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The Effect of Sulfoxides on the Stereoselective Construction of Tetrahydrofurans: Total Synthesis of (+)-Goniothalesdiol

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Abstract: Good to excellent stereoselectivities were achieved in the reductive cyclization (with Et_3SiH/trimethylsilyl trifluoromethanesulfonate (TMSOTf)) of enantiopure hydroxy sulfinyl ketones en route to 2,5-*cis*-disubstituted tetrahydrofuran skeletons. Electrostatic effects of the exocyclic sulfoxide, which stabilized the reactive intermediate oxocarbenium conformations, were responsible for the observed stereocontrol. A model is proposed to explain the results. The use of this reaction and the asymmetric β-ketosulfoxide reduction as key steps facilitated the total enantioselective synthesis of the natural β-C-aryl glycoside (+)-goniothalesdiol.

Keywords: electrostatic interactions · enantioselectivity · goniothalesdiol · natural products · oxocarbenium ions

Introduction

Stereoselective approaches to substituted tetrahydrofuran and -pyran derivatives continue to attract considerable attention due to the widespread appearance of these structural motifs in a number of natural products that exhibit important biological properties, such as C-glycosides or nucleosides,[1] potent antitumor agents, annonaceous acetogenins,[2] the polyether antibiotics,[3] some macrolide antibiotics,[4] and the brevetoxins.[5]

The various strategies currently available for the stereoselective syntheses of these heterocyclic systems have been recently reviewed.[3c,6] One of them, the Et_3SiH/trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed synthesis of ethers by reductive condensation of carbonyl compounds and alkoxysilanes[7] or alcohols[8] has been applied by us to the asymmetric synthesis of a number of different sized cyclic ethers. The Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure β-hydroxy sulfinyl ketones, in turn accessible through the well-established diastereoselective reduction of an adequately functionalized enantiopure β-ketosulfoxide,[9] facilitated the synthesis of 5-,[10] 6-,[10,11] 7-,[12] and 8-membered[13] cyclic ethers with 2,ω-*cis* disubstitution in a highly diastereoselective manner. We have tested the validity of our asymmetric approach by completing the total enantioselective synthesis of structurally simple natural products such as (−)-centrolobine,[10,11] (+)-*cis*-6-(methyltetrahydropyran-2-yl)acetic acid,[10] and (+)-isolaurepan.[12] Later, we extended this methodology to the total enantioselective synthesis of (+)-goniothalesdiol,[14] a natural product that has four stereogenic centers in a 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran structure.[15] The first synthetic approach to this class of compounds was reported by Yoda et al.,[16] who carried out an asymmetric synthesis of (+)-5-epigoniothalesdiol[17] from D-tartaric acid by using a Lewis acid promoted reductive cleavage of the lactol **1** (see Scheme 1) to generate the tetrahydrofuran ring in 15 steps and 29% overall yield. As depicted in Scheme 1, the ionic reductive cleavage of the OH in the OTBS-protected lactol **1** led to the stereoselective formation of the 2,5-*trans*-tetrahydrofuran derivative **2**.

Later, Yoda's group published the synthesis of the unnatural (−)-enantiomer of goniothalesdiol through a 16-step reaction sequence (overall yield 10.3%), again based on a Lewis acid promoted reductive deoxygenation of the highly functionalized lactol **3** with opposite configuration at C-4 and C-5, and with the OH at C-4 protected as an acetal

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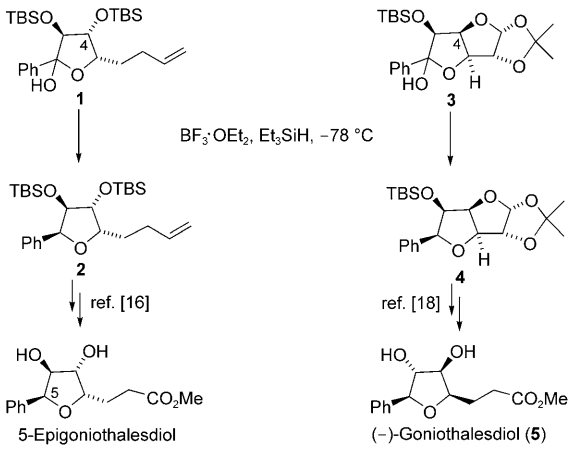


Scheme 1. Ionic reductive cleavage of the OH in lactols **1** and **3** en route to 5-epigoniothalesdiol and (−)-goniothalesdiol. TBS = *tert*-butyl dimethylsilyl.

(Scheme 1).[18] The *cis*-2,5-disubstituted tetrahydrofuran derivative **4** was, in this case, the major diastereomer observed. The opposite diastereoselectivity achieved in the reduction step of compounds **1** and **3** showed that the stereochemical course of the reaction was highly dependent on the nature of the OH protecting groups, and/or the relative stereochemistry of C-4 of the precursor.

Since then, many research groups have reported their studies on the stereoselective synthesis of tetrahydrofurans, and several new syntheses of natural (+)-goniothalesdiol have been published.[19–23] In all cases, long synthetic pathways and/or low yields were reported, which shows the difficulty of asymmetric synthesis of these kinds of compounds. Until now, the shortest and most efficient total synthesis of (+)-**5** was reported by Britton et al. in 2010[24] from methyl 5-oxopentanoate. It featured an organocatalytic asymmetric α-chlorination and a microwave-assisted cyclization of a chlorotriol precursor (4 steps, 49 % overall yield).

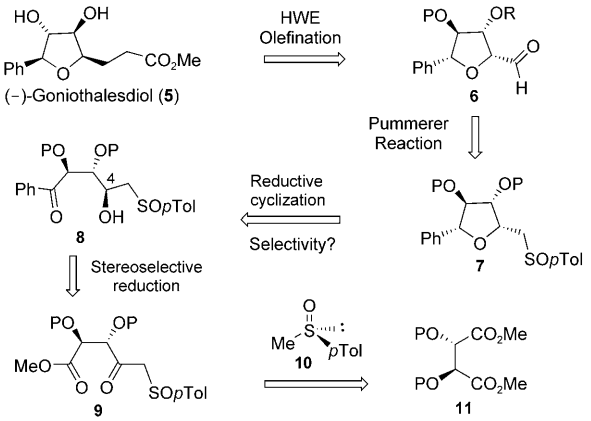
When we were developing our total enantioselective synthesis of (+)-goniothalesdiol, we observed several interesting features related to the reactivity of the substrates and the stereoselectivity of the cyclization step. The proposed mechanism[10–13] for the reductive cyclization involves the formation of an intermediate cyclic oxocarbenium ion, which undergoes nucleophilic attack from Et_3SiH to give the cyclic ether. Other similar reactions that give rise to cyclic ethers, such as the Mead reductive cyclization of ketones that have a β-lactone three carbon atoms distant from the alcohol,[25,26] and the nucleophilic substitution of γ-lactols and cyclic acetals,[27–29] also proceed via these intermediates.[30–32] The study of oxocarbenium ion reactivity is of huge interest because these ions occur as intermediates in many interesting synthetic and bioorganic reactions, including the formation and cleavage of glycosides.

The factors influencing the reactivity and stereoselectivity of various substituted cyclic oxocarbenium ions have been studied extensively by Woerpel et al.[28,30a–b,31–33] These mechanistic studies established the electronic effects of the ring substituents in the cyclic oxocarbenium ion as the main factors that control the stability of the reactive conformations and, as a consequence, the stereoselectivity of the nucleophilic additions.

Bearing in mind all the preceding work, we could not easily predict the stereoselectivity of the reductive cyclization key step because it appears to be mainly dependent on the nature of the substituents. We now report a full account of the total enantioselective synthesis of (+)-goniothalesdiol, including our conclusions on the relative influence of oxygenated substituents in the intermediate cyclic oxocarbenium ion versus the exocyclic sulfur function on the control of the stereochemical course of the reductive cyclization. We also saw that the relative configuration of a sulfoxide situated on the acyclic precursor had a central role in the control of the stereochemical course of the reduction step.

