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2-(Trimethylsilyloxy)furan as a Dianion Equivalent: A Two-Step Synthesis of Functionalized Spirocyclic Butenolides

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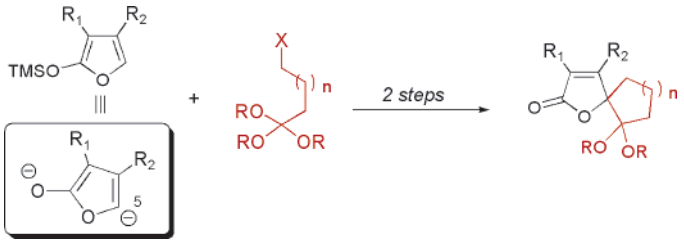
ABSTRACT



The use of 2-(trimethylsilyloxy)furan derivatives as dianion equivalents leads to a general and connective spiroannulation protocol for the efficient preparation of spirocyclic butenolides.

Among the plethora of heterocyclic subunits present in biologically active natural or synthetic products, spirobutenolides of the general formula **1** (Figure 1) occupy a cardinal position. The number of strategies reported in the literature for their assembly is a clear testimony to their importance.[1]

In addition, the unusually high number of molecules displaying useful biological activities and embodying the basic structure of **1** further illustrates the unique properties of this class of compounds. Representative examples including man-made molecules, such as the remarkably active acaricides and insecticides spirodiclofen (**2**) and spiromesifen (**3**),[2] the spirocyclic neuropeptide Y antagonist (**4**),[3] and naturally occurring substances, such as spirofragilide (**5**)[4] or the recently isolated lambertellol A (**6**),[5] are collected in Figure 1.

The ubiquitous presence of this subunit coupled with its interesting biological properties triggered our interest, and the possibility of assembling spirocyclic butenolides **1** in a connective manner was envisioned. Moreover, we were particularly intrigued by the likelihood of generating more richly functionalized analogues of **1**, such as **7** (Scheme 1). Indeed, a literature survey revealed that most of the procedures employed to date either relied upon multistep sequences or allowed little functionalization of the final adducts.

Guided by our previous experience in the preparation of carbospirocycles,[6] we envisaged the use of 2-(trimethylsilyloxy)furan (**9**, R = H) as the template upon which a novel spiroannulation strategy could be implemented. Our proposed approach is presented in Scheme 1. It was anticipated that adducts **8**, available through Lewis acid mediated condensa-

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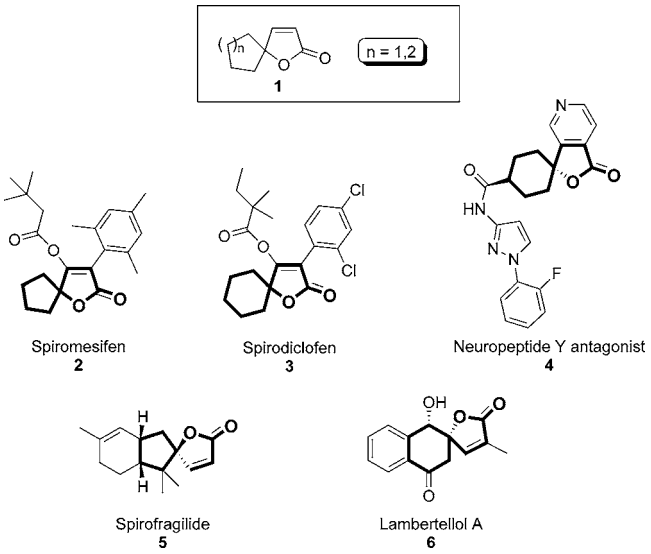
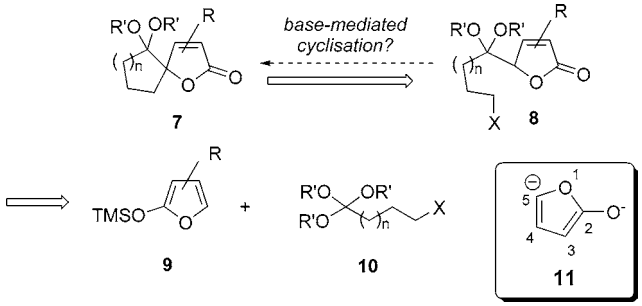


