Stereochemistry of the Silylcarbinol to Silyl Ether Rearrangement[1]

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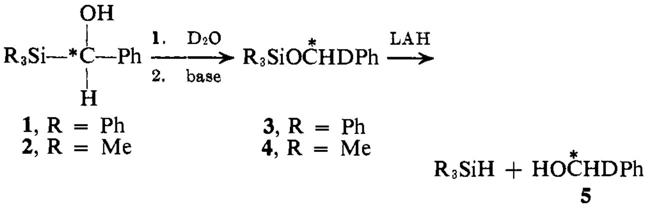
Abstract: (*R*)-(+)-Phenyltriphenylsilylcarbinol (**1**) was exchanged with D_2O and the resulting O-deuterated derivative was rearranged in the presence of triethylamine to give (+)-benzyl-α-*d* triphenylsilyl ether (**3**) which was chiral by virtue of deuterium substitution at the benzylic position. This ether, on reductive cleavage by lithium aluminum hydride, gave (*S*)-(+)-benzyl-α-*d* alcohol (**5**). The silylcarbinol to silyl ether rearrangement must therefore proceed with inversion at carbon contrary to the stereochemistry previously claimed for this type of rearrangement. The comparable base-catalyzed rearrangement of (*S*)-(−)-phenyltrimethylsilylcarbinol-*O-d* (**2**) was very much slower but was shown to proceed with inversion at carbon as well. The previously reported erroneous conclusion that the silylcarbinol (**7**) to silyl ether (**8**) rearrangement proceeds with retention of configuration at carbon was based upon a prediction of configuration resulting from the application of Cram's rule to the addition of methylmagnesium iodide to the chiral methyl-α-naphthylphenylsilyl phenyl ketone (**6**). This prediction must also be incorrect. Thus in this previous study two incorrect stereochemical assignments were used to rationalize the known configurations of the products (**9** and **10**). Quite apparently the application of Cram's rule to the reactions of such silyl ketones is unwarranted at this time.

The necessity of determining the configuration of optically active phenyltriphenylsilylcarbinol (**1**) and phenyltrimethylsilylcarbinol (**2**), products of asymmetric Grignard reductions,[3] led us to consider the base-catalyzed silylcarbinol to silyl ether rearrangement. This rearrangement has been shown to be highly stereoselective[4] and reportedly proceeds with retention of configuration both at silicon and carbon.[5] We reasoned that if this reaction could be applied to the chiral secondary carbinols **1** and **2** which had been suitably substituted with deuterium, the resulting benzyl-α-*d* silyl ethers **3** and **4** would be chiral by virtue of deuterium substitution. The absolute configuration and enantiomeric purity of these ethers could then be determined by hydrogenolysis with lithium aluminum hydride (LAH) to give benzyl-α-*d* alcohol (**5**) whose absolute configuration and maximum rotation have been established. From these results the configuration of the starting carbinols **1** and **2** could be deduced if the stereochemistry of the rearrangement were known unequivocally.



$$R_3Si{-}\overset{OH}{\underset{H}{{}^{*}C}}{-}Ph \xrightarrow[2.\ \text{base}]{1.\ D_2O} R_3SiO\overset{*}{C}HDPh \xrightarrow{\text{LAH}} R_3SiH + HO\overset{*}{C}HDPh$$

1, R = Ph; **2**, R = Me; **3**, R = Ph; **4**, R = Me; **5**

Brook and coworkers[4,5] have studied the conversion of optically active methyl-α-naphthylphenylsilyl phenyl ketone (**6**) to the mixture of diastereomeric silylcarbinols **7** by treatment with methyl Grignard reagent. The configuration of the ketone **6** is firm, being founded upon the X-ray diffraction determination[6] of the absolute configuration of (+)-methyl-α-naphthylphenylsilane and the known stereochemistry of its chemical correlation[7] with **6**. The configurations of the silicon center in diastereomers **7a** and **7b** were shown to be unchanged from that in **6**; *i.e.*, the rearrangement went with retention of configuration at silicon. The configuration at the newly created chiral carbon center was inferred by a presumed analogy with the corresponding type of reaction in the carbon series. When optically active **6** was used as the starting material, a mixture (**7a** + **7b**) was obtained with one form predominating over the other by a ratio of approximately 80:20 as determined by nmr measurements. Configuration **7b** was assigned to the predominant diastereomer by applying Cram's rule[8] based on the open-chain model for Grignard additions to chiral ketones. This mixture of diastereomers **7a** and **7b** was then rearranged by base catalysis to the silyl ethers **8** which were reductively cleaved to the silane, **9**, and phenylmethylcarbinol (**10**) which had an excess of the levorotatory isomer whose configuration is known to be *S* as shown. Furthermore, the enantiomeric purity of **10** was about 60%, indicating that, within experimental error, the rearrangement was 100% stereoselective (after correcting for the 80:20 diastereomeric ratio of the starting material). Thus, knowing the absolute configuration of the starting material **6**, the absolute configuration of the product **10**, and that the conversion of **8** to **10** does not disturb the asymmetry at carbon, and assuming the validity of the application of Cram's rule in an example such as this, the configuration of the predominant diastereomeric silyl ether must be **8a**. Brook and coworkers deduced from this that the rearrangement proceeded with retention of configuration at carbon as well as retention of configuration at silicon, *i.e.*, **7b** → **8a**.

