Pergamon

Tetrahedron, Vol. 53, No. 48, pp. 16597-16606, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)01039-9

Preparation and Synthetic Utility of Oxasilacyclopentane Acetals Derived from Siliranes

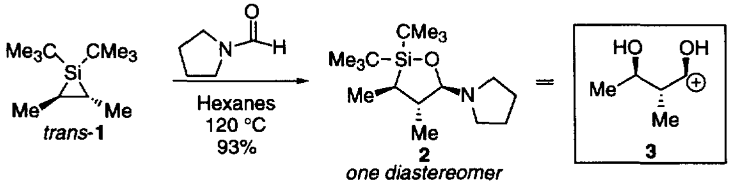
Jared T. Shaw and K. A. Woerpel*

Department of Chemistry, University of California,
Irvine, California 92697-2025, USA

Abstract: The insertion of formamides into a C–Si bond of silirane *trans*-**1** provides a facile route to the oxasilacyclopentane acetate **5** (86% overall yield). Stereoselective carbon-carbon bond formation on the derived oxonium ion was achieved by addition of the silyl enol ether of acetophenone (92:8 selectivity, 79% yield) and 3-pentanone (92:5:3 selectivity, 100% yield). These results demonstrate the potential of siliranes as intermediates in organic synthesis. © 1997 Elsevier Science Ltd.

Although the reactions of three-membered rings such as cyclopropanes[1] and epoxides[2] have been used to great advantage in organic synthesis, the chemistry of siliranes (silacyclopropanes) has not been applied for synthetic purposes, despite the unique reactivity of these strained systems.[3-13] The lack of methodology employing siliranes is due to limited investigations of key reactivity issues such as the stereoselectivity of ring-opening reactions.[14-16] In order to address these issues, we are developing new ring-opening reactions of siliranes and studying their stereochemistry.[16-18] The long-term goal of these studies is to introduce the reactions of siliranes as new methods for organic synthesis.

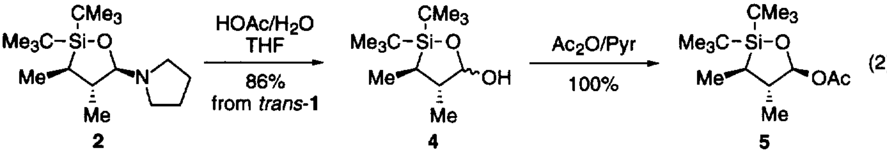
While exploring insertion reactions of silirane *trans*-**1**[19] with aldehydes,[16] we discovered that formamides insert into the C–Si bond to produce *N*,*O*-acetals such as **2** in high yield and with excellent stereoselectivity (eq 1).[17] The efficiency of this process led us to investigate these transformations as new methods for stereoselective synthesis. In this paper we describe how the amide insertion product **2** serves as a synthon for the chiral dihydroxy carbocation **3**. The products generated from this chemistry are structurally related to the acetate-terminated polypropionate natural products, including lankamycin[20] and oleandamycin.[21]



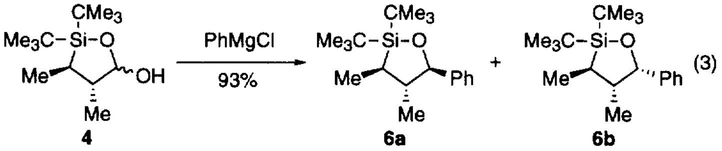
(1)

Results and Discussion

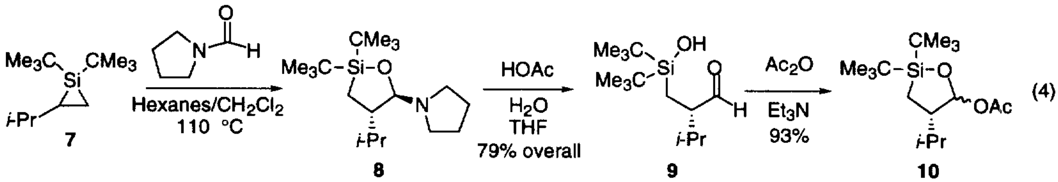
The insertion of 1-formylpyrrolidine into silirane *trans*-**1** proceeds cleanly in hexanes at 120 °C in a sealed tube to provide the *N*,*O*-acetal **2** as a single product. The progress of the reaction was monitored in C_6D_{12} (sealed NMR tube) by ^1H NMR spectroscopy to determine a 93% yield versus internal standard. Because the acetal **2** was sensitive to the presence of even trace amounts of acid such as found in $CDCl_3$, it was hydrolyzed with AcOH in THF/H_2O to afford the hemiacetal **4** as a 4:1 mixture of anomers (eq 2, 86% overall yield from silirane *trans*-**1**). Acylation of hemiacetal **4** with Ac_2O provided a single acetate **5** (by ^1H and ^{13}C NMR spectroscopy) in quantitative yield after chromatography (eq 2). This acetate became the focus of subsequent reactivity studies because it resembles the ribofuranosyl acetates which have been utilized previously for stereoselective carbon-carbon bond formation.[22,23]

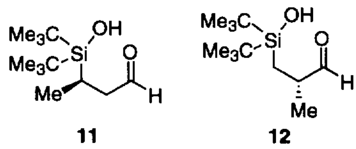


The stereochemistry of the oxasilacyclopentanes **2**, **4**, and **5** was determined by chemical and spectroscopic methods. The relative configuration of the two methyl-bearing stereocenters of hemiacetal **4** was determined to be trans by treatment with PhMgCl to afford a mixture of the benzyl ethers **6** (eq 3), whose structures we have proven unambiguously.[16] Assignments of the stereochemistry at the acetal centers of **2**, **4**, and **5** were made by comparison of coupling constant data with that obtained for the stereochemically related phenyl derivatives **6**.[16,17] The stereochemistry at the labile acetal carbon, although critical to mechanistic investigations of the insertion reaction,[17] is unimportant for synthesis objectives, because the stereocenter was isomerized in each manipulation.

