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Synthesis of *dl*-12-epiverticillol☆

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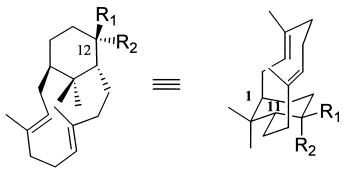
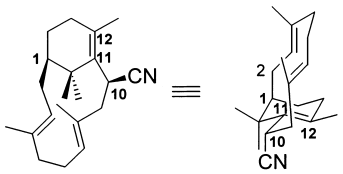
Abstract—The first synthesis of 12-epiverticillol **2**, a constituent of a moss, *Jackiella javanica*, was elaborated in a *dl*-form by setting up 10-cyanoverticillene **3** as a key intermediate. The C1–C2 bond of the intermediate **3** is forced to take axial orientation as in the case of the verticillol. 10-cyanoverticillene **3** was converted to γ-lactone **11**, the cyclohexane ring of which was disclosed to take a boat conformation. Decarbonylation was achieved by application of Wilkinson's catalyst to formyl MOM ether **25** derived from **11**, and final deprotection furnished the objective **2**. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The diterpene alcohols, verticillol **1**[2] and 12-epiverticillol **2**,[3] are a constituent of an evergreen wood of conifer *Sciadopitys vertilillata* and a moss, *Jackiella javanica*, respectively. These natural products have a unique structure, in which the homogeranyl unit is attached in a 1,3-IN OUT fashion to a cyclohexanol possessing geminal dimethyl groups at the center of the IN OUT bonding. The bicyclic verticillol is biogenetically related to a monocyclic cembrene skeleton and is the putative biogenetic precursor of tricyclic taxane nucleus.[4,5] In spite of the early discovery of verticillols, there had been no report on the complete synthesis of the natural products excepting the construction of the hydrocarbon, verticillene.[6] The novel IN-OUT structure of verticillols as well as their biogenetical relation with the bioactive taxane-type compounds[7] prompted us to elaborate the synthetic route of verticillols, in which 10-cyanoverticillene **3** was settled as key intermediate. The C1–C2 bond of the intermediate **3** is forced to take axial orientation as in the case of verticillols. By virtue of the cyano group, introduction of the hydroxyl group with concomitant *trans* protonation at the tetrasubstituted C11–C12 double bond is expected feasible. Subsequent removal of a carbonyl unit derived from the cyano group may lead to verticillols. This paper describes the first synthesis of *dl*-12-epiverticillol **2** from the key intermediate **3** (Fig. 1).



Verticillol (**1**) : R_1=OH, R_2=Me
12-Epiverticillol (**2**) : R_1=Me, R_2=OH



10-Cyanoverticillene (**3**)

Figure 1. Structure of verticillols and 10-cyanoverticillene.

2. Results and discussion

In our previous paper,[8] construction of the intermediate **3** was demonstrated as depicted briefly in Scheme 1. The coupling reaction of chloro ester **4** and geranyl cyanide **5** proceeded smoothly in the presence of $SnCl_4$, affording axial and equatorial chlorides, **6** and **7** in moderate yield as a whole. After separation of each isomer, the individual was submitted to dehydrochlorination reaction under different conditions, furnishing the tetrasubstituted olefinic product **8** from each isomer. By the conventional reactions, **8** was converted to allyl chloride **9**, from which the key intermediate **3** was prepared by the action of $LiN(TMS)_2$

☆ This constitutes Part 62 of the series Cyclization of Polyenes. For Part 61; Ref. 1.

Keywords: diterpene; synthesis; 1,3-IN OUT ring system; polysubstituted cyclohexane; precursor of taxane; chair/boat conformational change.

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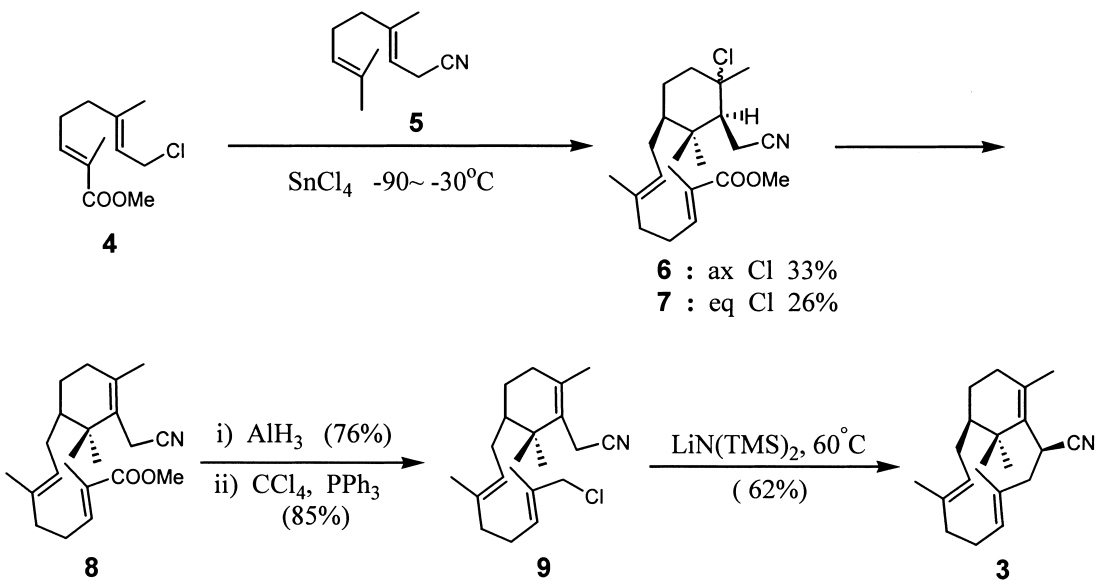
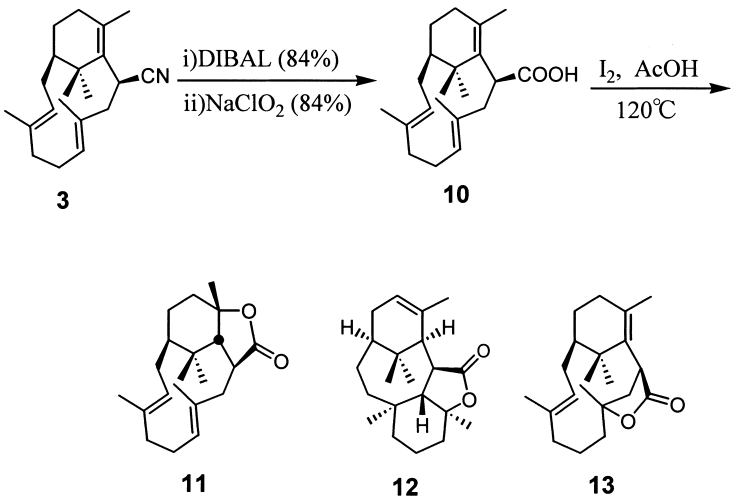


Scheme 1.



Scheme 2.

