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Synthesis of α-Unsubstituted Aldol Adducts Utilizing Enantiomerically Pure β-Keto δ-Dioxolane Sulfoxides

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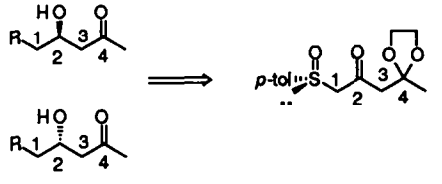
Abstract: We report an efficient means to synthesize either enantiomer of α-unsubstituted aldol adducts in high enantiomeric excess through the use of β-keto δ-dioxolane sulfoxide **4**. Through a short sequence of reactions, α-unsubstituted aldol products are obtainable in high yield.

The aldol reaction has become one of the most widely used reactions in organic synthesis to form carbon-carbon bonds with oxygen functionality in the 1,3 positions in a highly stereoselective manner.[1a-f] However, when chiral α-unsubstituted enolates are employed, the stereoselectivity of the reaction decreases resulting in the formation of both enantiomers of the aldol product.[2a,b] Researchers have developed successful methodologies to address this problem, including the use of new chiral auxiliaries and chiral bases.[2a,b] In this paper, we are reporting an approach to the synthesis of enantiomerically pure α-unsubstituted aldol adducts through the use of β-keto δ-dioxolane sulfoxides, as shown in Scheme 1.

The reduction of β-keto sulfoxides is a reliable and highly diastereoselective reaction.[3] By placing a masked carbonyl group at the δ-position, the aldol carbon backbone is then in place, and through several simple transformations, a variety of aldol substrates is obtainable. Since this study began, Solladie has recently reported the use of β,δ-diketo sulfoxides in synthesis,[4] but we wanted to investigate the reduction of β-keto δ-dioxolane sulfoxides. With the δ-ketone protected as its ketal, it will not interfere with subsequent reactions, and thus the functionalized sulfoxide can serve as a more versatile intermediate in organic synthesis.

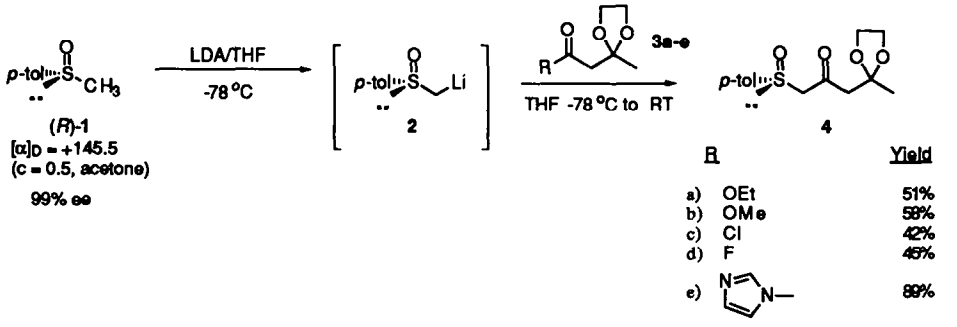
Scheme 1



Initial attempts to synthesize the β-keto δ-dioxolane sulfoxide **4** led to disappointing results, as illustrated in Scheme 2. For example, treatment of *R*(+)-methyl *p*-tolyl sulfoxide[5] with LDA and acylation of the resulting sulfinyl anion with the ethyl or methyl ketal ester derived from ethyl acetoacetate and methyl acetoacetate, respectively led to poor yields of **4**.[3a, 6a,b] The acid chloride and fluoride derived from 1,3-dioxolane-2-methyl-2-acetic acid and cyanuric chloride[6c] or cyanuric fluoride[6d] respectively, led to even

