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ent-Verticillane-type diterpenoids from the Japanese liverwort *Jackiella javanica*

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Abstract

Three *ent*-verticillane diterpenoids and two *ent*-sesquiterpenoids were isolated from the Japanese liverwort *Jackiella javanica* Schiffn. together with five known *ent*-verticillane and three *ent*-kaurane diterpenoids, and three sesquiterpenoids. Five *ent*-verticillane epoxides were synthetically prepared from *ent*-verticillols action to clarify the absolute configuration of natural *ent*-9,10-epoxyverticillol. Their structures were established by extensive NMR spectroscopic and X-ray crystallographic analyses.
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Keywords: *Jackiella javanica*; Liverwort; *ent*-Verticillane; *ent*-Kaurene; Diterpenoid; Sesquiterpenoid

1. Introduction

As part of a search for novel compounds and biologically active substances in the Hepaticae, we are currently studying the chemical constituents of liverworts. Liverworts are rich sources of a wide range of terpenoids and aromatic compounds, some with interesting biological activities (Asakawa, 1982, 1995, 1999). A number of unusual compounds found in the liverworts are valuable for chemosystematic studies (Asakawa, 2004). Additionally, it is known that differences in the main components are occasionally observed in the same species in different geographical locations (Asakawa, 1982, 1995; Nagashima and Asakawa, 1998).

Jackiella javanica Schiffn. grows on wet rocks and is distributed in Southeast Asia, Taiwan and Japan. The principal constituents of the species are *ent*-verticillane diterpenoids (Harrison et al., 1984; Nagashima et al., 1990, 1997), the putative biosynthetic precursors of taxanes (Koepp et al., 1995). We now report the further fractionation of the ether extract of the Japanese *J. javanica* which resulted in the isolation and identification of three new *ent*-verticillane diterpenoids **1**–**3** in addition to five previously known *ent*-verticillane **4**–**8**, three *ent*-kaurane diterpenoids **9**–**11** and five sesquiterpenoids **12**–**16**. In this communication, we report the structure characterization of three new diterpenoids.

2. Results and discussion

The ether extract of *J. javanica* was fractionated by chromatography on silica gel and preparative HPLC to afford three new *ent*-verticillane diterpenoids (**1**–**3**), along with five known *ent*-verticillanes (**4**–**8**), three *ent*-kaurene diterpenes (**9**–**11**), and five sesquiterpenes (**12**–**16**). The known *ent*-verticillanes and *ent*-kauranes were determined as *ent*-verticillol (**4**), *ent*-5-epi-verticillol (**5**), *ent*-verticillanediol (**6**), *ent*-5-epi-verticillanediol (**7**) and *ent*-isoverticillenol (**8**) (Harrison et al., 1984; Nagashima et al., 1990), as well as *ent*-kauren-15-one (**9**) (Matsuo

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et al., 1977), *ent*-11α-hydroxykauren-15-one (**10**) (Connolly and Thornton, 1973; Benés et al., 1977) and *ent*-16-kauren-15α-ol (**11**) (Matsuo et al., 1977) by comparison of spectroscopic data with those of authentic samples isolated in a previous study of *J. javanica*. Moreover, the known sesquiterpenoids, *ent*-spathulenol (**14**) (Asakawa et al., 1980), *ent*-globulol (**15**) (Toyota et al., 1999) and (+)-α-cadinol (**16**) (Kalsi et al., 1979) were identified by the comparison of their spectroscopic data with reference data.

The IR spectrum of **1** confirmed the presence of a hydroxyl group (3447 cm^{-1}) and its EI-MS spectrum gave a molecular ion peak at *m/z* 288 $[M]^+$. The high-resolution EI-MS (HR-EI-MS) spectrum showed the molecular formula as $C_{20}H_{32}O$, indicating that **1** possessed five degrees of unsaturation. As the ^1H and ^{13}C NMR spectra (Tables 1 and 2) of **1** were similar to those of compounds **4**–**8**, the structure of **1** was considered likely to be a verticillane diterpenoid. The ^1H NMR spectrum showed two tertiary methyls (δ 0.79, 0.87), three olefinic methyls (δ 1.51, 1.60, 1.77) and three olefinic protons (δ 4.82 *d*, 5.30 *d*, 5.35 br *s*). DEPT spectra of **1** confirmed the presence of three trisubstituted olefinic carbons (δ 120.4, 123.1, 129.7 each CH, 132.9, 133.7, 136.3 each C) and a quaternary carbon bearing a hydroxy group (δ 75.7), as well as five methyls, six methylenes, one methine and one quaternary carbon.

Analysis of ^1H–^1H COSY and HMQC spectra of **1** showed the presence of four partial segments: (i) –C=CH–CH_2–; (ii) –CH–CH_2–CH_2–; (iii) –C=CH–CH_2–; (iv) –C=CH–CH_2–. The connectivity between these fragments was established from the HMBC spectrum. Thus, the structure was confirmed to be a verticillane like compound with a hydroxyl group at C-2, and three double bonds at C4–C5, C9–C10 and C13–C14. Moreover, the absolute stereochemistry was assumed to be the same as *ent*-verticillane diterpenoid by the co-occurrence with the known *ent*-verticillanes **4**–**8**. The NOESY spectrum of **1** showed NOE correlations between: (i) H-4 and H-18, H-3; (ii) H-10 and H-6, H-8α, H-11α, H-12α, and H-18; (iii) H-14 and H-6, H-12α; (iv) H-6 and H-7α, H-10, H-14, and H-16; (v) H-16 and H-6, H-7β, H-15β, H-17, H-19, and H-20; (vi) H-17 and H-16, H-7α, H-7β, and H-3; (vii) H-11β and H-19, H-20. However, the stereochemistry of the tertiary hydroxy group at C-2 remained to be clarified. Therefore, an X-ray crystallographic analysis of **1** was carried out. An ORTEP diagram is shown in Fig. 1 and reveals the beta (*ent*-alpha) configuration of the hydroxy group. Thus, the structure of **1** is *ent*-verticilla-4,9,13-trien-2α-ol.

