Letter

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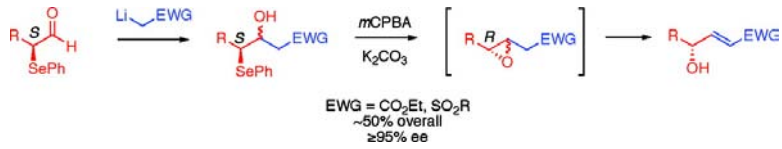

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Asymmetric, Organocatalytic, Three-Step Synthesis of γ-Hydroxy-(*E*)-α,β-Unsaturated Sulfones and Esters

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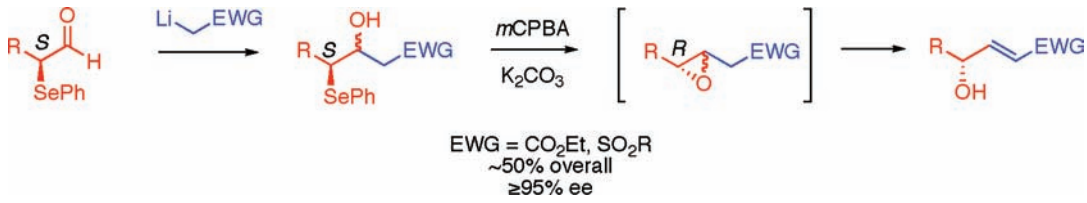
ABSTRACT



Efficient and enantiocontrolled synthesis of γ-hydroxy-α,β-unsaturated sulfones and esters are reported through the reaction of enantioenriched α-selenyl aldehydes with EWG-stabilized carbanions and then a one-pot selenide oxidation, in situ epoxide formation, and final in situ epoxide opening.

While studying the metabolites of certain vitamin D_3 analogues, we became interested in the synthesis of γ-hydroxy-α,β-unsaturated sulfones and esters. γ-Hydroxy-α,β-ethylenic sulfones have previously been used as substrates in stereocontrolled processes such as conjugate additions and cycloaddition reactions,[1] as substrates for preparation of enatiomerically pure polypropionate chains or amino alcohol units,[2] and also as intermediates in alkaloid syntheses.[3] γ-Hydroxy-α,β-enoates have been used as sources of α,β-epoxyesters, which are highly versatile functionalities and can be converted into a number of compounds by opening the oxirane[4] and as intermediates in natural product syntheses.[5] Use of both of these γ-hydroxy-α,β-unsaturated systems as substrates for stereoselective radical reactions has been explored.[6] General methodologies for the asymmetric synthesis of these systems, however, are limited in scope.[7] Based on the utility of such systems in highly stereocontrolled processes[1] and as intermediates in natural product syntheses,[3,5] we set out to design a simple, asymmetric general strategy for their synthesis.

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Table 1. Reaction Results from Scheme 1

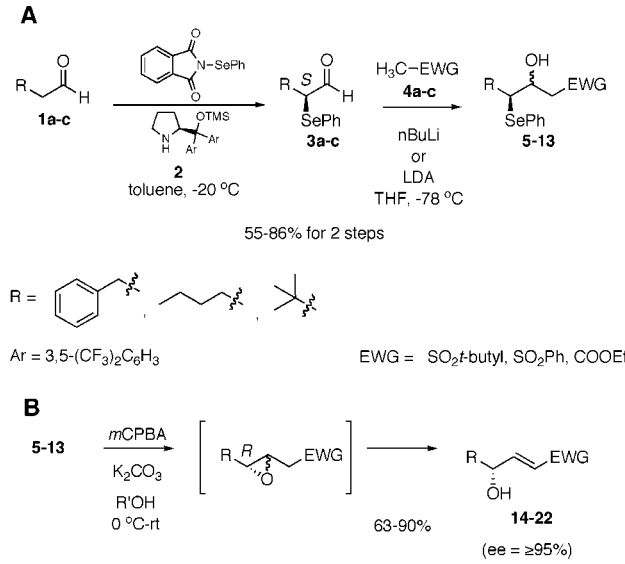
compd (A, B)	R	EWG	A (yield, %)	B (yield, %)	ee (%)
5, **14**	Bn (**1a**)	SO_2t-butyl (**4a**)	84	70	99[a]
6, 15	Bn (**1a**)	SO_2Ph (**4b**)	79	90	95[b]
7, 16	Bn (**1a**)	COOEt (**4c**)	77	73	96[a]
8, 17	*n*-butyl (**1b**)	SO_2t-butyl (**4a**)	86	91	95[b]
9, 18	*n*-butyl (**1b**)	SO_2Ph (**4b**)	85	86	97[a]
10, 19	*n*-butyl (**1b**)	COOEt (**4c**)	50	67	95[a]
11, 20	*t*-butyl (**1c**)	SO_2t-butyl (**4a**)	82	63	96[a]
12, 21	*t*-butyl (**1c**)	SO_2Ph (**4b**)	75	69	99[a]
13. 22	*t*-butyl (**1c**)	COOEt (**4c**)	85	N/A	N/A

[a] ee values determined using chiral HPLC. [b] ee values determined through ^{1}H NMR analysis of crude reaction mixture of γ-hydroxy alcohols with (*S*)-Mosher acid chloride.

