Bull. Chem. Soc. Jpn., **69**, 221—228 (1996)

Synthesis of 10-Cyanoverticillene and Its Reactions Directed toward the Verticillol Synthesis[1)]

Tadahiro Kato,* Takumi Hirano, Masahiro Hoshikawa, and Tadao Uyehara†

Department of Chemistry, Faculty of Science, Science University of Tokyo, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162

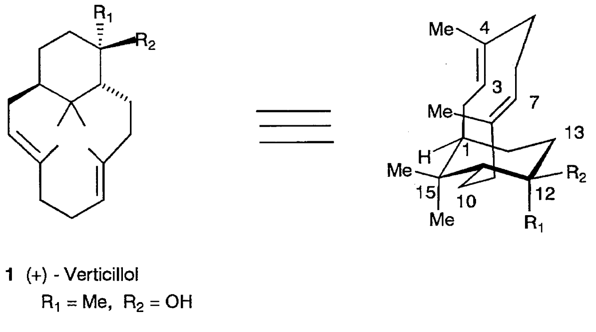
†Department of Chemistry, Faculty of Engineering, Utsunomiya University, 350 Minemati, Utsunomiya, Tochigi 321

(Received September 1, 1995)

Directed toward the synthesis of verticillols, 10-cyanoverticillene **8** was settled as a key intermediate. Bond formation of cyano chloride **7** possessing secoverticillane skeleton to the key intermediate **8** with LiN(TMS)$_2$ at 60 °C proceeded smoothly with moderate yield. The tetrasubstituted double bond of **8** was selectively oxidized, providing the epoxyverticillene derivatives **15** and **16**. Hydride reduction of the epoxides were attempted, giving unexpected results. Synthesis of *dl*-verticillene **13** was also presented.

More than three decades ago, Sumimoto et al. described the isolation and structural elucidation of verticillol **1**[2)] obtained from an evergreen wood of conifer *Sciadopitys vertilillata* (Fig. 1). More recently, Asakawa et al. reported the elucidation of 12-epiverticillol **2**[3)] isolated from a moss, *Jackiella javanica*. These natural products have a unique structure, in which homogeranyl unit is attached in an 1,3-IN OUT fashion to a chair–cyclohexanol possessing geminal dimethyl groups at the center of the IN OUT bondings. The bicyclic verticillols are biogenetically related to monocyclic cembrene skeletons and is the putative biogenetic precursor of tricyclic taxane nucleus.[4)]

Inspite of the early discovery of verticillols, there had been no report on the synthesis of the natural products excepting the construction of the hydrocarbon, verticillene.[5)] The novel IN OUT structure of verticillols led us to design our synthetic strategy to settle 10-cyanoverticillene **8** as a key intermediate, in which C1–C2 bond is forced to take axial orientation as in the case of verticillols. By virtue of cyano group, functionalization of tetrasubstituted C11–C12 double bond is expected feasible. Furthermore, Lewis acid promoted cyclization of the bicyclic intermediate **8** and its derivatives to a taxane skeleton is much interested from biogenetical viewpoints. This paper reports on the preparation of the key intermediate **8** and several reactions directed toward the synthesis of verticillols.



1 (+) - Verticillol
R$_1$ = Me, R$_2$ = OH

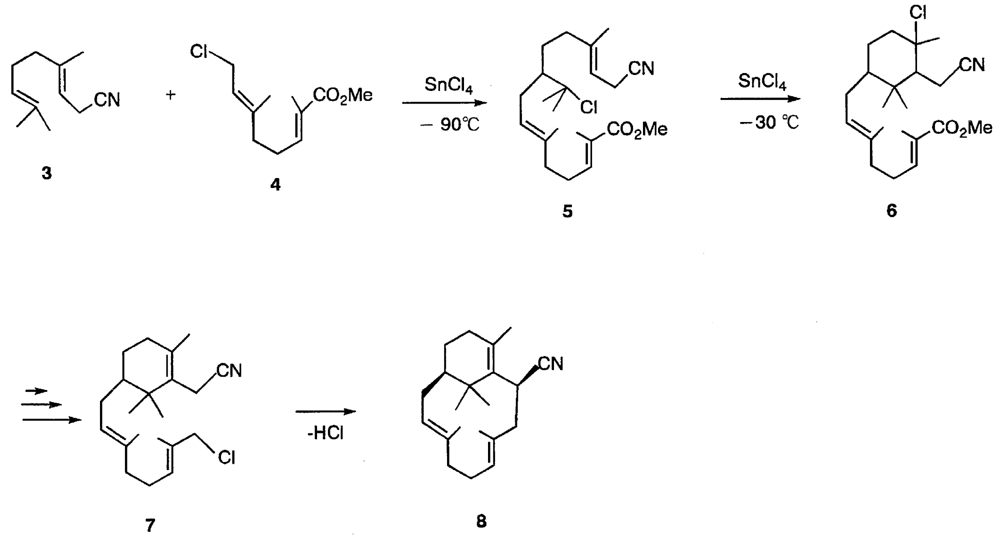
2 12-epi-Verticillol
R$_1$ = OH, R$_2$ = Me

Fig. 1. Structure of verticillols (**1** and **2**).

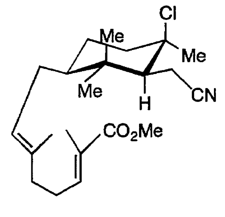
Results and Discussion

Our overall strategy for the synthesis of the intermediate **8**, as depicted in Scheme 1, was to utilize the regioselective coupling reaction of two geranyl units **3** and **4** to acyclic chloride **5** and successive ring formation reactions. The requisite allyl chloride **4** was prepared from geranyl acetate as follows. The terminal vinylic methyl group of E geometry was subjected to the sequential oxidation reactions with SeO$_2$ and ^{t}BuOOH[6)] to allyl alcohol followed by PCC treatment[7)] to formyl group and then with NaClO$_2$ to the corresponding carboxylic acid.[8)] Alkaline hydrolysis of the acetate group and then esterification with CH$_2$N$_2$ afforded the hydroxy methyl ester, which was transformed to the allyl chloride **4** by treatment with CCl$_4$ and triphenylphosphine. The elaboration of the reactions leading to the formation of monocyclic chloride **6** had been demonstrated in our previous studies.[9)] Thus, the coupling reaction of geranyl cyanide **3** with the allyl chloride **4** was carried out by the action of SnCl$_4$, first at −90 °C and then at −30 °C to furnish axial and equatorial chlorides **6a** and **6b** in 34 and 25% yields, respectively after separation with SiO$_2$ column chromatography.

