

Synthesis and chemistry of tetronic acids

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1. Introduction.

Tetronic acids (4-hydroxy-2(5H)-furanones) form a subclass of β -hydroxybutenolides with the generic structure **1**.¹ The best known

members of this family are vitamin C (ascorbic acid) **2** and pennicillic acid **3**. A great number of these compounds and their metabolites are found in many natural products, which exhibit a wide array of biological properties.² The aim of this review is to cover the current synthetic methodologies developed to build these molecules and their specific chemistry more than biological and pharmaceutical aspects of these products.

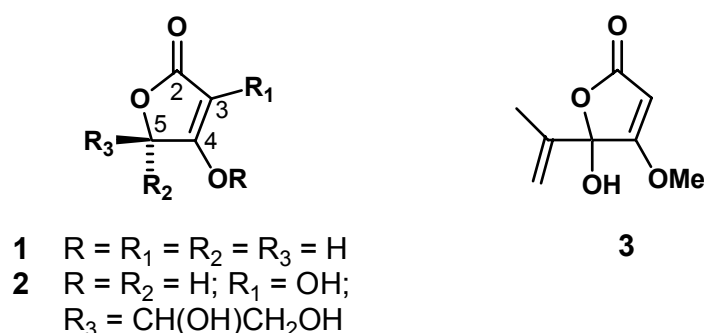


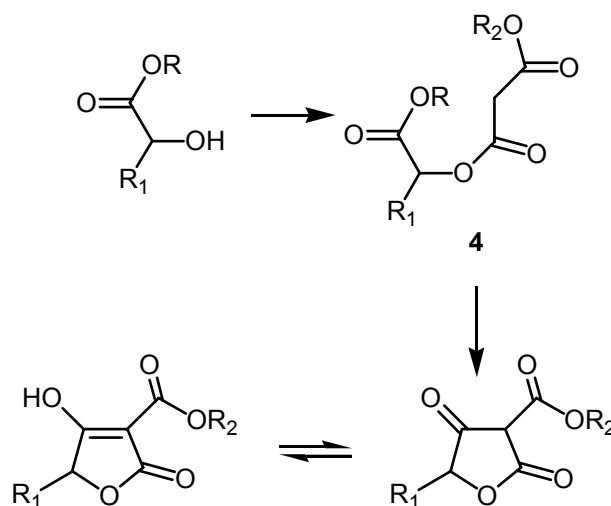
Figure 1

2. Synthesis of tetronic acids

2.1. Base-promoted Dieckman cyclization.

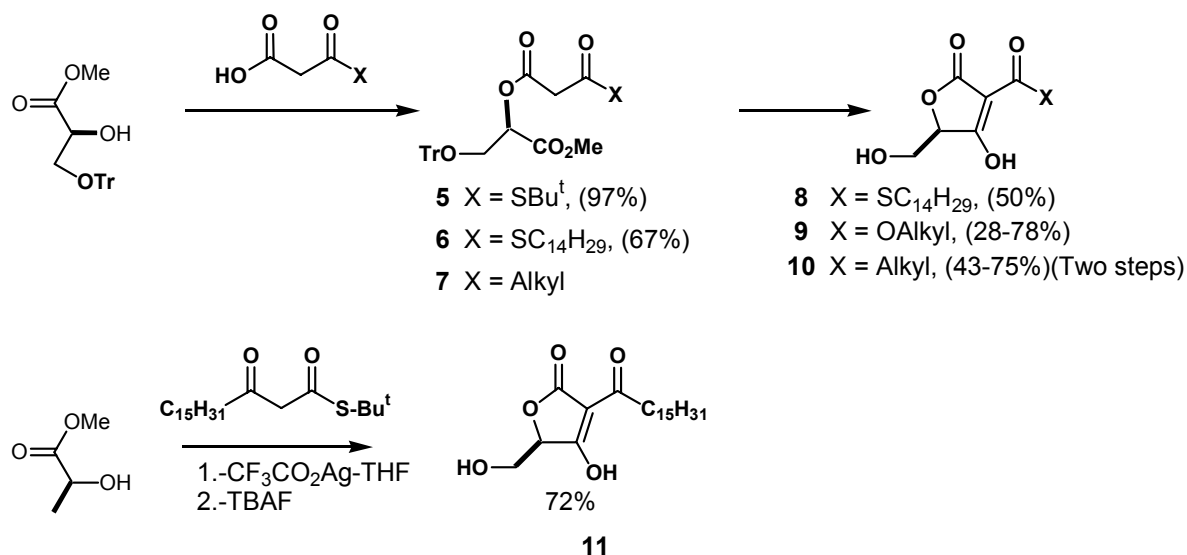
3,5-Disubstituted tetronic acids present medicinal interest as potential antibiotic, antiviral and antineoplastic agents.²⁻⁷ Among them, the 3-acyl derivatives comprise a structural motif present in a great number of active natural products. The base-promoted Dieckmann cyclization of glycolyl acetoacetates **4** (Scheme 1) is one of the most synthetically useful methods for the preparation of these 3-acyl derivatives.^{8-14,26,28} The ability of these intermediates to cyclize is highly dependent on the presence of substituents at the α' -position. Thus, while the cyclization of α' -substituted glycolyl acetoacetates is a very easy process, the unsubstituted

derivatives require vigorous reaction conditions to success. A wide structural variety of glycolyl acetoacetate intermediates are easily obtained by simple acylation of the suitable α -hydroxy acid with a malonate monoester derivative. Optically active α -hydroxy acids are readily accessible from natural sources and they comprise a very good resource of chiral starting materials for the stereoselective synthesis of these 3-acyl derivatives. Structurally simple chiral 3-acyl-5-substituted derivatives have been synthesized from (S)-glyceric acid,⁷ (L)-threonic acid,¹⁵ (R,R)-tartaric acid¹⁶ or (s)-lactic acid.^{7,17}



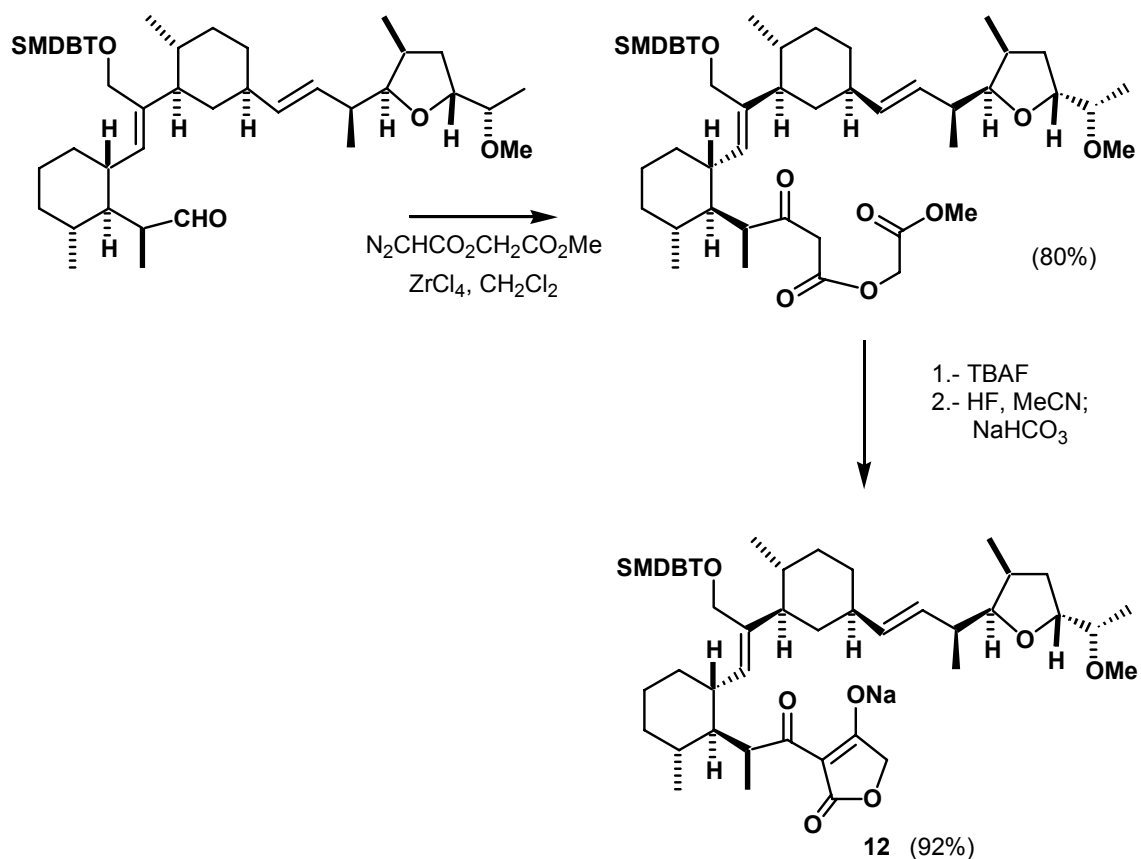
Scheme 1

The power of this methodology has been confirmed by the construction of a library of chiral 3-acyl-5-substituted tetronic acids focused on inhibitors of tyrosine and dual-specificity protein phosphatase.⁷ The 3-acyl-5-substituted tetronic acid derivatives **8-11** were readily synthesized from (S)-glyceric acid and (s)-lactic acid by means of a tetrabutylammonium fluoride-promoted Dieckman cyclization¹⁸ of the suitable glycolyl acetoacetate intermediates **5-7** in moderate to good yields (Scheme 2).



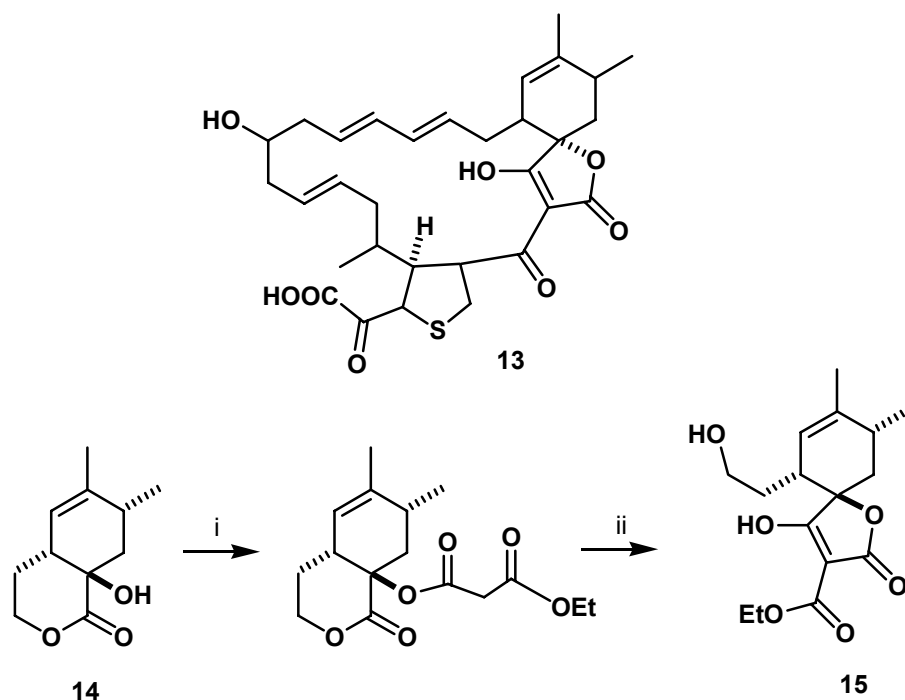
Scheme 2

The base-promoted Dieckmann cyclization is also the preferred synthetic method to construct the 3-acyl-5-substituted tetronic acid core in more complex molecules. Thus, the final stage of the first total synthesis of the antibiotic polyether ionophore tetronasin (**12**)¹⁹ was the challenging installation of the 5-unsubstituted 3-acyl tetronic acid core. This was accomplished in two steps by installation of the required β -keto ester intermediate by a Zirconium catalyzed C-H insertion reaction of the methyl (diazoacetoxy)acetate unit and a tetrabutylammonium fluoride-promoted intramolecular Dieckmann cyclization to afford tetronasin (**12**) in 72 % yield (Scheme 3).



