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# Recent advances in the synthesis of naturally occurring tetronic acids

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ABSTRACT

During the last decades the interest towards natural products containing the tetronic acid moiety augmented significantly, due to their challenging structures and to the wide range of biological activities they display. This increasing enthusiasm has led to noteworthy advances in the development of innovative methodologies for the construction of the butenolide nucleus. This review provides an overview of the progress in the synthesis of tetronic acid as a structural key motif of natural compounds, covering the last 15 years. Herein, the most representative synthetic pathways towards structurally diverse natural tetronic acids are grouped according to the strategy followed. The first part describes the functionalization of a preformed tetronic acid core by intermolecular reactions (cross-coupling reactions, nucleophilic substitution, multicomponent reactions) whereas the second part deals with intramolecular approaches (Dieckmann, cycloaddition or ring expansion reactions) to construct the heterocyclic core. This rational subcategorization allowed us to make some considerations about the best approaches for the synthesis of specific substrates, including modern intriguing methodologies such as microwave irradiation, solid phase anchoring, bio-transformations and continuous flow processes.

## 1. Introduction

Tetronic acids are a class of naturally occurring five membered heterocycles (4-hydroxy-[5H]furan-2-ones) synthesized by a variety of marine and terrestrial species, such as bacteria, molds, algae, fungi, lichens and sponges [1,2]. Several hundred naturally occurring tetronic acids and 4-*O*-substituted derivatives (i.e., tetronates) are known to date, vitamin C [3] and penicillic acid [4] being undoubtedly the most important representatives (Fig. 1). Tetronic acid derivatives and their metabolites have attracted significant attention due to their broad range of biological activities, which cover antibiotic, [5,6] anti-HIV-1 protease, [7] anticoagulant, [8] antiepileptic, [9] antibacterial, [10] antifungal, [11] insecticidal, [12] analgesic, [13] anti-inflammatory [14] and anticancer activities [15].

The high incidence of multi-faceted biological activities and the challenging structural features have stimulated intense efforts towards a deep investigation of tetronic acid-containing natural compounds. A steadily increasing number of reports have been dealing with the isolation of new derivatives and the evaluation of their medicinal potential as well as with the development and refinement of synthetic strategies.

Tetronic acid can exist either in keto- or enol-form (Fig. 2). In certain natural products the tetronic core constitutes the main structural feature of the molecule, while in other ones tetronic acid is fused to more complex structural motifs such as alkaloids, macrolides, terpenes, and tannins. The most frequent and pharmacologically most interesting derivatives are those featuring 3-acyl residues. This has been explained by the ability of these compounds to chelate indispensable metal ions and to mimic phosphate groups in the binding site of kinases and phosphatases [2].

The intense synthetic interest on such compounds, mainly related to their use as a privileged structure in drug discovery, has led to the development of several innovative methodologies for the construction of the tetronic core, as well as the total synthesis of tetronic acid-containing natural compounds themselves [16,17,18,2,19,20,5,21,22].

This review aims to be a concise and critical update of the most recent advances in the synthesis of tetronic acid nucleus as a structural key motif of natural molecules, which could be of interest for the wide scientific community of researchers working in the field of natural compounds, including synthetic organic and medicinal chemists. In this context, synthetic procedures to obtain fused heterocycles incorporating the tetronic fragment will be reported as well. A categorization of the synthetic approaches has been attempted, based on the strategy followed to construct the functionalized tetronic core. Similar approaches

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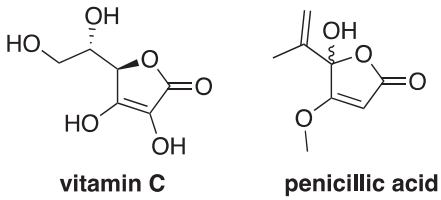


**Fig. 1.** Naturally occurring tetronic acid derivative vitamin C and penicillic acid.

are grouped and discussed collectively. The review incorporates the relevant literature of the last 15 years.

## 2. Synthetic strategies

The tetronic acid containing compounds have been constructed following two main approaches. The first one is based on the functionalization of a preformed tetronic acid core by intermolecular approaches, such as cross-coupling reactions, nucleophilic substitutions or multicomponent reactions. The second one relies on the obtainment of the 5-membered ring by intramolecular approaches, such as Dieckmann reactions, cycloadditions or ring expansion reactions (Fig. 2).

### 2.1. Intermolecular approaches

#### 2.1.1. Multicomponent reactions

Several groups have recently reported the synthesis of tetronate containing derivatives by multicomponent reaction approaches (MCR), in which the skeleton was built in one single step. Metal-based catalysts were often employed, so to increase the sustainable aspect of this kind of protocol, characterized by a substantial atom economy and, consequently, by a very reduced formation of waste products. This approach was mainly used to obtain polycyclic compounds containing the tetronate moiety. The classic multicomponent, one-pot protocol, was modulated depending on the number of condensed rings and the type of substituents, enhancing the reaction conditions through the use of different catalysts. In 2008, Shaabani et al. prepared 4*H*-furopyrans by condensation of isocyanides **1**, dialkylacetylene dicarboxylates **2** and tetronic acid **3** (Fig. 3a) [23]. The proposed mechanism involved the initial formation of a Michael-type vinylisonitrilium cation, which could be successively attacked by the anion of the tetronic acid leading to a keteneimine. Isomerization produced the fused heterocyclic system. In this way 4*H*-furo pyrans **4** were synthesized, containing the same diester motif - derived from the use of symmetric acetylene dicarboxylates - but various *N*-substitution due to the use of different isocyanides.

A MCR approach was exploited also by Shearer et al. for the synthesis of tricyclic furochromenes **8b**, starting from tetronic acid **3**, aromatic aldehydes **6** and β-diketones **5** [24]. In particular, the product of Knoevenagel condensation **7a** in presence of a catalytic amount of pyrrolidine, was further subjected to Michael addition to give the homodimeric product **7b**. In contrast, when a stoichiometric amount of pyrrolidine was used, together with $InCl_3$ as the catalyst, the *N*-pyrrolidine addition product **8a** was favored, to further allow incorporation of tetronic acid. Treatment in acidic conditions and subsequent dehydration led to the desired aryl chromene derivative **8b**. (Fig. 3b) Substituted furochromene derivatives like **8b** were also obtained by Ganja et al, following a similar approach (Fig. 3c), through MCR using $Y_2O_3$/hydroxyapatite as heterogeneous catalyst [25]. In these conditions the polycyclic compounds were formed within minutes at room temperature. The interaction between the catalyst cation and the substrate was favored, probably thanks to the mixed oxides properties (from metal oxides and pure oxides). To further improve the yield of such an approach, protic polar solvents were exploited, necessary for the condensation to happen. The mixed catalyst was easily recovered after any cycle and efficiently reused at least for other 6 times, affording differently substituted furochromene derivatives. The one-pot condensation approach was employed not only for the synthesis of polycyclic compounds but also for the obtainment of 3-substituted tetronic acids. Rezayan et al. synthesized dihydropyridine and dihydroisoquinoline derivatives by a three components reaction [26]. After condensation between isoquinoline **9** (or quinoline) with conjugated alkyne **2**, tetronic acid **3** worked as the nucleophile towards the quinolinium (or isoquinolinium) intermediate. Following this protocol, it was possible to prepare a 3-heteroaromatic-substituted tetronic acid **10**, under neutral conditions, by exploiting the ability of tetronic acid to tautomerize and stabilize very efficiently the structure through H-bond formation. (Fig. 4).

#### 2.1.2. Metalation

Metalation represented the key step for the functionalization at C(5) of tetronic acids in numerous recent works, especially through aldol condensations, in order to have access to biologically active natural products. Methylene methyl tetronate **11** was used as a common building block for the synthesis of structurally different natural compounds endowed with biological activity.

A structurally intriguing class of natural compounds is represented by the spirotetronate polyketides (e.g., chlorothricolides, kijanimicin, okilactomicins, abyssomicins) which are characterized by the presence of a five-membered tetronic acid moiety spirolinked to a cyclohexene ring. Among them, okilactomicins are a family of natural metabolites from *Streptomyces griseoflavus* consisting of fused rings (one of them is a 13-member ring) and exhibiting antitumor, antibacterial and cholesterol level control activities [27,28,29]. In 2012, Niu and Hoye reported their developments towards total synthesis of **okilactomicin D** starting from polyenal **12**, which was treated with lithiated methyl tetronate **11** to afford the aldol ready to be oxidized to 3-acyl tetronate **13** [30]. The generation of the spiro portion was achieved by a diastereoselective (8:1) intramolecular Diels Alder reaction in refluxing toluene. The most abundant diastereoisomer was demethylated with LiCl with formation of **okilactomicin D** in good yield. It is worth to note that more polar solvent mixtures for the cycloaddition strongly accelerated the reaction rate, maintaining the same diastereoisomeric ratio, but lowering the yields of isolable product (Fig. 5a).

A key intermediate for the synthesis of **abyssomicin C**, another natural spirotetronate showing activity on methicillin resistant mycobacteria and inhibiting PABA, was prepared following a similar strategy [31]. Aldehyde **14** was condensed with methylene tetronate **11** in presence of LDA. Deprotection and oxidation of the secondary alcohol groups of **16**, followed by exposure to high temperatures to favor the

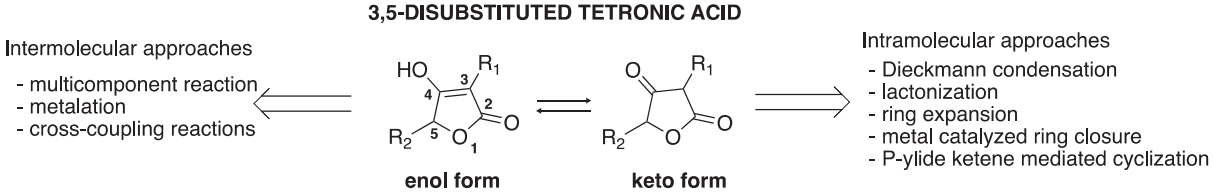


**Fig. 2.** Characteristic keto-enol tautomerism in tetronic acid derivatives and their sub-categorized synthetic approaches.

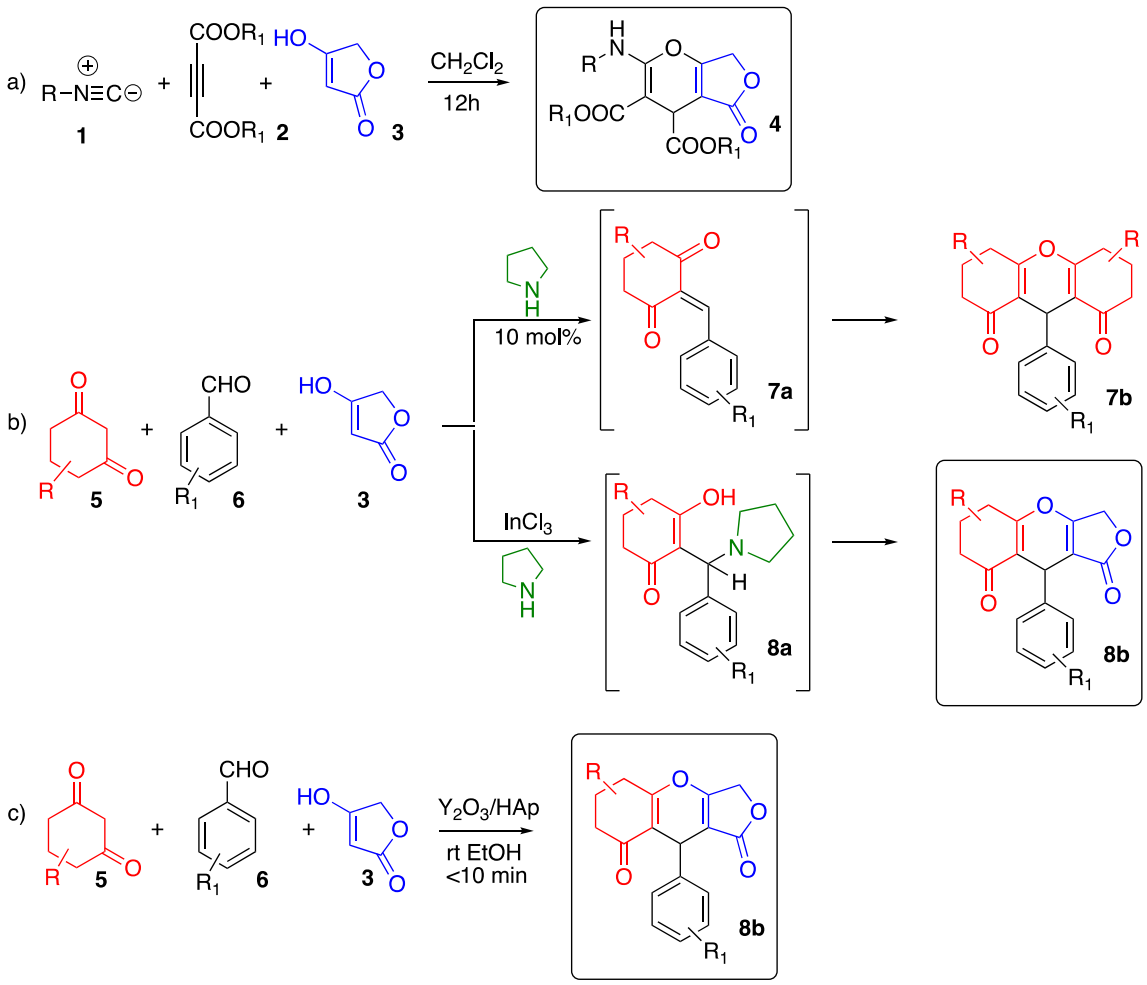


**Fig. 3.** Examples of furochromene derivatives, containing a tetronate core, prepared by multicomponent reaction approach (MCR).

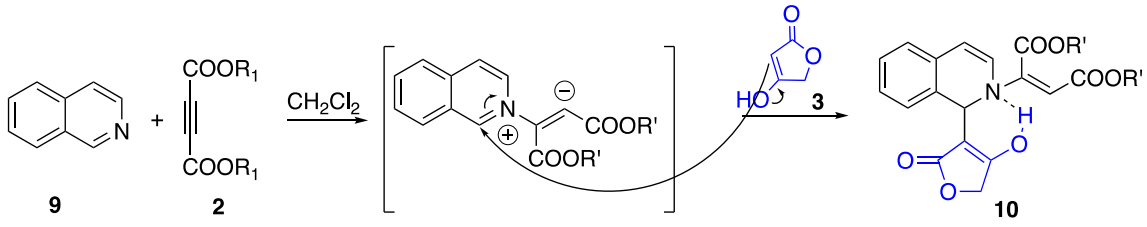


**Fig. 4.** Synthesis of 3-dihydroisoquinoline substituted tetronic acid, exploiting a three-component reaction method.

intramolecular Diels Alder reaction, gave compound **17**. This resulting fused tricycle (one of them consisting of 11 atoms), having the correct stereochemistry and skeleton of the desired natural compound, was identified as the key intermediate for the total synthesis of **abyssomicins** (Fig. 5b). Analogously to what here above described, methylene methyl tetronate **11** was used also for the construction of the bicyclic nucleus of **phaeosphaeride A**, a cytotoxic natural compound extracted from fungus *Phaeosphaeria avenaria* [32]. The most significative steps towards its preparation involved the deprotonation of the vinyl proton by treatment of tetronate **11** with LDA, so that condensation with acetonide-protected aldehyde **18** could give access to the corresponding tetronate aldol **19** with good stereoselectivity (Fig. 5c). Conversion to the corresponding tetramate nucleus was performed in presence of methoxylamine, to give **20** as a suitable precursor to desired **phaeosphaeride A**. The same approach exploiting different diastereoisomers allowed to obtain analogues of phaeosphaeride A, which showed inhibition of STAT3-dependent transcriptional activity in a dose-dependent manner and exhibited antiproliferative effects against selected cancer cell lines [33].

During their studies aimed at investigating the antioxidant activity of pulvinic acids, Habrant et al performed SAR studies on simplified pulvinic analogues (derivatives **26**) [34]. To this purpose, methyl tetronate **21** was variously functionalized, exploiting once again the metalation at C(5) to afford compounds containing the exocyclic double bond. Tetronic derivative **21** was protected as benzyl ether under Mitsunobu conditions, and the obtained product **22** was deprotonated using LDA. Subsequent addition of keto esters **23** provided alcohols **24**, which were then dehydrated with trifluoroacetic anhydride to give, after deprotection, simplified analogues **26** (simplified pulvinic acids I) (Fig. 6).

Soda et al. used a furan intermediate as key precursor for the introduction of a tetronate moiety within the synthesis of antitussive and insecticidal protostemonine, a stemoamide analogue, and other

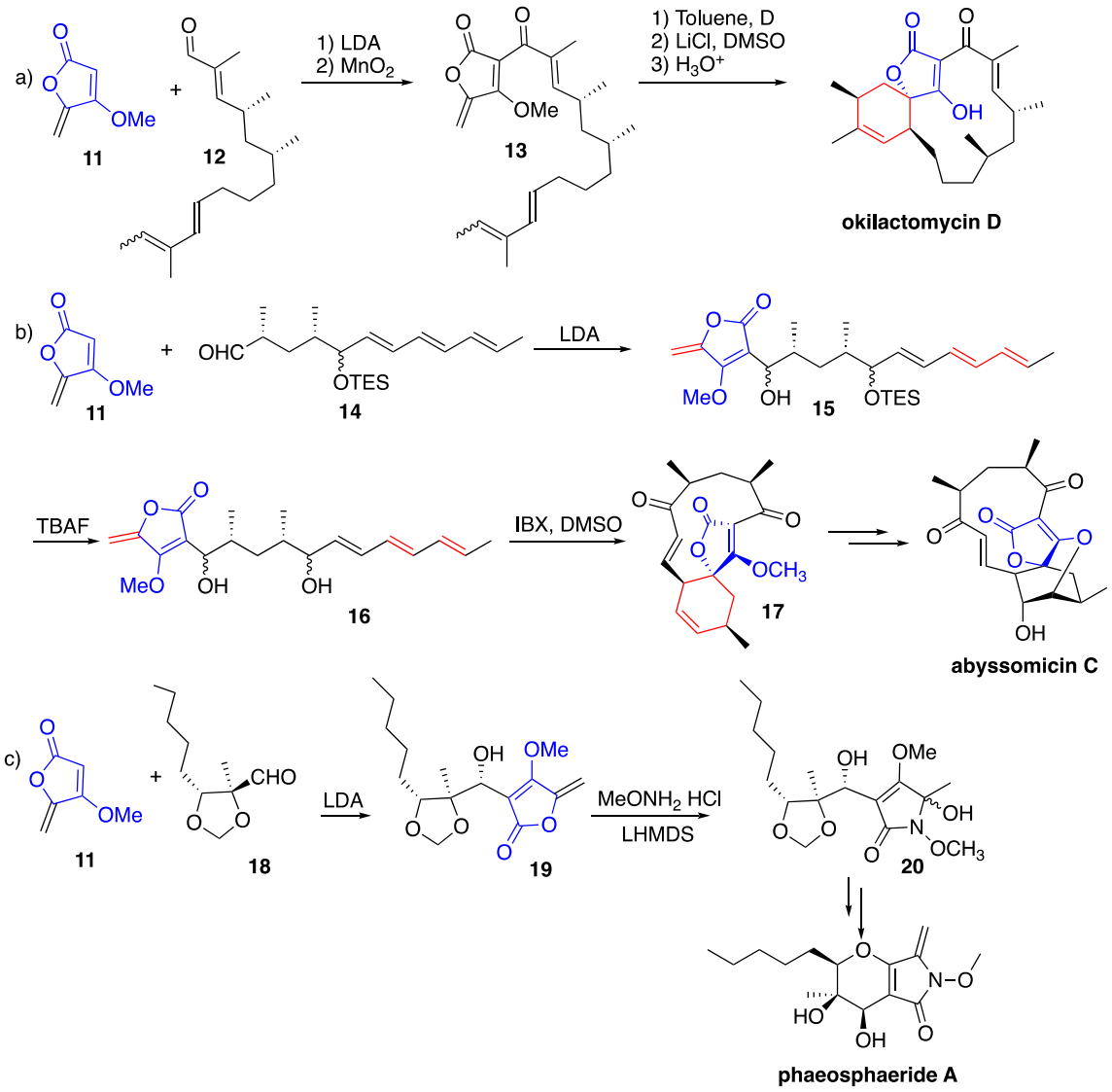


**Fig. 5.** Metalation and subsequent aldol reaction involving alkylidene tetronate **11** for the preparation of valuable natural products (**okilactomicin D**, abyssomicin intermediate **17** and **phaeosphaeride A**).

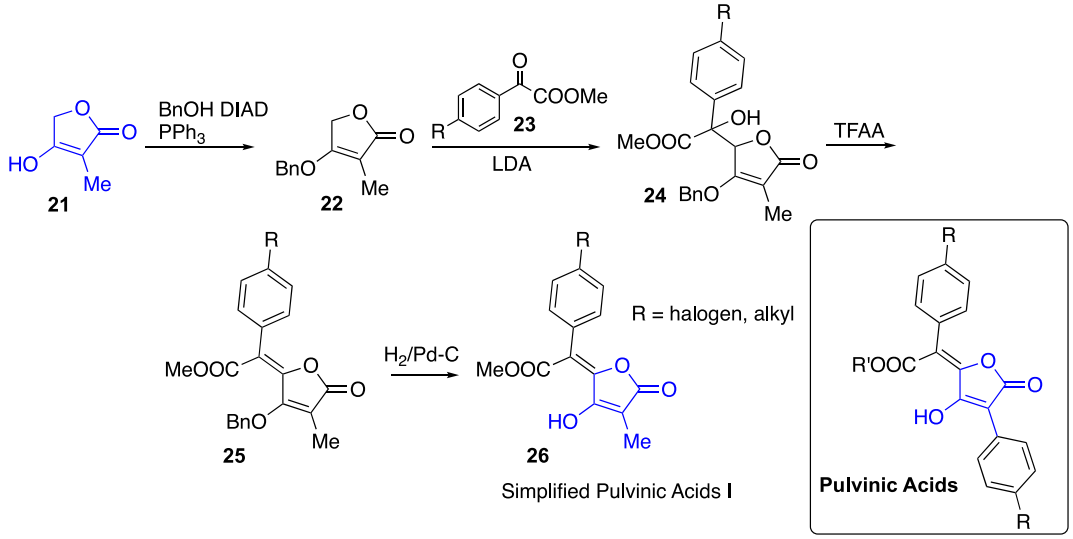


**Fig. 6.** Preparation of pulvinic acid analogues **26**, by metalation of methyl tetronic acid **21**.

correlated alkaloids (Fig. 7) [35]. The Authors proposed an easy preparation of the tricyclic **stemoamide**, which was then treated with DIBAL-H to convert the lactone to hemiacetal **27**. The tetronate moiety was installed with 2-siloxyfuran **28** in a one-pot process in the presence of $BF_3{\cdot}Et_2O$ via an oxocarbenium ion. A bromide group was regioselectively introduced on the resulting tetracyclic intermediate **29** with NaHMDS and bromine. The obtained intermediate **30** was then used to prepare either *E*- or *Z*-tetrasubstituted olefins **31** or **32**, respectively, by using stereodivergent conditions. The elimination of bromide with AgOTf at 40 °C provided protostemonamide **31** as the kinetic product with 3:1 diastereoselectivity. In contrast, after the elimination with AgOTf, the further addition of TfOH initiated the isomerization of the *Z*-olefin to the *E*-olefin, providing isoprotostemonamide **32** as the thermodynamic product with 4:1 diastereoselectivity. Protostemonamide and isoprotostemonamide were then converted to **protostemonine**, **isoprotostemonine** and other pyrrole-containing stemonine-like alkaloids [21].