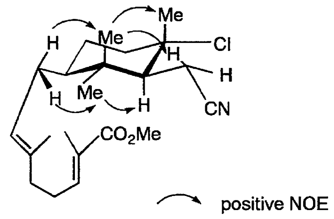
The structure of the chlorides was elaborated by chemical and spectral evidence. As expected, dehydrochlorination of **6a** with LiCl in DMF at 100 °C afforded tetrasubstituted cyano ester **9** exclusively while equatorial isomer **6b** afforded a 1 : 1 mixture of dehydrochlorination products **10** and **11** under the same conditions. NOE experiment of the equatorial chloride **6b** supported the assigned stereostructure as shown in Chart 1. The conditions of the selective conversion of the equatorial chloride **6b** to the tetrasubstituted product **9**



Scheme 1.



6a



6b

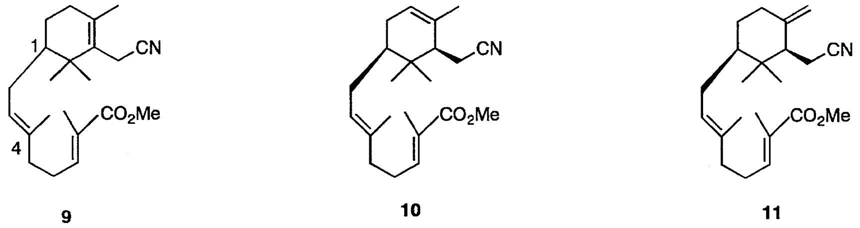


Chart 1.

was explored. When **6b** was treated with anhydrous $ZnCl_2$ at room temperature for 2 d, a mixture of **9** and 4-chloro derivative[10] of **9** was formed in a moderate yield. In the meanwhile, **6b** afforded a 1 : 1 mixture of **9** and **10** when the reaction was carried out in the presence of 2-methyl-2-butene.[11] These facts suggested that, on treatment of **6b** with $ZnCl_2$, a mixture of **9** and **10** was formed, the latter being transformed to the thermodynamically more stable tetrasubstituted isomer **9** by addition/elimination of HCl during the prolonged reaction time. When **6b** was reacted with $ZnCl_2$ for 2 d and then stirred for a day after addition of 2-metyl-2-butene, the tetrasubstituted product **9** was isolated in 86% yield.

The cyanoester **9** was converted to cyano chloride **7** by sequential reactions of AlH_3 reduction to allyl alcohol followed by chlorination with CCl_4 and triphenylphosphine. The requisite C–C bond formation of the cyano chloride **7** under basic conditions was dependent on the reaction temperature. As summarized in Table 1, the yield of cyanoverticillene **8** increased when reaction temperature was elevated and the reaction proceeded with 73% yield when **7** was slowly added to THF solution of lithium bis(trimethylsilyl)amide at 60 °C.[12] The temperature dependence of the yield of **8** is explained by enhancement of thermodynamically less stable axial conformer **7B** at higher temperature. The C–C bond

Table 1. Temperature Dependence of the Yield of Cyanoverticillene **8**

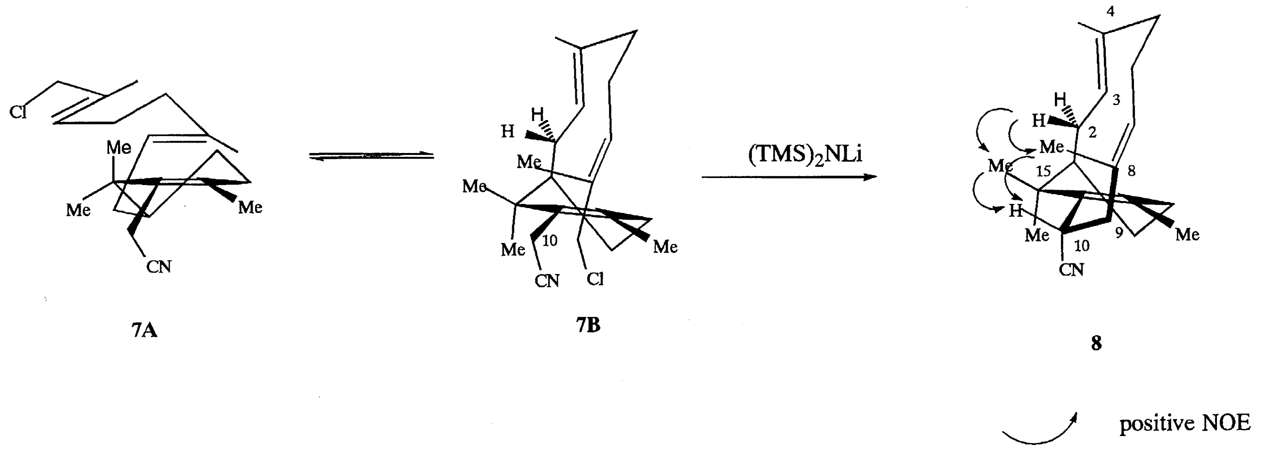
Run	Temp/°C	Yield of **8** (%)	Conditions
1	−78→0	15	a
2	0	25	b
3	25	31	b
4	60	73	b

a) THF solution of $(TMS)_2NLi$ was dropped to THF solution of cyano chloride **7** at −78 °C and the temperature was raised to 0 °C. b) THF solution of cyano chloride **7** was slowly added to the stirred THF solution of $(TMS)_2NLi$ at the temperature listed in the Table 1.

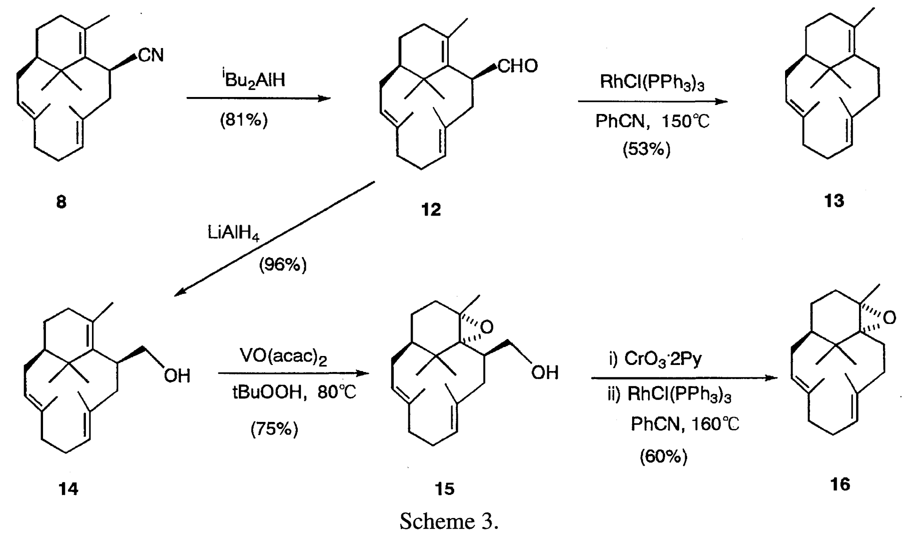
formation takes place easily from the axial conformation, giving the cyanoverticillene **8** as a single stereoisomer. The stereochemistry of **8** was deduced from ^{1}H NMR spectra, in which 10-proton shows positive NOE with 8- and 15-methyl groups. The olefinic protons at 3- and 7-positions appear at $\delta = 5.08$ and 4.82 as broad doublets with $J = 12.0$ and 11.2 Hz, respectively. These coupling modes are quite similar with those of natural verticillol **1**, which showed signals at $\delta = 5.63$ (d, $J = 12.0$ Hz) and 4.88 (d, $J = 10.5$ Hz). These facts indicate the stereochemistry of **8** as depicted in Scheme 2. The stereochemistry at C-10 position of **8** may be controlled by 15-gem. dimethyl group during the C–C bond formation.

