Published in final edited form as:

Org Lett. 2008 October 16; 10(20): 4685–4687. doi:10.1021/ol8020513.

Asymmetric, Organocatalytic, 3-Step Synthesis of γ -Hydroxy-(*E*)- α - β -Unsaturated Sulfones and Esters

Kimberly S. Petersen and Gary H. Posner

Department of Chemistry, Johns Hopkins University, 3400 Charles St., Baltimore, MD 21218

Abstract

EWG = CO₂Et, SO₂R
~50% overall
□95% ee

Efficient and enantiocontrolled synthesis of γ -hydroxy- α,β -unsaturated sulfones and esters are reported through the reaction of enantioenriched α -selenenyl 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 D₃ analogs, 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 enantiomerically 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 oxirane⁴ 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 processes¹ and as intermediates in natural product syntheses,^{3,5} we set out to design a simple, asymmetric general strategy for their synthesis.

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 -selenenyl- β -hydroxy sulfones or esters. Oxidation

Correspondence to: Gary H. Posner.

ghp@jhu.edu.

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>.

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).

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 (*t*-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 aldehyde⁹ 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 ($\geq 95\%$). The *(E)*-geometry of the new carbon-carbon double bond in products **14-22** was confirmed by 1H NMR spectroscopy ($J_{\alpha,\beta} = 14-16$ 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 acetate (**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.

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 aldehydes¹⁰ we decided to explore the feasibility of such a system in the reaction 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 one gram 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 6 steps and 32% overall yield from (*S*)-glycidol.^{5a} Using the methodology described here we have prepared intermediate ester **23** in only 4 steps and in 47% overall yield and 97% ee (Scheme 4).

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 gram. This 3-step process works on a variety of substrates with high overall yields ($\sim 50\%$) and excellent control of absolute stereochemistry (ee values $\geq 95\%$). 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank the NIH (CA 93547) for financial support and the ACS (predoctoral fellowship to K.S.P.).