A similar approach was used for the synthesis of **stemofoline** and **methoxystemofoline** alkaloids, as acetylcholine esterase inhibitors [36]. An adequately protected fused tricycle bearing an aldehyde (**34**) represented the suitable intermediate for the introduction of the tetronate core. In this case, functionalization at C(5) was made possible by using a lithiated furan derivative (**33**). Further oxidation and thiocarbonation of the resulting intermediate **36** afforded a 1:1 ratio of methoxy and isomethoxystemofolines (*Z* and *E* isomers), derived from the thiocarbonate group elimination and consequent double bond formation (Fig. 8).

The first synthesis ever reported of sesteterpene **palinurin** exploited an enantioselective 3-methyl tetronic acid **21** functionalization, using optically pure methyl prolinol **38** to obtain **39** [37]. Reaction of the iminoenolate on allyl bromide **40** gave 5-alkyl derivative **41**, followed by *O*-TBS deprotection and hydrolysis to tetronic acid **42** and further protected via Mitsunobu reaction in presence of methanol, prior to oxidation of the residual primary hydroxyl group to afford the aldehyde **43**. Olefination reaction with previously prepared phosphonate **44** and final demethylation to tetronic acid afforded the product **palinurin**, known as anti-inflammatory and antibacterial agent (Fig. 9). In this case it is evident how metalation could lead to 5-alkyl instead of 5-alkylidene derivatives, exploiting a $S_N2$-like reaction on bromide **40** rather than the more deeply investigated aldol condensation.

Metalation process adopted in presence of continuous flow conditions and different bases [38,39] improved yields and selectivity during the synthesis of various butenolides. Ganiek et al. exploited this kind of approach [40] by treatment of acrylate **46** with a strong base such as TMPMgCl LiCl **47** (described to allow magnesiation and activation of the ester portion towards ring closing, intermediate **48**), in presence of the appropriate aldehyde **49**, to afford 5-aryl tetronate **50** in mild conditions and low reaction times. Further metalation of the resulting aryl butenolide, using again TMP metal-chloride, allowed cross coupling reactions with suitable electrophiles, so to give 3-functionalized 5-aryl tetronates **52** (Fig. 10).

### 2.1.3. *Metal catalyzed C—C cross coupling reactions*

Pd-catalyzed cross coupling reactions were mainly used to obtain 3-arylsubstituted tetronates, in some cases after the introduction of 5-arylidene moieties by metalation reactions, as described in the previous chapter. Antane et al. performed the synthesis of differently substituted pulvinones by the functionalization of bromo methyl tetronate **53** (Fig. 11a) [41]. Condensation with available aldehydes gave, after dehydration, 5-arylidene tetronates **55**. Suzuki coupling between selected arylboronates and the bromo derivatives afforded tetronates ready to undergo demethylation, with obtainment of tetronic acids-containing pulvinones. MIC and biological antibacterial activity of the obtained compounds were also reported. Tetronate **53** was also subjected to Suzuki coupling in presence of $Pd(PPh_3)_4$, $Na_2CO_3$ and MW irradiation in dioxane/water mixture as the solvent, in order to obtain a series of 3-aryl tetronates **56**, investigated as antifungal and anti-inflammatory compounds by Song et al. (Fig. 11b) [42]. Interestingly, in 1989 compound **53** was employed for the synthesis of the key fragment of **tetronasin** and **tetronomycin**, naturally occurring products with antibacterial activity, due to their polyether ionophore portion [43]. The starting substrate, bromotetronic acid **53**, was methylated and stannylated at C(3) to give **57**. 3-acyl tetronates **58** were obtained by a Pd-catalyzed cross-coupling reaction (Fig. 11c). This work represents, to the best of our knowledge, the only one example of 3-acylation of the tetronate core via cross coupling reactions.

Following similar strategies 5-arylidene tetronates were prepared from commercially available tetronates (Fig. 12a) [44]. Functionalization at C(5) of tetronate **3** was obtained by treatment with suitable aromatic aldehydes. Satisfying diastereoselectivity towards the formation of desired *Z* isomer was achieved by one-pot treatment of alkyl tetronates with an excess of DBU as the base. Successive bromination of **59** was performed using excess of $Br_2$, affording 3-bromotetronates **60** as substrates for further cross coupling reactions. Interestingly, changing the concentration and the stoichiometric amount of $Br_2$, it was possible to preferentially brominate C(3) on tetronate moiety **59**, rather than

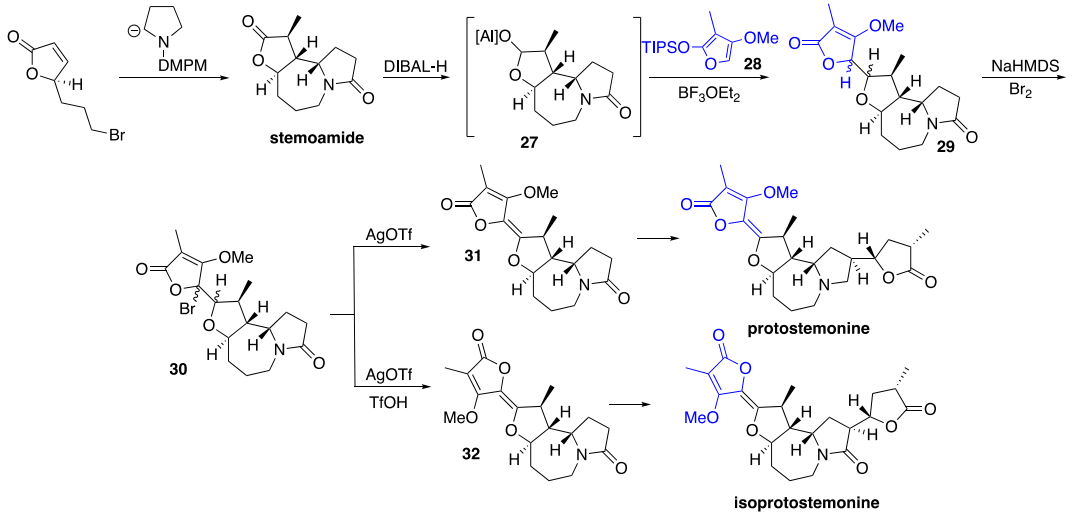


**Fig. 7.** Treatment of **stemoamide** with furan derivative tetronate **28** gave access to intermediates for the synthesis of natural **protostemonine** and **isoprotostemonine**.

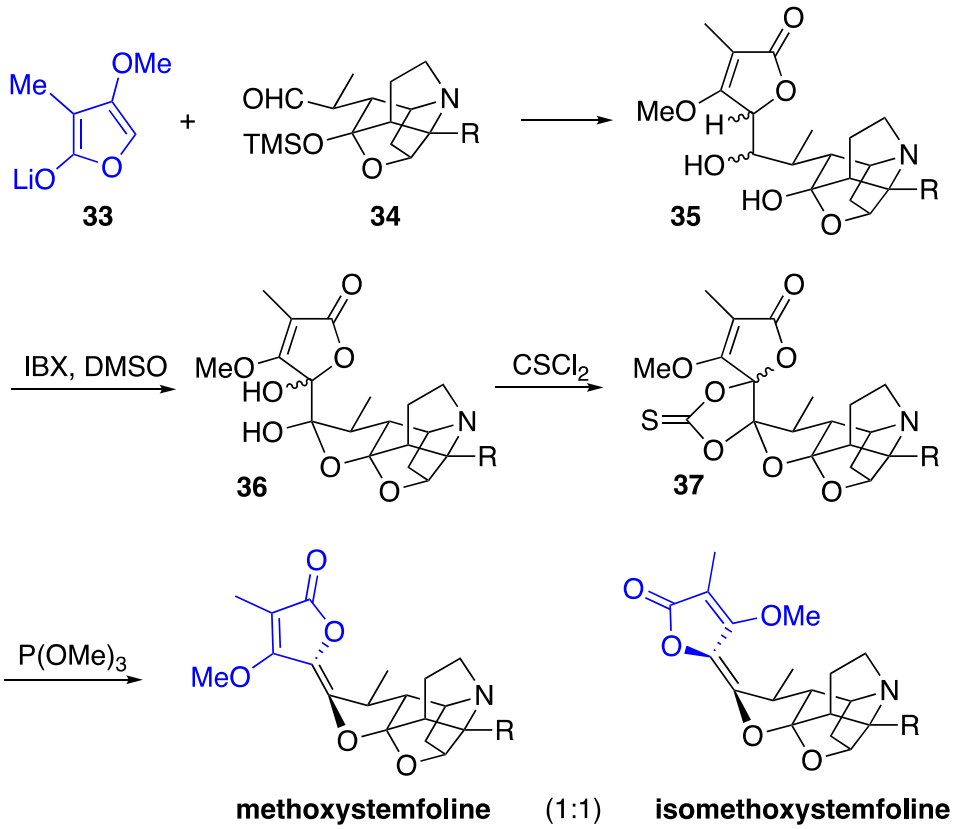


**Fig. 8.** Approach for the synthesis of **methoxystemfoline** and **isomethoxystemfoline** starting from furan-tetronate **33**.

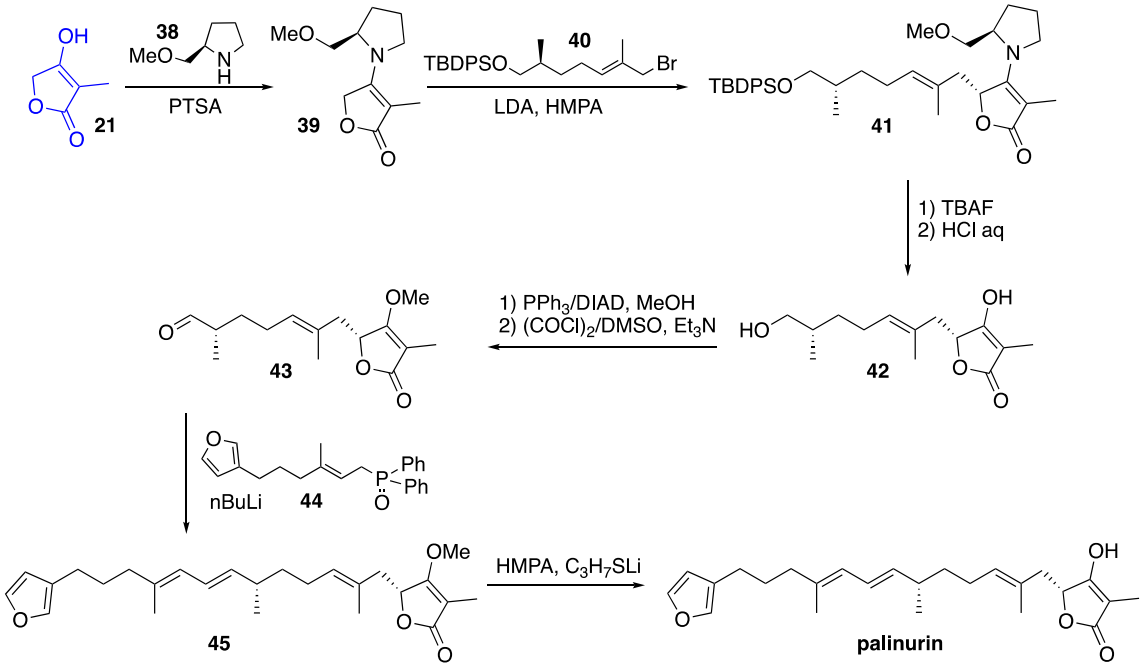


**Fig. 9.** Enantioselective **palinurin** synthesis by metalation and functionalization of tetronic acid **21**.

both C(3) and the exocyclic double bond. Treatment with an excess of DBU allowed dehydrohalogenation and exocyclic double bond was restored (**62**). Sonogashira cross coupling reactions afforded the halide substitution and setting of the suitable aryl group (compounds **61** and **63**). To give more value to the biological importance of such derivatives, Sonogashira cross-coupling products, bearing a triple bond, were subjected to 1,3-dipolar cycloaddition reactions with benzyl azide, showing the possibility to synthesize 1,2,3-triazoles as potentially antiviral and antimicrobial compounds [45]. Manchoju et al. introduced the 5-arylidene group converting, at first, tetronic acid **3** to diazotetronic acid **64** (upon treatment with tosyl azide) and, then, performing aldol condensation with the suitable benzaldehyde in presence of $TiCl_4$ (**65**)

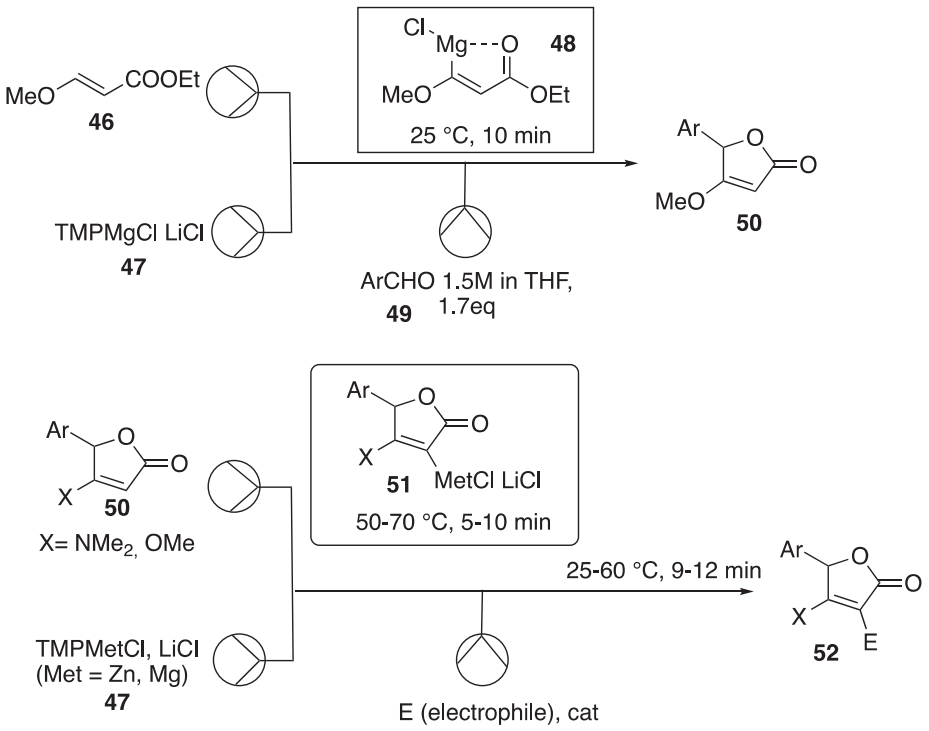


**Fig. 10.** Continuous flow-mediated synthesis of 3-substituted tetronate **52**.

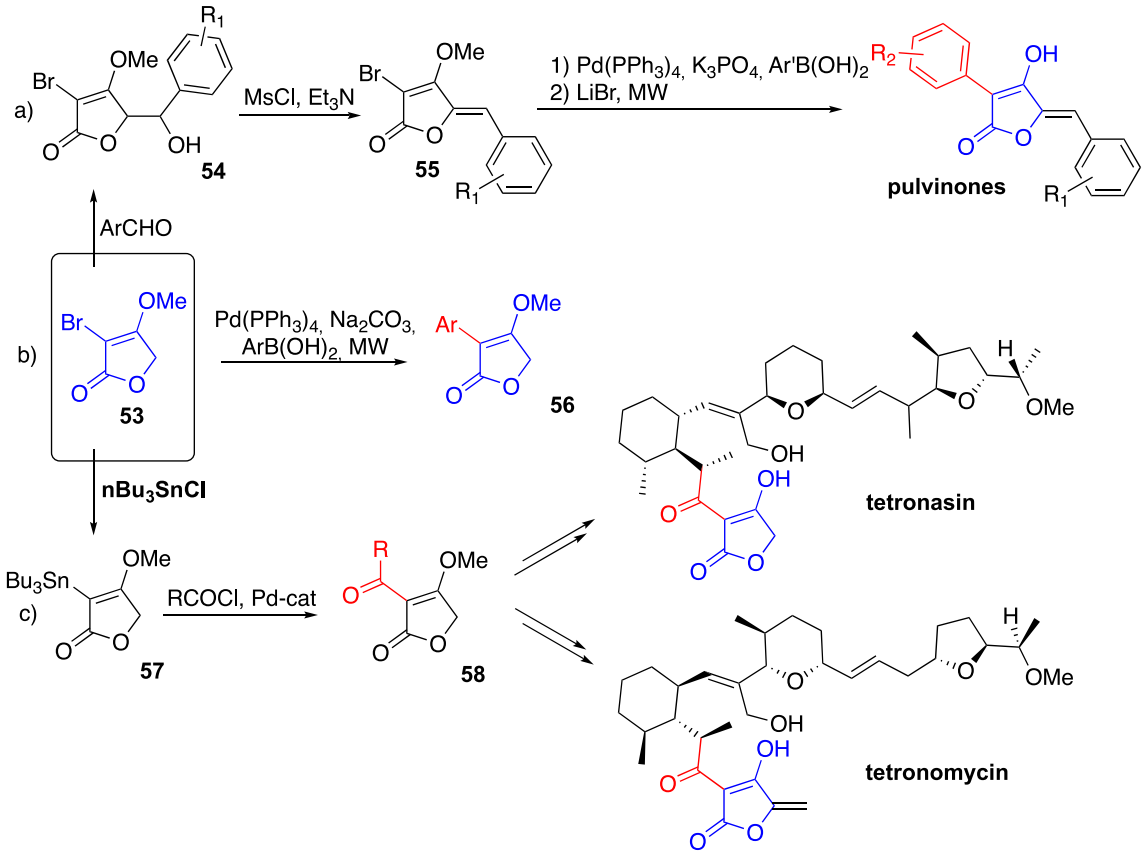


**Fig. 11.** 3-Arylation and 3-acylation methodologies on bromotetronate **53** for the synthesis of natural **pulvinones** (pathway a) and metabolites **tetronasin** and **tetronomycin**.

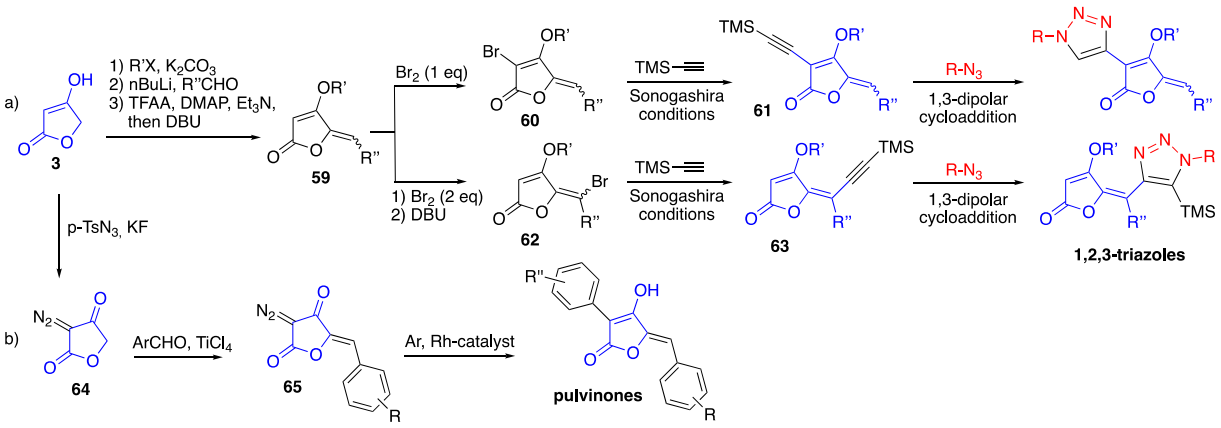


**Fig. 12.** Preparation of 5-arylidene derivatives by metal-catalyzed C—C cross coupling.

[46]. Afterward, 3-arylation was carried on in presence of rhodium-based catalysts to afford desired pulvinone analogues, endowed with a wide range of biological activities, from antibacterial to anti-inflammatory to anticoagulant (Fig. 12b).

During their investigation about pulvinic acids as antioxidant compounds, Habrant et al prepared simplified analogues with only one aromatic ring (Compound **70**, Fig. 13) [34]. Regioselective addition of methyl propionate zinc enolate was performed to methoxymaleic anhydride **66** gave intermediates **67**, successively dehydrated to afford the 5-alkylidene derivatives of methyl tetronate **68**. To note, in this case the precursor of the tetronic acid skeleton was subjected to the nucleophilic attack by metalated methyl propionate. Iodination of the enol double bond of **68**, followed by Suzuki cross coupling and demethylation, gave the desired simplified 3-arylpulvinic acid **69**. When dilactone **71** was used as the starting material, nucleophilic substitution by *O*- or *N*-nucleophiles was performed, with the latter reacting with complete selectivity towards the less hindered lactone to afford **74**. Attempts with 2 equivalents of MeLi as *C*-nucleophile resulted in double methylation of **71** and subsequent formation of the tertiary alcohol **75**, isolated in good yield (Fig. 14).

Cross coupling reactions appeared one of the most affordable methods for one of the final steps towards the preparation of **chalcitrin**. The interest for this natural compound recently increased, due to its potential biological activity as a metal chelator. Since the compound is isolated in disappointing amounts from *Chalciporus piperatus*, Yang et al. proposed a total synthesis in which the key intermediate is represented by condensed tetracycle **76** (Fig. 15) [47]. Further functionalizations were necessary to stannylate the isolated double bond, to perform a Stille-like cross-coupling between **77** and 3-iodotetronate **78**. Unfortunately, this first attempt did not furnish the tetracycle-substituted tetronate **79**, so that stannylation was set again, this time on the tetronate moiety (**80**), ready to react with iodinated **76**. Thus, the desired intermediate **79** was obtained, suitable for debenzylation by $BBr_3$ to afford the expected **chalcitrin**, in higher amounts compared to extraction from natural sources.

Zhu et al. reported the synthesis of **11-demethoxy-16-*epi*-myrtoidine**, analogue of alkaloid **myrtoidine** (active as antimalarial) consisting of a fused hexacyclic nucleus and isolated from the stem bark of *Strychnos myrtoides* (Fig. 16) [48]. Reaction between protected indole **81** and dimethyl α-methylene malonate resulted in the formation of the tetracyclic intermediate **82**, further converted to ester **83** upon decarboxylation and change of the protecting group (from tosylate to *t*-butoxycarbonyl group). Allyl bromide **85** was obtained by reduction of vinyl ester **84** with DIBAL-H and bromination via Appel reaction. The nucleophilic substitution with 3-bromotetronic acid led to intermediate **86**, followed by a radical cyclization reaction to give the product **87**. Pyrrolidine *N*-deprotection and methylation followed by indole *N*-deprotection and acetylation gave the desired demethoxymyrtoidine analogue.

Jin et al. exploited gold-based catalysis to perform *6-endo dig* cyclizations starting from propargyl vinyl ethers **88**, to have access to different important classes of heterocycles [49]. To test the possibility to obtain 6-endo products instead of 5-exo ones, previously synthesized aryl or alkyl propargyltetronates **89** were heated in DCE in presence of Au catalyst, to obtain the corresponding pyrans **90** in good yields and high selectivity towards the *E* isomers. According to the proposed reaction mechanism, the initial coordination and activation of the triple bond of **89** (**II**) was followed by the insertion on the enolic double bond (**III**). Then, keto-enol tautomerism allowed the formation of the allene lactone intermediate **IV**, in which the enolic oxygen was capable to afford the ring closing (**V**), followed by Au elimination (**VI**) and formation of the desired product **VII** (Fig. 17a).

