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Chiral Silicon Groups as Auxiliaries for Enantioselective Synthesis: Access to Optically Active Silanes by Biotransformation and the Enantiospecific Preparation of (*R*)-(+)-1-Phenylethanol

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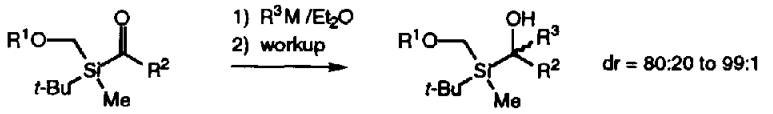
Abstract: The synthesis of the optically active alkoxymethyl-substituted acetylsilanes (+)-**3** and (–)-**3** was achieved by the bioreduction of (±)-**3** with resting cells of *Trigonopsis variabilis* to the diastereoisomeric alcohols (+)-**4** and (+)-**5**. These two compounds were separated by chromatography and separately reoxidized to the desired optically active silyl ketones. As a simple example of the use of chiral alkoxymethyl-substituted silyl groups as auxiliaries for the synthesis of enantiomerically enriched silicon-free compounds, the chelate controlled 1,2-addition of phenyl lithium to (–)-**3** and the stereospecific conversion of the corresponding major addition product to (*R*)-(+)-1-phenylethanol (+)-**10** is presented.

INTRODUCTION

We have previously demonstrated that chiral alkoxymethyl-substituted silicon groups can efficiently transfer stereochemical information from a silicon to a carbon center:[2,3] for instance, the 'chelate-controlled' addition of several organometallic species to the carbonyl group of chiral acylsilanes **1** afforded the corresponding α-hydroxysilanes **2** with diastereoisomeric ratios (dr) up to >98:2 (Scheme 1). Such α-hydroxysilanes can serve as versatile starting materials for further stereoselective transformations.[4] The use of chiral silanes for the enantioselective synthesis, however, has been limited so far due to the restricted access to optically active material.



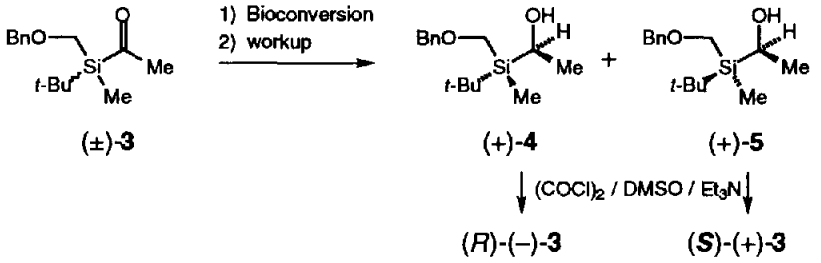
1 **2**

Scheme 1

To introduce chiral silicon auxiliaries as tools for the synthesis of optically active silicon-free molecules, it was imperative to develop an efficient method to attain enantiomerically pure compounds possessing a stereogenic silicon center. In this paper we present a handy method for the preparation of the two optical antipodes (+)-**3** and (–)-**3** (Scheme 2). In the key step, the enantioselective bioreduction of acylsilanes is applied; a reaction, which was described earlier by Tacke and Syldatk *et al.* for silyl ketones differing from ours.[5-7]

RESULTS AND DISCUSSION

Bioconversion—The racemic (±)-**3** is accepted by several microorganisms as a substrate. It is reduced stereoselectively to the α-hydroxysilanes (+)-**4** and (+)-**5** (Scheme 2). Preliminary screening experiments revealed that best results with respect to chemical and stereochemical yields of the compounds (+)-**4** and (+)-**5** were obtained with cells of *Trigonopsis variabilis* (DSM 70714) as the biocatalyst.



Scheme 2

The bioconversion of (±)-**3** was studied more thoroughly with two cell preparations: with resting free and resting immobilized cells (calcium-alginate matrix) of *T. variabilis*. Both systems delivered the two alcohols (+)-**4** and (+)-**5** in high chemical (67–99%) and stereochemical yields (up to >96% ee, see below). The use of immobilized cells, however, proved to be advantageous for several reasons.

(1) The immobilized cells gave particularly higher yields of the reduction products (95% *vs.* 70%), and, which is even more important, the enantiomeric purities of the products (+)-**4** and (+)-**5** were reproducible and distinctively higher when the reactions are performed with immobilized cells. The graph on the left side of Figure 1 depicts the conversions of (±)-**3** into (+)-**4** and (+)-**5** as a function of the reaction time with the two systems (identical conditions and catalyst concentrations). As can be recognized, the reaction rate, particularly in the initial period of the conversion, is lower when the transformation is performed with immobilized cells: the diffusion of the rather non-polar substrate through the hydrophilic calcium alginate matrix represents most probably the limiting factor.

