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Silylene-Mediated Ring Contraction of Homoallylic Ethers To Form Allylic Silanes

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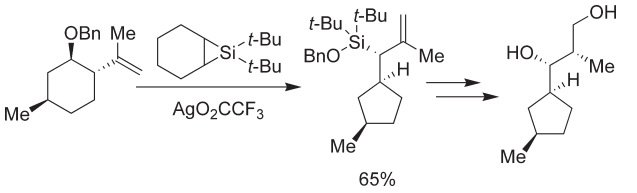
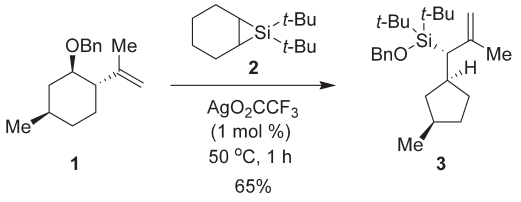
Received May 26, 2009



(−)-Isopulegol derivatives undergo a ring contraction under silylene-mediated conditions to provide cyclopentane products. Silylene transfer to other homoallylic ethers did not provide the ring contraction products. Allylic silane products were elaborated to determine the stereochemical course of the ring contraction reaction. A mechanism for the transformation is proposed.

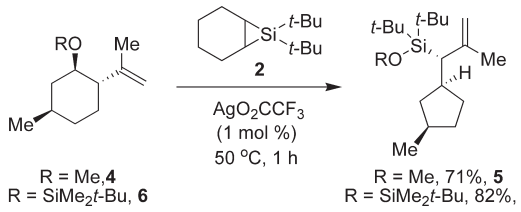
Cyclopentane units are found in many natural and non-natural products, including alkaloids, steroids, prostaglandins, triquinanes, and guaianes.[1−6] The ring contraction of a six-membered carbocyclic compound is an efficient way to assemble a cyclopentane because the reorganization of the bonds can occur with high selectivity.[7−12] This reorganization leads to compounds not easily accessed by other syntheses.[13] In this paper, we report the ring contraction of six-membered carbocyclic homoallylic ethers to form five-membered carbocyclic allylic silanes by treatment with silylene intermediates.

As part of our investigations into silylene transfer reactions to homoallylic ethers,[14] we examined the reaction of (−)-isopulegol derivative **1** under the optimized reaction conditions. Subjection of benzyl ether **1** to cyclohexene silacyclopropane **2** and AgO_2CCF_3 did not provide the expected silylmethyl allylic silane product. Instead, the five-membered ring allylic silane product **3** was isolated as a single stereoisomer (eq 1).



(1)

Alteration of the protecting group on the homoallylic ether provided similar ring contraction products. When alkyl ether **4** was treated to the reaction conditions, allylic silane **5** was observed (eq 2). Treatment of silyl ether **6** to the reaction conditions provided allylic silane **7** (eq 2). Both allylic silanes were found to be predominantly one stereoisomer, as indicated by ^{1}H NMR and ^{13}C NMR spectroscopy.[15,16]



(2)

A variety of homoallylic ethers were subjected to the reaction conditions, but they did not undergo rearrangement. *epi*-Isopulegol derivative **8** underwent silylene transfer to the alkene[17] to form silacyclopropane **9** as a mixture of diastereomers that was not stable to purification (eq 3). The product did not undergo further transformations upon heating. The same result was observed with both five-membered ring ether **10** and seven-membered ring ether **12** (eq 4). The lack of ring contraction of the five-membered ring silacyclopropane **11** (eq 4) may be the result of too much ring strain involved in contraction to the four-membered ring.[18] Differences in conformational preferences and flexibility between six- and seven-membered rings may cause the seven-membered ring

