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## SULFUR-MEDIATED SYNTHESIS OF SUBSTITUTED TETRAHYDROFURANS: APPLICATION TO THE SYNTHESIS OF GONIOFUFURONE

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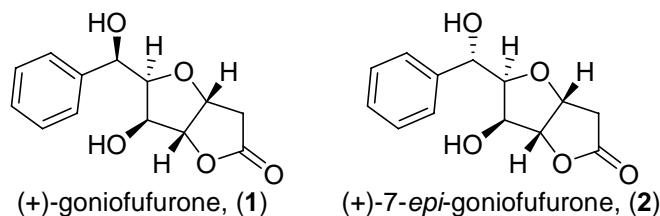
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**Abstract** – An efficient strategy for the synthesis of densely functionalized 2,5-*trans*-disubstituted-tetrahydrofurans (**4**), from sulfinyldienols is described. Further transformations of this substrate have resulted in a new synthesis of goniofufurone (**1**) by means of silylated lactone (**11**), also readily available from D-xylose.

### INTRODUCTION

Asian trees of the genus *Goniothalamus* (Annonaceae) have been recognized as a source of therapeutic agents in folk medicine. In 1972, Geran *et al.* found that the ethanolic extract of the stem bark of *Goniothalamus giganteus* Hook F. & Thomas showed cytotoxic activity during an *in vivo* antileukemic screening.<sup>1</sup> Subsequent bioactivity-directed studies by McLaughlin's group on the ethanolic extracts of these plants led to the discovery of novel styryllactones which were found to possess significant cytotoxicities against several human tumors.<sup>2</sup> Among these styryllactones, (+)-goniofufurone (**1**),<sup>2a</sup> and its stereoisomer, (+)-7-*epi*-goniofufurone (**2**),<sup>2b</sup> (Scheme 1) have attracted much attention from the biological and synthetic points of view due to their significant activity and selectivity toward several human tumor cell lines such as human lung carcinoma, and they have become interesting synthetic targets for a number of groups. Thus, Shing completed the first synthesis of (+)-goniofufurone (**1**) starting from D-glycero-D-glyco-heptono- $\gamma$ -lactone.<sup>3a</sup> Most of the subsequent syntheses started from different natural products, particularly carbohydrates. On the other hand, Zhou's synthesis relied on a Sharpless asymmetric epoxidation,<sup>4a</sup> whereas Roberts used a Julia-Colonna asymmetric epoxidation,<sup>4b</sup> and Hanaoka used a highly diastereoselective aldol reaction.<sup>5</sup> In connection with our involvement in organosulfur

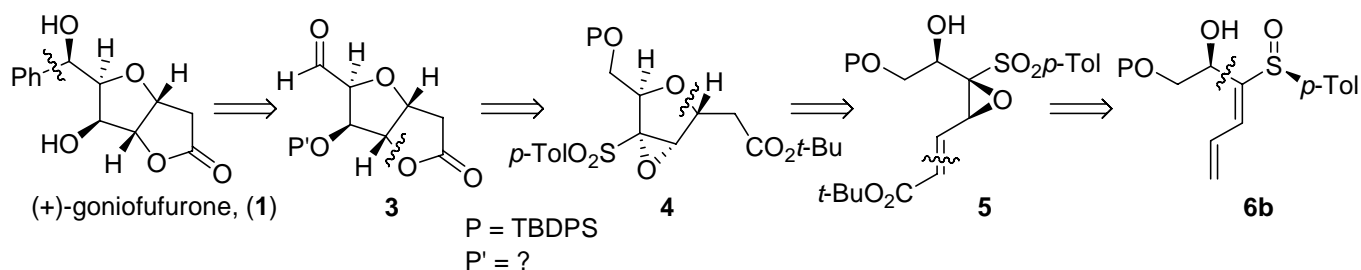
chemistry,<sup>6</sup> we report herein substantial extensions of our methodologies to prepare substituted tetrahydrofurans from  $\alpha$ -hydroxysulfinyldienes,<sup>7</sup> that have resulted in a synthesis of (+)-goniofufurone (**1**) and (+)-7-*epi*-goniofufurone (**2**).



