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EPI-NEOVERRUCOSANE- AND *ENT*-CLERODANE-TYPE DITERPENOIDS AND *ENT*-2,3-SECOAROMADENDRANE- AND CALAMENENE-TYPE SESQUITERPENOIDS FROM THE LIVERWORT *HETEROSCYPHUS PLANUS*

TOSHIHIRO HASHIMOTO, ICHIZEN NAKAMURA, MOTOO TORI, SHIGERU TAKAOKA and YOSHINORI ASAKAWA*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan

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Key Word Index—*Heteroscyphus planus*; Lophocoleaceae; Jungermanniales; Hepaticae; heteroscyphones A–D; heteroscyphol; 13-epi-neoverrucosan-5β,20-diol; 13-epi-neoverrucosan-5β-ol; plagiochilines L and M; (+)-7-hydroxycalamenene; (+)-5,8-dihydroxycalamenene; neoverrucosane-, *ent*-spiroclerodane- and *ent*-clerodane-type diterpenoids; *ent*-2,3-secoaromadendrane- and calamenene-type sesquiterpenoids; chemosystematics.

Abstract—The four new *ent*-spiroclerodane-type diterpenoids, heteroscyphones A–D, a new *ent*-clerodane-type diterpenoid, heteroscyphol, a new neoverrucosane-type diterpenoid, 13-epi-neoverrucosan-5β,20-diol, two new *ent*-2,3-secoaromadendrane-type sesquiterpenoids, plagiochilines L and M, and a new calamenene-type sesquiterpenoid, (+)-5,8-dihydroxycalamenene, have been isolated from the liverwort *Heteroscyphus planus*, together with the previously known 13-epi-neoverrucosan-5β-ol, plagiochiline C and (+)-7-hydroxycalamenene and their absolute stereostructures established by a combination of chemical transformation, NMR spectrometry and X-ray crystallographic analysis. This is the first isolation of the *ent*-2,3-secoaromadendrane-type sesquiterpenoids from the Lophocoleaceae. *Heteroscyphus planus* is chemically similar to *Plagiochila* species belonging to the chemotype I (2,3-secoaromadendrane-type).

INTRODUCTION

Recent studies of liverworts have shown them to be rich sources of terpenoids and lipophilic aromatic compounds [1]. Recently, we reported that the liverwort *Heteroscyphus coalitus* (=*H. bescherellei*) (Lophocoleaceae) produced the *ent*-clerodane-type diterpenoid, (+)-junceic acid (**18**) [2]. We further investigated the chemical constituents of Japanese *Heteroscyphus planus* and found that this liverwort contained verrucosane-, clerodane- and spiroclerodane-type diterpenoids, 2,3-secoaromadendrane- and calamenene-type sesquiterpenoids [3–5]. In this paper, we report the isolation and characterization of a few verrucosane-type diterpenoid, four new highly oxygenated *ent*-spiroclerodane-type diterpenoids, a new *ent*-clerodane, two new *ent*-2,3-secoaromadendrane-type sesquiterpenoids, and a new calamenene-type sesquiterpenoid, together with the previously known, 13-epi-neoverrucosan-5β-ol (**2**) [6, 7], plagiochiline C (**10**) [1], and (+)-7-hydroxycalamenene (**12**) [8] and to discuss the chemosystematics of the Lophocoleaceae including *H. planus*.

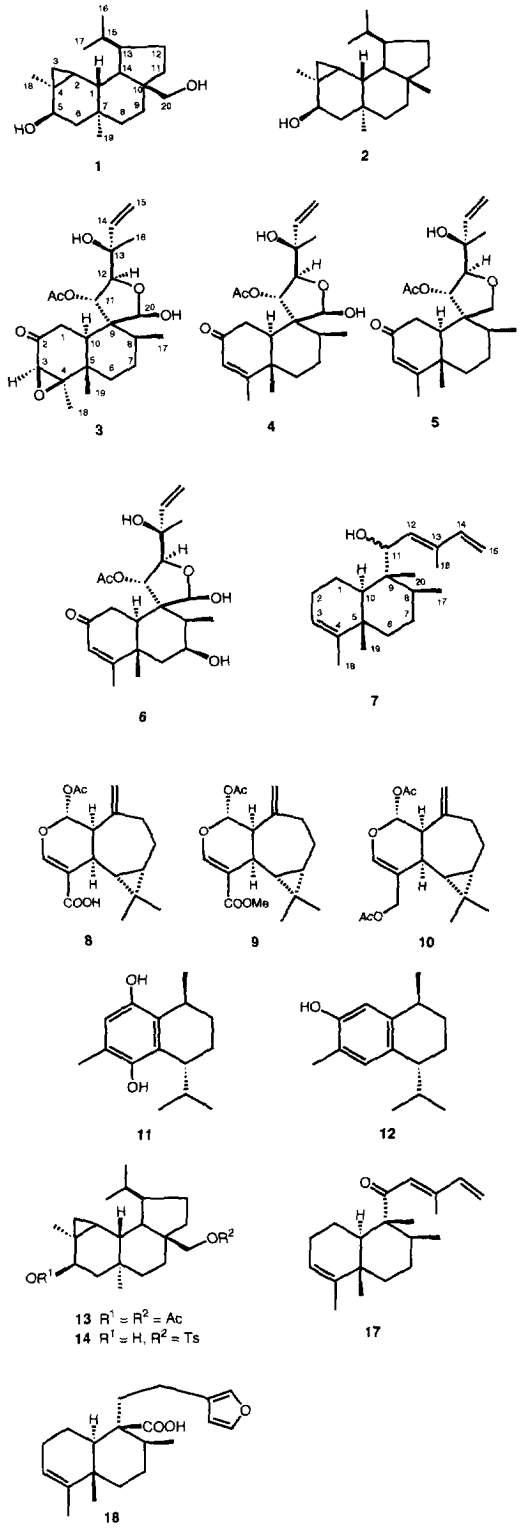
*Author to whom correspondence should be addressed.