Recent reports on the organocatalytic, asymmetric α-selenenylation of aldehydes in high yields (>85%) and high enantiomeric excess (>95%)[8] gave us an entry point to control absolute stereochemistry in our γ-hydroxy-α,β-unsaturated systems. Such α-selenylated aldehydes could easily undergo an aldol-type reaction with an electron-withdrawing group (EWG)-stabilized carbanion to give a diastereomeric pair of γ-selenyl-β-hydroxy sulfones or esters. Oxidation of the selenide and treatment with mild base could give a β,γ-epoxide which, upon further treatment with base could rearrange into the desired enantiomerically enriched γ-hydroxy-α,β-unsaturated ester or sulfone with the overall inversion of stereochemistry (Scheme 1, Table 1).

In order to examine the scope of this reaction, we chose three aldehydes (3-phenylpropanal, hexanal, and 3,3-dimethylbutanal) and three EWG-stabilized methyl groups (*tert*-butyl methyl sulfone, phenyl methyl sulfone, and ethyl acetate). Using the methodology of Tiecco and Marini[8b] to make α-selenyl aldehydes **3a**−**c**, we were able to react the crude α-selenyl aldehyde[9] with lithiated EWG-stabilized methyl groups **4a**−**c** to give diastereomeric compounds **5**−**13** (Scheme 1, A) in 55−86% yields. γ-Selenyl-β-hydroxy sulfones and esters **5**−**13** underwent oxidation and spontaneous cyclization with *m*-CPBA and K_2CO_3 to give the transient β,γ-epoxide which immediately rearranged in situ to yield exclusively the γ-hydroxy-(*E*)-α,β-unsaturated sulfone or ester **14**−**22** (Scheme 1, B) in 63−90% yields and excellent ee's (≥95%). The (*E*)-geometry of the new carbon−carbon double bond in products **14**−**22** was confirmed by ^{1}H NMR spectoscopy ($J_{\alpha,\beta}$ = 14−16 Hz). α-Selenyl aldehyde **3c** derived from 3,3-dimethylbutanal underwent reaction sequence A (Scheme 1) in high yield with all three EWG-stabilized carbanions (**4a**−**c**), but γ-selenyl-β-hydroxy ester **13** derived from reaction with ethyl aceate (**4c**) decomposed under the reaction conditions used in reaction sequence B (Scheme 1). Also, substituted EWG-stabilized methyl groups such as propionates were explored, but no substantial selectivity in *E*/*Z* double bond formation was seen.

Scheme 1. Synthesis of γ-Hydroxy-α,β-unsaturated Sulfones and Esters from α-Selenyl Aldehydes[11]



Our success using α-selenenylated aldehydes led us to investigate other leaving groups alpha to the aldehyde and whether a one-pot 3-step procedure might be possible (Scheme 2). Given the precedent for the enantioselective organocatalytic α-chlorination of aldehydes[10] we decided to explore the feasibility of such a system in the reaction

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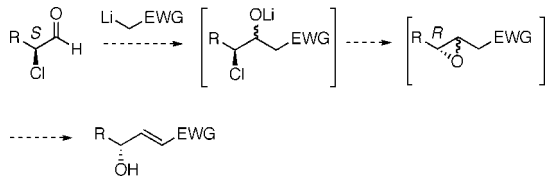
Scheme 2. Plan for One-Pot Procedure



sequence. Individually, each step in the reaction sequence with an α-chloro aldehyde appeared to work, but a one-pot procedure could not be achieved successfully. Ultimately, this strategy was not pursued due to the instability and volatility of the α-chlorinated aldehydes and the superior results with the α-selenyl systems.

Confirmation of absolute stereochemistry was first achieved by reducing α-selenyl aldehydes **3a**−**c** with $NaBH_4$ and comparing optical rotations with published values.[8b] An X-ray crystal structure was also obtained for γ-hydroxy-α,β-unsaturated sulfone **15**, which confirms the *R* configuration of the γ-hydroxy carbon (Figure 1).

Further proving the value of this synthetic method, scale up of the procedure to 1 g was readily accomplished with no erosion of ee (97%) and in 59% overall yield for γ-hydroxy-α,β-unsaturated sulfone **14**.[11]

γ-Hydroxy ether-α,β-unsaturated ester **23** (Scheme 3) is a key intermediate in a recent synthesis of the biologically active alkaloid (+)-α-conhydrine (**24**).[5a] Intermediate **23** was prepared in six steps and 32% overall yield from (*S*)-glycidol.[5a] Using the methodology described here, we have prepared intermediate ester **23** in only four steps and in 47% overall yield and 97% ee (Scheme 4).

