EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201500663

A Rapid Entry to Diverse γ-Ylidenetetronate Derivatives through Regioselective Bromination of Tetronic Acid Derived γ-Lactones and Metal-Catalyzed Postfunctionalization

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Keywords: Synthetic methods / Halogenation / Cross-coupling / Cycloaddition / Lactones / Oxygen heterocycles

The synthesis of a series of diverse methyl and benzyl γ-ylidenetetronate derivatives was accomplished through the condensation of methyl and benzyl tetronates with (hetero)aryl aldehydes in a new two- or three-step aldolisation/dehydration sequence. The bromination of methyl and benzyl γ-ylidenetetronates occurred under mild conditions to provide the corresponding C-3-brominated γ-unsaturated lactones. Di- and tribrominated γ-lactones were prepared under slightly different conditions. Some brominated materials were employed in representative Stille, Suzuki–Miyaura, and Sonogashira cross-coupling reactions to yield functionalized methyl and benzyl γ-ylidenetetronate derivatives. Compounds that resulted from the Sonogashira cross-coupling reactions were desilylated and converted into 1,2,3-triazole derivatives through a copper(I)-catalyzed 1,3-dipolar cycloaddition reaction with benzyl azide.

Introduction

γ-Lactones derived from tetronic acids, γ-ylidenetetronates, and tetronic acid derivatives, which are isolated from natural sources or synthesized as potential chemotherapeutic agents, have been known to display interesting biological activity (Figure 1).[1] In connection to our work, some noteworthy examples of γ-lactones from natural sources include a group of 5-arylidenetetronates that can be extracted from fungal sources.[1a–1f] Pulvinic acid derivatives and pulvinone analogues are representative examples of this family of compounds, with some having radioprotective and antioxidant properties[2a–2c] as well as anti-influenza A virus (H1N1) activity.[2d] Non-natural 5-arylidenetetronates have been developed as potent antibacterials and inhibitors of bacterial peptidoglycan biosynthesis.[3]

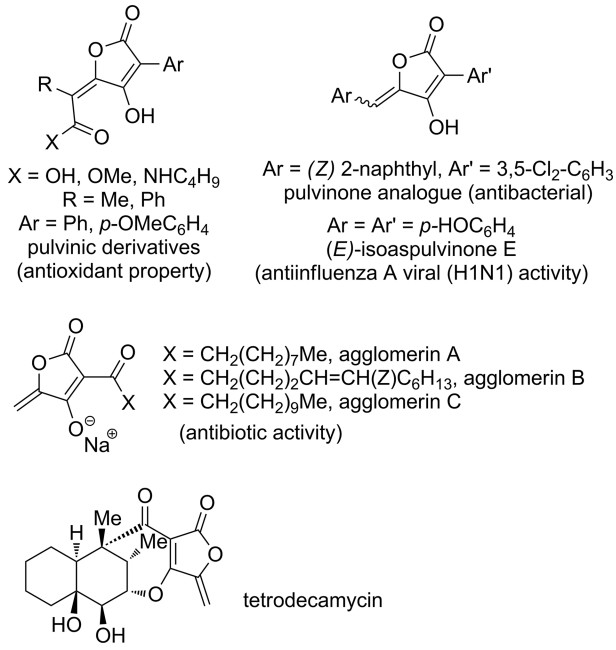

Figure 1. γ-Ylidenetetronate and tetronic acid derivatives from natural sources or designed as chemotherapeutic agents.

In our current research program directed towards the synthesis and biological evaluation of new therapeutic agents as possible anti-infective agents, halogenated γ-lactones derived from tetronic acids were identified as useful synthetic platforms for the preparation of diverse γ-ylidene-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500663.

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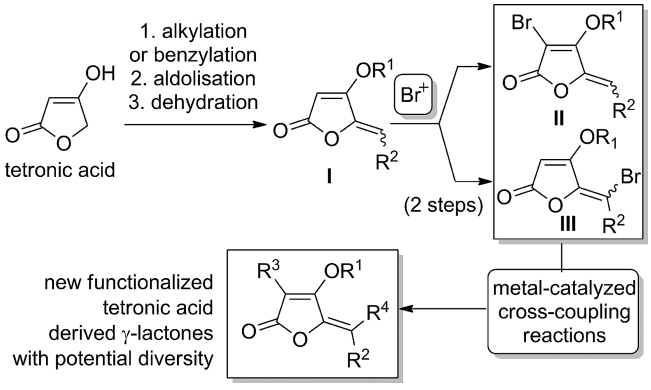
tetronates (R^1, R^2, R^3, and R^4, Scheme 1) prepared by a metal-catalyzed cross-coupling postfunctionalization step.[4] These halogenation sequences, which are relatively rare in the literature,[5] start from γ-benzylidene tetronates, and the resulting products are used in the development of new valuable organic entities and chemotherapeutic agents.



Scheme 1. General access to the targets.

Herein, we disclose our results for the synthesis of γ-lactones that are derived from methyl and benzyl tetronates, the regioselective bromination of these γ-lactones, and their use in specific Stille,[6] Suzuki–Miyaura,[7] and Sonogashira[8] cross-coupling reactions. To demonstrate the synthetic utility of our strategy, examples of Cu^I-catalyzed 1,3-dipolar cycloadditions of acetylenic-derived γ-benzylidene tetronates with benzyl azide[9] are also presented. These cycloaddition reactions provide access to pharmaceutically relevant 1,2,3-triazoles,[10] which contain the tetronic acid derived motif.

Results and Discussion

The starting methyl and benzyl tetronates **1a** and **1b** were either commercially available (i.e., **1a**, R^1 = Me) or known (i.e., **1b**, R^1 = Bn).[5b,5c] New lactones **1c** and **1d** were prepared in a similar manner to **1b** in unoptimized yields of 50 and 37%, respectively, by treating *p*-fluoro- and *p*-methoxybenzyl chlorides (1.1 equiv.) with potassium carbonate (2.0 equiv.) in *N*,*N*-dimethylformamide (DMF) at room temperature. Aldehydes **2**–**20** (see Figure 2), which were to be used in the aldolisation/dehydration sequence (Scheme 1, general structure **I**) were either commercially available (i.e., **2**–**6** and **8**–**20**) or prepared by using a known procedure (i.e., **7**).[11]

The first approach (method A) to prepare γ-ylidenetetronates **I** follows literature procedures that were developed for analogues of **I**.[1j,5b,5c] Tetronates **1a**–**1d** were treated with *n*BuLi (1.1 equiv.) and aldehydes **2**–**15** (1.5 equiv.) in tetrahydrofuran (THF) at –78 °C to room temperature (overnight) to yield the corresponding aldol adducts **21**–**41** as diastereoisomeric mixtures in good yields, after workup and filtration through silica gel (Scheme 2).

The aldol adducts were converted directly into γ-lactones **42**–**64** by a two-step/one-pot sequence that proceeded

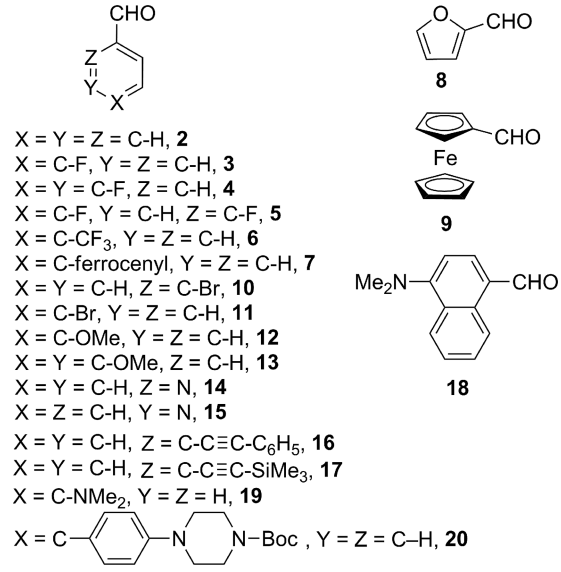
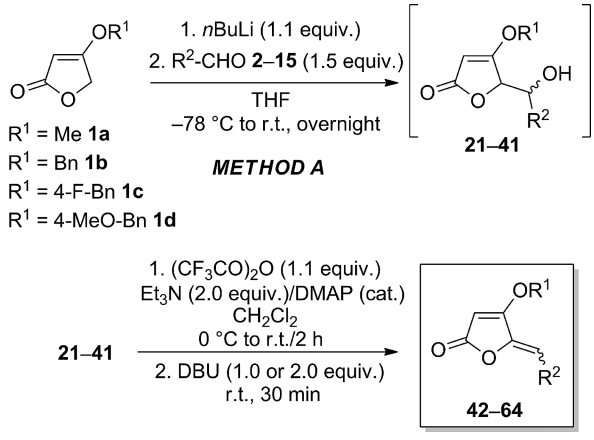


Figure 2. Structures of the aldehydes **2**–**20** used in the aldolisation processes.