Scheme 3

5,5-Spirobicyclic-3-acyl tetronic acid is a structural motif present in the brain-type cholecystokinin (CCK) receptor antagonist tetronothiodin (**13**).²⁰ Recently, an isomeric oxaspirobicyclic tetronic acid core **15** has been synthesized.²¹ The final stage of this stereoselective synthesis required the formation of the tetronic acid ring on the hydroxy lactone **14**, which was accomplished in two steps by direct acylation of the free hydroxy group of **14** with ethyl malonyl chloride and a base-promoted Dieckmann cyclization of this intermediate to deliver the required spirotetronic acid unit. Remarkably, only potassium bis(trimethylsilyl)amide was able to give the expected cyclization (Scheme 4).



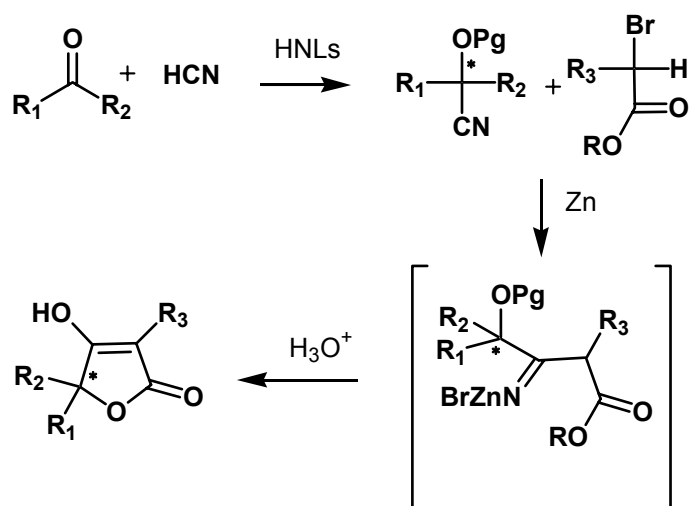
(i) Ethyl malonyl chloride, 2,6.-di-tert-butyl-4-methyl pyridine, CH_2Cl_2 , 5h, 98%;
(ii) KHMDS (2 equiv), -78°C then RT overnight, 91%.

Scheme 4

2.2. Cyclization of γ -oxygenated or γ -halogenated β -ketoester.

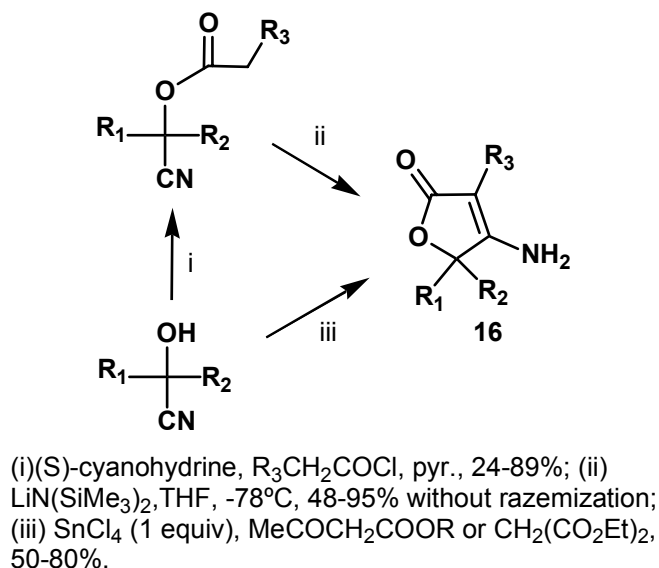
Suitable β -ketoester derivatives bearing a γ -halogen atom²²⁻²⁴ or a γ -oxygenated function²⁵⁻²⁹ have been widely used as tetronic acid precursors.

Optically active 3,5-disubstituted tetronic acids are directly synthesized by the Blaise reaction³⁰ of Reformatsky reagents with chiral cyanohydrins (Scheme 5) and acid hydrolysis of the γ -hydroxy^{25a-h} and γ -silyloxy β -ketoester²⁷ generated intermediates. Optically pure cyanohydrins are readily accessible by the hydroxynitrile lyases (HNLs)-catalyzed addition of hydrocyanic acid to aldehydes and prochiral ketones.³¹



Scheme 5

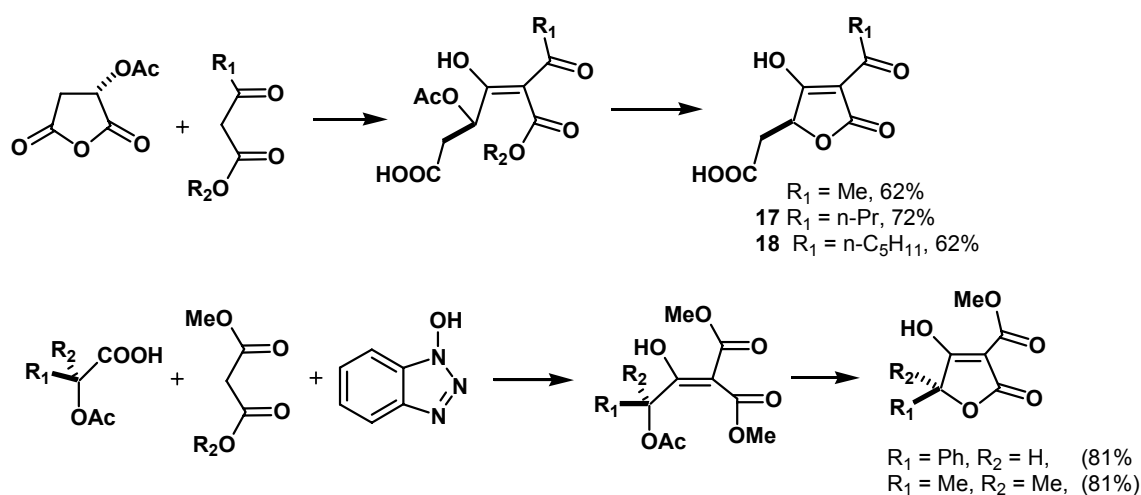
The intramolecular version of the Blaise reaction on the O-acetylated cyanohydrins affords the 4-amino-2(5H)-furanones **16** in good yields.^{32,33} Alternatively, the tin (IV) chloride-promoted reaction of α -hydroxy nitriles with α -dicarbonyl compounds directly delivers **16** in moderate yields³⁴ (Scheme 6).



Scheme 6

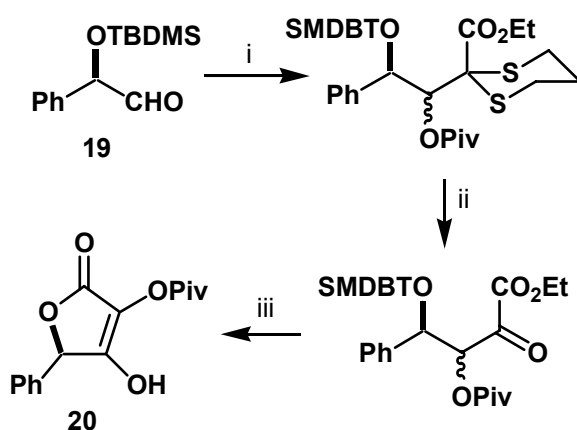
Optically pure γ -acetoxy- β -hydroxy- β -ketoester can be synthesized from the “chiral pool” by a C-acylation reaction of an active methylene

compound with the N-hydroxybenzotriazole ester of an appropriate chiral O-protected α -hydroxy acid^{26a,b} or by regioselective ring opening of (S)-malic acid anhydride^{26c} with the anion of a β -ketoester (Scheme 7). Base or acid-promoted cyclization of these intermediates affords the chiral 5-substituted 3-acyl tetronic acids. The method allows an easy and efficient access to the natural (S)-carlosic (**17**) and (S)-viridicatic acids (**18**). Also, N-protected L-maleimides have been transformed into chiral 5-substituted-4-amino 2(5H) furanones.³⁵



Scheme 7

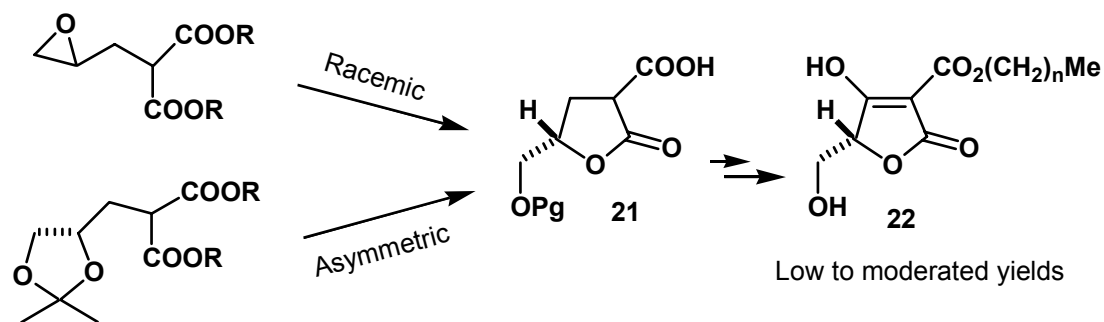
The important and stereogenically labile 5-aryl-3-hydroxy tetronic acids have been obtained in enantiomerically pure form by condensation of the enantiomerically pure silyl-protected mandelaldehydes^{27a} **19** with the anion of ethyl 1,3-dithiane-2-carboxylate in the presence of pivaloyl chloride (Scheme 8). Dithiane hydrolysis and tetrabutylammonium fluoride-promoted lactonization delivered the target 5-aryl-2(5H)-furanone **20** in 85-90% yield. Remarkably, the pivaloyl group migrates from position 4 to position 3 during this tetrabutylammonium fluoride-promoted lactonization.



(i) Ethyl 1,3-dithiane-2-carboxylate, LDA, Cl-Piv, -78°C , 50-60%;
(ii) NCS, AgNO₃, aq. MeCN, 80-90%; (iii) TBAF, THF, 85-90%.