Results and Discussion

Our retrosynthetic approach to (+)-**5** is shown in Scheme 2. We proposed to obtain (+)-**5** from aldehyde **6** through a Horner–Wadsworth–Emmons (HWE) olefination to complete the C-2 carbon chain from an adequately protected diol derivative. The aldehyde group of **6** could proceed from the CH_2SOp-Tol substituent of the tetrahydrofuran deriva-

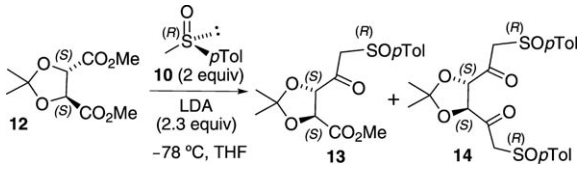


Scheme 2. Retrosynthesis of (+)-goniothalesdiol (**5**). Tol = tolyl.

Abstract in Spanish: *Se han conseguido entre buenas y excelentes estereoselectividades, controladas por el sulfóxido, en la ciclación reductora de hidroxisulfinil cetonas enantiopuras para generar el esqueleto de tetrahidrofuranos* cis*-2,5-disustituidos. Los efectos electrostáticos por parte del sulfóxido exocíclico, estabilizando el ion oxocarbenio intermedio, son los responsables del estereocontrol observado. Se propone un modelo que explica los resultados experimentales. El uso de esta reacción y de la reducción asimétrica de β-ceto sulfóxidos como etapas clave, ha permitido la síntesis total enantioselectiva del β-C-aril glicósido natural (+)-goniothalesdiol.*

tive **7** by a Pummerer reaction.[34] We envisaged the formation of the heterocyclic moiety through the Et_3SiH/TMSOTf-promoted reductive cyclization reaction from β-hydroxy sulfinyl ketone **8**, which ought to be easily available through the well-established stereoselective reduction of enantiopure β-keto sulfoxides.[9] The β-ketosulfoxide (+)-(S*R*)-**9** could be prepared, in turn, by the procedure reported by Solladié et al.,[35] based on the condensation of dihydroxy-protected dimethyl tartrate **11** and the lithium anion derived from (+)-(*R*)-methyl *p*-tolyl sulfoxide **10**.[36]

We initially planned to use the commercially available (+)-dimethyl 2,3-O-isopropylidene-D-tartrate (**12**) as the starting material (Scheme 3 and Table 1). The reaction of **12** with the anion derived from enantiomerically pure (−)-(S*R*)-methyl *p*-tolyl sulfoxide (**10**)[36] and LDA to give the monocondensed product (**13**) was not easy to control. The addition of diester **12** (1 equiv) to a solution of two equivalents of the lithium anion derived from (S*R*)-**10** in THF at −78 °C (Table 1, entry 1), gave rise to the doubly condensed product **14**, which was isolated in 34% yield. To avoid the formation of **14**, we decided to use only one equivalent of **10** and two equivalents of LDA, but we did not observe any improvement. After several trials in which we changed the relative molar ratio of the sulfinyl carbanion and other experimental parameters, we obtained a mixture of **13** and **14**, in 36 and 16% yield, respectively, by using two equivalents of sulfoxide **10** and excess LDA (2.3 equiv), and adding the previously generated α-sulfinyl carbanion at −60 °C to the solution of diester **12** (Table 1, entry 2). Through these experiments, we established that the slow addition of the anion derived from **10** to the solution of **12** was essential to improve the ratio of **13** to **14**. Finally, compound (2*S*,3*S*,S*R*)-**13** could be isolated pure in 90% yield by adding the anion previously formed from **10** (2 equiv) and LDA (2.2 equiv) in THF at −78 °C to diester **12** (1 equiv; 0.1 M in THF) over three hours (Table 1, entry 3).

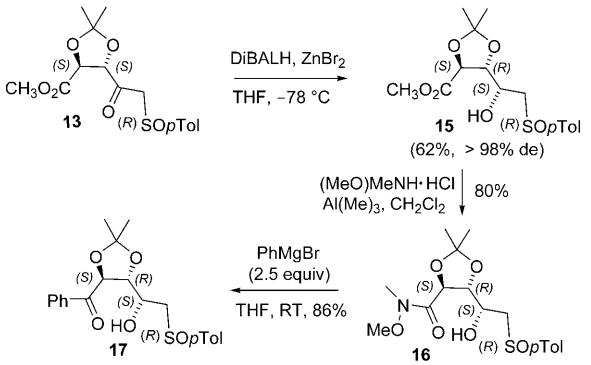


Scheme 3. Synthesis of β-ketosulfoxide **13** from diester **12**. LDA = lithium diisopropylamide.

Table 1. Reaction of diester **12** and (S*R*)-methyl *p*-tolyl sulfoxide **10**.

Entry	Isolated yield [%]	*T* [°C]	Experimental conditions
1	34 (**14**)	−78	addition of **12** to the anion of **10**
2	36 (**13**), 16 (**14**)	−60	addition of the anion of **10** to **12**
3	90 (**13**)	−78	slow addition of the anion of **10** to **12** (2.5 mL h^{-1})

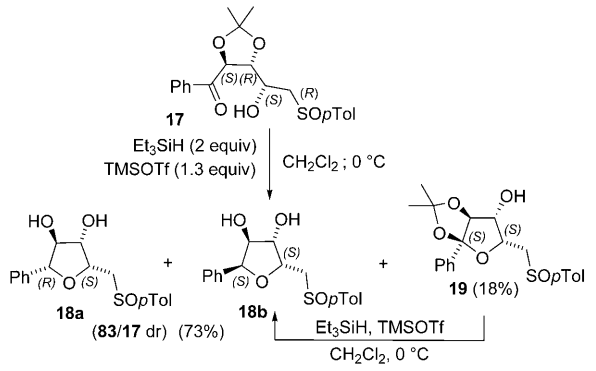
With β-ketosulfoxide **13** in hand, we effected its reduction with diisobutylaluminum hydride (DIBALH) in the presence of $ZnBr_2$ to afford β-hydroxysulfoxide (2*S*,3*R*,4*R*,S*R*)-**15** (Scheme 4). Again, the order of addition of the reactants was essential to achieve good yields and stereoselectivities. When DIBALH was added to a mixture of β-ketosulfoxide **13** and $ZnBr_2$, a moderate diastereoselectivity (78% diastereomeric excess (de)) resulted. Nevertheless, when β-ketosulfoxide **13** and $ZnBr_2$ (4 equiv in THF) was added to a DIBALH solution, β-hydroxysulfoxide (2*S*,3*R*,4*R*,S*R*)-**15** could be obtained in a completely diastereoselective way (>98% de) in 62% yield. The absolute configuration at the new hydroxylic center formed was established by ^{1}H NMR spectroscopy as *R*, which was expected on the basis of the mechanism proposed for the reduction of such β-ketosulfoxides.[9] From the numerous examples of reductions of β-ketosulfoxides reported, a noticeable difference in the nonequivalence of the methylene hydrogen atoms α to the sulfoxide for the *R*,(S)*R* and the *S*,(S)*R* epimers has been observed. For the *R*,(S)*R* configuration, the $\Delta\nu$ value between these two hydrogen atoms is smaller (35–50 Hz) than in the *S*,(S)*R* diastereomer (80–98 Hz).[9,10,35] For β-hydroxysulfoxide **15**, $\Delta\nu = 35$ Hz; thus, the 2*S*,3*R*,4*R*,(S)*R* absolute configuration was assigned. The configuration of the minor diastereomer was assigned as 2*S*,3*R*,4*S*,(S)*R* on the base of its higher $\Delta\nu$ value (96.5 Hz).



Scheme 4. Synthesis of hydroxy sulfinyl ketone **17**.

