Synthesis and Biological Properties of 2(5*H*)-Furanones Featuring Bromine Atoms on the Heterocyclic Ring and/or Brominated Substituents

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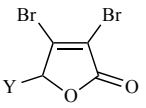
Abstract: This review with 263 references deals with the synthesis of unnatural and natural 2(5*H*)-furanone derivatives featuring bromine atoms on the heterocyclic ring and/or brominated substituents, which have been described in the literature since 1951 up to February 2016. The review has been organized on the basis of seven classes of brominated furanone derivatives that were synthesized. Where possible, experimental details of the syntheses have been reported. Furthermore, the biological properties of the target compounds, including their mutagenic, cytotoxic, enzymatic, anti-inflammatory and photosynthetic inhibitory activities have been summarized, paying particular attention on the compounds that have demonstrated antimicrobial properties via inhibition of quorum sensing and biofilm formation

Keywords: *Brominated 2(5H)-furanone derivatives, Regioselectivity, Marine natural products, Bioactivity, Antimicrobials, Quorum quenching*

1. INTRODUCTION

In the last four decades the chemistry of 2(5*H*)-furanones (also referred as 2-butenolides) has received great interest and has experienced a remarkable expansion as evidenced by numeous reviews [1–18]. This interest is largely justified by the fact that these heterocycles include biologically active natural compounds and substances possessing interesting biological properties such as mutagenic, cytotoxic, anti-inflammatory, fungicidal and antibacterial activities. Furthermore, intense research has been conducted on the synthesis of brominated 2(5*H*)-furanone derivatives as some compounds of this class have been found capable to block the bacterial quorum sensing (QS), *i.e.* the cell-to-cell communication of bacteria that include antibiotic resistant species [19,20], enhancing bacterial clearance [21] and preventing swarming motility [22] and the production of QS-regulated virulence factors, notably biofilm formation [22–26].

However, no updated review regarding a comprehensive description of the syntheses of natural and unnatural brominated 2(5*H*)-furanone derivatives and the biological properties associated to some of these heterocyclic compounds has been published so far. Only two reviews, which were published in 2004 and 2011 respectively, deal with the synthetic aspects of 3,4-dibromo-5-hydroxy-2(5*H*)-furanone (mucobromic acid) (**1**) [10,14] and 3,4-dibromo-2(5*H*)-furanone (**2**) (Figure 1)[14].



1 : Y = OH (mucobromic acid)
2 : Y = H

Figure 1. Structures of compounds **1** and **2**

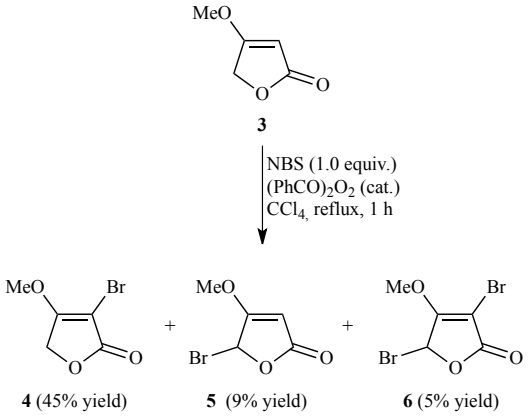
This review with 263 references aims to provide a thorough insight of the synthesis of 2(5*H*)-furanones with bromine atoms on the heterocyclic ring and/or brominated substituents that include natural products and unnatural compounds used in the literature as versatile synthetic intermediates. The review also focuses on the biological properties of the synthesized compounds with particular attention to those of the brominated compounds that have been found capable of interfering with the QS system of bacteria, especially of those that are cause of mortality and morbidity in human beings. The literature data on these topics have been organized on the basis of the structures of the target compounds and have been subdivided in the following sections interposed between the introduction and conclusion: i) synthesis and bioactivity of 2(5*H*)-furanone derivatives with one bromine atom on the heterocyclic ring; ii) synthesis and bioactivity of 2(5*H*)-furanone derivatives with two bromine atoms on the heterocyclic ring; iii) synthesis and bioactivity of 2(5*H*)-furanone derivatives possessing one bromine atom on the heterocyclic ring and monobrominated substituents; iv) synthesis and bioactivity of 2(5*H*)-furanone derivatives featuring one bromine atom on the heterocyclic ring and dibrominated substituents; v) synthesis and bioactivity of 2(5*H*)-furanone derivatives featuring two bromine atoms on the heterocyclic ring and brominated substituents; vi) synthesis and bioactivity of 2(5*H*)-furanones with monobrominated substituents; and vii) synthesis and bioactivity of 2(5*H*)-furanones with di-, tri- and tetra-brominated substituents.

The literature has been surveyed from 1951 until the end of February 2016.

2. SYNTHESES AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES WITH ONE BROMINE ATOM ON THE HETEROCYCLIC RING

2.1. SYNTHESIS AND BIOACTIVITY OF 3-BROMO-2(5*H*)-FURANONE DERIVATIVES

In 1979, Reffstrup and Boll investigated the bromination reaction of 4-methoxy-2(5*H*)-furanone (**3**), a commercially available compound, and found that treatment of **3** with 1.0 equiv of NBS in CCl_4 under reflux in the presence of catalytic amount of benzoyl peroxide gave a mixture of three brominated compounds which were easily separated and identified as 3-bromo-4-methoxy-2(5*H*)-furanone (**4**), 5-bromo-4-methoxy-2(5*H*)-furanone (**5**) and 3,5-dibromo-4-methoxy-2(5*H*)-furanone (**6**) (Scheme 1) [27]. Compound **4**, which was the main component of the mixture, was isolated in 45% yield [27].



Scheme 1. Bromination of compound **3**

It is interesting to note that compound **5**, which was isolated in 9% yield, was used as direct precursor to the aglycone **7** (Figure 2) [27] of the antibiotic glycoside narthecide, which was isolated from *Narthecium ossifragrum* [28].

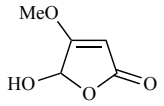


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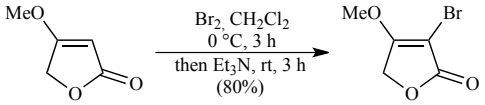
Figure 2. Structure of aglycone **7**

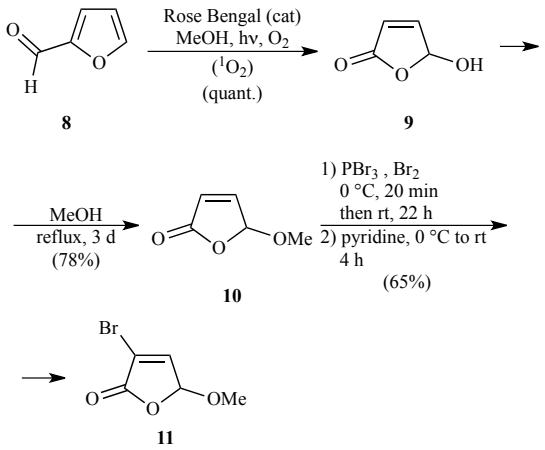
In 2006, Heo and coworkers synthesized compound **4** in 80% yield via addition of bromine to **3** and subsequent Et_3N-mediated elimination of hydrobromic acid (Scheme 2) [29]. The synthesis was carried out according to a protocol described in the literature for the one-pot preparation of α-bromoenones from the corresponding enones [30].



3 **4**

Scheme 2. High yielding synthesis of 3-bromo-4-methoxy-2(5*H*)-furanone (**4**)

In 2013, Vasamsetty, Khan and Mehta synthesized 3-bromo-5-methoxy-2(5*H*)-furanone (**11**) via a four-step protocol in which commercially available furfural (**8**) was the starting material (Scheme 3) [31].

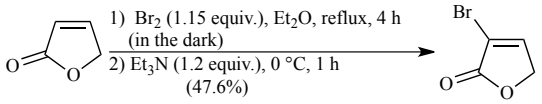


8 **9** **10** **11**

Scheme 3. Synthesis of 3-bromo-5-methoxy-2(5*H*)-furanone (**11**)

Thus, Rose Bengal sensitized photo-oxidation of **8** according to the literature [32] gave 5-hydroxy-2(5*H*)-furanone (**9**) in quantitative yield, which was acetalyzed with methanol providing compound **10** in high yield. The subsequent bromine addition to **10** through a modified literature procedure [33], followed by pyridine-mediated *in situ* dehydrobromination of the resulting compound led to **11** in 65% yield [31].

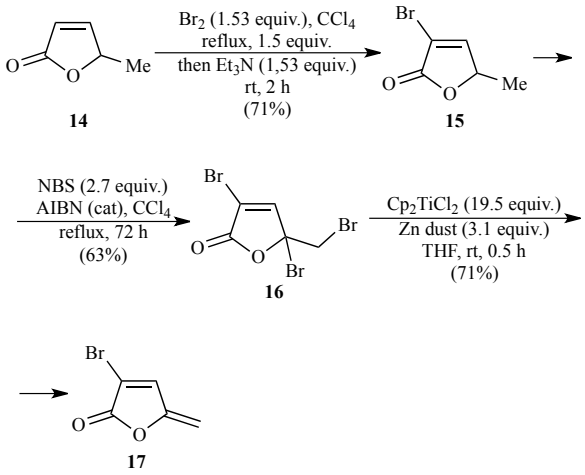
In 2015, Zhao, Yang, Li and coworkers described that 3-bromo-2(5*H*)-furanone (**13**) could be obtained from 2(5*H*)-furanone (**12**) in 47.6% yield by addition of bromine to **12** in Et_2O under reflux, followed by Et_3N-mediated dehydrobromination of the resulting adduct (Scheme 4)[34].



12 **13**

Scheme 4. Synthesis of 3-bromo-2(5*H*)-furanone (**13**)

Several years earlier, a similar procedure had been employed by de Echagüen and Ortuño for the synthesis of 3-bromo-5-methyl-2(5*H*)-furanone (**15**) from 5-methyl-2(5*H*)-furanone (**14**) (Scheme 5) [35]. However, in this case, CCl_4 had been used in place of Et_2O as the solvent for the reaction with bromine.



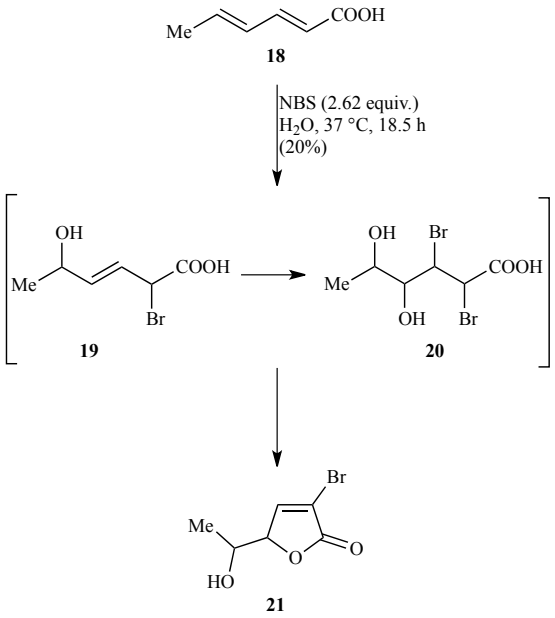
14 **15** **16** **17**

Scheme 5. Synthesis of compounds **15** and **17**

Compound **15** was then employed as the starting material for a two-step synthesis of 3-bromo-5-methylene-2(5*H*)-furanone (**17**) involving the AIBN–mediated reaction of **15** with 2.7 equiv of NBS in CCl_4 under reflux and the reductive debromination of the resulting compound **16** by using zinc dust in THF in the presence of a catalytic amount of Cp_2TiCl_2 (Scheme 5) [35].

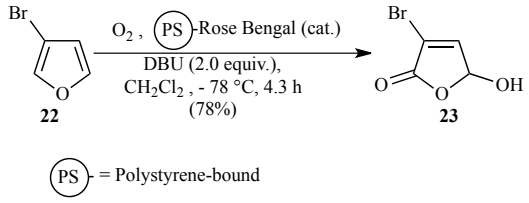
In 1990, Sánchez-Ferrando and coworkers synthesized a 1 : 1 mixture of *erythro*- and *threo*-3-bromo-5-(1-hydroxyethyl)-2(5*H*)-furanone (**21**) in 20% yield by treatment of sorbic acid (**18**) with 2.62 equiv of NBS in water at 37 °C for 18.5 h (Scheme 6) [36]. These authors

speculated that the formation of **21** could take place from intermediates **19** and **20** (Scheme 6) [36].



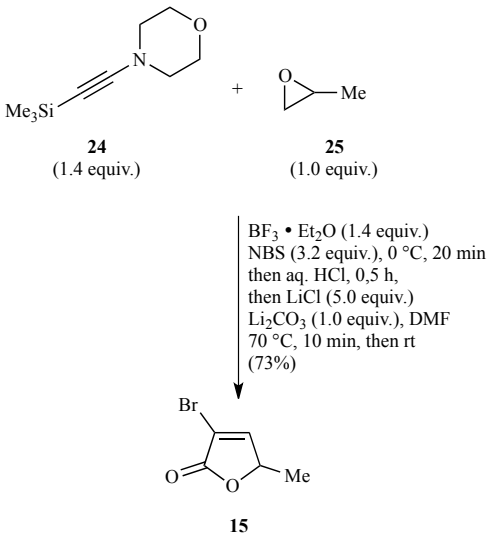
Scheme 6. Synthesis of 3-bromo-5-(1-hydroxyethyl)-2(5*H*)-furanone (**21**)

In 2006, 3-bromo-5-hydroxy-2(5*H*)-furanone (**23**) was obtained in 78% yield by Riccio and coworkers via photooxidation of 3-bromofuran (**22**) in CH_2Cl_2 at – 78 °C in the presence of 2 equiv of DBU (Scheme 7) [37].



Scheme 7. Synthesis of 3-bromo-5-hydroxy-2(5*H*)-furanone (**23**)

In 2008, 3-bromo-5-methyl-2(5*H*)-furanone (**15**) was also prepared in 73% yield from ynamine **24** and propylene oxide (**25**) [38] by using the method of Jacobsen [39] as shown in Scheme 8.



Scheme 8. Synthesis of compound **15** from ynamine **24** and propylene oxide (**25**)

Notably, compound **15** was also synthesized in 20-52% yield from α-angelica lactone (**26**) (Figure 3) by isomerization and subsequent addition of bromine-dehydrobromination [40,41].

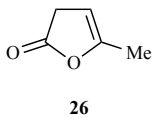
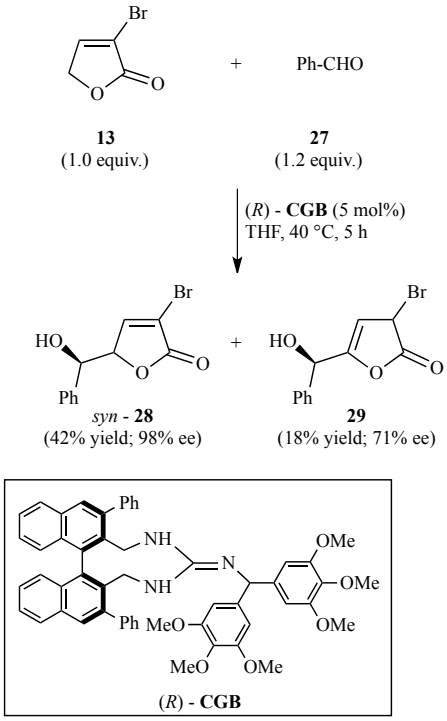


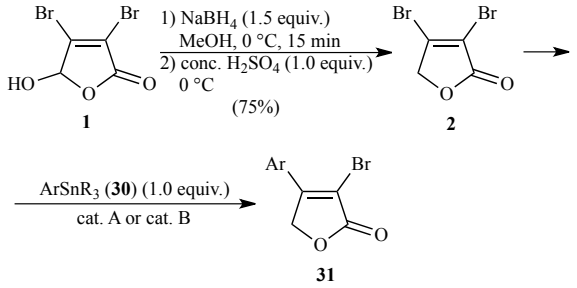
Figure 3. Structure of α-angelica lactone (**26**)

In 2010, Terada and coworkers investigated the axially chiral guanidine base (*R*)-**CGB**-catalyzed asymmetric vinylogous aldol reaction of 3-bromo-2(5*H*)-furanone (**13**) with benzaldehyde (**27**) and found that treatment of **13** with 1.2 equiv of **27** in THF at – 40 °C in the presence of 5 mol% (*R*)-**CGB** led to *syn*-3-bromo-5-(1-hydroxybenzyl)-2(5*H*)-furanone (**28**) in 42% yield with 98% ee together with β,γ-unsaturated lactone **29** in 18% yield and 71% ee (Scheme 9) [42].



Scheme 9. Synthesis of (*R*)-3-bromo.5-(1-hydroxybenzyl)-2(5*H*)-furanone *syn*-(**28**) and lactone **29**

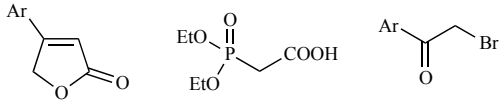
In 2000, our research group prepared 3,4-dibromo-2(5*H*)-furanone (**2**) in 75% yield by the reaction of mucobromic acid (**1**) with 1.5 equiv. of $NaBH_4$ in methanol at 0 °C for 15 min, followed by the addition of 1.0 equiv of concd. sulfuric acid, and found that **2** was able to undergo Pd-catalyzed reaction with equimolar amounts of aryl(trialkyl)stannanes **30a–e** in NMP at room temperature to provide regioselectively 4-aryl-3-bromo-2(5*H*)-furanones **31a–e** in yields ranging from 58 to 76% (Scheme 10) [43]. The catalyst system that was used for the cross-coupling reactions consisted of 5 mol% $PdCl_2(PhCN)_2$ and 10 mol% $AsPh_3$ (*catalyst A*) or was obtained by treatment of 2.5 mol% $Pd_2(dba)_3$ with 10 mol% $AsPh_3$ (*catalyst B*). We also found that compounds **31** could be used as direct precursors to 3-unsubstituted-4-aryl-2(5*H*)-furanones **32** (Figure 4), a class of compounds that, in 2001, were synthesized in excellent yields by halolactonization of 2,3-allenoic acids followed by a Suzuki-type coupling reaction with arylboronic acids [44] and, in 2009, were prepared by the reaction of diethylphosphonoacetic acid (**33**) with phenacyl bromides **34** (Figure 4), followed by an intramolecular Horner-Emmons type cyclization [45].



Entry	**30**		Catalyst [(a)]	Reaction time (h)	Product	
	Ar	R			**31**	Yield%
1	Ph	Bu	*A*	93	**31a**	76
2	Ph	Me	*A*	39	**31a**	70
3	Ph	Bu	*B*	94	**31a**	67
4	4-$MeSC_6H_4$	Me	*B*	22	**31b**	59
5	4-$MeOC_6H_4$	Bu	*B*	89	**31c**	68
6	3-FC_6H_4	Bu	*B*	89	**31d**	58
7	4-MeC_6H_4	Bu	*B*	112	**31e**	73

(a) *Cat. A* = 5 mol% $PdCl_2(PhCN)_2$ + 10 mol% $AsPh_3$; *Cat. B* : 2.5 mol% $Pd_2(dba)_3$ + 10 mol% $AsPh_3$

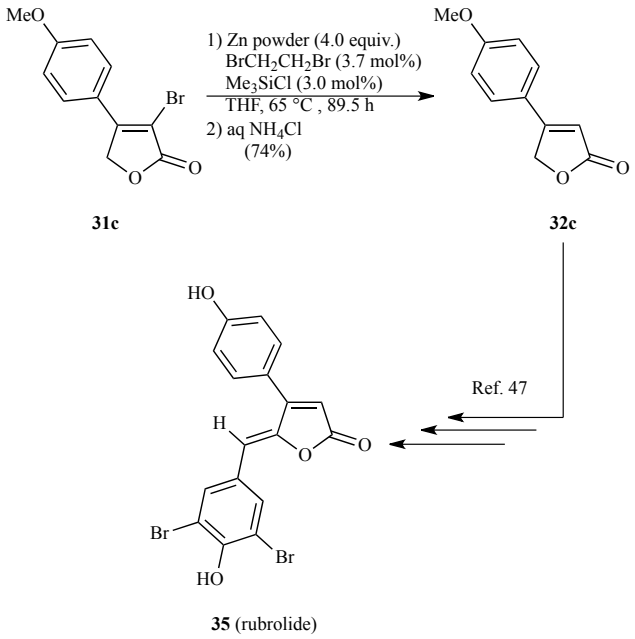
Scheme 10. Synthesis of 3,4-dibromo-2(5*H*)-furanone (**2**) and its regioselective Pd-catalyzed monoarylation reaction with aryl(trialkyl)stannanes



32 **33** **34**

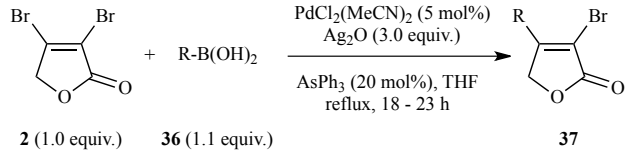
Figure 4. Structures of compounds **32–34**

In a typical example, we found that treatment of **31c** with 4.0 equiv of zinc powder, which was activated with 3.7 mol% 1,2-dibromoethane and then with 3.0 mol% Me_3SiCl [46] in THF at 65 °C for 89.5 h followed by hydrolysis gave 4-(4-methoxyphenyl)-2(5*H*)-furanone (**32c**) in 74% yield (Scheme 11) [43]. It is worth noting that compound **32c** had previously been employed as a precursor to rubrolide C (**35**) [47], a metabolite of the colonial tunicates *Ritterella rubra* [48] and *Synoicum blochmanni* [49], which was shown to exhibit antibacterial activity against *Staphylococcus aureous* (MIC = 11 *μg/di*sc) and *Bacillus subtilis* (MIC = 11 *μg/di*sc) and moderate but selective inhibition of protein phosphatases 1 and 2A [48].



Scheme 11. Synthesis of compound **32c**, a precursor to rubrolide C (**35**)

In 2001, we developed an unprecedented, general and efficient procedure for the regioselective synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones **37** [50]. We found that the reaction of 3,4-dibromo-2(5*H*)-furanone (**2**) with 1.1 equiv of alkylboronic acids **36** in THF under reflux for 18-23 h in the presence of 3.0 equiv of Ag_2O, 5 mol% $PdCl_2(MeCN)_2$ and 20 mol% $AsPh_3$ proceeded regioselectively providing the cross-coupling products **37** in yields ranging from 69 to 79% (Scheme 12) [50]. Notably, the cross coupling reaction appeared suitable to prepare multigram quantities of compounds **37** and in all cases examined it did not provide any trace of symmetrical 3,4-dialkyl-2(5*H*)-furanones [50].



37	R	Reaction time (h)	Yield%
37a	*n*-Oct	22	71
37b	*t*-BuO$(CH_2)_6$	23	70
37c	*t*-BuOCH(Me)$(CH_2)_5$	23	69
37d	*n*-Bu	18	79

Scheme 12. Regioselective synthesis of 4-alkyl-3-bromo-2(5*H*)-furanones **37**

One year later, as part of an effort to explore the use of 3,4-dibromo-2(5*H*)-furanone (**2**) for the selective synthesis of nostoclides I (**38a**) and II (**38b**) (Figure 5), which are a pair of cytotoxic compounds produced by a cyanobacterium *Nostoc* sp. [51], we planned to prepare 3-bromo-4-isopropyl-2(5*H*)-furanone (**37e**) (Figure 4) as a useful precursor to these natural products [52].

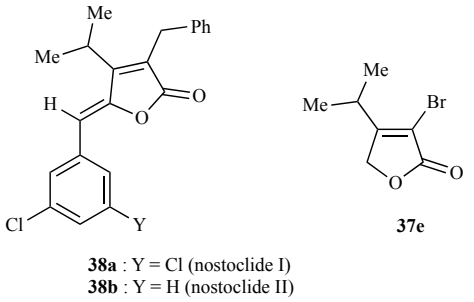
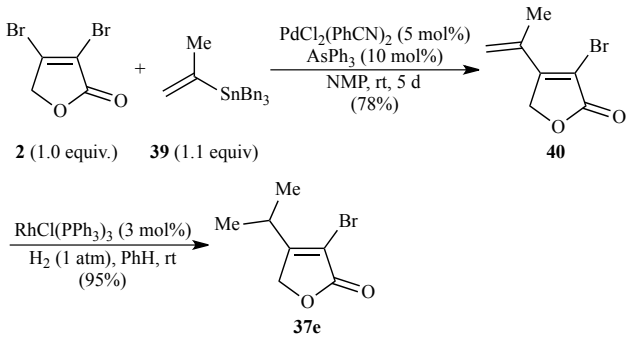


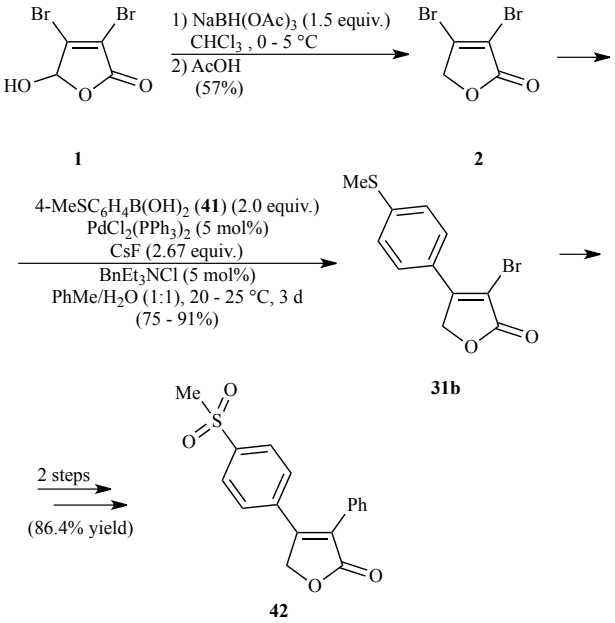
Figure 5. Structures of compounds **38a**, **38b** and **37e**

Unfortunately, the reaction of **2** with 1.1 equiv of isopropylboronic acid under the experimental conditions developed to prepare compounds **37a-d** [50] did not occur at all. Nevertheless, compound **37e** could be synthesized in 74% overall yield by the two-step route shown in Scheme 13 [52].



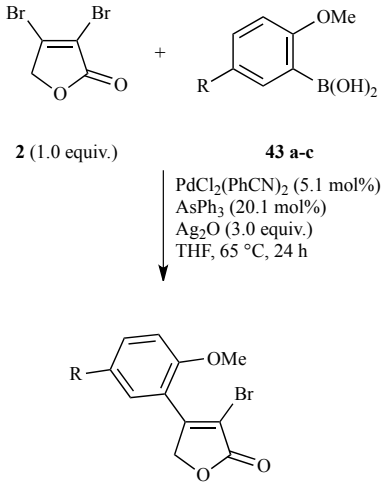
Scheme 13. Two-step synthesis of 3-bromo-4-isopropyl-2(5*H*)-furanone (**37e**)

Still in 2002, Zhang and coworkers described the preparation of 3,4-dibromo-2(5*H*)-furanone (**2**) in 57% yield by treatment of mucobromic acid (**1**) with 1.5 equiv of sodium triacetoxyborohydride in $CHCl_3$ at 0–5 °C followed by addition of acetic acid [53]. Compound **2** was then reacted with 2.0 equiv of 4-(methylthio)phenylboronic acid (**41**) in a 1 : 1 mixture of toluene and water at 20–25 °C for 3 days in the presence of 5 mol% $PdCl_2(PPh_3)_2$, 5 mol% $BnEt_3NCl$ and 2.67 equiv of CsF producing 3-bromo-4-(4-methylthiophenyl)-2(5*H*)-furanone (**31b**) in 75-91% yield (Scheme 14). Compound **31b** was then used as an advanced precursor to Vioxx® (**42**) (Scheme 14), an anti-inflammatory drug launched by Merck, which, however, in 2004, was withdrawn from the market worldwide.



Scheme 14. Synthesis of compound **31b**, an advanced precursor to Vioxx® (**42**)

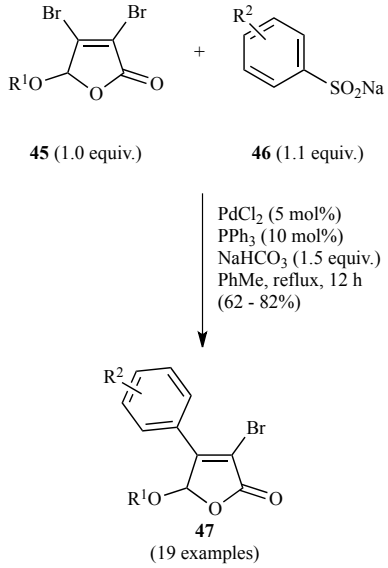
In 2014, 4-aryl-3-bromo-2(5*H*)-furanones **44a–c** were synthesized in modest yields by Barbosa and coworkers through a $PdCl_2(PhCN)_2/AsPh_3$-catalyzed Suzuki-Miyaura reaction of **2** with 4-arylboronic acids **43a–c** in THF at 65 °C in which Ag_2O was used as the base (Scheme 15) [54].



44	R	Yield%
44a	H	35
44b	Me	37
44c	Cl	26

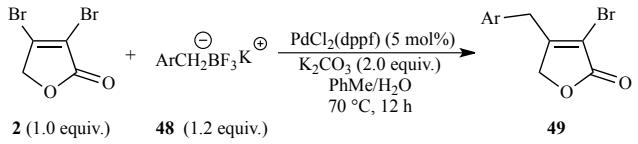
Scheme 15. Synthesis of 4-aryl-3-bromo-2(5*H*)-furanones **45a–c**

More recently, Wang and coworkers developed an efficient protocol for the synthesis of 5-alkoxy-4-aryl-3-bromo-2(5*H*)-furanones **47** [55]. It involved the $PdCl_2/PPh_3$-catalyzed desulfitative regioselective arylation of 5-alkoxy-3,4-dibromo-2(5H)-furanones **45** with sodium arylsulfinates **46** as aryl source (Scheme 16). The reaction was carried out in toluene under reflux using $NaHCO_3$ as the base providing compounds **47** in yields ranging from 62 to 82% [55].



Scheme 16. Synthesis of 5-alkoxy-4-aryl-3-bromo-2(5*H*)-furanones **47**

Still in 2015, Hu and coworkers demonstrated that 4-arylmethyl-3-bromo-2(5*H*)-furanones **49** could be prepared in satisfactory yields by reacting 3,4-dibromo-2(5*H*)-furanone (**2**) with 1.2 equiv of potassium arylmethyltrifluoroborates **48** in a 1 : 1 mixture of toluene and water at 70 °C for 12 h in the presence of 5 mol% $PdCl_2$(dppf) and 2.0 equiv of K_2CO_3 (Scheme 17) [56]. The potassium arylmethyltrifluoroborates that were not commercially available were prepared prepared according to a literature procedure [57].

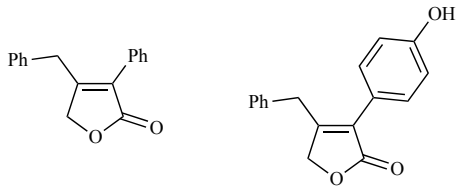


49	Ar	Yield%
49a	Ph	68
49b	4-MeC_6H_4	56
49c	3-MeC_6H_4	55
49d	4-$MeOC_6H_4$	60
49e	4-ClC_6H_4	57

Scheme 17. Regioselective synthesis of 4-arylmethyl-3-bromo-2(5*H*)-furanones **49**

It deserves to be noted that compound **49a** was used as a precursor of gymnoascolide (**50**) (Figure 6) [56], a butenolide isolated from the Australian soil ascomycete *Gymnoascus reessii* [58], as well as of eutypoid (**51**)

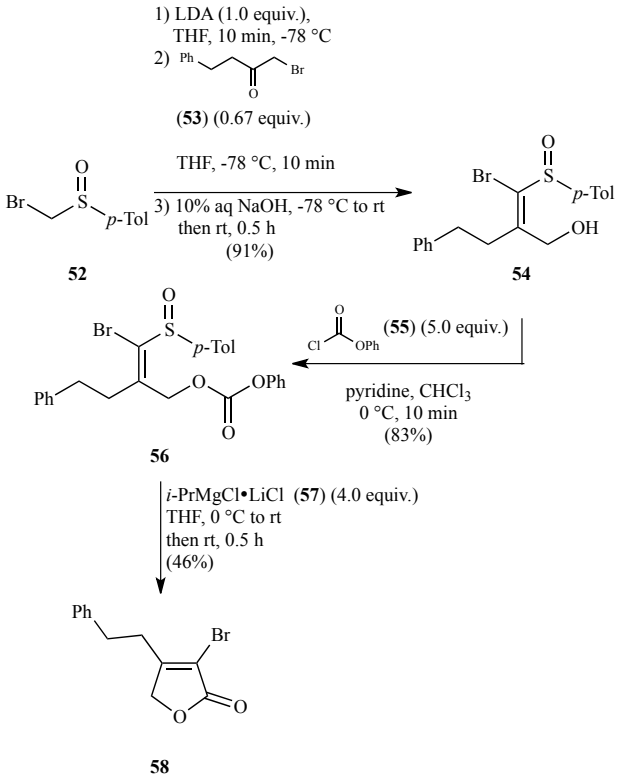
(Figure 6), a metabolite of the mangrove fungus *Eutypa* sp. (# 424) [59.]



50 (gymnoascolide A) **51** (eutypoid A)

Figure 6. Structures of naturally-occurring compounds **50** and **51**

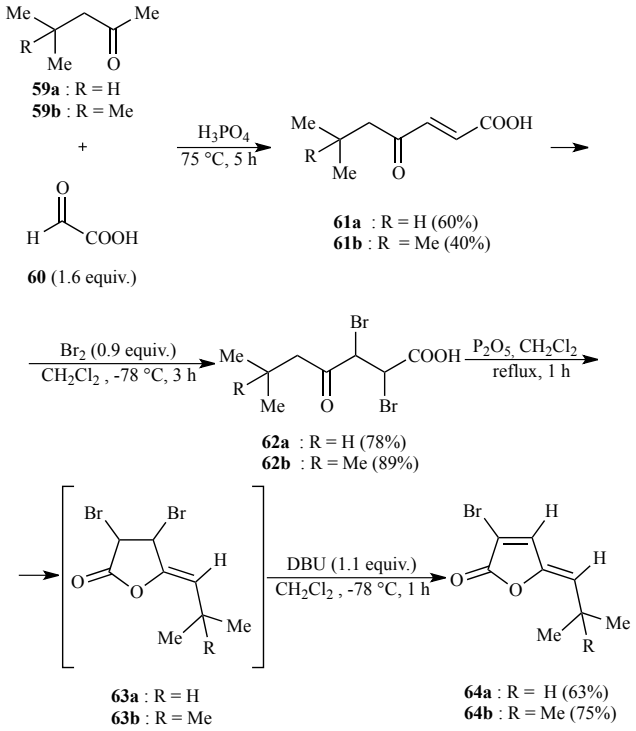
In the same year, Kimura, Satoh and coworkers described a three-step synthesis of 3-bromo-4-(2-phenylethyl)-2(5*H*)-furanone (**57**) in which bromomethyl *p*-tolyl sulfoxide (**52**) was the starting material (Scheme 18) [60].



Scheme 18. Three-step synthesis of compound **57**

The synthesis began with the reaction of **52** with LDA in THF at –78 °C and addition of 1-bromo-4-phenylbutan-2-one (**53**) to the resulting lithium derivative, followed by basification with aqueous NaOH, which gave 1-bromo-3-hydroxyprop-1-enyl *p*-tolyl sulfoxide (**54**) in 91% yield. The subsequent reaction of **54** with phenyl chloroformate (**55**) in $CHCl_3$ in the presence of pyridine gave sulfoxide **56** in 83% yield. Finally, the nucleophilic cyclization of the magnesium alkylidene carbenoid generated from **56** and *i*-PrMgCl·LiCl (57) provided compound **58** in 46% yield (Scheme 18) [60].

Six years earlier, as part of a study on the synthesis of brominated furanones, which are quorum quenching compounds that inhibit biofilm formation and the expression of virulence in *in vitro* and *in vivo* models, Kumar and coworkers had synthesized 3-bromo-5-(2-methylpropylidene)-2(5*H*)-furanone (**64a**) and 3-bromo-5-(2,2-dimethylpropylidene)-2(5*H*)-furanone (**64b**) via a multi-step route in which 2-pentanones **59a** and **59b**, respectively, were used as starting materials (Scheme 19) [61]. The first step of the developed protocol involved the regioselective condensation of ketones **59a** and **59b** with glyoxylic acid (**60**). Addition of bromine to the resulting compounds **61a** and **61b**, respectively, provided the dibromo derivatives **62a** and **62b**, respectively, which underwent dehydration by treatment with P_2O_5 leading to 3,4-dibromodihydrofuran-2-ones **63a** and **63b**, respectively, which unfortunately proved to be difficult to isolate and purify.

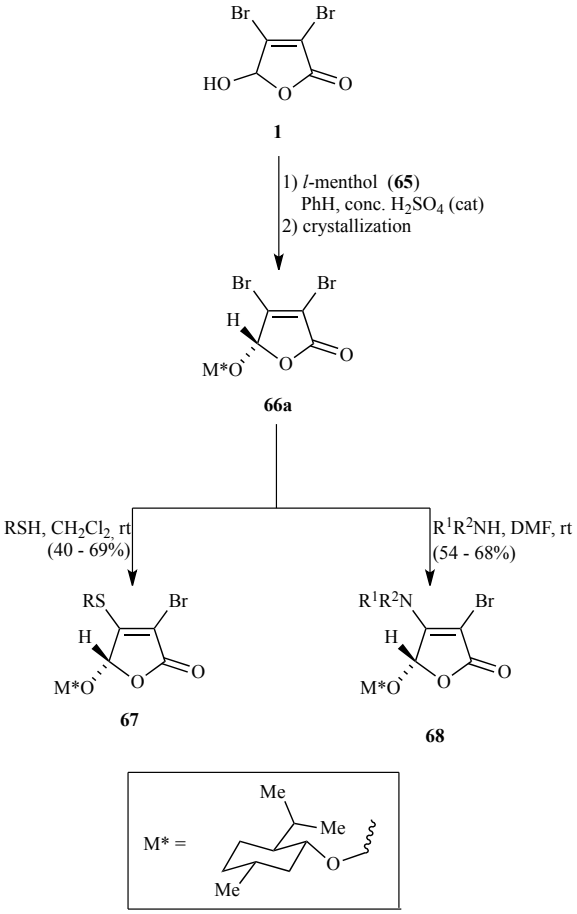


Scheme 19. Regioselective synthesis of 3-bromo-2(5*H*)-furanones **64a** and **64b**

Therefore, these crude products were reacted with DBU in $CHCl_3$ at – 78 °C to give the target compounds **64a** and **64b** in 29.5% and 26.6% overall yield, respectively, based on the starting ketones **59a** and **59b**, respectively [61]. The biological activity of compounds **64a** and **64b** however was not evaluated.