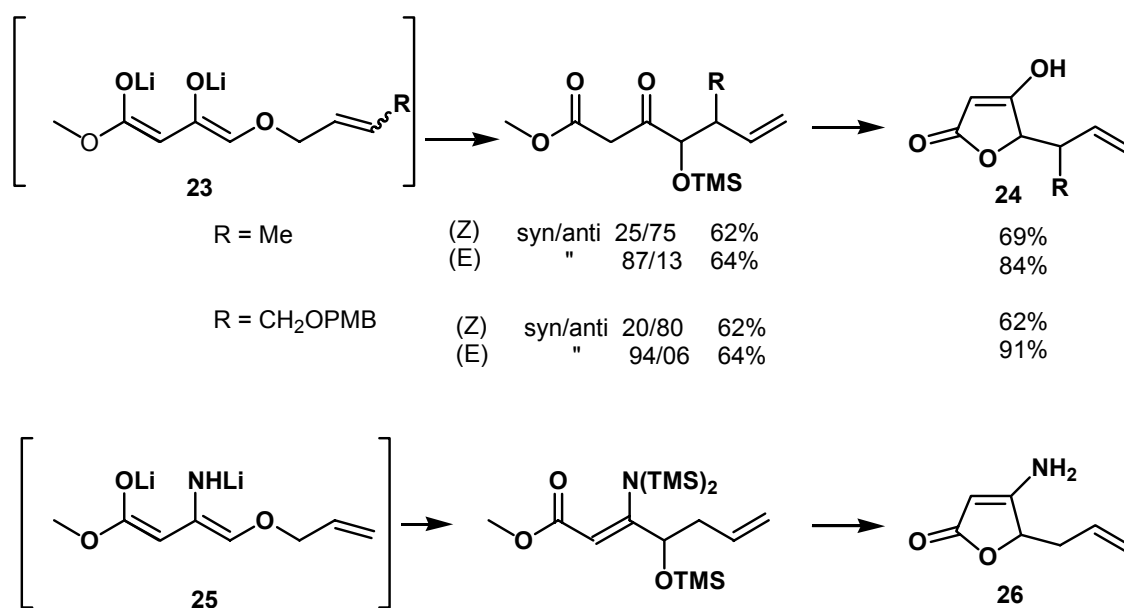
Scheme 8

Natural 3-alkanoyl-5-hydroxymethyl tetronic acids comprise an important group of biologically active molecules. Access to this group of derivatives has been accomplished²⁸ in good yields from diethyl allylmalonate by simple epoxidation, hydrolysis and acid-promoted lactonization, or from optically active glycerol acetonide by hydroxyl activation, malonate alkylation, hydrolysis and acid-promoted-lactonization (Scheme 9). In both cases, the produced 5-substituted-3-carboxy lactones **21** have to be further elaborated to the target tetronic acids **22**.



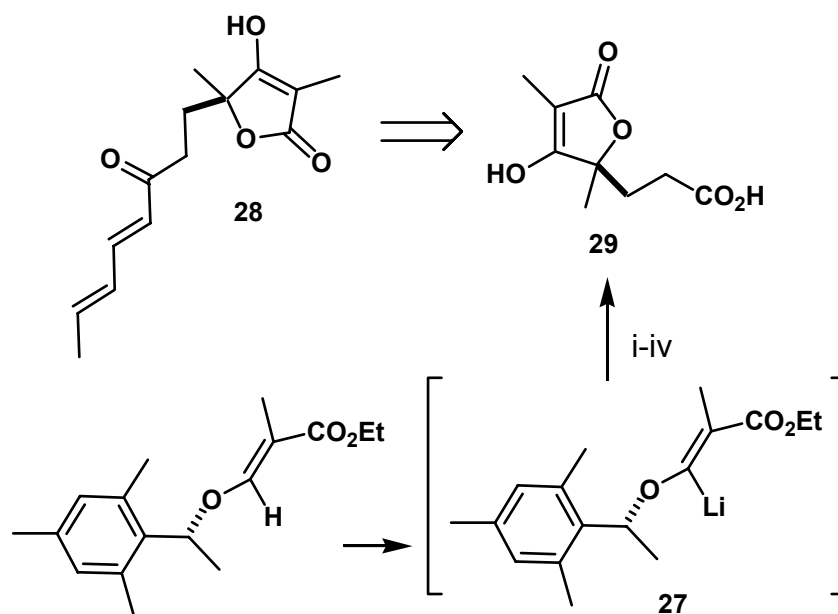
Scheme 9

γ -allyloxy- β -keto ester dianions **23** rearrange to γ -hydroxy- β -keto ester derivatives which form 5-substituted tetronic acid **24** by simple lactonization²⁹ (Scheme 10). Alternatively, the γ -allyloxy- β -enamino ester dianions **25** rearrange to the γ -hydroxy- β -enamino ester derivatives, which can be subsequently lactonized to the corresponding 4-amino-2(5H)-furanones **26**.³⁶



Scheme 10

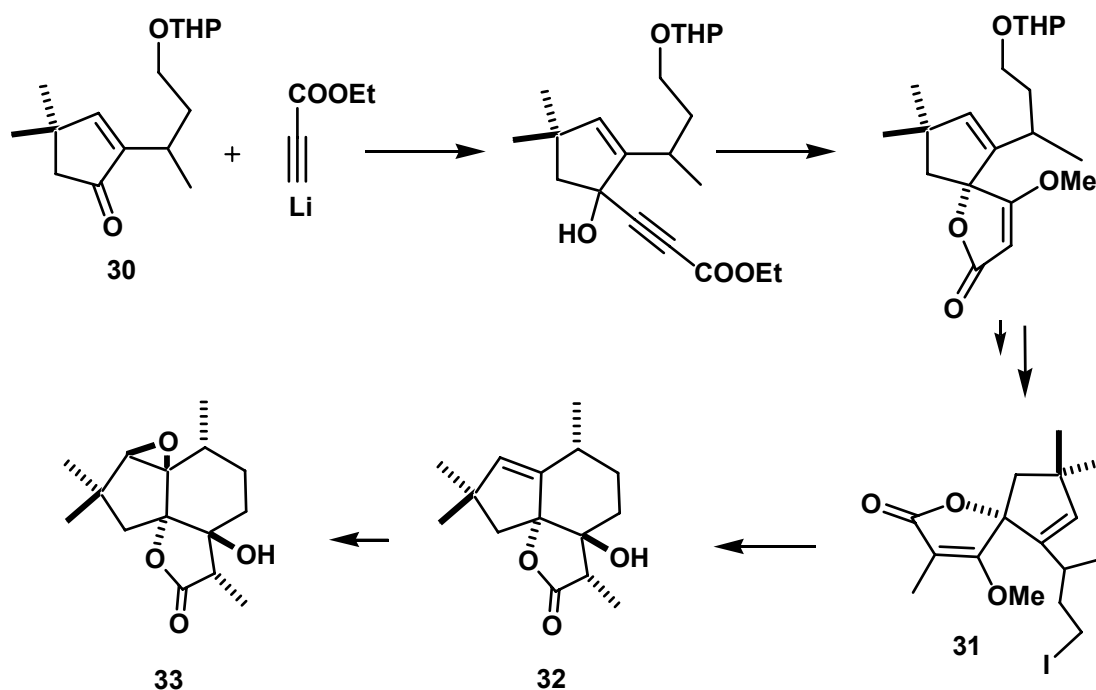
β -C-lithiated acrylates are suitable C₃ building blocks for the synthesis of structurally important 3,5-disubstituted or 3,5,5-trisubstituted tetronic acids.³⁷ In particular, a chiral ethyl 3-lithio-2-methyl-3-(1-phenylethoxy) acrylate **27** has been used to synthesize **29**,³⁸ a known (-)-vertinolide (**28**) precursor (Scheme 11).



(i) LDA, THF, -100°C; then MeCOCH₂CH₂CO₂Et, -100°C, 68%, 4.5:1 diastereomeric mixture; (ii) NaOH, MeOH, quant.; (iii) LDA, THF, -90°C, MeI, 85 %; (iv) Me₃SiCl, CH₂Cl₂, RT, quant.

Scheme 11

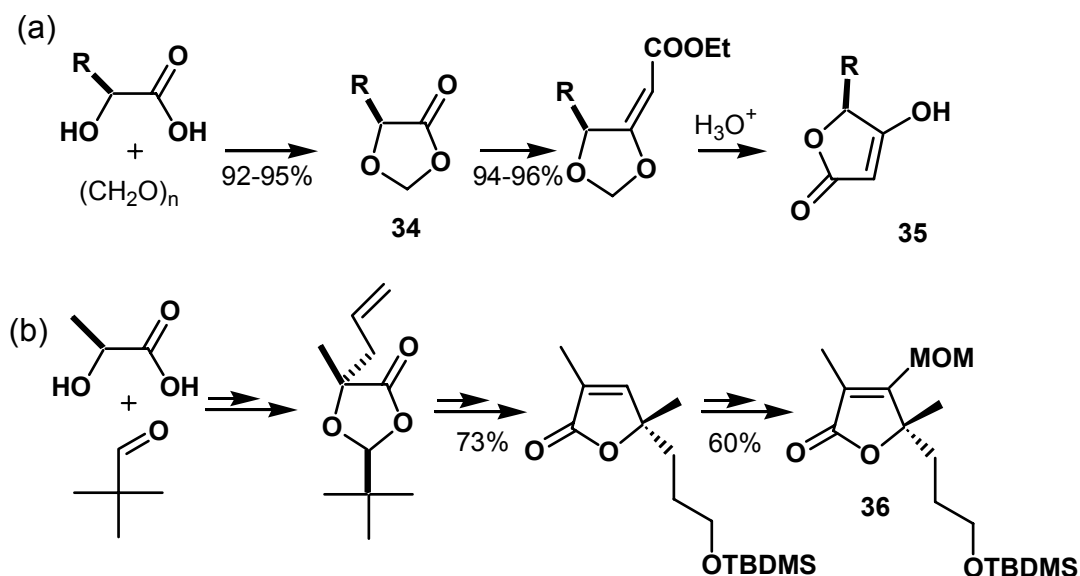
Methyl 3-substituted 5,5-spiro tetronates are good radical acceptors. This property has been exploited in the synthesis of the epoxy-lactone alliacolide (**33**)³⁹ which makes use of a stereoselective intramolecular radical cyclization onto an enolic double bond as a key step to elaborate the tricycle core of this molecule. The strategy requires a spiro-annulation of the tetronic ring system onto the substituted cyclopentenone **30**, a radical cyclization from the iodo **31** and a stereocontrolled epoxidation of the β-hydroxy intermediate **32** to give the target alliacolide (**33**) (Scheme 12).



Scheme 12

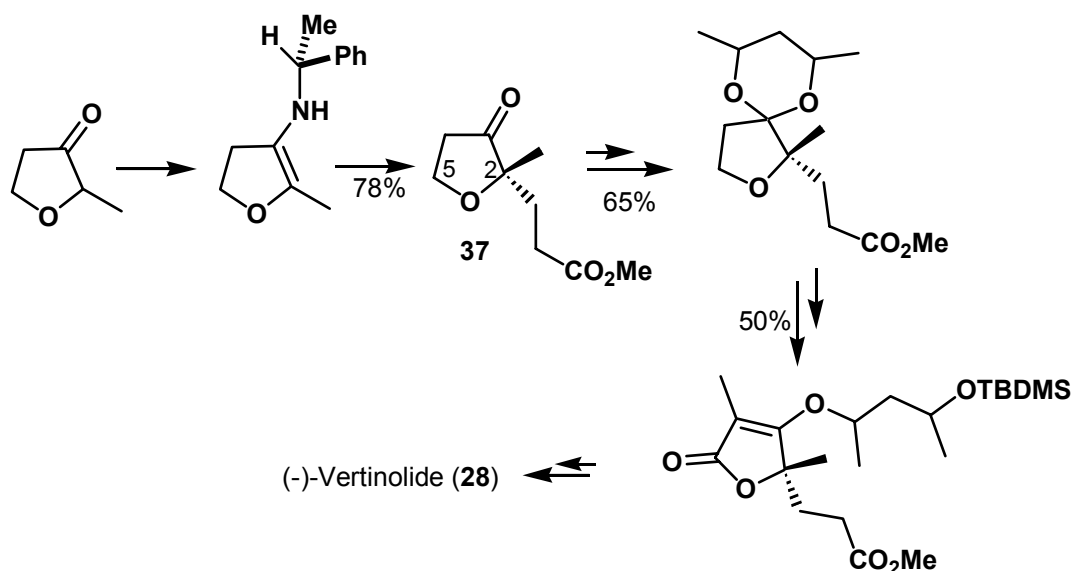
2.3. Synthesis from other heterocycles.