Directed toward the synthesis of verticillols, we next carried out the epoxidation of 11–12 double bond by virtue of cyano group of **8** and attempted the reductive ring opening of the epoxide ring. The selective hydride attack at 11 position from β side might be promising from stereoelectronic effect,[13] leading to 12-epiverticillol **2**. Reduction of the cyano group with ^{i}Bu$_2$AlH furnished 10-formylverticillene **12**, which was converted to the hydrocarbon **13** by the action of Wilkinson's catalyst.[14] The NMR signals of the hydrocarbon **13** was in agreement with (±)-verticillene reported by Pattenden.[5] This evidence confirms the structure of the 10-cyanoverticillene **8** and its derivatives derived therefrom. 11,12-Epoxy-11,12-dihydroverticillene **16** was prepared from the formyl derivative **12** by sequential reactions of reduction with LiAlH$_4$ to alcohol **14** followed by Sharpless epoxidation to epoxy alcohol **15**, which in turn was oxidized to formyl epoxide and then submitted to deformylation, providing the epoxide **16** (Scheme 3).

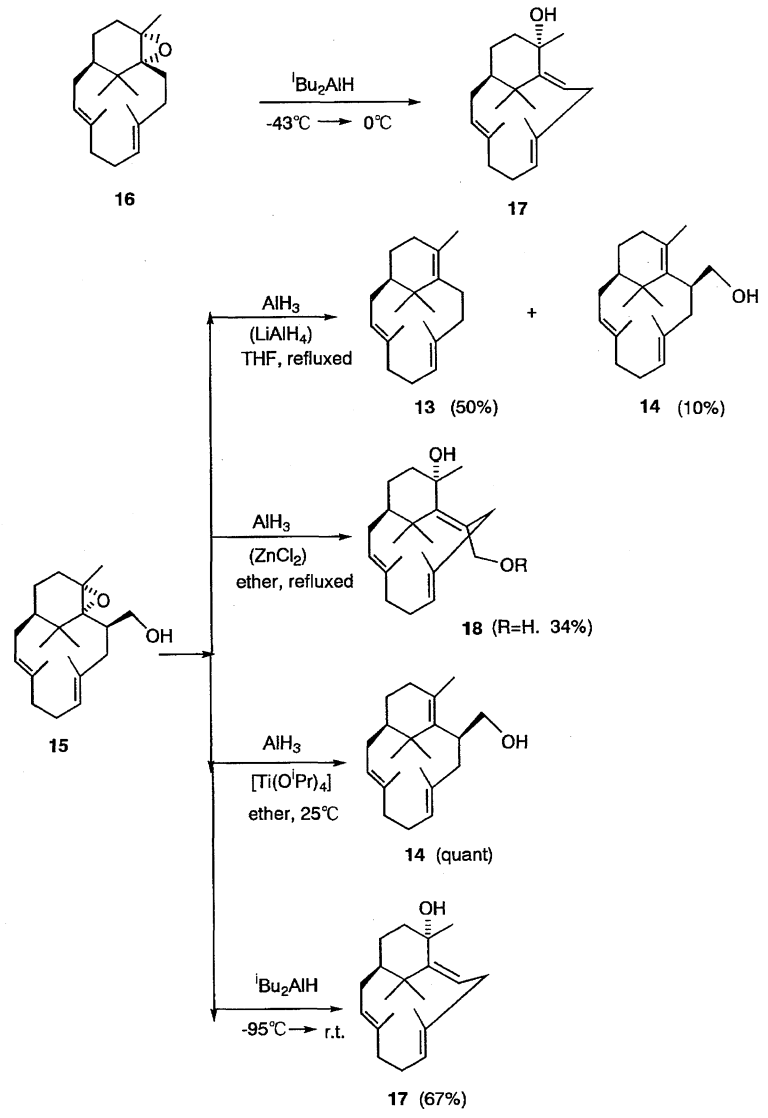
Starting from epoxides **15** and **16**, reactions with reducing reagents are examined under several conditions (Scheme 4). Treatment of epoxide **16** with ^{i}Bu$_2$AlH under several conditions led to the formation of allyl alcohol **17** as a sole product, indicating ^{i}Bu$_2$AlH acted merely as a Lewis acid. The geometry of newly formed trisubstituted double bond of **17** was estimated by observation of positive NOE between 10-proton and 15-methyl group. On treatment of **16** under Birch conditions (Li in EtNH$_2$), deoxygenation took place to afford verticillene **13**. Expecting the neighboring effect of the hydroxymethyl group, epoxy alcohol **15** was then submitted to the hydride reagents. When **15** was treated with AlH$_3$ in the presence of LiAlH$_4$, the major products were a mixture of **13** and **14**, in which the epoxide ring was reduced to the double bond. In addition, the hydroxymethyl group was missed in the formation of **13**. The dehydroxymethyl-



Scheme 2.



Scheme 3.



Scheme 4.

ation was also observed on treatment with ^{i}Bu$_2$AlH to afford **17** in 67% yield. When reacted with AlH$_3$ in the presence of ZnCl$_2$, triene diol **18** (R = H) was the major isolable product derived from the epoxide ring opening. The structure was confirmed by transforming it to the corresponding trifluoroacetate **18** (R = COCF$_3$). Treatment with AlH$_3$ in the presence[15] of Ti(O^{i}Pr)$_4$ resulted in the exclusive formation of the deoxygenated product **14**.

