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DITERPENOIDS FROM THE JAPANESE LIVERWORT *JUNGERMANNIA INFUSCA**

IN HONOUR OF PROFESSOR G. H. NEIL TOWERS 75TH BIRTHDAY

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Key Word Index—*Jungermannia infusca*; Jungermanniaceae; liverwort; bis-norclerodane-type; clerodane-type; labdane-type; *ent*-kaurane-type; diterpenoid; bis-norditerpenoid; absolute configuration; x-ray analysis.

Abstract—A new bis-norclerodane-type and two new clerodane-type diterpenoids were isolated from the Japanese liverwort, *Jungermannia infusca*, together with twelve known clerodane-, labdane- and *ent*-kaurane-type diterpenoids. These structures were determined by the use of NMR spectroscopic techniques, chemical degradation and X-ray crystallographic analyses. The presence of (+)- and (−)-isoabienol were confirmed by chiral HPLC analysis. © 1998 Elsevier Science Ltd. All rights reserved

INTRODUCTION

As part of a search for new biologically active substances in the Hepaticae, we are continuing to study the chemical constituents of liverworts. *Jungermannia* species belonging to the Jungermanniales. These are a rich source of diterpenoids of the clerodane-, labdane-, pimarane- and *ent*-kaurane-types [1, 2]. Each species is morphologically small, therefore, their identification is quite difficult. During the course of the investigation of the chemical constituents of *J. infusca*, it was found that there are at least four chemotypes of this liverwort [3]. In order to clarify the presence or the absence of new chemo-types of *J. infusca*, the chemical constituents of specimens collected in Okayama prefecture, Japan were reinvestigated. In this paper, the isolation and characterization of two new clerodane-types (**1**,**2**), a new bis-norclerodane-type diterpenoid **3** and twelve previously known clerodane- (**4**–**9**), labdane- (**10**–**14**) and *ent*-kaurane-type diterpenoids (**15**) are described. The absolute configurations of **7** and **10** [4] were established by X-ray crystallographic analysis of their derivatives.

RESULTS AND DISCUSSION

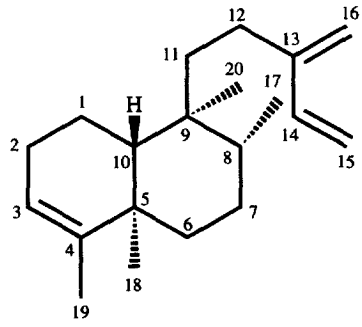
The new compounds **1**–**3** were isolated from the ether extract of *J. infusca* by a chromatographic separation (silica gel, Sephadex LH-20 and preparative HPLC), together with six previously known clerodanes **4**–**9**, five labdanes **10**–**14**, and an *ent*-kaurane-type diterpenoid **15** whose spectral and physical data were identical with those of authentic samples.

Compounds **7** and **8**, 13*E*-symphyoreticulic and 13*Z*-symphyoreticulic acids were isolated from *J. infusca* which had been collected in a different locality [3] and their relative stereochemistry was established by complete assignments of their ^{1}H and ^{13}C NMR spectra. These compounds have previously been reported as present in the Compositae [4]. However, neither their optical rotation nor ^{1}H and ^{13}C NMR spectroscopic data have been reported, except for the ^{1}H NMR spectrum analysis of 13*Z*-symphyoreticulic acid. In order to obtain further evidence of the structures of both compounds, an X-ray analysis of a single crystal of the carbamate **16** of **7** was carried out (see Section 3, Experimental). The Eta is 2.066 (alternative chirality: −2.136) and its absolute stereochemistry is depicted in Fig. 1. Thus, the structure of **7** was established to be an *ent*-clerodane-type diterpenoid and its geometrical isomer, **8**, was proposed to have the same absolute configuration. Additionally, compound **18** [3] had also been previously isolated from other *J. infusca* samples [3], together with **7**–**9**. The spectral data of the diol derivative of **18** were in agreement with those of the diol derivative of **7**. Thus, the absolute configuration of **18** and its geometrical isomer **9** were the same as **7**.

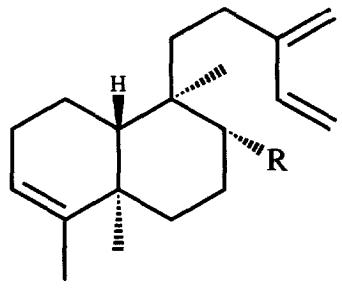
The isolation of (+)-gomeraldehyde (**10**) ([α]$_D$

* This paper is dedicated, with best wishes, to Professor G. H. Neil Towers on the occasion of his 75th birthday.

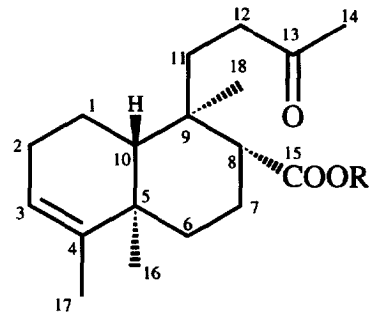
† Author to whom correspondence should be addressed.



