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Regioselective bromination of tetronic acid-derived γ-lactones and metal-catalyzed post-functionalization: an efficient access to new γ-ylidenetetronate derivatives

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ABSTRACT

The synthesis of several methyl and benzyl γ-ylidenetetronates was accomplished and the bromination reactions of these derivatives, using bromine or *N*-bromosuccinimide (NBS), were found to occur under mild conditions. Several new brominated γ-unsaturated lactones derived from tetronic acid were prepared in moderate to good yields, with some of them characterized by single crystal X-ray diffraction. A preliminary reactivity study of two bromine-derived γ-benzylidene methyl tetronates, in Sonogashira cross-coupling reactions, with also preparation of 1,2,3-triazole-derived γ-benzylidene methyl tetronate under Cu(I)-catalyzed condition, was performed with an indication that these brominated γ-benzylidene tetronates are useful platforms to produce diversified γ-lactones.

γ-Lactones derived from tetronic acids and derived molecules, are structures that occur naturally with various biological activities and are promising compounds that can be used in a number of synthetic useful reactions to prepare bioactive materials (Fig. 1).[1] In our current research program directed to the synthesis and biological evaluation of new therapeutic agents, halogenated γ-lactones derived from tetronic acids were identified as useful synthetic intermediates, with the aim to prepare a set of molecules with some diversity (R^1, R^2, R^3, and R^4), through for example, metal-catalyzed cross-coupling post-functionalization (Scheme 1). These halogenation sequences starting from the γ-benzylidenetetronates and use of the resulting products in the development of new valuable organic entities and chemotherapeutic agents are relatively scarce in the literature.[2]

In this Letter, we disclose our preliminary results directed to the synthesis of γ-lactones derived from methyl and benzyl tetronates, their regioselective bromination, and their use in Sonogashira[3] cross-coupling reactions. In order to demonstrate the synthetic utility of our strategy, an example of Cu(I)-catalyzed 1,3-dipolar cycloaddition with benzyl azide as 1,3-dipole, using an acetylenic-derived methyl γ-benzylidene-derived tetronate,[4] is also

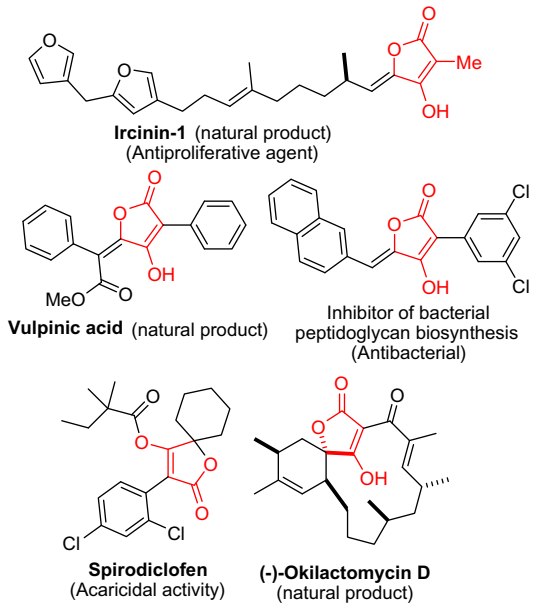

Figure 1. Natural and bioactive tetronic acid derivatives.

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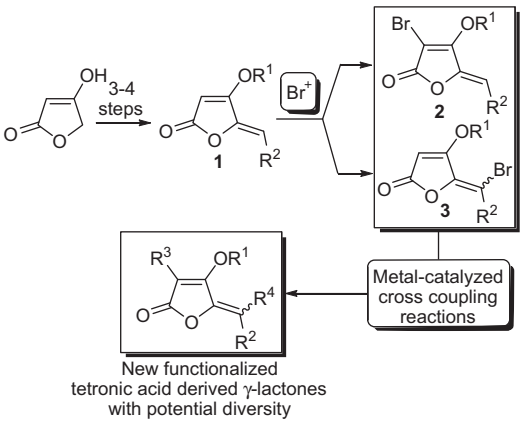
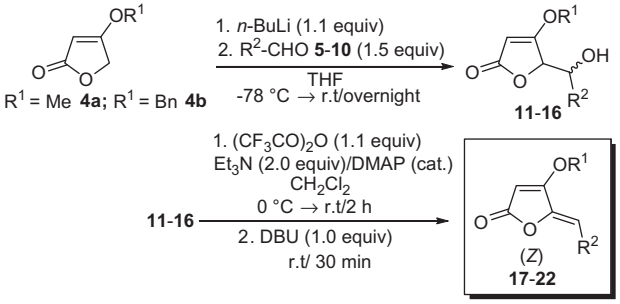


Scheme 1. General access to the targets.

presented giving access to a pharmaceutical relevant 1,2,3-triazole tetronic acid-derived γ-lactone derivative.

Starting lactones of general structure **1** (Scheme 1) were prepared, following literature procedures developed with some analogues,[2b,c,5] using either methyl tetronate (commercially available) or known benzyl derivative.[2b,c] The benzyl derivative was easily prepared in 60% yield by the reaction of benzyl bromide (1.1 equiv) and potassium carbonate (K_2CO_3) (2.0 equiv) in *N*,*N*-dimethylformamide (DMF). Treating tetronates **4** (**4a**, R^1 = Me, **4b**, R^1 = Bn) with *n*-BuLi (1.1 equiv) and aldehydes (1.5 equiv) **5**–**10** in tetrahydrofuran (THF) from −78 °C to room temperature (overnight) gave the aldols adducts **11**–**16** as diastereoisomeric mixtures (1/1) in good to excellent yields, after column chromatography purification (Scheme 2 and Table 1). These alcohols **11**–**16** were then transformed into the corresponding γ-lactones **17**–**22**, in moderate to good yields (Table 1), following a two-steps/one-pot sequence through esterification with trifluoroacetic anhydride



Scheme 2. γ-Lactone synthesis from methyl or benzyl tetronates.

