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A Rational Approach to Chiral α-Hydroxy Aryl Ketones from Chiral Aryl Epoxides via Regioselective, Stereo Retentive Oxidative Epoxide Opening: Its Application to the Synthesis of Antifungal Sch 42427/SM 9164.

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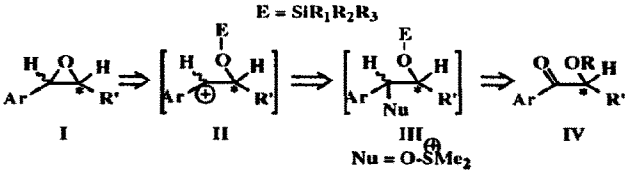
Abstract: A new, mild method for the direct conversion of chiral aryl epoxides to hydroxy-protected chiral α-hydroxy aryl ketones with complete retention of the chiral center and good regioselectivity has been established. An application of this new reaction to the synthesis of antifungal Sch 42427/SM 9164 is also described.

Chiral α-hydroxy aryl ketones are intermediates of interest for the synthesis of natural/biologically active compounds.[1] To this end a direct hydroxylation of aryl ketones[1a-c] with good to excellent enantiomeric excesses (*ee*), or a selective oxidation of optically active diols in moderate to good yields has been described.[1d] For the synthesis of Sch 42427/SM 9164 (1) *O*-protected α-hydroxy ketone **6** is a key intermediate of interest.[2,3] We report here a novel approach to the synthesis of such compounds.

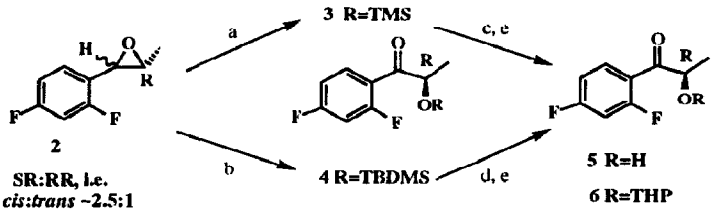
In recent years elegant catalytic methods for the preparation of chiral aryl epoxides with excellent *ees* have been introduced.[4] The availability of these chiral epoxides makes them attractive starting materials for the synthesis of α-hydroxy aryl ketones. Additionally, a practical synthesis of chiral epoxide **2** needed for the synthesis of **1** has been published where the chiral center of (S)-2-chloropropionic acid was manipulated to generate the aromatic epoxide **2** preserving the *ee* at the chiral center.[3] Although oxidative opening of epoxides to α-hydroxy ketones under strongly acidic conditions has been reported,[5] this method does not predict the regio chemical or the chiral outcome, and has been usually used to open either the symmetrical epoxides, or primary aryl epoxides. In fact, the use of DMSO/BF_3•Et_2O or variations thereof led[5a,b] to ~5% yield of the desired alcohol **5**. The use of DMSO/CF_3SO_3H,[5c] after some optimization, resulted in 35-40% of the desired alcohol **5**.[6] This is not surprising in view of the reported instability of α-hydroxy arylketones in general, and of compound **5** in particular to strong acid or to oxidizing conditions.[7] We sought to develop mild conditions in which the stereo *and* regiochemistry could be controlled, and whereby α-hydroxy aryl ketones could be generated as hydroxy-protected species so as to improve their stability. This article describes these findings.