Scheme 1

## RESULTS AND DISCUSSION

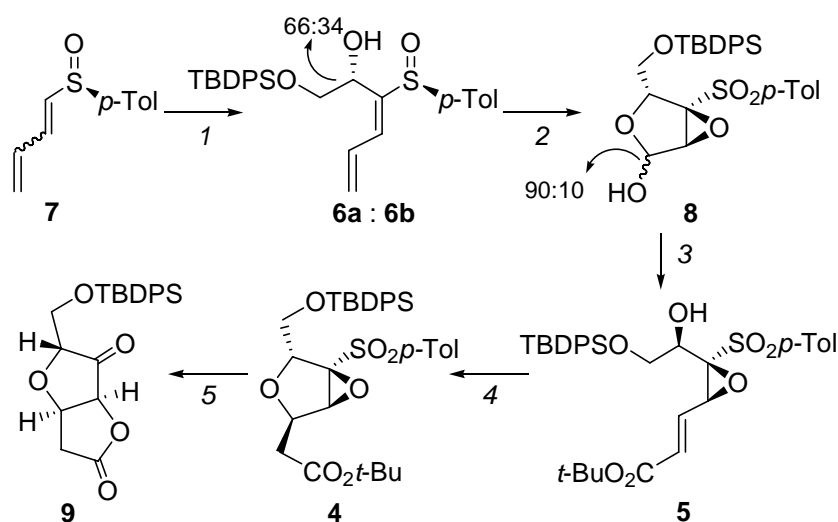
Our retrosynthetic analysis (Scheme 2) was designed with introduction of the aryl ring at the end of the sequence to facilitate the preparation of analogs at the aryl moiety for preliminary biological testing. Another key point was to develop a selective route to 2,5-*trans*-disubstituted-tetrahydrofurans functionalized at C-3 and C-4 to complement our prior efforts on this field.<sup>7</sup> Thus, **1** could derive from aldehyde (**3**), similarly to a previous report,<sup>3j</sup> and **3** should be available from tetrahydrofuran (**4**) through an unprecedented sulfonyloxirane cleavage with concurrent lactonization to render a ketolactone, reduction of the ketone and selective oxidation of the primary alcohol. Sulfonyltetrahydrofuran (**4**) could be obtained by stereoselective intramolecular Michael addition of oxiranylenoate (**5**), that could derive from  $\alpha$ -hydroxysulfinyldiene (**6b**) by our metal-catalyzed oxidation/epoxidation to produce a vinyl oxirane, followed by oxidative-cleavage and a Wittig reaction. Diene (**6b**) could be prepared through a condensation of the corresponding aldehyde and metalated 1-sulfinylbutadiene, available in a single step by the protocol of Craig.<sup>8</sup>



Scheme 2

To establish the viability and stereoselectivity of the sequence, it was decided to use initially racemic materials. Thus, lithiation of the racemic mixture of sulfinyldienes (**7**) (*E/Z* mixture),<sup>8</sup> (Scheme 3), with concurrent isomerization to the *E* geometry,<sup>7</sup> followed by reaction with

*t*-butyldiphenylsilyloxyacetaldehyde,<sup>9</sup> yielded the readily separable mixture of diastereoisomers (**6a**) and (**6b**) (66:34) that could be interconverted by a Mitsunobu protocol.<sup>10</sup> At this stage, the synthesis was pursued with the mixture and the treatment of the **6a/6b** mixture with *t*-BuOOH and VO(acac)<sub>2</sub> led to oxidation at sulfur and hydroxyl-directed epoxidation at the more electron deficient double bond with complete regio- and stereoselectivity.<sup>11</sup> Ozonolysis of the labile vinyloxirane intermediate gave lactol (**8**) that readily reacted with stabilized ylide Ph<sub>3</sub>PCHCO<sub>2</sub>*t*-Bu to give the desired *E*-enoate (**5**). Optimal conditions to trigger the desired intramolecular Michael addition of **5** entailed the use of Triton B to form 2,5-*trans*-tetrahydrofuran (**4**) as a single isomer.<sup>12</sup> Finally, we were pleased to find that the treatment of **4** with MgBr<sub>2</sub> gave lactone (**9**), with the fused furano-furone core of (+)-goniofufurone (**1**), through epoxysulfone cleavage and lactonization, thus validating our original hypothesis. To our knowledge this process is unprecedented, with related cyclizations in the literature using more nucleophilic alcohols, thus generating cyclic ethers, instead of lactones.<sup>13</sup>