Following a reported protocol, Boufroua et al recently described the preparation of condensed bicyclic tetronates starting from allyl acetates

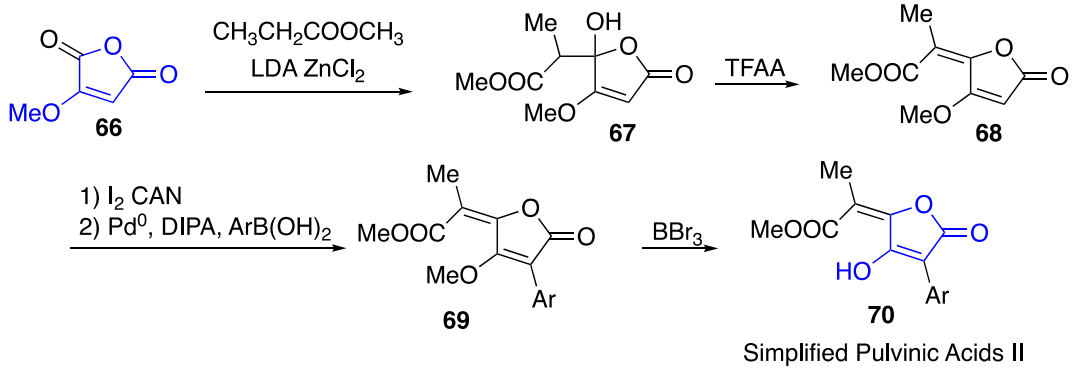


**Fig. 13.** Synthesis of simplified **pulvinic acids** by Suzuki cross-coupling on intermediate **68**.

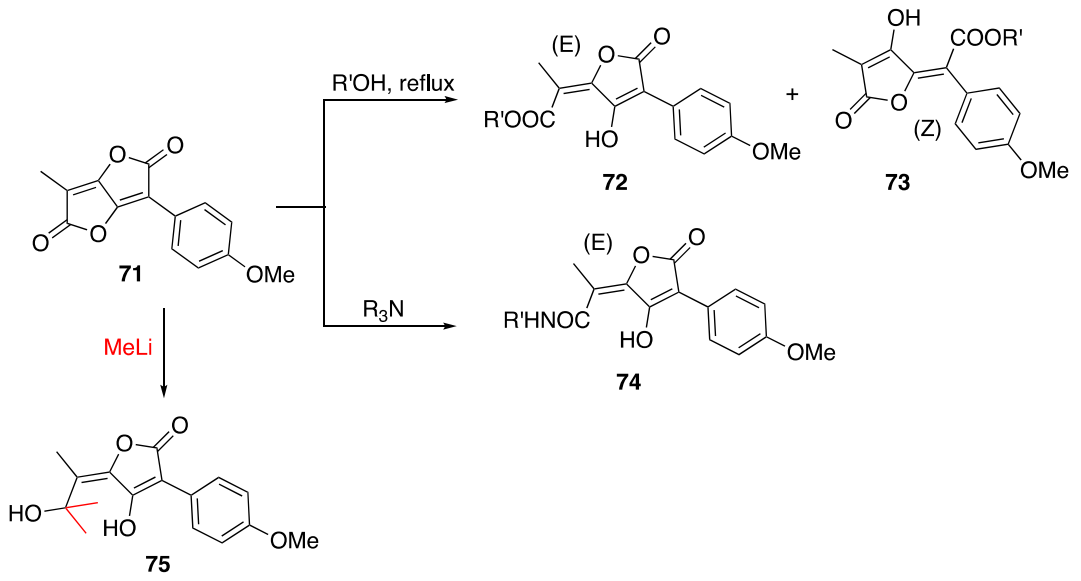


**Fig. 14.** Nucleophilic attacks performed on dilactone **71**.

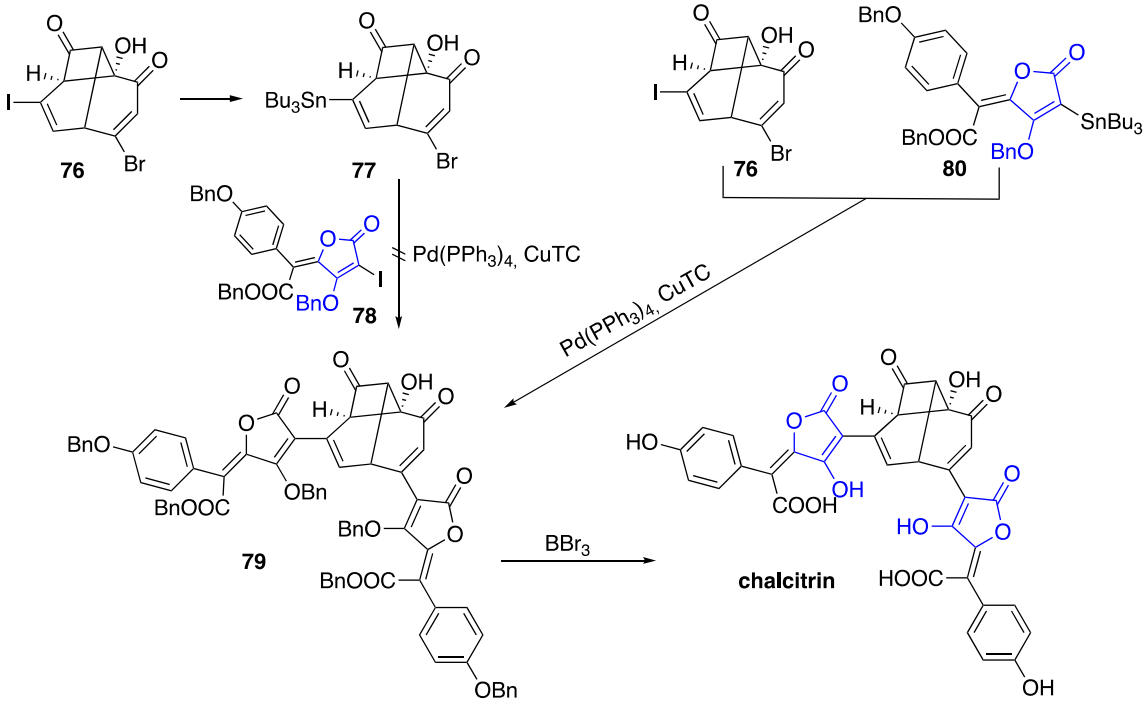


**Fig. 15.** Pd-catalyzed cross-coupling attempts for the synthesis of **chalcitrin**.

and tetronic acid [50]. Using indium triflate as the catalyst, α-allylation of **3** resulted in intermediate **92**, followed by cyclization of the enolic tetronate form, to afford bicyclic **93** (Fig. 17b).

As reported above, it is evident that metal-catalyzed cross coupling reactions represented a very important approach towards the formation of 3-acylated and 3-arylated product, exploiting the already formed tetronate moiety. This is possible because of the enolic double bond, susceptible of halogenation or metalation, so that new C—C bonds could be easily installed. On the other hand, unsubstituted C(5) represents the most reactive position, when aldol condensation is used for the alkylidene group to take place and, at the same time, the most nucleophilic carbon when the furan intermediate is involved.

### 2.2. *Intramolecular cyclization*

In this chapter the construction of the tetronate moiety from linear precursors will be discussed. The reported approaches exploit the advantageous energetic conditions to the 5-member ring closing. The condensation took place thanks to the presence of an adequate "trigger": a base for methylene active compounds or transesterification substrates; catalyst-based multiple bond activation for *endo*- and *exo*- cyclizations and rearrangements; heating, to favor the ring closure without any chemical reactant required. As a result, several pharmacologically active compounds from natural sources were synthesized and studied, to afford the same tetronic scaffold by following different pathways or exploiting the same approach for the formation of structurally diverse moieties.

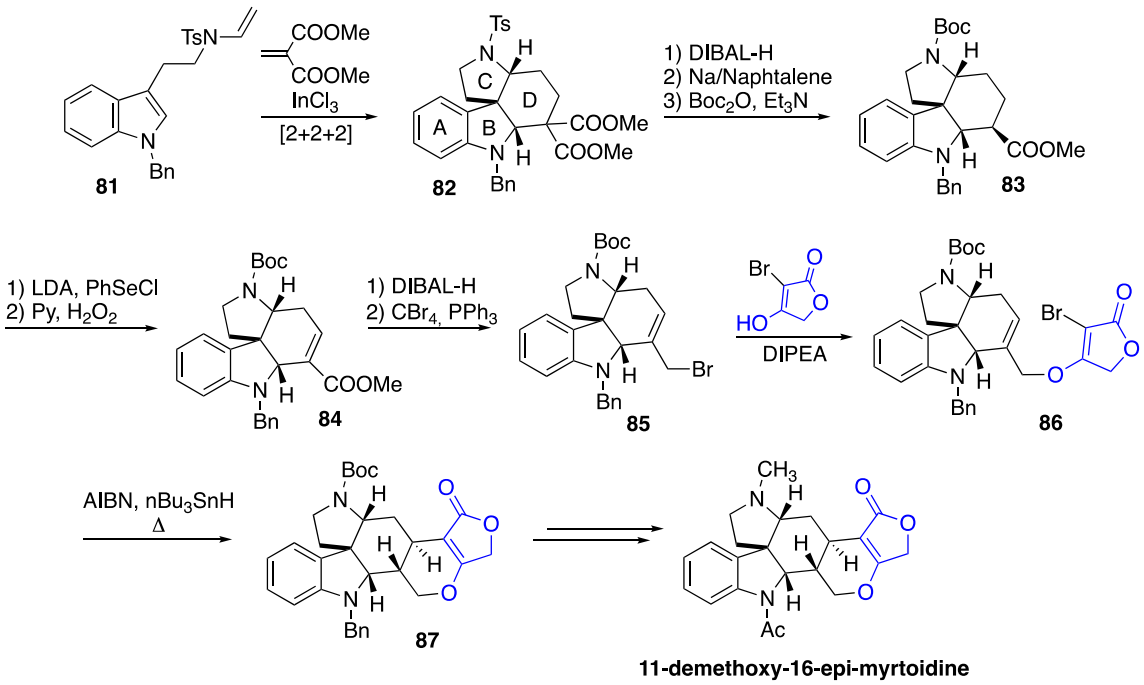


**Fig. 16.** Total synthesis of **myrtoidine** analogue, exploiting radical cyclization to obtain the condensed tetronate moiety.

*2.2.1. Dieckmann condensation*

Synthesis of natural pulvinones via intermolecular methods has been already discussed in the previous chapter, in which the functionalization at C(3) and C(5) of the commercially available tetronic nucleus was described. Pulvinones were also prepared by intramolecular approaches, and Dieckmann condensation was one of the most convenient and exploited ways for the preparation of this class of natural compounds. Bernier et al. in 2007 prepared differently substituted pulvinones with a mixed approach in which aryl halides **94** were treated with acyloxycinnamates **95** under Heck conditions [51]. The resulting acrylates **96** were subjected to a hydrolysis/transesterification sequence, after which the obtained arylacetic esters **97** were exposed to alkaline conditions, so that Dieckmann condensation could take place, to afford the desired pulvinones (Fig. 18a).

In a similar way pulvinone analogues were prepared starting from α-hydroxyester **98** (obtained by Lewis acid-mediated alcoholysis in presence of methyl 3-phenylglycidate) by Nadal and coworkers [52]. Esterification of the secondary alcohol with appropriate arylacetic acids gave access to **99**, readily α-deprotonated in presence of LHMDS to favor Dieckmann condensation, with subsequent obtainment of several differently substituted pulvinones in high yields and with almost complete diastereoselectivity (Fig. 18b). Lastly, the synthetic approach described by Xu et al. to obtain the same pulvinone skeleton exploited the condensation between ethyl chloroacetate **101** and arylacetic acid **100** [53]. The resulting 3-aryl tetronic acid **103** was converted into methyl tetronate, while the introduction of the 5-arylidene substituent took place by aldol condensation, as previously reported, to give the 5-arylidene derivatives. Final enolate deprotection in presence LiBr gave pulvinones (Fig. 18c).

Trying to synthesize new analogues of azaprostanoid (a potent antiaggregatory agent), Pashkovskii et al. functionalized the tetronic core, prepared starting from Meldrum acid as the precursor [54]. In particular, acylation of the cyclic dione **104** was performed, followed by decarboxylation and alkyl chain rearrangement to give **106**. Transesterification to compound **107** and Dieckmann condensation upon TBAF exposure highlighted how 3-acyl tetronic acid **108** resulted from the introduction of the acyl chain in the former steps and subsequent intramolecular rearrangement, rather than through a late-stage intermolecular reaction. Conversion of the exocyclic carbonyl to methylene afforded 3-alkyl derivative **109**, appropriately functionalized for the preparation of enaminotetronate **110** as oxa-aza prostanoid analogue (Fig. 19).

Tetrocarcins are a widely represented class of natural compounds showing the tetronic nucleus [55]. Their bioactivity, especially against gram positive bacteria, leukemia and carcinoma, justified the increased interest towards viable synthetic pathways to afford the aglycone portion, the spirotetronate **(+)-tetronolide**. In 2006, Boeckman et al. revised the previously reported approaches for the total synthesis of this key intermediate, describing their efforts to find the best protocol for the preparation of enantiomerically pure tetronolide [56]. The first aim was to synthesize the two portions **111** and **112**, identified as direct precursors of the desired aglycone skeleton. In particular, cyclohexene derivative **111** was prepared starting from stannylation of divinyl ether **113**, further carboxylated and condensed with optically pure (-)-lactam **116** to give imide **117**, brominated on the less hindered double bond, to afford the unstable dibrominated product **118** (Fig. 20).

Coupling with dienol ester **119** allowed the isolation of acetal **120** with excellent diastereoselectivity, so that imide cleavage and intramolecular cycloaddition could give the bicyclic system, as a 1:5 mixture of diesters **121a** and **121b**. Epoxidation and ring opening afforded allyl alcohol **122**, then chemoselectively hydrolyzed and converted to protected primary alcohol **123**. MOM derivatization of the residual secondary hydroxyl group and dioxolane opening gave the desired allyl ether **111**. On the other hand, polyunsaturated dioxolenone **112** was prepared by condensation between lithium enolate of imide **124** and allyl iodide **125**, further reduced and *O*-protected to give **127** (Fig. 21). Double bond epoxidation, followed by primary alcohol benzylation, gave **128**, which after epoxide opening by $Me_3Al$, MOM protection and debenzylation, afforded **130**. Oxidation to aldehyde allowed HWE reaction with phosphonate **131** to obtain triene **132**, further subjected to the same protocol of deprotection-oxidation-HWE reaction with **134** to afford the desired dioxolenone **112**. Reaction between **111** and **112** afforded intermediate β-keto ester **135**, in which the *i*Pr-ester was converted into the more reactive methyl ester. Dieckmann condensation allowed the construction of the spirotetronic acid core, showing an exocyclic enol ether double bond at C(3) (compound **136**).

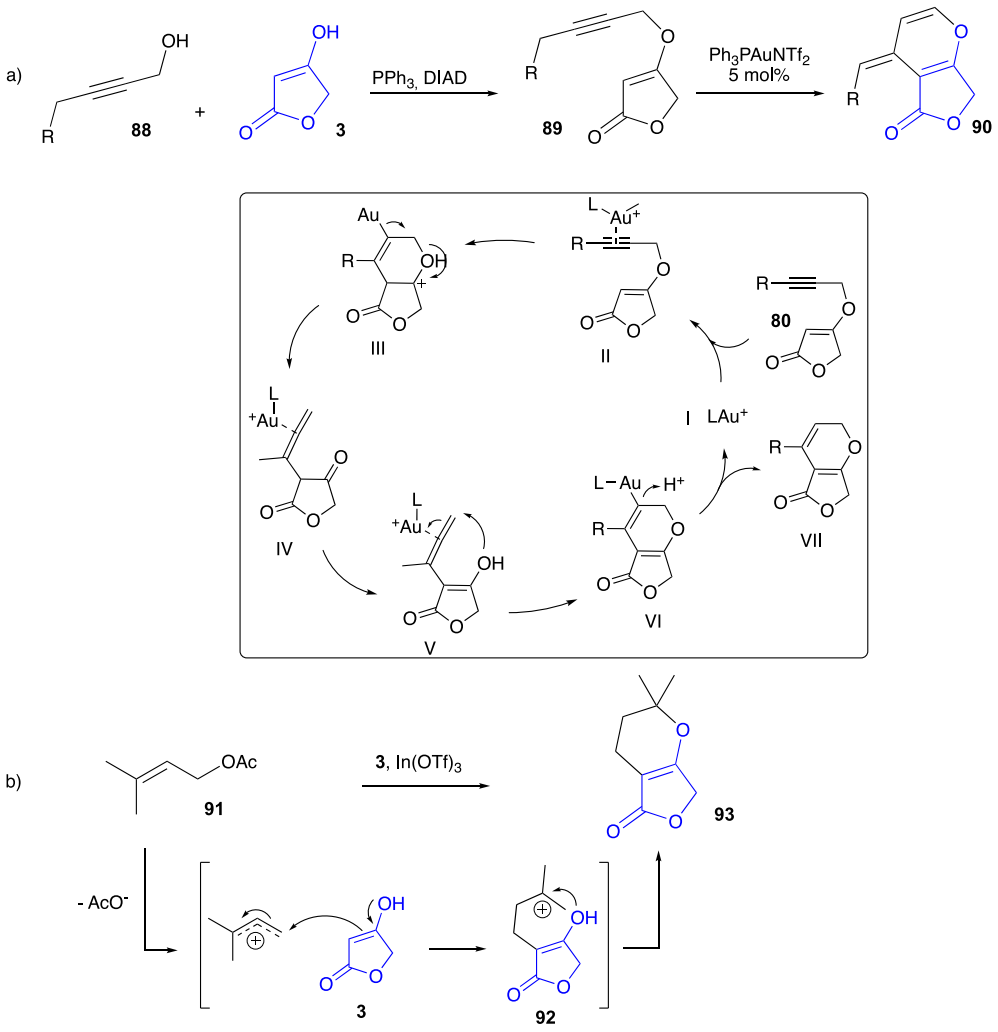


**Fig. 17.** Au-catalyzed cyclization to pyran **90** and its proposed reaction mechanism (a); In-based ring closing reaction on tetronic acid **3** in presence of allyl acetate substrate **91**.

Oxidation of the primary alcohol to aldehyde **137** and subsequent Wittig olefination afforded α,β-unsaturated aldehyde **138** which, upon MPM cleavage and conversion of primary alcohol to chloride **139**, allowed sulfonylation reaction and isolation of the stable sodium salt **140**. Julia olefination, performed in presence of NaO*t*Am, resulted in macrocyclization. Oxidation and desulfonylation gave **141**. Enantioselective ketone reduction, followed by MOM protection afforded **142**, which was desilylated, oxidized and completely deprotected, to afford optically pure **(+)-tetronolide**, in which the 5-spiro-3-acyl tetronic acid core acts as a connector between the four condensed rings (Fig. 22).

Nodulisporacid A is a natural antiplasmodial agent isolated from marine fungi *Nodulisporium* Sp. CRIF1 [57]. From the structural point of view, it is worth to note the presence of three stereogenic centers and the presence of a 1:1 ratio between *Z*- and *E*- isomers. The approach followed by Sumiya et al. for its synthesis provided for a *one-pot* reaction between a suitable aldehyde, diketene and dimethyl (*S*)- malate (Fig. 23) [58]. In particular, (*R*)-glyceraldehyde acetonide **143** underwent Grignard reaction with **144** and oxidation to ketone **145**, further attacked by MeLi in presence of $SnCl_4$. Protection as TBS ether and acetonide cleavage gave **147**. A three-component reaction with diketene **148** and malate **149**, in presence of $TiCl_4$, gave the linear intermediate **150**, ready to undergo Dieckmann condensation upon treatment with TBAF, so that the acyl tetronic acid skeleton of **151** could be set. Contingent TBS deprotection favored intramolecular cyclization of γ-hydroxy ketone of **151** to 2,5-dihydrofuran, whose acidic hydrolysis afforded **nodulisporacid A**.

A total synthesis approach for pulvinic acid derivative **methyl bovinate** was reported by Besl et al. [59]. In this work, the key intermediate 4,5-dimethoxy-benzaldehyde-2-menthylester **152** was treated with pyrandione **153** in acidic conditions, allowing aldol condensation and further rearrangement to terphenyl quinone **154**, in alkaline environment. Oxidative rearrangement according to Wikholm conditions [60] favored the condensation of the hydroxy terphenyl quinone to dilactone **155** which, in presence of KOH in methanol, underwent ring opening and formation of two diastereoisomers **156a** and **156b** (15:85 ratio). The main product **156b** was isolated, so that dealkylation and lactonization could give the desired **methyl bovinate** (Fig. 24a). Hereafter the mechanism for dilactone **155** obtainment is reported (Fig. 24b): oxidation by DMSO afforded sulfur salt **158**, readily attacked by acetic anhydride. Intramolecular rearrangement on the resulting ketene of **159** resulted in tetronic acid derivative **160**, whose enol portion was able to condense on the residual anhydride, with subsequent formation of dilactone **162**.

Other methyl ester analogues of pulvinic acids, namely **vulpinic acid derivatives**, were prepared by Nadal et al starting from methyl tartrate **163** (Fig. 25) [61]. Mono-esterification was performed in presence of suitable arylacetic acids, so that treatment with LHMDS afforded, after dehydration, 5-alkylidenetetronic acids **166**, in which the *Z* isomer was obtained with high diastereoselectivity. Generation of the sodium salt of the resulting butenolide was crucial to perform the

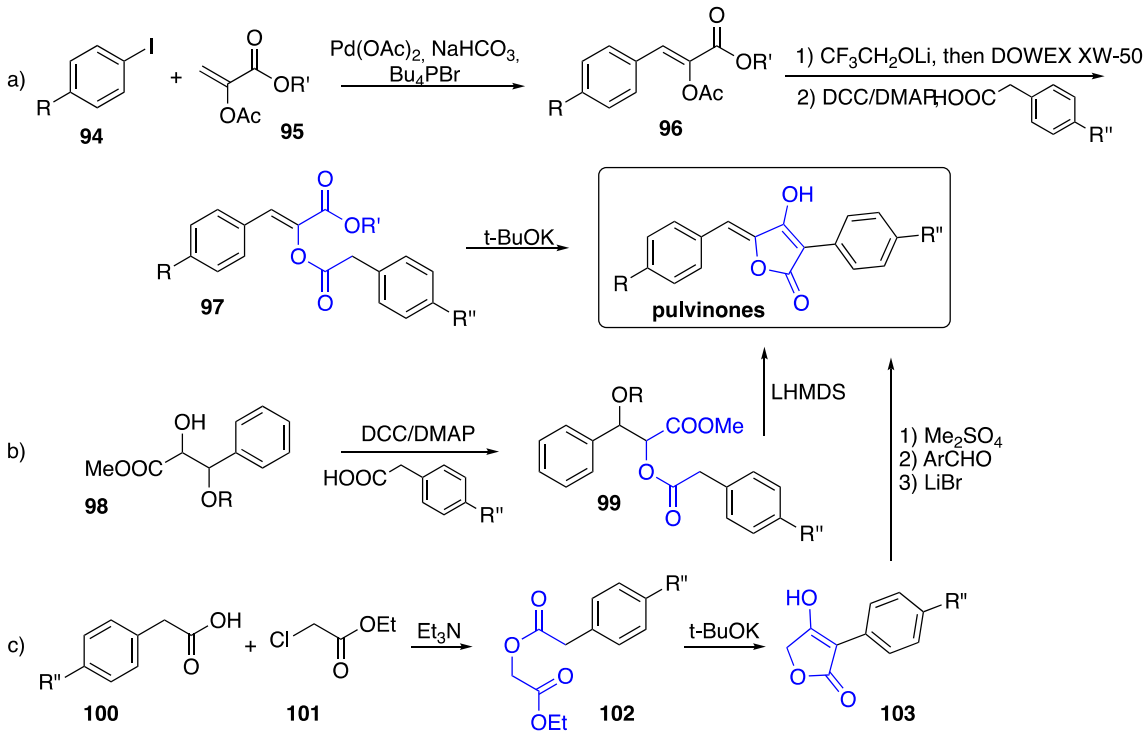


**Fig. 18.** Different intramolecular approaches for the synthesis of **pulvinones** exploiting Dieckmann condensation.

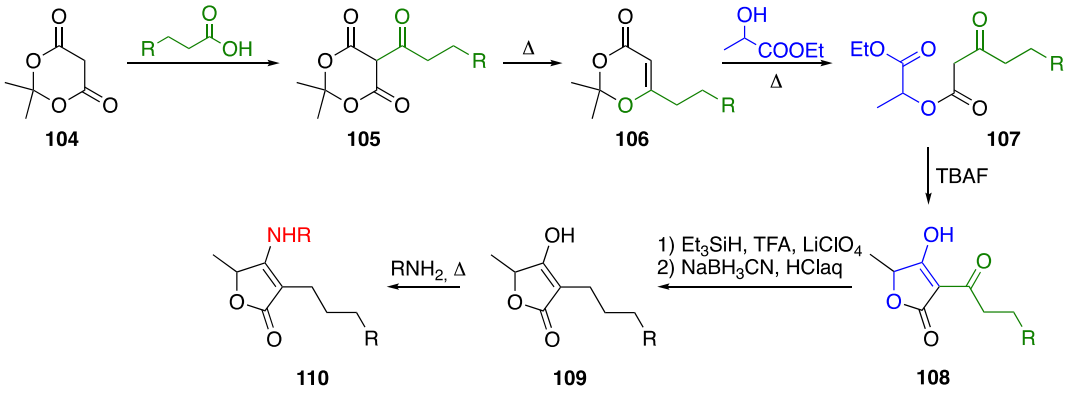


**Fig. 19.** Functionalization of Meldrum's acid **104** to tetronic acid **109**, as useful intermediate for the synthesis of oxa-aza prostanoid analogue **110**.

iodination of the exocyclic double bond (**167**), allowing Suzuki-Miyaura coupling between different aryl boronates and iodinated substrates, with subsequent obtainment of differently substituted vulpinic acid analogues **168**.