According to our retrosynthetic analysis, we needed to transform the ester function of (2*S*,3*R*,4*R*,(S)*R*)-**15** into phenyl ketone derivative **17** (Scheme 4). We thus decided to proceed via the *N*-methyl-*N*-methoxyamide (Weinreb amide **16**) intermediate, to avoid overreaction of the ester with the phenyl Grignard. Thus, upon reaction of **13** with *N*-methyl methylhydroxylamine hydrochloride in the presence of excess $AlMe_3$ at room temperature,[37] Weinreb amide **16** was obtained pure, in 80% yield. Finally, enantiomerically pure hydroxysulfinyl ketone **17** resulted, in 86% yield, after reaction of **16** with an excess of PhMgBr (Scheme 4).

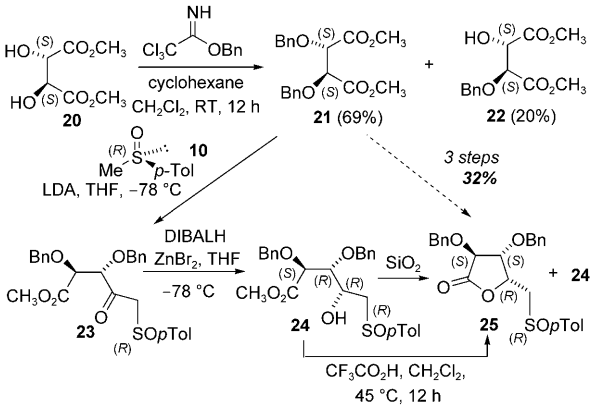
We then tried to generate the tetrahydrofuran ring by reductive cyclization of isopropylidene-protected hydroxy sulfinyl ketone **17** (Scheme 5). Upon treatment of **17** with TMSOTf and Et_3SiH, under the typical conditions previous-



Scheme 5. Reductive cyclization of isopropylidene-protected derivative **17**. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

ly used by us to generate various-sized cyclic ethers,[10–13] protected lactol **19** and a mixture of tetrahydrofuran epimers **18a** and **18b**, without the isopropylidene protecting group, were formed. This mixture could be separated by chromatography to isolate **18a** and **18b** (83:17 diastereomeric ratio (d.r.)) in 73% yield, and pure **19** in 18% yield. Although **19** was further transformed into **18** (**18a**/**18b**: 83:17) by treatment with Et_3SiH/TMSOTf, these results were not useful overall, because we needed the OH groups of **18** protected for further manipulation. Working at lower temperatures (−78 °C), protected lactol **19** could be achieved as the major product. Further investigations into experimental conditions to achieve the reductive cyclization without losing the *trans*-acetonide were unsuccessful. This may be due to the presence of the acetonide group, which would lower the conformational flexibility of the intermediate oxocarbenium ion, thus hindering its formation.

To avoid deprotection and transketalization under the acidic conditions of the reductive cyclization, we decided to change the acetonide into two benzyl (Bn) ethers, intuitively more robust protecting groups (Scheme 6). The benzylation of commercially available (−)-(2*S*,3*S*)-dimethyl D-tartrate (**20**) by treatment with NaH, benzyl bromide, and catalytic tetra-*n*-butyl ammonium iodide in THF, led to dibenzyl

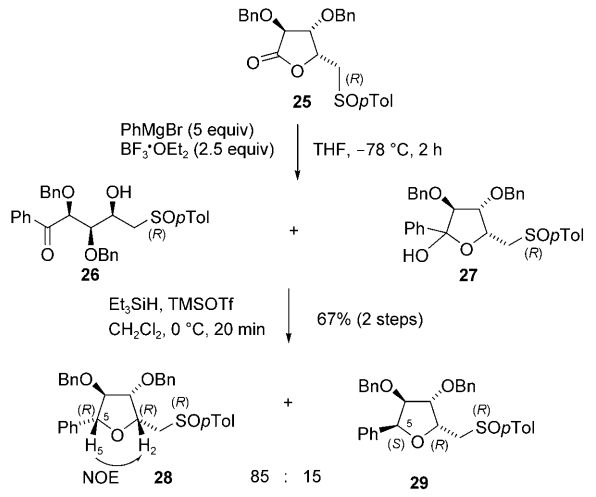


Scheme 6. Synthesis of benzyl-protected lactone **25**. TFAA = trifluoroacetic anhydride.

ether **21** in only 15% yield. Better yields were achieved by reaction of **20** with benzyl trichloroacetimidate in the presence of triflic acid.[38] Under these conditions, dibenzyl ether (2*S*,3*S*)-**21** could be isolated in 69% yield, although the concomitant formation of monobenzyl ether **22** could not be avoided (20% yield, Scheme 6). The reaction between the lithium anion of (S*R*)-methyl *p*-tolyl sulfoxide **10** and dibenzyl-protected dimethyl tartrate (*S*,*S*)-**21** was carried out under the optimized conditions established above for the reaction of **12**. The addition of two equivalents of the anion generated from (S*R*)-**10** and LDA to diester **21**, gave rise to β-ketosulfoxide (2*S*,3*S*,S*R*)-**23** (Scheme 6). Nevertheless, chromatographic purification on silica gel produced partial degradation, which gave a low yield of **23**. The reaction was also shown to be sensitive to temperature and difficult to scale up. The best conditions were 1.2 mmol of **21** at −78 °C for the reaction, and demetalated silica gel[39] for the chromatographic purification; however, only a maximum 57% yield of **23** could be obtained. To increase the overall yield of the stepwise synthesis, we decided to avoid purification and use the crude mixture directly.

Thus, the reduction of the crude mixture containing β-ketosulfoxide **23** with DIBALH in the presence of $ZnBr_2$ afforded, exclusively, carbinol (2*S*,3*R*,4*R*,S*R*)-**24**, with *R* absolute configuration at the newly created C-4 stereogenic center. This result showed that the well-established protocol to reduce β-ketosulfoxides could work efficiently, even in molecules with other oxygenated centers α to the carbonyl group that could compete with the sulfoxide in the diastereocontrol of the process.[40] When the resulting carbinol (**24**) was purified by chromatography, the silica gel catalyzed its partial transformation into lactone (3*S*,4*S*,5*R*,S*R*)-**25** (Scheme 6). Several attempts to protect the OH group of **24** led to the exclusive formation of lactone **25**. Direct transformation of the ester function of **24** to a Weinreb amide (MeONHMe·HCl, Me_3Al) was unsuccessful, and only gave lactone **25**. We then decided to take advantage of the easy formation of **25**, which could be obtained by reducing the crude reaction mixture with CF_3COOH.[41] After flash chromatography, lactone **25** was isolated pure in 32% overall yield for the three steps, which included condensation with lithium methyl *p*-tolylsulfoxide, DIBALH reduction, and lactonization, from tartrate derivative **21**.

With lactone **25** in hand, we directed our efforts to the introduction of the phenyl substituent and the stereoselective construction of the 2,5-*cis* tetrahydrofuran skeleton required en route to goniothalesdiol (Scheme 7). We first attempted to introduce the phenyl group at C-2 by using PhLi, or PhLi in the presence of two different Lewis acids (Me_2AlCl, $BF_3{\cdot}OEt_2$), without success. The use of PhMgBr as nucleophile gave rise, in 80% conversion, to a mixture of hydroxy phenyl ketone (2*S*,3*R*,4*R*,S*R*)-**26**, and cyclic hemiketal (3*S*,4*S*,5*R*,S*R*)-**27**, as a mixture of epimers at C-2. The addition of Lewis acids such as $ZnBr_2$ or TMSOTf to activate the lactone did not improve the results. Complete transformation of **25** was achieved by addition of five equivalents of PhMgBr in the presence of $BF_3{\cdot}OEt_2$ but, after SiO_2 flash

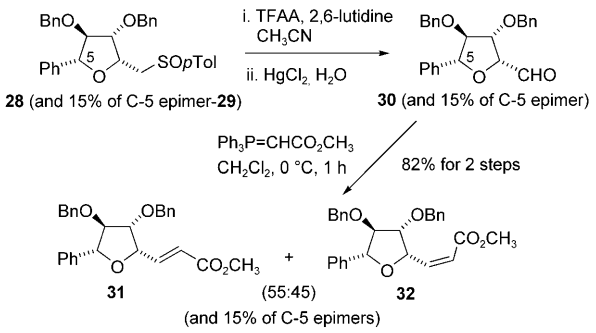


Scheme 7. Synthesis of benzyl-protected tetrahydrofuran derivatives **28** and **29**.

chromatography, we obtained a poor yield of a mixture of **26** and **27**. These low chemical yields prompted us to again use the crude mixture without further purification in the next step (Scheme 7).