Scheme A

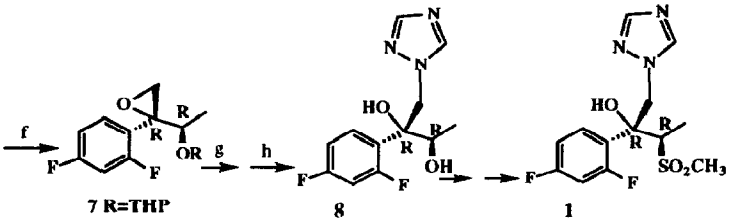


This work was based on the following rationale (**Scheme A**). The opening of aromatic epoxide **I** should be favored towards the formation of the benzylic carbonium ion intermediate equivalent of **II**.[8] Although DMSO is not a

strong nucleophile, in the absence of other nucleophiles it should suffice to trap the carbonium ion. Since sulfoxonium intermediate such as **III** can be oxidized,[9] and DMSO is inexpensive, it appeared to be a good solvent of choice to examine this hypothesis. Next, it was imperative that the oxygen anion of **II** is trapped quickly, without generating another nucleophile stronger than DMSO, to obtain the synthetically versatile oxygen-protected product. Furthermore, it would be synergistic to have a moiety in this trapping reagent that would enhance the epoxide opening as the opening of epoxide in DMSO is slow, and requires heat.[5] Commercially available trimethylsilyl triflate (TMSOTf), and *t*-butyldimethylsilyl triflate (TBDMSOTf) meet these requirements, where the silyl moiety can coordinate with the epoxide oxygen to facilitate ring opening, and silylate the oxygen (as triflate is a good leaving group). The triflate anion thus generated is a weak nucleophile that would not interfere with DMSO's ability to trap the carbonium ion of **II** (and in fact stabilize **III** by forming its salt). Finally, it also appeared that the chirality of the carbon bearing the R' group can be preserved during the above reaction for the following reasons. Abstraction of the tertiary hydrogen on the stereogenic center carrying a bulky trialkylsilyl- protected oxygen would be a much less favored process over either the removal of one of the six more acidic primary hydrogens on the methyl groups of **III** which subsequently would pull the benzylic hydrogen via a five-membered transition state (such transition statet has been postulated previously)[9] or to the removal of the benzylic hydrogen directly, either of which would lead to the oxidized product **IV**. In fact, the results of this study indicate that the chirality remains intact during the above transformation.



Scheme B



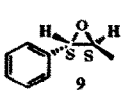
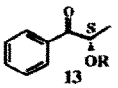
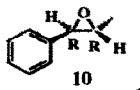
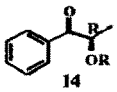
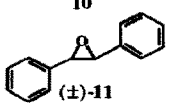
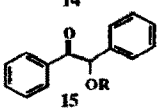
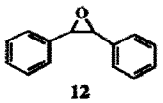
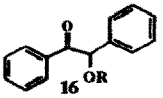
a) (i) DMSO, 1.2eq.TMSOTf, RT; (ii) CH_2Cl_2, -78°C, 5eq Et_3N, 78%; b) (i) DMSO, 1.2eq.TBDMSOTf, RT; (ii) CH_2Cl_2, -78°C, 5eq.Et_3N. 80%; c) MeOH, aq. citric acid, RT, 90%; d) MeOH, 4N HCl, 0°C, 85%; e) DHP, PPTS, RT, quant.; f) Me_3SOI/DMSO/60% NaH then add **6** in THF, RT;g) DMF/sodium triazole, 70°C; h) aq. HCl or pTSA/MeOH/H_2O, 60% for three steps (from **6**)

The desired epoxide **2** (prepared as in ref. 3, % *ee* at the center of interest ≥ 96 with a *cis:trans* ratio of ~2.5:1) was used to evaluate the above hypothesis. As indicated in **Scheme B**, the conversion of epoxide **2** to the *O*-protected α-hydroxyketones **3** (with TMSOTf), and **4** (with TBSMSOTf) in DMSO proceeded in good yields[10] with retention of chirality [%*ee* ~94 as judged by ^1H NMR with Eu(hfc)$_3$][13] at the alcohol carbon. Although, in theory, both **3**, and **4** could be used for the preparation of **1**,[11] for the purpose of meeting the delivery needs of **1**, and to demonstrate the

usefulness of this reaction, they were deprotected to obtain **5**, again in good yields. The *%ee* of **5**, obtained from either **3** or **4** was ≥94 (chiral HPLC)[12] confirming the *%ee* established by NMR above. Furthermore, with known chemistry, **5** was transformed to the tetrahydropyranyl-protected alcohol **6** which, in turn, was converted to the key advanced intermediate **7** (with expected threo:erythro ratio of 7:1)[2,3] for the synthesis of **1**. The details of the conversion of alcohol **6** to **1** via the diol derived from **7** along with an independent chiral synthesis of **6** will be published in a separate paper.