Scheme 2. Synthesis of 5-arylidenetetronates (method A) from methyl and benzyl tetronate (DMAP = 4-(dimethylamino)pyridine.

through an esterification with trifluoroacetic anhydride and an elimination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base[5b,5c] in dichloromethane. Compounds **42**,[1i,1j] **43**,[3a] and **51**[1i] are known compounds or have been previously reported in the literature. Compounds **42**, **44**, **47**–**54**, **56**, **58**, **60**, **61**, **63**, and **64** were obtained as the (*Z*) stereoisomer (in our preliminary communication,[4] the (*Z*) stereochemistry of ferrocenyl derivative **50** was confirmed by single-crystal X-ray diffraction analysis). Compounds **43**, **45**, **46**, **55**, **57**, **59**, and **62** were obtained as two stereoisomers after column chromatography (in favor of the thermodynamically more stable (*Z*) stereoisomer; Scheme 2 and Table 1). By using aldehyde **9**, we directly obtained the ferrocenyl dehydrated compounds **50** and **61** (Table 1, Entries 9 and 20) without isolation of the aldol products. Pyridinyl derivatives **59** and **60** (Table 1, Entries 18 and 19) were found to be unstable during the aldolisation/dehydration sequence. In addition, the dehydration reactions of products that were formed from substituted benzyl te-

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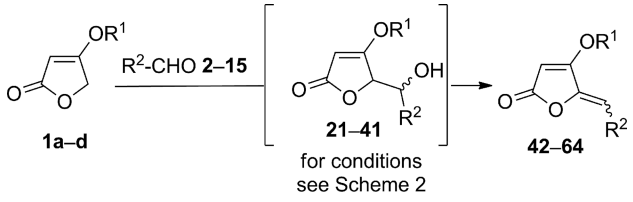
tronates **1c** and **1d** (Table 1, Entries 21–23) were less efficient than the dehydration reactions of substrates prepared from **1a** and **1b**. However, the aldolisation reactions worked equally well in all cases. Because some of the yields (overall yields for the aldolisation/dehydration sequence) presented in Table 1 were only moderate, we studied a model reaction and determined that slight changes in the reaction conditions for the aldolisation and dehydration steps (performing the reaction at room temperature for 2.5 h for the esterification and using of 2.0 equiv. of DBU for 45 min for the dehydration) could provide **44** in a more satisfactorily 53% isolated yield (compared with 28% yield; Table 1, Entry 3) with a *Z*/*E* ratio of 19:1. Although this optimization study was only carried out with tetronate **1a** and aldehyde **3**, there is hope that some of the yields provided in Table 1 can indeed be improved.

Table 1. Synthesis of 5-arylidenetetronates (method A) from methyl and benzyl tetronates.

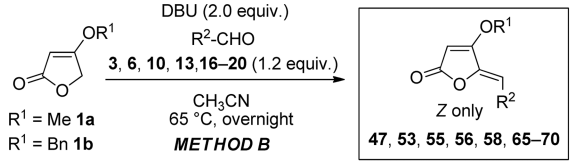


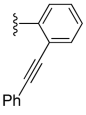
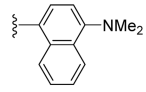
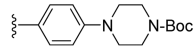
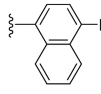
Entry	R^1	R^2	Compound [% yield][a]	*Z*/*E*[b]
1	Me	C_6H_5	**42** (39)	[c]
2	Me	4-BrC_6H_4	**43** (44)	89:11
3	Me	4-FC_6H_4	**44** (28)	[c]
4	Me	3,4-$F_2C_6H_3$	**45** (32)	96:4
5	Me	2,4-$F_2C_6H_3$	**46** (60)	88:12
6	Me	4-$CF_3C_6H_4$	**47** (43)	[c]
7	Me	4-FcC_6H_4[c,d]	**48** (65)	[c]
8	Me	2-furanyl	**49** (46)	[c]
9	Me	Fc[d]	**50** (95)[e]	[c]
10	Me	3,4-$(MeO)_2C_6H_3$	**51** (39)	[c]
11	Bn	C_6H_5	**52** (47)	[c]
12	Bn	2-BrC_6H_4	**53** (54)	[c]
13	Bn	4-BrC_6H_4	**54** (40)	[c]
14	Bn	4-FC_6H_4	**55** (85)	95:5
15	Bn	4-$CF_3C_6H_4$	**56** (57)	[c]
16	Bn	4-$MeOC_6H_4$	**57** (36)	85:15
17	Bn	3,4-$(MeO)_2C_6H_3$	**58** (18)	[c]
18	Bn	2-pyridinyl	**59** (43)	81:19
19	Bn	3-pyridinyl	**60** (13)	[c]
20	Bn	Fc[d]	**61** (54)[e]	[c]
21	4-F-Bn	4-$MeOC_6H_4$	**62** (27)	93:7
22	4-F-Bn	4-$CF_3C_6H_4$	**63** (14)	[c]
23	4-MeO-Bn	4-$CF_3C_6H_4$	**64** (21)	[c]

[a] Overall isolated yield (aldolisation/dehydration sequence) after silica gel chromatography. [b] Ratio of stereoisomers. [c] Only (*Z*) isomer was identified. [d] Fc = ferrocenyl. [e] Obtained directly without isolation of the aldol.

This first approach gave the desired molecules of general structure **I**, but a more practical approach that avoids cryogenic temperatures and the use of *n*BuLi, especially for possible scaleup, was envisaged. A one-pot procedure (method B) that uses DBU (2 equiv.) as the base, aldehydes **3**, **6**, **10**, **13**, and **16**–**20** (1.2 equiv.), and tetronates **1a** and **1b** in acetonitrile (65 °C, overnight) was discovered and applied to the synthesis of γ-lactones **47**, **53**, **55**, **56**, **58**, and **65**–**70** (Table 2). All the final products were obtained in moderate to good yields as (*Z*) isomers as confirmed by single-crystal X-ray diffraction analysis of compound **66** (Figure 3).[12] In the reaction with aldehyde **17** (Table 2, Entry 9), the trimethylsilyl group was removed during the aldolisation/dehydration sequence, and the final product **69** was isolated in only 22% yield. Replacing DBU with other bases (i.e., K_2CO_3, NaH) or changing the solvents (THF, MeOH, CH_2Cl_2) gave only the aldol products along with incomplete conversion of the starting materials. In addition, performing the reaction in neat DBU at room temperature or 65 °C provided only the aldol product. Therefore CH_3CN was critical for the successful outcome of the aldolisation/dehydration reaction sequence. It possible that the cyanomethyl anion (pK_a of CH_3CN = 31.3) generated in the course of the reaction induces the dehydration of the resulting aldol, with both steps occurring at 65 °C

Table 2. Synthesis of 5-arylidenetetronates from methyl and benzyl tetronates (method B).



Entry	R^1	R^2	Compound (yield %)[a]
1	Me	4-$CF_3C_6H_4$	**47** (30)
2	Me		**65** (73)
3	Me		**66** (63)
4	Bn	2-BrC_6H_4	**53** (38)
5	Bn	4-FC_6H_4	**55** (58)
6	Bn	4-$CF_3C_6H_4$	**56** (33)
7	Bn	4-$NMe_2C_6H_4$	**67** (30)
8	Bn		**68** (46)
9[b]	Bn		**69** (22)
10	Bn	3,4-$(MeO)_2C_6H_3$	**58** (57)
11	Bn		**70** (72)

[a] Isolated yield after silica gel chromatography. Only (*Z*) isomer was isolated. [b] 2-[(Trimethylsilyl)ethynyl]benzaldehyde (**17**) was used.

