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Enantioselective synthesis of 2-(2-hydroxyethyl)allylsilanes from chiral β-hydroxyesters

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Abstract: The synthesis of chiral (2-substituted-2-hydroxyethyl)allylsilanes by cerium mediated trimethylsilylmethylmagnesium chloride addition on chiral β-hydroxyesters is described. © 1997 Elsevier Science Ltd

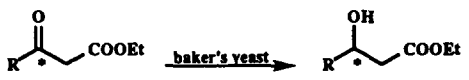
Allylsilyl derivatives are nucleophilic substrates which are widely used for carbon–carbon bond formation in intermolecular or intramolecular reactions with electrophiles.[1,2] In previous work, we have investigated the intramolecular cyclization of an allylsilyl group to an α-acyliminium ion as part of synthetic approaches to alkaloids.[3] The first step of these syntheses was a Mitsunobu reaction between cyclic imides and 2-(2-hydroxyethyl)allylsilanes. Such reagents have previously been obtained by lithiation[4] then silylation[5] of 3-methylhomoallylic alcohols,[3a,6] by ring opening of epoxides with Grignard or cuprate reagents derived from 2-haloallylsilane,[7] by addition of bifunctional reagents as mixed allylsilane/allylorganometallic compounds on aldehydes[8] and by indium mediated allylsilylation of carbonyl compounds.[9] None of these methods has been applied to the enantioselective synthesis of these compounds.

We report here the enantioselective synthesis of 2-(2-hydroxyethyl)allylsilanes starting from chiral β-hydroxyesters. The allylsilane functionality is introduced by cerium mediated trimethylsilylmethylmagnesium chloride addition on the ester group.[10]

The non racemic chiral starting materials were hydroxyesters **1a–c** which were prepared by baker's yeast microbial reduction of the corresponding ketoesters. The results are summarized in Table 1.

The hydroxy functionality was then protected. An O-protecting group that could be removed under conditions that would not affect the allyltrimethylsilyl group was required. Allyl, tetrahydropyranyl and t-butyldimethylsilyl protecting groups were used but they could not be removed efficiently during the hydrolysis step. Trimethylsilyl was found to be the most effective protecting group. Thus, treatment of hydroxyesters **1a–c** with trimethylsilyl chloride afforded ethers **2a–c** in 85–97% yield.

Table 1.



Hydroxyester	$[\alpha]_D$	ee %	Absolute configuration	yield %
R = CH_3 **1a**	+40 (c 1.3, $CHCl_3$)	91	S	61
R = C_6H_5 **1b**	-48 (c 0.052, $CHCl_3$)	95	S	65
R = 3,4-$(OMe)_2C_6H_3$ **1c**	+24.5 (c 0.7, $CHCl_3$)	80	R	46

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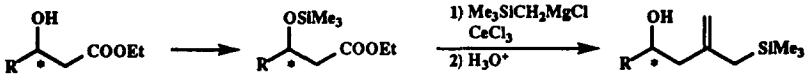
Table 2. Synthesis of Hydroxyallylsilanes 3a–c

Hydroxyallylsilane		$[\alpha]_D$	ee %	Absolute configuration	yield %
R = CH_3	**3a**	-25 (c 1.26, $CHCl_3$)	91	S	100
R = C_6H_5	**3b**	-30 (c 0.1.52, $CHCl_3$	95	S	77
R = 3,4-$(OMe)_2C_6H_3$	**3c**	+17.5 (c 0.78, $CHCl_3$	80	R	97



1a-c **2a-c** **3a-c**

The cerium reagent derived from $CeCl_3$ and trimethylsilylmethylmagnesium chloride was reacted with esters **2a–c**. After aqueous acidic workup, this reaction gave hydroxyallylsilanes **3a–c** with good to excellent yields. Table 2 summarizes the results.

The structures were confirmed by comparison of spectroscopic data with those of racemic samples.[9] The enantiomeric excess was determined by analyzing the diastereomeric ratio of the corresponding (S)-α-methoxy-α-trifluoromethyl-α-phenylacetate (MTPA ester).[13]

In conclusion, we describe the first enantioselective synthesis of (2-substituted-2-hydroxyethyl)allylsilanes by cerium mediated trimethylsilylmethylmagnesium chloride addition on the ester group of optically active β-hydroxyesters. Chiral (2-substituted-2-hydroxyethyl)allylsilanes were obtained with excellent chemical yields and good enantiomeric excesses. These compounds are useful intermediates in alkaloid synthesis.