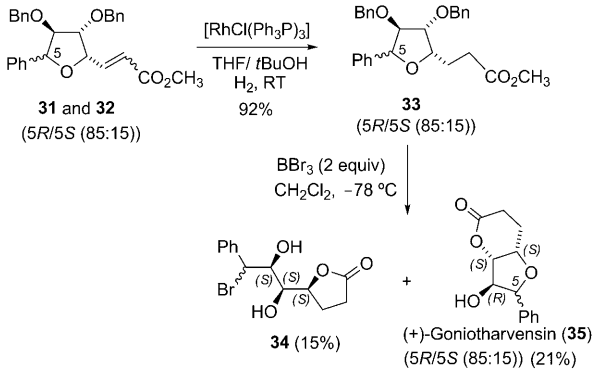
Thus, treatment of the mixture of **26** and **27** under the conditions used for the reductive cyclization (TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 20 min) led, in 67 % yield, to a mixture of *cis*-2,5-disubstituted tetrahydrofuran **28** and the corresponding *trans* diastereoisomer **29** (**28**/**29** 85:15). Tetrahydrofuran derivatives **28** and **29** resulted from the reductive cyclization of hydroxy sulfinyl ketone **26** and/or the reductive deoxygenation of lactol **27** by Et_3SiH and TMSOTf acting as a Lewis acid. The *cis* relative configuration of the 2,5-substituents of **28** was established from an NOE spectroscopy experiment, which demonstrated the close spatial arrangement of the two hydrogen atoms H2 and H5 situated on the carbon atoms adjacent to the heterocyclic oxygen atom. Diastereoisomers **28** and **29** could not be separated at this stage, so we continued the synthesis towards **5** with this mixture, which could be separated in the final step.

As shown in Scheme 8, the *p*-tolyl sulfinylmethyl group present in tetrahydrofuran **28** and C5 epimer **29**, was subjected to Pummerer reaction conditions,[34,42] followed by hydrolysis with $HgCl_2$ to cleave the intermediate hemithioacetal. The aldehyde (2*R*,3*S*,4*R*,5*R*)-**30** and its C-5 epimer were obtained as an 85:15 mixture and were shown to be very unstable. Thus, without further purification, the mixture was submitted to a Wittig reaction with $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2. After chromatographic purification, a 55:45 mixture of the corresponding *trans* and *cis* olefins (2*S*,3*R*,4*R*,5*R*)-**31** and (2*S*,3*R*,4*R*,5*R*)-**32**, which resulted from major epimer **28** and an analogue ratio of the olefins proceeding from minor epimer **29**, was isolated in 82 % overall yield for the last two steps starting from sulfoxides **28** and **29**.



Scheme 8. Synthesis of olefins **31** and **32**.

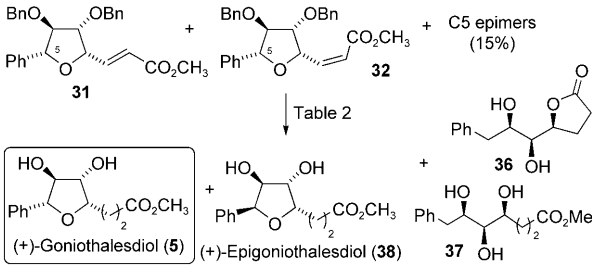
At this point, we considered simultaneously performing the reduction of the double bonds of the olefins and deprotection of the benzyl alcohols to complete the synthesis. However, the known fragility of the *C*-arylglycoside bond under hydrogenolytic conditions (H_2, Pd/C, MeOH)[43] prompted us to try a stepwise hydrogenation and deprotection. We first hydrogenated the double bonds of the mixture of **31** and **32** (and the C-5 epimers) by using the Wilkinson catalyst $[RhCl(Ph_3P)_3]$[44] in THF/*t*BuOH under H_2 to give hydrogenated derivatives **33** in 92 % yield (Scheme 9). We



Scheme 9. Hydrogenation and deprotection of olefins **31** and **32**.

then attempted to selectively cleave the benzylic ethers of **33** with BBr_3 in CH_2Cl_2. These conditions have been reported to avoid undesired byproducts derived from the benzylic C–O heterocyclic-bond breaking.[45] However, treatment of **33** with BBr_3 in CH_2Cl_2 at −78 °C was unsuccessful, and gave rise to compound **34** (15 % yield), together with natural (+)-goniotharvensin (**35**) and its C-5 epimer in 21 % yield.

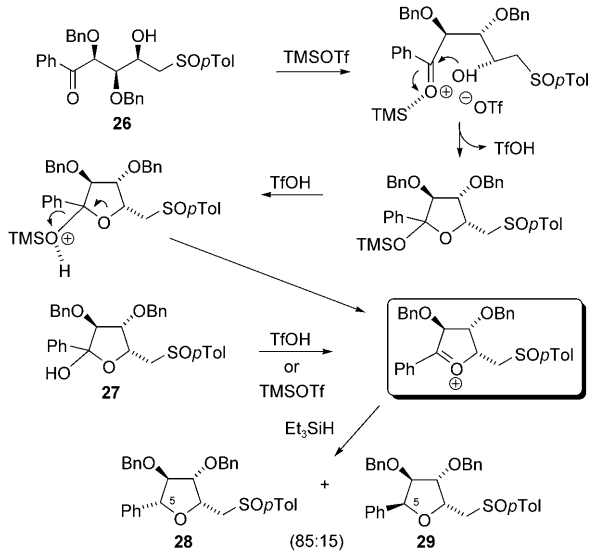
We then returned to simultaneous hydrogenation and deprotection. We initially used the conditions reported by Yoda et al.[18] for a similar transformation. Treatment of the mixture of olefins **31** and **32** with MeOH/HCOOH (4.4 %) in the presence of a catalytic amount (0.2 equiv) of Pd black at 50 °C left the starting materials unchanged. When the amount of Pd was increased to 10 equivalents, the formation of compound **36** was observed, which resulted from the reductive cleavage of the O–C5 benzylic bond of the tetrahydrofuran ring, followed by lactonization, together with hydroxy ester precursor **37**. The two compounds were isolated as a 50:50 mixture in 86 % yield (Scheme 10 and Table 2).



Scheme 10. Direct transformation of olefins **31** and **32** into **5**.

Table 2. Experimental conditions for the transformation of olefins **31** and **32** into (+)-goniothalesdiol (**5**).

Experimental conditions	Products [%]			
	5	**38**	**36**	**37**
Pd black (10 equiv), EtOH/HCOOH (10%), RT, 12 h	–	–	(50:50, 86% yield)	
Pd black (1.2 equiv), MeOH/HCOOH (4.4%), 55°C, 6 h	41	9	35	–



Scheme 11. Mechanism of the transformation of **26** and **27** into tetrahydrofuran C5 epimers **28** and **29**. TfOH = trifluoromethanesulfonic acid.

