An Unprecedented Domino Double Allylsilane [3+2] Cycloaddition/Wagner–Meerwein Rearrangement/Friedel–Crafts Alkylation/Elimination Reaction Sequence Leading to a Novel Pentacyclic Ring System**

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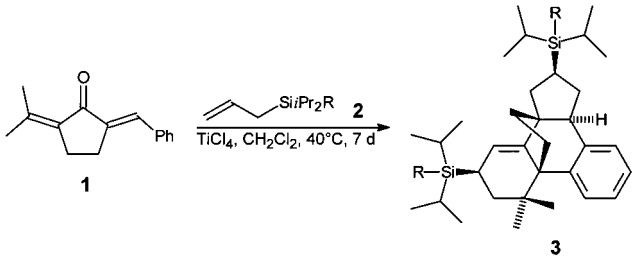
The Lewis acid promoted [3+2] cycloaddition of allylsilanes to electron-deficient olefins has become a powerful method for the stereoselective formation of silylcyclopentanes.[1–3] For projected applications to organic synthesis it was important that we could demonstrate for the first time the application of a modified Fleming–Tamao oxidation[4] to the oxidative cleavage of carbon–silicon bonds with sterically very demanding silyl groups, such as triphenylsilyl, *tert*-butyldiphenylsilyl, and diisopropylphenylsilyl.[5] Thus, the cycloaddition products can be transformed to the corresponding hydroxycyclopentanes with retention of configuration. Domino reactions offer the advantage of executing multistep transformations without intermediate workup and therefore can be applied to the one-pot synthesis of polycyclic ring systems.[6] We have already shown that the Lewis acid/Lewis base complex resulting from the first cycloaddition of an allylsilane can be exploited for consecutive transformations prior to hydrolytic workup. The Lewis acid promoted reaction of allylsilanes was used for a domino [3+2] cycloaddition with 3-butyn-2-one to bicyclo[3.3.0]octanes[7] and for a domino [2+2] cycloaddition with methyl propynoate to bicyclo[2.2.0]-hexanes.[8] The diastereoselective spiroannulation by [3+2] cycloaddition of allylsilanes and 2-alkylidenecycloalkan-1-ones was also extended to consecutive cycloadditions by using 2,5-diisopropylidenecyclopentanone as substrate.[9] In an extension of these previous findings we wanted to utilize the titanium tetrachloride complex resulting from the cycloaddition for additional carbon–carbon bond formations, for example by electrophilic aromatic substitution. In this context we investigated the cyclopentane spiroannulation by double allylsilane [3+2] cycloaddition at 2(*E*)-benzylidene-5-isopropylidenecyclopentanone (**1**).

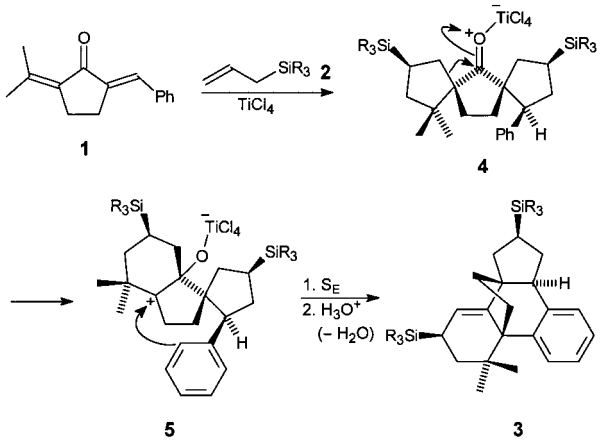
Compound **1** was prepared by aldol condensation of 2-isopropylidenecyclopentanone with benzaldehyde.[10] The titanium tetrachloride promoted reaction of **1** with the allylsilanes **2** was thought to proceed by a sequential annulation of two equivalents of the allylsilane. However, reaction of **1** with an excess of allyltriisopropylsilane (**2a**) at room temperature led to an inseparable mixture of mono-



Scheme 1. Lewis acid promoted domino reaction of the cross-conjugated dienone **1** with the allylsilanes **2**.