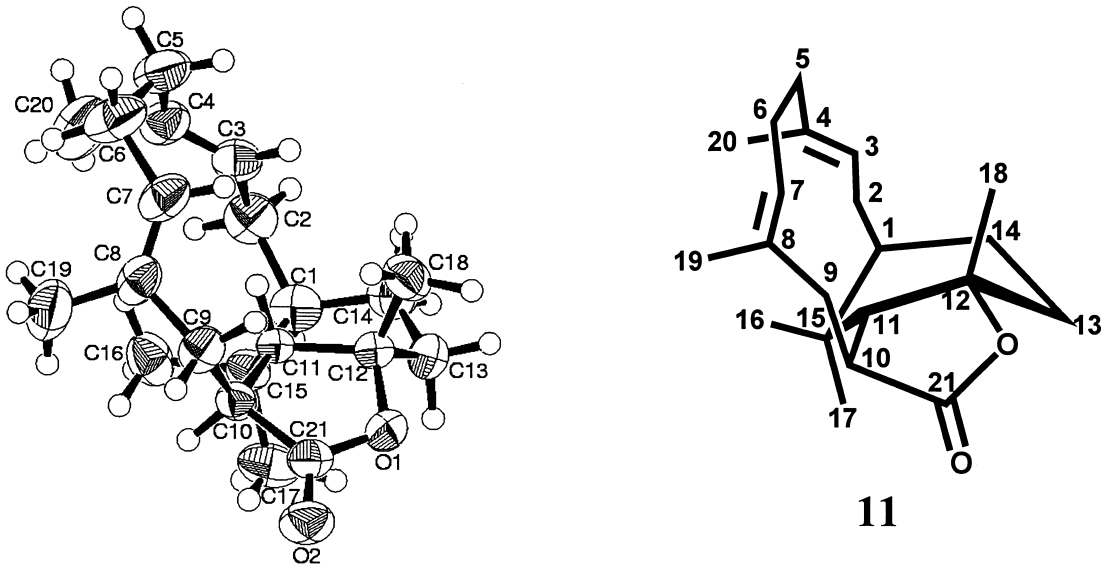
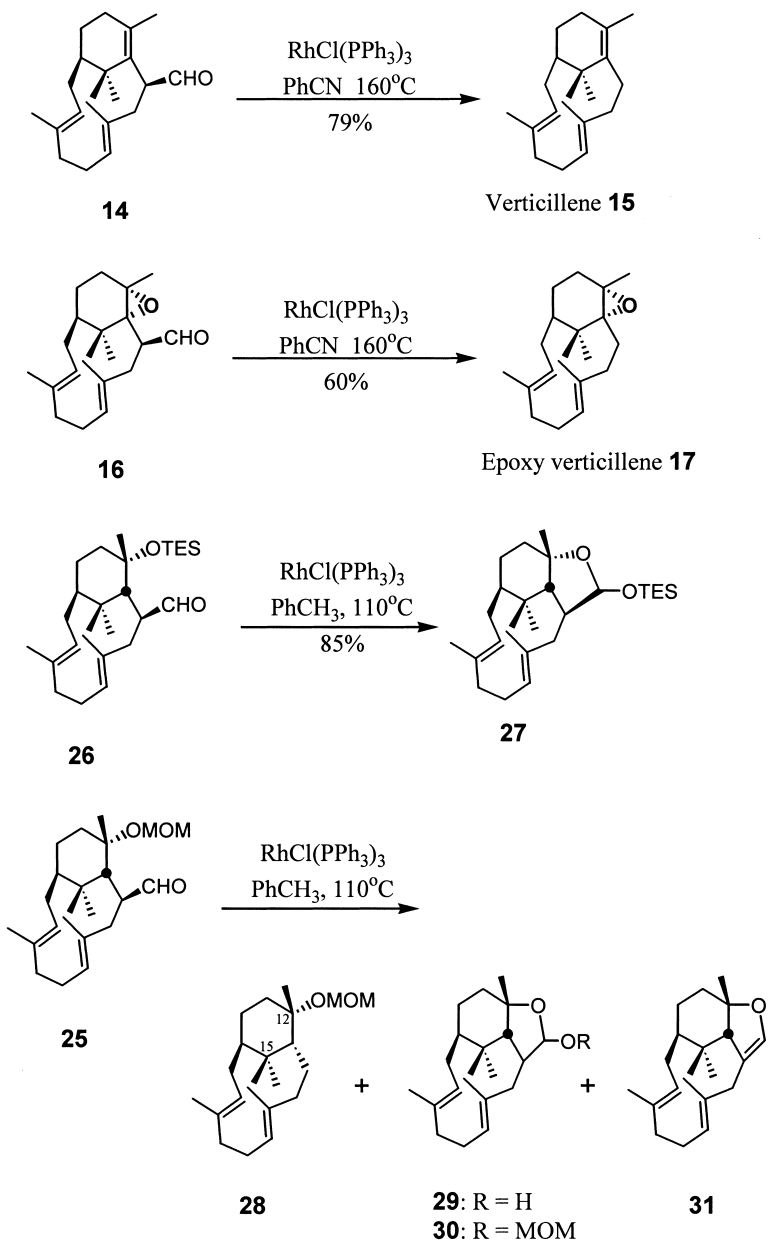


Figure 2. A perspective ORTEP drawing of γ-lactone **11**.

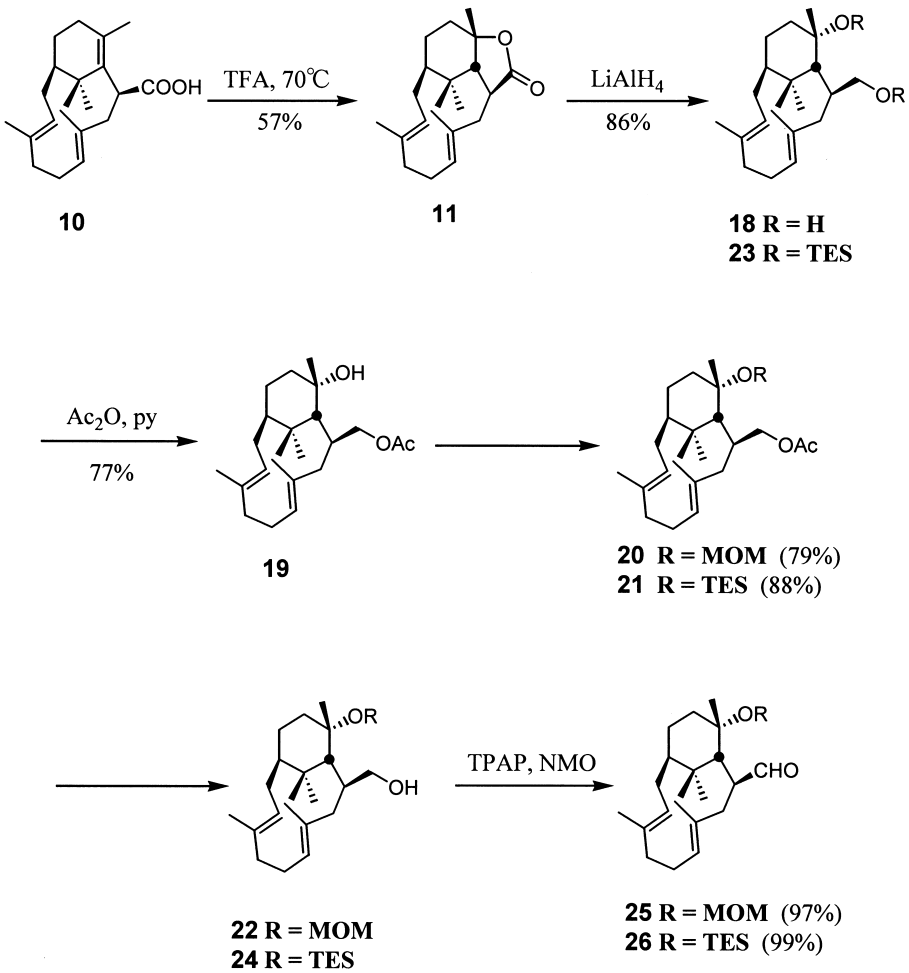


Scheme 3.

at 60°C. The high temperature of 60°C was crucial for the effective construction of the intermediate **3**, the stereochemistry being evaluated by NOE experiments.