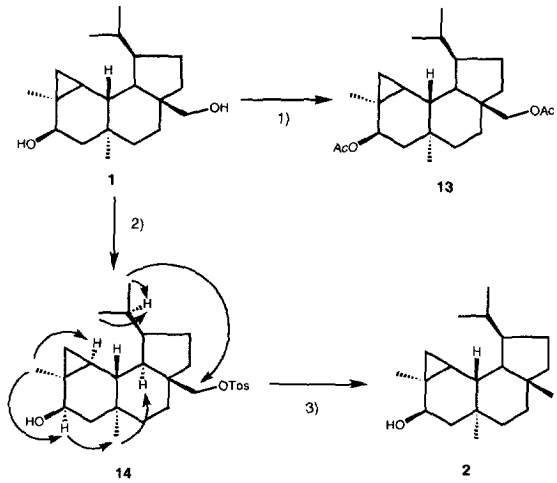
RESULTS AND DISCUSSION

The fresh liverwort, *Heteroscyphus planus*, was extracted with ether. Chromatography of the crude extract on silica gel and Sephadex LH-20 gave a new epi-neoverrucosane-type diterpenoid, 13-epi-neoverrucosan-5β,20-diol (**1**), four new *ent*-spiroclerodane-type diterpenoids, heteroscyphones A–D (**3–6**), a new *ent*-clerodane-type diterpenoid, heteroscyphol (**7**), two new *ent*-2,3-secoaromadendrane-type sesquiterpenoids, plagiochilines L (**8**) and M (**9**), and a new calamenene-type sesquiterpenoid, (+)-5,8-dihydroxycalamenene (**11**), together with the previously known 13-epi-neoverrucosan-5β-ol (**2**) [6, 7], plagiochiline C (**10**) [1], (1*S*, 4*R*)-(+)-7-hydroxycalamenene (**12**) [6], of which heteroscyphone A (**3**) was the major component.

Verrucosanes

13-epi-Neoverrucosan-5β,20-diol (**1**), mp 157–159°, $C_{20}H_{34}O_2$ ([M]$^+$ at *m/z* 306.2559) contained a primary (δ_H3.45 *d*, *J* = 11 Hz, 3.67 *d*, *J* = 11.2 Hz), and a secondary hydroxyl group (δ_H4.03, *dd*, *J* = 11, 7 Hz) which were confirmed by the acetylation to give a diacetate (**13**), $C_{24}H_{38}O_4$ ([M]$^+$ at *m/z* 390.2770) (δ_H 2.05, 2.06 each 3H,





Scheme 1.

s). The presence of the two tertiary methyls, an isopropyl group and two protons on a cyclopropane ring was also confirmed by the ^{1}H NMR spectrum (Table 1). The signal patterns of the ^{1}H NMR spectra were very similar to those of 13-epi-neoverrucosan-5β-ol (**2**), except for the presence of the primary hydroxyl group, indicating that **1** might be a 13-epi-neoverrucosane-type diterpenoid possessing a 5β-hydroxyl group and a primary hydroxyl group at C-10, C-15 or C-20. This assumption was further confirmed by chemical transformation as follows. Tosylation of **1** with tosyl chloride in pyridine gave a mono tosylate (**14**), followed by reduction with Zn–NaI in hexamethylphosphoramide (HMPA) [9] to afford 13-epi-neoverrucosan-5β-ol (**2**) [6, 7] as shown in Scheme 1. The location of the primary hydroxyl group at C-20 was confirmed by the NOESY spectrum of **1** in which NOEs were observed between H-20 and H-15, H-16 and H-17. The NOE experiment (Scheme 1) of the tosylate (**14**) in which the NOEs were observed between (i) H-15 and H-16, (ii) H-16 and H-20, (iii) H-15 and H-17, (iv) H-2 and H-18, (v) H-5 and H-18, (vi) H-5 and H-19, and (vii) H-14 and H-19, further supported the stereostructure of **1**. On the basis of the above chemical and spectral data, the structure of **1** was established to be 13-epi-neoverrucosan-5β,20- diol.

