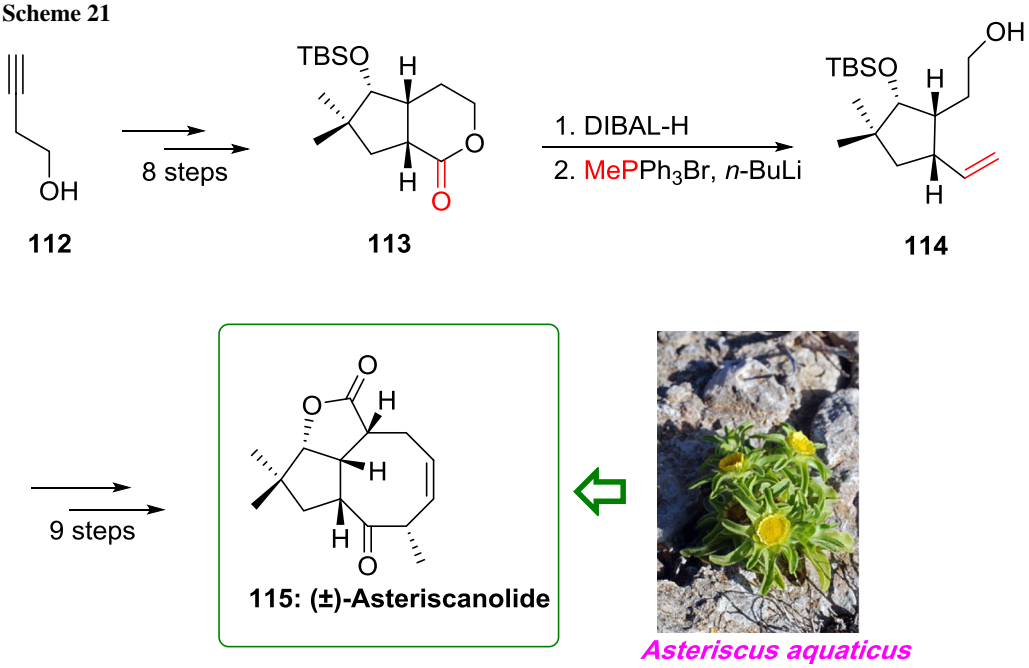
Scheme 20



to obtain the essential C1–C13 and C14–C22 segments of the antitumor natural product phostriecin. Wittig reaction, Browns' alkoxy allylboration, CBS reduction, and R ring-closing metathesis were considered as key steps. Total synthesis of phostriecin (**111**) was commenced from diol **107**, which afforded alcohol **108** upon one step. Next, oxidation reaction of the resultant primary alcohol **108** with 2-iodoxybenzoic acid (IBX)–DMSO afforded aldehyde that has been exposed to two-carbon Wittig reaction with (triphenylphosphoranylidene)acetaldehyde (**109**) under reflux in benzene to give the corresponding α,β-unsaturated aldehyde **110** in 76% yield. Finally, upon several steps, α,β-unsaturated aldehyde **110** provided phostriecin (**111**) (Scheme 20) [122].

The first member of the humulanolide class of natural products that was isolated and fully identified was asteriscunolide A (**115**). This natural product having an 11-membered ring was isolated from *Asteriscus aquaticus* in 1982 [123]. In the following study, the same plant species permitted for the extraction of asteriscunolides B, C, and D [124], and the stereochemical aspects of asteriscunolides A, B, C, and D have been demonstrated using X-ray diffraction analysis [125]. In 2000, Kraft and co-workers demonstrated the

Scheme 21



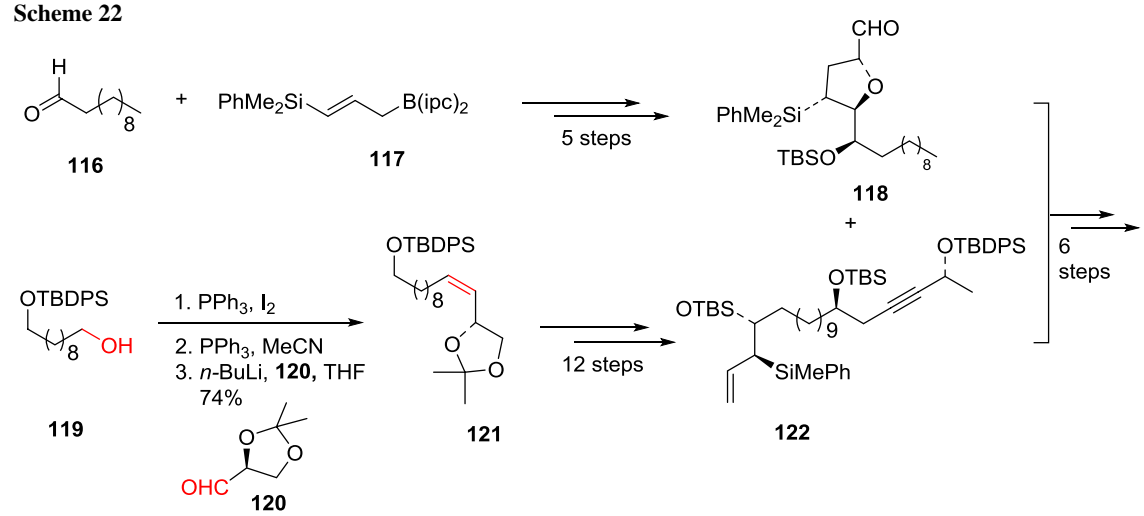
total synthesis of asteriscanolide [126]. An intermolecular Pauson–Khand cycloaddition and a ring-closing metathesis reaction were considered as main steps. Remarkably, the latter of these two steps led to the construction of an eight-membered ring having an "in–out" intra-bridgehead relationship. Based on this method, total synthesis of asteriscunolide A (**115**) was commenced from 3-butyn-1-ol (**112**), which afforded lactone **113** in 90% yields, then the reduction of lactone **113** provided. After several steps, alkene **114** gave (±) asteriscanolide (**115**) (Scheme 21) [127].

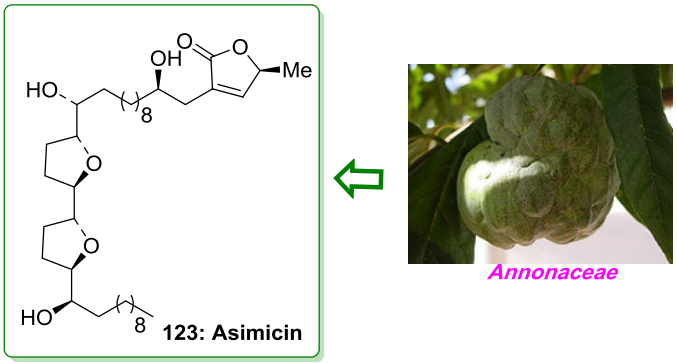
The annonaceous acetogenins, a structurally varied group of naturally occurring compounds, have been extracted from the Annonaceae group. Various members of this group show remarkable antitumor property in human tumor cell lines [72]. Initially, Roush and co-workers demonstrated a highly asymmetric method for the synthesis of asimicin (**123**) [128, 129]. The same research group in 2005 successfully accomplished an extremely enantioselective synthesis of asimicin (**123**). They predicted that the *bis*-tetrahydrofuran part of asimicin might be provided from two sequential chelate-controlled [3 + 2] annulation of allylsilanes and suitably functionalized aldehydes. The reaction between **122** and **118** under chelate-controlled conditions gave the anticipated stereochemically matched compound. Indeed, this achievement opened a gateway for a broader investigation of [3 + 2] annulation reactions of chiral aldehydes and chiral allylsilanes. The formation of the highly substituted allylsilane **122** that includes functionality required for providing the butenolide at a later step of the synthesis was started by transformation of **119** (provided by monosilylation of 1,10-decanediol) to the primary iodide in excellent yield. Reaction of the iodide with triphenylphosphine and Wittig reaction with (*S*)-glyceraldehyde acetonide (**120**) [130] gave compound **121**. Upon several steps, the latter was transformed to allylsilane **122**. On the other hand, the formation of aldehyde **118** was started by the reaction between undecanal (**116**) and (*E*)-γ-silylallylborane (**117**), provided by (−)-Ipc$_2$BOMe [131]. Next, the reaction between allylsilane **122** and aldehyde **118**, upon several steps, afforded asimicin (**123**) (Scheme 22) [132].

The coumarins, a great class of natural products, were extracted from plant species [133]. 4′-Demethylmacrophyllol (**127**) was isolated from the *Hydrangea macrophylla* subsp. *serrata* as a glucoside form, which was called macrophylloside B [133]. The smooth hydrolysis of macrophylloside **B** with sulfuric acid afforded D-glucose scaffold and an aglycone 4′-demethylmacrophyllol. Güneş and co-workers in 2007 demonstrated a short and significant synthesis of 4′-demethylmacrophyllol (**127**) through Wittig reaction in four steps. Total synthesis of 4′-demethylmacrophyllol (**127**), 8-hydroxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-isochroman-1-one, was accomplished starting from 4-benzyloxy-3,5-dimethoxybenzaldehyde (**125**) and a phosphonium salt **124** in four steps with an overall yield of 44%. Based on this method, the first step of the formation was a carbonyl olefination reaction of 4-benzyloxy-3,5-dimethoxybenzaldehyde (**125**) and the phosphonium salt **124** [134] to afford a mixture of *E/Z* stilbene ester **126** in a yield of 86%. Upon three steps, 4′-demethylmacrophyllol (**127**) has been produced in 44% overall yield (Scheme 23) [135].

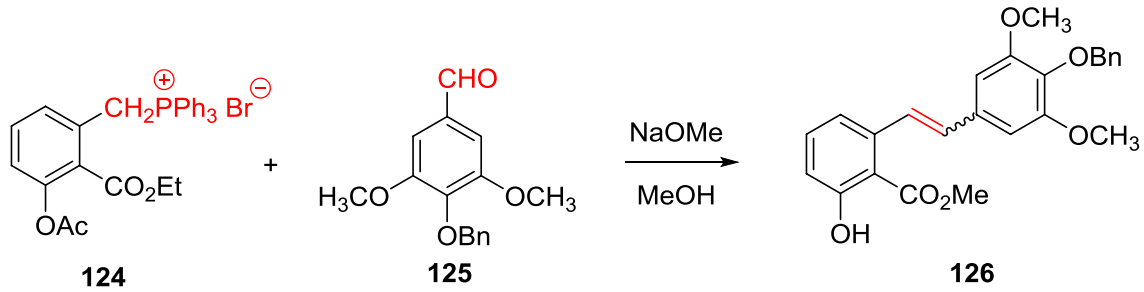
Myxobacteria, a rich repertoire of innumerable secondary metabolites, contain efficient structures and widespread