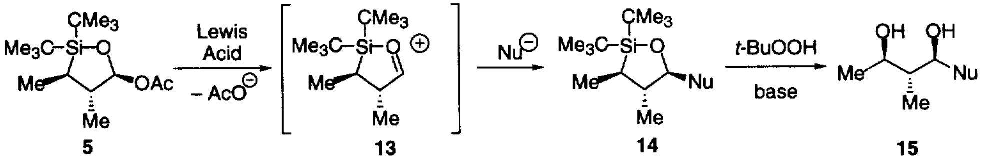


The cyclic hemiacetal form observed for the hydrolysis product **4** was not always preferred for the oxasilacyclopentane system. When isopropyl-substituted *N,O*-acetal **8**, prepared by reaction of silirane **7** with 1-formylpyrrolidine, was treated with acid, a siloxy aldehyde was observed as the major product by ^1H NMR spectroscopy. The siloxy aldehyde form **9** also predominates in related silanes **11** and **12**.[24] Although not observed, the cyclic hemiacetal structure for **9** is kinetically accessible.[25] Upon treatment of the aldehyde **9** with Ac_2O, acylation of the minor hemiacetal form occurs to provide acetate **10**. The silanol moiety of **9** must be sterically and electronically[26] less nucleophilic than the hemiacetal hydroxyl group.



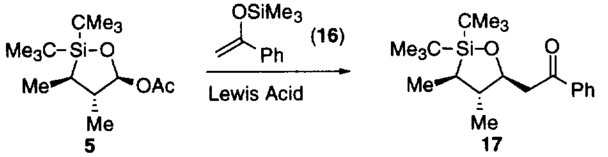


The facile preparation of acetates **5** with high stereoselectivity encouraged us to consider how the reactivity of these products could result in synthetic applications of siliranes. If **5** were to act as a precursor to oxonium ion[27] **13** (eq 5), then attack by carbon nucleophiles from the sterically more accessible β-face would form a new carbon-carbon bond to afford oxasilacyclopentane **14**.[28,29] Oxidation of the oxasilacyclopentane **14** to the 1,3-diol[30] **15** using our recently reported conditions[31] would demonstrate that siliranes can be employed for stereoselective synthesis.



(5)

The addition of silylenol ether **16**[32] to the acetate **5** (eq 6, Table 1) was examined to demonstrate the concept embodied in eq 5. When acetate **5** was treated with $ZnBr_2$ in either $MeNO_2$ or CH_2Cl_2 at low temperature (entries 1-2), a mixture of ketones was formed with low diastereoselectivity. Only marginally better stereoselectivity was observed when $SnBr_4$ was employed (entry 3), although the major product was the opposite diastereomer to the one obtained with $ZnBr_2$ (entry 2). Considerably higher stereoselectivity (92 : 8) was observed when $SnCl_4$ was employed as Lewis acid (entry 4).

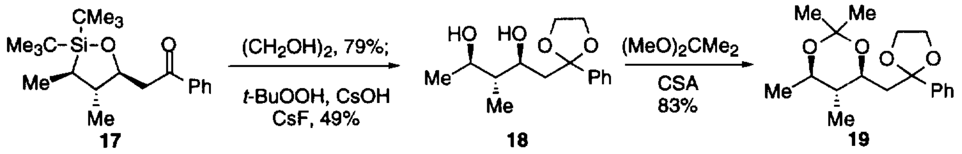


(6)

Table 1. Addition of 1-Trimethylsilyloxy-1-phenylethene to **5** (eq 6).

Entry	Solvent	Temperature (°C)	Lewis Acid	Selectivity (% yield)
1	$MeNO_2$	–20	$ZnBr_2$	48 : 52
2	CH_2Cl_2	–78	$ZnBr_2$	40 : 60
3	CH_2Cl_2	–78	$SnBr_4$	65 : 35
4	CH_2Cl_2	–78	$SnCl_4$	92 : 8 (79%)

The preparation of diol **18** from oxasilacyclopentane **17** demonstrates that siliranes have potential to be intermediates for organic synthesis (eq 7). Protection of the carbonyl followed by oxidation of the C–Si bond under conditions developed in our laboratories for hindered alkoxysilanes[31] led to diol **18**. The relative stereochemistry of the two hydroxy groups was proven by formation of the acetonide **19** and subsequent analysis by ^{13}C NMR spectroscopy.[33,34]



(7)

The acetate substrates **5** can also be used to synthesize products containing four contiguous stereocenters with high stereoselectivity. Addition of the silylenol ether of 3-pentanone (**20**) to acetate **5** in the presence of a Lewis acid led to predominately one ketone **21** (eq 8, Table 2) along with two minor isomers (**22** and **23**). For most conditions investigated, facial selectivity (**21** + **22** : **23**) on the putative oxonium ion **13** was higher ($\geq$91%) than for the acetophenone enolate **16** (eq 6, Table 1). Trimethylsilyl enol ethers delivered increased stereoselectivity at the stereocenter α to the carbonyl group as compared to the corresponding Si(*t*-Bu)Me$_2$ derivatives (entries 1,2). In addition, the (*E*)-enol ethers[35] were more stereoselective than the corresponding (*Z*)-isomers (compare entries 4 and 5). The high stereoselectivity and yield of these reactions make them attractive for the construction of stereochemically interesting structures.

