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

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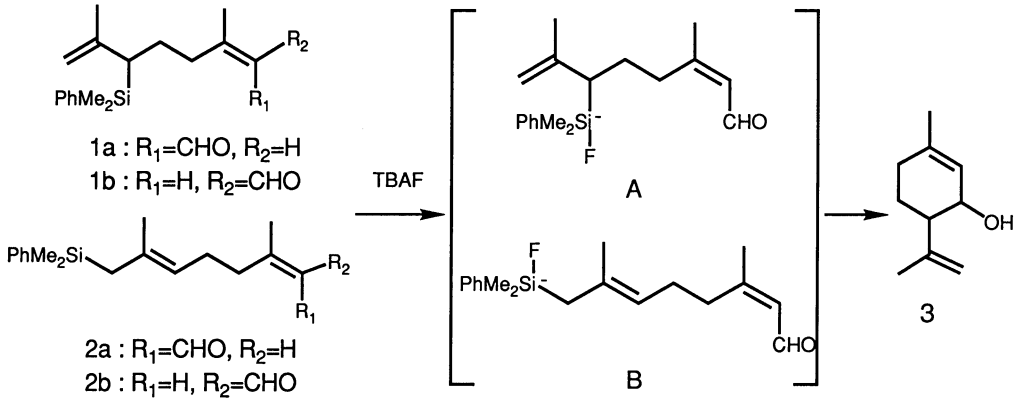
(Received October 16, 1991)

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.

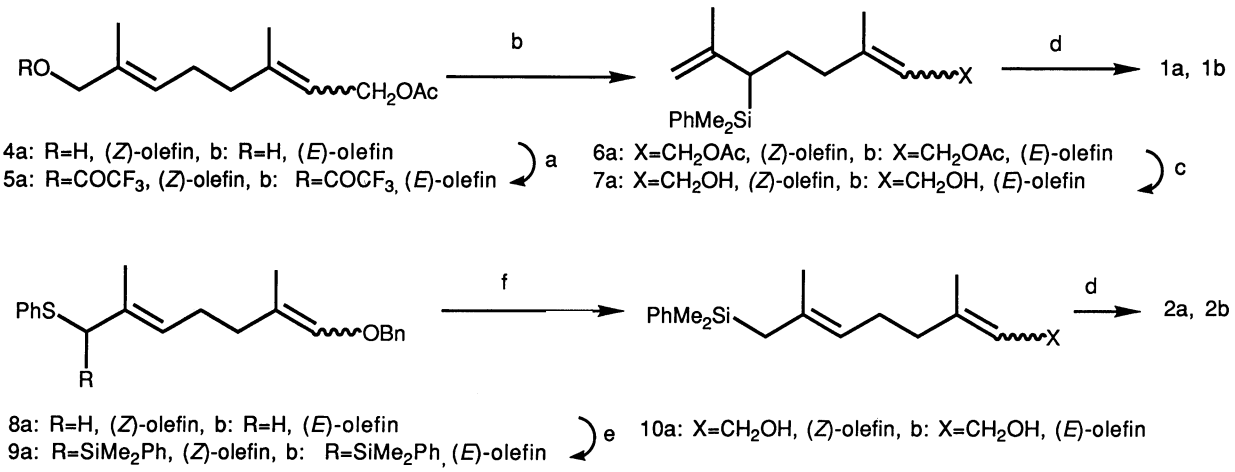
Although C–C bond formation with allylsilanes has become one of the useful and important methodologies in organic synthesis,[1] regio- and stereoselectivities in intramolecular cyclization of polyfunctionalized substrates have not yet well-documented. In the presence of fluoride ion, allylsilanes react 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 cylization 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.



(a) Trifluoroacetic anhydride, Et_3N, CH_2Cl_2, -15°C; (b) $(PhMe_2Si)_2CuLi$, THF, -15°C; (c) K2CO3, MeOH; (d) PDC, CH_2Cl_2; (e) (i) n-BuLi, DABCO, HMPA, THF, -78°C (ii) $PhMe_2SiCl$; (f) Li, NH_3

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**/%	*cis*:*trans*
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 ^{1}H 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% isolalted 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 cylization 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 cylization 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 cylization reaction of **2** might be slower than that of **1** and the ratio of *cis*-isomer increased.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ 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×1.2 m). Compounds **1b**, **2b**, and **5b**—**10b** were synthesized as described for **1a**, **2a**, and **5a**—**10a**, respectively.

(2*Z*,6*E*)-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}; ^{1}H 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).

(2*E*,6*E*)-3,7-Dimethyl-8-trifluoroacetoxy-2,6-octadienyl Acetate (5b). Yield 79% from **4b**. IR (neat) 1786, 1740 cm^{-1}; ^{1}H 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-diemthylphenylsilyl-2,7-octadienyl Acetate (6a). To a solution of **5a** in THF (24 ml) was added 24 ml of THF solution of $(Me_2PhSi)_2CuLi$–LiCN (ca 25 mmol)[8)] at −78 °C. The reaction mixture was stirred for 18 h and quenched with 10 ml of H_2O. 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}; ^{1}H 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$^+$). ^{1}H 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 K_2CO_3 (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$^+$); ^{1}H 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$^+$); ^{1}H 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-dimethylphenysilyl-2,7-octadienal (1a). A solution of **7a** (126 mg, 0.44 mmol) and pyridinium dichromate (200 mg, 0.53 mmol) in CH_2Cl_2 (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}; ^{1}H 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 $C_{18}H_{26}OSi$: M, 286.1753.

(*E*)-3,7-Dimethyl-6-dimethylphenylsilyl-2,7-octadienal (1b). Yield 83% from **7b**. IR (neat) 1740 cm^{-1}; ^{1}H 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 $C_{18}H_{26}OSi$: M, 286.1753.

Benzyl (2*Z*,6*E*)-3,7-Dimethyl-8-dimethylphenylsilyl-8-phenylthio-2,6-octadienyl Ether (9a). To a solution of **8a**, diazabicylo[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}; ^{1}H 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 $C_{31}H_{38}OSSi$: M, 486.2376.

Benzyl (2*E*,6*E*)-3,7-Dimethyl-8-dimethylphenylsilyl-8-phenylthio-2,6-octadienyl Ether (9b). Yield 43% form **8b**. IR (neat) 1250 cm^{-1}; FDMS m/z 486 (M$^+$); ^{1}H 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).

(2*Z*,6*E*)-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}H NMR ($CDCl_3$) δ=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 $C_{18}H_{28}OSi$: M, 288.1910.

(2*E*,6*E*)-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}H NMR δ=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).

(2*Z*,6*E*)-3,7-Dimethyl-8-dimethylphenylsilyl-2,6-octadien-1-al (2a) and (2*E*,6*E*)-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}H NMR δ=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 $C_{18}H_{26}OSi$: M, 286.1753.

2b: IR ($CHCl_3$) 1714 cm^{-1}; FD-MS m/z 286 (M^+); ^{1}H NMR δ=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}H NMR spectrum of the reaction mixtures. The structure of *cis*-and *trans*-isopiperitenol were established as their benzoates[9] prepared from the reaction mixture of **2a** by benzoylation 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}H NMR δ= 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 $C_{10}H_{16}O$: M, 152.1201.

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