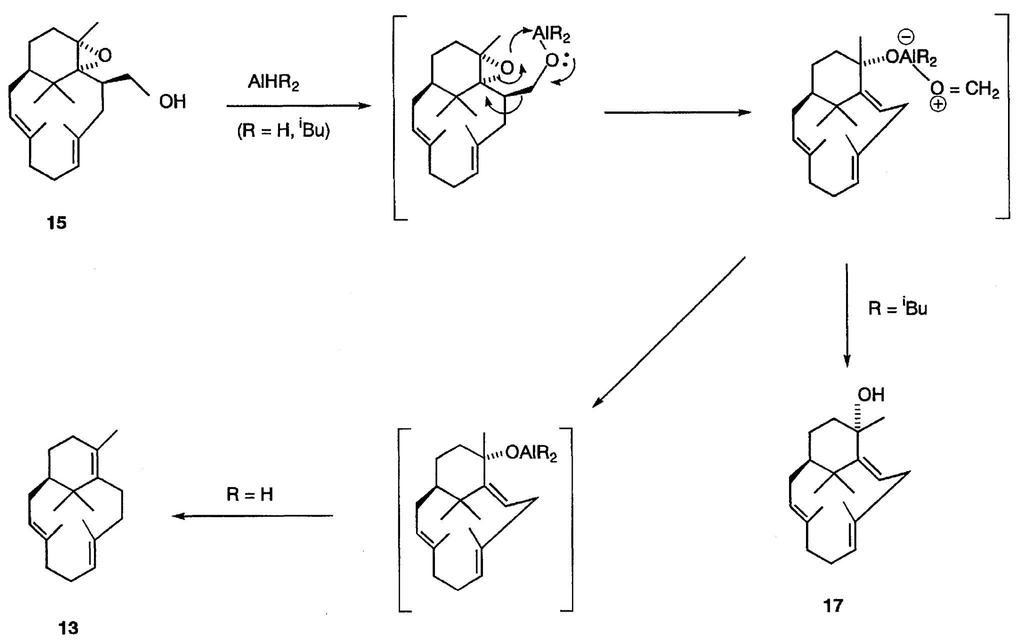
Although trials of the selective reduction of the epoxide ring with alanes were all unsuccessful, probably owing to the steric hindrance, we have observed the unexpected dehydroxymethylation, which may proceed through a route shown in Scheme 5. The involvement of the ate complex of **17** as an intermediate for the formation of the hydrocarbon **13** is supported by the facts that allyl alcohol **17** was quantitatively transformed to **13** by the action of AlH$_3$ in refluxing THF.

By the present study, we have explored a simple route to synthesize 10-cyanoverticillene **8**, from which *dl*-verticillene **13** was prepared. We have also observed some unexpected reactions of the epoxides **15** and **16** derived from the intermediate **8**.

Experimental

Melting points (measured on Yanaco-MP) are uncorrected. Unless otherwise noted, ^{1}H NMR and ^{13}C NMR spectra were recorded on solutions in CDCl$_3$ with SiMe$_4$ as internal standard with JEOL spectrometers. Chemical shifts are reported in δ-units with δ_H (^{1}H NMR) and δ_C (^{13}C NMR), and *J*-values are in Hz. The mass spectra were measured with Hitachi M-80 and M-80A spectrometers. The usual work-up involved dilution of the reaction mixture with water, extraction with diethyl ether (ether), washing of the organic extract with water and brine, followed by drying over Na$_2$SO$_4$, and evaporation at aspirator pressure. Column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70—230 mesh), the weight of the silica gel and elution solvents being indicated in parentheses.

Methyl 8-Hydroxy-2,6-dimethylocta-2*E*,6*E*-dienoate. To a stirred CH$_2$Cl$_2$ (5 cm^3) solution of SeO$_2$ (5.5 mg, 0.05 mmol), salicylic acid (36 mg, 0.26 mmol) and 70% aqueous ^{t}BuOOH (1.3 cm^3, 9.5 mmol) was added CH$_2$Cl$_2$ (1 cm^3) solution of geranyl acetate (500 mg, 2.55 mmol) at room temperature and the stirring was



Scheme 5.

continued overnight. The reaction mixture was diluted with diethyl ether, and the ether solution was successively washed with 0.1 M NaOH solution (M = mol dm^{-3}) and then brine, dried over $MgSO_4$, and volatile materials were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 cm^3) and the solution was added to a stirred mixture of pyridinium chlorochromate (PCC) (550 mg, 2.55 mmol) and AcONa (215 mg, 2.62 mmol) in CH_2Cl_2 (10 cm^3). After stirred for 30 min, the mixture was dissolved in diethyl ether and filtered through a pad of SiO_2. The volatile materials were removed and chromatography (30 g; hexane–AcOEt, 10 : 1) yielded recovered geranyl acetate (173 mg, 35%) and formyl acetate (8-acetoxy-2,6-dimethylocta-2*E*,6*E*-dienal) (197 mg, 37%). To an ice cooled ᵗBuOH solution of formyl acetate (11.2 g, 53.2 mmol) and 2-methyl 2-butene (87 cm^3) was added aqueous solution (55 cm^3) of a mixture of $NaClO_2$ (7.5 g, 83 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (7 g, 45 mmol) and the mixture was stirred for 2 h under ice cooling. The reaction mixture was extracted with diethyl ether and the ether solution was washed with aq NaOH solution. From the ether solution was obtained recovered formyl acetate (3.4 g). The aq NaOH solution was, after being kept for 3 h at room temperature, acidified with aq HCl and extracted with diethyl ether. From the ether solution was obtained hydroxy acid (8-hydroxy-2,6-dimethylocta-2*E*, 6*E*-dienoic acid) (7.4 g). Excess CH_2N_2 in diethyl ether was added to diethyl ether solution of the hydroxy acid to give methyl ester in quantitative yield. Hydroxy ester. ^{1}H NMR (60 MHz, CCl_4) δ_H = 1.69 (3H, s), 1.82 (3H, s), 3.69 (3H, s), 4.05 (2H, d, *J* = 7 Hz), 5.40 (1H, t, *J* = 7 Hz), and 6.67 (1H, t, *J* = 7 Hz). EIMS Found: *m*/*z* 198. Calcd for $C_{11}H_{18}O_3$: M, 198.

Methyl 8-Chloro-2,6-dimethylocta-2*E*,6*E*-dienoate 4. A mixture of hydroxy ester (16.6 g, 83.6 mmol) and triphenylphosphine (28.5 g, 109 mmol) in CCl_4 (30 cm^3) was refluxed for 1 h before being cooled to room temperature. Hexane (100 cm^3) was added to the mixture and the resultant white powder was removed by filtration. The mother liquid was concentrated under reduced pressure. Hexane (100 cm^3) was again added to the residue and the mixture was kept in refrigerator for several hours. The precipitated white powder was removed by filtration. By several repeats of this procedure, crude allyl chloride **4** (17.3 g, 96%) was obtained as colorless oil. ^{1}H NMR (90 MHz, CCl_4) δ_H = 1.78 and 1.80 (each 3H, s), 3.66 (3H, s), 3.99 (2H, d, *J* = 7.8 Hz), 5.42 (1H, t, *J* = 7.8 Hz), and 6.57 (1H, m). EIMS Found: *m*/*z* 216. Calcd for $C_{11}H_{17}ClO_2$: M, 216.