This conclusion rests on knowing with certainty the configuration at carbon of the silylcarbinol **7**. Contrary to the statement[5] that "The absolute configura-

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(2) Taken from the Ph.D. Thesis of M. S. B., Aug 1970.

(3) (a) M. S. Biernbaum and H. S. Mosher, *Tetrahedron Lett.*, 5789 (1968); (b) M. S. Biernbaum and H. S. Mosher, *J. Org. Chem.*, **36**, 3168 (1971).

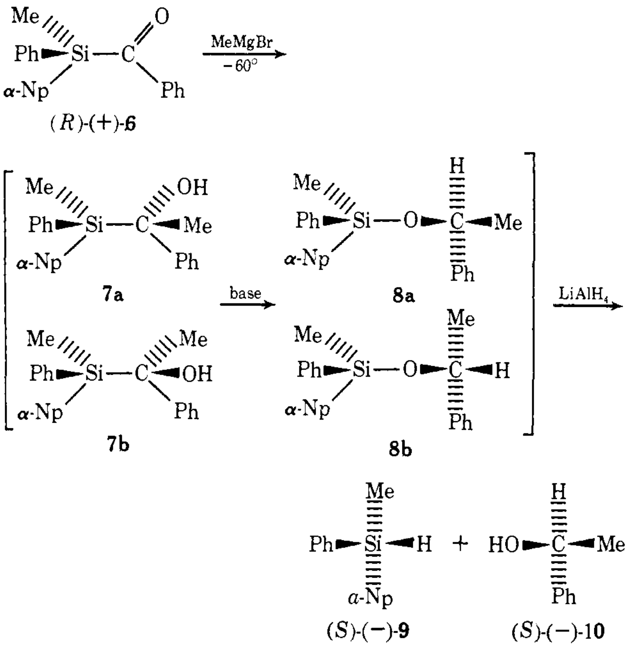
(4) A. G. Brook, C. E. LeGrow, and D. M. McRae, *Can. J. Chem.*, **45**, 239 (1967), and references therein.

(5) A. G. Brook, C. M. Warner, and W. W. Limburg, *ibid.*, **45**, 1231 (1967).

(6) Y. Okaya and T. Ashida, *Acta Crystallogr.*, 20, 461 (1966).

(7) L. H. Sommer, "Stereochemistry, Mechanism, and Silicon," McGraw-Hill, New York, N. Y., 1965.

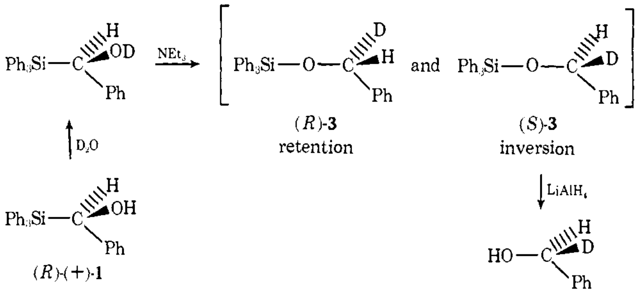
(8) D. J. Cram and F. A. Abd ElHafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).



tion of the predominant diastereomer formed by the addition of methyl Grignard reagent to the ketone (**6**) can be predicted reliably from Cram's rule of asymmetric induction," we regarded this conclusion with considerable reservation. Extrapolation of Cram's rule to include a case where the α-carbon is replaced with silicon seems unwarranted until experimental support for such a conclusion under these special circumstances can be gathered. The analogous reaction for the conversion of **6** to **7**, where carbon replaces silicon, has not been reported. Although it seems quite logical to assume that α-naphthyl would act as though it were a larger group than phenyl in application of Cram's model, this is something which should be checked experimentally. No such examples have been reported to our knowledge. Furthermore, the carbon-silicon bond is longer than the carbon-carbon bond. This could easily have a determining effect on the steric control of asymmetric induction in **6** → **7**, as could also the availability of empty d orbitals of silicon which are not available for coordination with the reagent in the carbon analog. In short, the basis upon which the configuration of the predominant product epimer of the reaction **6** → **7** is assigned is insecure and the configurational assignment of **7b** to the predominant product is equivocal. The conclusion that the silylcarbinol to silyl ether rearrangement (**7** → **8**) proceeds with retention of configuration is not proven.

