

Synthesis of ($\pm$)-Isopiperitenol by Fluoride Ion Mediated Cyclization of Allylsilane Moiety Incorporated in Terpene Aldehydes

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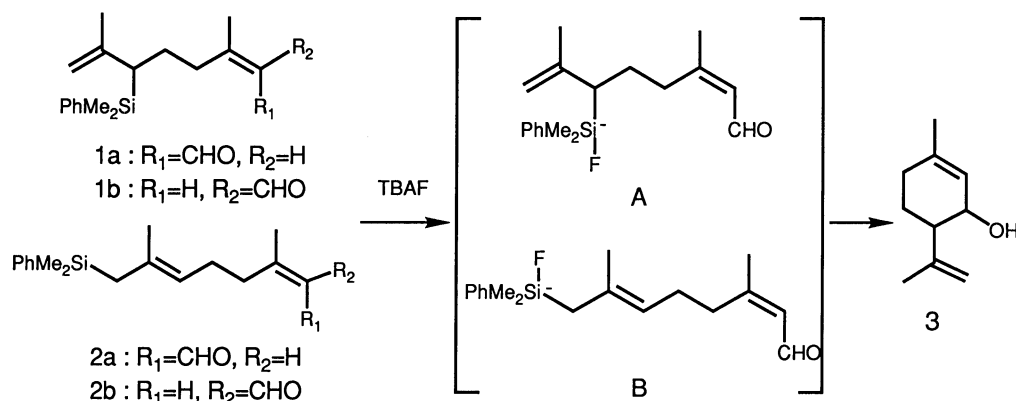
Synopsis. Fluoride ion mediated cyclization of aldehydes (**1** and **2**) having regioisomeric allylsilane functionalities gave a mixture of *cis*- and *trans*-isopiperitenol (**3**). The aldehydes (**1**) reacted faster and showed better stereoselectivity than the regioisomeric aldehydes (**2**) regardless of geometry of the double bond at an unsaturated aldehyde.

Although C–C bond formation with allylsilanes has become one of the useful and important methodologies in organic synthesis,¹⁾ regio- and stereoselectivities in intramolecular cyclization of polyfunctionalized substrates have not yet well-documented. In the presence of fluoride ion, allylsilanes react at either α - or γ -site of the

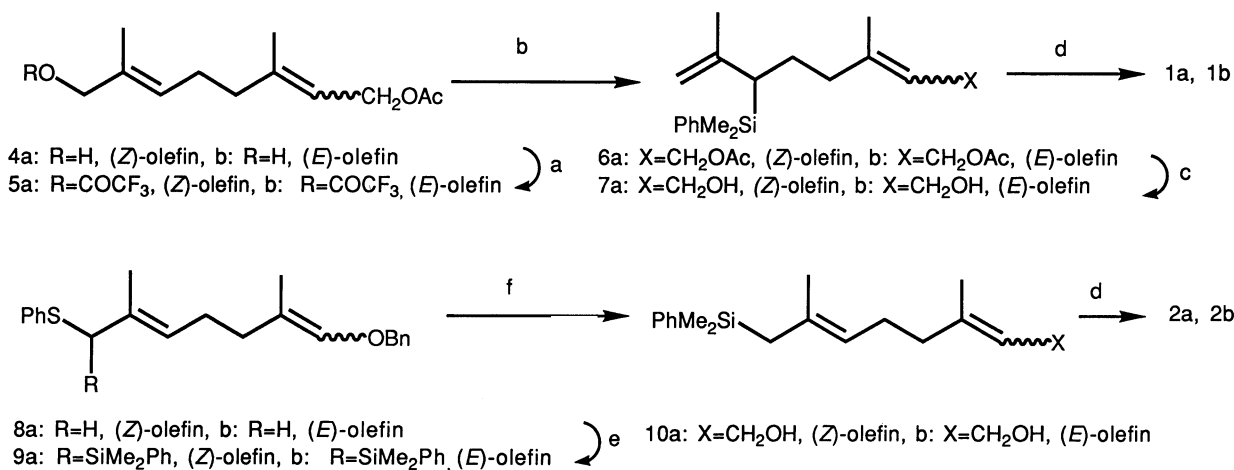
allylsilane, depending upon the structure of molecules.^{2–5)} We synthesized aldehydes (**1** and **2**) having regioisomeric allylsilane moieties and examined fluoride ion mediated cyclization reactions.