The ^1H NMR spectrum (Table 1) of compound **2** displayed an olefinic proton (δ 5.89 br *d*) and five tertiary methyls. The ^{13}C NMR spectrum (Table 2) showed the presence of trisubstituted olefinic carbons (δ 128.0, 133.1), two quaternary carbons (δ 62.1, 66.3) bearing the oxygen atoms as well as five methyls, seven methylenes, three methines and a quaternary carbon. The HR-EI-MS spectrum of **2** showed the molecular formula as $C_{20}H_{34}O_2$, indicating four degrees of unsaturation. Furthermore, the IR spectrum exhibited the presence of a

Table 1
^1H NMR spectroscopic assignments of **1**–**3**(600 MHz, $CDCl_3$)

H	1	2	3
2		1.46 br *s*	1.51 *m*
3	2.28 2H, br *s*	1.59–1.65 *m*	1.67 *dd* (13.7, 6.3), α
		1.91–1.97 *m*	2.08 *ddddd* (13.7, 13.7, 13.7, 6.3, 1.6), β
4	5.35 br *s*	1.66–1.73 *m*	2.35 *ddd* (13.7, 13.7, 6.3), α
		1.91–1.97 *m*	2.30 *ddd* (13.7, 6.3, 1.6), β
6	3.17 *apparent* br *d*	2.23 *d* (8.5)	2.69 *d* (10.4)
7	1.45 *ddd* (13.7, 13.7, 4.9)[a], α	1.50–1.58 2H, *m*	1.46 *m*, α
	1.34 *m*, β		1.33 *ddd* (13.2, 13.2, 1.6), α
8	2.22 *ddd* (12.9, 12.9, 4.9), α	1.66–1.73 *m*	1.85 *ddd* (13.2, 13.2, 2.7), α
	2.12 *m*, β	1.99 *dt* (13.7, 3.8)	1.96 *m*, β
10	4.82 *d* (11.8)	2.93 *d* (9.3)	4.70 br *d* (11.8)
11	2.02 *m*, α	1.59–1.65 *m*	2.25 br *d* (13.2), α
	2.47 *apparent dd* (12.9, 2.7), β	1.91–1.97 *m*	2.59 *ddd* (13.2, 13.2, 11.8), β
12	1.94 *ddd* (12.9, 12.9, 3.0), α	2.31 *ddd* (13.2, 13.2, 2.7), α	4.17 *dd* (11.0, 4.4)
	2.15 *m*, β	2.24 *m*, β	
14	5.30 *d* (12.1)	5.89 br *d* (12.9)	5.83 br *d* (12.6)
15	2.00 br *d* (14.8), α	2.72 *dddd* (14.6, 12.9, 6.0, 1.4), α	1.95 *m*, α
	2.68 *apparent dd* (14.8, 12.1), β	1.89 br *d* (14.6), β	2.75 *dddd* (14.3, 12.6, 4.1, 1.4), β
16	0.87 *s*	0.96 *s*	0.87 *s*
17	0.79 *s*	0.80 *s*	0.74 *s*
18	1.77 *s*	1.27 *s*	4.53 *q* (1.6)
			4.82 *q* (1.6)
19	1.51 *s*	1.25 *s*	1.58 *t* (1.4)
20	1.60 *s*	1.61 *s*	1.63 *t* (1.6)

[a] *J* values (Hz) in parenthesis.

Table 2
^{13}C NMR spectroscopic assignments of **1**–**3**, **12**, **13** and **17**–**23** (100 MHz, $CDCl_3$)

C	1	2	3	12	13	17	19	20	21	22	23
1	40.7	37.4	37.7	30.6	79.1	37.7	37.1	36.8	36.1	36.9	36.7
2	75.7	43.9	45.0	31.8	32.0	45.0	44.2	42.9	43.3	42.5	42.7
3	40.4	28.1	29.9	29.4	35.1	29.8	26.6	28.2	26.3	27.5	26.2
4	120.4	41.4	36.1	34.8	146.3	36.0	39.2	41.1	38.7	41.4	39.0
5	136.3	75.5	149.0	31.9	55.9	148.9	73.4	75.4	73.2	75.1	72.9
6	40.5	45.2	42.5	16.9	67.0	42.6	43.6	46.1	43.5	46.6	45.5
7	21.6	21.1	20.0	45.2	49.4	20.0	20.4	21.7	21.3	21.3	20.5
8	39.2	39.9	37.4	20.4	18.2	37.5	40.5	40.4	39.8	39.1	40.0
9	132.9	62.1	135.6	33.6	36.3	136.5	62.0	133.9	133.6	61.7	61.5
10	129.7	66.3	123.5	31.3	41.7	122.5	66.9	129.6	129.8	65.5	66.4
11	26.7	26.3	34.7	74.1	26.0	31.9	26.1	24.4	24.4	24.0	23.8
12	40.4	38.7	80.4	27.8[a]	21.1	81.4	38.8	40.5	40.7	37.9	38.1
13	133.7	133.1	134.8	27.4[a]	16.2	130.9	133.4	63.5	63.4	63.2	63.0
14	123.1	128.0	129.5	20.6	11.6	131.6	127.8	64.3	64.3	64.7	64.4
15	42.7	33.6	32.9	18.7	107.8	32.8	33.9	34.9	34.9	34.3	34.6
16	21.1	29.4	27.6			27.6	29.3	28.9	28.7	30.6	30.4
17	18.3	24.8[a]	24.3			24.2	25.6	25.6	26.0	24.4	25.3
18	23.0	24.9[a]	105.6			105.7	33.0	24.5	32.1	25.4	32.8
19	15.8	16.6	15.8			15.9	16.4	16.4	16.7	16.9	16.8
20	15.3	15.2	9.6			10.4	15.3	15.8	15.8	15.8	15.8
OCO*CH$_3$*						21.4					
O*C*OCH$_3$						170.2					

[a] May be interchanged in the vertical column.

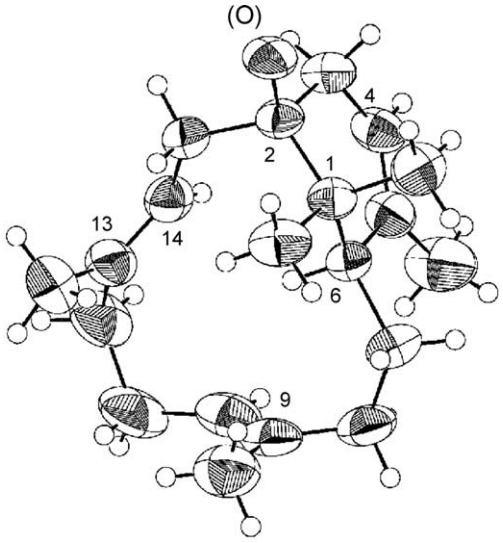


Fig. 1. ORTEP drawing of **1**. Anisotropic ellipsoids are represented by a 50% probability level.

hydroxyl group. The above spectroscopic data suggested the presence of a tertiary hydroxy group and an epoxide in the molecule. Detailed analysis of the spectroscopic data suggested that the structure is 9,10-epoxyverticillol, which has already been reported as a reaction product from verticillol (**18**) (Begley et al., 1990). The ^{13}C NMR data of **2** are identical with reference data (Begley et al., 1990). As the assignment of ^{13}C NMR signals has not been mentioned in the literature, the complete assignment of **2** was achieved by the analysis of ^{1}H–^{1}H COSY, HMQC and HMBC spectra.

