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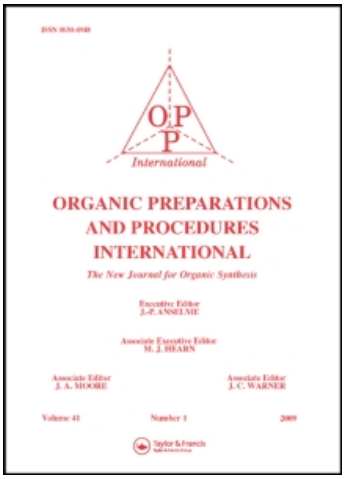

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SYNTHESIS AND CHEMISTRY OF TETRONIC ACIDS

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SYNTHESIS AND CHEMISTRY OF TETRONIC ACIDS

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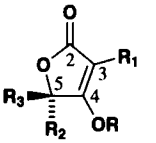
INTRODUCTION

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 reactivity rather than the biological and pharmaceutical aspects of these products.



1 $R = R_1 = R_2 = R_3 = H$
2 $R = R_2 = H$; $R_1 = OH$;
$R_3 = CH(OH)CH_2OH$

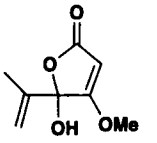


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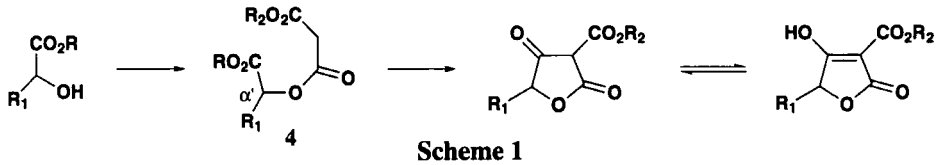
Figure 1

I. SYNTHESIS OF TETRONIC ACIDS

1. Base-promoted Dieckman Cyclization

3,5-Disubstituted tetronic acids present medicinal interest as potential antibiotic, antivirial and antineoplastic agents.[2-7] Among them, the 3-acyl derivatives comprise a structural

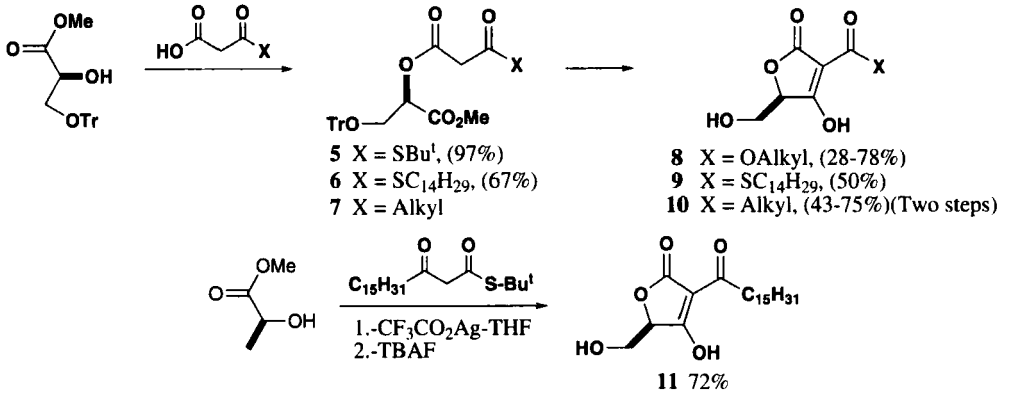
motif present in a great number of active natural products. The base-promoted Dieckmann cyclization of glycolyl acetoacetates **4** (*Scheme 1*) is one of the most synthetically useful methods for the preparation of these 3-acyl derivatives.[8-14,26,28] The ability of these intermediates



Scheme 1

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 source 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 acid[16] or (s)-lactic acid.[7,17]

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 cyclization[18] of the suitable glycolyl acetoacetate intermediates **5-7** in moderate to good yields (*Scheme 2*).[7]



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

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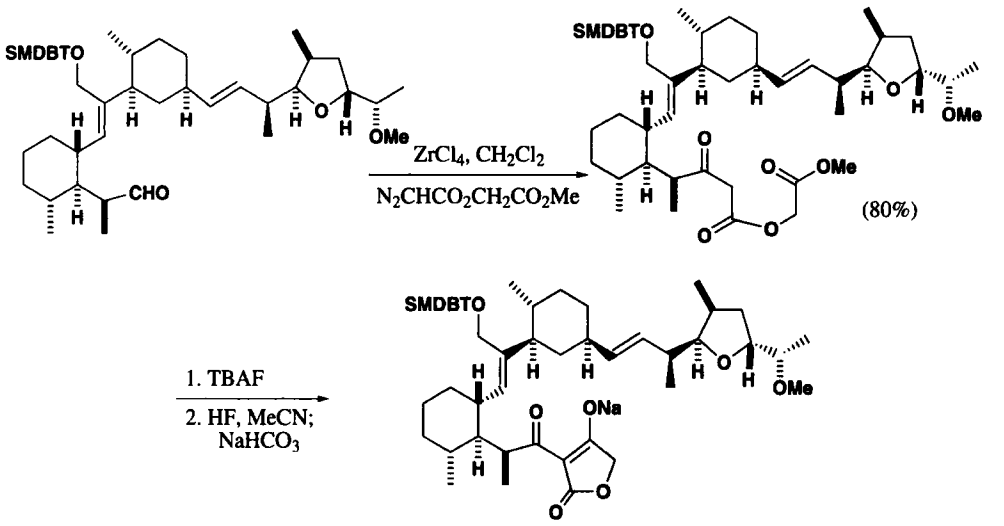
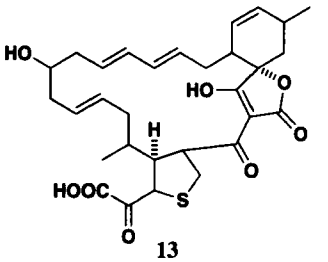
challenging installation of the 5-unsubstituted 3-acyl tetronic acid core. This was accomplished in two steps by installation of the required β-keto ester intermediate by a zirconium-catalyzed C-H insertion reaction of the methyl (diazoacetoxy)acetate unit and a tetrabutylammonium fluoride-promoted intramolecular Dieckmann cyclization to afford tetronasin (**12**) in 72% yield (*Scheme 3*).



Scheme 3 **12** (92%)

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 oxaspirobicylic 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 led to the expected cyclization (*Scheme 4*).



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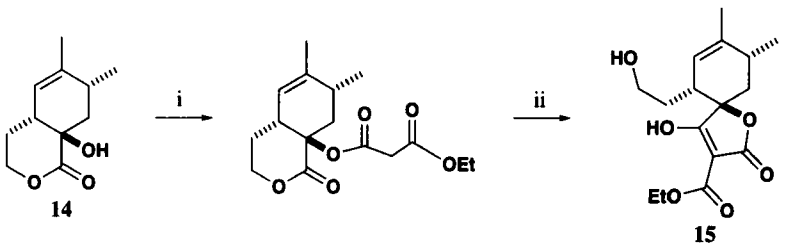

14 **15**

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

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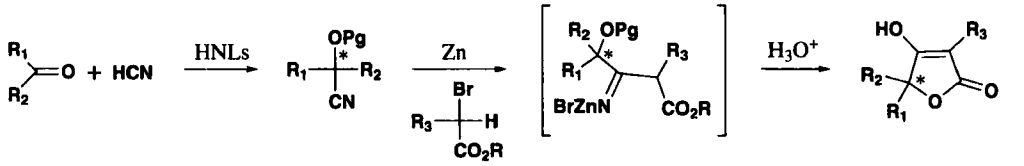
2. Cyclization of γ-Oxygenated or γ-Halogenated β-Ketoester

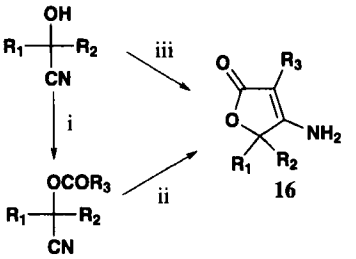
Suitable β-ketoester derivatives bearing a γ-halogen atom[22-24] or a γ-oxygenated function[25-29] have been widely used as tetronic acid precursors.

