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Synthesis and Trimethylaluminum Additions on γ-Hydroxy-δ-sulfinyl and Sulfonyl Enoates

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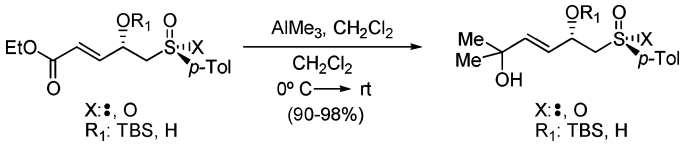
ABSTRACT



The stereoselective synthesis of epimeric (*R*)- and (*S*)-γ-hydroxy-δ-p-tolylsulfinyl (or sulfonyl) enoates is reported. Reaction with $AlMe_3$ occurred exclusively at the ester goup allowing a clean and high-yielding access to enantiopure 1,4-diols bearing a tertiary carbinol.

The ambiphilic character of organoaluminum reagents as well as their oxyphilicity[1] have been successfully utilized in interesting synthetic applications. Aluminum derivatives react very efficiently with β-ketosulfoxides,[2] giving excellent asymmetric inductions in DIBALH reductions[3] and in addition reactions,[4] which are a consequence of an efficient association between the sulfinyl oxygen and the organoaluminum compounds. Recently, we reported that organoaluminum reagents react with (*R*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinols,[5] leading to the 1,4-conjugate addition products in a highly chemoselective and π-facial diastereoselective manner with good yields and mild conditions. This high reactivity was surprising because such an easy conjugate addition had only been found in a few cases for simple alanes reacting with enones that can adopt an s-*cis* conformation[6] or cyclopentenones with a hydroxy group at the δ-position[7] or in the presence of some transition metals.[8] The existence of an OH at C-4 and a sulfoxide in the remote position from the α,β-unsaturated moiety of the *p*-quinol seemed to play an essential role in assisting the transfer of the alkyl group. The role of the γ-hydroxy group in directing the site and face selectivity of 1,4-conjugate additions had been pointed out in reactions of similar *p*-quinol derivatives[9,10] and acyclic

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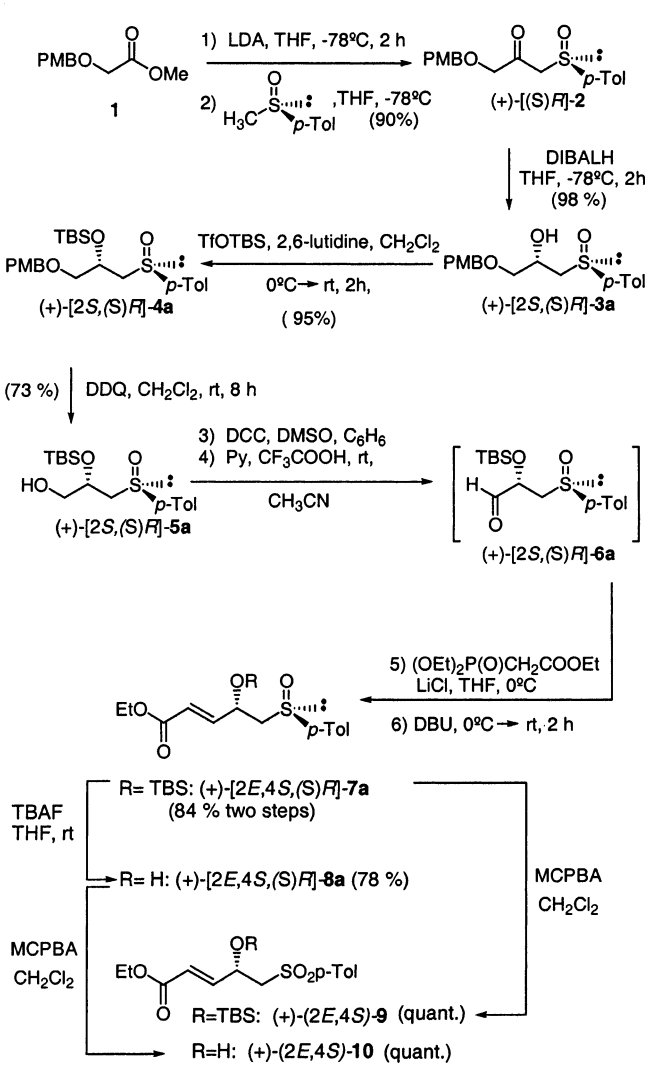
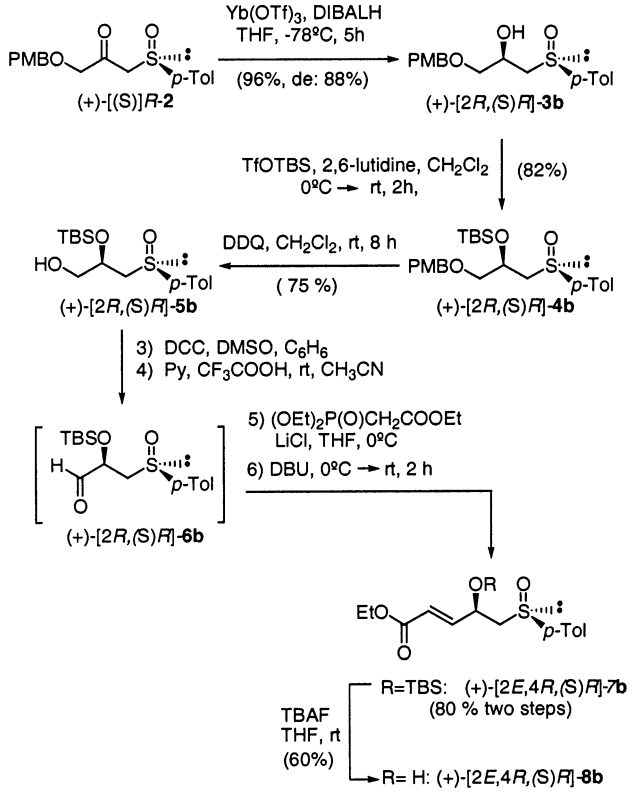
Scheme 1. Synthesis of γ-Hydroxy-δ-sulfinyl and Sulfonyl Enoates **8a**, **9**, and **10**



