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HYDROXYL-DIRECTED CYCLOPROPANATION OF Z-ALLYL-SILANES

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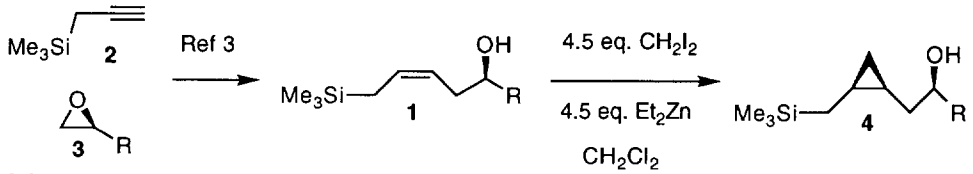
Summary: Z-5-Hydroxy-alk-2-enyl-silanes of general structure **1** are cyclopropanated by an excess of CH_2I_2 / Et_2Zn in good yield and excellent stereoselectivity. Ensuing protodesilylation, however, lacks efficient regiocontrol and affords syn-products **5** in modest yield but high stereochemical purity.

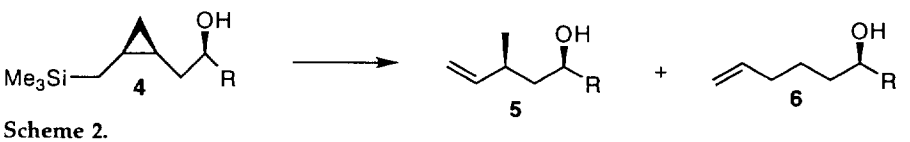
Hydroxyl-directed reactions are proven to be a powerful method in controlling relative stereochemistry in open chain compounds.[1] One of the frequently and successfully applied examples includes the directed cyclopropanation.[2] In connection with our interest in allylsilanes of general structure **1**[3] we briefly examined their stereoselective cyclopropanation.

The substrates **1** were readily available from propargyl-trimethyl-silane **2** and the corresponding epoxides **3** as previously described.[3] We found that the double bond can easily be cyclopropanated under Furukawa conditions[4] in reasonable yield and satisfying stereoselectivity. Treatment with 4-5 eq. of Et_2Zn and equimolar amounts of CH_2I_2 in CH_2Cl_2 at -18° - 5° yielded the cyclopropanes **4** as summarized in Table 1. The relative stereochemistry was presumed to be syn based on mechanistic considerations. As shown below, this turned out to be correct.



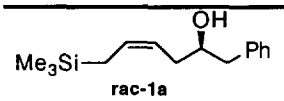
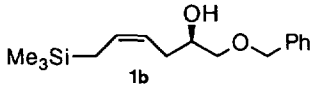
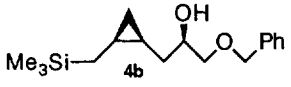
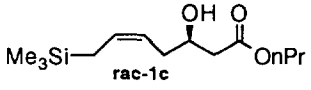
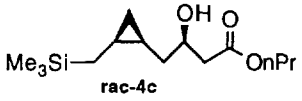
Scheme 1.

For purpose of chemical correlation as well as to demonstrate their usefulness as synthetic building blocks, we tried to protodesilylate cyclopropanes **4** regioselectively. However, this proved to be much more cumbersome than anticipated from literature precedents.[5] Neither of the methods screened so far with **rac-4a, rac-4a'**, or **rac-4a"** (cf. Table 2) provided the desired syn-configurated olefins **5** in satisfying selectivity. In all cases, substantial amounts of the straight chain product **6**, derived from electrophilic attack at the methine carbon, were formed. Even non-chelating Lewis acids, like BF_3·AcOH, turned out to be only marginally selective, while BCl_3, at low temperature, led to nearly regiorandom mixtures. Whereas the hydroxyl-protected isomers **5a'** and **6a'** were obtained as inseparable mixtures, the free alcohols **5** and **6** could fortunately enough be separated readily by flash or MPL chromatography.[6]



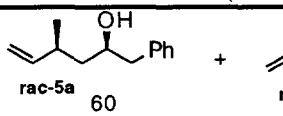
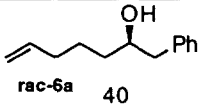
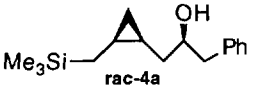
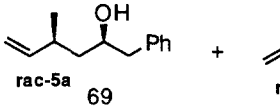
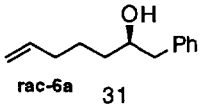
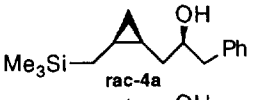
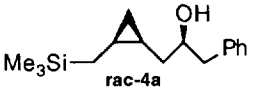
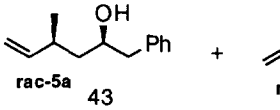
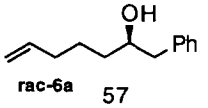
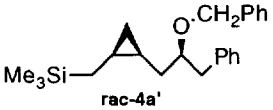
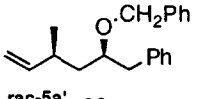
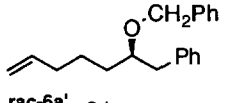
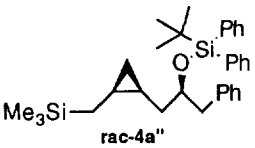
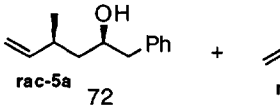
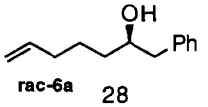
Scheme 2.