Optically active 3,5-disubstituted tetronic acids are directly synthesized by the Blaise reaction[30] of Reformatsky reagents with chiral cyanohydrins (*Scheme 5*) and acid hydrolysis of the γ-hydroxy[25a-h] and γ-silyloxy β-ketoester[27] 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-acylated 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 yields[34] (*Scheme* 6).



i)(S)-cyanohydrin, R_3CH_2COCl, pyr., 24-89%; ii) $LiN(SiMe_3)_2$,THF, -78°C, 48-95% without razemization; iii) $SnCl_4$ (1 equiv), $MeCOCH_2COOR$ or $CH_2(CO_2Et)_2$, 50-80%

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]

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

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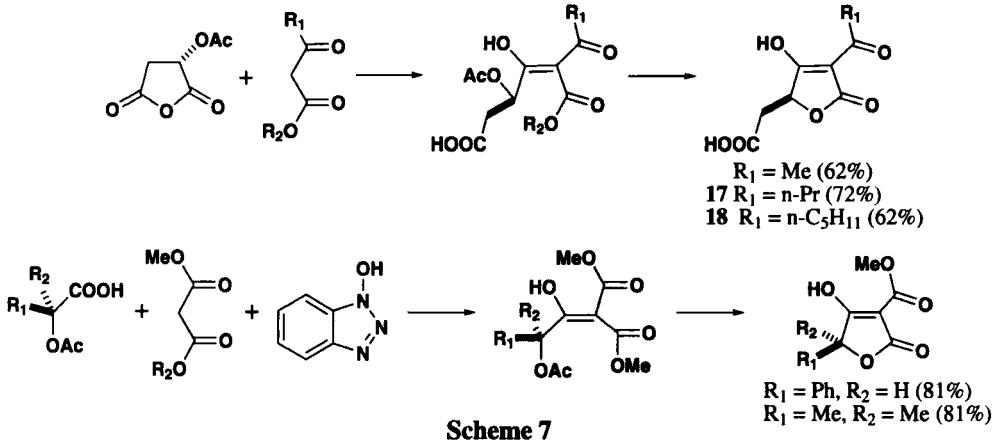

Scheme 7

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.

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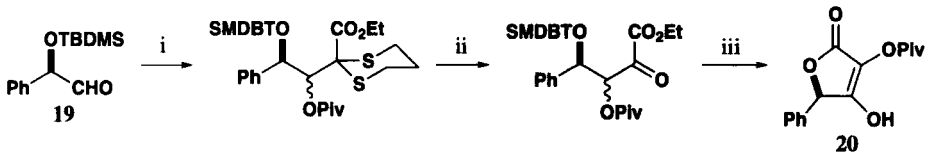
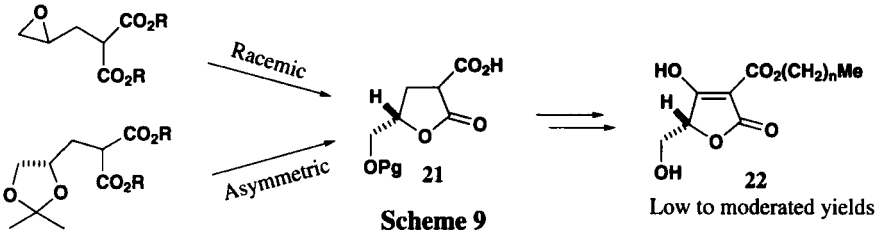


i)Ethyl 1,3-dithiane-2-carboxylate, LDA, Cl-Piv, -78°C,50-60%; ii)NCS, $AgNO_3$, aq. MeCN, 80-90%; iii) TBAF,THF, 85-90%

Scheme 8

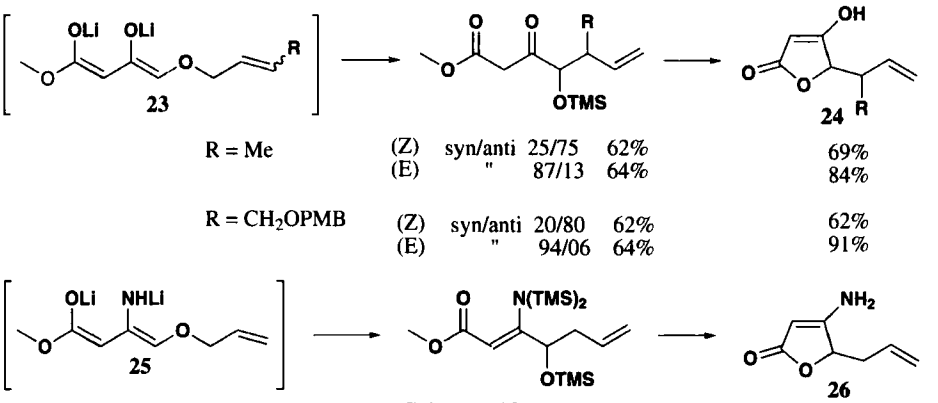
Natural 3-alkanoyl-5-hydroxymethyl tetronic acids comprise an important group of biological active molecules. Access to this group of derivatives has been accomplished[28] in good yields from diethyl allylmalonate by simple epoxidation, hydrolysis and acid-promoted lactonization, or from optically active 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

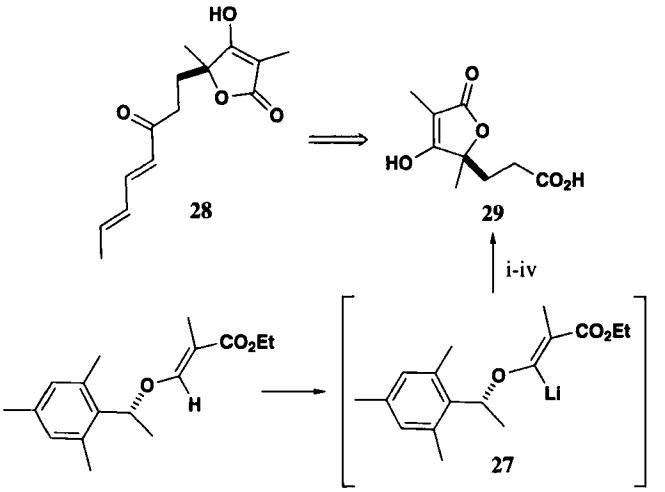
γ-allyloxy-β-keto ester dianions **23** rearrange to γ-hydroxy-β-keto ester derivatives which form 5-substituted tetronic acid **24** by simple lactonization[29] (*Scheme 10*). Alternatively,

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 C_3 bulding 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 $MeCOCH_2CH_2CO_2Et$, -100°C, 68%,4.5:1 diastereomeric mixture; ii) NaOH, MeOH, quant.; iii) LDA,THF,-90°C, MeI, 85 %; iv) Me_3SiCl, CH_2Cl_2, RT, quant

Scheme 11

Methyl 3-subsituted 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

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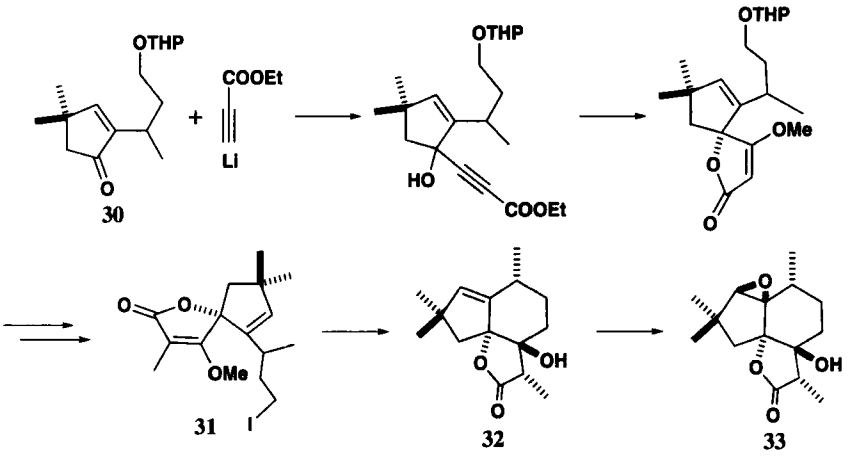
tetronic ring system onto the substituted cyclpentenone **30**, a radical cyclization from the iodo **31** and a stereocontrolled epoxidation of the β-hydroxy intermediate **32** to give the target alliacolide (**33**) (*Scheme 12*).



