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Preparation of a 'Si-centered' chiral auxiliary by resolution

Michael Trzoss, Jie Shao and Stefan Bienz*

University of Zurich, Organic Chemistry, Winterthurerstr. 190, Zurich CH8057, Switzerland

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Abstract—(*R*)- and (*S*)-[(benzyloxy)methyl](*tert*-butyl)methylsilane [(−)-(*R*)-**1** and (+)-(*S*)-**1**], possessing a stereogenic center at the Si-atom, were prepared in highly enantiomerically enriched form by resolution via diastereomeric silyl ethers. Conversion of the hydrosilanes into different functionalized chiral silanes by direct or stepwise substitution of the (Si)–H-atom was shown to proceed with high stereoselectivity (96–98% stereoselectivity under optimized conditions) thus allowing the preparation of substrates where the chiral silicon moiety can act as a chiral auxiliary for stereoselective transformations.

1. Introduction

We have previously shown that chiral silicon groups can efficiently be used as chiral auxiliaries for stereoselective transformations.[1–6] Of particular interest was silicon group **A** containing a 'Si-centered' stereogenic, which was used as an auxiliary for the asymmetric nucleophilic addition of organometallics to the carbonyl groups of acylsilanes **2**[2–5,7] and, more recently, also of α- and β-silyloxy carbonyl derivatives **3** and **4** (Fig. 1).[8] The stereoselectivities obtained by these reactions were high with a number of useful transformations being performed with the respective addition products.

While the use of racemic material was for the most part sufficient for our initial studies (concerning primarily of the investigation of stereochemical efficiency of newly designed chiral auxiliaries), access to the enantiomerically pure auxiliaries and starting materials is imperative for establishing new chemical methods for general application. For auxiliary **A** we have shown that enantiomerically highly enriched acylsilanes (−)-(*R*)- and (+)-(*S*)-**2** are accessible by Si-specific biocatalytic reduction of the respective racemate, chromatographic separation of the obtained diastereomeric α-hydroxysilanes, and re-oxidation of the latter.[3,9] The biotransformation was high yielding and as a result scaled-up to batches of 30 g,

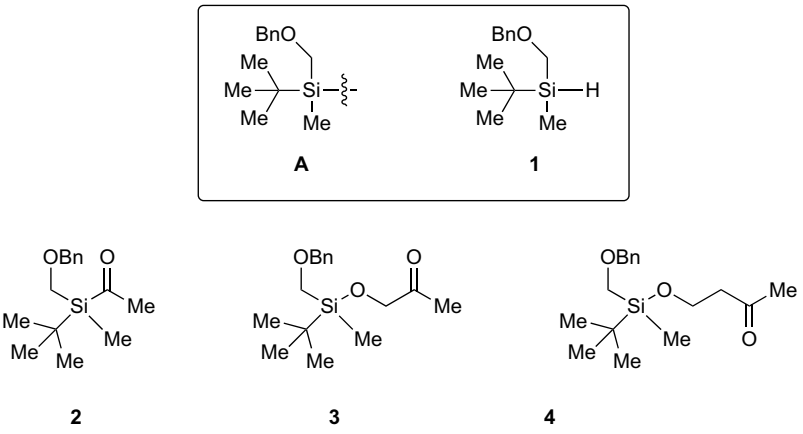

Figure 1.

* Corresponding author. Tel.: +41-1-635-4245; fax: +41-1-635-6812; e-mail: sbienz@oci.unizh.ch

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allowing the preparation of reasonable amounts of material with this process in one cycle. However, the procedure itself is not open to the general chemical community since it requires access to rather large reactors along with a knowledge of handling microorganisms. We thus searched for an alternative method for the preparation of enantiomerically pure silicon compounds **A** and considered hydrosilane **1** as a suitable target. Hydrosilane **1** is largely configurationally stable[10] and is suitable as a starting material for the preparation of silanes with different functionalities.