The cyano group of **3** was transformed to the carboxyl group by sequential reactions of diisobutylaluminum hydride (DIBAL) reduction to a formyl group followed by oxidation with $NaClO_2$, providing verticillene-10-carboxylic acid **10**. The lactone formation at 12 position of the carboxylic acid **10** seems a promising procedure for the introduction of a hydroxyl group with concomitant *trans* protonation at the 11 position. For this purpose, we have explored the lactonization conditions of typical β,γ-enoic acids and found that iodine in refluxing acetic acid is an alternative reagent for the lactonization.[9] Application of our conditions to the acid **10** afforded three kinds of γ-lactones, **11**–**13** in 20, 28 and 8% yields, respectively (Scheme 2). Although lactonization of **10** proceeded partly in the expected manner, the yield of the objective **11** was still unsatisfactory. We, therefore, continued to develop other lactonization conditions and found that γ-lactone **11** was provided in 57% yield when **10** was refluxed in trifluoroacetic acid. Under these conditions, the isomeric lactones **12** and **13** were not formed. The structure including stereochemistry of the resultant lactone **11** was unequivocally demonstrated by X-ray chrystallographic analysis. It is noteworthy that the cyclohexane ring of γ-lactone **11** exists as a boat conformation, the ORTEP drawing being depicted in Fig. 2.

The remaining step of the synthesis is the exploitation of effective removal of the carbonyl group from **11**. Removal of the formyl group from 10-formyl verticillol protected as MOM or TES ether by the action of Wilkinson's catalyst[10] seemed possible since deformylation of 10-formyl verticillene **14** and its epoxy derivative **16** proceeded smoothly as illustrated in Scheme 3, affording deformylated products

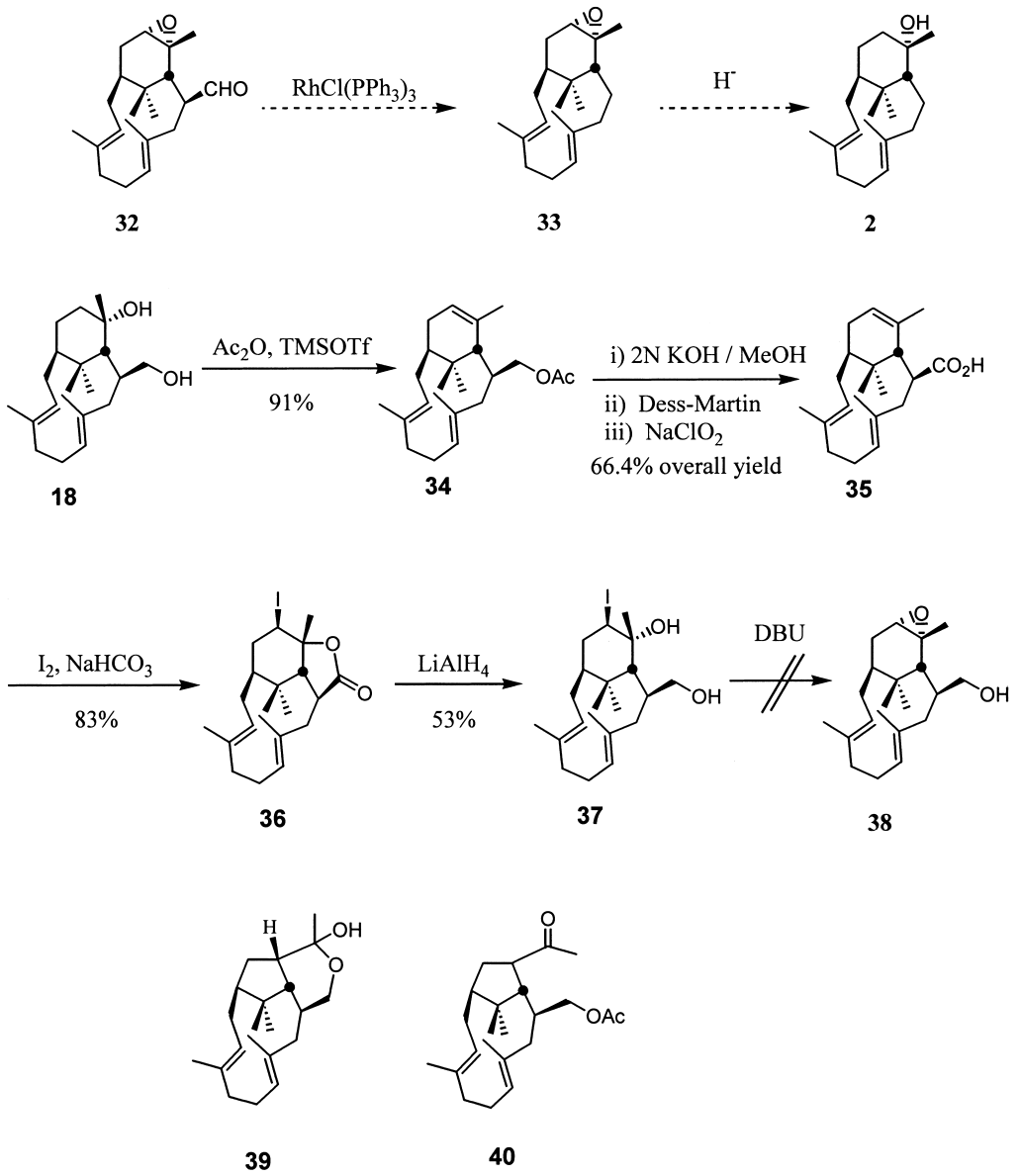


Scheme 4.

15 and **17** in moderate yields in our model experiments.[8] 12-Epoxy derivative **32** in Scheme 5 was also selected as an alternative candidate for the deformylation-precursor. Reduction of **11** with $LiAlH_4$ afforded diol **18**, the primary hydroxyl group being selectively acetylated to give monoacetate **19**. The tertiary hydroxyl group could be protected with either methoxymethyl (MOM) or triethylsilyl (TES) groups to give **20** and **21**, respectively, by the action of MOMCl and pyridine at 60°C or TESOTf and lutidine at −78°C in practical yields in each reaction as illustrated in Scheme 4. In the case of the TES group, selective deprotection of the acetate group to the hydroxyl group was unsuccessful by means of K_2CO_3 in MeOH at room temperature or $LiAlH_4$ at 0°C. The former treatment gave the diol **18** exclusively while the latter reaction resulted in the complete recovery of the starting material **21**. When MOM was applied as a protecting group, hydrolysis with KOH in MeOH proceeded smoothly to give 10-hydroxymethyl MOM ether **22** from acetoxy MOM ether **20**. The corresponding TES ether **24** was provided through bis-TES ether **23**, prepared from the diol **18** by the action of excess TESOTf in the presence of Et_3N. Selective removal of the TES group from the 10-hydroxymethyl TES moiety was successfully achieved by treatment with PPTS in MeOH–CH_2Cl_2 solution[11] to give mono-TES ether **24**. Oxidation of the hydroxymethyl group of both MOM and TES ethers **22** and **24** to the formyl group proceeded in high yields by the aids of tetrapropylammonium perruthenate (VII) (TPAP) and *N*-methylmorpholine *N*-oxide (NMO),[12] affording formyl ethers **25** and **26**, respectively.

Although our model experiments suggested that it was easy task to remove the formyl group from MOM ether **25** or TES ether **26** by the action of Wilkinson's catalyst, it was soon found that the deformylation was troublesome as shown in Scheme 3. Application of the catalyst to TES ether **26** resulted in the predominant formation of lactol **27** as its TES ether while the reaction of MOM ether **25** was highly capricious and gave a mixture of products, from which lactone **11**, lactols **29** and **30**, and dihydrofuran **31** were characterized in addition to the objective **28** in variable yields. The deformylation reaction was quite subtle, the maximum yield of **28** being 12%, and sometimes the compound **28** could not be formed at all depending on the reaction conditions such as temperature, solvent and reaction time. Trials of decarbonylation with other methods[13] were all unsuccessful.