Spiro-clerodanes and clerodane

Heteroscyphone A (**3**), $C_{22}H_{32}O_7$ ([M]$^+$ at *m/z* 408.2166, mp 217.5–220°) showed the presence of a tertiary hydroxyl group (3250 cm^{-1}; δ_C 73.3, *s*), a ketone (1740 cm^{-1}; δ_C 201.2, *s*), an acetoxyl (1720 cm^{-1}; δ_H 1.99, *s*), a hemiacetal group (δ_C 101.2, *d*) which was confirmed by the formation of a γ-lactone (**15**), $C_{22}H_{30}O_6$ (1760 cm^{-1}; δ_C 173.8, *s*) by oxidation with pyridinium chlorochromate (PCC)–Al_2O_3. The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of **3** contained three tertiary methyls, a secondary methyl, a vinyl group, three methylenes and two methines, two methines bearing ether oxygen and three quaternary carbons one of which possessed an ether oxygen. The degree of unsaturation was seven and thus **3** was a tetracyclic diterpenoid by considering each functional group. The ^{1}H–^{1}H, ^{13}C–^{1}H 2D NMR spectra and HMBC experiments showed the connectivity of each carbon as shown in Fig. 1. Miyashita

Table 1. ^{1}H NMR spectral data for **1–15** (TMS–$CDCl_3$)*

H	1	2	3	4	5	6†	7	8	9	10	11	12	13	14	15
1	—	1.42, 1.72 (each *m*)	—	—	—	1.53 (*m*)	2.72 (*dd*, 10, 3)	2.71 (*dd*, 10, 3)	—	—	—	1.38 1.78 (*m*)	—	1.26 (*m*)	—
2	—	—	—	—	—	—	6.73 (*d*, 10)	6.70 (*d*, 11)	—	—	—	—	—	0.59 (*m*)	—
3	0.28 (*t*, 5)	3.00 (*s*)	5.73 (*s*)	5.74 (*s*)	5.67 (*s*)	2.29 (*m*)	7.48 (*s*)	7.36 (*s*)	—	—	0.49 (*m*)	2.99 (*s*)	5.69 (*d*, 7)	0.25 (*t*, 5)	0.25 (*t*, 5)
5	4.04 (*dd*, 11, 8)	—	—	—	—	—	2.56 (*dd*, 10, 3)	2.55 (*dd*, 10, 3)	—	—	5.31 (*dd*, 10, 8)	—	—	4.02 (*dd*, 11, 8)	4.02 (*dd*, 11, 8)
6	—	2.96 (*m*)	—	—	—	1.07 (*m*) 1.63 (*dt*, 13, 3)	0.46 (*t*, 9)	0.45 (*t*, 10)	—	—	—	—	—	—	—
7	—	1.60 (*m*)	—	—	—	1.51 (*m*)	0.92 (*m*)	0.86 (*m*)	6.51 (*s*)	6.68 (*s*)	—	1.54 (*m*)	—	—	—
8	—	1.44 (*m*)	—	—	—	1.25 (*m*)	0.99 (*m*)	0.96 (*m*)	—	—	—	—	—	—	—
9	—	—	—	—	—	—	2.04 (*m*) 2.33 (*m*)	2.05 (*m*) 2.30 (*m*)	1.20 (*d*, 7)	1.07 (*d*, 7)	—	—	—	—	—
10	—	1.78 (*m*)	—	—	—	1.55 (*m*)	—	—	—	—	—	—	—	—	—
11	—	5.80 (*d*, 6)	5.91 (*d*, 5)	5.59 (*d*, 6)	6.15 (*d*, 6)	4.53 (*d*, 10)	1.03 (*s*)	1.01 (*s*)	0.81 (*d*, 7)	0.88 (*d*, 7)	—	5.56 (*d*, 7)	5.61 (*d*, 7)	—	—
12	—	3.81 (*d*, 6)	3.81 (*d*, 5)	3.68 (*d*, 7)	4.04 (*d*, 6)	5.05 (*d*, 11)	1.11 (*s*)	1.11 (*s*)	0.96 (*d*, 7)	1.08 (*d*, 6)	—	4.00 (*d*, 7)	4.03 (*d*, 7)	—	—
13	—	—	—	—	—	—	—	—	2.20 (*s*)	1.94 (*s*)	—	—	—	1.03 (*m*)	—
14	—	5.75 (*dd*, 17, 11)	5.79 (*dd*, 17, 11)	5.80 (*dd*, 17, 11)	5.94 (*dd*, 17, 11)	6.41 (*dd*, 17, 11)	4.77 (*d*, 2) 4.81 (*s*)	4.76 (*d*, 2) 4.80 (*s*)	—	—	—	5.71 (*dd*, 17, 11)	5.71 (*dd*, 17, 11)	1.66 (*dd*, 13, 7)	—
15		5.14 (*d*, 11) 5.43 (*dd*, 17, 11)	5.14 (*d*, 11) 5.47 (*d*, 17)	5.13 (*dd*, 11, 1) 5.38 (*dd*, 17, 11)	5.13 (*d*, 11) 5.49 (*d*, 17)	5.59 (*d*, 10)						5.19 (*d*, 11)	5.18 (*d*, 11)	1.87 (*m*)	
16	0.84 (*d*, 7)	1.36 (*s*)	1.44 (*s*)	1.44 (*s*)	1.31 (*s*)	1.75 (*s*)	—	3.73 (*s*)			0.89 (*d*, 7)	1.43 (*s*)	1.44 (*s*)	0.70 (*d*, 7)	0.86 (*d*, 7)
17	0.94 (*d*, 7)	5.25 (*s*)	—	3.92 (*d*, 10) 4.00 (*d*, 10)	6.44 (*d*, 6)	0.95 (*s*)					0.95 (*d*, 7)	—	—	0.86 (*d*, 7)	0.70 (*d*, 7)
18	1.22 (*s*)	1.01 (*d*, 7)	1.05 (*d*, 7)	1.09 (*d*, 6)	1.36 (*d*, 7)	0.89 (*s*)					1.13 (*s*)	1.01 (*d*, 7)	1.05 (*d*, 7)	1.23 (*s*)	1.23 (*s*)
19	0.85 (*s*)	1.27 (*s*)	1.86 (*s*)	1.85 (*s*)	1.99 (*s*)	1.55 (*s*)					0.91 (*s*)	1.28 (*s*)	1.88 (*s*)	0.79 (*s*)	0.79 (*s*)
20	3.45 (*d*, 11) 3.67 (*dd*, 11, 2)	1.20 (*s*)	1.16 (*s*)	0.91 (*s*)	1.54 (*s*)	1.00 (*s*)					3.97 (*d*, 11) 4.13 (*dd*, 11, 2)	1.43 (*s*)	1.39 (*s*)	3.85 (*d*, 10) 4.00 (*dd*, 10, 1)	3.85 (*d*, 10) 4.00 (*dd*, 10, 1)
2-Ac							2.13 (*s*)	2.11 (*s*)							
11-Ac		1.99 (*s*)	1.98 (*s*)	2.02 (*s*)	2.04 (*s*)	—						2.04 (*s*)	2.04 (*s*)	—	
20-Ac											2.06 (*s*)			—	