Coupling Reaction of Geranyl Cyanide 3 and Allyl Chloride 4. An anhydrous CH_2Cl_2 (75 cm^3) solution of geranyl cyanide **3** (5.65 g, 34.6 mmol) and allyl chloride **4** (5 g, 23.1 mmol) was cooled at −90 °C and pre-cooled CH_2Cl_2 (19 cm^3) solution of $SnCl_4$ (3.33 cm^3, 27.8 mmol) at −90 °C was added under stirring. The temperature of the reaction mixture was gradually raised to −30 °C. After the stirring was continued for 3 h at −30 °C, pyridine (5 cm^3) in CH_2Cl_2 (5 cm^3) was added to quench the reaction. The reaction mixture was diluted with ether and filtered through a pad of SiO_2. The volatile materials were removed and chromatography (400 g; first hexane : AcOEt, 30 : 1 and then 15 : 1) yielded axial chloride **6a** (2.98 g, 34%) and equatorial chloride **6b** (2.19 g, 25%) as colorless oil. Axial chloride **6a**. ^{1}H NMR (90 MHz) δ_H = 0.86, 1.06, 1.62, 1.68, 1.76, and 3.74 (each 3H, s), 5.16 (1H, bt, *J* = 7.2 Hz), and 6.74 (1H, bt, *J* = 7.2 Hz). ^{13}C NMR (50 MHz) δ_C = 168.6 (s), 135.2 (s), 127.5 (s), 121.2 (s), 74.2 (s), 38.7 (s), 142.1 (d), 124.6 (d), 55.4 (d), 48.4 (d), 42.9 (t), 38.4 (t), 28.8 (t), 27.1 (t), 23.2 (t), 15.1 (t), 51.7 (q), 34.1 (q), 28.5 (q), 16.1 (q), 15.9 (q), and 12.4 (q). Equatorial chloride **6b**. ^{1}H NMR (400 MHz) δ_H = 0.80, 1.19, 1.52, 1.60, 1.84, and 3.76 (each 3H, s), 2.15 (2H, bt, *J* = 7.5 Hz), 2.29 (2H, q, *J* = 7.5 Hz), 2.47 (1H, dd, *J* = 6.9, 17.7 Hz), 2.82 (1H, dd, *J* = 3.0, 17.7 Hz), 5.14 (bt, *J* = 7.5 Hz), and 6.74 (1H, bt, *J* = 7.5 Hz). ^{13}C NMR (50 MHz) δ_C = 168.6 (s), 135.3 (s), 127.6 (s), 121.0 (s), 75.6 (s), 40.4 (s), 142.0 (d), 124.4 (d), 57.1 (d), 48.3 (d), 44.8 (t), 38.3 (t), 28.4 (t), 27.0 (t), 25.5 (t), 14.9 (t), 51.7 (q), 28.9 (q), 25.2 (q), 16.1 (q), 16.0 (q), and 12.5 (q). EIMS of **6a** and **6b**: 379 (M$^+$), 343, 311, 230, (base peak), 149, and 114. HRMS Found: *m*/*z* **6a**, 379.2268; **6b**, 379.2273. Calcd for $C_{22}H_{34}ClNO_2$: M, 379.2280.

Dehydrochlorination of Chlorides 6a and 6b. With LiCl in DMF. 6a. A mixture of axial chloride **6a** (5 g, 13.2 mmol) and LiCl (5.03 g, 118.7 mmol) in *N*,*N*-dimethylformamide (DMF) (88 cm^3) was warmed at 100 °C for 3 h. After being cooled to room temperature, the reaction mixture was diluted with ether, washed with aq $NaHCO_3$ and then brine, dried over $MgSO_4$, and ether was removed. Chromatography (200 g; hexane–AcOEt, 10 : 1) yielded dehydrochlorinated product **9** (4.34 g, 96%) as colorless oil.

6b. A mixture of equatorial chloride **6b** (177 mg) and LiCl (180 mg) in DMF (3 cm^3) was warmed at 100 °C for 3 h, treated as described in the case of **6a**, and a 1 : 1 mixture of **10** and **11** was obtained in 98% yield. The mixture was separated by 10% $AgNO_3$–SiO_2 chromatography with hexane–AcOEt 10 : 1.

With $ZnCl_2$. After a mixture of equatorial chloride **6b** (5 g, 13.2 mmol) and anhydrous $ZnCl_2$ (2.0 g, 14.7 mmol) in CH_2Cl_2 (182 cm^3) was stirred at room temperature for 2 d, 2-methyl-2-butene (18.2 cm^3) was added and the stirring was continued for 24 h. The usual work-up and chromatography (hexane–AcOEt, 10 : 1) afforded the cyano ester **9** (3.89 g, 86%). **9**. ^{1}H NMR (90 MHz, CCl_4) $\delta_H = 0.90$, 1.13, 1.63, 1.74, 1.80, and 3.66 (each 3H, s), 2.90 (2H, bs), 5.10 (1H, bt, $J = 6.8$ Hz), and 6.57 (1H, bt, $J = 6.0$ Hz). ^{13}C NMR (50 MHz) $\delta_C = 168.6$ (s), 134.8 (s), 133.7 (s), 127.7 (s), 127.5 (s), 119.2 (s), 38.3 (s), 142.2 (d), 125.0 (d), 45.3 (d), 38.4 (t), 32.1 (t), 28.6 (t), 27.2 (t), 23.0 (t), 16.5 (t), 51.7 (q), 26.0 (q), 21.2 (q), 20.2 (q), 16.1 (q), and 12.5 (q). Cyano ester **10**. ^{1}H NMR (90 MHz, CCl_4) $\delta_H = 0.80$, 1.05, 1.61 (each 3H, s), 1.80 (6H, bs), 3.64 (3H, s), 5.07 (1H, bt, $J = 6.8$ Hz), 5.47 (1H, m), and 6.57 (1H, t, $J = 6$ Hz). Cyano ester **11**. ^{1}H NMR (90 MHz, CCl_4) $\delta_H = 0.60$, 1.10, 1.59, 1.80, and 3.66 (each 3H, s), 4.63 and 4.93 (each 1H, bs), 5.08 (1H, bt, $J = 6.8$ Hz), and 6.57 (1H, bt, $J = 6.0$ Hz). HRMS Found: *m/z* **9**, 343.2516; **10**, 343.2500; **11**, 343.2489. Calcd for $C_{22}H_{33}NO_2$: M, 343.2511.

