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A facile enantioselective synthesis of 2-(2-aminoethyl)allylsilanes, new synthons for piperidine synthesis

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Abstract—The synthesis of chiral (2-substituted-2-aminoethyl)allylsilanes by cerium mediated trimethylsilylmethylmagnesium chloride addition to the ester group of non racemic chiral β-aminoesters is described.

The piperidine ring is a structural subunit found in a large number of naturally occurring alkaloids. The stereoselective synthesis of functionalized piperidines has received considerable attention due to the broad range of their biological activity and their versatility as key synthetic intermediates.[1] As part of our program to expand the synthetic utility of allylsilyl functionalized substrates for the synthesis of piperidine-containing natural products,[2,3] we have imagined a scheme where the piperidine ring would be formed by a Mannich type intramolecular cyclisation reaction starting from substituted aminoethylallylsilyl derivatives. In this paper, we report the enantioselective synthesis of these aminoallylsilanes.

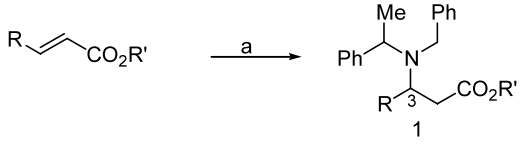
In a previous publication,[4] we have described the enantioselective synthesis of hydroxyethylallylsilyl derivatives. They were prepared from chiral hydroxyesters, the allylsilyl functionality was introduced by cerium mediated trimethylsilylmethylmagnesium chloride addition to the ester group. We thought that such a reaction could be extended to aminoesters and this article describes the successful application of this strategy to the synthesis of aminoethylallylsilanes.

The non racemic chiral starting materials were aminoesters **1a–e** which were prepared by Michael conjugate addition of lithium (*R*) or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-ethylenic esters (Scheme 1) according to Davies' procedure.[5]

The results are summarized in Table 1.

Aminoesters **1** were obtained with good to excellent yields and high diastereoselectivity. The absolute configuration of the new stereogenic center of the major diastereomer was assigned by analogy with Davies' work.[5]

The synthesis of the target molecules was carried out as shown in Scheme 2



Scheme 1. *Reagents and conditions*: (a) (*R*) or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine, *n*-BuLi, THF, 0°C, 1 h.

Table 1. Preparation of β-aminoesters **1**

	R	R′	Yield (%)	Diastereomeric purity
(3*R*,α*R*)-**1a**	Me	Et	83	91:9
(3*S*,α*S*)-**1a**	Me	Et	85	91:9
(3*R*,α*R*)-**1b**	Pr	Et	79	91:9
(3*S*,α*S*)-**1b**	Pr	Et	70	91:9
(3*R*,α*R*)-**1c**	C_9H_{19}	Et	71	90:10
(3*S*,α*S*)-**1c**	C_9H_{19}	Et	69	90:10
(3*R*,α*R*)-**1d**	$C_{11}H_{23}$	Et	88	90:10
(3*S*,α*S*)-**1d**	$C_{11}H_{23}$	Et	76	90:10
(3*S*,α*R*)-**1e**	Ph	Me	86	92:8
(3*R*,α*S*)-**1e**	Ph	Me	79	92:8

Keywords: allylsilane; organocerium; amine; diastereoselectivity.
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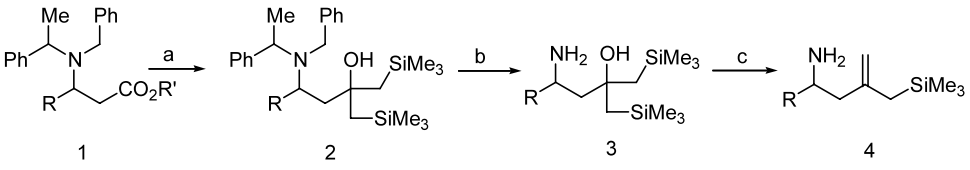

Scheme 2. *Reagents and conditions*: (a) Me_3SiCH_2MgCl, $CeCl_3$, THF, rt, 3 days; (b) $Pd(OH)_2$, H_2, MeOH, H_2O, AcOH, THF, 24 h; (c) HCl 1N, diethyl ether, 0°C, 1–24 h.

In a first step, the cerium reagent derived from cerium chloride and trimethylsilylmethylmagnesium chloride[4] was reacted with the ester group of the starting materials to result in the formation of the tertiary alcohols **2**[6] with very good yields. The aqueous acidic workup of the reaction had to be performed in mild conditions (HCl 1N, $t<-5$°C for 1 h) to prevent elimination of trimethylsilanol. Debenzylation of **2** was performed at room temperature under hydrogen (3.5 atm) with Pearlman's catalyst to give aminoalcohols **3**[7] in generally good to excellent yields. The relatively moderate yields in the phenyl substituted compound **3e** have been attributed to partial cleavage of the molecule under the hydrogenolysis conditions. In the last step, tertiary alcohols **3** were treated with HCl 1N at 0°C for 1–24 h to give aminoallylsilanes **4**[8] in good to excellent yields. The results are summarized in Table 2.

