1
Tetronic Acids

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1.1
Introduction

Tetronic acids belong to the class of 4-hydroxybutenolides that are characterized by a 4-hydroxy-2(5*H*)-furanone ring, as it can be seen in the generic structure of Scheme 1.1 [1]. This type of five-membered vinylogous acids can be met in two main tautomeric forms (**1** and **2**) with enol structure **1** being the one that predominates. Tetronic acid is a substructural element of many natural products of various classes such as alkaloids, terpenes, macrolides, and tannins. Two well-known natural products of this class are ascorbic acid (**3**) and penicillic acid (**4**). In many cases, its presence in natural products is connected with a wide range of significant biological properties and, therefore, the synthesis of these compounds has attracted synthetic interest for more than a century. In the following section, a synopsis of the natural occurrence, biological activities, and biosynthetic considerations of tetronic acid natural products will be attempted and a more thorough analysis of the synthetic strategies toward such compounds will be presented. Categorization of tetronic structures is based on 5-position's substitution and discussion on synthetic routes toward these compounds will be limited on total syntheses with main focus to the construction of tetronic ring.

1.2
Natural Occurrence, Biological Activities, and Biosynthesis

A large group of tetronic natural products isolated from numerous fungi, molds, and lichens are pulvinic acids (**16**) and their decarboxylated analogs, pulvinones (**14**) [2]. The first pulvinic derivative was isolated by Berbet in 1831 from the lichen *Cetraria vulpina*, whereas the first pulvinone was isolated by Gill in 1973 by the mushroom *Boletus elegans* [3]. Pulvinic dimers such as norbadione A (from bolete *Xerocomus badius* [4]) and sclerocitrin (from puffball *Scleroderma citrinum* [5]) have also been isolated and they have been biosynthetically linked with the dimerization of xerocomic acid by an ingenious mechanism proposed

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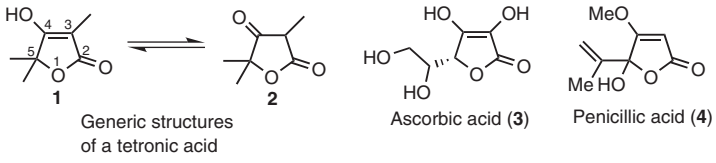
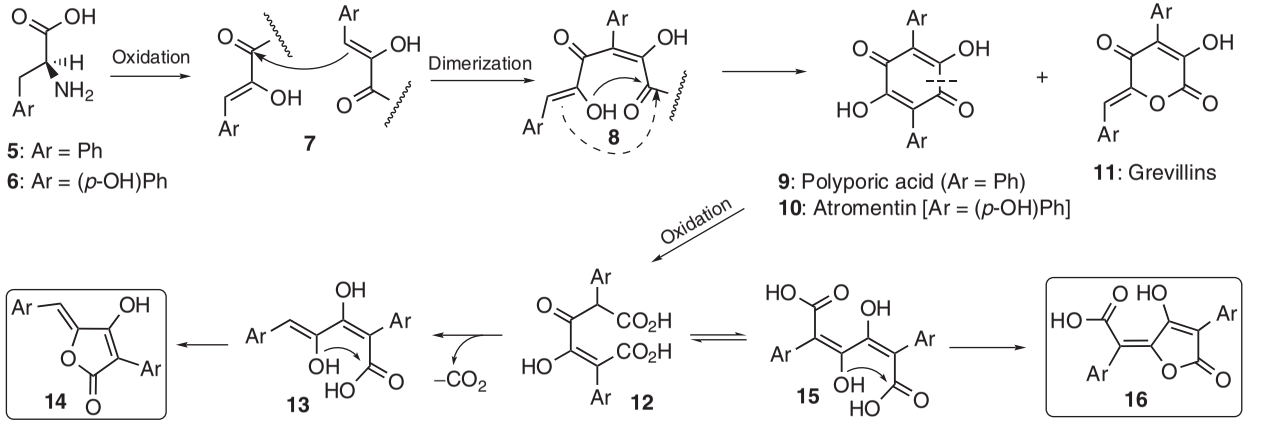


Scheme 1.1 Generic structure of a tetronic acid and structures of ascorbic acid (**3**) and penicillic acid (**4**).

by Steglich *et al.* [5]. Vulpinic acid and analogs have displayed anti-inflammatory, antipyretic, and analgesic properties, but several of these compounds are cytotoxic [6]. Norbadione A, di-O-methyl atromentic acid, and derivatives exhibit marked antioxidant and radioprotective properties [7], whereas variegatic and xerocomic acids are inhibitors of cytochrome P450 enzymes [8]. In addition, norbadione A acts as a strong Cs^{2+} chelator and has been studied for applications in ^{137}Cs decontamination [9]. Biosynthetically, pulvinic acids and pulvinones are related to terphenylquinones (**9** and **10**) and grevillins (**11**), two isomeric classes of natural products that stem from the dimerization of arylpyruvates **7** that directly connects them with the shikimate pathway (Scheme 1.2) [2a]. This was supported by feeding experiments that established L-phenylalanine and L-tyrosine as essential building blocks for their biosynthesis [10] as well as the identification of the atromentin's gene cluster that delineated the biogenetic relation of tyrosine with **10** [11].

3-Acyl tetronic acids are probably the biologically most interesting class of tetronic acid natural products. For example, tetronasin [12], an ionophore antibiotic produced from *Streptomyces longisporoflavus*, is used as an animal-feed supplement and interferes with the selective permeation of ions across lipid bilayers causing depolarization of the membrane and death [13]. This molecule tends to bind metal ions by using its 3-acyl-tetronic moiety. RK-682, a simple 3-palmitoyl-5-hydroxymethylene tetronic acid isolated from various *Actinomycetes* and *Streptomycetes* sources [14], is a potent inhibitor of HIV-1 protease [14a] and various protein tyrosine kinases and phosphatases [14b] (including VHR and cdc25B) by acting as a phosphate mimic. In 2010, Sun *et al.* [15] reported the full reconstruction of RK-682 biosynthesis by using recombinant enzymes via a pathway that shares many common features with that of spirotetronate antibiotics that will be discussed later. Indications from feeding/NMR (nuclear magnetic resonance) experiments have shown that the biosynthesis of relevant agglomerins [16] may follow a similar pathway that is based on the incorporation of a glyceryl unit into the tetronic ring [17]. On the contrary, in 1962, an alternative route has been proposed by Bentley *et al.* [18] for the biosynthesis of 3-acyl tetronic acids isolated from molds (carlic, carolic, and carlosic acids) that involves enzymatic acylation of γ-methyl tetronic derivatives derived from C4-dicarboxylic acids.

A group of tetronic acid natural products with challenging structural patterns from both synthetic and biosynthetic viewpoints and interesting antibiotic and antitumor properties are the spirotetronic natural products. Tetrocarcin A (TCA) is produced by *Micromonospora chalcea* NRRL 11289 and possesses a polycyclic



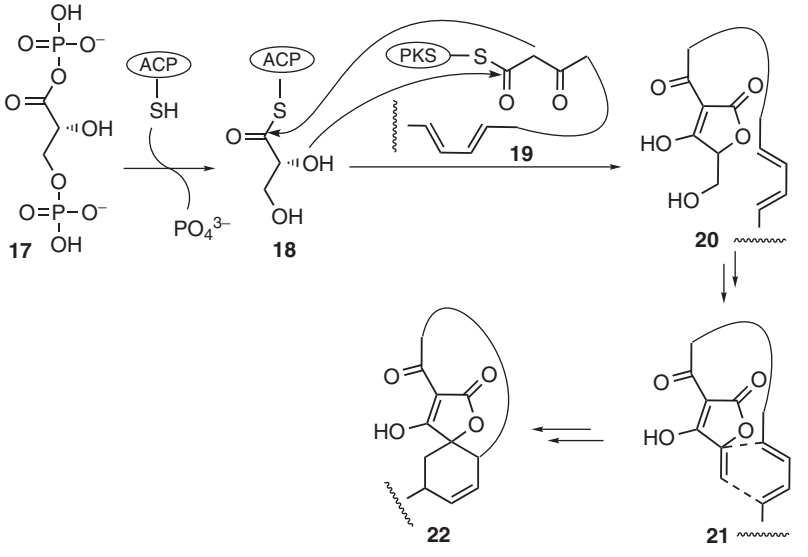
Scheme 1.2 Biosynthesis of pulvinic acids (**16**) and pulvinones (**14**).

aglycon (tetronolide) that features a *trans*-decalin system and a tetronate moiety spiro linked with a cyclohexene ring and two sugar side chains heavily responsible for their biological activity [19]. TCA-induced apoptosis in tumor cells [20] can be mediated by (i) antagonizing the mitochondrial functions of proteins of the Bcl-2 family (natural apoptosis inhibitors) in HeLa cells [20a], (ii) activating the caspase-dependent cell death pathway via endoplasmic reticulum stress in lymphomas [20b,c], and (iii) inhibiting the phosphorylation of factors involved in phosphatidylinositol 3-kinase/Akt signaling in human breast cancer cells [20d]. On bioassay using experimental mouse models, TCA exhibited remarkable antitumor activities without significant myelosuppression and associated nephrotoxicity [21]. Arisostatins A and B, two tetrocarcins of similar biological properties, have been isolated in 2000 from *Micromonospora* sp. TP-A0316 [22]. Recent results have indicated that arisostatin A induces apoptosis in HN-4 cells by mediating loss of mitochondrial transmembrane potential, release of cytochrome C into cytosol and generation of reactive oxygen species [23]. More than 60 structurally related compounds have been reported from strains of various Gram-positive bacteria (Actinomycetes) and nearly all of them possess antibacterial and antitumor activities. Well-known examples include the first member to be discovered in this family, chlorothricin [24], as well as kijanimicin [25], lobophorins A–F [26], MM46115 [27], and versipelostatin [28]. Chlorothricin acts as an inhibitor of pyruvate carboxylase that catalyzes the anaplerotic CO_2 fixation on synthetic media and it is able to inhibit cholesterol biosynthesis via the mevalomalonate pathway [29]. Kijanimicin has a broad spectrum of antimicrobial activity against Gram-positive bacteria, anaerobes, and the malaria parasite *Plasmodium falciparum* and also shows antitumor activity [25, 30]. Interestingly, lobophorins A and B exhibit anti-inflammatory and not antibiotic properties, based on experiments performed in the PMA-induced mouse ear edema model [26a]. Versipelostatin down-regulates the expression of GRP78, a molecular chaperone in the endoplasmic reticulum that plays an important role as a surviving factor in solid tumors because of its acquisition of a resistant mechanism against both chemotherapy and hypoglycemic stress [28, 31]. Later, it was demonstrated that versipelostatin can specifically inhibit the activation of the unfolded protein response (UPR), in response to glucose deprivation [31]. The result of versipelostatin action is enhanced sensitivity to glucose deprivation with enhanced cell death after exposure to the drug in the glucose-deprived state.

Another group of structurally related spirotetronate macrolides lacking the decalin core include spirotetronic tetramers quartromicins [32], spirohexenolides [33], and abyssomicins [34]. Spirohexenolide A displays strong cytotoxicity in the NCI-60 cell line and low toxicity in mice [33], whereas quartromicins exhibit antiviral activity against herpes simplex virus type 1, influenza virus type A, and HIV [32]. Natural atropoisomers abyssomicin C and atrop-abyssomicin C display significant antibiotic activity against a variety of Gram-positive bacteria, including methicillin- and vancomycin-resistant *Staphylococcus aureus* strains, with the second being the most active [34a, 35]. These molecules are the first natural products able to inhibit the *p*-aminobenzoic acid (*p*ABA), a constituent of the folate pathway, by covalently

binding to aminodesoxychorismate synthase via a Michael addition of a cysteine nucleophile [36].

Initial results from feeding experiments complemented by the identification of the gene clusters [37] of chlorothricin [37a], kijanimicin [37b], TCA [37c], abyssomicin [37d], and quartromicin [37e] as well as the related non-spiro tetronates tetronomycin [38] and RK-682 [15] have contributed to the elucidation of a reasonable biosynthetic route for the tetronate moiety (Scheme 1.3). In particular, a polyketide unit (**19**), synthesized by a module type I polyketide synthase (PKS), and a glycerol derived 3-carbon unit bound to an acyl carrier protein, ACP (glyceryl-*S*-ACP, **18**) are combined to form the tetronate moiety. The latter is synthesized by an FkbH-like glyceryl-*S*-ACP synthase that catalyzes D-1,3-bisphosphoglycerate dephosphorylation and transfer to ACP. In the case of RK-682, the formation of the C–C and C–O bonds of the tetronic ring seems to be mediated by the action of the same synthase, but it is not clear in what order and whether this is also the case for other tetronic natural products. In the case of kijanimicin and TCA, an FAD-dependent oxidoreductase has been suggested to be involved in the dehydration and subsequent intramolecular (or intermolecular, in the case of quartromicins) Diels–Alder reaction, but it is still not clear whether such processes are catalyzed or spontaneous (e.g., a similar gene was not found in the case of abyssomicin). It should be noted that similar Diels–Alder reactions have been proposed for the biosynthesis of spirotetronic sesterterpenes ircinianin and wistarin [39]. In this case, the unprecedented occurrence of both wistarin enantiomers in nature may imply that this process is enzyme catalyzed. Finally, feeding/NMR experiments with versipelostatin imply the intermediacy of a glycerol unit in its biosynthesis, although no genetic data are still available [40].



Scheme 1.3 Biosynthetic route toward spirotetronates.

1.3
5-Ylidene Tetronic Natural Products

1.3.1
Pulvinic Acids and Pulvinones

The representative examples of this family, as shown in Figure 1.1, are pulvinic acids (X = OH), vulpinic acids (X = OMe), and pulvinones (analogs lacking carboxyl or ester group). These compounds constitute a large group of 5-arylidenetetronates and can be extracted from lichenous and higher fungal sources [2a]. Since the pioneering synthesis of vulpinic acid (**24**) by Volhard in 1894 [41], the total synthesis of many members of this family has been described (Figure 1.1).

