First Practical Asymmetric Synthesis of a New Tetrasubstituted Tetrahydrofuran, (–)-Goniothalesdiol

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Abstract: An efficient and practical strategy has been developed for the construction of the antipode of 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran, goniothalesdiol, isolated from the bark of the Malaysian tree. The synthetic process is based on the convenient manipulation via Lewis acid-induced deoxygenation of the highly functionalized lactone derived from D-glucuronolactone.

Key words: goniothalesdiol, tetrasubstituted tetrahydrofuran, stereoselective deoxygenation, trisubstituted γ-lactone, D-glucuronolactone

Substituted tetrahydrofurans feature in many biologically potent natural products such as annonaceous acetogenins,[1] macrolides,[2] cytotoxic polyethers,[3] marine toxins,[4] pheromones,[5] and epoxylipids.[6] To fully exploit the opportunities offered by these compounds requires access to synthetic methodology capable of targeting chiral substituted tetrahydrofurans. In this conncetion many strategies have been explored in developing synthetic routes to these compounds and the natural products themselves. However, most methods were concerned with the construction of 2,5-disubstituted furans, while few focused on tri- and tetrasubstituted ones,[7] since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol (Figure 1). We have recently succeeded in the development of novel and stereoselective asymmetric syntheses of biologically active tri-[8a,b] and tetrasubstituted[8c] furan-type of natural products through elaboration of commercially available materials based on new routes exploited in this laboratory.

On the other hand, another type of dihydroxylated tetrahydrofuran, (+)-goniothalesdiol (**1**), was first isolated in 1998 from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae).[9] This was revealed to have significant cytotoxicity against P388 mouse leukemia cells and strong insecticidal activities,[9] and a new addition to the styryl-type lactone series.[10] However, no report concerning the total synthesis of the (–)-enantiomer of **1** as well as the natural product itself, to our knowledge, has been appeared to date despite these pharmacological activities and interesting structural features except our asymmetric synthesis of 2-epigoniothalesdiol (**2**) starting from D-tartaric acid.[11] We wish to communicate herein the first novel and practical asymmetric synthesis of the antipode of natural **1** by means of requisite elaboration of the functionalized lactone derived from D-glucuronolactone whose outlined synthetic pathway is described in Scheme 1 together with the preceding method of 2-epiform.

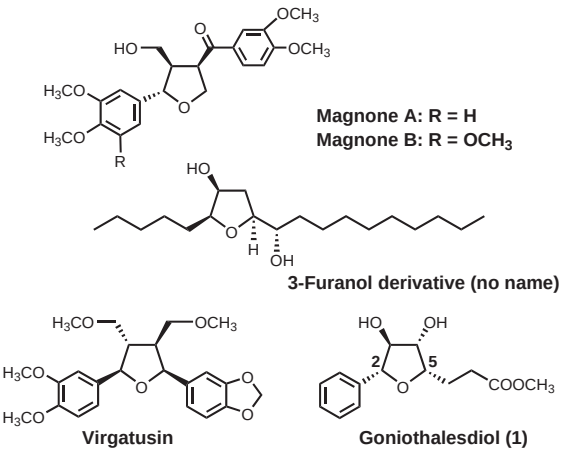
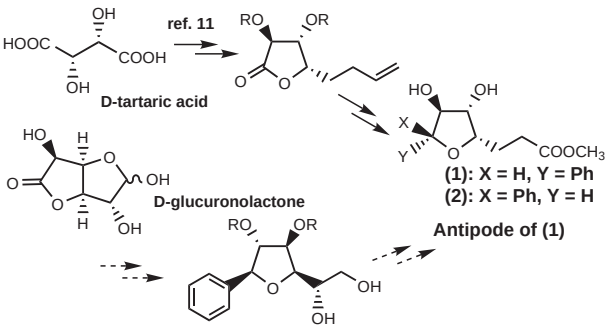


Figure 1



Scheme 1

As shown in Scheme 2, three hydroxyl groups of conveniently functionalized D-glucuronolactone were protected successively through acetonide formation followed by silylation to give the lactone **4**. To begin with, treatment of **4** with Grignard reagents in the presence of $CeCl_3$[12] at low temperature provided the labile hemiketal intermediates, which were readily effected by $BF_3{\cdot}OEt_2$-promoted hydrogenation with Et_3SiH[13] at the same temperature, leading directly to the tetrahydrofuran derivatives **5a** and **5b**, respectively. The reactions in both cases proceeded within 5 minutes in high yields with complete stereoselectivity

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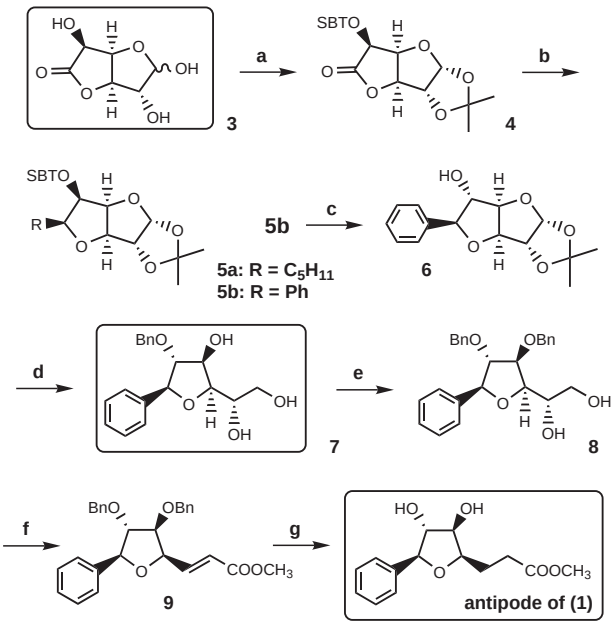
(determined by ^{13}C NMR analysis) and no other product was observed. Stereochemistry of the new asymmetric center in **5a** was unambiguously determined to be *S*,[14] and **5b** was also estimated to have the same configuration based on the similarity of its spectral data and confirmed after completion of the synthesis of (–)-**1**.