Reliable configurational assignments can be made on the basis of asymmetric synthesis only after considerable correlative experimental evidence or well-precedented mechanistic studies; *a priori*, such assignments have 50:50 chance of being correct. Such a warning against unjustified extrapolation of empirically derived conformational rules from one system to another has been made before.[9] Unwarranted predictions based on Cram's rule or any other empirical correlation scheme are no less objectionable even when the prediction turns out to be correct; in the present case the prediction is almost certainly wrong.[10]

We have investigated the rearrangement of the secondary carbinol **1** to the ether **3**, anchoring our study on the absolute configuration of (*R*)-(+)-**1** which has now been determined by an X-ray diffraction study[11] on the *p*-bromobenzoate ester of phenyltriphenylsilylcarbinol and on the known absolute configuration of benzyl-α-*d* alcohol (**5**).[12] (*R*)-(+)-Phenyltriphenylsilylcarbinol, which was obtained by resolution[3] and was at least 95% enantiomerically pure, was exchanged with D_2O and treated with anhydrous triethylamine in a dry nitrogen atmosphere in chloroform solvent for 5 days at 49°. A quantitative yield of crude benzyl triphenylsilyl ether (**3**) was obtained, $[\alpha]^{24}\text{D}$ +0.79 ± 0.1° (*c* 10.1, $CHCl_3$). The ether **3** was converted, by treatment with lithium aluminum hydride, into a mixture of triphenylsilane (**11**, 61% yield) and benzyl-α-*d* alcohol (**5**, 45% yield), which was purified by preparative gas chromatography to give (*S*)-(+)-benzyl-α-*d* alcohol, 90 ± 10% enantiomerically pure.[13]



Since the configuration of (+)-benzyl-α-*d* alcohol is firmly established[11] as *S*, the benzyl triphenylsilyl ether **3** must also have the *S* configuration since the C-O bond is not disturbed by the LAH reduction. Therefore, configurations of starting materials and products are known and the pathway of the rearrangement, **1** → **3**, must involve *inversion of configuration at carbon*, not retention! Based on the close analogy of reactions **1** → **3** and **7** → **8**, the first of which is now unequivocally established as proceeding by inversion, one can logically assume that the second also proceeds by inversion at carbon,[10] contrary to the earlier conclusion.[5] These results also require that the major diastereomer obtained by the addition of methylmagnesium bromide to the silyl ketone (*R*)-(+)-**6** must have configuration **7a** instead of **7b** as previously assigned. Accordingly, the very dubious application of Cram's rule to this particular system gave the incorrect configurational assignment.

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[9] (a) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. S. Simmons, and A. G. Ternay, Jr., *J. Amer. Chem. Soc.*, 87, 1958 (1965); (b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 36, 341.

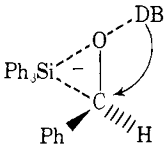
[10] This error has now been corrected: A. G. Brook and J. D. Pascoe, *J. Amer. Chem. Soc.*, 93, 6224 (1971).

[11] H. Hope, private communication; we are greatly indebted to Professor Hope for this determination; K. Black and H. Hope, *ibid.*, 93, 3053 (1971).

[12] V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *ibid.*, 88, 3595 (1966).

[13] This determination of enantiomeric purity is based on the direct comparison of the ORD curves of this sample and an authentic sample of the pure enantiomer obtained by fermentation.[12] The determination takes into consideration the 91% deuterium incorporation as measured by mass spectrographic analysis. The large uncertainty is due to the small amount of material available and its rather low rotation. The experimental results are compatible with a 100% stereoselective rearrangement if one allows rather generous limits of error during the ORD measurements.

Although these results establish that this rearrangement proceeds with inversion at the carbon center, they do not reveal the fine details of the rearrangement—in particular the extent to which the protonated base assists in the dynamics of bond formation–bond rupture and the degree of synchronicity involved. For instance, they do not distinguish between a base-assisted migration of deuterium from oxygen to carbon within a tight ion pair a, or discreet reprotonation in a less intimate solvent-separated ion pair b, or a rather free carbanion shielded in front by the leaving silicon atom and reprotonated from the back at a rate faster than rotation about the C–O bond c.