(2) The immobilized cells, embedded in the alginate matrix, are more stable than the free cells. The free resting cells of *T. variabilis* have to be used immediately after harvesting. Upon their storage at 4°C for one day only, the enzymatic activity dropped already to 60%; freezing them reduced the activity even to 10%. Though not stable for several months, the storage of immobilized cells for two weeks at 4°C did not visibly affect their enzymatic activity. As another consequence of the increased stability of the immobilized cells, they can be repetitively used for several subsequent biotransformations. It is recognized from the right-side graph in Figure 1, that a drop of enzymatic activity is not observed till after three biotransformations; after approximately 15 to 16 transformations, the relative activity seems to be stabilized at 27%. It is supposed that several enzyme systems participate at the bioreduction of (±)-**3** and that not all of them are deactivated to the same extent in the course of the reactions. That in fact more than one oxido-reductase system is present in *T. variabilis* was shown with the unsuccessful reduction of (±)-**3** in presence of a partially purified enzyme that was active towards other acylsilanes.[5]

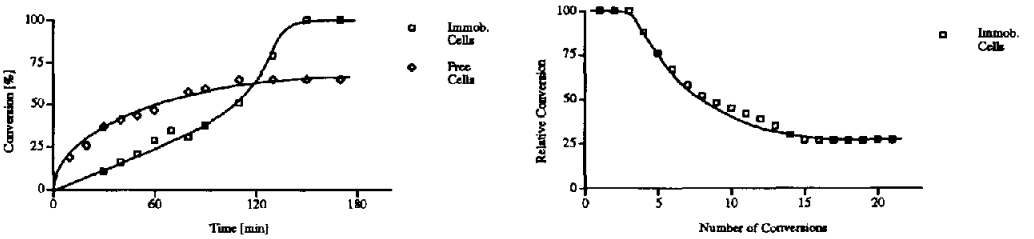


Figure 1 Left-side graph: comparison of the conversion curves of the transformations with free resting cells and immobilized resting cells of *T. variabilis*. Right-side graph: dependency of the relative biocatalytic activities of immobilized resting cells of *T. variabilis* as a function of the number of transformations with the same cell preparation.

(3) The use of immobilized cells facilitates the workup procedure. When working with free resting cells, the isolation of the reduction products was difficult because of the formation of persistent emulsions in the extraction step. This problem was particularly distinctive in large-scale transformations. When working with immobilized cells the extraction step could be omitted. The alginate pearls containing the biocatalyst can readily be filtered off the reaction broth and reused, and the cell-free aqueous filtrate is subsequently passed through a column of Amberlite XAD-2 to quantitatively collect the organic products by adsorption.

An obstacle in the bioreductions of the acylsilanes is the pronounced substrate inhibition, which is often observed in such transformations. In the case of acylsilanes, it is readily recognized from the Michaelis–Menten plot (initial specific biocatalyst's activity[8] *vs.* substrate concentration, Figure 2) that the biocatalyst's initial activity decreases with increasing substrate concentration. The biotransformation, however, is still performed reasonably fast with substrate concentrations up to 1 g/l.

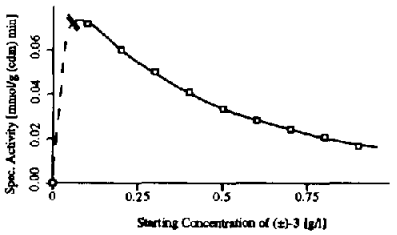
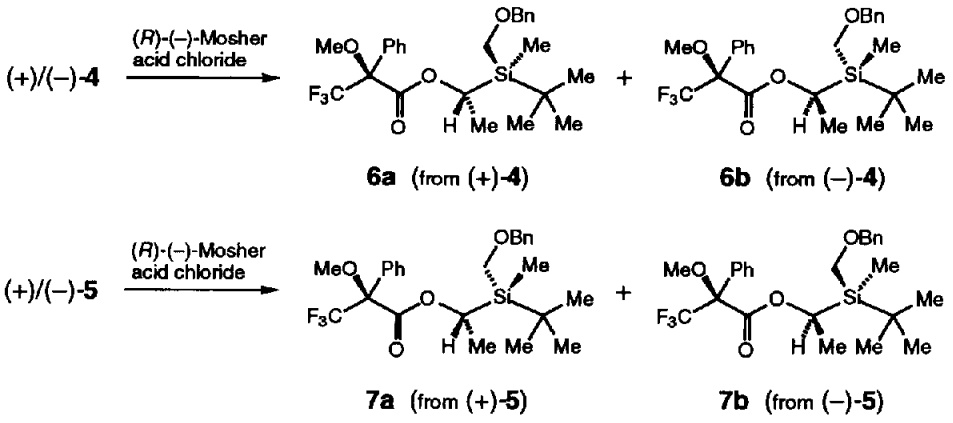


Figure 2 Michaelis-Menten plot for the bioreduction of (±)-**3** with immobilized cells of *T. variabilis* revealing a distinctive substrate inhibition.

Enantiomeric Purities and Absolute Configurations—The alcohols (+)-**4** and (+)-**5** were separated by low-pressure liquid chromatography on silica gel and were further investigated separately. The enantiomeric purities and the absolute configurations at the chiral carbinol centers of the two compounds were determined by the Mosher method:[9] treatment of enriched (+)-**4** and (+)-**5** with (*R*)-(–)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (Mosher acid chloride) gave mainly rise to the two products **6a** and **7a**, respectively (Scheme 3).