Since chiral 1-phenylpropylene oxides **9** and **10** (*%ee* >98, both with *trans* configuration) are commercially available, they were converted to the known chiral α-hydroxy ketones **13** and **14** (R=H for both),[1] respectively, to further the above reaction. As shown in **Table 1**, both reactions proceeded in very good yields of the desired products

Table 1: Epoxides to α-hydroxy ketones: Additional examples.

Substrate	Product	Yield; Chirality (*%ee*)[a]
 **9**	 **13**	**80%; S (>96)**
 **10**	 **14**	**83%; R (>96)**
 **(±)-11**	 **15**	**71%; NA**
 **12**	 **16** R = TMS	**85%; NA** NA= not applicable

a) The details of yields and *%ees* are described in the text.

(R = TMS) retaining the *%ees* at the alcohol center. Both of these compounds were deprotected (MeOH, aq. citric acid as described in **Scheme B**) to their alcohols, and were subjected to chiral HPLC[12] which confirmed the *ees* as well as the chiralities (by comparision with the authentic alcohols made by the procedure of Davis[1]). Next, this reaction was applied to sterically demanding (and commercially available) stilbene oxides **11**, and **12**. Again, the expected products were obtained in excellent yields. It is interesting to note that the *cis* epoxide **12** led to better yields than the *trans* epoxide **11**. This is of special interest for the synthesis of **1**, as the preparation of **2** from α-haloketone[3] allows for a manipulation of *cis* vs. *trans* stereochemistry. It is conceivable that **2** with *cis:trans* ratio of >5:1 may yet lead to better isolated yields of **3** and **4** than the one depicted in **Scheme B**. Also under consideration is the use of cosolvents (e.g., CH_2Cl_2, Tol., *t*-BuOMe, etc.) that would allow a temperature below 15°C for the above reaction, possibly improving the overall yeilds of this reaction. Work in this regard will be described in the future.

In summary, a new procedure for the conversion of chiral arylepoxides to *O*-protected chiral α–hydroxy arylketones in very good to excellent yields, has been established.[14] This new method has been applied to the synthesis of Sch 42427.

Acknowledgments: We thank Dr. Mohinder Puar for ascertaining *ees* of the silyl-protected alcohols with ^{1}H-NMR.

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6 The rest of the mass was accounted for by the diol (~25%) and the benzylic hydroxy ketone (~30%) generated from either 3or 5 (ref.7). Additionally, two byproducts in small amounts were also formed in these reactions.

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10 The unoptimized yields reported in this manuscript represent the product content in the worked up reactions. The rest of the mass balance was accounted for by the unreacted substrates (in small amounts), the hydrolyzed products, and the regio isomers. A detailed account will be available in a full paper.

11 This would be ideal as it would save steps for deprotection/protection with a new group.

12 Chiracel OB®, 220nm, 4-7% *i*-PrOH/hexane, flow ~0.7-1.1 ml/min. The base line separations of the enantiomers were established by using the racemic alcohols (prepared according to ref. 7a).

13 Enantiomeric excesses by ^{1}H NMR (Varian XL-400 MHz) were determined in $CDCl_3$.

14 Recently, and subsequent to the completion of this work, a similar procedure for the synthesis of α-hydroxy acylsilanes has been used: Wicha, J.; Raube P. *J. Org. Chem.*, **1994**, *59*, 4355.

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