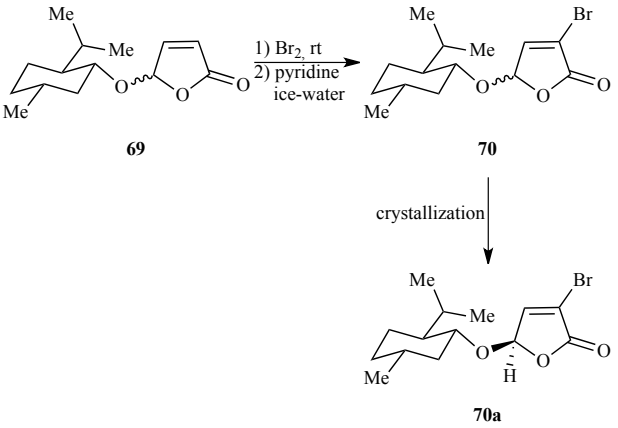
Over the past 20 years, significant attention has also been paid to the synthesis of enantiomerically pure 5-alkoxy-3-bromo-2(5*H*)-furanones. In 1995, Chen and

coworkers prepared enantiomerically pure 5-(*l*-menthyloxy)-3,4-dibromo-2(5*H*)-furanone (**66a**) by acetalyzation of mucobromic acid (**1**) with *l*-menthol (**65**) in the presence of a catalytic amount of concd. sulfuric acid (Scheme 20) [62]. Crystallization of the resulting epimeric mixture allowed to obtain enantiomerically pure **66a** in 33% yield. The subsequent tandem Michael addition-elimination reaction of **66a** with thiols or amines then yielded 5-alkoxy-3-bromo-2(5*H*)-furanones **67** and **68** respectively, in good yields with de > 98% (Scheme 20) [62].



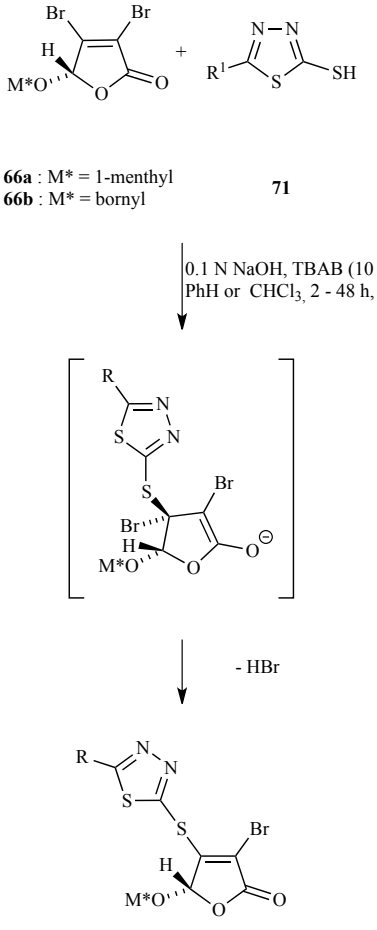
Scheme 20. Synthesis of chiral 5-alkoxy-3-bromo-2(5*H*)-furanones **67** and **68**

In 1998, Huang and Chen synthesized 5(*R*)-[(1*R*,2*S*,5*R*)-(–)-menthyloxy]-3-bromo-2(5*H*)-furanone (**70a**) in 46% yield with de > 98% by crystallization of an epimeric mixture of 5-(*l*-menthyloxy)-3-bromo-2(5*H*)-furanone (**70**), which was obtained via addition of bromine to an epimeric mixture of 5-(*l*-menthyloxy)-2(5*H*)-furanone (**69**) followed by pyridine-mediated elimination of hydrogen bromide (Scheme 21) [63].



Scheme 21. Synthesis of 5(*R*)-[(1*R*,2*S*,5*R*)-(–)-menthyloxy]-3-bromo-2(5*H*)-furanone (**70a**)

In 2009, Li, Shao and coworkers synthesized a series of chiral 2,5-disubstituted 1,3,4-thiadiazoles **72** possessing a 2(5*H*)-furanone moiety according to the procedure depicted in Scheme 22 [64]. Specifically, acetalyzation of mucobromic acid (**1**) with (–)-menthol [63] and (+)-borneol [65] followed by separation of the resulting diastereomers allowed to obtain enantiomerically pure compounds **66a** and **66b** respectively. The subsequent tandem Michael addition–elimination reactions of these compounds with 2-mercapto-1,3,4-thiadiazoles **71** then gave compounds **72a-l** in good to excellent yields (Scheme 22) [64].

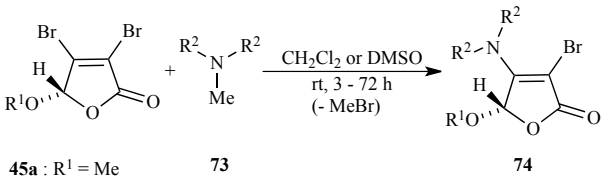


72	M*	R	Yield%
72a	1-menthyl	Ph	98
72b	1-menthyl	4-ClC_6H_4	95
72c	1-menthyl	2-HOC_6H_4	96
72d	1-menthyl	4-HOC_6H_4	66
72e	1-menthyl	4-$(NO_2)C_6H_4$	83
72f	1-menthyl	4-$MeOC_6H_4$	92
72g	1-menthyl	2-furyl	75
72h	1-menthyl	4-pyridyl	83
72i	1-menthyl	3-pyridyl	89
72j	bornyl	2-furyl	60
72k	bornyl	4-pyridyl	69
72l	bornyl	3-pyridyl	69

Scheme 22. Synthesis of compounds **72 a-l**

It was then discovered that all compounds **72a-l** exhibited anticancer activity against human epitheloid cervix carcinoma (HeLa) cells and that compound **72e** possessed the best inhibitory activity with an IC_{50} of 0.9 μM [64].

In 2013, a series of 5-alkoxy-4-amino-3-bromo-2(5*H*)-furanones of general formula **74** which included chiral derivatives were synthesized in modest to good yields by Fan, Li and coworkers using a one-pot protocol involving the regioselective transalkylation of *N*-methyl tertiary amines **73** with 5-alkoxy-3,4-dibromo-2(5H)-furanones **45a**, **66a** and **66b** [66]. As shown in Scheme 23, the reactions generally occurred in CH_2Cl_2 or DMSO at room temperature producing compounds **74a-j** in yields ranging from 35 to 87% [66]. Notably, compound **74b** in which R^1 = menthyl and R^2 = Me was found to posses a significant anticancer activity against HeLa cell lines (IC_{50} = 0.19 μM/L) [66].



45a : R^1 = Me
66a : R^1 = menthyl
66b : R^1 = bornyl

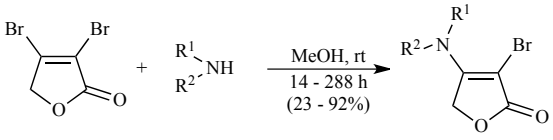
73 **74**

74	R^1	R^2	Solvent	Reaction time (h)	Yield%
74a	Me	Me	CH_2Cl_2	3	87
74b	menthyl	Me	CH_2Cl_2	3	86
74c	bornyl	Me	CH_2Cl_2	3	84
74d	Me	$(CH_2)_5$	DMSO	24	39
74e(*)	menthyl	$(CH_2)_5$	DMSO	24	43
74f	bornyl	$(CH_2)_5$	DMSO	24	45
74g	Me	$(CH_2)_4$	DMSO	3	53
74h	menthyl	$(CH_2)_4$	DMSO	9	63
74i	Me	$(CH_2)O(CH_2)$	DMSO	26	55
74j(*)	menthyl	$(CH_2)O(CH_2)$	DMSO	72	72

(*) Reaction carried out at 60 °C

Scheme 23. Synthesis of 5-alkoxy-4-amino-3-bromo-2(5*H*)-furanones **74a-j**

Two years earlier, Cunha and coworkers had reported that a variety of 4-amino-3-bromo-2(5*H*)-furanones of general formula **76** could be obtained by treatment of 3,4-dibromo-2(5*H*)-furanone (**2**) with primary and secondary amines **75** at room temperature (Scheme 24) [67]. The reactions were generally carried out by treatment of **2** with 2.0 equiv of amines **75** in methanol providing compounds **76** in yields ranging from 23 to 92% but, in some cases, high yields of compounds **76** were obtained by the reaction of **2** with 1.0 equiv of **75** and 1.0 equiv of $NaHCO_3$ [67].

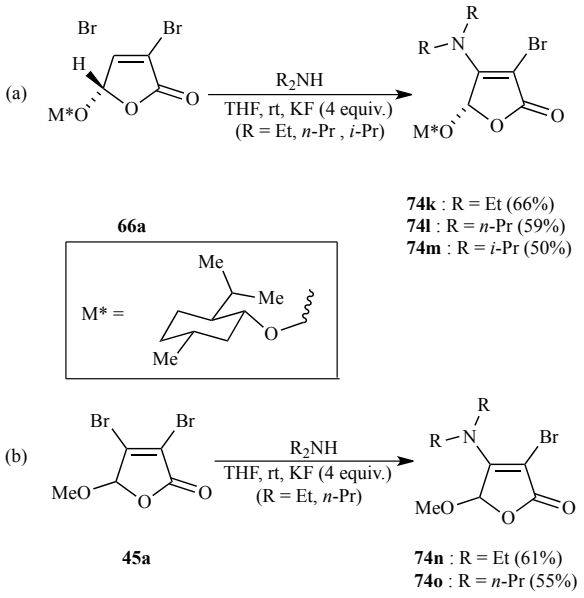


2 (1.0 equiv.) **75** (2.0 equiv.) **76** (10 examples)

Scheme 24. Synthesis of 4-amino-3-bromo-2(5*H*)-furanones **76**

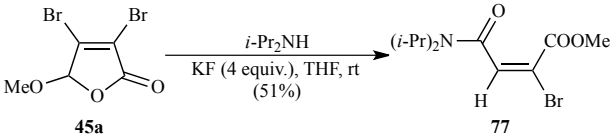
It was found that *para*-substituted anilines afforded generally better yields of compounds **76** than *ortho*-substituted ones and that their reactions occurred in shorter times [67].

In 2012, Wang and coworkers synthesized 5-alkoxy-4-dialkylamino-3-bromo-2(5*H*)-furanones **74k**, **74l** and **74m** in satisfactory yields by regioselective reaction of 3,4-dibromo-5-menthyloxy-2(5*H*)-furanone (**66a**) with diethyl-di-*n*-propyl- and diisopropylamine, respectively, in THF at room temperature using KF as the base (Scheme 25, eq. a) [68].



Scheme 25. Synthesis of 5-alkoxy-4-dialkylamino-3-bromo-2(5*H*)-furanones **74k-o**

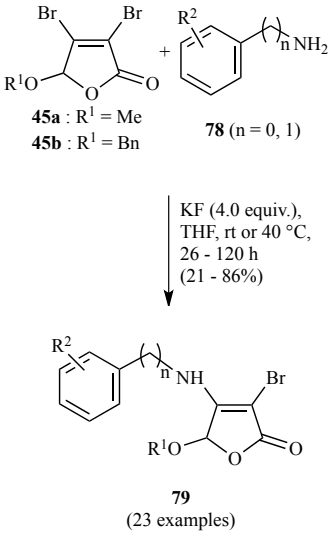
Furthermore, compounds **74n** and **74o** were prepared in 61 and 55% yield respectively, by tandem Michael addition-elimination reactions of 3,4-dibromo-5-methoxy-2(5*H*)-furanone (**45a**) with diethyl- and di-*n*-propylamine, respectively (Scheme 25, eq. b) [68]. However, the reaction between **45a** and diisopropylamine in THF at room temperature in the presence of KF, unexpectedly, gave methyl (*E*)-2-bromo-4-(diispropylamino)-4-oxobut-2-enoate (**77**) in 51% yield (Scheme 26) [68].



Scheme 26. Synthesis of compound **77** from **45a** and diisopropylamine

Wang and coworkers also investigated the bioactivity of compounds **74** on adenocarcinoma human alveolar basal epithelial (A549) cells *in vitro* and found that some of these compounds had anticancer activity and that their inhibition activity increased with sample concentration. Interestingly, menthyloxy and methoxy substituents at position 5 had not influence on the inhibition [68].

One year later, Wang and coworkers synthesized twenty three 5-alkoxy-4-amino-3-bromo-2(5*H*)-furanones **79** containing aryl rings by treatment of 5-alkoxy-3,4-dibromo-2(5*H*)-furanones **45a** and **45b** with primary amines **78** bearing aryl functionality in THF at room temperature or 40 °C using KF as the base (Scheme 27) [69]. The resulting tandem Michael addition-elimination reactions provided compounds **79** in 21–86% yield (mostly over 64%) [69].



Scheme 27. Synthesis of 5-alkoxy-4-amino-3-bromo-2(5*H*)-furanones **79**

In the last two decades, significant attention has also been devoted to the synthesis of (*Z*)-3-bromo-5-ylidene-2(5*H*)-furanones **80** (Figure 7).

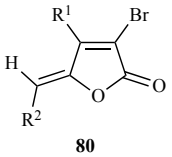
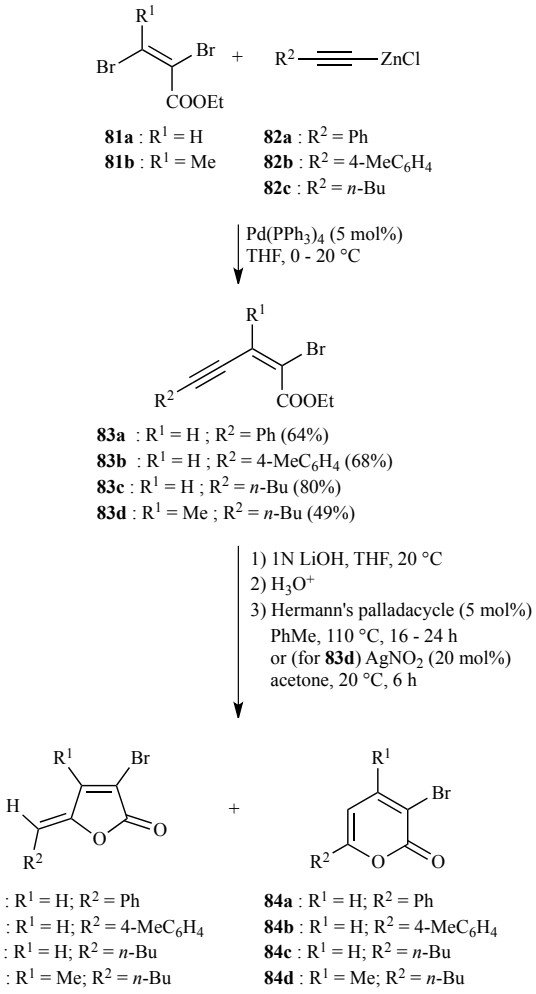


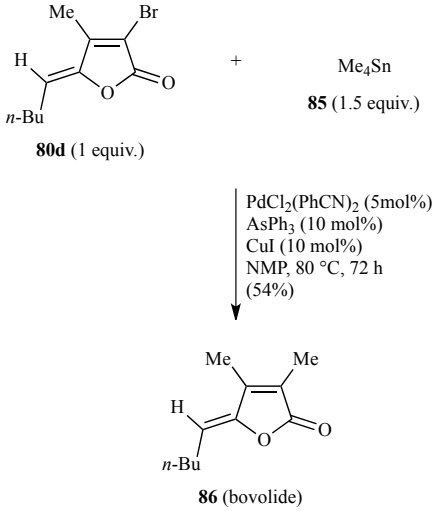
Figure 7. Structure of compounds **80**

In 1998, our research group described the synthesis of compounds **80a-d** via the route outlined in Scheme 28 [69]. In particular, according to the general procedure which we had previously developed for the regioselective and stereospecific monoarylation, monoalkynylation and monoalkylation of stereodefined 2,3-dibromo-2-alkenoates [70–72], stereoisomerically pure compounds **81a** and **81b** were reacted with 1.3 equiv of alkynylzinc chlorides **82a**, **82b** and **82c** in THF at 0–20 °C in the presence of 5 mol% $Pd(PPh_3)_4$ to give stereoisomerically pure compounds **83a–d** in yields ranging from 49 to 80%.



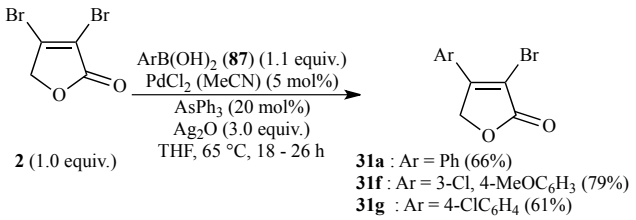
Scheme 28. Regioselective synthesis of (*Z*)-3-bromo-5-ylidene-2(5*H*)-furanones **80a–d**

These ethyl 2-bromo-2-en-4-ynoates were then converted into the required compounds **80a-d** by saponification with 1N LiOH, followed by acidification and lactonization of the resulting crude carboxylic acids by heating their toluene solution under argon at 110 °C for 16–24 h in the presence of 5 mol% *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (Herrmann's palladacycle). Compounds **80a, 80b, 80c** and **80d** were so obtained in 45, 36, 50 and 25% yield, respectively. Notably, compounds **80a–c** were obtained together with 3–6% of the corresponding 3-bromo-2*H*-pyran-2-ones **84a–c**, but **80d** was obtained together with a significant amount of pyranone **84d**, which was isolated in 45% yield. Nevertheless, when the cyclization reaction of the crude carboxylic acid derived from **83d** was carried out in acetone at 20 °C for 6 h in the presence of 20 mol% $AgNO_3$ a mixture of **80d** and **84d** in ca. 79 : 21 ratio was obtained from which pure **80d** was isolated in 52% yield [69]. Compound **80d** was then used as direct precursor to bovolide (**86**), a natural compound first found in butter [73]. In fact, the reaction of **80d** with 1.5 equiv of tetramethyltin (**85**) in NMP at 80 °C for 72 h in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% $AsPh_3$ and 10 mol% CuI gave **86** in 54% yield (Scheme 29) [69].



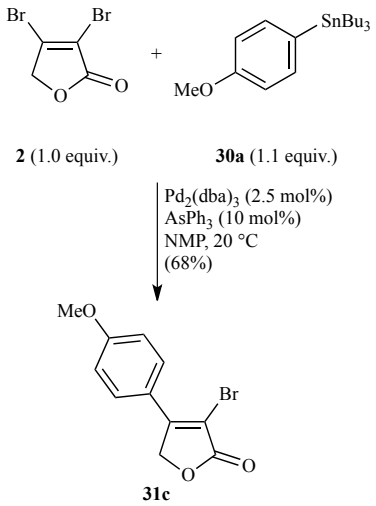
Scheme 29. Synthesis of bovolide (**86**)

In 2001, 4-aryl-3-bromo-2(5H)-furanones **31** were synthesized by our research group using a novel protocol that involved the $PdCl_2(MeCN)_2/AsPh_3$-catalyzed regioselective Suzuki-Miyaura reaction of 3,4-dibromo-2(5*H*)-furanone (**2**) with 1.1 equiv of arylboronic acids (**87**) in THF at 65 °C and 3.0 equiv of Ag_2O [74]. Scheme 30 depicts the synthesis of compounds **31a**, **31f** and **31g** in 66%, 79% and 61% yield, respectively, according to this protocol.



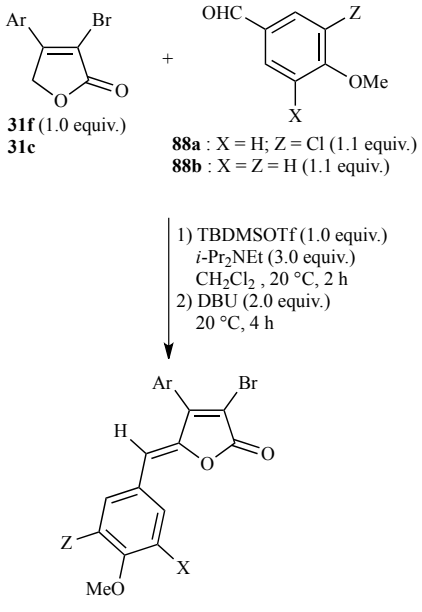
Scheme 30. Synthesis of compounds **31a**, **31f** and **31g** via regioselective Suzuki-Miyaura reaction

On the other hand, the Stille-type reaction of **2** with 1.1 equiv of (4-methoxyphenyl)tributyltin (**30a**) in NMP at room temperature in the presence of a $Pd_2(dba)_3/AsPh_3$ catalyst system provided regioselectively 3-bromo-4-(4-methoxyphenyl)-2(5*H*)-furanone (**31c**) in 68% yield (Scheme 31) [74].



Scheme 31. Synthesis of compounds **31c** via a Stille-type coupling reaction

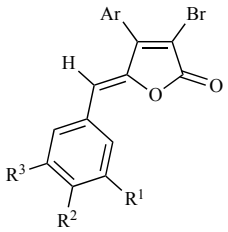
Compounds **31f** and **31c** were then used as advanced precursors to (*Z*)-4-aryl-5-(1-arylmethylene)-3-bromo-2(5*H*)-furanones **89a** and **89b**, respectively. In particular, **31f** and **31c** were treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and diisopropylethylamine yielding the corresponding silyl ethers that were not isolated, but immediately reacted with aldehydes **88a** and **88b**, respectively. The resulting compounds were not isolated, but submitted to reaction with DBU providing compounds **89a** and **89b** in 95% and 99% yield, respectively (Scheme 32) [74].



89	Ar	Z	Yield%
89a	3-Cl, 4-$MeOC_6H_3$	Cl	95
89b	4-$MeOC_6H_4$	H	99

Scheme 32. Stereoselective synthesis of (*Z*)-4-aryl-5-(1-arylmethylene)-3-bromo-2(5*H*)-furanones **89a** and **89b**

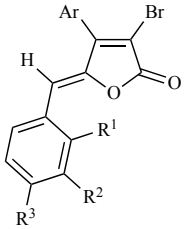
In 2012, our protocol [74] was employed by Barbosa, Forlani and coworkers to prepare (*Z*)-4-aryl-5-(1-arylmethylene)-3-bromo-2(5*H*)-furanones **90a–k** (Figure 8) in modest to satisfactory yields starting from 3,4-dibromo-2(5*H*)-furanone (**2**) [75]. Notably, all compounds **90**, except **90j**, appeared capable to interfere with the photosynthetic electron transport chain in the chloroplasts. The IC_{50} values of the most active compounds, **90b** and **90c**, were only 1 order of magnitude higher than those of commercial herbicides sharing the same mode of action [75].



90a : Ar = 2-MeO, 4-FC_6H_3 ; R^1 = H; R^2 = R^3 = OCH_2O
90b : Ar = 2-MeO, 4-FC_6H_3; R^1 = R^2 = H; R^3 = NO_2
90c : Ar = 2-MeO, 4-FC_6H_3; R^1 = R^2 = H ; R^3 = CF_3
90d : Ar = 2-$MeOC_6H_4$; R^1 = H; R^2 = R^3 = OCH_2O
90e : Ar = 2-$MeOC_6H_4$; R^1 = R^2 = H ; R^3 = NO_2
90f : Ar = 2-$MeOC_6H_4$; R^1 = R^2 = H ; R^3 = CF_3
90g : Ar = 2-$MeOC_6H_4$; R^1 = R^2 = R^3 H
90h : Ar = 2-$MeOC_6H_4$; R^1 = OH; R^2 = R^3 = H
90i : Ar = 2-MeO, 4-FC_6H_4 ; R^1 = OH ; R^2 = R^3 = H
90j : Ar = 2-$MeOC_6H_4$; R^1 = R^2 = H ; R^3 = OH
90k : Ar = 2-MeO, 4-FC_6H_3 ; R^1 = R^2 = H ; R^3 = OH

Figure 8. Structures of compounds **90a–k**

In 2015, the same research group synthesized stereoisomerically pure compounds (*Z*)-**91a** and (*Z*)-**91c–j** and (*E*)*(Z*)-**91b** (Figure 9) by the same procedure used in 2012 to prepare **90a–k** [75].

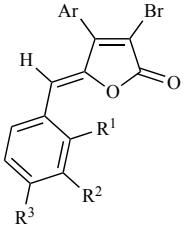


(*Z*)-**91a** : Ar = 2-MeO, 5-ClC_6H_3 ; $R^1 = R^2$ = H ; R^3 = F
(*E*)/(*Z*)-**91b** : Ar = 2-MeO, 5-ClC_6H_3; $R^1 = R^2$ = H; $R^3 = NO_2$
(*Z*)-**91c** : Ar = 2-MeO, 5-ClC_6H_3 ; $R^1 = R^2$ = H; $R^3 = CF_3$
(*Z*)-**91d** : Ar = 2-MeO, 5-ClC_6H_3 ; $R^1 = R^3$ = ; $R^2 = NO_2$
(*Z*)-**91e** : Ar = 2-MeO, 5-BrC_6H_3 ; $R^1 = R^2$ = H; $R^3 = CF_3$
(*Z*)-**91f** : Ar = 2-MeO, 5-BrC_6H_3; R^1 = Br; $R^2 = R^3$ = H
(*Z*)-**91g** : Ar = 2-MeO, BrC_6H_3; $R^1 = R^2$ = ; R^3 = F
(*Z*)-**91h** : Ar = 2_MeO, 5-BrC_6H_3 ; R^1 = Cl; $R^2 = R^3$ = H
(*Z*)-**91i** : Ar = 2-MeO, 5-BrC_6H_3 ; R^1 = R^3 = H; R^2 = OMe
(*Z*)-**91j** : Ar = 2-MeO, 5-BrC_6H_3; $R^1 = R^3$ = H; R^2 = F

Figure 9. Structures of compounds (*Z*)-**91a**, (*Z*)-**91c–j**, and (*E)(*Z)-**91b**

All these substances were then evaluated for their abilities of interfering with the light-driven reduction of ferricyanide by isolated spinach chloroplasts and it was found that at 10 μM compound (*E)(*Z)-**91b** showed the highest effectiveness and that compounds (*Z*)-**91c**, (*Z*)-**91e** and (*Z*)-**91g** were very active [75].

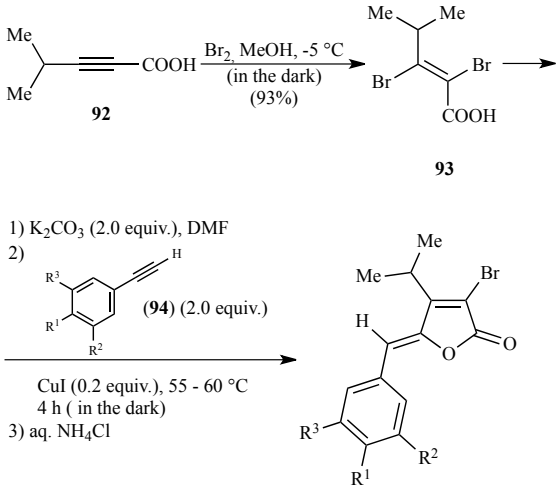
In the same year, Barbosa and coworkers also investigated the photosynthetic inhibitory activity of rubrolide analogues different from compounds **91a–j** and discovered that (*Z*)-4-aryl-5-(arylmethylene)-3-bromo-2(5*H*)-furanones **91k–s** (Figure 10) were capable of inhibiting the basal, uncoupled and phosphorylating electron transfer [76]. Thus, these compounds acted as inhibitors of the Hill reaction, *i.e.* the light-driven transfer of electrons by chloroplasts in photosynthesis that results in the cleavage of water molecules and liberation of dioxygen [77].



91k : Ar = Ph; $R^1 = R^2$ = H; R^3 = F
91l : Ar = Ph; $R^1 = R^3$ = H; R^2 = OMe
91m : Ar = 2-$MeOC_6H_4$; $R^1 = R^2$ = H; R^3 = Et
91n : Ar = 4-FC_6H_4; $R^1 = R^2$ = H; R^3 = Et
91o : Ar = 2-$MeOC_6H_4$; $R^1 = R^2$ = H; R^3 = OH
91p : Ar = 2-$MeOC_6H_4$; $R^1 = R^3$ = OMe; R^2 = H
91q : Ar = 2-HOC_6H_4; $R^1 = R^3$ = OH; R^2 = H
91r : Ar = 2-MeO,4-FC_6H_3; $R^1 = R^2$ = H; R^3 = OH
91s : Ar = 2-HO, 4-FC_6H_4; $R^1 = R^3$ = OH; R^2 = H

Figure 10. Structures of compounds **91k–s**

In 2013, Ngi, Thibonnet and coworkers developed a new route to (*Z*)-5-[1-(aryl)methylene]-3-bromo-4-isopropyl-2(5*H*)-furanones **95** in which 4-methyl-2-pentynoic acid (**92**) was the starting material (Scheme 33) and used these compounds as precursors to nostoclide analogues [78].



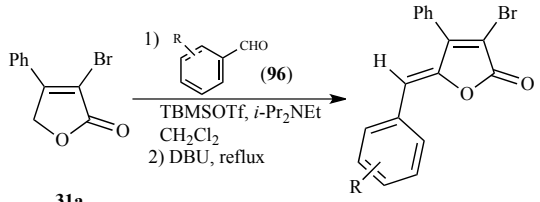
95	R^1	R^2	R^3	Yield%
95a	H	H	H	65
95b	OH	H	H	38
95c	OH	Cl	Cl	25
95d	OH	H	Cl	28
95e	OMe	H	Cl	65
95f	OMe	Cl	Cl	68

Scheme 33. Stereoselective synthesis of (*Z*)-5-[1-(aryl)methylene]-3-bromo-4-isopropyl-2(5*H*)-furanones **95a–f**

Specifically, addition of bromine to **92** using a previously reported protocol [79] led to compound **93** in 93% yield. A mixture of **93** and 2.0 equiv of K_2CO_3 in DMF was then stirred in the dark for 15 min and subsequently reacted with 2.0 equiv of arylacetylenes **94** and 0.2 equiv of CuI at 55–60 °C for 4 h under stirring. Hydrolysis of the resulting mixtures with an aqueous NH_4Cl solution provided stereoselectively compounds **95a–f** in yields ranging from 25 to 68% [78]. Attempts were also made to convert compounds **95f** and **95e** into the corresponding *O*-demethylated derivatives **95c** and **95d**, respectively, but the efforts to carry out the demethylation reaction with BBr_3 or HBr in acetic acid were unsuccessful [78].

In 2015, Barbosa and coworkers synthesized (*Z*)-5-[1-(aryl)methylene]-3-bromo-4-phenyl-2(5*H*)-furanones **97a** and **97b** in 44% and 70% yield, respectively, via aldol

condensation of 3-bromo-4-phenyl-2(5*H*)-furanone (**31a**) with the required aryl aldehydes **96** (Scheme 34) [80].



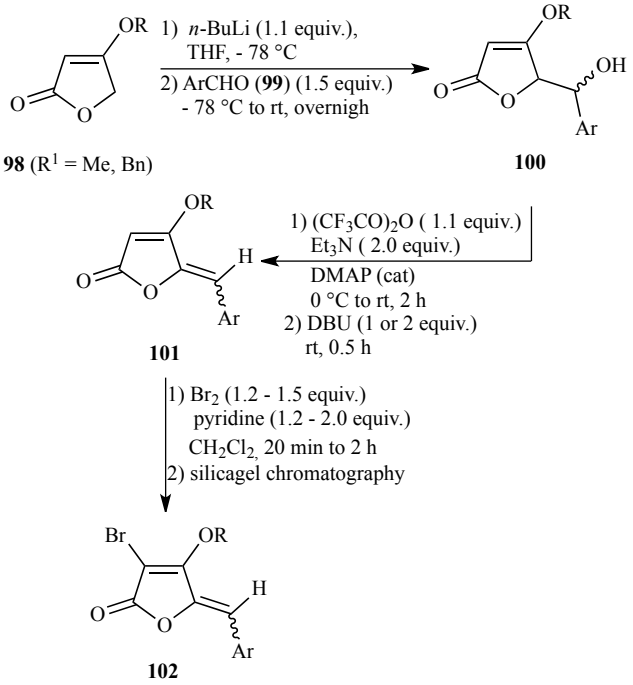
31a

97a : R = 4-F (44%)
97b : R = 3-MeO (70%)

Scheme 34. Stereoselective synthesis of (*Z*)-5-[1-(aryl)methylene]-3-bromo-4-phenyl-2(5*H*)-furanones **97a** and **97b**

Compounds **97a** and **97b**, which similarly to compounds **91** are analogues of rubrolides, a class of natural 2(5*H*)-furanones from marine invertebrates [81], were then assayed for their effect on non-cyclic electron transport from water to methylviologen under basal phosphorylation and uncoupled conditions and it was found that **97a** bearing a fluorine atom in the benzylidene group showed markedly higher activity than **97b** [80].

Still in 2015, Médebielle and coworkers carried out the synthesis of (*Z*)-4-alkoxy-5-[1(aryl)methylene]-3-bromo-2(5*H*)-furanones **102a–g** starting from 4-alkoxy-2(5*H*)-furanones **98** through the multistep route outlined in Scheme 35 [82]. The reaction of compounds **98** with *n*-BuLi and aldehydes **99** in THF yielded aldol adducts **100** which were directly converted to 4-alkoxy-5-[1-(aryl)methylene]-2(5*H*)-furanones **101a–g** via a two-step/one-pot sequence involving an esterification reaction with trifluoroacetic anhydride and a DBU-mediated elimination reaction. Compounds **101a** and **101c–g** were obtained as stereoisomerically pure *Z*-configured stereoisomers, but **101b** was obtained as a 96 : 4 mixture of *Z* and *E* stereoisomers, respectively. A bromine atom was then introduced on the C-3 position of compounds **101** by treatment with 1.2–1.5 equiv of bromine in the presence of pyridine. Purification of the resulting reaction mixtures by silica gel chromatography allowed to obtain stereoisomerically pure compounds (*Z*)-**102a–g** in yields ranging from 60 to 91% (Scheme 35) [82].



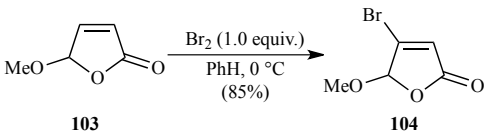
101	R	Ar	*Z/E*	Yield%
101a	Me	Ph	100 : 0	39
101b	Me	3,4-$F_2C_6H_3$	96 : 4	32
101c	Me	4-$CF_3C_6H_4$	100 : 0	43
101d	Me	3,4-$(MeO)_2C_6H_3$	100 : 0	39
101e	Bn	Ph	100 : 0	47
101f	Bn	4-$CF_3C_6H_4$	100 : 0	57
101g	Bn	3,4-$(MeO)_2C_6H_3$	100 : 0	18

102	equiv. of Br_2	R	Ar	Yield%
102a	1.5	Me	Ph	91
102b	1.5	Me	3,4-$F_2C_6H_3$	81
102c	1.2	Me	4-$CF_3C_6H_4$	62
102d	1.5	Me	3,4-$(MeO)_2C_6H_3$	60
102e	1.5	Bn	Ph	79
102f	1.5	Bn	4-$CF_3C_6H_4$	65
102g	1.2	Bn	3,4-$(MeO)_2C_6H_3$	64

Scheme 35. Synthesis of compounds **101a-g** and **102a-g**

2.2. SYNTHESIS AND BIOACTIVITY OF 4-BROMO-2(5*H*)-FURANONE DERIVATIVES

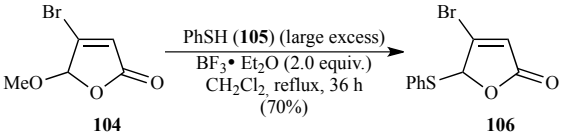
In 1953, Schenk synthesized 4-bromo-5-methoxy-2(5*H*)-furanone (**104**) in 85% yield by bromination of 5-methoxy-2(5*H*)-furanone (**103**) in benzene at 0 °C (Scheme 36)[83].



103 **104**

Scheme 36. Synthesis of 4-bromo-5-methoxy-2(5*H*)-furanone (**104**)

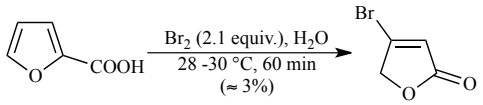
In 1996, Martin and coworkers converted compound **104** into 4-bromo-5-phenylthio-2(5*H*)-furanone (**106**) by treatment with a large molar excess of thiophenol (**105**) in CH_2Cl_2 under reflux in the presence of 2.0 equiv of $BF_3{\cdot}Et_2O$ (Scheme 37) [84].



104 **106**

Scheme 37. Synthesis of 4-bromo-5-phenylthio-2(5*H*)-furanone (**106**)

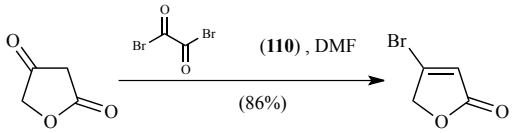
In 1963, Mabry reported that 4-bromo-2(5*H*)-furanone (**108**) could be obtained in a very low yield (ca. 3%) by the reaction of 2-furoic acid (**107**) with 2.1 equiv of bromine in water at 28–30 °C for 60 min (Scheme 38) [85].



107 **108**

Scheme 38. Synthesis of 4-bromo-2(5*H*)-furanone (**108**) from 2-furoic acid (**107**)

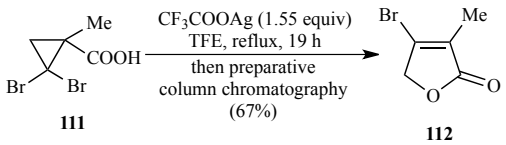
Nevertheless, in 1991, compound **108** was prepared by Jas in 86% yield on a 30 g scale by treatment of β-tetronic acid (2,4-(3*H*,5*H*-furandione) (**109**) with a Vilsmeier reagent prepared from oxalyl bromide (**110**) and DMF (Scheme 39) [86].



109 **108**

Scheme 39 Synthesis of 4-bromo-2(5*H*)-furanone (**108**) from β-tetronic acid (**109**)

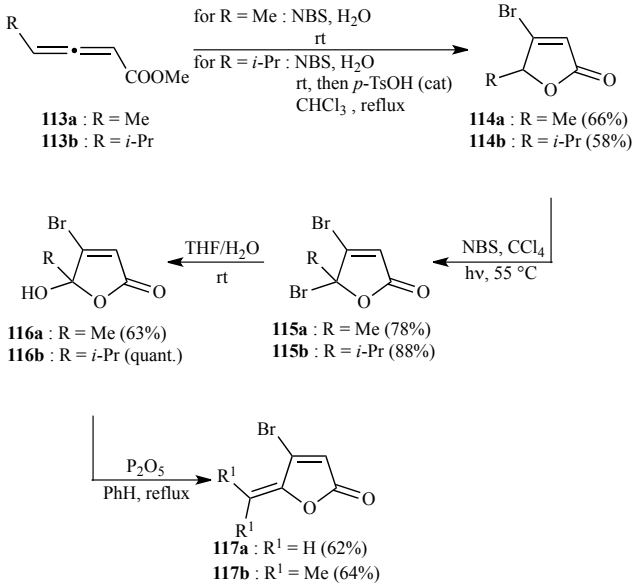
One year earlier, 4-bromo-3-methyl-2(5*H*)-furanone (**112**) had been synthesized by Svendson and Sydnes in 67% yield by treatment of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**111**) with 1.55 equiv of CF_3COOAg in 2,2,2-trifluoroethanol (TFE) under reflux for 19 h and chromatographic purification of the resulting crude reaction product (Scheme 40) [87].



111 **112**

Scheme 40. Synthesis of 4-bromo-3-methyl-2(5*H*)-furanone (**112**)

Again in 1990 Font, Gracia, and de March described an elegant method that allowed them to prepare 4-bromo-2(5*H*)-furanones **114a** and **114b**, 4-bromo-5-methylene-2(5*H*)-furanone (**117a**) and 4-bromo-5-isopropylidene-2(5*H*)-furanone (**117b**) in satisfactory yields starting from methyl 4-alkyl-2,3-butadienoates **113a** and **113b**, respectively (Scheme 41) [88].