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(Scheme 3). The fact that the dehydrated products were never formed in the reaction in neat DBU indicates that it probably is not involved in the dehydration step. This new procedure, which warrants further optimization, is more convenient that the previous approach (method A), as this one-pot procedure can be easily adapted to the preparation of milligram to gram quantities of 5-arylidenetetronates of general structure **I** after evaporation of the volatiles and purification by chromatography.

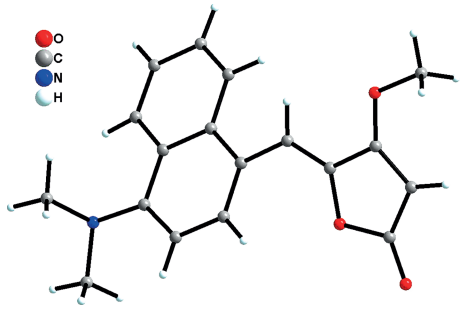
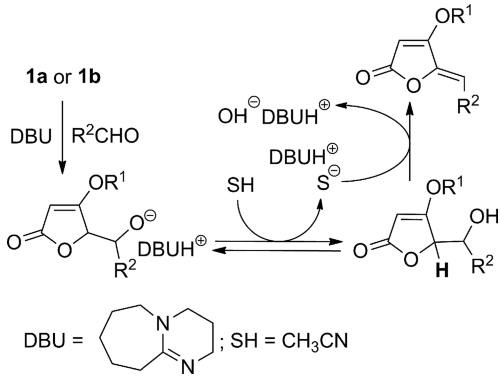


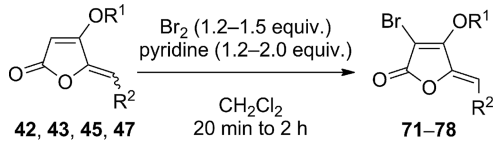
Figure 3. Single crystal X-ray diffraction analysis of (*Z*)-γ-lactone **66**.



Scheme 3. Proposed mechanism for the formation of the γ-lactones in CH_3CN in the presence of DBU (method B).

With a series of γ-unsaturated lactones obtained through two different procedures (methods A and B), we then pursued the preparation of the key brominated materials. We previously reported[4] feasibility studies of the reactions of γ-lactone **42** as a model compound with *N*-bromosuccinimide (NBS) and bromine. The introduction of a bromine atom at the C-3 position of γ-unsaturated lactones **42**, **43**, **45**, **47**, **51**, **52**, **56**, **58** was best achieved by using bromine (1.2–1.5 equiv.) in the presence of pyridine (1.2–2.0 equiv.) in anhydrous dichloromethane at room temperature for 20 min to 2 h (concentration of substrate c = 0.1 M). The resulting brominated materials **71**–**78** were obtained as the (*Z*) isomer in moderate to excellent yields after purification by column chromatography (Table 3). The stereochemistry and proof of structure **78** was established by using single-crystal X-ray diffraction analysis (Figure 4).[13]

Table 3. C-3 Bromination of 5-arylidenetetronate derivatives.



42, **43**, **45**, **47**, **51**, **52**, **56**, **58** → **71**–**78**

Entry	R^1	R^2	Compound [% yield][a][b]
1	Me	C_6H_5	**71** (91)[c],[8]
2	Me	4-BrC_6H_4	**72** (73)[c]
3	Me	4-$CF_3C_6H_4$	**73** (62)[d]
4	Me	3,4-$(MeO)_2C_6H_3$	**74** (60)[c]
5	Me	3,4-$F_2C_6H_3$	**75** (81)[c]
6	Bn	C_6H_5	**76** (79)[c]
7	Bn	4-$CF_3C_6H_4$	**77** (65)[c]
8	Bn	3,4-$(MeO)_2C_6H_3$	**78** (40)[c], **78** (64)[d]

[a] Isolated yield after silica gel chromatography. [b] Only (*Z*) isomer was identified. [c] Br_2 (1.5 equiv.) and pyridine (1.2 equiv.) were employed. [d] Br_2 (1.2 equiv.) and pyridine (2.0 equiv.) were employed.

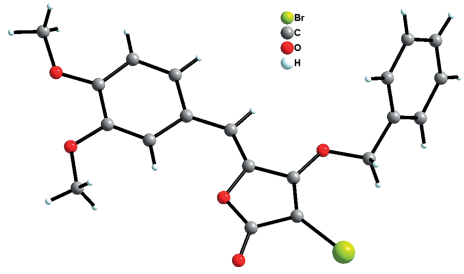


Figure 4. Single-crystal X-ray diffraction analysis of C-3-brominated (*Z*)-γ-lactone **78**.

Under slightly different conditions, the reaction was carried out by using bromine (1.0 equiv.) in the absence of pyridine in dichloromethane at 0 °C for 1 h. Under more dilute conditions (c = 0.02 M), the exocyclic dibromination of the two model γ-lactones **42**[4] and **52** was achieved diastereoselectively to provide dibrominated compounds **79** and **80** in moderate to good yields (Scheme 4). The stereochemistry of compound **79** was previously established[4] by single-crystal X-ray diffraction analysis. However, if lactones **42**, **47**, and **52** were treated with an excess amount of bromine (2.0 equiv.) without pyridine in the same solvent but at 0 °C to room temperature for 1 h (c = 0.1 M), tribrominated lactones **81**[4]–**83** were obtained in good yields (Scheme 4).

The results of the regioselective reactions with bromine in the presence or absence of pyridine deserve some comments. The combination of pyridine and bromine is the system of choice for the selective introduction of the bromine atom at the C-3 position of the methyl and benzyl tetronates (Table 3), without brominating the exocyclic double bond. Although the reasons of such selectively in the presence of pyridine remain unclear, a complex between pyridine and bromine (pyridinium tribromide or pyridinium hydrobromide perbromide)[14] might be the active species and, therefore, activate the C-3 position of the tetronate

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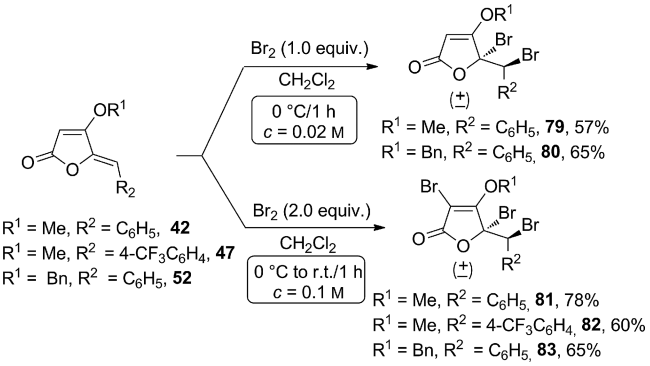
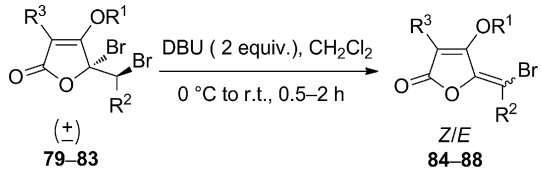


Scheme 4. Dibromination and tribromination reactions of γ-lactones **42**, **47**, and **52**.

through its enol ether moiety. Exocyclic bromination does not require such activation, as the critical factor to favor the dibromination over the tribromination reaction was the concentration of bromine (Scheme 4). The marked differences in reactivity underline the distinctions between bromine and the tribromide ion in an electrophilic attack.

From dibrominated lactones **79** and **80**, the corresponding exocyclic bromo-olefinic lactones **84** and **85** were prepared in excellent 88 and 85% yields by a base-induced [DBU (2.0 equiv.)] *anti* elimination of HBr (Table 4, Entries 1 and 2). The (*Z*) stereochemistry of **84** had already been established by single-crystal X-ray diffraction analysis, according to our preliminary communication.[4] The dibromination/base-promoted debromination sequence (i.e., **42**→**79**→**84**) can also be conducted in a one-pot procedure in 50% overall yield. However, the treatment of tribrominated **81**–**83** derivatives with DBU (2.0 equiv.) in dichloromethane (0 °C to room temperature) for 0.5 h gave mixtures of the corresponding (*Z*)- and (*E*)-bromo-olefinic lactones **86**–**88** in moderate to good yields after purification by silica gel chromatography (Table 4, Entries 3–5). The (*Z*) and (*E*) isomers of compound **85** were separated after two successive column chromatography procedures.