Chiral 2-dioxolanones **34** are very good suited synthons for the synthesis of natural occurring chiral substituted 2(5H)-furanones⁴⁰⁻⁴² (Scheme 13). They are very easily accessible from chiral α -hydroxy acids and aldehydes, and they can be homologated by means of a Wittig reaction and then rearranged to the tetronic acid derivative **35**⁴⁰ (Scheme 13, (a)) or they can be transformed into butenolides by a Wittig-Horner olefination reaction and further elaborated to 3,5,5-trisubstituted tetronic derivatives as **36**, precursor of the natural (-)-vertinolide (**28**)(Scheme 13, (b)).⁴¹



Scheme 13

A general protocol for the enantioselective construction of tetronic acids bearing a stereogenic center at C-5 has been reported.⁴³ The method is based on the readily preparation of highly optically pure 2,2-dialkyl- 4,5-dihydro-3-furanone **37** and its feasible oxidation at position C-5 (Scheme 14).

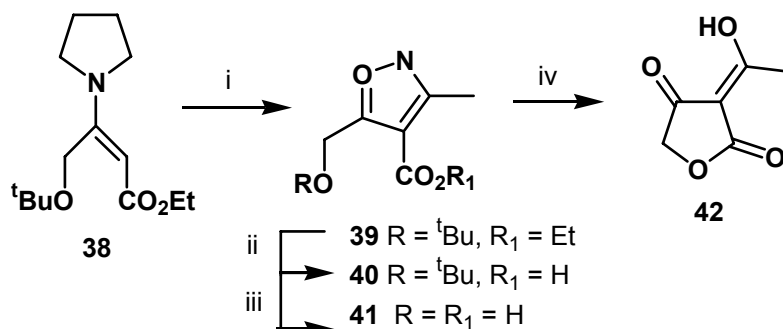


Scheme 14

Methoxide-mediated ring opening of 6-hydroxymethyl-1,3-dioxin-4-ones furnishes tetronic acid derivatives.⁴⁴ The reaction entails a ring opening to

a ketene intermediate and cyclization of this reactive intermediate to give the 2(5H)-furanone ring. 3-Mesityl-5,5-trisubstituted tetronic acids are obtained in good yields by reaction of the (chlorocarbonyl)mesitylketene with ketones.⁴⁵

The use of isoxazoles **41** as building blocks for the synthesis of 3-acyl-tetronic acids has been reported.⁴⁶ Alkyl isoxazole-4-carboxylate esters **39** are readily obtained by regioselective 1,3-dipolar cycloaddition of nitrile oxides with acetylene carboxylic acids or pyrrolidine enamines of protected γ -hydroxy- β -keto esters **38** (Scheme 15). Further transformations including deprotection of the oxygen substituent, lactonization, hydrogenation of the isoxazole ring and hydrolysis afford the tetronic acid derivative **42** in moderate yield.

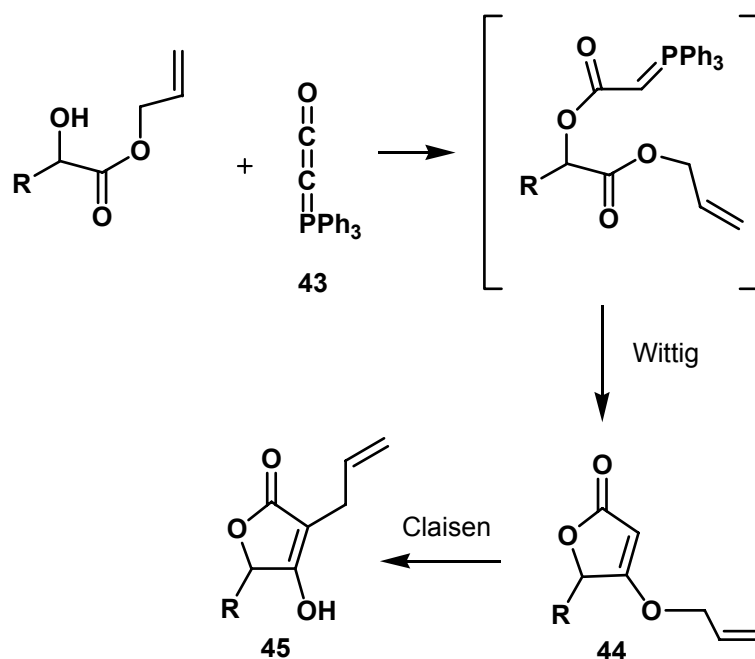


Scheme 15

2.4. One-pot synthesis.

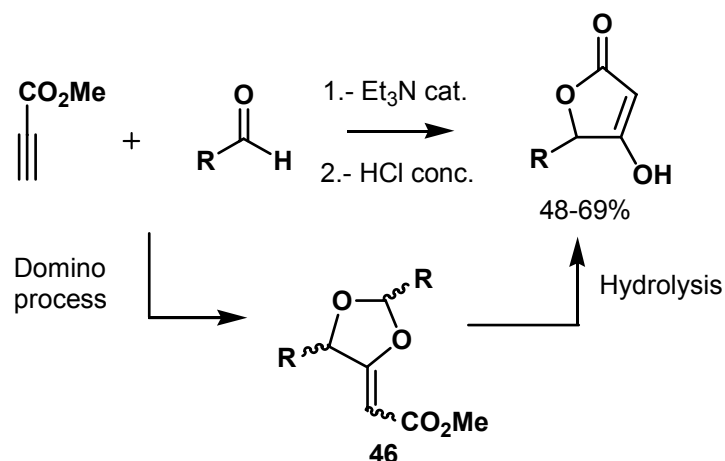
Two one-pot protocols for the synthesis of tetronic acid derivatives have been published.^{47,48} The first method⁴⁷ uses readily accessible allylic esters of α -hydroxy acids and keteneylidene triphenylphosphorane **43** to furnish 3-allyl tetronic acids **45** through a tandem Wittig-Claisen process

(Scheme 16). Esters other than allylic stop the process at the tetronate stage delivering the 5-substituted tetronate **44** in 80-90 % yield. Optically pure α -hydroxy esters like lactates, mandelates and malates deliver the 5-substituted tetronate derivatives with retention of the configuration at C-5 in the most cases.



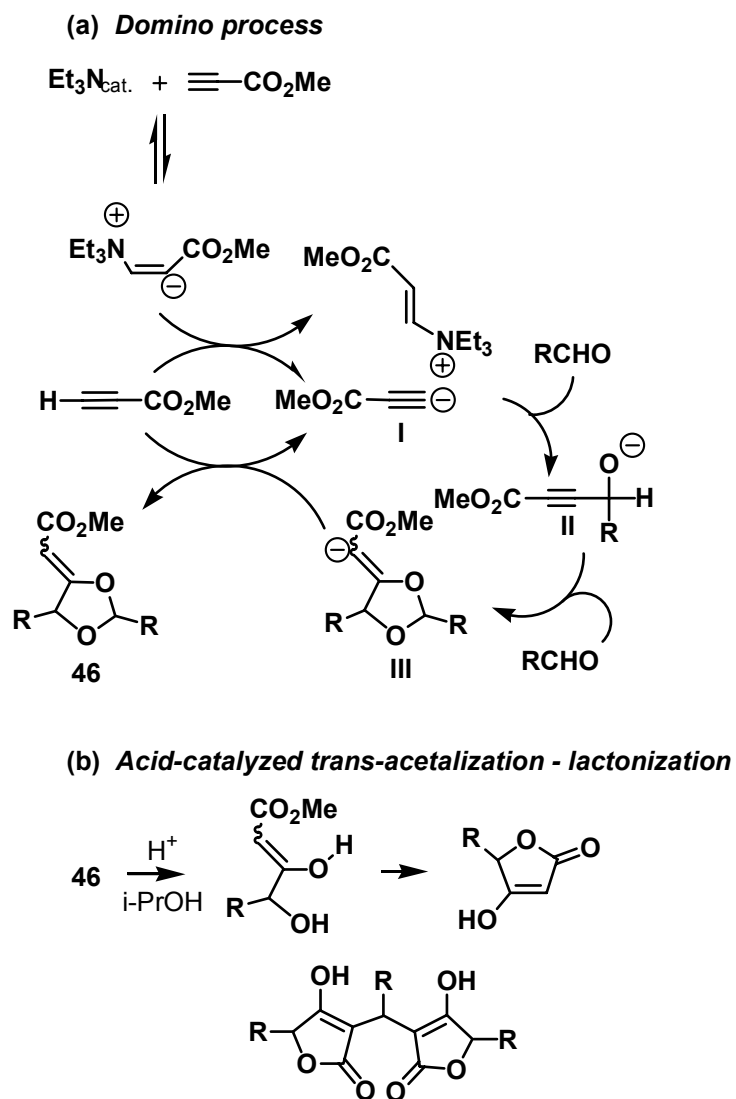
Scheme 16

The second one-pot protocol⁴⁸ furnishes 5-substituted tetronic acids from simple and commercial starting materials through two consecutive processes: a catalytic domino reaction to build a 1,3-dioxolane scaffolds **46**⁴⁹ and a two-step acid-catalyzed trans-acetalization-lactonization reaction to furnish the tetronic acid derivatives (Scheme 17). This chemical system works quite well for aliphatic aldehydes and it is a very good reaction manifold for the synthesis of 5-alkyl substituted tetronic acids. Scheme 18 outlines the proposed mechanism for the domino process:



Scheme 17

Triethyl amine triggers the domino process by a 1,4-addition to methyl propiolate to generate the ammonium acetylide **I**, which reacts with one molecule of aldehyde to give the ammonium alkoxide **II** which, in turn, reacts with another molecule of aldehyde to furnish the intermediate vinyl ammonium **III**. This anion deprotonates to the starting alkynoate generating the 1,3-dioxolanic scaffold **46** and acetylide **I** which reinitiates the cycle (Scheme 18, (a)). These 1,3-dioxolanic scaffolds **46** are built up in excellent yields and high efficiency: three bonds (two C-O bonds and one C-C bond) and one ring are created in just one synthetic step. Once these intermediates are formed, simple trans-acetalization liberates the required γ -hydroxy β -ketoester intermediates, which lactonize to furnish the 5-substituted tetronic acid derivatives (Scheme 18, (b)). Tetronic acid derivatives are quite reactive toward aldehydes to give dilactone compounds (see section 3.2).⁵⁰ Because the trans-acetalization reaction liberates one equivalent of aldehyde, the hydrolysis has to be run under controlled conditions.



Scheme 18

3. Reactivity of tetronic acids.

Tetronic acids have been modified according to the scheme outlined in figure 2.