Allylsilanes (**1** and **2**) were synthesized as shown in Scheme 2. Purity of these allylsilanes was more than 80% in every case.

Allylsilane (**1a**) cyclized readily in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) under reflux conditions for 1 h to yield a mixture of isopiperitenol (**3**) and its silyl ether. After treatment with an excess amount of TBAF, the reaction mixture was purified on a silica gel



Scheme 1.



Scheme 2.

Table 1. Fluoride Ion Mediated Cyclization of Silyl-substituted Aldehydes (**1** and **2**) in THF at 70°C^a

Substrate	TBAF/equiv	Time/h	Yield of 3 /%	<i>cis:trans</i>
1a	0.2	2	60	1:9
1b	0.2	2	41	1:9
2a	1.0	3	56	3:4
2b	1.0	3	34	3:4

a) Concentrations of substrates were 17 mM. Yields and *cis:trans* ratios were determined by GC based on an internal standard and by ¹H NMR analysis, respectively, after treatment with an excess amount of TBAF.

column to afford a 1:9 mixture of *cis*- and *trans*-isopiperitenol in 46% isolated yield. Results of cyclization reactions of isomeric allylsilanes (**1** and **2**) under the similar conditions were shown in Table 1.

Allylsilane **1b** having *E*-configuration cyclized more slowly than **1a** to give a 1:9 mixture of *cis*- and *trans*-isopiperitenol likewise **1a** but in lower yield, suggesting that the isomerization at the α,β -unsaturated aldehyde takes place faster than cyclization reactions.

In contrast to **1**, the regioisomeric terminally substituted allylsilanes (**2**) reacted very slowly under the same conditions and required a stoichiometric amount of TBAF to complete the reaction to form isopiperitenol (**3**) as a 3:4 mixture of *cis*- and *trans*-isomers. The difference on reactivity of these regioisomeric allylsilanes might suggest that the cyclization reaction involves a nonbasic hypervalent allyl silicate intermediates (**A** and **B** in Scheme 1) rather than allyl anions.^{6,7} Since the transition state from **2** leading to cyclization suffers from steric repulsion between allylsilyl group and carbonyl group, the cyclization reaction of **2** might be slower than that of **1** and the ratio of *cis*-isomer increased.

Experimental

¹H NMR spectra were recorded in CDCl₃ on a JEOL GX-400 (400 MHz) spectrometer. Chemical shifts (δ) are given in ppm from internal TMS and coupling constants (*J*) in Hz. IR spectra were taken on a Hitachi 270-30 spectrometer. Mass spectra were obtained on JEOL JMS-D-300 or JMS-HX-110 spectrometers. GC analyses were performed on a Hitachi 163 gas chromatograph using a column packed with XE-60 (ϕ 3 mm $\times$ 1.2 m). Compounds **1b**, **2b**, and **5b**—**10b** were synthesized as described for **1a**, **2a**, and **5a**—**10a**, respectively.

(2Z,6E)-3,7-Dimethyl-8-trifluoroacetoxy-2,6-octadienyl Acetate (5a). To a solution of **4a** (2.50 g, 11.8 mmol) and triethylamine (2.18 g, 21.5 mmol) in dichloromethane (20 ml) was added trifluoroacetic anhydride (7.06 g, 33.6 mmol) at -15°C and the mixture was stirred for 1 h. After usual workup the crude products were chromatographed on silica gel (EtOAc-hexane 1:1) to give **5a** as an oil (3.60 g, 99%). IR (neat) 1784, 1742 cm⁻¹; ¹H NMR δ =1.70 (3H, s), 1.77 (3H, s), 2.05 (3H, s), 2.1—2.3 (4H, m), 4.55 (2H, d, *J*=7 Hz), 4.71 (2H, s), 5.39 (1H, qt, *J*=1, 7 Hz), 5.56 (1H, m).