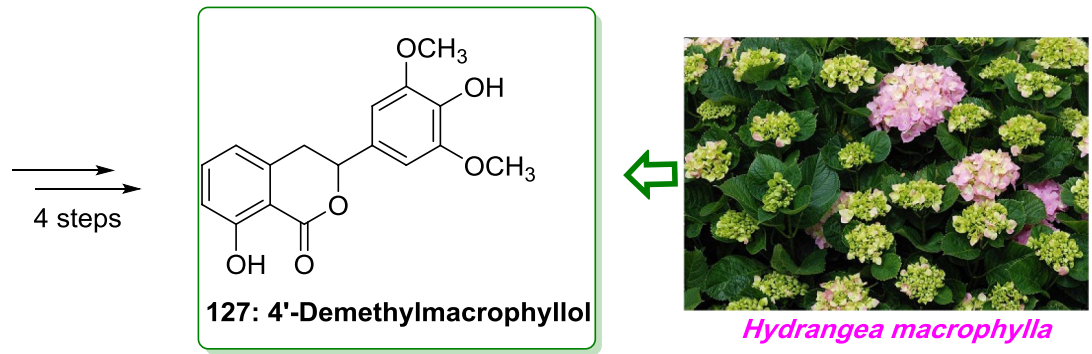
Scheme 22



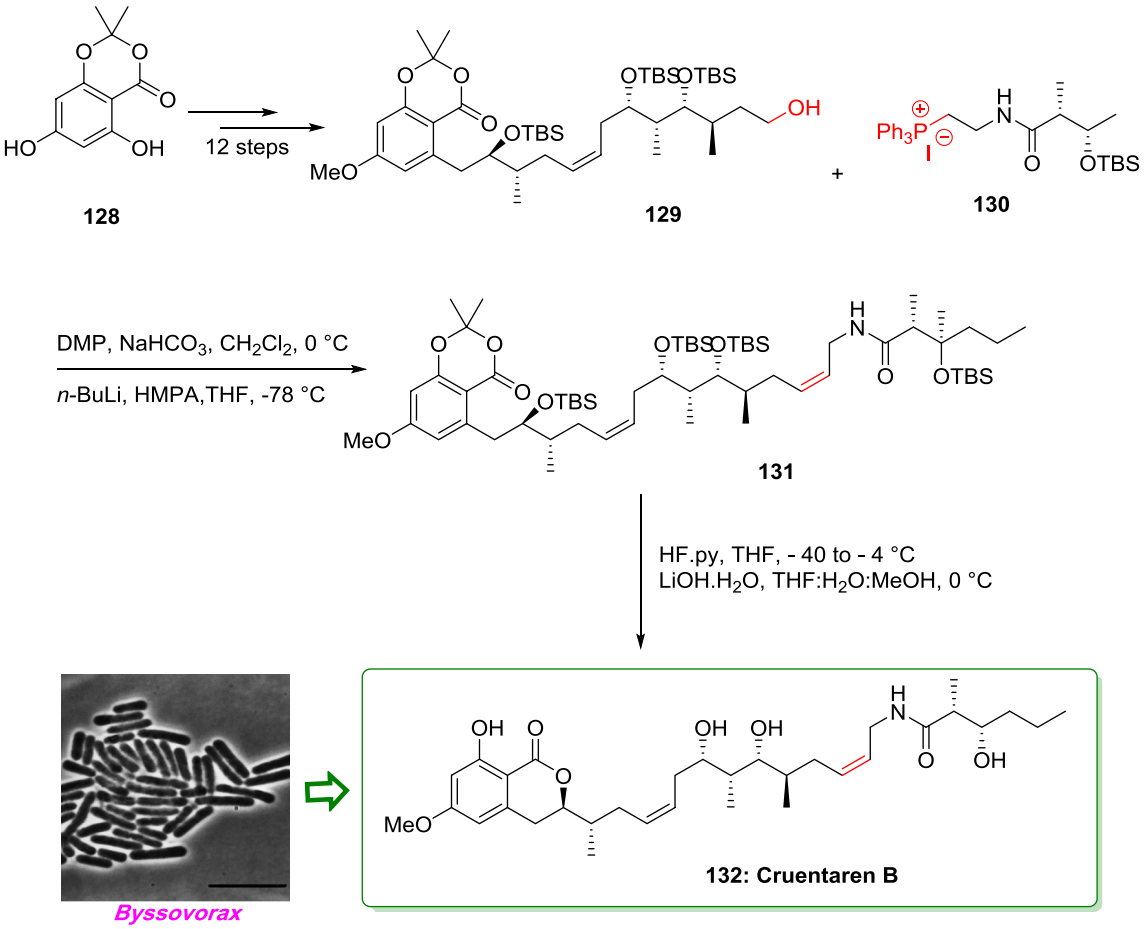


Scheme 23





Scheme 24

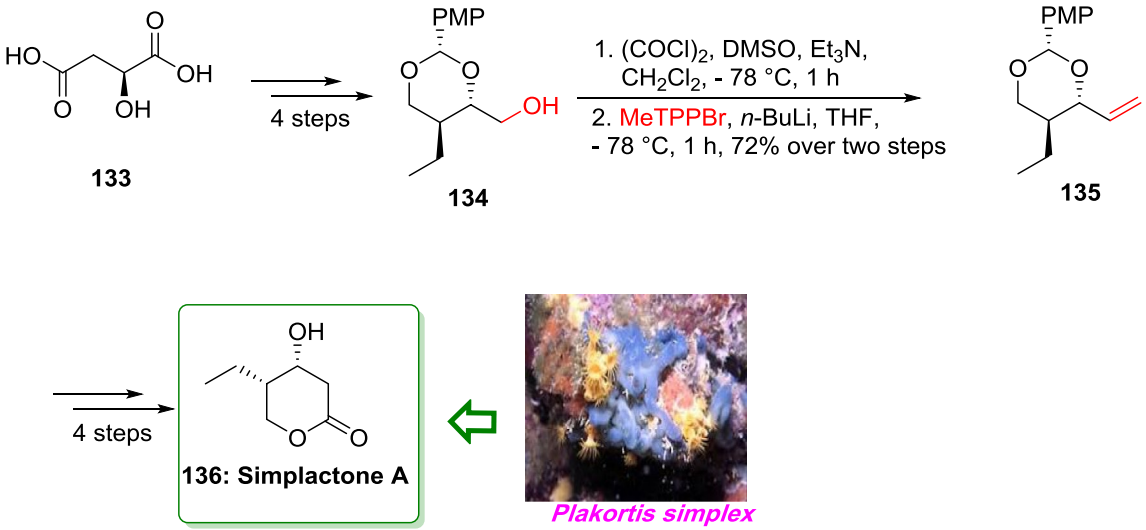


activities [135, 136]. Two examples of these molecules are benzolactones, cruentaren A and its ring-contracted congener cruentaren B (**132**) that were isolated from myxobacterium *Byssovorax cruenta* [137, 138]. Although cruentaren A powerfully prevented the growth of filamentous fungi and yeasts and also exhibited excellent cytotoxicity, cruentaren B demonstrated merely marginal cytotoxicity and no antifungal property [137]. Due to their unique structures and broad biological properties [139], cruentarens have fascinated the interest of synthetic chemists. Chakraborty and co-workers in 2008 demonstrated an efficient total synthesis of the cytotoxic natural product cruentaren B in 26 steps (longest linear sequence) with an overall yield of 7.1% [140]. Mitsunobu reaction, Stille coupling reaction, Brown's enantioselective crotylboration, Evans *syn*-aldol reaction, Mukaiyama–aldol reaction, a "non-Evans" *syn*-aldol reaction, and Wittig olefination reaction were known as the main steps for the construction of the natural product cruentaren [140]. Total synthesis of cruentaren B (**132**) was started from compound **128** that afforded the *Z*-olefin **129** in 88% overall yield upon several steps. Then reaction of the ylide, produced from **130**, with aldehyde in THF–HMPA provided the required *Z*-olefin in 64% yield, on the basis of recovered aldehyde. Next, the compound **131** was subjected to global deprotection of the TBS groups to give the desilylated product, in 92% yield that upon treatment with lithium hydroxide monohydrate in tetrahydrofuran gave the target product, cruentaren B (**132**), in 89% yield (Scheme 24) [140].

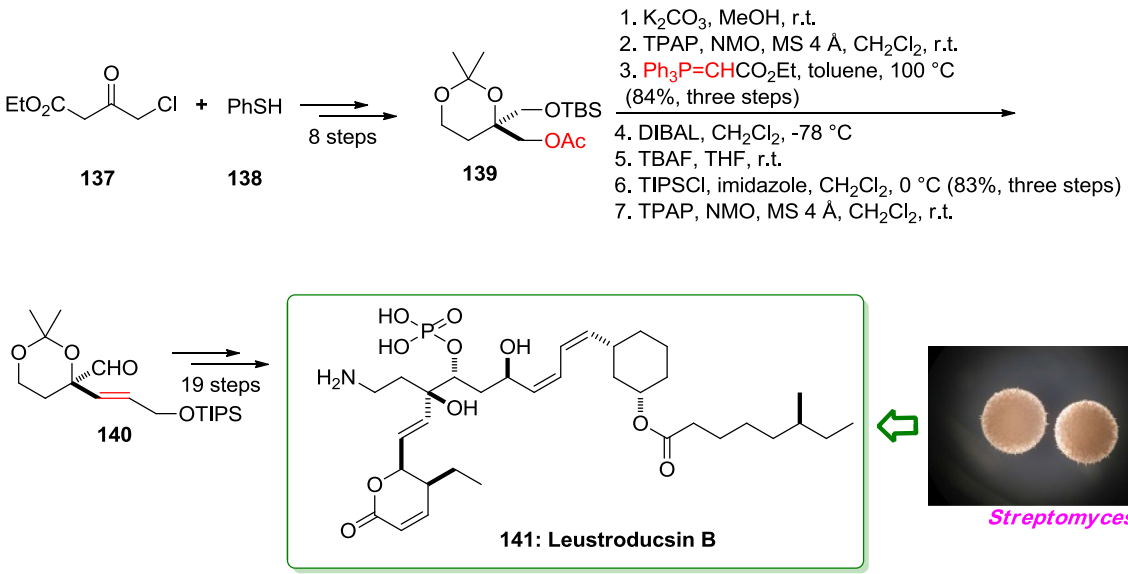
The δ-lactone simplactone A was isolated from the Caribbean sponge [141] *Plakortis simplex*. The facile and highly asymmetric method to the total synthesis of simplactone A was demonstrated by Kamal and co-workers in 2009 [142]. The main aspects of this synthetic method are enantioselective C-ethylation reaction, selective triol protection, and Wittig olefination reaction for the construction of the six-membered ring.

This group demonstrated an efficient synthetic way to simplactone A from market-purchasable (*S*)-malic acid (**133**) that afforded alcohol **134** upon several steps. Next, alcohol **134** (a six-membered acetal [143, 144] as *p*-methoxybenzylidene acetal **134**) was oxidized through Swern's oxidative reaction to make the relevant aldehyde that without purification on Wittig olefination reaction with MeTPPI and *n*-butyllithium in tetrahydrofuran afforded the olefin **135** in

Scheme 25



Scheme 26

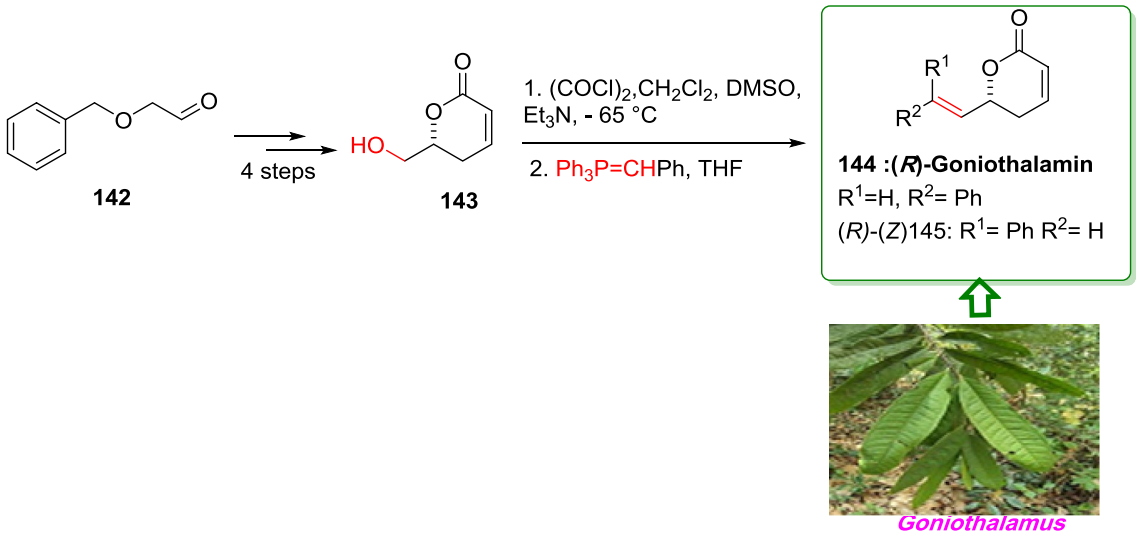


72% yield. After several steps, olefin **135** provided simplactone A (**136**) (Scheme 25) [142].

Containing pyrone as a moiety

Leustroducsin B (LSN-B, **141**), an effective colony-stimulating parameter inducer, was isolated by Sankyo and coworkers from the culture broth of *Streptomyces platensis* SANK 601 [145–148]. LSN-B containing a wide range of biological properties [149, 150] was established as a significant drug candidate. Leustroducsin B involves cytokine productions using NF-κB activation at the posttranscription level and at the transcription level [151]. Leustroducsin B (**141**) has been provided in 51% total yields in 16 steps using TBS ether as starting materials via Wittig reaction as the key step. Total synthesis of leustroducsin B has been achieved from the reaction of ethyl 4-chloroacetoacetate (**137**) and thiophenol (**138**) that after several steps gave TBS ether **139**. Next, elimination of the acetyl substituent of **139**, oxidation reaction of the alcohol to the expected aldehyde, and Wittig reaction using $Ph_3P{=}CHCO_2Et$ completed the corresponding α,β-unsaturated ester **140**. Then reduction of the ethyl ester and deprotection of the TBS substituent generated a diol in which less hindered allyl alcohol has been selectively protected as the TIPS ether. Next, the remaining alcohol has been oxidized to aldehyde **140** [152–154]. Finally, after several steps, aldehyde **140** provided natural product leustroducsin B (**141**) (Scheme 26) [155].

Scheme 27



Phytochemical investigations of the genus *Goniothalamus* have led to the extraction and identification of various compounds exhibiting a wide range of biological properties [156]. The styryl lactones were demonstrated principally in the genus *Goniothalamus* and the first styryl lactone known in the Annonaceae family was (*R*)-goniothalamin (**144**). This natural product exhibited in vitro cytotoxic effect particularly via inducing apoptosis on various cancer cell lines [157, 158]. This effect was selective for cancer cell lines without remarkable cytotoxicity to non-malignant cells [158]. In in vivo models, (*R*)-goniothalamin was demonstrated to contain tumoristatic and tumoricidal activity on Sprague–Dawley rats with 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumors [159].

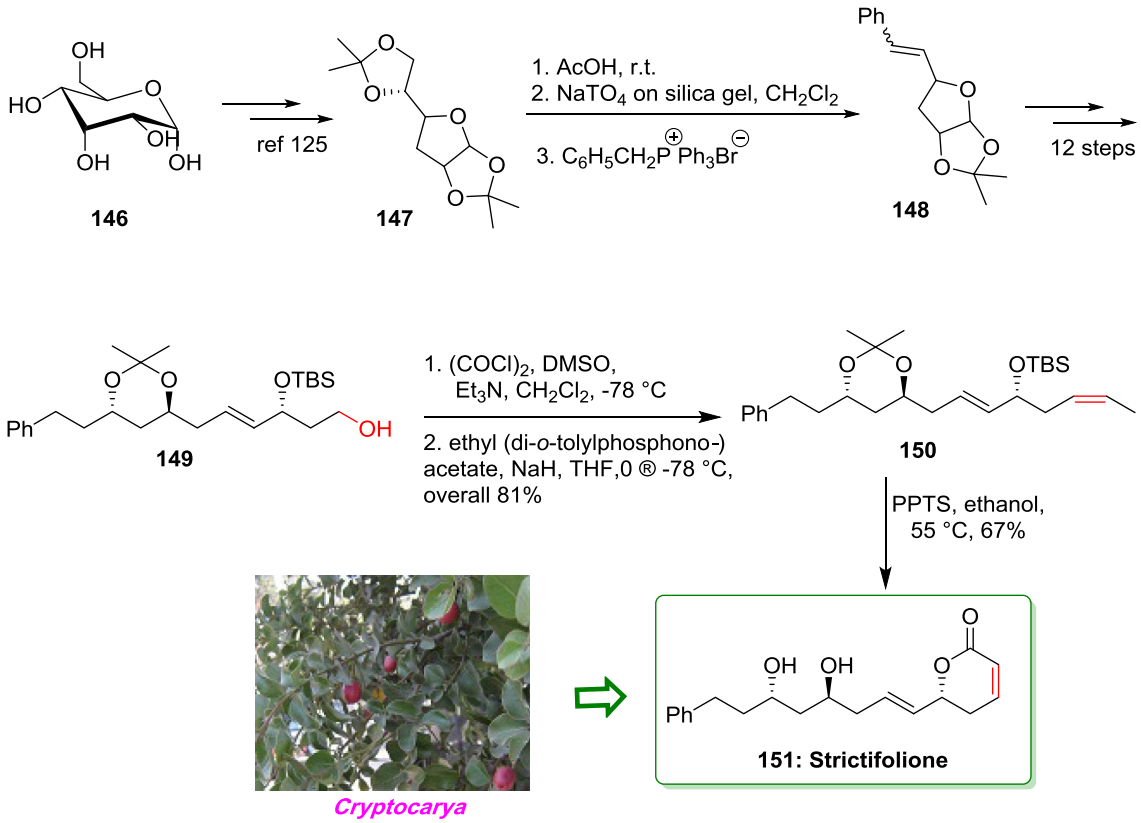
Total synthesis of (*R*)-goniothalamin (**144**) was achieved from benzyloxyacetaldehyde in 16 steps with 73% total yields. Catalytic enantioselective allylation reaction of α-benzyloxyacetaldehyde, ring-closing metathesis, and Wittig olefination reaction were considered as the key steps [160]. In this route, benzyloxyacetaldehyde (**142**) upon several steps gave *trans*-cinnamaldehyde (**143**). Next, Wittig olefination reaction of the relevant aldehyde with a solution of benzylidene triphenylphosphorane provided from the reaction of the triphenylphosphonium chloride and *n*-butyllithium in tetrahydrofuran gave a 1:3 molar ratio of (*R*)-goniothalamin (**144**) (13% yield) and its relevant *Z* isomer [(*Z*)-**145**, 40% yield] (Scheme 27) [160].

Strictifolione (**151**) that related to the class of 5,6-dihydro-δ-pyrones contains an alkyl side chain at the C6 position [161]. They showed a wide range of biological properties, attributed to their characteristic tendency to serve as suitable Michael acceptors. Strictifolione, isolated by Aimi and co-workers from the stem bark of *Cryptocarya strictifolia*, is known in the Indonesian tropical rainforests [162]. Total synthesis of strictifolione (**151**) was accomplished starting from D-glucose (**146**) in 67% total yields and 13 steps. D-Glucose, upon several steps afforded 3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**147**). Next, selective deprotection of the 5,6-*O*-isopropylidene group, sodium periodate-catalyzed oxidative removal, and Wittig olefination reaction with benzyltriphenylphosphorane provided an impure mixture of styrene derivative **148**. In the following, compound **148** afforded compound **149** after several steps. Then the free hydroxyl group of **149** has been efficiently exposed to Swern oxidation and Horner–Wadsworth–Emmons (HWE) reaction using ethyl (di-*o*-tolylphosphono)acetate and sodium hydride in tetrahydrofuran to provide only the *Z*-unsaturated ester **150**. Among a few reagents tested, pyridinium *p*-toluenesulfonate in EtOH at 55 °C efficiently deprotected both the TBS and the acetonide substituents. Furthermore, the lactonization step happened to furnish the total synthesis of strictifolione (**151**) (Scheme 28) [163].