*These assignments were established by the COSY, NOESY, NOE-difference, CH-COSY and HMBC experiments. Coupling constants (J in Hz) are given in parentheses.
†Measured in acetone-d_6.

Table 2. ^{13}C NMR spectral data for **3–9** and **15** (TMS–$CDCl_3$)*

C	3	4	5	6†	7	8	9	15
1	36.9	37.4	35.2	38.0	20.1	51.2	51.2	36.0
2	201.2	201.2	198.8	198.8	26.6	91.9	91.9	204.6
3	63.4	125.6	126.0	125.2	120.8	153.4	151.3	62.7
4	72.2	171.6	170.5	170.6	143.9	114.4	114.9	72.3
5	37.9	40.1	40.0	40.1	38.5	32.3	32.6	37.8
6	35.9	36.1	35.3	42.8	36.2	30.0	30.1	34.4
7	28.6	28.1	27.9	72.9	28.6	28.9	28.7	27.4
8	35.9	35.8	35.0	40.0	36.0	26.0	25.9	34.9
9	56.5	55.7	51.8	55.8	46.8	34.9	34.8	55.1
10	50.3	46.7	45.9	47.3	46.8	147.9	148.0	49.0
11	74.4	74.4	76.4	74.5	74.9	20.1	19.8	73.4
12	87.3	87.1	85.9	87.5	132.6	28.7	28.8	84 2
13	73.3	73.1	74.4	73.1	136.1	15.6	15.4	73.1
14	139.4	139.5	139.6	140.9	141.6	116.9	116.5	137.8
15	115.3	115.1	114.4	101.5	112.7	169.7	166.3	115.9
16	25.5	25.3	25.0	25.8	12.5	—	51.0	173.8
17	18.2	18.5	18.3	15.9	16.7	—	—	19.0
18	19.5	19.2	19.2	18.8	18.1	—	—	20.7
19	16.5	18.5	17.8	20.7	19.6	—	—	25.8
20	101.2	101.4	69.4	101.5	13.8	—	—	18.2
2-Ac (C=O)	—	—		—	—	169.7	169.5	—
2-Ac (Me)	—	—	—	—	—	20.9	20.8	—
11-Ac (C=O)	169.9	—	170.0	169.5	—	—	—	169.7
11-Ac (Me)	20.7	20.7	20.9	20.4	—	—	—	20.7

*These assignments were established by the DEPT, CH-COSY, HMBC experiments.
†Measured in acetone-d_6.

reaction [10] of **3** gave an α,β-unsaturated ketone (**4**), $C_{22}H_{32}O_6$ (1740 cm^{-1}; λ_{max} 236 nm), which was oxidized with PCC–Al_2O_3 to furnish a γ-lactone (**16**), $C_{22}H_{30}O_6$ ($[M]^+$ at m/z 390.2042; 1760 cm^{-1}) as shown in Scheme 2. Thus, the gross structure of **3** was depicted as shown in Fig. 1 and its relative stereochemistry was suggested by the NOE experiment in which NOEs were observed between (i) H-16 and H-14, (ii) H-16 and H-12, (iii) H-12 and H-14, (iv) H-1 and H-11, (v) H-11 and H-17, (vi) H-12 and H-18, (vii) H-17 and H-20, (viii) H-19 and H-20, and (ix) H-3 and H-19. Fortunately, a specimen of **3** suitable for X-ray crystal structure determination crystallized from ether. The crystal structure is shown in Fig. 2. The absolute configuration of **3** was based on its negative Cotton effect [298 nm ($\Delta\varepsilon$ − 1.81)]. On the basis of the above data, the structure of heteroscyphone A was established to be *ent*-spiroclerodane-type diterpenoid (**3**).