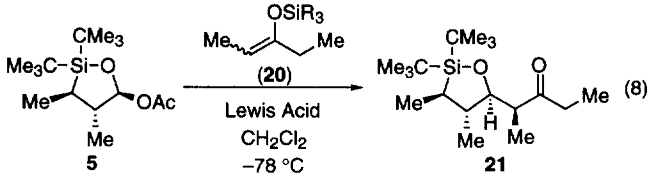
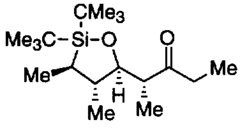
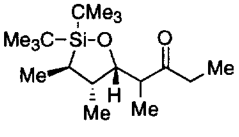
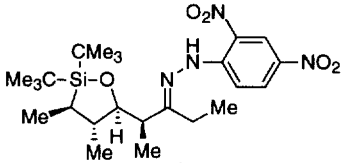


Table 2. Addition of silylenol ether **20** to **5** (eq 8).

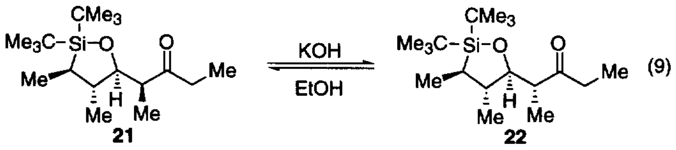
Entry	SiR$_3$	*E* : *Z*	Lewis Acid	**21** : **22** : **23**	(% yield)
1	Si(*t*-Bu)Me$_2$	90 : 10	SnBr$_4$	89 : 11 : 3	
2	Si(*t*-Bu)Me$_2$	90 : 10	SnCl$_4$	84 : 13 : 3	
3	SiMe$_3$	26 : 74	SnBr$_4$	89 : 7 : 4	
4	SiMe$_3$	26 : 74	SnCl$_4$	83 : 8 : 9	
5	SiMe$_3$	98 : 2	SnBr$_4$	92 : 5 : 3	(100%)


22

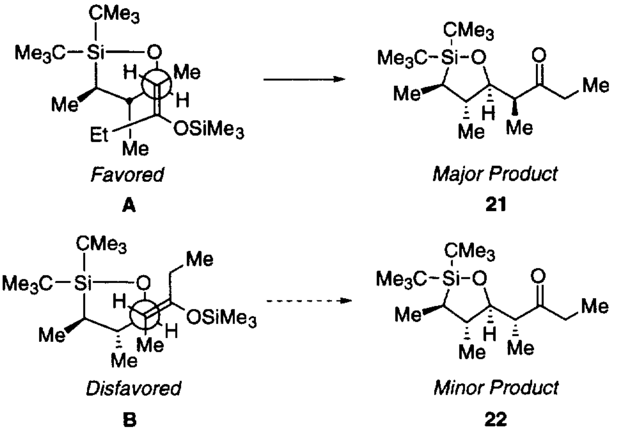

23


24
X-ray

The stereochemistry of ketones **21**-**23** was proven using a variety of methods. Because oxidation of the oxasilacyclopentane **21** would not provide information about the stereocenter α to the carbonyl, X-ray crystallography was chosen to be the most expedient method for structure elucidation. The 2,4-dinitrophenylhydrazone derivative **24** was crystalline and allowed unambiguous determination of the stereochemistry of the major product.[36] The stereochemical relationship between **21** and **22** was established by epimerization of **21** in base to afford a mixture of both ketones (eq 9). None of the third isomer (**23**) was observed by GC. These results indicate that **23** differs in stereochemistry from **21** and **22** at the ring juncture and must result from attack upon the alternate stereoface of the oxonium ion **13**. Due to the limited supply of **23**, the configuration of the stereocenter α to the carbonyl group of this stereoisomer has not been determined.



The preferential formation of ketone **21** can be rationalized by considering the two possible staggered transition structures **A** and **B**. In both structures, the hydrogen atom is directed toward the inside of the ring, which is the most sterically demanding position. The two structures **A** and **B** therefore represent synclinal versus antiperiplanar orientation of the alkene nucleophile to the oxygen atom of the electrophile.[37] Because the prochiral sp^2-hybridized nucleophile approaches the oxonium ion along the Bürgi-Dunitz trajectory,[38] the position antiperiplanar to the oxygen is more sterically crowded than the synclinal position.[39] In the case of enolate **20** and the oxonium ion **13**, we believe that **A** (depicted for the Z-enolate) positions the smaller alkenyl moiety (based on conformational A-values)[40] in the more sterically demanding antiperiplanar position as compared to the methyl group in this position for transition structure **B**. Further comment on this model must await investigations involving other nucleophiles.



