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Polysubstituted Oxygen Heterocycles by a Reformatsky-Type Reaction/Reductive Cyclization Approach from Enantiopure β-Ketosulfoxides

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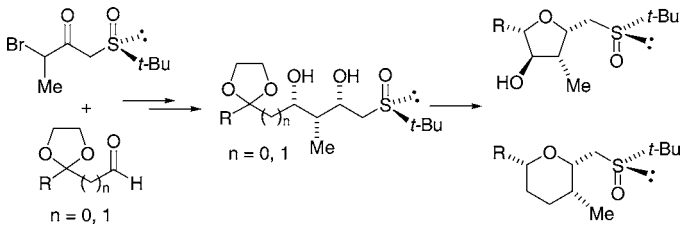
ABSTRACT



The stereoselective synthesis of tetrasubstituted tetrahydrofurans and trisubstituted tetrahydropyrans bearing a sulfoxide was achieved by reductive cyclization (Et_3SiH/TMSOTf) from the corresponding enantiopure hydroxy ketones protected as a dioxolane. These derivatives are easily accessible from a Reformatsky-type reaction between α-bromo-α′-sulfinyl ketones and protected α- or β-ketoaldehydes, followed by diastereoselective reduction of the resulting β-ketosulfoxide.

Stereoselective approaches to polysubstituted oxygen heterocycles continue to attract considerable attention due to the widespread appearance of these structural motifs in a large number of biologically active natural compounds, including structurally complex ionophore antibiotics,[1] marine macrolides,[2] brevetoxins,[3] and other polycyclic ethers.[4] Among the problems encountered when dealing with these structures, the stereoselective construction of tri- or tetrasubstituted tetrahydrofurans (THF) and tetrahydropyrans (THP) is one of the most challenging tasks that has been resolved using different strategies.[5] We have recently developed 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. In turn, these acyclic precursors were accessible through the well-established diastereoselective reduction of an adequately functionalized β-ketosulfoxide.[6] In spite of the important advances reached, efficient asymmetric syntheses of polysubstituted precursors were required to extend the method to structurally more complex cyclic ethers.

In connection with a project directed to extend the applications of sulfoxides in asymmetric synthesis,[7] we have recently described a highly stereoselective Reformatsky-type reaction of chiral nonracemic α-bromo-α′-sulfinyl ketones with aldehydes in the presence of SmI_2 giving access to

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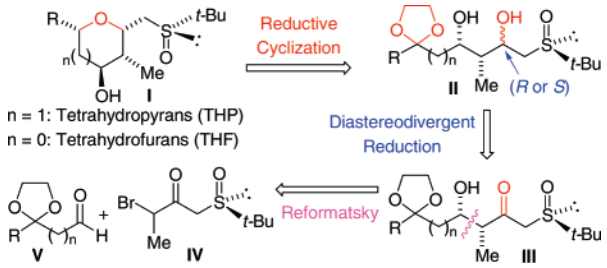
enantiomerically pure 2-methyl-1,3-diol moieties.[8] The short and efficient access to such highly substituted fragments encouraged us to check if the combination of the reductive cyclization and the Reformatsky-like process could open the way to the stereocontrolled synthesis of highly substituted oxygen heterocycles. We now report our preliminary results, evidencing that 2,3,6-trialkyl-substituted THP and 2,3,5-trialkyl-4-hydroxy-substituted THF are available in three steps starting from α-bromo-α′-sulfinyl ketones. Three or four new stereogenic centers can be created using an enantiomerically pure *tert*-butyl sulfoxide as the unique source of chirality. The accessibility of both diastereoisomeric hydroxy sulfinyl moieties by the well-established DIBALH and Lewis acid/DIBALH reduction[9] of the corresponding β-ketosulfoxides[10] prompted us to investigate the behavior of the acyclic derivatives bearing the two possible relative configurations at the β-hydroxysulfinyl moiety.

The retrosynthesis envisaged to THP or THF derivatives **I** (Scheme 1), based on the reductive cyclization process,

Scheme 1. Retrosynthetic Analysis for the Stereoselective Synthesis of Highly Substituted THP and THF Derivatives



required the preparation of acyclic dihydroxy ketones **II** ($n = 0, 1$), in turn available with both *R* or *S* configuration at the β-hydroxy sulfinyl moiety using the diastereodivergent reduction of monoprotected diketosulfoxides **III**. We envisaged the use of a SmI_2-promoted Reformatsky reaction to assemble the enantiopure bromosulfinyl ketone **IV** with protected α- ($n = 0$) or β- ($n = 1$) ketoaldehydes **V**. The synthetic versatility of the sulfoxide present in the final targets, which could be transformed into other functional groups, could increase the interest of our method later for future applications.