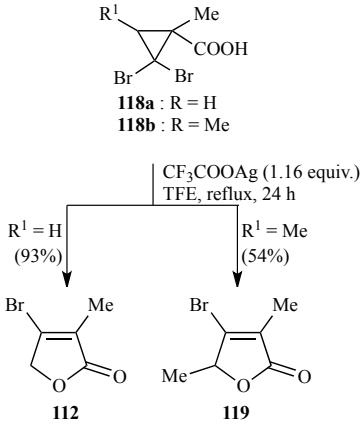


Scheme 41. Synthesis of 4-bromo-2(5*H*)-furanones **114a,b** and 4-bromo-5-ylidene-2(5*H*)-furanones **117a,b**

In particular, the reaction of **113a** with NBS in water at room temperature gave **114a** in 66% yield. On the other hand, **114b** was obtained in 58% yield by treatment of **113b** with NBS in water at room temperature and heating at reflux of a $CHCl_3$ solution of the resulting product in the presence of a catalytic amount of *p*-TsOH. Allylic bromination of **114a** with NBS under irradiation with an incandescent lamp afforded 4,5-dibromo-2(5*H*)-furanone **115a** in 78% yield, which was converted to 4-bromo-5-hydroxy-5-methyl-2(5*H*)-furanone (**116a**) in 63% yield by treatment with a mixture of THF and water. Finally, dehydration of **116a** with P_2O_5 in benzene under reflux gave **117a** in 62% yield. The same reaction sequence was then used to prepare **117b** from **114b**. In fact, allylic bromination of **114b** gave **115b** in 88% yield. Hydrolysis of this compound provided **116b** in quantitative yield,

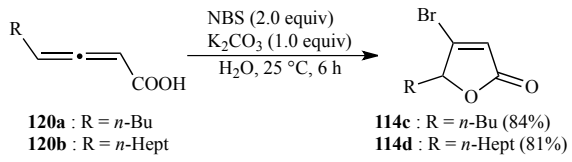
which was dehydrated with P_2O_5 in refluxing benzene giving rise to **119b** in 64% yield [88].

In 1998, Sydnes and coworkers reinvestigated the solvolysis of 2,2-dibromo-1-methylcyclopropane carboxylic acid (**118a**) in TFE in the presence of CF_3COOAg and found that the reaction in TFE under reflux for 24 h in the presence of 1.16 equiv of CF_3COOAg gave 4-bromo-3-methyl-2(5H)-furanone (**112**) in 93% yield (Scheme 42) [89]. The same reaction conditions were then used to prepare 4-bromo-3,5-dimethyl-2(5*H*)-furanone (**119**) in 54% yield from *trans*-2,2-dibromo-1,3-dimethylcyclopropanecarboxylic acid (**118b**) (Scheme 42) [89].



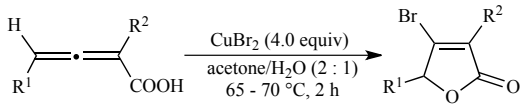
Scheme 42. Synthesis of 4-bromo-2(5*H*)-furanones **112** and **119**

It deserves also to be mentioned that, in the late 1990s and early 2000s, a significant contribution to the development of efficient and selective methods for the synthesis of variously substituted 4-bromo-2(5*H*)-furanones was given by the research group of Ma. In 1999, this group reported that 5-alkyl-4-bromo-2(5*H*)-furanones **114c** and **114d** could be synthesized in high yields by the reaction of allenecarboxylic acids **120a** and **120b**, respectively, with 2.0 equiv of NBS and 1.0 equiv of K_2CO_3 in water at 25 °C (Scheme 43) [90,91].



Scheme 43. Synthesis of 5-alkyl-4-bromo-2(5*H*)-furanones **114c** and **114d** fromn allenecarboxylic acids **120a** and **120b**, respectively

In the same year, Ma and Wu reported that 4-bromo-2(5*H*)-furanones **122a–f** could be obtained in high to excellent yields by treatment of 2,3-allenoic acids **121a–f** with 4.0 equiv of $CuBr_2$ in a 2 : 1 mixture of acetone and water at 65-70 °C for 2 h (Scheme 44) [92].

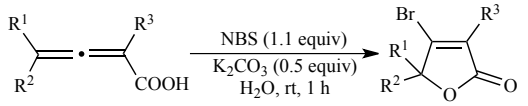


121 **122**

122	R^1	R^2	Yield%
122a	Ph	Me	96
122b	*n*-Hept	H	85
122c	*c*-C_6H_{11}	H	94
122d	Ph	*n*-Pr	99
122e	1-naphthyl	Me	89
122f	1-naphthyl	*n*-Pr	98

Scheme 44. Synthesis of 4-bromo-2(5*H*)-furanones **122a–f** from 2,3-allenoic acids **121a–f**

In 2001, Ma and Shi improved their protocol for the bromolactonization reaction of 2,3-allenoic acids with NBS and found that the reaction of carboxylic acids **123a–f** with 1.1 equiv of NBS and 0.5 equiv of K_2CO_3 in water at room temperature produced 4-bromo-2(5*H*)-furanones **124a–f** in yields ranging from 81 to 99% (Scheme 45) [93].

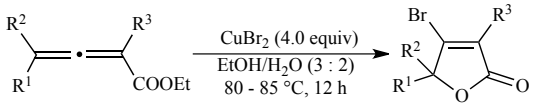


123 **124**

124	R^1	R^2	R^3	Yield%
124a	*n*-Bu	H	H	84
124b	*n*-Hept	H	H	81
124c	Ph	H	Me	94
124d	Ph	H	*n*-Pr	99
124e	1-naphthyl	H	Me	98
124f	Ph	Me	H	99

Scheme 45. Synthesis of 4-bromo-2(5*H*)-furanones **124a–f** by bromolactonization of 2,3-allenoic acids **123a–f** with NBS/K_2CO_3 in water

Again in 2001, Ma and Wu demonstrated that ethyl 2,3-allenoates **125**, which were the precursors to compounds **123**, could be directly used as substrates of bromolactonization reactions with $CuBr_2$ [94]. In particular, it was found that compounds **125** with different substitution patterns were able to react with 4.0 equiv of $CuBr_2$ in a 3 : 2 mixture of EtOH and water at 80–85 °C for 12 h to give 4-bromo-2(5*H*)-furanones **124** in yields ranging from 40 to 97%. As shown in Scheme 46, this protocol was used for the synthesis of compounds **124g–q** [94].

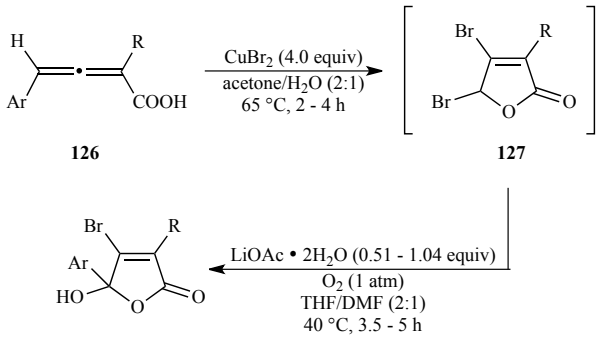


125 **124**

124	R^1	R^2	R^3	Yield%
124g	*n*-Hex	H	*n*-Pr	95
124h	*n*-Hex	H	Bn	97
124i	*i*-Pr	H	Bn	78
124j	*i*-Pr	H	*n*-Pr	68
124k	*i*-Pr	H	Me	86
124l	Me	H	Me	72
124m	Me	H	*n*-Pr	84
124n	Me	Me	Me	68
124o	Me	Me	*n*-Pr	66
124p	*n*-Pr	H	allyl	54
124q	Ph	H	Me	40

Scheme 46. Bromolactonization of ethyl 2,3-allenoates **125** with $CuBr_2$

Finally, in 2004, Ma and coworkers synthesized 3-alkyl-5-aryl-4-bromo-5-hydroxy-2(5*H*)-furanones **128a–d** via sequential $CuBr_2$-mediated bromolactonization-hydroxylation of 4-aryl-2,3-allenoic acids **126a–d** (Scheme 47) [95].



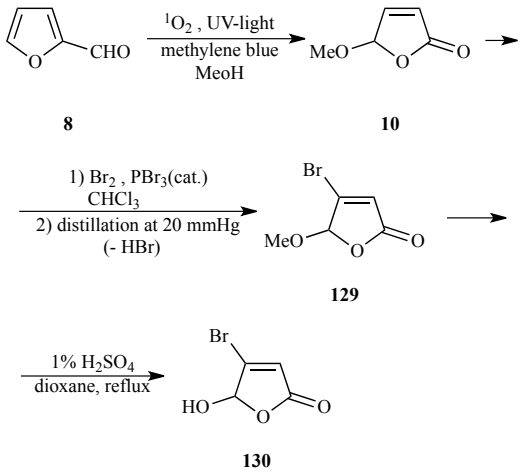
126 **127** **128**

128	Ar	R	equiv of LiOAc • H_2O	Yield%
128a	Ph	Me	1.04	54
128b	Ph	*n*-Pr	0.51	50
128c	Ph	Bn	1.00	49
128d	1-naphthyl	*n*-Pr	1.02	77

Scheme 47. Synthesis of 3-alkyl-5-aryl-4-bromo-5-hydroxy-2(5*H*)-furanones **128a–d**

Specifically, the crude 4-bromo-2(5*H*)-furanones (**127**), which were obtained by $CuBr_2$-mediated bromolactonization of compounds **126a–d** with 4.0 equiv of $CuBr_2$ in a mixture of acetone and water at 65 °C, were hydroxylated with dioxygen (1 atm) in the presence of 0.5–1.0 equiv of $LiOAc{\cdot}2H_2O$ in a mixture of THF and DMF at 40 °C leading to compounds **128a–d** in yields ranging from 49 to 77% [95].

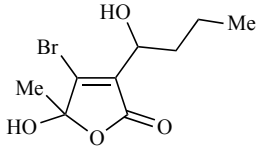
Previously, Lattermann and coworkers had briefly described a synthesis of 4-bromo-5-hydroxy-2(5*H*)-furanone (**130**) from furfural (**8**) without reporting the experimental conditions and yields of the employed reactions [96]. These authors found that furfural (**8**) was converted to 5-methoxy-2(5*H*)-furanone (**10**) by treatment with singlet oxygen using methylene blue as sensitizer in methanol (Scheme 48). Addition of bromine to a $CHCl_3$ solution of **10** in the presence of a catalytic amount of PBr_3, followed by distillation under vacuum of the resulting compound with elimination of HBr gas gave crystalline 4-bromo-5-methoxy-2(5*H*)-furanone (**129**). Finally, treatment of this compound with 1% sulfuric acid in dioxane under reflux produced compound **130** in a good yield (Scheme 48) [96].



8 **10** **129** **130**

Scheme 48. Synthesis of 4-bromo-5-hydroxy-2(5*H*)-furanone (**130**) from furfural (**8**)

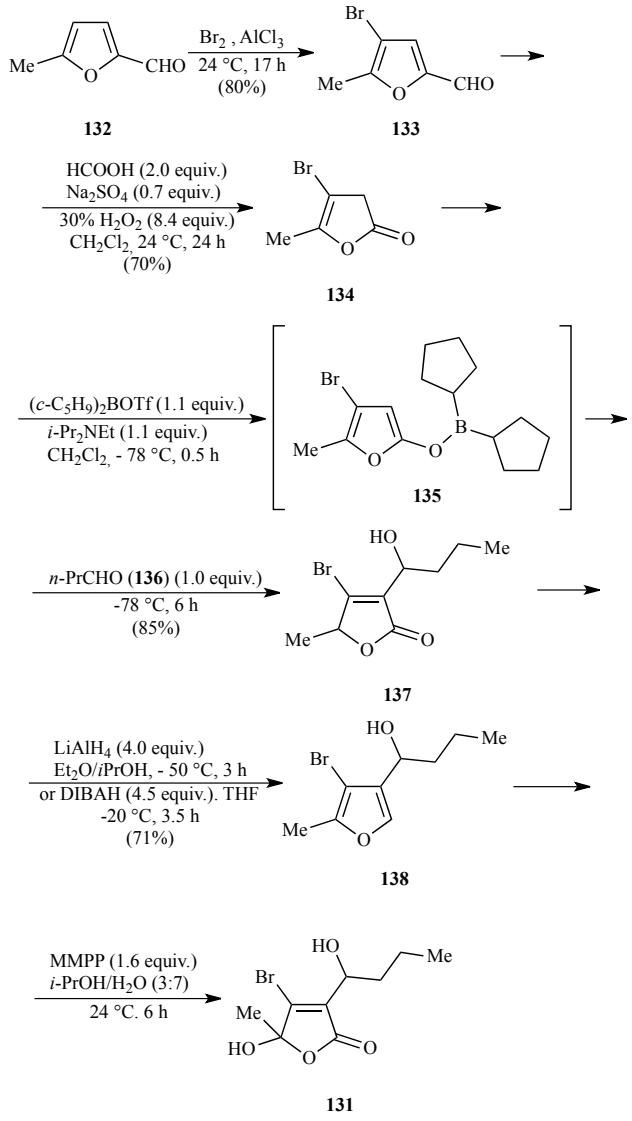
In the past years, studies have also been conducted on the synthesis of naturally-occurring 4-bromo-5-hydroxy-3-(1-hydroxybutyl)-5-methyl-2(5*H*)-furanone (**131**), a metabolite called bromobeckerelide (Figure 11) that was isolated from the marine red alga *Beckerella subcostatum* [95] and was found to exhibit remarkable activity against *Bacillus subtilis.* In fact, 0.5 mg of **131** caused 10 mm diameter of inhibitory zone (in the paper disk method) [97].



131 (bromo beckerelide)

Figure 11. Structure of bromobeckerelide (**131**)

In 1989, Jefford and coworkers accomplished the first total synthesis of **131** in five steps using 5-methylfurfural (**132**) as the starting material (Scheme 49) [98]. In this synthesis, for which the various steps were also briefly described by Jefford in 1993 [99], bromination of **132** under $AlCl_3$ catalysis gave 4-bromo-5-methylfurfural (**133**) in 80% yield.



Scheme 49. Total synthesis of bromobeckerelide (**131**) starting from 5-methylfurfural (**132**)

Bayer-Villiger oxidation of **133** gave lactone **134**, which was converted to a boron furanolate (**135**). The reaction of this crude compound with butanal (**136**) at – 78 °C generated 4-bromo-3-(1-hydroxybutyl)-5-methyl-2(5*H*)-furanone (**137**) in 85% yield. Reduction of **137** with $LiAlH_4$ in a mixture of Et_2O and *i*-PrOH at – 50 °C or with DIBAH in THF at – 20 °C gave furan **138** in 71% yield. Finally, smooth oxidation of **138** with magnesium monoperoxyphthalate (MMPP) in a mixture of *i*-PrOH and water [96] (or with *m*-chloroperbenzoic acid [97]) gave racemic bromobeckerelide (**132**) (Scheme 49) [98].

In 1993, bromobeckerelide (**131**) was synthesized by Katsumura, Ichikawa and Mori by photosensitized oxidation of the trisubstituted α-trialkylsilylfuran **139** (Figure 12), which was obtained by introduction of the required substituents into the furan ring via regioselective lithiation [100].

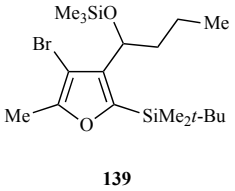
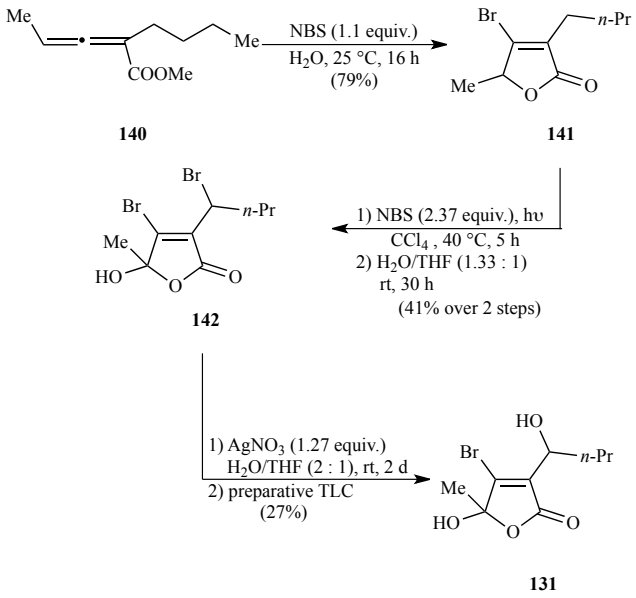


Figure 12. Structure of the trisubstituted α-trialkylsilylfuran **139**

Two years later, de March, Font and coworkers described a new synthesis of bromobeckerelide in which the target compound was obtained via a four-step route involving the use of methyl 2-butyl-2,3-pentadienoate (**140**) as the starting material (Scheme 50) [101].

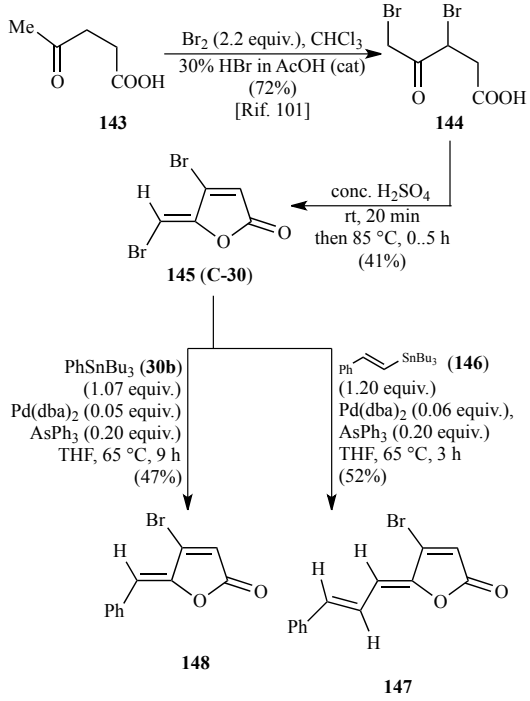


Scheme 50. Synthesis of bromobeckerelide (**131**) starting from methyl 2,3-allenoate **140**

In particular, the light protected reaction of **140** with 1.1 equiv of NBS in water at 25 °C gave 4-bromo-3-butyl-5-methyl-2(5*H*)-furanone (**141**) in 79% yield. A mixture of **141** and 2.37 equiv of NBS in CCl_4 was subsequently irradiated with a 500 W incandescent lamp at 40–45 °C and the resulting reaction mixture was filtered and concentrated and the residue was treated with a mixture

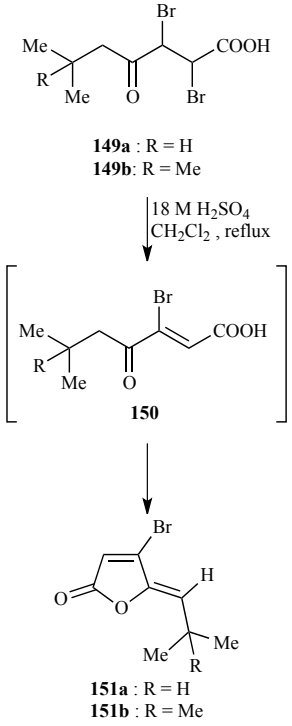
THF and water at room temperature providing pure 4-bromo-3-(1-bromobutyl)-5-hydroxy-5-methyl-2(5*H*)-furanone (**142**) in 41% yield. The final step of this route leading to **131** in 27% yield consisted of a light-protected reaction of **142** with 1.27 equiv of $AgNO_3$ in a mixture of THF and water for 2 d at room temperature, followed by TLC purification of the resulting product (Scheme 50) [101].

In 2004, Brückner and coworkers developed a regioselective route to (*Z*)-4-bromo-5-(*trans*-2-phenyl-2-propenylidene)-2(5*H*)-furanone (**147**) and (*Z*)-4-bromo-5-[1-phenyl(nethylene)]-2(5*H*)-furanone (**149**) that involved the use of levulinic acid (**143**) as the starting material (Scheme 51) [102]. Specifically, 3.5-dibromolevulinic acid (**144**) was prepared by bromination of **143** according to a protocol developed in 1997 by Read and coworkers [103]. The subsequent reaction of **144** with concd. sulfuric acid gave (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (**145**) (C-30) in 41% yield. A $Pd(dba)_2/AsPh_3$-catalyzed Stille-type cross-coupling reaction between **145** and (*E*)-2-phenylethenyltributyltin (**146**) then produced compound **147** in 52% yield. On the other hand, a $Pd(dba)_2/AsPh_3$-catalyzed Stille-type reaction of **145** with phenyltributyltin (**30b**) in THF at 65 °C for 9 h gave compound **148** in 47% yield (Scheme 51) [102]



Scheme 51. Regioselective synthesis of compounds **147** and **148**

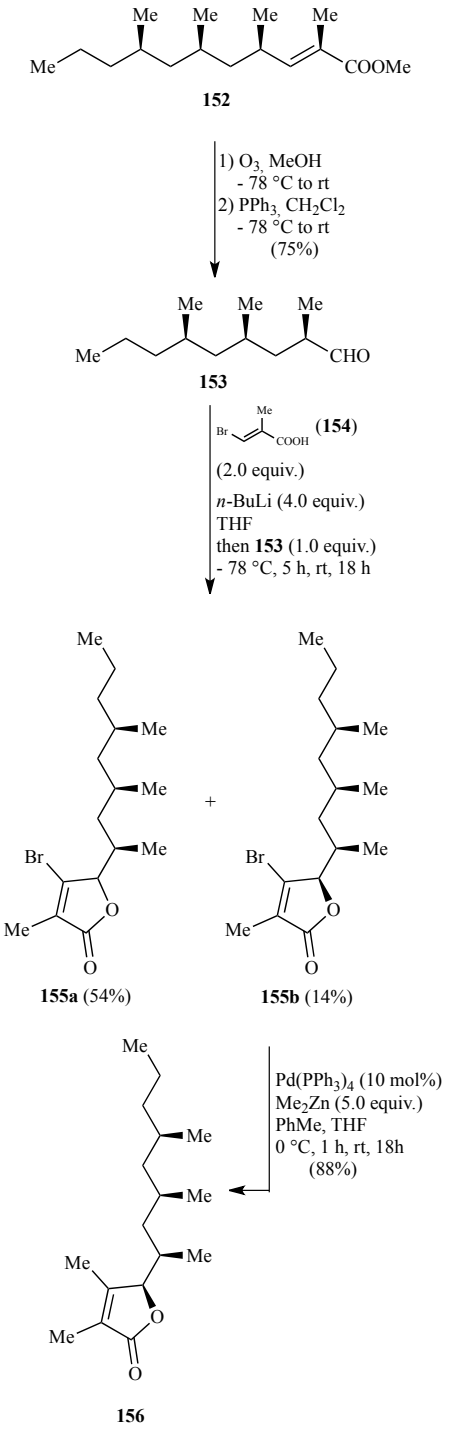
In 2009, Kumar and coworkers reported that (*Z*)-4-bromo-5-(2-methylpropylidene)-2(5*H*)-furanone (**151a**) and (*Z*)-4-bromo-5-(2,2-dimethylpropylidene)-2(5*H*)-furanone (**151b**) were available in 54 and 25% yield, respectively, by acid-promoted cyclization of dibromocarboxylic acids **149a** and **149b**, respectively (Scheme 52) [61]. The cyclization reaction was postulated to proceed via dehydration of the intermediate (*Z*)-3-bromo-4-oxo-2-alkenoic acids (**150**) [61].



Scheme 52. Synthesis of (*Z*)-4-bromo-5-ylidene-2(5*H*)-furanones **151a,b**

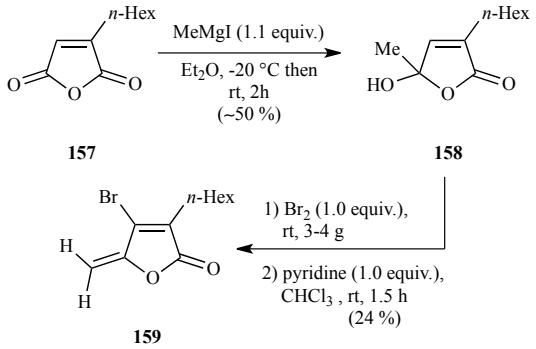
In the same year, Laschat and coworkers described an efficient synthesis of an 80 : 20 diastereomeric mixture of (5*R*)- and (5*S*)-4-bromo-3-methyl-5-[(1*R*,3R,5*R*)-1,3,5-trimethyloctyl]-2(5*H*)-furanone, (**155a**) and (**155b**), respectively [104], starting from the known preengland wax-derived methyl (2*E*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundec-2-enaote (**152**) (Scheme 53) [105]. Compound **152** was submitted to ozonolysis with reductive work-up with PPh_3 according to the method of Herber and Breit [106] providing aldehyde **153** in 75% yield. Compound **153** was then reacted with (*E*)-3-bromomethacrylic acid (**154**) in the presence of *n*-BuLi in THF at –78°C according to the procedure of Williams and coworkers [107] yielding an 80 : 20 diastereomeric mixture of compounds **155a** and **155b**, which were separated by chromatography and isolated in 54% and 14% yield, respectively. Compound **155b** was then used as direct precursor to (+)-capensifuranone (**156**) [104], the enantiomer of a compound that, in 1995, was isolated from *Siphonaria capensis,* a genus of cur-breathing sea snails from the South-East coast of South Africa [108]. In fact, the reaction of **155b** with 5.0 equiv of dimethylzinc in a mixture of toluene and THF at 0 °C in the presence of 10

mol% $Pd(PPh_3)_4$ gave **156** in 88% yield (Scheme 53) [104].



Scheme 53. Synthesis of 4-bromo-2(5*H*)-furanones **155a** and **155b** and (+)-capensifuranone (**156**)

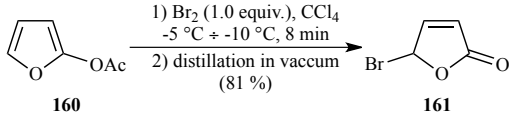
In 2010, De Keersmaecker and coworkers synthesized 4-bromo-3-hexyl-5-methylene-2(5*H*)-furanone (**159**) in 12% yield by using a three-step protocol in which *n*-hexylmaleic anhydride (**157**) was the starting material (Scheme 54) [109]. In particular, the reaction of **157** with 1.1 equiv of methylmagnesium iodide in Et_2O at –20 °C and then at room temperature gave regiospecifically compound **158** in 50% yield. The subsequent addition of bromine to **158** followed by dehydration and dehydrobromination with pyridine in $CHCl_3$ at room temperature gave compound **159** in 24% yield. Notably, this compound was found capable to inhibit *Salmonella typhimurium* strain ATCC14028 biofilm formation by 50% at a concentration of 100-250 μM. In addition, it was also found able to inhibit the QS regulated bioluminescence of *Vibrio harveyi* BB120 with an IC_{50} of 1.357 μM [109].



Scheme 54. Synthesis of 4-bromo-3-hexyl-5-methylene-2(5*H*)-furanone (**159**)

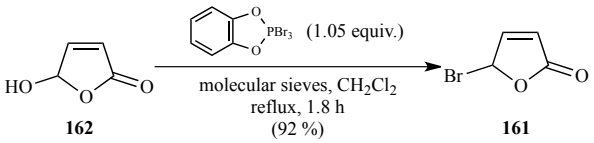
2.3. SYNTHESIS OF 5-BROMO-2(5*H*)-FURANONE DERIVATIVES

In 1952, racemic 5-bromo-2(5*H*)-furanone (**161**) was synthesized in 81% yield by the reaction of 2-acetoxyfuran (**160**) with an equimolar amount of bromine in CCl_4 at –5 ~ –10 °C followed by distillation of the resulting low boiling products (Scheme 55) [110].



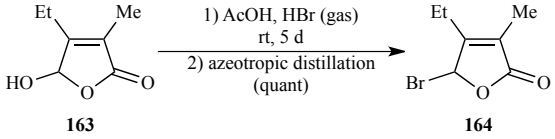
Scheme 55. Synthesis of racemic 5-bromo-2(5*H*)-furanone (**161**) from 2-acetoxyfuran (**160**)

In 1973, compound **161** was prepared in 91% yield by treatment of 5-hydroxy-2(5*H*)-furanone (**162**) with 1.03 equiv of pyrocatechol phosphorous tribromide in CH_2Cl_2 under reflux for 1.8 h in the presence of molecular sieves (Scheme 56) [111].



Scheme 56. Synthesis of racemic 5-bromo-2(5*H*)-furanone (**161**) from 5-hydroxy-2(5*H*)-furanone (**162**)

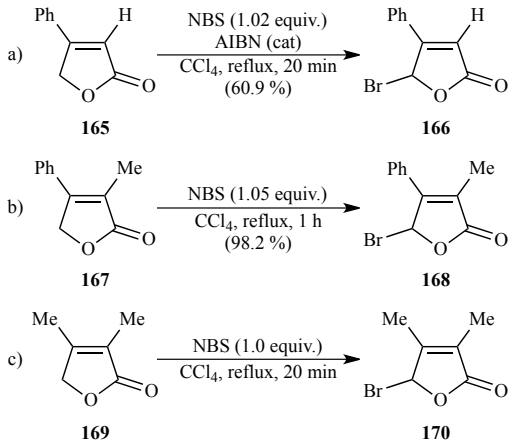
On the other hand, 5-bromo-4-ethyl-3-methyl-2(5*H*)-furanone (**164**) was obtained in quantitative yield by treatment of 4-ethyl-3-methyl-5-hydroxy-2(5*H*)-furanone (**163**) with glacial acetic acid containing HBr gas (40% by weight) for 5 d at room temperature (Scheme 57) [111].



163 **164**

Scheme 57. Synthesis of 5-bromo-4-ethyl-3-methyl-2(5*H*)-furanone (**164**)

In 1965, 5-bromo-4-phenyl-2(5*H*)-furanone (**166**) and 5-bromo-3-methyl-4-phenyl-2(5*H*)-furanone (**168**) were synthesized in 60.9% and 98.2% yield, respectively, by treatment of the corresponding 5-unsubstituted 2(5*H*)-furanones **165** and **167**, respectively, with 1.02–1.05 equiv of NBS in CCl_4 under reflux (Scheme 58, eqs. a and b) [112]. The bromination reaction of **165**, unlike that of **167**, was carried out in the presence of a catalytic amount of AIBN. It was also described that the reaction of 3,4-dimethyl-2(5*H*)-furanone (**169**) with 1.0 equiv of NBS in CCl_4 under reflux gave 5-bromo-3,4-dimethyl-2(5*H*)-furanone (**170**) (Scheme 58, eq. c) [112]. However, unfortunately, the yield of this reaction was not reported.



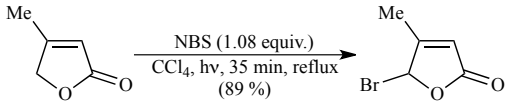
165 **166**

167 **168**

169 **170**

Scheme 58. Synthesis of 5-bromo-2(5*H*)-furanones **166**, **168** and **170**

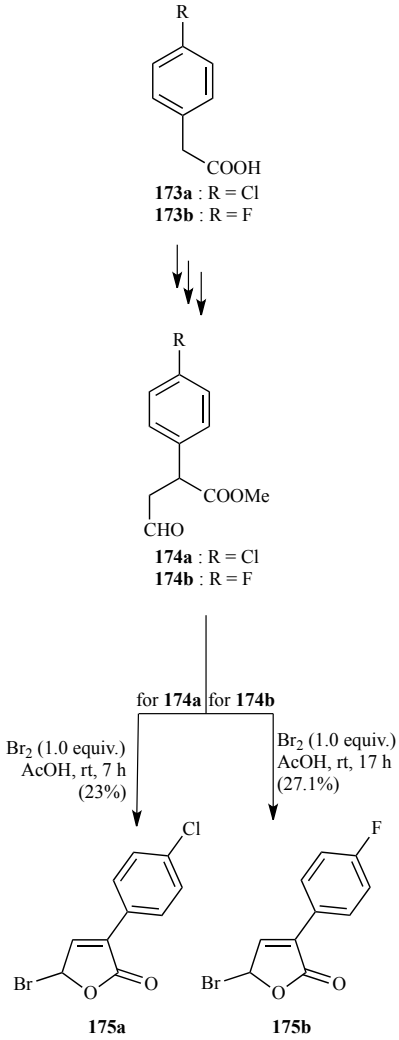
In 1976, 5-bromo-4-methyl-2(5*H*)-furanone (**172**) was prepared in 89% yield by reacting 4-methyl-2(5*H*)-furanone (**171**) with 1.08 equiv of NBS in CCl_4 under reflux and irradiation with a 100 W lamp (Scheme 59) [113].



171 **172**

Scheme 59. Synthesis of 5-bromo-4-methyl-2(5*H*)-furanone (**172**)

Two years later, Pettit and coworkers described that methyl 2-aryl-4-oxobutanoates **174a** and **174b**, which were prepared via a multi-step sequence from the corresponding arylacetic acids **173a** and **173b** respectively, underwent reaction with an equimolar amount of bromine in glacial acetic acid to produce 3-aryl-5-bromo-2(5*H*)-furanones **175a** and **175b** in 23% and 27.1% yield, respectively (Scheme 60) [114].

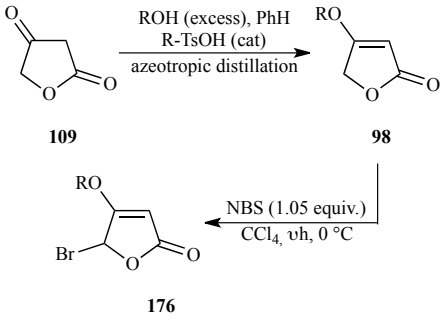


175a **175b**

Scheme 60. Synthesis of 3-aryl-5-bromo-2(5H)-furanones **175a** and **175b**

In 1989, Martin and coworkers described the synthesis of 4-alkoxy-2(5H)-furanones **98a–e** from β-tetronic acid (**109**) and their conversion to 4-alkoxy-5-bromo-2(5*H*)-furanones **176a–e** (Scheme 61) [115]. In particular, they

found that the reaction of **109** with 3.0 equiv of alcohols in the presence of a catalytic amount of *p*-TsOH, followed by removal of water by azeotropic distillation with benzene gave compounds **98** in yields ranging from 64 to 91%. Subsequent bromination of compounds **98a–e** with 1.05 equiv of NBS in CCl_4 at 0 °C under irradiation with a mercury high pressure lamp led to compounds **176a–e** in yields ranging from 25 to 83% (Scheme 61) [115].



176	R	Yield% of **98**	Yield% of **176**
176a	Me	81[(a)]	62
176b	CH_2=$CH(CH_2)_2$	91	25
176c	CH_2=$CHCH_2$	81	31
176d	$Me_3SiCH_2CH_2$	64	83
176e	$Me(CH_2)_4$	91	72

Scheme 61. Synthesis of 4-alkoxy-5-bromo-2(5*H*)-furanones **176a–e**

Finally, in concluding this subsection we wish to point out that, at the best of our knowledge, bioactivity data of 2(5*H*)-furanones featuring only one bromine atom on the heterocyclic ring have not been reported in the literature so far.

3. SYNTHESIS AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES WITH TWO BROMINE ATOMS ON THE HETEROCYCLIC RING

Mucobromic acid (**1**) is a dibrominated compound which can exist in an open-chain and in a ring form called 3,4-dibromo-5-hydroxy-2(5*H*)-furanone (Figure 13).

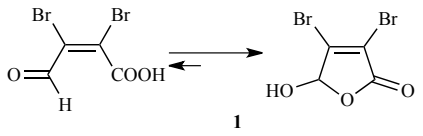
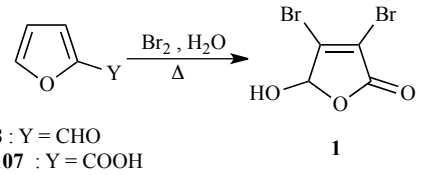


Figure 13. Chemical structure of mucobromic acid (**1**)

It is currently commercially available, but in the past years it was prepared by the reaction of furfural (**8**) [116] or 2-furoic acid (**107**) [117] with bromine in boiling water (Scheme 62).



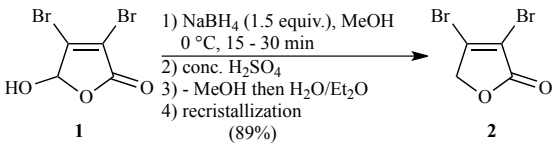
Scheme 62. Synthesis of mucobromic acid (**1**) from furfural (**8**) or 2-furoic acid (**107**)

In 1976, compound **1** was identified as a powerful inhibitor of tumoral and pancreatic *L*-asparagine synthetases [118] and, in 1994, it was found to be a potent bacterial mutagen with mean molar mutagenicity in the *Salmonella typhimurium* (TA100-S9) assay of 5.54 revertants/mmol [119].

In 2009, Marcos and coworkers [120] reported that **1**, which is a by product of water disinfection especially in surface water with high amount of bromide [121], is genetoxic leading to high levels of DNA breaks. More recently, Yang and coworkers found that **1** significantly inhibits the growth of two marine diatoms *Cylinthroteca* sp. and *Nitzschia closterium* and that the effect of this compound depends on the dose and diatoms species [120]. These authors further demonstrated that **1** is a quorum sensing inhibitor against the formation of *Cylinthroteca* sp. biofilms [122].

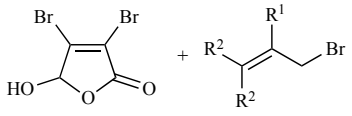
3,4-Dibromo-2(5*H*)-furanone (**2**) is another dibrominated compound the synthesis of which in the past years has been the subject of significant attention [43,53,23–126]. However, the synthetic procedures which date back to before the 1960s [124,125] are low yielding and involve the use of commercially unavailable starting materials and/or toxic reagents. Nevertheless, as already mentioned in subsection 2.1 of this review, in 2002, Zhang and coworkers synthesized **2** in 57% yield by reduction of mucobromic acid (**1**) with sodium triacetoxyborohydride in $CHCl_3$ followed by addition of acetic acid (Scheme 14) [53]. More recently, we prepared **2** in 89% yield on a multigram scale by treatment of **1** with 1.5 equiv of $NaBH_4$ in methanol followed by addition of 1.0 equiv of concd. sulfuric acid (Scheme 63) [126].

Lalonde and Leo had previously found that in the *Salmonella typhimurium* (TA100) assay compound **2** had a mean molar mutagenicity value of 1.18 revertants/nmol, lower than that of mucobromic acid (**1**) (5.54 revertants/nmol) [119].



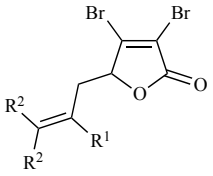
Scheme 63. Synthesis of 3,4-dibromo-2(5*H*)-furanone (**2**) via reduction of mucobromic acid (**1**) with $NaBH_4$

In 2003, 5-allyl-3,4-dibromo-2(5*H*)-furanones **178a–c** were synthesized in good yields by Zhang and coworkers via indium-mediated reaction of mucobromic acid (**1**) with 1.2 equiv of allyl bromides **177a–c** in a 1 : 1 mixture of THF and water in the presence of 10 mol% NH_4Cl (Scheme 64) [127].



1 (1.0 equiv.) **177**

In (1.2 equiv.)
NH_4Cl (10 mo%)
THF/H_2O (1:1)
0 °C to rt, 16 - 24 h



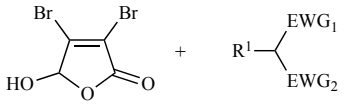
178

178	R^1	R^2	Yileld%
178a	H	H	70
178b	COOMe	H	74
178c	Me	H	61

Scheme 64. Synthesis of 5-allyl-3,4-dibromo-2(5*H*)-furanones **178a–c**

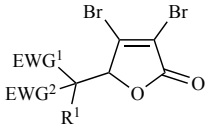
Interestingly, compounds **178a** and **178c** were also prepared in 75% and 41% yield, respectively, by treatment of **1** with the required allyl bromides in the presence of 10 mol% NH_4Cl and 1.2 equiv of tin, a metal much less expensive than indium, in a 1 : 1 mixture of THF and water [127].