systems[10] with Grignard and organolithium reagents. Nevertheless, the behavior of acyclic α,β-unsaturated systems bearing a γ-hydroxy-δ-sulfinyl moiety, similar to that found in [(*p*-tolylsulfinyl)methyl]-*p*-quinols, had never been investigated. The accessibility of both diastereomeric hydroxy sulfinyl moieties by the well-established DIBALH and $ZnBr_2$/DIBALH reduction of enantiomerically pure β-keto sulfoxides precursors[3] prompted us to investigate the behavior of the acyclic enoates **8**, bearing both possible relative configurations at the β-hydroxysulfinyl moiety, upon reaction with $AlMe_3$. The corresponding enantiopure hydroxy sulfone, easily available from the sulfoxides, was also of interest since the sulfonyl group[11] is very useful for further synthetic transformations. We now report on a new alkylation process on chiral epimeric sulfinyl enoates **8** and sulfone **10** (Scheme 1), in which the sulfur function has a pronounced effect in promoting the otherwise difficult addition to the ester.

Scheme 2. Synthesis of γ-Hydroxy-δ-sulfinyl Enoate **8b**



The synthetic sequence leading to enantiomerically pure ethyl 4-hydroxy-5-(*p*-tolylsulfinyl)-2-pentenoate [2*E*,4*S*,(S)-*R*]-**8a** is outlined in Scheme 1. Methyl *p*-methoxybenzyloxy acetate **1** was submitted to reaction with the lithium anion derived from [(S)*R*]-methyl *p*-tolylsulfoxide[12] to give the β-ketosulfoxide **2**,[13] whose reduction with DIBALH afforded [2*S*,(S)*R*]-**3a** as a single diastereomer in a 69% yield for the two steps. After protection of the secondary carbinol as a TBS (TfOTBS, 2,6-lutidine, 95% yield), the primary group of **4a** was deprotected with DDQ, giving rise to compound **5a** (73% yield). The unstable aldehyde **6a** resulting from Moffat oxidation of **5a** was immediately submitted to a Horner−Wadsworth−Emmons reaction to give the (*E*)-enoate **7a** in an 84% overall yield for two steps from **5a**. Enantiopure hydroxy pentenoate [2*E*,4*S*,(S)*R*]-**8a** was finally obtained after deprotection of the TBS group (TBAF, 78% yield). The respective sulfonyl derivatives **9** and **10** were furnished, in a quantitative yield, by oxidation of the sulfoxide moiety to sulfone when compound **7a** and free carbinol **8a** were treated with a solution of MCPBA in CH_2Cl_2.

