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

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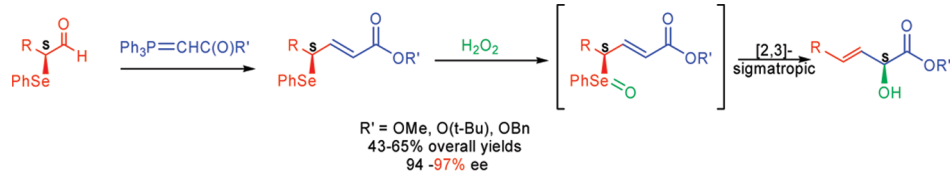
ABSTRACT



An efficient and enantiocontrolled three-step synthesis of α-hydroxy-(*E*)-β,γ-unsaturated esters is reported. Enantioenriched α-selenyl aldehydes, prepared in one step by asymmetric, organocatalytic α-selenylation of aldehydes, were directly subjected to a Wittig reaction followed by allylic selenide to selenoxide oxidation and final spontaneous [2,3]-sigmatropic rearrangement to yield the target compounds in 43−65% overall yield and in 94−97% ee.

Asymmetric synthesis utilizing organoselenium compounds has become increasingly popular in recent years.[1] Selenium incorporation can be done in either a nucleophilic or an electrophilic fashion.[2] Once selenium is introduced into the molecule, many different chemical transformations can occur including oxidations leading to either syn-elimination[3] or, in the case of an allylic selenide, [2,3]-sigmatropic rearrangement to give an allylic alcohol.[4] Pursuing our recently published work preparing chiral nonracemic γ-hydroxy-(*E*)-α,β-unsaturated sulfones and esters,[5] we have developed a complementary asymmetric synthetic method producing α-hydroxy-(*E*)-β,γ-unsaturated esters.

α-Hydroxy esters and their corresponding acids are key structural units of valuable synthetic intermediates as well as natural products.[1,6] On the basis of the utility of these structural units, we set out to design a simple, asymmetric general strategy for their synthesis. Suprisingly, most reports of selenium oxidation and [2,3]-sigmatroptic rearrangements have been done utilizing chiral oxidants as opposed to installing chirality prior to oxidation.[7] There have been a few reports involving diastereoselective oxidations of selenides containing chiral moieties,[8] but the scope is quite

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limited, with low to moderate yields and only modest diastereomeric excess (de). Other methods have also been reported using conformationally locked ring systems to induce stereocontrol.[9]

Recent reports on the organocatalytic, asymmetric α-selenenylation of aldehydes in high yields (>85%) and high enantiomeric excess (>95%)[10,11] gave an excellent method for controlling the absolute stereochemistry of our α-hydroxy-(*E*)-β,γ-unsaturated target systems.

We chose a variety of aldehydes (3-phenylpropanal, 2-cyclohexylethanal, *N*-Boc-4-piperidineethanal, hexadecanal, and 6-benzyloxyhexanal) as well as three different ester functional groups (OMe, O-*t*-butyl, and O-benzyl) to determine the generality of this reaction. α-Selenyl aldehydes **3a**−**e**, prepared according to an Italian protocol,[11] were immediately subjected in situ to a Wittig reaction to give the enantiomerically enriched compounds **5**−**11** (Scheme 1, A; Table 1) in 48−83% yields. Oxidation of the γ-seleneyl-(*E*)-α,β-unsaturated esters to the selenoxide using hydrogen peroxide caused spontaneous [2,3]-sigmatropic rearrangement to give the final enantioenriched α-hydroxy-(*E*)-β,γ-unsaturated esters (Scheme 1, B) in 63−90% yields and excellent ee's (≥94%). The exclusive (*E*)-geometry of the carbon−carbon double bond in intermediates **5**−**11** as well as the final products **12**−**18** was confirmed by ^{1}H NMR spectroscopy (J = 14−16 Hz). It is important to note that when α-hydroxy ester final products **12**, **13**, and **14** were dissolved in a variety of solvents (e.g., THF, $CHCl_3$, CH_3CN, and hexanes) at room temperature they were stable to racemization (as determined via chiral HPLC) for at least 24 h. We also used mCPBA as an oxidant of selenium, and we obtained a comparable yield and ee when compared to hydrogen peroxide (system tested was hexadecanal). The preferred method of oxidation remained hydrogen peroxide due to the convenience of the reaction conditions (nonanhydrous).