Two years later, Zhang and coworkers described that the synthesis of 5-substituted-3,4-dibromo-2(5*H*)-furanones of general formula **180** could be accomplished in good yields by the reaction of **1** with equimolar amounts of active methylene compounds **179** and 5 mol% $In(OAc)_3$ in toluene under reflux, with water separation by a Dean-Stark apparatus (Scheme 65) [128]. Various Lewis acids different from $In(OAc)_3$ were tested, but the latter compound turned out to be the most efficient catalyst [128].



1 (1.0 equiv.) **179** (1.0 equiv.)

$In(OAc)_3$ (5 mol%)
PhMe, reflux (- H_2O)

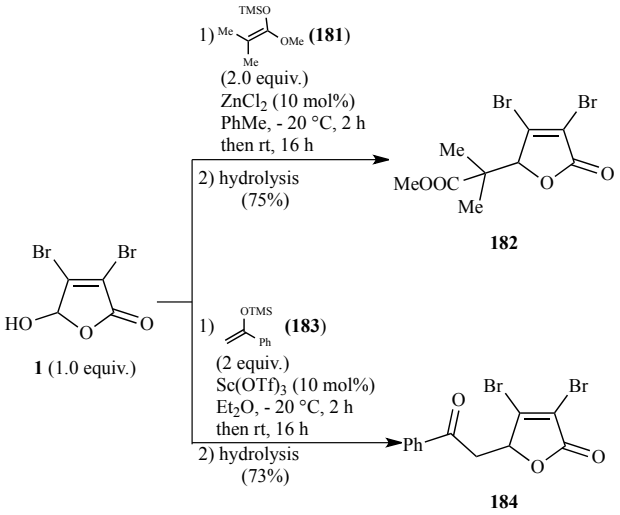


180

180	EWG^1	EWG^2	R^1	Yield%
180a	COOEt	COOEt	H	89
180b	COO*i*-Pr	COO*i*-Pr	H	91
180c	COOEt	COOBn	H	89
180d	COOEt	COOEt	Me	78
180e	H	H	COOH	60
180g	COO*n*-Oct	CN	H	69

Scheme 65. Synthesis of compounds **180a–f**

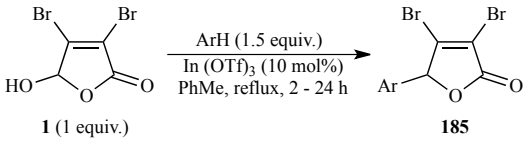
Zhang and coworkers also reported that the Mukaiyama aldol reaction of **1** with methyl trimethylsilyl dimethylketeneacetal (**181**) in toluene at –20 °C for 2 h and then at room temperature for 16 h in the presence of 10 mol% $ZnCl_2$, followed by hydrolysis gave compound **182** in 75% yield (Scheme 66) [129].



Scheme 66. Synthesis of compounds **182** and **184**

Moreover, they found that an analogous $Sc(OTf)_3$-catalyzed Mukaiyama aldol reaction between **1** and 1-phenyl-1-(trimethylsilyloxy)ethylene (**183**) in Et_2O at –20 °C for 2 h and then at room temperature for 16 h followed by hydrolysis produced 5-(benzoylmethyl)-3,4-dibromo-2(5*H*)-furanone (**184**) in 73% yield [129].

In 2007, in continuation of their studies on the selective synthesis of 5-substituted 3,4-dihalo-2(5*H*)-furanones, Zhang and coworkers synthesized 5-aryl-3,4-dibromo-2(5*H*)-furanones **185** via $In(OTf)_3$-catalyzed Friedel-Crafts-type reaction between 1.0 equiv of **1** with 1.5 equiv of electron-rich arenes in toluene under reflux.[130] This protocol allowed the synthesis of compound **185a**, **185b** and **185c** in 71%, 82% and 45% yield, respectively (Scheme 67) [130].

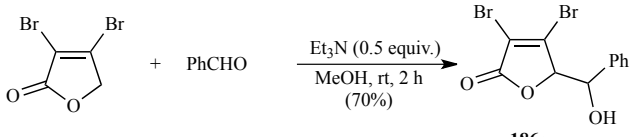


1 (1 equiv.) **185**

185	Ar	Yield%
185a	2,3,4-$(MeO)_3C_6H_2$	71
185b	2,3,6-$(MeO)_3C_6H_2$	82
185c	2,4,5-$(MeO)_3C_6H_2$	45

Scheme 67. Synthesis of 5-aryl-3,4-dibromo-2(5*H*)-furanones **185a–c**

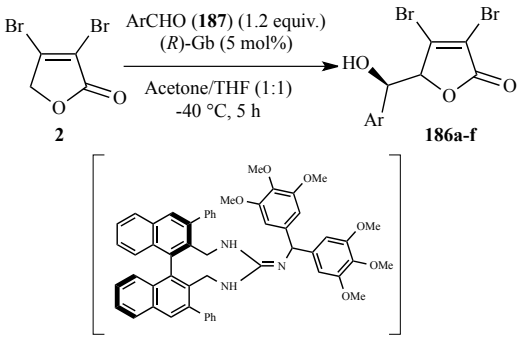
The same research group described that a 5 : 1 *syn/anti* steroisomeric mixture of 3,4-dibromo-5-[hydroxy(phenyl)methyl]-2(5*H*)-furanone (**187a**) was available in 87% yield by direct vinylogous aldol reaction of 3,4-dibromo-2(5*H*)-furanone (**2**) with benzaldehyde (**127**) in methanol at room temperature in the presence of 0.5 equiv of Et_3N (Scheme 68) [131].



2 (1.0 equiv.) **27** (1.1 equiv.) **186a** (*syn/anti* = 5 :1)

Scheme 68. Synthesis of 3,4-dibromo-5-[hydroxy(phenyl)methyl]-2(5*H*)-furanone (**186a**)

In 2010, Terada and coworkers reported the first enantioselective direct vinylogous reaction of **2** with aryl aldehydes [42]. The method, which involved the reaction of **2** with 1.2 equiv of aryl aldehydes in a 1 : 1 mixture of acetone and THF at –40 °C in the presence of 5 mol% the axially chiral guanidine base **(*R*)-Gb**, enabled efficient access to optically active compounds **186a–f** (Scheme 69) [42].



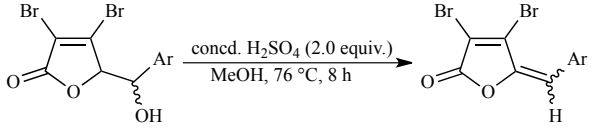
2 **186a-f**

186	Ar	Yield%	d.r. (*syn/anti*)	ee% *syn*	ee% *anti*
186a	ArPh	77	90:10	98	84
186b	2-MeC_6H_4	82	91:9	97	60
186c	4-MeC_6H_4	95	86:14	99	80
186d	4-$MeOC_6H_4$	58	87:13	97	80
186e	1-naphthyl	74	94:6	96	74
186f	2-furyl	79	85:15	97	88

Scheme 69. Enantioselective synthesis of compounds **186a–f**

These 3,4-dibromo-5-[hydroxy(phenyl)methyl]-2(5*H*)-furanones were obtained in high diastereoselectivity with excellent enantioselectivity for the major *syn*-stereoisomers [42].

In 2012, W.-M. Chen and coworkers synthesized stereoisomeric mixtures of 5-(arylmethylene)-3,4-dibromo-2(5*H*)-furanones **188a** and **188b** in 60% and 61% yield, respectively, by treatment of racemic *syn/anti* mixtures of compounds **186a** and **186b** with concd. sulfuric acid in methanol at 76 °C for 8 h (Scheme 70) [132].

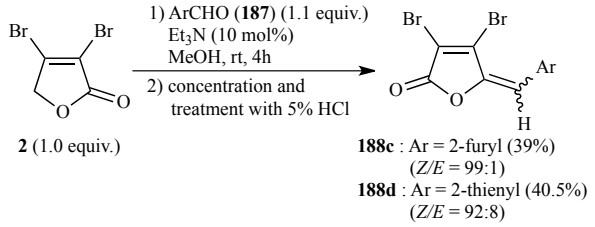


186a : Ar = Ph (*syn/anti* = 3:97)
186g : Ar = 4-$(NO_2)C_6H_4$ (*syn/anti* = 23 : 77)

188a : 60% (*Z/E* = 10 : 90)
188b : 61% (*Z/E* = 82 : 18)

Scheme 70. Synthesis of 5-(arylmethylene)-3,4-dibromo-2(5*H*)-furanones **188a** and **188b**

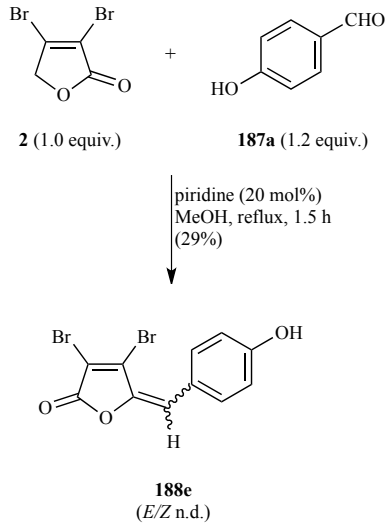
These authors also synthesized 3,4-dibromo-5-[(2-furyl)methylene]-2(5*H*)-furanone (**188c**) and 3,4-dibromo-5-[(2-thienyl)methylene]-2(5*H*)-furanone (**188d**) in 39 and 40.5% yield, respectively, by treatment of **2** with 1.1 equiv of the required heteroaryl aldehydes in methanol at room temperature in the presence of 10 mol% Et_3N, concentration of the resulting reaction mixtures and washing the residues with 5% HCl (Scheme 71) [132].



Scheme 71. Synthesis of compounds **188c** and **188d** from 3,4-dibromo-2(5*H*)-furanone (**2**)

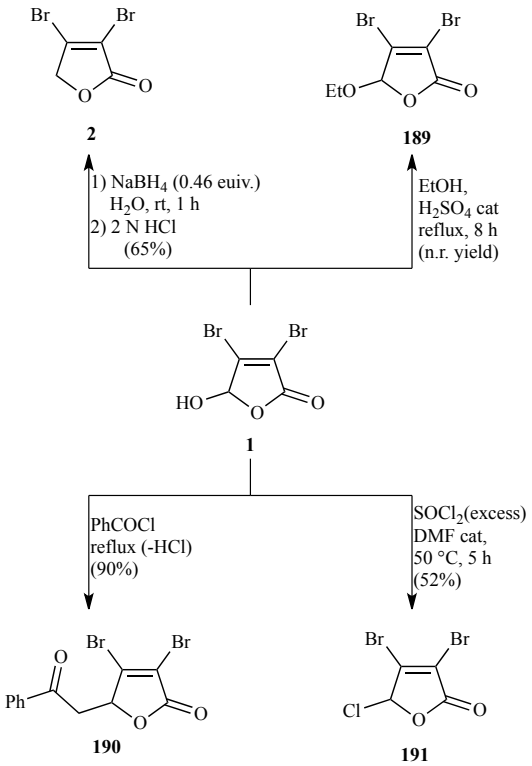
They finally synthesized 3,4-dibromo-5-(4-hydroxyphenyl)methylene]-2(5*H*)-furanone (**188e**) in 29% yield by the reaction of **2** with 1.2 equiv of 4-hydroxybenzaldehyde (**187**) and 20 mol% piperidine in methanol under reflux for 1.5 h under nitrogen atmosphere and concentration *in vacuo* of the resulting reaction mixture (Scheme 72) [132].

Notably, compounds **188a** and **188c** were found capable to exhibit remarkable effect of biofilm formation inhibition on *Pseudomonas aeruginosa* [130], a Gram-negative opportunistic pathogenic bacterium which colonizes most wounds forming biofilms making ineffective the clearance by immune defensive systems and antibiotherapy, thus causing wounds unhealed [133–135].



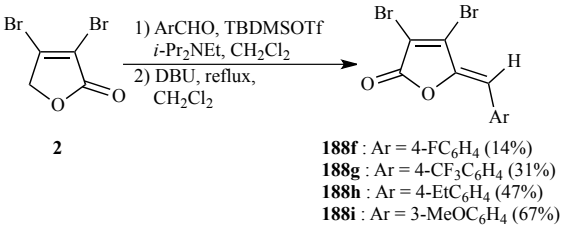
Scheme 72. Synthesis of compound **188e**

In 2011, Ramachandran and Sreekumar carried out the synthesis of the 3,4-dibromo-2(5*H*)-furanone derivatives **2**, **189**, **190** and **191** starting from mucobromic acid (**1**) via the one-step reactions depicted in Scheme 73 [136]. They also tested the antibacterial activity of these substances against *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and found that all synthesized compounds showed comparable activity against the Gram-negative bacteria *E. coli*, *P. vulgaris*, and *P. aeruginosa* [136].



Scheme 73. Synthesis of compounds **2, 189**, **190** and **191** from mucobromic acid (**1**)

Finally, in 2015, Barbosa and coworkers synthesized (*Z*)-5-(arylmethylene)-3,4-dibromo-2(5*H*)-furanones **188f–i** and evaluated the photosynthesis inhibition properties of these substances [78]. As outlined in Scheme 74, compounds **188f–i** were obtained in modest to satisfactory yields via aldol condensation of **2** with the required aryl aldehydes in CH_2Cl_2 solution in the presence of TBDMSOTf and *i*-Pr_2NEt.



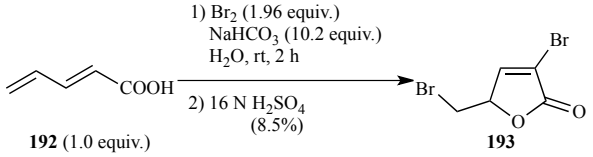
Scheme 74. Synthesis of (*Z*)-5-(arylmethylene)-3,4-dibromo-2(5*H*)-furanones **188f–i**

The resulting adducts, which were not isolated, were treated with DBU in CH_2Cl_2 under reflux providing compounds **188f**, **188g**, **188h** and **188i** in 14, 31, 47, and 67% yield, respectively. Remarkably, among these compounds, **188g** bearing the strong electron-withdrawing CF_3 group showed the highest photosynthesis inhibitory

activity and **188f** exhibited greater activity than **188h** in uncoupled electron flux [78].

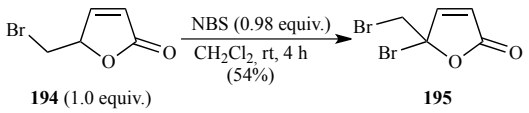
4. SYNTHESIS AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES FEATURING ONE BROMINE ATOM ON THE HETEROCYCLIC RING AND MONOBROMINATED SUBSTITUENTS

In 1982, 3-bromo-5-bromomethyl-2(5*H*)-furanone (**193)** was prepared in 8.5% yield by Font and coworkers via addition of 1.96 equiv of bromine to a stirred solution of 1.0 equiv of (*E*)-2,4-pentadienoic acid (**192**) and 10.2 equiv of $NaHCO_3$ in water at room temperature, followed by addition of 16 N sulfuric acid (to pH 2) to the resulting reaction mixture (Scheme 75) [137].



Scheme 75. Synthesis of 3-bromo-5-bromomethyl-2(5*H*)-furanone (**193**)

The same authors also synthesized 5-bromo-5-bromomethyl-2(5*H*)-furanone (**195**) in 54% yield by treatment of 5-bromomethyl-2(5*H*)-furanone **(194**) with NBS in CH_2Cl_2 at room temperature for 4 h (Scheme 76) [137].



Scheme 76. Synthesis of 5-bromo-5-bromomethyl-2(5*H*)-furanone (**195**)

In 1979, Beechan and Sims concisely described the first total synthesis of (*Z*)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (**196**) (Figure 14) [138], a naturally occurring fimbrolide isolated from the marine red alga *Delisea pulchra* [139–141] and *Delisea elegans* [142].

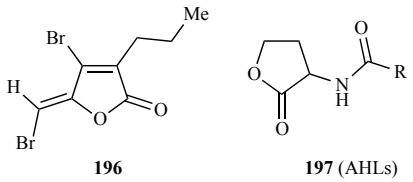
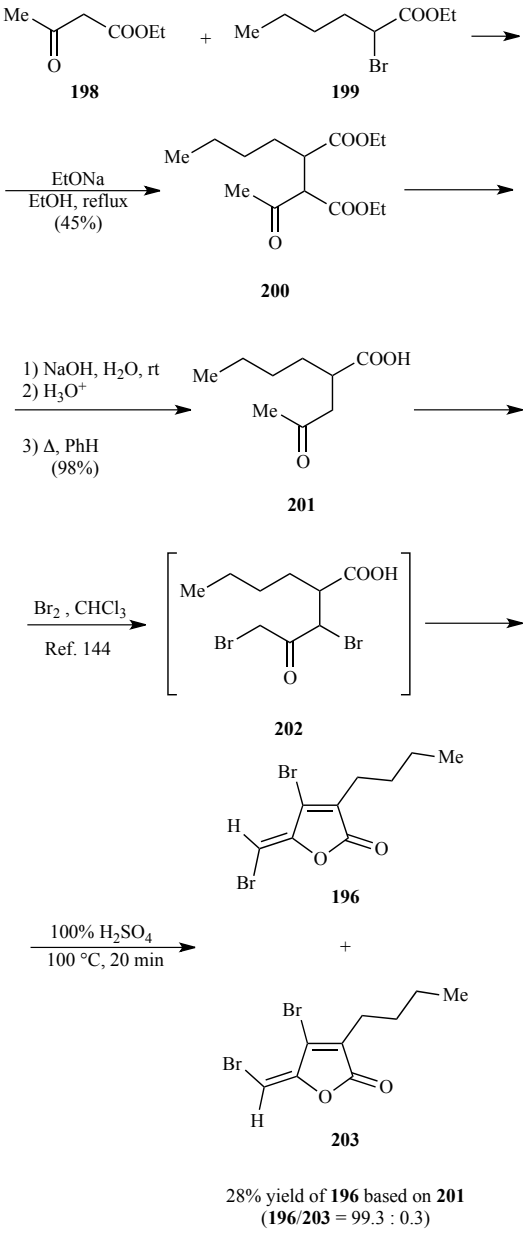


Figure 14. Structures of compounds **196** and AHLs

The synthesis of this natural compound, which has structural similarity to *N*-acyl homoserine lactones (AHLs) (Figure12), the most common quorum sensing (QS) signals in Gram-negative bacteria [143], commenced with the EtONa-mediated alkylation of ethyl acetoacetate (**198**) with commercially available ethyl 2-bromohexanoate (**199**) in EtOH under reflux (Scheme 77).

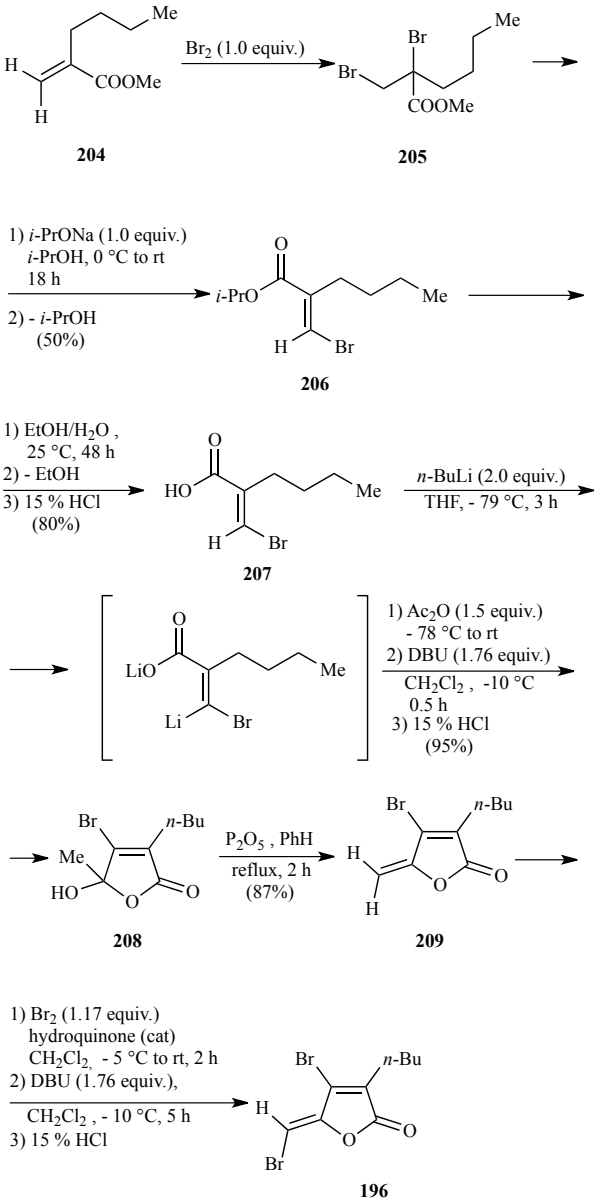


Scheme 77. First total synthesis of natural furanone **196**

The reaction gave compound **200** in 45% yield, which was converted to γ-ketoacid **201** by hydrolysis followed by decarboxylation of the resulting unstable dicarboxylic acid. Bromination of **201** in $CHCl_3$ solution according to the literature [144] gave crude dibromocarboxylic acid **202**, which on treatment with 40% sulfuric acid at 100 °C provided compound **196** in 28% yield based on **201**. As shown in Scheme 77, compound **196** was obtained together with a small amount of (*E*)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (**203**) [138], a natural product

which was isolated from *D. pulchra* [57,139] and *D. elegans* [142].

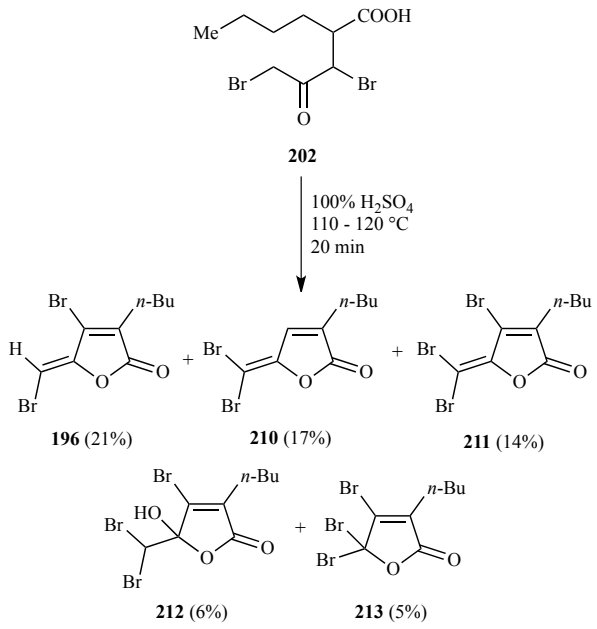
Another multi-step total synthesis of compound **196** was described in 1985 by Caine and Ukuchukvu (Scheme 78) [148]. It began with the addition of bromine to methyl 2-butylpropenoate (**204**).



Scheme 78. Total synthesis of compound **196** starting from ester **204**

The resulting compound was dehydrobrominated by treatment with *i*-PrONa in *i*-PrOH affording compound **206** in 50% yield. The latter was converted in high yield to the corresponding carboxylic acid **207** by treatment with aqueous EtOH at 25 °C for 48 h and removal of EtOH followed by acidification with 15% HCl. Compound **207** was then reacted with 2 equiv of *n*-BuLi in THF at –78 °C and the resulting organolithium derivative was treated with 1.5 equiv of Ac_2O in THF at –78 °C. Acidification of the reaction mixture with 15% HCl gave 2(5*H*)-furanone **208** in 45% yield, which was reacted with a mixture of P_2O_5 and benzene under reflux providing 4-bromo-3-butyl-5-methylene-2(5*H*)-furanone (**209**) in 87% yield. Finally, addition of bromine to **209** and dehydration of the resulting adduct with DBU in CH_2Cl_2 at –10 °C, followed by acidification with 15% HCl, gave the required compound **196** in 95% yield and 13.4% overall yield based on ester **204** (Scheme 78) [148].

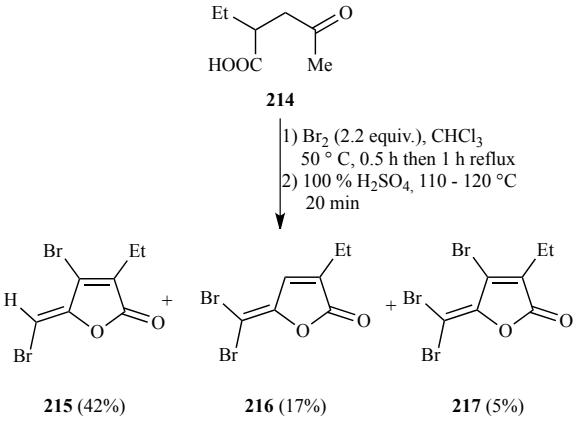
In 1997, Read and coworkers reinvestigated the cyclization reaction of crude dibromocarboxylic acid **202** with 100% sulfuric acid and found that the reaction at 110–120 °C for 20 min produced five products, compound **196** (which was erroneously called *E*-configured), 3-butyl-5-(dibromomethylene)-2(5*H*)-furanone (**210**), 4-bromo-3-butyl-5-(dibromomethylene)-2(5*H*)-furanone (**211**), 5-(bromomethyl)-3-butyl-4,5-dibromo-2(5*H*)-furanone (**212**), and 4-bromo-3-butyl-5-(dibromomethyl)-2(5*H*)-furanone (**213**) in 21%, 17%, 14%, 6%, and 5% yield, respectively (Scheme 79) [103].



Scheme 79. Products obtained by cyclization of crude **202** with 100% sulfuric acid

Read and coworkers also reported that the reaction of 2-ethyl-4-oxopentanoic acid (**214**) with 2.2 equiv of bromine in $CHCl_3$ at 50 °C, followed by treatment of the resulting crude dibromoacid with 100% sulfuric acid at 110–120 °C for 20 min gave a mixture of (Z)-4-bromo-5-(bromomethylene)-3-ethyl-2(5*H*)-furanone (**215**), 3-ethyl-5-(dibromomethylene)-2(5*H*)-furanone (**216**) and 4-bromo-

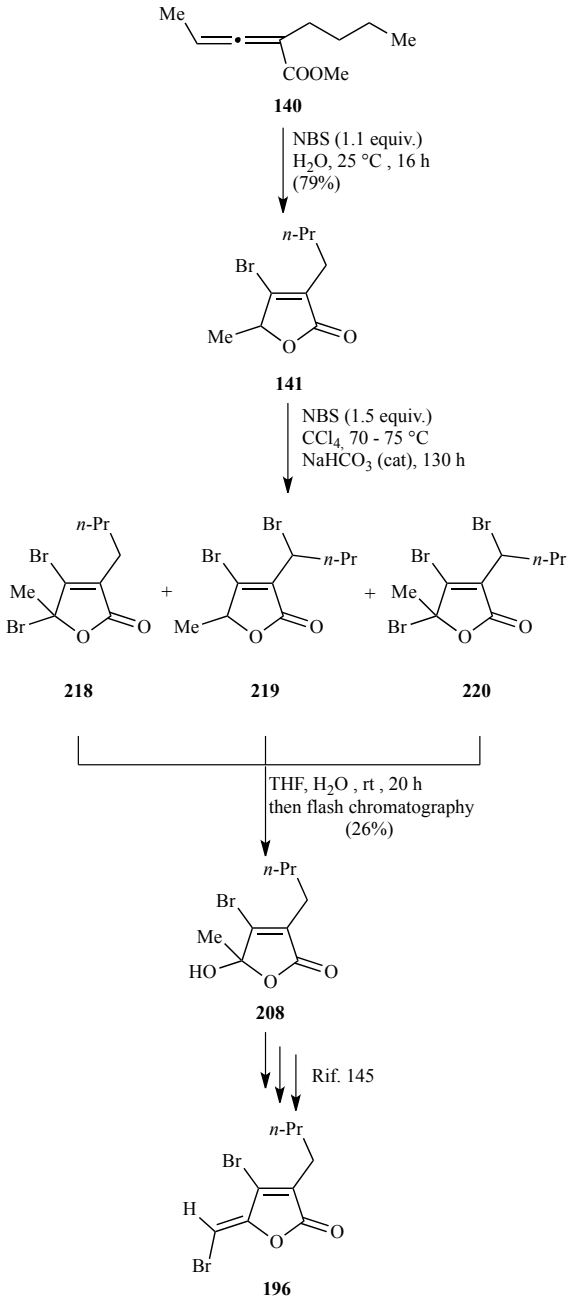
5-(dibromomethylene)-3-ethyl-2(5*H*)-furanone (**217**) from which compounds **215**, **216** and **217** were isolated in 42%, 17% and 5% yield, respectively (Scheme 80) [103].



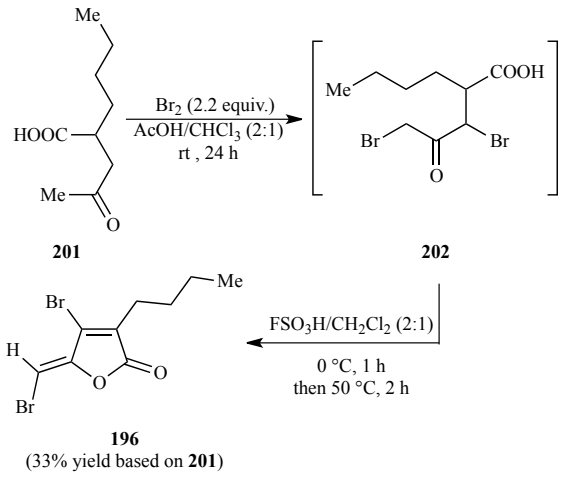
Scheme 80. Synthesis of compounds **215–217**

In 1995 by de March, Font and coworkers described a formal total synthesis of (*Z*)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (**196**) via a route involving the use of 4-bromo-3-butyl-5-methyl-2(5*H*)-furanone (**141**) as a key intermediate (Scheme 81) [101]. Compound **141**, which was prepared in 79% yield by bromination of methyl 2-butyl-2,3-pentadienoate (**140**) with 1.1 equiv of NBS in water at room temperature, was t reacted with 1.5 equiv of NBS in CCl_4 at 70–75 °C for 130 h in the presence of a catalytic amount of $NaHCO_3$ providing a mixture of compounds **141**, **218**, **219** and **220** in 9%, 31%, 19% and 17% yield, respectively. Hydrolysis of this mixture followed by purification of the resulting crude products by flash chromatography allowed to isolate 4-bromo-3-butyl-5-hydroxy-5-methyl-2(5*H*)-furanone (**208**) in 26% yield. According to the literature [145] compound **208** is an advanced precursor to fimbrolide **196**.

In 2009, Janda and coworkers described a further synthesis of compound **196** that involved a new interesting protocol for the cyclization reaction of dibromocarboxylic acid **202** (Scheme 82) [146]. In fact, crude dibromocarboxylic acid **202**, which was obtained by reacting ketoacid **201** with 2.2 equiv of bromine on a 2 : 1 mixture of AcOH and $CHCl_3$, was reacted with fluorosulfonic acid in CH_2Cl_2 at 0 °C for 1 h and then at 50 °C for 2 h providing **196** in 33% yield based on **201**. Notably, this cyclization protocol allowed to overcome the many problems related to the execution of the cyclization reaction making use of sulfuric acid at 110–120 °C, *i.e.* low yields due to both polymerization and decomposition and possible explosion of the reaction content when the reaction is carried out upon scale-up [146].



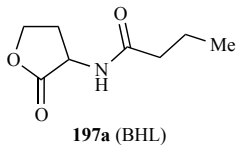
Scheme 81. Formal total synthesis of fimbrolide **196**



Scheme 82. Synthesis of natural fimbrolide **196** via FSO_3H-mediated cyclization of crude compound **202**

With regard to the bioactivity of 2(5*H*)-furanone derivatives featuring one bromine atom on the heterocyclic ring and mononobrominated substituents, it should be noted that since the late 1990s several studies have been conducted on the biological properties of (*Z*)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (**196**). In 1998, Kjelleberg and coworkers, in the context of an investigation on the role of putative extracellular signal molecules in the regulation of the carbon starvation response of marine *Vibrio* sp. strain S14, discovered that compound **196** inhibits the synthesis of proteins specifically induced upon carbon starvation [147].

In 2000, Givskov and coworkers found that **196** inhibits the swarmimg motility of the Gram-negative bacterium *Serratia liquefaciens* MG1 and demonstrated that this natural compound controls transcription of the QS regulated gene *swrA* in competition with the cognate signal molecule *N*-butanoyl-*L*-homoserine lactone (**197a**, BHL) (Figure 15) [148].



197a (BHL)

Figure 15. Structure of *N*-butanoyl-*L*-homoserine lactone (BHL)

In 2001, Wood and coworkers found that **196** inhibits swarming motility of the Gram-negative bacterium *Escherichia coli* at 13 μg/cm^2, but does not inhibit its growth rate at 13–52 μg/cm^2 or from 20 to 100 μg/mL [149]. In addition, they demonstrated that **196** is capable to inhibit the biofilm formation of *E. coli* decreasing the thickness of the biofilm by 55% at 60 μg/mL and descreasing the percentage of live cells by 87%.

In 2002, the same research group reported that **196** inhibits both the growth of the Gram-positive non-pathogenic bacterium *Bacillus subtilis* and its swarming motility in a concentration dependent way.[150] This research group also found that **196** is able to inhibit the biofilm formation of *B. subtilis* at 40 μg/mL decreasing the biofilm formation by 25% and reducing the percentage of live cells by 63 % [150]. These results were of significant interest since biofilm formation of *B. subtilis*, which is apparently dependent on LuxS- (*S*-ribosylhomocysteine lyase)-based QS by autoinducer 2 (AI-2), represents a continuous hygienic problem in the dairy industry and can lead to serious economic losses [151].

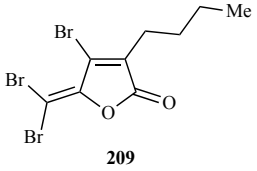
In 2004, in order to discover the mechanism of inhibition of the growth, swarming and biofilm formation in Gram-positive bacteria, Wood and coworkers investigated the gene expression profiles of *B. subtilis* grown with and without 5 μg/mL of compound **196** and found that this sublethal concentration led to the induction of specific genes involved in stress responses, fatty acid biosynthesis, lichenan degradation, transport and metabolism [152].

In the same year, Ren and Wood demonstrated that **196** is able to inhibit the mild steel corrosion induced by the Gram-positive sulphate-reducing bacterium *Desulfotomaculum orientis* [153]. In particular, they found that 20 and 40 μg/mL of **196** inhibited 58% and 96% of the *D. orientis* growth, respectively [153].

In 1998, Stintzi and coworkers showed that the siderophore synthesis in *Pseudomonas aeruginosa* may be regulated by QS [154] and, in 2005, Wood and coworkers evidenced the link between QS and siderophore synthesis of the Gram-negative pathogenic bacterium *Pseudomonas putida* F1 demonstrating that the QS disrupter **196** was able to inhibit the siderophore produced by this bacterium in a concentration dependent way, with 57% synthesis repressed by 100 μg/mL of **196** [155]. In contrast, 100 μg/mL of **196** were found to stimulate siderophore biosynthesis in the opportunistic human pathogen *Pseudomonas aeruginosa* PA01 about 3.5 fold [155,156].

Again in 2005, Jones and coworkers ascertained that compound **196** is able to reduce the growth of the Gram-positive bacterium *Bacillus anthracis* Sterne strain (the etiologic agent of anthrax) in a dose dependent manner [157]. In addition, Zang and coworkers reported that **196** covalently modifies and inactivates in a concentration dependent manner LuxS, the enzyme that produces autoinducer-2 (AI-2) [158], a signaling molecule that mediates inter-species QS among many bacteria [159].

In 2010, in the course of an investigation on the activity of brominated furanones on biofilm formation by *Salmonella typhimurium* ATCC 14028, De Keersmaecker and coworkers found that **196** is more active than the corresponding 3-alkyl-4-bromo-5-(dibromomethylene)-2(5*H*)-furanone **211** (Figure 16),[109] a natural product isolated fron *D. pulchra* [139–141] and *D. elegans* [142].



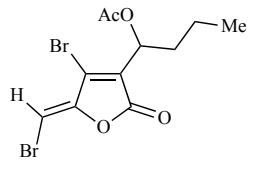
209

Figure 16. Structure of the natural compound **211**

Still in 2010, Ren and coworkers demonstrated the antifungal activity of naturally-occurring **196** on the Gram-positive bacterium *Candida albicans*, a causal agent of opportunistic oral and genital infections in humans, and found that 3 μg/mL of this furanone upregulates 32 genes of the pathogen with functions of stress response, NAPDH dehydrogenation and small molecule transport and represses 21 genes involved in cell-wall maintainance [160].

The year before, Landmann and coworkers had found that **196** is able to enhance the biofilm formation of *Staphylococcus epidermis* strain 1457, *S. epidermis* strain 047 and *S. aureus* at concentrations between 1.25 and 20 μM, which are 10 to 20% of the minimum inhibitory concentration (MIC) and correlate with an increase of polysaccharide intracellular adhesion, the major staphylococcal biofilms [161]. Notably, free, but not surface bound compound **196** was found to be toxic for staphylococci and eukaryotic cells to a similar extent, thus excluding a therapeutic application of this compound [161].

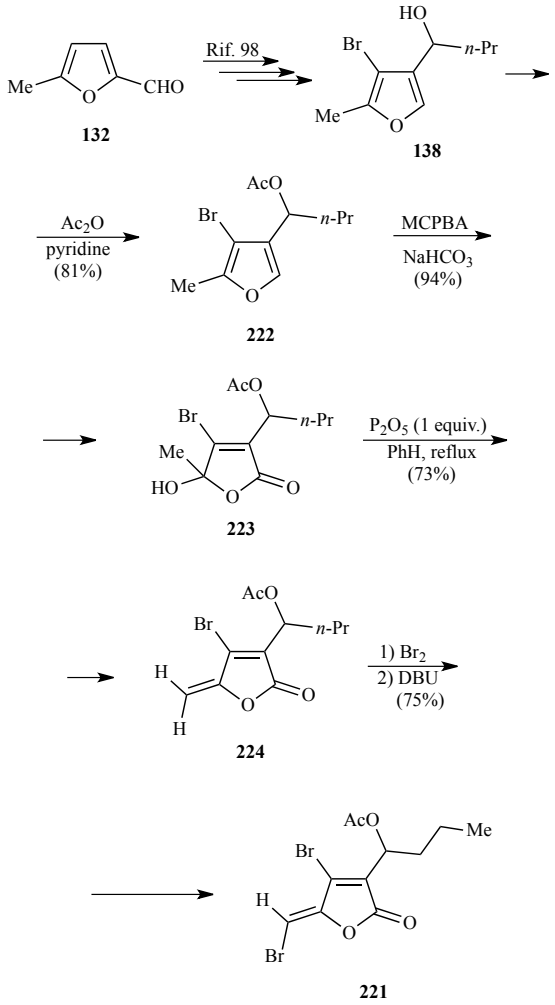
(*Z*)-3-(1-Acetoxybutyl)-4-bromo5-(bromomethylene) 2(5*H*)-furanone (**221**) (Figure 17) in another naturally occurring fimbrolide, isolated from *D. pulchra* [139-141] and *D. elegans* [142] that has been the subject of total synthesis.



