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Vinylsilane-mediated synthesis of styryl-lactone frameworks

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Dedicated to the memory of Dr. Cliff Soll, 1962–2014

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ABSTRACT

A general route to several styryl-lactone frameworks is presented. Starting from a known enol ether, stereoselective epoxidation and methanolysis yields a series of three distinct hydroxyacetals, each further functionalized by etherification with an allylic vinylsilane fragment. A highly efficient Lewis acid-promoted intramolecular annulation at the tethered oxocarbenium allows direct entry to *cis*-fused bicyclic ether cores. Further manipulation delivers a variety of additional styryl-lactone motifs and analogs; for example, simple allylic oxidation yields 3-deoxyisoaltholactone, in just five steps overall.

1. Introduction

Certain trees of the *Goniothalamus* genus, a group of Asian hardwoods of the *Annonaceae* family, have long been associated with traditional medicinal practices.[1] Their use as abortifacients, *anti*-rheumatics and insect repellents has inspired systematic investigation of the key agents responsible. For example, in a series of seminal efforts, McLaughlin and co-workers isolated and identified a number of the specific bioactive components from *Goniothalamus giganteus*.[2] Representative examples are shown in Fig. 1, each typically comprising a styrene unit appended to a hydroxylated γ- or δ-lactone fragment, albeit subtly differentiated by overall pattern. A common biosynthetic pathway has been proposed to account for this full range of skeletal variety,[2f,3] and many of these compounds have been isolated numerous times from multiple sources.[4] However, and more importantly, these so-called styryl-lactones have also proved inherently cytotoxic, exhibiting specific *anti*-tumor activity versus a number of human cell lines at the μg level.[5]

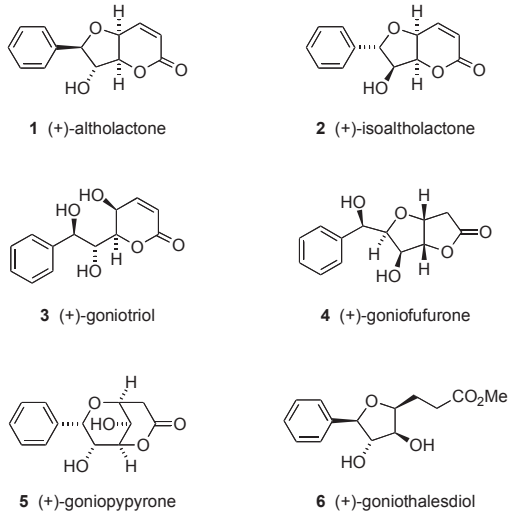

Fig. 1. Representative styryl-lactone architecture.

Taken as a whole, these factors have rendered styryl-lactones attractive targets for total synthesis and these efforts have been extensively reviewed.[6] To date, most synthetic approaches have started from the chiral pool (specifically, carbohydrate or tartrate)[7] though in recent years de novo synthesis has played an increasing

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role. For example, O'Doherty has developed an elegant and versatile route to the altholactone framework based on Sharpless asymmetric dihydroxylation of 2-vinylfuran, followed by Achmatowicz rearrangement.[8] In this fashion all four possible C2–C3 epimers of altholactone were synthesized, three of which are natural products in their own right. Several of these contrasting approaches are depicted in Fig. 2, with the key constituent pattern and its synthetic origin highlighted in each case.

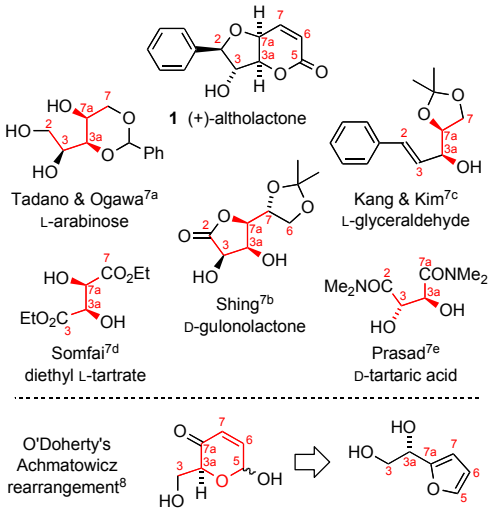


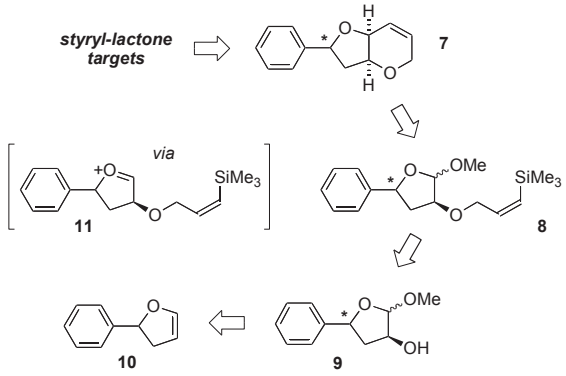
Fig. 2. Comparison of prior approaches to altholactone.[7,8]