In conclusion, the high stereoselectivities observed in the nucleophilic attack of silylenol ethers on acetate **5** derived from silirane *trans*-**1** demonstrate that the reactions of siliranes can be used in selective organic synthesis. We believe that the chemistry of siliranes will lead to new methods for the synthesis of polyoxygenated natural products. Future experiments from our laboratories will focus on other carbon-carbon bond-forming reactions of siliranes and their products (including acetate **5**) as well as the development of routes to enantiomerically pure materials.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 500 and 125 MHz, respectively, using a Nicolet Omega 500 spectrometer. Coupling constants are reported in Hertz. High resolution mass spectra were acquired on a VG Analytical 7070E or Fisons Autospec spectrometer, and were obtained by peak matching. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Melting points are reported uncorrected. Siliranes were stored and handled in an Innovative Technologies nitrogen atmosphere drybox.

1-Oxa-3,4-dimethyl-5-(1-pyrrolidino)-2,2-di(*tert*-butyl)silacyclopentane (2). *Trans*-silirane **1** (0.155 g, 0.781 mmol) was transferred to a reaction tube under inert atmosphere then treated with 1-formylpyrrolidine (0.75 mL, 7.37 mmol) and diluted in hexanes (1.5 mL). The tube was sealed and removed from the inert atmosphere then de-gassed by the method of freeze-pump-thaw (1 round). The tube was heated in an oil bath to 120 °C for 4 h then cooled, diluted in CH_2Cl_2 and reduced *in vacuo*. ^1H NMR ($CDCl_3$, 500 MHz) δ 4.23 (d, J = 9.6, 1 H), 3.50 (t, J = 6.4, 2 H), 3.43 (t, J = 6.6, 2H), 2.85 (m, 4H), 1.63 (m, 1H), 1.19 (d, J = 7.5, 3H), 1.06 (s, 9H), 1.00 (s, 9H), 0.97 (d, J = 6.4, 3H), 0.85 (m, 1H); IR (thin film) 2960, 2935, 2858, 1474, 1389, 1364, 934, 901, 854, 822, 697, 632; HRMS (CI/isobutane) calcd for $C_{17}H_{35}OSiN$ $(M+H)^+$ 297.2488, found 297.2492.

1-Oxa-3,4-dimethyl-5-hydroxy-2,2-di(*tert*-butyl)silacyclopentane (4). Unpurified **2** (*vide supra*) was dissolved in 10 mL of THF then treated with 1 mL of acetic acid and 1 mL of H_2O and stirred at room temperature for 10 h. The THF was removed *in vacuo* and the resultant material was dissolved in CH_2Cl_2 and washed with $NaHCO_3$ (sat., aq). The organic layer was filtered through a cotton plug and reduced *in vacuo*. Purification by flash chromatography (5:95-10:90 EtOAc/hexanes) yielded the product as a white solid (0.169 g, 86% from **1**, 4:1 mixture of anomers by ^1H NMR spectroscopy): mp 79-80 °C; ^1H NMR ($CDCl_3$, 500 MHz, major isomer) δ 4.86 (dd, J = 5.3, 7.5, 1H), 3.99 (m, 1H), 1.56 (m, 1H), 1.20 (d, J = 7.3, 3H), 1.09 (s, 9H), 1.06 (d, J = 7.0, 3H), 1.02 (s, 9H), 0.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, both isomers) δ 102.9, 98.9, 48.0, 44.9, 28.4, 28.0, 27.8, 27.7, 23.8, 21.5, 20.7, 20.1, 19.8, 15.5, 13.5, 12.8, 13.4; IR (KBr pellet) 3352, 2964, 2861, 1471, 1366, 1107, 971, 822, 700, 637 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{13}H_{29}O_2Si$ $(M-H)^+$ 243.1780, found 243.1781. Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 63.66; H, 11.33.

1-Oxa-3,4-dimethyl-5-acetoxy-2,2-di(*tert*-butyl)silacyclopentane (5). To a stirred solution of hemiacetal **4** (0.161 g, 0.66 mmol) in 10 mL of pyridine was added 4 mL of acetic anhydride. The reaction was stirred at room temperature for 12 h then reduced *in vacuo* and partitioned between CH_2Cl_2 and $NaHCO_3$ (sat., aq). The organic layer was recovered and the aqueous layer was extracted with 2x10 mL of CH_2Cl_2. The combined organic layers were filtered through a cotton plug and reduced *in vacuo*. Purification by flash chromatography (3:97-7:93 EtOAc/hexanes) yielded the product as a white solid (0.188 g, 100%): mp 85 °C; ^1H NMR ($CDCl_3$, 500 MHz,) δ 5.75 (d, J = 7.5, 1H), 2.10 (s, 3H), 1.78 (m, 1H), 1.21 (d, J = 7.5, 3H), 1.08 (s, 9H), 1.04 (s, 9H), 1.00 (d, J = 6.4, 3H), 0.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 100.7, 45.6, 27.7, 27.4, 23.4, 21.5, 21.1, 20.6, 15.1, 12.7; IR (KBr pellet) 2937, 2862, 1741, 1473, 1387, 1366, 1234, 1082, 1053, 1019, 1005, 988, 644, 624, 610, 699, 658, 636, 567, 469 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{13}H_{27}OSi$ $(M-OAc)^+$ 227.1831, found 227.1801. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 62.91; H, 10.56.