Scheme 3

Only traces of the diastereoisomeric compounds **6b** and **7b**—corresponding to dr's >98:2—were detected by ^{1}H NMR spectroscopy. Thus, the enantiomeric purities of the two starting compounds (+)-**4** and (+)-**5** exceeded 96% ee. The chemical shifts of the proton-containing groups attached to the carbinol carbon atoms—related to those of the Mosher ester derivatives of the respective optical antipodes—revealed for both compounds the *R* configuration at the stereogenic carbon centers. The spectra of the Mosher esters of (±)-**4** (**6a**/**6b**, 1:1) and (+)-**4** (**6a**/**6b** >98:2) are shown in Figure 3.

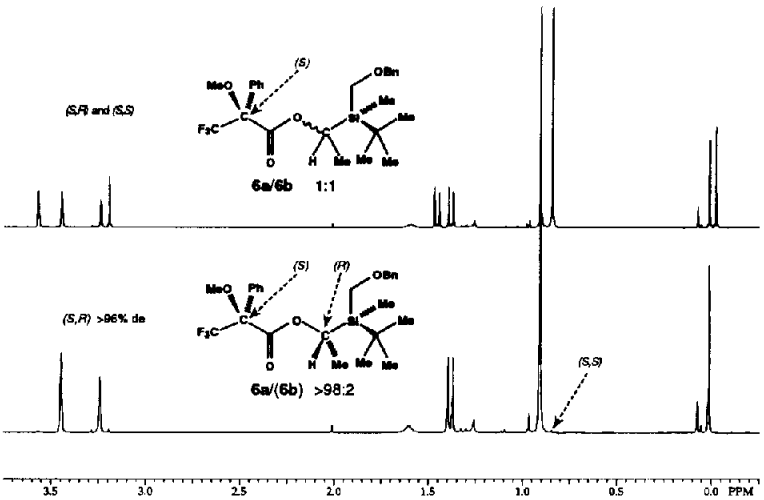
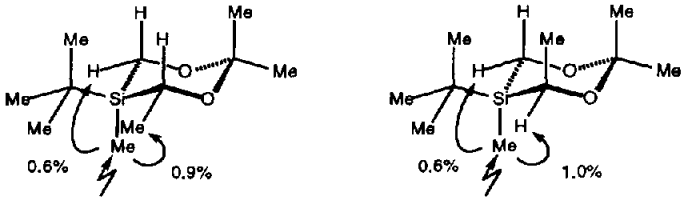


Figure 3. ^{1}H NMR of the Mosher esters of (±)-**4** (**6a**/**6b** 1:1) and of (+)-**4** (**6a**/**6b** >98:2) to establish the enantiomeric purity of (+)-**4** and the configuration at the stereogenic carbinol center.

The relative configurations of the silicon and carbon stereogenic centers—and therefrom the absolute configuration at the stereogenic silicon centers—were determined with nuclear Overhouser enhancement (NOE) NMR experiments, which were performed with the acetonides (±)-**8** and (±)-**9** (Figure 4). These compounds were obtained by hydrogenolysis of (±)-**4** and (±)-**5** and by the treatment of the two intermediary diols with acetone diethyl acetal and acid. Irradiation at the absorption frequencies of the Si*CH*$_3$ groups of the

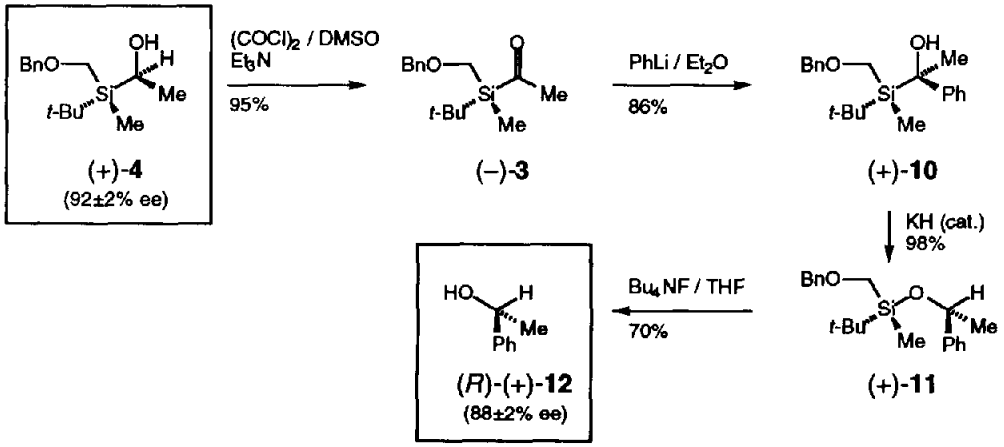
two rigid acetonides gave small but distinctive NOE responses at the signals deriving from the respective adjacent *cis*-configured groups. No enhancements of the respective *trans*-oriented groups, which should be arranged *antiperiplanar*, were detected. The absolute configuration at the stereogenic silicon center of (+)-**3** was confirmed by single crystal X-ray analysis of a derivative.[10]



(±)-**8** (±)-**9**

Figure 4 NOE responsive signals (irradiation at the $SiCH_3$ signal) for the determination of the relative configurations of the silicon and carbon stereogenic centers.