From 1894 (Volhard's syntheses of **23** and **24**) until the early 1970s, hydrolysis (for pulvinic acids) or methanolysis (for vulpinic acids) of dilactones of type **38** was the main synthetic strategy (Scheme 1.4) [42]. Volhard's dilactone approach was based on the condensation of diethyl oxalate and phenyl acetonitrile and subsequent acidic hydrolysis and dehydration [41]. Asano and Kameda [43] and Akermak [44] extended the methodology for unsymmetrical dilactones by the successive use of different aryl acetonitriles in the condensation step, but the final formation of two pulvinic isomers (**39** and **40**, $Ar_1 \neq Ar_2$) after dilactone opening was unavoidable. Alternative routes to access dilactones **38** have also been developed [45], with the most important being the biosynthetically inspired oxidative rearrangement of aryl hydroxyquinones such as polyporic acid **9** [45b,c] or atromentin **10** [45a]. Among the various conditions used for this oxidation, Moore's protocol [dimethyl

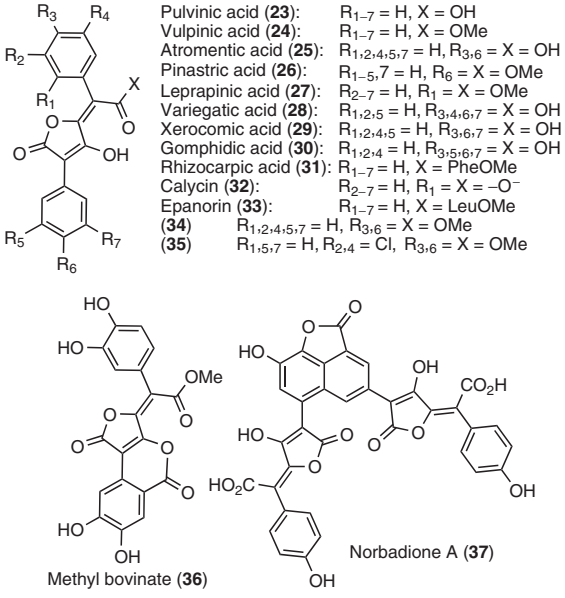
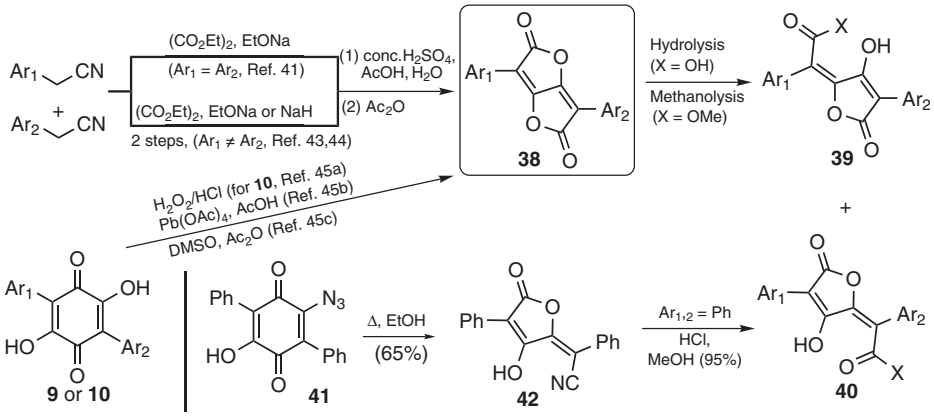


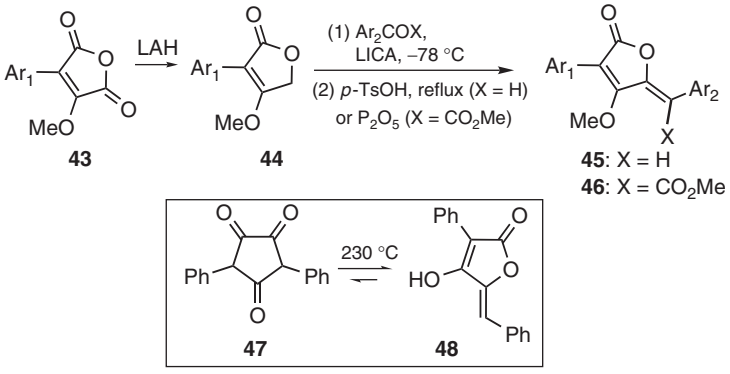
Figure 1.1 Structures of naturally occurring pulvinic acids.

sulfoxide/acetic anhydride (DMSO/Ac_2O)] was and still is the most widely used (i.e., Steglich's synthesis of methyl bovinate (**36**) in 2008 [46]). Dilactone strategy has been the basis for the total synthesis of a variety of pulvinic/vulpinic acids, such as atromentic (**25**) [42a], pinastric (**26**) [42b,c], leprapinic (**27**) [42d], variegatic (**28**) [42e], xerocomic (**29**) [42f], gomphidic (**30**) [42g], rhizocarpic (**31**) [42h] acids, calycin (**32**) [44], and epanorin (**33**) [42h]. Nevertheless, with the only exception of Moore's synthesis of vulpinic acid based on the thermal rearrangement of azidoquinone **41** to pulvinonitrile **42** followed by hydrolysis (Scheme 1.4) [47], no regiospecific methods have been reported during 80 years after Volhard's introduction of dilactone strategy.



Scheme 1.4 Pulvinic acid synthesis from dilactones **38** and azidoquinone **41**.

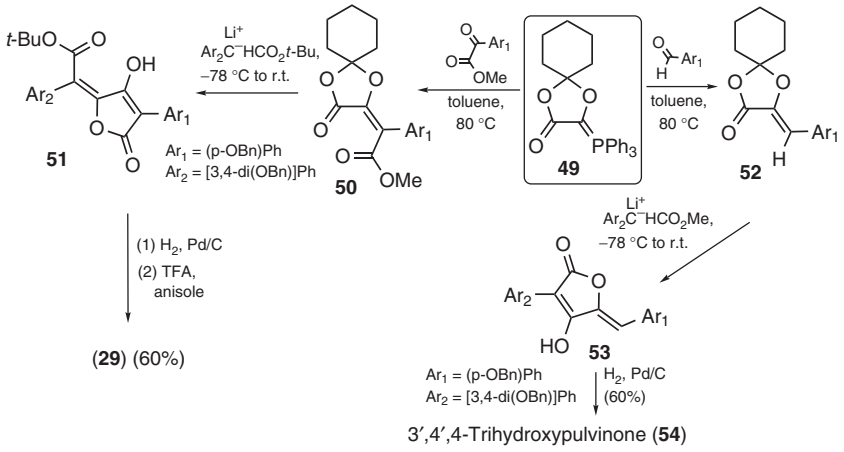
In 1975, Pattenden *et al.* reported the first regiospecific synthesis of permethylated pulvinic acids **46** [48] and pulvinones **45** [49] by condensation of **44** with aroyl formates and aryl aldehydes, respectively, followed by dehydration (Scheme 1.5). Interestingly, Pattenden's pioneering work allowed the first total synthesis of naturally occurring pulvinones, first isolated from natural sources in 1973 [3b] but



Scheme 1.5 Syntheses of pulvinic derivatives by Pattenden and Claisen.

already produced by Claisen in 1895 [50] from the thermal rearrangement of a symmetrical trione (**47** → **48**, Scheme 1.5).

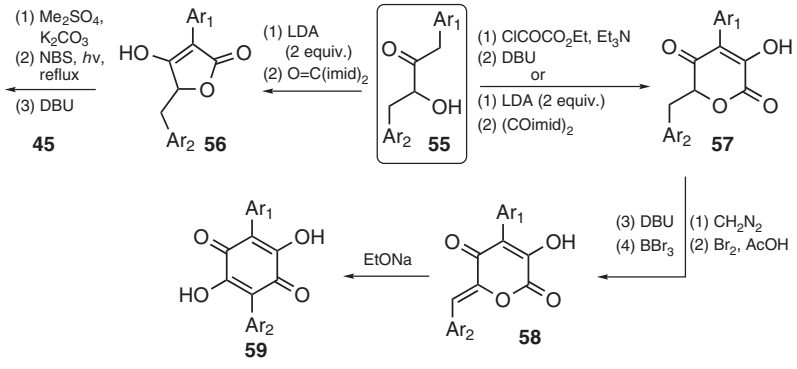
In 1984, Ramage *et al.* [51] have demonstrated that dioxolane phosphorane **49** can lead to pulvinic acids and pulvinones after olefination with α-ketoesters or aldehydes, respectively, and Claisen condensation with arylacetic esters (Scheme 1.6). In the case of pulvinic acids [51b], regiospecificity can be controlled by proper choice of ester groups, as this was outlined in the synthesis of xerocomic acid (**29**). Ramage's protocol was also used for the synthesis of multicolanic acid [51c], a tetronic metabolite found in *Penicillium multicolor*, which was previously synthesized by Pattenden via maleic anhydride chemistry [52]. In 2007, Bruckner's group modified Ramage's protocol by using similar phosphonates in order to replace the olefination step by a Horner–Wadsworth–Emmons (HWE) reaction [53].



Scheme 1.6 Syntheses of **29** and **54** by Ramage.

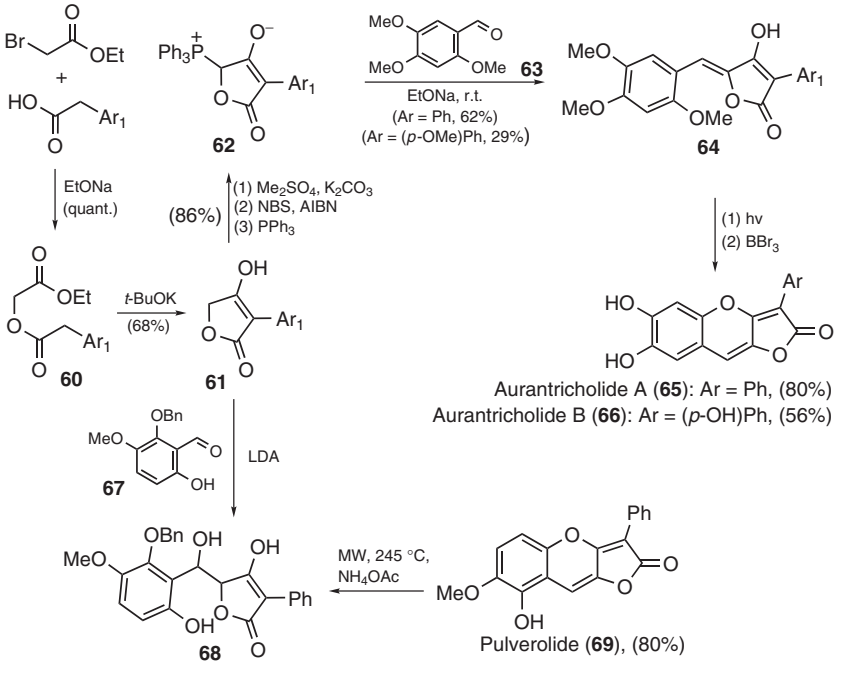
Working independently, Gill and Pattenden employed benzylacyloins (**55**) as synthetic precursors to obtain grevillins (**58**, pulvinic acids biosynthetic progenitors) and pulvinones **45**, (Scheme 1.7). Synthesis of pulvinones by Gill [54] was based on a previous report by Smith's group [55] and relies on the condensation of unsymmetrical bis-benzyl acyloins with carbonyldiimidazole. Similar condensation of **55** with oxalyldiimidazole (Gill's method [54]) or esterification with ethyloxalyl chloride followed by Dieckmann condensation (Pattenden's method [56]) led to grevillins (**58**) that rearrange to quinones **59** [57], affording pulvinic acids after application of Moore's protocol [45c].

In 1985, Campbell *et al.* [58] employed a Dieckmann condensation strategy to the synthesis of pulvinones. By this route, Campbell prepared tetronic acid **61** that can be either transformed to phosphorane **62** and utilized in Wittig reactions or condensed with arylaldehydes that can afford pulvinones after dehydration. The first route led Steglich's group in 2000 to the total synthesis of aurantricholides A (**65**) and B (**66**), two minor pigments of toadstool *Tricholoma aurantium* [59], whereas



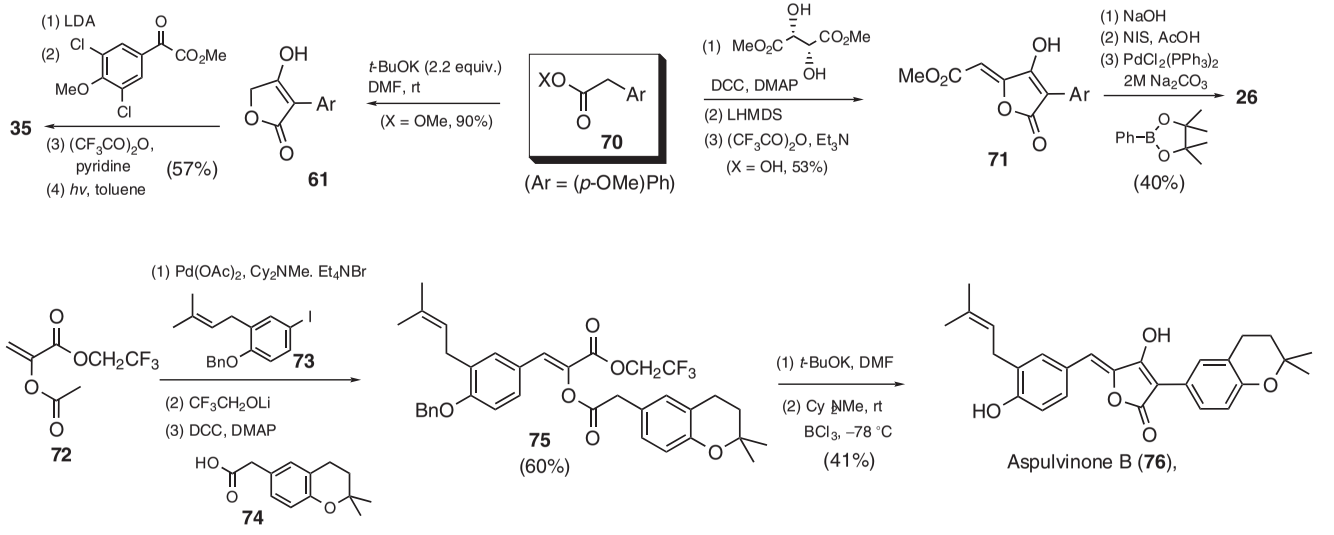
Scheme 1.7 Use of benzylacyloins in the synthesis of pulvinic derivatives.

the second one was used for the total synthesis of pulverolide (**69**), a pigment isolated from *Pulveroboletus ravenelii*, by Yang *et al.* [60] in 2010 (Scheme 1.8).



Scheme 1.8 Total syntheses of aurantricholides A and B and pulverolide.

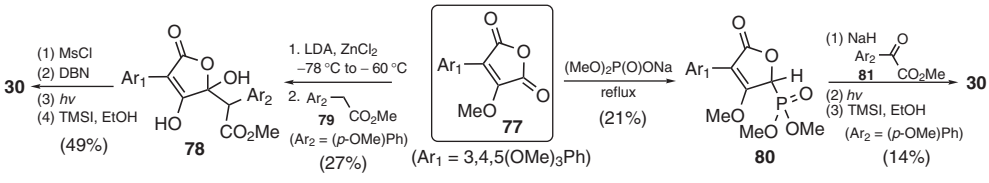
Furthermore, the Dieckmann condensation strategy has also been employed in the synthesis of pulvinic acids [61]. Interestingly, 30 years after the first relevant report by Weinstock *et al.* [61a], the group of Le Gall [61b] presented a versatile route for that purpose. Le Gall improved the synthesis of tetronic acid **61**, previously prepared by Campbell *et al.* [58], by devising a tandem transesterification/Dieckmann



Scheme 1.9 Total syntheses of aspulvinone B and pulvinic acids **26** and **35**.

condensation and offered the first total synthesis of **35** after application of Pattenden's arylidenation (Scheme 1.9) [48a]. Moreover, Le Gall *et al*. [61c] demonstrated that the use of aryl acetates of dimethyl tartrate can lead to tetronic acid **71** that can be coupled by aryl groups after iodination and Suzuki coupling reaction, thus affording pinastric acid (**26**). Recent reports on improved pulvinone synthesis based on Dieckmann condensation have also appeared [62] with that of Brückner's group succeeding on the total synthesis of several naturally occurring aspulvinones (i.e., aspulvinone B, Scheme 1.9) [62a]. Brückner introduced aryl groups of aspulvinones before the Dieckmann condensation by using a Heck reaction to 2-acetoxyacrylate **72** and subsequent esterification with arylacetic acids.

In 1991, Pattenden exploited the inherent regioselectivity of nucleophilic additions on β-methoxy maleic anhydrides to prepare gomphidic acid (**30**) by two different routes (Scheme 1.10) [63]. The first one involves an HWE reaction between phosphonate **80** and aryl pyruvate **81** [63b], and the second one is based on a Reformatsky-type reaction of **77** with zinc enolates derived from aryl acetate **79** [63c].