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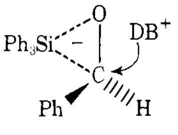

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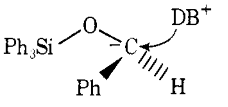

c

Experimental Section

Instruments. All nmr determinations were made on a Varian T-60 instrument in $CHCl_3$ or $CDCl_3$ solvent with chemical shifts, δ, reported in parts per million downfield from internal tetramethylsilane standard. Melting points were determined on a hot stage and are uncorrected. Rotations were taken on a Zeiss manual polarimeter which reads to 0.01° or on a Perkin-Elmer 141 electronic polarimeter which reads to 0.001° in center-filled tubes. The ORD measurements were made on a JASCO ORD/UV-5 instrument by Mrs. Ruth Records and the mass spectra were made by Dr. Alan Duffield at 12 eV on an Atlas AEI MS-9 instrument.

Rearrangement of (+)-Phenyltriphenylsilylcarbinol-*O-d* to (+)-Benzyl-*α-d* Triphenylsilyl Ether ((+)-3). The following experiment was preceded with an nmr study which showed that there was no exchange of the benzylic protons at δ 4.9 when a mixture of benzyl triphenylsilyl ether, triethylamine, and D_2O was allowed to stir in chloroform for 4 days.

A solution of resolved (+)-phenyltriphenylsilylcarbinol[3] [2.5 g, 6.8 mmol, $[\alpha]^{28}\mathrm{D}$ +47.1 ± 0.4° (*c* 4.67, $CHCl_3$)], maximum rotation[3] $[\alpha]^{22}\mathrm{D}$ +49.5 ± 1.1° (*c* 1.77, $CHCl_3$), in chloroform (11 ml), was shaken with D_2O (2.1 ml, 99.8% *d*, 0.11 mol); disappearance of the hydroxyl proton signal at δ 2.25 ($CHCl_3$) was instantaneous. Triethylamine (2 ml) was added, and the mixture was stirred first at room temperature overnight and then for 5 days at 49°, at which time the rearrangement was judged complete, based on the disappearance of the nmr signal for the carbinol benzylic proton at δ 5.3. Concentration of the reaction mixture under reduced pressure yielded a solid residue [2.5 g, $[\alpha]^{24}\mathrm{D}$ +0.79 ± 0.10° (*c* 10.12, $CHCl_3$)], which on recrystallization (hexane) yielded 1.6 g of white crystalline benzyl-*α-d* triphenylsilyl ether (+)-**3**: mp 83–85° (lit.[14] value for nondeuterated compound, 84.5–85.5°); ir (KBr) 1495, 1485, 1450, 1420 (Si–Ph), 1380, 1260, 1215, 1180, 1150, 1105 (Si–Ph), 1100, 1085, 1060, 1020, 995, 830, 820, 745, 705, and 695 cm^{-1}.

Lithium Aluminum Hydride Cleavage. To a mixture of lithium aluminum hydride (0.3 g, 8 mmol) in anhydrous diethyl ether (25 ml) was added a solution of the above benzyl-*α-d* triphenylsilyl ether [(+)-**3**, 1.48 g, 4 mmol] in dibutyl ether (80 ml). Enough diethyl ether was removed by distillation so that the internal temperature rose to 86°, where it was held for 21 hr under a dry nitrogen atmosphere. After hydrolysis (saturated $NaSO_4$ solution), the ether layer was dried ($MgSO_4$), concentrated, and distilled to give two colorless fractions: the first, 195 mg (45% crude yield), bp 80–100° (1.3 mm), which upon purification by glpc (5 × $^1/_4$ in. UCON Polar, 155°) yielded 96 mg (22% purified yield) of benzyl-*α-d* alcohol, (*S*)-(+)-**5**, and the second, triphenylsilane (**11**), 650 mg (61% yield), bp 140–150° (1.0 mm) (lit.[15] bp 152–167° (2 mm)); ir (KBr) 2120 (Si–H), 1420, 1100 cm^{-1} (Si–Ph). The benzyl-*α-d* alcohol, 91% d_1 as determined by mass spectrometry, was diluted 50:50 with isotopically normal benzyl alcohol to give $\alpha^{26}\mathrm{D}$ +0.33 ± 0.03° (l = $^1/_2$, neat, 45.5% d_1) which corresponds to $\alpha^{26}\mathrm{D}$ +1.45 ± 0.15° (l = 1, neat) when corrected to 1 deuterium atom/molecule. This corresponds to enantiomerically pure material based upon $\alpha^{24}\mathrm{D}$ +1.43 ± 0.01° (neat, l = 1)[12] for pure (*S*)-(+)-benzyl-*α-d* alcohol. From a direct ORD comparison (589–230 nm) of dilute ethanol solutions of enantiomerically pure benzyl-*α-d* alcohol, prepared by fermentation[12] and regenerated from the purified acid phthalate, it was concluded that this material was 90 ± 10% enantiomerically pure.