Scheme 2 Reagents and conditions: (a) 1. Acetone, H_2SO_4; 82%; 2. TBSCl, DMF, imidazole; quant.; (b) 1. Grignard reagents, $CeCl_3$, THF, –78 to –60 ºC; 2. Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 ºC; 78% (two steps) (**5a**); 79% (two steps) (**5b**); (c) 1. Bu_4NF, THF; 99%; 2. DEAD, Ph_3P, C_6H_5COOH, THF; 3. K_2CO_3, MeOH; 86% (two steps); (d) 1. NaH, $PhCH_2Br$, Bu_4NI, THF; 95%; 2. TFA, THF; 93%; 3. $LiAlH_4$, THF; 63%; (e) 1. $(CH_3)_2C(OCH_3)_2$, acetone, cat. PPTS; 74%; 2. NaH, $PhCH_2Br$, Bu_4NI, THF; 95%; 3. TFA, THF; 93%; (f) 1. $NaIO_4$, Et_2O–H_2O (1:1); 2. $(EtO)_2POCH_2COOCH_3$, NaH, THF; 77% (two steps); (g) Pd (black), 4.4% HCOOH–MeOH, 45 ºC; 66%.

Highly substituted five-membered ring oxocarbenium ions sometimes exhibit opposite stereoselectivities to what would be expected based upon a consideration of simple steric effects alone. However, in this case steric destabilization of the transition state leading to the *trans*-2,3-stereochemistry is presumably being observed due to the presence of the fused ring system.

In light of the above outcome, we turned our attention to the synthesis of the target compound. Thus, after removal of the protecting-TBS moiety in **5b**, the obtained product was subjected to Mitsunobu conditions with DEAD to afford the benzoyl ester intermediate, which was in turn hydrolyzed to the corresponding alcohol **6** in 86% yield (two steps) with complete inversion of configuration (determined by ^{13}C NMR analysis). With the desired contiguous stereogenic centers and functionalities in hand, the remaining side unit was then constructed as follows; benzyl protection of **6** necessary to resist changes in pH and acetonide deprotection with TFA yielded the diol derivative,[15] which was subsequently reduced with $LiAlH_4$ to give the triol **7** in reasonable yield. This was next effected by the reactions of chemoselective acetalization and benzylation, followed by deprotection of the acetonide again, leading to the corresponding diol product **8** in three steps. Then, **8** was cleaved with $NaIO_4$ to the crucial aldehyde and submitted to an olefination reaction with methyl diethylphosphonoacetate to provide the unsaturated methyl ester **9** in 77% yield (two steps). Finally, removal of the benzyl groups together with hydrogenation of **9** was performed employing Pd (black) in 4.4% HCOOH–MeOH[16] to complete the total synthesis of the (–)-enantiomer of natural goniothalesdiol **1**, $[\alpha]_D^{27.4}$ –7.1 (*c* 0.15, EtOH) [lit. $[\alpha]_D^{25}$ +7.5 (*c* 0.23, EtOH)],[9] in 66% isolated yield. The spectral data of synthesized (–)-**1** were completely identical to those of the reported natural compound.[9]

In summary this work constitutes the first efficient asymmetric synthesis of the enantiomer of natural goniothalesdiol from D-glucuronolactone and verifies the structure proposed in the literature for this compound. This will be widely applicable to the synthesis of other important tetrasubstituted tetrahydrofuran natural products.

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(14) The absolute *S*-configuration of the new asymmetric center in **5a** was proved by the transformation into the meso compound **12** through sequential seven steps as shown below (Figure 2).

(15) Coupling reaction of this diol intermediate **13** with Horner–Emmons reagent interestingly brought about the tricyclic

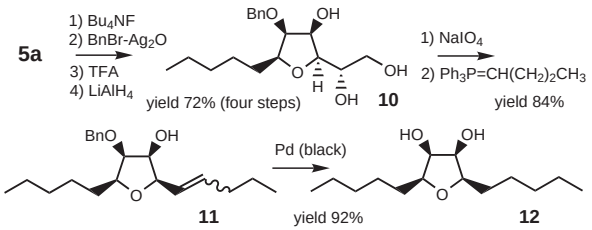

Figure 2

compound **15** directly in 75% isolated yield as a sole product. It is reasonable to assume that the formation of **15** would be resulted in the reaction through intramolecular Michael addition followed by cyclization of α,β-unsaturated ester **14** (Figure 3).

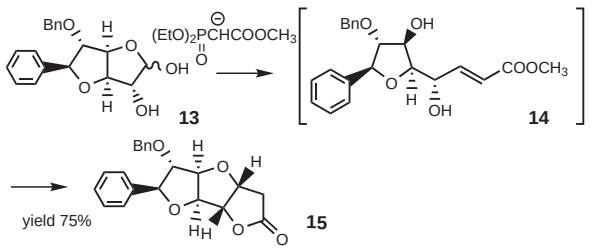

Figure 3

(16) Hydrogenation and simultaneous removal of the benzyl groups in **9** with Pd on carbon (10%) under H_2 atmosphere were proved to give a complex mixture. In addition, the hydrogenated final enantiomer of **1** was unstable and decomposed on standing.