Figure 1. Representative compounds bearing the spirobutenolide structure **1**.

tion of *ortho*-esters **10** with 2-(trimethylsilyloxy)furan derivatives **9**,[7] could serve as substrates for a base-mediated cyclization to spirobutenolides **7**. Such a strategy would imply the formal use of trimethylsilyloxy furan as the C-5 dianionic synthon **11**.[8]

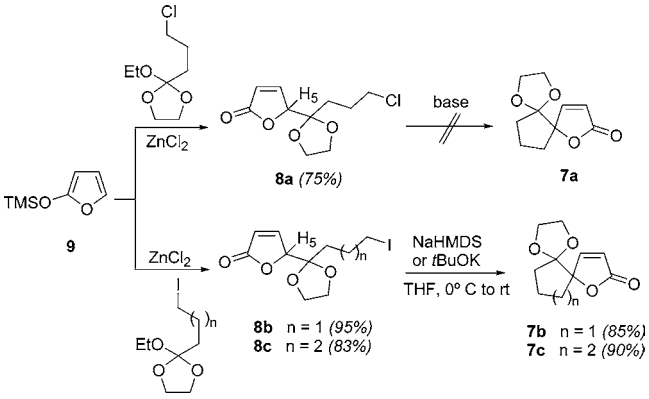
Scheme 1. Proposed Retrosynthetic Analysis of Functionalized Spirobutenolides **7**



Though attractive due to its simplicity and convergency, this approach did, however, raise some concerns. Indeed, from the onset, we were surprised at the lack of literature precedent on spirocyclization of compounds analogous to **8**.[9] Furthermore, Pelter et al. had previously shown that, under strongly basic conditions, adducts similar to **8** (R′ = Me) underwent alkoxy group elimination to form dienol ether derivatives.[10] Despite all these potential pitfalls, we now wish to report the successful application of this simple strategy for the efficient preparation of spirobutenolides, as depicted in Scheme 1.

We had previously shown that compounds such as **8a** could be readily produced, in one step and in high yields, through the $ZnCl_2$-promoted condensation of trimethylsilyloxy furan **9a** with *ortho*-ester **10a**.[7] With these substrates in hand, we next investigated their reactivity under basic conditions. To our disappointment, initial treatment of chlorinated **8a** with a variety of bases led only to the recovery of the starting material (Scheme 2).

Scheme 2. Initial Results on the Base-Promoted Spiroannulation of Butenolides **8a**,**b**



Interestingly, when iodinated derivatives **8b**,**c** were treated with base, rapid and complete transformation of these substrates into new products of similar polarity (TLC analysis) was observed. Following conventional aqueous workup, two new compounds, lacking the characteristic H-5 signal in their ^{1}H NMR spectrum and bearing a new quaternary carbon resonance at 94−95 ppm (APT/DEPT NMR), were obtained in excellent yields and without the need for further purification (Scheme 2). Extensive spectroscopic studies provided compelling evidence for the formation of the spirocyclic compounds **7b** and **7c**. Further investigations revealed NaHMDS and *t*-BuOK to be the most suitable bases for this reaction.

It is noteworthy that cyclization of butenolides **8** proceeds smoothly and in good yields regardless of the size of the ring being generated (five- vs six-membered). This observation is in sharp contrast to similar spiroannulations of the carbocyclic analogues of **8** for which the final cyclization is highly ring-size dependent.[6]

Subsequently, the scope and limitations of this novel approach toward spirobutenolides were investigated. Some

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(8) For reviews on the chemistry of trimethylsilyloxyfuran derivatives, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3211.

(9) For a rare example of aldol-mediated spirocyclization, see: (a) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61. For Mannich-based spirocyclizations, see: (b) Tokumaru, K.; Arai, S.; Nishida, A. *Org. Lett.* **2006**, *8*, 27. (c) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641. For a related cyclization, see: (d) Kobayashi, K.; Itoh, M.; Suginome, H. *Tetrahedron Lett.* **1987**, *28*, 3369.