Synthesis of (*R*)-(+)-1-Phenylethanol—To show with a simple example the synthetic potential of optically active chiral silyl auxiliaries for the stereoselective synthesis of optically active silicon-free organic molecules, carbinol (+)-**4** was converted to (*R*)-(+)-1-phenylethanol [(*R*)-(+)-**12**, Scheme 4]. Oxidation of the α-hydroxysilane (+)-**4** and (+)-**5** under Swern conditions delivered almost quantitatively and without racemization the acetylsilanes (–)-**3** and (+)-**3**, respectively.[11] Treatment of a sample of (–)-**3** (92±2% ee, from a conversion with free resting cells of *T. variabilis*) with phenyl lithium in diethyl ether provided 86% of α-hydroxysilane (+)-**10**. This compound was subsequently brought to reaction with a catalytic amount of potassium hydride to form, after Brook rearrangement,[12] the silyl ether (+)-**11** (98% yield). The silicon group of (+)-**11** was cleaved by the action of tetrabutyl ammonium fluoride (60–75% yield) to afford (*R*)-(+)-1-phenylethanol (*R*)-(+)-**12** with 88±2% enantiomeric excess. The conversion of (+)-**4** to (*R*)-(+)-**12** proceeded therefore with almost complete stereospecificity.



Scheme 4

EXPERIMENTAL

General Remarks. Where not remarked differently: all reactions were carried out under a blanket of inert gas. The solution of salts and acids used in the workup procedures were prepared in deionized water. During the workup, all extracts were dried over disodium sulfate prior to evaporation of the solvents *in vacuo*. Liquid chromatography was performed on Merck silica gel 60 (230–400 mesh), low-pressure liquid chromatography on Merck Lobar colums silica gel 60 (230–400 mesh), gas chromatography (GC) on a polar DB-wax column (60 m, inner diameter 0.25 mm, film 0.25μm; H_2 as the carrier gas with an average linear velocity (determined with butane) of 46.4 cm sec^{-1}). Infrared spectra (IR) were taken neat on a Perkin-Elmer 297 or 781 (frequencies given in cm^{-1}), ^1H (300 MHz) and ^{13}C NMR (50.4 MHz) on a Bruker AM-300 in $CDCl_3$ as the solvent (δ in ppm relative to the solvent: δ_H ($CHCl_3$) = 7.26, δ_C ($CDCl_3$) = 77.0; coupling constants (J) in Hertz, multiplicities of the ^{13}C NMR signals from DEPT experiments), mass spectra in *m/z* (rel.%) on a Varian MAT 112S (chemical ionization (CI-MS) with NH_3 as the reactant gas).

Cultivation and Immobilization of Trigonopsis variabilis *(DSM 70714).*

Cultivation. *T. variabilis* was cultivated in a medium containing 2% malt extract, 2% glucose, 1% bacto peptone, and 0.5% yeast extract. The medium was adjusted to pH 6.8 with diluted HCl or NaOH and autoclaved for 20 min. A preculture was prepared by inoculation of 100 ml of the complex medium with fresh cells from an agar plate (swab of inoculation loop). Incubation was performed in a 400 ml Erlenmeyer shaking-flask, which was shaken at 170 rpm at 30°C for 40 h. 10 ml portions of the preculture were used to inoculate 400 ml portions of medium in 2 l Erlenmeyer shaking-flasks (for large-scale cultivations in bioreactors equipped with pH- and O_2-control, the respective amounts were scaled-up linearly). After incubation for 24 h at 30°C, the cells, being in the exponential growth phase, were collected by centrifugation (at 3000 x *g*, 40 min). They were washed with 0.9% brine and separated from the aqueous medium by centrifugation to give a cell wet mass (cwm) of 8–15 g per 400 ml batch. The ratio 'cell wet mass'/'cell dry mass' of 4.16 was determined by lyophylization of a sample of wet cells. The wet cells were either used directly for bioconversions or were immobilized as described below.

Immobilization. A 'homogeneous' cell/sodium alginate suspension was prepared at 23°C by the admixture of 20 g of a suspension of freshly harvested cells (10 g cwm in 10 ml of H_2O) to 60 g of a homogeneous aqueous soln. of sodium alginate (2% in deionized H_2O; heating and vigorous stirring is required to dissolve completely the sodium alginate). This suspension was added by means of a pump dropwise *via* a capillary to a carefully stirred $CaCl_2$ soln. (2% in H_2O), where the calcium alginate pearls with a load of 12.5% of resting cells (relative to cwm) precipitated. The detachement of small droplets from the capillary was supported by a stream of air; the capillary size as well as the fluid and air flows were adjusted in a way that the size of pearls did not exceed *ca.* 1 mm in diameter. To force a complete crosslinking, the pearls were kept in the $CaCl_2$ soln. for another 30 min at ambient temperature. Then the immobilized cells were collected by filtration, they were washed with H_2O and suspended in an aqueous soln. of 20% glucose, 0.9% NaCl, and 0.05 % $CaCl_2$. They can either be used immediately for biotransformations or stored at 4°C for later transformations.