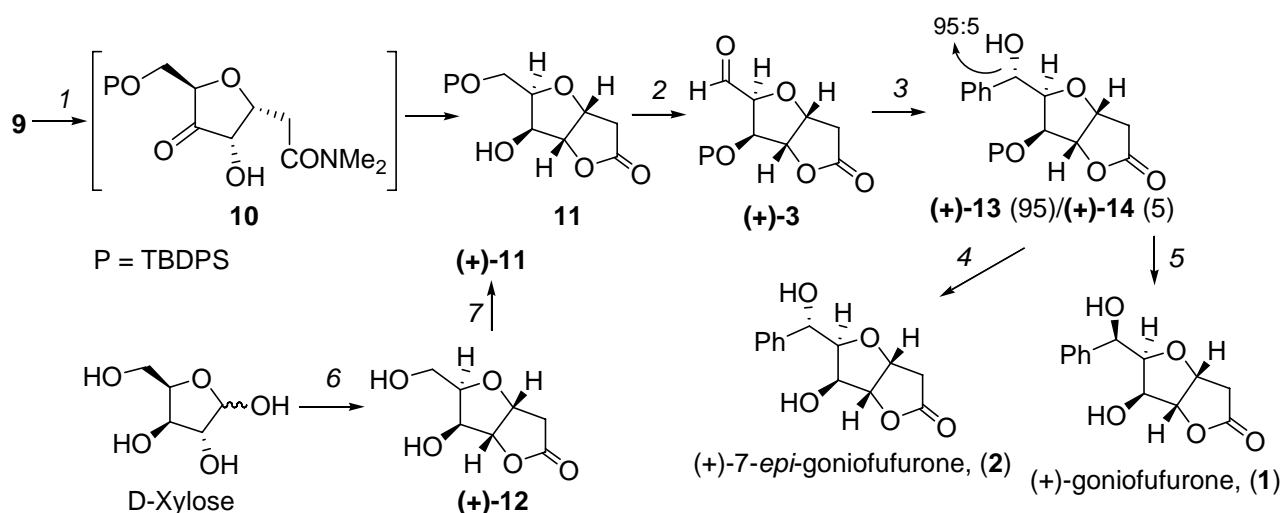


Scheme 3. Reagents and conditions: **1**. (a) LDA, THF, -78 °C. (b) TBDPSOCH<sub>2</sub>CHO, THF, -78 °C, 30 min, 76%. **2**. (a) 5% VO(acac)<sub>2</sub>, *t*-BuOOH, C<sub>6</sub>H<sub>6</sub>, rt, 5 h 30 min. (b) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 1:1, -78 °C, 15 min; then, SME<sub>2</sub>, -78 to 0 °C, 2 h, 42% two steps. **3**. Ph<sub>3</sub>PCHCO<sub>2</sub>*t*-Bu, C<sub>6</sub>H<sub>6</sub>, 0 °C to rt, 3 h, 30 min, 82%. **4**. Triton B, MeOH, rt, 16 h, 72%. **5**. MgBr<sub>2</sub>, Et<sub>2</sub>O, rt, 72%.

Reduction of ketone (**9**) under a variety of conditions, afforded the undesired epimer at the carbinol center as major product.<sup>14</sup> After considerable experimentation, lactone opening to afford dimethylamide (**10**), followed by hydroxyl-directed ketone reduction<sup>15</sup> and acid-catalyzed cyclization led to the desired alcohol (**11**) as single isomer (Scheme 4). Seeking additional structural confirmation for **11**, furanolactone (+)-(**12**) was prepared by the methodology described by Galbis,<sup>3j,16</sup> that entails the condensation of D-xylose and Meldrum's acid. Selective protection of the primary hydroxyl group as a

*t*-butyldiphenylsilyl ether gave (+)-**11**, that had identical spectral features to the racemic material. It was then decided to continue the synthetic sequence with the optically pure material.