**Pulverolide**, an antibacterial butenolide analogue extracted from *Pulverobuletus ravanelii*, shows a particular tricyclic core, in which the tetronate nucleus bears a phenyl group at C(3) [62]. Because of its rarity, the total synthesis of this natural compound was undertaken and reported by Yang and co-workers [63]. The approach was similar to the one previously described for the preparation of pulvinones (Fig. 17c). More specifically, condensation between bromoethyl acetate and phenylacetic acid in potassium carbonate, followed by lactonization, afforded tetronic acid **169**, which, upon lithiation and subsequent reaction with the appropriate aldehyde, gave the aldol adduct **170**. In this case, microwave irradiation at 245 °C in ammonium acetate allowed ring condensation to **171** and dehydration (**172**), while final debenzylation afforded the desired tricyclic **pulverolide** (Fig. 26).

Recently, Bao et al. designed dual antifungal compounds, merging the pharmacophores of **pulvinic acid** and **azoxystrobin** [64]. In order to achieve this purpose, methyl glycolate **173** was condensed with arylacetic acid methyl esters **174** affording tetronic acids **176**, via Dieckmann condensation. Finally, enol functionalization with the proper bromo derivative **177** afforded a series of target compounds **178**. Antifungal activity evaluation showed that electron-withdrawing groups on the aromatic ring of the acrylate moiety positively affected the potency of this new class of compounds (Fig. 26a).

Another class of potentially bioactive butenolides was obtained by Matsuo et al. exploiting the reactivity of dithiomalonates for a stereoselective synthesis of 3-alkoxycarbonyltetronic acid derivatives [65]. In particular, it was observed that monoester **182** was formed by condensation between methyl glycerate **179** and diphenyl dithiomalonate **180** in presence of Cu catalysts **181.** Further deprotonation resulted in intramolecular cyclization, while primary alcohol deprotection and alcoholysis of the sulphurated portion afforded the desired optically pure 3-*t*-butoxycarboxyl-5-alkyltetronic acid **183** (Fig. 27b). Antioxidant and anti-inflammatory 3,5-diarylsubstituted tetronic acid analogues **186** were prepared by Weber et al. starting again from arylacetic acids [66]. α-Aryl α-bromoacetate **184** was reacted with the arylacetic

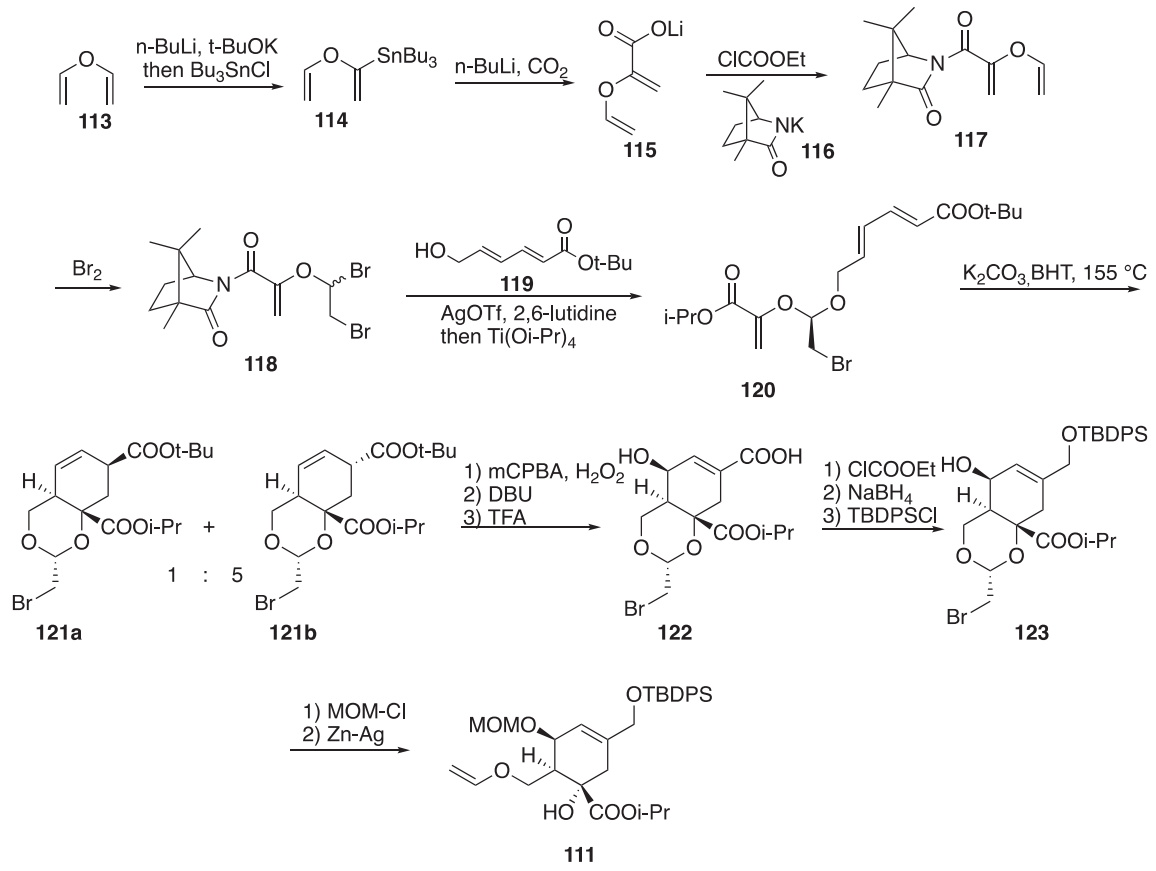


**Fig. 20.** Preparation of cyclohexene derivative **111**, as useful intermediate for the synthesis of **(+)-tetronolide**.

precursor in alkaline environment to give **185**, ready to undergo cyclization upon treatment with NaH (Fig. 27c).

The biosynthetic pathway towards the formation of the tetronate core of antiviral **quartromicin** was *in-depth* analyzed by Wu and coworkers, in order to better comprehend the key step, essential for the formation of the alkylidenetetronate nucleus [67]. For this purpose, the skeleton of butenolide **192** was prepared starting from β-ketothioester **187** (already reported in literature), [68] which was treated with β-hydroxyester **188** in presence of $AgCOOCF_3$. The resulting linear intermediate **189** was then exposed to TBAF, so that desilylation of the hydroxy group and rearrangement to tetronic acid **190** took place and favored *O*-acetylation to **191a**. Treatment with hydrolase QmnD4 afforded the elimination product **192a**, showing the exocyclic double bond necessary for the four *intermolecular* Diels Alder reactions to take place. In particular, cycloaddition between the unsaturated chain (diene) of one molecule and the exocyclic double bond (dienophile) of another molecule allowed the formation of the spirotetronate moiety, as subunit of quartromicin structure (Fig. 28a). With similar purposes, Lees et al. investigated the deacetylase role of natural lyase (exclusively present in spirotetronate biosynthetic pathways) [69]. Enantiomerically pure tetronates were prepared and acetylated, following the above reported protocol so that, after acyl tetronic acid **191b** formation, the acetoxy substituent could be eliminated in presence of DBU as the base, resulting in an exocyclic double bond at C(5). Comparison between naturally occurring and synthetic **192b** revealed identical structures, proved to be the direct precursor for the *intramolecular* Diels Alder cycloaddition leading to **193**, late intermediate for the synthesis of **abyssomicins C** (Fig. 28b).

The same TBAF-mediated Dieckmann condensation above reported was used by He et al., in an effort to accomplish the total synthesis of antimicrobial **tetrodecamycin** [70]. *Cis*-decalin derivative **194** was reacted with ethyl acetate and oxidized to give β-ketoester **195**, which underwent transesterification with methyl (*S*)-lactate, in presence of catalytic nitrobenzeneboronic acid (NBBA). The resulting diastereoisomers **196a** and **196b** were then treated with an excess of TBAF, to give the suitable tetronic acid intermediates **197a** and **197b.** Unfortunately, intramolecular condensation attempts to obtain the tetracyclic structure did not give the active **tetrodecamycin**, because of the lack of reactivity of the *cis*-decalin double bond towards oxidative cyclizations to fused *trans*-decalin (Fig. 29).

An interesting class of tetronate-containing compounds is represented by spirohexenolides, which possess cell growth inhibition activity, with low toxicity for healthy cells. In their work, Jones et al. reported the synthesis of the key intermediate for the preparation of **spirohexenolide B**, compound **202**, exploiting cycloaddition reactions between a suitable diene and dienophile [71]. In particular, conjugated trienic alcohol **198** underwent Diels Alder reaction with α-acetoxyacrolein to give cyclohexene aldehyde **199**, further converted to methyl ester **201**. Dieckmann condensation upon LHMDS-mediated deprotonation of the acetyl group afforded 3-unsubstituted spirotetronate **202**, which after further steps gave the desired natural compound (Fig. 30).

### 2.2.2. *Lactonization*

Another extensively used approach towards the formation of tetronate derivatives was based on lactonization: intramolecular transesterifications or nucleophilic substitution reactions allowed the obtainment of differently substituted tetronic acid analogues, resulting in the development of new protocols towards their preparation.

Athanasellis and coworkers reported in 2002 the synthesis of 3-acyl tetronic acids, avoiding cross-coupling reactions or any other intramolecular methodology until here described [72]. Activation of *O*-acetylated α-hydroxyacid **203** was performed with HOBt and followed by the nucleophilic attack of methylene active compounds, such as

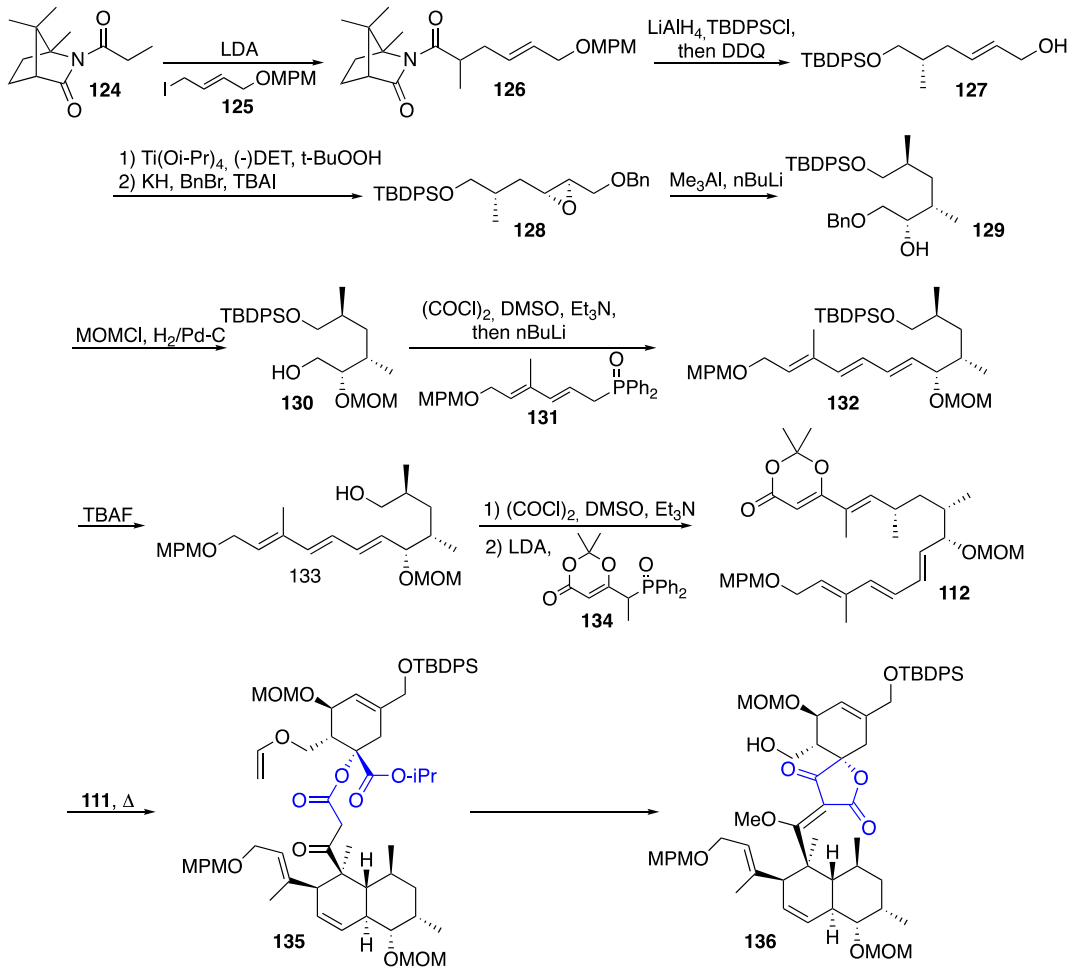


**Fig. 21.** Preparation of 3-alkylidenetetronic acid intermediate **136** by Dieckmann cyclization.

malonates or acetoacetate derivatives **205**. Resulting aldol condensation product **206**, upon deacetylation, allowed the formation of 3-functionalized tetronic acids **207** (Fig. 31). It is worth to note that only the glycolic acid derivative was able to afford in one step the corresponding tetronic acid, while all of the α-substituted glycolic acids required an acidic treatment to favor the rearrangement to **207**. Reaction of methylene active compounds with protected α-hydroxyacids was exploited also by Mitsos et al. but using NHS-activation in order to obtain product **206** [73]. Cyclization upon deprotection in alkaline environment afforded 3-acyl or 3-alkoxycarbonyltetronic acids with no racemization, so that 5-phenyl 3-acyl- (or 3-alkoxycarbonyl)tetronic acids could be prepared in a stereoselective way. More recently, activation of α-substituted glycolic acid **208** in form of cyclic carbonate **209** was reported by Prousis et al. [74]. Also in this case, treatment with methylene active compounds **205** furnished intermediates **206**, ready to undergo intramolecular transesterification, affording optically pure 5-monosubstituted 3-acyltetronic acids **207**. Due to its importance in cell wall building and maintenance, UPPS was evaluated as a target for the exertion of antibacterial activity of tetramic and tetronic acid derivatives [75]. For the preparation of a set of compounds presenting the tetronate moiety, Peukert et al. used the same approach, so that the resulting 3-methoxycarbonyltetronic acid (**207**, Y = OMe) could be treated with different aromatic amines, affording 3-amidotetronic acids **210** as potential UPPS inhibitors in the context of antibacterial chemotherapy (Fig. 31).

Solid-phase synthesis of bioactive acyltetronic acids was reported as an easy process, suitable for immobilization, functionalization and cleavage of the desired compound. According to Matiadis and co-workers, carbonate-activated Wang resin **211** was treated with (*S*)-mandelic or (*S*)-lactic acid to afford a new carbonate bond upon the polymer (**212**) [76]. Condensation with dialkyl malonate in presence of HOBt afforded the α,β-unsaturated diester **213**. Treatment with TFA allowed the release from the resin and cyclization to optically pure tetronic acids **214** (Fig. 32).

Tetronic acid derivatives were found to be very useful as radical scavengers, with antioxidant and, in particular, radioprotective properties against γ-irradiation. In this context, **norbadione A** was identified as a potent antioxidant agent, however too toxic to be used in therapy. Alternatively, its pulvinic substructure **xerocomic acid** was used as a model for the preparation of analogues with radioprotective and antioxidant activity (Fig. 33) [77].

A crucial symmetrical bis-lactone moiety **220** was prepared by Le Roux et al., [78] by condensing phenylacetonitrile **215** and diethyl oxalate **216**, resulting in iminotetronic intermediate **218**: hydrolysis to substituted tetronic acid **219**, followed by lactonization, afforded the desired product **220**, ready to undergo nucleophilic attack by substituted amines, to afford **221** (Fig. 34). Unsymmetrical bis-lactone **225** was prepared by Korovitch et al. through the reaction between phenylacetate **222** and ethyl glycolate **223** by intramolecular transesterification. The resulting tetronic acid **224**, protected in form of methyl tetronate, was functionalized at C(5) through aldol condensation with methyl pyruvate. Ester hydrolysis and subsequent annulation afforded the unsymmetrical bis-lactone **227**. Interestingly, the reaction with different *N*-based nucleophiles was described, resulting in different sets of 5-amidotetronic acids, bearing crown ether (**228**) or dimer moieties (**229**), with potential antioxidant activity (Fig. 35) [79].

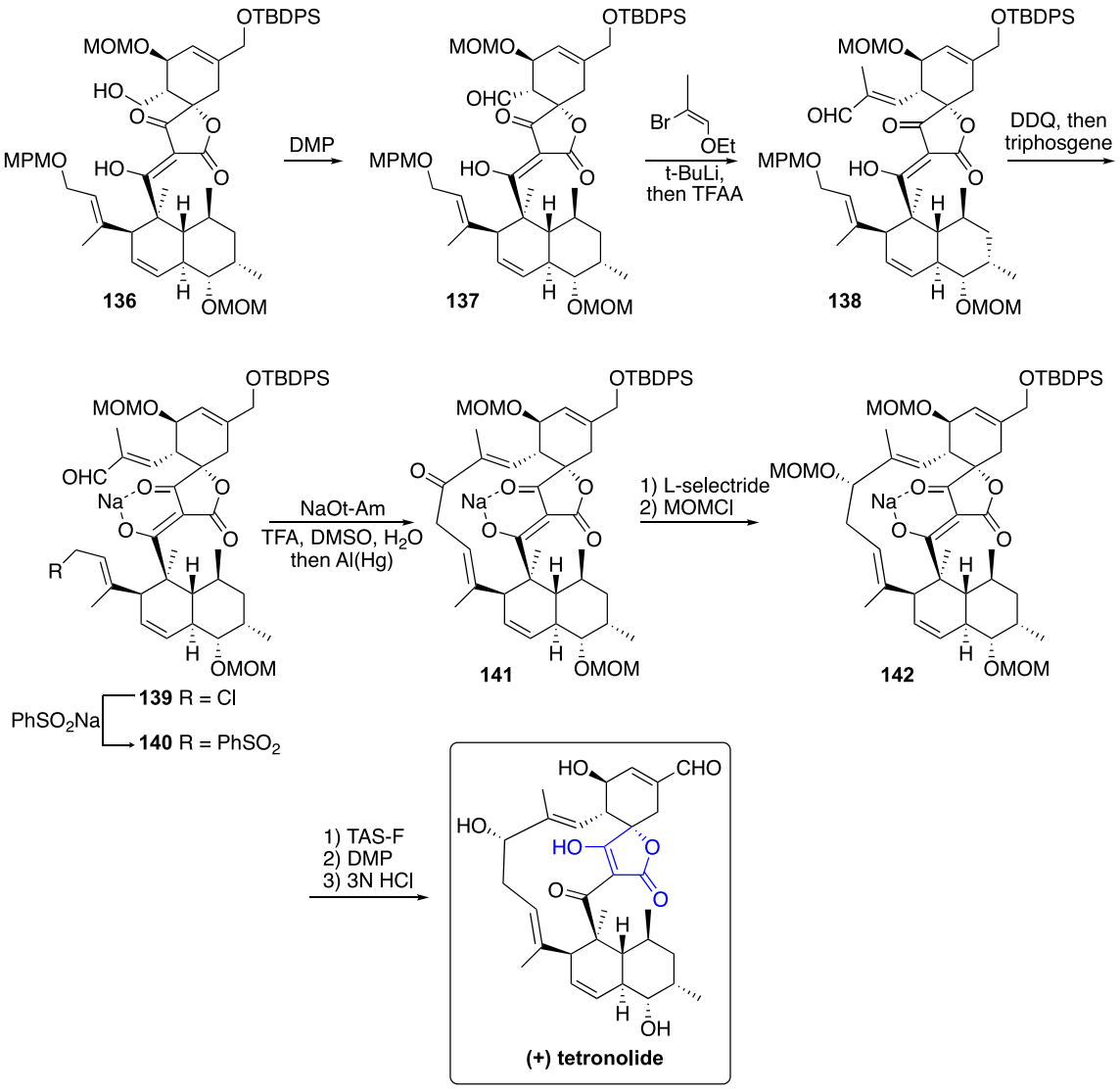


**Fig. 22.** Conversion of intermediate **136** to optically pure **(+)-tetronolide**.

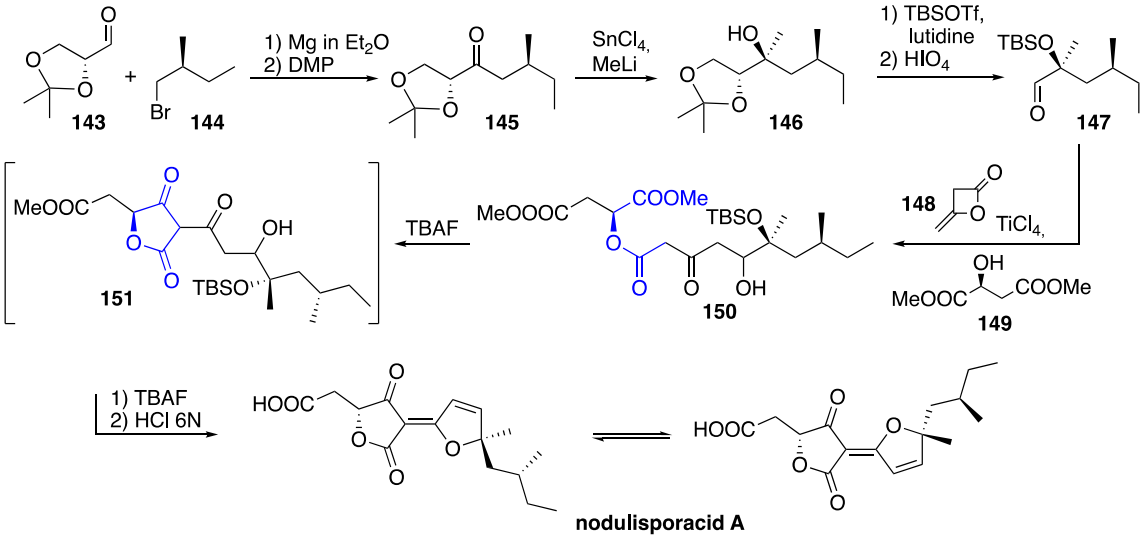


**Fig. 23.** Functionalization of protected glyceraldehyde **143**, as optically pure starting material for the preparation **of nodulisporacid A**.