(2E,6E)-3,7-Dimethyl-8-trifluoroacetoxy-2,6-octadienyl Acetate (5b). Yield 79% from **4b**. IR (neat) 1786, 1740 cm⁻¹; ¹H NMR δ =1.69 (3H, s), 1.70 (3H, s), 2.08 (2H, m), 2.18 (2H, m), 4.59 (2H, d, *J*=7 Hz), 4.71 (2H, s), 5.34 (1H, qt, *J*=1, 7 Hz), 5.54 (1H, qd, *J*=1, 7 Hz).

(Z)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadienyl Acetate (6a). To a solution of **5a** in THF (24 ml) was added

24 ml of THF solution of (Me₂PhSi)₂CuLi-LiCN (ca 25 mmol)⁸ at -78°C. The reaction mixture was stirred for 18 h and quenched with 10 ml of H₂O. Usual workup gave the residue, which was chromatographed on silica gel (toluene-hexane 7:3) to afford **6a** as an oil (2.1 g, yield 54%). IR (neat) 1740 cm⁻¹; ¹H NMR δ =0.27 (3H, s), 0.31 (3H, s), 1.56 (3H, s), 1.62 (3H, s), 1.5—1.7 (2H, m), 1.96 (3H, s), 1.9—2.1 (2H, m), 4.44—4.55 (2H, m), 4.54 (1H, br s), 4.77 (1H, br s), 5.31 (br t, *J*=7 Hz), 7.31 (3H, m), 7.48 (2H, m).

(E)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadienyl Acetate (6b). Yield 38% from **5b**. IR (neat) 1740 cm⁻¹; FDMS *m/z* 330 (M⁺). ¹H NMR δ =0.26 (3H, s), 0.31 (3H, s), 1.54 (6H, s), 2.05 (3H, s), 1.9—2.1 (5H, m), 4.50 (1H, s), 4.55 (2H, d, *J*=7 Hz), 4.74 (1H, s), 5.54 (1H br t, *J*=7 Hz), 7.34 (3H, m), 7.50 (2H, m).

(Z)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadien-1-ol (7a). A solution of **6a** (303 mg, 0.92 mmol) and K₂CO₃ (110 mg, 0.80 mmol) in MeOH (10 ml) was stirred at room temperature for 12 h. After usual workup, chromatography of the residue on silica gel (toluene-ethyl acetate 4:1) yielded **9a** (222 mg, 84%). IR (neat) 3341 cm⁻¹; FDMS *m/z* 288 (M⁺); ¹H NMR δ =0.26 (3H, s), 0.30 (3H, s), 1.09 (1H, br s), 1.57 (3H, s), 1.61 (3H, s), 1.5—1.75 (3H, m), 1.9—2.1 (2H, m), 4.02 (2H, d, *J*=7 Hz), 4.53 (1H, br s), 4.76 (1H, br s), 5.37 (1H, br t, *J*=7 Hz), 7.34 (3H, m), 7.49 (2H, m).

(E)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadien-1-ol (7b). Yield 86% from **6b**. IR (neat) 3352 cm⁻¹; FDMS *m/z* 288 (M⁺); ¹H NMR δ =0.26 (3H, s), 0.30 (3H, s), 1.16 (1H, br s), 1.56 (6H, s), 1.60—2.15 (5H, m), 4.12 (2H, d, *J*=7 Hz), 4.50 (1H, br s), 4.74 (1H, br s), 5.32 (1H, qt, *J*=1, 7 Hz), 7.35 (3H, m), 7.50 (2H, m).

(Z)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadienal (1a). A solution of **7a** (126 mg, 0.44 mmol) and pyridinium dichromate (200 mg, 0.53 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 2 h. After usual workup, the reaction mixture was chromatographed on silica gel (hexane-EtOAc 4:1) to give **1a** (140 mg, 88%). IR (neat) 1742 cm⁻¹; ¹H NMR δ =0.28 (3H, s), 0.32 (3H, s), 1.57 (3H, s), 1.4—1.8 (3H, m), 1.82 (3H, d, *J*=1 Hz), 2.4—2.7 (1H, m), 4.54 (1H, br s), 4.81 (1H, br s), 5.82 (1H, d, *J*=8 Hz), 7.35 (3H, m), 7.48 (2H, m), 9.82 (1H, d, *J*=8 Hz), HRMS, Found: *m/z* 286.1759. Calcd for C₁₈H₂₆OSi: M, 286.1753.