To evaluate our retrosynthetic approach to the tetrahydropyranyl derivatives, we decided to synthesize two series of analogues bearing a methyl and a propyl substituent due to the accessibility of the required β-ketoaldehydes, easily prepared as protected dioxolanes using known methods.[11]

Enantiomerically pure γ-bromo-β-ketosulfoxide **3**, necessary for the Reformatsky-like reaction, was synthesized, as previously reported,[8b,12] by reaction of the lithium anion derived from (*R*)-methyl *tert*-butyl sulfoxide (**2**) with methyl 2-bromopropionate **1**, in 95% yield (Scheme 2). The SmI_2-promoted reaction between **3** and the aldehyde **4** gave the Reformatsky adduct **5** with 73% yield and 93:7 dr. It is worth mentioning that the success of this transformation required the use of a recently prepared SmI_2/THF solution. The analogue reaction with aldehyde **6** led to hydroxy β-ketosulfoxide **7** in 86% yield and 93:7 dr (Scheme 2).

The reduction of **5** and **7** with DIBALH gave rise to the exclusive formation of 1,3-*syn*-diol derivatives **8** and **9** as a consequence of the hydride attack from the *re* face of the carbonyl group directed by the sulfoxide.[9] When the reduction was carried out with DIBALH/$Yb(OTf)_3$, the corresponding *anti*-2-methyl-1,3-diols **10** and **11** were formed with good yields and selectivities (Scheme 2). We were able to obtain diastereomerically pure **8**, **9**, **10**, and **11** after chromatographic separation. The absolute configuration of the major diastereomer **11** was confirmed by X-ray diffraction (Figure 1).[13]

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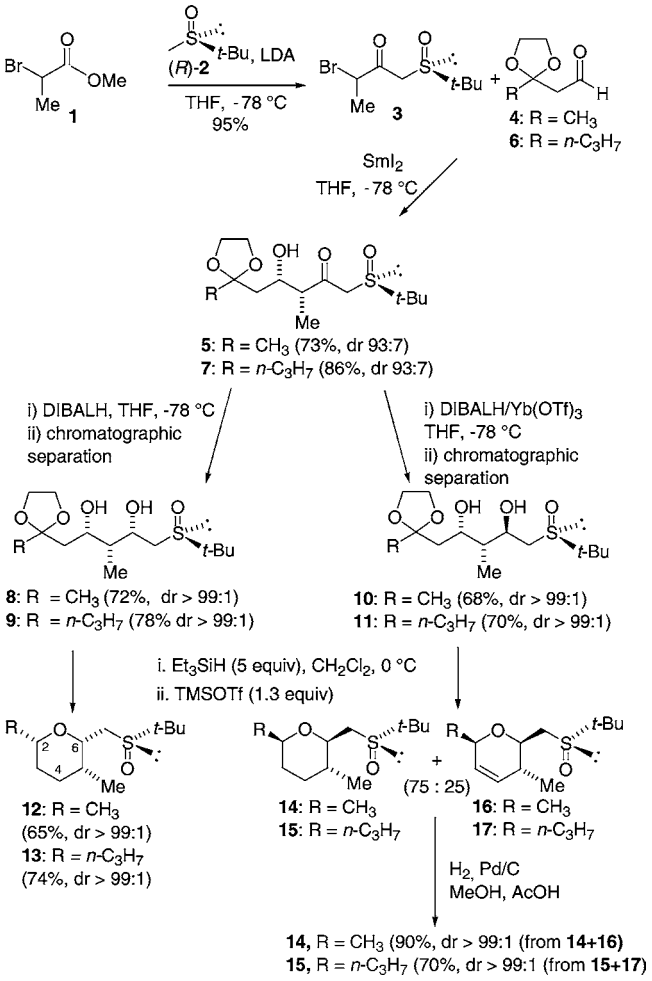
Scheme 2. Stereoselective Synthesis of Trisubstituted THPs **12**−**15**