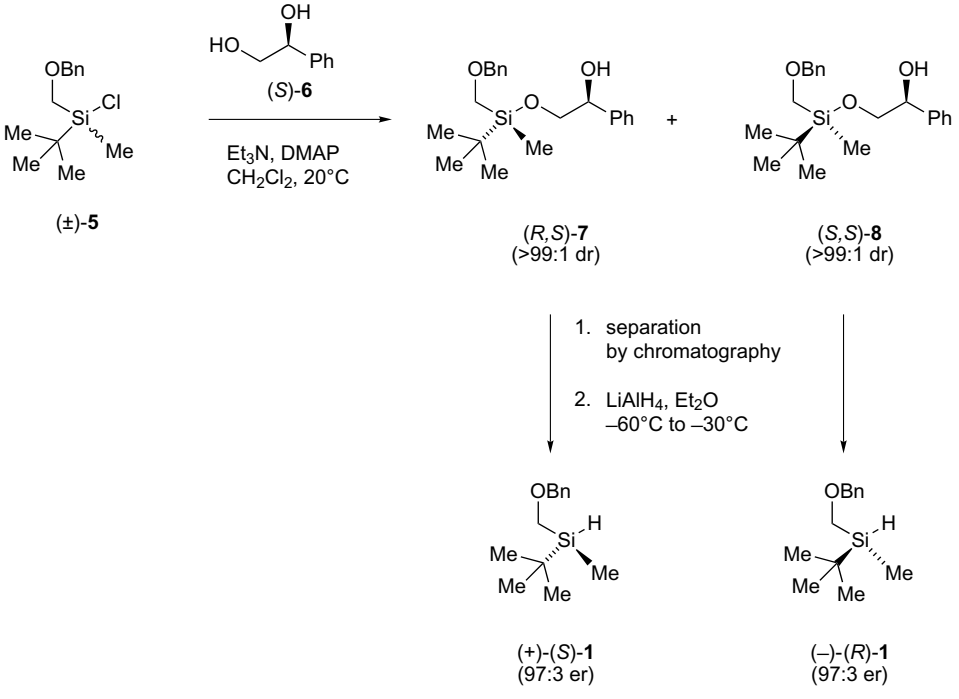
Herein we report a novel and convenient route to the enantiomerically highly enriched hydrosilanes (−)-(*R*)- and (+)-(*S*)-**1**, and show that these hydrosilanes can in fact be converted stereospecifically into several functionalized compounds such as acylsilanes, halogenosilanes, and silyl ethers.

2. Results

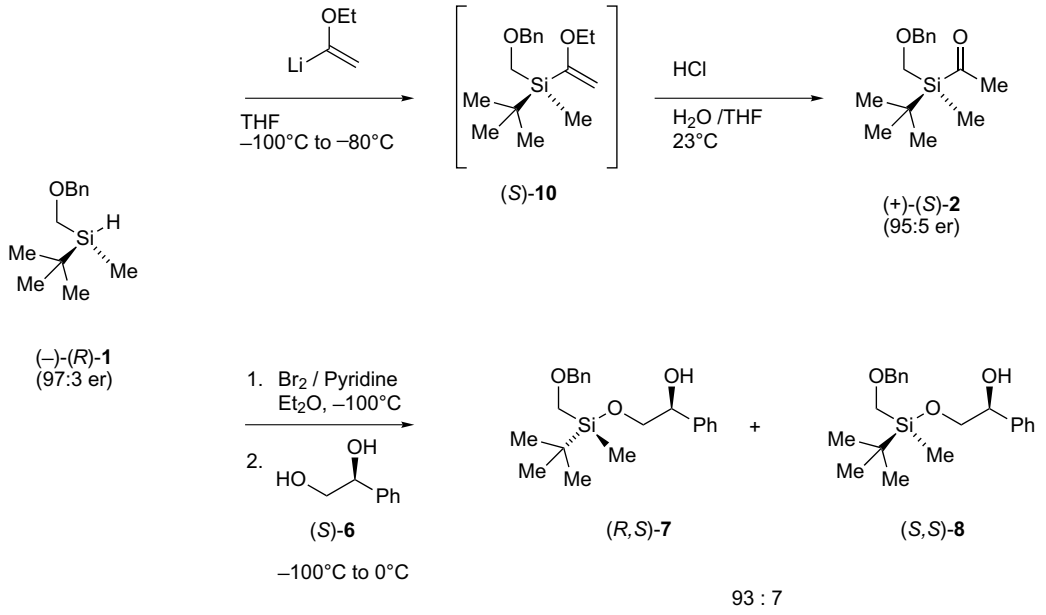
During earlier investigations we noticed that diastereomeric silyl ethers **7** and **8** (obtained as racemates by the addition of phenylmagnesium bromide to a racemic aldehyde precursor) could be readily separated by flash chromatography,[8] which would thus allow the resolution of the silicon auxiliary when the respective mono-silyl ethers of racemic chlorosilane (±)-**5** with enantiomerically pure diols (*R*)- or (*S*)-**9** were prepared (Scheme 1).