Scheme 12

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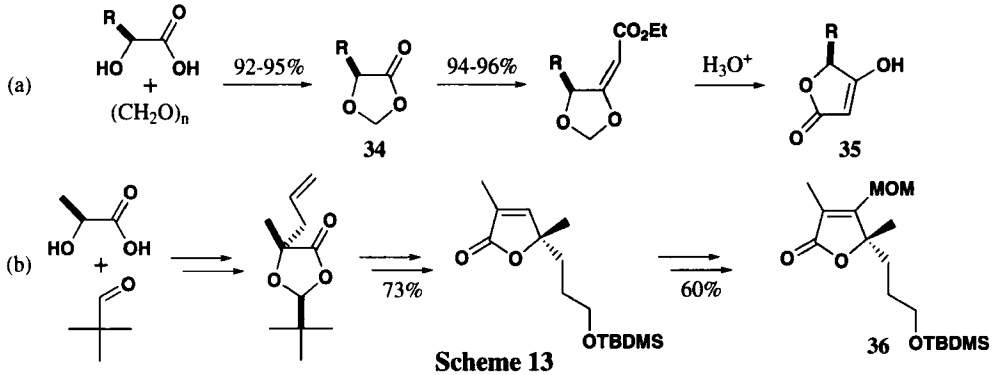
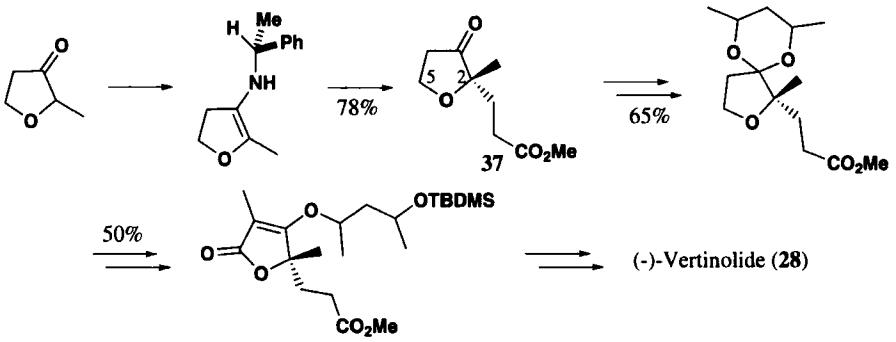
3. Synthesis from Other Heterocycles

Chiral 2-dioxolanones **34** are synthons well-suited for the synthesis of natural occurring chiral substituted 2(5H)-furanones[40-42] (*Scheme 13*). They are very readily 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 such as **36**, precursor of the natural (-)-vertinolide (**28**)(*Scheme 13*, (b)).[41]



Scheme 13

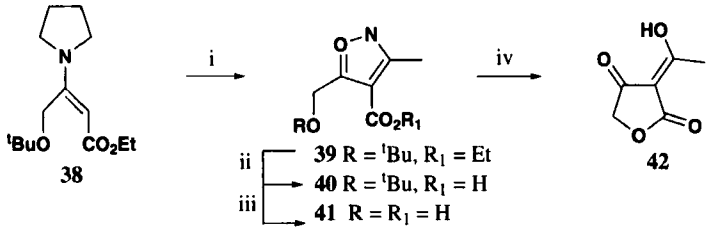
A general protocol for the enantioselective construction of tetronic acids bearing a stereogenic center at C-5 has been reported.[43] The method is based on the straightforward preparation of highly optically pure 2,2-dialkyl- 4,5-dihydro-3-furanone **37** and its feasible oxidation at position C-5 (*Scheme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



i) $EtNO_2$, Et_3N, $POCl_3$, 0-5°C, 63%; ii) NaOH aq. (2M), reflux, 94%; iii) CF_3CO_2H, 46%; iv) 1) H_2, Pd-C, RT, 2) NaOH aq. (2M), RT, 42%

Scheme 15

4. One-pot Synthesis

Two one-pot protocols for the synthesis of tetronic acid derivatives have been published.[47,48] The first method[47] 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 proceed to 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-subsituted tetronate derivatives with retention of the configuration at C-5 in most cases.

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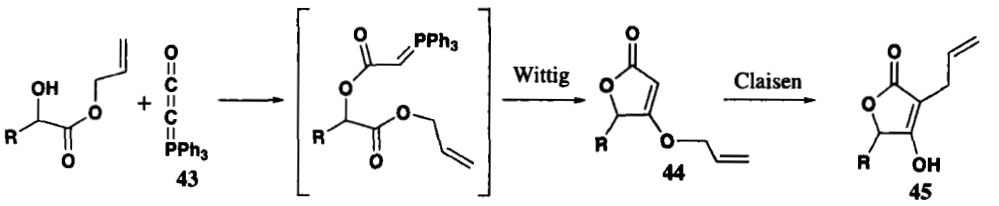
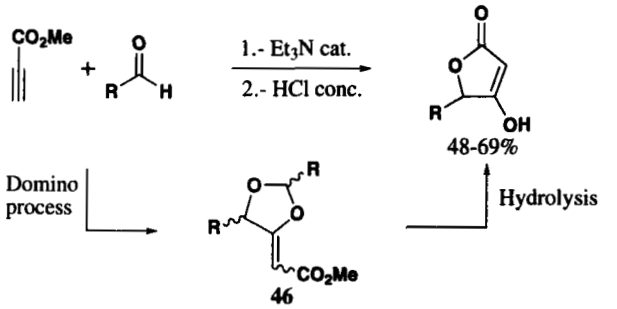


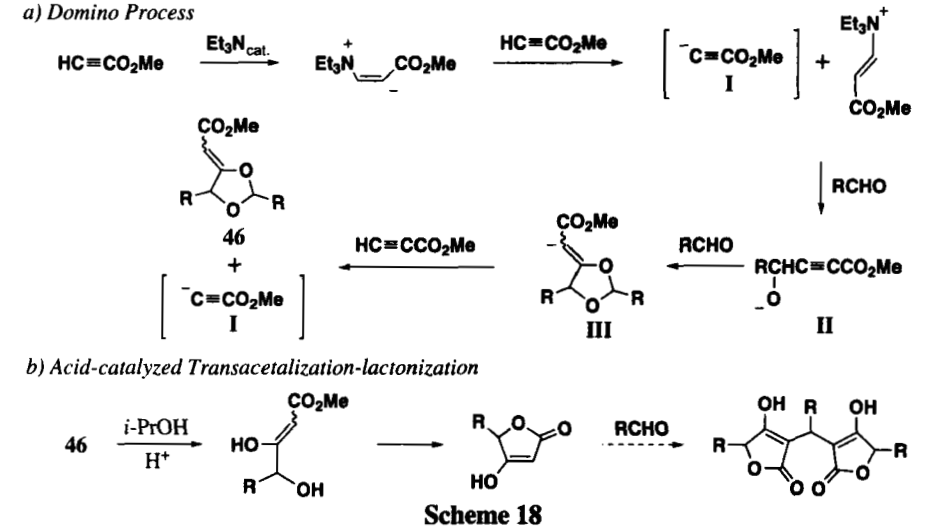
Scheme 16

The second one-pot protocol[48] furnishes 5-substituted tetronic acids from simple commercially available starting materials through two consecutive processes: a catalytic domino reaction to build a 1,3-dioxolane scaffold **46**[49] and a two-step acid-catalyzed trans-acetalization-lactonization reaction to furnish the tetronic acid derivative (*Scheme 17*). This chemical system



Scheme 17

works quite well for aliphatic aldehydes and it is an excellent reaction manifold for the synthesis of 5-alkyl substituted tetronic acids. *Scheme 18* outlines the proposed mechanism for the domino process.



Scheme 18

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Triethylamine 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*). 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 acid-catalyzed transacetalization liberates the required γ-hydroxy β-ketoester intermediates, which lactonize to furnish the 5-substituted tetronic acid derivatives (*Scheme 18*). Since tetronic acid derivatives are quite reactive toward aldehydes to give dilactone compounds (see section **II.2**)[50] and the transacetalization reaction liberates one equivalent of aldehyde, the hydrolysis has to be performed under pH controlled conditions.

II. REACTIVITY OF TETRONIC ACIDS

Tetronic acids have been modified according to the *Scheme* outlined in *Figure* 2.

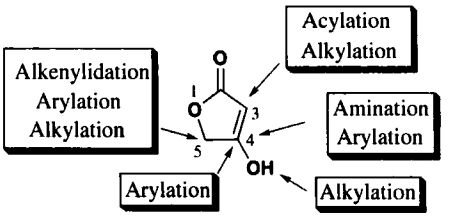
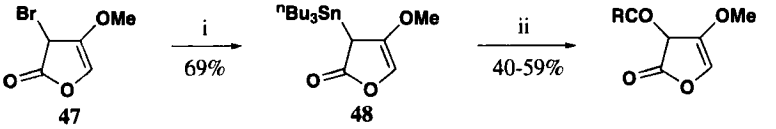


Figure 2

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 works 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 useful reaction because it affords mixtures of mono and diacylated products.[55] The problems associated with substituents on 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



47 **48**

i) $Na^+[Nap]^-$, nBu_3SnCl, THF,-78°C to RT; ii) RCOCl, trans-$Bn(Cl)Pd(PPh_3)_2$(cat.), $C_2H_4Cl_2$, 60°C