(E)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadienal (1b). Yield 83% from **7b**. IR (neat) 1740 cm⁻¹; ¹H NMR δ =0.28 (3H, s), 0.35 (3H, s), 1.56 (3H, s), 1.5—1.7 (3H, m), 2.04 (3H, d, *J*=1 Hz), 1.9—2.1 (1H, m), 2.25 (1H, m), 4.53 (1H, br s), 4.78 (1H, br s), 5.80 (1H, qd, *J*=1, 8 Hz), 7.35 (3H, m), 7.49 (2H, m), 9.95 (1H, d, *J*=8 Hz). HRMS, Found: *m/z* 286.1748. Calcd for C₁₈H₂₆OSi: M, 286.1753.

Benzyl (2Z,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-8-phenylthio-2,6-octadienyl Ether (9a). To a solution of **8a**, diazabicyclo[2.2.2]octane (463 mg, 2.22 mmol) and hexamethylphosphoric triamide (0.385 ml, 2.0 mmol) in 50 ml THF was added 0.65 M *n*-BuLi (1.24 ml, 2.0 mmol, 1 M=1 mol dm⁻³) at -78°C and the mixture was stirred for 1 h. Chlorodimethylphenylsilane (0.34 ml, 2.0 mmol) was added and the reaction mixture was stirred for 45 min. The reaction was quenched with 5% citric acid solution. After usual workup the reaction mixture was chromatographed on silica gel to furnish **9a** as a colorless oil (478 mg, 54%). IR (neat) 1250 cm⁻¹; ¹H NMR δ =0.45 (6H, s), 1.51 (3H, s), 1.66 (3H, s), 1.86—1.98 (4H, m), 3.39 (1H, s), 3.93 (2H, d, *J*=6.5 Hz), 4.47 (3H, s), 5.09 (1H, br t, *J*=7 Hz), 5.36 (1H, br t, *J*=6.5 Hz), 7.07—7.37 (13H, m), 7.56—7.59 (2H, m). HRMS, Found: *m/z* 486.2394. Calcd for C₃₁H₃₈OSSi: M, 486.2376.

Benzyl (2E,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-8-phenylthio-2,6-octadienyl Ether (9b). Yield 43% from **8b**. IR (neat) 1250 cm⁻¹; FDMS *m/z* 486 (M⁺); ¹H NMR δ =0.41

(3H, s), 0.45 (3H, s), 1.53 (3H, s), 1.55 (3H, s), 1.86—1.90 (2H, m), 2.00—2.06 (2H, m), 3.40 (1H, s), 3.98 (2H, d, $J=7$ Hz), 4.49 (2H, s), 5.13 (1H, br t, $J=7$ Hz), 5.32 (1H, qt, $J=1, 7$ Hz), 7.07—7.38 (13H, m), 7.57—7.60 (2H, m).

(2Z,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-2,6-octadien-1-ol (10a). A solution of benzyl ether **9a** (48 mg, 0.1 mmol) in THF (5 ml) was added to a solution of Li (6 mg, 1 mmol) in liquid ammonia (20 ml) at -78°C . After 15 min ammonium chloride was added to the reaction mixture and warmed up to room temperature. Usual workup and chromatography on silica gel gave **10a** as a colorless oil (21.4 mg, 75%). IR (neat) 3352 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) $\delta=0.28$ (6H, s), 1.25 (1H, br s), 1.50 (2H, d, $J=1$ Hz), 1.70 (3H, s), 1.73 (3H, d, $J=1.5$ Hz), 2.05—2.06 (4H, m), 4.08 (2H, qd, $J=1, 7$ Hz), 5.09 (1H, brs), 5.42 (1H, dt, $J=1.5, 7$ Hz), 7.31—7.36 (3H, m), 7.48—7.51 (2H, m). HRMS Found: m/z 288.1905. Calcd for $\text{C}_{18}\text{H}_{28}\text{OSi}$: M, 288.1910.