1-Oxa-3,4-dimethyl-5-phenyl-2,2-di(*tert*-butyl)silacyclopentane (6a, 6b). To a stirred solution of **4** (0.128 g, 0.524 mmol) in 5 mL of THF cooled to -78 °C was added a solution of phenylmagnesium chloride (2.6 mL, 2.0 M in THF). The reaction was stirred at that temperature for 15 min. then warmed to room temperature for 15 min. The flask was fitted with a condenser and the reaction was heated to reflux for 3 h then cooled to room temperature and quenched with the addition of HCl (3 mL, 10% aq). After the reaction had stirred for 1 h, it was diluted in 20 mL of hexanes and washed with 3x10 mL of Na_2HPO_4 (sat., aq). The resulting hexanes solution was filtered through a pad of Na_2SO_4 and reduced *in vacuo* to a clear oil. Purification by flash chromatography (2:98-3:97 EtOAc/hexanes) yielded the product (0.148 g, 93%) as a clear oil. Analysis by gas chromatography indicated that the two diastereomers were formed in >99% isomeric purity in a 70:30 (**6a**:**6b**) ratio.

6a: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.20 (m, 5H), 5.26 (d, J = 8.8, 1H), 2.40 (m, 1H), 1.26 (d, J = 7.4, 3H), 1.17 (s, 9H), 1.15 (s, 9H), 1.15 (m, 1H), 0.61 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.8, 127.7, 127.5, 126.9, 83.4, 44.0, 29.1, 28.6, 24.2, 22.6, 20.6, 17.5, 14.2; IR (thin film) 3117, 2962, 2933, 2858, 1473, 1387, 1363, 1072, 1017, 841, 822, 700 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{33}OSi$ $(M\text{-}t\text{Bu})^+$ 247.1517, found 247.1517. Anal. Calcd for $C_{19}H_{32}SiO$: C, 74.93; H,10.59. Found: C, 74.86; H, 10.64.

6b: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.25 (m, 5H), 4.24 (d, J = 10.0, 1H), 1.62 (m, 1H), 1.25 (d, J = 7.4, 3H), 1.19 (s, 9H), 1.09 (s, 9H), 1.05 (m, 1H), 0.88 (d, J = 6.1, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.3, 128.2, 127.4, 126.6, 86.7, 49.4, 28.2, 27.9, 26.0, 21.5, 21.4, 15.2, 12.7; IR (thin film) 3117, 2932, 2857, 1492, 1472, 1386, 1363, 1063, 1021, 848, 822, 750 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{33}OSi$ $(M\text{-}t\text{Bu})^+$ 247.1517, found 247.1522. Anal. Calcd for $C_{19}H_{32}SiO$: C, 74.93; H, 10.59. Found: C, 74.69; H, 10.68.

1-Oxa-4-isopropyl-5-(1-pyrrolidino)-2,2-di(*tert*-butyl)silacyclopentane (8). Silirane **7** (0.139 g, 0.654 mmol) was transferred to a reaction tube under inert atmosphere then treated with 1-formylpyrrolidine (0.360 mL, 3.73 mmol) and diluted in a mixture of CH_2Cl_2 and hexanes (50:50, 1.8 mL). The tube was sealed and removed from the inert atmosphere then de-gassed by the method of freeze-pump-thaw (1 round). The tube was heated in an oil bath to 110 °C for 8 h then cooled, diluted in 20 mL of 10:90 triethylamine/hexanes and washed with 3x10 mL of water. The organic layer was filtered through Na_2SO_4 and reduced *in vacuo* to yield the product as a clear oil: ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 4.50 (d, *J* = 9.9, 1 H), 2.85 (m, 4H), 1.92 (m, 1H), 1.82 (m, 1H), 1.74 (m, 4H), 1.63 (m, 1H), 1.01 (s, 9H), 0.99 (s, 9H), 0.93 (d, *J* = 6.8, 3H), 0.80 (d, *J* = 6.8, 3H), 0.65 (dd, *J* = 7.6, 14.7, 1H), 0.55 (dd, *J* = 12.8, 14.7, 1H); IR (thin film) 2959, 2857, 1472, 1415, 1386, 1364, 1173, 1152, 1011, 904, 861, 823, 760, 738, 621 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{17}H_{35}OSiN$ $(M)^+$ 311.2644, found 311.2634.

Siloxyaldehyde 9. Unpurified **8** (*vide supra*) was dissolved in 10 mL of THF then treated with 1 mL of acetic acid and 1 mL of H_2O and stirred at room temperature for 10 h. The THF was removed *in vacuo* and the resultant material was dissolved in MTBE and washed with Na_2HPO_4 (sat., aq). The organic layer was filtered through Na_2SO_4 and reduced *in vacuo*. Purification by flash chromatography (5:95-10:90 EtOAc/hexanes) yielded the product as a clear oil (0.134 g, 79% from **7**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (d, *J* = 2.0, 1H), 2.55 (m, 1H), 2.18 (m, 1H), 2.14 (s, 1H), 1.04 (d, *J* = 7.1, 3H), 1.01 (s, 9H), 1.00 (s, 9H), 0.93 (d, *J* = 6.8, 3H), 0.89 (dd, *J* = 11.7, 15.1, 1H), 0.62 (dd,*J* = 2.3, 15.1, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.8, 53.8, 30.2, 27.7, 27.53, 27.48, 27.4, 20.2, 18.6, 4.8; IR (thin film) 3420 (br), 2961, 2933, 2889, 2860, 2713, 1715, 1471, 1389, 1366, 1013, 967, 939, 824, 762, 734 cm^{-1}. Anal. Calcd for $C_{14}H_{32}O_2Si$: C, 65.06; H, 11.80. Found: C, 65.01; H, 11.80.