Bioconversion of (±)-3 to (+)-4 and (+)-5

Bioconversion. (a) With resting free cells: A suspension of 2.5 g (cwm) of freshly harvested cells of *T. variabilis* in 250 ml of a 0.1M Tris buffer at pH 7 containing glucose (20%) was prewarmed in a 2 l Erlen-

meyer shaking-flask for 2 min at 37°C with shaking (170 rpm). 125 mg (0.47 mmol) of (±)-**3** were added and incubation was continued. Samples were taken in intervals of 15–20 min, extracted with hexane and analyzed by GC (isothermal at 200°C, r_t [(±)-**3**] = 7.35, r_t [(+)-**4**] = 11.98, r_t [(+)-**5**] = 13.03). After the reaction was complete (*ca.* 2 h), the cells were removed by centrifugation (at 3000 x *g*, 40 min) and the reaction products extracted (persistent emulsions!) from the supernant liquid with ethyl acetate. For the extraction of the alcohols (+)-**4** and (+)-**5** from the cell mass, the latter was washed several times with hexane, too. The combined organic extracts gave, after filtration through silica, 85 mg (67%) of a 1:1 mixture of (+)-**4** and (+)-**5**, which were separated by low-pressure liquid chromatography (ethyl acetate/hexane 1:25).

(b) With resting immobilized cells: A suspension of 10 g of immobilized cells in 250 ml of 0.1 M Tris buffer at pH 7.5 containing glucose (20%) and $CaCl_2$ (0.05%) was prewarmed in a 2 l Erlenmeyer shaking-flask for 2 min at 37°C with shaking (170 rpm). 125 mg (0.47 mmol) of (±)-**3** were added and the incubation continued. Samples were taken in intervals of 15–20 min, extracted with hexane and analyzed by GC. After the reaction was complete (*ca.* 2.5 h), the alginate pearls were filtered off with a sieve and washed several times with 50 ml portions of hexane. The aqueous soln. was passed through Amberlite XAD-2 (10 g) to adsorb quantitatively the reduction products, and the resin was eluted with 300 ml of hexane. The combined hexane fractions contained 125 mg (99%) of a 1:1 mixture of (+)-**4** and (+)-**5**, which were separated as above.

(Si*R*,1*R*)-(+)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}ethanol (+)-4. $[\alpha]_D^{23}$ = 16±2 (c = 0.8, THF). Enantiomeric purity (determined by the Mosher method, see below) >96% ee. IR (film): 3420*s* (br.), 3060*w*, 3020*w*, 2950*s*, 2929*s*, 2880*s*, 2850*s*, 2800*m*, 1495*w*, 1470*s*, 1460*s*, 1450*s*, 1430*m*, 1380*m*, 1360*m*, 1300*w*, 1250*m*, 1200*w*, 1090*s*, 1070*s*, 1030*s*, 1005*m*, 975*m*, 935*w*, 900*w*, 885*m*, 825*s*, 800*m*, 780*m*, 765*m*, 730*s*, 695*s*. ^{1}H-NMR: 7.38–7.28 (*m*, 5 arom. H); 4.50 (*s*, PhC*H*$_2$O); 3.78 (*q*, *J* = 7.5, C*H*(OH)CH$_3$); 3.50, 3.38 (*AB*, *J* = 12.6, SiCH$_2$O); 3.16 (*d*, *J* = 4.1, OH); 1.32 (*d*, *J* = 7.6, CH(OH)C*H*$_3$); 0.95 (*s*, C(C*H*$_3$)$_3$); 0.01 (*s*, SiC*H*$_3$). ^{13}C-NMR: 137.8 (*s*, arom. C); 128.3 (*d*, 2 arom. C); 127.6 (*d*, 3 arom. C); 77.5 (*t*, PhCH$_2$O); 61.1 (*t*, SiCH$_2$O); 58.7 (*d*, SiCH(OH)); 27.0 (*q*, C(CH$_3$)$_3$); 20.3 (*q*, C(OH)CH$_3$); 16.5 (*s*, *C*(CH$_3$)$_3$); –10.9 (*q*, SiCH$_3$). CI-MS: 284 (100, [*M* + 1 + NH$_3$]$^+$), 267 (35, [*M* + 1]$^+$). Anal. calc. for $C_{15}H_{26}O_2Si$ (266.459): C 67.62, H 9.84; found: C 67.40, H 9.56.

(Si*S*,1*R*)-(+)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}ethanol (+)-5. $[\alpha]_D^{23}$ = 12±2 (c = 1.9, THF). Enantiomeric purity (determined by the Mosher method, see below) >96% ee. IR (film): 3420*s* (br.), 3060*w*, 3020*w*, 2950*s*, 2920*s*, 2880*s*, 2850*s*, 2800*m*, 1495*w*, 1470*s*, 1460*s*, 1450*s*, 1430*m*, 1380*m*, 1360*m*, 1300*w*, 1250*m*, 1200*w*, 1090*s*, 1070*s*, 1030*s*, 1005*m*, 975*m*, 935*w*, 900*w*, 885*m*, 825*s*, 800*m*, 780*m*, 765*m*, 730*s*, 695*s*. ^{1}H-NMR: 7.38–7.28 (*m*, 5 arom. H); 4.48 (*s*, PhC*H*$_2$); 3.71 (*q*, *J* = 7.6, C*H*(OH)CH$_3$); 3.46, 3.29 (*AB*, *J* =12.7, SiC*H*$_2$O); 2.34 (*d*, *J* = 4.1, OH); 1.40 (*d*, *J* = 7.5, CH(OH)C*H*$_3$); 0.98 (*s*, *C*(CH$_3$)$_3$); 0.06 (*s*, SiC*H*$_3$). ^{13}C-NMR: 138.2 (*s*, arom. C); 128.3 (*d*, 2 arom. C); 127.6 (*d*, 2 arom. C); 127.5 (*d*, arom. C); 77.5 (*t*, PhCH$_2$O); 60.9 (*t*, SiCH$_2$O); 60.5 (*d*, SiCH(OH)); 27.4 (*q*, C(CH$_3$)$_3$); 20.6 (*q*, C(OH)CH$_3$); 16.9 (*s*, *C*(CH$_3$)$_3$); –10.3 (*q*, SiC*H*$_3$). CI-MS: 284 (100, [*M* + 1 + NH$_3$]$^+$), 267 (10, [*M* + 1]$^+$), 221 (8). Anal. calc. for $C_{15}H_{26}O_2Si$ (266.457): C 67.62, H 9.84; found: C 65.98, H 9.41.