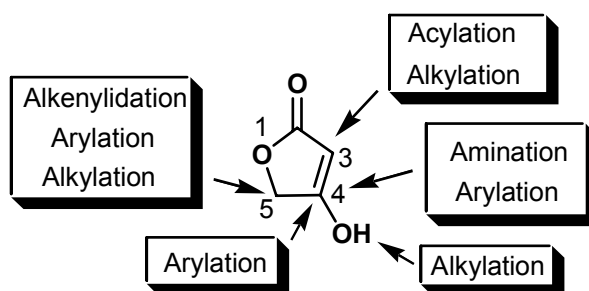
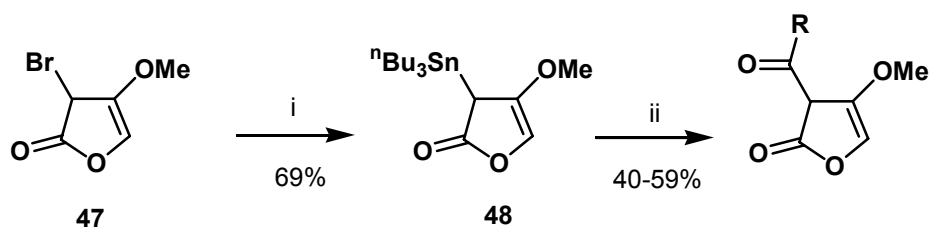


Figure 2

3.1. 3-Acylation.

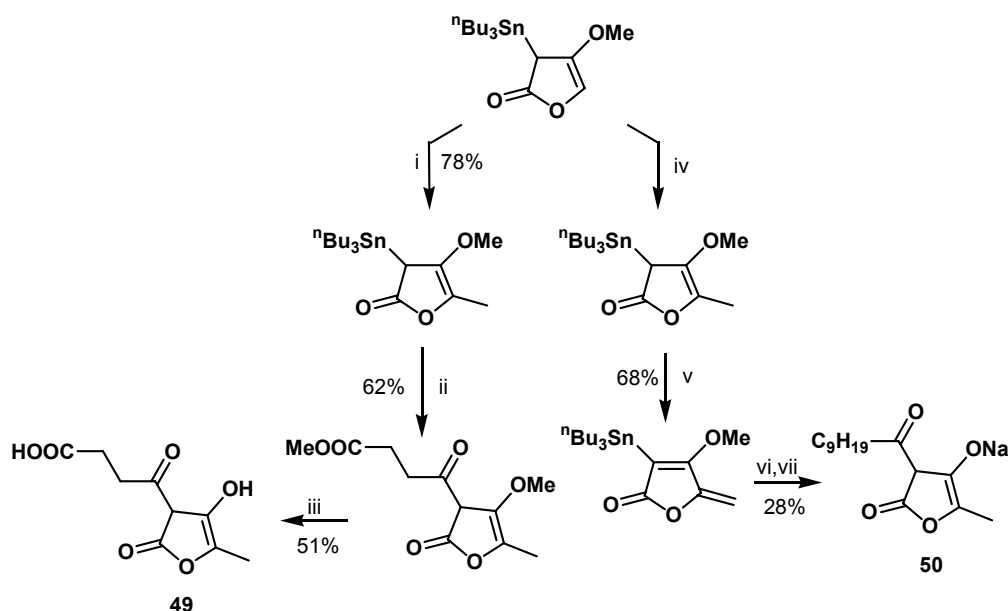
The direct acylation at the C-3 position by coupling of an acid chloride and a 3-metallated tetronate derivative is a feasible process.⁵¹⁻⁵³ It has been shown that this process fits well for the 5-substituted tetronates, but it fails when this C-5 position is vacant due to the preferential C-5 deprotonation when unsubstituted tetronates are treated with strong bases.^{52,54} On the other hand, the regioselective acylation of a 3,5-tetronate dianion is not a practicable reaction because it affords mixtures of mono and diacylated products.⁵⁵ These problems associated with the substitution grade of the tetronate molecule can be overcome by means of a palladium catalyzed acylation of a 3-tri-(n-butylstannyl) tetronate derivative **48**,⁵⁶ which is obtained in a straightforward fashion from the readily available 3-bromo tetronate **47**⁵⁷ (Scheme 19). In addition, the stability of the C-Sn bond permits functionalization of the tetronate ring system to allow the preparation of the 5-substituted-3-stannyl tetronates. Palladium-promoted acylation of these derivatives furnishes the



(i) $\text{Na}^+[\text{Nap}]^-$, $n\text{Bu}_3\text{SnCl}$, THF, -78°C to RT; (ii) RCOCl , $\text{trans-Bn}(\text{Cl})\text{Pd}(\text{PPh}_3)_2$ (cat.), $\text{C}_2\text{H}_4\text{Cl}_2$, 60°C

Scheme 19

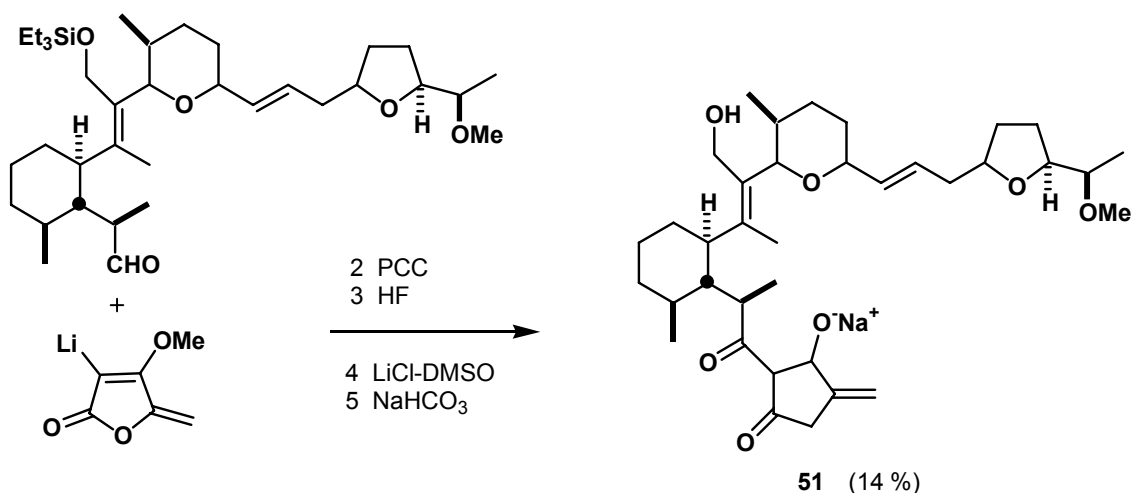
corresponding 3-acyl-5-substituted tetronates. This protocol has been exploited for the effective total synthesis of the fungal metabolite (±)-carolinic acid (**49**) as well as the antibiotic agglomerin A (**50**)⁵⁶ (Scheme 20).



(i) LDA, THF, -78°C, MeI; (ii) MeO₂CCH₂CH₂COCl, trans-Bn(Cl)Pd(PPh₃)₂(cat.), C₂H₄Cl₂, 60°C; (iii) HCl 3N; (iv) LDA, THF, -78°C, Me₂NCH₂⁺I⁻; (v) 1) MeI, MeOH, 2) NaOH 1M; (vi) H₁₉C₉COCl, trans-Bn(Cl)Pd(PPh₃)₂(cat.), C₂H₄Cl₂, 60°C; (vii) NaOH (1M), MeOH

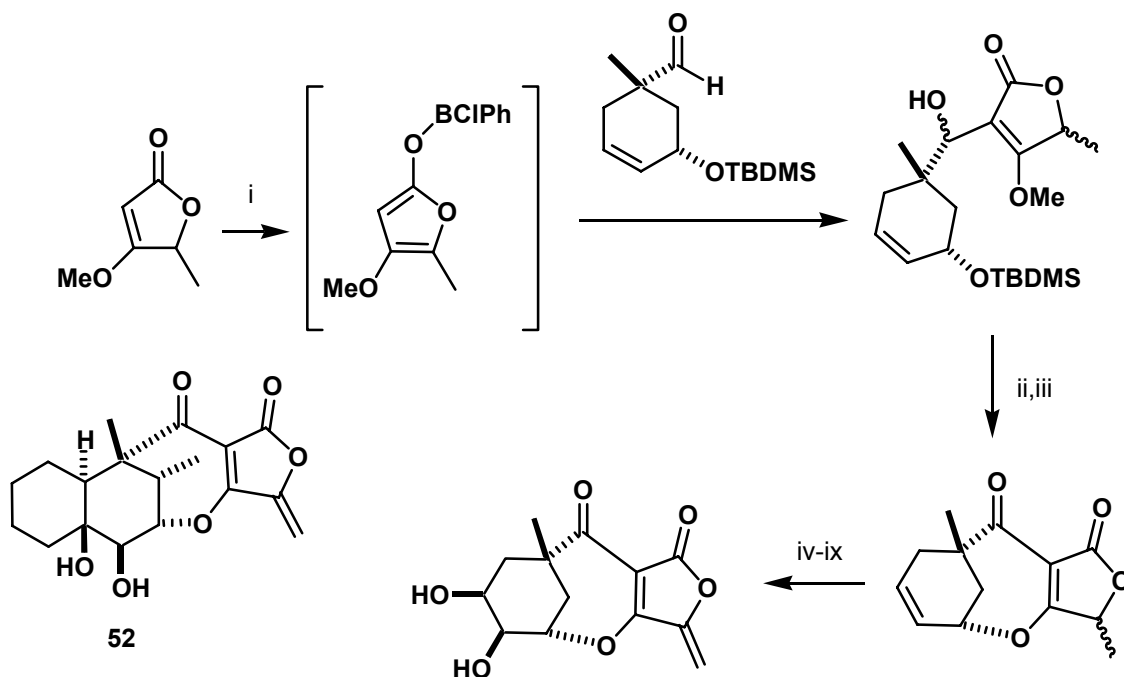
Scheme 20

In some cases, the formation of the 3-lithium salt is the best option. That was the case with the final stage of the total synthesis of the acyltetronic acid ionophore antibiotic tetronomycin (**51**)^{58,59} (Scheme 21).



Scheme 21

Boron enolates have proved to be a very good option to achieve C-3 acylation. Thus, these anolates have been used to build the tricycle core of the novel poliketide antibiotic tetrodecamycin (**52**)^{60,61} (Scheme 22).

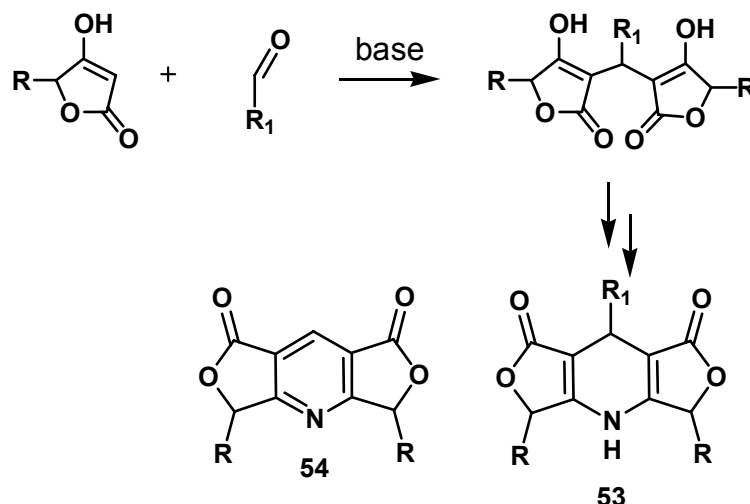


(i) 1) PhBCl_2 , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , -78°C , 2) -78°C to RT, 86%; (ii) IBX, DMSO, RT, 91%; (iii) cat. Concd H_2SO_4 , CH_2Cl_2 , RT, 89%; (iv) 1) LiHMDS, -78°C , 2) N-phenylmercaptophthalimide, -78°C , 87%; (v) 1) OsO_4 , pyridine, CCl_4 , RT, 2) aq. NaHSO_3 , 87%; (vi) TBDMSOTf, lutidine, CH_2Cl_2 , -78°C , 92%; (vii) MCPBA, CH_2Cl_2 , -20°C ; (viii) BaCO_3 , benzene, 27% for the 2 steps; (ix) HF, MeCN, 0°C , 100%.