The structure of **2** was confirmed by oxidation of *ent*-verticillols. Oxidation of a mixture of *ent*-verticillol (**4**) and *ent*-5-epi-verticillol (**5**) (Harrison et al., 1984; Nagashima et al., 1990) with *m*-chloroperbenzoic acid (MCPBA) which gave six epoxy derivatives **2** and **19**–**23**. The spectroscopic data of derivative **2** were completely identical with those of the natural product. Thus **2** was established to be (9*S*, 10*S*)-*ent*-9,10-epoxyverticillol.

The other derivatives were also identified as (9*S*, 10*S*)-*ent*-9,10-epoxy-5-epiverticillol (**19**), (13*S*, 14*S*)-*ent*-13,14-epoxyverticillol (**20**), (13*S*, 14*S*)-*ent*-13, 14-epoxy-5-*epi*-verticillol (**21**), (9*S*, 10*S*:13*S*,14*S*)-*ent*-9,10:13,14-diepoxyverticillol (**22**), and (9*S*, 10*S*:13*S*, 14*S*)-*ent*-9,10:13,14-diepoxy-5-epi-verticillol (**23**) by analysis of ^{1}H–^{1}H COSY, HMQC, HMBC and NOESY spectra. The enantiomers of **20** and **22** have also been reported as reaction intermediates (Begley et al., 1990), with their ^{1}H and ^{13}C NMR spectra were identical with those of **20** and **22**. The complete ^{13}C NMR spectroscopic assignments for compounds **2** and **19**–**23** are reported for the first time by the present experiments. Furthermore, the X-ray crystallographic analyses (shown in Figs. 2–4) reveal the relative stereochemistry for compounds **2**, **21** and **22**.

The IR spectrum of **3** showed the presence of a hydroxyl group (3269 cm^{-1}) and its EI-MS exhibited the molecular ion peak at *m*/*z* 288 [M]$^{+}$. The ^{1}H NMR spectrum (Table 1) confirmed the presence of an *exo*-methylene (δ 4.53, 4.82 each *q*), two olefinic protons (δ 4.70, 5.83 each br *d*), a methine proton (δ 4.17 *dd*) bearing a hydroxyl group, and four tertiary methyls. The ^{13}C

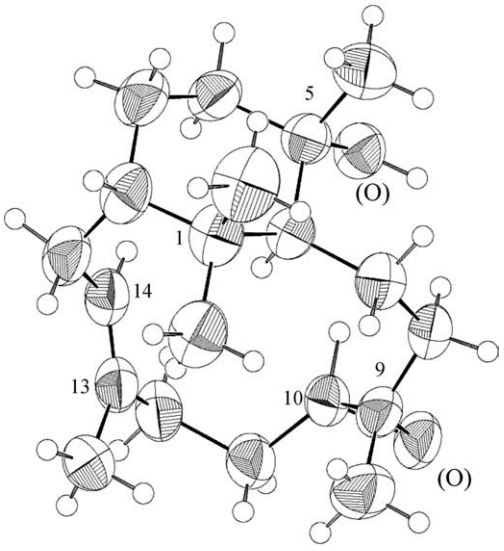


Fig. 2. ORTEP drawing of **2**. Anisotropic ellipsoids are represented by a 50% probability level.

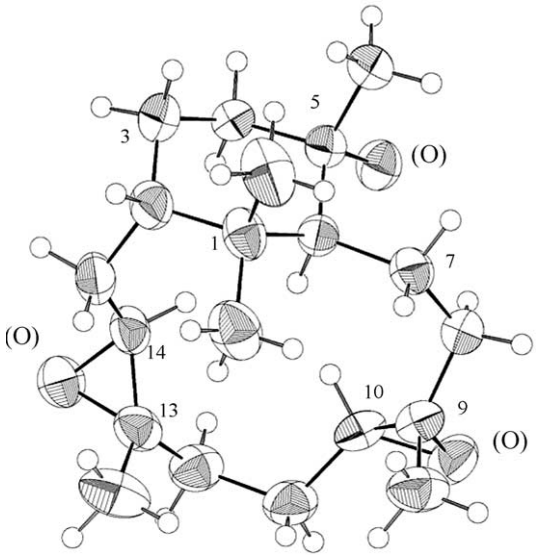


Fig. 4. ORTEP drawing of **22**. Anisotropic ellipsoids are represented by a 50% probability level.

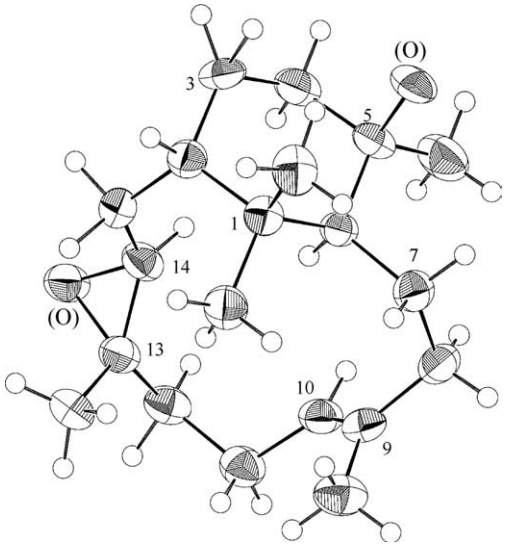


Fig. 3. ORTEP drawing of **21**. Anisotropic ellipsoids are represented by a 50% probability level.

NMR (Table 2) and DEPT spectra of **3** showed four trisubstituted olefinic carbons (δ 123.5, 129.5, 134.8, 135.6), *exo*-methylene carbons (δ 105.6, 149.0), and a methine (δ 80.4) bearing a hydroxyl group as well as four methyls, six methylenes, two methines, and a quaternary carbon.