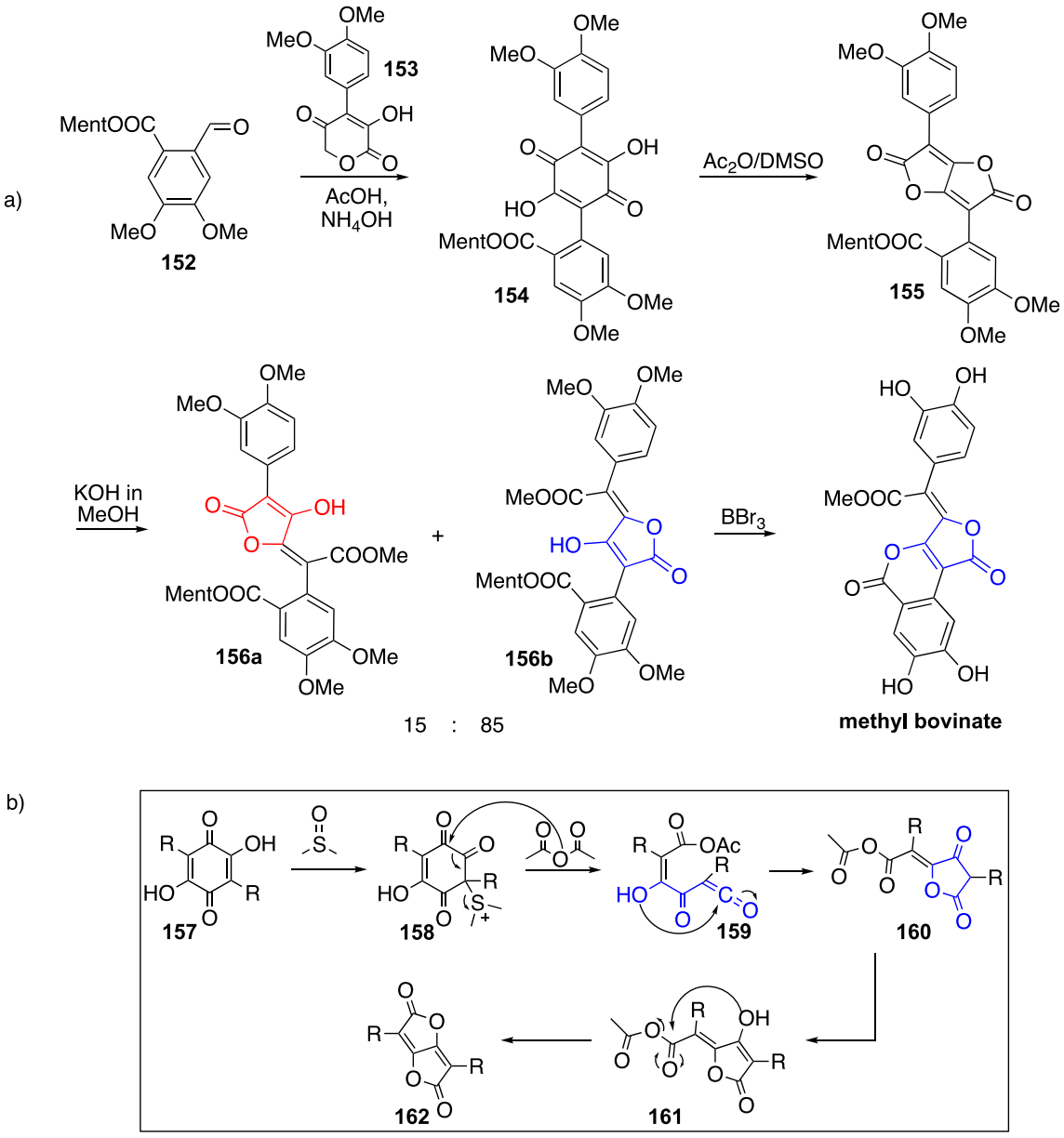


**Fig. 24.** Synthesis of natural **methyl bovinate** by Wikholm rearrangement to dilactone **155**, followed by ring opening and condensation (a); detailed mechanism of Wikholm oxidation in presence of $Ac_2O$ and DMSO (b).

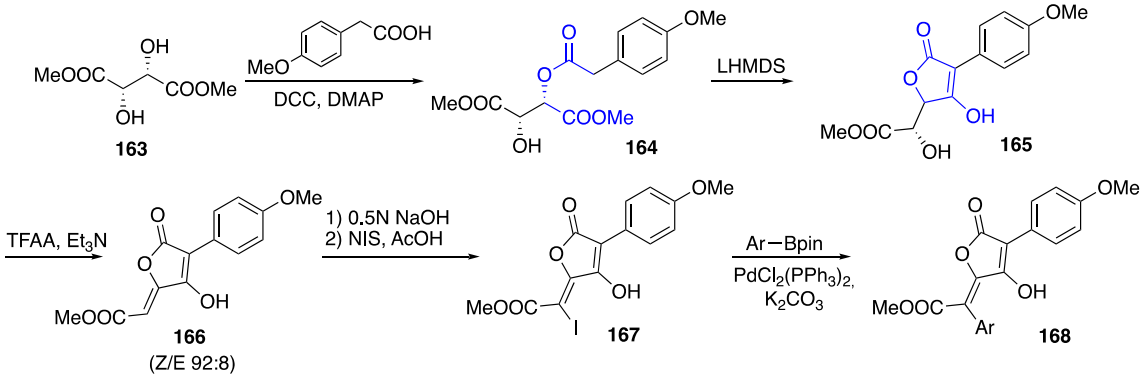


**Fig. 25.** Preparation of **vulpinic acid** analogues **168** starting from methyl tartrate **163**.

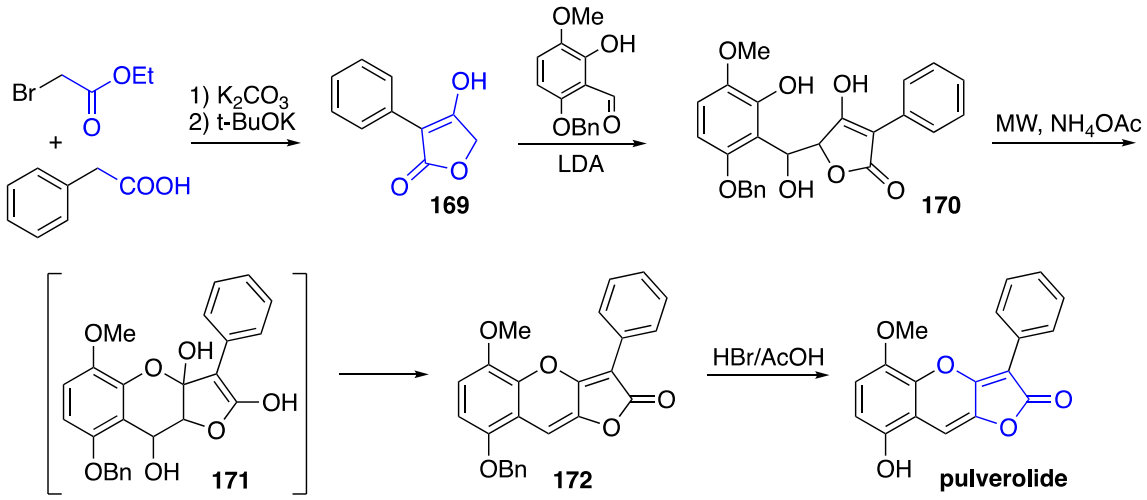


**Fig. 26. Pulverolide** synthesis exploiting a microwave-mediated intramolecular condensation/dehydration.

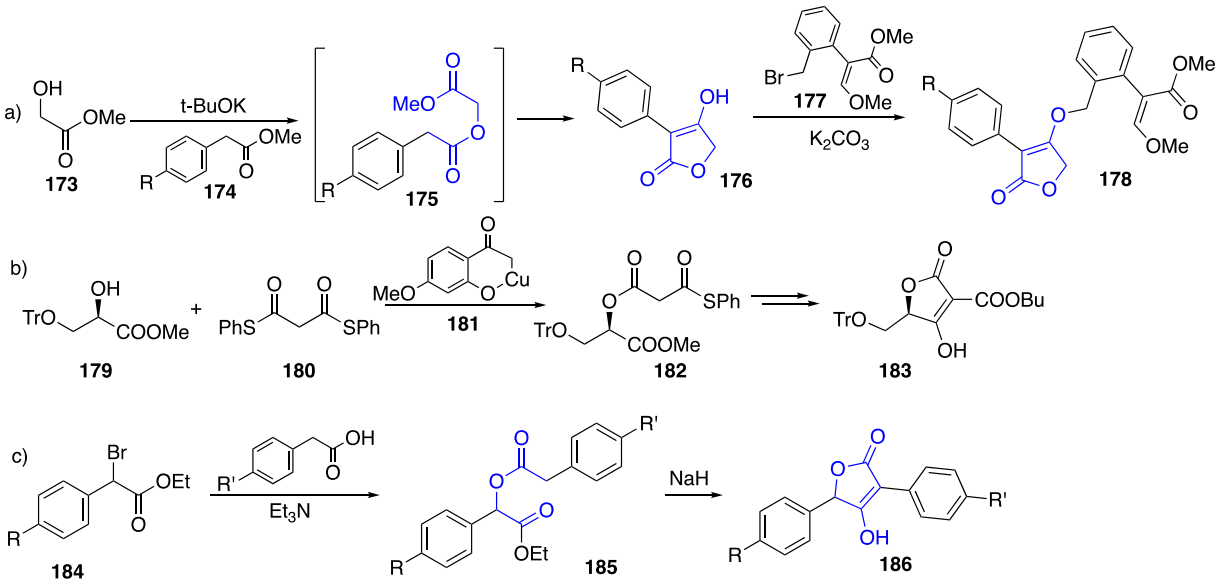


**Fig. 27.** Different synthetic approaches towards the formation of 3-aryl tetronate **178**, 3-butoxycarbonyl tetronic acid **183** and 3,5-diaryl tetronic acid **186**.

Jones et al. focused their attention on the preparation of several thiolactomycin derivatives, as growth inhibitors of *Plasmodium falciparum* and potential antimalarial agents [80]. Double alkylation of β-ketoester **230** resulted in compound **231**, ready to be brominated at C (4) to afford **232**. Base-catalyzed cyclization gave access to the appropriately substituted tetronic acid core **233** (Fig. 36).

Bisorbibutenolides belong to the class of bisorbicillinoids, isolated from fermentation of *Trichorderma* Sp. USF-2690 and known as potent antioxidant agents [81]. From the biosynthetic point of view, it was hypothesized that bisorbicillinol could represent the common intermediate for the formation of other bisorbicillinoids. Hong et al. focused their attention on the synthesis of such a scaffold [82]. Pyruvaldehyde di-isopropyl acetal **234** was enantioselectively functionalized to afford tertiary alcohol **235**, further protected and subjected to chain elongation to give **236**. Olefination of the carbonyl group, protection of the tertiary alcohol and ketal deprotection afforded **238**, ready to undergo aldol condensation with acetoacetate derivative **239** and methylene oxidation so to obtain **240**. Condensation and ring closing, followed by PMB deprotection and [4 + 2] cycloaddition gave access to the quinol system of sorbicillinol **242**. Final treatment with KHMDS allowed the formation of the tetronate moiety by lactonization and formation of **bisorbibutenolide** (Fig. 37).

Polyketide **mycosporulone** is a natural compound extracted from fungi, with antibacterial, antimycotic and anticancer activity [83]. It consists of a spiro moiety, in which one of the two rings involved is a methylenetetronic acid. According to Jung et al., conjugated ketoester **243** underwent aldol condensation in presence of propionaldehyde, so that cyclohexanone **244** was obtained (Fig. 38) [84] Enolization of the keto group in presence of DIPEA/TIPSOTf afforded silyl enol ether **245**, ready to react with (*R*)-glyceraldehyde acetonide to give a diastereoisomeric mixture of aldols **246a** and **246b**. Isolated **246b** was oxidized to ketone **247**, further treated with DMDO to afford acyloin **248**, deprotected from the acetonide and cyclized by transesterification to deliver spirotetronate **mycosporulone**.

After isolation from *Litsea rotundifolia*, **rotundifolide A** and **B** were characterized and showed significant *in vitro* inhibition of PTP1B enzyme [85]. According to the work of Zhao et al., synthesis of the tetronate moiety was achieved after elongation and terminal TMS-alkyne installation to give **249** [85]. α-Deprotonation and treatment with *O*-protected lactaldehyde (**250**), followed by acidification, allowed the ring closure to afford β-hydroxylactone **252**, further oxidized to **rotundifolide A** (Fig. 39). **Rotundifolide B** was prepared following the

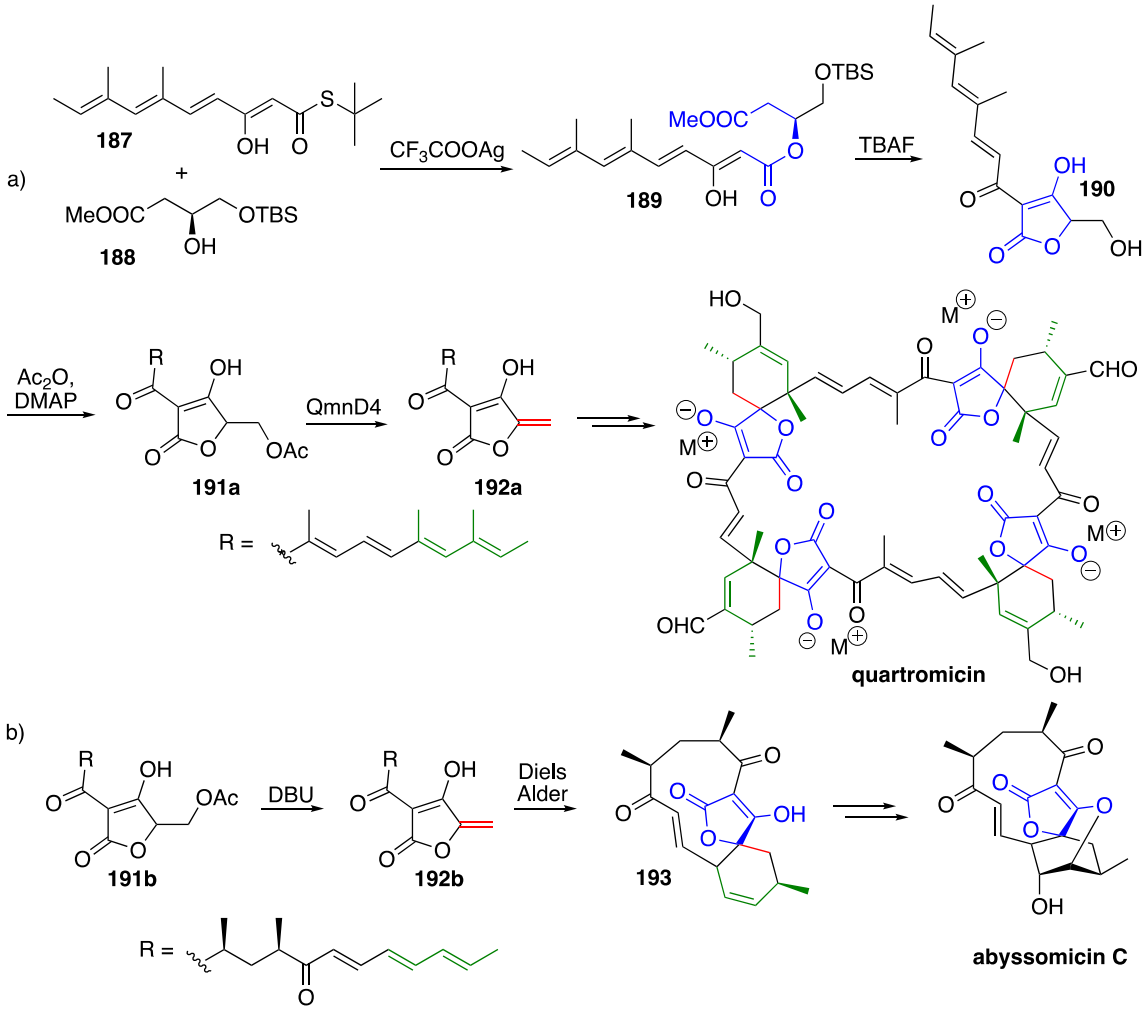


**Fig. 28.** Chemical preparation of 5-alkilidene tetronic acids **192a** and **192b** as precursors for the biosynthesis of **quartromicin** and **abyssomicins C**.

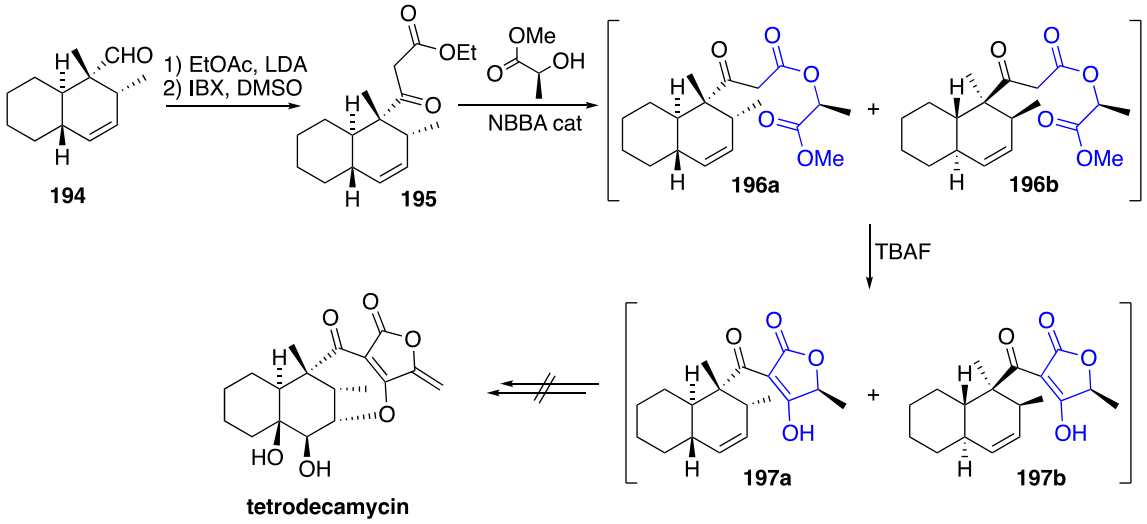


**Fig. 29.** Attempted approach to the synthesis of optically active **tetrodecamycin** from 3-acyltetronic acid intermediates **197a** and **197b**.

same procedure, but starting from **253**, with a terminal double bond instead of the alkyne group.

Kapferer et al. prepared in an enantioselective way tetronate analogues of natural butenolides from *Plagiomnium undulatum* [86]. For this purpose, heptanal **254** was treated with malonic acid to give the corresponding β,γ-unsaturated diacid **255**, which was decarboxylated and esterified to **256**, then α-methylated to **257**. Dihydroxylation of the double bond favored the ring closure of **258**, affording the γ-hydroxylactone **259**, further oxidized to obtain the optically pure tetronic derivative **260** (Fig. 40). The same protocol was successfully applied also

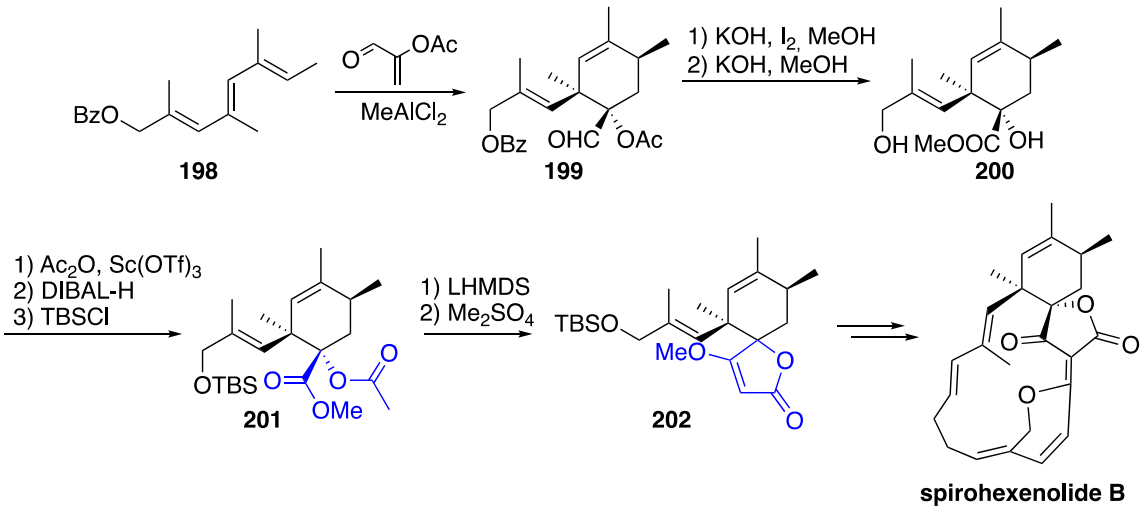


**Fig. 30.** Key steps towards the preparation of **spirohexenolide B**, involving Dieckmann condensation to methyl tetronate **202**.

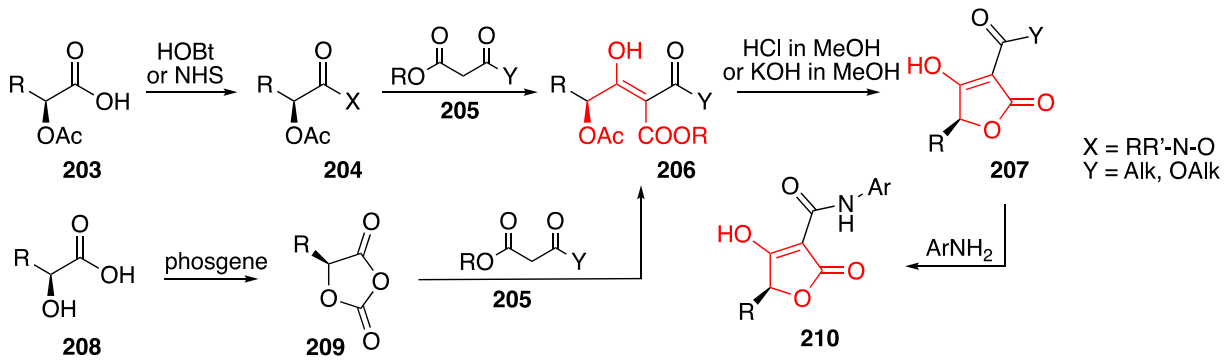


**Fig. 31.** Synthesis of 3-functionalized tetronic acids **207** and **210** by treatment with methylene active compound **205** and subsequent lactonization.

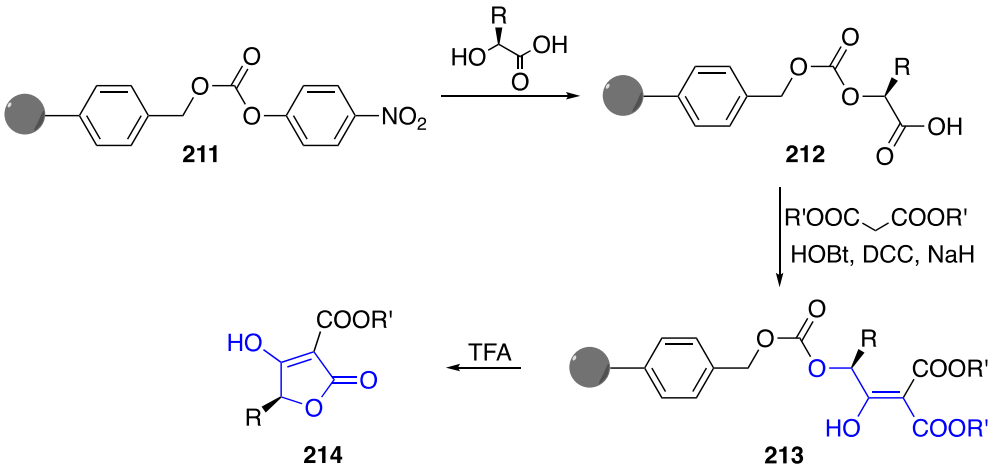


**Fig. 32.** Solid-phase synthesis of alkoxycarbony tetronic acids **214** starting from α-hydroxy acids.

for the synthesis of 5,5-disubstituted analogues.