The spectral data of heteroscyphone **B** (**4**), $C_{22}H_{32}O_6$ ($[M]^+$ at m/z 392.2199, mp 211.5–214°), resembled those of **3**, except for the presence of a trisubstituted double bond in place of the epoxide ring, indicating that **4** was the desepoxy compound of **3**. This presumption was supported by the chemical transformation as shown in Scheme 2. The spectral data of the α,β-unsaturated ketone which was obtained from **3** by the Miyashita reaction [10] were identical to those of the natural product (**4**).

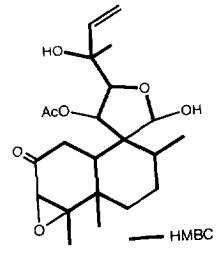
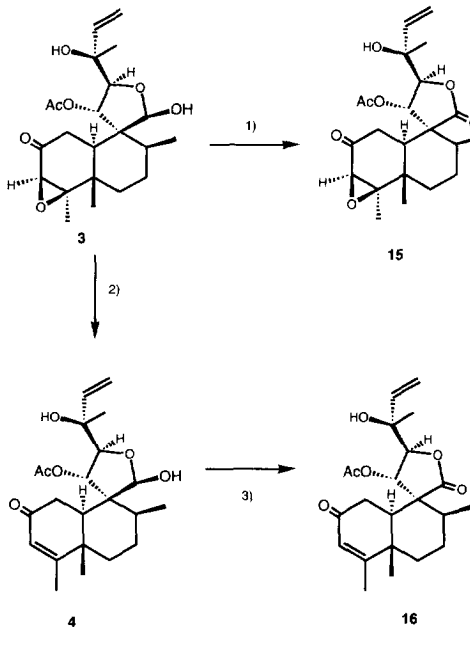


Fig. 1. HMBC of **3**.

The absolute configuration of **4** was also established by the negative Cotton effect at 329 nm ($\Delta\varepsilon$ −1.41).

Heteroscyphone C (**5**), $C_{22}H_{32}O_5$ ($[M]^+$ at m/z 376.2222, mp 72–74°), decreased one oxygen compared with **4**. The ^1H and ^{13}C NMR of **5** were similar to those of **4**, except for the presence of an additional methylene group [δ_H3.92, 4.00 (*d*, J = 10 Hz); δ_C69.4, *s*) bearing an ether oxygen in place of the hemiacetal group, showing that **5** might be a deoxy derivative of **4**. This assumption was further confirmed by the 2DNMR (^1H–^1H, ^{13}C–^1H) and NOE experiments (Fig. 3) of **5**. On the basis of the above spectral data and the negative Cotton effect at 329 nm ($\Delta\varepsilon$ −1.73), the structure **5** was given to heteroscyphone C.



Scheme 2.

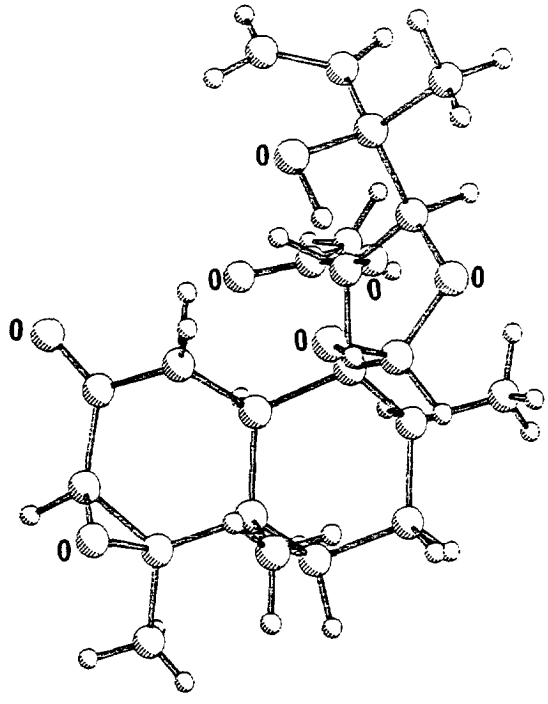


Fig. 2. ORTEP drawing of heteroscyphone A (**3**).

Heteroscyphone D (**6**), $C_{22}H_{32}O_7$ ($[M-H_2O]^+$ at m/z 390.2012, mp 138–140.5°), increased one oxygen compared with **4**. The ^1H and ^{13}CNMR spectra (Tables 1 and 2) were similar to those of **4** except for the presence of a methine (δ_H4.15, *m*, δ_C72.9, *d*) bearing a hydroxyl group, suggesting that **6** possessed the same structure as **4**, with the secondary hydroxyl group at C-6 or C-7. The position of an axial hydroxyl group at C-7 was confirmed by HMBC experiment, the presence of the lower shift of H-17 (Δ −0.34) and H-19 (Δ −0.38) by the β-axial hydroxyl group at C-7 and the presence of the NOEs between H-1 and H-7. The absolute configuration was also established by the negative Cotton effect at 333 nm ($\Delta\varepsilon$ −1.29).