At this stage, we set up an alternative candidate **32** as the deformylation precursor, which would provide 12-epivertiicillol **2** through the hydride reduction of the epoxy group of the expected product **33** as illustrated in Scheme 5. The successful deformylation of **16** to **17** in the model experiment in Scheme 3 encouraged us to prepare the



Scheme 5.

candidate **32** from epoxy alcohol **38** following the route shown in Scheme 5. By treatment of diol **18** with Ac_2O in the presence of TMSOTf,[14] selective dehydration of the *tert*-OH group took place easily to afford the corresponding acetate **34** in high yield. The sequential reactions of hydrolysis followed by two-step oxidation provided carboxylic acid **35**, an isomer of the original carboxylic acid **10**. Iodo-lactonization reaction proceeded smoothly to furnish iodo-lactone **36**, which in turn was reduced to iodo-diol **37**. Conversion of **37** to the epoxide **38** was unsuccessful by treatment with DBU, which afforded the ring contracted product **39** as its ketol form. The ketol **39** was transformed, as expected, to the methyl ketone **40** by Ac_2O treatment. The failure of epoxide formation may be due to the predominant existence of **37** as a boat conformation, in which both iodine and hydroxyl groups exist as equatorial configuration, preventing epoxide ring formation. Attempt of direct epoxidation of primary alcohol derived from **34** by alkaline hydrolysis gave no clear product corresponding to epoxy alcohol **38** by application of Sharpless epoxidation under several conditions.

Failure of epoxide formation from **37** compelled us to adopt the MOM ether **28** as the synthetic precursor although its yield was less than 12%. The deprotection of the MOM group of **28** was also not easy task. Treatment of **28** with such acidic reagents as aq HCl or TMSI[15] accompanied the exclusive dehydration to verticillene **41**. Deprotection of MOM group was finally achieved by assistance of $BF_3{\cdot}Et_2O$ in ether,[16] providing 12-epiverticillol **2** and verticillene **41** in 33 and 61% conversion yields, respectively. The NMR spectra of the purified compound were identical with the reported values[3b] of 12-epiverticillol **2**.

It should be pointed out that the target molecule possesses a 1,2,3,3,4-substituted cyclohexan-1-ol ring system,[17] in which the homogeranyl unit is appended at 2 and 4 positions in OUT-IN fashion, and chair-boat conformational change

is feasible in such polysubstituted cyclohexane ring, as observed in the case of γ-lactone **11**. It seems of interest to reveal the exact conformation of the cyclohexane ring of 12-epiverticillol itself.

3. Experimental

3.1. General

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 an internal standard with JEOL spectrometers. Chemical shifts are reported in δ-units and shown with δ_H and δ_C in the ^{1}H NMR and ^{13}C NMR, and *J*-values are in Hz. The mass spectra were measured with Hitachi M-80 and M-80A spectrometers. The infra-red spectra were measured with Hitachi 270-30 spectrometer in solution. The characteristic absorption bands were reported with cm^{-1}, the solvent being indicated in parentheses. The usual work-up in the experimental sections involved dilution of the reaction mixture with water, extraction with diethyl ether (ether), washing of the organic extracts with water and brine, followed by drying over Na_2SO_4, and evaporation at aspirator pressure. The reaction was monitored by SiO_2 TLC and column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70–230 mesh).

3.2. Procedures described in Scheme 4

3.2.1. Lactonization of 10-carboxylverticilla-3,7,11-triene 10 with trifluoroacetic acid. A 1 ml of trifluoroacetic acid solution of 10-carboxylverticillene **10** (23 mg, 0.07 mmol) was refluxed for 30 min and the mixture was treated by usual work-up to afford γ-lactone **11** (13 mg, 57%). Mp 169–170°C (hexane). IR ($CC1_4$) 2936, 1766, 1450, 1384, 1272 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 0.62 (3H, s), 0.93 (3H, s), 1.53 (6H, s), 1.55 (3H, s), 2.15 (1H, t, *J*=13 Hz), 2.56 (1H, s), 2.61 (1H, dd, *J*=13, 5.5 Hz), 4.96 (1H, bd, *J*=11.0 Hz), and 5.32 (1H, bd, *J*=11.0 Hz). δ_C (125 MHz, $CDC1_3$) 180.0 (s), 134.3 (s), 132.3 (d), 131.7 (s), 123.3 (d), 85.8 (s), 46.7 (d), 41.8 (t), 41.3 (t), 40.1 (d), 40.0 (d), 34.4 (s), 32.6 (t), 31.4 (t), 29.3 (q), 28.3 (q), 26.5 (t), 25.6 (q), 23.3 (t), 16.3 (q), and 15.9 (q). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10. 19. Found: C, 79.52; H. 10.05. HI-EI-MS. Found: *m/z* 316.2400. Calcd for $C_{2l}H_{32}O_2$: M^+, 316.2402.

3.3. Crystallographic data for *dl*-lactone 11

$C_{2l}H_{32}O_2$, *M*=316.48, Triclinic, space group *P*1− (#2), *a*=8.843(6), *b*=13.73(1), *c*=7.977(5) Å, α=97.96(5)°, β=99.96(5)°, γ=102.00(6)°, *V*=917(1) Å^3, *Z*=2, *F*(000)=348.00, D_{calc}=1.145 g cm^{-3}, μ(Mo Kα)=0.71 cm^{-1}, *T*=296(2) K, radiation=0.71069 Å, *R*1=0.054 for $I>2.0\sigma(I)$, *wR*2=0.049 for all data (4219 reflections), GOF=1.57 (337 parameters), crystal dimensions 0.65×0.25×0.25 mm^3. A quality single crystal of **11** (colorless prism) was mounted on a glass fiber. Diffraction data were measured on a Rigaku AFC-5S diffractometer with graphite monochromated Mo Kα radiation. The data reduction, structure solution, and refinements were performed using teXsan. Data deposited at the Cambridge Crystallographic Data Centre; deposition number CCDC 191161.

3.3.1. 10-Hdroxymethylverticilla-3,7-dien-12-ol 18. After a mixture of γ-lactone **11** (180 mg, 0.57 mmol) and $LiAlH_4$ (103 mg, 2.71 mmol) in anhydrous THF (1 ml) was refluxed for 1 h, the mixture was quenched with AcOEt. Usual work-up followed by SiO_2 column chromatography with hexane–AcOEt (15:1) and then (1:1) afforded diol **18** (157 mg, 86%). Mp 141–143°C (hexane).IR ($CC1_4$): 3444 cm^{-1}. δ_H (400 MHz): 0.75 (3H, s), 1.20 (3H, s), 1.41 (3H, s), 1.52 (3H, s), 1.54 (3H, s), 2.68–2.77 (1H, m), 3.69 (1H, dd, *J*=11.6, 5.0 Hz), 3.97 (1H, dd, *J*=11.6, 8.0 Hz), 4.86 (1H, br d, *J*=11.0 Hz), and 5.44 (1H, br d, *J*=12.4 Hz). δ_C (100 MHz): 133.1 (s), 133.0 (s), 129.9 (d), 127.4 (d), 74.6 (s), 66.1 (t), 45.3 (d), 44.4 (d), 44.2 (t), 41.9 (t), 41.1 (t), 37.0 (s), 36.6 (d), 34.1 (t), 33.0 (q), 28.6 (q), 28.3 (q), 26.7 (t), 26.3 (t), 16.4 (q), and 15.1 (q). Anal. calcd for $C_{21}H_{36}O_2$: C, 76.20; H, 10.56. Found: C, 76.52; H. 10.25. HR-MS Found: *m/z* 320.2715. Calcd for $C_{2l}H_{36}O_2$: M^+, 320.2715.