Altholactone itself, **1**, was first isolated by Loder and Nearn in 1977 from the bark of an unnamed *Polyalthia* species of New Guinea. After extensive spectroscopic and chemical studies its structure was proposed correctly as shown.[9] Eight years later, McLaughlin unknowingly re-isolated the identical compound from the stem bark of *G. giganteus*, naming it goniothalenol.[2a,10] X-ray studies corroborated Loder's original assignment, and a simple brine shrimp lethality test revealed initial cytotoxicity, subsequently confirmed versus murine P388 leukemia. A full screen of the NCI Human Tumor Panel followed with IC_{50} values in the 10^{-5} to 10^{-7} M range.[10] Specific mode of action has been attributed to apoptosis induced by oxidative stress.[11] Antiplasmodial and antimycobacterial activity have also been demonstrated.[12] The overall structure features a *cis*-fused hexahydro-2*H*-furo[3,2-*b*]pyran at its core. This *cis*-[5,6] framework is also present in isoaltholactone **2**, initially isolated from three separate members of the *Goniothalamus* genus; once again structure was confirmed by X-ray.[13] Though merely epimeric at C2 and C3, cytotoxicity was described as marginal.[10] While introductory SAR investigations have since ensued,[14] clearly a potentially versatile synthetic approach leading to further analogs would be much valued.

We recently developed a general methodology for the concise assembly of *cis*-fused bicyclic ether arrays clearly applicable to this class of target systems.[15] Indeed our subsequent efforts have culminated in a concise synthesis of 3-deoxyisoaltholactone.[16] In this full paper, we now report a detailed account of these studies based around the rapid construction of a central *cis*-fused bicyclic framework, and resulting in the synthesis of several additional representative styryl-lactone motifs.

2. Results & discussion

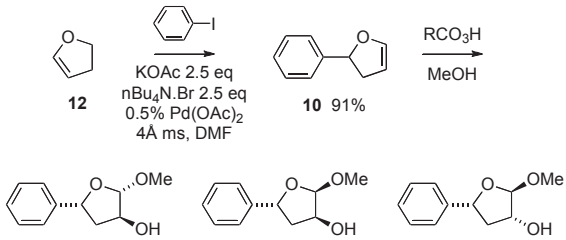
Our overall approach is illustrated in Scheme 1 and hinges on construction of *cis*-[5,6] core **7**. The key step—an intramolecular vinylsilane annulation at a tethered oxocarbenium, **11**—is fundamental to construction of the central *cis*-fused bicyclic framework **7**.[17] Whereas intermolecular C-glycosidation of furanose acetals is subject to subtle stereoelectronic effects, as elegantly delineated by Woerpel,[18] in this instance the intramolecular nature of the cyclization ensures *syn*-delivery. As previously illustrated,[15] each vinylsilane precursor **8** is readily available by simple etherification with hydroxyacetals such as **9**, which in turn arise from selective oxidation of the corresponding dihydropyran **10**.



Scheme 1. Overall approach to styryl-lactone core.

2.1. Synthesis of hydroxyacetal precursors

In the event, our approach was reduced to practice by first subjecting 4,5-dihydrofuran **12** to Jeffery's Heck arylation with concomitant olefin migration, Scheme 2.[19] For initial exploratory studies, a relatively non-selective epoxidation/solvolysis was employed in order to access all possible stereoisomers for comparative studies. Thus, simple peracetic acid epoxidation followed by methanolysis under basic conditions[20] yielded an initially complex mixture of hydroxyacetals **9abc** in 3:1:1 ratio and 72% overall yield. However, careful separation by flash chromatography (gradient elution with $CHCl_3$–acetone mixtures) yielded each distinct hydroxyacetal for further study. Stereochemistry of each was established by extensive NMR studies, including NOEs, and are illustrated as shown.[21] **9a** and **9b** were the product of epoxidation *anti* to the phenyl substituent, whereas **9c** arose from the minor *syn*-pathway. These stereochemical assignments were borne out by subsequent conversion to the bicyclic systems (vide infra, Sect. 2.2). As the remotely monosubstituted DHF **10** has proven an excellent substrate for stereocontrol during other face-selective reaction processes,[22] we were confident we could later adapt existing



RCO_3H Conditions	Overall yield	9a : 9b : 9c
AcOOH, 0 °C to rt	72%	3 : 1 : 1
m-CPBA, 0 °C to rt	82%	6 : 1 : 2
m-CPBA, –40 °C to rt	85%	10 : 1 : 1.5
m-CPBA, –63 °C to rt	82%	11 : 1 : 1.7

Scheme 2. Synthesis & identification of hydroxyacetal precursors.