3-Prenylated coumarin derivatives, a distinctive group of natural coumarins, were found with a prenylated side chain in the coumarin scaffold. Noticeably, they were broadly applied in the fields of medicine, biology, and polymer science [164, 165]. Xiao-Ping and co-workers tried to produce a wide range of phebaclavin A–H group that have been extracted from the aerial parts of *Phebalium clavatum* by Muyard and co-workers [166]. Mali and co-workers synthesized a number of 3-allylcoumarin derivatives using Wittig reaction followed by photochemical cyclisation [167].

Also, the total synthesis of phebaclavin A (**157**) and phebaclavin C (**159**) has been achieved and reported for the first time in 2005 by Xiao-Ping and co-workers. It should be mentioned that phebaclavin A (**157**) and C_2 were provided in 60% and 58% total yields over five steps using market purchasable aldehyde as starting materials.

Scheme 28

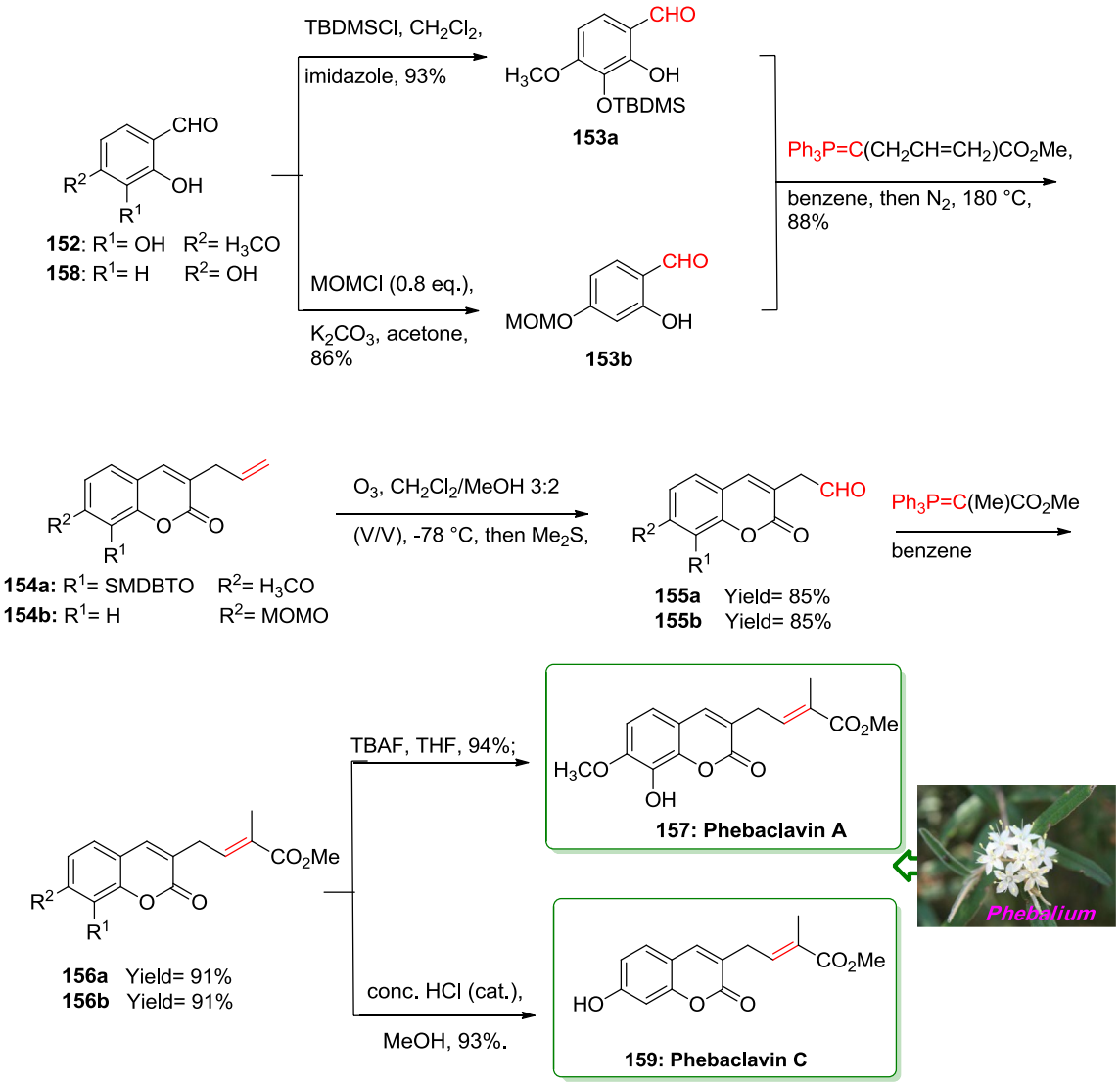


Noticeably, the total synthesis benefits Wittig reaction twice and solvent-free cyclizing as the main step. Remarkably, the Wittig reaction was the fastest and most significant method to provide 3-prenylated coumarins [168]. In this method, 2,3-dihydroxy-4-methoxybenzaldehyde (**152**) and 2,4-dihydroxybenzaldehyde (**158**) were selected as the starting material [168]. The reaction of **152** and *t*-butyldimethylsilyl chloride (TBDMSCl) using imidazole in anhydrous dichloromethane afforded the monosilylated product aldehyde **153a** in 93% yield. The reaction of this aldehyde with $Ph_3P{=}C(CH_2CH{=}CH_2){-}CO_2Me$ [70] with subsequent solvent-free cyclization [169] of the Wittig product gave the 3-allylcoumarin (**154a**) in over 88% yield. Next, ozonolysis in the presence of Me_2S of **154a** afforded aldehyde **155a** [170] in 85% yield. In the following, Wittig reaction of **155a** and $Ph_3P{=}C(Me)CO_2Me$ in dry benzene afforded the ester **156a** as a single product. Then compound **156a** has been reacted with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran to give the phebaclavin A (**157**) as the sole product with the yield of 94% (Scheme 29) [168].

On the other hand, for the formation of phebaclavin C, aldehyde **158** was protected selectively with methoxymethyl substituent (MOM) using chloromethyl methyl ether (MOMCl) to make **153b** [171] in the yield of 86%. Next, the reaction of aldehyde **153b** with $Ph_3P{=}C(CH_2CH{=}CH_2){-}CO_2Me$ followed by solvent-free cyclization of resultant ester afforded the 3-allylcoumarin (**154b**) in over 88% yield. In the following, ozonolysis and reduction with Me_2S of **154b** afforded aldehyde **155b** in 85% yield. Then Wittig reaction of **155b** with $Ph_3P{=}C(Me)CO_2Me$ in dry benzene afforded ester **156b** as a single product. Compound **153b** produced the *E*-configuration **156b** in total yield of 72%. Lastly, compound **156b** has been refluxed using conc. HCl (cat.) in methanol to provide the desired phebaclavin C (**159**) in moderate yield (93%) [168].

Naturally occurring α,β-unsaturated lactones exhibit diverse pharmacological activities, whereas some show antitumor properties, and a few comprise stimulating activities [161]. Outstanding among them include a polyoxygenated chain linked along with α,β-unsaturated lactone scaffold containing antifungal and antimicrobial property, or cytotoxicity against human tumor cells [87, 172]. (−)-Synrotolide [89], a naturally occurring compound containing α-pyrone moiety, was isolated from *Syncolostemon rotundifolius*, and shares structural analogs along with (−)-spicigerolide [87]. Enantioselective total synthesis of synrotolide as its diacetate using diastereoselective Grignard reaction-favored (*Z*)-Wittig olefination reaction, enantioselective allylation, and ring-closing metathesis as main steps was demonstrated by Krishna and co-workers in 2007 [173]. Total synthesis of synrotolide (**163**) was commenced from D-ribose (**160**). Upon several steps, D-ribose afforded compound **161** that

Scheme 29

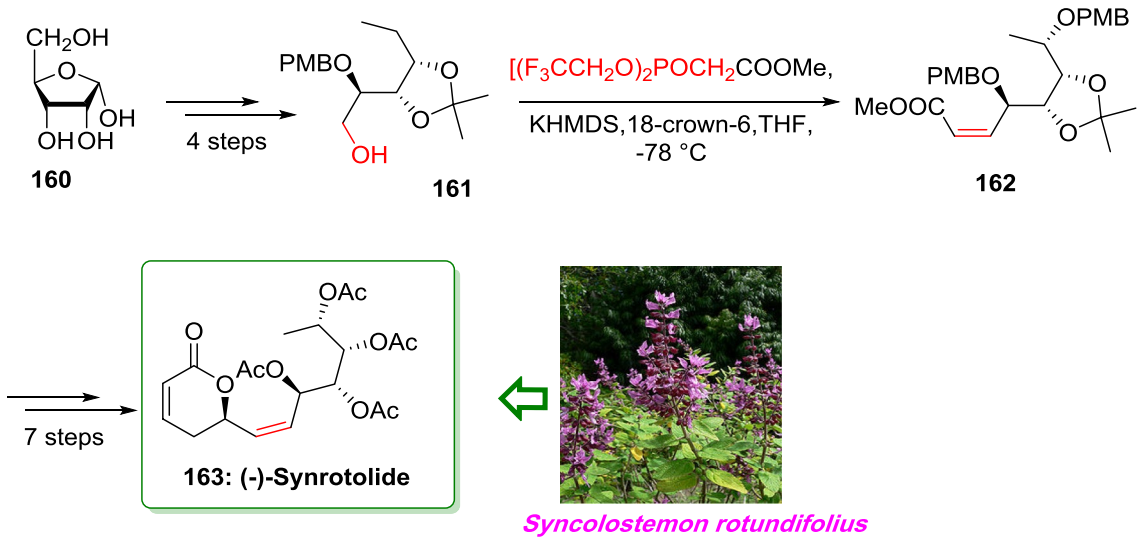


has been oxidized to an aldehyde via Swern reaction and exposed to a Wittig olefination reaction to give the corresponding α,β-unsaturated ester **162** in 88% yield mostly as the (*Z*)-isomer. After several steps, α,β-unsaturated ester **162** afforded synrotolide (**163**) (Scheme 30) [173].

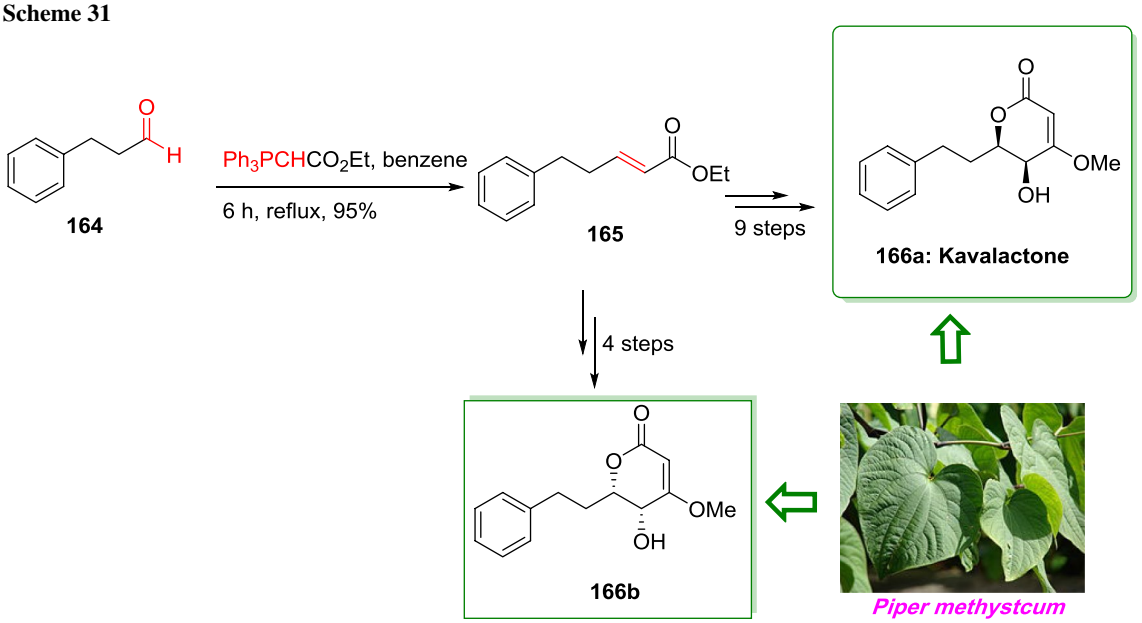
Kavalactones, isolated from the kava plant *Piper methysticum* (Piperaceae), are known frequently in the South Pacific islands [174]. The extract of this plant includes at least six pharmacologically potent compounds known as kavapyrones [175] that mediate the local anesthetic sedating, muscle relaxant, anticonvulsive, and sleep inspiring effect of the plant [176]. The potential application of this kava extract is known in the reaction of fear- and anxiety-correlated disorders [177]. In clinical trials, kava was known to be superior to placebo, significantly released anxiety and also tension [178]. In 2007, Kamal and co-workers demonstrated a short and significant linear total synthesis of both the stereoisomers of dihydrokawain-5-ol with excellent *ees*. The main reactions of the synthetic method are Sharpless enantioselective dihydroxylation and Wittig olefination reaction [179]. Therefore, total synthesis of target product **166a** was started from the market purchasable hydrocinnamaldehyde (**164**). Upon Wittig olefination reaction of the latter with the stabilized ylide (ethoxycarbonylmethylene)triphenylphosphorane under reflux in benzene the *E* isomer in the form only α,β-unsaturated ester **165**. Lastly, α,β-unsaturated ester **165** afforded kavalactone (**166a**) upon several steps. Similarly, the other stereoisomer dihydrokawain-5-ol (**166b**) was provided from hydrocinnamaldehyde (**164**) (Scheme 31) [179].

Fraxinol occurs naturally in *Seriphidium santolium* [180], *Fraxinus ornus* [181], *Corchorus olitorius* [182], *Pelargonium reniforme* [183], and *Toddalia asiatica* [184], a plant indigenous to southern Africa. Furthermore, *Pelargonium reniforme* includes 5,6,7-trimethoxycoumarin [185].