Table 4. Elimination reactions of di- and tribrominated γ-lactones **79**–**83**.

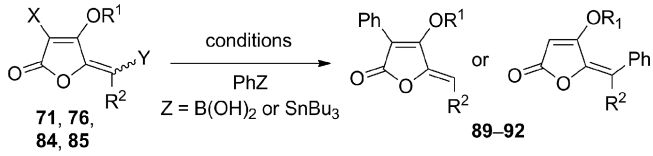


Entry	R^1	R^2	R^3	Compound [% yield][a]	*Z*/*E*[b]
1	Me	C_6H_5	H	**84** (88)	[c]
2	Bn	C_6H_5	H	**85** (85)	1/0.3
3	Me	C_6H_5	Br	**86** (62)	≈1:1
4	Me	4-$CF_3C_6H_4$	Br	**87** (60)	≈1:0.6
5	Bn	C_6H_5	Br	**88** (81)	≈1:0.3

[a] Isolated yield after silica gel chromatography. [b] Ratio of stereoisomers. [c] Only (*Z*) isomer present.

The brominated γ-benzylidene methyl and benzyl tetronates were then used in several typical Suzuki–Miyaura, Stille, and Sonogashira cross-coupling reactions (Tables 5 and 6).

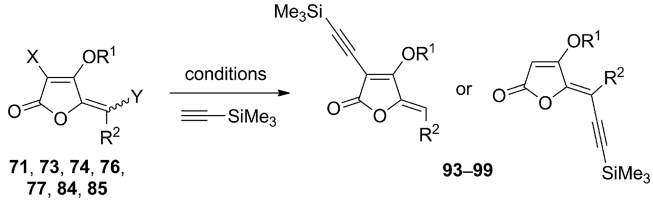
Table 5. Suzuki–Miyaura[a] and Stille[b] cross-coupling reactions.



Entry	R^1	R^2	X, Y	Suzuki–Miyaura product [% yield][c]	Stille product [% yield][c]
1	Me	C_6H_5	Br, H	**89** (99)	**89** (74)
2	Bn	C_6H_5	Br, H	**90** (47)	**90** (67)
5	Me	C_6H_5	H, Br	**91** (96)	**91** (74)
6	Bn	C_6H_5	H, Br	–	**92** (61)

[a] Reagents and conditions: $PhB(OH)_2$ (2 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), and K_2CO_3 (2 equiv.) in PhMe at 75 °C overnight. [b] Reagents and conditions: $PhSnBu_3$ (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) in PhMe at 75 °C overnight. [c] Isolated yield.

Table 6. Sonogashira cross-coupling reactions.[a]



Entry	R^1	R^2	X, Y	Compound [% yield][b]
1	Me	C_6H_5	Br, H	**93** (78)
2	Me	4-$CF_3C_6H_4$	Br, H	**94** (73)
3	Me	3,4-$(MeO)_2C_6H_3$	Br, H	**95** (93)
4	Bn	C_6H_5	Br, H	**96** (93)
5	Bn	4-$CF_3C_6H_4$	Br, H	**97** (82)
6	Me	C_6H_5	H, Br	**98** (82)[c]
7	Bn	C_6H_5	H, Br	**99** (83)[c]

[a] Reagents and conditions: Trimethylsilylacetylene (1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (0.1 equiv.), CuI (0.1 equiv.), and Et_3N (2 equiv.) in PhMe at 75 °C overnight. [b] Isolated yield. [c] Only one isomer (*Z*) was obtained.

For the Suzuki–Miyaura cross-coupling reactions, phenyl boronic acid [$PhB(OH)_2$, 2.0 equiv.] was used as the coupling partner with C-3-brominated derivatives **71** and **76** and exocyclic brominated γ-benzylidene methyl and benzyl tetronates **84** and **85** in the presence of $Pd(PPh_3)_4$ (0.1 equiv.) and anhydrous K_2CO_3 (2.0 equiv.) in toluene at 75 °C overnight (Table 5). Moderate to excellent yields were achieved for coupling products **89**–**92**.

Alternatively, these C-3 arylated γ-benzylidene methyl and benzyl tetronates could be prepared by a Stille coupling reaction using $PhSnBu_3$ (2.0 equiv) and $Pd(PPh_3)_4$ (0.1 equiv.) in toluene at 75 °C overnight (Table 5). Gen-

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erally, both the Suzuki–Miyaura and Stille reactions gave good yields, but they were substrate dependent.

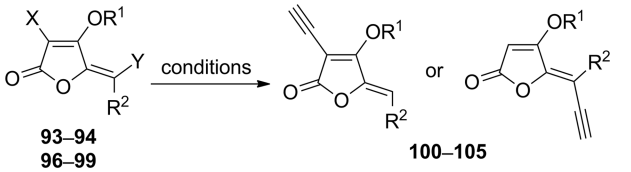
A Sonogashira cross-coupling reaction was attempted by using trimethylsilylacetylene (1.5 equiv.) as the coupling partner with C-3-brominated derivatives **71**, **73**, **74**, **76**, and **77** and exocyclic brominated derivatives **84** and **85** as the starting materials. The C-3 and exocyclic coupled products **93**–**99** were prepared in good to excellent yields by using $Pd(PPh_3)_2Cl_2$ (0.1 equiv.) in the presence of CuI (0.1 equiv.) and Et_3N (2 equiv.) in toluene at 75 °C overnight (Table 6). Compounds **93** and **98** were previously prepared under slightly different conditions (Et_3N was used as the solvent at 50 °C), as described in our preliminary communication.[4] Here, compounds **98** (Table 6, Entry 6) and **99** (Table 6, Entry 7) were obtained as a single isomer with the proposed (*Z*) configuration. There was noticeably no erosion of stereochemistry in the cross-coupling reaction of enantiopure **84** to give **98**, and the reaction that gave **99** was also remarkably stereospecific despite that the starting material **85** was present as a *Z*/*E* (1:0.3) mixture.

Notably, the cross-coupling reactions of exocyclic halogenated γ-benzylidene tetronates are not common, although a Suzuki–Miyaura reaction of an iodoalkene derivative of tetronic acid was recently used in the preparation of vulpinic acid.[15]

The Sonogashira coupling products **93**, **94**, and **96**–**99** were desilylated to provide acetylenic compounds **100**–**105** in moderate to good yields. The desilylation proceeded extremely fast (5 min) by using tetrabutylammonium fluoride (1.1 equiv.) in THF at 0 °C (Table 7). When the reaction was performed at room temperature, lower product yields resulted, whereas performing the reaction longer than 5 min (either at 0 °C or room temperature) produced several side products. The desilylation did occur by using K_2CO_3 as a base in MeOH, but the addition of the methoxide anion to the exocyclic bond also occurred.

Compound **100**–**102**, **104**, and **105** were then employed in a copper(I)-catalyzed 1,3-dipolar cycloaddition with benzyl azide (1.5 equiv.) as a model 1,3-dipole reaction. This transformation was attempted in a solvent mixture (*t*BuOH/CH_2Cl_2/H_2O, 1:0.5:1.0 v/v/v) with sodium L-ascorbate (0.1 equiv.) as the reductant and $CuSO_4 \cdot 5H_2O$ (0.05 equiv.) as the copper source at room temperature overnight. The use of dichloromethane as a cosolvent was critical to achieve the best yields of unknown 1,2,3-triazole derivatives **106**–**110** (Table 8). Because 1,2,3-triazole skeletons have been recognized as privileged scaffolds in many medicinal-oriented research programs,[10] the combination of such heterocyclic units with a tetronic acid unit and their derivatives may offer great potential in the development of new chemotherapeutic agents.