Table 1 Cyclopropanation of Allylsilanes 1.

Substrate	Conditions[a]	Product	Isolated Yield(%)	GC-Purity(%)[b]
 rac-1a	A	 rac-4a	82	97
 1b	A	 4b	82	96
 rac-1c	A	 rac-4c	64	95

[a]Conditions A: 4-4.5 eq. of CH_2I_2 / 4-4.5 eq. of Et_2Zn, CH_2Cl_2, -18°-5°, 5-6h; in toluene, the reaction is significantly slower. [b]According to ^1H NMR products 4 contain small amounts of an unidentified impurity not visible in GC which is easily separated after protodesilylation.

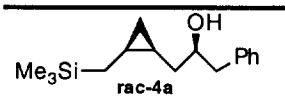
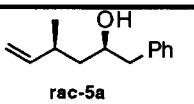
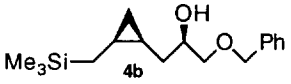
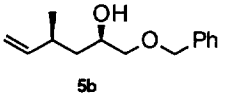
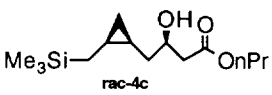
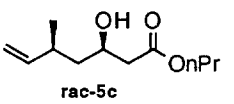
Table 2 Protodesilylation of Cyclopropyl-methyl-silane **4a**.

Substrate	Reagents	Products (GC-Ratio)
 rac-4a	CF_3COOH/ CH_2Cl_2 -10°-0°	 rac-5a 60 +  rac-6a 40
 rac-4a	BF_3·AcOH/ CH_2Cl_2 0°-RT	 rac-5a 69 +  rac-6a 31
 rac-4a	ZnI_2/EtOEt RT	Slow Decomposition
 rac-4a	BCl_3/ CH_2Cl_2 -78°	 rac-5a 43 +  rac-6a 57
 rac-4a'	CF_3COOH/ CH_2Cl_2 -10°-0°	 rac-5a' 69 +  rac-6a' 31
 rac-4a''	BF_3·AcOH/ CH_2Cl_2 0°-RT[a]	 rac-5a 72 +  rac-6a 28

a) The TBDPS-protecting group was split off nearly quantitatively under these conditions.

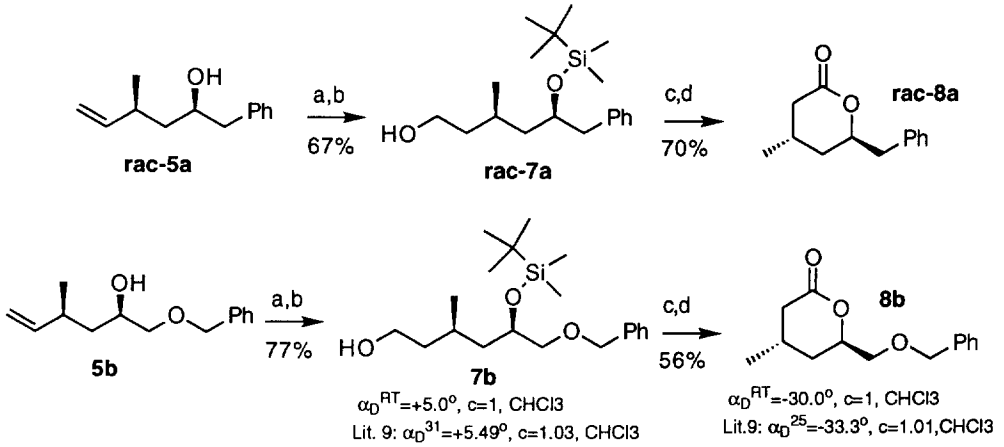
Based on these experiences, all three cyclopropyl-methyl-silanes **4** were processed on a preparative scale with BF_3·AcOH as compiled in Table 3. Unfortunately, the regioisomeric ratio turned out to be even slightly worse with the higher oxygenated substrates. Consequently, the syn-alcohols **5** could only be isolated in moderate yield but high stereochemical purity.

Table 3 Preparative Protodesilylation of Cyclopropyl-methyl-silanes **4**.

Substrate	Reagents	GC-Ratio 5:6	Product 5	Isol.Yield of 5 (%)
 rac-4a	BF_3·AcOH/ CH_2Cl_2[a]	71:29	 rac-5a	53
 4b	BF_3·AcOH/ CH_2Cl_2[a]	50:50	 5b	41
 rac-4c	BF_3·AcOH/ CH_2Cl_2[a]	47.5:52.5	 rac-5c	37

a) 3 eq., -20° to -5°, 2.5h.