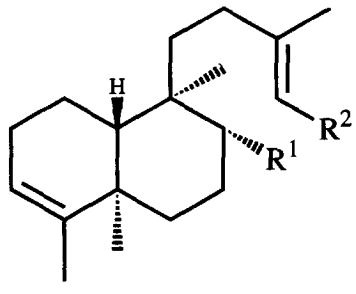
1



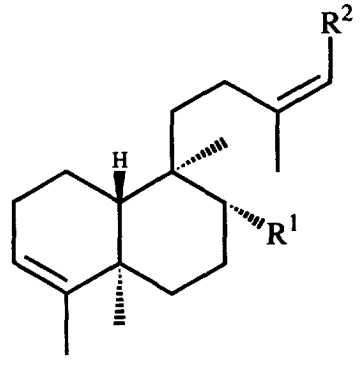
2 R=CH_2OH
5 R=CHO
6 R=COOH



3 R=H
20 R=CH_3



4 R^1=COOH, R^2=CH_2OH
7 R^1=COOH, R^2=CHO
16 R^1=R^2=$CH_2OCONHC_6H_4Br$
18 R^1=R^2=CHO
21 R^1=$COOCH_3$, R^2=CH_2OH



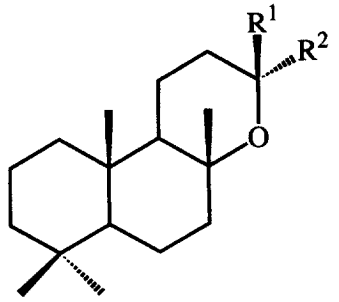
8 R^1=COOH, R^2=CHO
9 R^1=R^2=CHO
17 R^1=R^2=$CH_2OCONHC_6H_4Br$

+22.0°) and (+)-*epi*-gomeraldehyde (**11**) ($[\alpha]_D$ +27.6°) was previously reported from *J. infusca* [5], *Sideritis* species [6, 7] ($[\alpha]_D$ not given) and *Baccharis* species [8] (**10**: $[\alpha]_D$ −16°). In order to clarify their absolute configuration, the X-ray crystallographic analysis of carbamate **19** derived from **10** was carried out. The Eta was 0.901 (alternative chirality; −0.900) and the absolute structure of **19** is depicted in Fig. 2. Thus, the absolute configuration of **10** was established and its 13-epimer, (+)-*epi*-gomeraldehyde (**11**) [6] was supported to be the same as that of **10**.

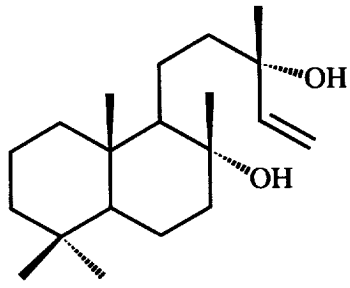
The mass spectrum of **1** showed *m/z* 272[M]$^+$ and its molecular formula, $C_{20}H_{32}$ (calculated 272.2504), was confirmed by GC–HR mass spectrum. The ^{1}H NMR spectrum (Table 1) of **1** indicated the presence of a secondary methyl, an olefinic methyl, two tertiary methyls, *terminal*-vinylic protons (δ 5.05 *d*, 5.22 *d*, 6.37 *dd*) and two olefinic protons (δ 4.98 2H, *s*, 5.23 1H *s*). The ^{13}C NMR spectrum (Table 2) of **1** showed 20 carbons, and its DEPT spectrum indicated the presence of four methyls, six methylenes, two methines and two quaternary carbons, together with trisubstituted olefinic carbons (δ 120.4 *d*, 144.5 *s*), an *exo*-methylene (δ 115.5 *t*, 147.6 *s*) and *terminal*-vinylic carbons (δ 112.9 *t*, 139.0 *d*). Since the above spectral data were similar to those of the clerodane-type diterpenoids **5**–**9**, compound **1** was suggested to be a clerodane-type diterpene hydrocarbon. From the detailed analysis of ^{1}H–^{1}H COSY, HSQC and HMBC spectra (Table 3), the structure of **1** was supported to be clerod-3, 13(16), 14-triene. The stereochemical structure of **1** was clarified as follows. In the difference NOE spectrum, correlations were observed between: H-20 and H-17, and H-20 and H-18. The $LiAlH_4$ reduction of compound **5**, which was isolated from the present species, gave a monoalcohol **2** [3]. Tosylation and further reduction afforded a hydrocarbon whose spectral data and optical rotation were identical with those of the natural hydrocarbon **1**. Thus, the structure of **1** was supported to be *ent*-clerod-3, 13(16),14-triene, considering the co-occurrence of the related clerodane diterpenoids **7**–**9** in the present species.

The spectral data of **2** were completely identical with those of the hydrogenated derivative from compounds **5** or **6** [3]. However, compound **2** was newly isolated from liverworts as a natural product.