annulated species. In order to affect the sequential [3+2] cycloaddition at **1** the reaction was performed with a large excess of **2a** for seven days in dichloromethane under reflux (see Experimental Section). Using these reaction conditions we isolated, after hydrolytic workup and purification by chromatography on silica gel, the pentacyclic bis(triisopropylsilyl) derivative **3a** (R = *i*Pr) as a single diastereoisomer in 47% yield (Scheme 1). The structural assignment for **3a** is based on the spectral data and has been confirmed by an X-ray crystal structure determination of the corresponding epoxide (see below). From the reaction of **1** and allyldiisopropylphenylsilane (**2b**) the analogous bis(diisopropylphenylsilyl) derivative **3b** (R = Ph) was obtained stereoselectively in 25% yield.[11] Since it has been demonstrated recently that the diisopropylphenylsilyl group can be converted to a hydroxy group by a modified Fleming–Tamao oxidation,[5] compound **3b** was of interest with respect to further functionalizations of the novel carbon framework.

The unexpected formation of the novel pentacyclic ring system can be rationalized by the following mechanism (Scheme 2). A consecutive twofold [3+2] cycloaddition of the allylsilane **2** to the two exocyclic double bonds of **1** provides the Lewis acid complex **4**. The configuration of this intermediate is in agreement with the results of our previous investigation on the spiroannulation by [3+2] cycloaddition of allylsilanes.[9] Thus, the sequential [3+2] cycloaddition proceeds by an approach of both allylsilane moieties to the cross-conjugated dienone from the same face *syn* to each other. Both silyl groups are oriented *anti* relative to the carbonyl group, as found for most [3+2] cycloadditions of allylsilanes. Moreover, the [3+2] cycloaddition was already shown to be



Scheme 2. Proposed mechanism for the domino reaction of the dienone **1** with the allylsilanes **2**.

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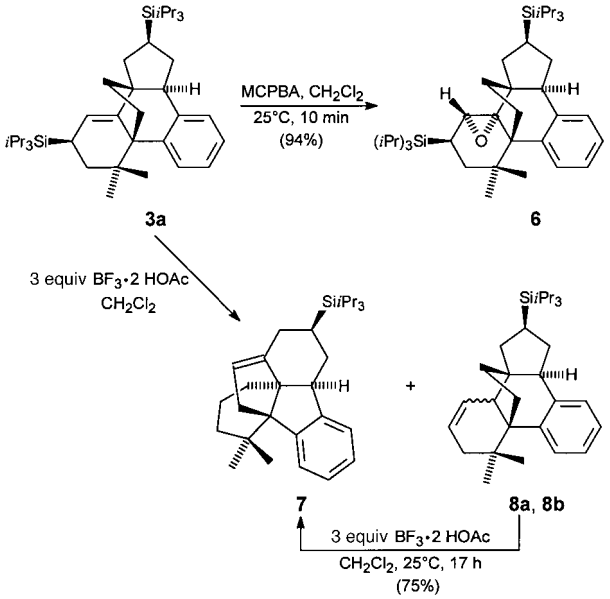
highlystereospecific with respect to the transformation of stereochemistry present in the exocyclic double bond to the product.[9] The coordination to the Lewis acid in **4** initiates a ring enlargement by Wagner–Meerwein rearrangement to the carbenium ion **5**. The geminal dimethyl group adjacent to the spiro carbon atom causes a steric repulsion which perhaps represents the driving force for this rearrangement. Acid-catalyzed rearrangements of dispiroketones are well-known by the work from Fitjer et al.[12] The resulting tertiary carbocation **5** effects an intramolecular Friedel–Crafts alkylation, and finally, elimination of water on hydrolytic workup generates the double bond. Thus, the relative configuration of the five stereogenic centers present in the product is established by the double [3+2] cycloaddition of the allylsilane and preserved during the subsequent stereospecific intramolecular reaction steps.

Compound **3a** was stereoselectively transformed into the crystalline epoxide **6** (m.p. 156 °C) by epoxidation of the double bond using *m*-chloroperbenzoic acid (MCPBA; Scheme 3). The X-ray structure analysis of the epoxide **6** confirmed the structure of the novel pentacyclic ring system,



Scheme 3. Reactions of compound **3a** with electrophiles.

the configuration of the five stereogenic centers already present in **3a**, and the configuration of the oxirane ring (Figure 1).[13] The two triisopropylsilyl groups and the ethano bridge resulting from the original five-membered ring of **1** are all on the same side of the molecule. As anticipated the epoxidation of the allylsilane double bond in **3a** took place stereoselectively *anti* relative to the silyl group.

