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Total Stereoselective Synthesis of (+)-Goniothalesdiol

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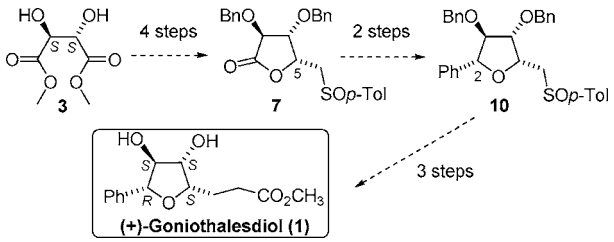
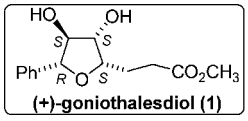
ABSTRACT

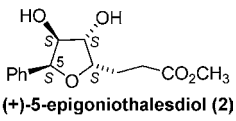


The stereoselective synthesis of (+)-goniothalesdiol (1) was accomplished in nine steps starting from commercially available (−)-(2*S*,3*S*)-dimethyl D-tartrate (3). The key features were a completely diastereoselective reduction of a *β*-ketosulfoxide to generate the stereogenic center at C-5 in 7 and formation of the 2,5-*cis*-substituted tetrahydrofuran ring in 10 from a stereoselective Et_3SiH/TMSOTf-promoted reductive cyclization/deoxygenation.

The genus *Goniothalamus* (Annonaceae) is well-known as an interesting source of various bioactive compounds such as acetogenins,[1] alkaloids,[2] styryl lactones,[3] and flavanoids.[4] Recently, a new natural 2,3,4,5-tetrasubstituted tetrahydrofuran derivative, (+)-goniothalesdiol (**1**), was isolated from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae) and was revealed to have significant cytotoxicity against P388 mouse leukemia cells and insecticidal activities.[5] The structure and relative stereochemistry of **1** was assigned on the basis of ^{1}H and ^{13}C NMR spectroscopy, and the absolute configuration was confirmed by semisynthesis from natural (+)-goniothalenol (altholactone).[5]

The first approach to this class of compounds was published by Yoda,[6] who carried out an asymmetric synthesis of (+)-5-epigoniothalesdiol (**2**) from D-tartaric acid via a Lewis acid promoted hydrogenation reaction.





Since then, four syntheses of the bioactive metabolite goniothalesdiol have been described. The first total synthesis

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of the natural enantiomer (+)-**1**, reported in 2002 by Gracza, started from D-mannitol and required 11 steps, one of which was nonstereoselective (it generated a 50:50 mixture of stereoisomers).[7a] This approach, based on a palladium(II)-catalyzed oxycarbonylation methodology for the construction of the tetrahydrofuran ring, was completed with a 0.5% overall yield. More recently, the same author has reported an optimized synthesis of (+)-**1** that proceeded in 10 steps and 1% overall yield.[7b] The second preparation of goniothalesdiol, published by Yoda, provided (−)-**1**, the unnatural enantiomer, through a lengthy 16-step reaction sequence that was based on a Lewis acid induced deoxygenation of a highly functionalized lactone derived from D-glucurolactone.[8] Another approach to (+)-**1** was reported by Cardá and Marco in 2004 and was based on stereoselective *anti* aldol reactions of L-erythrulose derivatives.[9] This formal synthesis of goniothalesdiol allowed the preparation, in 11 steps, of a lactone intermediate (7.6% overall yield), which could be converted into (+)-**1** by means of three additional transformations (2% overall yield). Very recently,[10] Yadav has described the last synthesis of (+)-goniothalesdiol employing Sharpless catalytic asymmetric epoxidation and Sharpless asymmetric dihydroxylation reactions, in 11 steps, starting from cinnamyl alcohol.