The IR and ^{13}C NMR (Table 2) spectra of **3** showed



10 R^1=CH_3, R^2=CH_2CHO
11 R^1=CH_2CHO, R^2=CH_3



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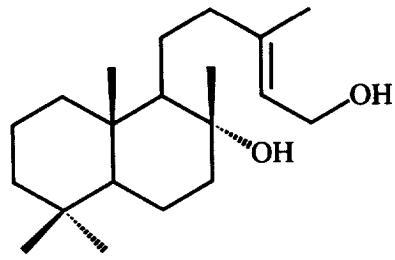

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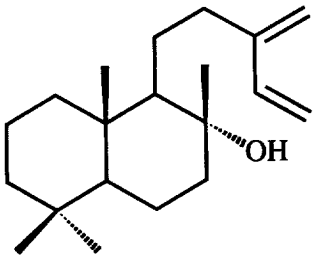

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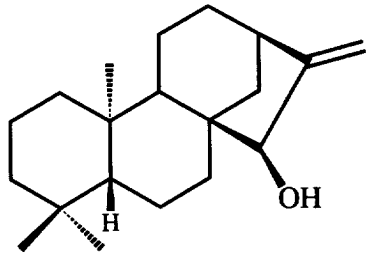

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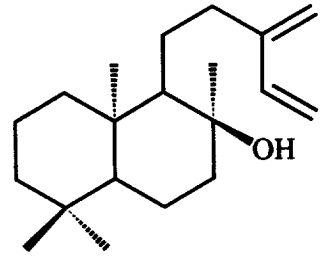

22

the presence of carboxylic acid and carbonyl (3600–2400, 1730, 1720 cm^{-1}, δ 179.5, 209.4 each *s*) groups. The EIMS and CIMS (CH_4) of **3** showed *m/z* 274[M–CH_3]$^+$ and a quasi-molecular ion at *m/z* 293, [M + H]$^+$ respectively. Thus, the molecular weight of **3** was shown to be 292. Methylation of **3** by CH_2N_2 gave a monomethyl ester **20** (δ_H 3.65 3H, s). The ^{1}H NMR spectrum (Table 1) of **3** also showed the presence of two tertiary methyls (δ 0.97, 1.06), an olefinic methyl (δ 1.59), an acetyl group (δ 2.17), and an olefinic proton (δ 5.20). The ^{13}C NMR spectrum (Table 2) displayed 18 carbons and its DEPT spectrum showed the presence of four methyls, six methylenes, two methines and two quaternary carbons, together with an ester carbonyl, a ketone carbonyl and trisubstituted olefinic carbons (δ 120.6 *d*, 143.6 *s*). The above spectral evidence and CIMS showed that the molecular formula of **3** should be $C_{18}H_{28}O_3$. The ^{1}H–^{1}H COSY spectrum suggested the presence of three partial segments, [A] –CH–CH_2–CH_2–CH=C–, [B] –CH–CH_2–CH_2– and [C] –CH_2–CH_2–. In order to clarify the connectivity of each partial structure, the HMQC and HMBC spectra of **3** were measured. The detailed analysis of the HMBC spectrum as shown in Table 4 suggested that the structure of **3** was a bis-norclerodane-type diterpenoid. The NOEs in the NOESY spectrum of **3** were observed between: H-16 and H-18, H-16 and H-1α, H-16 and H-7α, H-18 and H-7α, H-8 and H-10, H-8 and H-6β, H-6β and H-10 and H-8 and H-7β, respectively. Thus, the stereostructure of bis-norinfuscaic acid was depicted as **3**.

The EIMS of **4** showed *m/z* 320[M]$^+$ and its molecular formula was deduced to be $C_{22}H_{30}O_5$ (*m/z* 320.2378) by the HRMS. The IR and ^{13}C NMR spectra indicated the presence of primary hydroxyl and carboxylic acid groups (3600–2400, 1700 cm^{-1}; δ 59.4 *t*, 179.7 *s*). The ^{1}H and ^{13}C NMR spectra (Tables 1–2) exhibited the presence of a methylene (δ_H 4.14 2H *d*; δ_c 59.4) bearing a hydroxyl group, two trisubstituted olefinic carbons (δ_H 5.20 *br s*, 5.42 *br t*; δ_c 120.7, 123.2 each *d*, 140.4, 143.7 each *s*) and an ester carbonyl carbon, together with four tertiary methyls, six methylenes, two methines and two quaternary carbons. Compound **4** was treated with CH_2N_2 to give a monomethyl ester **21**, the spectral data of which were agreement with those of the methyl ester of bacchasalicylic acid isolated from the Compositae [9]. Since the ^{1}H and ^{13}C NMR data of bacchasalicylic acid (**4**) [9] have not been reported, the complete assignments of the ^{1}H and ^{13}C NMR spectra of **4** were carried out by the detailed analysis of 2D COSY and the data are shown in Tables 1–2.