We next investigated the feasibility of achieving further transformations at the pentacyclic ring system by using the silyl groups. We expected a chemoselective reaction of the silyl group at the six-membered ring because it constitutes an allylsilane which has been generated in the final elimination step of the domino reaction. In fact, protodesilylation of **3a** with the boron trifluoride/acetic acid complex provided the olefins **7** and **8**, which are exclusively desilylated at the six-

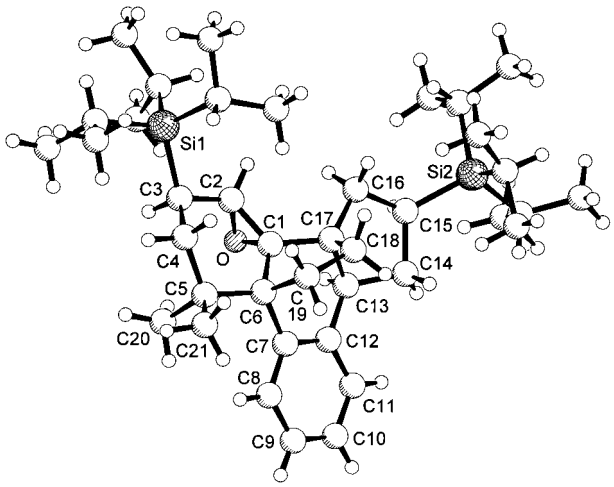


Figure 1. Molecular structure of **6** in the crystal. Selected bond lengths [Å]: Si1–C3 1.901(3), Si2–C15 1.884(3), C1–C2 1.465(4), C1–O 1.438(3), C2–O 1.461(3), C2–C3 1.519(4), C3–C4 1.544(4), C4–C5 1.548(4), C5–C6 1.573(4), C1–C17 1.520(3), C1–C6 1.538(4), C6–C7 1.555(4), C12–C13 1.501(4), C13–C14 1.531(4), C13–C17 1.531(4), C14–C15 1.561(4), C15–C16 1.576(4), C16–C17 1.538(4), C17–C18 1.549(4), C18–C19 1.542(4), C6–C19 1.549(4).

membered ring (Scheme 3, Table 1). The cyclohexenes **8** with an isomerized double bond compared to **3a** were obtained as a mixture of two diastereoisomers **8a** and **8b**, initially formed

Table 1. Protodesilylation of compound **3a**.

Reaction conditions	**7**, Yield [%]	**8a**, Yield [%]	**8b**, Yield [%]
25 °C, 30 min	5	64	22
25 °C, 1 h	10	58	29
−5 °C, 22 h	36	31	22
25 °C, 48 h	54	–	24

in a ratio of about 3:1. In contrast to the epoxidation, the protodesilylation of the allylsilane **3a** does not provide only one diastereoisomer. This lack of stereoselectivity is ascribed to the fact that two different mechanisms can be involved in the protodesilylation of 3,3-disubstituted allylsilanes. One follows the expected S_E2' course, the alternative pathway proceeds by a protonation at C-2, followed by an incompletely stereoselective 1,2-hydride shift and loss of the silyl moiety.[14] A detailed study of the protodesilylation revealed that only the major diastereoisomer **8a** slowly isomerizes to the thermodynamic product **7** on prolonged reaction times, while **8b** remains unchanged. Evidently **8a** represents the kinetic product of the reaction. In fact, on treatment with the boron trifluoride/acetic acid complex the isolated product **8a** is smoothly converted to the cyclopentene **7** in 75% yield.[11]

Finally, treatment of the bis(diisopropylphenylsilyl) derivative **3b** with a large excess of the hydrotetrafluoroboric acid/dimethyl ether complex led unexpectedly to Wagner–Meerwein rearrangement with concomitant double protodesilylation of the pentacyclic framework and afforded directly the olefin **9** in 59% yield (Scheme 4, Figure 2).[11,13]

In conclusion, we found a domino reaction of allylsilanes which provides stereoselectively the disilyl derivatives **3** containing a novel pentacyclic ring system with five stereogenic centers, two of them quaternary. Regio- and stereoselective transformations at the pentacyclic framework were shown.