Cyano Chloride 7. To a stirred diethyl ether (100 cm^3) solution of cyano ester **9** (5 g, 14.6 mmol) was dropped an ether solution (198 cm^3) of AlH_3 freshly prepared from $LiAlH_4$ (2.5 g, 65.9 mmol) and anhydrous $ZnCl_2$ (5.07 g, 37.2 mmol) in diethyl ether (198 cm^3) at −78 °C under argon atmosphere. After being stirred for 3 h at −78 °C, the reaction was quenched with AcOEt and then MeOH. The reaction mixture was passed through a pad of SiO_2 and the filtrate was evaporated. Chromatography (hexane–AcOEt, 5 : 1) of the residue yielded allyl alcohol (4.0 g, 87%). A mixture of the allyl alcohol (4.1 g, 12.9 mmol) and triphenylphosphine (4.41 g, 16.8 mmol) in CCl_4 was refluxed for 1 h under argon atmosphere. After being cooled to room temperature, hexane was added and the precipitated white powder was removed by filtration. By repeats of addition of hexane and removal of white powder, pure cyano chloride **7** (3.6 g, 83%) was obtained. **7**. ^{1}H NMR $\delta_H = 0.87$, 1.12, 1.61 (each 3H, s), 1.72 (6H, s), 3.00 (2H, s), 4.00 (2H, s), 5.12 (1H, bt, $J = 7.2$ Hz), and 5.50 (1H, bt, $J = 5.4$ Hz). EIMS Found: *m/z* 333 (M), 162, 160, 135, 133, and 121 (base peak). Calcd for $C_{21}H_{32}ClN$: M, 333.

10-Cyanoverticillene 8. 1.5 M hexane solution (3.93 cm^3) of ^{n}BuLi was added to THF solution (20 cm^3) of $(TMS)_2NH$ (1.32 cm^3, 6.28 mmol) at 0 °C under argon atmosphere and the mixture was stirred for 1 h. The flask of the mixture was transferred to oil bath at 60 °C. THF solution (60 cm^3) of the cyano chloride **7** (395.5 mg, 1.18 mmol) was gradually dropped to the warmed mixture during 1 h and the stirring was continued for further 2 h at the same conditions. MeOH was added and volatile materials were removed under reduced pressure. The residue was diluted with ether, passed through a celite layer, and the ether was removed. Chromatography (hexane–AcOEt, 20 : 1) gave 10-cyanoverticillene **8** (258 mg, 73%), mp 149—150 °C (hexane). ^{1}H NMR (400 MHz) $\delta_H = 0.85$ [15-Me (eq)], 1.11 [15-Me (ax)], 1.49 (4-Me), 1.53 (8-Me), 1.90 (12-Me), 2.63 (2α-H, dddd, $J_{2\alpha,14} = 2.0$, $J_{2\alpha,1} = 6.3$, $J_{2\alpha,3} = 12.0$, $J_{2\alpha,2\beta} = 15.2$ Hz), 2.90 (9β-H, t, $J = 12.8$ Hz), 3.43 (10α-H, dd, $J_{10\alpha,9\alpha} = 4.0$, $J_{10\alpha,9\beta} = 12.8$ Hz), 4.82 (7-H, bd, $J = 11.2$ Hz), and 5.08 (3-H, bd, $J = 12.0$ Hz). ^{13}C NMR (50 MHz) $\delta_C = 132.9$ (s), 132.0 (s), 131.3 (s), 128.6 (s), 122.9 (s), 37.7 (s), 132.1 (d), 126.1 (d), 42.6 (d), 27.3 (d), 42.0 (t), 39.9 (t), 33.8 (t), 32.2 (t), 26.7 (t), 26.6 (t), 32.6 (q), 24.2 (q), 22.0 (q), 16.5 (q), and 15.3 (q). Found: C, 84.55; H, 10.53; N, 4.65%. Calcd for $C_{21}H_{31}N$: C, 84.71; H, 10.50; N, 4.71%. EIMS Found: *m/z* 297 (M), 282 (100), 159 (69), 146 (54), and 135 (29).

Reduction of 10-Cyanoverticillene 8. 10-Formylverticillene 12. To a cooled toluene (2 cm^3) solution of 10-cyanoverticillene **8** (51 mg, 0.17 mmol) at −78 °C was added 1.5 M toluene solution (172 µl, 0.26 mmol) of diisobutylaluminium hydride (DIBAH) at the same temperature and the mixture was stirred for 1 h. Aqueous NH_4Cl and then 1 M HCl solutions were successively added to the mixture and the mixture was poured into water after stirred for 5 min. The usual work-up and chromatography (5 g, hexane–AcOEt, 15 : 1) yielded 10-formylverticillene **12** (42 mg, 81%). Colorless prisms, mp 108—110 °C (hexane). ^{1}H NMR (90 MHz) $\delta_H = 0.91$ (3H, s), 1.08 (3H, s), 1.58 (9H, bs), 3.18 (1H, dd, $J = 6.0$, 9.8 Hz), 4.75 (1H, bd, $J = 10.5$ Hz), 5.10 (1H, bd, $J = 12.0$ Hz) and 9.53 (1H, s). Found: C, 79.55, H, 10.44%. Calcd for $C_{21}H_{32}O$: C, 79.70; H, 10.19%. EIMS Found: *m/z* 300 (M), 271 (100), 161 (38), 149 (34), and 136 (58).

10-Hydroxymethylverticillene 14. To an ether (10 cm^3) solution of 10-formylverticillene **12** (163 mg, 0.54 mmol) was added $LiAlH_4$ (20 mg, 0.54 mmol) and the mixture was stirred until completion of reduction monitored by TLC. AcOEt (0.5 cm^3) was added and the mixture was filtered through a pad of SiO_2. The residue, obtained by evaporation of the volatile materials, was chromatographed (hexane–AcOEt, 10 : 1) to give hydroxymethylverticillene **14** (157 mg, 96%) as colorless needles, mp 89—91 °C. ^{1}H NMR (90 MHz) $\delta_H = 0.90$ and 1.03 (each 3H, s), 1.50 (3H, t, $J = 1.5$ Hz), 1.55 and 1.69 (each 3H, s), 3.65 (2H, m), 4.77 (1H, bd, $J = 10.5$ Hz), and 5.09 (1H, bd, $J = 12.0$ Hz). Found: C, 83.15, H, 11.06%. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33%. EIMS Found: *m/z* 302 (M), 271 (100), 147 (44), and 133 (53).

Verticillene 13. A mixture of 10-formylverticillene **12** (106.1 mg, 0.35 mmol) and $RhCl(PPh_3)_3$ (420 mg, 0.45 mmol) in benzonitrile (1 cm^3) was stirred first at room temperature for 20 min and then at 150 °C for 10 min under argon atmosphere. After being cooled to room temperature, the reaction mixture was chromatographed (10 g; hexane) to elute oilly hydrocarbon **13** (51 mg, 53%). ^{1}H NMR (90 MHz) $\delta_H = 0.86$ and 0.96 (each 3H, s), 1.52 (6H, bs), 1.68 (3H, bs), 4.69 (1H, bd, $J = 9.8$ Hz), and 5.15 (1H, bd, $J = 12.0$ Hz). ^{13}C NMR (50 MHz) $\delta_C = 136.0$ (s), 132.8 (s), 131.5 (s), 126.3 (s), 37.0 (s), 128.5 (d), 126.7 (d), 42.7 (d), 40.1 (t), 38.5 (t), 34.1 (t), 31.4 (t), 27.5 (t), 26.1 (t), 26.0 (t), 32.8 (q), 24.5 (q), 21.7 (q), 16.6 (q), 15.4 (q). HRMS Found: *m/z* 272.2498. Calcd for $C_{20}H_{32}$: M, 272.2504. LRMS Found: 272 (M), 257 (64), 189 (64), 161 (45), 148 (37), 147 (36), and 134 (100).