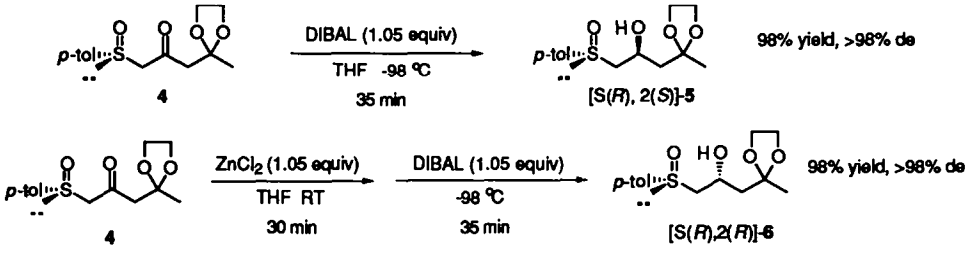
poorer yields of product, most likely due to the difficulty in the purification of these unstable acid halides. However, β-keto δ-dioxolane sulfoxide **4** could be formed in very high and reproducible yield in a one-pot reaction by treating the lithio carbanion of *R*(+)-methyl *p*-tolyl sulfoxide **2** with the imidazolide prepared in situ from 1,3-dioxolane-2-methyl-2-acetic acid and 1,1' -carbonyldiimidazole.[6e]

Scheme 2



Stereoselective reduction of the β-ketone was carried out according to Solladie's procedure.[3b] When a solution of **4** (1.0 eq) in anhydrous THF was added to a precooled solution of DIBAL (1.0 eq, -78 °C), the hydroxy sulfoxide **5** was obtained in 98% yield and 94% diastereoselectivity. On the other hand, if DIBAL (1.05 eq) was added dropwise to a precooled solution of **4** (1.0 eq) in THF and $ZnCl_2$ (1.05 eq, -78 °C), we obtained the hydroxy sulfoxide **6** in 98% yield and 94% diastereoselectivity. The ketal functionality is not affected under these reaction conditions, nor does it interfere with the stereoselectivity of the reduction reaction. Interestingly, we found that in both cases if the reductions are carried out using the above procedures but at a lower temperature (-98 °C), the stereoselectivity increases to >98% d.e. without a deleterious effect on the chemical yield of the reaction as depicted in Scheme 3. The products of these lower temperature reactions are pure by high field ^1H NMR (300 MHz) displaying a single set of peaks with almost no detectable trace of a minor diastereomer. HPLC was also used to corroborate these results. The absolute stereochemistry of the β-hydroxy δ-dioxolane sulfoxides was determined by mechanistic considerations[7,8] and by ^1H NMR analysis of the nonequivalent protons of the CH_2 group α to the sulfoxide and the CH_2 group α to the 1,3 dioxolane moiety in both $CDCl_3$ and DMSO-d_6.[7,8]

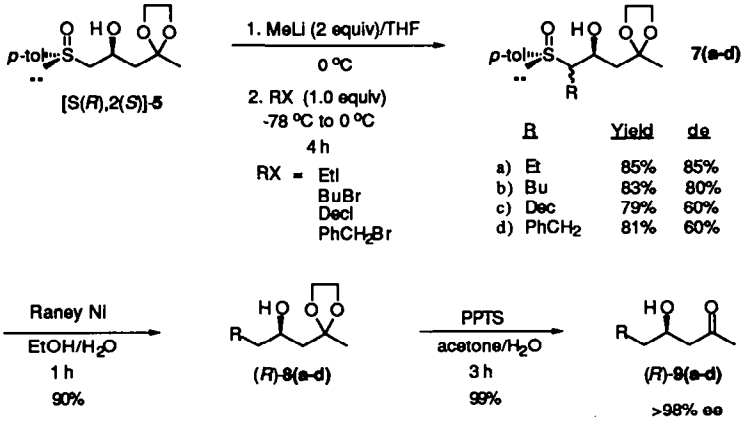
Scheme 3



With the δ-carbonyl functionality properly protected, β-hydroxy δ-dioxolane sulfoxides **5** and **6** could be regioselectively alkylated by treatment with MeLi (2 eq) in THF and quenching the resulting dianion with a variety of simple alkyl halides to yield sulfoxides **7a-d** in good yields as illustrated in Scheme 4.[9] The stereoselectivity of these alkylation reactions was not exceedingly high, ranging from 85% d.e. in the ethyl case to 60% d.e. in the decyl and benzyl cases. Because the stereochemistry at this newly alkylated center is inconsequential for the synthesis of α-unsubstituted aldol adducts, the low diastereoselectivity did not pose a problem, but we are currently investigating ways to improve the selectivity of this reaction for use in future synthetic efforts.[10]