1-Oxa-4-isopropyl-5-acetoxy-2,2-di(*tert*-butyl)silacyclopentane (10). To a stirred solution of aldehyde **9** (0.362 g, 1.40 mmol) in 15 mL of CH_2Cl_2 was added 1 mL of acetic anhydride, 2 mL of triethylamine, and a spatula tip of DMAP. The reaction was stirred at room temperature for 12 h then reduced *in vacuo* and partitioned between MTBE and NaH_2PO_4 (sat., aq). The organic layer was washed with 2x10 mL of NaH_2PO_4 (sat., aq). The organic layer was filtered through Na_2SO_4 and reduced *in vacuo*. Purification by flash chromatography (3:97-5:95 EtOAc/hexanes) yielded the product as a clear oil (0.391 g, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer) δ 5.99 (d, *J* = 7.3, 1H), 2.07 (s, 3H), 1.88 (m, 1H), 1.68 (m, 1H), 1.04 (s, 9H), 1.02 (d, *J* = 7.5, 3H), 1.02 (s, 9H), 0.91 (d, *J* = 6.4, 3H), 0.89 (m, 1H), 0.58 (dd, *J* = 12.1, 15.0, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz, major isomer) δ 170.5, 99.2, 49.7, 28.0, 27.45, 27.38, 27.3, 21.2, 20.2, 19.8, 18.7, 6.7; IR (neat) 2960, 2934, 2892, 2860, 1750, 1471, 1367, 1223, 1091, 1017, 1008, 827, 769, 740, 625 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{14}H_{29}OSi$ $(M-OAc)^+$ 241.1988, found 241.1978. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.88. Found: C, 64.13; H, 10.88.

1-Oxa-3,4-dimethyl-5-(3-phenyl-(1-oxoethyl))-2,2-di(*tert*-butyl)silacyclopentane (17). To a stirred solution of acetate **5** (0.172 g, 0.60 mmol) in 6 mL CH_2Cl_2 at -78 °C was added $SnCl_4$ (0.60 mL, 1 M, CH_2Cl_2) followed by 1-phenyl-1-trimethylsiloxyethylene (0.246 mL, 1.20 mmol). The reaction was warmed to room temperature for 3h then diluted in CH_2Cl_2 and poured into $NaHCO_3$ (sat., aq). The organic layer was recovered and the aqueous layer was extracted with 2x10 mL of CH_2Cl_2. The combined organic layers were filtered through a cotton plug and reduced *in vacuo*. Purification by flash chromatography (2:98-3:97 EtOAc/hexanes) yielded the product as a clear oil (0.165 g, 79%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 4.96 (m, 1H), 3.09 (dd, *J* = 6.3, 16.2, 1H), 2.99 (dd, *J* = 6.9, 16.2, 1H), 2.26 (m, 1H), 1.19 (d, *J* = 4.0, 3H), 1.04 (s, 18H), 0.94 (m, 1H), 0.92 (d, *J* = 6.8, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 137.4, 132.7, 128.5, 128.0, 42.7, 42.2, 28.6, 28.3, 22.0, 21.8, 20.0, 14.9, 12.6; IR (thin film) 2934, 2857, 1688, 1598, 1581, 1473, 1448, 1386, 1364, 1290, 1210, 1180, 1025, 822, 743, 697, 635 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{22}H_{35}O_2Si$ $(M+H)^+$ 347.2406, found 347.2405. Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.78; H, 9.89. Found: C 72.68; H 9.86.

Ethylene Glycol Acetal of 17 (18). To a stirred solution of ketone **17** (0.187 g, 0.540 mmol) in 10 mL of benzene was added 2 mL of ethylene glycol and 0.005 g of camphorsulfonic acid. The flask was fitted with a Dean/Stark trap (1 g of 4Å molecular sieves added to trap) and a reflux condenser then the mixture was heated to reflux for 5 days. The reaction was diluted MTBE and washed with 3x20 mL of Na_2HPO_4 (sat., aq). The organic layer was separated, filtered through a layer of Na_2SO_4 and reduced *in vacuo*. Purification by flash chromatography (10:90 EtOAc/hexanes) yielded the product as a clear oil (0.165 g, 79%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.25 (m, 3H), 4.04 (m, 2H), 3.84 (m, 1H), 3.73 (m, 1H), 3.40 (m, 1H), 2.16 (m, 1H), 2.09 (m, 1H), 1.27 (m, 1H), 1.12 (d, *J* = 7.5, 3H), 0.90 (d, obscured, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.9, 127.5, 127.3, 126.1, 110.0, 79.4, 64.5, 64.2, 47.4, 47.0, 27.9, 27.8, 25.1, 21.0, 15.8, 12.9; IR (neat) 3028, 2958, 2884, 2857, 1472, 1386, 1354, 1167, 1074, 1048, 987, 954, 898, 871, 822, 764, 700, 633, 618 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{39}O_3Si$ $(M+H)^+$ 391.2668, found 391.2663. Anal. Calcd for $C_{23}H_{38}O_3Si$: C, 70.72; H 9.81. Found: C, 70.91; H 9.70.