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(2) For examples of marine natural products, see: Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48.
(3) For examples of sesquiterpenoids, see: Fraga, B. M. *Nat. Prod. Rep.* **2001**, *18*, 650–673.
(4) For examples of monoterpenoids, see: Grayson, D. H. *Nat. Prod. Rep.* **2000**, *17*, 385–419.
(5) For examples of diterpenoids, see: Hanson, J. R. *Nat. Prod. Rep.* **2002**, *19*, 125–132.
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(11) Ferraz, H. M. C.; Silva, L. F., Jr. *Tetrahedron Lett.* **1997**, *38*, 1899–1902.
(12) Mathew, F.; Myrboh, B. *Synth. Commun.* **1996**, *26*, 1097–1101.
(13) For a review concerning ring contractions, see: Silva, L. F., Jr. *Tetrahedron* **2002**, *58*, 9137−9161.
(14) Cleary, P. A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 5531–5533.
(15) The relative configurations of **5** and **7** were assigned based on comparisons of their ^{1}H NMR and ^{13}C NMR spectra to those of allylic silane **3**.
(16) Allylic silane **7** was difficult to purify, so we have not been able to identify minor components of the reaction mixture.
(17) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993–10002.
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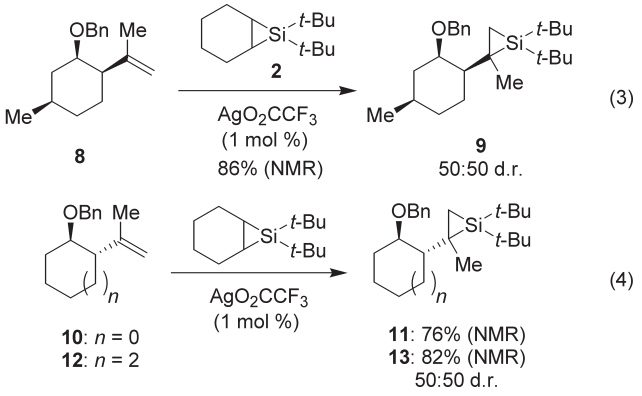
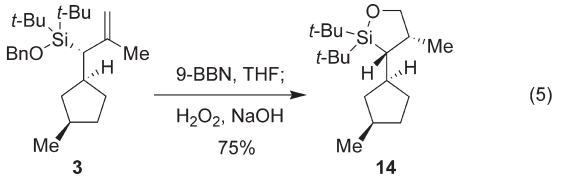
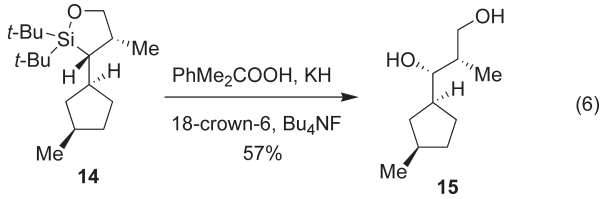
Published on Web 08/14/2009 DOI: 10.1021/jo901111j

system of silacyclopropane **13** to align orbitals differently,[19] thus preventing ring contraction.



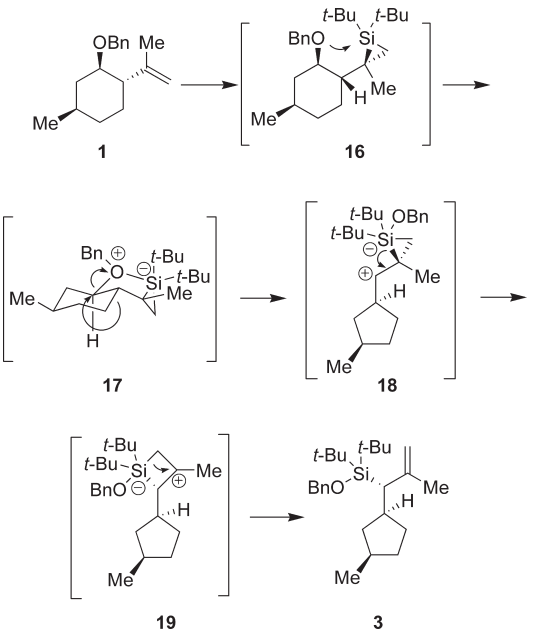
The structure and relative stereochemistry of allylic silane **3** was determined by X-ray crystallography of a derivative. Allylic silane **3** underwent hydroboration, followed by oxidation, to form oxasilacyclopentane **14** as a single isomer (eq 5).[20] Oxasilacyclopentane **14** was then subjected to modified Tamao−Fleming oxidation conditions[21−23] to remove the di-*tert*-butylsilylene moiety, providing diol **15** (eq 6). The stereochemistry and connectivity of diol **15** was established by X-ray crystallography.[24]





A stepwise mechanism is proposed to account for the contraction of the original six-membered ring to form the five-membered ring (Scheme 1). Silylene transfer to the double bond of **1** would form silacyclopropane adduct **16** as one diastereomer.[25] The oxygen atom can then complex to the Lewis-acidic silicon atom[26] to form the conformationally

SCHEME 1. Proposed Mechanism for the Formation of Allylic Silane 3



favored trans-fused ring system **17**.[27,28] The analogous structure for the cis-fused ring system (**20**) derived from alkene **8** appears to encounter steric hindrance due to a *t*-Bu group being forced over the cyclohexane ring (Figure 1).[29] The ring-contracting step forms silacyclopropylcarbinyl cation **18** with inversion of configuration. Carbocation **18** undergoes silacyclopropylcarbinyl cation rearrangement[30,31] to form ylide **19**. The nucleophilic pentavalent silicon atom can then reform the terminal alkene, providing allylic silane **3**.[30,31]

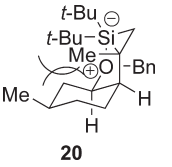


FIGURE 1. Proposed conformation of ylide **20**.