Continuing with the synthesis of aldol compounds, α-alkyl-β-hydroxy-δ-dioxolane sulfoxides **7a-d** were treated with Raney Nickel in the presence of aqueous EtOH to remove the sulfur auxiliary, producing hydroxy ketals **8a-d** in high yield (90%). Mild deprotection of the ketal using PPTS in acetone/ H_2O gave aldol adducts **9a-d**[11] in almost quantitative yield and in >98% e.e. as determined by ^1H NMR analysis of their MTPA esters.[12]

Scheme 4



In conclusion, we have demonstrated that it is possible to synthesize either enantiomer of simple α-unsubstituted aldol adducts in very high enantiomeric excess and in high purity through an efficient and short series of reactions utilizing a common starting material. Although, the enantiomerically pure sulfoxide auxiliary is not recoverable in the above reaction scheme, it is important to note that sulfoxide **4** is readily available from inexpensive and commercially available starting materials.

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8. ^1H, ^{13}C, DEPT-90 and DEPT-135 spectra were recorded on a Bruker ARX 300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard.
   ^1H NMR ($CDCl_3$, 300 MHz) [S(*R*),2(*S*)]-**5** δ 7.54 (AA'BB', 1H, J = 8.1 Hz, C2 andC2'), 7.33 (AA'BB', 1H, J = 8.0 Hz, C3 and C3'), 4.50 (m, 1H, C*H*OH), 4.09 (s, 1H, OH), 3.95 (m, 4H), 2.86 (AB from ABX , 2H, J_{AB} = 13.1, J_{AX} = 9.2, J_{BX} = 3.2, *p*-tolSOCH_2), 2.42 (s, 3H), 1.87 (m, 2H, CH_2CHOH), 1.33 (s, 3H).
   ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.6, 140.7, 109.6 (quaternaries), 64.7 (CH), 129.9, 124.1 (CH, double signal), 64.6, 64.3, 64.0, 44.4 (CH_2), 24.1, 21.4 (CH_3). Anal. Calcd for $C_{14}H_{20}O_4S$ (284.37): C, 59.13; H, 7.09. Found: C, 59.00; H, 6.98.
   ^1H NMR ($CDCl_3$, 300 MHz) [S(*R*),2(*R*)]-**6** δ 7.57 (AA'BB', 1H, J = 8.1 Hz, C2 andC2'), 7.33 (AA'BB', 1H, J = 8.1 Hz, C3 and C3'), 4.28 (m, 1H, C*H*OH), 3.96 (m, 5H, OCH_2CH_2O, OH), 3.00 (AB from ABX , 2H, J_{AB} = 13.1 , J_{AX} = 7.2, J_{BX} = 4.3, *p*-tolSOCH_2), 2.42 (s, 3H), 2.03 (ABX, 2H, J =14.6, J = 8.8, J = 3.1, CH_2CHOH), 1.35 (s, 3H).
   ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.6, 140.7, 109.6 (quaternaries), 64.7 (CH), 129.9, 124.1 (CH, double signal), 64.6, 64.3, 64.0, 44.4 (CH_2), 24.1, 21.4 (CH_3). Anal. Calcd for $C_{14}H_{20}O_4S$ (284.37): C, 59.13; H, 7.09. Found: C, 59.24; H, 7.16.
9. It is important to note that the alkylation reaction proceeds equally well with both hydroxy sulfoxides **5** and **6** but only the [S(*R*),2(*S*)]-**5** isomer is depicted in Scheme 4 for simplicity.
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11. All compounds and intermediates reported herein have been fully characterized by spectroscopic means as well as by combustion or high resolution mass spectral analysis.
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