3.3.2. 10-Acetoxymethylverticilla-3,7-dien-12-ol 19. A mixture of diol **18** (157 mg, 0.49 mmol), pyridine (0.28 ml, 3.43 mmol) and Ac_2O (0.23 ml 2.45 mmol) in CH_2Cl_2 (4 ml) was stirred at room temperature until complete conversion to monoacetate. The reaction was monitored by SiO_2 TLC. An excess MeOH was added to remove an excess Ac_2O. The mixture was diluted with water, and extracted with ether. The combined ether solutions were washed with aqueous $CuSO_4$ and then treated by usual work-up. Silica gel column chromatography with hexane–AcOEt (15:1) and then (10:1) afforded monoacetate **19** (134 mg, 77%). Mp 155–157°C (hexane). IR (CCl_4): 2932, 1732 cm^{-1}. δ_H (400 MHz); 0.78 (3H, s), 0.94 (1H, s, OH), 1.18 (3H, s), 1.34 (3H, s), 1.51 (3H, s), 1.35–1.50 (3H, m), 1.54 (3H, s), 1.83 (1H, br d, *J*=14.9 Hz), 1.97–2.10 (5H, m), 2.07 (3H, s), 2.23 (1H, s), 2.15–2.45 (4H, m), 2.71 (1H, dddd, *J*=14.6, 12.7, 6.4, 1.2 Hz), 4.19 (1H, t, *J*=11.3 Hz), 4.77 (1H, dd, *J*=11.3, 3.2 Hz), 4.87 (1H, br d, *J*=10.3 Hz), and 5.45 (1H, br d, *J*=12.7 Hz). δ_C (100 MHz): 171.4 (s), 133.2 (s), 133.0 (s), 130.2 (d), 127.4 (d), 74.1 (s), 68.2 (t), 45.0 (d), 43.7 (d), 42.9 (t), 42.0 (t), 41.2 (t), 37.4 (s), 34.2 (d), 34.0 (t), 33.6 (q), 28.7 (q), 27.6 (q), 26.6 (t), 26.3 (t), 21.3 (q), 16.2 (q), and 15.2 (q). Anal. calcd for $C_{23}H_{38}O_3$:C, 76.20; H, 10.56. Found: C, 75.98; H. 10.38. HR-MS Found: *m/z* 362.2808. Calcd for $C_{23}H_{38}O_3$: M^+, 362.2821.

3.3.3. 10-Acetoxymethyl-12-methoxymethyloxyverticilla-3,7-diene 20. After a mixture of monoacetate **19** (134 mg, 0.37 mmol), diisopropylethylamine (4 ml) and chloromethyl methyl ether (1 ml) was kept at 60°C overnight, the mixture was treated by usual work-up. Silica gel column chromatography with hexane–AcOEt (15:1) gave 10-acetoxymethyl MOM ether **20** (118 mg, 79%). Mp 101–103°C (MeOH). IR (CCl_4): 1738, 1238, 1028 cm^{-1}. δ_H (400 MHz): 0.77 (3H, s), 1.16 (3H, s), 1.34 (3H, s), 1.51 (3H, s), 1.54 (3H, s), 2.07 (3H, s), 2.34–2.45 (1H, m), 2.67–2.75 (1H, m), 3.44 (3H, s), 4.11 (1H, t, *J*=11.2 Hz), 4.66 (1H, d, *J*=7.3 Hz), 4.68 (1H, d, *J*=7.3 Hz), 4.79 (1H, dd, *J*=11.2, 2.6 Hz), 4.88 (1H, bd, *J*=10.2 Hz), and 5.48 (1H, bd, *J*=12.0 Hz). δ_C (100 MHz): 171.5 (s), 133.2 (s), 133.1

(s), 130.2 (d), 127.5 (d), 90.3 (t), 79.4 (s), 68.4 (t), 56.6 (q), 45.6 (d), 45.0 (d), 42.8 (t), 41.3 (d), 37.6 (s), 35.4 (t), 34.2 (t), 34.1 (t), 28.9 (q), 28.5 (q), 27.8 (q), 26.8 (t), 26.4 (t), 21.2 (q), 16.3 (q), and 15.2 (q). Anal. Calcd For $C_{25}H_{42}O_4$:C, 73.85; H, 10.41. Found: C, 73.54; H. 10.25. HR-MS Found: *m/z* 406.3078. Calcd for $C_{25}H_{42}O_4$: M^+, 406.3083.

3.3.4. 10-Hydroxymethyl-12-(methoxymethyloxy)verticilla-3,7-diene 22. A solution of 10-acetoxymethyl MOM ether **20** (118 mg, 0.29 mmol) in 2 M KOH–MeOH (5 ml) was stirred for 6 h at room temperature. The mixture was treated by the usual work-up, and silica gel column chromatography with hexane–AcOEt (5:1), and then (1:1) afforded 10-hydroxymethyl MOM ether **22** (106 mg, 100%). Mp 72–74°C (hexane). IR (CCl_4): 3644, 3520 cm^{-1}. δ_H (500 MHz): 0.76 (3H, s), 1.20 (3H, s), 1.40 (3H, s), 1.52 (3H, s), 1.54 (3H, s), 3.44 (3H, s), 3.55–3.60 (1H, m) 3.99–4.03 (1H, m), 4.70 (1H, d, *J*=7.3 Hz), 4.74 (1H, d, *J*=7.3 Hz), 4.86 (1H, bd, *J*=10.7 Hz), and 5.46 (1H, bd, *J*=12.6 Hz). δ_C (125 MHz): 133.3 (s), 133.2 (s), 129.9 (d), 127.4 (d), 90.5 (t), 80.9 (s), 66.1 (t), 56.6 (q), 46.3 (d), 45.0 (d), 43.8 (t), 41.1 (t), 37.3 (d), 37.1 (s), 35.5 (t), 34.2 (t), 28.7 (q), 28.5 (q), 28.0 (q), 26.8 (t), 26.3 (t), 16.4 (q), and 15.2 (q). Anal. Calcd for $C_{23}H_{40}O_3$: C, 75.77; H 11.06. Found: C, 75.50; H. 10.85. HR-MS Found: *m/z* 364.2982. Calcd for $C_{23}H_{40}O_3$: M^+, 364.2977.

3.3.5. 10-Acetoxymethyl-12-(triethylsilyloxy)verticilla-3,7-diene 21. To a CH_2Cl_2 (1 ml) solution of monoacetate **19** (6.1 mg) and 2,6-lutidine (0.5 ml) was added triethylsilyl trifluoromethanesulfonate (0.5 ml) at −78°C and the mixture was stirred at the same temperature for 2 h. After the reaction was quenched with MeOH at −78°C, water was added, and extracted with ether. The combined ether solutions were washed with sat.aq. NH_4Cl solution. Usual work-up and silica gel column chromatography with hexane–AcOEt (15:1) afforded triethylsilyl ether **21** (7.0 mg, 88%). δ_H (90 MHz): 0.66 (6H, q, *J*=6.8 Hz), 0.79 (3H, s), 0.98 (9H, t, *J*=6.8 Hz), 1.17 (3H, s), 1.36 (3H, s), 1.52 (3H, s), 1.56 (3H, s), 1.92 (3H, s), 4.08 (1H, t, *J*=8 Hz), 4.79 (1H, dd, *J*=2.7, 10.8 Hz), 4.88 (1H, bd, *J*=10.8 Hz), and 5.44 (1H, bd, *J*=10.8 Hz).

3.3.6. 10-Triethylsilyloxymethyl-12-triethylsilyloxyverticilla-3,7-diene 23. To a stirred mixture of diol **18** (42 mg, 0.13 mmol) and triethylamine (0.18 ml, 1.31 mmol) in CH_2Cl_2 (1.5 ml), TMSOTf (0.15 ml, 0.655 mmol) was added at 0°C, and then the mixture was stirred at room temperature for 10 min. After sat. aq. NH_4Cl solution was added, the mixture was worked up as usual and the resulting residue was purified by SiO_2 column chromatography with hexane–AcOEt (50:1) to afford bis-TES ether **23** (60 mg, 83%). White powder. δ_H (400 MHz): 0.61, 0.64 (each 6H, q, *J*=8.0 Hz), 0.75 (3H, s), 0.97 (18H, t, *J*=8.0 Hz), 1.11 (3H, s), 1.34 (3H, s), 1.50 (3H, s), 1.53 (3H, s), 3.64 (1H, t, *J*=10.6 Hz), 4.20 (1H, dd, *J*=10.6, 3.4 Hz), 4.83 (1H, br d, *J*=10.8 Hz), and 5.45 (1H, br d, *J*=11.2 Hz).