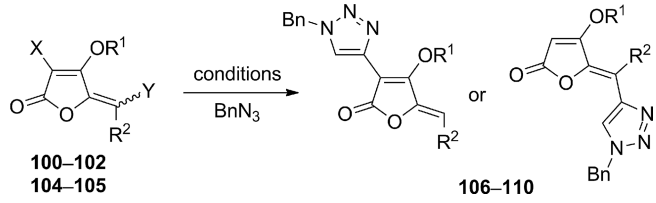
Table 7. Desilylation reactions of Sonogashira coupling products.[a]



Entry	R^1	R^2	X, Y	Compound [% yield][b]
1	Me	C_6H_5	Me_3Si–C≡C–, H	**100** (83)[8]
2	Me	4-$CF_3C_6H_4$	Me_3Si–C≡C–, H	**101** (89)
3	Bn	C_6H_5	Me_3Si–C≡C–, H	**102** (80)
4	Bn	4-$CF_3C_6H_4$	Me_3Si–C≡C–, H	**103** (56)
5	Me	C_6H_5	H, Me_3Si–C≡C–	**104** (81)[c]
6	Bn	C_6H_5	H, Me_3Si–C≡C–	**105** (50)[c]

[a] Reagents and conditions: Bu_4NF (1.1 equiv.), THF, 0 °C, 5 min. [b] Isolated yield. [c] Only the (*Z*) isomer was obtained.

Table 8. Copper(I)-catalyzed 1,3-dipolar cycloaddition reactions.[a]



Entry	R^1	R^2	X, Y	Compound [% yield][b]
1	Me	C_6H_5	HC≡C–, H	**106** (41)[4]
2	Me	4-$CF_3C_6H_4$	HC≡C–, H	**107** (66)
3	Bn	C_6H_5	HC≡C–, H	**108** (62)
4	Me	C_6H_5	H, HC≡C–	**109** (66)
5	Bn	C_6H_5	H, HC≡C–	**110** (68)

[a] Reagents and conditions: BN_3 (1.5 equiv.), sodium L-ascorbate (0.1 equiv.), and $CuSO_4 \cdot 5H_2O$ (0.05 equiv.) in *t*BuOH/CH_2Cl_2/H_2O (1:0.5:1.0 v/v/v) at room temp., overnight. [b] Isolated yield.

Conclusions

A new one-pot synthesis that is readily amenable for scaleup has been presented for γ-benzylidene methyl and benzyl tetronates. The bromination of several γ-benzylidene tetronate derivatives have also been performed selectively under mild conditions to provide access to useful molecular entities for postfunctionalization. The Suzuki–Miyaura, Stille, and Sonogashira cross-coupling reactions of the brominated derivatives were employed as model coupling partners to readily provide additional diversity. The resulting Sonogashira products were useful for the syntheses of biologically relevant 1,2,3-triazole-derived γ-benzylidene methyl and benzyl tetronates. Most of the materials described herein are new compounds, and the methods can be employed for the preparation of new chemotherapeutic agents as well as for the design of new scaffolds and organic substances for materials science. Many of the yields are not yet optimized, and there is certainly room for improvement. We are currently studying the scope and limitations of these cross-coupling reactions by using various boronic acids and alkyne coupling partners. Preliminary biological evaluations of some of these materials as well as new derivatives are currently under way, and complete biological data will be presented in future papers.

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Experimental Section

General Methods: Solvents were distilled before use. Reagents were obtained commercially and used without further purification. The ^{1}H, ^{19}F, and ^{13}C NMR spectroscopic data were recorded with a Bruker Avance 300 spectrometer (in $CDCl_3$ unless otherwise cited) at 300, 282, and 75 MHz, respectively. Chemical shifts are reported in ppm [s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), br. (broad)] relative to the solvent peak (δ_H = 7.26 ppm for $CHCl_3$, δ_C = 77.0 ppm for $CDCl_3$) or $CFCl_3$ (δ_F = 0.00 ppm for ^{19}F NMR spectra). Coupling constants (*J*) are reported in Hertz. TLC was performed on Merck silica Gel 60 F254 plates with detection by UV light. Silica gel column chromatography was performed on Macherey–Nagel silica gel 60*M* (0.04–0.063 mm). The solvents that were employed for chromatography, workup, and recrystallization are dichloromethane (DCM), ethyl acetate (AcOEt), hexane (HX), and petroleum ether (PE). Mass spectra were recorded with a Finnigan MAT 95 [EI or ESI+]. Melting points were measured in capillary tubes on a Büchi apparatus. Compounds **1a**, **1b**, **2**–**6**, **8**–**15**, and **16**–**20** were commercially available. Compound **7** was prepared as described in ref.[15] Compounds **42**[1i,1j] and **51**[1i,1j] are known compounds with spectroscopic data, whereas compound **43** is mentioned in the literature[3a] with no data available. Compounds **71**, **79**, **84**, **86**, **93**, **98**, **100**, and **106** have already been described in our preliminary communication.[4]

Typical Procedure for the Synthesis of the Starting Benzyl Lactone Derivatives 1b–1d: To a suspension of tetronic acid (5.0 g, 50 mmol) and anhydrous K_2CO_3 (13.8 g, 100 mmol) in dry DMF (100 mL) was added 4-methoxybenzyl chloride (7.46 mL, 55 mmol) at room temperature under argon, and the resulting suspension was stirred overnight. The DMF was then removed under reduced pressure, and water (50 mL) was added. The aqueous phase was then extracted with AcOEt (3 × 50 mL), and the combined organic layers were washed with brine (1 × 50 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. Recrystallization from AcOEt afforded the desired compound as a colorless solid.

4-(4-Fluorobenzyloxy)furan-2(5*H*)-one (1c): Colorless solid (50% yield); m.p. 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.15–7.07 (m, 2 H), 5.19 (s, 1 H), 5.03 (s, 2 H), 4.67 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 173.3, 163.1 (d, *J* = 248.7 Hz), 130.2 (d, *J* = 8.8 Hz), 129.8 (d, *J* = 3.3 Hz), 115.9 (d, *J* = 22.2 Hz), 89.8, 73.8, 67.9 ppm. HRMS (ESI+): calcd. for $C_{11}H_9FNaO_3$ [M + Na]$^+$ 231.0428; found 231.0418.

4-(4-Methoxybenzyloxy)furan-2(5*H*)-one (1d): Colorless solid (37% yield); m.p. 88–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.7 Hz, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 5.18 (s, 1 H), 4.99 (s, 2 H), 4.64 (s, 2 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 173.4, 160.3, 130.0, 125.7, 114.2, 89.5, 74.4, 67.9, 55.3 ppm. HRMS (ESI+): calcd. for $C_{12}H_{12}NaO_4$ [M + Na]$^+$ 243.0628; found 243.0630.

General Procedure for the Aldol Reactions: (see Scheme 2, method A). To a solution of the lactone (7.0 mmol) in dry THF (70 mL) was slowly added *n*BuLi (1.0 M solution in hexane, 7.7 mmol, 1.1 equiv.) at –78 °C under argon. The mixture was stirred at –78 °C for 15 min, and then the aldehyde (10.5 mmol, 1.5 equiv.) was added at –78 °C. The resulting mixture was then warmed to room temperature and then stirred at this temperature overnight. Water (20 mL) was added, and the aqueous phase was extracted with AcOEt (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The crude product was passed through a short column of silica gel (mixture of PE and AcOEt), and the crude aldol adducts were determined to be sufficiently pure for use in the dehydration step by the ^{1}H and ^{19}F NMR spectroscopic data. The crude aldol product (5.30 mmol) was dissolved in dry DCM (40 mL, 0.13 M), and a catalytic amount of DMAP (0.53 mmol, 0.1 equiv.) was added. Freshly distilled triethylamine (10.6 mmol, 2.0 equiv.) was then added, and the resulting mixture was cooled to 0 °C. Trifluoroacetic anhydride (TFAA, 5.83 mmol, 1.1 equiv.) was added dropwise, and the solution was warmed to room temperature over 2 h. DBU (10.6 mmol, 2.0 equiv.) was added, and the mixture was stirred at room temperature for 0.5 h. Water (20 mL) was added, and the aqueous layer was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine (40 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(*Z*)-5-(4-Fluorobenzylidene)-4-methoxyfuran-2(5*H*)-one (44): Purification by silica gel column chromatography (PE/AcOEt, 2:1) afforded **44** (28% yield) as a white solid; m.p. 155–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.69 (m, 2 H), 7.09–7.01 (m, 2 H), 6.16 (s, 1 H), 5.26 (s, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 168.5, 162.8 (d, *J* = 249.4 Hz), 141.8 (d, *J* = 2.7 Hz), 132.3 (d, *J* = 8.3 Hz), 128.6 (d, *J* = 3.5 Hz), 115.8 (d, *J* = 21.6 Hz), 106.5, 88.1, 59.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.68 (m) ppm. HRMS (ESI+): calcd. for $C_{12}H_9FNaO_3$ [M + Na]$^+$ 243.0428; found 243.0427.