The synthesis of epimer [2*E*,4*R*,(S)*R*]-**8b** was achieved by a similar reaction sequence from the hydroxy sulfoxide [2*R*,-(S)*R*]-**3b** (Scheme 2). Surprisingly, the attempts to synthesize

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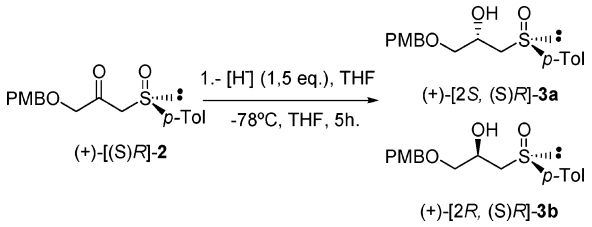
Table 1. Reduction of [(S)*R*]-*β*-ketosulfoxide **2** with Hydrides



entry	hydride	**3a**:**3b**	yield (%)
1	$ZnCl_2$/DIBALH[a]	50:50	62
2	$ZnBr_2$/DIBALH[a]	67:33	65
3	ZnI_2/DIBALH[a]	50:50	60
4	$LiAlH_4$	24:76	41
5	$NaBH_4$	36:64	99
6	Bu_4NBH_4	38:72	99
7	$Yb(OTf)_3$/DIBALH[a]	8:92	96

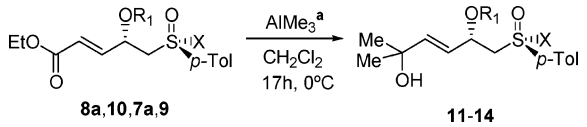
[a] DIBALH (1 M in heptane); dr was determined by ^{1}H NMR from the crude reaction mixture.

[2*R*,(S)*R*]-**3b** by the DIBALH/ZnX_2 (X = Cl, Br, I)[3] reduction of *β*-ketosulfoxide **2** were poorly stereoselective and led to an almost equimolecular mixture of (2*R*)- and (2*S*)-diastereomers **3a** and **3b**, respectively (Table 1, entries 1−3).[14] The presence of an oxygenated function at C-1 of the *β*-keto sulfoxide **2**, which could compete with the sulfinyl oxygen in the chelation with the Zn atom, could be in the origin of this lack of selectivity.

To improve these results, we checked other hydrides such as $LiAlH_4$ (Table 1, entry 4), $NaBH_4$ (Table 1, entry 5), and Bu_4NBH_4 (Table 1, entry 6). In all cases, the major formation of [2*R*,(S)*R*]-**3b** was observed, but the diasteromeric ratio was not in the range of utility. Finally, the treatment of *β*-ketosulfoxide **2** with $Yb(OTf)_3$[15] and DIBALH (Table 1, entry 7) afforded a mixture of [2*R*,(S)*R*]-**3b** and its epimer in a **3b**/**3a** ratio of 92:8. The epimers could not be separated at this stage since the mixture was isolated in a 96% yield by flash column chromatography.

The absolute configuration at the hydroxylic carbons of epimeric carbinols **3** could be deduced not only from the mechanism already proposed for the reduction of such *β*-ketosulfoxides[3,16] but also from the ^{1}H NMR spectra of the products. From the numerous examples of reduction of

Table 2. Reactions of **8a**, **10**, **7a**, and **9** with $AlMe_3$



entry	enoate	product	yield (%)
1	**8a** (X = **:** ; R_1 = H)	**11**	90
2	**10** (X = O; R_1 = H)	**12**	98
3	**7a** (X = **:** ; R_1 = TBS)	**13**	96
4	**9** (X = O; R_1=TBS)	**14**	98

[a] A 2 M solution in heptanes (4 equiv) was added to a 0.2 M solution of enoate **8a**, **10**, **7a**, or **9** in CH_2Cl_2 at 0 °C.

β-ketosulfoxides reported, a noticeable difference in the nonequivalence of the methylene hydrogens α to the sulfoxide for the [*R*,(S)*R*]- and [*S*,(S)*R*]-epimers has been observed. For the [*R*,(S)*R*]-configuration, the $\Delta\nu$ value between these two hydrogens is smaller {$\Delta\nu$ = 26 Hz in [*R*,(S)*R*]-**3b**} than in the [*S*,(S)*R*]-diastereomer {$\Delta\nu$ = 81 Hz in [*S*,(S)*R*]-**3a**}.

Compound **3b** was transformed into **7b** and **8b** (Scheme 2) following a reaction sequence similar to that used for the epimers **7a** and **8a** shown in Scheme 1. Compound **7b** was obtained diastereomerically pure by chromatographic purification of the crude resulting from the olefination reaction.