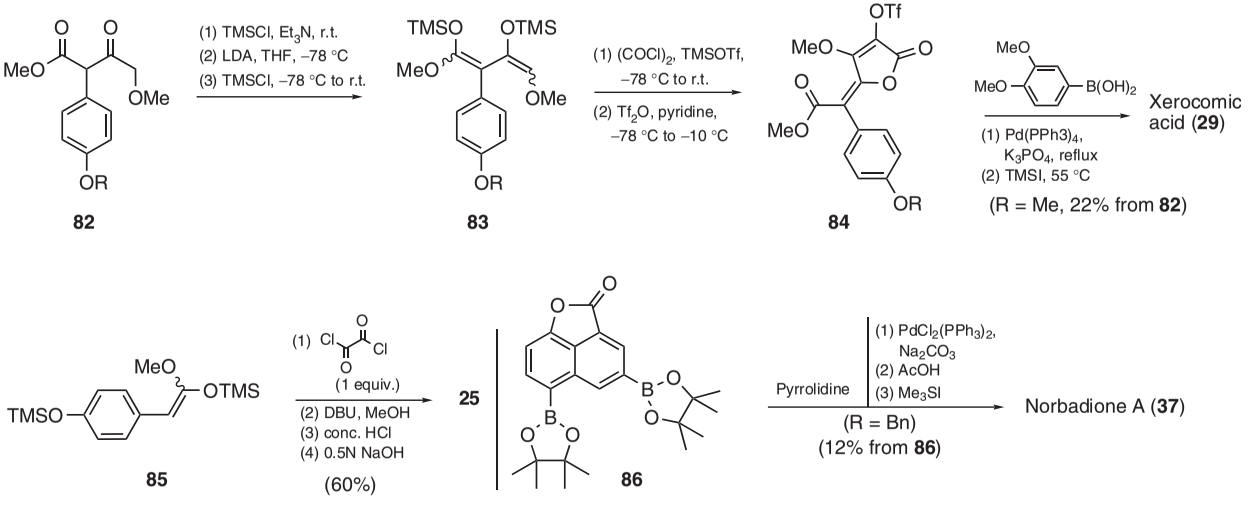
Scheme 1.10 Total syntheses of gomphidic acid by Pattenden.

In a series of reports, Langer's group studied the synthesis of pulvinic acids via a TMSOTf-catalyzed [3+2] cyclization of 1,3-bis-(trimethylsilyloxy)-1,3-dienes (e.g., **83**) with oxalyl chloride followed by Suzuki coupling of product triflates (Scheme 1.11) [64]. Langer's versatile method was applied to the synthesis of almost all natural pulvinic acids (e.g., xerocomic acid **29**), including norbadione A (**37**) by Le Gall *et al*. [65]. In a modification of Langer's protocol, Mioskowski dimerized simple silyl ketene acetals (e.g., **85**) to obtain symmetrical pulvinic acids via an uncatalyzed reaction with $(COCl)_2$ (Scheme 1.11) [66].

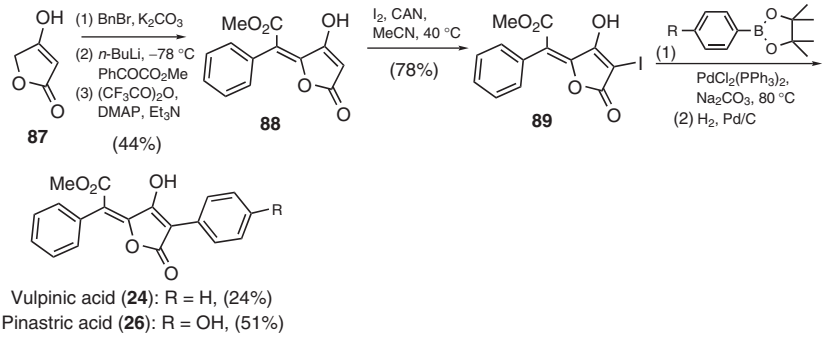
In 2006, Le Gall *et al*. [67] presented a conceptually different approach for the synthesis of pulvinic acids, starting from commercial tetronic acid **87** (Scheme 1.12). The protocol involves application of Pattenden's arylidenylation by aroyl formates, iodination, and aryl coupling by Suzuki reaction. The utility of Le Gall's method was exemplified by the synthesis of vulpinic (**24**) and pinastric (**26**) acid.

1.3.2 Agglomerins

Agglomerins constitute a group of 3-acyl-5-methylidene tetronic acids with antibiotic activity [16]. Synthetic efforts toward agglomerins started by Ley and coworkers



Scheme 1.11 Application of Langer's chemistry to the synthesis of pulvinic derivatives.



Scheme 1.12 Le Gall's synthesis of pulvinic acids.

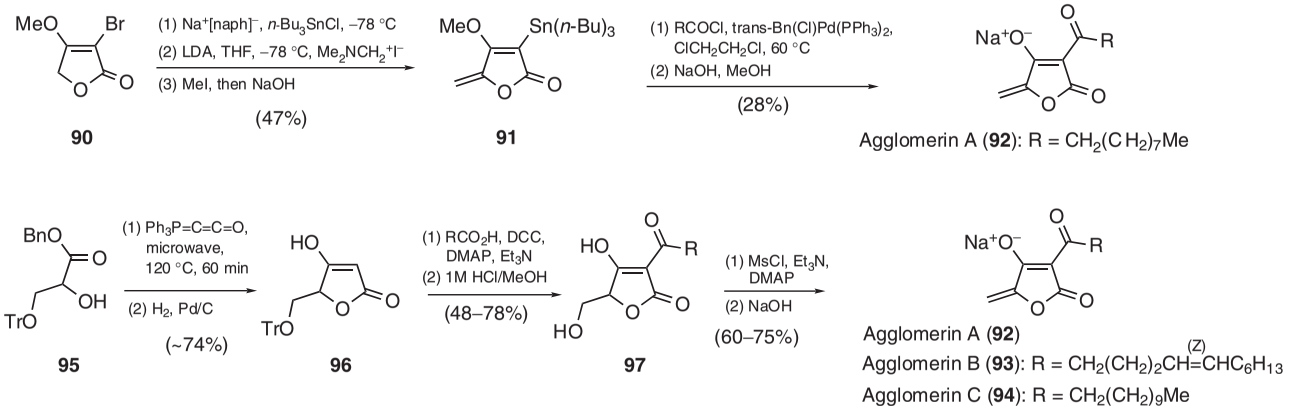
[68] who successfully applied a Pd-catalyzed acylation on stannyl tetronate **91** toward the synthesis of agglomerin A (Scheme 1.13) (**92**). In 2005, Schobert's group prepared agglomerins A–C (**92–94**) following a triphenylphosphoranylidene/glycerate **95** Wittig cyclization and a DCC-mediated 3-acylation of **96** [69], according to Yoshii's protocol (Scheme 1.13) [70].

1.3.3
Tetronomycin

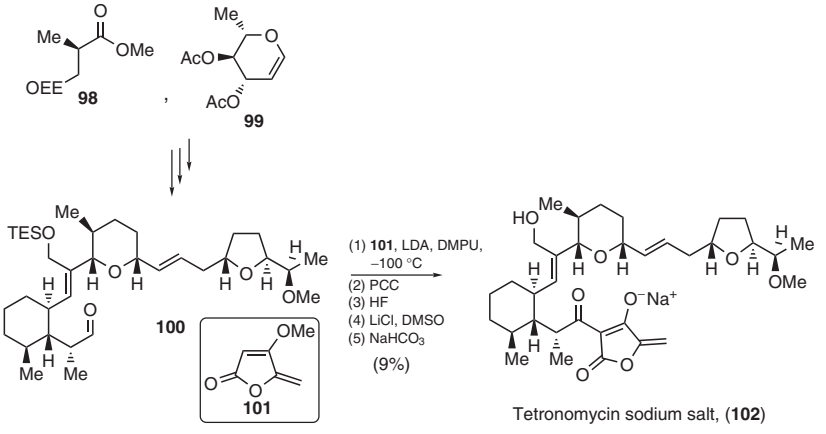
Tetronomycin (**102**), a structurally challenging 3-acyltetronic acid ionophore antibiotic, was isolated from a *Streptomyces* strain in the early 1980s [71]. The only total synthesis reported so far was accomplished in 1992 by Yoshii and coworkers (Scheme 1.14) [72]. By using as chiral building blocks the ethoxyethyl ether **98** and L-rhamnal diacetate **99**, Yoshii reached aldehyde **100**, a suitable precursor for the installation of the tetronic moiety. This was achieved by a reaction with the lithium anion of methyl tetronate **101** at −100 °C that led to the target after pyridinium chlorochromate (PCC) oxidation and careful deprotection.

1.3.4
Stemofoline Alkaloids

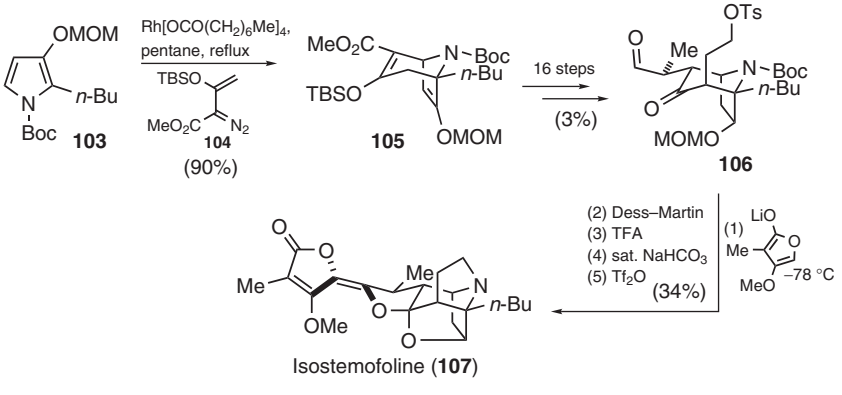
Stemofoline alkaloids constitute a group of natural products isolated from *Stemona* plants that have been used in Chinese and Japanese folk medicines as cough-relief agents and insecticides [73]. These molecules are characterized by a rigid polycyclic core bearing a pendant methyl tetronate. Synthetic attempts toward these targets were mainly focused on the construction of the bridged alkaloid nucleus [74], whereas racemic total synthesis of isostemofoline (**106**) by Kende *et al.* [75] and asparagamine A (**116**) and isodidehydrostemofoline (**117**) by Overman *et al.* [76] have been reported. Kende's synthesis is based on an Rh-catalyzed [4+3] cycloaddition of vinyl diazoester **104** with pyrrole intermediate **103** (Scheme 1.15), whereas Overman's approach utilizes a



Scheme 1.13 Total syntheses of agglomerins A–C.



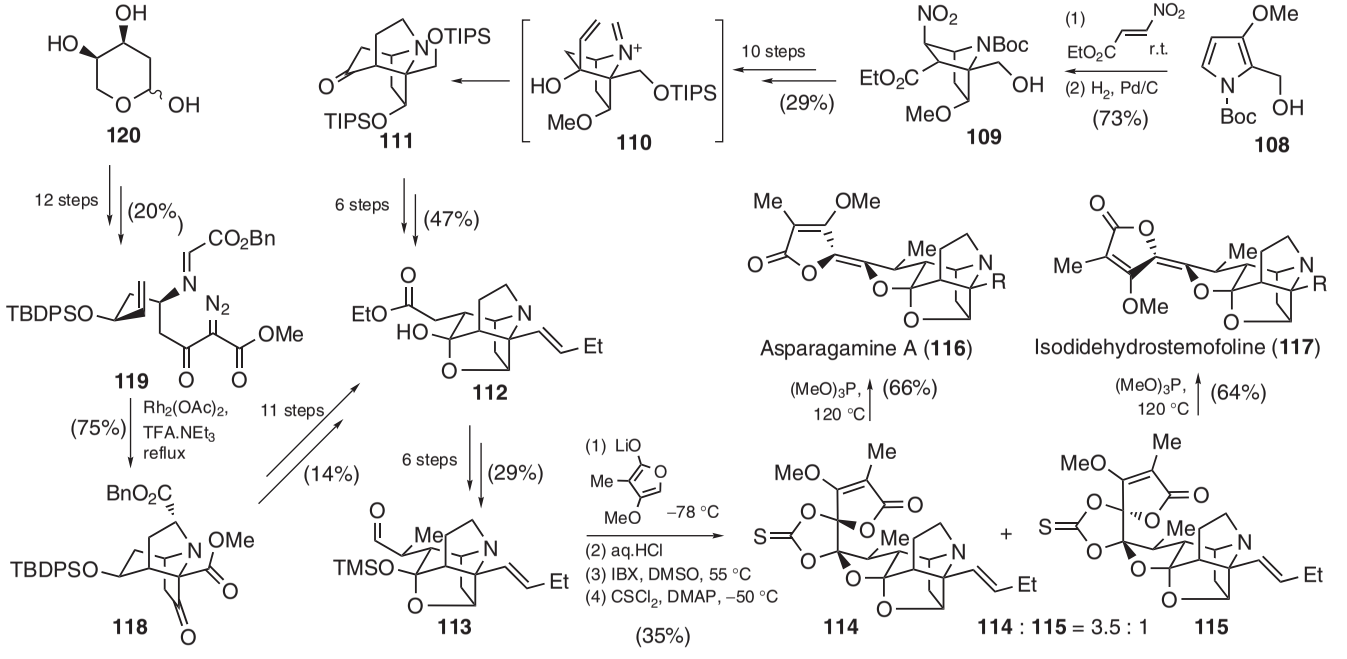
Scheme 1.14 Total syntheses of tetronomycin.



Scheme 1.15 Kende's total syntheses of isostemofoline.

Diels–Alder reaction between ethyl (*E*)-3-nitroacrylate and **108** and an aza-Cope–Mannich reaction as key steps to form the main polycyclic framework (Scheme 1.16).

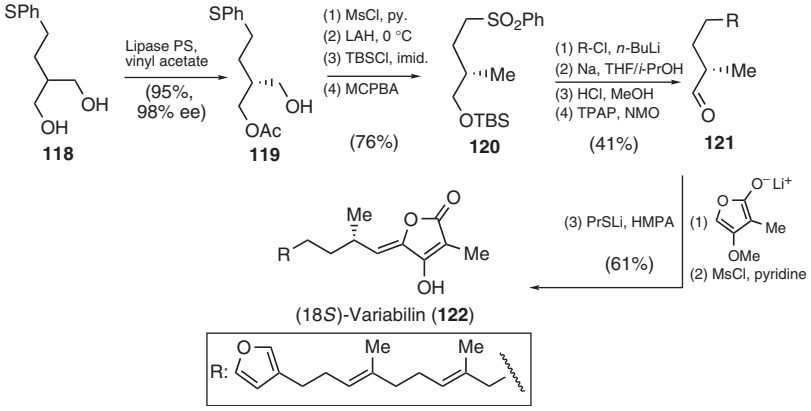
Interestingly, both researches employed the same technique to install the methyl tetronate ring, that is, addition of the lithium anion of 4-methoxy-3-methyl-2(5*H*)-furanone to an aldehyde (**106** or **113**), but Kende used a Tf_2O-mediated dehydration to finish the synthesis, whereas Overman obtained the final structures after a Corey–Winter reaction to form the dialkoxy alkene unit (Scheme 1.16). In 2012, Martin *et al.* [77] managed to prepare enantioselectively Overman's intermediate **113** by an elegant cascade of reactions that culminates in the intramolecular dipolar cycloaddition of **119**, prepared from 2-deoxy-D-ribose (**120**) (Scheme 1.16).



Scheme 1.16 Racemic and enantioselective syntheses of **116** and **117**.