3.3.7. 10-Hydroxymethyl-12-triethylsilyloxyverticilla-3,7-diene 24. Pyridinium *p*-toluenesulfonate (PPTS, 2.7 mg, 0.011 mmol) was added to a stirred solution of bis-TES ether **23** (60 mg, 0.11 mmol) in a mixed solvents of CH_2Cl_2 (0.8 ml) and MeOH (2.4 ml) at 0°C and the mixture was kept at 0°C for 10 min. The reaction was quenched with sat. aq. $NaHCO_3$ solution and treated by usual work-up. Column chromatography with hexane–AcOEt (15:1) and then (3:1) afforded mono-TES ether **24** (42 mg, 88%). White powder. δ_H (400 MHz): 0.68 (6H, q, *J*=8.0 Hz), 0.74 (3H, s), 0.98 (9H, t, *J*=8.0 Hz), 1.16 (3H, s), 1.39 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 2.71 (1H, dt, *J*=13.8, 6.4 Hz), 3.55 (1H, dd, *J*=11. 1, 7.0 Hz), 4.14 (1H, dd, *J*=11.1, 6.4 Hz), 4.84 (1H, br d, *J*=10.2 Hz), and 5.14 (1H, br d, *J*=12.2 Hz). δ_C (100 MHz): 133.3 (s), 133.0 (s), 129.7 (d), 127.3 (d), 78.6 (s), 65.9 (t), 46.3 (d), 45.2 (d), 43.4 (t), 41.1 (t), 40.6 (t), 37.6 (d), 37.2 (s), 34.2 (t), 33.3 (q), 28.7 (q), 28.0 (q), 26.9 (t), 26.2 (t), 16.3 (q), 15.1 (q), 7.3 (q, 3C), and 6.9 (t, 3C).

3.3.8. 10-Formyl-12-methoxymethyloxyverticilla-3,7-diene 25. After a mixture of MOM ether **22** (106 mg, 0.29 mmol), *N*-methylmorpholine-*N*-oxide (NMO, 52 mg, 0.44 mmol) and tetrapropylammonium perruthenate (VII) (TPAP, 5.3 mg, 0.015 mmol) in CH_2Cl_2 (1 ml) was stirred at room temperature for 4 h, the mixture was diluted with ether. The ether solution was successively washed with aqueous Na_2SO_3 solution, brine, aqueous $CuSO_4$ solution, and then brine. After being dried over Na_2SO_4, ether was removed and the residue was submitted to a silica gel column chromatography with hexane–AcOEt (40:1) then (10:1) to provide formyl MOM ether **25** (103 mg, 97%). Mp 112–114°C (hexane). IR ($CC1_4$): 1712, 1046, 1028 cm^{-1}. δ_H (500 MHz): 0.83 (3H, s), 1.24 (3H, s), 1.26 (3H, s), 1.49 (3H, s), 1.56 (3H, s), 2.53 (1H, s), 3.37 (3H, s), 4.51 (1H, d, *J*=7.5 Hz), 4.65 (1H, d, *J*=7.5 Hz), 4.92 (1H, br d, *J*=10.5 Hz), 5.46 (1H, br d, *J*=12.5 Hz), and 10.08 (1H, s). δ_C (125 MHz): 205.4 (d), 133.7 (s), 132.2 (s), 131.0 (d), 127.2 (d), 90.7 (t), 79.4 (s), 56.6 (q), 49.7 (d), 47.9 (d), 44.3 (d), 41.2 (t), 39.5 (t), 37.1 (s), 34.7 (t), 34.0 (t), 28.7 (q), 28.5 (q), 27.0 (q), 26.7 (t), 26.4 (t), 16.3 (q), and 15.2 (q). Anal. calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 75.88; H. 10.42. HR-MS Found: *m/z* 362.2794. Calcd for $C_{23}H_{38}O_3$: M^+, 362.2821.

3.3.9. 10-Formyl-12-triethylsilyloxyverticilla-3,7-diene 26. Procedure was similar with those described in the preparation of **25**. TES ether **24** (19.2 mg, 0.044 mmol) afforded **26** (19 mg, 100%) after column chromatography. **26**: White powder. δ_H (400 MHz): 0.63 (6H, q, *J*=8.0 Hz), 0.80 (3H, s), 0.95 (9H, t, *J*=8.0 Hz), 1.238 (3H, s), 1.244 (3H, s), 1.48 (3H, s), 1.55 (3H, s), 4.88 (1H, br d, *J*=10.5 Hz), 5.43 (1H, br d, *J*=12.0 Hz), and 10.14 (1H, br s).

3.4. Procedures described in Scheme 3

3.4.1. Reaction of 10-formyl-12-triethylsilyloxyverticilla-3,7-diene 26 with Wilkinson's catalyst. A mixture of formyl TES ether **26** (20 mg, 0.05 mmol) and $RhCl(PPh_3)_3$ (56 mg, 0.06 mmol) in toluene (3 ml) was stirred at 110°C overnight. The residue obtained by evaporation of the solvent was chromatographed on SiO_2 column with hexane–AcOEt (100:1) to afford lactol TES ether **27** (17 mg, 85%). White powder, δ_H (500 MHz): 0.60 (3H, s), 0.63 (6H, q, *J*=7.9 Hz), 0.85 (3H, s), 0.96 (9H, t, *J*=8.0 Hz), 1.39 (3H, s), 1.50 (3H, s), 1.56 (3H, s), 4.90 (1H, br d, *J*=11.6 Hz), 5.14 (1H, br d, *J*=12.2 Hz), and 5.48 (1H, d, *J*=6.4 Hz). δ_C (125 MHz): 134.6 (s), 133.6 (s), 130.5 (d),

123.7 (d), 100.2 (d), 82.8 (s), 51.8 (d), 42.3 (d), 41.32 (t), 41.28 (s), 40.9 (d), 34.44 (t), 34.35 (t), 31.5 (t), 29.8 (q), 29.7 (q), 26.4 (t), 25.6 (q), 24.4 (t), 16.5 (q), 16.3 (q), 6.9 (q, 3C), and 5.0 (t, 3C).