After several experiments, the best results were obtained with Pd black (1.2 equiv) in MeOH/HCOOH (4.4%) at 55°C for 6 h. Following purification by flash chromatography, we isolated (2*S*,3*S*,4*R*,5*R*)-**5** in 41% yield, lactone (2*R*,3*S*,4*S*)-**36** in 35% yield, and (2*S*,3*S*,4*R*,5*S*)-**38** in 9% yield. The last compound was formed as a consequence of the presence of the C-5 epimers in the initial mixture of heterocyclic olefins **31** and **32**. Our synthetic **5** ($[\alpha]_D^{20}=+6.4$ ($c=0.36$ in EtOH); lit:[15] $[\alpha]_D^{20}=+7.5$ ($c=0.23$ in EtOH), lit:[19a] $[\alpha]_D^{20}=+6.5$ ($c=0.6$ in EtOH), lit:[19b] $[\alpha]_D^{20}=+6.9$ ($c=0.38$ in MeOH), lit:[18] $[\alpha]_D^{20}=-7.1$ ($c=0.15$ in EtOH, for the enantiomer)), showed identical physical and spectroscopic parameters to those reported for the natural (+)-goniothalesdiol (**5**).[15]

Thus, the total enantioselective synthesis of the natural tetrahydrofuran derivative (+)-**5** was finally complete in nine steps and 5% overall yield from commercially available (−)-dimethyl D-tartrate. The stereoselective construction of the *cis*-2,5-disubstituted tetrahydrofuran moiety was accomplished by the Et_3SiH/TMSOTf-promoted reductive cyclization/deoxygenation of the mixture of **26** and **27**.

A mechanistic pathway explaining the convergent evolution of this mixture into tetrahydrofuran C-5 epimers **28** and **29** is shown in Scheme 11. Initial activation of the carbonyl group of hydroxysulfinylketone **26** by TMSOTf, which acts as a Lewis acid, favors intramolecular nucleophilic addition of the OH to give an intermediate mixed-acetal precursor of the cyclic oxocarbenium intermediate. Either TMSOTf or the Brønsted acid previously liberated could activate the transformation of lactol **27** into the same cationic intermediate. The common oxocarbenium ion later reacts with Et_3SiH to give the final cyclic ethers as a mixture of C5 epimers **28** and **29** (85:15, respectively). The intriguing stereochemistry of the last step deserves some comments.

The stereochemical course of the reductive cyclization/deoxygenation: As mentioned above, the mechanism and stereochemistry of nucleophilic substitutions of tetrahydrofuran and -pyran acetals, which likely occur through the intermediate formation of cyclic oxocarbenium ions, have been extensively studied by Woerpel et al.[28,30–33] The main conclusions reached are that electrostatic effects of the various ring substituents define a reactive conformation for the oxocarbenium intermediate, which undergoes a stereoelectronically governed face-selective attack of the nucleophile.[46] The stereoselectivity was shown to be only slightly affected by the solvent, the Lewis acid, the leaving group, and the nucleophile. In connection with our work, the most significant results correspond to the study of variously substituted ribose-derived acetals,[28] as well as tetrahydropyranyl oxocarbenium ions with an exocyclic alkoxyalkyl substituent.[31a,b] The model proposed by Woerpel et al. assumes that the stereoselectivity of the overall process depends on the conformational preference of the alkoxy group situated at C-3[47] of the five-membered ring oxocarbenium ion. As shown in Figure 1, the most stable and reactive conformer of the intermediate is **38**, which has the axial C-3 benzyloxy substituent. This is due to the electrostatic interaction that arises between the electronegative axial oxygen and the close positive charge of the cationic carbon. The inside face

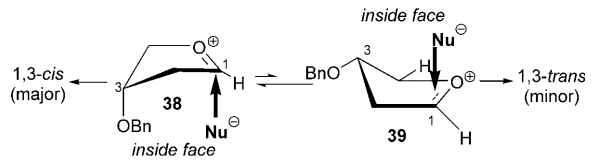
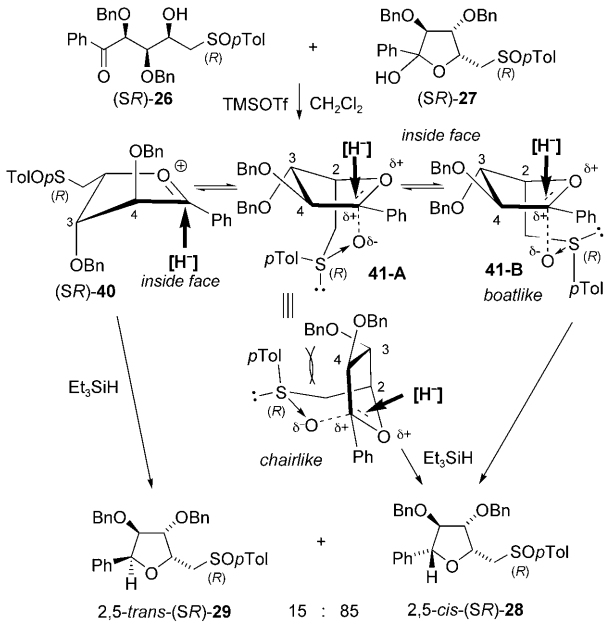


Figure 1. Woerpel's stereochemical model for reactions of five-membered oxocarbenium ions with nucleophiles.[28]

attack of the nucleophile, which is favored by stereoelectronic effects, supports the formation of the 1,3-*cis* disubstituted compound as the major product.

Exocyclic electrostatic interactions have also been shown to contribute to the conformational stability of tetrahydropyran oxocarbenium ions.[31a,b] In such cases, the stereochemical course of the nucleophilic approach is also governed by stereoelectronic effects. When polysubstituted derivatives react, in accordance with the Curtin–Hammet principle, the reactive conformation cannot be the most stable due to the interactions developing in the transition state.

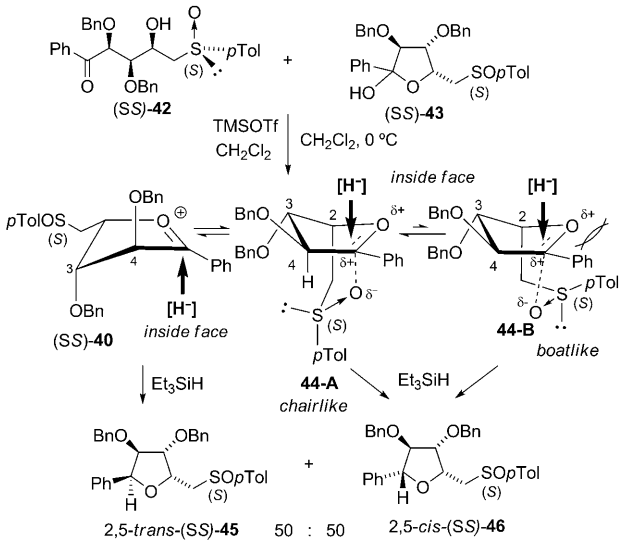
In our case, as shown in Scheme 12, the intermediate oxocarbenium ion that results from the treatment of the mixture of **26** and **27** with TMSOTf, could adopt the envelope conformation (S*R*)-**40**, with both OBn substituents in the



Scheme 12. Stereochemical model justifying the major formation of *cis*-2,5-tetrahydrofuran (S*R*)-**28** from the mixture of (S*R*)-**26** and (S*R*)-**27**.

axial position. In accordance with Woerpel's assumption, this conformation must be stabilized by the electrostatic interaction that exists between the electronegative oxygen of the C-3 benzyloxy group and the positive charge at the cationic carbon center, although the axial OBn at C-4 would slightly decrease the stability.[28] Nevertheless, the favored inside attack of the nucleophile (Et_3SiH) on this conformer (S*R*)-**40** only explains the formation of minor 2,5-*trans* (S*R*)-**29** tetrahydrofuran epimer. The formation of major 2,5-*cis*-disubstituted diastereomer (S*R*)-**28**, experimentally observed by us (**28**/**29** 85:15), must be due to the presence of the exocyclic polar sulfoxide in the starting substrates. Assuming that electrostatic effects have the most significant influence over the control of the conformational equilibria, we propose that the envelope conformers (**41**), with two OBn equatorial substituents and the *p*-tolylsulfinylmethyl group in the axial position at C-2, could be the most stable. The electronegative sulfinyl oxygen plays an essential role in the electrostatic stabilization of **41**, because it can interact through space with the positively charged cationic carbon C-5 to generate a six-membered ring. Two possible conformers could be considered for the new ring of the associated intermediate. Chairlike conformation **41-A** shows two severe 1,3-diaxial interactions between the *p*-tolyl group and the C2–C3 and C4–C5 axial bonds of the oxocarbenium ring, which do not exist in the boatlike conformer **41-B**. Although the favored inside-facial attack of the hydride from the top face of both conformers would justify the major formation of *cis*-2,5-disubstituted derivative **28**, reaction through conformer **41-B**, in which the bulky *p*-tolyl group shows no destabilizing interactions, must be preferred.