Up to now, we had always applied the reductive cyclization of β-hydroxy sulfinyl ketones to the free carbonyl derivatives.[6] We then tried to deprotect the dioxolane group of **8**, but all attempts were unsuccessful due to the formation of complex reaction mixtures where different cyclized hemiacetals and mixed acetals were detected. Taking into account that the reductive cyclization of hydroxy ketones was proposed to occur from the intermediate formation of a cyclic oxocarbenium ion resulting from a mixed acetal,[6d] we decided to check the reductive cyclization on the dioxolane itself. To our delight, upon treatment of **8** with an excess of Et_3SiH in CH_2Cl_2 at 0 °C and further addition of TMSOTf, a clean reaction mixture resulted in a very short time (30 min), from which tetrahydropyran **12** could be isolated in 65% yield as a unique diastereomer. The structural assignment of **12** (^{1}H NMR NOESY and COSY experiments) revealed the *cis* disposition of the substituents situated at C-2 and C-6 on the heterocycle, as well as the lack of the free hydroxy group, non-engaged in the cyclization process, situated at the β-carbon of the dioxolane moiety in the precursor **8**. A similar result was obtained when the *syn*-1,3-diol **9** was treated with Et_3SiH/TMSOTf, giving in this case **13**, lacking the OH at C-4, isolated in 74% yield. The behavior of epimeric acyclic *anti*-1,3-diols **10** and **11** when treated with Et_3SiH/TMSOTf was similar, furnishing, respectively, a 75:25 mixture of tetrahydropyrans **14** or **15** and dihydropyrans **16** or **17**, as unique diastereoisomers. These results evidenced that the loss of the β-OH was independent of its relative stereochemistry and suggested the favored elimination to a double bond as the driving force for this behavior. On this basis, we propose the mechanism indicated in Scheme 3 to explain the observed results. Activation of the

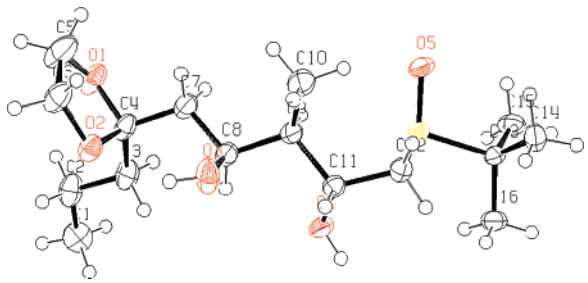
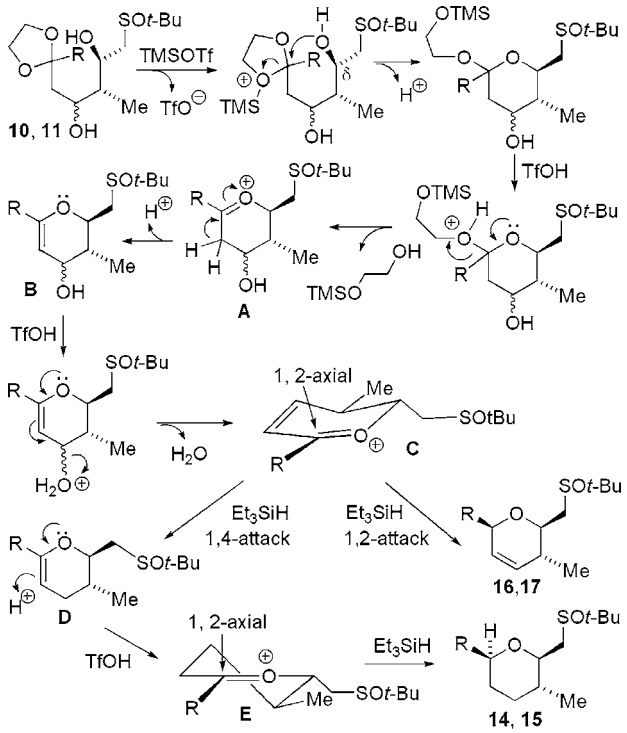


Figure 1. X-ray structure of **11**.

Scheme 3. Mechanistic and Stereochemical Pathway Explaining the Formation of **14**−**17**



ketal of **10** and **11** by the TMSOTf favors the dioxolane ring opening and subsequent nucleophilic attack of the OH at the

(13) We thank Dr. André DeCian for assistance with the analysis of the crystal structure (Service commun Rayons X, 4 rue Blaise Pascal 67070 Strasbourg cedex e-mail: sercomrx@chimie.u-strasbg.fr).