Scheme 30



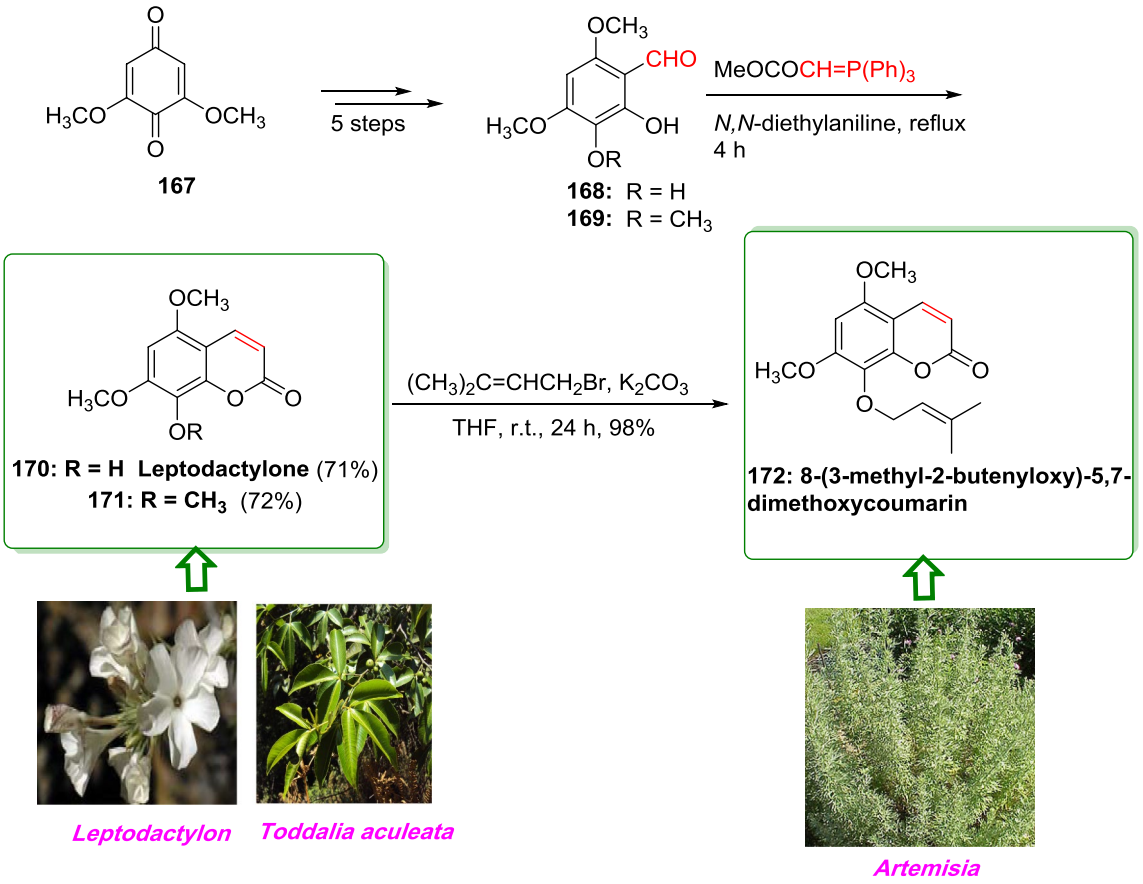
Scheme 31



Leptodactylone (**170**) was known in *Leptodactylon* sp. [186] and *Ruta sp. Tene* 29662 [186]. Besides, the latter *Ruta sp. Tene* 29662 includes 5,7,8-trimethoxycoumarin (**171**), isolated from *Toddalia aculeate* [187]. Artanin **172**, a coumarin hemiterpene ether, is a natural constituent of *Artemisia* sp. [188]. The formation of five naturally occurring polyoxygenated coumarins was demonstrated by Kimpe and co-workers in 2008. It concerns two 5,6,7-trioxygenated coumarins, containing 6-hydroxy-5,7-dimethoxycoumarin (fraxinol) and 5,6,7-trimethoxycoumarin, and three 5,7,8-trioxygenated coumarins, for example, 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone, **170**), 5,7,8-trimethoxycoumarin (**171**) [189].

Remarkably, the above-mentioned coumarins are known in nature as secondary plant metabolites. The main aspect of this synthetic method is the construction of the desired tetraoxygenated benzaldehydes that are transformed to the corresponding coumarins through a Wittig reaction. Total synthesis of five trioxygenated coumarins was started from market purchasable 2,6-dimethoxybenzoquinone (**167**). Upon several steps, 2-hydroxy-3,4,6-trimethoxybenzaldehyde (**169**), small quantities of a dihydroxylated side product were provided that showed to be 2,3-dihydroxy-4,6-dimethoxybenzaldehyde (**168**) [190]. Both 2-hydroxybenzaldehydes **168** and **169** were transformed into the desired coumarins through the Wittig

Scheme 32



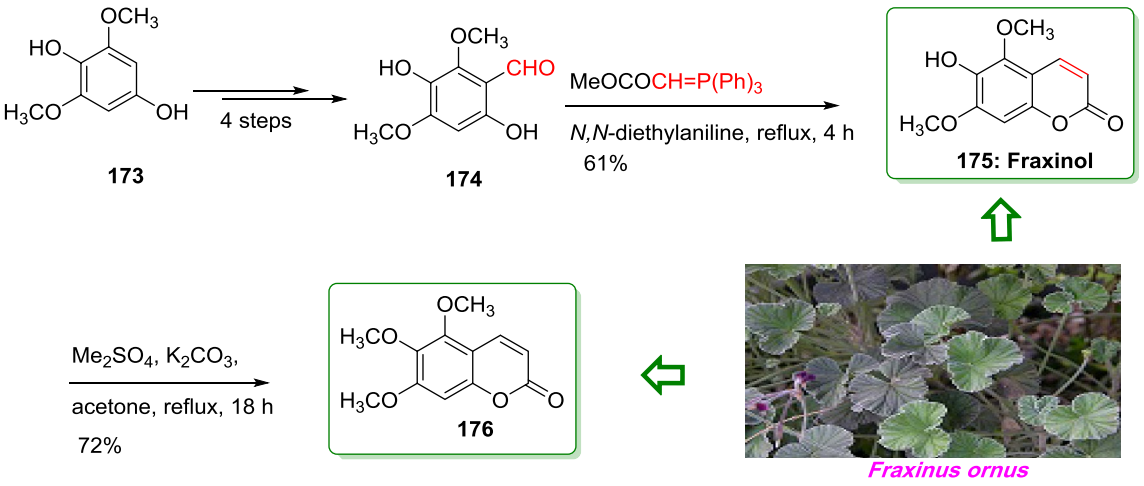
reaction. In this route, the natural trioxygenated coumarins 8-hydroxy-5,7-dimethoxycoumarin (leptodactylone, **170**) and 5,7,8-trimethoxycoumarin (**171**) have been provided in 71 and 72% yield, respectively. Prenylation of the 8-hydroxy group of leptodactylone (**170**) with excess prenyl bromide in the presence of K_2CO_3 in tetrahydrofuran at room temperature gave 8-(3-methyl-2-butenyloxy)-5,7-dimethoxycoumarin (artanin, **172**) in 98% yield (Scheme 32) [189].

On the other hand, total synthesis of **175** and **176** was started from 2,6-dimethoxybenzene-1,4-diol (**173**). After several steps, 3,6-dihydroxy-2,4-dimethoxybenzaldehyde (**174**) has been provided in 97% yield. Next, Wittig reaction of 3,6-dihydroxy-2,4-dimethoxybenzaldehyde (**174**) and methyl (triphenylphosphoranylidene)acetate in *N*,*N*-diethylaniline provided 6-hydroxy-5,7-dimethoxycoumarin (fraxinol, **175**) in 61% yield. Next, methylation reaction of 6-hydroxy-5,7-dimethoxycoumarin (**175**) afforded 5,6,7-trimethoxycoumarin (**176**) in 72% yield [189]. Up to 2008, this method was the first total synthesis of artanin (**172**). The formation of leptodactylone (**170**) and 5,7,8-trimethoxycoumarin (**171**) has been demonstrated in six steps from pyrogallol in overall yields of below 1% [186]. Moreover, coumarin **171** was provided in two steps from 2,4-dihydroxy-3,6-dimethoxybenzaldehyde in 4% yield. Noticeably, the syntheses of leptodactylone (**170**), fraxinol (**175**), and 5,6,7-trimethoxycoumarin (**176**) were demonstrated previously in poor yields (51–55%) using an unusual reaction that includes the transfer of the C3 part of cinnamic acid onto the related phenols. Moreover, 5,6,7-trimethoxycoumarin (**176**) was provided in 46% yield through a palladium catalyzed coupling reaction between 3,4,5-trimethoxyphenol and ethyl propynoate (Scheme 33) [189, 191].

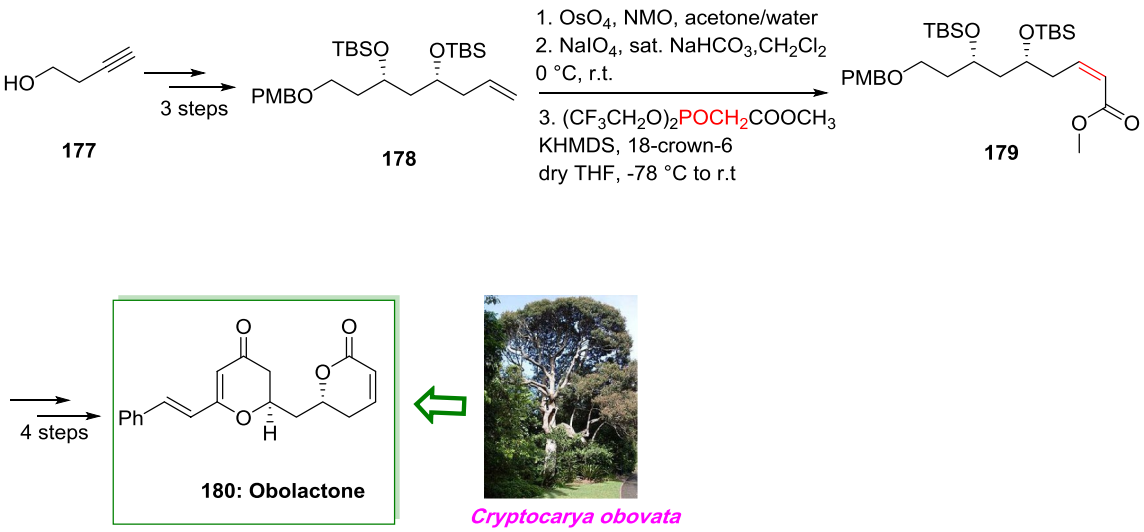
In 2004, natural product obolactone (**180**) has been extracted by Guéritte and co-workers from *Cryptocarya obovate* [192]. Obolactone is unique in the sense that two dihydropyrones, specifically a γ-pyrone and α-pyrone, are connected via a methylene bridge thus demonstrating a rare structural scaffold. Krishna and co-workers in 2010 reported the total synthesis of **180** via a Brønsted acid-catalyzed tandem cyclization reaction as the key step.

For the construction of obolactone (**180**), this synthetic method was commenced with the market-purchasable homopropargyl alcohol **177,** which after two steps transformed into compound **178**. Since the terminal olefin present in **178** has been considered as the protected carbonyl group, its dihydroxylation and oxidative elimination afforded the desired aldehyde using Wittig olefination reaction [193] to give the α,β-unsaturated ester **179** (70%, over three steps)

Scheme 33

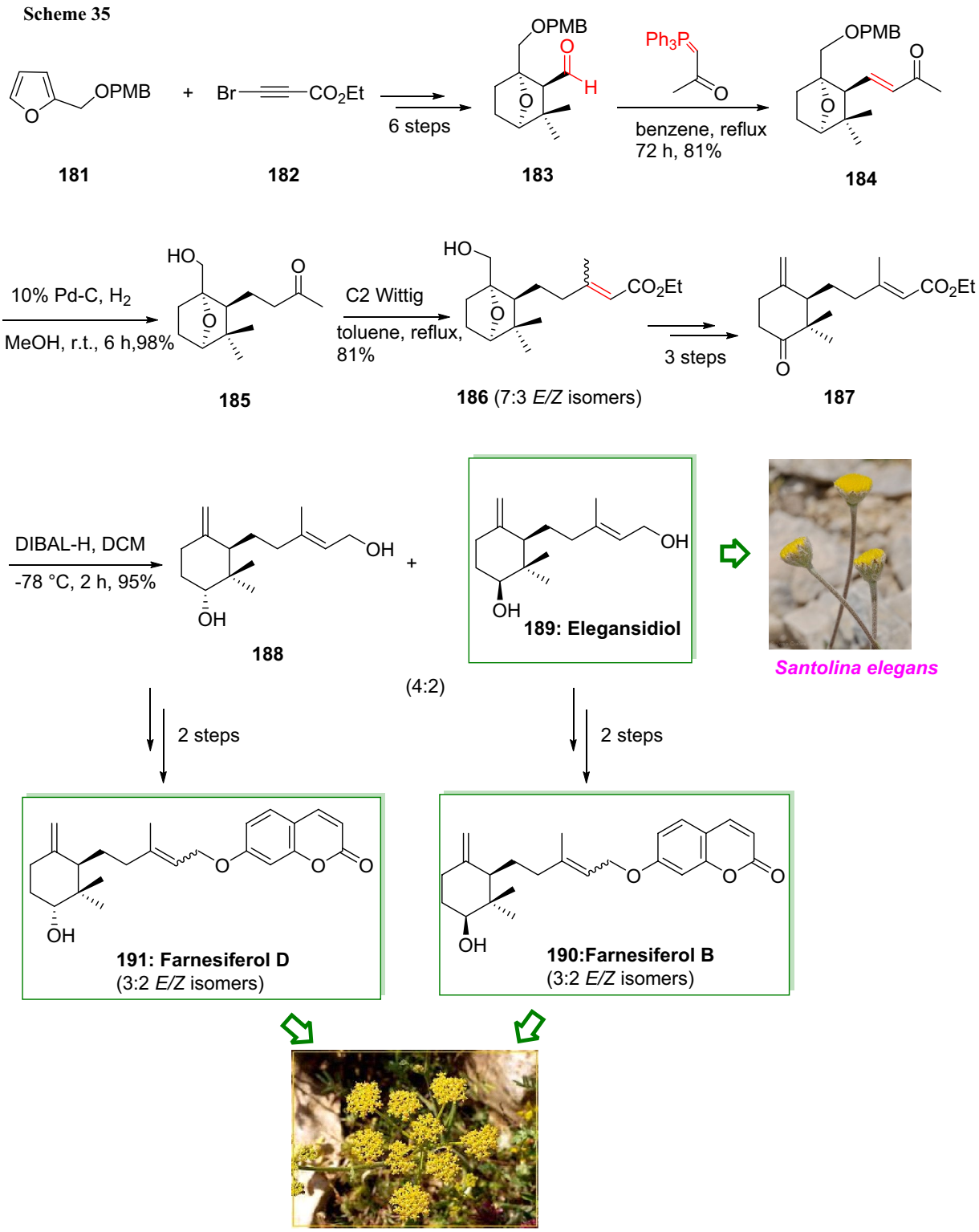


Scheme 34



mostly as the (*Z*)-isomer. Lastly, upon several steps, compound **179** afforded the desired naturally occurring compound **180** (75%) via a multiple reaction set, specifically silyl deprotection-tandem ring-closing reactions (Scheme 34) [194].