The presence of a secondary hydroxyl group was revealed by formation of a monoacetate **17**, the ^{1}H and ^{13}C NMR spectra of which showed the presence of an acetyl group (δ_H 2.04 *s*; δ_C 21.4 CH_3, 170.2 C) (Table 2). The ^{1}H NMR spectrum of **3** was similar to those of **4**–**8**, suggesting an *ent*-verticillane diterpenoid. The analyses of ^{1}H–^{1}H COSY and HMQC spectra of **3** confirmed three partial segments: (i) –C=CH–CH_2–CH–CH_2–CH_2–; (ii) –CH–CH_2–CH_2–; (iii) –C=CH–CH_2–CH(O)– (Fig. 5). Again HMBC correlations, as shown in Fig. 5, enabled the structure to be assembled as in **3**, verticilla-5(18), 9, 13-trien-12β-ol. The relative stereochemistry was clarified by NOESY spectra of the original compound and its monoacetate **17** (Fig. 6).

Although the absolute configuration of **3** has not been verified by independent evidence, its was presumed to be an *ent*-verticillane diterpenoid to take into account the coexistence of *ent*-verticillanes **4**–**8**. Thus,

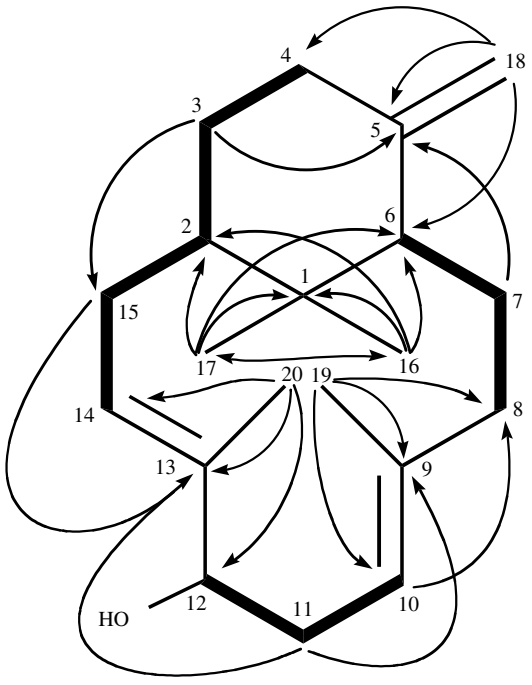


Fig. 5. ^{1}H–^{1}H COSY (Bold lines) and ^{1}H–^{13}C correlations (arrows) of **3**.

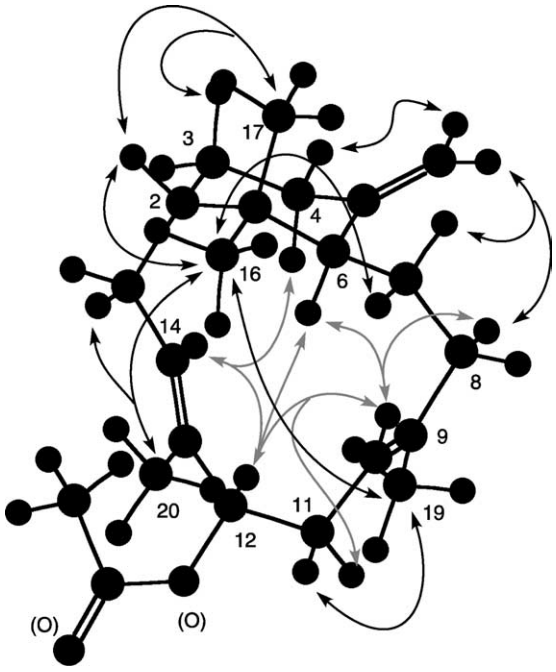


Fig. 6. NOE correlaions of **17** by NOESY spectrum.

structure **3** was established to be *ent*-verticilla-4(18),9,13-trien-12α-ol.

The ^{1}H and ^{13}C NMR data of compound **12** were identical with those of (+)-cubeban-11-ol (Weyerstahl et al., 1998) except for the specific optical rotation [(+)-**12** $[\alpha]_D^{20} + 31.8^\circ$ *c* 0.6; *ent*-**12** $[\alpha]_D^{20} - 60.1^\circ$ *c* 0.29, each $CHCl_3$]. As the sign of the specific optical rotation was opposite, the structure of **12** was established to be *ent*-cubeban-11-ol.

The ^{1}H and ^{13}C NMR spectroscopic data of **13** was incomplete accord with those of (+)-4(15)-eudesmene-1β,6α-diol (Hu et al., 1996; Kitajima et al., 2002) except for the specific optical rotation [(+)-**13** $[\alpha]_D^{23} + 32^\circ$ *c* 0.6; *ent*-**13** $[\alpha]_D^{12} - 31.5^\circ$ *c* 0.13 each MeOH]. Thus **13** was established to be *ent*-4(15)-eudesmene-1β,6α-diol.

The present *J. javanica* produces *ent*-verticillanes as the main components. Thus it is reconfirmed that the presence of *ent*-verticillane-type diterpenoids is a significant chemical marker of *J. javanica*. This work reports the first occurrence of *ent*-sesquiterpenoids **12** and **13** as natural products from liverworts.

3. Experimental

3.1. General

Melting points: uncorrected. ^{1}H and ^{13}C NMR: 400 and 600 MHz (^{1}H NMR), and 100 and 150 MHz (^{13}C NMR). Chemical shift values are expressed in δ (ppm) downfield from tetramethylsilane as an internal standard (^{1}H NMR), and δ 77.03 (ppm) from $CHCl_3$ as a standard (^{13}C NMR). TLC: visualized under UV (254 nm) light and by spraying with 10% H_2SO_4 or Godin reagent (Godin, 1954), followed by heating. MeOH–CH_2Cl_2 (1:1) was used for Sephadex LH-20. $CHCl_3$ for the optical rotations.

3.2. Plant material

J. javanica Schiffn. (931136) was collected in Kagoshima pref., Japan, 1993, and identified by Dr. M. Mizutani (Hattori Botanical laboratory, Japan), and a voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Tokushima Bunri University.