Epoxidation of 10-Hydroxymethylverticillene 14. A mixture of 10-hydroxymethylverticillene **14** (34 mg, 0.11 mmol), $VO(acac)_2$ (5 mg), and 70% ^{t}BuOOH (55 µl, 0.55 mmol) in benzene (5 cm^3) was refluxed 10 min. The direct chromatography of the cooled reaction mixture (hexane–AcOEt, 10 : 1) yielded epoxy alcohol **15** (26 mg, 75%) as colorless oil. ^{1}H NMR (400 MHz) $\delta_H = 1.05$ (3H, s), 1.06 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 1.57 (3H, s), 3.40 (1H, bs), 3.50 (1H, t, $J = 10.0$ Hz), 4.99 (1H, bd, $J = 11.0$ Hz), and 5.39 (1H, bd, $J = 12.0$ Hz). ^{13}C NMR (50 MHz) $\delta_C = 133.1$ (s), 132.7 (s), 71.0 (s), 66.2 (s), 36.8 (s), 129.1 (d), 126.5 (d), 41.8 (d), 39.8 (d), 67.9 (t), 39.6 (t), 39.0 (t), 34.2 (t), 32.0 (t), 25.9 (t), 25.6 (t), 28.4 (q), 25.3 (q), 23.4 (q), 17.0 (q), 15.8 (q). HRMS Found: *m/z* 318.2549. Calcd for $C_{21}H_{34}O_2$: M, 318.2559. LRMS: *m/z* 318 (M; 5), 250 (63), 157 (41), 148 (36), and 135 (100).

Verticillene Epoxide 16. To a CH_2Cl_2 (2 cm^3) solution of $CrO_3 \cdot Py_2$ (192 mg, 0.74 mmol) was added CH_2Cl_2 (1 cm^3) solution of epoxy alcohol **15** (29.6 mg, 0.09 mmol) and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with ether and the ether solution was passed through a pad of SiO_2 eluted with ether. Evaporation of the volatile materials gave formyl epoxide (27.8 mg). A mixture of formyl epoxide (27 mg) and $RhCl(PPh_3)_3$ (163 mg) in benzonitrile (1 cm^3) was stirred at 160 °C for 5 min. The direct chromatography (hexane–AcOEt, 60 : 1) of the cooled reaction mixture yielded verticillene epoxide **16** (15 mg, 60%) as colorless oil. ^{1}H NMR (90 MHz) $\delta = 1.00$ (3H, s), 1.03 (3H, s), 1.49 (3H, s), 1.55 (6H, s), 5.00 (bd, $J = 9.0$ Hz), 5.37 (1H, bd, $J = 12.0$ Hz). HRMS Found: *m/z* 288.2465. Calcd for $C_{20}H_{32}O$: M, 288.2453. LRMS (%): *m/z* 288 (M; 10), 221 (39), 152 (68), 148 (46), and 135 (100).

Reaction of Verticillene Epoxide 16. With AlH_3. To a diethyl ether solution (5 cm^3) of AlH_3 freshly prepared from $LiAlH_4$ (20 mg) and anhydrous $ZnCl_2$ (40 mg) in ether (7 cm^3) was added diethyl ether solution (1 cm^3) of verticillene epoxide **16** (11 mg) under argon atmosphere at 0 °C and the mixture was stirred overnight at the same temperature. After cooling, MeOH (0.2 cm^3) was added and the mixture was passed through a pad of SiO_2 with ether. The residue, obtained by evaporation of the volatile materials, was chromatographed (2 g; hexane–AcOEt, 10 : 1) to isolate recovered verticillene epoxide **16** (3.0 mg) and allyl alcohol **17** (3.9 mg).

With ^{i}Bu$_2$AlH. To a 1.5 M toluene solution (50 µl) of ^{i}Bu$_2$AlH (DIBAH) was added toluene solution (1 cm^3) of verticillene epoxide **16** (5.7 mg) under argon atmosphere at −43 °C and the mixture was stirred overnight at the same temperature. After elevating the temperature to 0 °C, MeOH (0.2 cm^3) was added and the mixture was passed through a pad of SiO_2 with ether. The residue, obtained by evaporation of the volatile materials, was chromatographed (2 g; hexane–AcOEt, 10 : 1) to isolate the allyl alcohol **17** (4.5 mg). ^{1}H NMR (400 MHz) $\delta_H = 1.12$, 1.36, 1.55, 1.58, and 1.66 (each 3H, s), 2.51 (1H, dd, $J = 6.0$, 16.0 Hz), 3.23 (1H, dd, $J = 12.0$, 16.0 Hz), 5.15 (1H, ddq, $J = 4.5$, 5.2, 1.5 Hz), 5.19 (bd, $J = 11.0$ Hz), and 5.63 (1H, dd, $J = 6.0$, 16.0 Hz). ^{13}C NMR (25 MHz) $\delta_C = 146.4$ (s), 133.6 (s), 132.4 (s), 72.9 (s), 40.0 (s), 127.0 (d), 126.3 (d), 125.3 (d), 43.5 (d), 41.2 (t), 39.2 (t), 36.1 (t), 32.2 (t), 24.1 (t), 22.8 (t), 35.2 (q), 31.1 (q), 29.9 (q), 17.6 (q), and 14.9 (q). HRMS Found: *m/z* 288.2448. Calcd for $C_{20}H_{32}O$: M, 288.2453. LRMS (%): *m/z* 288 (M; 100), 273 (38), 270 (54), 255 (52), 187 (44), 159 (40), 147 (49), 136 (59), and 121 (67).

With Li-Ethylamine. After a mixture of verticillene epoxide **16** (6.9 mg) and Li (5 mg) in ethylamine (5 cm^3) was stirred at room temperature until blue color appeared, aq NH_4Cl was added to the mixture. The usual work-up and chromatography (2 g; hexane) yielded verticillene **13** (5 mg).

Reaction of Epoxy Alcohol 15. With AlH_3 To a THF solution (5 cm^3) of AlH_3 freshly prepared from $LiAlH_4$ (40 mg) and anhydrous $ZnCl_2$ (60 mg) in THF was added THF solution (1 cm^3) of epoxy alcohol **15** (26 mg) under argon atmosophere and the mixture was refluxed for 1 h. After cooling, MeOH (0.2 cm^3) was added and the mixture was passed through a pad of SiO_2 with ether. The residue, obtained by evaporation of the volatile materials, was chromatographed (benzene) to isolate verticillene **13** (11.4 mg), 10-hydroxymethylverticillene **14** (2.3 mg) and recovered epoxy alcohol **15** (7.0 mg).