Scheme 19

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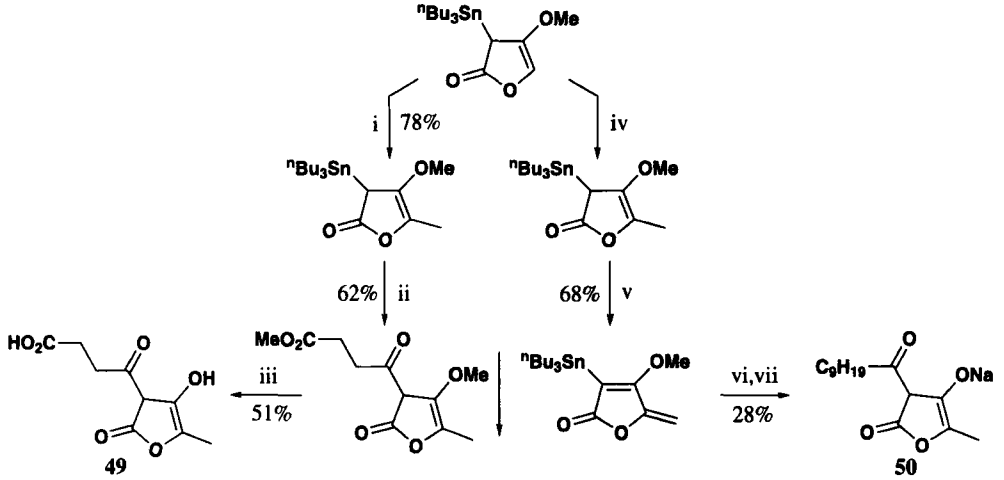
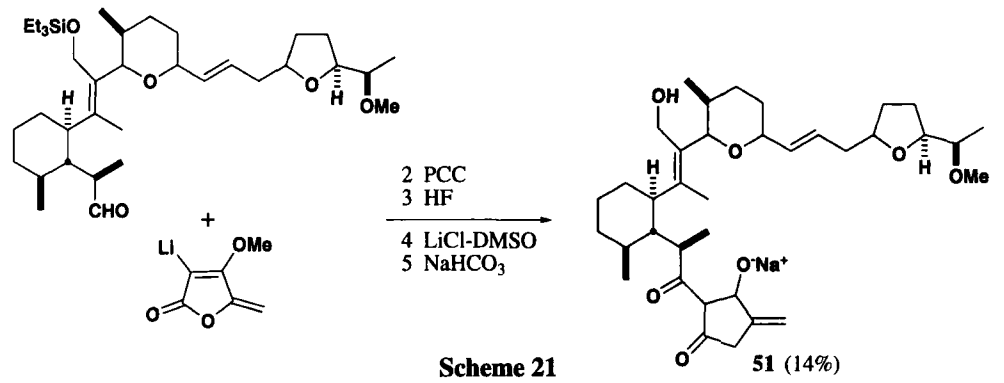
bond permits functionalization of the tetronate ring system to allow preparation of the 5-substituted-3-stannyl tetronates. Palladium-promoted acylation of these derivatives furnishes the corresponding 3-acyl-5-susbstituted tetronates. This protocol has been exploited for the effective total synthesis 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) $MeO_2CCH_2CH_2COCl$, trans-Bn(Cl)Pd(PPh_3)$_2$(cat.),$C_2H_4Cl_2$, 60°C; iii) HCl 3N; iv) LDA, THF, -78°C, $Me_2NCH_2^+I^-$; v) 1) MeI, MeOH, 2) NaOH 1M; vi) $H_{19}C_9COCl$, trans-Bn(Cl)Pd(PPh_3)$_2$(cat.), $C_2H_4Cl_2$, 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 antibioic tetronomycin (**51**)[58,59] (*Scheme 21*). Boron enolates have proved to be very good options to achieve C-3



Scheme 21

51 (14%)

acylation. Thus, these enolates have been used to build the tricycle core of the novel poliketide antibiotic tetrodecamycin (**52**)[60,61](*Scheme 22*).

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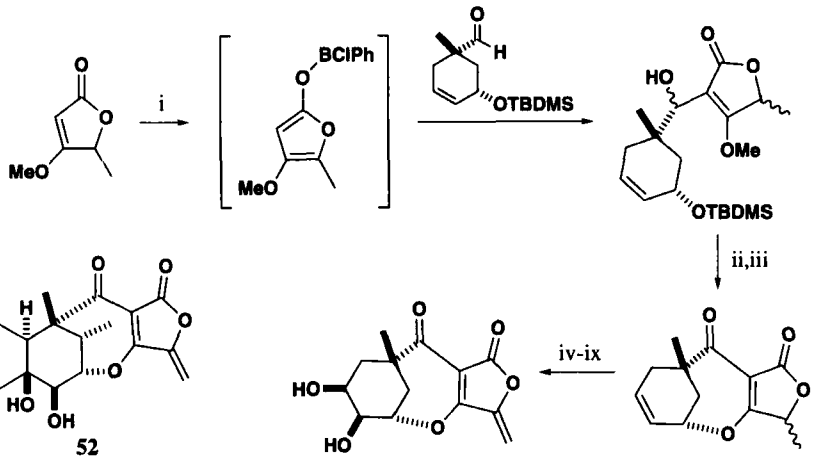
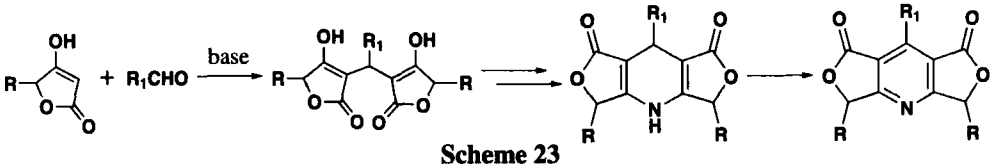


i) 1) $PhBCl_2$, i-Pr_2NEt, CH_2Cl_2, -78°C, 2) -78°C to RT, 86%; ii) IBX, DMSO, RT, 91%; iii) cat. Conc. H_2SO_4, CH_2Cl_2, RT, 89%; iv) 1) LiHMDS, -78°C, 2) N-phenylmercaptophthalimide, -78°C, 87%; v) 1) OsO_4, pyridine, CCl_4, RT, 2) aq. $NaHSO_3$, 87%; vi) TBDMSOTf, lutidine, CH_2Cl_2, -78°C, 92%; vii) MCPBA, CH_2Cl_2, -20°C; viii) $BaCO_3$, benzene, 27% for the 2 steps; ix) HF, MeCN, 0°C, 100%

Scheme 22

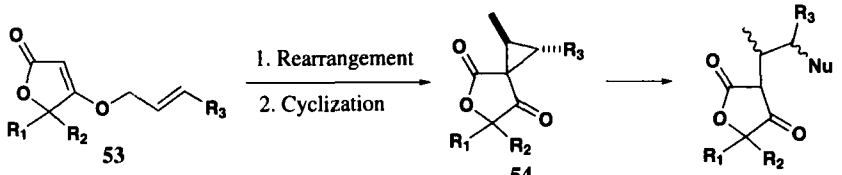
2. 3-Alkylation

Tetronic acids are quite reactive toward aldehydes furnishing *bis*-furanones[50,62-64] which, in turn, are easily transformed into fused-heterocycles[65-67] (*Scheme 23*).



Scheme 23

Allyl tetronates **53** 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*).



R_1	R_2	R_3
-$(CH_2)_5$-		Ph
H	Ph	Ph

42-80 %

Nu	Config.
OR_4	*syn*
NR_4R_5	*syn*
SR_4	*syn*
R_4	*syn/anty*

Scheme 24

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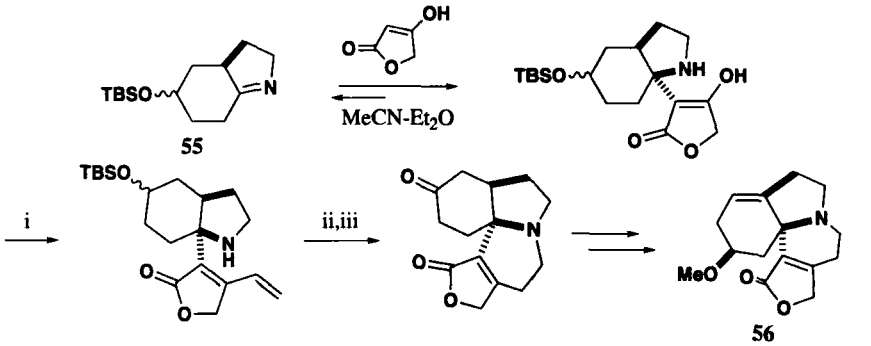
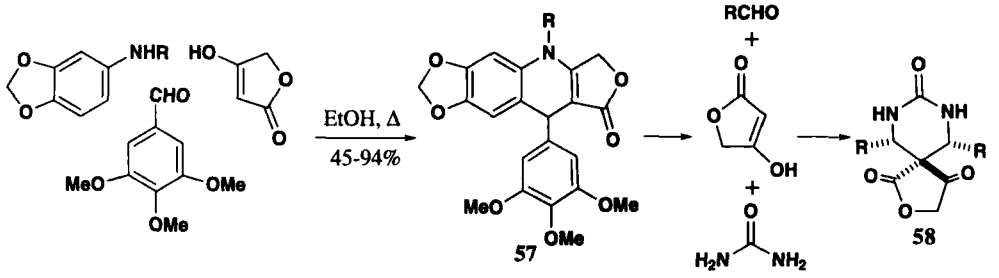
Coupling of tetronic acids and imines furnishes the versatile C-3 amino-alkyl tetronic acids which can be further transformed into more sophisticated compounds. This is illustrated in the first synthesis of the alkaloid cocculidine (**56**), which utilizes a coupling reaction of the bicyclic imine **55** and tetronic acid to install 3 of the 4 rings present in the molecule[69] (*Scheme 25*).



i) 1) Boc_2O, cat. DMAP, CH_2Cl_2, RT, 2) Tf_2O, pyr., CH_2Cl_2, -78°C to RT, 8h, 3) n-$Bu_3SnCH{=}CH_2$, $(Ph_3P)_2PdCl_2$, DMF, 35°C, 4h; ii) TFA (neat) then H_2O, 5 steps, 52%; iii)TPAP, NMO, 4 a MS, CH_2Cl_2-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



Scheme 26

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 as potential scaffolds for further reactions *via* the remaining functional groups in a domino strategy (*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.