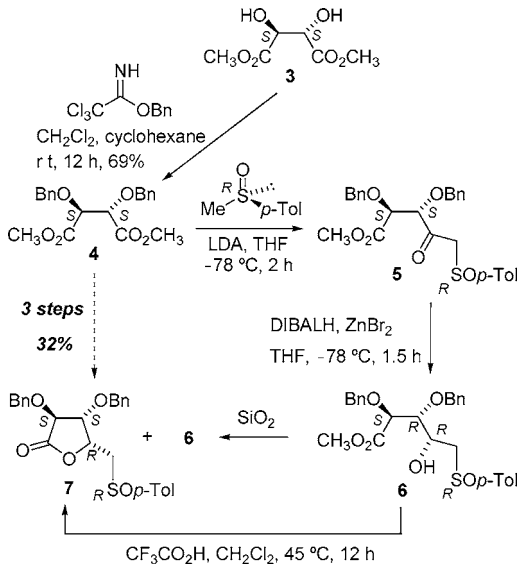
In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[11] we have recently described a highly stereoselective approach to different sized *cis*-disubstituted cyclic ethers based on the Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure hydroxy sulfinyl ketones which are, in turn, accessible through the well established diastereoselective reduction of an adequately functionalized β-ketosulfoxide.[12]

In this paper, we extend the scope of this methodology to the efficient construction of a natural product bearing a tetrasubstituted tetrahydrofuran structure and four stereogenic centers.

The stereoselective total synthesis of natural (+)-goniothalesdiol (**1**) that we are reporting proceeds in a nine-step reaction sequence and exploits the diastereoselective reduction of a β-ketosulfoxide and a *cis*-stereoselective Et_3SiH/TMSOTf-promoted reductive cyclization/deoxygenation to generate, respectively, the stereogenic centers at C-5 and C-2 of the tetrahydrofuran ring.

Our asymmetric synthesis of (+)-goniothalesdiol (**1**) started with the protection of commercially available (−)-(2*S*,3*S*)-dimethyl D-tartrate (**3**) with benzyl trichloroacetimidate in the presence of triflic acid[13] to afford, in 69% yield, the dibenzyl ether derivative (2*S*,3*S*)-**4** (Scheme 1).[14]

Scheme 1. Synthesis of Sulfinyl Lactone (3*S*,4*S*,5*R*,S*R*)-**7** from Commercially Available (−)-(2*S*,3*S*)-dimethyl D-tartrate (**3**)



The addition of 2 equiv of the anion generated from enantiomerically pure (−)-(S*R*)-methyl-*p*-tolyl sulfoxide[15] and LDA to the diester **4** gave rise to the corresponding β-ketosulfoxide (2*S*,3*S*,S*R*)-**5**, together with several byproducts (Scheme 1). The reaction was shown to be very sensitive to factors such as temperature, scale-up of the reaction and partial degradation during chromatographic purification. Under the best conditions (−78 °C, 1.2 mmol of compound **4** and use of demetalated silica gel for column chromatography), the maximum yield achieved for derivative **5** was 57%. For this reason, we decided to reduce the carbonyl group using the isolated, but nonpurified, crude reaction mixture of compound **5**.

Thus, the reduction of the crude β-keto sulfoxide **5** with diisobutylaluminum hydride (DIBALH) in the presence of $ZnBr_2$ afforded, in a completely diastereoselective way, alcohol (2*S*,3*R*,4*R*,S*R*)-**6**, bearing the *R* absolute configuration at the newly created C-4 stereogenic center. This result evidenced that the well-established protocol to reduce β-ketosulfoxides, first reported in 1985 by Solladié,[16] is

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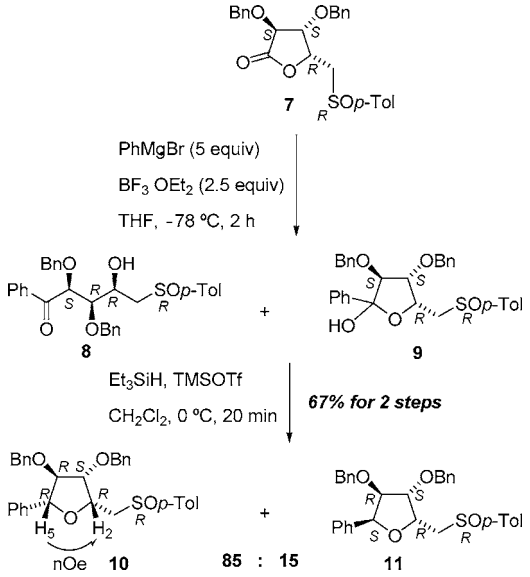
working efficiently even in molecules with other oxygenated centers α to the carbonyl group, which could compete with the sulfoxide in the diastereocontrol of the process.[17] Nevertheless, attempts at purification of carbinol **6** by silica gel chromatography led to partial transformation into lactone (3*S*,4*S*,5*R*,S*R*)-**7** (Scheme 1). Moreover, several attempts at protecting the OH group of compound **6** led to the exclusive formation of lactone **7**. Due to the easy transformation of **6** into **7**, we decided to optimize this process by working with the nonpurified crude reaction mixture obtained from the reduction step. Under the best conditions (trifluoroacetic acid[18] in CH_2Cl_2 at 45 °C for 12 h), lactone **7** could be isolated pure, after flash chromatography, with a 32% yield for the three-step reaction sequence starting from tartrate derivative **4** (Scheme 1).