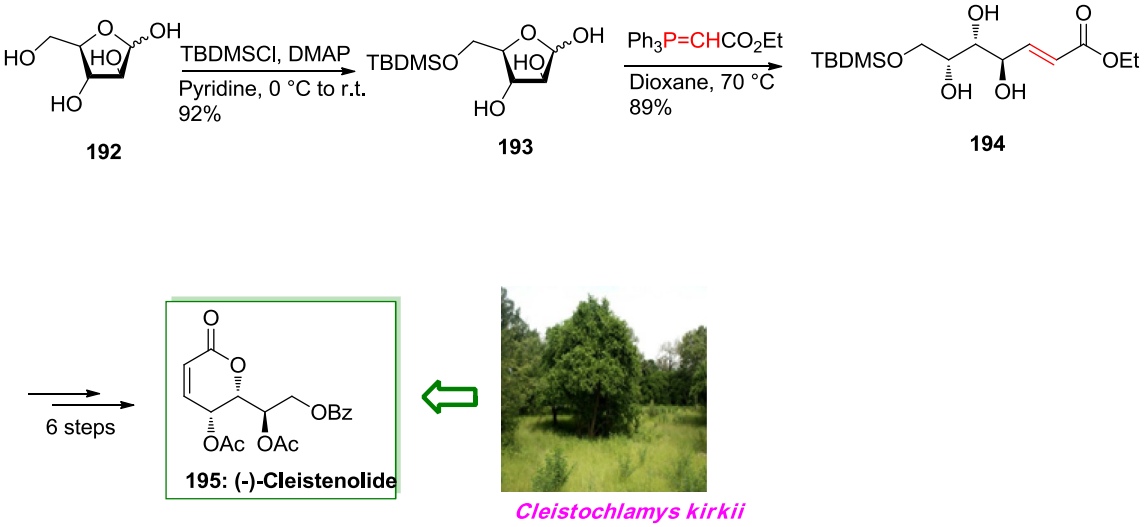
Monocarbocyclic terpenoids have fascinated significant attention due to their presence as component in natural products with remarkable biological properties [195]. Elegansidiol, an oxygenated monocyclic sesquiterpenoid containing a 3-substituted 2,2-dimethyl-4-methylenecyclohexanol part was isolated a decade back [196]. This part is being commonly isolated as a structural scaffold in various other natural products. Few samples include achilleol A, achilleol [197, 198], cordiaquinone C [199], farnesiferol B (**190**) and D (**191**) are also biologically potent derivatives [200]. In this route, farnesiferol B (**190**), D (**191**), and elegansidiol (**189**) were produced from a main intermediate **187** in three to four steps. Elegansidiol was transformed into farnesiferol B (**190**) in two steps. Therefore, this strategy commenced with the reaction of furfuryl ether **181** and ethyl bromopropiolate (**182**) and upon several steps afforded compound **183**. Next, compound **183** was exposed to a Wittig reaction with 1-(triphenylphosphoranylidene)-2-propanone to make the corresponding α,β-unsaturated ketone **184**. In the following, one-pot olefin reduction and PMB deprotection of **184** using palladium/C in MeOH gave alcohol **185** in good yield. The ketone has been exposed to 2-C Wittig reaction with stable ylide (carbethoxymethylene)triphenylphosphorane in toluene to make the α,β-unsaturated ester **186**. Upon three steps, compound **186** afforded the main intermediate **187** and has been reduced with diisobutylaluminium hydride to afford the elegansidiol (**189**) accompanied by its other



diastereomer **188** in 4:2 ratio. While elegansidiol (**189**) was used for the construction of farnesiferol B (**190**), the other diastereomer **188** was used for the total synthesis of natural product farnesiferol D (**191**) [201] (Scheme 35).

The family Annonaceae contains over 2000 species [72], several of them suffered species extinction before being well explored. A significant range of these compounds isolated show imperative biological properties [202]. In 2007, Nkunya and co-workers identified a component, cleistenolide

Scheme 36



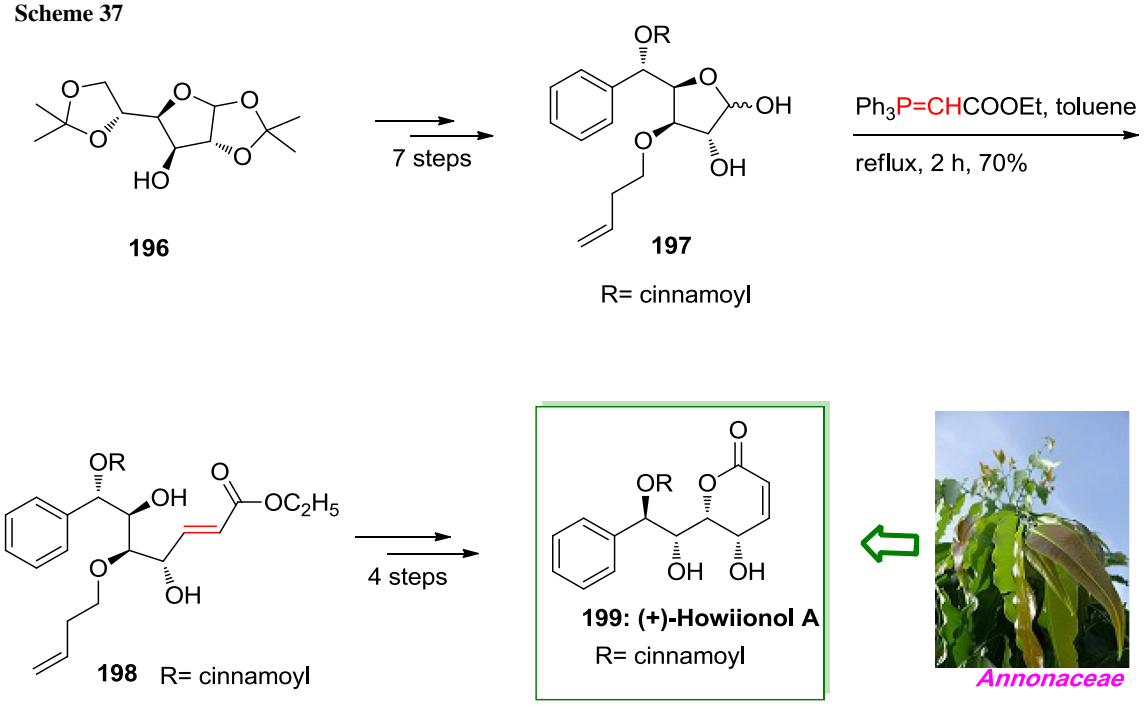
(**195**) from the Annonaceae, *Cleistochlamys kirkii* Oliver, a plant species known in Mozambique and Tanzania [203]. A facile enantioselective total synthesis of cleistenolide **195** was performed in eight steps and 49% overall yield starting from the natural chiral template D-arabinose (**192**). Wittig olefination reaction, selective 1,3-transacetal construction, and modified Yamaguchi esterification were considered as key steps. In this route, D-arabinose was transformed to 5-*O*-silyl aldehyde **193** in a yield of 92% upon one step. Next, Wittig olefination reaction of aldehyde **193** and ethyl (triphenylphosphoranylidene)acetate [204] in dioxane gave the α,β-unsaturated ester **194** in 89% yield. Lastly, the α,β-unsaturated ester **194** was transformed into (−)-cleistenolide (**195**) in 91% yield upon several steps (Scheme 36) [205].

Styryl lactone (+)-howiionol A (**199**) is natural product extracted from the *Annonaceae* class. The cytotoxic ethyl acetate soluble styryl lactones (+)-crassalactone B and (+)-crassalactone C were isolated from the leaves and twigs of *Polyalthia crassa* along with (+)-goniofufurone [206, 207] and (+)-howiionol A [208]. Total synthesis of (+)-howiionol A (**199**) is natural product, extracted from the Annonaceae class, was commenced from market purchasable D-(+)-glucose (**196**) that after several steps afforded diol **197** in 70% yield. Next, diol **197** using Wittig reaction with (ethoxycarbonylethylene)triphenylphosphorane in toluene provided ester **198** in 72% yield (no cyclized product was detected). Lastly, after four steps, compound **198** was transformed into (+)-howiionol A (**199**) in 74% yield (Scheme 37) [209].

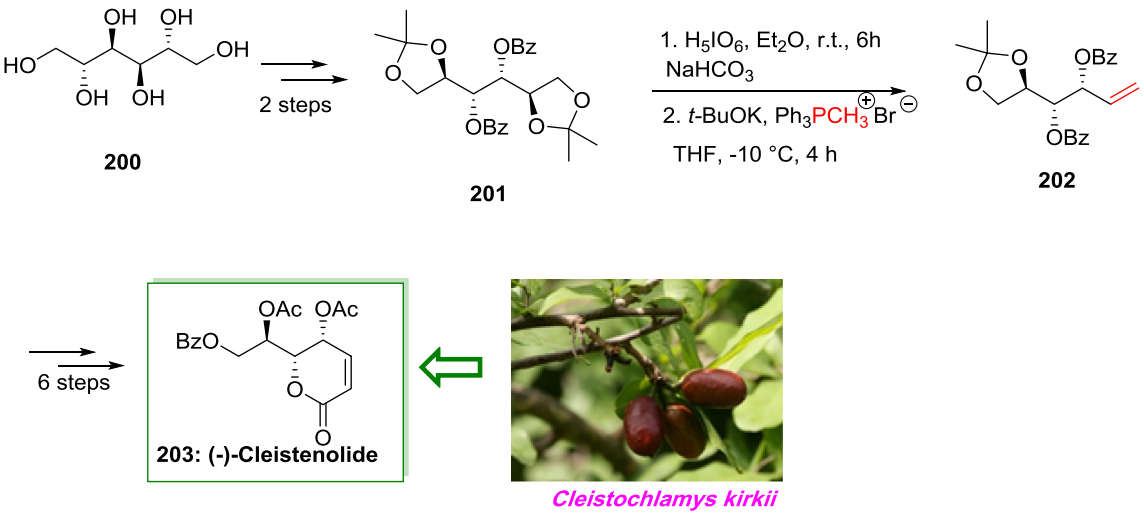
(−)-Cleistenolide and (−)-cleistodienol, natural products isolated from the medicinal plant *Cleistochlamys kirkii,* are known in Mozambique and Tanzania [203]. (−)-Cleistenolide, a six-membered lactone, having a 5,6-dihydro-2*H*-pyran-2-one scaffold exhibited in vitro antifungal property against *Candida albicans* and antibacterial property against *Staphylococcus aureus* and *Bacillus anthracis*. The extracts of this plant are used in traditional medicine as a medicine for treatment of tuberculosis, rheumatism, and wound infections [210]. A concise and significant total synthesis of (−)-cleistenolide (**203**) was accomplished starting D-mannitol in nine steps with an overall yield of 23.6%. The chiron method for the construction of (−)-cleistenolide contains a one-C-atom Wittig olefination, a selective allylic triethylsilyl protection, and a Grubbs-mediated ring-closure metathesis (RCM) reaction as the main steps (Scheme 39) [211]. Total synthesis of (−)-cleistenolide (**203**) was started from D-mannitol (**200**) that after two steps transformed into 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-benzoyl-protected derivative **201** in 91% yield. Then compound **201** was reacted with orthoperiodic acid (H_5IO_6) followed by sodium bicarbonate in diethyl ether at ambient temperature to afford the corresponding aldehyde [212] that has been transformed into alkene **202** through a Wittig reaction. Lastly, after three steps, alkene **202** provided the natural product (−)-cleistenolide (**203**) in 85% yield (Scheme 38) [211].

Substituted α,β-unsaturated δ-lactones (for example, styryl lactones), a significant group of natural products, exhibit a wide series of potent biological properties [213]. Cryptocaryalactones are natural germination inhibitors without effect on corn [214]. (+)-(6*R*,2′*S*)-Cryptocaryalactone was isolated from *Cryptocarya bourdillonii* GAMB (Lauraceae) in 1972 by Govindachari [215] and its absolute stereochemistry was developed by Meyer via enantioselective synthesis [216]. The total synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone was performed using enantioselective acetate aldol reaction. Noticeably, Still–Gennari reaction, Evans acetal intramolecular oxa-Michael reaction, and lactonization reaction are

Scheme 37



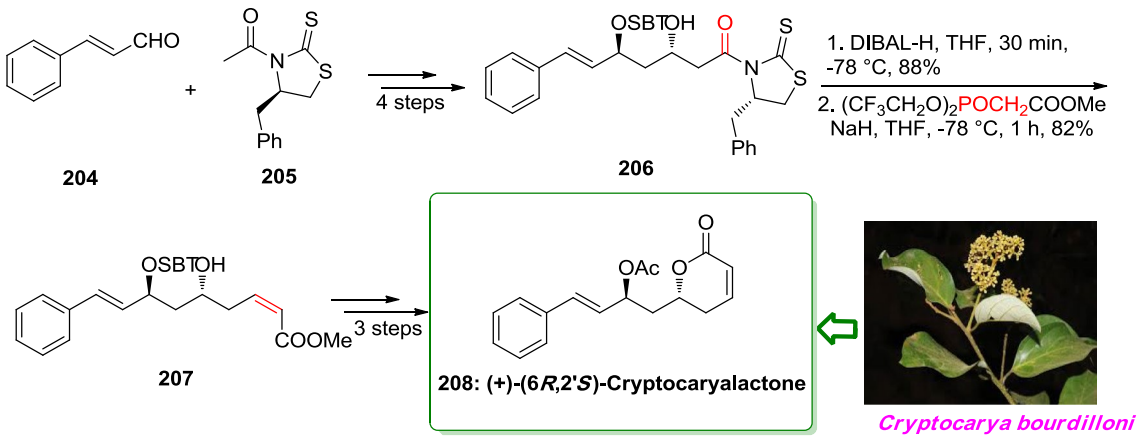
Scheme 38



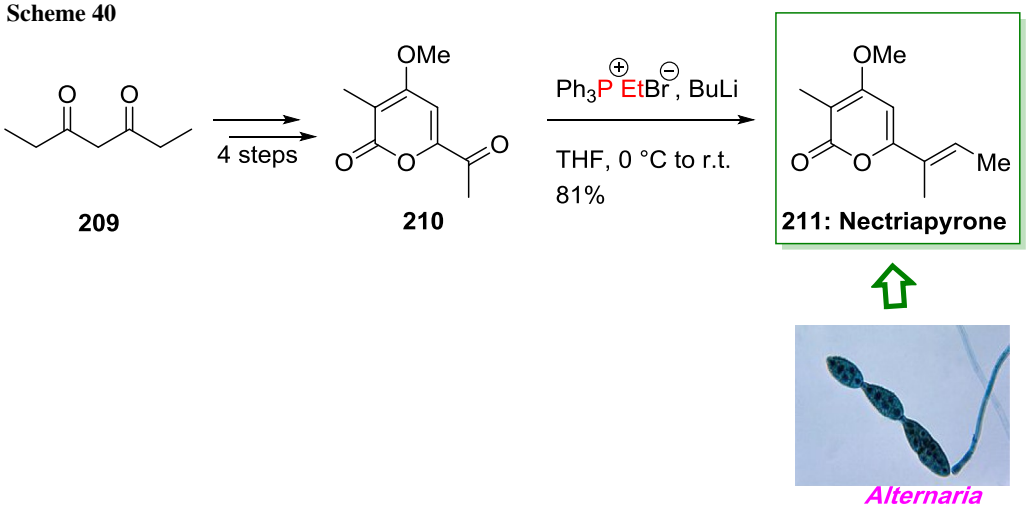
the key steps in the synthesis of the target natural product (+)-(6*R*,2′*S*)-cryptocaryalactone (**208**) [217]. In this pathway, total synthesis of (+)-(6*R*,2′*S*)-cryptocaryalactone (**208**) was started from the reaction of *trans*-cinnamaldehyde (**204**) and (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (**205**) that afforded compound **206** upon several steps. Next, compound **206** was reacted with diisobutylaluminium hydride to make the desired aldehyde. The latter has been exposed to Still–Gennari–Wittig olefination with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate [193] in tetrahydrofuran to give the corresponding α,β-unsaturated ester **207** completely as the (*Z*)-isomer in 82% yield. After several steps, the α,β-unsaturated ester **207** provided (+)-(6*R*,2′*S*)-cryptocaryalactone (**208**) in 85% yield (Scheme 39) [217].