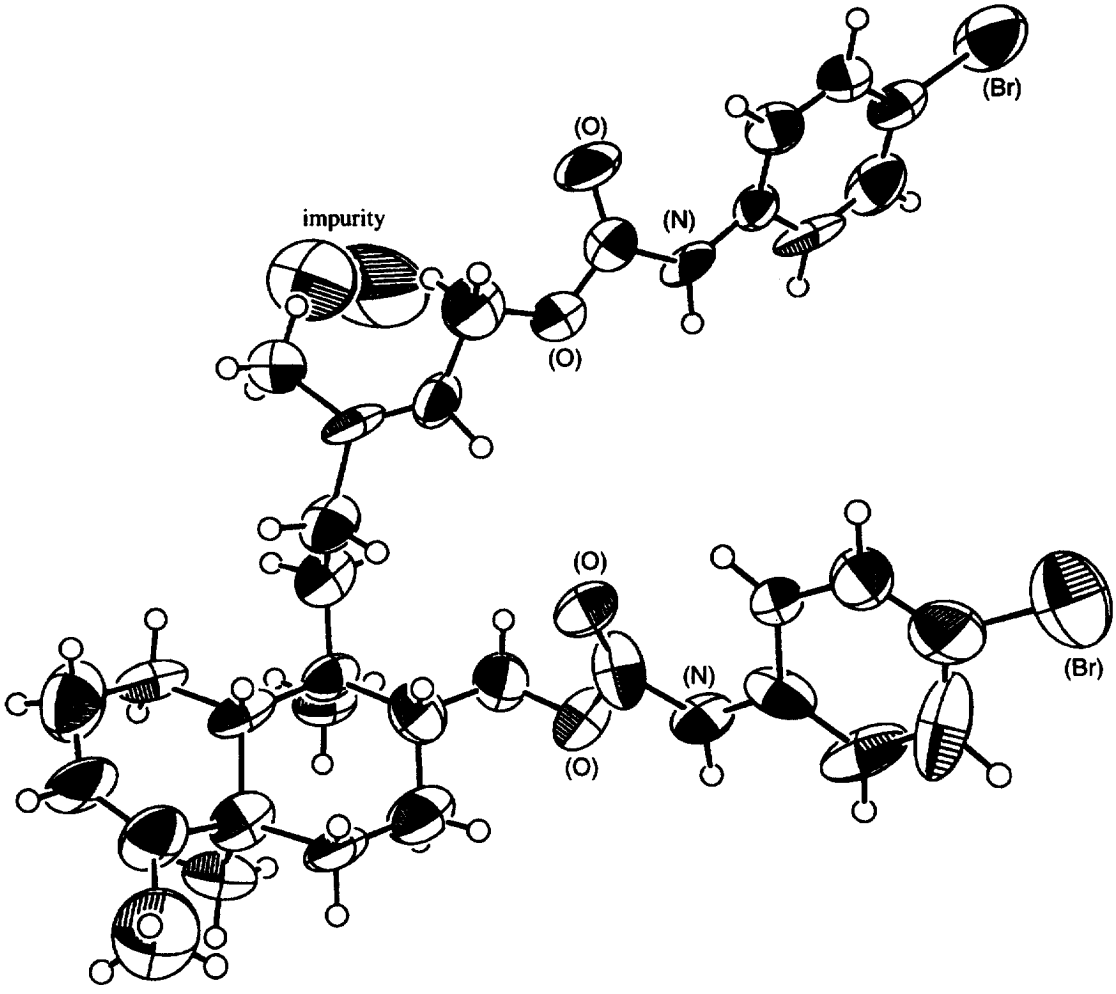

Fig. 1. The ORTEP Depiction of **16**.

The spectral data of **14** ($[\alpha]_D$ +7.0°, $CHCl_3$) were completely identical with those of isoabienol ($[\alpha]_D$ +29.09°, solvent was not given [10]) isolated from *Abies sibirica* (Pinaceae) and its absolute structure was shown to be the normal labdane-type by the formation of the known lactones [10]. Isoabienol has been isolated from *Pinus sylrestris* (Pinaceae) [11] and *Sagittaria trifolia* (Alismataceae) [12], respectively and the negative optical rotation ($[\alpha]_D$ −6.4° [11] and −6.2° [12], each $CHCl_3$) has been reported. However, its structure has been depicted as normal labdane-type in spite of the opposite sign of $[\alpha]_D$ [10]. Considering the co-occurrence of the normal labdane-type, (+)-gomeraldehyde (**10**) and its epimer (**11**), 13-*epi*-sclareol (**12**) and its analogue (**13**), and positive optical rotation of **14**, the absolute structure of **14** must be normal labdane-type. Furthermore, the analysis of **14** by chiral HPLC indicated that it contained a very small amount (*ca.* 0.2%) of its enantiomer **22**.

It has been known that there are at least four chemo-types: (i) kaurane-type, (ii) kaurane-type glucoside, (iii) labdane- and clerodane-type, and (iv) bis(bibenzyl)-type, of *J. infusca* in Japan [13]. The present sample of *J. infusca* biosynthesizes labdane- and clerodane-type diterpenoids as the main components, and thus this species belongs to the third chemo-type. Liverworts are very interesting chemically, because sometimes the same species produce both normal and enantiomeric mono- and sesquiterpenoids. The different species belonging to the same genus occasionally produce normal or enantiomeric sesquiterpenoids [1, 2]. Diterpenoids of *Jungermannia* liverworts are biogenetically quite interesting. *J. hattoriana* produces both labdane-type, with a 10β-Me, and the (−)-pimarane-type diterpenoids, with a 10α-Me [14]. *J. infusca* elaborates both the normal labdane-type and the *ent*-clerodane-type diterpenoids.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded at 200, 400 and 600 MHz (^1H NMR) and 100, 150 MHz (^{13}C NMR), respectively. Chemical shift values were