(2E,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-2,6-octadien-1-ol (10b). Yield 81% from **9b**. IR (neat) 3340 cm^{-1} ; FDMS m/z 286 (M^+-2); $^1\text{H NMR}$ $\delta=0.27$ (6H, s), 1.50 (s, 2H), 1.66 (3H, s), 1.69 (3H, s), 1.94—2.11 (4H, m), 4.13 (2H, d, $J=7$ Hz), 4.92 (1H, br t, $J=7$ Hz), 5.39 (1H, dt, $J=1, 7$ Hz), 7.30—7.39 (3H, m), 7.48—7.52 (2H, m).

(2Z,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-2,6-octadien-1-al (2a) and (2E,6E)-3,7-Dimethyl-8-dimethylphenylsilyl-2,6-octadienal (2b). Alcohols **10a** and **10b** were oxidized as described for **9a** to give **2a** (83%) and **2b** (82%), respectively.

2a: IR (CHCl_3) 1716 cm^{-1} ; $^1\text{H NMR}$ $\delta=0.27$ (6H, s), 1.50 (3H, s), 1.70 (2H, s), 1.95 (3H, d, $J=1$ Hz), 2.20 (2H, q, $J=8$ Hz), 2.53 (2H, t, $J=8$ Hz), 4.91 (1H, qt, $J=1, 8$ Hz), 5.86 (1H, br d, $J=8$ Hz), 7.31—7.37 (3H, m), 7.48—7.52 (2H, m), 9.90 (H, d, $J=8$ Hz); HRMS Found m/z 286.1759, Calcd for $\text{C}_{18}\text{H}_{26}\text{OSi}$: M, 286.1753.

2b: IR (CHCl_3) 1714 cm^{-1} ; FD-MS m/z 286 (M^+); $^1\text{H NMR}$ $\delta=0.28$ (6H, s), 1.50 (3H, s), 1.62 (2H, s), 2.14 (3H, d, $J=1$ Hz), 2.09—2.18 (4H, m), 4.87 (1H, br s), 5.86 (1H, br d, $J=8.5$ Hz), 7.32—7.36 (3H, m), 7.48—7.52 (2H, m), 9.98 (1H, d, $J=8.5$ Hz).

Cyclization of Allylsilanes 1 and 2 Mediated by TBAF. A THF solution of allylsilane (17 mM) and TBAF (3.4 mM for **1** and 17 mM for **2**) was heated at 70°C for **2** or 3 h. After treated with excess amount of TBAF, the reaction mixture was analyzed by GC using geranyl acetate as an internal standard. The cis to trans ratios were determined by $^1\text{H NMR}$ spectrum of the reaction mixtures. The structure of cis- and trans-isopiperitenol were established as their benzoates⁹⁾ prepared

from the reaction mixture of **2a** by benzylation followed by separation with HPLC.

Isolation of Isopiperitenol (3) from Cyclization Products of Allylsilane 1a. A solution of **1a** (37.6 mg, 0.13 mmol) in a mixture of THF (5 ml) and 0.05 M TBAF THF solution (0.4 ml, 0.02 mmol) was refluxed for 1 h. Upon cooling the reaction mixture, 0.05 M TBAF THF solution (3 ml, 0.15 mmol) was added. Usual workup gave a residue, which was chromatographed on silica gel (benzene-EtOAc 4:1) to give a 1:9 mixture of cis- and trans-isopiperitenol (9.1 mg, 46%).

trans-Isopiperitenol: IR (neat) 3592 cm^{-1} ; $^1\text{H NMR}$ $\delta=1.4$ —1.8 (3H, m), 1.70 (3H, s), 1.73 (3H, s), 1.95 (1H, m), 2.08 (1H, ddd, $J=12, 9, 3$ Hz), 4.12 (br d, $J=9$ Hz), 4.85 (1H, s), 4.89 (1H, t, $J=1.5$ Hz), 5.45 (1H, br s). HRMS, Found: m/z 152.1192. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$: M, 152.1201.

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