Hence, enantiomerically pure diol (*S*)-**6**, which is commercially available, was treated with chlorosilane (±)-**5** in the presence of Et_3N and DMAP, which gave an 87% yield of the two optically active ethers (*R*,*S*)-**6** and (*S*,*S*)-**7**. Additional products that can be silylated at the secondary alcohol group of the diol were not obtained in this reaction. After separation of the diastereomeric products, the reduction of (*R*,*S*)-**7** and (*S*,*S*)-**8** with $LiAlH_4$ in Et_2O at low temperatures afforded stereoselectively, the respective hydrosilanes (+)-(*S*)-**1** and (−)-(*R*)-**1** with enantiomeric ratios (er) of 97:3 (together with diol (*S*)-**9**, which could be recovered). The enantiomeric purities of the two hydrosilanes were determined by means of ^1H NMR spectroscopy, performed in the presence of the Pirkle reagent.[11] Since the conversion of silyl ethers into hydrosilanes is known to proceed with retention of configuration, the relative configurations of (*R*,*S*)-**7** and (*S*,*S*)-**8** were deduced on the basis of the already known reduction products (+)-(*S*)- and (−)-(*R*)-**1**,[5] respectively.

To prove the viability of compounds **1** to be used as starting materials for the preparation of differently functionalized enantiomerically enriched chiral silanes, hydrosilane (*R*)-**1** was treated with freshly prepared 1-ethoxyvinyllithium at −100 °C in THF to deliver vinyl ether (*S*)-**10**, which was directly hydrolyzed by treatment with diluted aqueous HCl to afford the (*S*)-configured acylsilane (+)-**2** (Scheme 2). Starting from (−)-(*R*)-**1** of 97% enantiomeric ratio (er), (*S*)-**2** of 95% er was obtained, showing that the substitution reaction proceeded to 98% with retention of configuration. The enantiomeric ratio of acylsilane **2** was determined, as previously described, by ^1H NMR of the Mosher ester derivatives of the separated corresponding diastereomeric alcohols that were obtained by reduction of a sample of the ketone with $LiAlH_4$.[4]



Scheme 1.



Scheme 2.

Lower selectivity was observed for the conversion of enantiomerically enriched hydrosilanes **1** into silyl ethers. Treatment of (−)-(*R*)-**1** (er 97:3) with Br_2 at −100 °C in the presence of pyridine followed by the addition of enantiomerically pure diol (*S*)-**6** gave, after gradual warm-up of the mixture to 0 °C and aqueous work-up, silyl ethers (*R*,*S*)-**7** and (*S*,*S*)-**8** in diastereomeric ratios (dr) of 80:20 to 93:7, depending on the solvent used. In CH_2Cl_2, the formation of the silylether from the intermediary bromosilane proceeded rather rapidly even at −60 °C, while the same transformation proceeded more slowly, but with higher selectivity, even when it was warmed to 0 °C, when Et_2O was used as the solvent. The overall reaction, with retention of the configuration in the first and inversion of configuration in the second step, proceeded with 82–96% overall stereoselectivity. The loss of stereochemical information during the process was probably due to partial racemization of the bromosilane in the presence of Br^- that is formed during the bromination and subsequent substitution steps rather than to a nonselective substitution reaction itself.

3. Conclusion

We have shown herein that 'Si-centered' chiral silicon group **A** can be prepared in the form of hydrosilanes (−)-(*R*)- and (+)-(*S*)-**1** in highly enantiomerically enriched forms. Transformation into differently functionalized silanes can be effected with moderate to high stereoselectivity, too, depending on the reaction conditions used. Direct substitution of the hydrosilane by treatment with a nucleophile seems to be advantageous over a stepwise procedure, where racemization of the intermediary species is possible.