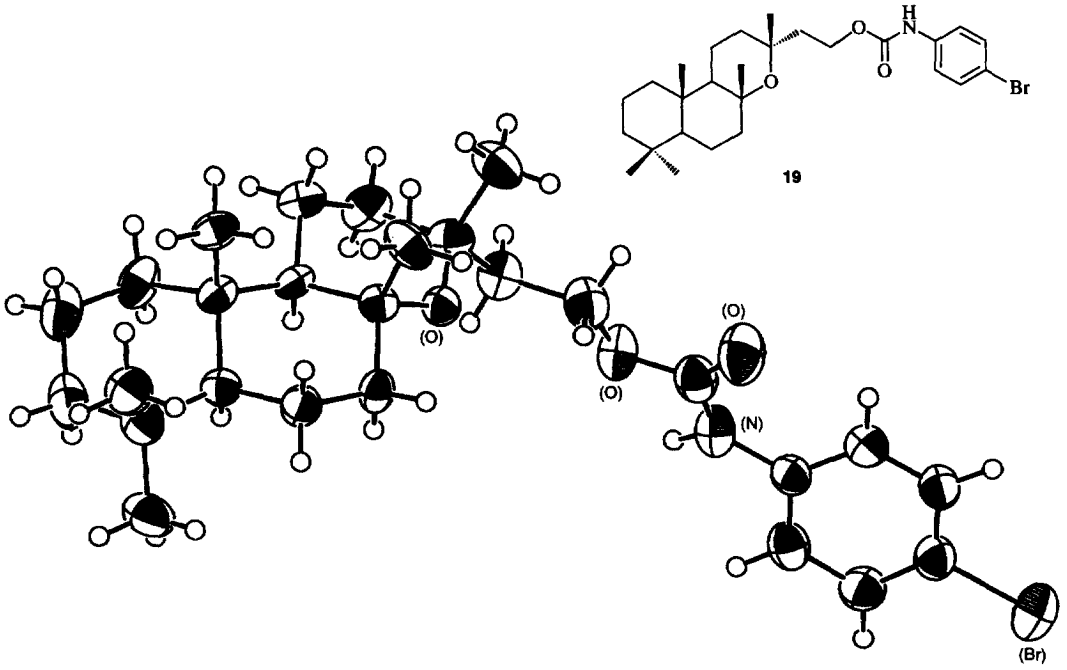

Fig. 2. The ORTEP Depiction of **19**.

Table 1. ^{1}H NMR Spectroscopic data of **1**, **3**, **4** and **20** (600 MHz, $CDCl_3$)

H	1	3	4	20*
1	1.40–1.49 *m*	1.45 *dddd*, J = 12.1, 12.1, 12.1, 6.3 H_z	1.39–1.49 *m*	1.33–1.50, 2H, *m*
	1.53–1.61 *m*	1.57*m*	1.56–1.64*m*	
2	2.05 2H,*m*	1.98*m*	2.01*m*	1.96*m*
		2.07*br d*	2.08*m*	2.07*m*
3	5.23*s*	5.20*br s*	5.20*br s*	5.19*br s*
6	1.21*ddd*, J = 12.9, 12.9, 5.4 Hz	1.81d*t*, J = 14.3, 3.6 Hz, α	1.79d*t*, J = 13.2, 3.3 Hz, α	1.15*ddd*, J = 13.6, 13.6, 3.6 Hz
	1.72 *td*, J = 12.7, 3.4 Hz	1.16*ddd*, J = 13.7, 13.7, 3.6 Hz, β	1.17*ddd*, J = 13.5, 13.5, 3.6 Hz, β	1.75–1.83*m*
7	1.40–1.49 2H, *m*	1.97*m*, α	1.97*dddd*, J = 13.7, 13.7, 13.7, 3.3 Hz, α	1.63*dq*, J = 14.5, 3.9 Hz
		1.70*dq*, J = 14.3, 3.6 Hz, β	1.69*dq*, J = 14.3, 3.6 Hz, β	1.99*m*
8	1.53–1.61*m*	2.36*dd*, J = 12.9, 3.6 Hz	2.49*dd*, J = 12.9, 3.3 Hz	2.37*dd*, J = 12.7, 3.4 Hz
10	1.40–1.49*m*	1.28*dd*, J = 12.1, 1.6 Hz	1.39–1.49*m*	1.27*dd*, J = 12.2, 2.0 Hz
11	1.40–1.49*m*	1.60*m*	1.39–1.49*m*	1.56*m*
	1.53–1.61*m*	1.84*m*	1.56–1.64*m*	1.75–1.83*m*
12	2.01*ddd*, J = 13.4, 13.4, 4.9 Hz	2.25*ddd*, J = 16.8, 12.1, 4.9 Hz	1.84*ddd*, J = 12.9, 12.9, 4.7 Hz	2.22*ddd*, J = 16.6, 12.2, 4.9 Hz
	2.10*ddd*, J = 13.4, 13.4, 4.2 Hz	2.60*ddd*, J = 16.8, 11.8, 4.4 Hz	2.10*ddd*, J = 12.9, 12.9, 3.6 Hz	2.57*ddd*, J = 16.1, 12.2, 3.9 Hz
14	6.37*dd*, J = 17.6, 10.7 Hz	2.17 3H, *s*	5.42*br t*, J = 6.9 Hz	2.17 3H, *s*
15	5.05*d*, J = 10.7 Hz		4.14 2H, *d*, J = 6.9 Hz	
	5.22*d*, J = 17.6 Hz			
16	4.98 2H, *s*	1.06 3H, *s*	1.68 3H, *s*	1.06 3H, *s*
17	0.82 3H,*d*, J = 6.6 Hz	1.59 3H, *s*		1.59 3H, *s*
18	1.01 3H, *s*	0.97 3H, *s*	1.06 3H, *s*	0.93 3H, *s*
19	1.60 3H, *s*		1.59 3H, *br s*	
20	0.72 3H, *s*		0.94 3H, *s*	
COOMe				3.65 3H, *s*