(11) Procedure for the Synthesis of **14**. A solution of 3-phenylpropanal, **1a** (90%, 1.2 mL, 9.4 mmol), and catalyst **2** (0.7 g, 1.2 mmol) in toluene (20 mL) was stirred at rt under Ar for 30 min. The reaction mixture was cooled to −20 °C, and *N*-(phenylseleno)phthalimide (3.4 g, 11.2 mmol) was added. After the mixture was stirred for 2 h, the contents of the flask were filtered and rinsed with hexanes, the solvent evaporated (avoid heat!), and the crude mixture (**3a**) dried under vacuum for 1 h to get rid of all toluene. To an ice-cooled solution of methyl *tert*-butyl sulfone, **4a** (4.0 g, 29.4 mmol), in anhydrous THF (30 mL) under Ar was added *n*-BuLi (1.5 M in hexanes, 18.8 mL, 28.1 mmol) dropwise and the mixture stirred for 30 min. The reaction mixture was cooled to −78 °C, and a solution of crude **3a** (9.4 mmol) in 10 mL THF was added via cannula. After being stirred at −78 °C for 1 h, the mixture was quenched by addition to water (50 mL) and extracted with Et_2O (3 × 30 mL). The organics were combined, rinsed with brine (30 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (25% EtOAc in hexanes) to give **5** (3.4 g, 84% yield), which was used directly in the next step. To a solution of **5** (2.5 g, 5.9 mmol) in MeOH (20 mL) was added K_2CO_3 (3.2 g, 23.5 mmol), and the reaction mixture was stirred for 20 min. The mixture was cooled to 0 °C, and *m*-CPBA (77%, 2.6 g, 11.8 mmol) was added. The solution was allowed to warm slowly to rt and stirred for a total of 1.5 h. The reaction mixture was then added to a saturated solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organics were combined, dried over $MgSO_4$, filtered, concentrated, and chromatographed (30% EtOAc in hexanes) to give **14** (1.1 g, 70% yield) as a white solid: $[\alpha]^{24}_D$ −1.9 (*c* 1.35, $CHCl_3$); IR (neat, cm^{-1}) 3483 (brs), 3061 (w), 2980 (w), 2929 (w), 1630 (w), 1453 (w), 1297 (m), 1272 (m), 1200 (w), 1108 (m), 835 (w), 702 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27 (m, 5H), 6.95 (dd, 1H, *J* = 14.8, 3.6 Hz), 6.53 (dd, 1H, *J* = 14.8, 2.0 Hz), 4.65 (m, 1H), 2.99 (dd, 1H, *J* = 14.0, 5.2 Hz), 2.84 (dd, 1H, *J* = 13.6, 8.0 Hz), 2.09 (brs, 1H), 1.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.05, 136. 23, 129.42, 128.82, 127.14, 123.47, 71.26, 58.42, 42.85, 23.22; HRMS calcd for $C_{14}H_{20}O_3S$ [MH^+] 269.1211, found 269.1211; mp = 81−83 °C.

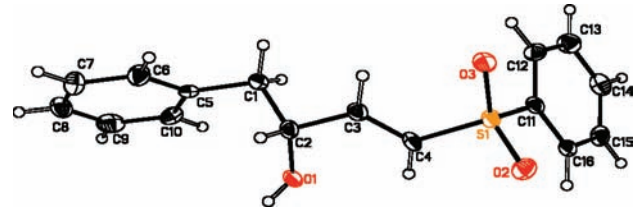
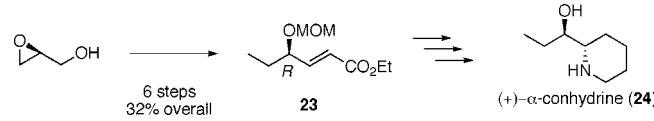
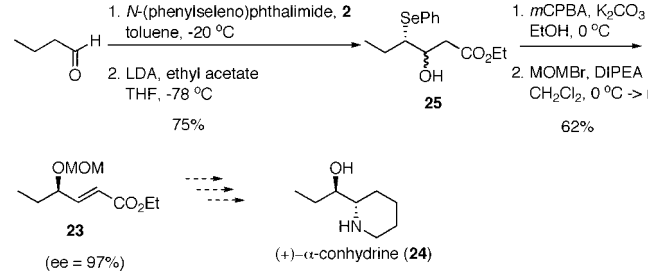


Figure 1. Crystal structure of **15** (confirms *R* configuration at the γ-hydroxy carbon atom).

Scheme 3. Synthesis of (+)-α-Conhydrine (**24**) Using Key Intermediate γ-Hydroxy Ether-α,β-Unsaturated Ester **23**[5a]



Scheme 4. Formal Synthesis of (+)-α-Conhydrine (**24**)



In summary, we report an efficient and generalized procedure for the synthesis of γ-hydroxy-α,β-unsaturated sulfones and esters of high enantiomeric purity that is easily scaled to amounts >1 g. This three-step process works on a variety of substrates with high overall yields (∼50%) and excellent control of absolute stereochemistry (ee values ≥95%). We have shown the application of this methodology to a formal synthesis of the natural product (+)-α-conhydrine. Undoubtedly, this methodology could be expanded to the preparation of other γ-hydroxy-α,β-unsaturated compounds with other EWGs, such as nitro or cyano.

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Supporting Information Available: Experimental procedures and spectra of γ-hydroxy-α,β-unsaturated sulfones and esters. This material is available free of charge via the Internet at http://pubs.acs.org.

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