With lactone **7** in hand, we next directed our efforts to introduction of the phenyl substituent and stereoselective construction of the 2,5-*cis* tetrahydrofuran skeleton of the natural product (Scheme 2). Our first attempts at introducing

Scheme 2. Synthesis of Sulfinyl 2,5-*cis*-Tetrahydrofuran (2*R*,3*S*,4*R*,5*R*,S*R*)-**10** from Sulfinyl Lactone (3*S*,4*S*,5*R*,S*R*)-**7**



the phenyl ring at C-2 using PhLi alone or in the presence of different Lewis acids (Me_2AlCl, $BF_3{\cdot}OEt_2$) were unsuccessful. Nevertheless, the use of PhMgBr as nucleophile, gave rise, with an 80% conversion, to a mixture of hydroxy phenyl ketone (2*S*,3*R*,4*R*,S*R*)-**8**, as the minor compound, and cyclic hemiketal (3*S*,4*S*,5*R*,S*R*)-**9**, as a mixture of epimers at C-2, albeit in low yields (30−40%), after chromatographic purification. Although the use of additives such as $ZnBr_2$ or TMSOTf did not enhance the effectiveness of the reaction, the addition of 5 equiv of PhMgBr in the presence of $BF_3{\cdot}OEt_2$ led to total conversions and yields approaching 60% after SiO_2 flash chromatography.

Due to the reduced chemical yields observed when chromatographic purification of derivatives **8** and **9** was attempted, we again decided to use this mixture without purification for the next step of the reaction sequence (Scheme 2). Thus, the treatment of the mixture of **8** and **9** under the typical conditions used for reductive cyclization of hydroxy sulfinyl ketones developed by us (TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 20 min) led to stereoselective formation of the 2,5-*cis* tetrahydrofuran (2*R*,3*S*,4*R*,5*R*,S*R*)-**10**, in 85% yield, together with 15% of the 2,5-*trans* derivative (2*R*,3*S*,4*R*,5*S*,S*R*)-**11** (Scheme 2). Tetrahydrofuran derivatives **10** and **11** resulted from the reductive cyclization of hydroxy sulfinyl ketone **8** and the reductive deoxygenation of hemiketals **9** by Et_3SiH and TMSOTf acting as a Lewis acid. The *cis* relative stereochemistry of derivative **10** was determined from a NOESY experiment which demonstrated the close spatial proximity between the two protons H_2 and H_5 situated on the carbons adjacent to the heterocyclic oxygen atom (Scheme 2). The stereochemical course of this reaction is the same to that previously observed by us in unsubstituted 5-keto-2-hydroxypentyl sulfoxides[12c] and by Yoda in systems with a CH_2OBn at C-4,[19] but opposite to that achieved by the same author on a derivative bearing a OTBS group at C-4.[6] Both diastereoisomers **10** and **11** could not be separated at this stage, and we continued the reaction sequence toward (+)-goniothalesdiol (**1**) with this mixture until the final separation at the last step of the synthesis.