Infectopyrone, a 2-pyrone, was first isolated from *Alternaria infectoria*. It can be isolated from *Stemphylium* and *Ulocladium* sp. Podlech and co-workers in 2012 reported the total synthesis of the 2-pyrone naturally occurring compounds nectriapyrone, aplysiopsenes A–C, *ent*-aplysiopsene D, phomapyrones A and D, and of 8,9-dehydroxylarone using Wittig olefination initiating from vermopyrone. This group selected vermopyrone (**210**), an appropriate initiating

Scheme 39



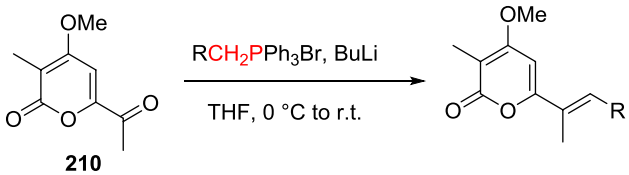
Scheme 40



precursor, for the aplysiopsenes using a Wittig olefination method. Noticeably, vermopyrone was provided by Coleman and co-workers [218] in four steps initiating from 3,5-heptanedione (**209**). They commenced with the synthesis of nectriapyrone (**211**), a pyrone first reported by Boll in 1976 and co-workers in 6% yield over four steps [219]. Vermopyrone (**210**) underwent the Wittig reaction with an ylide provided from the relevant ethylphosphonium salt to afford nectriapyrone (**211**) with an *E/Z* selectivity of 7:3, in which the natural *E* isomer was separated using chromatography. The yield of compound **211** was calculated, which showed significant increased (44%) in yield over five steps (Scheme 40) [220].

Aplysiopsenes were provided through similar olefination reaction. In this route, the reaction of vermopyrone (**210**) and the relevant phosphorous ylides (provided from butyl lithium and the phosphonium bromides) led to the formation of desired aplysiopsenes with 33-80% yield as mixtures of diastereoisomers. Noticeably, after separation by chromatography the *E*-configured aplysiopsenes A–C were obtained in

Scheme 41



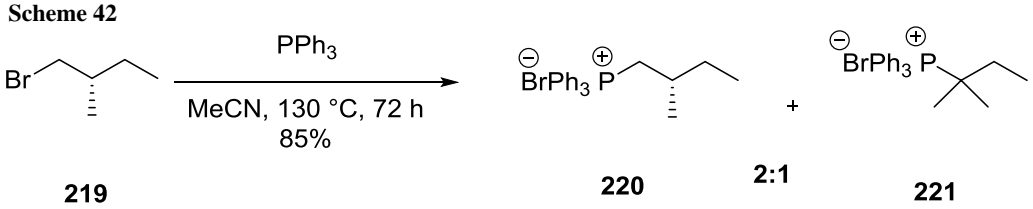
18–56% yield, respectively, over five steps. Worthy to mention that in spite of the stability of the precursor vermopyrone (**210**) at room temperature at least for some weeks, the product, aplysiopsene, was relatively unstable (Scheme 41, Table 1) [220].

Enantioselective pure synthesis of (*S*)-2-methylbut-1-yl-triphenylphosphonium bromide (**220**), which was the Wittig precursor for the olefination to aplysiopsene D (**215**), was straightforward. The normal approach [221] for the reaction of bromide [218] and triphenylphosphine afforded the phosphonium salt **220** along with a rearranged product

Table 1 Wittig reactions toward 2-pyrone-derived natural products **211**–**218**

Product	R	Yield/%	*E/Z*	Yield *E*/%
Nectriapyrone (**211**)	Me	81	7:3	57
Aplysiopsene A (**212**)	Et	76	7:3	53
Aplysiopsene B (**213**)	^{i}Pr	44	4:6	18
Aplysiopsene C (**214**)	Pr	80	7:3	56
(*ent*)-Aplysiopsene D (**215**)	^{s}Bu	33	1:1	17
Phomapyrone A (**216**)	(*E*)-But-2-en-2-yl	78	9:11	35
Phomapyrone D[a] (**217**)	Ac	84	7:3	59
8,9-Dehydroxylarone (**218**)	(*E*)-Propen-1-yl	70	7:3	49

Scheme 42

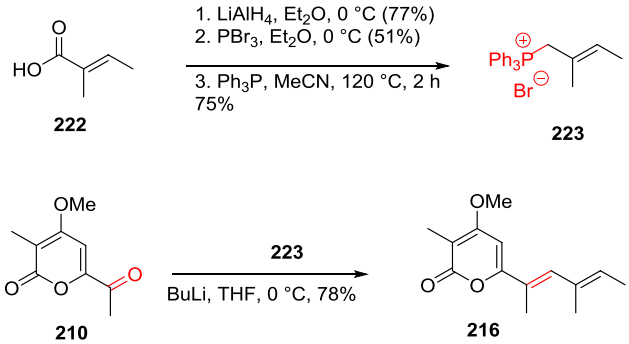


221 in a 2:1 ratio. This by-product was not stated in the reported synthesis of the phosphonium salt **220** [221, 222]. The synthesis of aplysiopsene D (**215**) were performed with this mixture (4 equiv.), but with a relatively poor yield. The olefination reaction afforded 33% of a 1:1 mixture, which after chromatographic purification led to a 17% yield of the natural product. Noticeably, the total synthesis of aplysiopsene D (**215**) was achieved with 9% yield in five steps. It should be mentioned that the specific rotation of the natural product, (*S*)-aplysiopsene D, was reported by Ciavatta and co-workers [223], which was opposite to that of the synthesized (*S*)-aplysiopsene; therefore, the obtained product was an R-configured compound, in fact, is *ent*-aplysiopsene D [220] (Scheme 42).

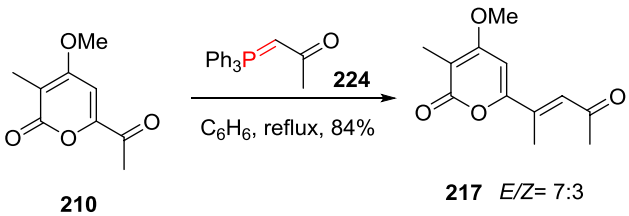
Phomapyrone A (**216**) was provided based on the method used for the aplysiopsenes. The required phosphorus ylide was constructed from (*E*)-1-bromo-2-methylbut-2-ene provided from tiglic acid (**222**) with minor modification [224]. The reaction of vermopyrone (**210**) and the ylide obtained from the phosphonium salt [224] afforded an olefinated product as a mixture of diastereoisomers (*E/Z* = 9:11) with 78% yield. Remarkably, isolation of the isomers finished the *E* isomer phomapyrone A (**216**) with 35% yield and a total yield of 19% over five steps [220] (Scheme 43).

Synthesis of phomapyrone D (**217**) was not probable through the developed method. Once the ylide **224** was synthesized using deprotonation of acetonyl(triphenylphosphonium) bromide with butyl lithium, a low 12% yield of the *Z* isomer was provided in the following olefination reaction. Notably, the modification of this method using precipitation of the ylide **224** with aqueous NaOH followed via Wittig reaction in benzene resulted in the effective synthesis of phomapyrone D (**217**) in 84%

Scheme 43



Scheme 44



yield for the *E/Z* mixture of diastereoisomers and in 59% yield for the *E* isomer, required for the natural products (Scheme 44) [220].

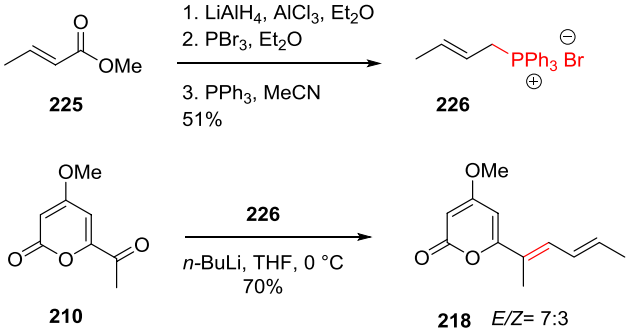
The synthesis of 8,9-dehydroxylarone (**218**) was commenced from market-purchasable crotyl bromide (technical quality, *E/Z* = ~ 5:1) that afforded the phosphonium salt. The Wittig olefination reaction was effective but led to a 64% yield of an inseparable mixture of four diastereoisomeric dehydroxylarones. Isomerically pure (*E*)-methyl

crotonate (**225**) as precursor for the Wittig salt, gave pure (*E*)-(but-2-en-1-yl)triphenylphosphonium bromide (**226**) in 51% yield over three steps that was converted into 8,9-dehydroxylarone (**218**) through Wittig olefination with 70% yield and with an *E/Z* ratio of 7:3. Lastly, the pure naturally occurring compound was provided in 49% yield [220] (Scheme 45).

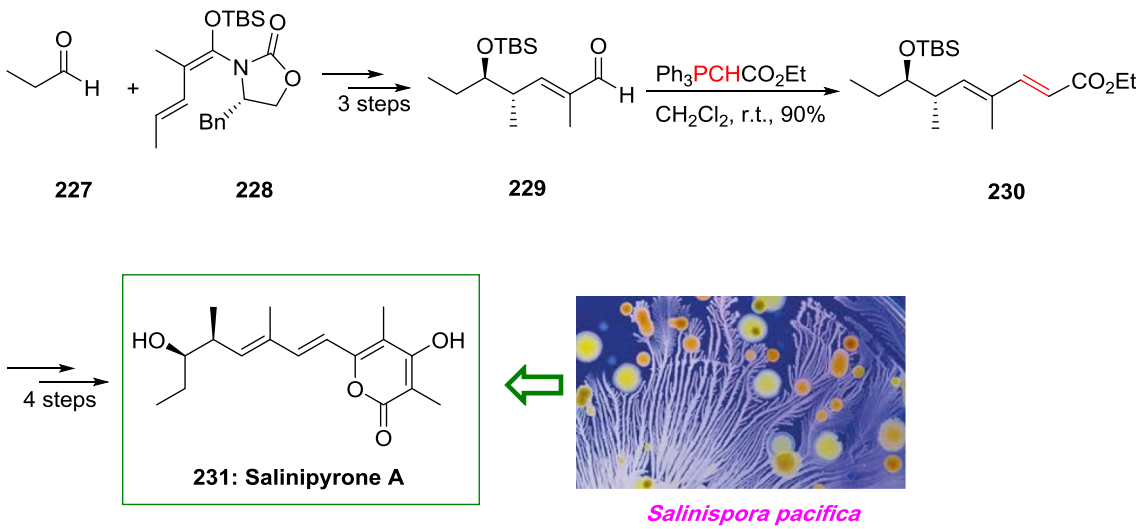
Consequently, this group reported a signification approach toward nectriapyrone (**211**), aplysiopsenes A-C, phomapyrone A (**216**), D (**217**), and 8,9-dehydroxylarone (**218**) and (*rac*)-9-*O*-methyl phomapyrone C merely separated by column chromatography, which essential in virtually all total syntheses [220]. Polyketides, a great class of natural products, were provided through step-wise decarboxylative Claisen type condensation reaction of acyl-CoA precursors that were catalyzed by polyketide synthases (PKSs). A wide range of type I polyketides containing antitumor property were isolated from marine actinomycetes [225, 226]. Four type I polyketides, salinipyrones A and B and pacificanones A and B were extracted from cultures of the obligate marine actinomycete *Salinispora pacifica* CNS-237 [227]. Meshram and Ramesh demonstrated the first asymmetric total syntheses of salinipyrone A (**231**) [228]. Main conversions in this approach involved formation of δ-hydroxy-α-methyl-α,β-unsaturated carbonyl part through the vinylogous Mukaiyama aldol reaction and a seven-step synthetic reaction with 14% overall yield starting from vinylketene silyl N,O-acetal **228** [228]. Total synthesis of salinipyrone A (**231**) was started from vinylketene silyl N,O-acetal (**228**) propionaldehyde (**227**) that afforded compound **229** upon three steps. Next, compound **229** was homologated to (*E*)-α,β-unsaturated ester **230** (90% yield) through Wittig olefination reaction with $Ph_3P{=}CHCO_2Et$ in dichloromethane. Upon several steps, (*E*)-α,β-unsaturated ester **230** generated salinipyrone A (**231**) in 90% yield (Scheme 46) [228].

Gymnoconjugatin A (**238**) and B (**239**) were isolated from the soil microbe of *Gymnoascus reessii* accompanied by various polyenyl-pyrroles containing auxarconjugatin A isorumbrin. The first total synthesis of gymnoconjugatin A and B demonstrated by Coleman and Walczak [218] was relied on Stille, and also Suzuki–Miyaura coupling reactions using boron/tin hetero-bis-metallated butadiene. A concise total synthesis of the microbial natural products gymnoconjugatin A and B were achieved using furfural and *trans*-methyl crotonate via Horner–Wadsworth–Emmons (HWE) and Wittig reactions. Total synthesis of gymnoconjugatin A (**283**) and B (**239**) was commenced from furfural **232** that produced aldehyde **233** upon three steps. Next, aldehyde **233** underwent Horner–Wadsworth–Emmons (HWE) olefination with phosphonate **235** to give the corresponding tetraene ester **237** [229] in poor yields. However, a decent yield can be obtained through coupling reaction of **233** with stable phosphorus ylide **235** (provided in three steps from methyl crotonate including bromination, construction of Wittig salt and then ylide) in MeOH. The similar sequence was used for

Scheme 45



Scheme 46

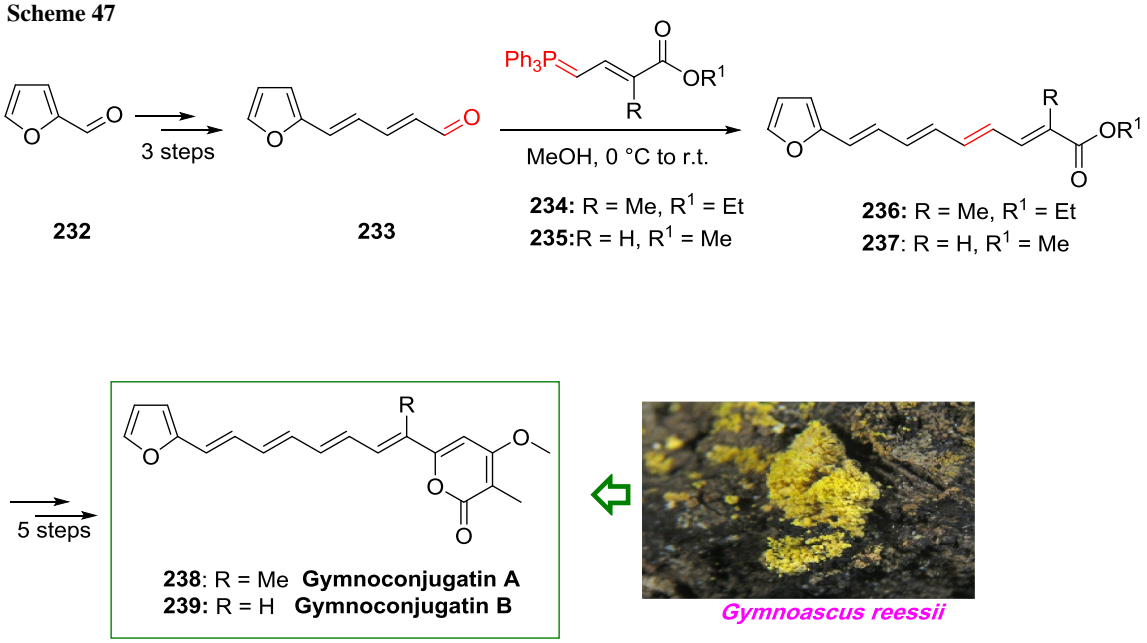


the formation of *trans*-tetraene ester **236** through reacting aldehyde **233** with phosphorus ylide **235**. Remarkably, the required phosphorus ylide **234** has obtained from market purchasable ethyl tiglate via allylic bromination reaction and Wittig reaction in 48% yield. Upon several steps, ester **236** and compound **237** afforded gymnoconjugatin A and B (Scheme 47) [230].