To clarify the influence of the relative configuration of the sulfoxide on the stereochemistry of the reductive cyclization, we synthesized compound (S*S*)-**42**, the sulfinyl epimer of (S*R*)-**26**, by using a procedure similar to that described above, starting from dimethyl dibenzyltartrate (*S*,*S*)-**21** and (S*S*)-methyl *p*-tolyl sulfoxide (S*S*)-**10** (see the Supporting Information for details). The resulting mixture of hydroxyl sulfinyl ketone (S*S*)-**42** and hemiketal (S*S*)-**43** was subjected to reductive cyclization conditions (TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C), which led to formation of a 50:50 mixture of *trans*-2,5-(S*S*)-**45** and *cis*-2,5-(S*S*)-**46** diastereomers (Scheme 13).



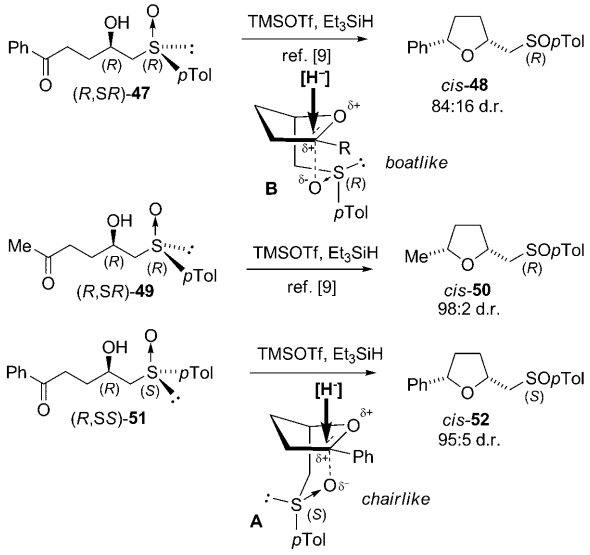
Scheme 13. Stereochemical course of the reaction of the mixture of (S*S*)-**42** and (S*S*)-**43** with Et_3SiH/TMSOTf.

Again, three different conformations of the intermediate could react with the hydride (Et_3SiH), once the cyclic oxocarbenium ion was formed from **42** and **43** in the presence of TMSOTf: 1) the envelope conformer (S*S*)-**40**, analogous to (S*R*)-**40** (Scheme 12), which is stabilized by the electrostatic interaction between the axial C-3 OBn and the positive charge; and the substituents with OBn in the diequatorial dispositions, 2) **44-A**; and 3) **44-B**, which are also stabi-

lized by the electrostatic effect of the sulfynyl oxygen. Boatlike conformer **44-B** is strongly destabilized by the *p*-tolyl group, and can be disregarded as a reactive conformation. Chairlike structure **44-A**, shows no steric destabilizing interactions, since the bulky *p*-tolyl group is equatorial, but the spatial proximity of the nonbonding electron pairs at the sulfoxide and the oxygen of the C3 OBn could slightly destabilize it. Thus, assuming similar stability and/or reactivity of both (S*S*)-**40** and **44-A**, the favored inside attack of the hydride would explain the formation of a 50:50 mixture of *cis* and *trans* diastereomers (S*S*)-**45** and (S*S*)-**46**.

Other data that reinforce the role of electrostatic effects correspond to the results shown in Scheme 1 reported by Yoda et al. en route to 5-epigoniothalesdiol.[16] The ionic deoxygenation of lactol **1**, which has a similar structure and stereochemistry to **26** and **27** but lacks the sulfoxide, in the presence of Et_3SiH and $BF_3{\cdot}OEt_2$, afforded a product with stereochemistry that can be explained on the basis of the electrostatic effect of the C-3 substituent. This is in agreement with Woerpel's model, if one assumes a reactive conformation similar to **40**. The presence of the sulfoxide in lactol **27** allows inversion of the stereochemistry, and leads to the correct configuration of the natural product.

The role of the sulfoxide in the control of the reactive conformation and stereochemistry, is also evident from the results indicated in Scheme 14. The reductive cyclization (Et_3SiH/TMSOTf) of phenyl hydroxysulfinyl ketone (*R*,S*R*)-**47**, previously reported by us,[10] led to a 84:16 mixture of diastereoisomers, in which the 2,5-*cis* disubstituted tetrahydrofuran *cis*-**48**, was the major one. The methyl ketone analogue (*R*,S*R*)-**49** reacted even more stereoselectively, and gave rise to exclusive formation of the diastereomer *cis*-**50**. The stabilization of the reactive conformation of the cyclic oxocarbenium ion by the electrostatic effect of the sulfoxide explains these results. The bicyclic envelope–boatlike conformation **B** (Scheme 14) must react stereoselectively at the top face, which is in accordance with the favored inside attack of the nucleophile. The phenyl group, present in the intermediate that results from (*R*,S*R*)-**47** (**B**, R = Ph) could partially delocalize the positive charge, thus slightly reducing the electrostatic stabilization by the sulfinyl oxygen. On the other hand, the donating character of the methyl group of the intermediate that arises from (*R*,S*R*)-**49** can concentrate the charge at the cationic center. This would increase the electrostatic stabilization of **B** (R = Me), which is then formed in a highly diastereoselective manner.



Scheme 14. Role of the sulfoxide in the control of the reactive conformation of oxocarbenium ions.

We also synthesized compound (*R*,S*S*)-**51** (see the Supporting Information for details), the sulfur epimer of phenyl sulfinyl hydroxy ketone (*R*,S*R*)-**47**. Reductive cyclization gave rise to the *cis*-2,5-disubstituted tetrahydrofuran *cis*-**52** in a high d.r. (95:5) (Scheme 14). This stereoselectivity must be a consequence of the fact that the reaction occurs through an oxocarbenium ion with a chairlike conformation such as **A**, which is electrostatically stabililized. Comparison between the chairlike conformer **A**, generated from (*R*,S*S*)-**51**, and the boatlike analogue **B**, which results from (*R*,S*R*)-**47**, explains the higher stereoselectivity obtained from **A** due to the higher stability of a chair relative to a boat, which has greater torsional strain. Moreover, the reactive conformation **A**, which has no alkoxy substituents on the oxocarbenium ring, must be more stable than conformation **44-A** in the reaction of the dibenzyloxy-substituted derivative (S*S*)-**42**, due to the absence of repulsions in **44-A** between the nonbonded electron pairs of the benzyl oxygen and the sulfoxide. This also explains the decreased stereoselectivity observed from (S*S*)-**42**.