In order to determine unequivocally the relative configuration, rac-**5a** and **5b** were transformed into the lactones **rac-8a** and **8b**, respectively, according to Scheme 3. Standard silylation followed by hydroboration with 9-BBN and oxidative work-up afforded the primary alcohols **rac-7a** and **7b**,[7] which were oxidized in one pot to the corresponding acids with PDC in DMF. CF_3COOH - induced cleavage of the protecting group and concomitant ring closure[8] lead to the target compounds **rac-8a** and **8b**.

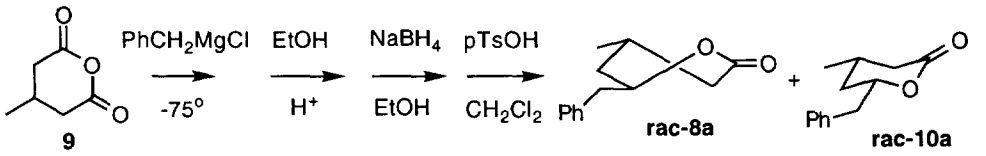


a) 1.5 eq. TBDMS-Cl, 3 eq. imidazole, DMF, RT, 15h; b) 2.6 eq. 9-BBN, THF, RT, 15h; 6N NaOH, 30% H_2O_2; c) 3.5 eq. PDC, DMF, RT, 7h; d) CF_3COOH, 11 vol% H_2O, 24h, RT.

Scheme 3.

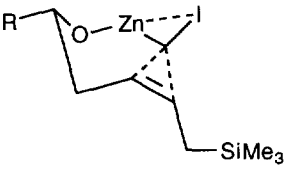
In order to corroborate the assigned structures an authentic mixture (1.7:1) of **rac-8a** and **rac-10a** was independently synthesized from 3-methyl-glutaric anhydride (**9**).[10] The NMR spectrum clearly identified the minor component as

rac-10a, with the chair form prevailing having both substituents in an equatorial position, whereas the major product **rac-8a**, indistinguishable from the above prepared compound, exists predominantly in a twist-boat conformation.



Scheme 4.

The stereochemical outcome can be rationalized assuming a six-membered, chairlike transition state where the substituent R adopts an equatorial position. This model is reminiscent of the transition state proposed by Mihelich et al. for the V^{5+}-catalyzed epoxidation of homoallylic alcohols.[11]



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6. Medium pressure liquid chromatography on a *Lobar* ®*LiChroprep* ® Si 60 column from E. Merck, Darmstadt.
7. I thank Prof. K. Ogasawara and Prof. S. Takano for reference spectrum of **7b**.
8. R. Baker, W. J. Cummings, J. F. Hayes, and A. Kumar, *J. Chem. Soc., Chem. Commun.* **1986**, 1237.
9. S. Takano, Y. Shimazaki, Y. Iwabuchi, and K. Ogasawara, *Tetrahedron Lett.* **1990**, *31*, 3619.
10. Due to different cyclization rates in the lactonization step and possible enrichment during purification, this ratio (1.7:1) does not exactly reflect the selectivity of the $NaBH_4$ reduction.
11. E. D. Mihelich, K. Daniels, and D. J. Eickhoff, *J. Am. Chem. Soc.* **1981**, *103*, 7690.
12. ***Typical procedure:*** **rac-4a**. To a solution of **rac-1a** (1.11 g, 4.47mmol, 96% pure according to GC[13]) in 24 ml of CH_2Cl_2 was added at 0° 17.9 mmol Et_2Zn (17.9 ml 1M [hexane]). After stirring for 1/4 h the mixture was cooled to -18° and 17.9 mmol of CH_2I_2 were added (4.79 g, 1.44 ml). The internal temperature was then slowly raised within 5h to +5°. After quenching with sat. aq. NH_4Cl solution the mixture was extracted with Et_2O, washed twice with H_2O, dried over Na_2SO_4 and concentrated i.V. Flash chromatography of the crude product (SiO_2, hexane/AcOEt=93/7) yielded 960 mg of the cyclopropane **rac-4a**.
rac-5a. 530 mg (2.02 mmol) of **rac-4a** were dissolved in 9 ml of CH_2Cl_2 and cooled to -75°. BF_3·AcOH (3 eq., 6.06 mmol, 1.138 g) was added and the cooling bath interchanged after 5 min. (ice/MeOH, T=-20°). The temperature was then allowed to slowly rise to -5° (2 1/2h). The reaction mixture was poured onto crashed ice/dil. aq. NaOH, extracted with Et_2O, washed with H_2O, dried over Na_2SO_4 and concentrated i.V. Flash chromatography of the crude product (SiO_2, pentane/AcOEt=9/1) yielded 204 mg of (2RS, 4SR)-4-methyl-1-phenyl-hex-5-en-2-ol (**rac-5a**) as colourless oil.
13. 25m capillary column *HP Carbowax 20M*.

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