Mosher Esters 6a, 6b, 7a, and 7b

General Procedure. The soln. of 5–10 mg (0.02–0.04 mmol) of the corresponding silylalcohol **4** or **5**, 1.2 equivalents of the (*R*)-(–)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (Mosher acid chloride) and a catalytic amount of 4-dimethylaminopyridine (*ca.* 1 mg) in 2 ml of THF/Et$_3$N (1:1) was stirred at 23°C

for 2 h. Water was added, the organic layer separated, and the aqueous phase extracted with ether (2 ml). The combined organic layers gave after chromatography (hexane) 55–65% of the corresponding Mosher ester derivatives **6a**, **6b**, **7a**, or **7b** as colorless oils. The diastereoisomeric ratios were determined by integration of the signals of the CH_3Si and the $(CH_3)_3C$ groups.

(1*R*,2*R*)-2-(Benzyloxy)methyl-1,2,3,3-tetramethyl-2-silabutyl (*S*)-α-Methoxy-α-trifluoromethylphenylacetate 6a. 7.50–7.24 (*m*, 10 arom. H); 5.18 (*q*, *J* = 7.5, C*H*CH_3); 4.41, 4.37 (*AB*, *J* = 13.8, PhCH_2O); 3.43 (*s*, CH_3O); 3.24, 3.20 (*AB*, *J* = 14.9, SiCH_2O); 1.37 (*d*, *J* = 7.5, CHCH_3); 0.89 (*s*, C(CH_3)$_3$); 0.00 (*s*, SiCH_3).

(1*S*,2*S*)-2-(Benzyloxy)methyl-1,2,3,3-tetramethyl-2-silabutyl (*S*)-α-Methoxy-α-trifluoromethylphenylacetate 6b. 7.53–7.24 (*m*, 10 arom. H); 5.19 (*q*, *J* = 7.3, C*H*CH_3); 4.41 (*s*, PhCH_2O); 3.55 (*s*, CH_3O); 3.18 (*s*, SiCH_2O); 1.44 (*d*, *J* = 7.3, CHCH_3); 0.83 (*s*, C(CH_3)$_3$); –0.04 (*s*, SiCH_3).

(1*R*,2*S*)-2-(Benzyloxy)methyl-1,2,3,3-tetramethyl-2-silabutyl (*S*)-α-Methoxy-α-trifluoromethylphenylacetate 7a. 7.50–7.24 (*m*, 10 arom. H); 5.19 (*q*, *J* = 7.5, C*H*CH_3); 4.41 (*s*, PhCH_2O); 3.43 (*s*, CH_3O); 3.24, 3.21 (*AB*, *J* = 14.3, SiCH_2O); 1.37 (*d*, *J* = 7.5, CHCH_3); 0.89 (*s*, C(CH_3)$_3$); 0.00 (*s*, SiCH_3).

(1*S*,2*R*)-2-(Benzyloxy)methyl-1,2,3,3-tetramethyl-2-silabutyl (*S*)-α-Methoxy-α-trifluoromethylphenylacetate 7b. 7.53–7.24 (*m*, 10 arom. H); 5.19 (*q*, *J* = 7.4, C*H*CH_3); 4.39 (*s*, PhCH_2O); 3.55 (*s*, CH_3O); 3.18 (*s*, SiCH_2O); 1.44 (*d*, *J* = 7.4, CHCH_3); 0.83 (*s*, C(CH_3)$_3$); –0.04 (*s*, SiCH_3).

Acetonides (±)-8 and (±)-9

(*S,*S**)-5-*tert*-Butyl-2,2,4,5-trimethyl-5-sila-1,3-dioxane (±)-8.** A soln. of 55 mg (0.21 mmol) of (±)-**4** in 3 ml of EtOH with 5 mg of Pd/C (10%) was kept at 23°C under H_2 until no more gas was consumed (approx. 2 h). The catalyst was filtered off and the solvent was evaporated to give 37 mg of a crude diol. This compound was dissolved in 1.5 ml of dry acetone and reacted at 23°C for 2 h with 65 mg (0.62 mmol) of acetone dimethylacetal and 3 mg of *p*-toluene sulfonic acid. It was poured on 3 ml of an ice-cold $NaHCO_3$ soln., the acetone was evaporated, and the aqueous residue extracted with Et_2O. Evaporation of the solvent and chromatography (ethyl acetate/hexane 1:20) of the residue gave 20 mg (0.09 mmol, 45%) of (±)-**8** as a colorless oil. ^{1}H NMR: 3.72 (*q*, *J* = 5.8, SiC*H*CH_3); 3.47, 3.30 (*AB*, *J* = 11.4, SiCH_2O); 1.41, 1.37 (2*s*, C(CH_3)$_2$); 1.26 (*d*, *J* = 5.8, SiCHCH_3); 0.83 (*s*, SiC(CH_3)$_3$); 0.02 (*s*, SiCH_3). NOE experiments: irradiation at 0.02; responsive signals at 3.30 (0.6%, eq. H) and at 1.26 (0.9%, eq. CH_3); irradiation at 0.83; responsive signals at 3.72 (0.9%, eq. H), at 3.47 (1.0%, ax. H), at 3.30 (0.6%, eq. H), and at 0.02 (0.6%).