Conclusion

We have reported the total enantioselective synthesis of the natural (+)-goniothalesdiol (**5**) based on the asymmetric reduction of β-ketosulfoxide **23**, and the Et_3SiH/TMSOTf-promoted reductive cyclization of phenyl hydroxyl sulfinyl ketone **26**, starting from commercially available (−)-dimethyl D-tartrate. The synthesis was completed in nine steps and 5% overall yield. The success of the synthetic sequence lies in the protecting groups of the tartrate hydroxyl groups and the presence of the sulfoxide in **23** and **26**. The stereochemical course of the reductive cyclization/deoxygenation reaction allowed us to put forward the essential role of the sulfoxide in stabilizing the reactive conformation of the five-membered oxocarbenium ring intermediate. Based on Woerpel's model, we proposed that electrostatic interactions of the exocyclic sulfoxide define the reactive conformation. On changing the relative configuration of the sulfoxide in (S*R*)-**26**, which gave rise to (S*S*)-**42** in a 85:15 d.r., a significant drop in stereoselectivity was observed (50:50 d.r.). This clearly shows the role of the sulfoxide in defining the stereochemistry of the final products. Reductive cyclizations of hydroxy sulfinyl ketones **47**, **49** and **51**, which lack the benzyloxy substituents, were highly stereoselective (up to 98:2

d.r.). Thus, the presence of OBn substituents on the oxocarbenium ring also influenced the relative stability of the reactive conformations.

Experimental Section

General: Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. All reactions were monitored by TLC, which was performed on precoated sheets of silica gel 60. Flash column chromatography was carried out on silica gel 60 (230–400 mesh; Merck). Eluting solvents are indicated in the text. The apparatus for inert-atmosphere experiments was dried by flaming in a stream of dry argon. Diisopropylamine was freshly distilled over KOH before use. NaH was washed before use with several portions of hexane. CH_2Cl_2 was predried over $CaCl_2$, distilled over P_2O_5, and carefully stored under argon. Dry THF was distilled from sodium/benzophenone ketyl. All other reagent-quality solvents were predried over activated molecular sieves and stored under argon. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and drying of solvent with $MgSO_4$. For the synthesis and characterization of compounds **13**–**19**, **21**–**27**, **30**–**35**, **37**, **42**, **43**, and **51**, see the Supporting Information.

Method A: Synthesis of β-ketosulfinyl esters: A solution of *n*BuLi (2.5 M in hexanes; 2.3 equiv) was added to a solution of dry diisopropylamine (2.2 equiv) in THF (0.7 M) at −40 °C, under argon. The mixture was stirred for 45 min before the dropwise addition of a solution of (S*R* or S*S*)-methyl-*p*-tolylsulfoxide[40] (2 equiv) in THF (0.75 M). After stirring for 1 h at this temperature, the reaction was cooled to −78 °C, and the resulting anion was slowly added (2.5 mL h^{-1}) to a solution of the corresponding ester (1 equiv) in THF (0.9 M). The reaction was stirred at this temperature for the time indicated in each case. The mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ethyl acetate. After workup and flash chromatography, the corresponding pure β-ketosulfinyl esters were obtained.

Method B: Synthesis of β-hydroxysulfinyl esters by reduction of β-ketosulfinyl esters: A solution of the β-ketosulfoxide (1 equiv) and dry $ZnBr_2$ (4.5 equiv) in THF (0.1 M) was added dropwise at −78 °C to a solution of DIBALH (1.5 M in toluene, 3 equiv) in THF (0.1 M), under argon. The resulting mixture was stirred at the same temperature for 2 h and quenched with saturated Na-K tartrate. After workup, the crude β-hydroxysulfoxides and/or the corresponding lactones were purified by flash chromatography.

Method C: Synthesis of sulfinyl hydroxy ketones and the corresponding sulfinyl lactols from sulfinyl lactones: Boron trifluoride etherate (2.5 equiv) was added at −78 °C to a solution of the sulfinyl lactone (1 equiv) in THF (0.06 M) under argon. After stirring for 1.5 h, a solution of phenyl magnesium bromide (1 M) in toluene (5 equiv) was added dropwise at −78 °C. The resulting mixture was stirred for 2 h at the same temperature and hydrolyzed with saturated aqueous NH_4Cl. After extraction with EtOAc, washing with brine, and workup, the resulting equilibrium mixture of sulfinyl hydroxyketone and the corresponding hemiketal were used in the next reaction without further purification.

Method D: Synthesis of tetrahydrofurans by reductive cyclization of sulfinyl hydroxy ketones and/or reductive deoxygenation of sulfinyl lactols: Et_3SiH (2 equiv) and TMSOTf (1.3 equiv) were successively added dropwise to a solution of the corresponding hydroxy ketone in CH_2Cl_2 (0.04 M) at 0 °C under argon. The mixture was stirred at the same temperature for the time indicated in each case and quenched with water. After workup and flash chromatography, pure tetrahydrofuran derivatives were obtained.

Compound 28: Compound **28** was prepared according to method D (stirring for 20 min). After flash chromatography (eluent CH_2Cl_2/Et_2O 12:1), a nonseparable mixture of (2*R*,3*S*,4*R*,5*R*,S*R*)-**28** and (2*R*,3*S*,4*R*,5*S*,S*R*)-**29** (85:15, respectively) was obtained as a colorless oil (67% yield for the two last steps starting from lactone **25**). R_f = 0.5 (hexane/EtOAc 1:3); $[\alpha]_D^{20}$ (mixture of compounds **28**/**29** 85:15) = +52 (c = 0.73 in $CHCl_3$); ^{1}H NMR ($CDCl_3$; major diastereomer **28**): δ = 2.41 (s, 3H), 3.21–3.51 (AB part of ABX system, J_{AB} = 12.8, J_{AX} = 6.7, J_{BX} = 7.1 Hz, $\Delta\nu$ = 66.6 Hz, 2H), 4.00 (dd, J = 3.9, 1.0 Hz, 1H), 4.10 (dd, J = 4.0, 1.0 Hz, 1H), 4.27 (td, J = 6.8, 3.9 Hz, 1H), 4.41 and 4.53 (AB system, J = 11.5 Hz, 2H), 4.50 (s, 2H), 4.78 (d, J = 3.9 Hz, 1H), 7.20–7.53 ppm (m, 19H); ^{1}H NMR (minor diastereomer **29**): δ = 2.41 (s, 3H), 3.12–3.43 (AB part of ABX system, J_{AB} = 12.9, J_{AX} = 6.9, J_{BX} = 7.2 Hz, $\Delta\nu$ = 79.2 Hz, 2H), 3.96 (br d, J = 4.2 Hz, 1H), 4.14 (br d, J = 4.7 Hz, 1H), 4.50 and 4.60 (AB system, J = 11.7 Hz, 2H), 5.18 (d, J = 3.5 Hz, 1H), 7.20–7.53 ppm (m, 19H); ^{13}C NMR ($CDCl_3$; major diastereomer **28**): δ = 21.4, 56.4, 71.5, 72.0, 76.0, 83.3, 86.1, 89.2, 124.2, 126.3, 127.6, 127.8, 127.9, 128.4, 128.5, 129.9, 137.3 (2C), 140.0, 140.4, 141.5 ppm; MS (EI): *m*/z (%): 512 $[M]^+$ (0.4), 496 (4), 387 (1), 197 (5), 181 (5), 139 (8), 91 (100); HRMS (EI) *m*/z: calcd for $C_{32}H_{32}O_4S$: 512.20213 $[M]^+$; found: 512.20227.