(*Z*)-4-(Benzyloxy)-5-(3,4-dimethoxybenzylidene)furan-2(5*H*)-one (58): Purification by silica gel column chromatography (PE/AcOEt, from 3:1 to 1:1) afforded **58** (18% yield) as a yellow solid; m.p. 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (m, 5 H), 7.39–7.38 (m, 1 H), 7.30–7.27 (m, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.23 (s, 1 H), 5.30 (s, 1 H), 5.13 (s, 2 H), 3.92 (s, 3 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 168.6, 149.8, 148.8, 140.7, 133.9, 128.9, 128.7, 127.9, 125.3, 124.3, 112.6, 110.8, 107.9, 88.4, 74.0, 55.71, 55.68 ppm. HRMS (ESI+): calcd. for $C_{20}H_{18}NaO_5$ [M + Na]$^+$ 361.1046; found 361.1034.

General Procedure for the One-Pot Aldolisation/Dehydration Reaction Sequence: (see Table 2, method B). Under argon, the lactone (4.38 mmol) and the aldehyde (5.26 mmol, 1.2 equiv.) were dissolved in CH_3CN (15 mL). DBU (8.76 mmol, 2 equiv.) was then added, and the mixture was stirred at 65 °C overnight. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography.

(*Z*)-4-Methoxy-5-[2-(phenylethynyl)benzylidene]furan-2(5*H*)-one (65): Purification by silica gel column chromatography (PE/AcOEt, 5:1) afforded **65** (73% yield) as a white solid; m.p. 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.1 Hz, 1 H), 7.46–7.43 (m, 3 H), 7.28–7.14 (m, 5 H), 6.84 (s, 1 H), 5.18 (s, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 168.5, 142.9, 133.6, 132.3, 131.5, 130.4, 128.7, 128.6, 128.4, 123.8, 123.0, 105.3, 94.9, 88.4, 87.4, 59.4 ppm. HRMS (ESI+): calcd. for $C_{20}H_{14}NaO_3$ [M + Na]$^+$ 325.0835; found 325.0835.

(*Z*)-4-(Benzyloxy)-5-[4,4-(dimethylamino)benzylidene]furan-2(5*H*)-one (67): Purification by silica gel column chromatography (PE/AcOEt, 3:1) afforded **67** (30% yield) as a yellow wax. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 9.0 Hz, 2 H), 7.43 (m, 5 H), 6.67 (d, *J* = 9.0 Hz, 2 H), 6.22 (s, 1 H), 5.24 (s, 1 H), 5.11 (s, 2 H), 3.01 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 169.3, 150.6, 139.1, 134.2, 132.2, 128.9, 128.8, 127.9, 120.2, 111.8, 109.1, 87.7, 73.9, 40.0 ppm. HRMS (ESI+): calcd. for $C_{20}H_{20}NO_3$ [M + H]$^+$ 322.1438; found 322.1427.

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General Procedure for the C-3-Bromination Reactions: (see Table 3). To a solution of the lactone (0.145 mmol) and pyridine (0.290 mmol, 2 equiv.) in DCM (1.45 mL, 0.1 M) was slowly added bromine (0.174 mmol, 1.2 equiv.) at room temperature under argon. The resulting solution was stirred at room temperature for 1 h. The reaction was quenched with a saturated solution of $Na_2S_2O_3$ (20 mL), and the resulting mixture was extracted with DCM (3× 20 mL). The combined organic phases were dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(*Z*)-3-Bromo-5-(4-bromobenzylidene)-4-methoxyfuran-2(5*H*)-one (72): Purification by silica gel column chromatography (PE/AcOEt, 4:1) afforded **72** (73% yield) as a white solid; m.p. 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 2 H), 6.19 (s, 1 H), 4.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 163.3, 142.4, 132.0, 131.9, 130.8, 123.6, 107.4, 80.8, 59.8 ppm. HRMS (ESI+): calcd. for $C_{12}H_8Br_2NaO_3$ [M + Na]$^+$ 380.8732; found 380.8733.

(*Z*)-5-Benzylidene-4-(benzyloxy)-3-bromofuran-2(5*H*)-one (76): Purification by silica gel column chromatography (PE/AcOEt, 5:1) afforded **76** (79% yield) as a white solid; m.p. 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 6.3 Hz, 2 H), 7.46 (m, 5 H), 7.39–7.33 (m, 3 H), 6.30 (s, 1 H), 5.75 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 162.8, 142.2, 134.5, 131.8, 130.6, 129.3, 129.1, 128.8, 128.7, 128.0, 108.9, 81.6, 73.7 ppm. HRMS (ESI+): calcd. for $C_{18}H_{13}BrNaO_3$ [M + Na]$^+$ 378.9940; found 378.9926.

General Procedure for the Exocyclic Dibromination Reactions: (see Scheme 4). To a solution of the lactone (0.495 mmol) in DCM (25 mL, 0.02 M) was slowly added bromine (1 drop 3 min^{-1}, 0.495 mmol, 1 equiv.) at 0 °C under argon, and the resulting solution was stirred for 1 h at this temperature. The reaction was quenched at 0 °C with a saturated aqueous $Na_2S_2O_3$ solution (30 mL), and the resulting mixture was extracted with DCM (3× 30 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(±)-4-(Benzyloxy)-5-bromo-5-[bromo(phenyl)methyl]furan-2(5*H*)-one (80): Purification by silica gel column chromatography (DCM/PE, 2:1) afforded **80** (65% yield) as a white solid; m.p. 155–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.62 (m, 2 H), 7.50–7.45 (m, 5 H), 7.40–7.38 (m, 3 H), 5.39 (s, 1 H), 5.38 (s, 1 H), 5.27–5.26 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 167.6, 135.9, 133.1, 130.0, 129.5, 129.4, 129.0, 128.4, 128.2, 90.2, 89.5, 75.6, 52.4 ppm. HRMS (ESI+): calcd. for $C_{18}H_{14}Br_2NaO_3$ [M + Na]$^+$ 458.9202; found 458.9221.

General Procedure for the Tribromination Reactions: (see Scheme 4). To a solution of the lactone (0.108 mmol) in DCM (1.1 mL, 0.10 M) was slowly added bromine (0.216 mmol, 2.0 equiv.) at 0 °C under argon. The resulting solution was then slowly warmed to room temperature over 1 h. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL), and the mixture was extracted with DCM (3× 20 mL). The combined organic phases were dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(±)-3,5-Dibromo-5-{bromo[4-(trifluoromethyl)phenyl]methyl}-4-methoxyfuran-2(5*H*)-one (82): Purification by silica gel column chromatography (PE/AcOEt, 2:1) afforded **82** (60% yield) as a white solid; m.p. 109–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.4 Hz, 2 H), 7.65 (d, J = 8.4 Hz, 2 H), 5.36 (s, 1 H), 4.52 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 164.4, 139.3, 131.6 (q, J = 32.6 Hz), 130.5, 128.8 (q, J = 280.1 Hz), 125.5 (q, J = 3.7 Hz), 89.2, 81.6, 61.0, 51.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.88 (s) ppm. HRMS (ESI+): calcd. for $C_{13}H_8Br_3F_3NaO_3$ [M + Na]$^+$ 528.7868; found 528.7880.