Experimental

Optical rotations were measured on a Jasco Dip-370 polarimeter. Infrared spectra (IR) were obtained using a Perkin-Elmer 881 spectrophotometer. NMR spectra in $CDCl_3$ were recorded on a Brucker AC 400 spectrometer operating at 400.13 MHz for ^1H NMR and 100.61 MHz for ^{13}C NMR. TLC analyses were performed on Merck $60F_{254}$ silica gel plates and were visualized using iodine. Flash column chromatography was carried out using Merck silica gel (grade 60, 230–400 mesh).

Ethyl (S)-(+)-3-hydroxybutanoate ***1a***

Compound **1a** was prepared by baker's yeast microbial reduction of ethyl acetylacetate according to the published procedure.[11] $[\alpha]_D$ +40 (c 1.3, $CHCl_3$)[lit.[11] ($[\alpha]_D$ +43.5 (c 1.0, $CHCl_3$)]; 91% ee. Its enantiomeric purity was determined by specific rotation.

Ethyl (S)-(−)-3-hydroxy-3-phenylpropanoate ***1b***

Compound **1b** was prepared by baker's yeast reduction of ethyl benzoylacetate under fermenting conditions with cyclohex-2-enone, as previously described.[12] $[\alpha]_D$ −48 (c 0.052, $CHCl_3$) (lit.[14] $[\alpha]_D$ −51 (c 1.5, $CHCl_3$); 95% ee. The enantiomeric excess was determined by ^1H NMR analysis of the Mosher derivative.

Ethyl (R)-(+)-3-hydroxy-3-(3,4-dimethoxyphenyl)propanoate ***1c***

Compound **1c** was prepared by baker's yeast reduction of ethyl 3-oxo-3-(3,4-dimethoxyphenyl)propanoate, as previously described.[12] $[\alpha]_D$ +24,5 (c 0.7, $CHCl_3$); 80% ee. The enantiomeric excess was determined by ^1H NMR analysis of the Mosher derivative.

General procedure for preparation of silylethers ***2a–c***

Alcohol (1eq) was dissolved in dry THF. Triethylamine (4eq) was added, followed by trimethylchlorosilane (4eq). The reaction mixture was stirred at room temperature for 24 hours, was then diluted with ethyl acetate:hexane 5:5, washed with water and brine and extracted with ethyl acetate:hexane

5:5. The combined organic phase was dried with magnesium sulfate and evaporated to give the crude product. It was chromatographed on silica gel using ethyl acetate:hexane 3:7 as eluent.

Ethyl (S)-(+)-3-(trimethylsilyloxy)butanoate ***2a***

Yield 90%; $[\alpha]_D$ +21 (c 3.05, $CHCl_3$); IR (CCl_4, cm^{-1}) 1730; ^1H NMR 0.05 (s, 9H), 1.15 (d, J =6.8, 3H), 1.20 (t, J =7.2, 3H), 2.35 (dd, J =6.8, J =16.0, 1H), 2.45 (dd, J =8.0, J =16.0, 1H), 4.10 (m, 2H), 4.25 (m, 1H); ^{13}C NMR 0.2, 14.3, 24.0, 44.9, 60.4, 65.8, 171.7.

Ethyl (S)-(−)-3-phenyl-3-(trimethylsilyloxy)propanoate ***2b***

Yield 85%; $[\alpha]_D$ −66 (c 1.5, $CHCl_3$); IR (CCl_4, cm^{-1}) 1737; ^1H NMR 0.01 (s, 9H), 1.28 (t, J =7.1, 3H), 2.58 (dd, J =4.1, J =14.7, 1H), 2.70 (dd, J =9.3, J =14.7, 1H), 4.15 (m, 2H), 5.15 (dd, J =4.1, J =9.3, 1H), 7.22–7.40 (m, 5H); ^{13}C NMR 0.2, 14.5, 46.5, 60.7, 72.2, 126.0, 127.7, 128.6, 144.2, 171.4.