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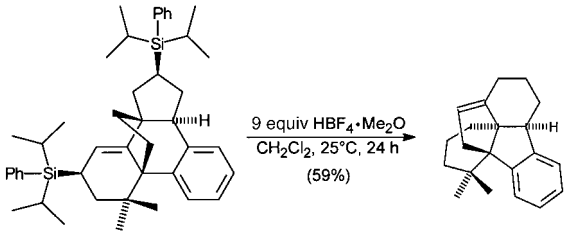

3b **9**

Scheme 4. Wagner–Meerwein rearrangement with double protodesilylation of the bis(diisopropylphenylsilyl) derivative **3b**.

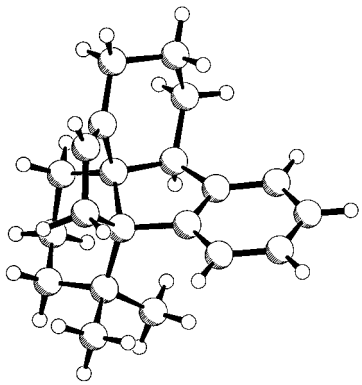

Figure 2. Molecular structure of **9** in the crystal.

Experimental Section

3a: A solution of **1** (200 mg, 0.94 mmol) in dry dichloromethane (5 mL) was added to a solution of titanium tetrachloride (0.11 mL, 195 mg, 1.03 mmol) in dry dichloromethane (5 mL) under argon atmosphere at room temperature. After addition of a solution of allyltriisopropylsilane (**2a**) (1.35 mL, 1.11 g, 5.61 mmol) in dry dichloromethane (5 mL) the reaction mixture was heated at reflux. Over the next five days additional allyltriisopropylsilane (**2a**) (1.15 mL, 950 mg, 4.80 mmol) was added in three portions. After a total reaction time of seven days the mixture was hydrolyzed by addition of an aqueous solution of ammonium chloride. The organic layer was separated, the aqueous layer was extracted five times with dichloromethane, and the combined organic layers were dried over magnesium sulfate. Removal of the solvent in vacuo and flash chromatography (hexane) of the residue on silica gel afforded the pentacyclic compound **3a** (260 mg, 47 %) as a colorless solid, m.p. 58 °C. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): $\delta = 10.95$ (3 CH), 11.24 (3 CH), 16.44 (CH), 19.24 (6 CH_3), 19.32 (6 CH_3), 19.59 (CH), 25.47 (CH_3), 28.90 (CH_3), 32.24 (CH_2), 34.27 (CH_2), 34.38 (CH_2), 34.91 (C), 36.67 (CH_2), 41.56 (CH_2), 51.33 (C), 56.19 (C), 57.01 (CH), 111.97 (CH), 125.19 (CH), 125.33 (CH), 126.96 (CH), 127.85 (CH), 139.70 (C), 145.01 (C), 147.49 (C); MS (105 °C): *m/z* (%): 590 [M^+] (9), 547 (13), 391 (33), 197 (10), 157 (100); elemental analysis (%) calcd. for $C_{39}H_{66}Si_2$: C 79.24, H 11.25; found: C 79.12, H 10.64.