In summary, silylene transfer to (−)-isopulegol derivatives provided allylic silanes by a ring contraction. Similar five- and seven-membered ring systems underwent silylene transfer to the alkene but did not provide ring contraction products. A mechanism for the transformation was proposed utilizing a silylene ylide intermediate and a silacyclopropylcarbinyl rearrangement.

Experimental Section

Allylic Silane 3. To a solution of homoallylic ether **1** (0.394 g, 1.60 mmol) in 8.0 mL of toluene was added cyclohexene silacyclopropane **2** (0.470 g, 2.09 mmol). AgO_2CCF_3 (0.004 g,

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(24) The details of the crystallographic studies are provided as Supporting Information.
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0.02 mmol) was then added. The brown solution was then placed under an Ar atmosphere and allowed to stir for 1 h at 50 °C, at which point the mixture was concentrated in vacuo. Purification by flash chromatography (hexanes) provided 0.402 g (65%) of **3** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.35 (m, 4H), 7.19−7.23 (m, 1H), 4.91−5.01 (m, 2H), 4.74−4.76 (m, 2H), 2.22−2.32 (m, 1H), 2.01−2.07 (m, 2H), 1.80−1.93 (m, 1H), 1.61−1.77 (m, 5H), 1.02−1.29 (m, 20H), 0.89 (d, J = 6.6, 3H), 0.71−0.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 142.1, 128.3, 126.8, 126.2, 113.2, 66.6, 44.7, 43.7, 41.1, 34.3, 32.4, 32.3, 30.1, 29.8, 25.0, 23.8, 23.2, 21.5; IR (thin film) 2951, 2860, 2360, 1112, 820, 726 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{42}OSiNa$ $(M + Na)^+$ 409.2903, found 409.2910.

Homoallylic Ether 4. To a 0 °C solution of sodium hydride (0.710 g, 29.6 mmol) in 50 mL of THF was added (−)-isopulegol (2.50 mL, 14.8 mmol) dropwise followed by methyl iodide (1.01 mL, 16.3 mmol). The reaction mixture was warmed to room temperature and stirred for 12 h. The solution was then cooled to 0 °C and diluted with 20 mL of H_2O. The aqueous layer was extracted twice with 20 mL of EtOAc. The combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (95:5 hexanes/EtOAc) provided 2.35 g (95%) of **4** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77−4.79 (m, 2H), 3.33 (s, 3H), 3.08−3.13 (m, 1H), 2.15−2.17 (m, 1H), 1.98−2.03 (m, 1H), 1.73 (s, 3H), 1.61−1.67 (m, 3H), 1.33−1.44 (m, 2H), 0.93−0.96 (m, 3H), 0.82−0.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 110.9, 80.7, 56.1, 51.9, 39.2, 34.6, 31.6, 31.3, 22.4, 19.6; IR (thin film) 2923, 2869, 1454, 1371, 1106, 885 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{20}ONa$ $(M + Na)^+$ 191.1412, found 191.1419.

Allylic Silane 5. To a solution of homoallylic ether **4** (0.017 g, 0.01 mmol) in 0.7 mL of benzene-d_6 was added cyclohexene silacyclopropane **2** (0.029 g, 0.13 mmol). AgO_2CCF_3 (0.001 g, 0.005 mmol) was then added. The brown solution was then heated for 1 h at 50 °C, at which point the mixture was concentrated in vacuo. Purification by flash chromatography (hexanes) provided 0.022 g (71%) of **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72−4.77 (m, 2H), 3.62 (s, 3H), 2.26−2.29 (m, 1H), 2.09−2.12 (m, 1H), 1.93−2.00 (m, 2H), 1.82 (s, 3H), 1.67−1.75 (m, 2H), 1.14−1.20 (m, 3H), 1.10 (s, 9H), 1.09 (s, 9H), 0.98−1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 113.1, 53.1, 44.3, 43.4, 41.3, 34.4, 32.5, 32.2, 30.1, 29.6, 27.1, 24.9, 23.1, 21.7; IR (thin film) 2948, 2859, 1469, 1189, 1116, 819 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{37}OSi$ $(M - H)^+$ 309.2614, found 309.2623.