3.3. Extraction and isolation

J. javanica (1.03 kg) was extracted with Et_2O (10 L) for 3 weeks. The crude extract (23.6 g) was divided into 12 fractions by column chromatography (C.C.) on silica gel using a *n*-hexane–EtOAc gradient solvent system. Fr. 4 was divided into eight subfractions after Sephadex LH-20 (MeOH–CH_2Cl_2 1:1) and silica gel C.C. (*n*-hex.–Et_2O 17:3). From Fr. 4–2, *ent*-kauren-15-one (**9**) (20.2 mg) was purified by C.C. on silica gel (*n*-hex.–EtOAc 7:3) and finally preparative HPLC (Nucleosil 50-5, *n*-hex.–EtOAc 1:1). Fr. 4–6 was subjected to further silica gel, Lobar column and preparative HPLC (Nucleosil 50-5, *n*-hex.–Et_2O 17:1) to yield *ent*-5-epi-verticillol (**5**) (552.6 mg) and *ent*-16-kauren-15α-ol (**11**) (12.5 mg). Fr. 4–7 was applied to silica gel and reverse phase silica gel chromatography (Cosmosil 75C_{18}-OPN, MeOH and/or CH_3CN) to give *ent*-verticillol (**4**) (87.5 mg), *ent*-verticillanediol (**6**) (171.3 mg), *ent*-isoverticillenol (**8**) (367.8 mg), *ent*-cubeban-11-ol (**12**) (10.8 mg), *ent*-spathulenol (**14**) (452.1 mg). Fr. 7 was applied to a Sephadex LH-20 and silica gel C. C. to give twelve subfractions. Fr. 7–8 was repeatedly subjected to chromatography on silica gel and preparative HPLC (NUCLEOSIL 50-5, *n*-hex.–Et_2O 7:3) to yield *ent*-verticilla-4(18),9,13-trien-12α-ol (**3**) (11.7 mg), *ent*-globulol (**15**) (17.5 mg) and (+)-α-cadinol (**16**) (17.2 mg). Fr. 10 was purified by Sephadex LH-20, silica gel and preparative HPLC (NUCLEOSIL 50-5, *n*-hex.–EtOAc 9:1 and/or CHEMCOSORB 5-ODS-H, CH_3CN) to give *ent*-verticilla-4,9,13-trien-2α-ol (**1**) (32.2 mg), *ent*-5-epi-verticillanediol (**7**) (1.6 g), *ent*-11α-hydroxy-16-kauren-15-one (**10**) (16.4 mg) and *ent*-4(15)-eudesmene-1β,6α-diol (**13**) (1.6 mg). (9*S*, 10*S*)-*ent*-9,10-epoxyverticillol (**2**) (3.3 mg) was isolated from Fr. 11 by C.C. on silica gel and Sephadex LH-20.

3.4. Ent-verticilla-4,9,13-trien-2α-ol (*1*)

Colorless crystals (from *n*-hexane); m.p. 93–95 °C; $[\alpha]_D^{20} - 208.9^\circ$ (*c* 2.83); HR-EIMS: found 288.2466, $C_{20}H_{32}O$ requires 288.2453; FTIR ν_{max} cm^{-1}: 3447

(OH); For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2; EIMS *m/z* (rel. int.): 288[M]$^+$(38), 273(5), 245(3), 219(4), 191(6), 177(9), 161(11), 150(90), 137(77), 123(63), 109(100), 95(64), 81(99), 67(43), 55(36), 43(41). Crystal data: triclinic, $P\bar{1}$, a = 13.087 (4) Å, b = 13.257 (5) Å, c = 13.507 (7) Å, α = 63.14°, β = 66.257 (2)°, γ = 67.477 (2)°, V = 1854.62 (13) Å^3, Z = 4, Mo Kα radiation, λ = 0.71073, DIP image plate, refinement on F^2, fullmatrix least-squares refinement, R(gt) = 0.0598, wR(gt) = 0.157, S(ref) = 1.116, 10942 reflections, 757 parameters, only coordinates of H atoms refined, Cell refinement, Scalepack (HKL); data reduction, maXus; program used to refine structure, *SHELXL*-97.

3.5. (9*S*,10*S*)-Ent-9,10-epoxyverticillol (**2**)

Colorless crystals (from *n*-hexane); m.p. 157–158 °C; $[\alpha]_D^{18}$ − 114.2° (*c* 1.81); HR-EIMS: found 306.2543, $C_{20}H_{34}O_2$ requires 306.2559; FTIR ν_{max} cm^{-1}: 3420 (OH); For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2; EIMS *m/z* (rel. int.): 306[M]$^+$(6), 288(15), 273(14), 233(10), 215(12), 189(19), 177(97), 161(26), 149(26), 137(72), 135(62), 121(82), 107(69), 95(84), 81(80), 69(75), 55(58), 43(100). Crystal data: monoclinic, $P2_1$, a = 8.4830 (5) Å, b = 9.5790 (5) Å, c = 11.4310 (10) Å, α = 90.00°, β = 94.816 (2)°, γ = 90.00°, V = 925.59 (11) Å^3, Z = 2, Mo Kα radiation, λ = 0.71073, DIP image plate, refinement on F^2, fullmatrix least-squares refinement, R(gt) = 0.0632, wR(gt) = 0.1579, S(ref) = 1.111, 1814 reflections, 199 parameters, 1 restraints, only coordinates of H atoms refined, Cell refinement, Scalepack (HKL); data reduction, maXus; program used to refine structure, *SHELXL*-97.

3.6. Ent-verticilla-4(18),9,13-trien-12α-ol (**3**)

Colorless crystals (from *n*-hexane); m.p. 116–117 ° C; $[\alpha]_D^{17}$ − 150.8° (*c* 0.91); HR-EIMS: found 288.2452, $C_{20}H_{32}O$ requires 288.2453; FTIR ν_{max} cm^{-1}: 3269 (OH); For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2; EIMS *m/z* (rel. int.): 288[M]$^+$(28), 273(15), 255(27), 245(10), 220(17), 205(35), 189(31), 175(19), 161(26), 149(24), 135(37), 121(58), 107(56), 93(79), 84(100), 81(61), 69(47), 55(47), 41(50).

3.7. Ent-cubeban-11-ol (**12**)

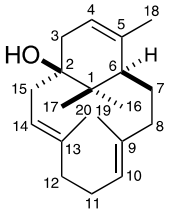
Amorphus; $[\alpha]_D^{20}$ − 60.1° (*c* 0.29); HR-EIMS: found 222.1982, $C_{15}H_{26}O$ requires 222.1984; FTIR ν_{max} cm^{-1}: 3334 (OH); ^{1}H NMR (600 MHz): δ 1.72–1.75 (2H, *m*, H-2), 0.72 (1H, *m*, H-3α), 1.54 (1H, *m*, H-3β), 2.27 (1H, *m*, H-4), 1.01 (1H, *m*, H-5), 0.86 (1H, *t*, *J* = 4.1 Hz, H-6), 1.80 (1H, *m*, H-7), 0.93 (1H, *m*, H-8), 0.90 (1H, *m*, H-9), 1.84 (1H, *m*, H-10), 1.23 (3H, *s*, H-12 or H-13), 1.24 (3H, *s*, H-13 or H-12), 1.03 (1H, *d*, *J* = 6.9 Hz, H-14), 1.00 (3H, *d*, *J* = 6.6 Hz, H-15); For ^{13}C NMR spectrum, see Table 2; EIMS *m/z* (rel. int.): 222[M]$^+$(8), 204(5), 163(100), 149(21), 135(8), 121(15), 107(82), 93(24), 81(27), 59(38), 43(24).