1.3.5
Variabilin

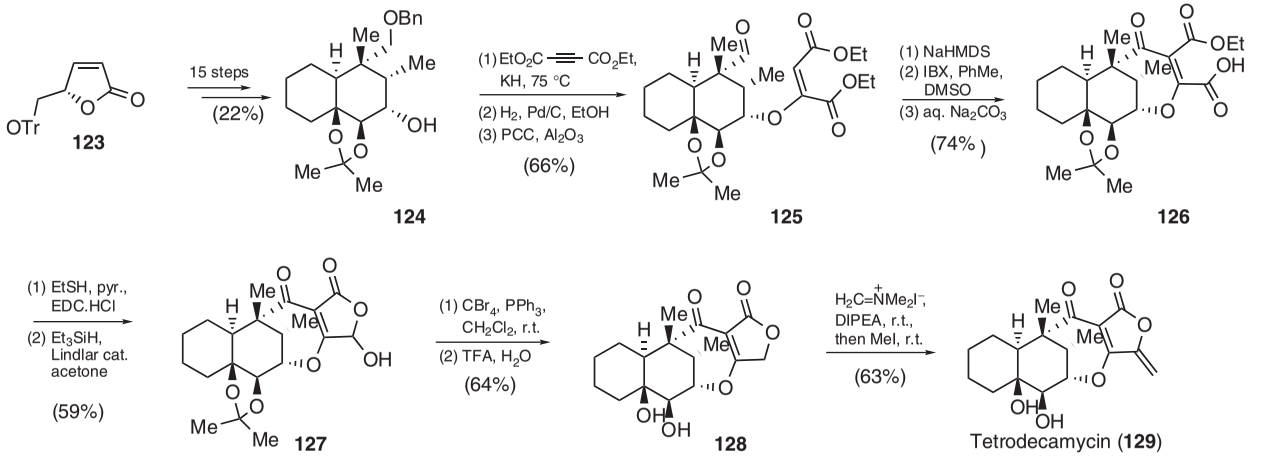
The bioactive marine furanosesterterpene tetronic acid (18*S*)-variabilin (**122**) [78] has been synthesized by Takabe *et al.*, 30 years after its first isolation (Scheme 1.17) [79]. Stereochemical control was achieved by enzymatic desymmetrization of propanediol **118**, whereas the tetronic core was introduced via an aldol condensation/mesylation/elimination sequence.



Scheme 1.17 Total synthesis of variabilin.

1.3.6
Tetrodecamycin

Tetrodecamycin (**129**) is a polyketide antibiotic isolated in 1994 from the culture broth of *Streptomyces nashvillensis* MJ885-mF8 and was found to exhibit promising antibacterial activity against Gram-positive bacteria [80]. Owing to its challenging decalin core structure doubly anchored with a 5-methylene tetronate, a number of model studies have been published by the groups of Paintner, Barriault, and Tchabanenko mainly focused on the decalin core of the molecule [81], whereas Paintner investigated also the attachment of tetronic ring by using a novel 3-hydroxyalkylation reaction of boron 4-methoxy-2-furanolates [82]. The first enantioselective total synthesis of tetrodecamycin reported by Tatsuta *et al.* [83] in 2006, included a very interesting strategy to introduce a tetronate ring on the decalin structure **124** obtained from carbohydrate derivative **123**. According to Scheme 1.18, compound **124** was transformed in three steps to aldehyde **125** that was annulated to afford the third ring of the target via a sodium hexamethyldisilazide (NaHMDS)-mediated Baylis–Hillman type reaction. Finally, the inventive formation of the tetronic ring of tetrodecamycin relies on the reduction of carboxylic acid **126** that leads to hemiacetal **127** and a novel deoxygenation operation using CBr_4 and PPh_3.

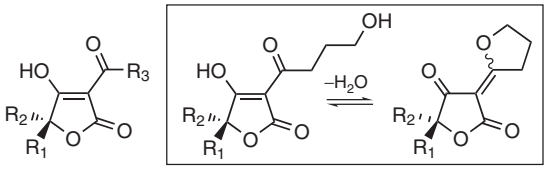


Scheme 1.18 Total synthesis of tetrodecamycin.

1.4
5-Monosubstituted Tetronic Natural Products

1.4.1
Carlic, Carlosic, Carolic, Carolinic, and Viridicatic Acids

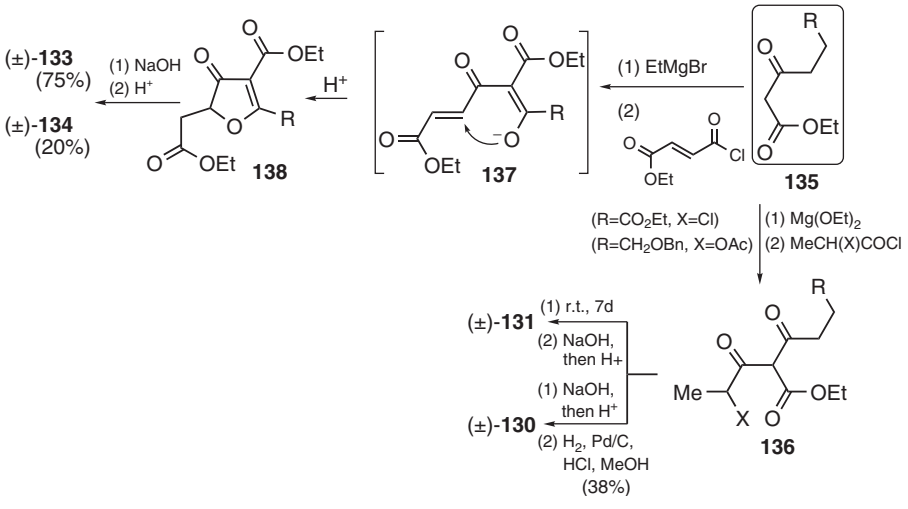
A number of fungal 5-substituted 3-acyl tetronic acid metabolites, as shown in Scheme 1.19, have attracted significant attention during the development of new synthetic protocols in the field of tetronic acids.



Carolic acid (**130**): $R_1 = H$, $R_2 = Me$, $R_3 = CH_2(CH_2)_2OH$
Carolinic acid (**131**): $R_1 = H$, $R_2 = Me$, $R_3 = CH_2CH_2CO_2H$
Carlic acid (**132**): $R_1 = CH_2CO_2H$, $R_2 = H$, $R_3 = CH_2(CH_2)_2OH$
Carlosic acid (**133**): $R_1 = CH_2CO_2H$, $R_2 = H$, $R_3 = CH_2CH_2Me$
Viridicatic acid (**134**): $R_1 = CH_2CO_2H$, $R_2 = H$, $R_3 = CH_2(CH_2)_3Me$

Scheme 1.19 Structures of carolic, carolinic, carlic, carlosic and viridicatic acids.

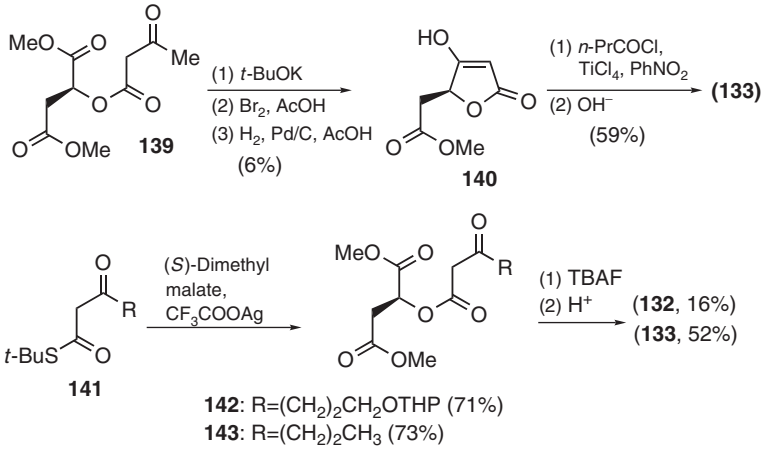
The first syntheses of racemic carolinic acid (**131**) by Haynes *et al.* [84], carolic acid (**130**) by Sudo *et al.* [85], and carlosic (**133**) and viridicatic (**134**) acids by Svendsen and Boll [86] were based on a C5–O1 disconnection of the tetronic ring. The main difference of these strategies is that cyclization by Haynes and Sudo proceeds via an intramolecular substitution, whereas Svendsen and Boll perform



Scheme 1.20 First racemic syntheses of **130**, **131**, **133**, and **134**.

a Michael addition for the same purpose (Scheme 1.20). Notable feature of the latter syntheses is the alkaline-induced rearrangement of the initial condensation products (**138**) to the final tetronic acid metabolites **133** (R = *n*-propyl) and **134** (R = *n*-pentyl).

Aiming to a C3–C4 stereoselective disconnection approach, Bloomer and Kappler [87] managed to cyclize malic derivative **139**, as shown in Scheme 1.21. Deacetylation toward **140** followed by an *O*-acylation/Fries rearrangement sequence with butyryl chloride/$TiCl_4$/$PhNO_2$ afforded (*S*)-carlosic acid [87b]. Following similar protocols, the syntheses of (*R*)-carolic acid and (±)-carlic acid have also been achieved [87a,c]. Some years later, Ley *et al.* [88] performed the synthesis of (*S*)-carlosic and (*S*)-carlic acids by a fluoride-induced cyclization of malic derivatives **142** and **143** derived from the transesterification of β-ketothiesters **141** with (*S*)-dimethyl malate (Scheme 1.21).

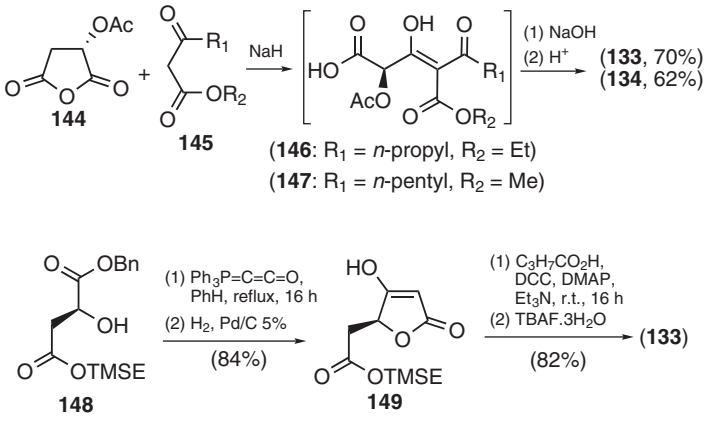


Scheme 1.21 Use of malic derivatives in the synthesis of **132** and **133**.

An extension of the use of malic derivatives by Mitsos *et al.* [89] includes the regioselective ring opening of malic anhydrides **144** by β-ketoesters **145** that successfully leads to (*S*)-carlosic and (*S*)-viridicatic acids (Scheme 1.22). Finally, Schobert and Jagusch [90] employed their methodology of constructing tetronic structures from α-hydroxyesters and $Ph_3P{=}C{=}C{=}O$ to the efficient synthesis of (*S*)-carlosic acid, as shown in Scheme 1.22.

1.4.2
RK-682

RK-682 (**152**), a simple 3-alkanoyl-5-hydroxymethyltetronic acid, was structurally elucidated by Sodeoka *et al.* [91] through its total synthesis starting from the D-mannitol derived glycerate **150** and subsequent application of Ley's synthetic protocol (Scheme 1.23) [88]. Two years later, Ohta and coworkers [92] prepared



Scheme 1.22 Synthesis of **133** and **134** by Mitsos and Schobert.

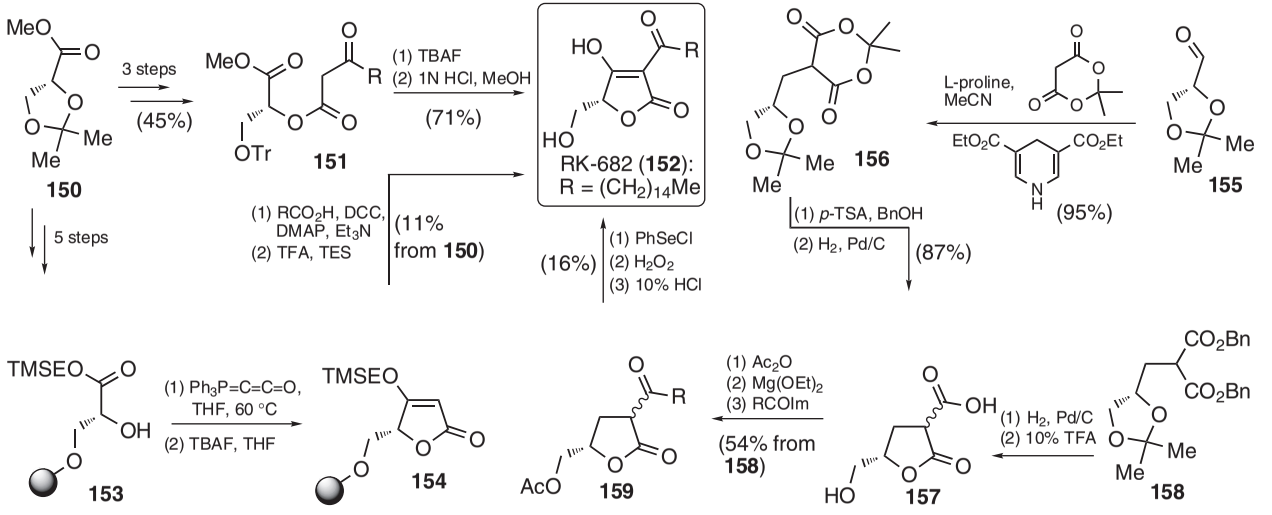
RK-682 and other related HIV-1 protease inhibitors by a modified Masamune acylation of lactone **157** (**157** → **159**) followed by a phenylselenylation strategy to create the double bond of the tetronate. The convergence of Ohta's strategy was recently recognized by Ramachary's group who developed an organocatalytic method for the synthesis of intermediate **156**, also providing a formal synthesis of RK-682 as well as agglomerins (**92–94**) [93]. As RK-682 can be considered as a hydrated agglomerin-related precursor, Schobert and Jagusch [69] applied their protocol for agglomerin synthesis to the preparation of RK-682 on solid phase (Scheme 1.23).

1.4.3
Massarilactone B

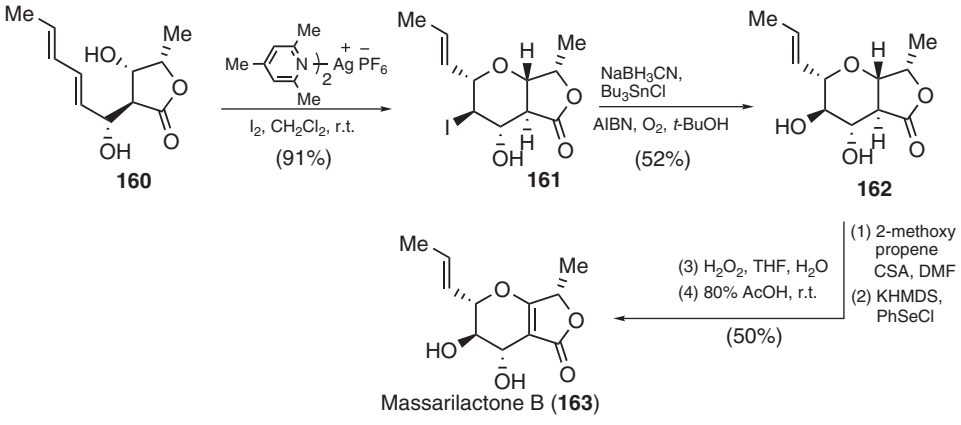
Massarilactone B (**163**), a bicyclic tetronate with antibacterial activity [94], was synthesized by Snider and Gao, as shown in Scheme 1.24 [95]. Key features of the synthesis are the highly diastereoselective iodoetherification of intermediate **160** and the establishment of the tetronic core at **162** through an elimination process.