1-(1,3-Dioxolan-2-yl)-1-phenyl-4-methyl-hexan-3,5-diol (19). To a stirred solution of $CsOH \bullet H_2O$ (0.730 g, 4.35 mmol) and *tert*-butylhydroperoxide (0.48 mL, 4.35 mmol; 90% aq) in 5 mL of NMP was added oxasilacyclopentane **18** (0.155 g, 0.435 mmol) in 3 mL of NMP. CsF (0.330 g, 2.17 mmol) was added and the reaction was heated to 70 °C for 10 h. The reaction was quenched with $Na_2S_2O_3$ (10 mL, 1.3 M aq) and diluted in MTBE. The aqueous layer was removed and the organic layer washed with 6x10 mL of H_2O. The organic layer was filtered through a cotton plug and reduced *in vacuo*. Purification by flash chromatography (30:70-50:50 EtOAc/hexanes) yielded the product as a clear oil (0.057 g, 49%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (m, 2H), 7.36 (m, 3H), 4.13 (br s, 2H), 4.09 (m, 2H), 3.87 (m, 2H), 3.78 (m, 2H), 2.24 (dd, *J* = 1.2, 15.1, 1H), 1.99 (dd, *J* = 9.6, 15.1, 1H), 1.48 (m, 1H), 1.15 (d, *J* = 6.3, 3H), 0.73 (d, *J* = 6.8, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.7, 128.3 (128.343), 128.3 (128.251), 125.4, 110.9, 73.0, 71.3, 64.6, 63.9, 45.1, 44.4, 21.0, 12.8; IR (thin film) 3444 (br), 3080, 3029, 2969, 2892, 1448, 1416, 1379, 1313, 1274, 1212, 1134, 1040, 946, 920, 826, 768, 734, 705 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{15}H_{21}O_3(M-OH)^+$ 249.1491, found 249.1502. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C 67.52; H, 8.39.

Acetonide of 19. To a stirred solution of **19** (0.042 g, 0.16 mmol) in 1 mL of acetone was added 2 mL of 2,2-dimethoxypropane followed by 0.002 g of camphorsulfonic acid. The reaction was quenched after 5 min with several drops of triethylamine then reduced *in vacuo*. Purification by flash chromatography yielded the product as a clear oil (0.040 g, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (m, 2H), 7.30 (m, 3H), 4.05 (m, 1H), 4.00 (m, 1H), 3.78 (m, 2H), 3.52 (m, 2H), 2.18 (dd, *J* = 1.9, 14.8, 1H), 2.08 (dd, *J* = 8.1, 14.9, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 1.13 (d, *J* = 6.0, 3H), 0.74 (d, *J* = 6.8, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.2, 127.8, 127.6, 126.0, 109.8, 97.5, 70.8, 64.5, 64.2, 44.0, 40.6, 30.0, 20.0, 19.1, 12.5; IR (thin film) 3060, 3028, 2988, 2936, 2889, 1448, 1378, 1261, 1202, 1177, 1054, 1043, 965, 906, 764, 734, 704, 618 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{18}H_{27}O_4$ $(M+H)^+$ 307.1909, found 307.1908. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H 8.55. Found: C, 70.67; H 8.59.

1-Oxa-3,4-dimethyl-5-(2-(3-oxopentyl))-2,2-di(*tert*-butyl)silacyclopentane (21). To a stirred solution of acetate **5** (0.114 g, 0.398 mmol) in 4 mL of CH_2Cl_2 at -78 °C was added $SnBr_4$ (0.40 mL, 1 M, CH_2Cl_2) followed by 3-trimethylsiloxy-2-pentene (0.25 mL, 1.6 mmol, density of 1.0 assumed). The reaction was stirred for 20 min at that temperature then warmed to room temperature for 1 h. The reaction was diluted in CH_2Cl_2 and poured into $NaHCO_3$ (sat., aq). The organic layer was recovered and the aqueous layer was extracted with 2x10 mL of CH_2Cl_2. The combined organic layers were filtered through a cotton plug and reduced *in vacuo*. Purification by flash chromatography (2:98-3:97 EtOAc/hexanes) yielded the product as a clear oil (0.125 g, 100%, 92:5:3 selectivity by GC): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.71 (dd, *J* = 7.7, 10.5, 1H), 2.57 (m, 3H), 1.57 (m, 1H), 1.21 (d, *J* = 7.6, 3H), 1.12 (d, *J* = 6.8, 3H), 1.03 (s, 9H, overlapping with m, 3H), 0.99 (s, 9H), 0.93 (d, *J* = 6.4, 3H), 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.8, 83.3, 49.4, 43.2, 33.2, 27.9, 27.8, 25.4, 21.3, 15.3, 12.6, 9.0, 7.9; IR (thin film) 3086, 3060, 2934, 2857, 1688, 1598, 1474, 1448, 1386, 1364, 1290, 1210, 1180, 1025, 1007, 897, 822, 743, 697, 635 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{27}O_2Si$ (M-*t*Bu)$^+$ 255.1780, found 255.1774. Anal. Calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 69.27; 11.70.

Acknowledgments. This research was supported by the National Institutes of Health (GM-54909) and by University of California Cancer Research Coordinating Committee funds. Acknowledgment is also made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank the American Cancer Society (for a Junior Faculty Research Award to K.A.W.) and the U.S. Department of Education (in the form of a GAANN fellowship to J.T.S.). The contributions of

Dr. Joseph Ziller (for crystallographic analysis) and Dr. John Greaves (for mass spectrometric data) are gratefully acknowledged.