Allylic Silane 7. To a solution of homoallylic ether **6** (0.027 g, 0.01 mmol) and cyclohexene silacyclopropane **2** (0.029 g, 0.13 mmol) in 0.7 mL of benzene-d_6 was added AgO_2CCF_3 (0.001 g, 0.005 mmol). The brown solution was then heated for 1 h at 50 °C, at which point the mixture was concentrated in vacuo. Purification by flash chromatography (hexanes) provided 0.034 g (82%) of **7** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68−4.80 (m, 2H), 2.26−2.32 (m, 1H), 1.91−1.96 (m, 2H), 1.82 (s, 3H), 1.69−1.72 (m, 2H), 1.08 (s, 18H), 1.02−1.06 (m, 5H), 0.97−0.98 (m, 2H), 0.94 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.2, 114.8, 44.7, 40.7, 33.7, 33.0, 31.3, 30.1, 29.6, 29.2, 28.2, 27.5, 27.1, 21.5, −1.3, −1.4; IR (thin film) 2952, 2859, 1469, 1253, 1043, 833 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{50}OSi_2Na$ $(M + Na)^+$ 433.3298, found 433.3295.

Oxasilacyclopentane 14. To a 0 °C solution of allylic silane **3** (0.440 g, 1.10 mmol) in 3.8 mL of THF was added 9-BBN (6.8 mL of a 0.5 M solution in THF, 3.3 mmol) dropwise. The reaction mixture was allowed to warm to room temperature for 8 h. After the solution was cooled to 0 °C, 1.5 mL of NaOH (3 N) and 1.5 mL of 30% H_2O_2 were added. The heterogeneous mixture was warmed to room temperature and stirred for an additional 3 h. The mixture was then saturated with K_2CO_3 and diluted with 5 mL of CH_2Cl_2. The layers were separated, and the organic layer was washed with 5 mL of brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (95:5 hexanes/EtOAc) provided 0.250 g (75%) of **14** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82−3.86 (m, 1H), 3.70−3.72 (m, 1H), 2.23−2.31 (m, 1H), 2.04−2.13 (m, 1H), 1.86−1.97 (m, 3H), 1.72−1.82 (m, 1H), 1.35−1.37 (m, 1H), 1.16−1.26 (m, 2H), 1.11 (s, 9H), 1.00−1.05 (m, 15H), 0.83−0.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.9, 45.4, 38.8, 37.0, 36.0, 34.6, 33.7, 33.3, 29.6, 29.0, 22.3, 21.3, 21.1, 17.0; IR (thin film) 2948, 2859, 1377, 1080, 985, 822 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{37}OSi$ $(M + H)^+$ 297.2614, found 297.2613. Anal. Calcd for $C_{18}H_{36}OSi$: C, 72.60; H, 12.24. Found: C, 72.84; H, 12.30.

Diol 15. To a solution of KH (0.120 g, 2.90 mmol) in 1.5 mL of THF was added 18-crown-6 (0.780 g, 2.90 mmol). The solution was cooled to 0 °C, and cumene hydroperoxide (88%, 0.49 mL, 2.9 mmol) was added dropwise. The cooling bath was removed, and oxasilacyclopentane **14** (0.150 g, 0.490 mmol) was added by way of cannula in 0.5 mL of THF. The reaction mixture was heated to 50 °C for 2 h, and Bu_4NF (1.47 mL of a 1.00 M solution in THF, 1.47 mmol) was added. After 12 h, the mixture was cooled room temperature, and the solution was diluted with 2 mL of saturated sodium thiosulfate and 5 mL of CH_2Cl_2. The layers were separated, and the organic layer was washed with 5 mL of brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (70:30 hexanes/EtOAc) provided 0.480 g (57%) of diol **15** as a white solid: mp 97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72−3.75 (m, 1H), 3.64−3.68 (m, 1H), 3.56−3.59 (m, 1H), 1.89−2.33 (m, 4H), 1.69−1.81 (m, 2H), 1.56−1.66 (m, 1H), 1.10−1.29 (m, 3H), 0.84−1.04 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.9, 68.1, 44.4, 40.3, 37.7, 34.8, 33.8, 28.1, 21.0, 9.3; IR (thin film) 3307, 2917, 2861, 1454, 1029, 820 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{20}O_2Na$ $(M + Na)^+$ 195.1361, found 195.1366. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.49; H, 11.83.

Acknowledgment. This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health (GM-54909). L.E.B. thanks the Department of Education (GAANN) for a predoctoral fellowship. K.A.W. thanks Amgen and Lilly for awards to support research. We thank Dr. Phil Dennison (UCI) for assistance with NMR spectroscopy, Dr. Joseph W. Ziller (UCI) for X-ray crystallography, and Dr. John Greaves and Ms. Shirin Sorooshian (UCI) for mass spectrometry.

Supporting Information Available: Complete experimental procedures, X-ray data, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.