References

- (1). (a) Barton DL, Conrad PC, Fuchs PL. *Tetrahedron Lett* 1980;21:1811–1814.. (b) Trost BM, Seoane P, Mignani S, Acemoglu M. *J. Am. Chem. Soc* 1989;111:7487–7500.
- (2). (a) Carretero JC, Dominguez E. *J. Org. Chem* 1993;58:1596–1600.. (b) de Blas J, Carretero JC, Dominguez E. *Tetrahedron Lett* 1994;35:4603–4606.. (c) Dominguez E, Carretero JC. *Tetrahedron* 1994;50:7557–7566..
- (3). (a) Rojo J, Garcia M, Carretero JC. *Tetrahedron* 1993;49:9787–9800.. (b) Carretero JC, Arrayas RG. *J. Org. Chem* 1998;63:2993–3005.. (c) de Vincent J, Arrayas RG, Canada J, Carretero JC. *Synlett* 2000:53–56.. (d) Iradier F, Arrayas RG, Carretero JC. *Org. Lett* 2001;3:2957–2960. [PubMed: 11554817]. (e) Krafft ME, Kyne GM, Hirosawa C, Schmidt P, Abboud KA, L'Helias M. *Tetrahedron* 2006;62:11782–11792..
- (4). (a) Rodriguez S, Vidal A, Monroig JJ, Gonzalez FV. *Tetrahedron Lett* 2004;45:5359–5361.. (b) Rodriguez S, Kneeteman M, Izquierodo J, Lopez I, Gonzalez FV, Peris G. *Tetrahedron* 2006;62:11112–11123.. (c) Lopez I, Rodriguez S, Izquierodo J, Gonzalez FV. *J. Org. Chem* 2007;72:6614–6617. [PubMed: 17655257].
- (5). (a) Jamieson AG, Sutherland A. *Org. Lett* 2007;9:1609–1611. [PubMed: 17371038]. (b) Kotkar SP, Suryavanshi GS, Sudalai A. *Tet. Asym* 2007;18:1795–1798.. (c) Varseev GN, M. ME. *Org. Lett* 2007;9:1461–1464. [PubMed: 17378570]. (d) Taber DF, Reddy PG, Arneson KO. *J. Org. Chem* 2008;73:3467–3474. [PubMed: 18341286].
- (6). (a) Morikawa T, Washio Y, Harada S, Hanai R, Kayashita T, Nemoto H, Shiro M, Taguchi T. *J. Chem. Soc. Perkin Trans. I* 1995:271–281.. (b) Charlton MA, Green JR. *Can. J. Chem* 1997;75:965–974.. (c) Ogura K, Kayano A, Akazome M. *Bull. Chem. Soc. Jpn* 1997;70:3091–3101..
- (7). (a) Ogura K, Shibuya N, Iida H. *Tetrahedron Lett* 1981;22:1519–1522.. (b) Pyne SG, Spellmeyer DC, Chen S, Fuchs PL. *J. Am. Chem. Soc* 1982;104:5728–5740.. (c) Fuchs PL, Hutchinson DK. *J. Am. Chem. Soc* 1985;107:6137–6138.. (d) Ryu I, Kusumoto N, Ogawa A, Kambe N, Sonoda N. *Organometallics* 1989;8:2279–2281.. (e) Dominguez E, Carretero JC. *Tetrahedron* 1990;46:7197–7206.. (f) Burgess K, Cassidy J, Henderson I. *J. Org. Chem* 1991;56:2050–2058.. (g) Trost BM, Grese TA. *J. Org. Chem* 1991;56:3189–3192.. (h) Wnuk SF, Dalley NK, Robins M. *Can. J. Chem* 1991;69:2104–2111.. (i) Barton DL, Gero SD, Quiclet-Sire B, Samadi M. *Tetrahedron Asymmetry* 1994;5:2123–2126.. (j) Zoller T, Uguen D. *Eur. J. Org. Chem* 1999:1545–1550.. (k) de la Rosa VG, Ordonez M, Llera JM. *Tetrahedron Asymmetry* 2000;2000:2991–3001.. (l) Marcus J, Van Meurs PJ, Van den Nieuwendijk MCH, Porchet M, Brussee J, Van der Gen A. *Tetrahedron* 2000;56:2491–2495.. (m) Pedersen TM, Hansen EL, Kane J, Rein T, Helquist P, Nourby PO, Tanner D. *J. Am. Chem. Soc* 2001;123:9738–9742. [PubMed: 11583534]. (n) Rodriguez S, Vidal A, Monroig JJ, Gonzalez FV. *Tetrahedron Lett* 2004;45:5359–5361..
- (8). (a) Sunden H, Rios R, Cordova A. *Tetrahedron Lett* 2007;48:7865–7869.. (b) Tiecco M, Carlone A, Sternativo S, Marini F, Bartoli G, Melchiorre P. *Angew. Chem. Int. Ed* 2007;46:6882–6885..
- (9). Column chromatography of the α -selenyl aldehydes, even using florisil led to erosion of enantiomeric purity.
- (10). (a) Brochu MP, Brown SP, MacMillan DWC. *J. Am. Chem. Soc* 2004;126. (b) Halland N, Braunton A, Bachmann S, Marigo M, Jorgensen KA. *J. Am. Chem. Soc* 2004;126:4790–4791. [PubMed: 15080678].
- (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 stirring 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 *t*-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 stirring at -78 °C for 1 h the mixture was quenched by addition to water (50 mL) and extracted with Et₂O (3 × 30 mL). The organics were combined, rinsed with brine (30 mL), dried over MgSO₄, 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 K₂CO₃ (3.2 g, 23.5 mmol) and the reaction mixture was stirred for 20 min. The mixture was cooled to 0 °C and mCPBA (77%, 2.6 g, 11.8 mmol) was added. The solution was allowed to warm slowly to rt and stirred a total of 1.5 h. The reaction mixture was then added to a sat. solution of NaHCO₃ (25 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The organics were combined, dried over MgSO₄, filtered, concentrated, and chromatographed (30% EtOAc in hexanes) to give **14** (1.1 g, 70% yield) as a white solid. [α]_D²⁴ -1.9 (*c* 1.35, CHCl₃); 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₄H₂₀O₃S [MH⁺]: 269.1211, found 269.1211; MP = 81-83 °C

A

55-86% for 2 steps

$\text{Ar} = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$ $\text{EWG} = \text{SO}_2t\text{-butyl, SO}_2\text{Ph, COOEt}$ **B** **Scheme 1.**Synthesis of γ -hydroxy- α,β -unsaturated sulfones and esters from α -selenyl aldehydes¹¹

Scheme 2.

Plan for one pot procedure

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**)

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

Table 1

Reaction results from Scheme 1

compound (A, B)	R	EWG	A (yield%)	B (yield%)	ee
5, 14	Bn (1a)	SO ₂ - <i>t</i> -butyl (4a)	84	70	99 [*]
6, 15	Bn (1a)	SO ₂ Ph (4b)	79	90	95 ^{**}
7, 16	Bn (1a)	COOEt (4c)	77	73	96 [*]
8, 17	<i>n</i> -butyl (1b)	SO ₂ - <i>t</i> -butyl (4a)	86	91	95 ^{**}
9, 18	<i>n</i> -butyl (1b)	SO ₂ Ph (4b)	85	86	97 [*]
10, 19	<i>n</i> -butyl (1b)	COOEt (4c)	50	67	95 [*]
11, 20	<i>t</i> -butyl (1c)	SO ₂ - <i>t</i> -butyl (4a)	82	63	96 ^{**}
12, 21	<i>t</i> -butyl (1c)	SO ₂ Ph (4b)	75	69	99 [*]
13, 22	<i>t</i> -butyl (1c)	COOEt (4c)	85	N/A	N/A

* ee values determined using chiral HPLC.

** ee values determined through ¹H NMR analysis of crude reaction mixture of γ -hydroxy alcohols with (S)-Mosher acid chloride.