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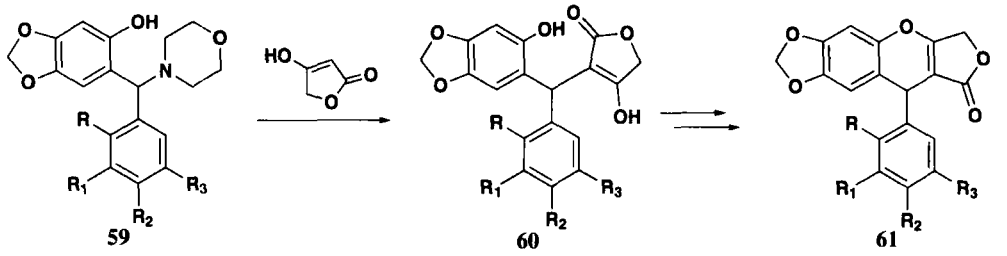
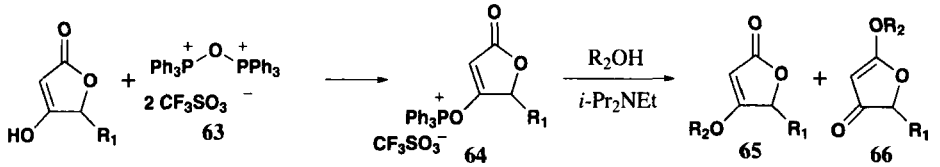


Scheme 27

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. 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 yield 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 do not react. This method has been adapted to the chemo- and regioselective alkylation of L-ascorbic acid and derivatives.[77] The other efficient and versatile method[76] is based on the formation of a very reactive 4-O-phosphonium ether methanesulfonate salt derivative **64** by reaction of tetronic acid with the triphenylphosphonium anhydride trifluoromethanesulfonate (**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 regioslectivity (*Scheme 28*).



Scheme 28

4. 4-Amination

4-Amino-2(5H)-furanones are biologically active molecules[78] which are either obtained by enamine formation from the suitable tetronic acid precursor[79] 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

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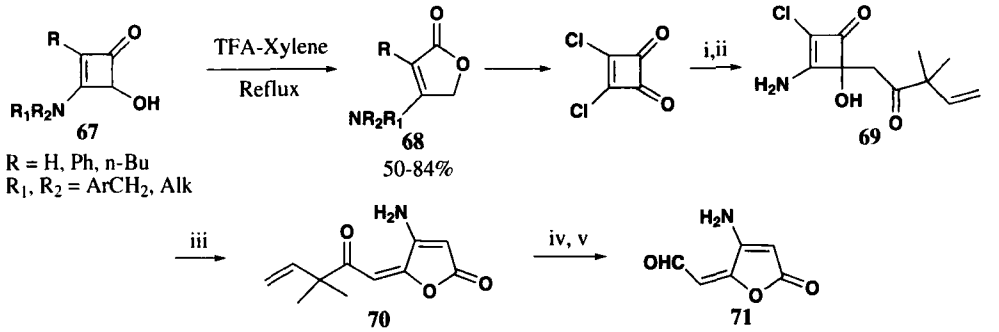
3-amino 4-hydroxy-cyclobutenone **67** (*Scheme 29*). Thus, while the trifluoroacetic acid-promoted rearrangement of 4-hydroxy-cyclobutenone **67** affords the 3-substituted-4-amino-2(5H)-furanone

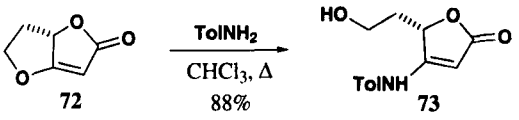


67 **68** **69** **70** **71**

i) CH_2=CH($OSiMe_3$)CMe_2CH=CH_2, $TiCl_4$,-78°C, 69%; ii) NH_3, EtOH, 45%; iii) pyridine, xylene, reflux, 85%; iv) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH-CH_2Cl_2, 80%; v) $Pb(OAc)_4$, CH_2Cl_2, 65%

Scheme 29

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*).

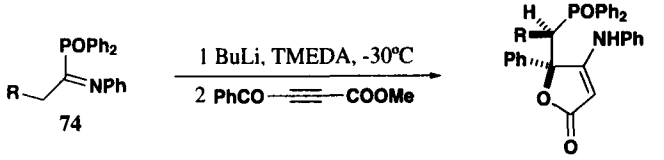


72 **73**

Scheme 30

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*).

The 1,3-cycloaddition of lithiated phosphazene derivatives **74** with benzoyl methyl propiolate has been reported[87] to give the phosphorous-containing 4-amino-2(5H)-furanones **75** and **76** in moderate yield and good diastereoselectivity (*Scheme 31*).



74

75 R = H (50%)
76 R = Me (45%)

Scheme 31

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

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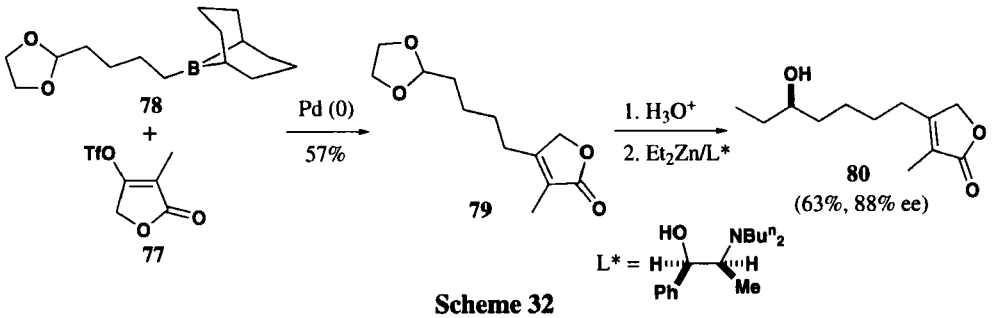
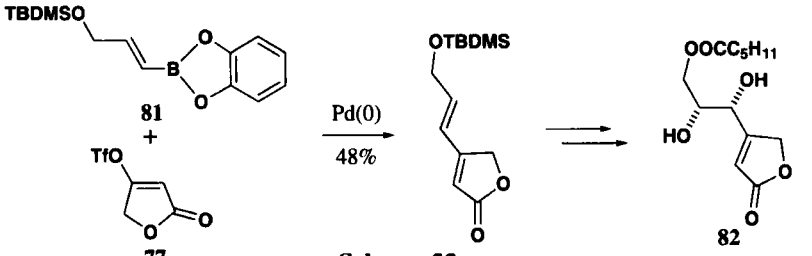
mainly by transition metal-catalyzed cross-coupling reactions. The Pd(0)-catalyzed cross-coupling (Suzuki) reaction of tetronic acid triflates **77** with 9-alkyl-9-borabicyclo[3.3.1]nonanes **78** affords the 4-alkyl-2(5H)-furanones **79** in moderate to good yield and tolerates a range of functionalities.[89] 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



Scheme 32

alkenylboronates **81** and tetronic acid 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 with $AsPh_3$ as a ligand (63-85%).[91] The coupling reaction conditions has also been applied to alkenylboronic acids affording



Scheme 33

the 4-substituted-2(5H)-furanones with retention of the configuration of the alkenyl group and better yields than the 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, especially 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 in 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 skeleton[97] (*Scheme 34*).