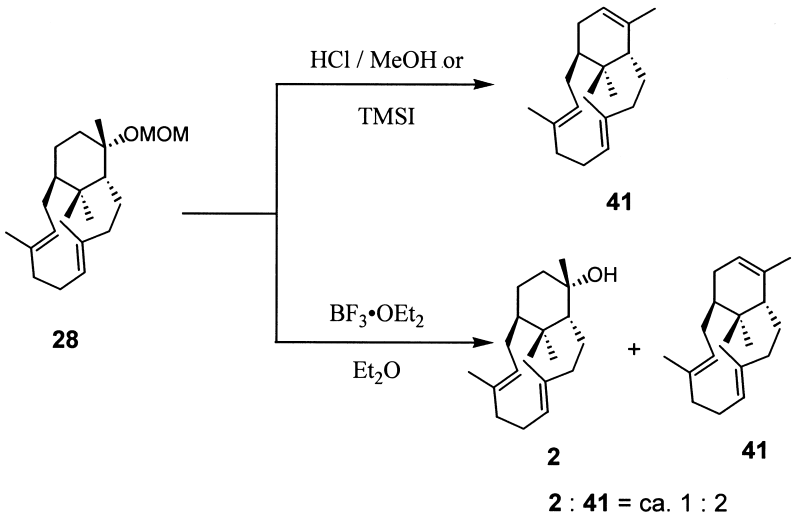
3.4.2. 12-Methoxymethyloxy-verticilla-3,7-diene 28. A mixture of formyl MOM ether **25** (103 mg, 0.28 mmol) and $RhCl(PPh_3)_3$ (260 mg, 0.28 mmol) in toluene (4 ml) was stirred at 110°C overnight, and the residue obtained by evaporation of the solvent was chromatographed on SiO_2 column with hexane–AcOEt (80:1), and then (1:1) to afford MOM ether **28** (5.6 mg, 6%), γ-lactone **11** (18 mg, 20%), dihydrofuran **31** (14 mg, 17%), lactol **29** (16 mg, 18%), and lactol MOM ether **30** (10 mg, 10%). **28**: colorless oil. δ_H (500 MHz): δ 0.65 (3H, s), 0.96 (3H, s), 1.23 (3H, s), 1.50 (3H, s), 1.54 (3H, s), 2.38 (1H, q, J=12.0 Hz), 2.70 (1H, dt, J=7.0, 13.4 Hz), 3.39 (3H, s), 4.66 and 4.68 (each 1H, d, J=7.1 Hz), 4.80 (1H, d, J=11.3 Hz), and 5.49 (1H, d, J=11.6 Hz). δ_C (125 MHz): 133.4 (s), 132.9 (s), 129.6 (d), 127.7 (d), 90.5 (t), 78.8 (s), 55.7 (q), 43.9 (d), 43.7 (d), 41.4 (t), 40.8 (t), 40.3 (t), 36.4 (s), 34.3 (t), 34.2 (q), 27.9 (q), 27.4 (t), 26.8 (t), 26.6 (q), 20.3 (t), 16.3 (q), and 15.3 (q). HR-MS Found: m/z 334.2864. Calcd for $C_{22}H_{38}O_2$: M^+, 334.2872. **29**: IR (CCl_4): 3616, 3396, 2920, 1744, 1482, 1446, and 1392 cm^{-1}. δ_H (400 MHz): 0.63 (3H, s), 1.04 (3H, s), 1.31 (3H, s), 1.51 (3H, s), 1.57 (3H, s), 2.55 (1H, d, J=6.6 Hz, OH), 4.90 (1H, bd, J=11.7 Hz), 5.10 (1H, dd, J=6.6, 2.7 Hz), and 5.31 (1H, bd, J=11.5 Hz). HR-MS Found: m/z 318.2564. Calcd for $C_{21}H_{34}O_2$: M^+, 318.2559. **31**: colorless oil. δ_H (400 MHz): 0.85 (3H, s), 1.00 (3H, s), 1.23 (3H, s), 1.57 (3H, s), 1.61 (3H, s), 2.46 (1H, ddd, J=13.9, 12.0, 4.4 Hz), 2.73 (1H, s), 2.70 (1H, d, J=14.4 Hz), 2.76 (1H, d, J=14.4 Hz), 5.09 (1H, t, J=7.8 Hz), 5.33 (1H, d, J=12.0 Hz), and 6.20 (1H, s). HR-MS Found: m/z 300.2444. Calcd for $C_{21}H_{32}O$: M^+, 300.2450. **30**: δ_H (400 MHz): 0.63 (3H, s), 0.86 (3H, s), 1.41 (3H, s), 1.51 (3H, s), 1.57 (3H, s), 3.39 (3H, s), 4.64 (1H, d, J=6.6 Hz), 4.93 (1H, br d, J=11.3 Hz), 4.95 (1H, d, J=6.6 Hz), 5.33 (1H, br d, J=11.6 Hz), and 5.34 (1H, d, J=6.6 Hz).

3.5. Procedures described in Scheme 5

3.5.1. 10-Acetoxymethylverticilla-3,7,12-tiene 34. To a stirred mixture of **18** (47 mg, 0.15 mmol) and Ac_2O (0.11 ml, 1.16 mmol) in CH_2Cl_2 (3 ml), TMSOTf (0.15 ml of a 0.1 M CH_2Cl_2 solution, 0.015 mmol) was added at room temperature, and then the stirring was continued for 20 min. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and treated by usual work-up. Column chromatography with hexane–AcOEt (50:1) afforded **34** (46 mg, 91%). δ_H (400 MHz): 0.88 (3H, s), 0.91 (3H, s), 1.54 (3H, s), 1.59 (3H, s), 1.75 (3H, s), 2.07 (3H, s), 2.26–2.30 (1H, m), 2.62–2.70 (1H, m), 3.24 (1H, br s), 4.06 (1H, dd, J=11.0, 7.8 Hz), 4.18 (1H, dd, J=11.0, 2.0 Hz), 4.94 (1H, br d, J=11.7 Hz), 5.28 (1H, br d, J=12.0 Hz) and 5.50 (1H, br s).

3.5.2. 10-Carboxylverticilla-3,7,12-tiene 35. After a solution of **34** (18 mg, 0.05 mmol) in 2 M KOH–MeOH (1 ml) was stirred for 30 min at room temperature, and subsequent usual work-up afforded 10-hydroxymethyl derivative (14 mg, 93%). White powder. δ_H (500 MHz): 0.89 (3H, s), 0.96 (3H, s), 1.55 (3H, s), 1.59 (3H, s), 1.71 (3H, s), 2.63–2.70 (1H, m), 3.19 (1H, bs), 3.60 (1H, dd, J=10.1, 7.6 Hz), 4.93 (1H, bd, J=10.3 Hz), 5.28 (1H, bd, J=11.9 Hz), and 5.47 (1H, bs). δ_C (125 MHz): 134.3 (s), 133.6 (s), 133.0 (s), 131.0 (d), 124.6 (d), 124.3 (d), 67.0 (t), 45.2 (t), 43.7 (d), 41.3 (d), 41.0 (t), 38.1 (d), 36.4 (s), 34.1 (t), 30.7 (t), 27.8 (q), 26.3 (t), 25.5 (q), 25.1 (q), 16.0 (q), and 15.2 (q). HR-MS Found: m/z 302.2614. Calcd for $C_{21}H_{34}O$: M^+, 302.2610. The CH_2Cl_2 solution of Dess–Martin periodinane (77 mg, 0.18 mmol) was added to the vigorously stirred mixture of the hydroxymethyl derivative (46 mg, 0.15 mmol) and pyridine (0.06 ml, 0.74 mol) in CH_2Cl_2 (2 ml) solution at room temperature and the stirring was continued for 1 h. After dilution with ether, aq $Na_2S_2O_3$ and then aq. $NaHCO_3$ solutions were successively added and the reaction mixture was stirred for an additional 10 min. The mixture was worked up as usual and the resulting residue was purified by SiO_2 column chromatography with hexane–AcOEt (15:1) to afford formyl derivative (39 mg, 86%). Mp 142–144°C (hexane). δ_H (270 MHz, $CDCl_3$): 0.88 (3H, s), 0.98 (3H, s), 1.52 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 3.47 (1H, bs), 4.93 (lH, bd, J=11.8 Hz), 5.29 (1H, bd, J=12.0 Hz), 5.57 (1H, bs), and 9.95 (1H, s). HR-MS Found: m/z 300.2447. Calcd for $C_{21}H_{32}O$: M^+, 300.2453. To a stirred solution of the formyl derivative (89 mg, 0.30 mmol) and 2-methyl-2-butene (0.4 ml) in *tert*-BuOH (2 ml) was dropped a mixture of NaH_2PO_4 (39 mg, 0.33 mmol) and $NaClO_2$ (53 mg, 0.59 mmol) in aqueous solution (0.4 ml) at 0°C and the stirring was continued for 1 h at the same temperature. After being stirred for 17 h at room temperature, the reaction mixture was acidified by adding 4N aq. HCl, extracted with ether, and the ether solution was worked up as usual to obtain the carboxylic acid **35** (77.0 mg, 83%). Mp 196–200°C (hexane). δ_H (500 MHz, $CDCl_3$): 0.86 (3H, s), 0.91 (3H, s), 1.55 (3H, s), 1.58 (3H, s), 1.84 (3H, s), 3.26 (1H, bs), 5.01 (1H, bd, J=8.6 Hz), 5.32 (1H, bd, J=11.9 Hz), 5.14 (1H, bd, J=10.5 Hz), and 5.48 (1H, bs). δ_C (125 MHz, $CDCl_3$): 182.0 (s), 134.4 (s), 133.1 (s), 132.1 (d), 132.0 (s), 124.5 (d), 122.9 (d), 43.5 (d), 43.1 (t), 41.0 (d), 40.8 (t), 39.0 (d), 36.1 (s), 33.8 (t), 30.4 (t), 27.8 (q), 26.4 (t), 26.1 (q), 25.1 (q), 15.7 (q), and 15.2 (q). Anal. calcd for $C_{21}H_{32}O_2$:C, 79.70; H, 10.19. Found: C, 79.42; H. 10.10. HR-MS Found: m/z 316.2406. Calcd for $C_{21}H_{32}O_2$: M^+, 316.2402.