4. Experimental

4.1. General

Unless otherwise stated: manipulations were carried out under Ar in oven-dried glass equipment. For reactions, Et_2O was freshly distilled from Na with benzophenone ketyl as indicator; CH_2Cl_2 was freshly distilled from CaH_2; benzene (Anal. Grade) was stored over Na. All organic solvents were distilled prior to use. Extracts were washed with satd aq NH_4Cl solution and brine and dried over $MgSO_4$. Solutions for work-up procedures were prepared in deionized H_2O. Chromatography: Merck silica gel 60 (40–63 μm). Mp: Mettler FP5/FP52. IR spectra: neat liquid films between NaCl plates; Perkin–Elmer 297 or 781; in cm^{-1}, strong bands only. ^1H NMR spectra in $CDCl_3$; Bruker ARX-300 (300 MHz); δ in ppm relative to $CHCl_3$ (δ 7.26), J in Hz. ^{13}C NMR spectra in $CDCl_3$; Bruker ARX-300 (75.5 MHz); δ in ppm relative to $CDCl_3$ (δ 77.0); multiplicities from DEPT-135 and DEPT-90 experiments. Mass spectrometry (MS): Finnigan SSQ 700; chemical ionization (CI) with NH_3 as the reactant gas; quasi-molecular ions and characteristic fragments; in m/z (rel.%).

4.2. (Si*R*,1*S*)- and (Si*S*,1*S*)-2-{[[(Benzyloxy)methyl](*tert*-butyl)methylsilyl]oxy}-1-phenylethanol (*R*,*S*)-7 and (*S*,*S*)-8 and resolution

Et_3N (1.27 mL, 9.1 mmol), DMAP (0.1 g, 0.8 mmol), and (*S*)-1-phenylethane-1,2-diol (*S*)-**6** (1.08 g, 7.8 mmol) were added at 0 °C successively to a stirred solution of *rac*-[(benzyloxy)methyl](*tert*-butyl)chloro(methyl)silane (±)-**5** (2.00 g, 7.8 mmol) in CH_2Cl_2 (30 mL). The mixture was warmed to 23 °C and stirred for an additional 3 h. It was quenched with satd aq NH_4Cl solution, extracted with Et_2O, and chromatographed (hexane/Et_2O 3:1) to

provide silylethers (*R*,*S*)-**7** (1.21 g, 3.4 mmol) and (*S*,*S*)-**8** (1.22 g, 3.4 mmol) in 87% overall yield.

(*R*,*S*)-**7**: $[\alpha]_D^{23} = 42.4$ (*c* 1.23, $CHCl_3$, 100:0 er). IR: 3440 br, 2930, 2860, 1100 br, 1070, 700. ^{1}H NMR: 7.31–7.18 (m, 10 arom H); 4.75–4.71 (m, C*H*OH); 4.46 (s, PhCH_2); 3.85 (d, $J = 1.9$, OH); 3.81 (dd, $J_1 = 10.5$, $J_2 = 3.1$, SiOC*H*H); 3.56 (dd, $J_1 = 10.5$, $J_2 = 9.0$, SiOCH*H*); 3.25, 3.15 (AB, $J = 13.1$, $SiCH_2$); 0.87 (s, *t*-Bu); 0.10 (s, SiMe). ^{13}C NMR: 140.4, 138.0 (2s, 2 arom C); 128.3, 128.1, 127.9, 127.6 (4d, 4×2 arom C); 127.5, 126.2 (2d, 2 arom C); 77.2 (t, PhC_2); 74.5 (d, CHOH); 70.2 (t, SiOCH_2); 60.2 (t, $SiCH_2$); 25.9 (q, CMe_3); 18.1 (s, *C*Me$_3$); −8.1 (q, SiMe). CI-MS: 376 (100, $[M+NH_4]^+$); 358 (57, $[M+NH_4–H_2O]^+$).

(*S*,*S*)-**8**: $[\alpha]_D^{23} = +26.3$ (*c* 1.32, $CHCl_3$, 100:0 er). IR: 3440 br, 2930, 2860, 1100 br, 1070, 700. ^{1}H NMR: 7.31–7.17 (m, 10 arom H); 4.73–4.68 (m, C*H*OH); 4.47, 4.43 (AB, $J = 12.1$, PhCH_2); 3.85 (dd, $J_1 = 10.4$, $J_2 = 3.2$, SiOC*H*H); 3.61 (dd, $J_1 = 10.4$, $J_2 = 8.2$, SiOCH*H*); 3.45 (d, $J = 3.0$, OH); 3.27, 3.15 (AB, $J = 13.4$, $SiCH_2$); 0.87 (s, *t*-Bu); 0.09 (s, SiMe). ^{13}C NMR: 140.6, 138.2 (2s, 2 arom C); 128.3, 128.2, 127.8, 127.6 (4d, 4×2 arom C); 127.5, 126.2 (2d, 2 arom C); 77.3 (t, PhC_2); 74.4 (d, CHOH); 69.7 (t, $SiOCH_2$); 60.2 (t, $SiCH_2$); 26.1 (q, CMe_3); 18.2, (s, *C*Me$_3$); −7.8 (q, SiMe). CI-MS: 376 (100, $[M+NH_4]^+$); 358 (55, $[M+NH_4–H_2O]^+$).