(±)-4-(Benzyloxy)-3,5-dibromo-5-[bromo(phenyl)methyl]furan-2(5*H*)-one (83): Purification by silica gel column chromatography (DCM) afforded **83** (65% yield) as a white solid; m.p. 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H), 7.51–7.48 (m, 5 H), 7.39–7.37 (m, 3 H), 5.91–5.78 (m, 2 H), 5.32 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 164.8, 135.4, 133.7, 130.1, 129.7, 129.5, 129.0, 128.54, 128.48, 90.3, 81.9, 75.3, 52.7 ppm. HRMS (ESI+): calcd. for $C_{18}H_{13}Br_3NaO_3$ [M + Na]$^+$ 536.8307; found 536.8281.

General Procedure for the Elimination Reactions of Di- and Tribrominated Lactones: (see Table 4). To a solution of the brominated derivative (0.245 mmol) in DCM (5 mL, 0.05 M) was added DBU (0.588 mmol, 2 equiv.) at 0 °C under argon, and the resulting solution was warmed to room temperature and stirred for 0.5–2 h. The reaction was quenched with water (20 mL), and the mixture was extracted with DCM (3× 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

4-(Benzyloxy)-5-[bromo(phenyl)methylene]furan-2(5*H*)-one (85): Purification by silica gel column chromatography (PE/AcOEt, 1:1) afforded **85** (85% yield) as a mixture of *Z*/*E* (1:0.3) isomers. The (*Z*) and (*E*) isomers could be separated after a second column chromatography procedure (PE/AcOEt, 4:1). Data for (*Z*) isomer: White solid; m.p. 94–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2 H), 7.35–7.23 (m, 6 H), 6.84–6.81 (m, 2 H), 5.42 (s, 1 H), 4.89 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 166.6, 142.1, 135.7, 133.3, 129.8, 129.5, 128.5, 128.4, 128.0, 126.7, 109.0, 91.9, 73.9 ppm. HRMS (ESI+): calcd. for $C_{18}H_{13}BrNaO_3$ [M + Na]$^+$ 378.9940; found 378.9925. Data for (*E*) isomer: White solid; m.p. 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 2 H), 7.50–7.35 (m, 8 H), 5.50 (s, 1 H), 5.21 (s, 2 H) ppm. Selected ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 166.5, 140.4, 136.1, 133.8, 129.9, 129.7, 128.8, 128.1, 127.4, 108.5, 92.0, 74.6 ppm. HRMS (ESI+): calcd. for $C_{18}H_{13}BrNaO_3$ [M + Na]$^+$ 378.9940; found 378.9929.

3-Bromo-5-{bromo[4-(trifluoromethyl)phenyl]methylene}-4-methoxyfuran-2(5*H*)-one (87): Purification by silica gel column chromatography (DCM) afforded **87** (60% yield) as a mixture of *Z*/*E* (approximately 1:0.6) isomers (not separated); white solid. Data for *Z*/*E* isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.62 (m, 6 H), 7.50 (d, J = 8.1 Hz, 2 H), 4.48 (s, 3 H), 4.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 163.0, 162.9, 161.4, 142.1, 141.0, 139.4, 139.1, 131.5 (q, J = 32.5 Hz), 131.4 (q, J = 32.7 Hz), 130.2, 130.1, 125.1 (q, J = 3.8 Hz), 124.8 (q, J = 3.7 Hz), 123.5 (q, J = 271.0 Hz), 123.6 (q, J = 270.7 Hz), 107.7, 106.7, 84.65, 84.58, 60.1, 59.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.85 (s, minor), –62.98 (s, major) ppm.

General Procedure for Suzuki Coupling Reactions: (see Table 5). Brominated γ-benzylidene methyl or benzyl tetronate (0.196 mmol), K_2CO_3 (0.392 mmol, 2 equiv.), phenylboronic acid (0.392 mmol, 2 equiv.), and $Pd(PPh_3)_4$ (0.0196 mmol, 0.1 equiv.) were dissolved in toluene (2.0 mL, 0.1 M) under argon. The mixture was stirred overnight at 75 °C. The reaction was quenched with

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water (20 mL), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to afford the coupling product.

General Procedure for Stille Coupling Reactions: (see Table 5). Brominated γ-benzylidene methyl or benzyl tetronate (0.188 mmol), phenyltributylstannane (0.376 mmol, 2 equiv.), and $Pd(PPh_3)_4$ (0.0188 mmol, 0.1 equiv.) were dissolved in toluene (3 mL, 0.06 M) under argon. The mixture was stirred overnight at 75 °C. The reaction was quenched with water (20 mL), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to afford the coupling product.

(*Z*)-5-Benzylidene-4-(benzyloxy)-3-phenylfuran-2(5*H*)-one (90): Purification by silica gel column chromatography (PE/DCM, 1:1) afforded **90** (47% yield for Suzuki coupling; 67% yield for Stille coupling) as a white solid; m.p. 129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.1 Hz, 2 H), 7.56–7.53 (m, 2 H), 7.45–7.35 (m, 9 H), 7.21–7.20 (m, 2 H), 6.33 (s, 1 H), 5.07 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 162.6, 142.8, 134.9, 132.6, 130.5, 130.0, 129.2, 128.9, 128.8, 128.73, 128.65, 128.6, 128.4, 127.8, 108.2, 106.6, 74.6 ppm. HRMS (ESI+): calcd. for $C_{24}H_{18}NaO_3$ [M + Na]$^+$ 377.1148; found 377.1140.

5-(Diphenylmethylene)-4-methoxyfuran-2(5*H*)-one (91): Purification by silica gel column chromatography (DCM) afforded **91** (96% yield for Suzuki coupling; 74% yield for Stille coupling) as a yellow solid; m.p. 169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 8 H), 7.23–7.20 (m, 2 H), 5.31 (s, 1 H), 3.61 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 168.3, 139.3, 137.4, 136.6, 130.7, 130.5, 128.5, 128.1, 128.0, 127.6, 126.9, 90.1, 59.0 ppm. HRMS (ESI+): calcd. for $C_{18}H_{14}NaO_3$ [M + Na]$^+$ 301.0835; found 301.0833.

General Procedure for Sonogashira Coupling Reactions: (see Table 6). Brominated γ-benzylidene methyl or benzyl tetronate (0.355 mmol), CuI (0.036 mmol, 0.1 equiv.), and $Pd(PPh_3)_2Cl_2$ (0.036 mmol, 0.1 equiv.) were dissolved in toluene (3 mL, 0.1 M). Trimethylsilylacetylene (0.530 mmol, 1.5 equiv.) and freshly distilled Et_3N (0.710 mmol, 2 equiv.) were added, and the resulting mixture was stirred at 75 °C overnight. The reaction was quenched with water (20 mL), and the aqueous phase was extracted with AcOEt (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(*Z*)-4-Methoxy-5-[4-(trifluoromethyl)benzylidene]-3-[(trimethylsilyl)ethynyl]furan-2(5*H*)-one (94): Purification by silica gel column chromatography (PE/AcOEt, 4:1) afforded **94** (73% yield) as a yellow solid; m.p. 156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.1 Hz, 2 H), 7.59 (d, J = 8.1 Hz, 2 H), 6.25 (s, 1 H), 4.44 (s, 3 H), 0.23 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 166.4, 143.2, 135.5, 130.6, 130.4 (q, J = 28.3 Hz), 125.6 (q, J = 3.7 Hz), 123.8 (q, J = 271.0 Hz), 107.0, 104.6, 92.7, 88.7, 60.0, –0.53 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.83 (s) ppm. HRMS (ESI+): calcd. for $C_{18}H_{17}F_3NaO_3Si$ [M + Na]$^+$ 389.0791; found 389.0776.

(*Z*)-4-(Benzyloxy)-5-[1-phenyl-3-(trimethylsilyl)prop-2-ynylidene]-furan-2(5*H*)-one (99): Purification by silica gel column chromatography (PE/AcOEt, 4:1) afforded **99** (83% yield) as a beige solid; m.p. 141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2 H), 7.31–7.25 (m, 6 H), 6.90–6.87 (m, 2 H), 5.39 (s, 1 H), 4.90 (s, 2 H), 0.23 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.0, 147.4, 133.6, 133.4, 129.7, 128.48, 128.39, 128.3, 127.8, 126.8, 109.6, 108.7, 100.6, 92.2, 73.8, –0.31 ppm. HRMS (ESI+): calcd. for $C_{23}H_{22}NaO_3Si$ [M + Na]$^+$ 397.1230; found 397.1225.