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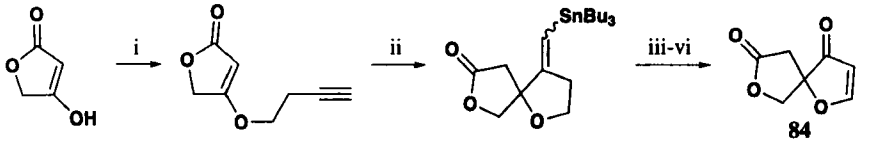


i) But-3-ynol, TsOH, PhH, 18 h, 76%; ii) Bu_3SnH, AIBN, PhH, reflux, 5 h, 71%; iii) HCl (1M), CH_2Cl_2, RT, 1 h, 100%; iv) O_3, -78°C, then DMS, -78°C to RT, 2 h, 79%; v) PhSeCl, THF, H_2O(cat), 5 days, 38%; vi) O_3, CH_2Cl_2, then purge N_2 and warm to RT, 12 h, 44%

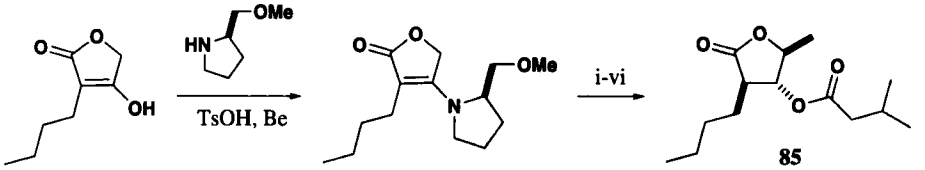
Scheme 34

6. 3,4-Diarylation

Unsymmetrical 3,4-disubstituted-2(5H)-furanones occur rarely in nature[98] but are reported to be useful as drugs and biocides. The 3,4-diaryl derivatives have been obtained from the 3,4-distannyl[99] or 3,4-dibromo[100] derivatives by a regioselective palladium-catalyzed cross-coupling reaction. Remarkably, the diminished reactivity of the C3-Sn bond relative to the C4-Sn makes this reaction quite regioselective and allows 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.

7. 5-Alkylation, Arylation and Alkenylidation

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-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) SmI_2 (4 equiv.), THF-DMAE, RT, 69%; vi) $(CH_3)_2CHCH_2COCl$, pyridine, 80%

Scheme 35

Methoxymethyl tetronates are easily alkylated at C-5 position by treatment with lithium dimethylisopropylamide and an electrophile. The aldol reaction of methoxymethyl 3-substituted tetronates **86** with aldehydes gives the corresponding chelation-controlled *threo*-adduct **87** as the main product, and which has been used in the stereocontrolled synthesis of the B-ring of the sesbanimide alkaloide (**88**)[103] (*Scheme 36*). On the other hand, methoxymethyl 3,5-dimethyl-tetronate **89** reacts with α,β-unsaturated ketone **90** to give (±)-vertinolide (**28**) in good yields[104] (*Scheme 37*).

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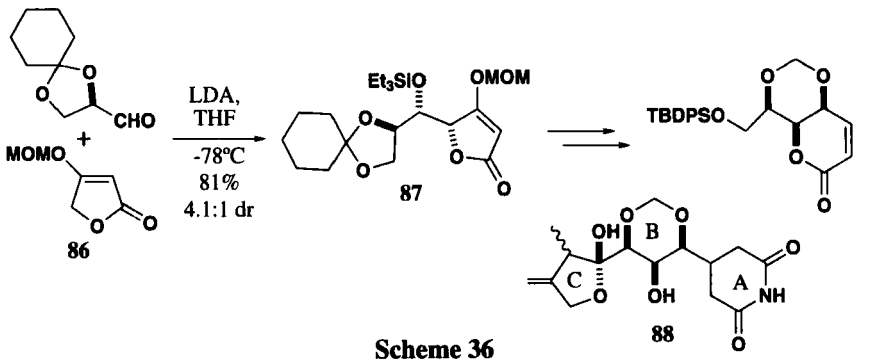
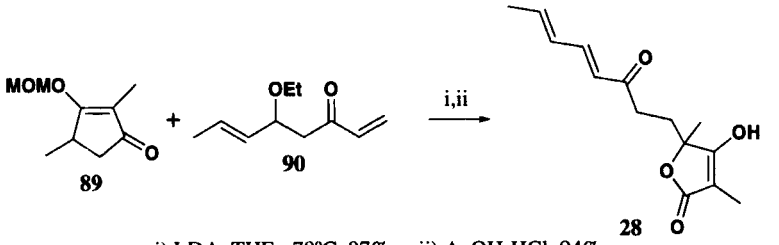


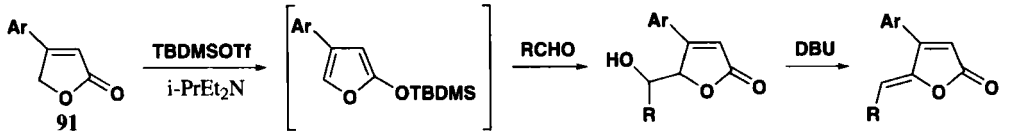
Scheme 36



i) LDA, THF, -78°C, 97%; ii) AcOH-HCl, 94%

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

Acknowledgements.- We thank the Spanish Ministerio de Ciencia y Tecnología (PPQ2002-04361-C04-03) by financial support. D. T. thanks the Instituto Canario de Investigación del Cáncer for a postdoctoral grant.

GLOSSARY OF ACRONYMS

AIBN = Azobis(isobutyronitrile)
BuLi = tert-Butyllithium
DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAE = N,N-Dimethylaminoethanol
DMAP = N,N-Dimethylaminopyridine
DMF = N,N-Dimethylformamide
DMS = Dimethylsulfide

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DMSO = Dimethylsulfoxide
IBX = 2-Iodobenzoic acid
KHMDS = Potassium *bis*(trimethylsilyl)amide
LDA = Lithium diisopropylamide
LHMDS = Lithium *bis*(trimethylsilyl)amide
MCPB = 3-Chloroperbenzoic acid
NCS = N-Chlorosuccinimide
NMO = 4-Methylmorpholine N-oxide
PCC = Pyridinium chlorochromate
Piv = Pivaloyl
PMB = 4-Methoxybenzyl
TBAF = Tetrabutylammonium fluoride
TBDMS = *tert*-Butyldimethylsilane
TBDMSOTf = *tert*-Butyldimethylsilyl trifluoromethanesulfonate
THF = Tetrahydrofuran
TFA = trifluoracetic acid
TMEDA = N,N,N',N'-Tetramethylethylenediamine
TMS = Trimethylsilyl
TPAP = Tetrapropylammonium perruthenate
TsOH = Methanesulfonic acid
Tr = Trityl

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REFERENCES

1. L. J. Haynes, J. R. Plimmer, *Q. Rev. Chem. Soc.*, **14**, 292 (1960); R. Brodersen, A. Kjaer, *Acta Pharmacol. Toxicol.*, **2**, 109 (1946).

2. G. Pattenden, *Fortsch. Chem. Org. Naturst.*, **35**, 133 (1978).

3. K. Rehse, J. Wagenknecht, *Arch. Pharm*, **312**, 164 (1979).

4. K. Arai, *Chem. Pharm. Bull.*, **37**, 3229 (1989).

5. B. E. Roggo, F. Petersen, R. Delmendo, H.-B. Jenny, H. H. Meter, J. Roesel, *J. Antibiotics*, **47**, 143 (1994).

6. M. Lang, J. Roesel, *Arch. Pharm.*, **326**, 921 (1993).

7. M. Sodeoka, R. Sampe, S. Kojima, Y. Baba, T. Usui, K. Ueda, H. Osada, *J. Med. Chem.*, **44**, 3216 (2001); M. Sodeoka, R. Sampe, S. Kojima, Y. Baba, N. Morisaki, Y. Hashimoto, *Chem. Pharm. Bull.*,**49**, 206 (2001); M. Sodeoka, R. Sampe,T. Kagamizono, H. Osada, *Tetrahedron Lett.*, **37**, 8775 (1996).

8. P. M. Boll, E. Sørensen, E. Balieu, *Acta Chem. Scand.*, **22**, 3251 (1968).

9. J. L. Bloomer, F. E. Kappler, *J. Chem. Soc., Perkin I*, 1485 (**1976**).

10. R. K. Boeckman Jr, R. B. Perni, J. E. Macdonald, A. J. Thomas, *Org. Synth.*, **66**, 194 (1988).

11. D. Ager, S. J. Mole, *Tetrahedron Lett.*, **29**, 4807 (1988).

12. K. Nomura, T. Lida, K. Hori, E. Yoshii, *J. Org. Chem.*, **59**, 488 (1994).

13. S. V. Ley, D. S. Brown, J. A. Clase, A. J. Fairbanks, I. C. Lennon, H. M. I. Osborn, E. S. E. Stokes, D. J. Wadsworth, *J. Chem. Soc.,Perkin I*, **15**, 2259 (1998); C. M. J. Fox, S. V. Ley, *Org. Synth.*, **66**, 108 (1988); P. M. Booth, C. M. J. Fox, S. V. Ley, *J. Chem. Soc., Perkin I*, 121 (**1987**).