* Measured at 400 MHz

Table 2. ^{13}C NMR Spectroscopic data of **1**, **3**, **4** and **20** (150 MHz, $CDCl_3$)

C	1	3	4	20*
1	18.3	17.8	17.9	17.9
2	26.9	26.6	26.6	26.7
3	120.4	120.6	120.7	120.6
4	144.5	143.6	143.7	143.6
5	38.2	37.8	37.8	37.9
6	36.8	35.5	35.6	35.8
7	27.5	21.5	21.6	21.7
8	36.3	49.2	48.9	49.4
9	38.8	38.2	38.6	38.4
10	46.5	46.5	46.3	46.7
11	37.5	33.2	38.5	33.6
12	24.7	37.5	32.8	37.7
13	147.6	209.4	140.4	208.9
14	139.0	30.0	123.2	30.0
15	112.9	179.5	59.4	174.7
16	115.5	19.9	16.4	20.1
17	16.1	17.9	179.7	18.1
18	20.0	19.8	20.0	20.0
19	18.0		17.8	
20	18.4		20.1	
CO_2Me				51.2

* Measured at 100 MHz.

Table 3. The long-range H–C correlations of **1**

H	C
6	5, 7, 8
12	11, 13, 14, 16
14	12, 13, 16
15	13, 14
16	12, 13, 14
17	7, 8, 9
18	4, 5, 6, 10
19	3, 4, 5
20	8, 9, 10, 11

Table 4. The long-range H–C correlations of **3**

H	C
8	9, 15
10	2, 5, 9, 16
12	9, 11, 13
14	12, 13
16	4, 5, 6, 10
17	3, 4, 5
18	8, 9, 10, 11

expressed in δ (ppm) downfield from tetramethylsilane as an internal standard (^1H 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 [15] followed by heating. MeOH–CH_2Cl_2 (1:1) was used for Sephadex LH-20. $[\alpha]_D$: $CHCl_3$. UV:EtOH.

Plant material

Jungermannia infusca (Mitt.) Steph. was collected in Tatsumitohge, Okayama in May, 1995, Japan and identified by Prof. H. Kitagawa (Nara University of Education, Japan). The voucher specimen was deposited at the Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and isolation

J. infusca dry material (227 g) was ground and extracted with Et_2O for 1 month. The crude extract (10.7 g) was divided into 12 fractions by CC on silica gel using a *n*-hexane-EtOAc gradient. Fr. 3 was chromatographed on SiO_2 (*n*-hexane-EtOAc) impregnated with 10% $AgNO_3$ to give *ent*-clerod-3,13(16),14-triene (**1**) (28 mg). Fr. 5 gave clerod-3,13(16),14-trien-17-al (**5**) (182 mg) and (+)-gomeraldehyde (**10**) (124 mg) [5] by rechromatography on Sephadex LH-20 and SiO_2 (*n*-hex.-Et_2O). Fr. 6 was rechromatographed on Sephadex LH-20, SiO_2 (*n*-hexane-Et_2O or *n*-hexane-EtOAc), MPLC (Lobar® column, *n*-hexane-Et_2O) and finally prep. HPLC (Nucleosil 50–5, *n*-hexane-Et_2O) to give (+)-isoabeinol (**14**) (377 mg) [10] ($[\alpha]_D$ +7.0°, *c* 5.40), **10** [5], (+)-*epi*-gomeraldehyde (**11**) (67 mg) [5] and *ent*-16-kauren-15α-ol (**15**) (4 mg) [16], respectively. (+)-Isoabeinol (**14**) was analyzed by chiral HPLC (Chiralcel OD-H, *n*-hexane-2-propanol, 9:1, flow 0.3 ml min^{-1}.) to establish the presence of a very small amount (*ca.* 0.2%) of **22**. Clerod-3, 13(16),14-trien-17-ol (**2**) (29 mg) [5] ($[\alpha]_D$ −45.0° *c* 1.71), *ent*-clerod-3, 13*Z*-diene-15, 17-dial (**9**) (15 mg) [5] and clerod-3,13(16),14-trien-17-oic acid (**6**) (631 mg) [5] were isolated by a combination of Sephadex LH-20, SiO_2 (*n*-hexane-EtOAc), MPLC (Lobar® column RP-18, CH_3CN) and prep. HPLC (NUCLEOSIL 50–5, *n*-hexane-EtOAc) of Fr. 7. Fr. **10** gave *ent*-clerod-3,13*E*-dien-15-al-17-oic acid (**7**) (32 mg) [5], *ent*-clerod-3,13*Z*-dien-15-al-17-oic acid (**8**) (179 mg) [5] and 13-*epi*-sclareol (**12**) (73 mg) by rechromatography on Sephadex LH-20, SiO_2 (*n*-hex.-Et_2O), MPLC (Lobar® column, *n*-hexane-EtOAc, *n*-hexane-Et_2O, CH_2Cl_2-EtOAc) and prep. HPLC (NUCLEOSIL 50–5, *n*-hexane-EtOAc). Bis-norinfuscaic acid (**3**) (15 mg), bacchasalicylic acid (**4**) (9 mg) [9] and 13*E*-labdene-8α,15-diol (**13**) (83 mg) [17] were purified by Sephadex LH-20, MPLC (Lobar® column RP-18, CH_3CN) and prep. HPLC (Chemcosorb 5-ODS-H, CH_3CN) of the Fr. 11.