4.3. (*R*)- and (*S*)-[(Benzyloxy)methyl](*tert*-butyl)methylsilane (−)-(*R*)-1 and (+)-(*S*)-1

A solution of the silylether (*S*,*S*)-**8** (500 mg, 1.39 mmol) in Et_2O (1 mL) was added at −60 °C to a stirred suspension of $LiAlH_4$ (53 mg, 1.39 mmol) in Et_2O (20 mL). The mixture was warmed to −30 °C and, after stirring for an additional 2 h, 5% aq H_2SO_4 solution was added to neutral pH. This was extracted with Et_2O and chromatographed (hexane/Et_2O 3:1) to afford hydrosilane (−)-(*R*)-**1** {291 mg, 1.31 mmol, 94%; $[\alpha]_D^{23} = -6.5$ (*c* 1.10, $CHCl_3$), 97:3 er} and diol (*S*)-**6** (177 mg, 1.28 mmol, 92%). Analogously, (+)-(*S*)-**1** was obtained from (*R*,*S*)-**7** in 94% yield {$[\alpha]_D^{23} = +6.5$ (*c* 1.10, $CHCl_3$), 97:3 er}. The spectroscopic data of (−)-(*R*)-**1** and (+)-(*S*)-**1**, except for chiroptical properties, were identical to those of (±)-**1** reported earlier;[1] the er were determined by ^{1}H NMR spectroscopy in presence of the Pirkle reagent.[11]

4.4. (*S*)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}ethanone (+)-(*S*)-2 from (−)-(*R*)-1

A solution of freshly prepared 1-ethoxyvinyllithium (3.15 mmol) in THF (8 mL) was slowly added at −100 °C to a stirred solution of hydrosilane (−)-(*R*)-**1** (200 mg, 0.90 mmol) in THF (10 mL). The mixture was allowed to warm to −60 °C and stirred at this temperature for an additional 5 h before it was quenched by the addition of satd aq NH_4Cl solution. After extraction with Et_2O, the crude product was dissolved in acetone (5 mL), after which 10% aq HCl solution (0.5 mL) was added and stirred for 1 h at 23 °C. Neutralization with satd aq $NaHCO_3$ solution, extraction with Et_2O, and chromatography (hexane/Et_2O 3:1) provided acylsilane (+)-(*S*)-**2** {202 mg, 0.76 mmol, 85%; $[\alpha]_D^{23} = -8.7$ (*c* 0.57, $CHCl_3$), 95:5 er}, which was spectroscopically identical with (±)-**2** reported earlier.[1] The er of the product was determined by means of ^{1}H NMR spectroscopy performed with the Mosher ester derivatives of the separated diastereomeric reduction products of (+)-(*S*)-**2** as reported earlier.[4]

4.5. (Si*R*,1*S*)-2-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl]oxy}-1-phenylethanol (*S*,*S*)-8 from (−)-(*R*)-1

A solution of Br_2 (0.74 mmol) in Et_2O (1 mL) was added dropwise at −100 °C to a stirred solution of hydrosilane (−)-(*R*)-**1** (150 mg, 0.67 mmol) and pyridine (107 mg, 1.34 mmol) in Et_2O (10 mL). After 30 min, (*S*)-1-phenylethane-1,2-diol (*S*)-**6** (121 mg, 0.88 mmol) was added at −100 °C and stirring was continued for an additional 2 h while the mixture was allowed to warm to −60 °C. Over a period of 4 h, the temperature was allowed to reach 0 °C and stirring continued at this temperature for an additional 3 h. Addition of satd aq NH_4Cl solution, extraction with Et_2O, and chromatography (hexane/Et_2O 3:1) provided silylether (*S*,*S*)-**8** (180 mg, 0.51 mmol) together with (*R*,*S*)-**7** and (14 mg, 0.04 mmol) corresponding to 82% overall yield and a dr of 93:7 (determined by ^{1}H NMR spectroscopy on the crude product).

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