Having synthesized the tetrasubstituted tetrahydrofuran **10**, with its four stereogenic centers with the correct absolute configuration of the natural product, we transformed its methylsulfinyl substituent at C-5 into the three-carbon chain bearing the methyl ester present in goniothalesdiol (**1**) (Scheme 3). Thus, treatment of sulfoxide **10** under the Pummerer reaction conditions[20] [(i) trifluoroacetic anhydride (TFAA), 2,6-lutidine; (ii) $HgCl_2$, H_2O] afforded the corresponding aldehyde (2*R*,3*S*,4*R*,5*R*)-**12**. This compound again proved to be very unstable and, without further purification, was submitted to the Wittig reaction with $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2 at 0 °C for 1 h. After chromatographic purification, a 55:45 mixture of the corresponding *trans* and *cis* olefins (2*S*,3*R*,4*R*,5*R*)-**13** and (2*S*,3*R*,4*R*,5*R*)-**14** was isolated with a 78% overall yield for the two last steps starting from sulfoxide **10** (Scheme 3).

To complete the synthesis it was necessary to deprotect the benzyloxy groups at C-3 and C-4 and reduce the double bond of derivatives (*E*)-**13** and (*Z*)-**14** (Scheme 3). These transformations had been previously reported by Yoda,[8] en route to the unnatural enantiomer (−)-goniothalesdiol, employing catalytic amounts of Pd (black) in 4.4% HCOOH−MeOH, a reaction that proceeded in 66% yield. Nevertheless, the application of such methodology to the mixture of (*E*)-**13** and (*Z*)-**14** was very troublesome and after much experimentation, we found the best conditions using Pd black (1.2 equiv) in a mixture of MeOH/HCOOH (4.4%) at 55 °C for 6 h. Under these conditions and after flash chromatog-

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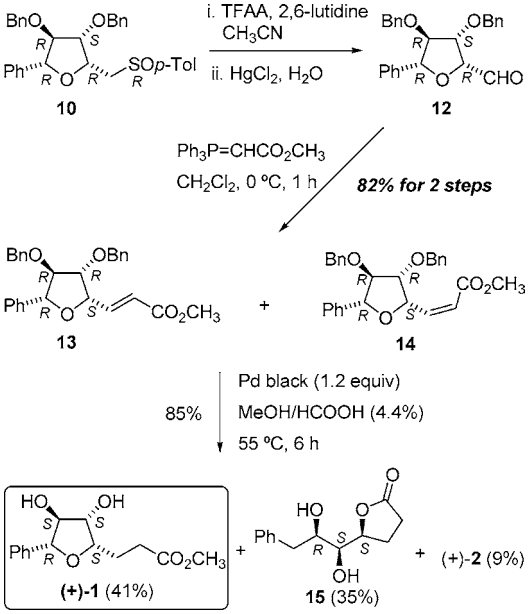
Scheme 3. Synthesis of (+)-Goniothalesdiol (**1**)



raphy, we could isolate three products: (+)-goniothalesdiol [(2*S*,3*S*,4*R*,5*R*)-**1**], in 41% yield, (2*R*,3*S*,4*S*)-**15**, formed by reductive opening of the tetrahydrofuran ring followed by lactonization, in 35% yield, and (+)-5-epigoniothalesdiol [(2*S*,3*S*,4*R*,5*S*)-**2**], in 9% yield, starting from the 85:15 mixture of tetrahydrofurans **10** and **11** (Schemes 2 and 3). Synthetic **1** {$[\alpha]^{20}_D = +6.4$ (*c* 0.36, EtOH)} {lit:[5] $[\alpha]^{20}_D = +7.5$ (*c* 0.23, EtOH), lit.[7a] $[\alpha]^{20}_D = +6.5$ (*c* 0.6, EtOH), lit.[7b] $[\alpha]^{20}_D = +6.9$ (*c* 0.38, MeOH), lit.[8] $[\alpha]^{20}_D = -7.1$ (*c* 0.15, EtOH)} showed physical and spectroscopic parameters identical to those described for the natural (+)-goniothalesdiol (**1**).[5]

In summary, we have reported a total stereoselective synthesis of natural (+)-goniothalesdiol (**1**) from commercially available (−)-dimethyl D-tartrate in nine steps and 5% overall yield. The key steps of our synthetic sequence were the diastereoselective DIBAL/$ZnBr_2$ reduction of a β-ketosulfoxide to generate the stereogenic center at C-2 and the Et_3SiH/TMSOTf-promoted reductive cyclization/deoxygenation which allowed the stereoselective formation of the *cis*-2,5-substitution of the tetrahydrofuran ring.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and copies of ^{1}H NMR, ^{13}C NMR and HRMS spectra for selected derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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