Table 2. Preparation of compounds **2**, **3**, and **4**

Aminoester **1**	Product **2**	Product **3**	Product **4**	
	Yield (%)	Yield (%)	Yield (%)	$[\alpha]_D$
(3*R*,α*R*)-**1a**	90	92	93	+20 (*c* 0.9; $CHCl_3$)
(3*S*,α*S*)-**1a**	86	91	Quant.	−21 (*c* 1.1; $CHCl_3$)
(3*R*,α*R*)-**1b**	76	83	75	+22 (*c* 1.1; $CHCl_3$)
(3*S*,α*S*)-**1b**	72	80	89	−21 (*c* 0.9; $CHCl_3$)
(3*R*,α*R*)-**1c**	82	88	Quant.	+18 (*c* 1.3; $CHCl_3$)
(3*S*,α*S*)-**1c**	71	89	84	−16 (*c* 1.9; $CHCl_3$)
(3*R*,α*R*)-**1d**	51	80	75	+12 (*c* 1,2; $CHCl_3$)
(3*S*,α*S*)-**1d**	73	82	78	−13 (*c* 1.0; $CHCl_3$)
(3*S*,α*R*)-**1e**	71	37	94	−10[a] (*c* 0.7; $CHCl_3$)
(3*R*,α*S*)-**1e**	68	44	90	+9[a] (*c* 1.0; $CHCl_3$)

[a] The enantiomeric purity was determined by HPLC using a Chiralcel OD column ($ee_{(3S,\alpha R)\text{-}\mathbf{1e}}=84\%$, $ee_{(3R,\alpha S)\text{-}\mathbf{1e}}=80\%$).

In conclusion, we have described the enantioselective synthesis of original 2-(2-aminoethyl)allylsilanes in three steps with good overall yields. These compounds will be used as new chiral starting materials for the synthesis of piperidine natural products.

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6. General procedure for preparation of **2**: Powdered $CeCl_3{\cdot}7H_2O$ (4.6 equiv.) was dried under vacuum (0.05 mmHg) for 3 days at 120°C while stirring. The flask was flushed with argon, then dry THF (110 ml) was added to form a white suspension which was stirred at room temperature for an additional 2 h. This slurry was cooled to −78°C and trimethylsilylmethylmagnesium chloride (4.6 equiv.) in THF was added dropwise over a period of 1–2 h. The cold mixture was stirred for 1 h and the ester (0.01 mol) in THF (10 ml) was added dropwise over 30 min. The resulting mixture was allowed to warm to room temperature and stirred for 3 days. The reaction mixture was then cooled to −10°C and hydrolyzed by dropwise addition of 1 M hydrochloric acid. The layers were separated and the aqueous layer was extracted with diethylether. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography. (3*R*,α*R*)-**2a**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.18–7.50 (m, 10H); 6.35 (s, 1H); 3.97 (q, 1H, $J=7.0$ Hz); 3.81 (AB system, 2H, $\Delta\nu=185$ Hz, $J_{AB}=12.8$ Hz); 3.34 (m, 1H), 2.03, (t, 1H, $J=13$ Hz), 1.42 (d, 3H, $J=7.0$ Hz), 1.14 (d, 3 H, $J=6.5$ Hz), 1.07 (dd, 1H, $J=13$ Hz, $J=1.9$ Hz); 0.84 (AB system, 2H, $\Delta\nu=43$ Hz, $J_{AB}=14.8$ Hz; 0.12 (AB system, 2H, $\Delta\nu=234$ Hz, $J_{AB}=14.8$ Hz), 0.07 (s, 9H); −0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6; 139.2; 129.8; 129.1; 128.7; 128.4;

127.4; 75.8; 56.2; 49.0; 48.9; 45.8; 34.9; 33.1; 18.7; 13.6; 1.1; 0.4.

7. General procedure for preparation of **3**: To a solution of **2** (1 g) in methanol (13 ml), acetic acid (0.31 ml), water (2.7 ml) and THF (2.4 ml) was added Pearlman's catalyst (0.3 g). The resultant mixture was stirred under 3.5 atm of hydrogen at room temperature for 24 h in a Parr apparatus. The mixture was filtered through Celite and concentrated. Then, the filtrate was washed with a saturated solution of sodium hydrogenocarbonate. Aqueous layer was extracted with methylene chloride then the organic layers were dried (K_2CO_3). (*S*)-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (m, 1H); 1.51 (dd, 1H, $J=14.7$ Hz, $J=2.5$ Hz), 1.45 (dd, 1H, $J=14.7$ Hz, $J=11.7$ Hz); 1.18 (AB system, 2H, $\Delta v=73$ Hz, $J=14.6$ Hz), 1.11 (d, 3H, $J=6.3$ Hz); 1.01 (AB system, 2H, $\Delta v=42$ Hz, $J=14.7$ Hz), 0.07 (s, 9H); 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 75.6; 50.8; 45.2; 35.00; 32.7; 28.0; 0.9; 0.6.
8. General procedure for preparation of **4**: A solution of HCl 1N (4.4 equiv.) was added slowly to a cooled (0°C) 0.5 M solution of **3** in ether and stirred at 0°C for 1 to 24 h. The excess of acid was neutralized with a saturated solution of sodium hydrogenocarbonate and the aqueous phase was extracted with three portions of ether, organic layers were collected and dried (K_2CO_3). (*S*)-**4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (s, 1H); 4.60 (s, 1H); 3.05 (m, 1H), 2.03 (dd, 1H, $J=13.6$ Hz, $J=4.6$ Hz), 1.86 (dd, 1H, $J=8.8$ Hz, $J=13.6$ Hz), 1,51 (AB system, 2H, $\Delta v=13$ Hz, $J_{AB}=13.4$ Hz), 1.35 (s, 2H); 1.07 (d, 3H, $J=6.4$ Hz); 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3; 109.6; 49.4; 44.6; 26.5; 23.9, –0.4.