Ethyl (R)-(+)-3-(3,4-dimethoxyphenyl)-3-(trimethylsilyloxy)propanoate ***2c***

Yield 98%; $[\alpha]_D$ +46 (c 1.4, $CHCl_3$); IR (CCl_4, cm^{-1}) 1737; ^1H NMR 0.05 (s, 9H), 1.23 (t, J =7.2, 3H), 2.55 (dd, J =4.2, J =14.6, 1H), 2.70 (dd, J =9.4, J =14.6, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.12 (m, 2H), 5.10 (dd, J =4.2, J =9.4, 1H), 6.75–6.95 (m, 3H); ^{13}C NMR 0.0, 14.3, 46.3, 55.8, 60.4, 71.8, 108.8, 110.7,117.7, 136.6, 148.3, 148.9, 171.1; Anal. Calcd for $C_{16}H_{26}O_5Si$ C, 58.87; H, 8.03; Si, 8.68. Found C, 58.91; H, 8.30; Si, 8.68.

General procedure for preparation of allylsilanes ***3a–c***

The literature procedure[10c] was modified as follows: powdered $CeCl_3.7H_2O$ (4.4eq) was dried under vacuum (0.5 mmHg), for 4 hours at 150°C then overnight at room temperature, while stirring. The flask was flushed with argon, then dry THF was added to form a white suspension which was stirred at room temperature for an additional 2 hours. This slurry was cooled to −78°C and trimethylsilylmethylmagnesium chloride (4.4eq) in THF (prepared from chloromethyltrimethylsilane and magnesium in THF) was added dropwise over a period of 40–60 min. The cold mixture was stirred for 1 hour more and the ester was added dropwise over 5 min. The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then cooled to 0–5°C and quenched by dropwise addition of chilled 1M hydrochloric acid, so that the internal temperature remained below 15°C. The layers were separated and the aqueous layer was extracted with diethylether. The combined organic layers were washed with saturated bicarbonate solution, dried with magnesium sulfate and concentrated. The crude product was chromatographed on silica gel using ethyl acetate:hexane 2:8 as eluent.

(S)-(−)-4-(Trimethylsilylmethyl)pent-4-en-2-ol ***3a***

Yield 100%; $[\alpha]_D$ −25 (c 1.26, $CHCl_3$); ee 90%; IR (CCl_4, cm^{-1}) 3560, 1650; ^1H NMR 0.00 (s, 9H), 1.20 (d, J =7.5, 3H),1.55 (AB spectrum, J =13.4, $\delta\nu$ =22.0, 2H), 1.96 (s broad, 1H), 1.99–2.15 (m, 2H), 3.75–3.95 (m, 1H), 4.74 (s, 1H), 4.75 (s, 1H); ^{13}C NMR −1.3, 22.8, 26.7, 48.4, 64.9, 110.3, 144.8.

(S)-(−)-1-Phenyl-3-(trimethylsilylmethyl)but-3-en-1-ol ***3b***

Yield 77%; $[\alpha]_D$ −30 (c 1.52, $CHCl_3$); ee 95%; IR (CCl_4, cm^{-1}) 3620, 3570, 1630; ^1H NMR 0.05 (s, 9H), 1.65 (AB spectrum, J =13.4, $\delta\nu$ =20.4, 2H), 2.35 (m, 3H), 4.80 (m, 3H), 7.25–7.40 (m, 5H); ^{13}C NMR −1.3, 26.6, 49.1, 71.2, 111.1, 125.8, 127.4, 128.4, 144.1, 144.4.

(R)-(+)-1-(3,4-Dimethoxyphenyl)-3-(trimethylsilylmethyl)but-3-en-1-ol ***3c***

Yield 97%; $[\alpha]_D$ +17.5 (c 0.78, $CHCl_3$); ee 80%; IR (CCl_4, cm^{-1}) 3620, 3560, 1630, 1595; ^1H NMR 0.05 (s, 9H), 1.59 (AB spectrum, J =13.4, $\delta\nu$ =20.4, 2H), 2.33 (d, J =6.7, 1H), 2.38 (s broad, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.73 (t, J =6.7, 1H), 4.73 (s, 1H), 4.79 (s, 1H), 6.80–6.95 (m, 3H); ^{13}C NMR −1.3, 26.5, 49.0, 55.8, 55.9, 71.1, 108.9, 110.9, 111.0, 118.0, 136.7, 144.5, 148.3, 149.0;

HRMS (EI) Found: $[M]^+$ 294.1646; $C_{16}H_{26}O_3Si$ requires M 294.1644; Anal. Calcd for $C_{16}H_{26}O_3Si$ C, 65.27; H, 8.91; Si, 9.51; Found C, 65.59; H, 8.97; Si, 9.87.

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