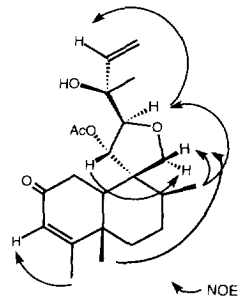


Fig. 3. Difference NOEs of **5**.

Heteroscyphol (**7**), $C_{20}H_{32}O$ ($[M]^+$ at m/z 288.2463), showed the presence of an olefin group (1610 cm^{-1}), a conjugated double bond (λ_{max} 232 nm), and an allylic secondary hydroxyl group (3400 cm^{-1}; δ_C74.9, *d*; δ_H4.53, *d*, J = 10 Hz) which was confirmed by the formation of an α,β-unsaturated ketone (**17**), $C_{20}H_{30}O$ ($[M]^+$ at m/z 286; λ_{max} 268 nm), by the oxidation of **7** with PCC–Al_2O_3. The ^1H NMR (Table 1) showed the presence of two tertiary methyls, two vinyl methyls, a methine bearing a trisubstituted double bond and a conjugated vinyl group. The HMBC spectrum of **7** indicated the connectivity between the conjugated double bond and the trisubstituted double bond and a vinyl group as well as that of A- and B-ring carbons, as shown in Fig. 4, indicating that **7** possessed the clerodane skeleton. The clerodane structure was further confirmed by the 2D (^1H–^1H and ^{13}C–^1H) NMR spectra. The relative stereochemistry of **7** was determined by the presence of NOEs (Fig. 5) between (i) H-1 and H-12, (ii) H-11 and H-17, (iii) H-11 and H-16, (iv) H-12 and H-14, (v) H-15 and H-16 and the absence of those between H-10 and H-18, H-19 and H-20, respectively. The absolute configuration of **7** was tentatively given by consideration of co-occurring the spiroclerodanes (**3–6**), although the stereochemistry at C-11 has not been clarified. Thus, the structure of heteroscyphol was characterized to be *ent*-cleroda-3,12(*E*),14-trien-11-ol (**7**).

Ent-2,3-*secoaromadendranes*

The IR spectrum of **8**, $C_{17}H_{22}O_5$ ($[M]^+$ at m/z 306.1494; mp 158–161°), indicated the presence of an ester group (1760 cm^{-1}) and a conjugated carboxylic acid (2930, 1680 cm^{-1}) which was confirmed by the formation of a mono methyl ester, $C_{18}H_{24}O_5$ ($[M]^+$ at m/z 320.1616; 1710 cm^{-1}; δ_H 3.73, *s*) which was identical with the natural plagiochiline M (**9**). The ^1H and ^{13}CNMR (Tables 1 and 2) and DEPT spectra of **8**, showed the

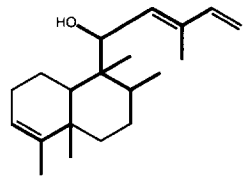


Fig. 4. HMBC of **7**.

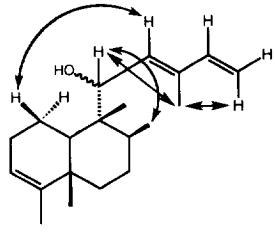


Fig. 5. Difference NOEs of **7**.

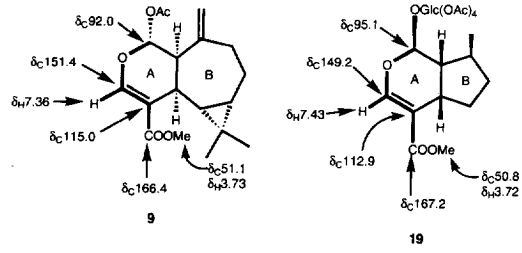


Fig. 6.

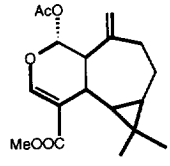


Fig. 7. HMBC of **9**.

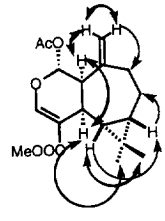
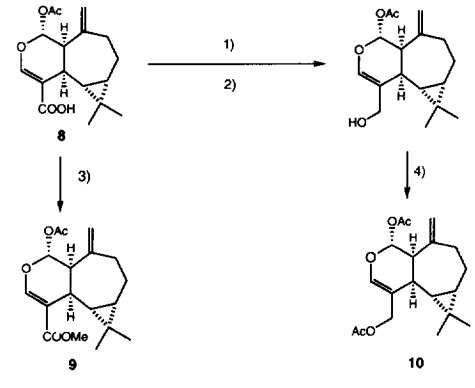


Fig. 8. Difference NOEs of **9**.