221

Figure 17. Structure of (*Z*)-3-(1-acetoxybutyl)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (**221**)

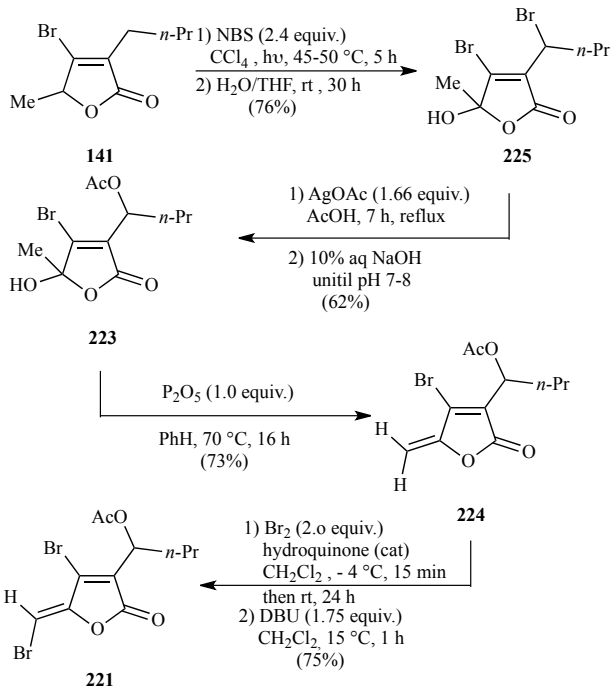
In 1993, Jefford briefly described a synthesis of **221** involving the use of 3-bromo-4-(1-hydroxybutyl)-2-methylfuran (**138**) (Scheme 83) [99], a compound available from 5-methylfurfural (**132)** according to the reaction sequence outlined in Scheme 49 [98]. Acetylation of **138** followed by double hydroxylation of the resulting acetate **222** gave 3-(1-acetoxybutyl)-4-bromo-5-hydroxy-5-methyl-2(5*H*)-furanone **223** in high yield.



Scheme 83. Stereoselective synthesis of (*Z*)-3-(1-acetoxybutyl)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (**221**)

The reaction of **223** with 1.0 equiv of P_2O_5 in benzene under reflux led to 3-(1-acetoxybutyl)-4-bromo-5-methylene-2(5*H*)-furanone (**224)** in 73% yield. Finally, addition of bromine to this compound, followed by DBU-mediated deydrobromination of the resulting adduct provided compound **221** in 75% yield (Scheme 83) [99].

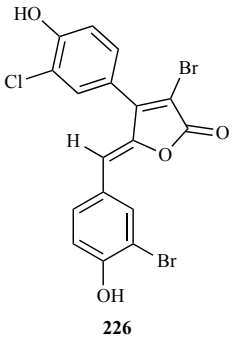
In 1995, de March, Font and coworkers described another synthesis of fimbrolide **221** (Scheme 84) [101].



Scheme 84. Synthesis of fimbrolide **221** starting from furanone **141**

The developed route involved the reaction of 4-bromo-3-butyl-5-methyl-2(5*H*)-furanone (**141**) [101] with 2.4 equiv of NBS in CCl_4 at 40–45 °C under irradiation for 5 h and hydrolysis of the resulting product providing compound **225** in 76% yield. Treatment of **225** with 1.46 equiv of AgOAc in glacial acetic acid followed by addition of 10% aqueous NaOH until pH 7-8 produced compound **223** in 62% yield, which was reacted with P_2O_5 in benzene at 70 °C producing **224** in 73% yield. Finally, addition of 2.0 equiv of bromine to a CH_2Cl_2 solution of **24** at –4 °C in the presence of a catalytic amount of hydroquinone and the subsequent dehydrobromination of the resulting adduct with 1.75 equiv of DBU in CH_2Cl_2 at –15 °C gave compound **221** in 75% yield [101].

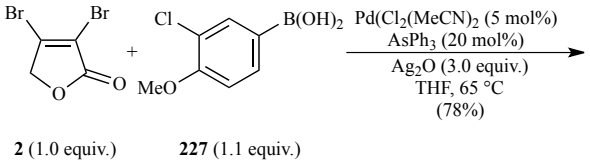
As regards the synthesis of naturally-occurring 2(5*H*)-furanone derivatives with one bromine atom on the heterocyclic ring and monobrominated substituents, it is worth noting that, in 2001, in connection with a project directed towards the synthesis of natural products and their analogues with potential cytotoxic activity against human tumor cell lines, our research group developed an efficient procedure for the synthesis of rubrolide N, a metabolite isolated from the marine ascidian *Synoicum blochmanni* to which the structure **226** (Figure 18) had been assigned by Salvá and coworkers [49].



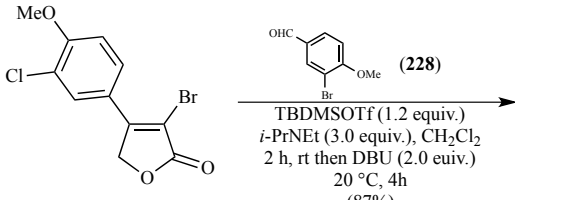
226

Figure 18. Proposed structure for rubrolide N

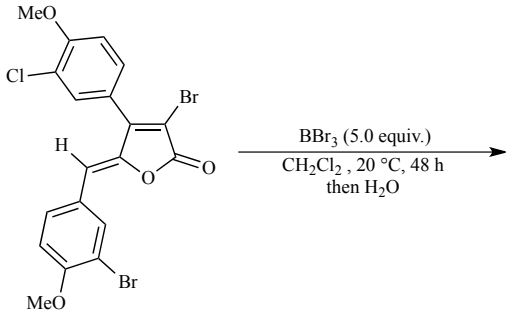
The synthesis of compound **225** was carried out by using the reaction sequence outlined in Scheme 85 [74].



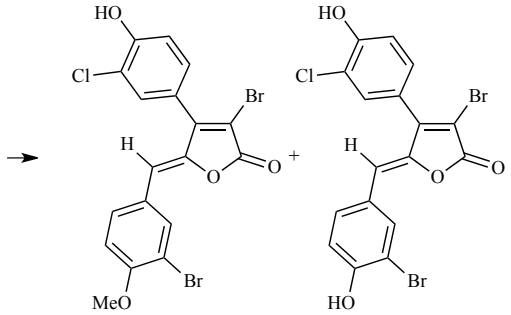
2 (1.0 equiv.) **227** (1.1 equiv.)



31f



229



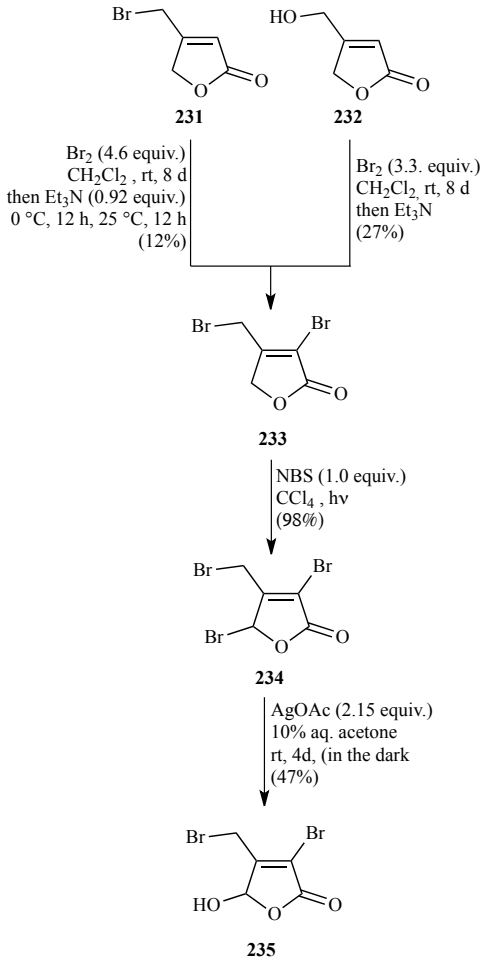
230 (51%) **226** (47%)

Scheme 85. Stereoselective synthesis of compound **225**

3,4-Dibromo-2(5*H*)-furanone (**2**) was submitted to a Suzuki-Miyaura reaction with 1.1 equiv of arylboronic acid **227** in THF at 65 °C in the presence of 3.0 equiv of Ag_2O, 0.5 mol% $PdCl_2(MeCN)_2$ and 20 mol% $AsPh_3$ providing 4-aryl-3-bromo-2(5*H*)-furanone **31f** in 78% yield. A CH_2Cl_2 solution of **31f** was then sequentially treated with 1.2 equiv of TBDMSOTf, 3.0 equiv of *i*-Pr_2NEt and 1.0 equiv of 3-bromo-4-methoxybenzaldehyde (**228**) at room temperature for 2 h and the resulting mixture was reacted with 2.0 equiv of DBU at 20 °C for 4 h affording selectively compound **229** in 87% yield. Finally, the reaction of **229** with 5.0 equiv of BBr_3 in CH_2Cl_2 at 20 °C for 48 h followed by hydrolysis led to a mixture of (*Z*)-3-bromo-4-(3-chloro-4-hydroxyphenyl)-5-[1-(1-bromo-4-methoxyphenyl)methylene]-2(5*H*)-furanone (**230**) and (*Z*)-3-bromo-4-(3-chloro-4-hydroxyphenyl)-5-[1-(3-bromo-4-hydroxyphenyl)methylene]-2(5*H*)-furanone (**226**) from which compounds **230** and **226** were isolated in 51% and 47% yield, respectively [74]. However, several NMR parameters of compound **226** did not match with those reported for the natural product with the structure of rubrolide N [49].

Many other syntheses of unnatural 2(5*H*)-furanone derivatives bearing one bromine atom on the heterocyclic ring and monobrominated substituents have been reported in the literature.

In 1997, as part of a study of the mutagenicity of halogen-substituted furanones, LaLonde and coworkers synthesized 3-bromo-4-(bromomethyl)-2(5*H*)-furanone (**233**), 3,5-dibromo-4-(bromomethyl)-2(5*H*)-furanone (**234**) and 3-bromo-4-(bromomethyl)-5-hydroxy-2(5*H*)-furanone (**235**) using 4-(bromomethyl)-2(5*H*)-furanone (**231**) or 4-(hydroxymethyl)-2(5*H*)-furanone (**232**) as the starting material (Scheme 86) [162]. Addition of 4.6 equiv of bromine to a CH_2Cl_2 solution of **231** followed by treatment with 0.92 equiv of Et_3N provided compound **233** in only 12% yield. Nevertheless, compound **233** was obtained in 27% yield by the reaction of **232** with 3.3 equiv of bromine at room temperature for 8 d followed by Et_3N-mediated dehydrobromination. The subsequent reaction of **233** with 1.0 equiv of NBS in CCl_4 under irradiation with an incandescent lamp gave compound **234** in 98% yield and 94% GC purity. Finally, treatment of **234** with 1.5 equiv of AgOAc in 10% aqueous acetone for 4 d at room temperature gave **235** in 47% yield [162].



Scheme 86. Synthesis of compounds **233, 234** and **235**

LaLonde and coworkers also evaluated the mutagenicity potency of compounds **233** and **235** in the Ames *Salmonella typhimurium* (TA100) assay and found that the mutagenicity value of **235** was 51.0 fold higher than that of **233**, but considerbly smaller than that observed for the H-by-OH replacement for the dichloride pair **236** and **237** (Figure 19) [162]. In fact, **237** had a mutagenicity value of 145 fold higher than that of **236** [162].

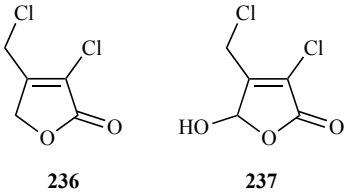
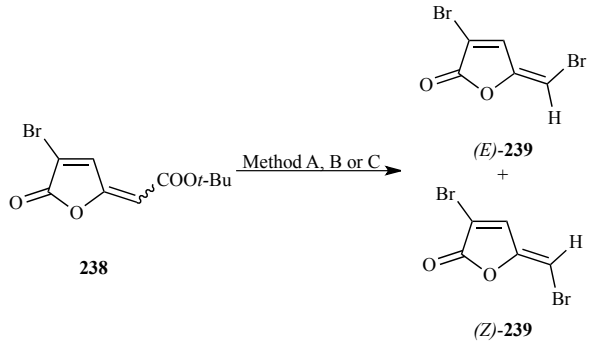


Figure 19. Structures of compounds **236** and **237**

In 2008, Benneche and coworkers carried out the synthesis of stereoisomeric mixtures of 3-bromo-5-(bromomethylene)-2(5*H*)-furanone **239** by using three different protocols (Scheme 87) [163]. The first protocol

(*Method* A) involved the cleavage of the *tert*-butyoxycarbonyl group of the α,β-unsaturated ester **238** by treatment with trifluoroacetic acid (TFA) and addition of bromine to the resulting compound, followed by reaction with Et_3N in DMF at room temperature. This one-pot protocol provided a 11 : 89 mixture of (*E*)- and (*Z*)-**239** in 56% yield, from which (*Z*)-**239** was isolated in 50% yield. The second protocol (*Method B*) consisted of treatment of a CCl_4 solution of **238** with bromine, addition of TFA to the resulting product, stirring the mixture at room temperature for 2 d, and evaporation of the solvent followed by addition of DMF and Et_3N at 0 °C. In this way a 60 : 40 mixture of (*E*)- and (*Z*)-**239** was obtained in 10% yield. In the third protocol (*Method C*) compound **238** was reacted with TFA in CH_2Cl_2 at room temperature, the reaction mixture was evaporated and treated with bis(2,4,6-trimethylpyridino)bromine(I) hexafluorophosphate in CH_2Cl_2 at 0 °C and after 2 h reacted with 1M HCl. This protocol allowed to obtain a mixture of (*E*)- and (*Z*)-**239** in a 2 : 98 ratio, respectively, from which compound (*Z*)-**239** was isolated in 48% yield [163].



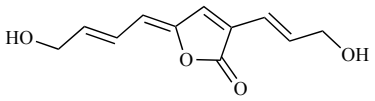
238

Method A : 1) TFA, CH_2Cl_2, 2 h; 2) Br_2 (4.0 equiv.), $CDCl_3$ rt, 2 - 3 d; 3) Et_3N (1.08 equiv.)
Method B : 1) Br_2 (1.1.equiv.), CCl_4 , rt, 2 h; 2) TFA, CH_2Cl_2 rt, 2 h; 3) Et_3N (1.08 equiv.), DMF, rt, 2 h
Method C : 1) TFA, CH_2Cl_2, rt, 2 h; 2) $Br^+(CoCl)_2PF_6^-$ (1.5 equiv.), CH_2Cl_2 , 2 h; 3) 1M HCl

Method	(*E*)/(*Z*)-**239**	total yield%	yiled% of (*Z*)-**239**
A	11:89	56	50
B	60:40	10	4
C	2:98	49	48

Scheme 87. Synthesis of compounds (*E*)- and (*Z*)-**239**

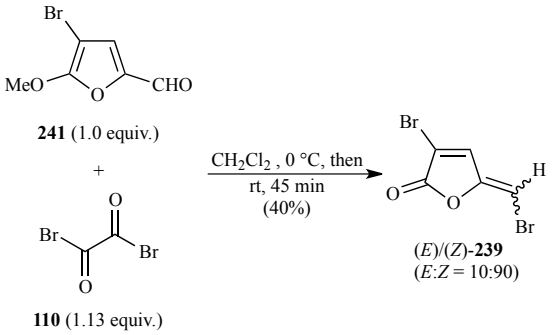
Notably, (*Z*)-**239**, which was a valuable intermediate to lissoclinolide (**240**), a metabolite of the tunicate *Lissoclinum patella* [164], at 60 μM was found to reduce significantly bioluminescence in the Gram-negative, bioluminescent, marine bacterium *Vibrio harveyi* BB170 compared to control without furanone [40]. About this result, it must be pointed out that the use of the bioluminescence reduction bioassay of *Vibrio harveyi* constitutes a direct method of detecting potentially biohazardous materials in water [165].



240

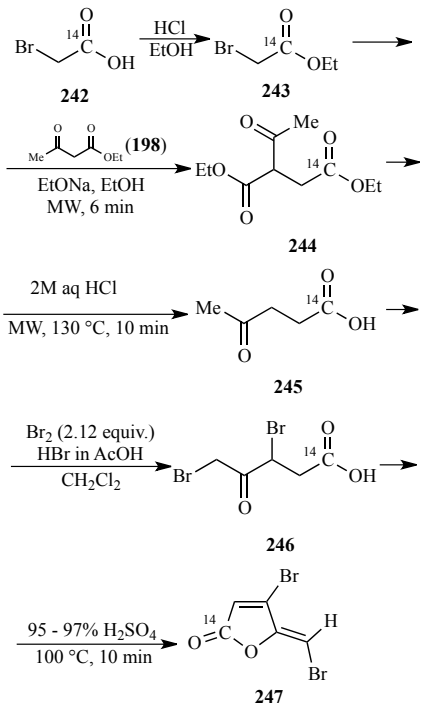
Figure 20. Structure of lissoclinolide (**240**)

In 2012, Benneche and coworkers reported that a mixture of (*E*)- and (*Z*)-**239** in a 10 : 90 ratio, respectively, was obtained in 40% yield by reacting 4-bromo-5-methoxyfurfural (**241**) with 1.3 equiv of oxalyl bromide (**110**) in CH_2Cl_2 at 0 °C and heating the resulting reaction mixture at room temperature for 45 min (Scheme 88) [166].



Scheme 88. Synthesis of (*E*)/(*Z*)-**239** from 4-bromo-5-methoxyfurfural (**241**)

As mentioned in Section 2.2, in 2004, Brückner and coworkers synthesized (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (**145**) (C-30) in 41% yield by the reaction of 3,5-dibromolevulinic acid (**144**) with concd. sulfuric acid at room temperature for 20 min and then at 85 °C for 0.5 h (Scheme 51) [102]. In the same year, Johansen and coworkers prepared (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-[2-^{14}C]furanone (**247**) in five steps in 7.7% overall yield starting from bromo[1-^{14}C]acetic acid (**242**) (Scheme 89) [167]. Microwave-accelerated condensation of ethyl bromo[1-^{14}C]acetate (**243**) with ethyl acetoacetate (**198**) and acidic hydrolysis of the resulting diester **244** followed by decarboxylation by microwave heating gave [1-^{14}C]levulinic acid **245**. Finally, the bromination reaction of **245** followed by sulfuric acid-mediated cyclization of the resulting dibrominated carboxylic acid **246** gave the targeted labelled 2(5*H*)-furanone **247** with a radiochemical purity higher than 97% and specific activity of 57 mCi/mmol [167].



Scheme 89. Synthesis of (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-[2-^{14}C]furanone (**247**)

In the last two decades, the bioactivity of (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (**145**) (C-30) has been the subject of several studies.

In 2004, Wu and coworkers demonstrated that this compound interfers with the action of *N*-acyl homoserine lactones by inhibiting *in vivo* gene expression regulated by QS systems in *Pseudomonas aeruginosa* [21]. Furthermore, these authors showed that **145** also exerts favourable therapeutic effects in *P. aeruginosa* lung infection in mice [21] reducing the inflammation *in vivo*. In fact, *N*-(3-oxododecanoyl)homoserine lactone, an important QS signal produced by *P. aeruginosa,* has been shown to have inflammatory effects [168].

In 2010. Roques and coworkers found that **145** is able to inhibit the growth and to restrict the number of adherent *P. aeruginosa* cells when added from the early stages of biofilm formation (*i.e.* adhesion and microcolony formation) in a dose dependent way [169].

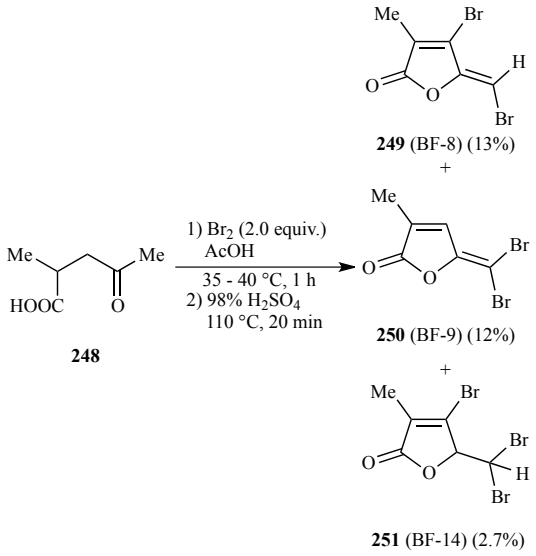
In 2013, Defoirdt and coworkers demonstrated that the QS-disrupter **145** increases the survival of giant freshwater prawn *Macrobrachium rosenbergii* larvae when challenged to pathogenic *Vibrio harveyi* [170].

In 2015, Chan and coworkers carried out a study in which they fabricated on microarc-oxidized titanium a new antibacterial agent, compound **145** loaded poly(*L*-lactic acid) nanoparticles, and found that this antibacterial coating produced a unique inhibition zone against *Stapylococcus aureus* throughout a 60-day period, which is long enough to prevent the infection around implants in the early and intermediates stages [171].

In the same year, Quan and coworkers incorporated for the first time compound **145** into Nafion polymer and investigated the antimicrobial and anti-biofilm properties of the resulting composite film against mixed culture and three strans of *P. aeruginosa*, *E. coli* and *Bacillus subtilis* [172]. The results indicated that **145** or Nafion alone could inhibit all colonization and that when **145** was incorporated into the Nafion polymer, synergetic anti-biofilm effects were obtained [172].

Finally, still in 2015, Li and coworkers obtained results showing that **145** efficiently inhibits biofilm formation by *Acidithiobacillus ferroxidans* (a Gram-negative bacterium commonly found in acid mine drainage and deep caves) and that the inhibition of biofilm formation is correlated with a decrease in the production of extracellular polymeric substance [173]. Notably, the reduction in the production of extracellular substances led to reduced biofilms on pentlandite, the most common terrestrial nickel sulfide, and to reduced pentantlandite attachment [173].

In 2008 Ren, Luk and coworkers synthesized (*E*)-4-bromo-5-(bromomethylene)-3-methyl-2(5*H*)-furanone (**249**) (BF-8) by bromination of 2-methyllevulinic acid (**248**), followed by oxidative ring closure under acidic conditions of the resulting dibrominated compound (Scheme 90) [174].



Scheme 90. Synthesis of compounds **249–251**

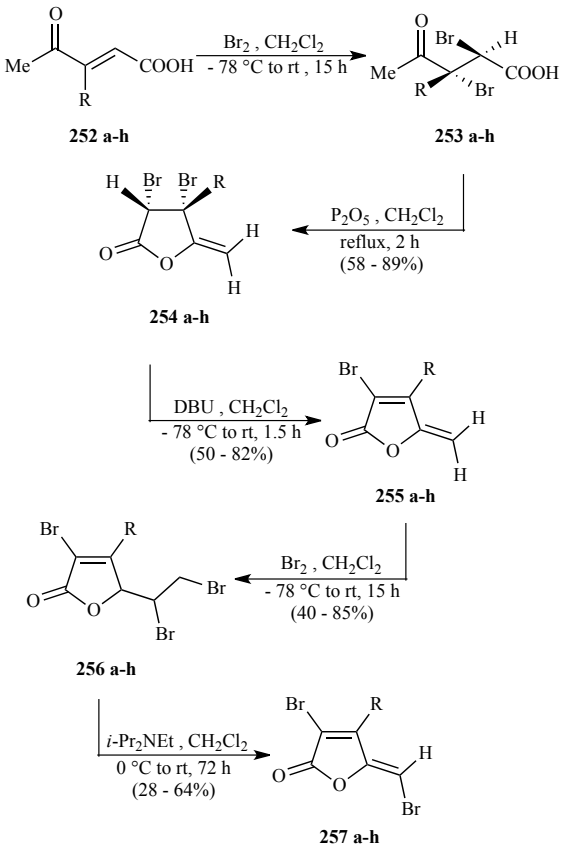
Notably, the reaction also produced 4-bromo-5-(dibromomethylene)-3-methyl-2(5*H*)-furanone (**250**) (BF-9) and 4-bromo-5-(dibromomethyl)-3-methyl-2(5*H*)-

furanone (**251**) (BF-14) in 12% and 2.7% yield, respectively (Scheme 90) [174]. Interestingly, compound **249** was found to exhibit significant inhibition activity for *E. coli* biofilm formation [174].

In 2012, Ren and coworkers showed that **249** could also act synergistically with antibiotics to enhance killing of *P. aeruginosa* PAO1 persister cells (a subpopulation of bacterial cells that are dormant and tolerant to antibiotics) and could also restore the susceptibility of isolated persister cells to antibiotics [175].

One year later, Ren and coworkers demonstrated that the QS inhibitor **249** (BF-8) could reduce persistance during the growth of *E. coli* and revert the antibiotic tolerance of its persister cells [176]. Again in 2013, the same research group characterized the effects of compound **249** on the mucoid strain *P. aeruginosa* PDO300 and found that this brominated furanone is able to reduce persistence during the growth of *P. aeruginosa* PDO300 and effectively to kill the persister cells isolated from this strain [177]. Furthermore, compound **249** was capable to inhibit biofilm formation of PDO300 and to reduce associated persistence [177].

In 2009, Kumar and coworkers carried out the synthesis of 4-substituted (*Z*)-3-bromo-5-(bromomethylene)-2(5*H*)-furanones **257a–h** by using the reaction sequence outlined in Scheme 91 [178]. Thus, addition of bromine to carboxylic acids **252**, followed by cyclodehydration of the resulting dibromolevulinic acids **253** with P_2O_5 in CH_2Cl_2 gave compounds **254** in moderate to good yields. Dehydrobromination of these substances with DBU in CH_2Cl_2 yielded 5-methylene-2(5*H*)-furanones **253**, which were reacted with bromine to give selectively compounds **256**. Finally, dehydrobromination of these substances with *i*-Pr_2NEt in CH_2Cl_2 provided compounds **257** stereoselectively and in moderate to satisfactory yields. For instance, the reaction of **256d** (R = *n*-Hex) with 3.4 equiv of *i*-Pr_2NEt in CH_2Cl_2 at room temperature for 72 h produced compound **257d** in 55% yield [178]. However, the stereoisomeric purities of compounds **257** were not reported [178].

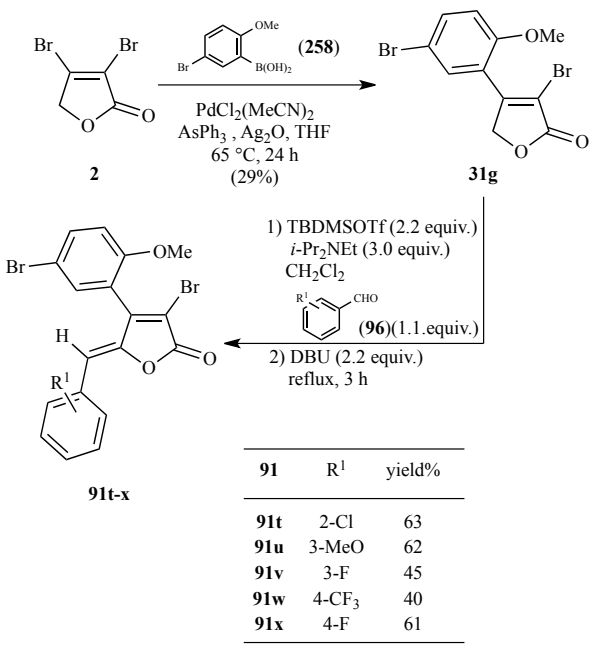


257	R
257a	Me
257b	*n*-Pr
257c	*n*-Bu
257d	*n*-Hex
257e	*n*-Hept
257f	*n*-Dec
257g	Ph
257h	Bn

Scheme 91. Synthesis of 4-substituted (*Z*)-3-bromo-5-(bromomethylene)-2(5*H*)-furanones **257a–h**

In 2015, Barbosa and coworkers synthesized (*Z*)-5-(1-arylmethylene)-3-bromo-4-(5-bromo-2-methoxyphenyl)-2(5*H*)-furanones **91k–o** via a route (Scheme 92) in which the first step was the $PdCl_2(MeCN)_2/AsPh_3$-catalyzed regioselective C-4 arylation reaction of 3,4-dibromo-2(5H)-furanone (**2**) with 5-bromo-2-methoxyphenylboronic acid (**258**) in THF at 65 °C in the presence of Ag_2O [76]. The resulting 3-bromo-4-(5-bromo-2-methoxyphenyl)-2(5*H*)-furanone (**31g**), which was obtained in 29% yield, was reacted with 2.2 equiv of TBDMSOTf, 3.0 equiv of *i*-Pr_2NEt and 1.1 equiv of the required aryl aldehydes in CH_2Cl_2 at room temperature and the crude reaction products were treated with 2.2 equiv of DBU under reflux providing compounds **91k–o** in 40–63% yield based on **31g** (Scheme 92) [76]. The lowest yield was obtained by

using an aryl aldehyde with the strong electron-withdrawing CF_3 substituent [76].

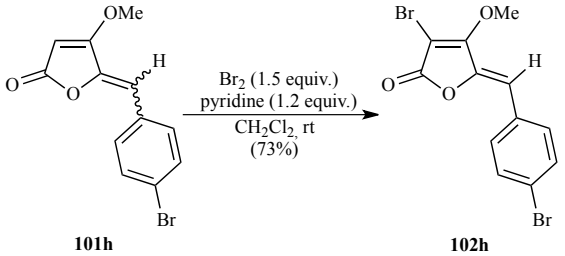


91	R^1	yield%
91t	2-Cl	63
91u	3-MeO	62
91v	3-F	45
91w	4-CF_3	40
91x	4-F	61

Scheme 92. Synthesis of (*Z*)-5-(1-arylmethylene)-3-bromo-4-(5-bromo-2-methoxyphenyl)-2(5*H*)-furanones **91t-x**

In 2016, Barbosa and coworkers found that compound **91n** caused a decrease in HL-60 cell viability followed by an increase in the apoptoric and necrotic cells in a concentration dependent manner [179].

The year before, Bouillon, Médebielle and coworkers prepared (*Z*)-3-bromo-5-(4-bromobenzylidene)-4-methoxy-2(5*H*)-furanone (**102h**) in 73% yield by treatment of a 89 : 11 (*Z*)/(*E*)- mixture of 5-(4-bromobenzylidene)-4-methoxy-2(5*H*)-furanone (**101h**) with 1.5 equiv of bromine and 1.2 equiv of pyridine in CH_2Cl_2 at room temperature (Scheme 93) [82].



Scheme 93. Synthesis of (Z)-3-bromo-5-(4-bromobenzylidene)-4-methoxy-2(5*H*)-furanone (**102h**)

The stereoisomeric mixture of compound **101h** was in turn prepared in 44% yield from 4-methoxy-2(5*H*)-furanone (**98a**) according to the reaction sequence outilined in Scheme 35 [82].

In concluding this section, it deserves also to be mentioned that, in 2001, our research group synthesized (Z)-3-bromo-4-(3-chloro-4-methoxyphenyl)-5-[1-(3-bromo-4-methoxyphenyl)methylene]-2(5*H*)-furanone (**229**) (Figure 18) in 87% yield by using the procedure developed to prepare compounds **89a** and **89b** (Scheme 32) [74]. Compound **229** was then *O*-demethylated by treatment with 5.0 equiv of BBr_3 in CH_2Cl_2 at room temperature for 48 h providing the rubrolide analogue **226** (Figure 21)in 51% yield [74].

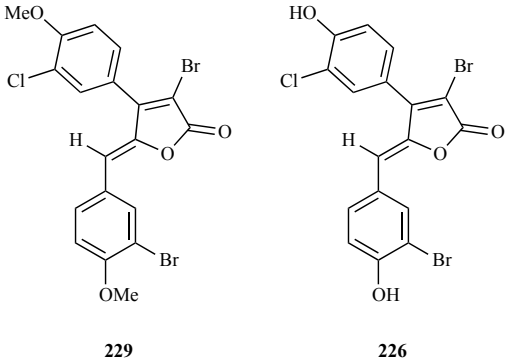


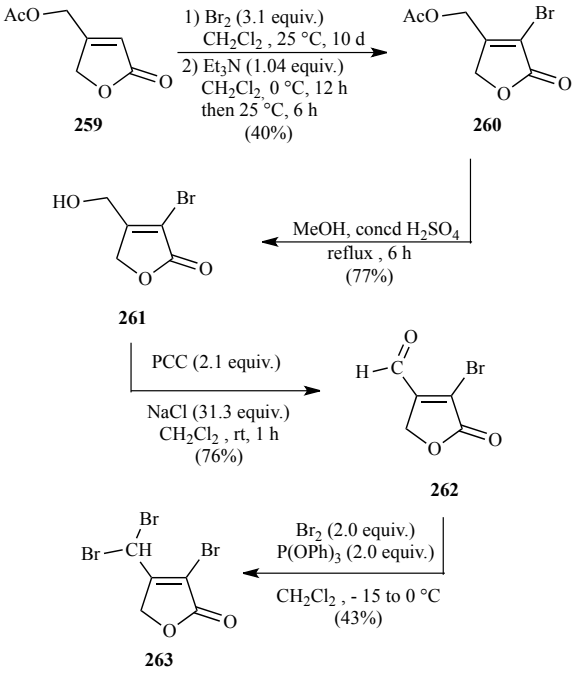
Figure 21. Structures of compounds **229** and **226**

Notably, compounds **229** and **226** proved to be highly cytotoxic for MCF-7, NCI-H460 and SF-268 cancer cell lines. In fact, their values for the growth reduction of any one of the cell lines were negative numbers, which indicated cell kill [74].

5. SYNTHESIS AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES FEATURING ONE BROMINE ATOM ON THE HETEROCYCLIC RING AND DIBROMINATED SUBSTITUENTS

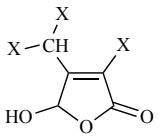
In 1997, 3-bromo-4-(dibromomethyl)-2(5*H*)-furanone (**261**) was synthesized by LaLonde and coworkers starting from 4-acetoxymethyl-2(5*H*)-furanone (**259**) via the route outlined in Scheme 94 [162]. In particular, the reaction of **259** with 3.1 equiv of bromine in CH_2Cl_2 for 10 d, followed by treatment with 1.04 equiv of Et_3N gave compound **260** in 40% yield. Acidic hydrolysis of the ester group of **260** in methanol furnished compound **261** in 77% yield. The subsequent reaction of **261** with a mixture of 2.1 equiv of pyridinium chlorochromate (PCC) and 31.3 equiv of NaCl in CH_2Cl_2 gave 3-bromo-4-formyl-2(5*H*)-furanone (**262**) in 76% yield. Finally, treatment of this compound with the reagent prepared from equimolar amounts of bromine and triphenylphosphite led to the target compound **263** in 53% yield (Scheme 94) [162]. It was then found that **263** was mutagenic in the *Salmonella typhimurium*

(TA100-S9) assay with a mean mutagenicity value of 82.4 revertants/mmol [162].



Scheme 94. Synthesis of 3-bromo-4-(dibromomethyl)-2(5*H*)-furanone (**263**)

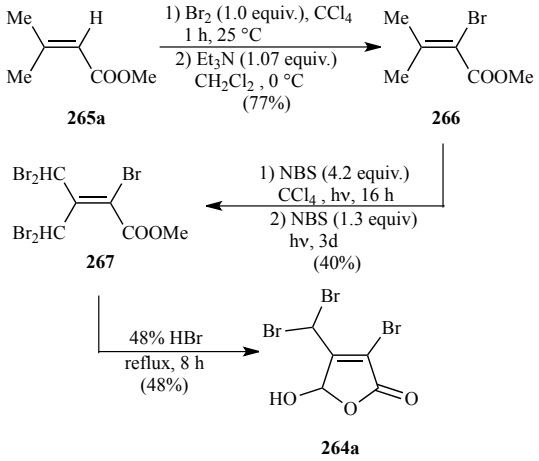
In 2000, 3-bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (**264a**) (Figure 22), which is the brominated analogue of the potent environmental mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (**264b**) (MX) (Figure 22) [180–182], was synthesized by the reaction sequence illustrated in Scheme 95 [183].



264a : X = Br
264b : X = Cl (MX)

Figure 22. Structures of compounds **264a** and **264b** (MX)

The synthesis began with the addition of bromine to methyl 3-methyl-2-butenoate (**265a**) and the subsequent dehydrobromination with Et_3N of the resulting adduct, which led to compound **266** in 77% yield.

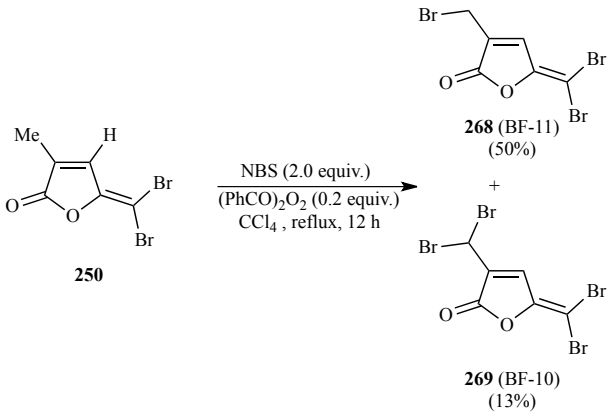


Scheme 95. Synthesis of 3-bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone **(264a)**

At first, three bromine atoms were introduced by treatment of this compound with 4.2 equiv of NBS in CCl_4 under irradiation for 6 h and. The subsequent introduction of the fourth bromine atom into the resulting product(s) was accomplished by treatment with 1.3 equiv of NBS in CCl_4 under irradiation for 3 d. In this way compound **267** was obtained in 40% yield. Finally, **267** was converted to 3-bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (**264a**) in 48% yield by treatment with 48% HBr under reflux for 8 h [183].

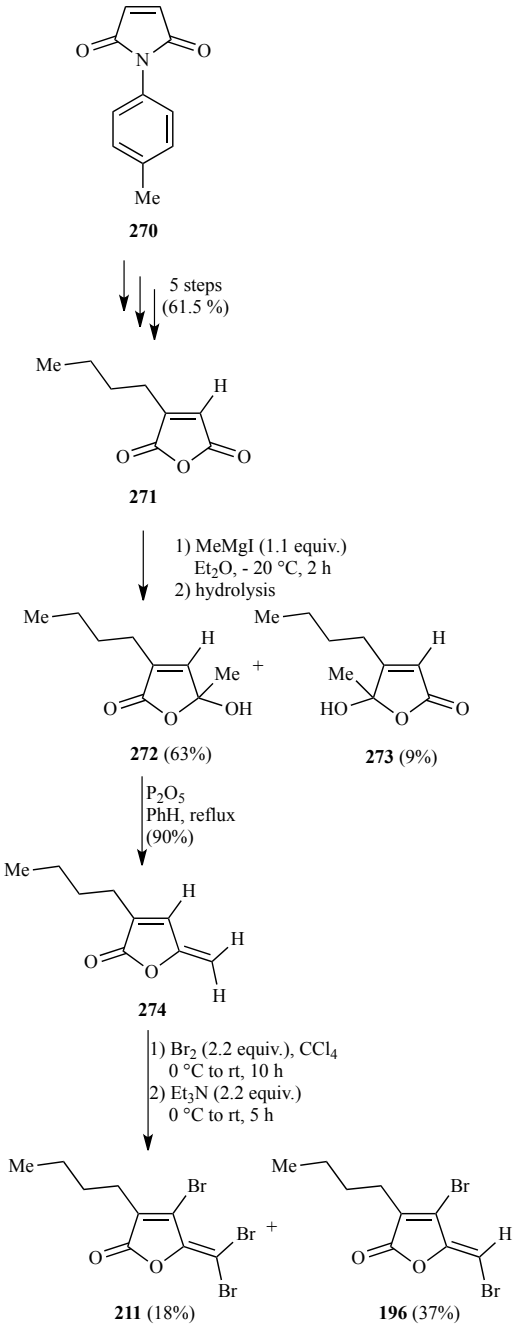
It is interesting to note that, previously, **264a** had been found to be present in chlorinated drinking waters in concentrations comparable to that of **264b** (MX) [184].