14. D. T. Witiak, A. K. Tehim, *J. Org. Chem.*, **55**, 1112 (1990).

15. P. Ge, K. L. Kirk, *J. Org. Chem. 1*, **61**, 8671 (1996).

16. S. Brandänge, L. Flodman, A. Norberg, *J. Org. Chem.*, **49**, 927 (1984).

17. W. R. Ewing, K. L. Bhat, M. Joullie, *Tetrahedron*, **42**, 5863 (1986).

18. For the use of tetrabutylammonium fluoride in base-promoted Dieckman cyclization, see: S. V. Ley, S. C. Smith and P. R. Woodward, *Tetrahedron*, **48**, 1145 (1992).

19. K. Hori, H. Kazuno, K. Nomura, E. Yoshii, *Tetrahedron Lett.*, **24**, 2183 (1993).

20. T. Murayama, Y. Matsumori, N. Iwata, M. Ito, T. Taniguchi, K. Chiara, T. Matsui, *Jap. J. Cancer Res.*, **87**, 743 (1996).

21. P. C. B. Page, H. Vahedi, K. J. Batchelor, S. J. Hindley, M. Edgar, P. Beswick, *Synlett*, 1022, (**2003**).

22. K. Takabe, N. Mase, M. Nomoto, M. Daicho, T. Tauchi, H. Yoda, *J. Chem. Soc., Perkin I*, 500 (**2002**).

23. T. Momose, N. Toyooka, Y. Takeuchi, *Heterocycles*, **24**, 1429 (1986).

24. A. Svendsen, P. M. Boll, *Tetrahedron*, **29**, 4251 (1973).

25. γ-hydroxy: (a) F. Effenberger, J. Roos, C. Kobler, H. Buhler, *Can. J. Chem.*, **80**, 671 (2002); (b) H. Búhler, A. Bayer, F. Effenberger, *Chem. Eur. J.*, **6**, 2564 (2000); (c) F. Effenberger, J. Syed, *Tetrahedron: Asymmetry*, **9**, 817 (1998);(d) M. J. J. Duffield, A. C. Regan, *Tetrahedron: Asymmetry*, **7**, 663 (1996); (e) I. W. Still, M. J. Drewery, *J. Org. Chem.*, **54**, 290 (1989); (f) T. Kitazume, *J. Fluorine Chem.* **35**, 287 (1987); (g) J. E. Wrobel, B. Ganem, *J. Org. Chem.*, **48**, 3761 (1983); (h) J. R. Anderson, R. L. Edwards, A. J. S. Whalley, *J. Chem. Soc., Perkin I*, 215 (**1982**);(i) N. Clemo, G. Pattenden, *Tetrahedron Lett.*, **23**, 585 (1982); (j)R. E. Damon, T. Luo, R. H. Schlessinger, *Tetrahedron Lett.*, **32**, 2749 (1976).

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26. γ-acetoxy: (a) G.Athanasellis, O. Igglessi-Markopoulou, J. Markopoulos, *Synlett*, 1736 (**2002**); (b) C. A. Mitsos, A. L. Zografos, O. Igglessi-Markopoulou, *J. Heterocycl. Chem.*, **39**, 1201 (2002); (c) C. A. Mitsos, A. L. Zografos, O. Igglessi-Markopoulou, *J. Org. Chem.*, **65**, 5852 (2000);(d) P. Pollet, S. Gelin, *Tetrahedron*, **34**, 1453 (1978).

27. γ-Silyloxy: (a) A. T. Hopper, D. T. Witiak, *J. Org. Chem.*, **60**, 3334 (1995); (b) L. R. Krepski, L. E. Lynch, S. M. Heilmann, J. K. Rasmussen, *Tetrahedron Lett.*, **26**, 981 (1985).

28. γ-Epoxy: M. Yamashita, H. Murai, A. Mitra, T. Yoshioka, I. Kawasaki, M. Gotoh, T. Higashi, S. Ohta, *Heterocycles*, **11**, 2327 (1998).

29. γ-Allyloxy: I. Pévet, C. Meyer, J. Cossy, *Tetrahedron Lett.*, **42**, 5215 (2001).

30. The Blaise reaction is the reaction of Reformatsky reagents with nitriles: E. E. C. Blaise, *Hebd. Séances Acad. Sci.*, **132**, 478 (1901); S. M. Hannick, Y. Kishi, *J. Org. Chem.*, **48**, 3833 (1983).

31. F. Effenberger, *Chimia*, **53**, 3 (1999); M. Schmidt, H. Griengel, *Top. Curr. Chem.*, **200**, 193 (1999).

32. H. Büler, A. Bayer, F. Effenberger, *Chem. Eur. J.*, **6**, 2564 (2000).

33. T. Hiyama, H. Oishi, Y. Suetsugu,, K. Nishide, H. Saimoto, *Bull. Chem. Soc. Jpn.*, **60**, 2139 (1987); T. Hiyama, H. Oishi, H. Saimoto, *Tetrahedron Lett.*, **26**, 2459 (1985).

34. A. C. Veronese, R. Callegari, A. Bretazo, *Heterocycles*, **32**, 2205 (1991).

35. Y. S. Lee, J. Y. Lee, D. W. Kim, H. Park, *Tetrahedron*, **55**, 4631 (1999).

36. I. Pévet, C. Meyer, J. Cossy, *Synlett*, 663 (**2003**).

37. A. Datta, R. R. Schmidt, *Synlett*, 429 (**1992**); A. Datta, R. R. Schmidt, *Tetrahedron Lett.*, **33**, 8035 (1992); H. Jatzke, U. Evertz, R. R. Schmidt, *Synlett*, 191 (**1990**).

38. A. Takaiwa, K. Yamashita, *Agri. Biol. Chem.*, **48**, 961 (1984).

39. M. Ladlow, G. Pattenden, *J. Chem. Soc., Perkin I*, 1107 (**1988**).

40. G. V. Reddy, V. Sreevani, D. S. Iyengar, *Tetrahedron Lett.*, **42**, 531 (2001).

41. K. Matso, Y. Sakaguchi, *Heterocycles*, **43**, 2553 (1996).

42. R. Ramage, G. J. Griffiths, F. E. Shutt, J. N. A. Sweeney, *J. Chem. Soc., Perkin I*, 1539 (**1984**).

43. D. Desmaele, *Tetrahedron*, **48**, 2925 (1992).

44. M. Sato, J. Sasaki, Y. Sugita, S. Yasuda, H. Sakoda, C. Kaneko, *Tetrahedron*, **47**, 5689 (1991).

Downloaded At: 19:32 26 January 2011

45. F. Lieb, J. Benet-Buchholtz, T. Facke, R. Fischer, A. Graff, I. M. Lefebvre, J. Stetter, *Tetrahedron*, **57**, 4133 (2001).

46. R. C. F. Jones, K. A. M. Duller, S. I. E. Vulto, *J. Chem. Soc., Perkin I*, 411 (**1998**);H. Kawakami,, S. Hirokawa, M. Asaoka, H. Takei, *Chem. Lett.*, 85 (**1987**).

47. R. Schobert, S. Mueller, H.-J. Bestmann, *Synlett*, 425 (**1995**).

48. D. Tejedor Aragón, G. V. López, F. García-Tellado, J.J. Marrero-Tellado, P. de Armas, D. Terrero, *J. Org. Chem.*, **68**, 3363 (2003).

49. D. Tejedor, F. García-Tellado, J.J. Marrero-Tellado, P. de Armas, *Eur. J. Chem.*, **9**, 3122 (2003); P. de Armas, F. García-Tellado, J.J. Marrero-Tellado, D. Tejedor, M. A. Maestro, J. González-Platas, *Org. Lett.*, **3**, 1905 (2001).

50. H. Zimmer, W. W. Hillstrom, J. C. Schmidt, P. D. Seemuth, R. Vögeli, *J. Org. Chem.* **43**, 1541 (1978) and references cited therein.

51. N. G. Clemo, G. Pattenden, *Tetrahedron Lett.*, **23**, 581 (1982).

52. O. Miyata, R. R. Schmidt, *Tetrahedron Lett.*, **23**, 1795 (1982).

53. K. Takeda, H. Kubo, T. Koizumi, E. Yoshii, *Tetrahedron Lett.*, **23**, 3173 (1982).

54. R. H. Schlessinger, E. J. Iwanowicz, J. P. Springer, *Tetrahedron Lett.*, **29**, 1489 (1988).

55. S. V. Ley, D. J. Wadsworth, *Tetrahedron Lett.*, **30**, 1001 (1989).

56. S. V. Ley, M. L. Trudell, D. J. Wadsworth, *Tetrahedron*, **47**, 8285 (1991).

57. K. Yamashita, A. Takaiwa, H. Nakada, *Agric. Biol. Chem.* **44**, 2931 (1980); W. D. Kumler, *J. Am. Chem. Soc.*, **60**, 859 (1938).

58. K. Hori, N. Hikage, A. Inagaki, S. Mori, K. Nombra, E. Yoshii, *J. Org. Chem.*, **57**, 2888 (1992).

59. For isolation and activity see: C. Keller-Juslén, H. D. King, M. Kuhn, H. R. Loosli, W. Pache, T. J. Petcher, H. P. Weber, A. J. Wartburg, *J. Antibiot.*, **35**, 142 (1982).