Scheme 1. Preparation of α-Hydroxy-(*E*)-β,γ-unsaturated Esters

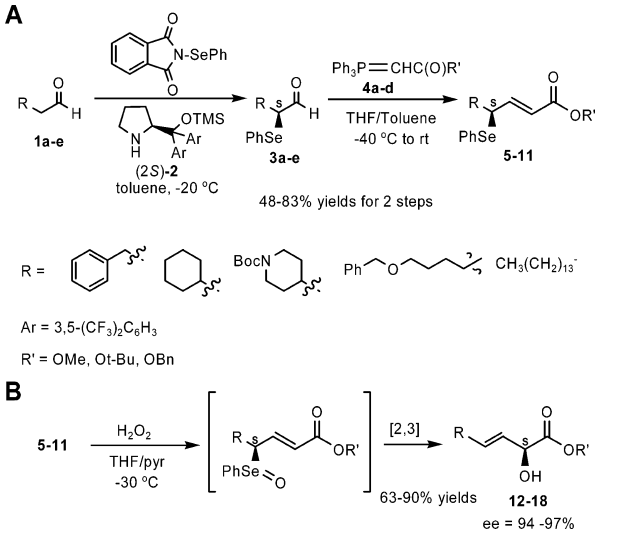


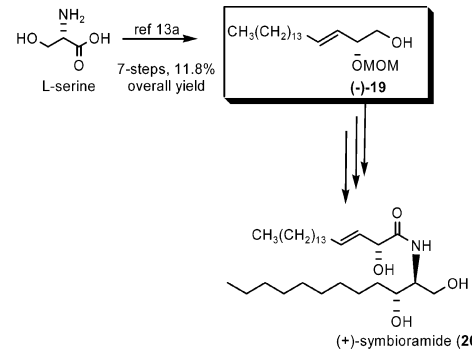
Table 1. Reaction Results from Scheme 1

compound			A	B	
(A,B)	R	R′	yield, %	yield, %	ee (%)[a]
5, **12**	Bn (**1a**)	OMe (**4a**)	73	87	95
6, **13**	Bn (**1a**)	O(*t*-Bu) (**4b**)	73	63	95
7, **14**	Bn (**1a**)	OBn (**4c**)	81	70	95
8, **15**	cyclohexyl (**1b**)	OBn (**4c**)	79	67	95
9, **16**	*N*-Boc-piperidine (**1c**)	OBn (**4c**)	83	67	94
10, **17**	$BnO(CH_2)_4$ (**1d**)	OBn (**4c**)	48	90	97
11, **18**[b]	$CH_3(CH_2)_{13}$ (**1e**)	OBn (**4c**)	77	83	95

[a] ee values determined using chiral HPLC and racemic standards. [b] Catalyst (2*R*)-**2** was used.

To illustrate the utility of this method for natural product synthesis, we completed a formal total synthesis of (+)-symbioramide (**20**), a naturally occurring bioactive ceramide composed of D-*erythro*-dihydrosphingosine and (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid.[12] We prepared key intermediate (−)-**19** that had been used in a recent synthesis[13] of this biologically active ceramide (Scheme 2). Intermediate (−)-**19** had been prepared in seven steps and 11.8% overall yield from L-serine.[13a] Using the new method described here, we prepared this intermediate monoprotected diol (−)-**19** in only 5 steps and in 28% overall yield and 95% ee (Scheme 3). It is important to note that, in order to achieve the natural stereochemistry at the chiral 2-position, we employed the