In 2008, Ren, Luk and coworkers reported that the reaction of 5-(dibromomethylene)-3-methyl-2(5*H*)-furanone (**250**) with 2.0 equiv of NBS in CCl_4 under reflux for 12 h, in the presence of 0.2 equiv of dibenzoyl peroxide, provided a mixture of 3-bromo-5-(dibromomethylene)-2(5*H*)-furanone (**268**) (BF-11) and 3-(dibromomethyl)-5-(dibromomethylene)-2(5*H*)-furanone (**269**) (BF-10) (Scheme 96) [174]. Column chromatography of this mixture allowed to obtain pure compounds **268** and **269** in 50% and 13% yield, respectively [174]. Compound **250** was in turn obtained in 18% yield by bromination of 2-methyllevulinic acid (**248**), followed by oxidative ring closure under acidic conditions of the resulting brominated derivative [174]. Data were also obtained suggesting that **268** is bactericidal to *Escherichia coli* [174].



Scheme 96. Synthesis of compounds **268** and **269**

One year earlier, Haval and Argade had described a synthesis of a mixture of naturally-occurring (*Z*)-4-bromo-5-(dibromomethylene)-3-butyl-2(5*H*)-furanone (**211**) and (Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5*H*)-furanone (**196**) via a multi-step reaction sequence in which *N*-(4-tolyl)maleimide (**270**) was used as the starting material (Scheme 97) [185]. Specifically, compound **270** was converted to 3-butylfuran-2,5-dione (**271**) in 61.5 % yield through a five-step sequence. The reaction of **271** with 1.1 equiv of methylmagnesium iodide in Et_2O at –20 °C followed by hydrolysis gave 3-butyl-5-hydroxy-5-methyl-2(5*H*)-furanone (**272**) and 4-butyl-5-hydroxy-5-methyl-2(5*H*)-furanone (**273**) in 62% and 9% yield, respectively. The subsequent treatment of compound **272** with P_2O_5 in benzene under reflux provided the expected butenolide **274**. Finally, addition of 2.2 equiv of bromine to **274** followed by reaction of the resulting adduct with 2.2 equiv of Et_3N in $CHCl_3$ gave a mixture of fimbrolides **211** and **196**, which were separated by HPLC using a known procedure [140]. Compounds **211** and **196** were so obtained in 18% and 37% yield, respectively (Scheme 97) [185]

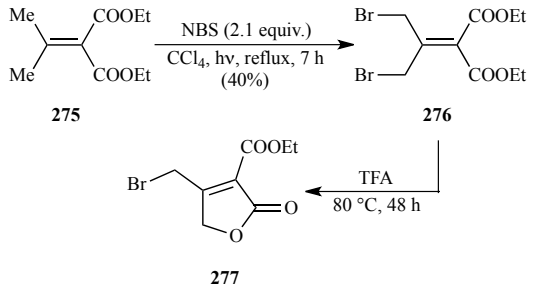


Scheme 97. Synthesis of naturally occurring fimbrolides **211** and **196**

It should be noted that Givskov and coworkers had previously found that compound **211**, similarly to **196**, is able to inhibit swarming motility of the Gram-negative bacterium *Serratia liquefaciens* MG1 and to control transcription of the QS regulated gene *swrA* in competition with the cognate signal molecule BHL [148].

6. SYNTHESIS AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES WITH MONOBROMINATED SUBSTITUENTS

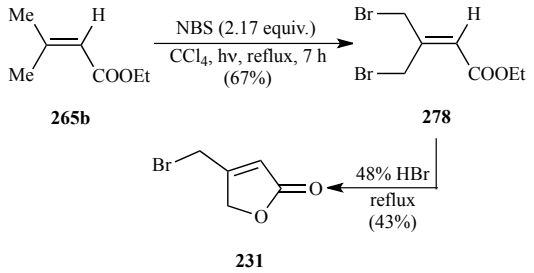
In 1966, 4-bromomethyl-3-ethoxycarbonyl-2(5*H*)-furanone **(277**) was synthesized in two steps starting from diethyl isopropylidenemalonate (**275**) (Scheme 98) [186].



Scheme 98. Synthesis of 4-bromomethyl-3-ethoxycarbonyl-2(5*H*)-furanone **(277**)

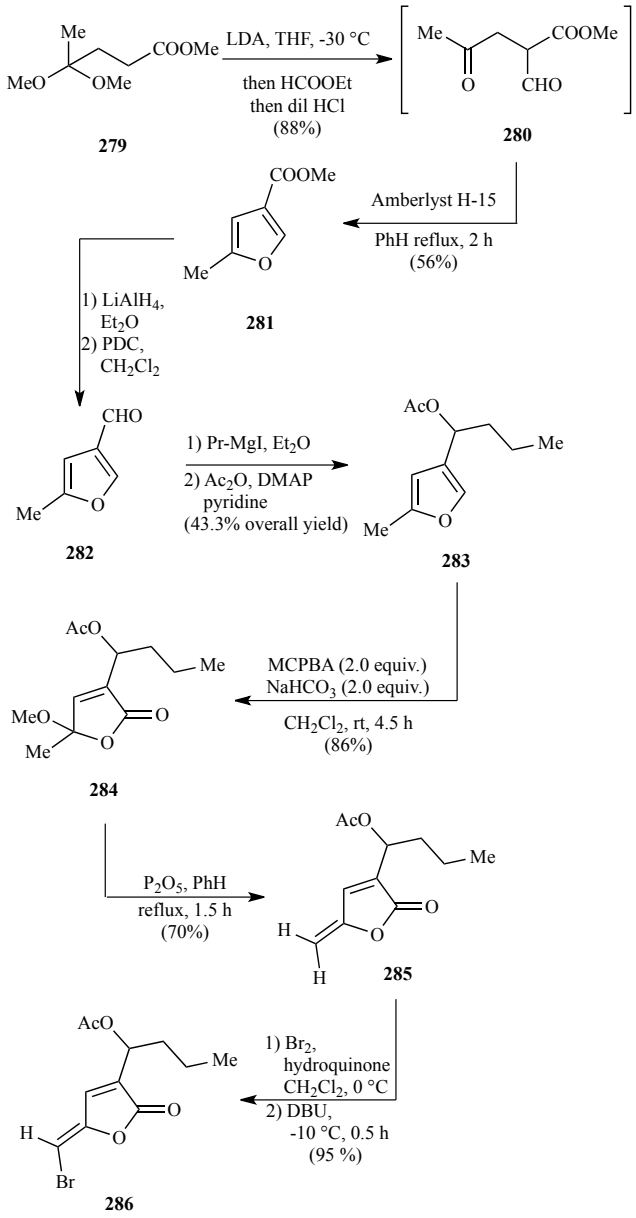
The reaction of **275** with 2.1 equiv of NBS in CCl_4 under reflux and irradiation with a 200 W lamp produced compound **276** in 40% yield. The subsequent reaction of **276** with trifluoroacetic acid at 80 °C for 48 h yielded the required compound **277** in 53% yield [186].

In 1976, Martin and coworkers carried out the synthesis of 4-bromomethyl-2(5*H*)-furanone (**231**) in 28.8% overall yield by treatment of ethyl 3-methyl-2-butenoate (**265b**) with 2.17 equiv of NBS in CCl_4 under reflux and irradiation with a 100 W lamp and cyclization of the resulting compound **278** by reaction with 48% HBr under reflux (Scheme 99) [113].



Scheme 99. Synthesis of 4-bromomethyl-2(5*H*)-furanone (**231**)

In 1983, Kotsuki, Monden and Ochi described an efficient synthesis of (*Z*)-3-(1-acetoxybutyl)-5-(bromomethylene)-2(5*H*)-furanone (**285**) in which methyl levulinate dimethyl ketal (**279**) was used as the starting material (Scheme 100) [187].

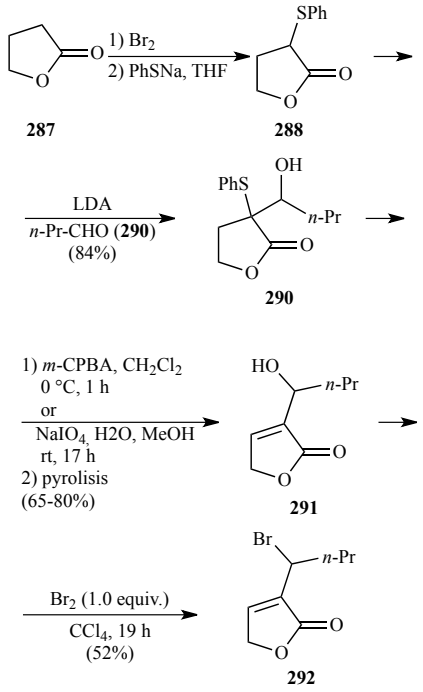


Scheme 100. Synthesis of (*Z*)-3-(1-acetoxybutyl)-5-(bromomethylene)-2(5*H*)-furanone (**286**)

Formylation of **279** and treatment of the resulting crude product **280** with Amberlyst H-15 produced methyl 5-methyl-3-furoate (**281**) in a satisfactory yield. Reduction of **281** with $LiAlH_4$ in Et_2O followed by oxidation of the resulting alcohol with pyridinium dichromate (PDC) in CH_2Cl_2 gave 5-methyl-3-formylfuran (**282**), which was then converted to compound **283** in 43.3% overall yield by treatment with propylmagmesium iodide and acetylation of the resulting alcohol. Oxidation of **283** with 2.0 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature in the presence of 2.0 equiv of $NaHCO_3$ led to a diastereomeric mixture of 2(5*H*)-furanone **284** in 86% yield. This compound was dehydrated with P_2O_5 in benzene under reflux providing 5-methylene-2(5*H*)-

furanone **285** in 70% yield. Finally, addition of bromine to **285** in the presence of a catalytic amount of hydroquininone and the subsequent dehydrobromination of the resulting adduct by treatment with DBU at –10 °C led to compound **286** in 95% yield (Scheme 100) [187].

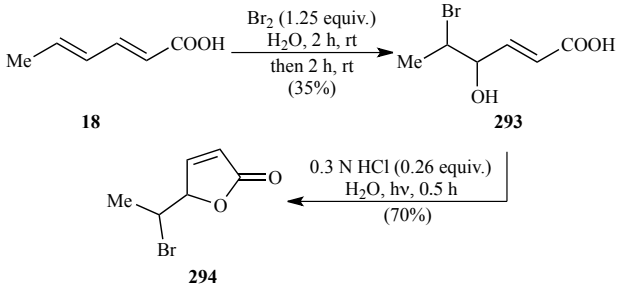
Four years later, Font and coworkers synthesized 3-(1-bromobutyl)-2(5*H*)-furanone (**292**) from commercially available γ-butyrolactone (**287**) through a route in which 3-(1-hydroxybutyl)-2(5*H*)-furanone (**291**) was the unexpected direct precursor to **292** (Scheme 101) [188].



Scheme 101. Synthesis of 3-(1-bromobutyl)-2(5*H*)-furanone (**292**)

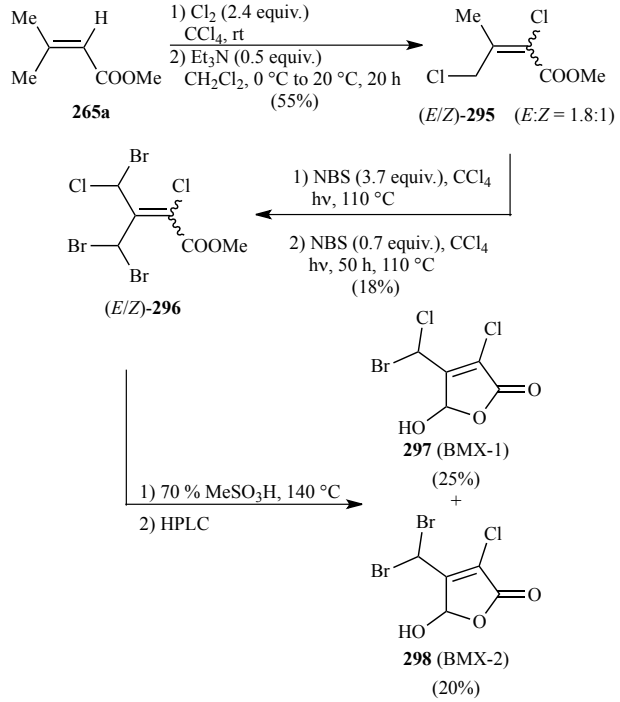
Specifically, lactone **287** was converted to 3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one (**288**) and the α-carbanion of this compound was reacted with butanal (**289**) providing compound **290** as a 1 : 1 diastereomeric mixture in 84% yield. Oxidation of **290** with *m*-CPBA in CH_2Cl_2 at 0 °C for 1 h or with sodium periodate in a 1 : 1 mixture of water and methanol at room temperature for 17 h, followed by pyrolysis of the resulting sulfoxide gave compound **291** in 65–80% yield. Finally, the substitution of the allylic hydroxyl group in **291** with bromine occurred unexpectedly under typical bromination conditions. In fact, treatment of **291** with 1.0 equiv of bromine in CCl_4 gave bromide **292** in 52% yield (Scheme 101) [188].

In 1995, Sánchez-Ferrando and coworkers reported a two-step synthesis of 5-(1-bromoethyl)-2(5*H*)-furanone (**294**) in which sorbic acid (**18**) was the starting material (Scheme 102) [36]. In particular, the reaction of **18** with 1.25 equiv of bromine in water at 85 °C for 1 h and then for 2 h at room temperature gave (*E*)-5-bromo-4-hydroxy-2-hexenoic acid (**293**) in 35% yield. The subsequent reaction of **293** in acidic water under UV irradiation provided compound **294** in 70% yield (Scheme 102) [36].



Scheme 102. Synthesis of 5-(1-bromoethyl)-2(5*H*)-furanone (**294**)

In 2000, 4-(bromochloromethyl)-3-chloro-5-hydroxy-2(5*H*)-furanone (**297**) (BMX-1) and 3-chloro-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (**298**) (BMX-2) were synthesized by Messeguer and coworkers from methyl-3-methyl-2-butenoate (**265a**) using the reaction sequence outlined in Scheme 103 [183, 189].

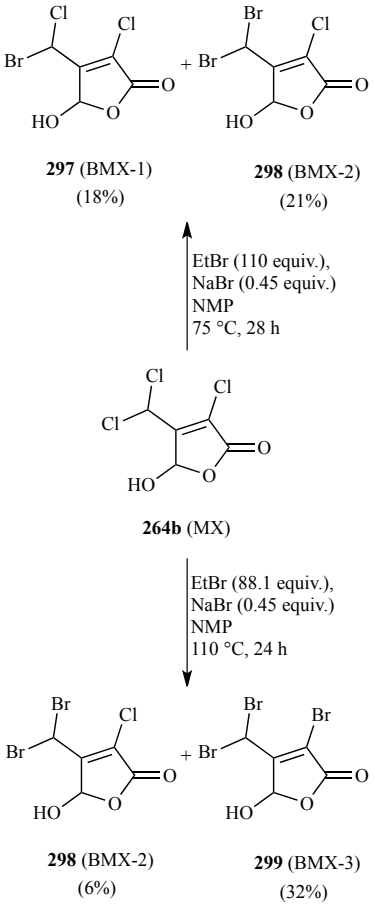


Scheme 103. Synthesis of compounds **297** (BMX-1) and **298** (BMX-2)

Chlorination of **265a** by treatment with 2.4 equiv of chlorine in CCl_4 solution at room temperature, followed by dehydrochlorination with 0.5 equiv of Et_3N in CH_2Cl_2 led in 55% yield to a stereoisomeric mixture of **295** in which

the *E*- and *Z*-stereoisomers were in a 1.8 : 1 ratio. This mixture was subjected to allylic bromination with an excess of NBS in the presence of light at 110 °C producing a mixture of (*E*)- and (*Z*)-**296** in a 1 : 1 ratio and in only 18% yield. Finally, hydrolysis and subsequent cyclization of this mixture by treatment with 70% methanesulfonic acid at 140 °C gave a mixture of compounds **297** (BMX-1) and **298** (BMX-2) from which pure compounds **297** and **298** were isolated in 25% and 20% yield, respectively, via reversed phase HPLC [183,189].

In 2003, Lumbard and coworkers described a simple synthesis of **297** (BMX-1), **298 (**BMX-2) and 3-bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (**299**) (BMX-3) from 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (**264b**) (MX) (Scheme 104) [190].

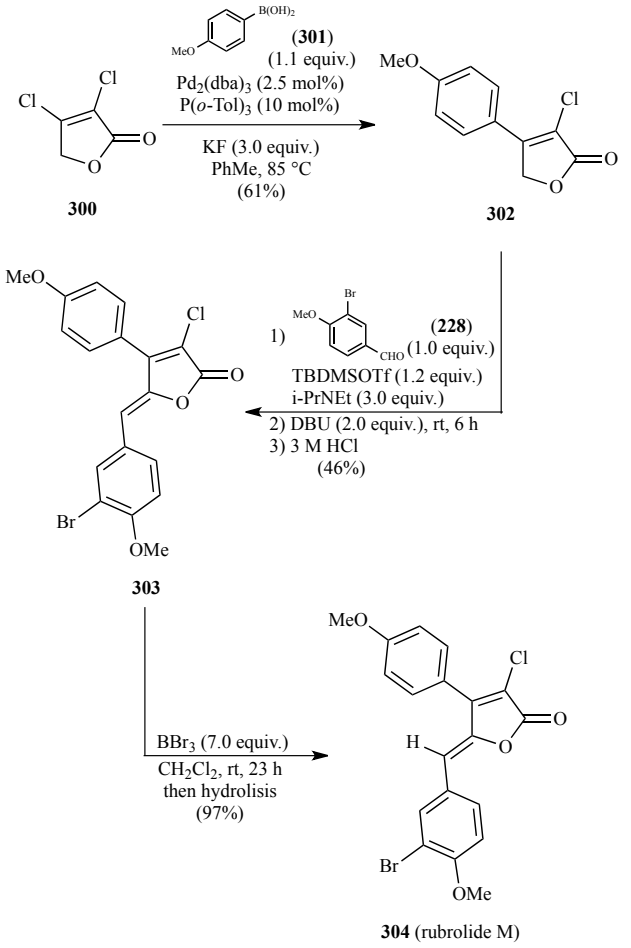


Scheme 104. Synthesis of compounds **297–299** from **264b** (MX)

They reported that the reaction of MX with 110 equiv of ethyl bromide and 0.45 equiv of NaBr in dry 1-methyl-2-pyrrolidinone at 75 °C for 28 h gave BMX-1 and BMX-2 in 18% and 21% yield, respectively. They also found that treatment of MX with 88.1 equiv of ethyl bromide and 2.0 equiv of NaBr in dry 1-methyl-2-pyrrolidinone at 100 °C for 24 h produced BMX-2 and BMX-3 in 6% and 32% yield, respectively (Scheme 104) [190].

In 2000, Messeguer and coworkers evaluated the mutagenic activity of compounds BMX-1, BMX-2 and BMX-3 by employing the Ames test with *Salmonella typhimurium* strain TA98 and TA100 and found that the mutagenic potencies in TA100 without S9 metabolic activation were 22.05 ± 3.15 revertants/ng for BMX-1 (**297**), 28.64 ± 2.65 revertants/ng for BMX-2 (**298**) and 37.29 ± 5.73 revertants/ng for BMX-3 (**299**) [189]. Notably, the mutagenic potencies proved to be six-to-nine fold lower in the TA98 strain without metabolic activation [189].

In 2002, our research group described the first synthesis of rubrolide M {(*Z*)-5-[1-(3-bromo-4-hydroxyphenyl)methylene]-3-chloro-4-(4-hydroxyphenyl)-2(5*H*)-furanone} (**304**) (Scheme 105) [123], a natural compound isolated from the ascidian *Synoicum blochmanni* [49].

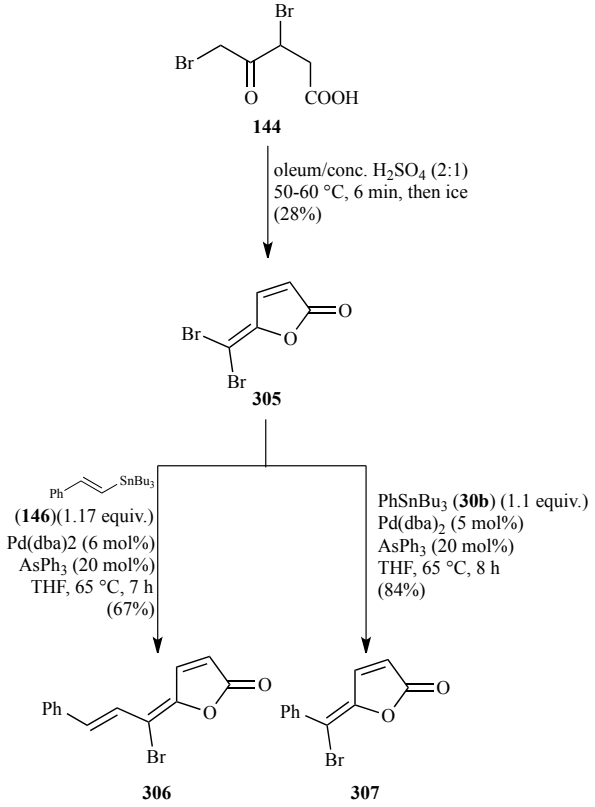


Scheme 105. Regio- and stereoselective synthesis of rubrolide M **(304)**

The stereo- and regioselective synthesis of **304** began with the Suzuki-Miyaura cross-coupling reaction of 3,4-dichloro-2(5*H*)-furanone (**300**) with 1.1 equiv of arylboronic acid **301** in the presence of KF as the base, a $Pd_2(dba)_3/P(o\text{-}Tol)_3$ catalyst system and using toluene as solvent, which gave compound **302** in 61% yield. This 2(5*H*)-furanone derivative was then treated with 1.2 equiv of TBDMSOTf, 3.0 equiv of *i*-Pr_2NEt and 1.0 equiv of 3-bromo-4-methoxybenzaldehyde (**228**) in CH_2Cl_2 at room temperature and the resulting crude aldol derivative was treated with 2.0 equiv of DBU at room temperature for 6 h. Acidification of the resulting reaction mixture led to conpound **303** in 46% yield, which on treatment with 7.0 equiv of BBr_3 in CH_2Cl_2 at room temperature, followed by hydrolysis provided rubrolide M (**304**) in 97% yield [123].

In 2003, we evaluated the cytotoxic activity *in vitro* of rubrolide M against the NCI three-cell line panel consisting of MCF-7, SF-268 and NCI-H460 cancer cells and found that this compound was significantly cytotoxic against all three cell lines [191].

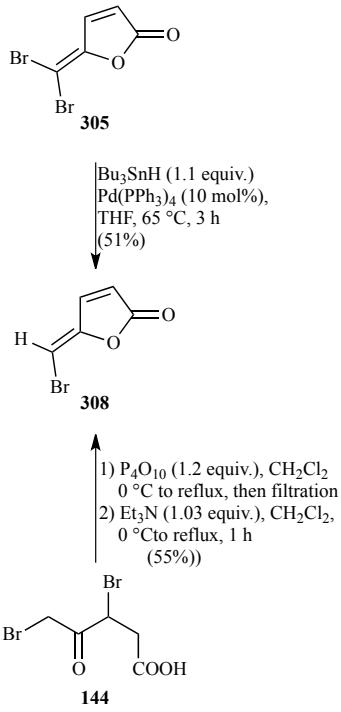
In 2004, Brückner and coworkers described low yielding stereoselective routes to (*Z*)-5-[*trans*-1-bromo-3-phenyl-2-propenylidene]-2(5*H*)-furanone (**306**) and (*Z*)-5-(1-bromo-1-phenylmethylene)-2(5*H*)-furanone (**308**) in which of 3,5-dibromolevulinic acid (**144**) was the starting material (Scheme 106) [102].



Scheme 106. Stereoselective synthesis of compounds **306** and **307**

The syntheses began with the reaction of easily accessible compound **144** [103,192] with a 2 : 1 mixture of oleum and concd. sulfuric acid at 50–60 °C for 6 min, which led to 5-(dibromomethylene)-2(5*H*)-furanone (**305**) in 28% yield. The subsequent $Pd(dba)_2/AsPh_3$-catalyzed Stille-type reaction of **305** with (*E*)-2-phenylethenyltributyltin (**146**) in THF at 65 °C produced stereoisomerically pure **306** in 67% yield. Furthermore, an analogous $Pd(dba)_2/AsPh_3$-catalyzed cross-coupling reaction of **305** with phenyltributyltin (**30b**) provided compound **307** in 84% yield [102].

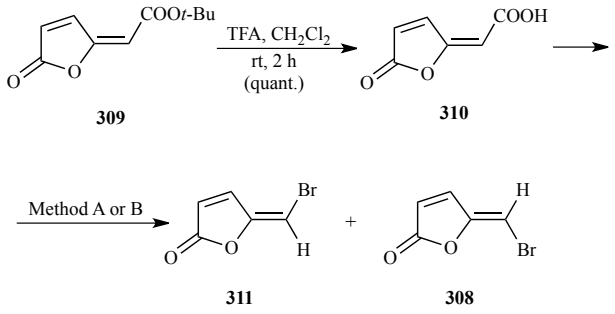
One year later, Brückner and coworkers synthesized (*Z*)-5-(bromomethylene)-2(5*H*)-furanone (**308**) in 51% yield by stereoselective reduction of 5-(dibromomethylene)-2(5*H*)-furanone (**305**) with 1.1 equiv of Bu_3SnH in THF at 65 °C in the presence of 10 mol% $Pd(PPh_3)_4$ (Scheme 107) [192]. Compound **308** was in turn obtained in 55% yield by treatment of 3,5-dibromolevulinic acid (**144**) with 1.2 equiv of P_4O_{10} in CH_2Cl_2 under reflux, followed by reaction with 1.03 equiv of Et_3N in CH_2Cl_2 at first at 0 °C and then under reflux for 1 h (Scheme 107) [192].



Scheme 107. Stereoselective synthesis of (*Z*)-5-(bromomethylene)-2(5*H*)-furanone (**307**)

In 2006, Benneche and coworkers developed a synthesis of (*Z*)-5-(bromomethylene)-2(5*H*)-furanone (**308**) and its (*E*)-stereoisomer, **311** (Scheme 108) [193] starting from the α,β-unsaturated ester **309** [194]. They reported that treatment of **309** with TFA in CH_2Cl_2 at room temperature for 2 h gave (*E*)-2-(5-oxofuran-2(5*H*)-ylidene)acetic acid

(**310**) in quantitative yield. They then found that addition of 4.0 equiv of bromine to **310** in $CDCl_3$ solution, followed by treatment of the resulting adduct with 1.08 equiv of Et_3N in a microwave oven for 1 mn in the presence of DMF (*Method A*) gave **311** in 7% yield together with **308** in 46% yield. On the other hand, the halodecarboxylation reaction of **310** with 1.07 equiv of bis(2,4,6-trimethylpyridino)bromine(I) hexafluorophosphate [$Br^+(coll)_2PF_6^-$] [195] in CH_2Cl_2 at 0 °C for 15 min and at room temperature for 2 h (*Method B*) gave stereoisomerically pure **311** in 22% yield (Scheme 108) [193].

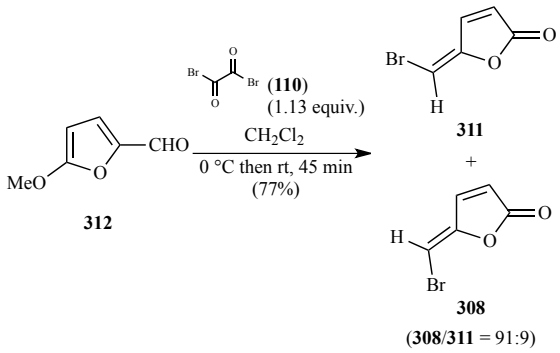


Method A: a) Br_2 (4.0 equiv.), $CDCl_3$, rt, 3 h;
b) Et_3N (1.08 equiv.), DMF, MW, 1 min
Method B: $Br^+(coll)_2PF_6^-$ (1.07 equiv.), CH_2Cl_2cf, 0 °C, 15 min, rt, 2 h

Method	Yield (%)	**311**/**308**
A	53	13/87
B	22	100/0

Scheme 108. Synthesis of (*E*)- and (*Z*)-5-(bromomethylene)-2(5*H*)-furanone, (**311**) and (**308**), respectively

More recently, Benneche and coworkers synthesized in 77% yield a mixture of (*E*)- and (*Z*)-5-(bromomethylene)-2(5*H*)-furanone in a 91 : 9 ratio, respectively, by reactiong 5-methoxyfurfural (**312**) with 1.13 equiv of oxalyl bromide (**110**) in CH_2Cl_2 (Scheme 109) [196].



Scheme 109. Synthesis of a mixture of (*E*)- and (*Z*)-5-(bromomethylene)-2(5*H*)-furanone from 5-methoxyfurfural (**312**)

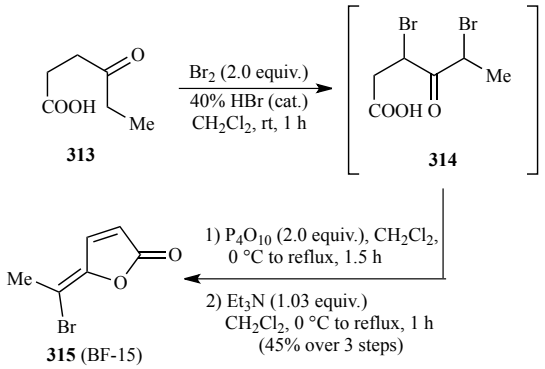
(*Z*)-5-(Bromomethylene)-2(5*H*)-furanone (**308)** has also been the subject a several studies concerning its biological activity. In 2002, Givskov and coworkers reported that this compound is capable of interfering with *N*-acyl homoserine lactone (AHL)-mediated QS in *Pseudomonas aeruginosa* and demonstrated that it specifically represses expression of a *PlasB-gfp* reporter fusion without affecting growth or protein synthesis and reduces the production of important virulence factors [197]. They also applied **308** to *P. aeruginosa* biofilms and found that the green fluorescent protein (Gfp) analysis that **308** penetrates microcolonies and blocks cell signaling and QS in most biofilm cells [197].

In 2004, Wu and coworkers showed that **308** interfers with the action of AHL molecules and inhibits gene expression regulated by QS systems in *P. aeruginosa in vivo* [168]. These authors also found that **308** exerts favourable therapeutic effects in *P. aeruginosa* lung infections in mice [168].

In 2007, Lönn-Stensrud and coworkers found that **308** inhibits biofilm formation and bioluminescence induction by *Streptococcus anginosus*, *S. intermedius* and *S. mutans* as well as bioluminescence induction by *Vibrio harveyi* BB152 [198].

In 2013, Vestby and coworkers investigated the use of compound **308** against the establishment of biofilm by *Salmonella* serotype Agona and *E. coli* O103:H2 and found that this brominated furanone inhibits biofilm formation without being bactericidal [199]. They also demonstrated that **308** effects both swimming and swarming motility without, however, affecting the expression of flagella [199].

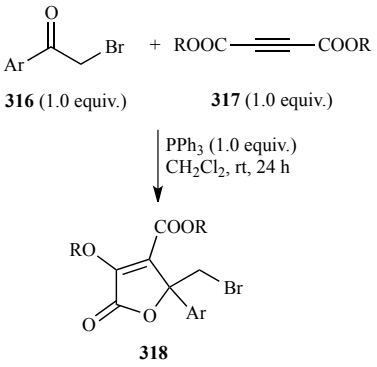
In the same year, Luk and coworkers carried out the synthesis of (*Z*)-5-(1-bromoethylidene)-2(5*H*)-furanone (**315**) in three steps and 45% overall yield starting from 4-oxohexanoic acid (**313)** (Scheme 110) [200]. In particular, a CH_2Cl_2 solution of **313** was reacted with 2.0 equiv of bromine and a catalytic quantity of 40% HBr at room temperature for 1 h. The resulting crude dibromocarboxylic acid **314** was dissolved in CH_2Cl_2 and treated with 2.0 equiv of P_4O_{10} at 0 °C for 0.5 h and then heated at reflux for 1.5 h. Finally, the solid intermediate, which was obtained by centrifugation of the reaction mixture, was reacted with 1.03 equiv of Et_3N at 0 °C for 1 h and under reflux for 1 h providing **315** (BF-15) in 45% yield based on **313** (Scheme 110) [200].



Scheme 110. Synthesis of (*Z*)-5-(1-bromoethylidene)-2(5*H*)-furanone (**315**)

Interestingly, compound **315** was found capable to inhibit the production of the virulence factor elastase B of *P. aeruginosa* PAO1 with little inhibition of biofilm formation [200].

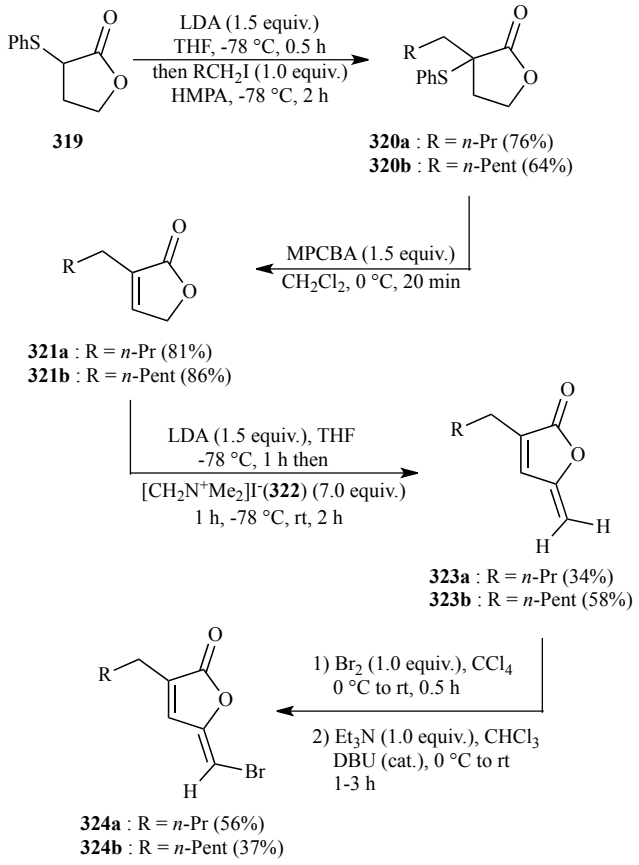
In 2012, 3-alkoxycarbonyl-5-aryl-5-bromomethyl-2(5H)-furanones **318** were synthesized by Hassanabadi and coworkers via a one-pot process involving the reaction of phenacyl bromides **316** with equimolar amounts of dialkyl acetylenedicarboxylates **317** and 1.0 equiv of PPh_3 in CH_2Cl_2 at room temperature for 24 h [201]. This protocol allowed the authors to prepare compounds **318a**, **318b** and **318c** in 88%, 6% and 92% yield, respectively (Scheme 111) [201].



318	R	Ar	Yield (%)
318a	Me	4-ClC_6H_4	88
318b	Et	4-ClC_6H_4	86
318c	*t*-Bu	4-ClC_6H_4	92

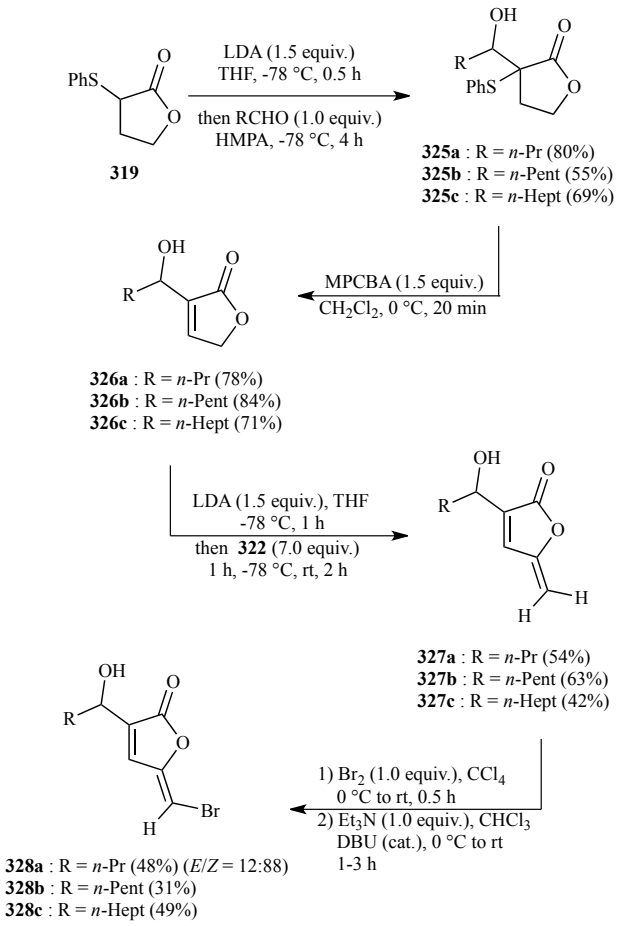
Scheme 111. One-pot synthesis of compounds **318a–c**

In 2013, Soulère, Queneau and coworkers carried out the synthesis of (Z)-3-alkyl-5-(bromomethylene)-2(5H)-furanones **324a** and **324b**, which are analogues of naturally-occurring bacterial QS inhibitors, via a novel reaction sequence in which α-phenylthio-γ-buryrolactone (**319**) was used as the starting material (Scheme 112) [202]. Specifically, treatment of **319** with LDA in THF at –78°C followed by addition of the required alkyl iodides in HMPA at –78 °C gave 3-alkyl-3-phenylthiodihydrofuran-2(3*H*)-ones **320a** and **320b** in good yields. Subsequent oxidation-elimination reaction of these substances by treatment with MCPBA in CH_2Cl_2 at 0 °C provided compounds **321a** and **321b** in 81% and 86% yield, respectively. They were converted to the corresponding 5-methylene-2(5*H*)-furanones **323a** and **323b** in 34% and 58% yield, respectively, by treatment with LDA in THF at –78 °C and then with dimethylmethylideneammonium iodide (**322**) (Eschenmoser's salt). Finally, a bromine addition-elimination sequence [185] allowed to obtain compounds **324a** and **324b** in 56% and 37% yield, respectively (Scheme 112) [202].



Scheme 112. Stereoselective synthesis of compounds **324a** and **324b**

Soulère, Queneau and coworkers also synthesized (*Z*)-5-(bromomethylene)-3-[1-(hydroxyalkyl)]-2(5*H*)-furanones **328a–c** through a route in which **319** was the starting material (Scheme 113).

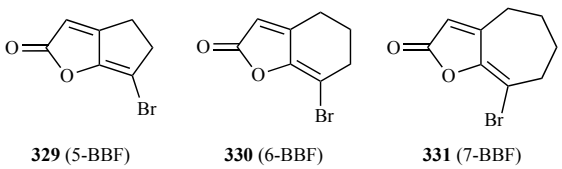


Scheme 113. Synthesis of (*Z*)-5-(bromomethylene)-3-[1-(hydroxyalkyl)]-2(5*H*)-furanones **329a–c**

The reaction of **319** with 1.5 equiv of LDA in THF at –78 °C for 0.5 h followed by addition of 1.0 equiv of the required alkyl aldehydes in HMPA at –78 °C produced compounds **325a–c** in yields ranging from 55% to 80%. An oxidative elimination reaction, which was carried out by treatment of **325a-c** with 1.5 equiv of MCPBA in CH_2Cl_2 at 0 °C gave 3-(1-hydroxyalkyl)-2(5*H*)-furanones **326a–c** in high yields. These compounds were then efficiently converted to the corresponding 5-methylene derivatives, **327a–c**, in satisfactory yields by using Eschenmoser's salt **322**. Finally, a bromine addition-elimination sequence, which was carried out by a procedure identical to that used to prepare compounds **324a,b**, provided **328a** in 48% yield and 88% stereoisomeric purity, and stereoisomerically pure compounds **328b** and **328c** in 31% and 49% yield, respectively (Scheme 113) [202].