General Procedure for the Desilylation Reactions: (see Table 7). To a solution of the silylated derivative (0.29 mmol) at 0 °C in THF (6 mL, 0.05 M) was slowly added tetra-*n*-butylammonium fluoride (TBAF, 0.1 M solution in THF, 0.31 mmol, 1.1 equiv.). The mixture was stirred at 0 °C for 5 min, and water (20 mL) was added. The aqueous layer was extracted with AcOEt (3 × 20 mL), and the combined organic phases were washed with water (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(*Z*)-3-Ethynyl-4-methoxy-5-[4-(trifluoromethyl)benzylidene]furan-2(5*H*)-one (101): Purification by silica gel column chromatography (from DCM/PE, 2:1 to DCM) afforded **101** (89% yield) as a yellow solid; m.p. 181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.1 Hz, 2 H), 7.60 (d, J = 8.1 Hz, 2 H), 6.29 (s, 1 H), 4.44 (s, 3 H), 3.40 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 166.7, 142.9, 135.4, 130.7, 130.6 (q, J = 32.4 Hz), 125.6 (q, J = 3.8 Hz), 123.8 (q, J = 277.0 Hz), 107.5, 87.3, 86.0, 72.2, 60.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.85 (s) ppm. HRMS (ESI+): calcd. for $C_{15}H_9F_3NaO_3$ [M + Na]$^+$ 317.0396; found 317.0385.

(*Z*)-5-Benzylidene-4-(benzyloxy)-3-ethynylfuran-2(5*H*)-one (102): Purification by silica gel column chromatography (PE/AcOEt, 5:1) afforded **102** (80% yield) as a brown solid; m.p. 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.72 (m, 2 H), 7.49–7.44 (m, 5 H), 7.40–7.32 (m, 3 H), 6.33 (s, 1 H), 5.80 (s, 2 H), 3.47 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 166.9, 141.5, 134.3, 131.9, 130.8, 129.4, 129.2, 128.8, 128.7, 128.3, 109.7, 87.0, 86.3, 74.3, 72.8 ppm. HRMS (ESI+): calcd. for $C_{20}H_{14}NaO_3$ [M + Na]$^+$ 325.0835; found 325.0827.

General Procedure for the Copper(I)-Catalyzed 1,3-Dipolar Cycloaddition: (see Table 8). To the solution of the alkyne (0.149 mmol) and benzyl azide (0.223 mmol, 1.5 equiv.) in *t*BuOH (1.0 mL) and DCM (0.5 mL) were successively added a solution of sodium L-ascorbate (0.0149 mmol, 0.1 equiv.) in water (0.5 mL) and a solution of $CuSO_4 \cdot 5H_2O$ (0.0074 mmol, 0.05 equiv.) in water (0.5 mL). The solution was stirred overnight at room temperature. The solvents were removed under reduced pressure, and water (10 mL) was added. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic phases were washed with water (10 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

(*Z*)-3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-4-methoxy-5-[4-(trifluoromethyl)benzylidene]furan-2(5*H*)-one (107): Purification by silica gel column chromatography (PE/AcOEt, 2:1) afforded **107** (66% yield) as a yellow solid; m.p. 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.86 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.41–7.31 (m, 5 H), 6.41 (s, 1 H), 5.57 (s, 2 H), 4.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 163.0, 144.3, 137.0, 135.9, 134.2, 130.5, 130.2 (q, J = 32.6 Hz), 129.2, 128.9, 128.2, 125.6 (q, J = 3.8 Hz), 124.0, 123.9 (q, J = 270.1 Hz), 106.9, 95.8, 62.2, 54.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.76 (s) ppm. HRMS (ESI+): calcd. for $C_{22}H_{16}F_3N_3NaO_3$ [M + Na]$^+$ 450.1036; found 450.1025.

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(*Z*)-5-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methylene]-4-methoxyfuran-2(5*H*)-one (109): Purification by silica gel column chromatography (PE/AcOEt, 1:1) afforded **109** (66% yield) as a yellow solid; m.p. 199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.40–7.30 (m, 10 H), 5.55 (s, 2 H), 5.26 (s, 1 H), 3.58 (s, 3 H) ppm. Selected ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 167.5, 139.0, 134.5, 132.8, 130.3, 129.0, 128.6, 128.3, 127.9, 127.5, 126.0, 117.5, 90.0, 59.1, 54.1 ppm. HRMS (ESI+): calcd. for $C_{21}H_{18}N_3O_3$ $[M + H]^+$ 360.1343; found 360.1346.

Single-Crystal X-ray Diffraction Analyses: Single-crystal X-ray studies were carried out by using a Gemini diffractometer and the related analysis software.[16] Absorption corrections based on the crystal faces were applied to the data sets (analytical).[17] The structures were solved by direct methods using the SIR97 program[18] combined with Fourier difference syntheses and refined against *F* using reflections with $[I/\sigma(I) > 3]$ by using the CRYSTALS program.[19] All atomic displacement parameters for non-hydrogen atoms were refined with anisotropic terms. The hydrogen atoms were theoretically located on the basis of the conformation of the supporting atom and refined by using the riding model.

Supporting Information (see footnote on the first page of this article): Experimental procedures, preparation of compounds, and ^{1}H, ^{19}F, and ^{13}C NMR spectra.

Acknowledgments

This work was supported by the Agence Nationale de la Recherche (ANR) (ANR-11-EMMA-04-QUINOLAC) and the Ministère de l'Enseignement Supérieur et de la Recherche (Ph. D. fellowship to S. I.). Additional support was provided by the Centre National de la Recherche Scientifique (CNRS) and the Université Claude Bernard Lyon 1 (UCBL). H. Y. and M. M. are grateful to the PICS exchange program of CNRS (grant number 05871) for fostering our international collaboration. The authors also thank Julien Bosson and Clément de Saint Jores for some materials syntheses and Florian Albrieux, Christian Duchet, Nathalie Enriques, and Reynald Hélye from the Centre Commun de Spectrométrie de Masse (CCSM) of Université Claude Bernard Lyon 1 for assistance and access to the mass spectrometry facility.

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[11] Compound **7**: CAS 1272–43–1; X. Yin, Y. Li, Y. Zhu, X. Jing, Y. Li, D. Zhu, *Dalton Trans.* **2010**, *41*, 9929–9935.

[12] Compound **66**: orthorhombic, *Pbca*, a = 15.375(1) Å, b = 12.338(1) Å, c = 15.512(1) Å, V = 2942.6(2) Å^3, refined formula: $C_{18}H_{17}NO_3$, molecular weight: 295.3 g mol^{-1}, Z = 8, d = 1.333 g cm^{-3}, μ = 0.091 mm^{-1}, $R[I/\sigma(I) > 3]$ = 0.0413, $Rw[I/\sigma(I) > 3]$ = 0.0456, S = 1.13, $\Delta\rho_{max}$ = 0.19 e-Å^{-3}, $\Delta\rho_{min}$ = –0.18 e-Å^{-3}, number refined parameters: 199, number reflections used: 2407. CCDC-1059356 (for **66**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] Compound **78**: monoclinic, $P2_1/n$, a = 12.2321(9) Å, b = 7.9932(5) Å, c = 18.823(1) Å, β = 101.404(6)°, V = 1804.1(2) Å^3, refined formula: $C_{20}H_{17}Br_1O_5$, molecular weight:

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417.26 g mol^{-1}, Z = 4, d = 1.536 g cm^{-3}, μ = 2.307 mm^{-1}, $R[I/\sigma(I) > 3]$ = 0.0363, $Rw[I/\sigma(I) > 3]$ = 0.0456, S = 1.10, $\Delta\rho_{max}$ = 0.25 e$^-$ Å^{-3}, $\Delta\rho_{min}$ = –0.39 e$^-$ Å^{-3}, number refined parameters: 235, number reflections used: 2099. CCDC-1061804 (for **78**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Received: May 22, 2015
Published Online: August 14, 2015

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