Trying to synthesize oxypyrimidine analogues as NNRTIs for the treatment of retroviruses, Radi et al. serendipitously discovered a pathway for the preparation of 5-aryltetronic acid, starting from substituted benzaldehyde **261** [87]. Conversion to propargylic *O*-acetylated product was allowed by terminal alkyne addition and *O*-acetylation (**262**), while oxidation of the triple bond to carboxylic derivative gave the suitable intermediate for acid activation and formation of α-methyl β-ketoester **263**. Exposure to alkaline environment for sodium in ethanol, in presence of *S*-methyl isothiourea did not afford the expected pyrimidinone, but the 5-aryl tetronic acid **264** in very good yield, as result of a simple deacetylation and further lactonization (Fig. 41).

According to Hirai et al, 3-acyltetronic acid derivatives could play a certain role as VHR inhibitors, since their enolate anion form is able to mimic the phosphate within the catalytic site of the enzyme [88]. The reported synthesis was based on intramolecular approach starting from

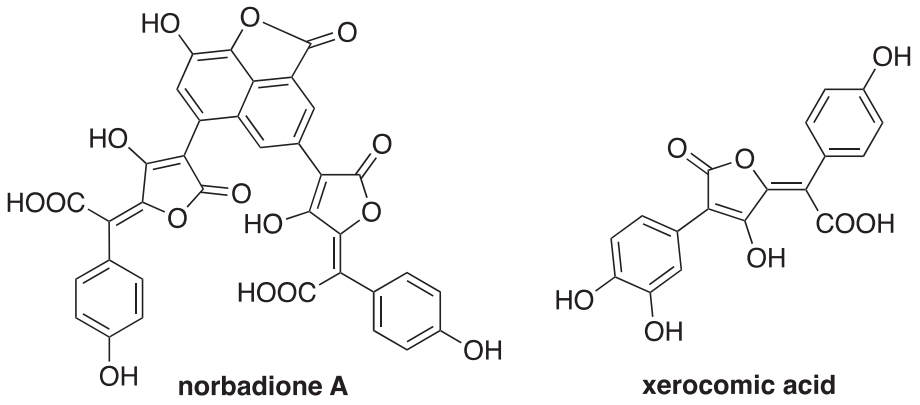


**Fig. 33.** Chemical structures of **norbadione A** and **xerocomic acid**.

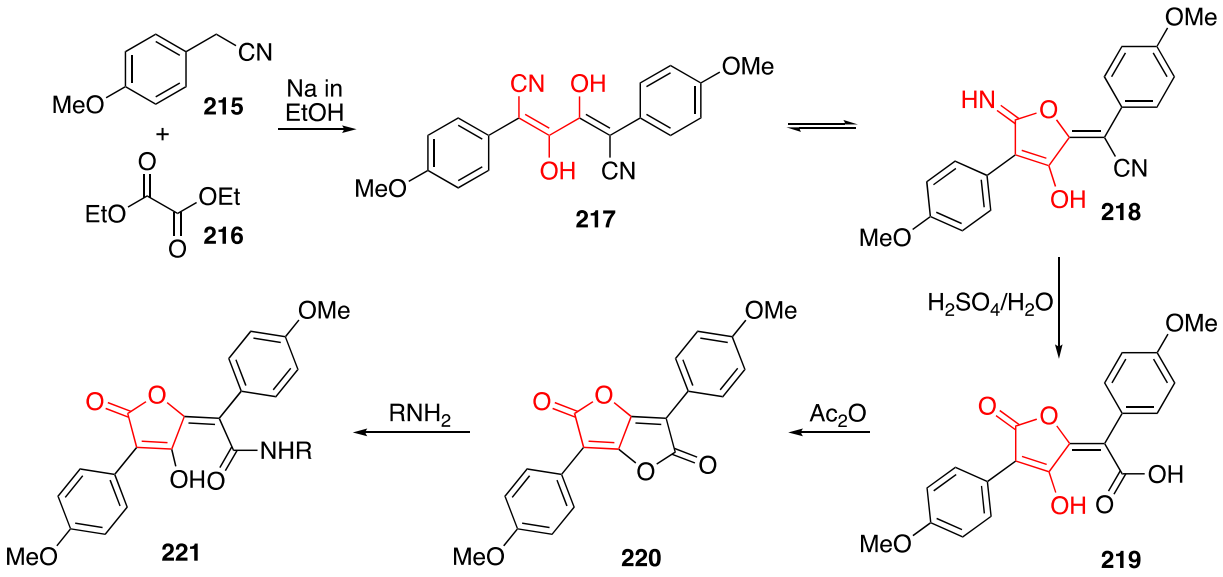


**Fig. 34.** Xerocomic acid analogue **221** preparation by dilactone **220** opening.

*O*-protected glycolaldehyde **265** and methyl propiolate to afford the corresponding propargyl secondary alcohol **266**. 1,4-addition of pyrrolidine and transesterification led to tetronic acid **268**, further acylated by fatty acids and *O*-deprotected to **269**. Treatment with an adequate amine allowed to obtain the corresponding enamine derivatives, both in *E*- and *Z*-forms (**270a** and **270b**, respectively), thanks to the H-bond interactions of the amino group with keto and lactone carbonyls (Fig. 42).

Hu and co-workers made efforts towards the synthesis of compounds with potential antifungal activity by merging the tetronic acid core with a phenylhydrazone portion, to evaluate a synergic effect between these two different motifs [89]. To this aim, ethyl chloroacetoacetate **271** was treated with KO*t*Bu and so that the resulting β-keto-γ-alkoxy ester **272** could be then converted into tetronic acid **3** after exposure to gaseous HCl. 3-alkylidenation was performed in presence of DMF-DMA, affording both *Z*- and *E*-isomers **273a** and **273b**, which equally reacted with phenyl hydrazine, to give the corresponding diastereoisomers **274a** and **274b**, in a 1:1 to 1:3 ratio between the possible tautomeric forms, based on NMR analysis (Fig. 43). *In vitro* essays demonstrated how the presence of halogen on the aromatic ring in ortho or meta position could further improve the antifungal activity of the condensed hydrazine derivatives.

Switching the analysis towards condensed polycycles, a few examples will be reported. Yamaguchi et al. described the conversion of isoprenyldihydrofuran moiety to fused bicyclic tetronate derivatives [90]. Intermolecular formation of 2,3-diethoxycarbonyl dihydrofuran **275** was followed by chemoselective MeMgBr treatment and subsequent formation of intermediate tertiary alcohol **276**. Intramolecular transesterification afforded bicyclic tetronate **277**, ready to undergo thermal ring expansion to the desired product **278** (Fig. 44).

The pyrone core is included in several natural products and represents an important scaffold in medicinal chemistry. Antibacterial **annularin F** (extracted from water fungus *Annulatascus triseptatus*) contains both pyrone and tetronic skeletons, synthesized starting from methyl acetoacetate. Kurdyumov et al. described the oxidation of methoxypyrone ester **279**, to obtain the formylated analogue **280** [91]. Further exposure to EtMgBr afforded secondary alcohol **281**, ready to undergo transesterification to 5-ethyltetronate derivative, racemic **annularin F** (Fig. 45).

Homologous isochromene dione, containing the tetronate moiety, was synthesized by Hussain and his group in an effort to prepare 3-substituted isocoumarins [92]. In particular, condensation of chloroacetyl chloride **282** with benzoyl acetic acid favored the intramolecular cyclization within acid **283** to benzolactone **284**, in which the residual carboxylic acid acted as the nucleophile towards the C-Cl bond, so that after dehydration, isochromene **285** was obtained (Fig. 46).

Exploiting MCR protocol, Moosazadeh et al. prepared natural compounds analogues, such as **massarilactone A** and **B**, endowed with antibacterial activity [93]. The authors developed and interesting and original method for the construction of polysubstituted furopyran

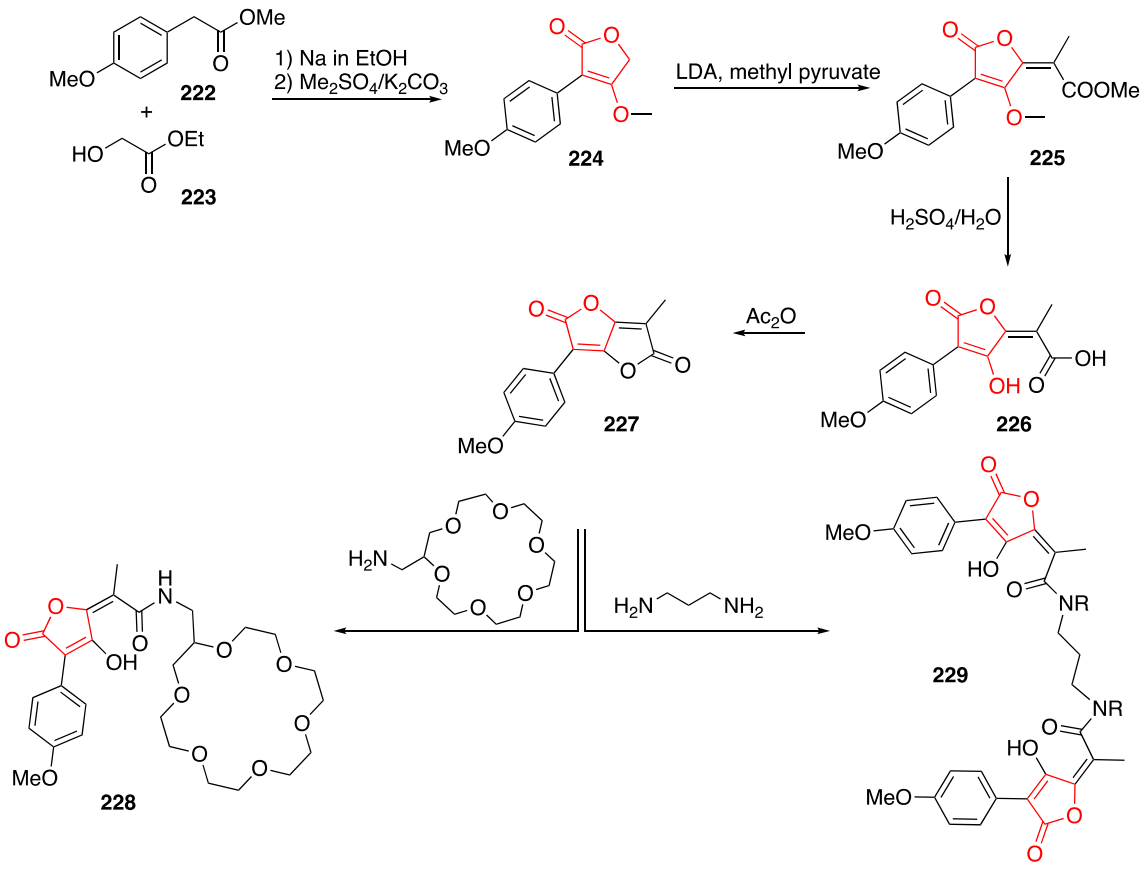


**Fig. 35.** Preparation of chelating and potential antioxidant **228** and **229** by reaction with unsymmetrical dilactone **227**.

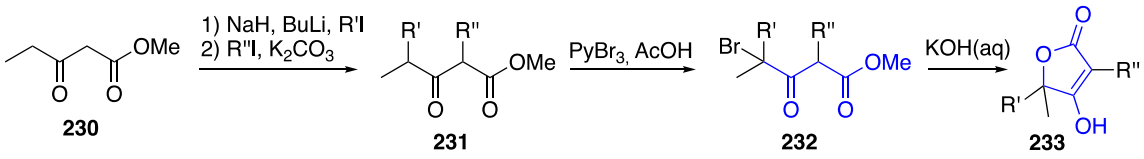


**Fig. 36.** 5-disubstituted tetronic acid **233** obtained by lactonization of brominated **232**.

derivatives, containing the fused tetronate skeleton using Meldrum acid (**287**) and isocyanide (**288**) in 1:6 ratio, in presence of substituted benzaldehydes in form of dimer, linked through a polyethylene glycol chain (**286**) (Fig. 47).

The proposed route to these products was based on a primary [4 + 1] cycloaddition of electron-deficient arylidene Meldrum acid heterodiene moiety **290** with the first isocyanide molecule to give an iminolactone intermediate **292** (Fig. 48). The second isocyanide attack might occur with subsequent five-membered ring cleavage and cyclization providing the diiminopyran intermediate **294**. Addition of a third (and last) equivalent of isocyanide molecule was necessary to install the tetronate fragment, since it gave intermediate **295** which, after cyclization consequent iminolactone isomerization, furnished product **296**. The obtained nitrilydene tetronates, in form of **289**, were successfully tested as potential antibacterial agents.

Fernandes et al. reported the preparation of 4-sulfonyloxy-butenolides, useful as potential antibacterial agents or as important synthesis intermediates, starting from γ-aryl-γ-hydroxy-α,β-acetylenic ester **297** [94]. In this context, sulfonic acid acted both as the activating acid towards the triple bond and as a nucleophile at C(4), giving different 5-aryl-4-sulfonyltetronates **299**. The same functionalization on aliphatic substrates (such as **300**) required the use of Pd as the metal catalyst, to better activate the triple bond and favor the sulfonic acid addition to give **301**. Further cross-coupling reactions on the resulting tosylates (Sonogashira, Suzuki) were performed, allowing the formation of variously 4-functionalized butenolides, like **302** and **303** (Fig. 49).

### 2.2.3. *Metal catalyzed ring closure*

Intramolecular cyclization catalyzed by the presence of metals is a highly represented method towards the formation of tetronic acid skeleton: Ag, Pd, Au were reported to favor 5-exo or 5-endo dig annulation, particularly useful for the preparation of 5-aryl or alkyl, 5-arylidene or alkylidene tetronic acid derivatives.

Sadamitsu et al. used $CO_2$ as low cost and easy-to-handle carbon source, to perform a one-step conversion of ynone **304** to biologically active tetronates [95]. Using MTDB as a base, it was possible to generate the enolate species that, in presence of high pressure of $CO_2$, underwent α-carboxylation to give **305**. Catalytic amount of silver acetate was essential for the triple bond activation, so that 5-*exo*-dig cyclization could take place and afford the alkylidene tetronate **306**. In these conditions, 6-endo dig derivatives could be generated, resulting in the corresponding hydroxypyrone **307** formation, mostly when sterically hindering α-substituents were present (Fig. 50). Years before, Yoshikawa et al. described in their work the synthesis of 5-arylidene and alkylidene derivatives by Ag-catalyzed rearrangement [96]. In particular, treatment of alkynone **308** with alkynoate **309** afforded with very high

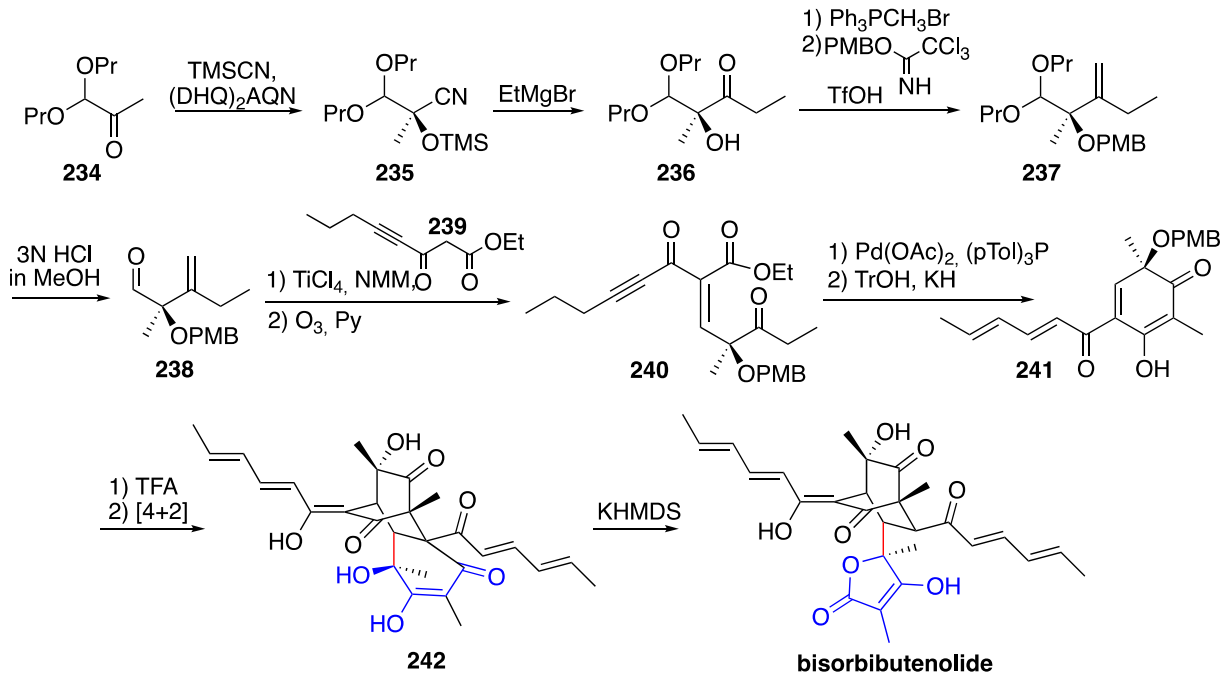


**Fig. 37.** Synthetic pathway towards the synthesis of **bisorbibutenolide** starting from protected pyruvaldehyde **234**.

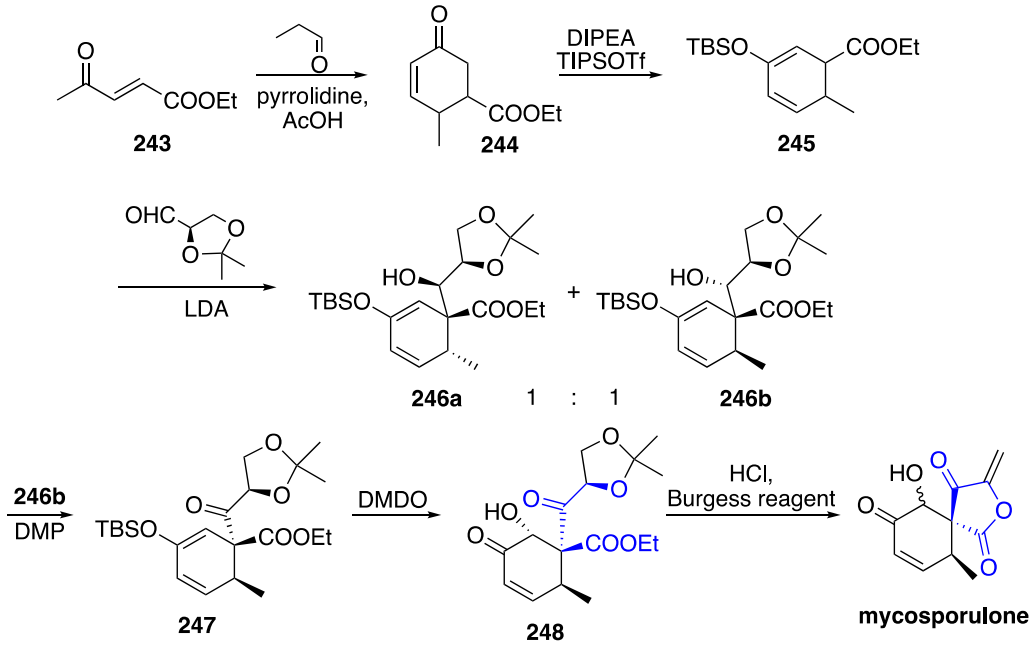


**Fig. 38. Mycosporulone** preparation going through intramolecular transesterification on cyclohexanone **248**.

diastereoselectivity enyne **310** as *E*-isomer, the only one suitable for the intramolecular rearrangement to desired tetronic acid **311**. Among the different solvents screened, DMF appeared to be the best one in terms of yields and isomeric ratio between tetronate **311** and pyrone adduct **307**. On the other hand, $Ag_2CO_3$ catalyzed selectively the 5-exo cyclization to **311**, whereas with $AgSbF_6$ 6-endo cyclization took place, favoring the pyrone moiety formation. In the same way Brönsted acids added to the reaction medium resulted in double activation (by $Ag^+$ and $H^+$) of the triple bond, making the δ-carbon more electrophilic than γ-carbon, to set endo cyclization and subsequent pyrone **307** delivery (Fig. 50). Following an analogue protocol, **aspulvinone E** was prepared in 3 steps, starting from α-substituted ethyl acetate **312** and the suitable terminal alkyne **313**, in presence of BuLi and $BF_3{\cdot}Et_2O$, so that ynone **314** could be α-carbonylated and converted to tetronate **315,** then deprotected to afford the desired product through a strongly shortened synthetic pathway, if compared to other methods previously reported in literature (Fig. 51).

During their studies about Michael addition of carboxylic acids to conjugated esters, Lu and coworkers explored the possibility to synthesize optically pure **pulveraven B**, using phenylacetic acid **316** as donor and cinnamate **317** as Michael acceptor [97]. Enantioselectivity of the addition was achieved thanks to the presence of a suitable chiral tetraamine in presence of BuLi, so that the *anti*-adduct **318** was obtained and underwent *in situ* aldol reaction with the aldehyde **319**.