presence of three tertiary methyls, three methylenes, six methines, an exomethylene, a trisubstituted double bond [δ_H7.36, *s*; δ_C153.4, *d*,114.4, *s*], an acetoxyl group, a hemiacetal [δ_H6.73, *d*, $J=10$ Hz; δ_C91.9, *d*]. The structure of the ring A in **9** was confirmed by the similarity of the ^{1}H and ^{13}C NMR spectra between **9** and iridoid glucoside, deoxyloganin tetraacetate (**19**) [11], as shown in each structure (Fig. 6). The NMR spectral data of the B-ring of **9** resembled those of the B-ring of plagiochiline C (**10**) [1] which co-occurred in the same plant. These spectral data led to the structure of **8** for plagiochiline L. The 2D NMR (^{1}H–^{1}H and ^{13}C–^{1}H) and HMBC spectra (Fig. 7) supported this structure. The relative stereochemistry of **9** was established by the presence of the NOEs (Fig. 8) between (i) H-3 and H-11, (ii) H-11 and H-7, (iii) H-8 and H-9, (iv) H-1 and H-5, (v) H-1 and H-11, (vi) H-6 and H-7, (vii) H-7 and H-8, (viii) H-5 and H-15, (ix) H-6 and H-15 and (x) H-9 and H-11. The structure of **8** was conclusively established by the following chemical transformation: treatment of **8** (Scheme 3) with oxalyl chloride and $NaBH_4$ [12], followed by acetylation without purification to give the known plagiochiline C (**10**) [1].



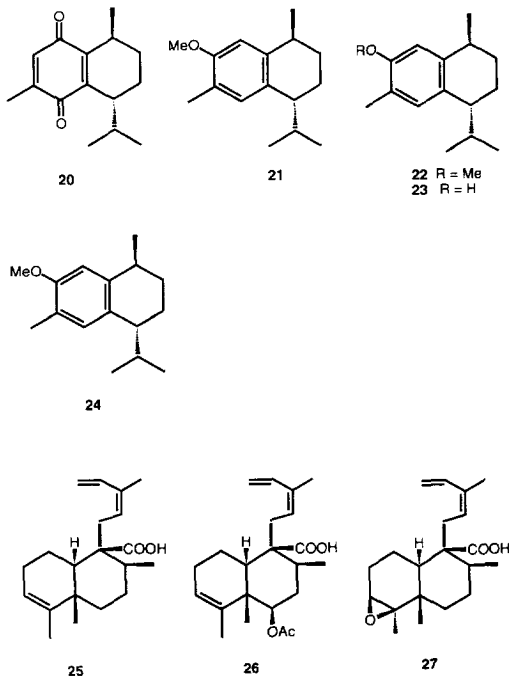
1) $COCl_2$ / THF, -30°, 1hr 2) $NaBH_4$ / DMF, -78 to -20°, 2hr
3) CH_2N_2 / Et_2O, r.t, 15min 4) Ac_2O / Py, r.t, 4hr

Scheme 3.

Calamenenes

The IR spectrum of **11**, $C_{15}H_{22}O_2$ ([M]$^+$ at *m/z* 234.1619), showed the presence of a hydroxyl (3450 cm^{-1}) and an aromatic group [λ_{max} 214 nm (log ε 4.20), 275 (3.33); 1500 cm^{-1}]. The ^{1}H NMR spectrum (Table 1) contained a methyl group (δ_H2.20, *s*) on a benzene ring, an isopropyl (δ_H0.81, 0.96, each *d*, $J=7$ Hz) and a secondary methyl group (δ_H1.20, *d*, $J=7$ Hz) and an isolated aromatic proton (δ_H6.51, *s*). The above molecular formula and spectral data led to the structure of 5,8-dihydroxycalamenene for **11**. This was further confirmed by the formation of 5,8-naphthoquinone from **11** by autooxidation. The absolute configurations at C-1 and C-4 were assigned to be 1*S* and 4*R* by consideration of co-occurring (1*S*, 4*R*)-7-hydroxycalamenene (**12**) in the same plant or its suspension cultured cell [8].

During the course of our investigation of *Heteroscyphus planus*, Nabeta *et al.* [8, 13] reported the isolation of the four calamenene-type sesquiterpenoids (**21**–**24**), and clerodane-type carboxylic acids (**25**–**27**) from *in vitro* cultured *H. planus* which might be the precursor of the



spiroclerodane-type diterpenoids. However, these diterpene acids and calamenenes have not been found in the field *H. planus* which contained **1–11**. We isolated the *ent*-clerodane-type diterpenoid, (+)-junceic acid (**18**) [2] from *H. coalitus* (*H. bescherellei*), but this furanoditerpenoid has not been isolated from *H. planus*.

The Jungermanniaceae [14–20], Schistochilaceae [21–23] and Lophoziaceae [24–27] in Hepaticae are rich sources of clerodane-type diterpenoids. This is the first report of the isolation of highly oxygenated clerodane diterpenoids possessing a spiro structure from the Hepaticae and *ent*-2,3-secoaromadendrane-type sesquiterpenoids from the Lophocoleaceae.