(*S,*R**)-5-*tert*-Butyl-2,2,4,5-trimethyl-5-sila-1,3-dioxane (±)-9.** Analogously to (±)-**8**, 12 mg (0.06 mmol, 52%) of (±)-**9** was obtained from 28 mg (0.11 mmol) of (±)-**5**. ^{1}H NMR: 3.59 (*q*, *J* = 6.0, SiC*H*CH_3); 3.54, 3.27 (*AB*, *J* = 11.4, SiCH_2O); 1.41, 1.34 (2*s*, C(CH_3)$_2$); 1.35 (*d*, *J* = 6.0, SiCHCH_3); 0.98 (*s*, SiC(CH_3)$_3$); –0.11 (*s*, SiCH_3). NOE experiments: irradiation at –0.11; responsive signals at 3.59 (01.0%, eq. H) and at 3.27 (0.6%); irradiation at 0.98; responsive signals at 3.45 (1.0%, ax. H), at 3.27 (0.6%, eq. H), at 1.35 (*ca.* 1%, ax. CH_3), at –0.11 (1.0%).

Synthesis of (R)-(+)-1-Phenylethanol (R)-(+)-12

(*R*)-(–)-[(Benzyloxymethyl)(*tert*-butyl)methylsilyl] Methyl Ketone (–)-3. A soln. of 65 mg (0.83 mmol) of $(CH_3)_2SO$ in 0.1 ml of CH_2Cl_2 was added slowly to a soln. of 52 mg (0.41 mmol) oxaylyl chloride in 2 ml of CH_2Cl_2 at –60°C. After 30 min, 100 mg (0.38 mmol) of (+)-**4** (>95% ee) in 0.4 ml of CH_2Cl_2 were

added, and after an additional 15 min, 0.26 ml (1.88 mmol) of Et_3N. The mixture was allowed to reach ambient temperature and water was added. Extraction with CH_2Cl_2 gave after chromatography (ethyl acetate/hexane 1:25) 95 mg (0.36 mmol, 95%) of (–)-**3** (>95% ee). $[\alpha]_D^{23}$ = 9.9±2 (c = 0.8, THF). IR (film): 3060*w*, 3030*w*, 2960*s*, 2930*s*, 2860*s*, 2810*m*, 1640*s* (C=O), 1495*w*, 1460*m*, 1430*w*, 1410*w*, 1380*w*, 1360*m*, 1340*m*, 1250*m*, 1200*w*, 1140*m*, 1090*s*, 1070*s*, 1030*w*, 1010*w*, 980*w*, 935*w*, 905*w*, 828*s*, 805*m*, 778*s*, 735*s*, 698*s*, 665*w*. ^{1}H-NMR: 7.30-7.29 (*m*, 5 arom. H); 4.51 (*s*, PhCH_2O); 3.45, 3.39 (*AB*, *J* = 13.0, SiCH_2O); 2.32 (*s*, COCH_3); 0.98 (*s*, C(CH_3)$_3$); 0.24 (*s*, SiCH_3). ^{13}C-NMR: 244.3 (*s*, *C*O); 138.8 (*s*, arom. C); 128.2 (*d*, 2 arom. C); 127.5 (*d*, 2 arom. C); 127.4 (*d*, arom. C); 77.0 (*t*, Ph*C*H_2O); 60.1 (*t*, Si*C*H_2O); 27.2 (*q*, C(*C*H_3)$_3$); 15.9 (*s*, *C*(CH$_3$)$_3$); -9.9 (*q*, Si*C*H_3). EI-MS: 264 (4, $M^{+\cdot}$), 249 (33), 221 (27), 173 (5), 151 (9), 149 (35), 135 (27), 73 (9), 65 (81), 63 (17), 57 (100), 43 (72). Anal. calc. for $C_{15}H_{24}O_2Si$ (264.44): C 68.13, H 9.15; found: C 68.32, H 9.30.

(*S*)-(+)-[(Benzyloxymethyl)(*tert*-butyl)methylsilyl] Methyl Ketone (+)-3. Analogously to (–)-**3**, Identical with (–)-**3** in all respects except for the specific rotation: $[\alpha]_D^{23}$ = 12±2 (c = 1.6, THF).