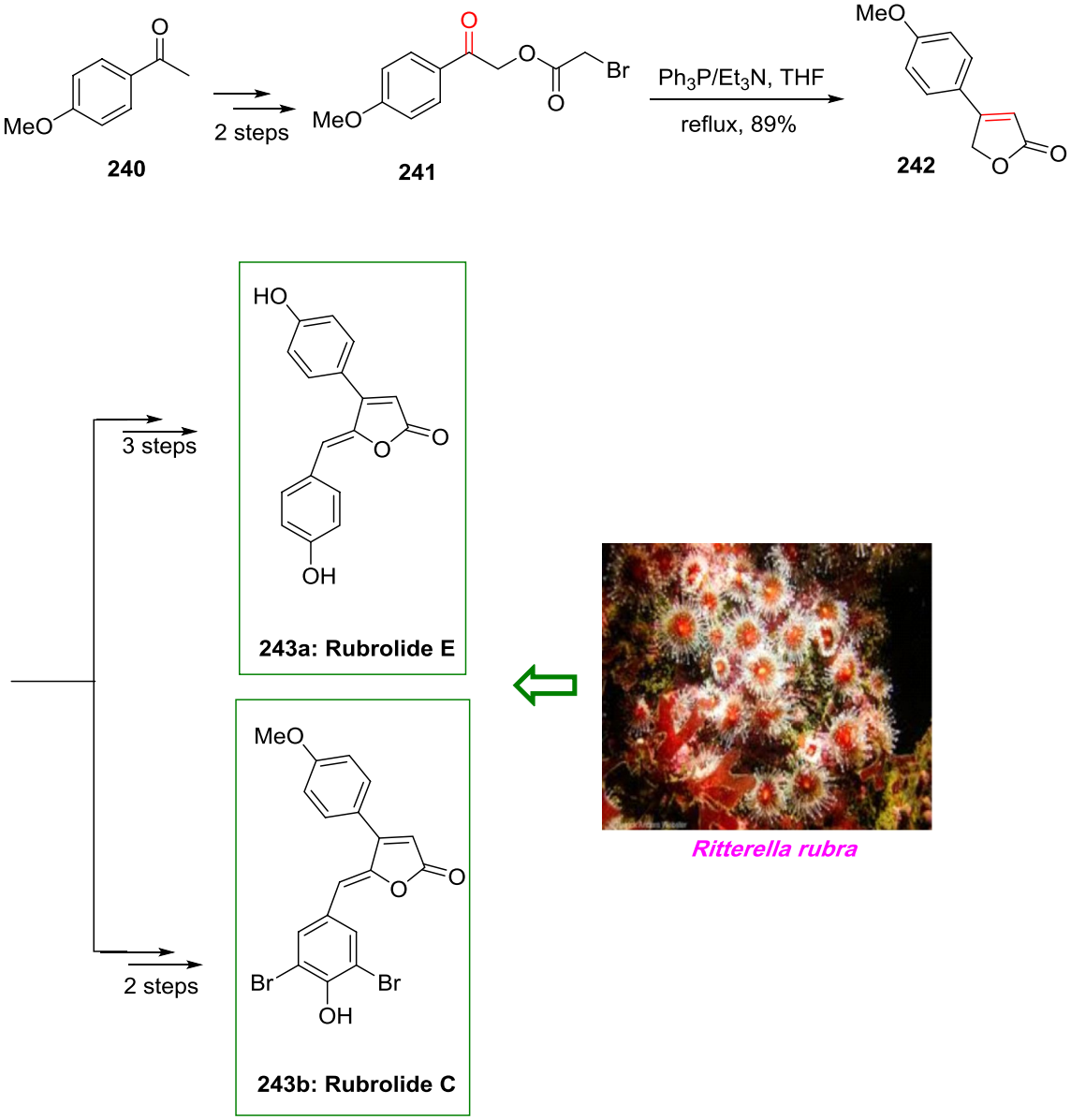
The γ-benzylidenebutenolide building blocks containing two 4-hydroxyphenyl scaffolds, with or without halogen atoms, is a usual structural aspect of a class of biologically potent marine ascidian metabolites named rubrolides [231]. The rubrolides without halogen atoms at C(3) of the butenolide scaffold are A, C, D, E, and J. Remarkably, rubrolides B, I, K, L, M, and O contain a Cl-atom at C(3) of the furan-2(5*H*)-one, whereas rubrolide N have 3-Br atom. Rubrolides A–H isolated in 1991 from the colonial tunicate *Ritterella rubra* [232, 233]. A short and significant four-step synthesis of rubrolide C (four steps; 46% overall yield) and E (four steps; 45% overall yield) was achieved from easily accessible starting precursors through an intramolecular Wittig reaction as a main step for the simple generation of 4-arylfuran-2(5*H*)-one. It should be mentioned that the probability of changing the groups on aromatic aldehydes and acetophenones makes this approach good for the synthesis of the desired target. Main reactions included in the formation of rubrolides C and E were atosyloxylation of aryl methyl ketone, intramolecular Wittig reaction, Knoevenagel condensation reaction, and demethylation. The synthesis of rubrolide E was started from 4-methoxyacetophenone (**240**) that provided 2-(4-methoxyphenyl)-2-oxoethyl 2-bromoacetate (**241**). The intramolecular Wittig reaction of **241** and triphenylphosphine/triethylamine in tetrahydrofuran gave 4-(4-methoxyphenyl)furan-2(5*H*)-one (**242**) in 89% yield. 4-(4-Methoxyphenyl)furan-2(5*H*)-one (**242**) afforded rubrolide E (**243a**) in 93% yield, upon several steps. Therefore, rubrolide E was provided in 45% overall yield in four steps. In a similar way, rubrolide C (**243b**) was provided in four steps in a 46% overall yield (Scheme 48) [234].

In 1972, Govindachari extracted (+)-(6*R*,20*S*)-cryptocaryalactone (**247**) from *Cryptocarya bourdillonii* GAMB (Lauraceae) [235]. The absolute stereochemistry of **247** has been identified by its enantioselective total synthesis [216]. Also, (−)-(6*S*,20*R*)-cryptocaryalactone (**248**) was isolated from *Cryptocarya moschata* [214] that shows anti-germination property. Remarkably, cryptocaryalactones are natural germination inhibitors without effect on corn [214]. In South Africa, Cryptocarya species were used as traditional remedies for the treatment of different diseases [236, 237]. An efficient chemoenzymatic pathway for the formation of cryptocaryalactone natural products using a kinetic resolution method as the main step was demonstrated by Reddy and co-workers in 2018 [238]. Total synthesis of (+)-(6*R*,20*S*)-cryptocaryalactone (**247**) was commenced from *trans*-cinnamaldehyde (**244**) that afforded *anti*-ethyl (*E*)-2-(2,2-dimethyl-6-styryl-1,3-dioxan-4-yl)acetate (**245**) upon several steps. The compounds (4*S*,6*S*)-**245** and (4*R*,6*R*)-**245** have been transformed into (+)-(6*R*,20*S*)-cryptocaryalactone (**247**) and (−)-(6*S*,20*R*)-cryptocaryalactone (**248**), respectively, using Wittig olefination, lactonization reaction, and acylation. The crude aldehyde has been exposed to (*Z*)-selective Wittig reaction with $(CF_3CH_2)_2POCH_2COOMe$ using sodium hydride to afford (*Z*)-olefine **246** and *ent*-**246** with excellent stereoselectivity in 65% and 62% yields over two steps. Lastly, the (*Z*)-olefine **246** and *ent*-**246** gave

Scheme 47



Scheme 48

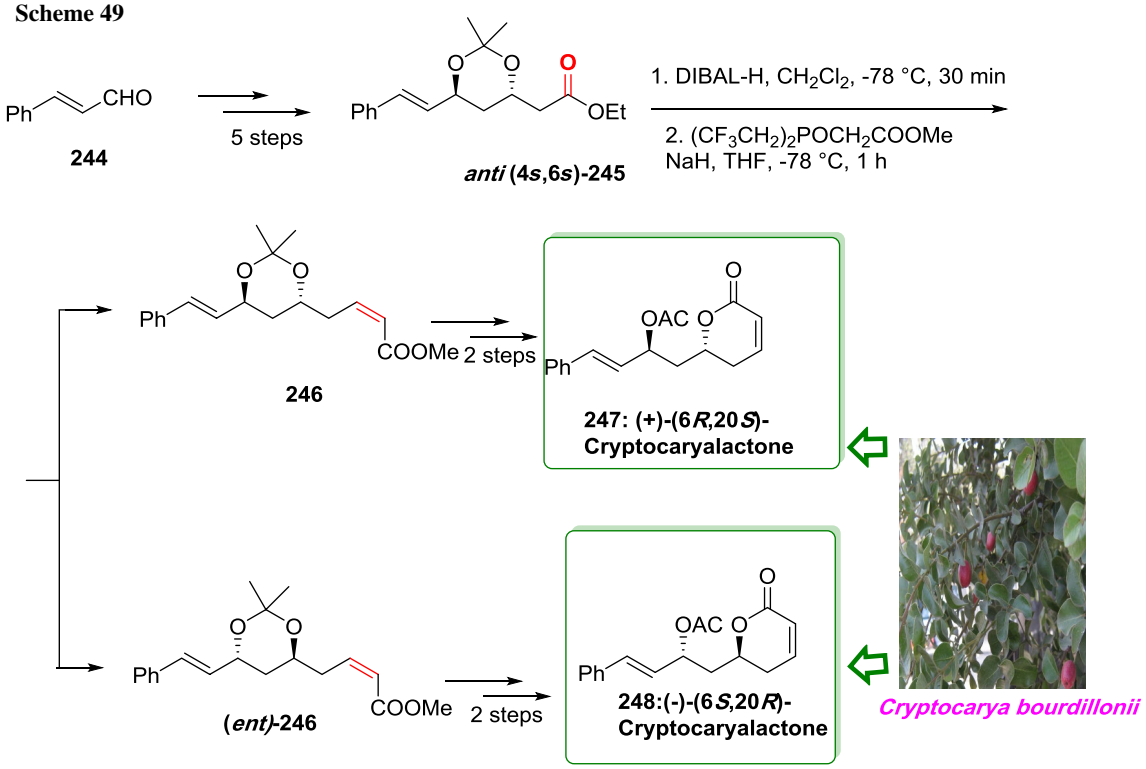


natural products (+)-(6*R*,20*S*) cryptocaryalactone (**247**) and (6*S*,20*R*)-cryptocaryalactone (**248**) in 85% and 86% yields (Scheme 49) [238].

Containing lactam as a moiety

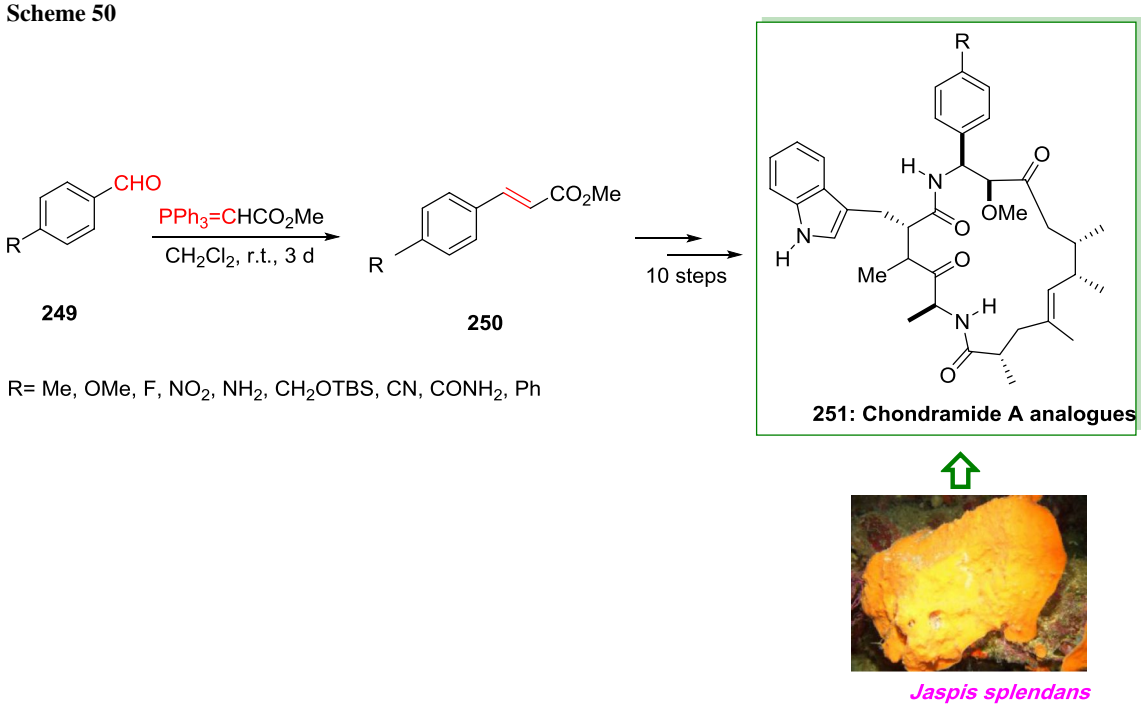
Cyclodepsipeptides, a unique group of secondary metabolites, involve unusual amino acids, such as N-methylated amino acids or D-amino acids and hydroxyl acids that commonly originated from the polyketide route. Various cyclodepsipeptides were isolated from marine sponges and exhibited fascinating biological properties such as antitumor or anti-HIV property. Cyclodepsipeptides, demonstrating antitumor property are the chondramides and the jasplakinolides. Noticeably, jasplakinolide was isolated from the marine sponge *Jaspis splendens* [239]. Also, it was known in a Jaspis sponge and called jaspamide [240]. Meanwhile, jasplakinolide was extracted from various other sponges. In contrast, so far only four natural chondramides were found specifically chondramides. They were isolated by the Höfle/Reichenbach et al. from myxobacteria [241]. The chondramides are quite analogous in structure to jasplakinolide, in which they include a tripeptide subunit comprising of an *N*-methyl-D-tryptophan, an L-β-tyrosine, and an L-alanine. Jasplakinolide and the chondramides vary principally in the hydroxy acid, which links the tripeptide unit to make the cyclodepsipeptide. While jasplakinolide involves an 8-hydroxy acid, in the chondramides the relevant

Scheme 49



sector is a 7-hydroxyacid. Therefore, jasplakinolide demonstrates a 19-membered macrocycle, whereas the chondramides are 18-membered. Total synthesis of chondramide A (**251**) was started from readily available aldehydes **249** that with the stabilized ylide [(carbomethoxy)methylene]-triphenylphosphorane [242] in CH_2Cl_2 gave *trans*-cinnamic esters **250** via Wittig reaction. After several steps, *trans*-cinnamic esters **250** afforded chondramide A analogs **251** in 20-67% yield (Scheme 50) [243].