Scheme 22

3.2. 3-Alkylation.

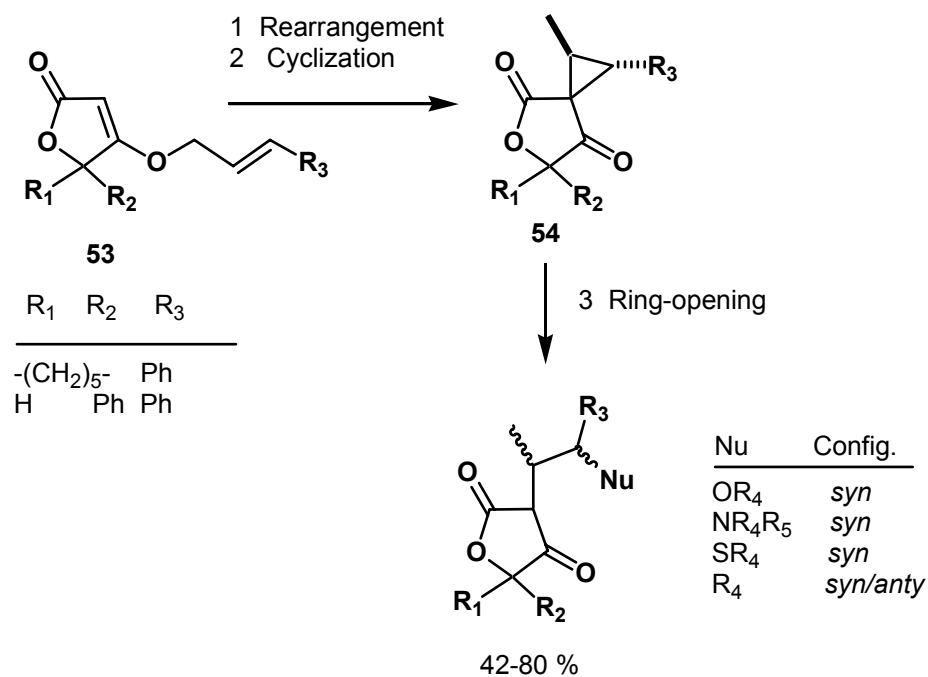
Tetronic acids are quite reactive toward aldehydes furnishing bis-furanones^{50,62-64} which in turn, are easily transformed into fused-heterocycles⁶⁵⁻⁶⁷ (Scheme 23).



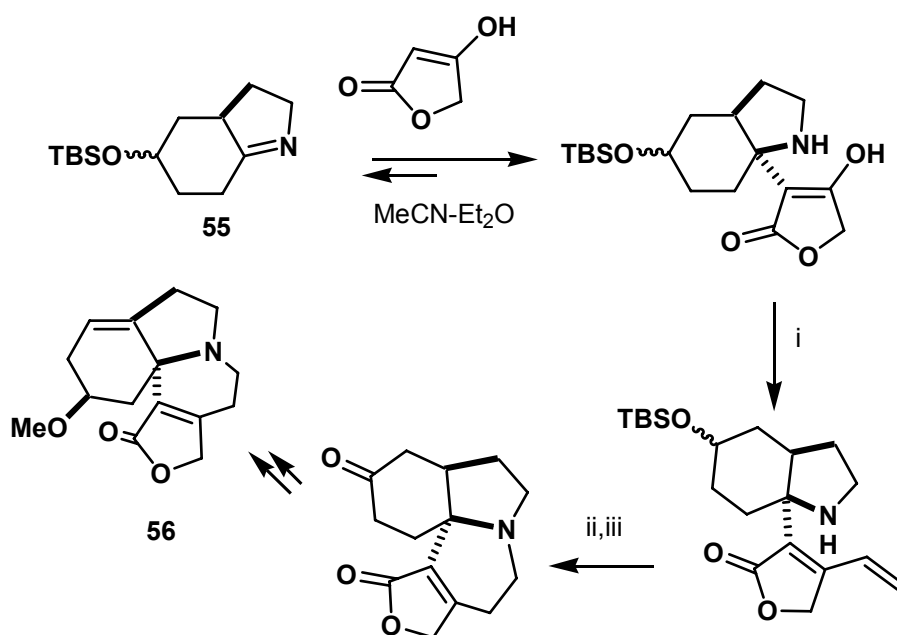
Scheme 23

Allyl tetronates **55** thermally rearrange to stable 3-(spirocyclopropyl)dihydrofuran-2,4-diones **54**, which are ring-opened with nucleophiles to give 3-substituted tetronic acids in good yields.⁶⁸ The one-pot procedure entails three different chemical processes: a Claisen-Conia rearrangement, a cyclization and a ring-opening reaction (Scheme 24).

Coupling of tetronic acids and imines furnishes the versatile C-3 amino-alkyl tetronic acids which can be further transformed into more sophisticated compounds. That is the case of the alkaloid cocculidine (**56**), whose first synthesis utilizes a coupling reaction of the bicyclic imine **55** and tetronic acid to install 3 of the 4 rings present in the molecule⁶⁹ (Scheme 25).



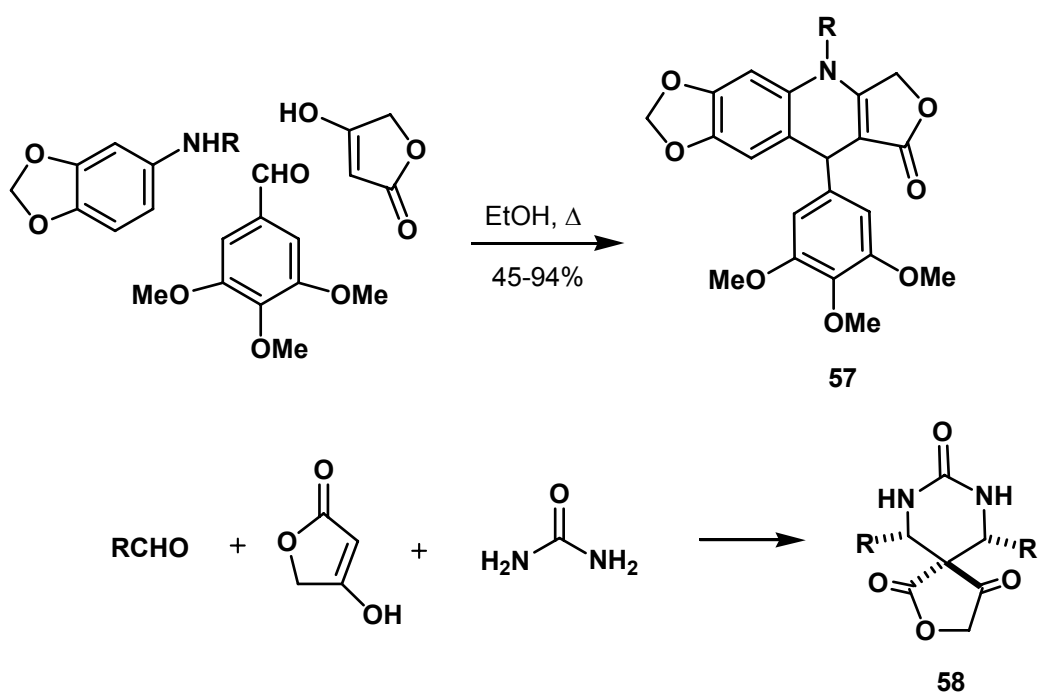
Scheme 24



(i) (1) Boc₂O, cat. DMAP, CH₂Cl₂, RT; (2) Tf₂O, pyr., CH₂Cl₂, -78°C to RT, 8h; (3) n-Bu₃SnCH=CH₂, (Ph₃P)₂PdCl₂, DMF, 35°C, 4h; (ii) TFA (neat) then H₂O, 5 steps, 52%; (iii) TPAP, NMO, 4 a MS, CH₂Cl₂-MeCN (10:1), 0°C to RT, 84%

Scheme 25

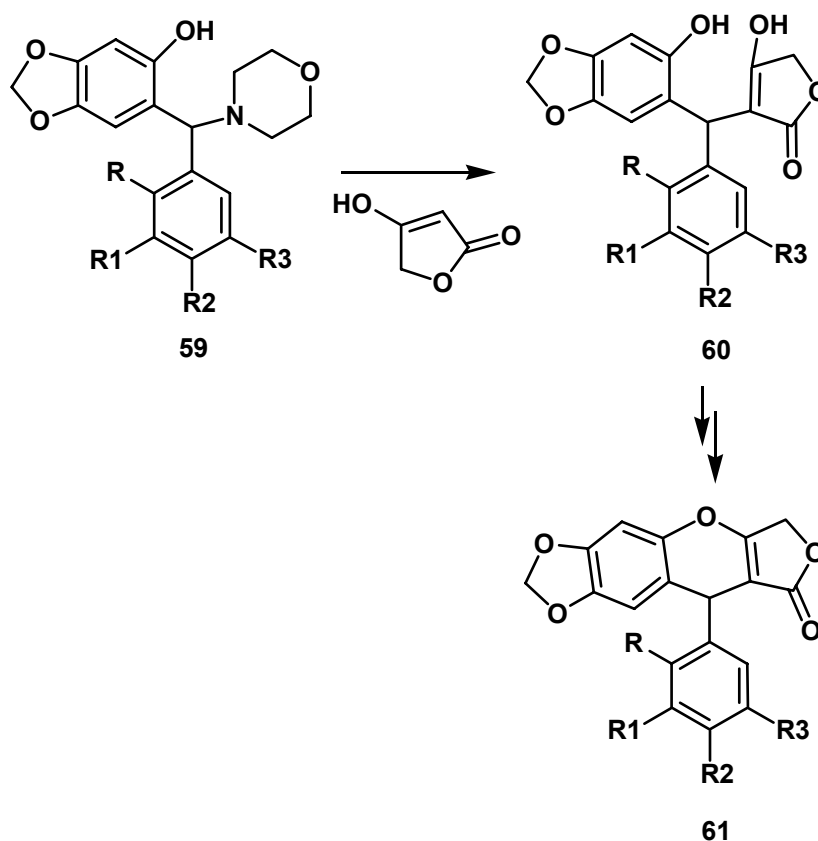
A convergent and one-pot method to prepare 4-aza-2,3-didehydropodophyllotoxin (**57**), analogues of microtubule assembly inhibitor pophyllotoxin, has been published.⁷⁰ The method comprises the one-pot reaction of tetronic acid, one aromatic amine and one aromatic aldehyde to give the 4-aza-2,3-didehydropodophyllotoxin (**57**) in excellent yield (Scheme 26). In a very similar manner, 3-spiro heterobicyclic tetronic acid **58** has been synthesized by the one-pot reaction of urea (1 mmol), aldehyde (2 mmol) and tetronic acid (1mmol).⁷¹ These molecules are suitable to be used as potential scaffolds to append other organic groups through remaining functional groups in a domino strategy (Scheme 26).



Scheme 26

Active antitumor agents based on the heterocyclic benzodioxole lactone **61** (Scheme 27) have been synthesized by coupling tetronic acid with morpholino Mannich bases **59** in aqueous acetic acid.⁷² The diol-

lactones **60** were transformed into the target **61** by acetylation, methylation and base-promoted cyclization.