Soulère, Queneau and coworkers also tested compounds **324a**, **324b**, **325a**–**b**, **328a-c**, and **329a-c** for their ability to inhibit the *Vibrio fischeri* QS system and found thay (*Z*)-3-butyl-5-(bromomethylene)-2(5*H*)-furanone (**325a**) with an IC_{50} of 0.6 μM was the most active compound among all these fimbrolide analogues. It was also verified that, for this substance, the bioluminescence inhibition did not result from antimicrobial activity rather than QS inhibition [202].

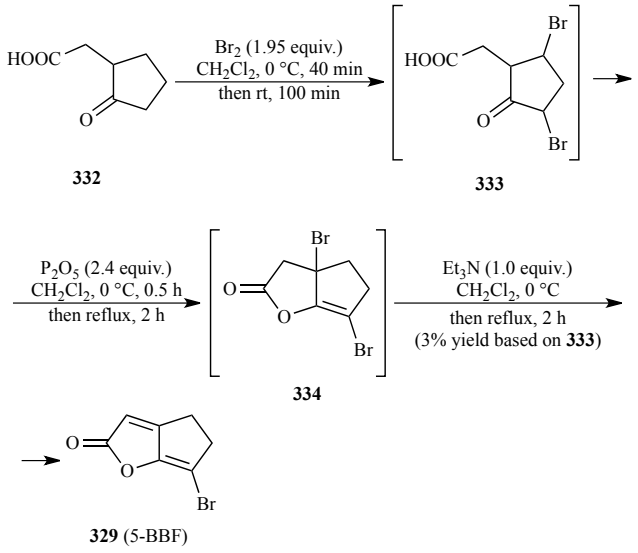
In 2014, in a study on the effect of bicyclic brominated furanones (BBF) on QS, Wang, Luk and coworkers synthesized compounds **329** (5-BBF), **330** (6-BBF) and **331** (7-BBF) (Figure 23) [25].



329 (5-BBF) **330** (6-BBF) **331** (7-BBF)

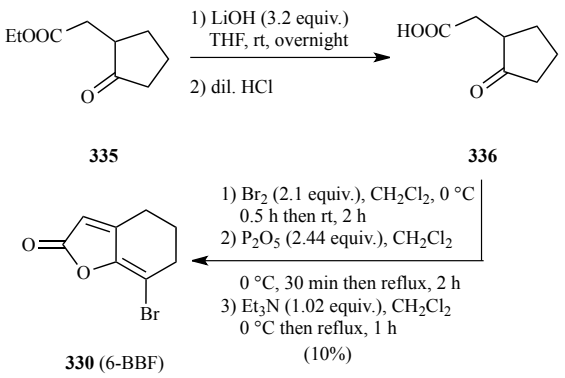
Figure 23. Structures of bicyclic brominated furanones **329–331**

The synthesis of compound **329** was carried out in only 3% yield by treatment of 2-oxocyclopentaneacetic acid (**332**) with 1.95 equiv of bromine at 0 °C for 40 min and then at room temperature for 100 min, followed by cyclization of the resulting dibrominated carboxylic acid **333** with P_2O_5 in CH_2Cl_2 at 0 °C for 0.5 h and then under reflux for 2 h. Finally, dehydrobromination of the resulting crude compound **334** by treatment with 1.04 equiv of Et_3N at first at 0 °C and then under reflux for 2 h gave compound **329** (5-BBF) (Scheme 114) [25].



Scheme 114. Synthesis of compound **329** (5-BBF)

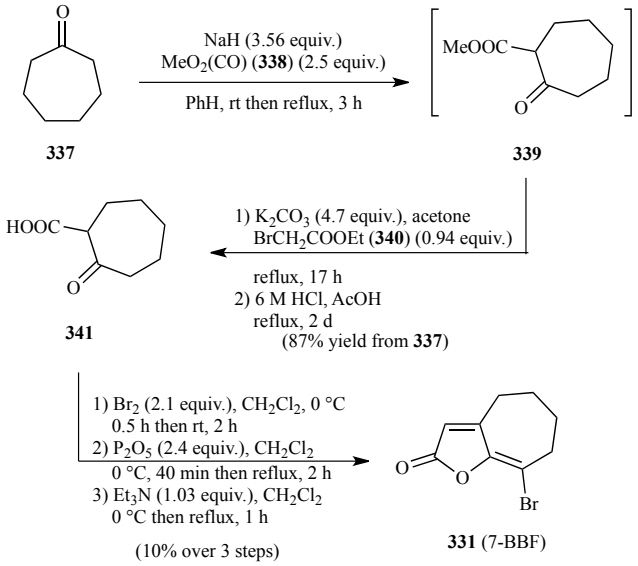
A similar reaction sequence involving 2-oxocyclohexaneacetic acid (**336**), which was obtained by saponification of the corresponding ethyl ester **335** allowed for the preparation of compound **330** (6-BBF) in 16% overall yield (Scheme 115) [25].



Scheme 115. Synthesis of compound **330** (6-BBF)

The synthesis of **331** (7-BBF) was instead carried out starting from cycloheptanone (**337**) (Scheme 116). Specifically, **337** was reacted with 3.56 equiv of NaH in benzene and the resulting enolate was treated with 2.5 equiv of dimethyl carbonate (**338**) providing crude methyl 2-oxo-1-cycloheptanecarboxylate (**339**). An acetone solution of **339** was then treated with 4.7 equiv of K_2CO_3 and 0.94 equiv of ethyl bromoacetate (**340**) and the resulting mixture was refluxed for 17 h. The oil, which was obtained after concentration of the reaction mixture, was treated with a mixture of 6 M HCl and acetic acid providing compound **341** in 87% yield based on **337**. Finally, dibromination of this intermediate, dehydration and Et_3N-mediated elimination produced compound **331** (7-BBF) in 10% yield (Scheme 116) [25].

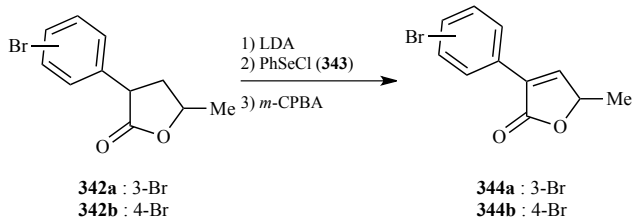
Next, 5-BBF, 6-BBF and 7-BBF were found to interfere with QS and QS-controlled activitites in Gram-negative bacteria. In fact, these compounds appeared able to inhibit biofilm formation by *E. coli* and *P. aeruginosa* and to inhibit elastase B production by *P. aeruginosa* at nonmicrobicidal concentrations [25]. The effect of compounds 5-BBF, 6-BBF and 7-BBF on biofilm formation of *P. aeruginosa* was investigated using a wild strain PA01-GFP, which constitutively expresses green fluorescence proteins [203] and enables easy and direct visualization of biofilm. In the initial screening, it was found that, at 400 μM, 6-BBF provided more inhibition than 5-BBF and 7-BBF. Results were also obtained showing that 6-BBF and 7-BBF exhibit antagonistic activities for the transcriptional activator LasR protein in the *lasI* QS circuit in *P. aeruginosa*, while 5-BBF is a strong agonist of the *rhil* QS circuit [25].



Scheme 116. Synthesis of compound **331** (7-BBF)

In the last two decades, significant interest has also been directed to the synthesis and evaluation of the biological properties of 2(5*H*)-furanones featuring monobrominated aryl substituents. In 2000, Pour and coworkers synthesized racemic 3-(3-bromophenyl)-5-methyl- and 3-(4-bromophenyl)-5-methyl-2(5*H*)-furanone, (**344a**) and (**344b**), respectively, by conversion of saturated lactones **342a** and **342b** with LDA, reaction of the resulting enolates with phenylselenyl chloride (**343**), and oxidation with MCPBA with spontaneous selenoxide elimination of the resulting α-selenyl derivatives (Scheme 117) [204].

Compounds **344a** and **344b** were then evaluated for their *in vitro* antifungal activity against a set of clinical isolates of human pathogenic fungi and it was found that their minimal inhibitory concentration (MIC) against *Candida albicans* after 24 h was 7.81 μmol/L for **344a** and 31.25 μmol/L for **344b**. In addition, the MIC values for **344a** and **344b** against *Trichophyton mentagrophytes* after 72 h were proven to be 31.25 and 6.25 μmol/L, respectively, and to double after 120 h [204].



Scheme 117. Synthesis of 3-(bromophenyl)-5-methyl-2(5*H*)-furanones **344a,b**

In 2001, Pour and coworkers prepared racemic 3-(4-bromophenyl)-5-(hydroxymethyl)-2(5*H*)-furanone (**347**)

(Figure 24) from the corresponding saturated lactone **346** (Figure 24) using a reaction sequence similar to that depicted in Scheme 117 [205]. Compound **346** was in turn synthesized from (4-bromophenyl)acetic acid (**345**) (Figure 24) via a five-step route [205].

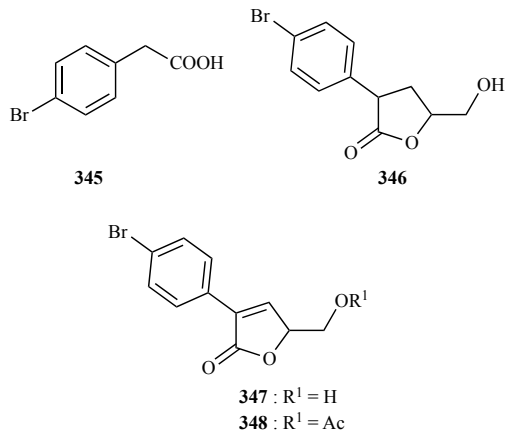


Figure 24. Structures of compounds **345–348**

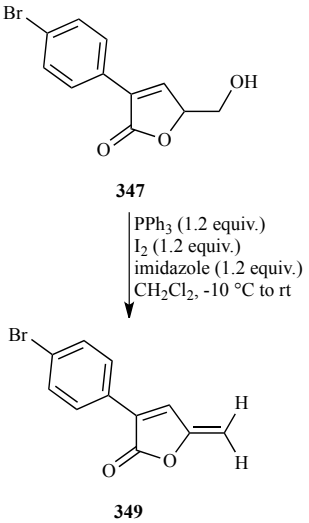
Compound **347** was subsequently converted to the corresponding acetate **348** (Figure 21) by acylation with acetyl chloride in CH_2Cl_2 at 0 °C in the presence of pyridine [205].

Compounds **347** and **348** were then evaluated for their antifungal activity against a set of human pathogenic fungi including the representatives of both yeast and filamentous strains and found that **347** exhibited a moderate antifungal effect which was much lower than that of the corresponding acetate **348**, a relatively lipophilic compound [205].

In 2004, compound **348**, also indicated as LNO18–22, was found to exhibit a broad spectrum of activity against a variety of pathogenic yeasts and molds including *Candida albicans*, *C. incospicua*, *C. krusei*, *Blastoschizomyces capitatus*, the *Trichosporon beigelii* complex, and *Aspergillus* species with decreased susceptibility to fluconazole [206].

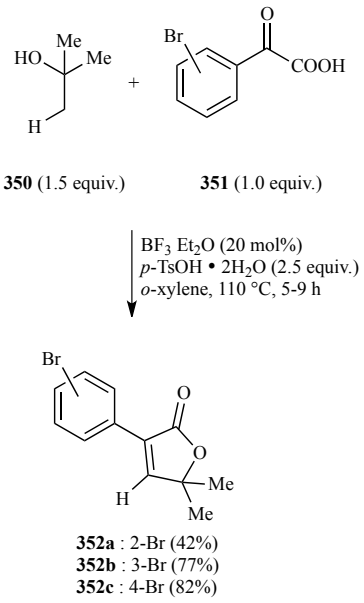
In 2006, the mechanism of action of **348** against *Candida albicans* was investigated by Vale-Silva and coworkers by using flow cytometry [207]. They determined that the potent fungicidal activity of this compound resulted in disruption of the plasmatic cell membrane of *C. albicans*.

Four years later, Pour and coworkers converted compound **347** to 5-methylene-3-(4-bromophenyl)-2(5*H*)-furanone (**349**) in 64% yield by treatment with 1.2 equiv of PPh_3, 1.2 equiv of iodine and 1.2 equiv of imidazole in dry CH_2Cl_2 at –10 °C and then at room temperature (Scheme 118) [208]. They then observed that **349** exhibited excellent activity against *C. albicans* ATCC44859 and *C. glabrata* strain and that this activity was identical to that of its precursor **347**. Compound **349** was also found to possess moderate cytostatic activity against CCRF-CEM cell lines. Moreover, cell cycle analysis of CCRF-CEM cells following treatment with **349** showed that this furanone is a necrotic agent [208].



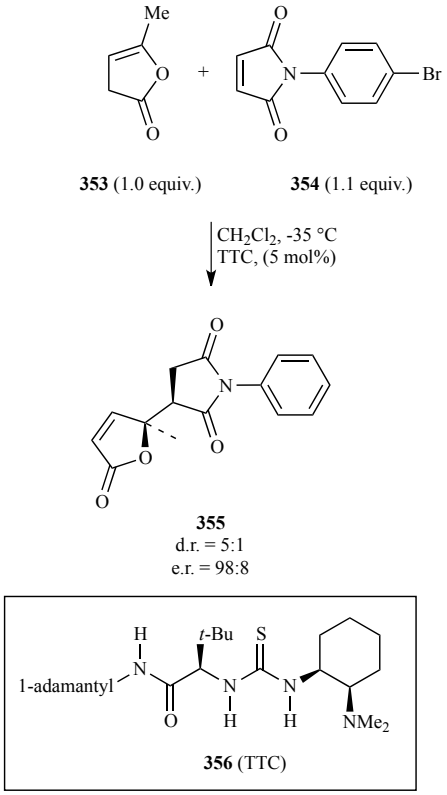
Scheme 118. Synthesis of 5-methylene-3-(4-bromophenyl)-2(5*H*)-furanone (**349**)

In 2015, 3-(bromophenyl)-5,5-dimethyl-2(5*H*)-furanones **352a–c** were efficiently synthesized by Mao and Zhu by using a practical and atom-economical method that involved the $BF_3{\cdot}Et_2O$ catalyzed, *p*-$TsOH{\cdot}2H_2O$-mediated annulation of 2-methylpropan-2-ol (**350**) with the required bromophenylglyoxylic acids **351** (Scheme 119) [209]. Specifically, the reaction of compounds **351a–c** with 1.5 equiv of **350** in *o*-xylene at 110 °C in the presence of 20 mol% $BF_3{\cdot}Et_2O$ and 2.5 equiv of *p*-$TsOH{\cdot}2H_2O$ produced compounds **352a**, **352b** and **352c** in 42%, 77% and 82% yield, respectively [209].



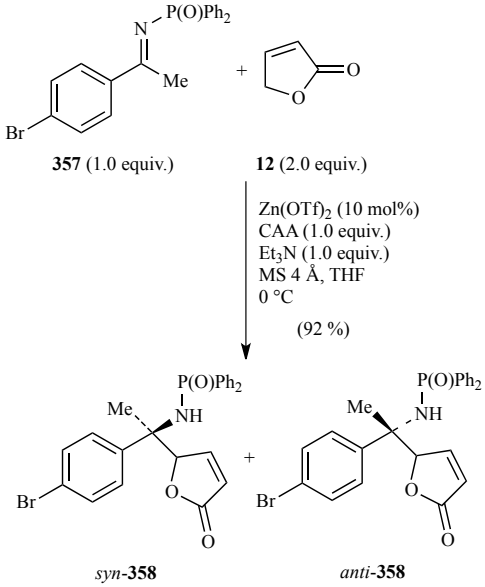
Scheme 119. Synthesis of 3-(bromophenyl)-5,5-dimethyl-2(5*H*)-furanones **352a–c**

In 2012, 2(5*H*)-furanone **355** was synthesized by Manna and Mukherjee in 93% yield with high diastereo- and enantioselectivity by asymmetric direct vinylogous Michael reaction between α-angelica lactone (**353**) and *N*-4-bromophenylmaleimide (**354**) in CH_2Cl_2 at –35 °C in the presence of 5 mol% the thiourea homochiral catalyst TTC (Scheme 120) [210].



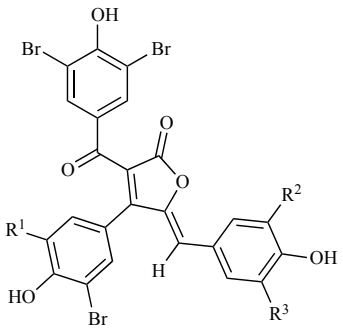
Scheme 120. Asymmetric synthesis of 2(5*H*)-furanone **355**

In 2015, Nakamura and coworkers reported that treatment of *N*-diphenylphosphinoylketimine **357** with 2.0 equiv of 2(5*H*)-furanone (**12**), 10 mol% $Zn(OTf)_2$, 10 mol% cinchona alkaloid amide (CAA) and 1.0 equiv of Et_3N in THF at 0 °C for 24 h in the presence of 4 Å molecular sieves produced in 92% yield a 1 : 99 mixture of *syn*- and *anti*-furanone **358** in which the e.r. for the *anti*-isomer was 93 : 7 (Scheme 121) [211]. Compound **357**, which was used in this asymmetric direct vinylogous Mannich reaction, was prepared from the corresponding methyl aryl ketone by using a literature procedure [212].



Scheme 121. Enantioselective synthesis of *anti*-2(5*H*)-furanone **358**

Still in 2015, Franck and coworkers synthesized some analogues of cadiolide A (**359a**), cadiolide B (**359b**) and cadiolide C (**359c**) (Figure 25) [213], three brominated, densely functionalized 2(5*H*)-furanone derivatives which were isolated in 1998 from an Indonesian ascidian of the genus *Botryllus* [214] and in 2012 from the Korean tunicate *Pseudodistoma antiboja* [215].

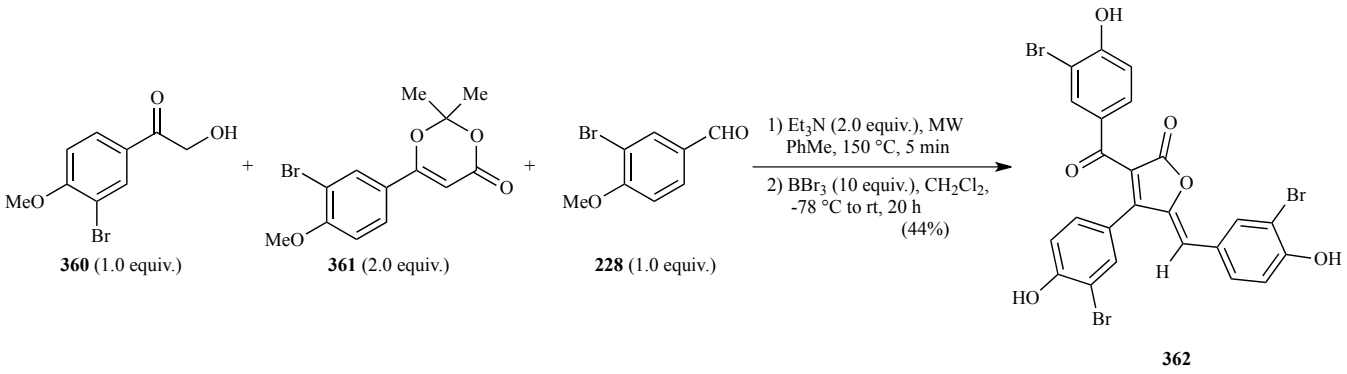


359a : R^1= Br; R^2=R^3= H (cadiolide A)
359b : R^1=R^2=R^3= Br (cadiolide B)
359c : R^1=R^2= H; R^3= Br (cadiolide C)

Figure 25. Structures of cadiolide A (**359a**), cadiolide B (**359b**) and cadiolide C (**359c**)

These analogues, which included 2(5*H*)-furanones featuring monobrominated phenyl substituents, were evaluated against four Gram-positive bacterial strains, *Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus* and *Enterococcus faecalis*, and four Gram-negative bacterial strains, *Salmonella typhi, E. coli* 100, *E. coli* 405 and *Erwinia carotovora*. Among the analogues with monobrominated substituents, (*Z*)-3-(3-bromo-4-hydroxybenzoyl)-5-(3-bromo-4-hydroxybenzylidene)-4-(3-bromo-4-hydroxyphenyl)-2(5*H*)-furanone (**362**) was the most potent compound with a MIC value of 1.95 μg/mL against *B. cereus*, *S. aureus*, *E. faecalis*, *S. typhi* and *E. coli* 405 [213].

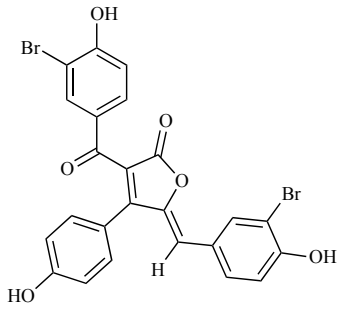
This compound was synthesized in 44% yield by a one-pot process involving the reaction of α-hydroxyketone **360** with 2.0 equiv of dioxinone **361**, 1.0 equiv of aldehyde **228** and 2.0 equiv of Et_3N in toluene at 150 °C under microwave irradiation for 15 min and the subsequent *O*-demethylation of the resulting crude product by treatment with 10 equiv of BBr_3 in CH_2Cl_2 at room temperature for 20 h (Scheme 122) [213].



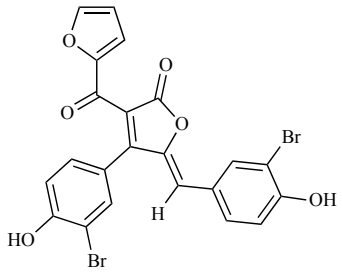
360 (1.0 equiv.) **361** (2.0 equiv.) **228** (1.0 equiv.) **362**

Scheme 122. One-pot synthesis of (*Z*)-3-(3-bromo-4-hydroxybenzoyl)-5-(3-bromo-4-hydroxybenzylidene)-4-(3-bromo-4-hydroxyphenyl)-2(5*H*)-furanone (**362**)

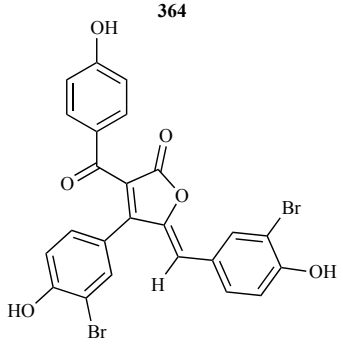
Interestingly, a similar one-pot procedure was used to prepare cadiolide analogues **363**, **364** and **365** (Figure 26) in 38%, 37% and 30% yield, respectively [213].



363



364



365

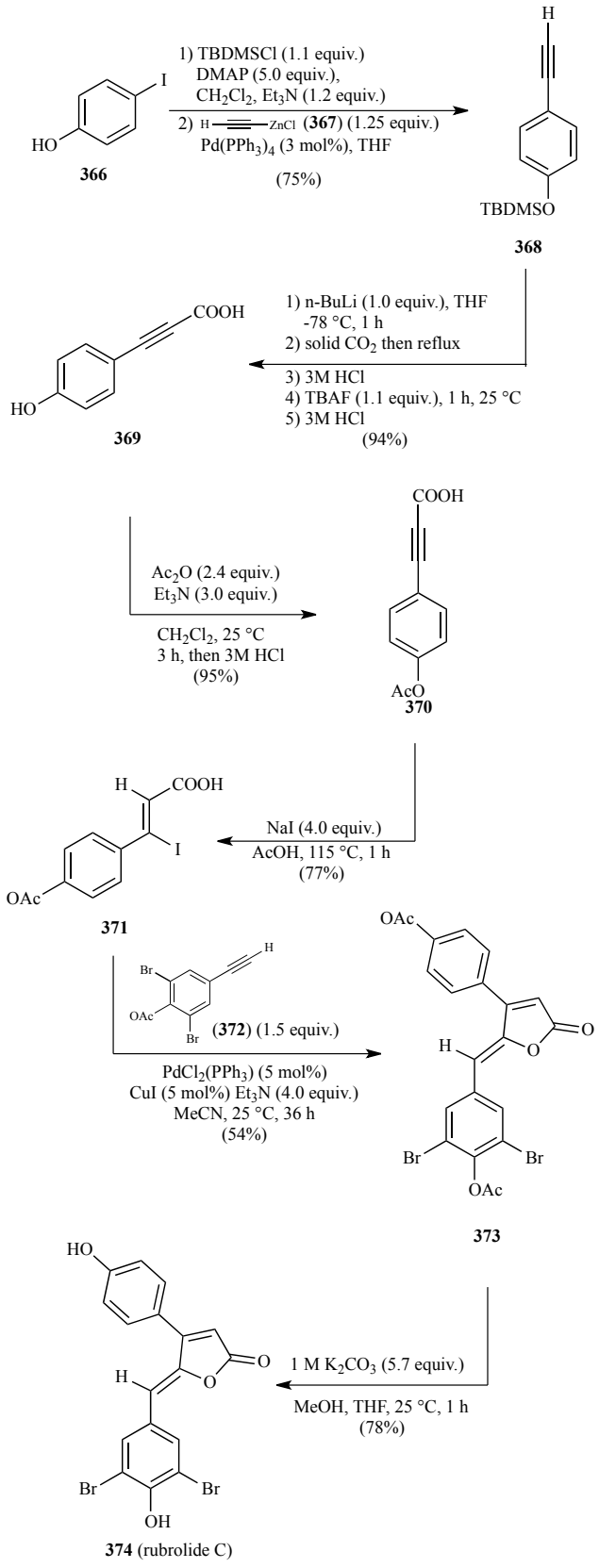
Figure 26. Structures of cadiolide analogues **363–365**

7. SYNTHESIS AND BIOACTIVITY OF 2(5*H*)-FURANONE DERIVATIVES FEATURING DIBROMINATED SUBSTITUENTS

As mentioned in Section 6, in 2004, Brückner and coworkers synthesized 5-(dibromomethylene)-2(5*H*)-furanone (**305**) by treatment of 3,5-dibromolevulinic acid (**144**) with a 2 : 1 mixture of oleum and concd. sulfuric acid at 50–60 °C (Scheme 106) [102].

In 2008, Ren, Luk and coworkers reported that the reaction of α-methyllevulinic acid (**248**) with 2 equiv of bromine at 35–40 °C for 1 h, followed by treatment of the resulting crude reaction mixture with 95–98% sulfuric acid at 110 °C for 20 min gave a mixture of 5-(dibromomethylene)-3-methyl-2(5*H*)-furanone (**250**) (BF-9), 4-bromo-5-(dibromomethyl)-3-methyl-2(5*H*)-furanone (**251**) (BF-14) and (*E*)-4-bromo-5-(bromomethylene)-3-methyl-2(5*H*)-furanone (**249**) (BF-8) in 12%, 2.7% and 13% yield, respectively (Scheme 90) [174]. These authors also found that the reaction of compound **250** with 2.0 equiv of NBS in CCl_4 under reflux for 12 h in the presence of a catalytic quantity of dibenzoyl peroxide gave 3-(dibromomethyl)-5-(dibromomethylene)-2(5*H*)-furanone (**269**) (BF-10) and 3-(bromomethyl)-5-dibromomethylene-2(5*H*)-furanone (**268**) (BF-11) in 13% and 50% yield, respectively (Scheme 96) [174]. Interestingly, compounds **250** (BF-9) and **269** (BF-10) exhibited strong biofilm inhibition by *E. coli* at 60 μg/mL without effects on *E. coli* growth [174].

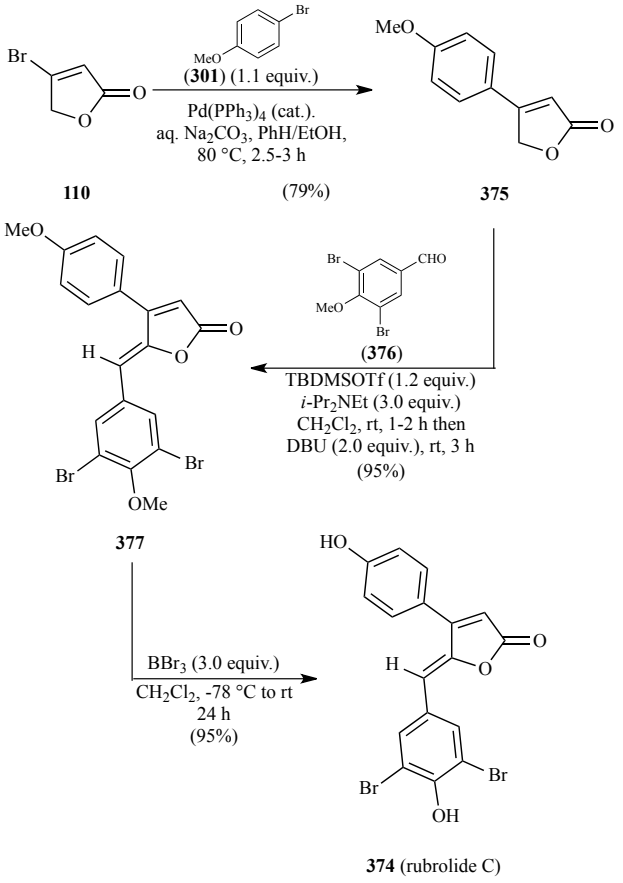
In 1997, Kotora and Negishi carried out the first total synthesis of rubrolide C (**374**) [216], a metabolite of the colonial tunicate *Ritterella rubra* which is a member of a family of compounds that are potent *in vitro* antibiotics and show moderate but selective inhibition of protein phosphatases I and 2A [48]. Scheme 123 outlines the reaction sequence used for the synthesis of this natural product.



Scheme 123. First total synthesis of rubrolide C (**374**)

Thus, protection of the phenol group of 4-iodophenol (**366**) as TBDMS ether, followed by Pd-catalyzed reaction with ethynylzinc chloride (**367**) gave 1-alkyne **368** in 75% yield. This compound was then converted to 3-(hydroxyphenyl)propynoic acid (**369**), which was reacted with Ac_2O and Et_3N ;in CH_2Cl_2 and subsequently with 3 M HCl providing 3-(4-acetoxyphenyl)propynoic acid (**370**) in 95% yield. Hydroiodination of **370** by treatment with NaI and AcOH at 115 °C gave stereoselectively and in a good yield (*Z*)-3-(4-acetoxyphenyl)-3-iodoprop-2-enoic acid (**371**) which underwent $PdCl_2(PPh_3)_2$/CuI-catalyzed cross-coupling/lactonization reaction by treatment witth 1-alkyne **372** in acetonitrile in the presence of Et_3N. The reaction led to rubrolice C diacetate (**373**) in 54% yield. Finally, treatment of **373** with 1 M K_2CO_3 in a mixture of MeOH and THF gave rubrolide C (**374**) in 78% yield [216].

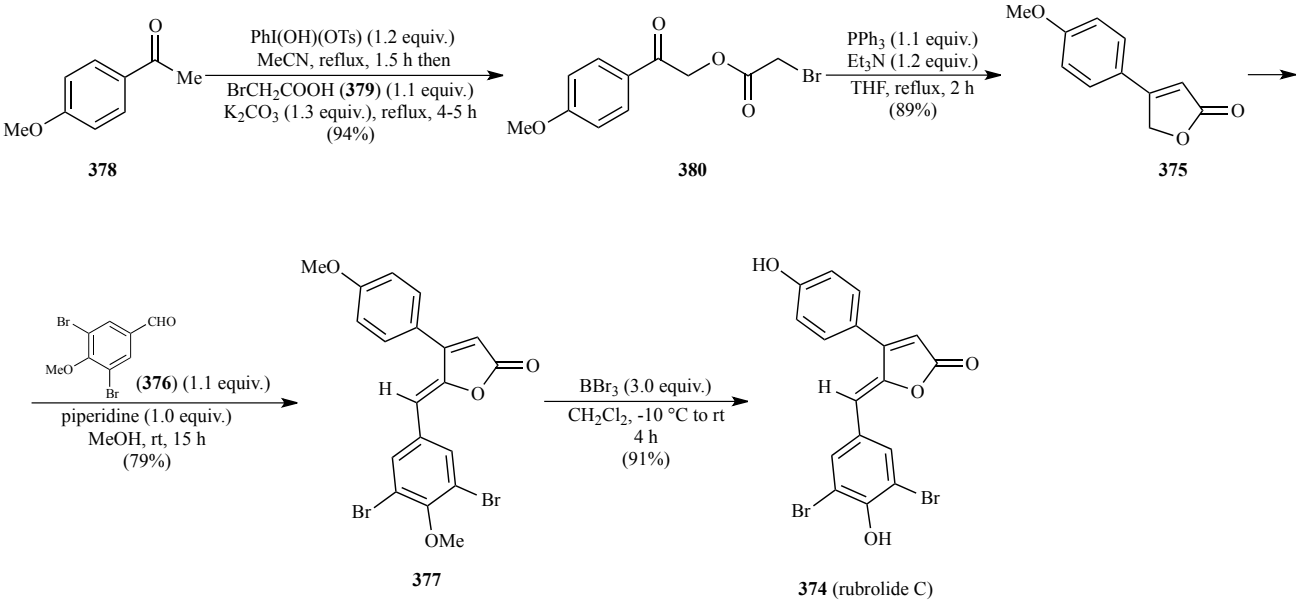
In 1998, Boukouvalas and coworkers described another synthesis of rubrolide C (Scheme 124) [47] that involved a lower number of steps compared to that reported by Kotora and Negishi [216] and was higher yielding. The Pd-catalyzed Suzuki-Miyaura cross-coupling of 4-bromo-2(5*H*)-furanone (**108**) with arylboronic acid **301**, which gave compound **375** in 79% yield, was first step of this new synthesis.



Scheme 124. Synthesis of rubrolide C (**374**) from 4-bromo-2(5*H*)-furanone (**110**)

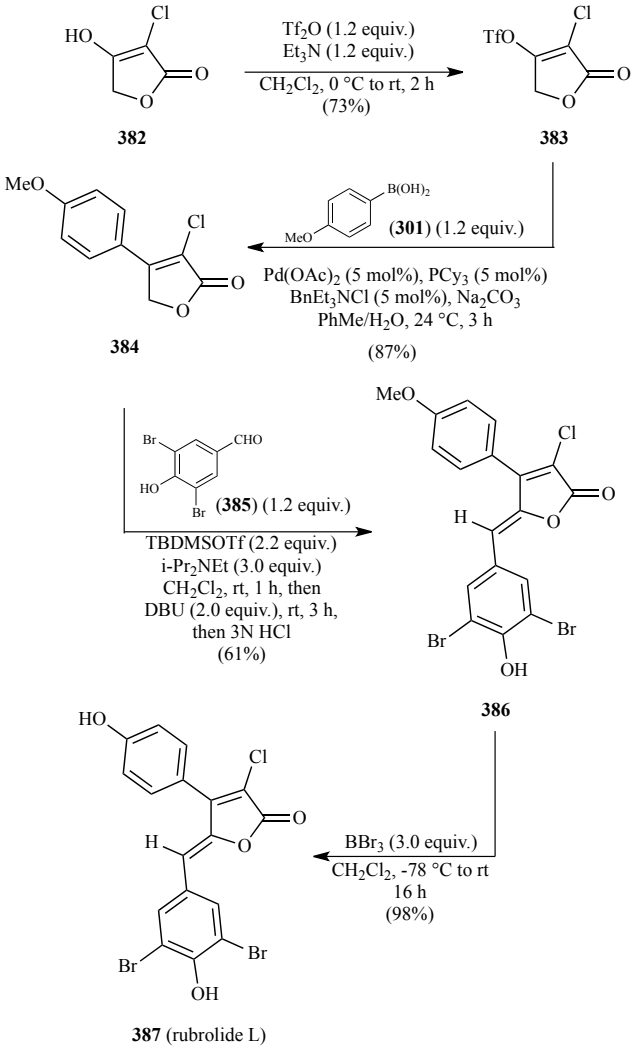
Aldolization of **375** with aldehyde **376** in the presence of TBDMSOTf and *i*-Pr_2NEt, followed by treatment with DBU gave stereoisomerically pure compound **377** in 95% yield. Finally, exposure of **377** to 3 equiv of BBr_3 in CH_2Cl_2 led to rubrolide C (**374**) in 95% yled [47].

More recently, Karade and coworkers reported a new efficient synthesis of rubrolide C (Scheme 125) in which the preparation of compound **374** via intramolecular Wittig reaction of 2-(4-methoxyphenyl)-2-oxoethyl 2-bromoacetate (**380**) with PPh_3 in the presence of Et_3N was a key step [217]. Conpound **380** was in turn obtained in 69% yield by treatment of 4-methoxyacetophenone (**378**) with 1.2 equiv of hydroxyl(tosyloxy)iodobenzene (known as Koser reagent) in acetonitrile under reflux, followed by entrapment of the resulting compound with bromoacetic acid (**379**) in the presence of K_2CO_3. The synthesis of rubrolide C was then completed in high yield by Knoevenagel condensation of **375** with aldehyde **376** and *O*-demethylation of the resulting compound **382** (Scheme 125) [217].



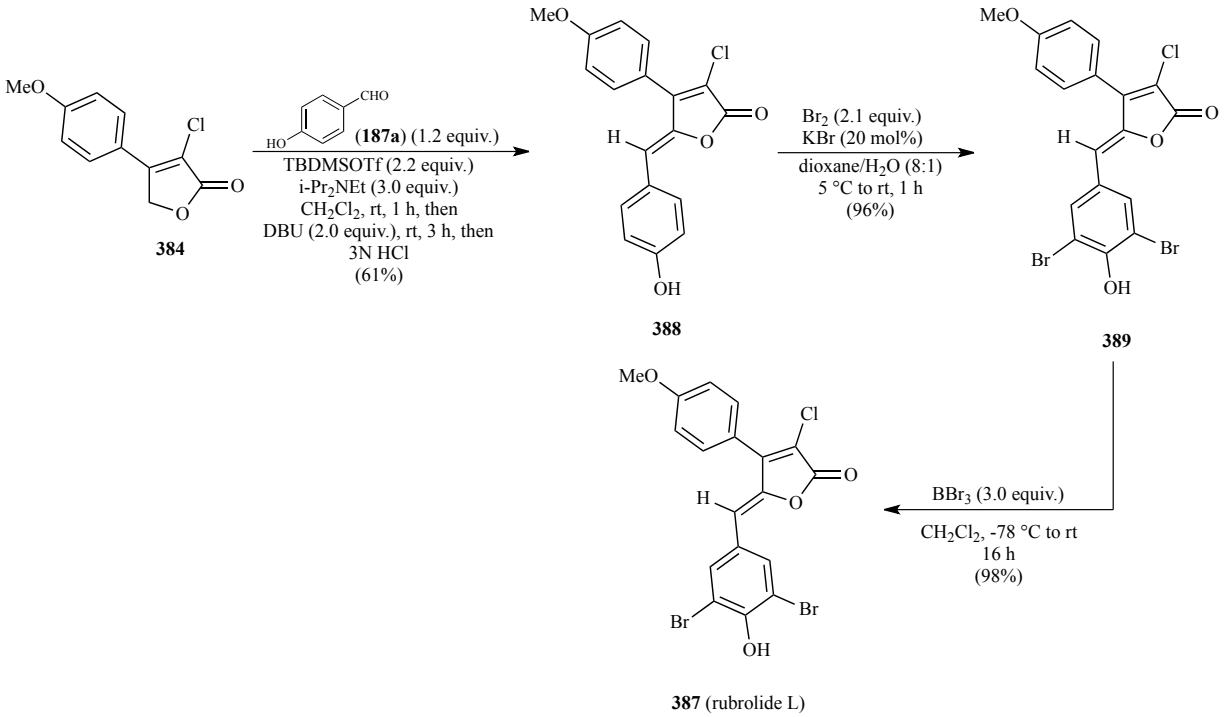
Scheme 125. Synthesis of rubrolide C (**374**) from 4-methoxyacetophenone (**378**)

In 2010, Boukouvalas and coworkers carried out the first synthesis of rubrolide L {3-chloro-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-4-hydroxyphenyl-2(5*H*)-furanone} (**387**) [218], an antitumor metabolite of the ascidian *Synoicum blochmanni* [49], which was found to inhibit human aldose reductase at submicromolar level [219]. The synthesis of **387** was achieved via two distinct pathways. In the first of these (Scheme 126), commercially available 3-chlorotetronic acid (**382**) was converted to triflate **383** in 73% yield. The chemoselective Suzuki-Miyaura cross-coupling reaction of **383** with 1.2 equiv of arylboronic acid **301** in a mixture of toluene an water in the presence of a $Pd(OAc)_2/PCy_3$ catalyst system, 5 mol% $BnEt_3NCl$ and Na_2CO_3 as the base gave 3-chloro-4-methoxyphenyl-2(5*H*)-furanone (**384**) in 87% yield. The subsequent aldolization reaction of **384** with aldehyde **385** in the presence of TBDMSOTf and *i*-Pr_2NEt, followed by treatment with DBU provided stereoisomerically pure **386** in 61% yield, which was then converted to rubrolide L (**387**) in 95% yield by BBr_3-mediated *O*-demethylation (Scheme 126) [218].