1.4.4
Annularins F, G, and H

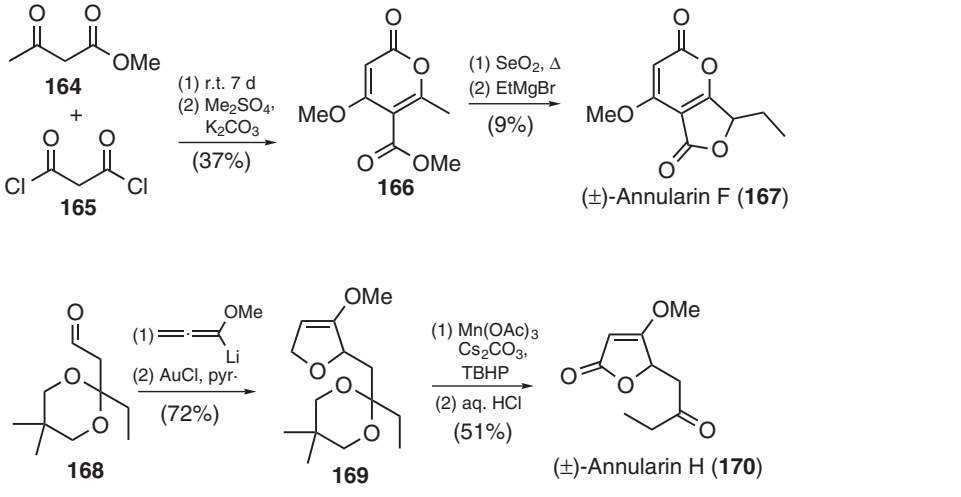
Annularins F (**167**), G (**172**), and H (**170**) are three polyketide metabolites, recently isolated from the organic extracts of the freshwater fungus *Annulatascus triseptatus* [96]. The first racemic synthesis reported for the antibacterial annularin F by Hsung *et al.* [97] involved a condensation of **164** and **165** toward pyrone **166** that was converted to **167** in two steps (Scheme 1.25). In 2007, Reissig *et al.* [98] produced racemic annularin H by a synthetic route based on the addition of lithium methoxyallene to aldehyde **168** followed by Au(I)-induced cyclization (Scheme 1.25).



Scheme 1.23 Various synthetic routes toward RK-682.



Scheme 1.24 Total synthesis of massarilactone B.

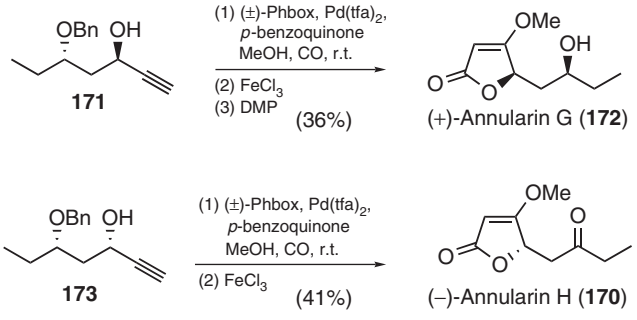


Scheme 1.25 Syntheses of racemic annularins F and H.

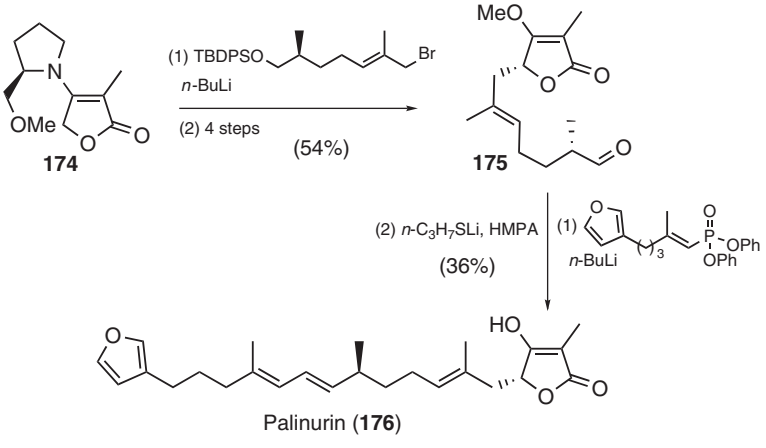
In 2010, Kato *et al.* [99] disclosed an enantioselective synthesis of annularin G and H, based on a Box-Pd(II)-catalyzed methoxycarbonylation of diastereoisomeric propargylic alcohols **171** and **173** (Scheme 1.26).

1.4.5 Palinurin

Palinurin (**176**), a linear furanosesterpene isolated from *Ircinia* sponges with anti-inflammatory and antibacterial properties [100], has been synthesized in 2009 by Fall's group [101]. The key step for the construction of the chiral tetronic acid moiety relies on the use of chiral pyrrolidine **174** (Scheme 1.27).



Scheme 1.26 Enantioselective synthesis of annularins G and H.



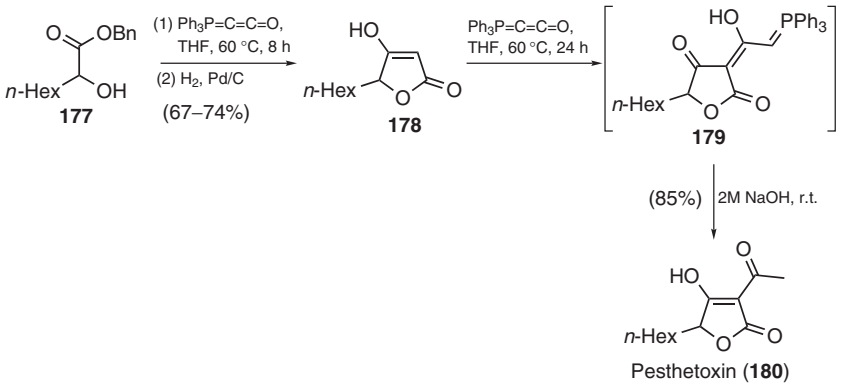
Scheme 1.27 Total synthesis of palinurin.

1.4.6
Pesthetoxin

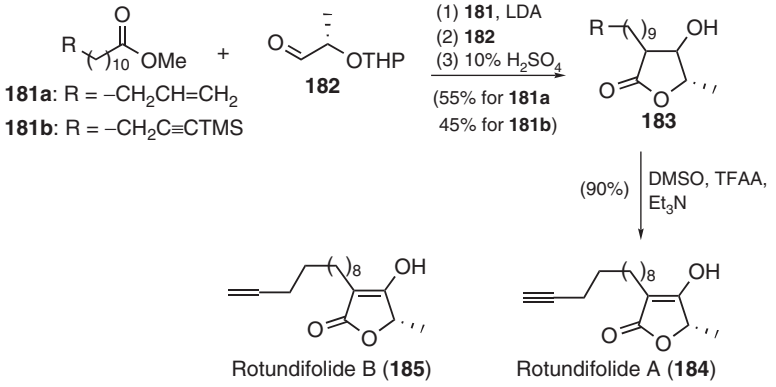
Pesthetoxin (**180**), a leaf necrosis inducing metabolite of the gray blight fungus *Pestalotiopsis theae* regularly infecting tea crops [102], was synthesized in a racemic form by Schobert *et al.* [103] in 2006 via the successive condensation of **177** with 2 equiv. of $Ph_3P{=}C{=}C{=}O$ and subsequent hydrolysis (Scheme 1.28).

1.4.7
Rotundifolides A and B

Rotundifolides A (**184**) and B (**185**), isolated from the bark of *Litsea rotundifolia* var. *oblongifolia*, were synthesized by the same group by a condensation of lactaldehyde **182** with suitable ester enolates and subsequent oxidation [104] (Scheme 1.29).



Scheme 1.28 Synthesis of racemic pesthetoxin.



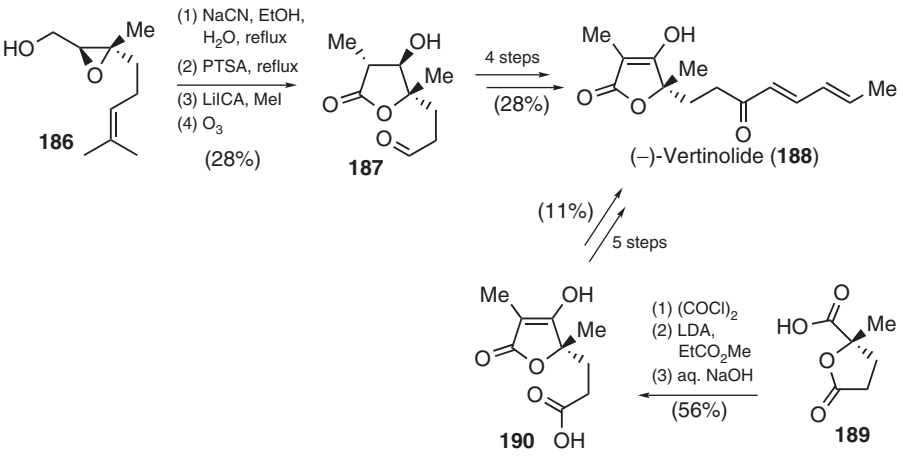
Scheme 1.29 Total synthesis of rotundifolides A and B.

1.5
5-Disubstituted Tetronic Natural Products

1.5.1
5-Dialkyl Tetronic Natural Products

1.5.1.1 Vertinolide

(−)-Vertinolide (**188**), a "vertinoid" fungal metabolite isolated from *Verticillium intertextum* in 1982 by Dreiding *et al.*, was first synthesized 1 year later by Ganem and Wrobel [105]. Special feature of their synthesis was the use of chiral sharpless epoxide **186** to provide vertinolide's precursor **187** after epoxide opening, lactonization, methylation, and ozonolysis (Scheme 1.30). The next year, Takaiwa and Yamashita [106] presented an alternative protocol based on homologation of **189** with the anion of methyl propanoate, followed by hydrolysis and relactonization to assemble vertinolide's core structure **190** (Scheme 1.30. In 1992, Schmidt *et al.* [107] synthesized Takaiwa's intermediate **190** by application of a stereoselective



Scheme 1.30 Vertinolide syntheses by Wrobel and Takaiwa.

version of his reaction between β-alkoxy vinyl carbanions and ketones toward tetronic acids.

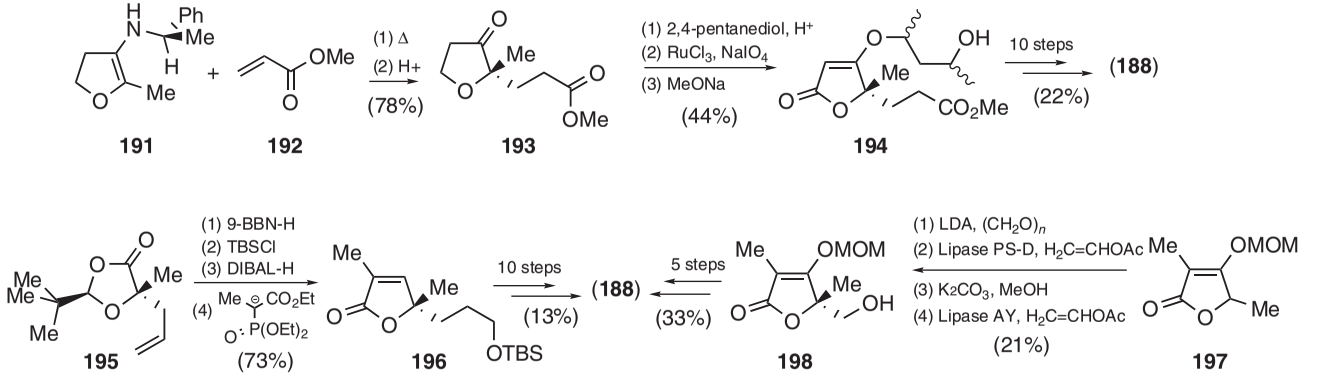
In 1992, Desmaële utilized enamine chemistry in a Michael addition to obtain chiral precursor **193** that gave vertinolide's tetronic ring (**194**) after ketalization, oxidation to lactone, and elimination (Scheme 1.31) [108]. After 4 years, Matsuo and Sakaguchi [109] employed their chiral 1,3-dioxolan-4-one **195** to obtain the central unsaturated lactone **196** after side-chain functionalization and condensation with triethyl-2-phosphonopropionate derived anion. Finally, in 2006, Takabe and coworkers [110], based on their previous work on the synthesis of racemic vertinolide, applied a lipase-catalyzed resolution on a 5-hydroxymethylene derivative of **197** to reach the natural enantiomer after five more synthetic steps (Scheme 1.31).

1.5.1.2 **Papyracillic Acid B**

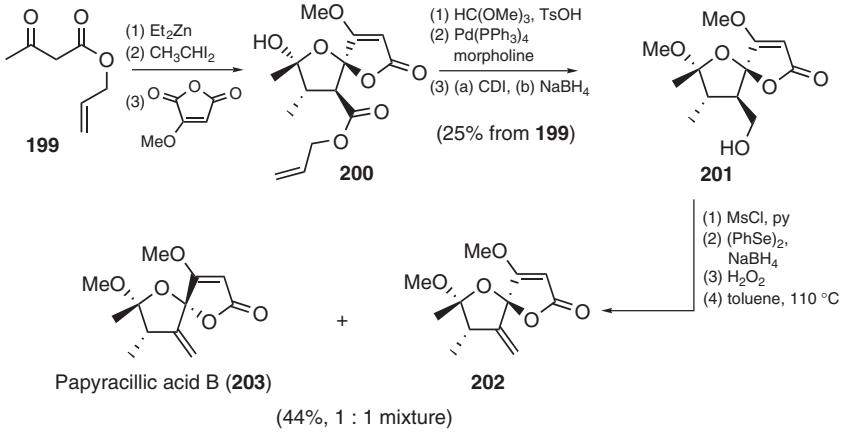
Papyracillic acid B (**203**), isolated from an endophytic fungus *Microsphaeropsis* sp., is a penicillic acid analog containing a spirofused cyclic ketal core appended with an exocyclic alkene [111]. Very recently, its racemic synthesis has been achieved by Zercher *et al*. [112] via a Zn-carbenoid-mediated chain extension–acylation reaction (Scheme 1.32). At the last step of Zercher's synthesis, paparycillic acid is obtained as 1 : 1 epimeric mixture with its C4 epimer, probably through an epimerization facilitated by exocyclic methylene group.