Ent-*clerod*-3,13(16), 14-*triene* (**1**)

$[\alpha]_D$ −33.9° (*c* 2.11); GCHRMS: found 272.2511 $C_{20}H_{32}$ requires 272.2504; UVλ_{max} nm (log ϵ): 225 (2.85) (*c* 1.1×10^{-3}); FTIR ν_{max} cm^{-1}: 1590, 1450, 1380, 990, 890; ^1H and ^{13}C NMR: Tabs. 1–2; GCMS *m/z* (rel. int.): 272[M]$^+$(2), 257(11), 243(5), 229(2), 217(2), 204(3), 189(100), 175(18), 173(14), 161(18), 147(18), 133(28), 120(51), 109(26), 107(55), 95(55), 79(27), 67(18), 55(16), 41(17).

Bis-norinfuscaic acid (**3**)

$[\alpha]_D$ −40.5° (*c* 6.12); CIMS (CH_4): 293; $[M+1]^+$; FTIR ν_{max} cm^{-1}: 3600–2400 *br*, 1730, 1710; ^1H and ^{13}C NMR: Tabs. 1–2; EIMS *m/z* (rel. int.): 274 [M-18]$^+$ (100), 259(11), 231(64), 213(37), 203(14), 188(22), 175(29), 159(16), 147(38), 132(25), 119(36), 107(41), 95(36), 81(22), 69(15), 55(13), 43(28).

Bacchasalicylic acid (**4**)

$[\alpha]_D$ −70.5° (*c* 2.90); HREIMS: found 320.2378 $C_{20}H_{32}O_3$ requires 320.2351; FTIR ν_{max} cm^{-1}: 3600–2400 *br*, 1700 (OH, COOH); ^1H and ^{13}C NMR: Tabs. 1–2; EIMS *m/z* (rel. int.): 320 [M]$^+$ (14), 302(19), 273(10), 259(13), 241(15), 221(40), 203(19), 189(9), 173(42), 159(22), 145(16), 133(32), 119(36), 107(59), 95(100), 81(40), 69(20), 55(25), 41(26).

Conversion of **5** *to* **1**

To a suspension of $LiAlH_4$ (10 mg) in dry Et_2O (3 ml) was added **5** (49 mg) in dry Et_2O and the mixture stirred at 0° for 30 min. Work-up as usual gave an alcohol **2** (48 mg). To compound **2** in pyridine (2 ml) was added *p*-toluenesulfonyl chloride (50 mg) with the mixture then stirred at room temp overnight. CC on Sephadex LH-20 of the reaction mixture gave a product which was reduced ($LiAlH_4$ in dry Et_2O) to afford a residue. Purification, using SiO_2, gave a hydrocarbon (11 mg), the spectral data and optical rotation of which were completely identical with those of **1**.

Methylation of **3**

Compound **3** (10 mg) and trimethylsilyl diazomethane (2 ml) in MeOH (2 ml) were stirred at room temp for 1 hr. The reaction residue was chromatographed on prep. TLC to give a methyl ester **20** (5 mg): $[\alpha]_D$ −53.7° (*c*1.8); HREIMS: found 306.2179, $C_{19}H_{30}O_3$ requires 306.2195; FTIR ν_{max} cm^{-1}: 1730, 1720 (C=O); ^1H and ^{13}C NMR: Tabs. 1–2; EIMS *m/z* (rel. int.): 306[M]$^+$ (21), 288(14), 274(100), 231(53), 213(27), 203(13), 188(20), 175(38), 159(16), 147(37), 132(23), 119(33), 107(41), 95(37), 81(22), 67(11), 55(15), 43(44).

Methylation of **4**

Compound **4** (9 mg) and trimethylsilyl diazomethane (2 ml) in MeOH (2 ml) was stirred at room temp for 1 hr to give a methyl ester **21** (9 mg). The ^1H and ^{13}C NMR spectrum of **21** was identical with that of bacchasalicylic acid methyl ester [9]: $[\alpha]_D$ −104.8° (*c* 2.7); HREIMS: found 334.2517, $C_{21}H_{34}O_3$ requires 334.2508; FTIR ν_{max} cm^{-1}: 3350 (OH), 1720 (C=O); ^{13}C NMR: δ 16.4, 18.0, 18.1, 20.1, 20.2, 21.9, 26.7, 33.0, 35.8, 37.9, 38.7, 39.0, 46.4, 49.2, 51.0, 59.5, 120.6, 123.3, 140.4, 143.7, 175.1; EIMS *m/z* (rel. int.): 334 [M]$^+$ (14), 316(14), 287(10), 269(7), 235(43), 217(8), 203(20), 187(9), 175(66), 159(20), 145(15), 119(29), 107(58), 95(100), 81(31), 69(14), 55(19), 41(16).