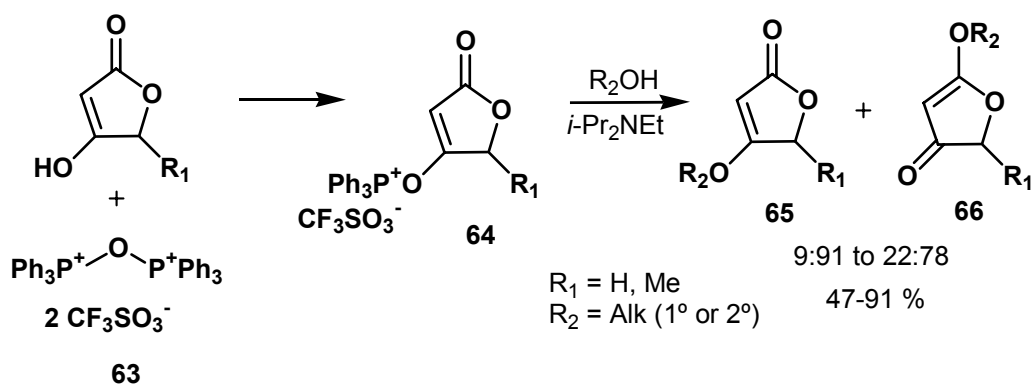
Scheme 27

An efficient method for the synthesis of 3-alkylated tetronic acids based on the selective NaBH_3CN reduction of a 3-acyl derivative has been described.⁷³

3.3. 4-O-Alkylation.

Regioselective 4-O-alkylation of tetronic acids has been the focus of many investigations.⁷⁴ Two general methods have been reported with synthetic value.^{75,76} The first one makes use of a Mitsunobu reaction for the high yielding regioselective O-alkylation of tetronic acids with primary and secondary alcohols. The reaction conditions are mild and compatible with a wide range of hydroxyl protecting groups. Tertiary alcohols fail to

give the reaction. This method has been adapted to the chemo- and regioselective alkylation of L-ascorbic acid and derivatives.⁷⁷ The other efficient and versatile method⁷⁶ is based on the formation of a very reactive 4-O-phosphonium ether methanesulphonate salt derivative **64** by reaction of tetronic acid with the triphenylphosphonium anhydride trifluoromethanesulphonate (**63**) (Hendrickson's reagent). This activated tetronate derivative **64** is able to react with stoichiometric amounts of primary or secondary alcohols to furnish the 4-O-alkylated tetronate **65** in excellent yields and high regioselectivity (Scheme 28).



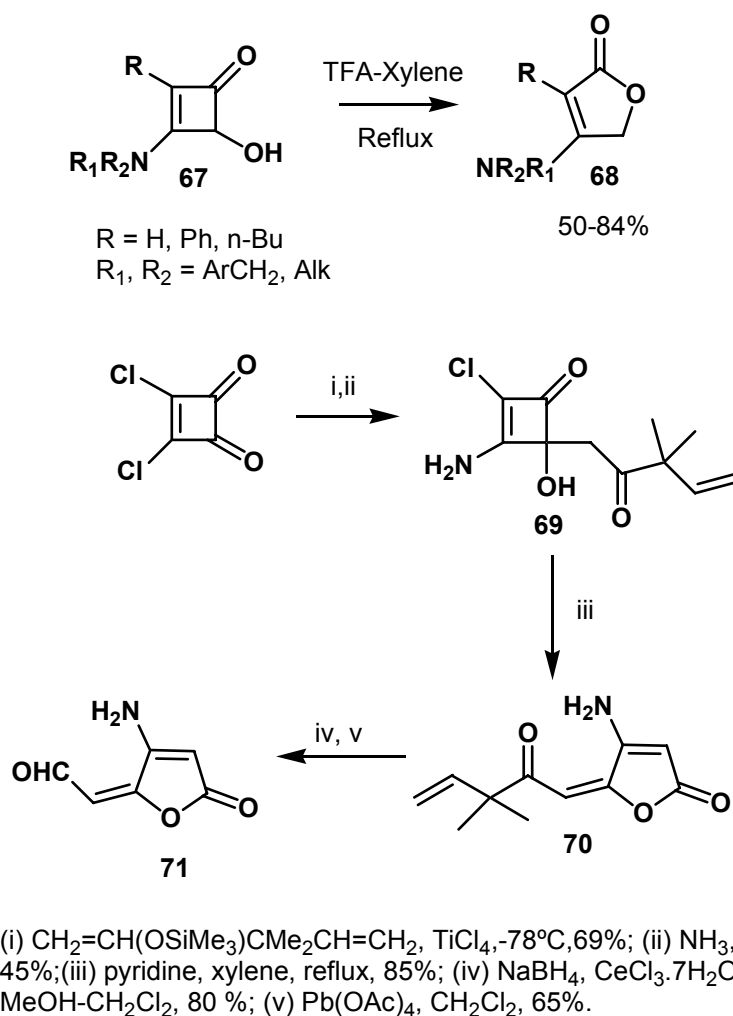
Scheme 28

3.4. 4-Amination

4-Amino-2(5H)-furanones are biologically active molecules⁷⁸ which are either obtained by enamine formation from the suitable tetronic acid precursor⁷⁹ or by direct synthesis. Some synthetic methods have already been mentioned in previous sections.

Simple unsubstituted 4-amino-2(5H)-furanones are very easily obtained from acetylenecarboxylates by aminoaddition, selective reduction of the enamine-intermediate and cyclization.⁸⁰ 5- or 3-Substituted derivatives can be obtained by ring-rearrangement of a suitable 3-amino 4-hydroxy-

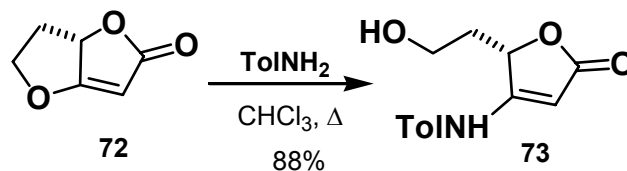
cyclobutenone **67** (Scheme 29). Thus, while the trifluoroacetic acid-promoted rearrangement of 4-hydroxy-cyclobutenone **67** affords the 3-substituted-4-amino-2(5H)-furanone **68**,⁸¹ the thermally-driven rearrangement of the 4-acylmethyl-2-chloro-3-amino-4-hydroxycyclobutane **69** produces the 5-acylmethyliden-4-amino-2(5H)-furanone **70**.⁸² This last rearrangement is a key step in the total synthesis of the natural product basidalin (**71**)⁸³ (Scheme 30).



Scheme 29

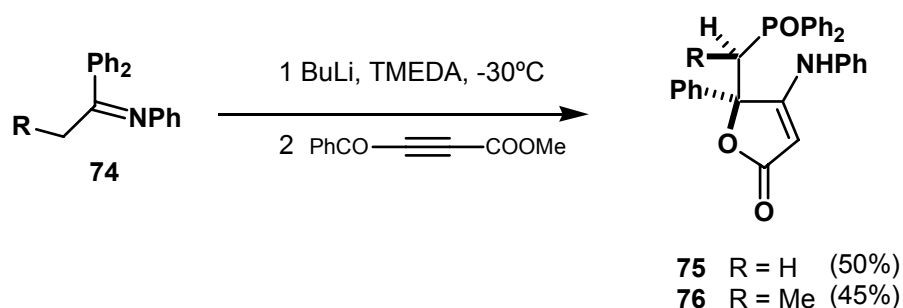
4-Azido-2(5H)-furanones, readily accessible from the 4-Br derivatives,⁸⁴ have been reported to be good precursors of 4-carbamoyl derivatives.⁸⁵

Also, bicyclic tetronate derivatives **72** have been used as suitable platforms for the synthesis of 5-substituted 4-amino-2(5H)-furanones **73**⁸⁶ (Scheme 30).



Scheme 30

The 1,3-cycloaddition of lithiated phosphazene derivatives **74** with benzoyl methyl propiolate has been reported⁸⁷ to give the phosphorous-containing 4-amino-2(5H)-furanones **75** and **76** in moderate yield and good diastereoselectivity (Scheme 31).

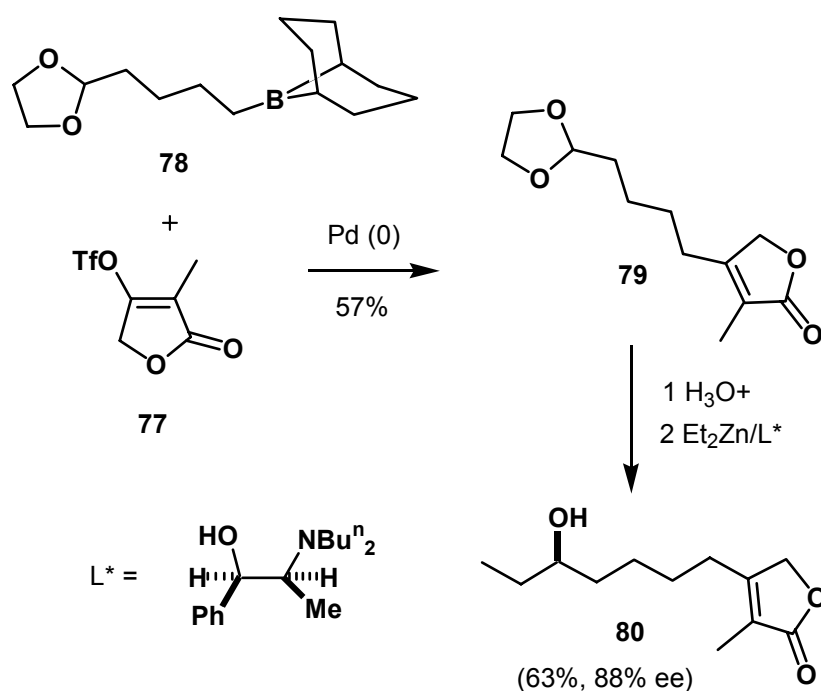


Scheme 31

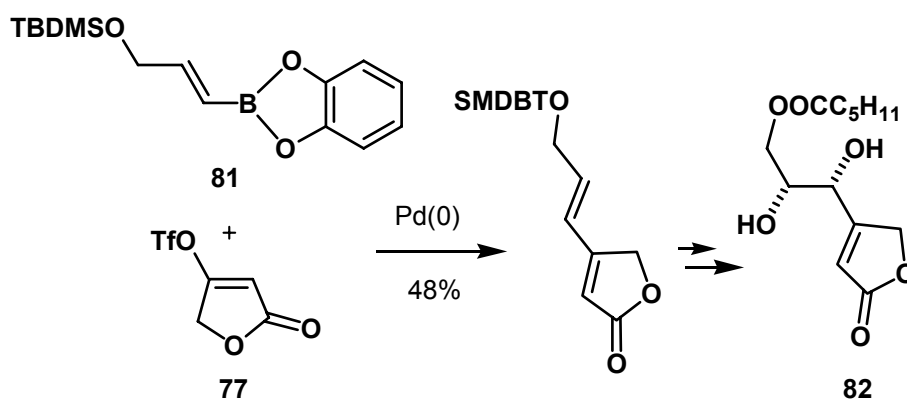
3.5. 4-Alkylation and 4-arylation.