1.5.1.3 **Bisorbibutenolide**

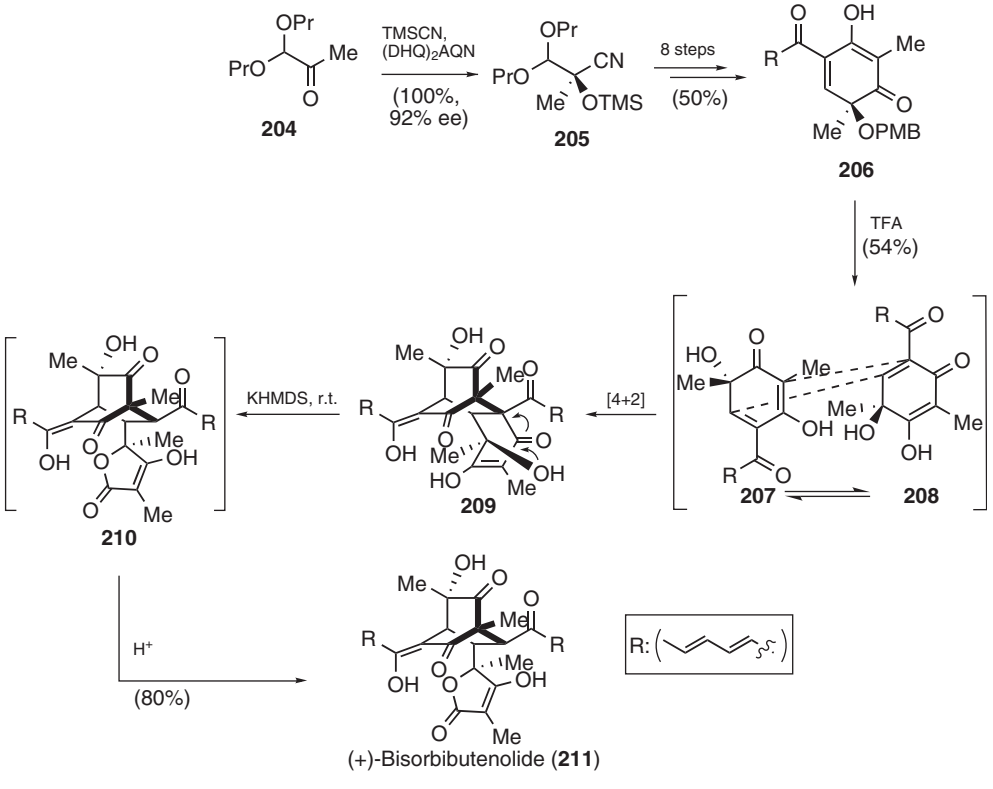
Bisorbibutenolide (or bislongiquinolide) (**211**), a member of sorbicilin-related natural products, is a biosynthetic product of bisorbicillinol (**209**), as it was reported in 1999 by Nicolaou *et al*. [113] in his inspiring work on this class of compounds. On the basis of biosynthetic considerations, Nicolaou converted **209** to **211** on treatment with potassium hexamethyldisilazide (KHMDS) in 80% yield (Scheme 1.33). Later in 2005, Deng *et al*. [114] prepared optically pure



Scheme 1.31 Synthetic routes toward vertinolide.



Scheme 1.32 Total synthesis of papyracillic acid B.



Scheme 1.33 Total synthesis of bisorbibutenolide.

bisorbibutenolide by controlling the stereochemistry of sorbicillinol (**207**) starting from a cinchona $(DHQ)_2AQN$-catalyzed cyanosilylation of **204–205**.

1.5.2 5-Spirotetronic Natural Products

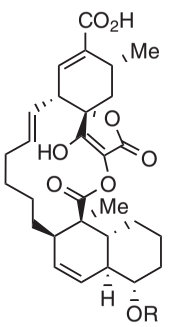
1.5.2.1 Spirotetronic Antibiotics

During the past three decades, a large amount of synthetic effort has been dedicated to studies on the spirotetronic antibiotics shown in Figure 1.2. These molecules share many structural similarities; however, some notable differences can also be detected. For example, all of them are 3-acyl tetronic derivatives with the exception of chlorothricolide (**212**) that bears an oxocarbonyl group at the same position. They all possess a macrocycle of different sizes spanning from the 13-membered ring in tetronolide (**215**) and kijanolide (**216**) to the impressive 32-membered ring of tetrameric quartromicins (**219–220**).

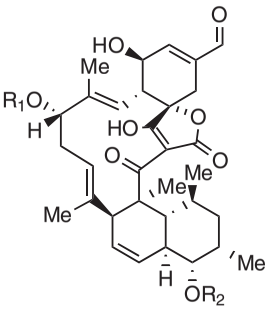
Synthetic studies mainly concern chlorothricolide, kijanolide, tetronolide, and quartromicins, while limited work has been done for versipelostatin (**218**) and spirohexenolide (**219**), the newer members of this family. Synthetic efforts have culminated in one total [115] and two analog syntheses [116, 117] of chlorothricolide, two total [118, 119] and one formal synthesis of tetronolide [120], one synthesis of a kijanolide analog [121] as well as numerous model or fragment syntheses on chlorothricolide [122–127], tetronolide [128–130], kijanolide [131–133], quartromicins [134, 135], versipelostatin [136], and spirohexenolide [137]. The discussion that follows will be limited only in the total and advanced analog syntheses mentioned earlier.

The first synthesis of an advanced analog of a spirotetronic antibiotic (**228**) was presented in 1986 by Ireland and Varney [116]. Ireland reached chlorothricolide's spirotetronic part via a route based on a Diels–Alder cycloaddition of maleic anhydride derivative **221** with 1,3-butadiene and a subsequent Dieckmann cyclization (Scheme 1.34). Coupling of the two chlorothricolide fragments **224** and **225** led to allyl carboxylate **226** that afforded the desired carbon macrocycle after a highly efficient Ireland–Claisen rearrangement. Transformation of **227** including an impressive radical decarboxylation led to the synthesis of protected dihydrochlorothricolide **228**.

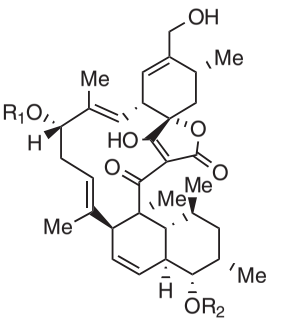
Significant advances in the synthesis of spirotetronic antibiotics were achieved during the following years because of the fundamental contribution of Yoshii and coworkers. In this context, in 1991, Yoshii *et al.* [118] presented the first total synthesis of a spirotetronic antibiotic, namely (+)-tetronolide (**215**). Yoshii performed an enantioselective synthesis of spirotetronic fragment **231** [128e] inspired by previous work of Schmidt on the reactions of vinyl carbanions using organocerium derivatives (Scheme 1.35) [126a]. Coupling of **231** with the octalin fragment **232** (prepared also enantioselectively by a Diels–Alder-based strategy) via an aldol type reaction furnished α-sulfonyl-ω-aldehyde **233** [128a], which was subjected to an elegant base-catalyzed macrocyclization [128c] for the assembly of the target macrocycle. It should be noted that, in 1997, Roush reported alternative



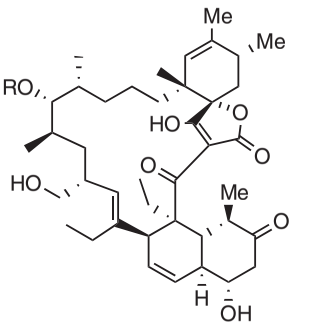
Chlorothricin (**212**): R=H
(–)-Chlorothricolide (**213**): R=A



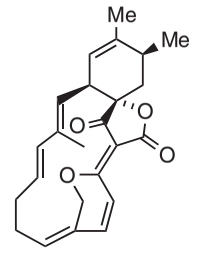
Tetrocarcin A (**214**):
R_1=B, R_2=C (X=H)
(+)-Tetronolide (**215**):
R_1=R_2=H



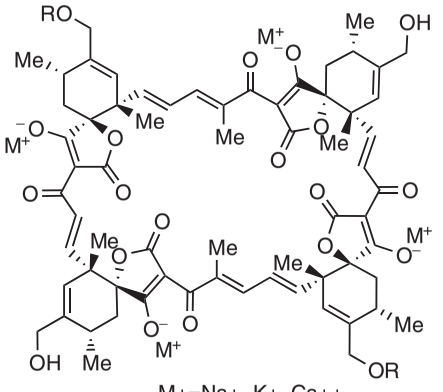
Kijanimicin (**216**):
R_1=B, R_2=C (X=D)
Kijanolide (**217**): R_1=R_2=H



Versipelostatin (**218**): R=E



Spirohexenolide B
(**219**)



M+=Na+, K+, Ca++

Quartromicin A_3 (**219**): R=F
Quartromicin D_3 (**220**): R=H

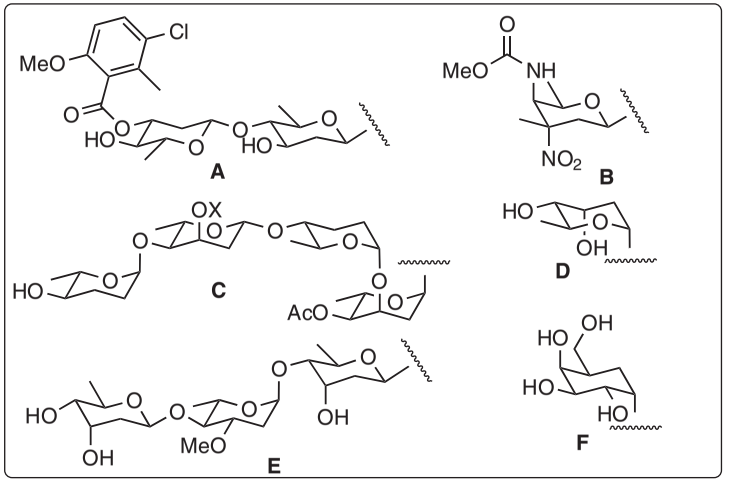
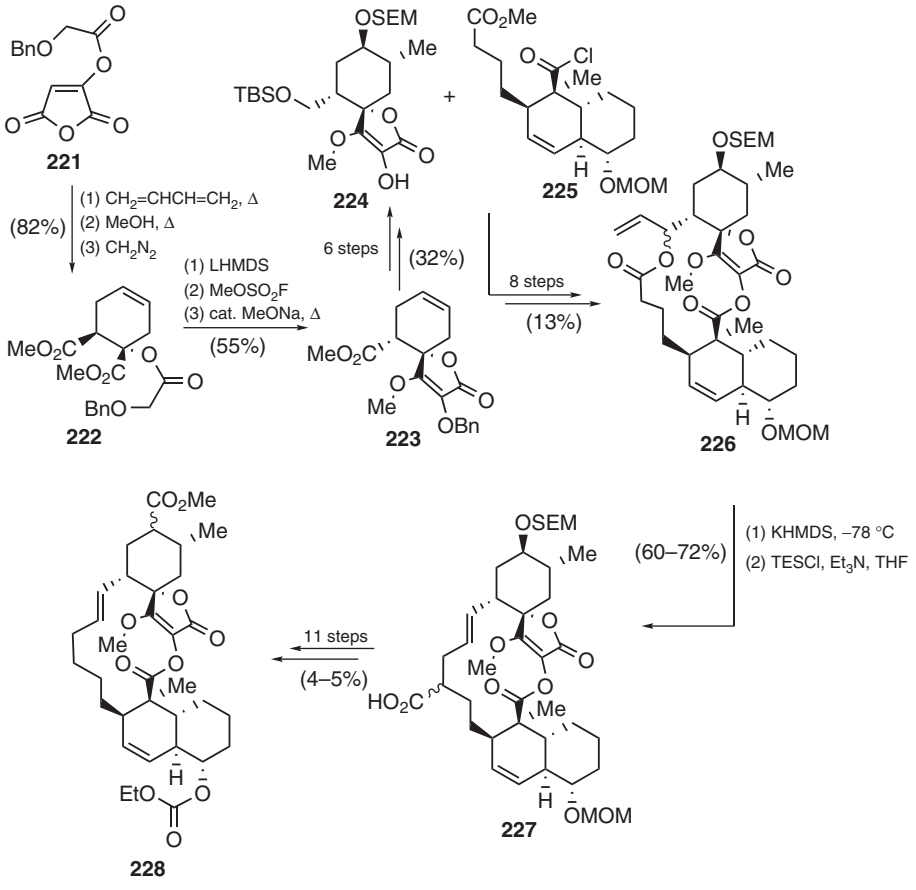


Figure 1.2 Spirotetronic antibiotics.

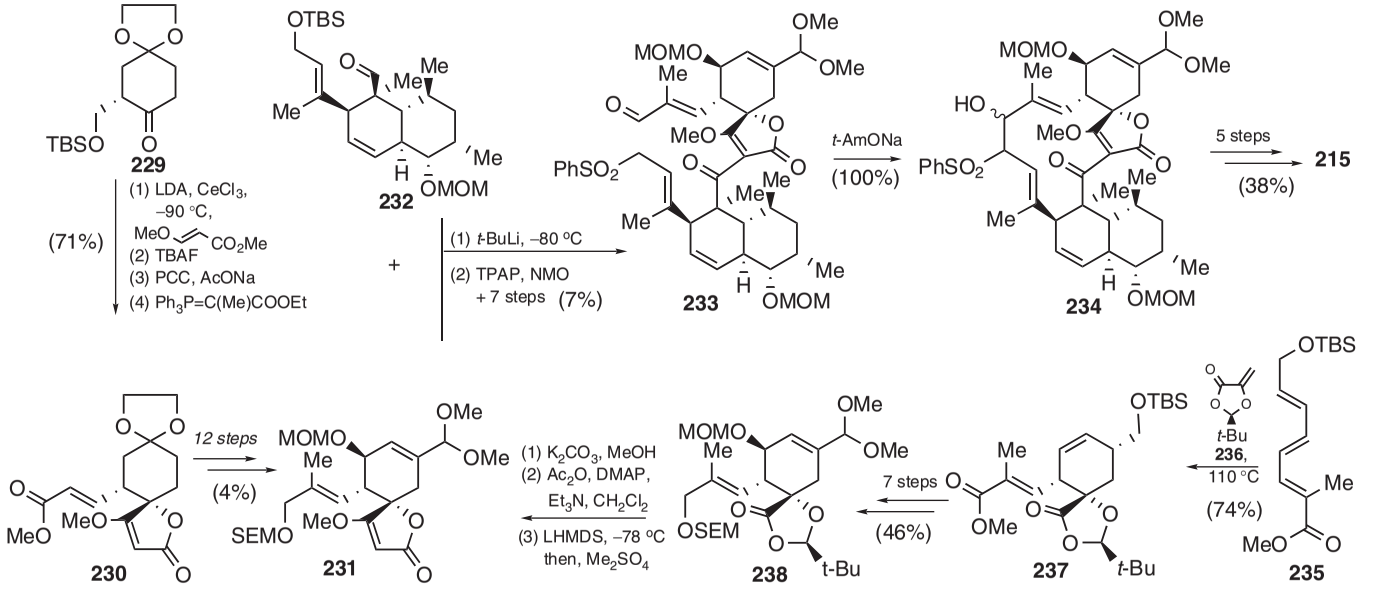


Scheme 1.34 Ireland's synthesis of chlorothricolide's analog **228**.

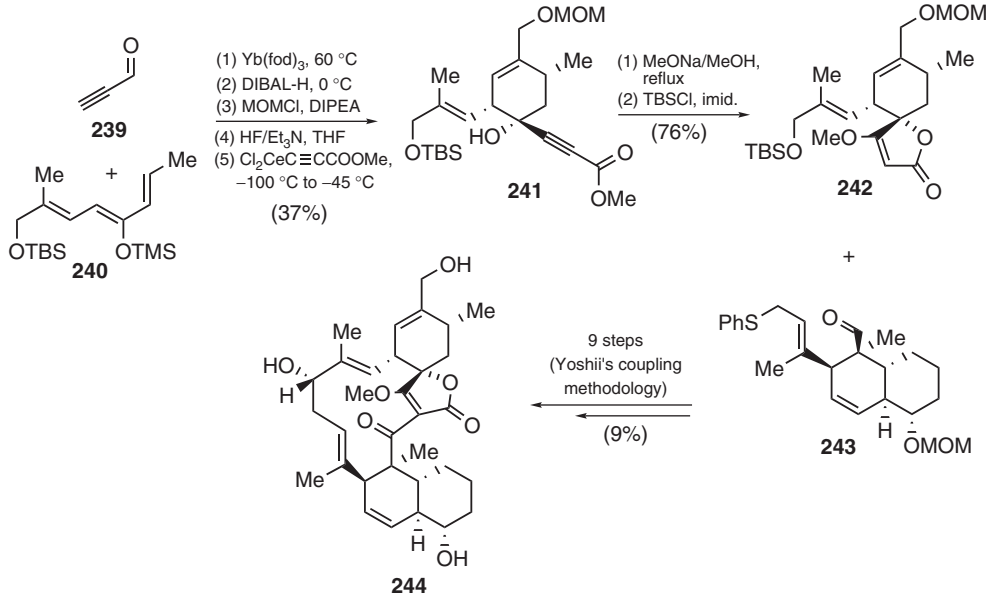
strategies for the enantioselective synthesis of Yoshii's tetronolide fragments [120a, 129b], thus accomplishing a formal synthesis of this molecule. Interestingly, for the spirotetronic part **231**, Roush employed an unexpectedly exo-diastereofacial selective Diels–Alder reaction between chiral dienophile **236** and triene **235**.