Scheme 2. Previously Published Synthesis of (+)-Symbioramide (**20**) Using Key Intermediate (−)-**19**



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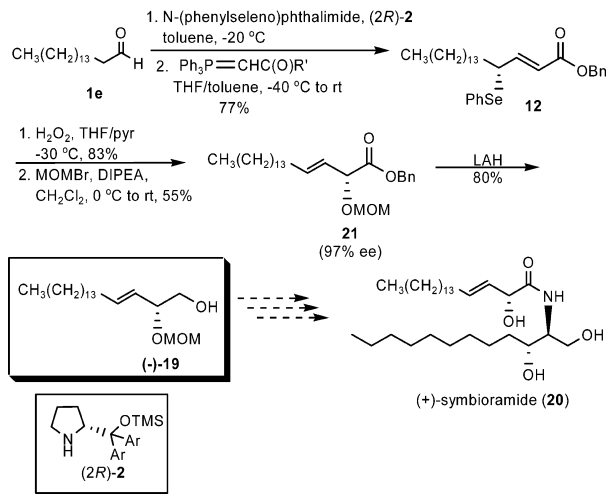
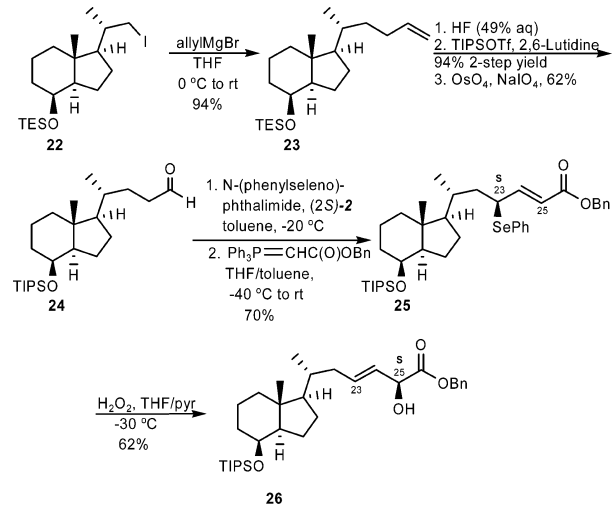
Scheme 3. Formal Total Synthesis of (+)-Symbioramide (**20**)



Scheme 4. Synthesis of a 23-(*E*)-ene-25(*S*)-hydroxy Vitamin D_3 Chiron



opposite proline-derived catalyst in the asymmetric α-selenenylation of hexadecanal. This formal total synthesis of (+)-symbioramide (**20**) allowed us to confirm the absolute stereochemistry of our final α-hydroxy carbonyl products. Previously published characterization of monoprotected diol (−)-**19** indicates that the absolute stereochemistry at the 2 position is *R*, with $[\alpha]_D = -77°$, matching our experimental data for intermediate (−)-**19** prepared via Scheme 3.

In one final example, we prepared also a vitamin D_3 chiron that incorporated a side chain with the structural motif generated via this synthetic method. An S_N2 displacement of iodide **22**[14] using allylmagnesium bromide yielded terminal olefin **23**. Oxidative cleavage afforded aldehyde **24**. Using the method described here (Scheme 4), we were able to prepare α-hydroxy-(*E*)-*β*,*γ*-unsaturated benzyl ester **26** as a single diastereomer. This fragment can be easily modified to prepare final C,D-ring side-chain modified vitamin D analogues.

In summary, we report an efficient, generalized, asymmetric, organocatalytic procedure for synthesis of α-hydroxy-(*E*)-*β*,*γ*-unsaturated esters in high enantiomeric purities. This three-step synthesis works with a variety of substrates, in good overall yields (46−65%), and with excellent control of absolute stereochemistry (ee values ≥94%). We have proven the utility of this method through a formal total synthesis of natural product (+)-symbioramide (**20**) as well as through the preparation of a 23-(*E*)-ene-25(*S*)-hydroxy building block useful for the synthesis of new vitamin D side-chain analogues.[15]

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

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