With the desired enoates in hand, we began the study of their reactions with organometallic reagents in order to determine the preference of the different reagents for 1,2- and 1,4-additions. We first tried the reaction of **8a** with BrMgMe (4 equiv in ether) and observed the formation of a (50:50) mixture of distereomeric 1,4-addition products at 0 °C and a mixture of 1,2- and 1,4-addition products at room temperature. Surprisingly, when a CH_2Cl_2 solution of **8a** was added over a 2 M solution of $AlMe_3$ in heptane (4 equiv), the clean formation of the tertiary carbinol [3*E*,5*S*,(S)*R*]-**11** (90% isolated yield) (Table 2, entry 1), resulting from a double addition on the ester group, was observed. The hydroxy sulfone **10** behaves similarly under the same conditions. The tertiary carbinol **12**, resulting from the exclusive addition of the $AlMe_3$ to the ester groups, was isolated in a 98% yield.

To know if the free OH had an essential role in these reactions, the TBS-protected sulfoxide **7a** and sulfone **9** were submitted to reaction with $AlMe_3$. Again, the corresponding tertiary carbinols **13** and **14** were formed in 96 and 98% yield, respectively. The reactivity shown by the aluminum reagent with the ester groups was rather surprising due to the inertness of such a functional group to these organometallic derivatives. The (4*R*)-epimeric enoate [2*E*,4*R*,(S)*R*]-**8b** did not react under the conditions where **8a** evolved in 17 h. Previous work had shown that ordinary esters are inert to $AlMe_3$ and reaction occurred only with $AlMe_3$/DMEDA complex in refluxing toluene.[17] The reactivity of the ester

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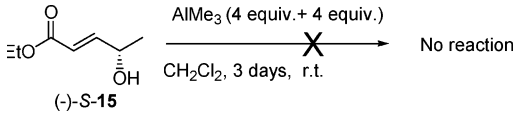
Scheme 3. Reactivity of (−)-**15** with $AlMe_3$



group is enhanced in glyconolactones[18] when the $AlMe_3$ can be intramolecularly complexed with a donating group proximal to the lactone, which assists the transfer of a methyl group.

In the case of substrates **8a**, **10**, **7a**, and **9**, the addition of $AlMe_3$ was only completed in the presence of an excess of the reagent.

With free OH derivatives **8a** and **10**, the first equivalent of $AlMe_3$ added to the reaction mixture must react with the OH to form an unreactive aluminum alkoxyde, which evolves into the double-addition product when an excess of the reactant is added. The presence of different basic centers in the starting molecules justifies the necessity of an excess of $AlMe_3$. The existence of the sulfur functions, which could also assist the transfer of the methyl group from $AlMe_3$, prompted us to investigate the role of the γ-oxygenated function in such a process on substrate **15**, which lacks the sulfur moiety. Under the conditions shown in Scheme 3, ethyl 4-hydroxy-2-pentenoate (2*E*,4*S*)-**15**[19] remained unchanged after 3 days at room temperature, even when 8 equiv of $AlMe_3$ were added. This lack of reaction pointed to an essential role of the sulfoxide or sulfone in assisting the aluminum reagent to transfer the methyl groups to the ester. A species such as **A** represented in Figure 1, where the electrophilic aluminum atom, associated to both the sulfinyl or sulfonyl oxygen and the ester, could be responsible for the observed results with the (4*S*)-epimer.

The inertness of the (4*R*)-epimer could be due to the unstability of the analogue species where the aluminum

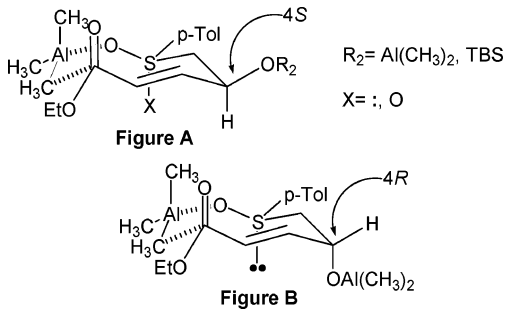


Figure 1. SOTol or SO_2Tol group assisting the transfer of Me from $AlMe_3$.

alkoxide substituent should adopt an unfavorable axial disposition (Figure 1,**B**).

The enantiopure 1,4-diol moiety present in compounds **11**−**14** is found in a group of natural products of the triterpenoid family.[20] The transformations reported here, allowing the synthesis of such fragments in mild conditions and high yields, open an easy access to the tertiary carbinol moiety from an α,β-unsaturated ester without competition with conjugate addition. $AlMe_3$, which fails to alkylate ordinary esters and γ-hydroxy-α,β-unsaturated analogues, is easily transferred in the presence of the sulfur function, whose role in assisting the transfer has been demonstrated.

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Supporting Information Available: Complete description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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