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[11] Selected data of the compounds **3b**, **7**, and **9**. **3b**: Colorless crystals, m. p. 62 °C; ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): $\delta = 10.60$ (CH), 10.80 (CH), 11.28 (CH), 11.52 (CH), 16.32 (CH), 18.40 (CH_3), 18.55 (CH_3), 18.78 (2 CH_3), 18.85 (CH), 18.99 (2 CH_3), 19.03 (2 CH_3), 25.48 (CH_3), 28.75 (CH_3), 31.33 (CH_2), 32.53 (CH_2), 33.60 (CH_2), 34.89 (C), 36.54 (CH_2), 41.01 (CH_2), 51.27 (C), 56.08 (C), 56.47 (CH), 111.44 (CH), 125.17 (CH), 125.34 (CH), 127.07 (CH), 127.51 (4 CH), 127.81 (CH), 128.65 (CH), 128.68 (CH), 134.50 (C), 134.96 (C), 135.37 (2 CH), 135.41 (2 CH), 139.68 (C), 144.97 (C), 148.17 (C); MS (140 °C): *m/z* (%) = 658 [M^+] (17), 615 (13), 468 (7), 425 (30), 191 (100), 149 (95), 121 (79); elemental analysis (%) calcd. for $C_{45}H_{62}Si_2$: C 82.00, H 9.48; found: C 81.97, H 9.62. **7**: Colorless oil; ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): $\delta = 11.09$ (3 CH), 12.72 (CH), 19.27 (6 CH_3), 21.86 (CH_2), 23.88 (CH_2), 25.95 (CH_3), 26.86 (CH_2), 28.26 (CH_3), 33.21 (CH_2), 36.13 (C), 37.55 (CH_2), 40.50 (CH_2), 45.53 (CH), 57.62 (C), 61.68 (C), 117.97 (CH), 122.81 (CH), 123.18 (CH), 125.87 (CH), 126.30 (CH), 144.85 (C), 150.68 (C), 151.35 (C); MS (50 °C): *m/z* (%): 434 [M^+] (13), 391 (71), 278 (100), 195 (60). **9**: Colorless crystals, m. p. 64 °C; ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): $\delta = 18.14$ (CH_2), 21.89 (CH_2), 23.89 (CH_2), 25.89 (CH_3), 26.88 (CH_2), 28.22 (CH_3), 31.10 (CH_2), 35.35 (C), 37.82 (CH_2), 37.93 (CH_2), 46.31 (CH), 57.25 (C), 61.79 (C), 117.84 (CH), 122.72 (CH), 123.32 (CH), 125.83 (CH), 126.28 (CH), 144.86 (C), 150.72 (C), 151.45 (C); MS (55 °C): *m/z* (%): 278 [M^+] 100), 263 (11), 207 (11), 195 (76); elemental analysis (%) calcd. for $C_{21}H_{26}$: C 90.59, H 9.41; found: C 90.23, H 9.21.
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[13] X-ray crystal structure analyses: **6**: $C_{39}H_{66}OSi_2$; $M = 607.10\ g\,mol^{-1}$, monoclinic, space group $P2_1/c$, $\lambda = 0.71073$ Å, $a = 14.099(2)$, $b = 20.267(3)$, $c = 13.030(3)$ Å, $\beta = 101.226(14)°$, $V = 3652.1(11)$ Å^3, $Z = 4$, $\mu = 0.125\ mm^{-1}$, $\rho_{calcd} = 1.104\ g\,cm^{-3}$, $T = 143(2)$ K, θ range: 3.11–25.01°; 6435 independent reflections; refinement method: full-matrix least squares on F^2; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0563$, $wR_2 = 0.1209$, maximal residual electron density: 0.433 e Å^{-3}. **9**: $C_{21}H_{26}$; $M = 278.42\ g\,mol^{-1}$, monoclinic, space group $P2_1/c$, $\lambda = 0.71073$ Å, $a = 13.523(2)$, $b = 8.7046(8)$, $c = 14.309(2)$ Å, $\beta = 111.670(10)°$, $V = 1565.3(3)$ Å^3, $Z = 4$, $\mu = 0.066\ mm^{-1}$, $\rho_{calcd} = 1.181\ g\,cm^{-3}$, $T = 200(2)$ K, θ range: 3.72–25.94°; 2973 independent reflections; refinement method: full-matrix least squares on F^2; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0373$, $wR_2 = 0.0979$, maximal residual electron density: 0.250 e Å^{-3}. All hydrogen atoms were determined by Fourier difference calculation and refined sotropically. Programs: G. M. Sheldrick, SHELXS-86 (Göttingen, **1986**), SHELXL-93 (Göttingen, **1993**); E. Keller, SCHAKAL-97 (Freiburg im Breisgau, **1997**). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-116375 (**6**) and -132639 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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