Although no total synthesis of kijanolide has ever been achieved, Yoshii managed to reach analog 26-*O*-methyl-28,29-bisnor-(±)-kijanolide (**244**) 3 years before the synthesis of tetronolide [121]. For the spirotetronic part, Yoshii applied Schmidt's chemistry by performing a reaction between a β,γ-unsaturated cyclohexanone and $Cl_2CeC{\equiv}CCOOMe$ followed by the base-catalyzed conversion of the resulting acetylenic carbinol **241** to spirotetronate **242** (Scheme 1.36).

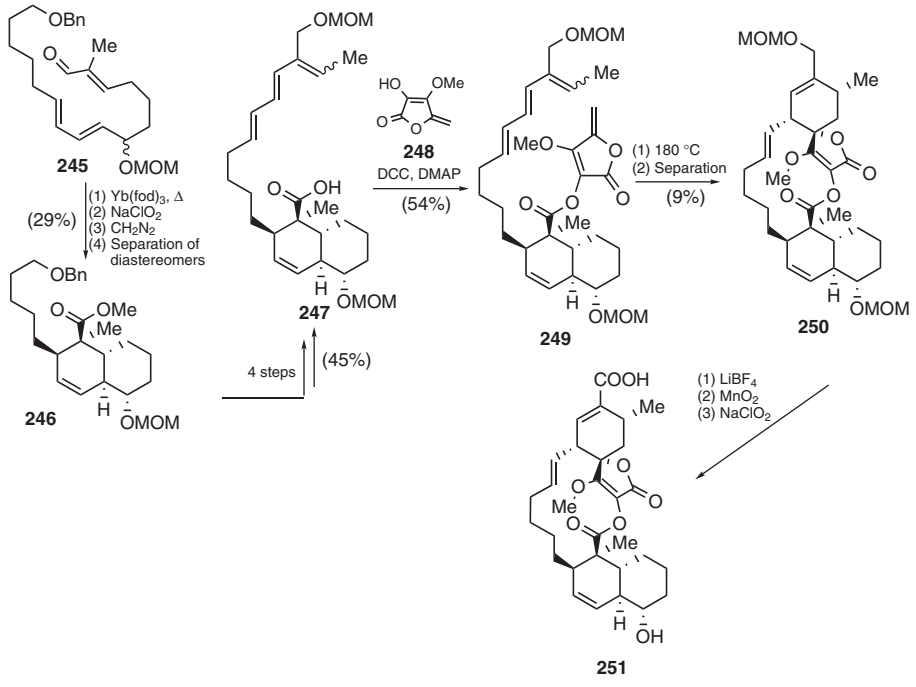
In addition, soon after Ireland's synthesis of chlorothricolide analog **228**, Yoshii and coworkers [117] made one step further by presenting the synthesis of (±)-chlorothricolide as its 24-*O*-methyl derivative **251** (Scheme 1.37). Yoshii succeeded in utilizing the same strategy as in the total synthesis of ircinianin for the key



Scheme 1.35 Yoshii's synthesis of (+)-tetronolide **215**.



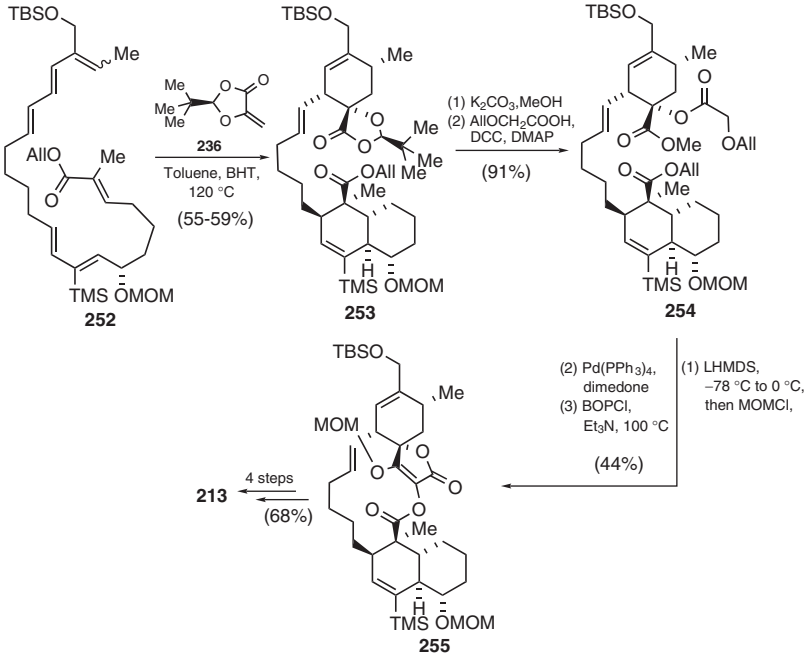
Scheme 1.36 Yoshii's synthesis of kijanolide's analog **244**.



Scheme 1.37 Yoshii's synthesis of chlorothricolide's analog **251**.

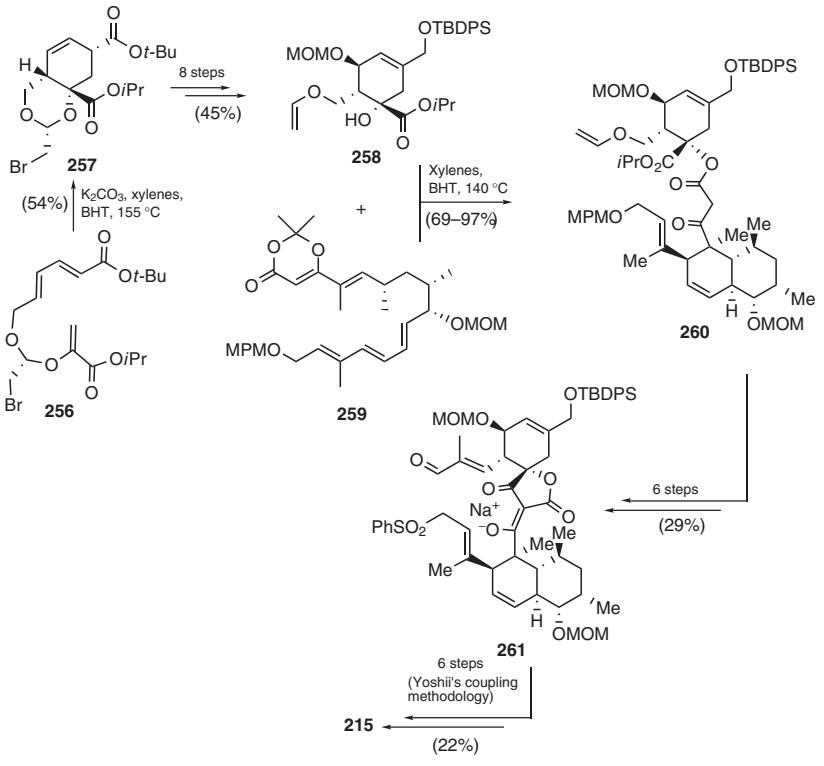
step [138], that is, an intramolecular Diels–Alder reaction (IMDA) of intermediate **249** bearing an appropriate diene and a methylene tetronate. Despite the poor diastereofacial selectivity of this step, and the low overall efficiency, Yoshii's inventive strategy remains a masterful application of stereoselection via intramolecular cyclization.

After 13 years of numerous synthetic studies, Roush's group presented, in 1998, [115b] a brilliant enantioselective approach for the first total synthesis of (−)-chlorothricolide (Scheme 1.38). Roush designed a masterful strategy to build in one step the carbocyclic part of chlorothricolide, installing simultaneously seven stereocenters in excellent stereo- and enantioselectivity and high yield (**252** → **253**). This step was the result of intensive investigations on the relative rates of various Diels–Alder inter- and intracyclizations and is based on the use of a novel chiral dienophile (**236**) [123e,g] and the asymmetric inducing effect of various substituents on the polyene precursor **252** [123f].



Scheme 1.38 Roush's total synthesis of (−)-chlorothricolide.

In 2006, Boeckman reported a highly convergent, enantioselective total synthesis of (+)-tetronolide. The synthesis highlights the use of several new methods, including camphor auxiliary-directed asymmetric alkylation for the construction of fragment **259**, the enantioselective preparation of acyclic mixed acetal **256** bearing chirality at the acetal center and the highly efficient connection of the two major precursors **258** and **259** via a ketene trapping/intramolecular [4+2] cycloaddition strategy (Scheme 1.39).



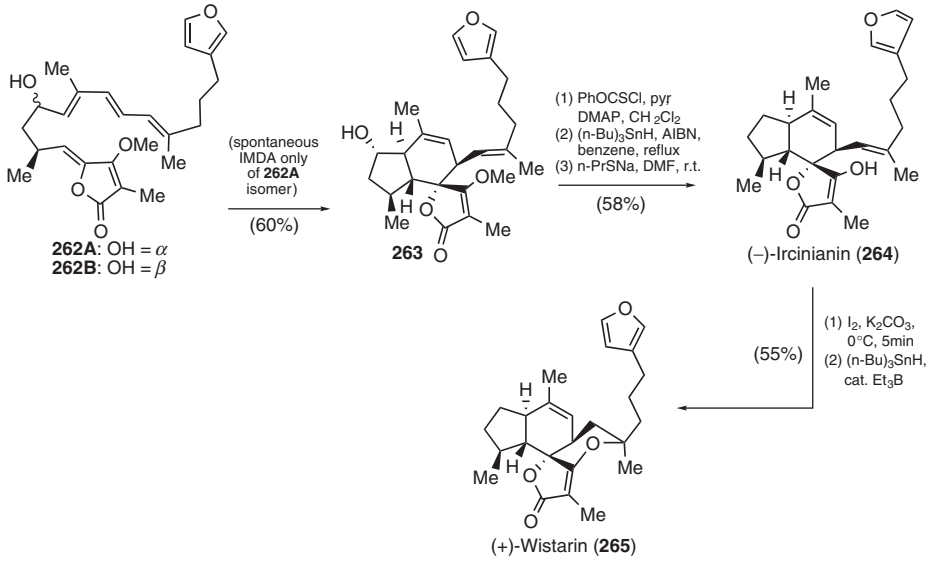
Scheme 1.39 Total synthesis of tetronolide by Boeckman.

1.5.2.2 Ircinianin and Wistarin

(−)-Ircinianin (**264**) and its cyclic isomer (+)-wistarin (**265**) were isolated from marine sponges of the genus *Ircinia* by the groups of Hofheinz and Gregson, respectively [39a,b]. Biosynthetic hypotheses of Hofheinz on the construction of the spirotetronic ring by an IMDA cyclization of an acyclic 8,11,13,20 tetraene precursor were verified by Yoshii *et al.* [138] in 1986 and inspired Uenishi *et al.* [139] in 1997 to develop the first enantioselective synthesis of (−)-ircinianin and (+)-wistarin. Uenishi observed that isomer **262A**, obtained from a Nozaki–Hiyama–Kishi coupling reaction, was spontaneously cyclized to **263**, whereas isomer **262B** remained unreacted under the same conditions (Scheme 1.40). (−)-Ircinianin was obtained after Barton deoxygenation of **263** and was transformed to (+)-wistarin via an iodoether ring formation/iodide radical hydrogenolysis reaction sequence.

1.5.2.3 Stemonamine Alkaloids

Alkaloids of the stemonamine group [73] stemonamide (**266**), isostemonamide (**267**), stemonamine (**268**), isostemonamine (**269**), maistemonamine (**270**), and isomaistemonamine (**271**) have attracted significant synthetic interest during the past decade that has resulted in numerous elegant total syntheses (Figure 1.3).



Scheme 1.40 Total synthesis of (−)-ircinianin and (+)-wistarin.

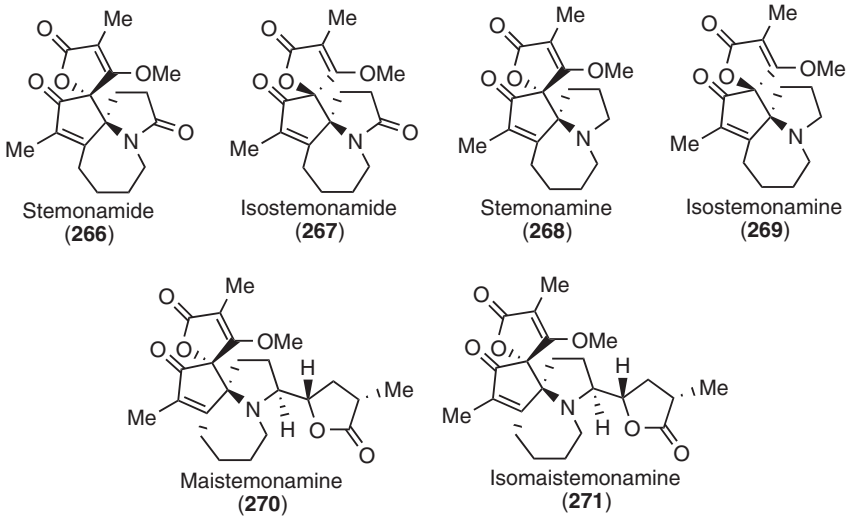
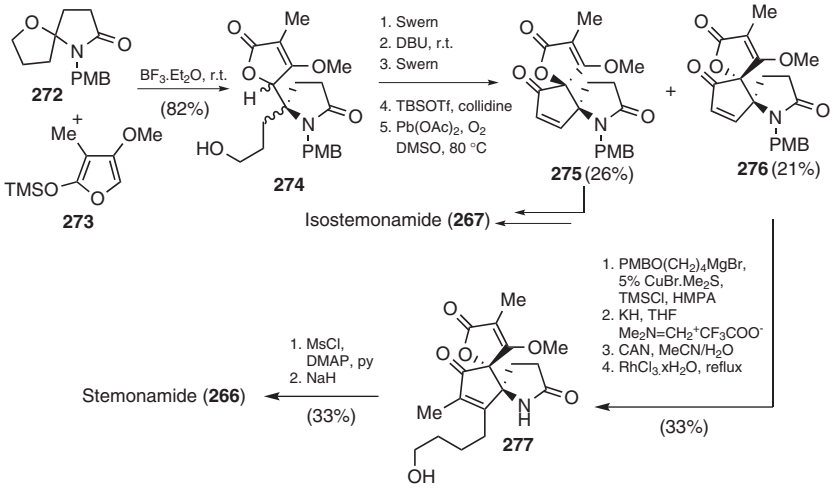


Figure 1.3 Stemonamine alkaloids.

In 2001, Kende's group [140] reported the first total synthesis of stemonamide and isostemonamide. Their synthesis took advantage of *N*-acyliminium ion chemistry for the construction of the spirotetronic core **274** (Scheme 1.41). The lack of stereoselectivity in the spirocyclization step enables the formation of precursors **275** and **276** for both natural products.