3.8. Ent-4(15)-eudesmene-1β,6α-diol (**13**)

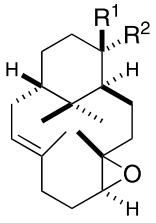
Amorphus; $[\alpha]_D^{26}$ − 36.8° (*c* 0.16, $CHCl_3$), $[\alpha]_D^{12}$ − 31.5° (*c* 0.13, MeOH); HR-EIMS: found 238.1930, $C_{15}H_{26}O_2$ requires 238.1933; FTIR ν_{max} cm^{-1}: 3402 (OH); ^{1}H NMR (400 MHz): δ 3.43 (1H, *dt*, *J* = 11.4, 4.8 Hz, H-1), 1.55 (1H, *m*, H-2α), 1.87 (1H, *m*, H-2β), 2.33 (1H, *ddd*, *J* = 13.2, 5.1, 1.8 Hz, H-3α), 2.07 (1H, *ddd*, *J* = 13.2, 13.2, 5.5 Hz, H-3β), 1.75 (1H, *d*, *J* = 9.9 Hz, H-5), 3.72 (1H, *dd*, *J* = 9.5, 8.1 Hz, H-6), 1.30 (1H, *m*, H-7), 1.26 (1H, *m*, H-8α), 1.53 (1H, *m*, H-8β), 1.90 (1H, *m*, H-9α), 1.22 (1H, *m*, H-9β), 2.25 (1H, *ddddd*, *J* = 7.0, 7.0, 7.0, 7.0, 2.6 Hz, H-11), 0.95 (3H, *d*, *J* = 7.0 Hz, H-12), 0.87 (3H, *d*, *J* = 7.0 Hz, H-13), 0.71 (3H, *s*, H-14), 4.75 (1H, *s*, H-15), 5.02 (1H, *s*, H-15); For ^{13}C NMR spectrum, see Table 2; EIMS *m/z* (rel. int.): 238[M]$^+$(8), 220(100), 202(32), 189(29), 177(60), 159(63), 153(41), 147(36), 139(25), 134(41), 123(72), 121(83), 117(13), 107(99), 93(64), 81(72), 77(27), 69(37), 55(48), 43(64).

3.9. Acetylation of **3**

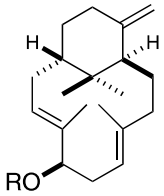
A solution of compound **3** (9 mg) in pyridine (1 ml) and Ac_2O (1 ml) was kept at room temperature overnight. H_2O was poured into the reaction mixture under cooling and extracted with Et_2O at three times. The residue after dried over with anhydrous $MgSO_4$ was removed the solvents to yield *ent*-12α-acetoxyverticilla-4(18),9,13-triene (**17**) (7.7 mg). Amorphous; $[\alpha]_D^{17}$ − 153.8° (*c* 0.26); HR-EIMS: found 330.2567, $C_{22}H_{34}O_2$ requires 330.2559; FTIR ν_{max} cm^{-1}: 1740, 1242, 1016; ^{1}H NMR (600 MHz): δ 1.51 (1H, *m*, H-2), 1.67 (1H, *dd*, *J* = 14.0, 6.3 Hz, H-3α), 2.06 (1H, *m*, H-3β), 2.36 (1H, *ddd*, *J* = 13.7, 13.7, 5.8 Hz, H-4α), 2.29 (1H, *m*, H-4β), 2.64 (1H, *d*, *J* = 12.9 Hz, H-6), 1.47 (1H, *m*, H-7α), 1.33 (1H, br *t*, *J* = 14.0 Hz, H-7β), 1.87 (1H , *ddd*, *J* = 13.2, 13.2, 2.7 Hz, H-8α), 1.95–1.99 (2H, *apparent* br *d*, H-8β, H-15α), 4.72 (1H, br *d*, *J* = 9.6 Hz, H-10), 2.26 (1H, *m*, H-11α), 2.63 (1H, *ddd*, *J* = 13.2, 13.2, 11.8 Hz, H-11β), 5.21 (1H, *dd*, *J* = 11.5, 4.4 Hz, H-12), 5.95 (1H, br *d*, *J* = 12.9 Hz, H-14), 2.72 (1H, *dddd*, *J* = 14.6, 12.6, 4.1, 1.6 Hz, H-15β), 0.86 (3H, *s*, H-16), 0.74 (3H, *s*, H-17), 4.82 (1H, *apparent q*, *J* = 1.9 Hz, H-18), 4.52 (1H, *apparent d*, *J* = 1.9 Hz, H-18), 1.59 (3H, *t*, *J* = 1.4 Hz, H-19), 1.61 (3H, *t*, *J* = 1.6 Hz, H-20), 2.04 (3H, *s*, –OCO*CH*$_3$). For ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 330[M]$^+$(14), 288(22), 270(40), 255(38), 220(40), 202(15), 189(20), 175(18), 161(22), 147(18), 135(28), 126(32), 121(41), 107(44), 93(59), 84(74), 77(25), 69(33), 55(42), 43(100).