3.5.3. Iodolactonization of 10-carboxylverticilla-3,7,12-tiene 35. To a stirred mixture of **35** (48 mg, 0.15 mmol) and $NaHCO_3$ (51 mg, 0.61 mmol) in acetone (0.5 ml) and H_2O (5 ml) was added iodine (38.5 mg, 0.152 mmol) at 0°C, and then the stirring was kept at 0°C for 15 h. The reaction mixture was quenched with an aq. $Na_2S_2O_3$ solution and extracted with ether. The organic phase was washed with brine, and dried, and evaporated. The residue was purified by SiO_2 chromatography eluted with hexane–AcOEt (10:1) to isolate **36** (56 mg, 83%). White powder. δ_H (270 MHz, $CDCl_3$): 0.71 (3H, s), 1.01 (3H, s), 1.54 (3H, s), 1.62 (3H, s), 1.64 (3H, s), 3.63 (1H, bs), 4.37 (1H, dd, J=13.4, 7.5 Hz), 5.08 (1H, bd, J=11.3 Hz), 5.26 (1H, bd, J=12.2 Hz). δ_C (68 MHz, $CDCl_3$): 178.1 (s), 134.8 (s), 132.3 (d), 131.9 (s), 126.5 (d), 84.0 (s), 46.4 (d), 46.1 (d), 42.4 (d), 42.1 (t), 41.5 (t), 40.0 (t), 34.6 (s), 32.7 (q), 31.9 (d), 31.6 (t), 26.7 (t), 25.8 (q), 25.5 (q), 16.5 (q), 15.6 (q). HR-MS Found: m/z 442.1365. Calcd for $C_{21}H_{31}IO_2$: M^+, 442.1369.



Scheme 6.

3.5.4. 10-Hydroxymethyl-13-iodoverticilla-3,7-dien-12-ol 37. $LiAlH_4$ (3.4 mg, 0.09 mmol) was added to the iodo-lactone **36** (39.0 mg, 0.09 mmol) in anhydrous THF (3 ml) at room temperature under nitrogen atmosphere, and the mixture was stirred for 17 h, and then quenched with AcOEt (1 ml) and MeOH (1 ml). Usual work-up followed by chromatography with hexane–AcOEt (20:1) and then (2:1) afforded iodo-diol **37** (21 mg, 53%). White powder. δ_H (270 MHz, $CDCl_3$): 0.75 (3H, s), 1.25 (3H, s), 1.52 (3H, s), 1.53 (3H, s), 1.55 (3H, s), 2.54 (1H, s), 2.73 (1H, tdd, J=12.5, 6.3,1.2 Hz), 3.10 (1H, tdd, J=14.0, 5.8, 1.2 Hz), 3.62 (1H, dd, J=11.7, 4.8 Hz), 4.01 (1H, dd, J=12.2, 7.4 Hz), 4.83 (1H, bd, J=10.7 Hz), 5.03 (1H, dd, J=14.0, 4.6 Hz), 5.33 (1H, bd, J=11.3 Hz). δ_C (68 MHz, $CDCl_3$): 134.4 (s), 133.0 (s), 130.1 (d), 126.2 (d), 75.8 (s), 66.1 (t), 57.6 (d), 49.4 (d), 43.9 (t), 43.7 (d), 42.5 (t), 41.0 (t), 38.1 (d), 37.6 (s), 33.9 (q), 33.5 (t), 28.2 (q), 28.0 (q), 26.3 (t), 16.5 (q), and 15.3 (q). HR-MS Found: m/z 446.1660. Calcd for $C_{21}H_{35}IO_2$: M^+, 446.1682.

3.5.5. Reaction of iodo-diol 37 with DBU. After a mixture of iodo-diol **37** (39 mg, 0.088 mmol) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (20 μl, 0.045 mmol) in toluene (3 ml) was kept at 110°C for 10 h, aq. NH_4Cl solution was added and then the mixture was extracted with ether. Usual work-up and SiO_2 column chromatography with hexane–AcOEt (10:1) gave the ring contracted product **39** (20 mg, 70%). δ_H (270 MHz, $CDCl_3$) 0.74 (3H, s), 1.03 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 1.59 (3H, s), 3.22 (1H, d, J=11.3 Hz), 4.10 (1H, dd, J=11.3, 3.2 Hz), 4.89 (1H, bd, J=11.3 Hz), and 5.12 (1H, bd, J=11.9 Hz). After a mixture of **39** (10 mg, 0.003 mmol), DMAP (trace), pyridine (10 μl, 0.126 mmol), and Ac_2O (14 μl, 0.157 mmol) in CH_2Cl_2 (3 ml) was stirred at room temperature overnight, MeOH was added. Usual work-up and then SiO_2 column chromatography with hexane–AcOEt (10:1) afforded acetoxy methyl ketone **40** (7 mg, 80%). δ_H (270 MHz, $CDCl_3$) 0.84 (3H, s), 1.16 (3H, s), 1.48 (3H, s), 1.58 (3H, s), 2.03 (3H, s), 2.29 (3H, s), 2.65 (1H, d, J=11.2 Hz), 3.15 (1H, q, J=9.3 Hz), 3.56 (1H, t, J=9.8 Hz), 4.30 (1H, dd, J=11.2, 2.4 Hz), 5.01 (1H, bd, J=11.4 Hz), and 5.14 (1H, bd, J=11.0 Hz). HR-MS Found: m/z 360.2646. Calcd for $C_{23}H_{36}O_3$: M^+, 360.2664.

3.6. Procedures described in Scheme 6

3.6.1. Reaction of 12-methoxymethyloxyverticilla-3,7-diene 28 with TMSI. A CH_2Cl_2 solution (1 ml) of TMSCl (1.6 μl, 0.013 mmol) was dropped to a stirred mixture of crude MOM ether **28** (3.9 mg, 0.012 mmol) and NaI (1.9 mg, 0.013 mmol) in CH_2Cl_2 (1 ml) and the mixture was kept at room temperature for 30 min. The usual work up and subsequent silica gel column chromatography gave hydrocarbon, verticilla-3,7,12-triene **41** (1.4 mg, 44%). Colorless oil. δ_H (90 MHz, $CDCl_3$): 0.75 (3H, s), 0.81 (3H, s), 1.27 (3H, s), 1.50 (3H, bs), 1.60 (3H, bs), 4.81 (1H, bd, J=10.2 Hz), and 5.18–5.50 (2H, m). HR-MS Found: m/z 272.2503. Calcd for $C_{20}H_{32}$: M^+, 272.2503.

3.6.2. 12-Epiverticillol 2. $BF_3{\cdot}OEt_2$ (0.003 ml, 0.02 mmol) was added to a stirred solution of MOM ether **28** (2 mg, 0.006 mmol) in Et_2O (0.5 ml) at 0°C, and the mixture was kept at 0°C for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution and treated by usual work-up. Column chromatography with hexane–AcOEt (20:1) and then (6:1) afforded 12-epiverticillol **2** (0.4 mg, 23%), hydrocarbon **41** (0.7 mg, 40%), and recovered MOM ether **28** (0.6 mg, 30%). **2** δ_H (500 MHz): 0.68 (3H, s), 0.98 (s, Me(16)), 1.21 (s, Me(18)), 1.51 (s, Me(19)), 1.54 (s, Me(20)), 2.69–2.73 (1H, m), 4.80 (1H, d, J=11.6 Hz), and 5.49 (1H, d, J=11.6 Hz).

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