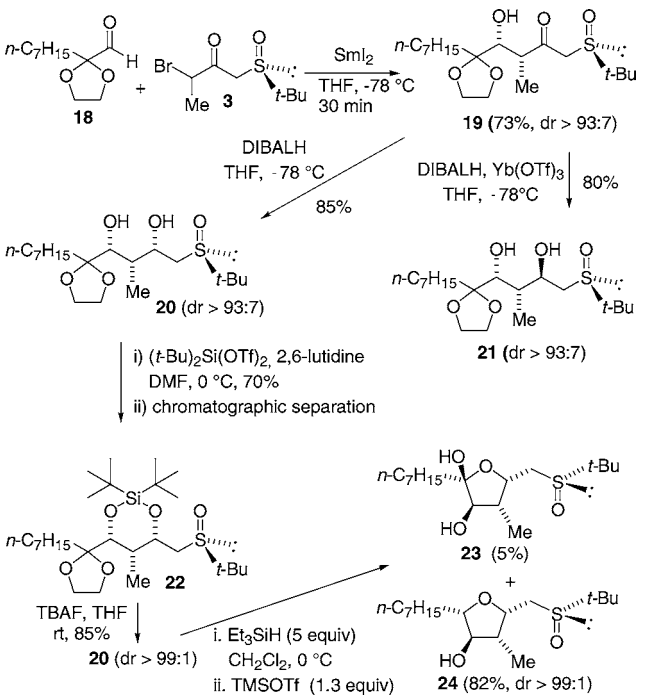
δ position to give an intermediate mixed ketal, precursor of the oxocarbenium ion **A**. The increased acidity of the CH_2 group situated vicinal to the hydroxy group facilitates the elimination of a proton to give the dihydropyran **B**. Protonation of the OH, which occurs independently of its configuration, was followed by H_2O elimination, producing the key oxonium intermediate **C**. The axial approach of Et_3SiH to the oxonium carbon (1,2-attack), favored by the higher stability of the half-chair-like transition state, explains the stereoselective formation of **16** and **17**, isolated in the reactions of **10** and **11**. The 1,4-attack of the Et_3SiH to intermediate **C** gives dihydropyran **D** whose protonation and subsequent stereoselective reduction justify the formation of **14** and **15** (Scheme 3).

The mixtures **14**/**16** and **15**/**17** were finally hydrogenated (H_2, Pd/C, MeOH/CH_3COOH) to afford saturated derivatives **14** and **15** in 90 and 70% yield, respectively.

En route to tetrahydrofuran derivatives, we applied a similar reaction sequence to the protected α-ketoaldehyde **18**,[8b] whose reaction with (*R*)-α-bromo-α′-*tert*-butylsulfinyl ketone **3** in the presence of SmI_2 gave rise to the Reformatsky adduct **19** in 73% yield as a 93:7 mixture of *syn* and *anti* diastereoisomers that could not be separated. Diastereoselective reduction of the β-ketosulfoxide moiety of **19**, either with DIBALH or with DIBALH/$Yb(OTf)_3$, afforded a similar nonseparable 93:7 mixture of 1,3-diols **20** and **21** with excellent yields (Scheme 4). In accordance with these results, both reductions must occur with a complete diastereoselection. We were able to obtain diastereomerically pure **20** after silylation to **22**, flash chromatography, and TBAF deprotection (Scheme 4). When we performed the Et_3SiH/TMSOTf-promoted reductive cyclization process on compound **20**, we were pleased to observe, together with a minor amount of cyclized hemiketal **23**, the formation of diastereo- and enantiomerically pure tetrasubstituted tetrahydropyran **24**, which was isolated in 82% yield. The relative and absolute configuration of **24** was established by ^1H NMR NOESY and COSY experiments. The reaction was again highly diastereoselective, leading to the exclusive formation of the 2,5-*cis*-disubstituted system. Stereoelectronic factors similar to those proposed in the case of intermediate **E** of Scheme 3 must be responsible for the observed stereochemical course.

In conclusion, the three-step sequence combining the asymmetric Reformatsky-like reaction between an enantiopure α-bromo-α′-sulfinyl ketone and an adequately protected ketoaldehyde, the diastereoselective reduction of the corresponding β-ketosulfoxide, and the Et_3SiH/TMSOTf-promoted reductive cyclization is an efficient route to enantiomerically pure highly substituted THF and THP derivatives. This strategy should allow the synthesis of biologically active molecules bearing such moieties. Moreover, the versatility of the sulfinyl group existing on the cyclic ethers increases the interest of this approach since it can be easily transformed into different groups.

Scheme 4. Stereoselective Synthesis of Tetrasubstituted THF **24**



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Supporting Information Available: Experimental procedures and compound characterization with copies of ^1H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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