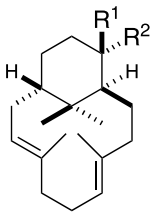
1



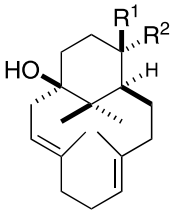
2 R^1=CH_3, R^2=OH
19 R^1=OH, R^2=CH_3



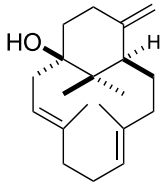
3 R=H
17 R=Ac



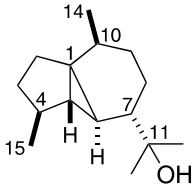
4 R^1=CH_3, R^2=OH
5 R^1=OH, R^2=CH_3



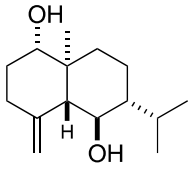
6 R^1=CH_3, R^2=OH
7 R^1=OH, R^2=CH_3



8



12



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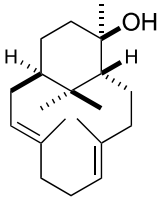
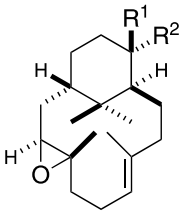
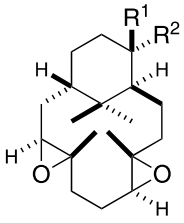


18



20 R^1=CH_3, R^2=OH
21 R^1=OH, R^2=CH_3



22 R^1=CH_3, R^2=OH
23 R^1=OH, R^2=CH_3

*3.10. Epoxidation of a mixture of **4** and **5***

To a mixture of **4** and **5**(ca 3:2) (104 mg) in CH_2Cl_2 (10 ml) was added MCPBA (119 mg), and stirred at 0 °C for 1 h. The reaction mixture was repeatedly chromatographed on silica gel and purified by preparative HPLC to yield six mono- and diepoxy compounds **2**(30.5 mg), **19**(2.3 mg), **20**(5.6 mg), **21**(11.4 mg), **22**(30.4 mg) and **23**(6.4 mg).

*3.10.1. (9S,10S)-Ent-9,10-epoxy-5-epi-verticillol (**19**)*

Colorless crystals (from *n*-hexane); m.p. 86–87 °C; $[\alpha]_D^{23}$ − 137.8° (*c* 0.19); HR-EIMS: found 306.2557, $C_{20}H_{34}O_2$ requires 306.2559; FTIR ν_{max} cm^{-1}: 3517 (OH); ^{1}H NMR (600 MHz): δ 1.53–1.58 (2H, *m*, H-2, H-4), 1.47 (1H, *m*, H-3α), 2.24–2.30 (2H, *m*, H-3β, H-12), 1.84–1.92 (2H, *m*, H-4, H-15α), 1.94 (1H, *d*, *J* = 8.2 Hz, H-6), 1.60–1.68 (2H, *m*, H-7α, H-11), 1.51 (1H, *m*, H-7β), 1.31 (1H, *m*, H-8α), 2.12 (1H, *dt*, *J* = 13.7, 3.6 Hz, H-8β), 2.70 (1H, *d*, *J* = 9.9 Hz, H-10), 1.93 (1H, *m*, H-11), 2.22 (1H, *ddd*, *J* = 13.5, 13.5, 2.5 Hz, H-12), 5.66 (1H, *d*, *J* = 14.6 Hz, H-14), 2.74 (1H, *dddd*, *J* = 14.6, 12.9, 6.6, 1.6 Hz, H-15β), 0.92(3H, *s*, H-16), 1.00 (3H, *s*, H-17), 1.19 (3H, *s*, H-18), 1.27 (3H, *s*, H-19), 1.61 (3H, *s*, H-20). For ^{13}C NMR: Table 2; EIMS *m*/*z* (rel. int.): 306[M]$^+$(16), 288(12), 273(10), 263(8), 245(8), 205(9), 189(14), 177(30), 161(21), 151(31), 135(62), 123(45), 121(58), 109(63), 95(74), 81(72), 69(63), 55(65), 43(100).

*3.10.2. (13S,14S)-Ent-13,14-epoxyverticillol (**20**)*

Colorless crystals (from *n*-hexane); m.p. 139–140 °C; $[\alpha]_D^{18}$ − 97.9° (*c* 0.38); CIMS (*iso*-butane): *m*/*z* 305 [M − H]$^+$; FTIR ν_{max} cm^{-1}: 3488 (OH); ^{1}H NMR (600 MHz): δ 1.58 (1H, *m*, H-2), 1.70 (1H, *m*, H-3α), 2.01 (1H, *m*, H-3β), 1.79 (1H, *m*, H-4α), 1.73 (1H, *m*, H-4β), 1.80 (1H, *m*, H-6), 1.59 (1H, *m*, H-7α), 1.36 (1H, *dddd*, *J* = 14.8, 14.8, 3.8, 1.6 Hz, H-7β), 2.24 (1H, *m*, H-8α), 2.11 (1H, *m*, H-8β), 5.02 (1H, *d*, *J* = 10.7 Hz, H-10), 2.13 (1H, *m*, H-11α), 2.30 (1H, *m*,

H-11β), 1.24 (1H, *m*, H-12α), 2.21 (1H, *m*, H-12β), 3.43 (1H, *d*, *J* = 9.9 Hz, H-14), 1.81–1.87 (2H, *m*, H-15, H-15′), 0.75 (3H, *s*, H-16), 0.84 (3H, *s*, H-17), 1.29 (3H, *s*, H-18), 1.60 (3H, *t*, *J* = 1.6 Hz, H-19), 1.25 (3H, *s*, H-20). For ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 288[M − 18]$^+$(19), 270(24), 255(27), 227(9), 215(8), 203(9), 187(16), 173(13), 159(18), 149(30), 134(100), 121(76), 109(46), 95(46), 81(57), 69(45), 55(40), 43(61).

3.10.3. (13S,14S)-Ent-13,14-epoxy-5-epi-verticillol (**21**)