References and Notes

1. Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198.
2. Padwa, A.; Murphree, S. S. In *Progress in Heterocyclic Chemistry*; H. Suschitzky and E. F. V. Scriven, Eds.; Pergamon: New York, 1994; Vol. 6; pp 56-73.
3. Seyferth, D.; Annarelli, D. C.; Vick, S. V.; Duncan, D. P. *J. Organomet. Chem.* **1980**, *201*, 179-195.
4. Seyferth, D.; Annarelli, D. C.; Shannon, M. L.; Escudie, J.; Duncan, D. P. *J. Organomet. Chem.* **1982**, *225*, 177-191.
5. Seyferth, D.; Annarelli, D. C.; Duncan, D. P. *Organometallics* **1982**, *1*, 1288-1294.
6. Seyferth, D.; Duncan, D. P.; Shannon, M. L.; Goldman, E. W. *Organometallics* **1984**, *3*, 574-578.
7. Seyferth, D.; Duncan, D. P.; Shannon, M. L. *Organometallics* **1984**, *3*, 579-583 and references cited therein.
8. Similar reactions have been observed for alkylidenesiliranes: Saso, H.; Ando, W.; Ueno, K. *Tetrahedron* **1989**, *45*, 1929-1940.
9. Kumarathasan, R.; Boudjouk, P. *Tetrahedron Lett.* **1990**, *31*, 3987-3990.
10. Ando, W.; Fujita, M.; Yoshida, H.; Sekiguchi, A. *J. Am. Chem. Soc.* **1988**, *110*, 3310-3311.
11. Kroke, E.; Willms, S.; Weidenbruch, M.; Saak, W.; Pohl, S.; Marsmann, H. *Tetrahedron Lett.* **1996**, *37*, 3675-3678.
12. Zhang, S.; Conlin, R. T. *J. Am. Chem. Soc.* **1991**, *113*, 4272-4278.
13. Belzner, J.; Ihmels, H.; Kneisel, B. O.; Gould, R. O.; Herbst-Irmer, R. *Organometallics* **1995**, *14*, 305-311.
14. Tortorelli, V. J.; Jones, M., Jr.; Wu, S.-h.; Li, Z.-h. *Organometallics* **1983**, *2*, 759-764.
15. Boudjouk, P.; Black, E.; Kumarathasan, R.; Samaraweera, U.; Castellino, S.; Oliver, J. P.; Kampf, J. W. *Organometallics* **1994**, *13*, 3715-3727.
16. Bodnar, P. M.; Palmer, W. S.; Shaw, J. T.; Smitrovich, J. H.; Sonnenberg, J. D.; Presley, A. L.; Woerpel, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 10575-10576.
17. Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 442-443.
18. Palmer, W. S.; Woerpel, K. A. *Organometallics* **1997**, *16*, 1097-1099.
19. Boudjouk, P.; Samaraweera, U.; Sooriyakumaran, R.; Chrusciel, J.; Anderson, K. R. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1355-1356.
20. Muntwyler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1972**, *55*, 460-472.
21. For a recent synthesis of oleandolide, see: Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287-11314.
22. Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett.* **1986**, *27*, 1011-1014.
23. Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chemistry Lett.* **1989**, 145-148.
24. For the related carbon systems, γ-hydroxyaldehydes preferentially adopt the tetrahydrofuran hemiacetal form: Stoddart, J. F. *Stereochemistry of Carbohydrates*; Wiley: New York, 1971, pp 29-31.
25. Hoveyda has invoked the interconversion of oxasilacyclopentane hemiacetals and β-siloxyaldehydes in the conversion of spirocyclic siloxanes to tetrahydropyran hemiacetals: Young, D. G. J.; Hale, M. R.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 827-830.
26. Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697-703.
27. Control experiments using both anomers of the methyl acetal corresponding to **5** indicate that an oxonium ion is a reactive intermediate. For a discussion of oxonium intermediates as intermediates in nucleophilic substitution reactions of acetals, see: Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116* 7915-7916.
28. Hoveyda has pioneered the use of oxasilacyclopentanes to control the stereochemistry of reactions on

exocyclic substituents: (a) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643-1645. (b) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1994**, *59*, 4370-4374.

29. Stereoselective nucleophilic addition to dioxasilacyclohexane carbocations was used for the formation of carbon-carbon bonds; the stereochemistry was controlled by stereoelectronic effects: Davis, A. P.; Hegarty, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 2745-2746.
30. The equivalence of oxasilacyclopentanes and 1,3-diols has been previously demonstrated. See, for example: Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487-6498.
31. Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044-6046.
32. Walshe, N.; Goodwin, G.; Smith, G.; Woodward, F. *Org. Synth.* **1986**, *65*, 1-9.
33. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.
34. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.
35. Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571-9574.
36. Hydrolysis of **24** with acid regenerated **21**, indicating that epimerization did not occur during the formation of the hydrazone.
37. Intramolecular additions of silylenol ethers to aldehydes in the presence of Lewis acids exhibit only a modest preference for antiperiplanar transition states: Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707-709.
38. For a recent overview of models for carbonyl addition, see: Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418-427.
39. Bassindale has proposed that this position is the most sterically hindered one in additions of prochiral nucleophiles to carbonyls: Bassindale, A. R.; Ellis, R. J.; Lau, J. C.-Y.; Taylor, P. G. *J. Chem. Soc., Chem. Commun.* **1986**, 98-100.
40. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994, pp 697.

(*Received* 1 *November* 1996; *accepted* 14 *April* 1997)