Rearrangement of (−)-Phenyltrimethylsilylcarbinol-*O-d*. A preliminary nmr study showed that there was no exchange of benzylic protons when the product, benzyl trimethylsilyl ether, was stirred with triethylamine and D_2O for 21 days.

A solution of phenyltrimethylsilylcarbinol[3] (**2**) (1.3 g, 7.2 mmol, $\alpha^{24}\mathrm{D}$ −29.88 ± 0.04° (neat), 33.3% enantiomerically pure) in deuteriochloroform (5 ml) was washed four times with 2-ml portions of 99.8% D_2O. After the final exchange, the solution was dried (Na_2SO_4), triethylamine (1.1 g) was added, and the reaction mixture, which was protected with a drying tube, was first heated at 61° for 5 days under which conditions only a trace of rearrangement took place. The mixture was then refluxed in a 91° oil bath for 70 days. During the first week a brown solid began to form and the mixture darkened upon continued reflux. Aliquots were removed periodically and monitored with nmr by observing the benzylic proton at δ 4.4 with the following results: 8th day, 25% of the carbinol had rearranged; 18th day, 49%; 29th day, 66%; 57th day, 85%; 70th day, no significant additional change. The reaction mixture was filtered and distilled to give a colorless liquid [0.56 g, $\alpha^{27}\mathrm{D}$ −4.53 ± 0.02° (l = $^1/_2$, neat)] which contained starting carbinol, silyl ether, and some benzyl alcohol. Because of the small amount of material this crude reaction product was cleaved by LAH reduction, as described for the benzyl triphenylsilyl ether, and purified by preparative glpc (Apiezon L, 5 ft × $^1/_4$ in., 155°) to give 32.5 mg (2.5% purified yield) of recovered phenyltrimethylsilylcarbinol [$[\alpha]\mathrm{D}$ −36 ± 7° (*c* 0.135, EtOH)], and benzyl-*α-d* alcohol (99 mg, 13% purified yield, 0.51 deuterium atom/molecule according to mass spectral analysis). The ORD of this sample compared with that of enantiomerically pure (+)-benzyl-*α-d* alcohol at 350, 300, and 280 nm showed that the sample was 15 ± 1.5% enantiomerically pure (*R*)-(−) isomer. Correcting for the 51% deuteration and 33% enantiomeric purity of the starting phenyltrimethylsilylcarbinol indicated that the rearrangement was 89 ± 10% stereoselective.

(+)-Benzyl-*α-d* Triphenylsilyl Ether. Benzyl-*α-d* alcohol (0.56 g), $\alpha^{24}\mathrm{D}$ +1.32 ± 0.02° (neat, l = 1), obtained from fermentation[12] and regenerated from the purified acid phthalate, was mixed with anhydrous pyridine (0.40 g) and ether (50 ml), and treated at 0° with freshly crystallized triphenylchlorosilane (1.50 g). The mixture was stirred for 4 hr at 0° and during 8 hr was allowed to warm to 30°. Pyridine hydrochloride (0.44 g) was removed by filtration and the filtrate washed at 0° (water, dilute HCl, water), dried ($MgSO_4$), and evaporated to give crystals which were recrystallized from *n*-hexane. The first crop (50 mg) proved to be triphenylsilanol. The main crop (650 mg), mp 79–84°, $[\alpha]^{20}\mathrm{D}$ +0.22 ± 0.01° (*c* 23.6, $CHCl_3$), was recrystallized: 320 mg, mp 83–84°, $[\alpha]^{20}\mathrm{D}$ +0.36 ± 0.01° (*c* 36, $CHCl_3$); Perkin-Elmer Model 421 photoelectric polarimeter reading to 0.002°.

Anal. Calcd for $C_{25}H_{21}DSiO$: C, 81.68; H, 6.32. Found: C, 81.83; H, 6.15.

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[14] A. G. Brook, C. M. Warner, and M. E. McGriskin, *J. Amer. Chem. Soc.*, 81, 981 (1959).

[15] H. H. Reynolds, L. A. Bigelow, and C. A. Kraus, *ibid.*, **51**, 3067 (1929).