Compound 5: Pd black (14 mg, 0.13 mmol, 1.2 equiv) was added to a solution of the crude mixture of (*E*)-**31** and (*Z*)-**32** (52 mg, 0.11 mmol, 1 equiv) in methanol (4 mL) and formic acid (176 μL) under argon. The flask was flushed again with argon, and the reaction mixture was stirred at 55 °C for 6 h. After cooling the reaction to room temperature and filtering over Celite, the solvent was evaporated. Purification by flash chromatography (eluent CH_2Cl_2/ethyl ether 3:1) allowed three compounds to be isolated: (+)-5-epi-Goniothalesdiol (**38**) as a colorless oil (2.6 mg, 9% yield), (*S*)-dihydro-5-[(1*S*,2*R*)-1,2-dihydroxy-3-phenylpropyl]furan-2(3*H*)-one (**36**) as a white solid (9.0 mg, 35% yield), and (+)-Goniothalesdiol (**5**) as a colorless oil (12.0 mg, 41% yield). R_f = 0.33 (CH_2Cl_2/ethyl ether, 3:1). $[\alpha]_D^{20}$ = +6.4 (c = 0.36 in EtOH); ^{1}H NMR ($CDCl_3$): δ = 2.04–2.17 (m, 2H), 2.28 (br s, 1H), 2.45–2.68 (m, 3H), 3.69 (s, 3H), 4.05–4.11 (m, 3H), 4.61 (d, J = 4.5 Hz, 1H), 7.28 (br d, J = 7.0 Hz, 1H), 7.34 (br t, J = 7.0 Hz, 2H), 7.42 ppm (br d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 23.7, 30.6, 51.9, 79.1, 80.7, 85.4, 86.2, 126.1, 127.8, 128.5, 140.0, 174.6 ppm; MS (FAB+): *m*/z (%): 267 $[M+1]^+$ (16), 152 (9), 120 (13), 107 (22), 89 (17), 77 (17); HRMS (FAB+): *m*/z: calcd for $C_{14}H_{18}O_5$: 267.12325 $[M+1]^+$; found: 267.12298.

Compound 38: R_f = 0.41 (CH_2Cl_2/ethyl ether, 3:1); $[\alpha]_D^{20}$ = +55 (c = 0.04 in EtOH) {lit:[16] $[\alpha]_D^{20}$ = +66.6 (c = 0.74, EtOH), lit:[19] $[\alpha]_D^{20}$ = +70.3 (c = 0.23, EtOH)}; ^{1}H NMR ($CDCl_3$): δ = 1.82–2.07 (m, 2H), 2.31 (br s, 1H), 2.35–2.64 (m, 2H), 2.99 (d, J = 3.7 Hz, 1H), 3.65 (s, 3H), 4.12 (broad s, 1H), 4.20 (br s, 1H), 4.25 (m, 1H), 5.3 (d, J = 3.4 Hz, 1H), 7.30 ppm (m, 5H).

Compound 36: M.p. 104–106 °C; R_f = 0.37 (EtOAc); $[\alpha]_D^{20}$ = +28.4 (c = 0.31 in EtOH); ^{1}H NMR ($CDCl_3$): δ = 2.06–2.26 (m, 2H), 2.37–2.62 (m, 2H), 2.64 (d, J = 5.8 Hz, 1H), 2.77–2.99 (AB part of ABX system, J_{AB} = 13.3, J_{AX} = 6.5, J_{BX} = 7.7 Hz, $\Delta\nu$ = 24.5 Hz, 2H), 3.39–3.43 (ddd, J = 5.7, 4.0, 3.2 Hz, 1H), 3.87–3.95 (m, 1H), 4.55 (td, J = 6.9, 3.9 Hz, 1H), 7.16–7.29 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 23.9, 28.2, 40.0, 72.7, 73.6, 81.5, 126.8, 128.7, 129.4, 137.3, 176.8 ppm; MS (FAB+): *m*/*z* (%): 237 $[M+1]^+$ (35), 201 (31), 167 (19), 149 (62), 107 (35), 91 (49) ; HRMS (ESI): *m*/z: calcd for $C_{13}H_{16}O_4+Na^+$: 259.0940 $[M+Na^+]$; found: 259.0941.

Compounds 45 and 46: Compound **45** was obtained from **42** and **43** by using method C (stirring for 20 min) as a 50:50 mixture of C-5 diastereomers **45** and **46**. Analytical samples of **45** and **46** were isolated by flash chromatography (eluent hex/EtOAc 1:2) as colorless oils.

*Compound **45***: R_f = 0.6 (hexane/EtOAc 1:2); $[\alpha]_D^{20}$ = −40 (c = 0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3H), 3.10–3.19 (AB part of ABX system, J_{AB} = 13.4, J_{AX} = 8.9, J_{BX} = 3.8 Hz, 2H), 3.97 (dd, J = 3.9 and 19.4 Hz, 1H), 4.23–4.46 (m, 4H), 4.5–4.7 (m, X part of ABX system, 1H), 7.13–7.56 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 21.4, 29.7, 71.4, 72.0, 75.6, 84.0, 86.3, 89.5, 124.0, 127.6, 127.8, 127.9, 128.4, 130.0, 140.2, 141.4, 141.5 ppm; MS (FAB+): *m*/z (%): 513.2 (100); HRMS (FAB+): *m*/z: calcd for $C_{32}H_{33}O_4S$: 513.2100 $[M+1]^+$; found: 513.2103.

*Compound **46***: R_f = 0.7 (hexane/EtOAc 1:2); $[\alpha]_D^{20}$ = −118 (c = 0.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H), 2.96–3.12 (AB part of ABX system, J_{AB} = 13.9, J_{AX} = 3.5, J_{BX} = 9.2 Hz, 2H), 4.06 (d, J = 3.3 Hz, 1H), 4.11–4.14 (m, 1H), 4.38–4.52 (AB system, J_{AB} = 11.7 Hz, 2H), 4.66–4.89 (AB system, J_{AB} = 11.6 Hz, 2H), 4.70 (s, 1H), 5.20–5.28 (X part of ABX system, J_{AX} = 3.5, J_{BX} = 9.2 Hz, 1H), 7.28–7.54 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): δ = 21.5, 29.7, 72.3, 75.3, 76.2, 79.2, 123.9, 127.0, 127.9, 128.3,

128.4, 130.2, 136.3, 1420.3 ppm; MS (EI): *m*/*z* (%): 513 $[M+H]^+$ (58), 451 (100), 217 (26), 149 (23); HRMS (ESI): calcd for $C_{32}H_{33}O_4S$: 513.2094 $[M+1]^+$; found: 513.2119.

Compound 52: Tetrahydrofuran **52** was obtained from (*R*,*SS*)-**51** by using method C (stirring for 1 h). Purification by flash chromatography (eluent hexane/EtOAc 1:3) gave a 95:5 mixture of diastereoisomers **52** and **53** in 52% yield. $R_f = 0.44$ (hexane/EtOAc 1:3); $[\alpha]_D^{20} = -50.0$ ($c = 0.04$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.66$–1.87 (m, 2H), 2.11–2.21 (m, 1H), 2.27–2.36 (m, 1H), 2.39 (s, 3H), 2.88–3.00 (AB part of ABX system, $J_{AB} = 6.8$, $J_{AX} = 5.1$, $J_{BX} = 4.9$ Hz, 2H), 4.48–4.94 (X part of ABX system, $J_{AX} = 5.1$, $J_{BX} = 4.9$ Hz, 1H), 4.92 (t, $J = 7.1$ Hz, 1H), 7.19–7.52 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 21.4$, 31.5, 33.9, 64.7, 73.7, 81.2, 123.8, 125.7, 127.3, 128.3, 130.0, 141.5, 142.5 ppm; MS (EI): *m*/z (%): 323 $[M+Na]^+$ (13), 301 $[M+H]^+$ (38), 139 (23); HRMS (ESI): calcd for $C_{18}H_{21}O_2S$: 301.1256 $[M+H]^+$; found 301.1268.

Compound ***53***: $[\alpha]_D^{20} = -161$ ($c = 0.65$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta =$ 1.19–1.37 (m, 1H), 1.71–1.83 (m, 1H, CH), 1.90–2.04 (m, 1H), 2.22–2.32 (m, 1H), 2.42 (s, 3H), 2.95–2.98 (m, 2H), 4.73–4.82 (m, 1H), 5.04 (t, $J =$ 7.2 Hz, 1H), 7.31–7.60 ppm (m, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 21.4$, 32.5, 35.3, 65.0, 73.7, 80.8, 123.8, 125.5, 127.4, 128.4, 130.0, 141.6, 142.8 ppm; MS (EI): *m*/*z* (%): 299 $[M+H-2H]^+$ (64), 159 (19), 139 (100); HRMS (ESI): calcd for $C_{18}H_{19}O_2S$: 299.1100 $[M+H-2H]^+$; found: 299.1095.

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