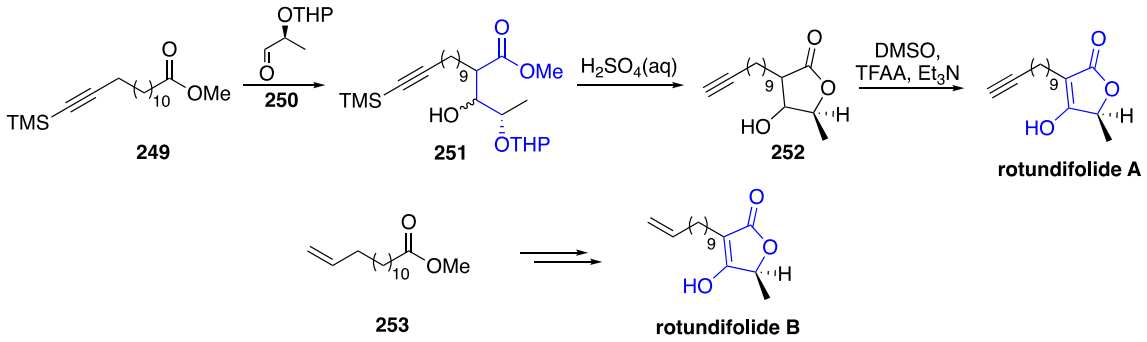


**Fig. 39.** Reported synthesis for **rotundifolide A** and **B**.

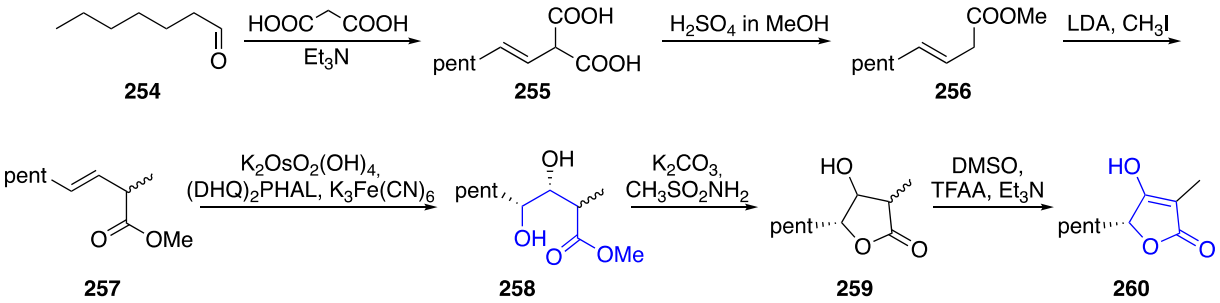


**Fig. 40.** Preparation of butenolide **260** by transesterification/oxidation protocol.

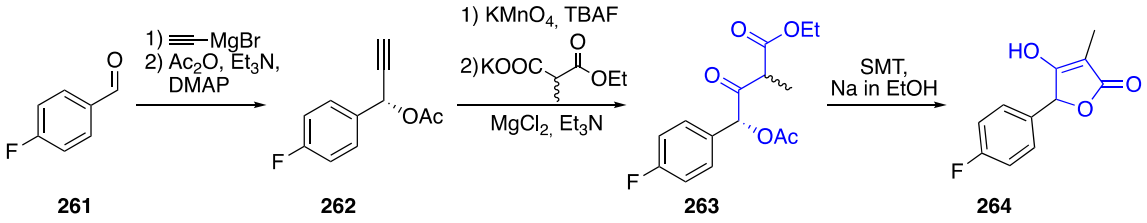


**Fig. 41.** Preparation of 5-aryltetronic acid **264** by functionalization of the triple bond of **262**.

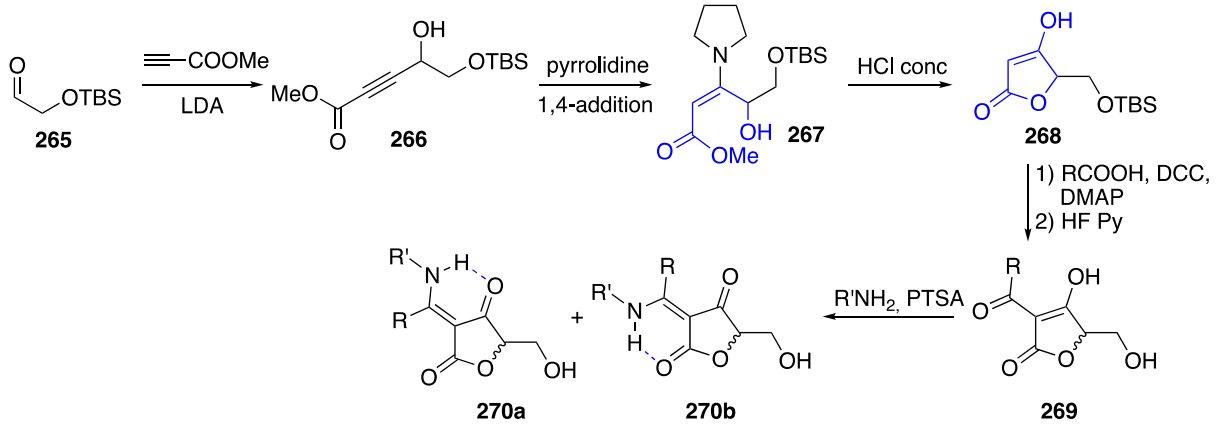


**Fig. 42.** Synthesis of 3-enamino derivatives **270a** and **270b** starting from 3-acyl tetronic acid **269**.

Esterification of the acidic portion afforded **320**, subjected to silyl ester cleavage, Ag-mediated 5-exo dig cyclization and final oxidation to the desired tetronate moiety, **pulveraven B** (Fig. 52).

Taking in consideration the synthesis of fused rings containing the tetronate core, several methods were proposed, always exploiting the presence of metal catalysts. Mancuso et al performed the construction of the tetronate core in dihydrofurofuranones thanks to the intramolecular reaction of *O*-alkynyl substituted phenols, such as **321** [98]. $PdI_2$ was used as the catalyst in order to activate the triple bond towards a 5-endo dig annulation, in presence of KI and DIPEA as the base (required to enhance the nucleophilicity of the phenolic OH) in an organic solvent. Palladiated benzofuran **322** was then subjected to carbonylation, by addition of a mixture CO/air, while subsequent Pd elimination from **323** allowed the obtainment of benzofurofuran **324**, together with a small

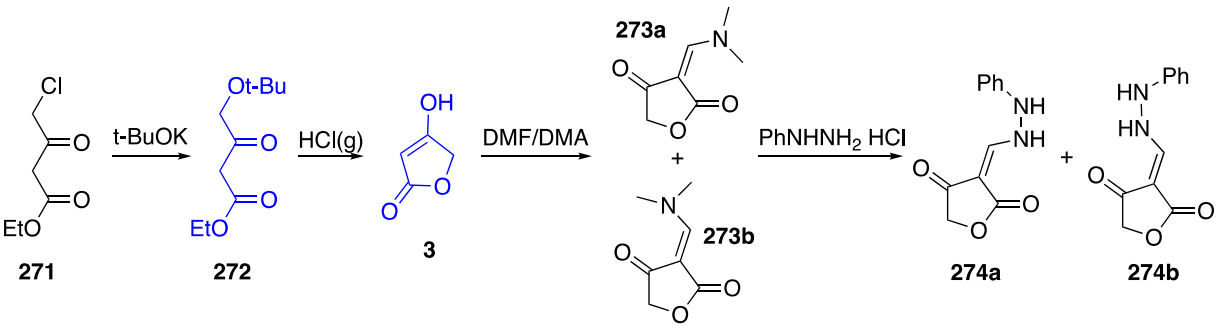


**Fig. 43.** Preparation of tetronic acid **3** starting from β-ketoester **271**, further functionalized to **274a** and **274b** phenylhydrazino isomers.

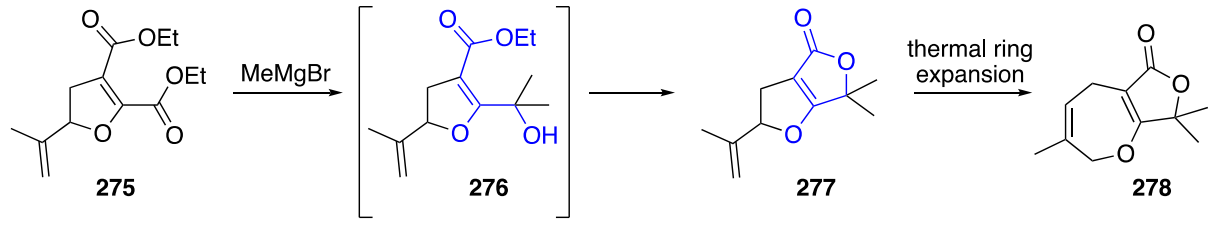


**Fig. 44.** Conversion of dihydrofuran **275** to tetronate derivative **278** by thermal ring expansion.

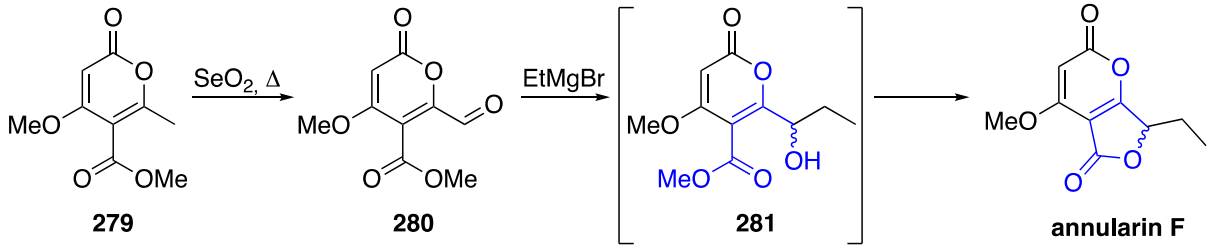


**Fig. 45.** Synthesis of **annularin F** starting from pyrone **279**.

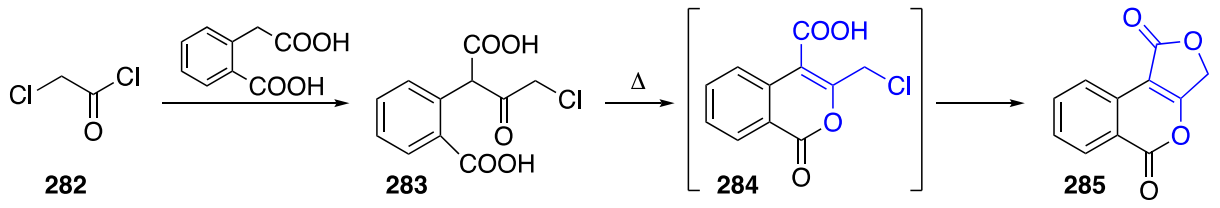


**Fig. 46.** Isochromene **285** construction from chloroacetyl chloride and benzoyl acetic acid.

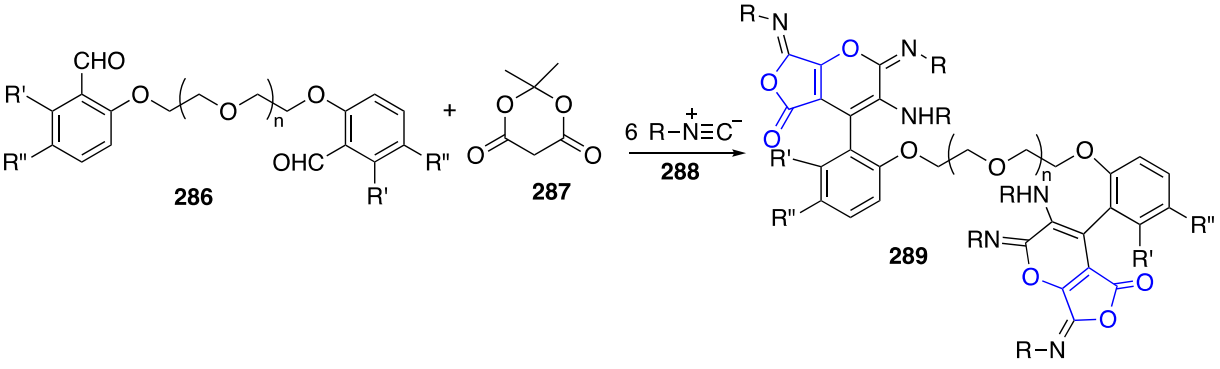


**Fig. 47.** Multicomponent reaction approach for the preparation of dimeric furopyran derivative **289**, using polyethylene glycol substrate **286**, Meldrum acid and isocyanide **288**.

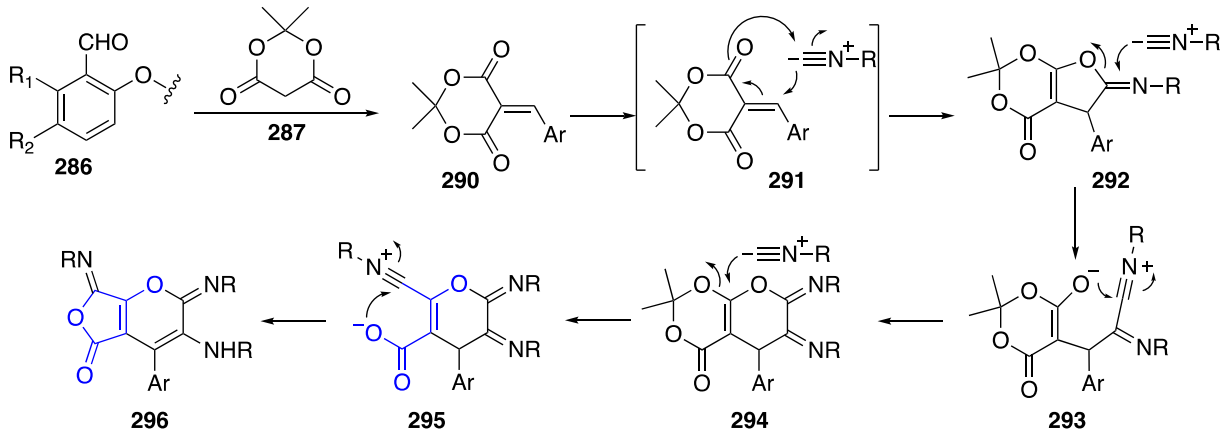


**Fig. 48.** Proposed mechanism for the conversion of benzaldehyde derivative **286** to nitrilydene tetronate **296**.

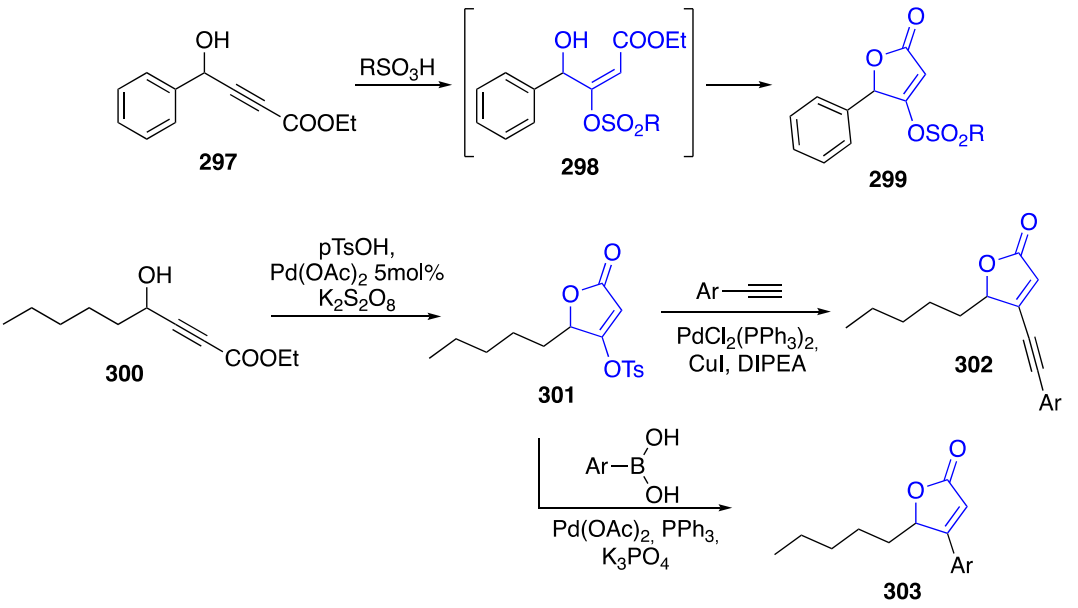

**Fig. 49.** Construction of butenolide derivatives **299** and intermediate **301**, as precursor for further functionalizations upon the scaffold, starting from propargyl alcohols **297** and **300**.

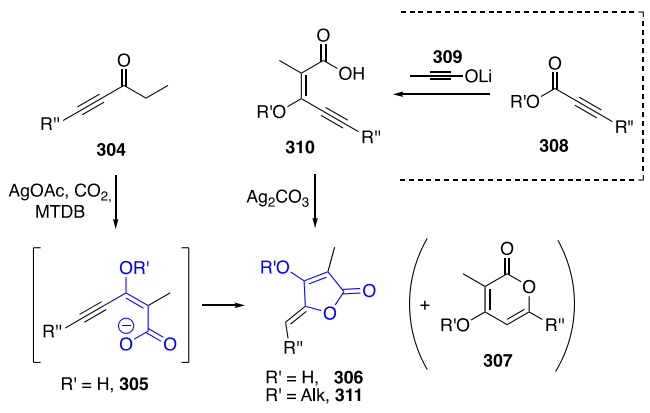


**Fig. 50.** Ag-catalyzed formation of tetronates exploiting the triple bond on **304** and **308.**

amount of benzofuran **325** (Fig. 53). The presence of a propargyl tertiary alcohol (or hindered secondary alcohol) was essential to favor the second cyclization, because of the rotamer effect increasing the reaction rate and disfavoring the formation of the byproduct **325**. Trying to extend the application to untraditional solvents, ionic liquids turned out to maximize the conversion of the substrate and improve the yield and selectivity of the cyclization towards desired **324.** It is worth noticing that the catalytic system was easily recycled and reused without losing activity up to six times, making the process more sustainable.

More recently, Kumar et al. reported a new strategy for the synthesis of the isocoumarinic moiety, avoiding multi step sequences and protection-deprotection protocols, starting from benzoic acid **326** and ethyl 4-hydroxy-4-methylpent-2-ynoate **327** [99]. In particular, $AgSbF_6$ was used as triple bond activator, sodium or lithium acetate were screened as bases, while Cu and Ag derivatives as oxidants, in presence of Rh-based catalyst. Among the others, the tetronate moiety **329** was isolated with good selectivity with respect to the lactone **330** when LiOAc acted as the base and $Ag_2CO_3$ was employed as the oxidant (Fig. 54). Differently functionalized hydroxy-alkynoates (**327** analogues) were studied, showing that the hindrance of the substituents carried by the tertiary alcohol carbon dramatically influenced the regioselectivity of the reaction, so that only tetronates **329** were generated following this approach.

Spiroketal **papyrallic acid** is isolated from ascomycete *Lachnum papyracaeum* and consists of a tetronate core connected with a

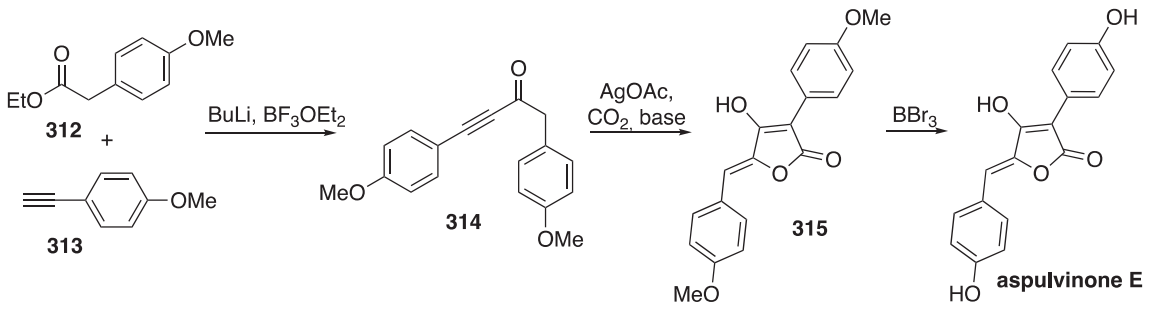


**Fig. 51.** Reported synthesis for **aspulvinone E**, in presence of $Ag_2CO_3$ as the catalyst.

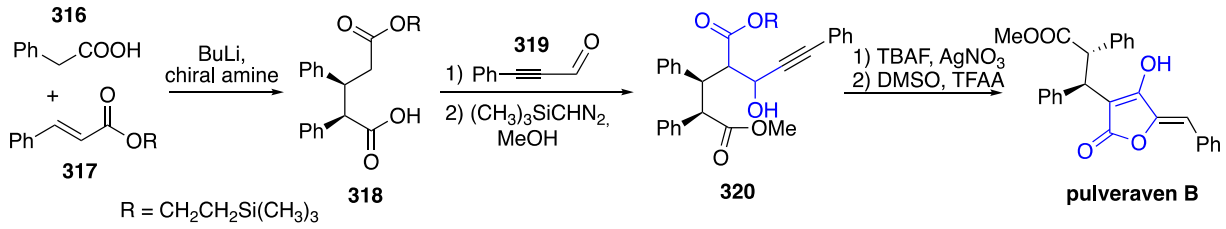


**Fig. 52.** Synthetic pathway towards enantiomerically pure **pulveraven B**.

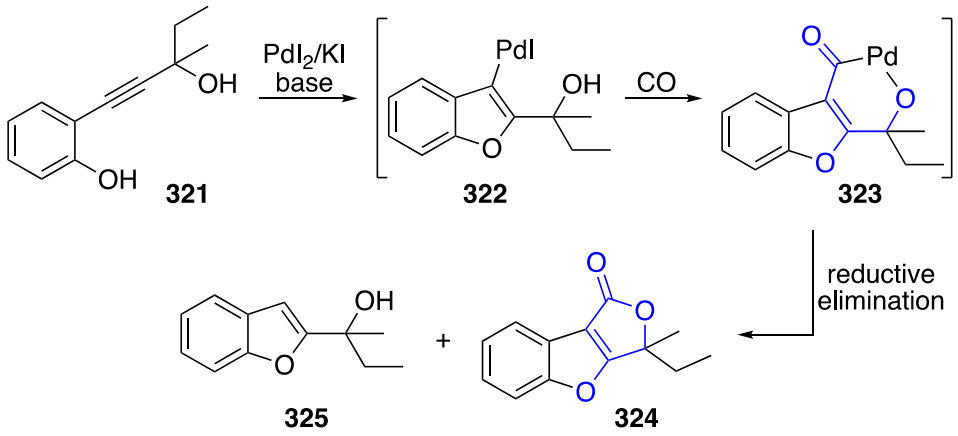


**Fig. 53.** Pd-based intramolecular cyclization to condensed tetronate **324**.

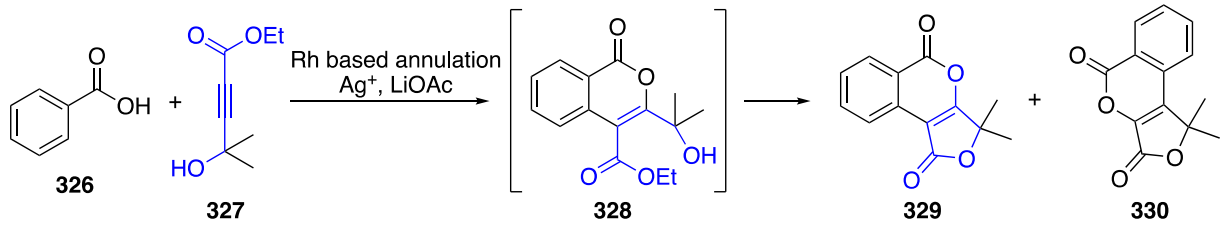


**Fig. 54.** Rh-catalyzed annulation between **326** and **327** to tetronate **329**.

hydroxytetrahydrofuran. Because of the cytotoxic activity, synthesis of papyrallic acid was strongly pursued during the last decades [100]. In particular, Mazzone and coworkers exploited their expertise in carbenoid homologation for the preparation of the bioactive product, starting from the treatment of methyl acetoacetate **331** with $Et_2Zn$ and $CH_3CHI_2$ to obtain the suitable substrate **332** for the condensation with methoxymaleic anhydride to spirotetronate **334** (Fig. 55) [101].

Using allyl acetoacetate **335** as substrate, chain elongation in presence of methoxymaleic anhydride gave hemiacetal **336**. Methylation gave **337**, further subjected to allyl cleavage to acid **338**, then reduced to primary alcohol and mesylated to **339**; subsequent $PhSe^-$ treatment gave **340**, ready to be converted in exocyclic methylene derivative upon heating, to afford a 1:1 mixture of **papyrallic acid B** and 4-*epi* papyrallic acid B (Fig. 56).