60. F. F. Paintner, L. Allmendinger, G. Bauschke, K. Polborn, *Synlett*, 1308 (**2002**).

61. For isolation and activity see: T. Tsuchida, H. Limuna, C. Nishida, N. Kinoshita, T. Sawa, M. Hamada, T. Takeuchi, *J. Antibiot.*, **48**, 1104 (1995).

62. J. M. Begley, G. N. Clemo, G. Patteden, *J. Chem. Soc., Perkin I*, 2393 (**1985**).

63. G. Maier, R. Wilmes, *Chem. Ber.*, **120**, 119 (1987).

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64. For a clay-catalyzed, microwave irradiated reaction of aldehydes and tetronic acid see: D. Villemin, B. Labiad, *Synthetic Comm.*, **20**, 3207 (1990).

65. K, Goerlitzer, J. Trittmacher, U. Bartke, *Pharmazie*, **57**, 606 (2002).

66. Y. Hitotsuyanagi, M. Kobayashi, M. Fukuyo, K. Takeya, H. Itokawa, *Tetrahedron Lett.*, **38**, 8295 (1997); D. G. Schmidt, P. D. Seemuth, H. Zimmer, *J. Org. Chem.*, **48**, 1914 (1983); I. Butula, D. Grguric, *Synthesis*, 808 (**1979**).

67. N. Martín, J. L. Segura, C. Seoane, J. L. Soto, M. Morales, M. Suárez, *Liebigs Ann. Chem.*, 827 (**1991**).

68. R. Schobert, G. J. Gordon, A. Bieser, W. Milius, *Eur. J. Org. Chem.*, 3637 (**2003**).

69. T. Kawasaki, N. Onoda, H. Watanabe, T. Kitahara, *Tetrahedron Lett.*, **42**, 8003 (2001).

70. C. Tratrat, S. Giorgi-Renault, H. Husson, *Org. Lett.*, **4**, 3187 (2002); for a stepwise method, see: Y. Hittsuyanagi, M. Fukuyo, K. Tsuda, M. Kobayashi, A. Ozeki, H. Itokawa, K. Takeya, *Bioorg. Med. Chem. Lett.*, **10**, 315 (2000).

71. G. Byk, H. E. Gottlieb, J. Herscovici, F. Mirkin, *J. Comb. Chem.*, **2**, 732 (2000).

72. L. Jurd, *J. Heterocycl. Chem.* **33**, 1227(1996).

73. F. S. Pashkovsky, I. P. Lokot, F. A. Lakhvich, *Synlett*, 1391 (**2001**).

74. For leading references, see: R. Schobert, S. Siegfried, *Synlett*, 686 (**2000**); T. Sato, Y. Koji, J. Otera, *Synlett*, 843 (**1995**); H. M. Hoffmann, B. Schmidt, S. Wolff, *Tetrahedron*, **45**, 6113 (1989).

75. J. S. Bajwa, R. C. Anderson, *Tetrahedron Lett.*, **31**, 6973 (1990).

76. F. F. Paintner, L. Allmendinger, G. Bauschke, *Synlett*, 83 (**2003**).

77. H. Tahir, O. Hindsgaul, *J. Org. Chem.*, **65**, 911 (2000).

78. T. Hiyama, H. Oishi, Y. Suetsugu, K. Nishide,. H. Saimoto, *Bull. Chem. Soc. Jpn.*, **60**, 2139 (19887); B. I. Dittmar, W. A. Price, (E. I. du Pont de Nemours) Ger. Off. 2516555 (**1975**) [*Chem. Abstr.*, **84**, 74087q (1976)] ; P. Gerike, (E. I. du Pont de Nemours) U.S. Reissue 27894 (**1974**) [*Chem. Abstr.*, **80**, 82435j (1974)].

79. T. Momose, N. Toyooka, T. Nishi, Y. Takeuchi *Hetrocycles*, **27**, 1907 (1988); for a synthetically relevant example, see: R. H. Schlessinger, A. M. M. Mjalli, A. D. Adams, *J. Org. Chem.*, **57**, 2992 (1992).

80. J. V. Greenhill, T.Tomassini, *Tetrahedron Lett.*, **31**, 2683 (1974).

81. J. Wang, X. Jiang, M. Chen, Z. Ge, Y. Hu, H. Hu, *J. Chem. Soc., Perkin I*, 66 (**2001**).

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82. Y. Yamamoto, M. Ohno, S. Eguchi, *Tetrahedron*, **50**, 7783 (1994).

83. H. Linuma, H. Nakamura, Y. Itaka, A. Obayashi, *J. Antibiot.*, **36**, 448 (1983).

84. E. M. Beccalli, E. Erba, P. Trimarco, *Synth. Commun.*, **30**, 629 (2000).

85. N. Shangguan, S. Katukojvala,, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.*, **125**, 7754 (2003).

86. A. Bertucco, J. Brennan, M. Fi, S. Kluge, P. J. Murphy, F. Pasutto, R. Signorini, H. L. Williams, *Tetrahedron*, **50**, 8237 (1994).

87. J. M. Álvarez-Gutierrez, F. López-García-Granda, A. Rodríguez-González, *J. Chem. Soc., Perkin I*, 4469 (**2000**).

88. For leading references, see: (a) F. Bellina, C. Anselmi, S. Viel, L. Mannina, R. Rossi, *Tetrahedron*, **57**, 9997 (2001) and references therein; (b) M. J. Ortega, E. Zubia, J. M. Ocafia, S. Naranjo, J. Salva, *Tetrahedron*, **56**, 3963 (2000); (c) S. L. Midland, J. J. Sims, *J. Org. Chem.*, **60**, 1118 (1995); (d) S. W. Miao, R. Andersen, *J. Org. Chem.*, **56**, 6275 (1991).

89. R. Grigg, P. Kennewell, V. Savic, *Tetrahedron*, **50**, 5489 (1994).

90. T. Honda, H. Mizutani, K. Kanai, *J. Org. Chem.*, **61**, 9374 (1996).

91. M. Yao, M. Deng, *J. Org. Chem.*, **65**, 5034 (2000).

92. For 4-bromo, see: (a) 38a; (b) E. Lattmann, R. H. Hoffmann, *Synthesis*, 155 (**2001**); (c) J. Boukouvalas, N. Lachance, M. Oullet, M. Trudeau, *Tetrahedron Lett.*, **39**, 7665 (1998).

93. For 4-stannyl, see : G. J. Hollingworth, G. Perkins, J. Sweeney, *J. Chem. Soc., Perkin I*, 1913 (**1996**).

94. J. Wu, Q. Zhu, L. Wang, R. Fathi, Z. Yang, *J. Org. Chem.*, **68**, 670 (2003).

95. P. G. Steel, *Chem. Commun.*, 2257 (**1999**).

96. For a very related radical spiro-annulation,see W. Zhang, *Tetrahedron Lett.*, **41**, 2523 (2000).

97. R. J. M. Gross, J. Fuscher, D.O'Hagan, *Chem. Commun.* 2255 (**1999**).

98. (a) A. Evidente, L. Sparapano, *J. Nat. Prod.*, **57**, 1720 (1994); (b) A. Evidente, G. Randazzo, A. Ballio, *J. Nat. Prod.*, **49**, 593 (1986); (c) L. Sparapano, A. Evidente, A. Ballio, A. Graniti, G. Randazzo, *Experientia*, **42**, 627 (1986); (d) P. Tantivatana, N. Ruangrungsi, V. Vaisiriroj, D. C. Lankin, N. S. Bhacca, R. P. Borris, G. A. Cordell, F. Johnson Le Roy, *J. Org. Chem.*, **48**, 268 (1983); R. Edwards, A. J. S. Whalley, *J. Chem. Soc., Perkin I*, 803 (**1979**).

99. R. Mabon, A. M. E. Richeceur, J. B. Sweeney, *J. Org. Chem.*, **64**, 328 (1999).

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100. (a) See reference 38a; (b) R. Rossi, F. Bellina, E. Raugei, *Synlett*, 1749 (**2000**).

101. R. Ramaje, G. J. Griffiths, F. E. Shutt, J. N. A. Sweeney, *J. Chem. Soc., Perkin I*, 1539 (**1984**).

102. K. Nishide, A. Aramata, T. Kamanaka, T. Inoue, *Tetrahedron*, **50**, 8337 (1994).

103. T. Honda, T. Yamada, T. Hayakawa, K. Kanai, *Tetrahedron: Asymmetry*, **5**, 247 (1994);T. Honda, T. Hayakawa, H. Kondoh, A. Okuyama, M. Tsubuki, *Chem. Lett.*,1861 (**1991**).

104. H. Takabe, N. Mase, M. Nomoto, M. Daicho, T. Tauchi, H. Yoda, *J. Chem. Soc., Perkin I*, 500 (**2002**).

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