After considerable experimentation with several protecting groups for the secondary alcohol of **11** that then allowed for selective deprotection of the primary alcohol, protection of the secondary alcohol as a TBDPS ether was examined. Subsequent selective desilylation of the primary silyl group with HF-pyridine complex followed by Swern oxidation gave aldehyde (+)-**3**. Treatment of this aldehyde with excess phenylmagnesium bromide led to the separable 95:5 mixture of diastereomeric alcohols (+)-**13** and (+)-**14** in moderate yield.<sup>17</sup> From the major product (+)-**13**, (+)-7-*epi*-goniofufurone (**2**), was easily obtained by deprotection of the hydroxyl group. On the other hand, (+)-goniofufurone (**1**) was synthesized via a three step sequence, oxidation of the 95:5 mixture followed by reduction and cleavage of the silyl protecting group. Synthetic **1** and **2** showed all spectroscopic data identical to those reported in the literature,<sup>2a,b</sup> including melting points and the sign of the optical rotation.<sup>18</sup>



Scheme 4. Reagents and conditions: 1. (a)  $\text{Me}_2\text{NH}$ , EtOH, rt, 2 h; then,  $\text{Bu}_4\text{NBH}_4$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 6 h 15 min, 53%. (b) PPTS, toluene, 80 °C, 3 h, 63%. 2. (a) TBDPSCl, imidazole, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 3 days, 86% and 14% of **11**. (b) HF·Pyr, THF, 0 °C, 3 h, 67% and 13% of starting material. (c)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , -60 °C, 35 min, 79%. 3.  $\text{PhMgBr}$ , THF, -20 to 0 °C, 2 h 45 min, 62%. 4. HF·Py, THF, 0 °C, 3 h, 30 min, 78%. 5. (a) PCC, 4 Å MS,  $\text{CH}_2\text{Cl}_2$ , rt, 70%. (b)  $\text{LiAlH}(\text{O}-t\text{-Bu})_3$ , THF, -20 °C, 2 h, 80%, 56% of (+)-**14** and 24% of (+)-**13**. (c) HF·Py, THF, 0 °C, 4 h, 71%. 6. (a) Meldrum's acid, *t*- $\text{BuNH}_2$ , DMF, 40 °C, 5 days, 61%. 7. TBDPSCl, imidazole, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 24 h, 90%.

To summarize, we have developed a novel entry to 2,5-*trans*-disubstituted-tetrahydrofurans functionalized at C-3 and C-4. This methodology relies on our metal-catalyzed oxidation/epoxidation of hydroxysulfinyldienes, followed by a stereoselective Michael cyclization of sulfonyloxiranylenoates and an unprecedented sulfonyloxirane cleavage with concurrent lactonization. These protocols have been

applied to the preparation of goniofufurone (**1**) and 7-*epi*-goniofufurone (**2**) through intermediate (**11**) that is also readily available from D-xylose. Further applications of these methodologies, as well as the preparation of analogs of goniofufurone (**1**), are being examined in our laboratories.

## ACKNOWLEDGEMENTS

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18. (1), mp 154-155 °C and  $[\alpha]_{\text{D}}^{20} = +8.9^\circ$  (c = 0.235 EtOH), lit.,<sup>2a</sup> mp 152-154 °C and  $[\alpha]_{\text{D}}^{20} = +9.0^\circ$  (c = 0.5 EtOH). (2), mp 192-193 °C and  $[\alpha]_{\text{D}}^{20} = +103.1^\circ$  (c = 0.32 EtOH), lit.,<sup>2b</sup> mp 190-192 °C and  $[\alpha]_{\text{D}}^{20} = +108^\circ$  (c = 0.2 EtOH).