### 2.2.4. *Ring expansion*

Another unconventional method towards the synthesis of tetronic acid analogues consists in the expansion of 4-member rings to the 5-member butenolide skeletons. In this context, Duffy et al. reported the preparation of the tetronic core starting from substituted diketene and

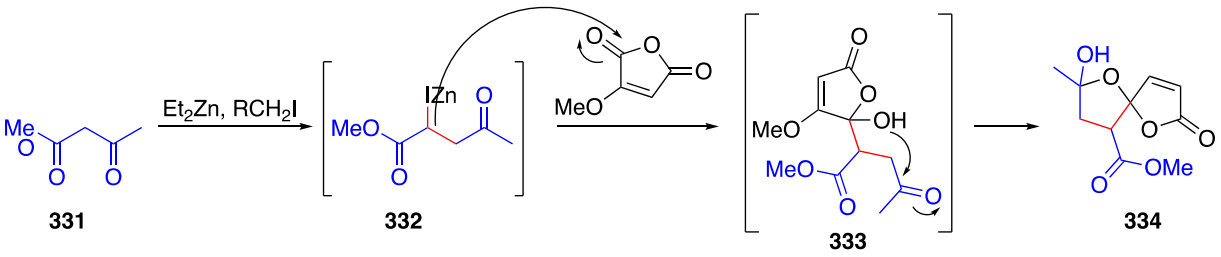


**Fig. 55.** Preparation of **334**, as **papyrallic acid** analogue.

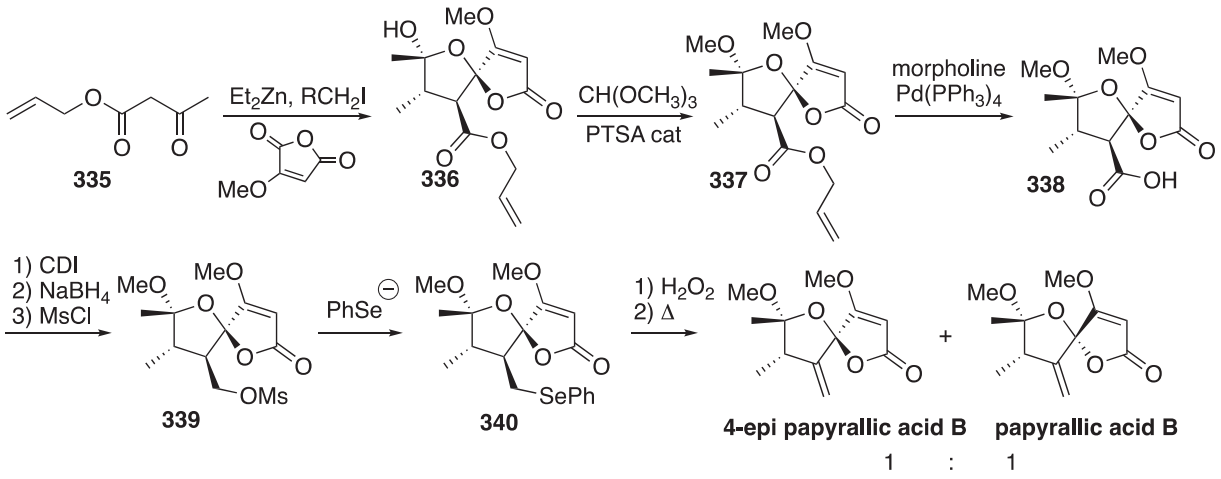


**Fig. 56.** Reported preparation for **papyrallic acid B.**

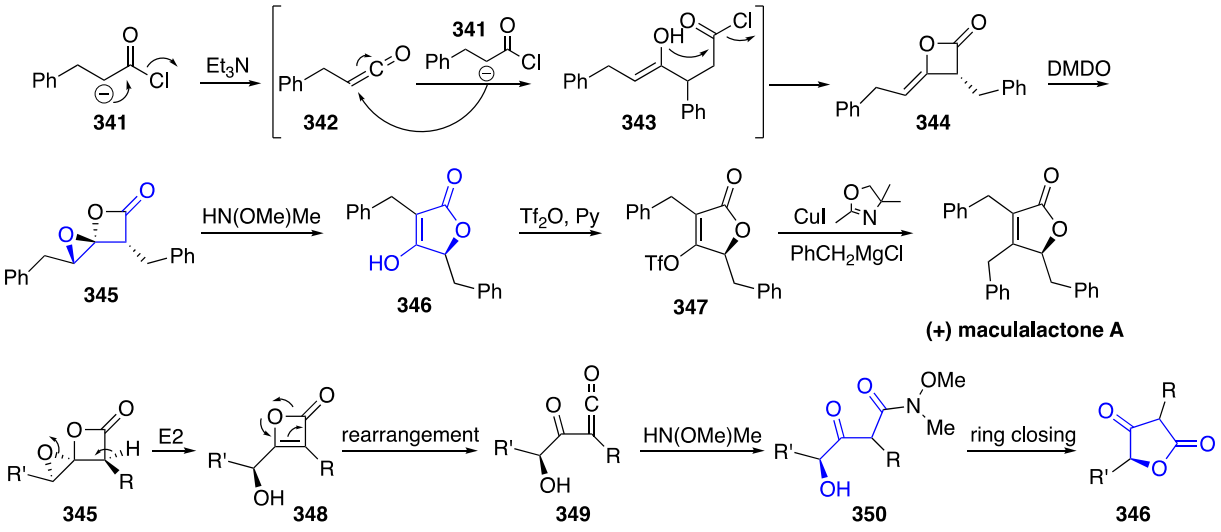


**Fig. 57.** Conversion of acyl chloride **341** to epoxy β-lactone **345**, as suitable intermediate for the synthesis of **(+)-maculalactone A** and the proposed reaction mechanism.

exploited it for the synthesis of bioactive antifouling agent, **(+)-maculalactone A** (Fig. 57) [102]. More specifically, suitable acyl chloride **341** underwent auto condensation to **344** in presence of triethylamine as the base. Epoxidation of the exocyclic double bond gave access to spiroepoxy β-lactone **345**, further treated with *N,O*-dimethylhydroxylamine, favoring the rearrangement to tetronate **346**. Final triflation and Negishi cross-coupling afforded enantiopure **(+)-maculalactone A**. From the mechanistic point of view, conversion of spiroepoxy β-lactone **345** to tetronate core **346** was favored by an E2 elimination upon secondary amine exposure, followed by *retro*-electrocyclic reaction to α-ketoketene **349** and formation of activated amide **350**. Ring closing by intramolecular esterification afforded desired **346**.

During their studies about the utility of alkoxycarbonyl di- and trifluorosemisquarates as building blocks for the preparation of bioactive compounds, Kurohara et al. were able to obtain 3-fluoroalkyltetronate derivatives [103,104]. The interest towards semisquarates is motivated by their characteristic structure, an unsaturated 4-membered ring **351** showing the α-diketo motif, ready to undergo ring expansion through radical oxidations. Mukayama reaction of silyl enol ether **352** with the diketone system selectively afforded tertiary alcohol **353**,

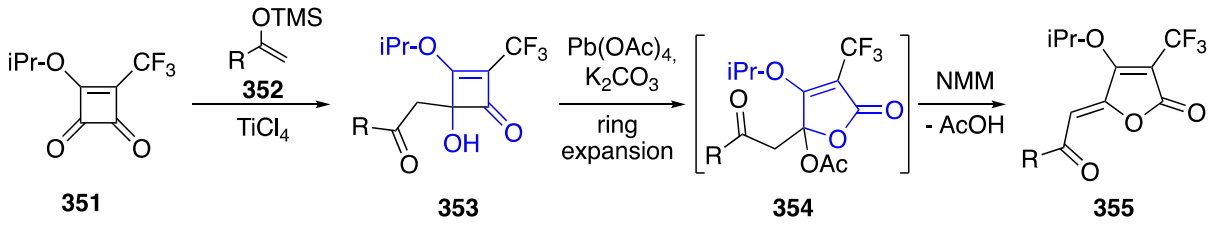


**Fig. 58.** Ring expansion of semisquarate **351** to tetronate **355**.

further treated with $Pb(OAc)_4$: this mild radical oxidation caused ring opening and subsequent rearrangement to 5-*O*-acetylated 5-substituted tetronate intermediate **354**. Then, exposure to potassium carbonate afforded with high diastereoselectivity *Z*-alkylidene tetronate **355**. Related compounds were obtained through Mukayama aldol reactions followed by $Pb(OAc)_4$ treatment and acetate elimination in presence of *N*-methylmorpholine (Fig. 58).

In an analogous way, modifications to α-hydroxycyclobutanone **356** were described by Gao et al. [105]. In order to exploit the electrocyclic ring expansion, different catalytic systems were screened and, among them, $Ni(cod)_2$ revealed to be the best one for this purpose, even though the presence of different ligands favored one particular type of rearrangement instead of another. More specifically, 5-isopropoxyfuranone **359** was obtained when a catalytic amount of $PPh_3$ was used; on the other hand, complete selectivity towards the formation of isopropoxytetronate **361** was registered when xantphos was employed. According to the hypothesized mechanism, $PPh_3$-mediated nickel insertion between ketene and enol (compound **357**) allowed the furanone formation through coordination and migration of the *O*-substituent (**358**), whereas H-migration took place in presence of xantphos (**360**), so that tetronate **361** could be obtained (Fig. 59).

The chemico physical properties of the pentafluorosulfanyl group ($SF_5$) recently made it one of the most interesting alternatives for the functionalization of compounds in pharmaceutical and agrochemical fields [106,107]. In order to better investigate the reactivity of such derivatives, Vida et al. went through the formation of tetronic derivatives as result of the oxidation of 4-pentafluorosulfanylphenol (or anisole) [108]. In particular, according to the hypothesized mechanism, treatment of **362** with hydrogen peroxide and sulfuric acid allowed ortho hydroxylation to **363** and further oxidation to diketone **364**, that underwent Bayer-Villiger ring expansion to afford anhydride **365**. Hydrolysis resulted in muconic acid **366**, ready to undergo conjugate addition of the carboxylic group, so to obtain pentafluorosulfanylderivative **367**. Final hydrolysis for 40 h at room temperature afforded tetronolactone **368**, as the main product of the reaction (Fig. 60).

### 2.2.5. *P-ylide ketene mediated cyclization*

Use of phosphorus ylide ketene for the synthesis of tetronic acid derivatives was exploited by several research groups, as a suitable alternative to the approaches until here reported. Generally, derivatization of a free hydroxy group is performed, so to obtain the triphenylphosphinoester undergoing Wittig-like reaction, essential for the formation of the enolic double bond. In order to investigate about a new synthetic pathway towards the synthesis of tetronic acid derivatives with biological activities, Schobert et al. compared solution and solid phase methodologies for the preparation of anticancer **RK-682** and antibacterial **agglomerins**. To this aim, *O*-trityl benzyl glycerate **369** in THF was treated with phosphorus ylide ketene under microwave irradiation [109]. The resulting tetronate **371** was debenzylated and subjected to acylation at C(3), while final detritylation afforded desired **RK-682** (Fig. 61). Agglomerins were prepared following the same protocol, but with final elimination of the primary hydroxyl, resulting in exocyclic double bond formation.

Alternatively, exploiting a solid phase approach, the diol TMES ester **372** was anchored on the trityl polystyrene resin via DMAP catalyzed etherification. Phosphorus ylide ketene treatment, followed by desilylation, afforded tetronic acid **373**, ready to be acylated and cleaved from the resin upon treatment with TFA/TESH in form of bioactive **RK-682** (Fig. 61). A different protocol was taken under consideration by the same group for the preparation of tetronic acid analogue of tipranavir (a HIV protease inhibitor) [110]. α-disubstituted benzyl glycolate **374** was treated with P ylide ketene under heating, so that condensation to tetronate **375** took place. Hydrogenation, followed by *O*-allylation with **376**, gave product **377**, while Claisen rearrangement at C(3) afforded **378**, thanks to the presence of ytterbium triflate under microwave irradiation. Cyclopropanation occurred at terminal double bond upon diethyl zinc/diiodomethane treatment, so that nitro reduction and subsequent sulfonylation allowed to collect the desired set of differently substituted sulfonamides **380** (Fig. 62).

Enantioselective synthesis of penicillic acid precursors, such as **carolinic acid**, a potential antibacterial agent, was performed by Linder et al. starting from enantiopure α-substituted glycolic acid benzyl ester **381** [111]. Treatment with phosphorus ylide ketene allowed to obtain the corresponding benzyl tetronate, readily hydrogenated to afford **382**, processed again with P ylide ketene so to deliver 3-acyl phosphine **383**, finally exposed to *t*-butyl glyoxylate. Hydrogenation of the double bond and ester hydrolysis ended with the obtainment of optically pure **(*R*)-**

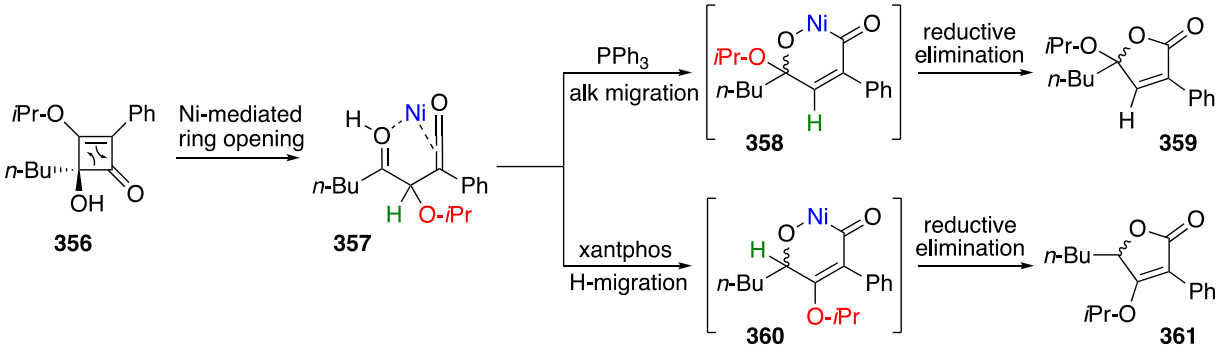


**Fig. 59.** Regioselective P-mediated formation of lactone **359** and tetronate **361** from α-hydroxycyclobutanone **356**.

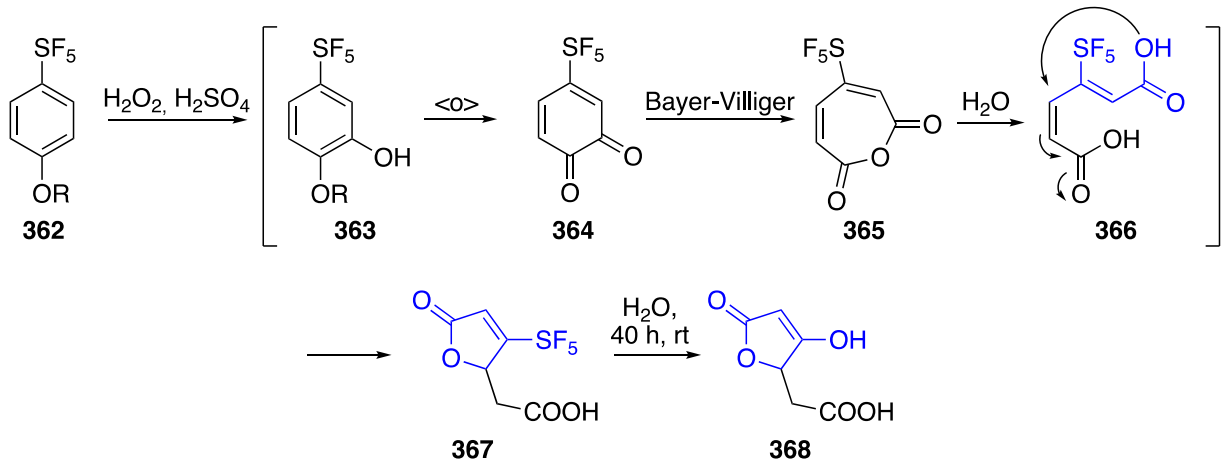


**Fig. 60.** Preparation of tetronolactone **368** starting from pentafluorosulfanyl derivative **362**.

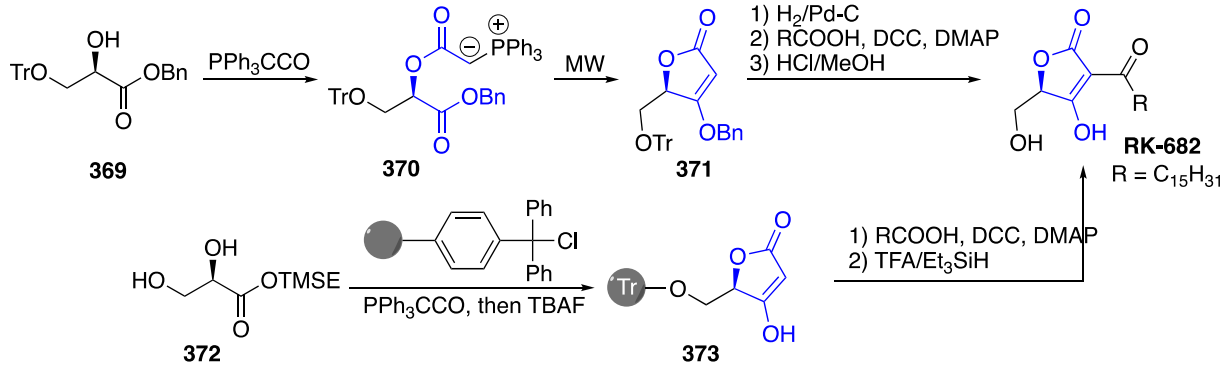


**Fig. 61.** Microwave-induced cyclization to optically pure **371** and solid-phase synthesis of **373**, as suitable intermediates for the preparation of **RK-682**.

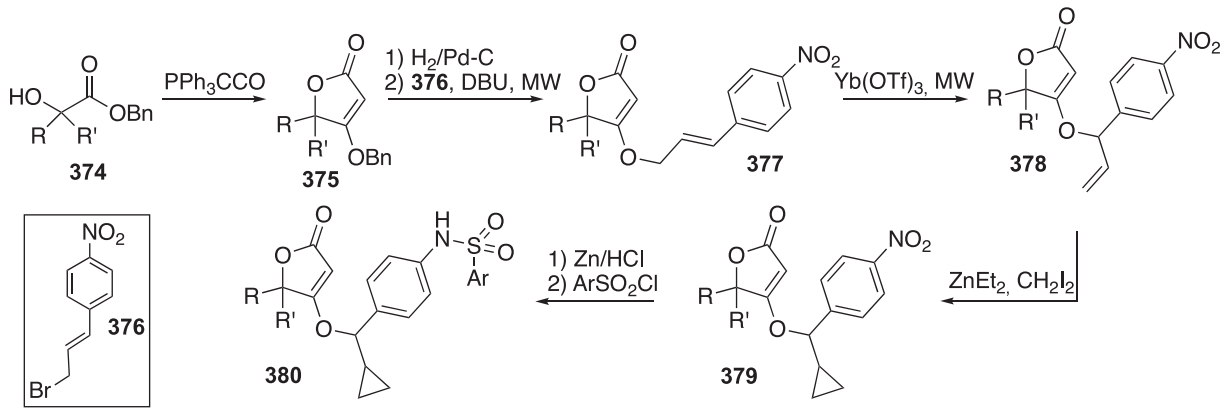


**Fig. 62.** Conversion of α-disubstituted benzyl glycolate **374** (via P ylide ketene) to potentially active sulfonamides like **380.**

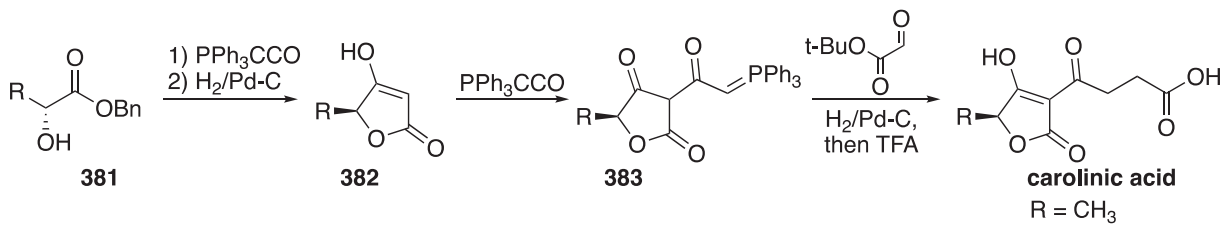


**Fig. 63.** Synthesis of enantiomerically pure **carolinic acid**.

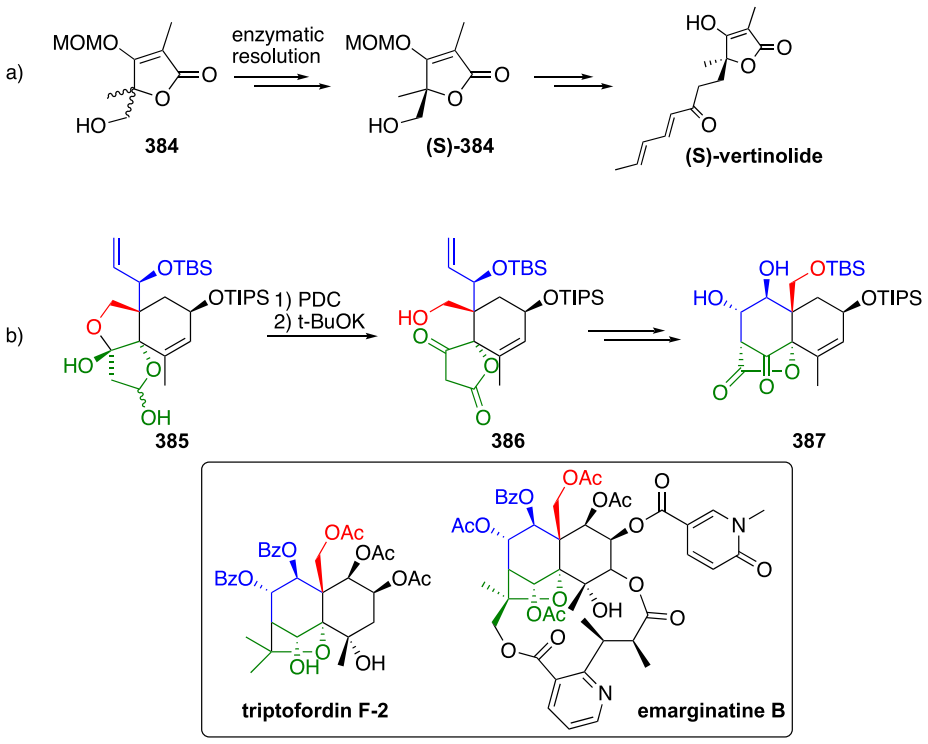


**Fig. 64.** Enzymatic resolution of **384** to **(S)-384**, as suitable intermediate for **(S)-vertinolide** (a); oxidation and rearrangement of hemiacetal **385** to **386**, useful for the preparation of **387** (b).

**carolinic acid** (Fig. 63).

Out of the categorization until here taken in consideration, a few more examples of conversion in tetronate nuclei are briefly reported below, as methodologically intriguing approaches towards the formation of substituted butenolides. In particular, enzymatic resolution was exploited by Tauchi et al. for the obtainment of enantiomerically pure **(S)-vertinolide**, with cytotoxic, antioxidant and antiviral potential activity [112]. (Fig. 64a) Besides, the preparation of the key intermediate for the synthesis of naturally occurring dihydro β-agarofurans **triptofordin F-2** and **emarginatine B**, active as cytotoxic molecules, [113] was afforded by a singular oxidation on hemiacetal skeleton and subsequent rearrangement (Fig. 64b). [114].

## 3. Conclusions

Tetronic acids are an important class of oxygen heterocycles that has evolved significantly in recent years, with numerous studies focusing on their diverse biological effects. For this reason, the development of new synthetic methods is a topic of growing interest for a great number of research groups. Many of the synthetic procedures used in the preparation of tetronic acid core have been known for a considerable time and are still in use because of their efficiency and simplicity. The main areas of current interest are the study of new methods based on step- and atom economy, exploiting the use of multicomponent strategies and the development of new catalytic reactions, continuous-flow synthesis, as well as microwave irradiation and immobilized reagents, to obtain a properly functionalized tetronic acid core. The significant advances of the past decade also reflect the impact of the recent developments in new methodologies that have enabled practical access to these simple but synthetically quite challenging ring systems.

We have put efforts in reviewing the state of art in an unprecedented way, trying to describe key synthetic developments of the last 15 years. We collected, at the best of our abilities, the chemical background behind the preparation of natural tetronate analogues, providing a compendium of diverse alternatives. In this context, a rational categorization in intermolecular and intramolecular approaches has been considered as the best solution, according to the different requirements of the scaffold. We hope that our work will assist interested readers in acquiring a systematic view of the field and inspire researchers to identify suitable synthetic routes to naturally occurring or bioinspired compounds containing the tetronic acid core.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

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