Conversion of **7** *and* **8** *to* **16** *and* **17**

To a suspension of $LiAlH_4$ (20 mg) in dry Et_2O (2 ml) was added a mixture of **7** and **8** (28 mg) in dry Et_2O and the mixture stirred at 0° for 2 hr. Work-up as usual gave a residue (48 mg) which was treated with 4-bromophenyl isocyanate (70 mg) and 1,4-diazabicyclo (2,2,2) octane (DABCO) (40 mg) in dry toluene (2 ml) and the mixture stirred at room temp overnight. The reaction mixture was chromatographed on SiO_2 (*n*-hexane-EtOAc) and finally purified by prep. HPLC (NUCLEOSIL 50–5, *n*-hexane-EtOAc) to yield the carbamates **16** (20 mg) and **17** (16 mg). Compound **16** was recrystallized from MeOH: **16**; ^1H NMR (400 MHz); δ 0.82 (3H, *s*), 1.02 (3H, *s*), 1.59 (3H, *s*), 1.75 (3H, *s*), 3.91 (1H, *dd*, *J*=11.0, 8.1Hz), 4.29 (1H, *dd*, *J*=11.0, 3.4 Hz), 4.66 (2H, *d*, *J*=7.3 Hz), 5.20 (1H, *br s*), 5.40 (1H, *br t*, *J*=7.3 Hz), 6.55 (1H, *s*), 6.65 (1H, *s*), 7.23–7.37 (4H, *m*), 7.40 (4H, *dd*, *J*=9.0, 2.7 Hz), **17**; ^1H NMR (200 MHz); δ 0.80 (3H, *s*), 1.04 (3H, *s*), 1.59 (3H, *s*), 1.79 (3H, *s*), 3.98 (1H, *dd*, *J*=11.0, 7.2 Hz), 4.30 (1H, *dd*, *J*=11.0, 3.5 Hz), 4.52 (1H, *dd*, *J*=11.9, 7.7 Hz), 4.75 (1H, *dd*, *J*=11.9, 7.4 Hz), 5.20 (1H, *br s*), 5.44 (1H, *br t*, *J*=7.3 Hz), 7.04 (1H, *s*), 7.16 (1H, *s*), 7.23–7.42 (8H, *m*).

Crystal data of **16**

Data collection: MXC(MAC Science). Cell refinement: MXC(MAC Science). Data reduction: *CRYSTAN*. Program used to solve structure: *CRYSTAN SIR*92. Refinement: Full matrix least square. Diffractometer: Mac Science MXC18. $C_{35}H_{44}N_2O_2Br_2$, MW=732, Monoclinic, C_2, a=27.747 (9), b=9.638 (4), c=14.350(2) Å, β=111.81 (3)°, V=3562.77 (2) Å^3, *Z*=4, D*x*=1.305 Mg cm^{-3}, D*m*=1.300 Mg cm^{-3}, Cu Kα radiation, λ=1.54178 Å, θ=25–30°, μ=32.257 mm^{-1}, F(000)=1512, Reflection: 1293, Parameter: 394, R_{int}=0.064, *R*=0.072, ωR=0.100, *S*=4.183, Eta=2.066 (alternative chirality: Eta= −2.136).

Conversion of **10** *to* **19**

To a suspension of $LiAlH_4$ (20 mg) in dry Et_2O (2 ml) was added compound **10** (50 mg) in dry Et_2O and the mixture stirred at 0° for 15 min. Work-up as usual gave a residue (48 mg). A sample of residue (20 mg), 4-bromophenyl isocyanate (26 mg) and DABCO (72 mg) in dry toluene (1 ml) were stirred at room temp for 50 min. The reaction mixture was chromatographed on SiO_2 (*n*-hexane-EtOAc) to give the carbamate **19** (25 mg) and recrystallized from *n*-hexane to give a single crystal: ^{1}H NMR (400 MHz); δ 0.76 (3H, *s*), 0.79 (3H, *s*), 0.85 (3H, *s*), 1.26 (3H, *s*), 1.83 (1H, *m*), 4.31 (2H, *m*), 6.56 (1H, *br s*), 7.27 (2H, *d*, J=9.3 Hz), 7.40 (2H, *d*, J=9.3 Hz).

Crystal data of **19**

Data collection: MXC(MAC Science). Cell refinement: MXC(MAC Science). Data reduction: *CRYSTAN*. Program used to solve structure: *CRYSTAN SIR*92. Refinement: Full matrix least square. Diffractometer: Mac Science MXC18. $C_{27}H_{40}O_3NBr$, MW=506, Orthorhombic, $P2_12_12_1$, a=19.978 (9), b=20.741 (8), c=6.170 (5) Å, V=2556.79 (2) Å^3, Z=4, Dx=1.314 Mg cm^{-3}, Dm=1.300 Mg cm^{-3}, Cu Kα radiation, λ=1.54178 Å, θ=20–30°, μ=23.974 mm^{-1}, F(000)=1072, Reflections: 1740, Parameter: 290, R_{int}=0.0, R=0.047, ωR=0.059, S=2.030, Eta=0.901 (alternative chirality: Eta= −0.900).

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