With AlH_3–$ZnCl_2$. Diethyl ether solution of AlH_3–$ZnCl_2$ was freshly prepared from $LiAlH_4$ (51.9 mg, 1.37 mmol) and anhydrous $ZnCl_2$ (111.4 mg, 0.82 mmol) in ether (5 cm^3) under argon atmosphere. To the AlH_3–$ZnCl_2$ mixture was added epoxy alcohol **15** (43.5 mg, 0.14 mmol) in ether (1 cm^3) and the mixture was refluxed for 12 h. After cooling, MeOH was added and the mixture was passed through a pad of SiO_2. Evaporation of volatile materials and chromatography (hexane–AcOEt, 3 : 1) yielded triene diol **18** (R = H) in 34% yield. After a mixture of the triene diol **18**, R = H (7.1 mg) and $(CF_3CO)_2O$ (56 µl) in CH_2Cl_2 (5 cm^3) was kept at 0 °C for 10 min, aqueous NaOH solution was added and the mixture was stirred for 30 min. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the volatile materials and chromatography (2 g; hexane–AcOEt, 10 : 1) yielded trifluoroacetate **18** (R = $COCF_3$) (7.9 mg) as colorless oil. ^{13}C NMR $\delta_C = 132.2$ (s), 132.0 (s), 131.2 (s), 130.9 (s), 73.8 (s), 48.3 (s), 128.1 (d), 123.3 (d), 42.2 (d), 72.3 (t), 41.1 (t), 37.9 (t), 36.4 (t), 33.3 (t), 25.7 (t), 14.3 (t), 27.9 (q), 27.4 (q), 23.5 (q), 16.5 (q), and 14.8 (q). EIMS (%) Found: *m/z* 414 (M; 21), 356 (72), 343 (87), 138 (88), and 81 (100). Calcd for $C_{23}H_{33}F_3O_3$: M, 414.

With AlH_3–Ti(O^{i}Pr)$_4$. To an ice-water cooled diethyl ether solution (2 cm^3) of **15** (13.6 mg) was added Ti(O^{i}Pr)$_4$ (19 µl) and the mixture was stirred for 10 min under ice cooling. A large excess of AlH_3 in diethyl ether was added under argon atmosphere and the mixture was stirred for 1.5 h. Aqueous NH_4Cl solution was added and the mixture was treated as usual to isolate 10-hydroxyverticillene **14** (13 mg).

With ^{i}Bu$_2$AlH. To a toluene (5 cm^3) solution of epoxy alcohol **15** (30.3 mg) was added 1.5 M toluene (254 µl) solution of ^{i}Bu$_2$AlH at −90 °C under argon atmosphere. The reaction temperature was raised gradually to room temperature with stirring and the stirring was continued overnight. The mixture was filtered through a pad of SiO_2. Evaporation of the combined ether solution and chromatography (hexane–AcOEt, 15 : 1) yielded allyl alcohol **17** (18.5 mg), 10-hydroxyverticillene epoxide (4.3 mg), and recovered **15** (3.6 mg). 10-Hydroxyverticillene epoxide. ^{1}H NMR (90 MHz) $\delta_H = 1.01$ (6H, s), 1.56 (9H, bs), 3.33 (1H, bs), 4.65 (1H, bdd, $J = 4.5$, 10.5 Hz), 4.99 (1H, bd, $J = 9.8$ Hz), and 5.33 (1H, bd, $J = 12.0$ Hz). ^{13}C NMR (50 MHz) $\delta_C = 133.6$ (s), 130.8 (s), 71.1 (s), 67.4 (s), 35.9 (s), 130.7 (d), 126.1 (d), 65.4 (d), 41.0 (d), 45.0 (t), 40.0 (t), 34.2 (t), 31.0 (t), 25.8 (t), 25.7 (t), 28.9 (q), 23.7 (q), 22.6 (q), 17.5 (q), and 15.7 (q). LRMS (%): *m/z* 304 (M; 18), 275 (56), 207 (27), 204 (41), 167 (31), and 137 (100). HRMS Found: *m/z* 304.2426. Calcd for $C_{20}H_{32}O_2$: M, 304.2402.

Reduction of Allyl Alcohol 17 with AlH_3. To a THF (5 cm^3) solution of allyl alcohol **17** (5.8 mg) was added under nitrogen atmosphere, a diethyl ether (5 cm^3) solution of AlH_3 freshly prepared from $LiAlH_4$ (20 mg) and $ZnCl_2$ (40 mg) in ether (15 cm^3). Ether was evaporated by warming the mixture gently and the resultant THF solution was stirred at 60 °C overnight under nitrogen atmosphere. After cooled to room temperature, MeOH was added and the mixture was filtered through a pad of SiO_2. The resultant product was identical with verticillene **13** via TLC and ^{1}H NMR.

References

1) This constitutes Part 52 of the series Cyclization of Polyenes. For Part 51, see : *J. Chem. Soc., Chem. Commun.*, **1994**, 311.

2) a) M. Sumimoto, Y. Ito, and H. Yokoi, "6th Symposium on the Chemistry of Natural Products," Abstr., p. 125 (1962); b) H. Erdtman, T. Norin, M. Sumimoto, and A. Morrison, *Tetrahedron Lett.*, **1964**, 3879; c) B. Karlsson, A. Pilotti, A. Söderholm, T. Norin, S. Sundin, and M. Sumimoto, *Tetrahedron*, **34**, 2349 (1978).

3) L. J. Harrison, M. Tori, Z. Hirayosi, and Y. Asakawa, "28th Symposium on the Chemistry of Perfume, Terpenes and Essential

Oil," Abstr., p. 285 (1984).

4) J. W. Harrison, R. M. Scrowston, and B. Lythgoe, *J. Chem. Soc. C*, **1966**, 1933; See also: C. S. Swindell, *Org. Prep. Proced. Int.*, **23**, 465 (1991).

5) C. B. Jackson and G. Pattenden, *Tetrahedron Lett.*, **26**, 3393 (1985).

6) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).

7) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.

8) B. S. Bal, W. E. Childers, Jr., and H. W. Pinnick, *Tetrahedron*, **37**, 2091 (1981).

9) a) T. Kato, H. Takayanagi, T. Suzuki, and T. Uyehara, *Tetrahedron Lett.*, **1978**, 1201; b) T. Kumagai, F. Ise, T. Uyehara, and T. Kato, *Chem. Lett.*, **1981**, 25.

10) The numbering was based on verticillene skeleton.

11) G. A. Kraus and B. Roth, *J. Org. Chem.*, **45**, 4825 (1980).

12) T. Takahashi, T. Nagashima, and J. Tsuji, *Tetrahedron Lett.*, **22**, 1359 (1981).

13) P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon Press, Oxford (1983), p. 165.

14) K. Ohno and J. Tsuji, *J. Am. Chem. Soc.*, **90**, 99 (1968).

15) M. Caron and K. B. Sharpless, *J. Org. Chem.*, **50**, 1557 (1985).