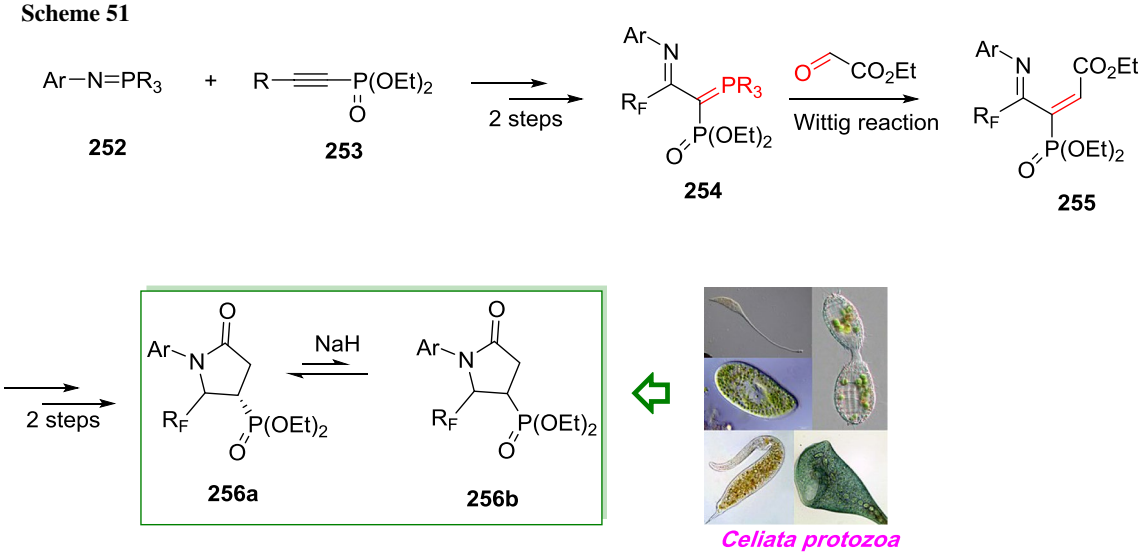
Scheme 50



Organophosphorus compounds are useful substrates in the synthesis of biochemical [244, 245] and especially β-aminophosphonates that are isosteres of β-amino acids, which are useful agrochemicals, enzyme inhibitors, pharmaceuticals [246, 247] and other biochemicals showing biological activities [248]. Various β-aminophosphonic acids were known as natural products [249, 250]. The parent acid has been initially isolated from *Celiata protozoa* [251], and afterwards this compound along with its various derivatives was isolated from microorganisms [252, 253]. γ-Lactams contain significant usages in the drug discovery, as main intermediates in the construction of pharmaceutically and biologically related compounds in the treatment of cancer, HIV [254], fungal infections [255], depression [255], neurodegenerative diseases [256], epilepsy [257]. The γ-lactam unit exhibited better prevention profiles of HDACs and cancer cell growth inhibitory properties [258]. In addition, γ-lactams are feasible glycinamide replacements in a wide range of cyclohexane-based CCR_2 antagonists [259]. Total synthesis of *trans*-γ-lactam was achieved from the reaction of phosphazenes **252** and polyfluoroacetylenephosphonates **253** that upon two steps gave diethoxyphosphinyl phosphoranes **254** in 65–80% yield. Noticeably, the Wittig reaction between ylides **254** and carbonyl compounds gave the related *E* isomer of 1-azadiene **255**, stereoselectively along with the relevant phosphine oxide. Upon several steps, 1-azadiene **255** afforded γ-lactams **256a/256b** as a mixture of *trans*- and *cis*-diastereoisomers in 90% yield (Scheme 51) [260].

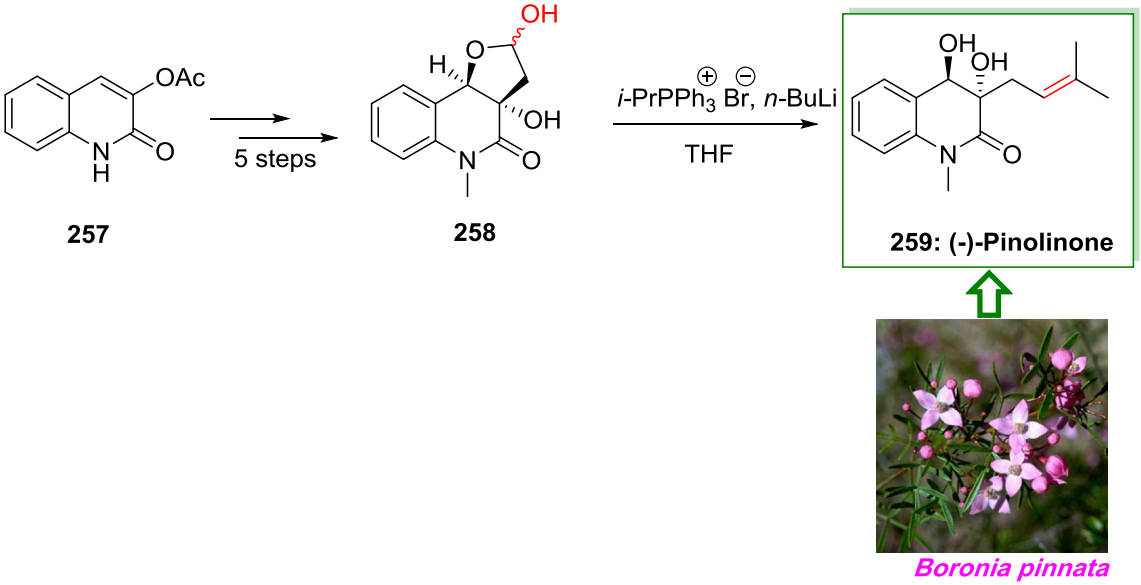
(−)-Pinolinone containing 3,4-dihydroquinolin-2(*1H*)-one scaffold was isolated from dried roots of *Boronia pinnata* Sm. (Rutaceae) [261]. It is a member of the group of 3-prenylated quinolin-2(*1H*)-ones, in which their various representatives were represented formerly [262]. However, merely one component of the plant genus Boronia was of interest [263]. It should be mentioned that 3,4-dihydroxylation is detected in various natural products 3,4-dihydroquinolin-2(1*H*)-ones which can be obtained from anthranilic acid. Although, most of these compounds contain an additional 4-aryl group obtained from an aromatic amino acid [264, 265]. Total synthesis of (−)-pinolinone (**259**) was started from 3-acetoxyquinolone (**257**) in six steps and in 17% overall yield. Additional main steps involved a selective ring expansion of the cyclobutane ring to a γ-lactone and

Scheme 51



R'	Ar	Yield /%
CF_3	*p*-MeO-Ph	76
CF_3	*p*-Me-Ph	65
CF_3	*p*-NO_2-Ph	80
C_2F_5	*p*-NO_2-Ph	68
CF_2H	*p*-NO_2-Ph	76

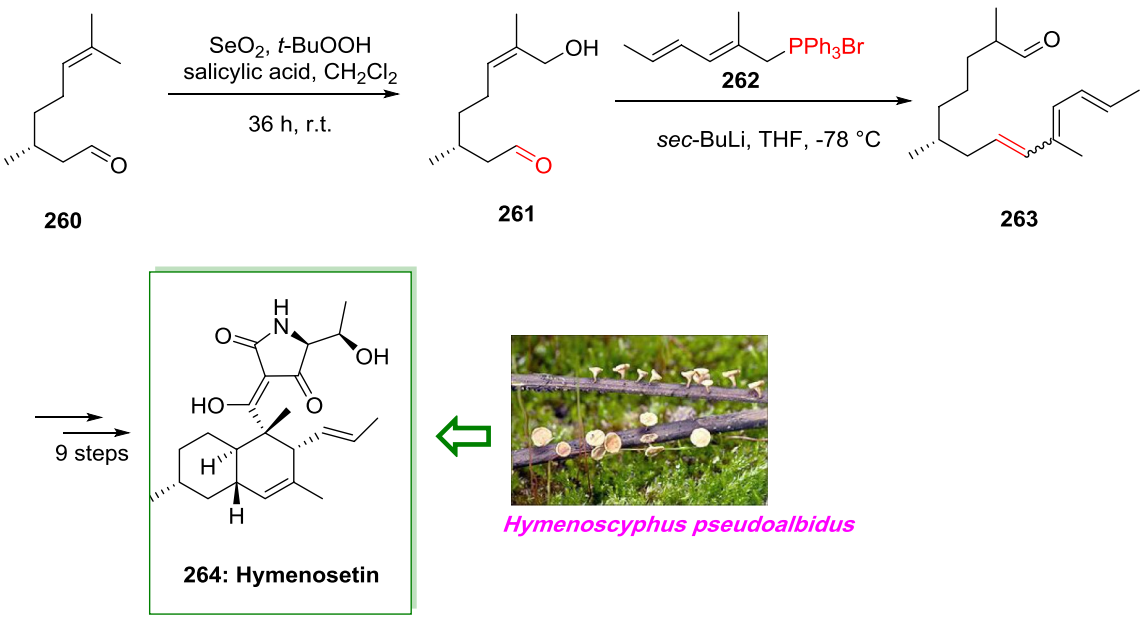
Scheme 52



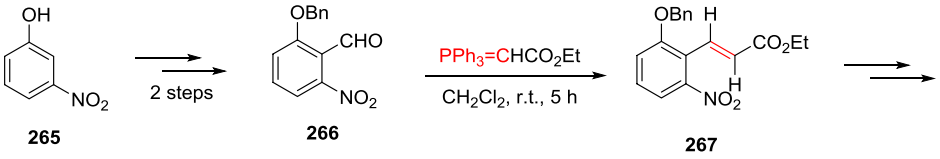
transformation of it using reduction/olefination reactions. In this method, 3-acetoxyquinolone upon several steps gave lactol **258** in 61% yields. Noticeably, lactol **258** should be in equilibrium with the γ-hydroxyaldehyde and hence expected being involved in Wittig reaction. Next, the reaction was accomplished by adding the lactol to an excess of the ylide in tetrahydrofuran as the solvent. Based on these conditions, a yield of 55% for the olefination and product **259** was exhibited to be identical to pinolinone (Scheme 52) [266].

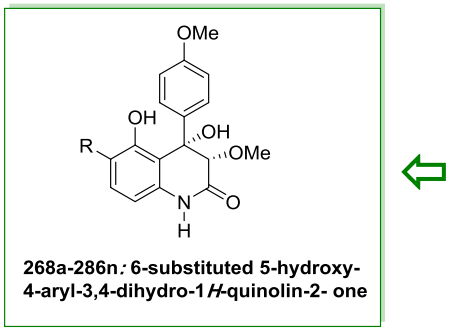
The 3-decalinoyltetramic acid, (−)-hymenosetin and its *N*-methyl analog were synthesized in 11 and 8 steps, respectively, from (+)-citronellal through an intramolecular Diels–Alder reaction as the main step. This approach exhibits the first sample for the construction of a 3-decalinoyltetramic acid with a free NH-scaffold. In 2014, Stadler and co-workers demonstrated the extraction of the novel fungal metabolite hymenosetin (**264**) from *Hymenoscyphus pseudoalbidus*, an aggressive species providing severe dieback of the European ash [267, 268]. In addition to cytotoxic and antifungal influences against the mouse fibroblast cell line L929, this compound exhibit significant biological properties against Gram-positive bacteria [268].

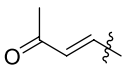
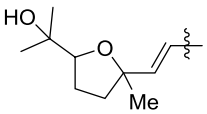
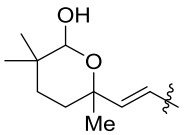
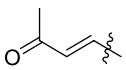
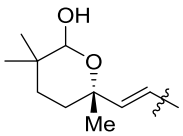
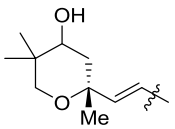
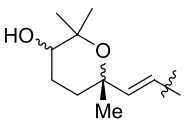
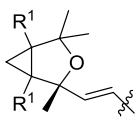
Scheme 53



Scheme 54





Product	R
Yaequinolone B (**268a**)	
Yaequinolone C (**268b**)	
Yaequinolone D (**268c**)	
Yaequinolone E (**268e**)	
Penigequinolone A (**268i**)	
Penigequinolone B (**268j**)	
Aspoquinolones A B (**268k,j**)	
R^1=α-H Aspoquinolone C (**268m**) R^1= β-H Aspoquinolone D (**268n**)	

Kauhl and co-workers demonstrated the extraction and structure clarification of hymenosetin from the ascomycete IBWF-E99318 (*Phoma* sp.). Total synthesis of (−)-hymenosetin (**264**) was started from (+)-citronellal (**260**) that gave allylic compound **261**. Next, Wittig reaction of the main product of the allylic oxidation **261** and **262** resulted in the corresponding triene alcohol **263** in 69% yield and satisfactory stereoselectivity (3:2 *E/Z*). After several steps, alcohols **263** afforded hymenosetin (**264**) in 70% yield. This product is a mixture of two major keto-enol tautomers (Scheme 53) [269, 270].

The 5-hydroxy-4-aryl-3,4-dihydro-1*H*-quinolin-2-ones, a small group of natural products, were isolated from fungal strains of *Penicillium* and *Aspergillus*. Some that contains an isoprenoid C-6 side chain are anthelmintics and insecticides. The total synthesis of **268** was accomplished successfully via the enantioselective formation of a β,β-diarylacrylates from 6-nitrosalicylaldehyde, via a Wittig olefination reaction, a Heck–Matsuda arylation reaction, and a selective Fe^0-catalyzed reductive cyclization reaction. Noticeably, installation of the 6-propenyl side chain was achieved by 5-*O*-allylation reaction of the heterocycle, Claisen rearrangement, and conjugative migration of the allyl double bond, as main steps. Besides, the Grubbs II-catalyzed olefin cross metathesis reaction of the 6-allyl scaffold with 2-methylbut-2-ene to make a precursor of peniprequinolone, was demonstrated. The quinoline unit is a remarkable heterocyclic structure known in various natural products and bioactive compounds [271, 272]. Fascinatingly, filamentous fungi were the source of moderately few quinolones [273, 274] although certain strains of *Penicillium* and *Aspergillus* provide 5-hydroxy-4-aryl-3,4-dihydro-1*H*-quinolin-2-ones, having a C-6 alkyl/alkenyl side chain that make a unique novel group of natural products.

The yaequinolones B–F, J_1, and J_2 (**268a**–**268g**) [265] were isolated from *Penicillium sp.* FKI-2140, together with nine relevant compounds, containing peniprequinolone (**268h**) and the penigequinolones A and B (**268i** and **268j**) [275, 276]. The cytotoxic and antifungal [277] **268h**, formerly demonstrated from *P. simplicissimum* and *P. namyslowskii* [278], was a nematicidal antibiotic against the root-lesion nematode *Pratylenchus penetrans* [279]. Total synthesis of (−)-hymenosetin (**268**) was started from 3-nitrophenol (**265**) that gave aldehyde **266** upon two steps. The Wittig reaction of aldehyde **266** and ethyl (triphenyl-λ5-phosphanylidene)acetate gave cinnamate **267** in 88% yield. Based on ^{1}H NMR results the stereochemistry of **267** was *E*. Upon several steps, cinnamate **267** produced 6-functionalized 5-hydroxy-4-aryl-3,4-dihydro-1*H*-quinolin-2- one (**268**) (Scheme 54) [280].

Conclusion

In summary, Wittig reaction or Wittig olefination is a reaction of a phosphonium ylide (frequently so-called Wittig reagent triphenyl) with an aldehyde or ketone to afford an alkene and triphenylphosphine oxide. In this review, we tried to underscore the implication and prominence of Wittig reaction as an exceptional reaction under new viewpoint, its uses in the chief and new field of total synthesis of natural products containing lactone, pyrone, and lactam as back bone. Remarkably, we tried to reveal how the Wittig reaction is playing a key role in the step (steps) of multistep total synthesis of naturally occurring compounds with miscellaneous biological potencies. As a matter of fact, currently, the Wittig reaction is one of the most momentous basic reactions in the total synthesis of the most significant class of naturally occurring compounds, containing lactones, pyrenes, and lactams as framework. The importantly compounds from biological aspects, issues, etc. are synthesized via Wittig reaction as a vivacious step in their multistep total synthesis.

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