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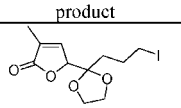
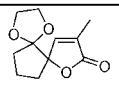
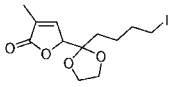
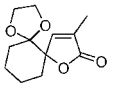
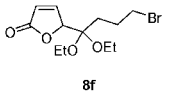
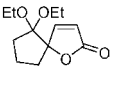
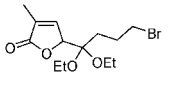
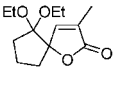
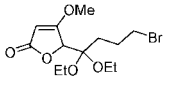
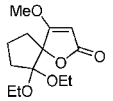
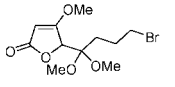
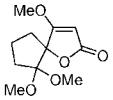
Table 1. Direct Spiroannulation of Butenolides[a]

entry	condensation product	spirobutenolide	yield (%)[b]
1	 **8d**	 **7d**	63
2	 **8e**	 **7e**	75
3	 **8f**	 **7f**	76
4	 **8g**	 **7g**	64
5	 **8h**	 **7h**	92
6	 **8i**	 **7i**	91

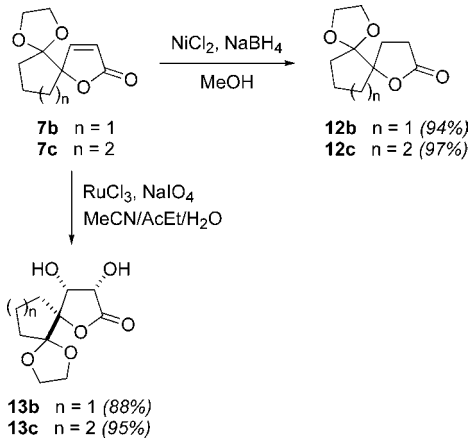
[a] All reactions performed in the presence of 1.3 equiv of *t*-BuOK or NaHMDS, in THF, from 0 °C to room temperature. [b] All yields refer to pure, isolated products.

pertinent examples are collected in Table 1. Interestingly, 3,5-disubstituted butenolides bearing a dioxolane protecting group are viable substrates, affording the annelated products **7d** and **7e** in good yields (entries 1 and 2). The smooth generation of spirobutenolides **7f**−**i** from diethyl- and dimethylketals **8f**−**i** was a pleasant surprise (entries 3−6). Indeed, not only did trimethylsilyloxyfuran derivatives condense efficiently with the triethyl- and trimethyl-substituted *ortho*-esters **10** (in stark contrast to other cyclic silyl enol ethers that afforded mostly, if not exclusively, the corresponding enol ester) but also the adducts **8f**−**i** underwent preferential cyclization rather than elimination of EtOH or MeOH, a process previously described by Pelter et al. Finally, interesting spirotetronic acid derivatives could be obtained by application of our protocol (entries 5 and 6).

The spirocyclic butenolides thus obtained proved surprisingly inert toward a wide variety of reagents (e.g., OsO_4, cuprates, high-order cuprates, cyanide, and malonate anions, etc.). However, simple though valuable synthetic transformations can be accomplished on these adducts provided a judicious choice of reaction conditions is made. Selected results are displayed in Scheme 3.

Thus, saturation of the butenolide C−C double bond could be smoothly accomplished through the use of $NiCl_2/NaBH_4$ and the spirocyclic γ-butyrolactones **12b** and **12c** were obtained in quantitative yields.[11] Similarly, the ruthenium-catalyzed dihydroxylation of the conjugated double bond of

Scheme 3. Functionalization of Spirocyclic Butenolides



7b and **7c** proved to be quite efficient providing diols **13b** and **13c**, again as the sole products, following extractive workup.[12] These diastereomerically pure diols, obtained in only three steps, could be interesting scaffolds en route to spiro-constrained DNA building blocks, popularized through the recent work of Paquette et al.[13]

In summary, we have successfully developed a concise and efficient access to the spirobutenolide framework. This new methodology hinges upon the use of 2-(trimethylsilyloxy)furan derivatives **9** as a synthon for dianions such as **11**, enabling this unprecedented, direct spiroannulation. The adducts thus obtained hold considerable potential as building blocks in synthesis. Current work focuses on the functionalization of these adducts, the establishment of an asymmetric version of this procedure, and its application to the stereocontrolled synthesis of biologically relevant substances. The results obtained during these investigations will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all spirocyclic products. This material is available free of charge via the Internet at http://pubs.acs.org.

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