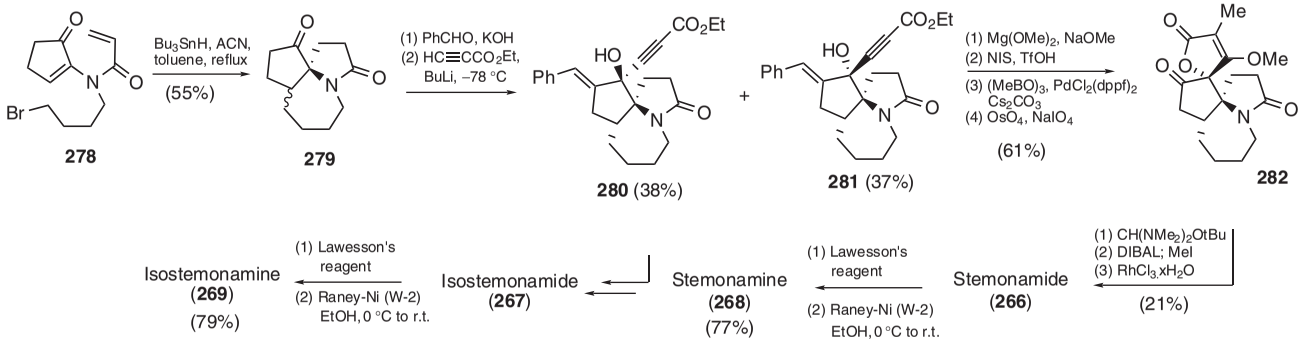
Scheme 1.41 Synthesis of stemonamide and isostemonamide by Kende.

Recently, both natural products were synthesized by Ishibashi *et al.* [141] using a radical cascade to build the fused tricyclic azepine unit **279**. The tetronic ring was introduced after reaction of **279** with ethyl propiolate and subsequent base-catalyzed cyclization. Ishibashi also succeeded to convert **266** and **267** to stemonamine and isostemonamine, respectively, by applying a novel chemoselective reduction, as shown in Scheme 1.42.

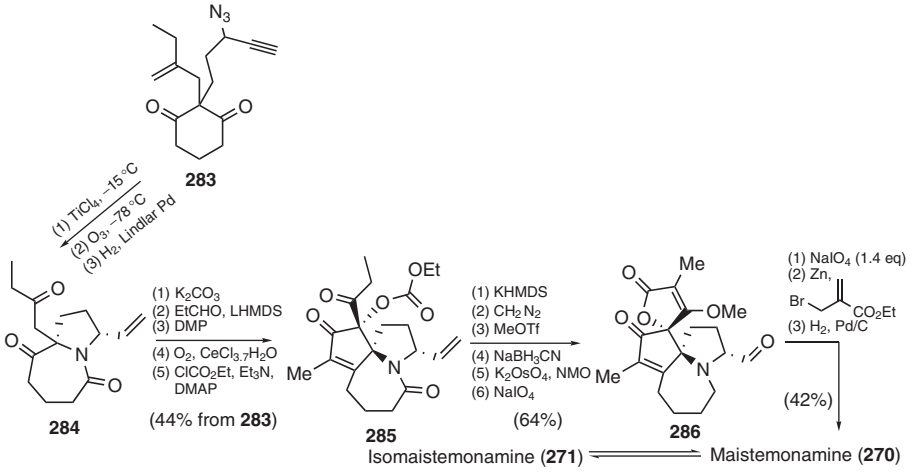
Very recently, Tu's group [142] utilized a methodology based on an intramolecular Schmidt cyclization to achieve the total synthesis of not only stemonamide **266** and stemonamine **268** but also maistemonamine **270** and isomaistemonamine **271**. The latter syntheses include a Dieckmann condensation for the assembly of the spirotetronic ring in **285** and a Reformatsky reaction for the construction of the pendant lactone in **270** (Scheme 1.43). Interestingly, Tu observed that maistemonamine was slowly converted to isomaistemonamine at room temperature, making feasible its isolation by crystallization.

1.5.2.4 **Abyssomicins**

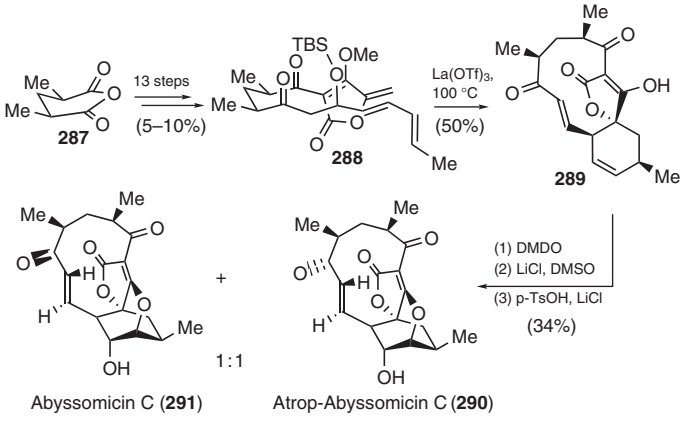
The biological properties and challenging structure of abyssomicin C have prompted researchers to pursue its total synthesis soon after its isolation. After several model studies [143], the first total synthesis of (−)-abyssomicin C was reported by Sorensen *et al.* [144] based on the biomimetic construction of carbocyclic skeleton **289** via a fascinating highly stereoselective IMDA macrocyclization of acyclic precursor **288** (Scheme 1.44). Interestingly, an atropoisomer of **291** was isolated, later characterized by Nicolaou *et al.* [35] as atrop-abyssomicin C (**290**). Following the same strategy, independent reports by Snider and Couladouros described alternative routes toward the preparation of precursor **288** [145].



Scheme 1.42 Synthesis of stemonamine alkaloids by Ishibashi.



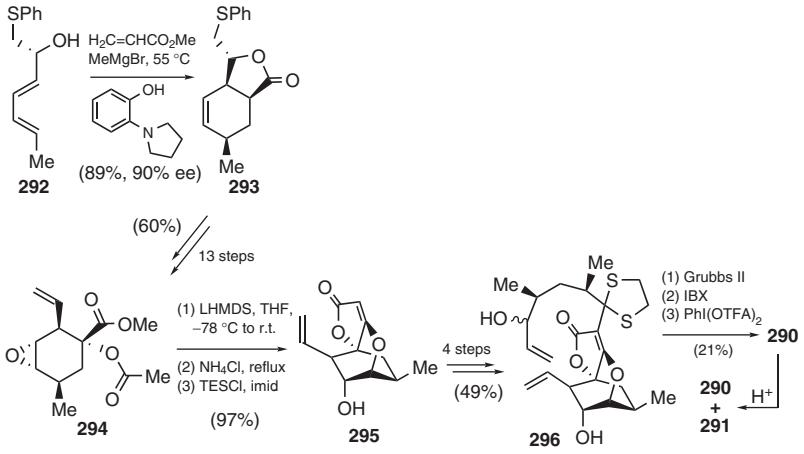
Scheme 1.43 Synthesis of maistemonamine and isomaistemonamine by Tu.



Scheme 1.44 Total synthesis of abyssomicin C and atrop-abyssomicin C by Sorensen.

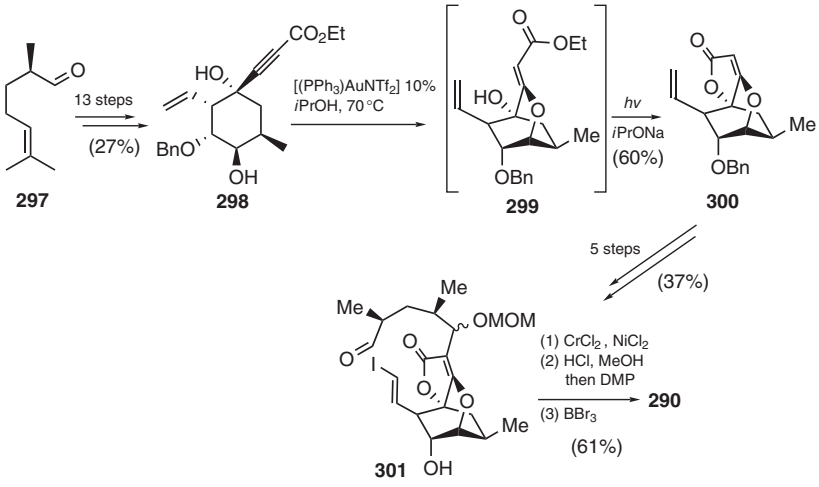
A conceptually different, convergent route was developed in 2006 by Nicolaou and Harrison [35, 146] for the enantioselective synthesis of **290** and **291**. On the basis of an enantioselective Mg(II)-templated Diels–Alder reaction between chiral dienol **292** and methyl acrylate and on previous model studies to build the spirotetronic core [143c], Nicolaou prepared a ring-closing metathesis (RCM) precursor (**296**) that smoothly afforded atropoisomer **290** after oxidation and deprotection (Scheme 1.45). Nicolaou also observed that **290** and **291** participate in an acid-catalyzed intercorversion leading to equilibrium mixtures of various ratios depending on the acidic media.

More recently, Bihelovic and Saicic [147] disclosed an enantioselective total synthesis of **290** that includes some very interesting features. Starting from (−)-norcitronellal (**297**), the authors built intermediate **298** that served as a substrate



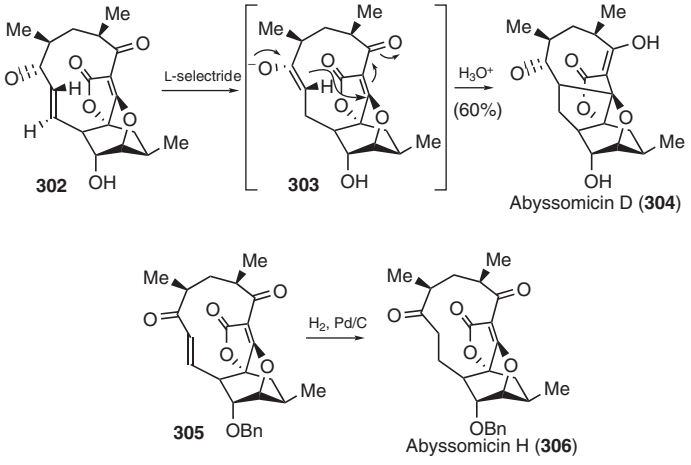
Scheme 1.45 Total synthesis of abyssomicin C and atrop-abyssomicin C by Nicolaou.

in a gold-promoted cascade leading to an one-pot spirotetronate formation of **300** (Scheme 1.46). The synthesis was completed by a remarkably efficient 11-membered ring closure in **301** by the Nozaki–Hiyama–Kishi reaction.



Scheme 1.46 Total synthesis of atrop-abyssomicin C by Bihelovic.

En route to the Nicolaou's and Bihelovic's syntheses of abyssomicins C, the synthesis of abyssomicin D (**304**) and H (**306**) has also been reported. Abyssomicin D was prepared by a 1,4-reduction of **302** with L-selectride [146], whereas reduction of the same bond in precursor **305** by Pd hydrogenation led to abyssomicin H [147] (Scheme 1.47).

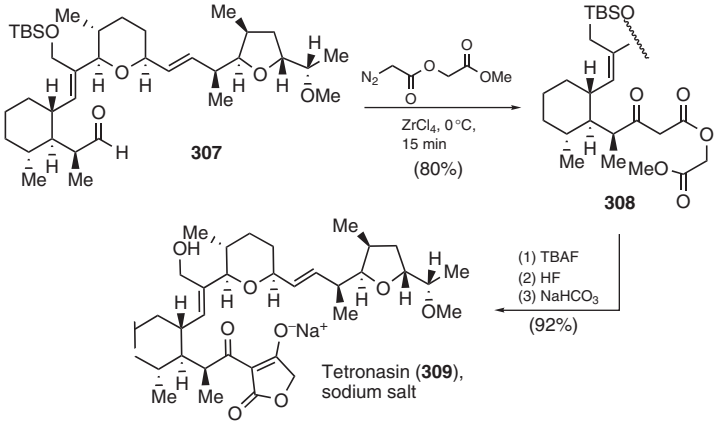


Scheme 1.47 Total synthesis of abyssomicins D and H.

1.6
5-Unsubstituted Tetronic Natural Products

1.6.1
Tetronasin

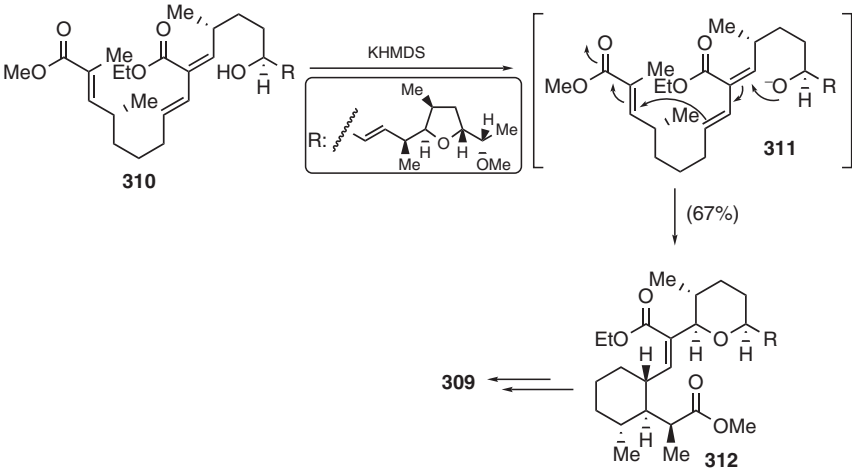
Following the total synthesis of tetronomycin **102**, Yoshii reported, in 1993, the total synthesis of the relevant ionophore, tetronasin (**309**) [148]. Interestingly, tetronasin (**309**) and tetronomycin (**102**) have opposite configurations at each of their 10 common chiral centers. In order to install the 5-unsubstituted tetronic ring at the final steps of the synthesis, Yoshii performed a Zr-catalyzed C–H insertion reaction between aldehyde **307** and methyl (diazoacetoxy)acetate to obtain β-keto ester **308**.



Scheme 1.48 Yoshii's total synthesis of tetronasin.

The synthesis was completed after a fluoride-induced Dieckmann reaction to form the tetronic ring (Scheme 1.48).

Five years later, Ley and coworkers [149] reported the total synthesis of tetronasin based on a biosynthetically inspired metal-templated polyene cyclization reaction of open chain precursor **310** (Scheme 1.49). By this transformation, Ley installed simultaneously four new stereocenters and obtained Yoshii's intermediate **312** with complete stereochemical control.



Scheme 1.49 Biomimetic synthesis of tetronasin by Ley.

1.7 Conclusions

For more than one century, the interesting properties and intriguing structural patterns of tetronic acid natural products have inspired many synthetic chemists to devise methodologies toward their total synthesis. Starting from the early contributions of Volhard and Haynes in the synthesis of vulpinic and carolinic acids, respectively, the research on this field has evolved innovative chemical methodologies for the preparation of tetronic rings, as described in the studies of Yoshii, Ley, Langer, and others. Such methodologies have provided outstanding total syntheses of complex structures, such as Yoshii's synthesis of tetronasin, tetronomycin, tetronolide, and ircinianin; Roush's synthesis of chlorothricolide; and Nicolaou's synthesis of bisorbibutenolide and abyssomicin C. The discovery of new natural products including a tetronic acid ring, combined with the biological properties of these compounds, implies that the interest of the synthetic community will continue to be intense in the following years. This is expected to lead to new strategies inspired by modern synthetic techniques, such as metal-catalyzed asymmetric synthesis or organocatalysis.

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