4-substituted-2(5H)-furanone is an ubiquitous subunit in many biologically active butanolide-containing natural products.⁸⁸ These important privileged fragments are synthesized mainly by transition metal-catalyzed cross-coupling reactions. The Pd(0)-catalyzed cross-coupling

(Suzuki) reaction of tetronic acid triflates **77** with 9-alkyl-9-borabicyclo[3.3.1]nonanes **78** affords the 4-alkyl-2(5H)-furanones **79** in moderate to good yield and tolerates a range of functionalities.⁸⁹ The potential of this reaction was further demonstrated by its application in the 3-step synthesis of the natural phytotoxin (-)-isoseiridine (**80**) (Scheme 32). Suzuki coupling of alkenylboronates **81** and tetronic acid



Scheme 32



Scheme 33

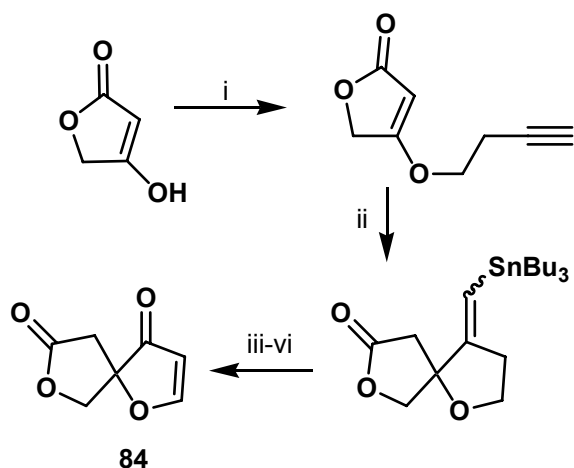
triflates **77** has been described in the preparation of syributin 1 (**82**)⁹⁰ (Scheme 33). Recently, the Pd(0)-catalyzed cross-coupling reaction of

cyclopropylboronic acids and tetronic acid triflates has been reported to succeed in the presence of AsPh_3 as a ligand (63-85%).⁹¹ The coupling reaction conditions has also been applied to alkenylboronic acids affording the 4-substituted-2(5H)-furanones with retention of the configuration of the alkenyl group and better yields than aforementioned methods. The palladium-catalyzed coupling reactions of 4-bromo and 4-stannyl tetronic acids derivatives with arylboronic acids have also been reported.^{92,93} Although these reactions proceed with reasonable efficiency (60-85%), the utility of these methods are limited by the harsh conditions required for the formation of the 4-bromo derivative and by the toxicity of the organotin by-products which are difficult to remove, specially on large scale reactions. Recently, 4-tosylate-2(5H)-furanones have been used as the tetronic partner in these palladium-catalyzed cross-coupling reactions with alkenyl and aromatic boronic acids, affording the 4-aryl(alkenyl)-2(5H)-furanone in moderate to good yields.⁹⁴ The major advantage of these derivatives resides on their stability and easy preparation.

Tetronates are good radical acceptors and this property has been exploited in the synthesis of longianone (**84**),^{95,96} a fungal metabolite possessing an unusual 1,7-dioxaspiro-[4,4]non-2-ene-4,8-dione skeleton⁹⁷ (Scheme 34).

3.6. **3,4-Diarylation.**

Unsymmetrical 3,4-disubstituted-2(5H)-furanones occur rarely in nature⁹⁸ but they are claimed as drugs and biocides. The 3,4-diaryl



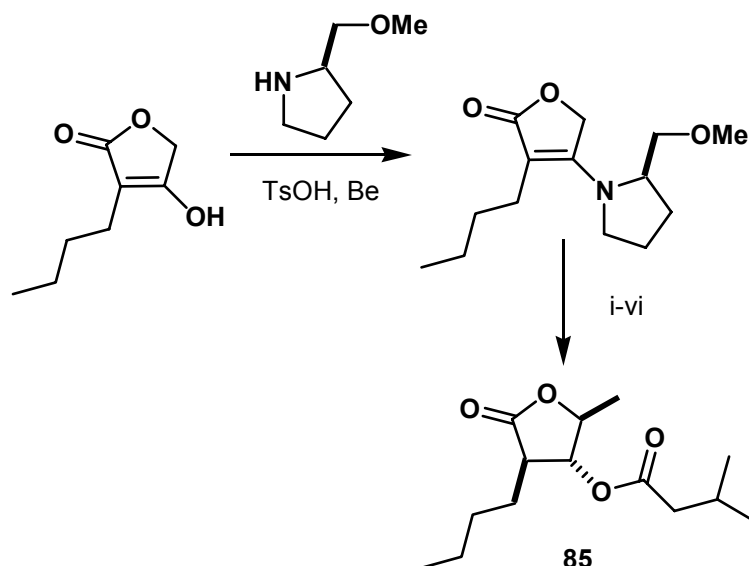
(i) But-3-ynol, TsOH, PhH, 18h, 76%; (ii) Bu_3SnH , AIBN, PhH, reflux, 5h, 71%; (iii) HCl (1M), CH_2Cl_2 , RT, 1h, 100%; (iv) O_3 , -78°C , then DMS, -78°C to RT, 2h, 79%; (v) PhSeCl , THF, H_2O (cat), 5 days, 38%; (vi) O_3 , CH_2Cl_2 , then purge N_2 and warm to RT, 12h, 44%.

Scheme 34

derivatives have been obtained from the 3,4-distannyl⁹⁹ or 3,4-dibromo¹⁰⁰ derivatives by a regioselective palladium-catalyzed cross-coupling reaction. Remarkably, the diminished reactivity of the C3-Sn bond regarding to the C4-Sn makes this reaction quite regioselective, allowing the preparation of the 4-aryl-3-bromo or 4-aryl-3-stannyl-2(5H)-furanones in moderate to good yields. These compounds can be further transformed into the 3,4-diaryl- or 4-aryl-2(5H)-furanones.

3.7. 5-Alkylation, arylation and alkenylation.

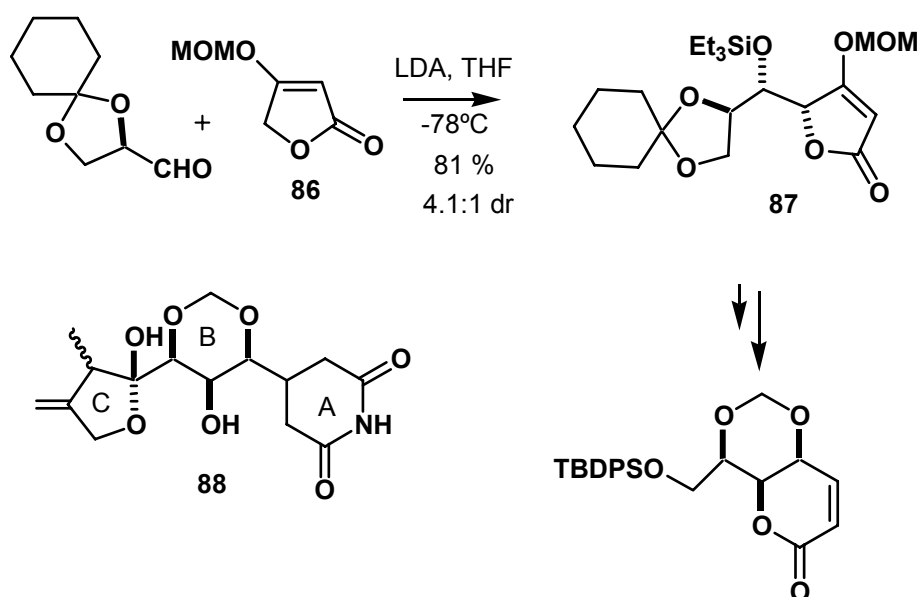
Fully functionalized tetronic acids are suitable precursors for the synthesis of the natural γ -lactones with three contiguous asymmetric centers. Alkyl substituents at the C-5 position of tetronic acids are easily introduced by a modified Ramage's method.¹⁰¹ This method has been applied to the asymmetric synthesis of (+)-blastmycinone (**85**)¹⁰² (Scheme 35).



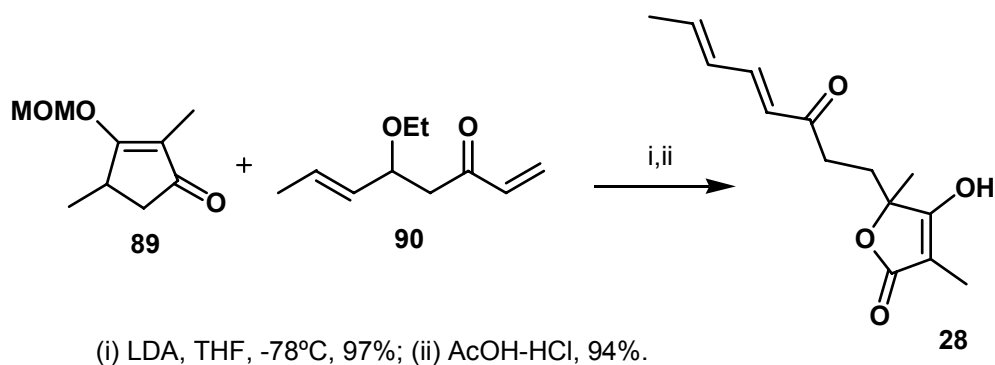
(i) $n\text{-BuLi}$, THF-HMPA, -78°C ; (ii) MeI , -98°C ; 91% (91:9 dr); (iii) NaBH_3CN , HCl (2N), MeOH , 45°C , 84%; (iv) NaOCl , pyridine; (v) Sml_2 (4 equiv.), THF-DMAE, RT, 69%; (vi) $(\text{CH}_3)_2\text{CHCH}_2\text{COCl}$, pyridine, 80%

Scheme 35

Methoxymethyl tetronates are easily alkylated at C-5 position by treatment with lithium dimethylisopropylamide and an electrophile. The aldolic reaction of methoxymethyl 3-substituted tetronates **86** with aldehydes gives the corresponding chelation-controlled *threo*-adduct **87** as the main product, and this fact has been used in the stereocontrolled synthesis of the B-ring of the sesbanimide alkaloids (**88**)¹⁰³ (Scheme 36). On the other hand, methoxymethyl 3,5-dimethyl-tetronate **89** reacts with α,β -unsaturated ketone **90** to give ($\pm$)-vertinolide (**28**) in good yields¹⁰⁴ (Scheme 37).

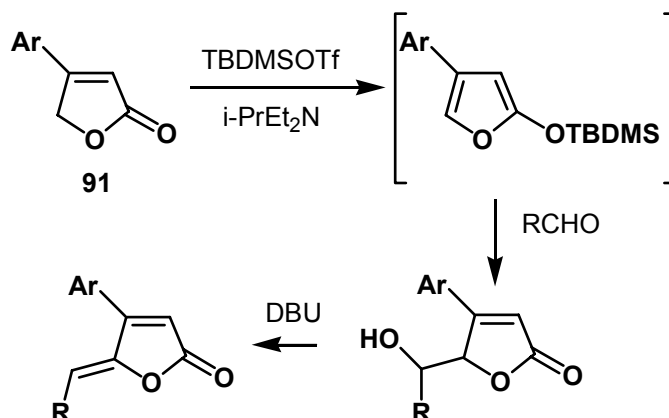


Scheme 36



Scheme 37

Finally, 4-aryl-2(5H)-furanones **91** are easily alkenylidated at C-5 position by treatment with tert-butyldimethylsilyltriflate in the presence of an aldehyde, followed by *in situ* DBU-promoted β -elimination^{88a,92c,94} (Scheme 38).



Scheme 38

4. References

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