Scheme 126. Synthesis of rubrolide L (**387**) using compound **386** as an advanced intermediate

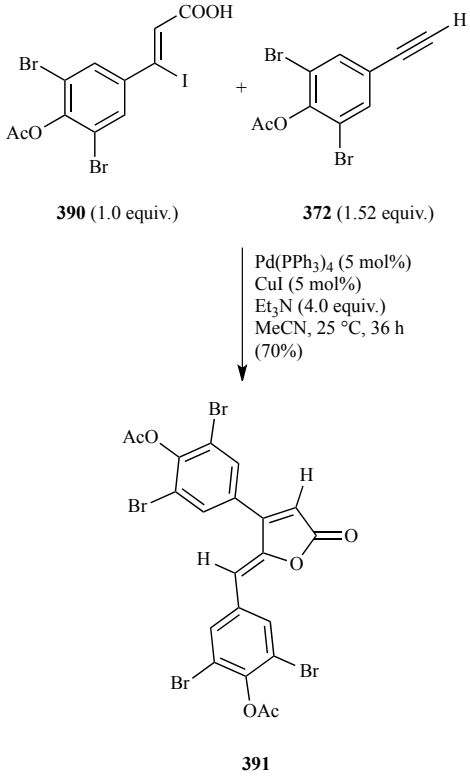
The second protocol used for the synthesis of **387** (Scheme 127) involved the conversion of compound **384** to (*Z*)-4-aryl-5-benzylidene-3-chloro-2(5*H*)-furanone **388**.



Scheme 127. Synthesis of rubrolide L (**387**) using compound **388** as an advanced intermediate

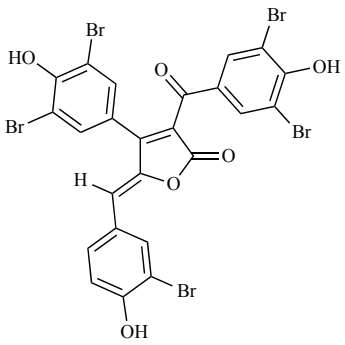
Bromination reaction of this compound using 2.0 equiv of bromine and 20 mol% KBr in a mixture of dioxane and water led to compound **389** in 96% yield. The synthesis of **387** was then completed in 95% yield by reacting **389** with 3 equiv of BBr_3 in CH_2Cl_2 [218].

On the other hand, a $Pd(PPh_3)_4$/CuI-catalyzed cross-coupling/lactonization reaction of (*Z*)-3-(4-acetoxy-3,5-dibromophenyl)-3-iodoprop-2-enoic acid (**390**) with 1-alkyne **372** was used in 1997 by Negishi and coworkers for the synthesis in 70% yield of rubrolide A diacetate (**391**) (Scheme 128) [216], the diacetyl derivative of a metabolite of the colonial tunicate *Ritterella rubra* [48] and the Australian ascidian *Synoicum prunum* [220].



Scheme 128. Synthesis of rubrolide A diacetate (**390**)

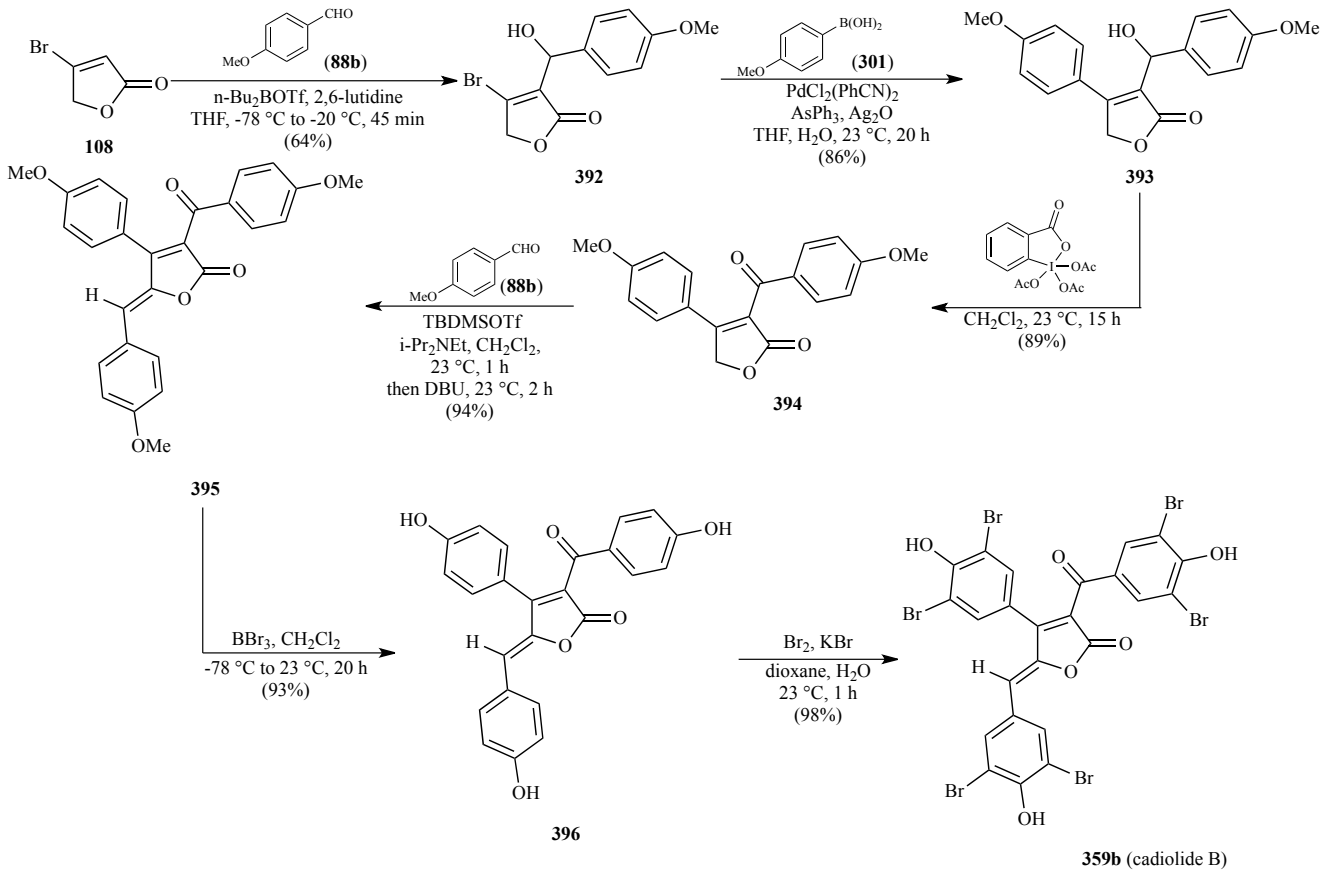
Even naturally-occurring cadiolides A (**359a**), B (**359b**), C (**359c**) (Figure 22) and cadiolide D (**359d**) (Figure 23) have been the subject of several synthetic studies.



359d (cadiolide D)

Figure 27. Structure of cadiolide D

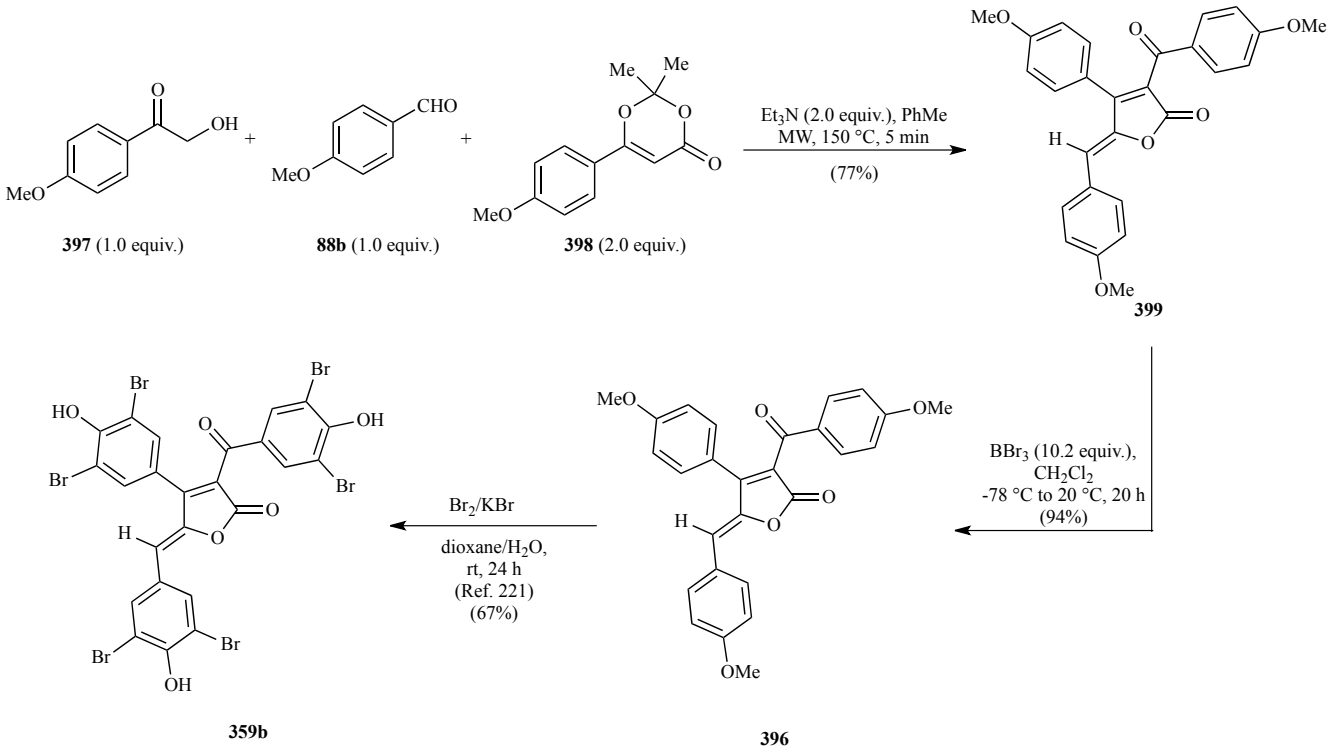
The first total synthesis of cadiolide B *i.e.* (*Z*)-3-(3,5-dibromo-4-hydroxybenzoyl)-4-(3,5-dibromo-4-hydroxyphenyl)-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2(5*H*)-furanone (**359b**) was carried out in 2005 by Boukouvalas and Poulet through the route outlined in Scheme 129 [221]. In particular, 4-bromo-2(5*H*)-furanone (**110**) was converted to compound **393** by using an improved literature protocol [222] that involved the formation of a dibutylboron 2-furanolate by treatment of **110** with *n*-Bu_2BOTf in the presence of 2,6-lutidine and the subsequent *in situ* aldolization reaction with 4-methoxybenzaldehyde (**91b**). The $PdCl_2(PhCN)_2/AsPh_3$-catalyzed Suzuki-type cross-coupling reaction of **393** with boronic acid **302** in THF in the presence of Ag_2O as the base gave alcohol **394**, which was subsequently oxidized with Dess-Martin periodinane providing ketone **395** in high yield. Aldol reaction of **395** with aldehyde **91b** in the presence of TBDMSOTf and *i*-Pr_2NEt, followed by *in situ* β-elimination with DBU gave stereoisomerically pure compound **396** in 94% yield. Next, compound **395** was fully *O*-demethylated by treatment with BBr_3 in CH_2Cl_2 and the resulting compound **397** was brominated with bromine/KBr providing cadiolide B (**359b**) in an excellent yield (Scheme 129) [221].



Scheme 129. First total synthesis of cadiolide B (**359b**)

In 2013, Leleu, Franck and coworkers described another synthesis of cadiolide B in which (*Z*)-3-(4-methoxybenzoyl)-5-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-2(5*H*)-furanone (**399**), which was used as an advanced intermediate, was obtained in 77% yield by reacting 1.0 equiv of α-hydroxyketone **397** with 1.0 equiv of aldehyde **88b** and 2.0 equiv of [6-(4-methoxyphenyl)-2,3-dimethyl-4*H*-1,3-dioxin-4-one] (**398**) in toluene at 150

°C under microwave irradiation in the presence of 2.0 equiv of Et_3N (Scheme 130) [223].

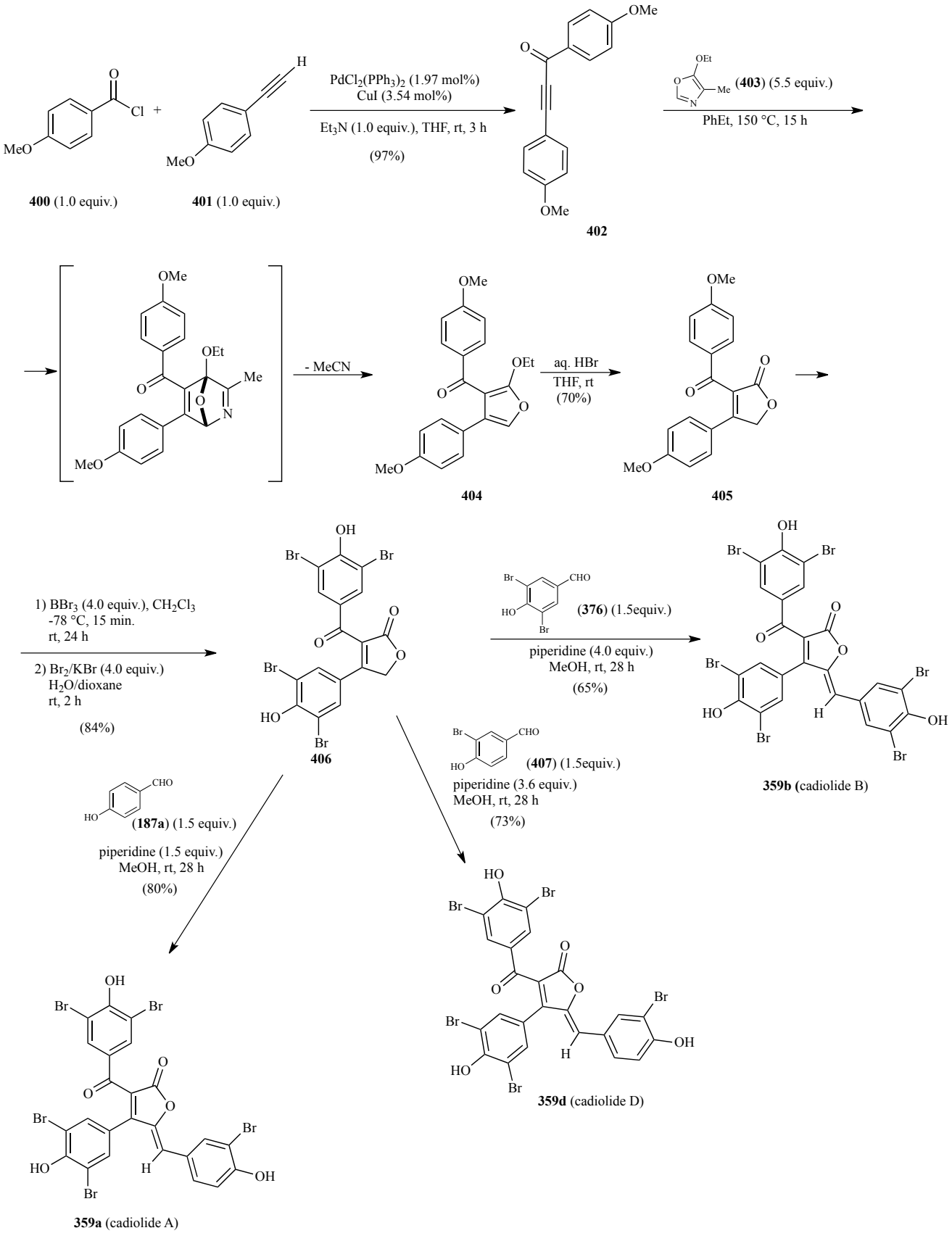


Scheme 130. Synthesis of cadiolide B (**359b**) via the microwave-promoted .

Compound **399** was converted into cadiolide B (**359b**) in 63% overall yield via a two-step route which was identical to that previously used by Boukouvalas and Poulet [221].

It deserves to be mentioned that, in 2014, that cadiolide B was found to exhibit antiviral activity against the Japanese encephalite virus at a concentration of 1 μg/mL [224].

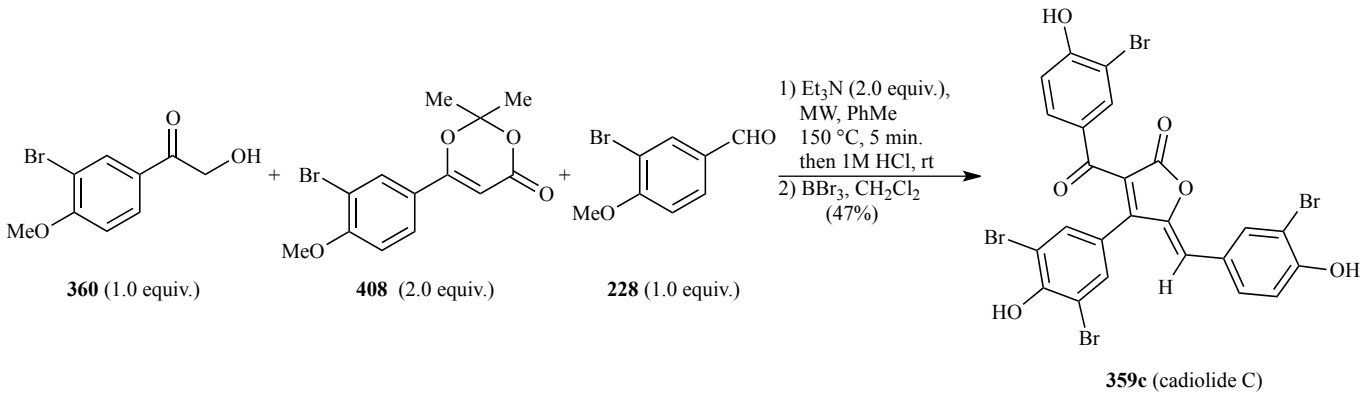
More recently, Boukouvalas and Thibault reported the first synthesis of cadiolides A (**359a**) and D (**359d**) and a new synthesis of cadiolide B (**359b**) [225]. As outlined in Scheme 131, these compounds were synthesized by using the "click–unclick" Dield-Alder cycloaddition--cycloreversion of commercially available 5-ethoxy-4-methyloxazole (**403**) with ynone **404**. The latter compound was prepared in 96% yield by $PdCl_2(PPh_3)_2$/CuI-catalyzed cross-coupling of commercially available 4-methoxybenzoyl chloride (**400**) with 4-methoxyphenylacetylene (**401**) in THF at room temperature in the presence of Et_3N as previously described [226–228]



Scheme 131. Stereoselective synthesis of cadiolides A (**359a**), B (**359b**) and D (**359d**)

Crude compound **404**, which was obtained from the reaction of **402** with **403**, was treated with aqueous HBr in THF at room temperature providing 3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2(5*H*)-furanone (**405**) in 70% yield. This compound was then treated with 4.0 equiv of BBr_3 in CH_2Cl_2 at –78 °C for 15 min and at room temperature for 24 h and the resulting crude product was reacted with a solution of 4 equiv of KBr_3, which was prepared *in situ* from bromine and KBr [221,229] in water and dioxane at room temperature. In this way 3-(3,5-dibromo-4-hydroxybenzoyl)-4-(3,5-dibromo-4-hydroxyphenyl)-2(5*H*)-furanone (**406**) was obtained in 84% yield. This compound was used as an advanced precursor to cadiolides A, B and D. Thus, by using classical Knoevenagel conditions (piperidine as base, methanol as solvent, room temperature) compound **406** was reacted with 4-hydroxybenzaldehyde (**187a**), 3,5-dibromo-4-hydroxybenzaldehyde (**376**) and 3-bromo-4-methoxybenzaldehyde (**407**) leading to stereoisomerically pure compounds **359a**, **359b** and **359d**, respectively, in 80%, 65% and 73% yield, respectively (Scheme 131) [225].

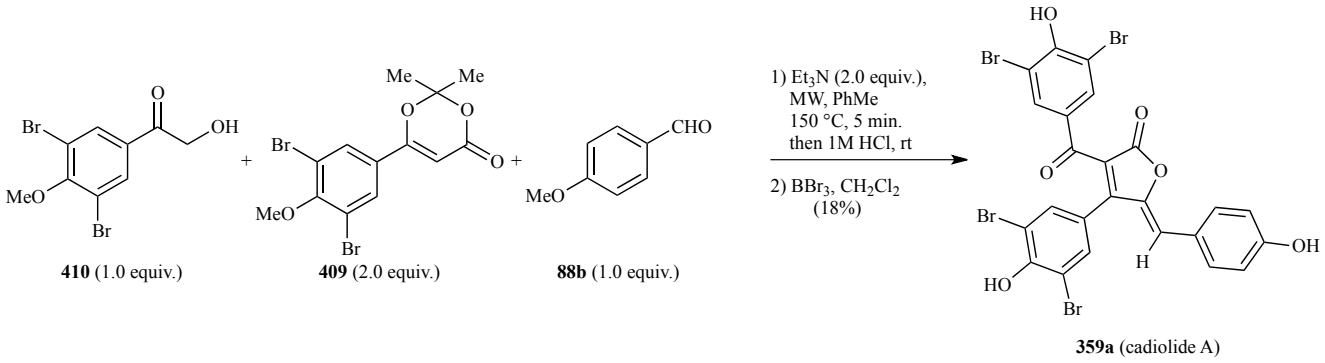
Furthermore, in 2015, cadiolides C (**359c**) and A (**359a**) were synthesized by Franck and coworkers [213] by using the one-pot reaction of α-hydroxyketones, dioxinones and aryl aldehydes, which they had previously employed in the synthesis of cadiolide B (**359b**) [223]. As shown in Scheme 132, cadiolide C (**359c**) was obtained in 47% yield by reacting 1.0 equiv of α-hydroxyketone **359**, 2.0 equiv of dioxinone **408** and 1.0 equiv of aldehyde **228** with 2.0 equiv of Et_3N in toluene under microwave irradiation at 150 °C for 5 min and treatment of the resulting reaction mixture with 1 M HCl followed by BBr_3-mediated *O*-demethylation of the resulting product [230].



Scheme 132. One-pot multicomponent synthesis of cadiolide C (**359c**)

A similar protocol allowed Franck and coworkers to obtain cadiolide A (**359a**) in 18% yield starting from α-hydroxyketone **410**, dioxinone **409** and aldehyde **88b** (Scheme 133) [213].

Notably, cadiolide C appeared capable to inhibit the bacterial growth of *Bacillus cereus* (CECT 148), *Salmonella typhi* (CECT 409) and *E. coli* 405 with a MIC value of 3.90 μg/mL and cadiolide A required the same concentration of tetracycline to inhibit the bacterial growth of *S. typhi* and *E. coli* 405 with a MIC value of 8.81 μg/mL [213].



Scheme 133. One-pot multicomponent synthesis of cadiolide A (**359a**)

Finally, in concluding this section, it is worth mentioning that, in 2013, Kutty, Kumar and coworkers designed, synthesized and evaluated some fimbrolide–nitric oxide donor hybrids as antimictrobial agents and found that 3-(1-nitroxybutyl)-5-(dibromomethylene)-2(5*H*)-furanone (**411a**), 3-(1-nitroxydodecyl)-5-(dibromomethylene)-2(5H)-furanone (**411b**) and 1-[5-(dibromomethylene)-2-oxo-2,5-dihydrofuran-3-yl]butyl 2-(nitrooxy)acetate (**412**) (Figure 28) were particularly effective as antimicrobial compared to the nonhybrid naturally-occurring fimbrolides as revealed by *Pseudomonas aeruginosa* QS reporte assays and biofilm inbition assays [230].

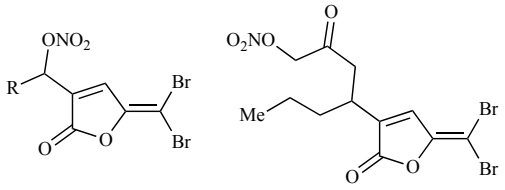
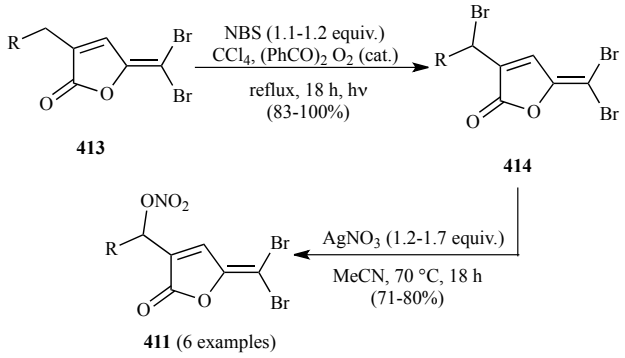
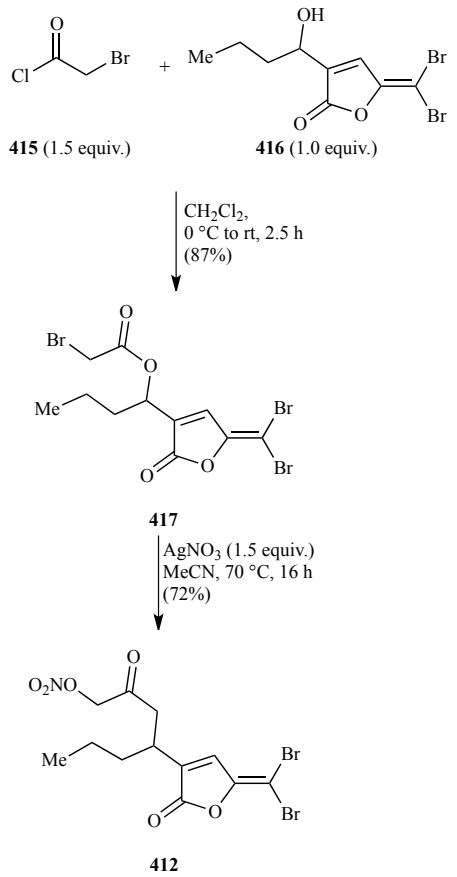


Figure 28. Structures of compounds **412a,b** and **413**

Compounds of general formula **411**, including **411a** and **411b**, were synthesized in high yields from the corresponding fimbrolide analogues **413** (Scheme 134) [230], which in turn were prepared by sulfuric acid-mediated cyclization of brominated 2-alkyllevulinic acids [103]. Allylic bromination of compounds **413** using NBS as the brominating reagent in the presence of benzoyl5peroxide gave compounds **413** in good to excellent yields, which were then converted to the corresponding nitrooxy-substituted fimbrolides **411** in 71–80% yield by treatment with 1.2–1.7 equiv of $AgNO_3$ in acetonitrile at 70 °C. On the other hand, the fimbrolide-nitrooxy derivative **412** was synthesized in 62.6 % overall yield via the two-step reaction sequence shown in Scheme 135 [231].

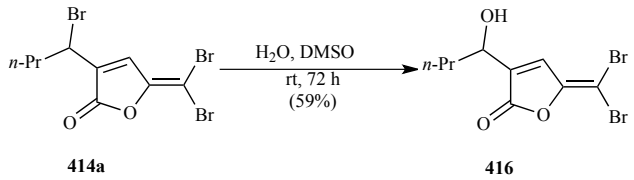


Scheme 134. Synthesis of fimbrolide-nitric oxide donor hybrids **411**



Scheme 135. Synthesis of compound **412**

Specifically, 1.0 equiv of 3-(1-hydroxybutyl)-5-(dibromomethylene)-2(5*H*)-furanone (**416**) was reacted with 1.5 equiv of bromoacetyl chloride (**415**) in CH_2Cl_2 providing compound **417** in 87% yield. The subsequent reaction of **417** with 1.5 equiv of $AgNO_3$ in acetonitrile under reflux gave compound **412** in 72% yield. Compound **416** was in turn obtained in 59% yield by treatment of bromofimbrolide **413a** with water in DMS at room temperature for 72 h (Scheme 136) [230].



Scheme 136. Synthesis of compound **416**

Notably, compounds **411** and **412** were proved capable to release in aqueous media nitric oxide [230], a compound which has been shown to influence biofilm dispersal in *P. aeruginosa* [231] and to control biofilm properties at picomolar to nanomolar concentrations [232]. It was also observed that the most potent and nonbactericidal compound in the biofilm inhibition assay was fimbrolide-NO donor hybrid compound **411b**, which showed a 73% decrease in biofilm biomass [230]

8. CONCLUSION

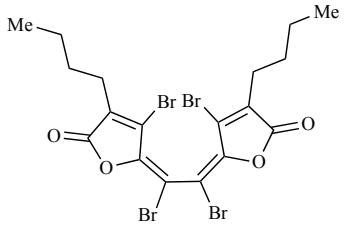
In this article, we have attempted to give a comprehensive overview of the several methodologies and strategies that have been developed and used in the literature since 1951 up to the end of February 2016 for the synthesis of natural and unnatural 2(5*H*)-furanone derivatives bearing bromine atoms on the heterocyclic ring and/or brominated substituents. Attention has also been placed to describe, albeit in summary form, the biological properties of the synthesized compounds, including their mutagenic, enzymatic, anti-inflammatory photosynthetic inhibitory activity, turning however more attention to those derivatives that demonstrated to exhibit antimicrobial activity via inhibition of quorum sensing and biofilm fomation.

In fact, as outlined in the previous sections of this review, in recent years numerous studies have been made on the identification and synthesis of brominated 2(5*H*)-furanone derivatives which, acting as QS inhibitors (also referred as quorum quenching (QQ) compounds, are able to fight bacterial pathogens, including those that have developed resistance to antibiotics by reducing their virulence and biofilm formation without affecting their growth. These studies have been largely justified by the fact that the approach involving the use of QQ compounds has been long considered less prone to cause resistance in bacterial populations than that based on the use of antibiotics [233–235], thereby producing significant benefits in areas such as human health, agricolture and industry.

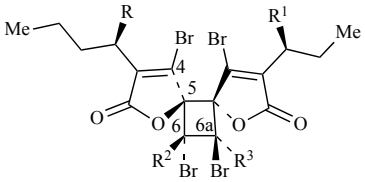
Unfortunately, in recent years, these expectations have been at least partially questioned by the fact that results have been obtained showing that some bacterial strains such as *Pseudomonas aeruginosa* PAO1 and PA14 can manifest resistance to QS inhibitors and, among these, (*Z*)-4-bromo-5-(bromomethylene)-2(5*H*)-furanone (C-30) (**145**) [236–238].

These data, however, do not prevent to suppose that it is possible to identify novel antimicrobial brominated 2(5*H*)-furanones that at appropriate concentrations are capable of controlling biofilm formation and virulence factors without the development of resistance. Moreover, it should be taken into account that a possible resistance to antibacterial brominated 2(5*H*)-furanone derivatives might be overcome by combining the administration of the antibacterial brominated furanones with that of efflux pump inhibitors [239,240].

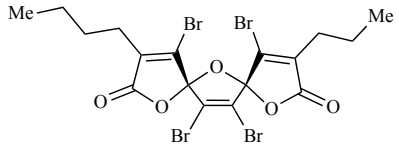
We therefore believe that it is important to actively continue the studies on the synthesis and evaluation of the antimicrobial activity of brominated 2(5*H*)-furanone derivatives also including among these substances the following natural compounds for which synthetic methods have not yet been reported and the biological properties have not yet been evaluated: (*Z,Z*)-5,5'-(1,2-dibromoethanediylidene)-bis(4-bromo-3-butyl)]-2(5*H*)-furanone (**417**) [142], pulchralides A (**418**), B (**419**) and C (**420**), acetoxyfimbrolide C_2 dimer (**421**), acetoxyfimbrolide *meso* dimer (**422**) [241], *cis*-4,11,12,13-tetrabromo-3,10-dibutyl-1,6,8-trioxadispiro[4.1.4.2]trideca-3,10,12-triene-2,9-dione (**423**) [142], and prunolides A (**424**) and B (**425**) [220] (Figure 29].



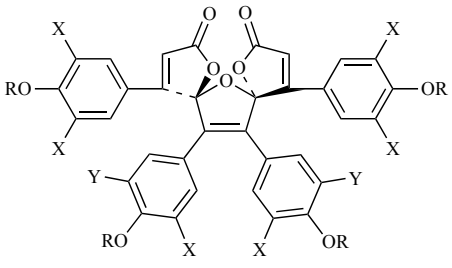
417



418 : R=R^1= OAc; R^2=R^3=H
(pulchralide A)
419: R=R^1=R^2=R^3=H
(pulchralide B)
420 : R=OAc; R^1=R^2=R^3=H
(pulchralide C)
421 : R=R^1= H; R^2=R^3=Br
(acetoxyfirubrolide C_2 dimer)
422 : C5 epimer of **420**
(acetoxyfirubrolide *meso* dimer)



423



424: R= H; X=Y= Br (prunolide A)
425 : R=Y= H; X= Br (prunolide B)

Figure 29. Structures of naturally-occurring compounds **419–427**

It is also our hope that the chemical and biological data reported in this review can be of help in designing efficient and versatile methods for the synthesis of these natural compounds and new, tunable, unnatural brominated 2(5*H*)-furanone derivatives possessing interesting biological properties.

LIST OF ABBREVIATIONS

Ac = acetyl
AHL = *N*-acyl homoserine lactone
AIBN = 2,2'-azobisisobutyronitrile
Ar = aryl
BHL = *N*-butanoyl-*L*-homoserine lactone
Bn = benzyl
Bu = butyl
coll = 2,4,6-trimethylpyridino
Cp = cyclopentadienyl
Cy = cyclohexyl
d = day
dba = dibenzoylacetone
DBU = 1,5-diazabicycloundec-7-ene
DIBAH = diisopropylaluminum hydride
DMF = *N,N*-dimethylformamide
DMSO = dimethyl sulfoxide
Et = ethyl
Hept = heptyl
Hex = hexyl
HMPA = hexamethylphosphoramide
IC_{50} = half maximal inhibitory concentration
LDA = lithium diisopropylamide
MCPBA = *m*-chloroperbenzoic acid
Me = methyl
MIC = minimum inhibitory concentration
MMPP = magnesium monoperoxyphthalate
MW = microwave
NAPDH = nicotinamide adenine dinucleotide phosphate
NBS = *N*-bromosuccinimide
NMP = *N*-methyl-2-pyrrolidone
Oct = octyl
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
Pent = pentyl
Ph = phenyl
Pr = propyl
QQ = quorum quenching
QS = quorum sensing
rt = room temperature
TBDMS = *tert*-butyldimethtylsilyl
TFA = trifluoroacetic acid
TFE = 2,2,2-trifluoroethanol
THF = tetrahydrofurane
TLC = tin-layer chromatography

TMS = trimethylsilyl
Tol = tolyl
p-Ts = *p*-toluenesulfonyl

CONFLICT OF INTEREST

The authors confirm that this article conent has no conflict of Interest.

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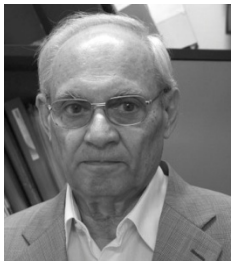
Biographical sketch



Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he again joined the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: i) new catalytic methods for the synthesis of oxygen-containing heterocycles; *ii)* the preparation of substances which exhibit significant cytotoxicity against human tumor cell lines and antivascular properties; *iii)* the study of new methodologies for carbon–carbon bond formation that involve the use of organometallic reagents; *iv)* palladium-catalyzed cross-coupling reactions; *v)* transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; *vi)* the design, development and applications of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct *C*- and *N*-arylation reactions of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides, and their application in the synthesis of bioactive natural and unnatural compounds. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of insect sex pheromone components, insecticidal carboxyamides, natural phototoxins, and naturally-occurring compounds of marine origin and their structural analogues possessing the 2(5*H)*-furanone ring. Professor Rossi, who has coauthored over 235 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry and the American Chemical Society. He is a reviewer for several international journals dealing with synthetic organic chemistry and organometallics.

Marco Lessi was born in Livorno (Italy) in 1979. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in June 2004 defending a thesis performed under the guidance of Professor Dario Pini. In January 2005, he began his PhD fellowship in the laboratory of Professor Pini and received his PhD degree in 2008, submitting a thesis on the preparation and applications of new insoluble polymer-bound (IPB) enantioselective catalytic systems. The studies were focused on the synthesis of transition metal complexes obtained from bisoxazoline and BINOL ligands. In the period January 2008–March 2009, Dr. Lessi worked for Solvay Solexis S.p.A. on the development of new routes for the preparation of high-fluorinated low-molecular-weight molecules and oligomers. In March 2009, he re-joined the University of Pisa, and at present he is an organic chemistry researcher, working in the group of Professor Bellina. The research interests of Dr. Lessi involve the development of novel and efficient protocols for highly selective transition metal-catalyzed direct C(sp^3)-H and C(sp^2)-H arylation reactions, and the discovery of new synthetic routes and applications of functionalized ionic liquids obtained from naturally-occurring building blocks.

Chiara Manzini was born in Lucca (Italy) in 1986 and graduated in Chemistry with first-class honours at the University of Pisa in 2011. In January 2012, she began his PhD fellowship in the laboratory of Professor Bellina and received his PhD degree in 2015, submitting a thesis on the on the development and application of new protocols for the selective arylation of *N*-containing heteroaromatics.

Giulia Marianetti was born in Lucca (Italy) in 1988 and graduated in Organic Chemistry with first-class honours at the University of Pisa in 2013. She currently holds a PhD scholarship at the Scuola Normale Superiore of Pisa under the supervision of Prof. Fabio Bellina and Prof. Vincenzo Barone. She is currently working on the synthesis and the computational studies of new organic fluorophores.

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992, he joined the University of Pisa as an Organic Chemistry Researcher in the Department of Chemistry and Industrial Chemistry. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry and, in January 2016, he became Full Professor of Organic Chemistry at the same University. His research interests were initially devoted to the synthesis of naturally occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of natural fungicidal derivatives of agrochemical interest. More recently, Prof. Bellina focused his attention on new protocols for regioselective transition metal-mediated carbon-carbon and carbon-heteroatom bond forming reactions, with a particular interest in the selective functionalization of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel protocols for the transition metal-catalyzed direct C–H and N–H bond arylation of heteroarenes with a focus on direct arylation reactions and cross dehydrogenative couplings, the alkynylation of (hetero)aromatic scaffolds, and on the application of these new procedures to the selective preparation of bioactive natural and synthetic compounds and to new organic chromophores.

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