(Si*R*,1*R*)-(+)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}-1-phenylethanol (+)-10. A 2 M soln. of PhLi in pentane (0.2 ml, 0.4 mmol) was added dropwise to a soln. of 80 mg (0.3 mmol) of (–)-**3** (92±2% ee) in 5 ml of hexane at –100°C. After 1 h, it was quenched with 3 ml of a sat. aqueous NH_4Cl soln. and extracted with Et_2O. Chromatography (ethyl acetate/hexane 1:25) gave 89 mg (0.26 mmol, 86%) of (+)-**10** as a colorless oil. $[\alpha]_D^{23}$ =20±2 (c = 0.8, THF). IR (film): 3450*s* (br.), 3080*w*, 3020*w*, 2950*s*, 2920*s*, 2850*s*, 2740*w*, 2710*w*, 1750*w*, 1600*m*, 1490*m*, 1470*m*, 1460*m*, 1450*m*, 1445*m*, 1430*w*, 1380*m*, 1310*m*, 1250*m*, 1200*w*, 1175*w*, 1155*w*, 1085*s*, 1065*s*, 1025*m*, 1005*w*, 935*w*, 910*w*, 895*m*, 825*s*, 805*m*, 785*m*, 745*s*, 715*m*, 700*s*. ^{1}H-NMR: 7.40–7.28 (*m*, 9 arom. H); 7.25–7.12 (*m*, arom. H); 4.55, 4.50 (*AB*, *J* = 11.8, PhCH_2O); 3.83 (*s*, OH); 3.41, 3.18 (*AB*, *J* = 12.6, SiCH_2O); 1.76 (*s*, C(OH)CH_3); 0.90 (*s*, C(CH_3)$_3$); 0.01 (*s*, Si)CH_3. ^{13}C-NMR: 148.2, 137.5 (2 *s*, arom. C); 128.4 (*d*, 2 arom. C); 127.9 (*d*, 2 arom. C); 127.8 (*d*, 3 arom. C); 125.1 (*d*, arom. C); 124.4 (*d*, 2 arom. C); 77.7 (*t*, Ph*C*H_2O); 70.6 (*s*, Si*C*(OH)); 61.3 (*t*, Si*C*H_2O); 28.8 (*q*, C(OH)*C*H_3); 27.4 (*q*, C(*C*H_3)$_3$); 18.1 (*s*, *C*(CH$_3$)$_3$); –9.0 (*q*, Si*C*H_3). CI-MS: 343 (10, $[M + 1]^+$), 342 (34, $[M - OH + NH_3]^+$), 326 (28), 325 (100, $[M - OH]^+$), 281 (18), 256 (21), 238 (36). Anal. calc. for $C_{21}H_{30}O_2Si$ (342.558): C 73.63, H 8.83; found: C 73.51, H 8.56.

(+)-{(*R*)-[(Benzyloxy)methyl](*tert*-butyl)methylsilyl} (*R*)-1-Phenylethyl Ether (+)-11. A reaction mixture consisting of 80 mg (0.24 mmol) of (+)-**10** and 15 mg of KH (20% in mineral oil, *ca.* 0.07 mmol) in 5 ml of THF at 23°C was stirred for 30 min and quenched with 3 ml of a sat. aqueous NH_4Cl soln. Extraction with Et_2O and chromatography (ethyl acetate/hexane 1:20) gave 78 mg (0.23 mmol, 98%) of (+)-**11** as a colorless oil. $[\alpha]_D^{23}$ = 47±2 (c = 0.7, THF). IR (film): 3050*w*, 3020*w*, 2950*s*, 2920*s*, 2880*m*, 2850*s*, 2800*w*, 1490*w*, 1470*m*, 1460*m*, 1450*m*, 1380*m*, 1365*m*, 1300*w*, 1280*w*, 1250*m*, 1205*m*, 1140*m*, 1110*s*, 1090*s*, 1070*s*, 1030*s*, 1000*m*, 960*s*, 935*w*, 900*w*, 830*s*, 800*m*, 770*s*, 730*s*, 695*s*, 675*m*.. ^{1}H NMR: 7.33–7.18 (*m*, 10 arom. H); 4.84 (*q*, *J* = 6.4, CHCH_3); 4.33 (*s*, PhCH_2O); 3.15, 3.09 (*AB*, *J* = 13.0, SiCH_2O); 1.40 (*d*, *J* = 6.4, C*H*CH$_3$); 0.93 (*s*, C(CH_3)$_3$); 0.14 (*s*, SiCH_3). ^{13}C NMR: 146.7, 138.9 (2*s*, arom C); 128.1, 128.0, 127.4 (3*d*, each 2 arom. C); 127.2, 126.7 (2*d*, arom. C); 125.2 (*d*, 2 arom. C); 77.0 (*t*, Ph*C*H_2O); 71.1 (*d*, OCH); 61.1 (*t*, Si*C*H_2O); 27.2 (*q*, CH*C*H_3); 26.1 (*q*, C(*C*H_3)$_3$); 18.2 (*s*, *C*(CH$_3$)$_3$); –7.5 (*q*, Si*C*H_3).

(*R*)-(+)-1-Phenylethanol (+)-12. A soln. of 78 mg (0.23 mmol) of (+)-**11** and 216 mg (0.68 mmol) of $Bu_4NF·3H_2O$ was stirred at 23°C for 2 h. Water was added and extracted with Et_2O to give, after chromatography (ethyl acetate/hexane 1:30), 17 mg(0.41 mmol, 60%) of (+)-**13** as a colorless liquid. The spectral data

was identical with that of an authentic sample; $[\alpha]_D^{23}$ =40±2 (c = 0.7, THF) corresponding to an optical purity of 88±2% (confirmed also with the Mosher method).

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