Colorless crystals (from *n*-hexane); m.p. 161 °C; $[\alpha]_D^{18}$ − 48.0° (*c* 0.33); HR-EIMS: found 306.2559, $C_{20}H_{34}O_2$ requires 306.2559; FTIR ν_{max} cm^{-1}: 3537 (OH); ^{1}H NMR (600 MHz): δ 1.58–1.66 (3H, *m*, H-2, H-4β, H-7α), 1.52 (1H, *d quint.*, *J* = 14.1, 2.5 Hz, H-3α), 2.29 (1H, *m*, H-3β), 1.80 (1H, *apparent ddd*, *J* = 12.9, 12.9, 4.7 Hz, H-4α), 1.56 (1H, *d*, *J* = 11.3 Hz, H-6), 1.38 (1H, *ddd*, *J* = 14.3, 14.3, 4.1 Hz, H-7β), 2.02 (1H, *ddd*, *J* = 13.5, 13.5, 4.1 Hz, H-8α), 2.13 (1H, *apparent* br *d*, H-8β), 4.86 (1H, *d*, *J* = 11.0 Hz, H-10), 2.12 (1 H, *apparent* br *d*, H-11α), 2.31 (1 H, *m*, H-11β), 1.19 (1H, *ddd*, *J* = 13.7, 13.7, 2.5 Hz, H-12α), 2.23 (1H, *ddd*, *J* = 13.7, 5.8, 2.2 Hz, H-12β), 3.19 (1H, *dd*, *J* = 9.9, 1.9 Hz, H-14), 1.83 (2H, *m*, H-15, H-15′), 0.71 (3H, *s*, H-16), 1.02 (3H, *s*, H-17), 1.22 (3H, *s*, H-18), 1.61 (3H, *t*, *J* = 1.6 Hz, H-19), 1.25 (3H, *s*, H-20). For ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 306[M]$^+$(3), 288(21), 270(15), 255(16), 215(9), 203(10), 187(12), 175(15), 161(21), 149(37), 134(69), 122(78), 109(70), 95(67), 81(68), 69(55), 55(46), 43(100). Crystal data: orthorhombic, $P2_12_12_1$, *a* = 9.5190 (6) Å, *b* = 13.6820 (7) Å, *c* = 14.1340 (11) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 1840.8 (2) Å^3, *Z* = 4, DIP image plate, refinement on F^2, fullmatrix least-squares refinement, *R*(gt) = 0.0789, *wR*(gt) = 0.1818, *S*(ref) = 1.182, 3479 reflections, 200 parameters, only coordinates of H atoms refined, Cell refinement, Scalepack (HKL); Data reduction, maXus; program used to refine structure, *SHELXL*-97.

3.10.4. (9S,10S:13S,14S)-Ent-9,10:13,14-diepoxyverticillol (**22**)

Colorless crystals (from *n*-hexane); m.p. 166–167 °C; $[\alpha]_D^{23}$ − 98.1° (*c* 0.87); FAB-MS (*m*-NBA) *m/z* : 345 [M + Na]$^+$, 361 [M + K]$^+$; FTIR ν_{max} cm^{-1}: 3465, 3374 (OH); ^{1}H NMR (600 MHz): δ 1.55–1.61 (2H, *m*, H-2, H-11), 1.65–1.76 (5H, *m*, H-3, H-4β, H-6, H-7α, H-8α), 1.97–2.02 (2H, *m*, H-3, H-11), 1.91 (1H, *ddd*, *J* = 13.2, 13.2, 4.1 Hz, H-4α), 1.52 (1H, *ddd*, *J* = 14.8, 14.8, 3.0 Hz, H-7β), 2.04 (1H, *dt*, *J* = 13.2, 3.6 Hz, H-8β), 2.96 (1H, *d*, *J* = 9.1 Hz, H-10), 1.36 (1H, *t*, *J* = 14.6 Hz, H-12α), 2.30 (1H, *ddd*, *J* = 14.6, 7.1, 1.6 Hz, H-12β), 3.51 (1H, *dd*, *J* = 8.8, 3.3 Hz, H-14), 1.84–1.87 (2H, *m*, H-15, H-15′), 0.97 (3H, *s*, H-16), 0.86 (3H, *s*, H-17), 1.304 (3H, *s*, H-18), 1.32 (3H, *s*, H-19), 1.297 (3H, *s*, H-20). For ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 304[M − 18]$^+$(2), 289(5), 271(6), 231(9), 189(10), 177(11), 175(20), 165(13), 161(21), 151(19), 147(23), 138(23), 135(78), 125(58), 121(59), 107(69), 95(76), 81(55), 69(58), 55(58), 43(100). Crystal data: orthorhombic, $P2_12_12_1$, *a* = 9.757 (4) Å, *b* = 14.289 (5) Å, *c* = 27.015 (2) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 3766.4 (3) Å^3, *Z* = 8, MoK α radiation, λ = 0.71073, DIP image plate, refinement on F^2, fullmatrix least-squares refinement, *R*(gt) = 0.0659, *wR*(gt) = 0.1790, *S*(ref) = 1.118, 6136 reflections, 415 parameters, 0 restraints, only coordinates of H atoms refined, Cell refinement, Scalepack (HKL); data reduction, maXus; program used to refine structure, *SHELXL*-97.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 263615 (13,14-epoxy-*ent*-5-epi-verticillol), 263616 (9,10-epoxy-*ent*-verticillol) and 263617 (9,10:13,14-diepoxy-*ent*-veticillol). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: 144 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.10.5. (9S,10S:13S,14S)-Ent-9,10:13,14-diepoxy-5-epi-verticillol (**23**)

Colorless crystals (from *n*-hexane); m.p. 179–180 °C; $[\alpha]_D^{23}$ − 44.1° (*c* 0.37); CIMS (*iso*-butane) *m/z* : 323 [M + H]$^+$; FTIR ν_{max} cm^{-1}: 3250 (OH); ^{1}H NMR (600 MHz): δ 1.67 (1H, br *s*, H-2), 1.54 (1H, *m*, H-3α), 2.31 (1H, *m*, H-3β), 1.85 (1H, *ddd*, *J* = 14.8, 14.8, 4.9 Hz, H-4α), 1.57–1.63. (2H, *m*, H-4β, H-11), 1.41 (1H, *d*, *J* = 8.2 Hz, H-6), 1.51 (1H, *ddd*, *J* = 15.1, 15.1, 3.3 Hz, H-7α), 1.76 (1H, *dddd*, *J* = 15.7, 8.0, 3.8, 3.8 Hz, H-7β), 1.25–1.27 (2H, *m*, H-8α, H-12α), 2.20 (1H, *dt*, *J* = 14.0, 3.8 Hz, H-8β), 2.66 (1H, *d*, *J* = 8.8 Hz, H-10), 2.01 (1H, *dd*, *J* = 16.8, 8.2 Hz, H-11), 2.33 (1H, *m*, H-12β), 3.22 (1H, *dd*, *J* = 8.0, 3.8 Hz, H-14), 1.86–1.88 (2H, *m*, H-15, H-15′), 0.95 (3H, *s*, H-16), 1.05 (3H, *s*, H-17), 1.19 (3H, *s*, H-18), 1.34 (3H, *s*, H-19), 1.29 (3H, *s*, H-20). For ^{13}C NMR: Table 2; EIMS *m/z* (rel. int.): 304[M − 18]$^+$(3), 279(10), 261(6), 219(8), 193(14), 175(30), 161(16), 149(22), 135(82), 125(49), 111(32), 109(69), 95(89), 81(54), 71(51), 69(58), 55(59), 43(100).

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