Table 1
Preparation of the γ-ylidenetetronates and precursors

R^1	R^2 in R^2 CHO	Aldol (% yield)[a]	γ-Lactone (% yield)[a]
Me	**5**: Ph	**11a** (93%)	**17a** (42%; 57%[b])
Me	**6**: 4-F-Ph	**12a** (82%)	**18a** (63%)[b]
Me	**7**: 3,4-OMe-Ph	**13a** (65%)	**19a** (60%)
Me	**8**: 3,4-F-Ph	**14a** (99%)	**20a** (34%)
Me	**9**: 4-CF_3-Ph	**15a** (67%)	**21a** (65%)
Me	**10**: Ferrocenyl	**16a**[c]	**22a** (99%)
Bn	**5**: Ph	**11b** (94%)	**17b** (50%)
Bn	**6**: 4-F-Ph	**12b**	**18b** (90%)
Bn	**7**: 3,4-OMe-Ph	(99%) **13b** (55%)	**19b** (33%)
Bn	**9**: 4-CF_3-Ph	**15b** (96%)	**21b** (32%)

[a] Isolated yield.
[b] Concd H_2SO_4 in dichloromethane at rt was used.
[c] Not formed (see text).

and elimination with 1,8-diazabicycloundec-7-ene (DBU) as a base,[2b,c] using dichloromethane as solvent. All the compounds **17**–**22** were obtained as a *Z* stereoisomer after column chromatography.[5] A minor *E* isomer was observed when R^1 = Me from the crude product (^{1}H NMR) but was not isolated during purification because of trace amount, while for γ-lactones with R^1 = Bn such isomer was not detected at all. The *Z* stereochemistry has been confirmed by single-crystal X-ray diffraction for the ferrocenyl-derived compound **22a** (Fig. 2)[6] which has been obtained directly during the aldolization process, without requiring the esterification/elimination step. Aldol products **11a** and **12a** can also be transformed into their corresponding unsaturated lactones **17a** and **18a** respectively, using H_2SO_4 in dichloromethane.[7] For γ-lactone **21b** the elimination step was not efficient compared with its methyl analogue **21a**, and in general the -OBn derivatives were found to be prone to some decomposition during the esterification/elimination step.

Bromination reactions were first performed on γ-lactone **17a** as a model compound and *N*-bromosuccinimide (NBS) as brominating reagent. Lithiation of **17a** using lithium diisopropylamide (LDA) in THF and trapping the C-3 lithium derivative with NBS in excess (2.3 equiv), gave **23a** in a moderate 52% isolated yield while using just NBS (2.5 equiv) in dichloromethane resulted in the dibromination on the exocyclic double bond with the formation of **24a** in a modest 24% yield (Scheme 3).

These results show that bromination on C-3 position can occur selectively through a previous activation (in this case with LDA). Otherwise, running the reaction with bromine (1.5 equiv) in the presence of pyridine (1.1 equiv) in dichloromethane at room temperature over 2 h (concentration of substrate, *C* = 0.1 M), gave **23a** in an excellent 91% isolated yield after column chromatography purification (Scheme 4). This optimized and more practical condition was found to be general, with some slight modifications, for a series of γ-lactones **17**–**21** giving the corresponding 3-brominated γ-lactones **23**, **25**–**28** in moderate to excellent yields (Table 2).[8]

When γ-lactone **17a** was reacted with bromine (1.0 equiv) in dichloromethane, without pyridine, at 0 °C (1 h) and quenching

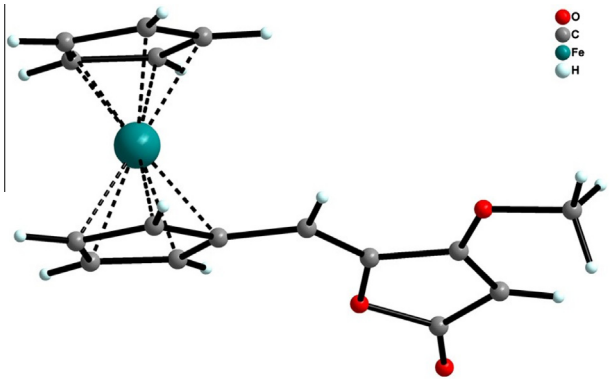
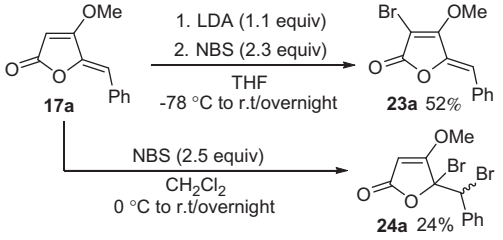


Figure 2. Single crystal X-ray diffraction of (*Z*)-γ-lactone **22a**.



Scheme 3. Bromination of γ-lactone **17a** using *N*-bromosuccinimide.