The Lophocoleaceae are divided into five genera: *Heteroscyphus*, *Chiloscyphus*, *Clasmatocolea*, *Leptoscyphus* and *Lophocolea*. *Heteroscyphus* is chemically quite different from *Chiloscyphus* and *Clasmatocolea* because the latter two genera elaborate mainly eudesmane-type sesquiterpene lactones [1]. *Lophocolea* is chemically close to *Chiloscyphus* and *Clasmatocolea* because it biosynthesizes eudesmane-type sesquiterpene lactones [28], although the content of the other sesquiterpenoids are different between these three genera. The present *H. planus* biosynthesizes highly oxygenated *ent*-clerodane-type diterpenoids (**3–6**), together with *ent*-2,3-secoaromadendrane-type sesquiterpenoids (**8** and **9**) which are significant chemical markers of the Plagiochilaceae and calamenene-type sesquiterpenoids widely distributed in the Jungermanniales. Thus, *H. planus* is chemically rather similar to *Plagiochila* species belonging to chemotype I which produce *ent*-2,3-secoaromadendranes, although clerodane-type diterpenoids have not been found in any *Plagiochila* species so far examined. *Heteroscyphus planus* is closely related with *H. coalitus* (=*H. bescherellei*) since both species elaborate *ent*-clerodane-type diterpenoids.

EXPERIMENTAL

Mps: uncorr. Solvents for spectral measurements were TMS–$CDCl_3$ or TMS–Me_2CO-d_6 [^{1}H NMR (400 and 200 MHz); ^{13}C NMR (50 MHz and 100 MHz)]; $CHCl_3$ ($[\alpha]_D$ and CD spectra); unless otherwise stated. EtOH (UV); $CHCl_3$–MeOH was used for Sephadex LH-20 CC.

Plant material. Heteroscyphus planus (Mitt.) Schiffn. was collected in Bizan, Tokushima in December, 1991 and identified by Dr M. Mizutani. A voucher specimen is deposited in the Institute of Pharmacognosy, Tokushima Bunri University.

Extraction and isolation. The fresh material (dry weight 566.7 g) was ground mechanically and the powder extracted with ether (2.5 l) for 10 days. After filtration and evapn of the solvent, the crude extract (11.63 g) was chromatographed on silica gel (347 g) using *n*-hexane–EtOAc gradient to give 46 frs: frs 9–13 gave plagiochiline M (**9**) (227 mg). Crystalline material from fr. 15 was filtered to give plagiochiline L (**8**) (456 mg). The mother liquor was rechromatographed on silica gel with *n*-hexane–EtOAc gradient to give plagiochiline C (**10**) [1] (280.5 mg). Frs 16 and 17 were rechromatographed on Sephadex LH-20 to give heteroscyphol (**7**) (227.5 mg) and (1*S*, 4*R*)-(+)-7-hydroxycalamenene (**12**) [8] (29.5 mg). Fr. 19 was treated in the same manner as described to give 13-epi-neoverrucosan-5β-ol (**2**) (127.8 mg) [6, 7]. (+)-5,8-Dihydroxycalamenene (**11**) (208.9 mg) was obtained from frs 23–25 as pure state. Fr. 32 was rechromatographed on silica gel with *n*-hexane–EtOAc gradient to give heteroscyphone A (**3**) (770.5 mg). Frs 33–37 contained diterpene mixts which were chromatographed on silica gel using the same solvent described above to give 13-epi-neoverrucosan-5β,20-diol (**1**) (127.8 mg), heteroscyphone B (**4**) (285 mg) and heteroscyphone C (**5**) (152 mg). Frs 45 and 46 gave heteroscyphone D (**6**) (76 mg).

13-epi-*Neoverrucosan-5*β,*20-diol* (**1**). Mp 220–221.5°; $[\alpha]_D$ +56.3 (*c* 0.77). IR ν_{max}^{KBr} cm^{-1}: 3300, 2900, 1460, 1030, 1010. ^{1}H NMR (Table 1). HRMS: found: 306.2567, $C_{20}H_{34}O_2$ requires 306.2559. EI-MS *m/z* (rel. int.): 306 $[M]^+$ (2), 288 (13), 273 (100), 257 (91), 245 (22), 230 (45), 215 (39), 201 (44), 187 (46), 175 (35), 161 (47), 149 (55), 135 (60), 119 (66), 107 (63), 95 (67), 81 (57), 69 (43), 55 (28), 41 (24). Anal. calcd for $C_{20}H_{34}O_2$; C; 78.38, H; 11.18; found: C; 78.14, H; 11.28.

Heteroscyphone A (**3**). Mp 217.5–220°; $[\alpha]_D$ +24.0 (*c* 0.98). IR ν_{max}^{KBr} cm^{-1}: 3250, 2930, 1740, 1720, 1440, 1360, 1230, 1020. CD: $\Delta\varepsilon$ 298 nm −1.81. ^{1}H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 408.2157, $C_{22}H_{32}O_7$ requires 408.2166. EI-MS *m/z* (rel. int.): 408 $[M]^+$ (1), 390 (1), 375 (2), 363 (0.8), 337 (42), 319 (11), 295 (6), 278 (100), 259 (15), 249 (20), 231 (37), 213 (20), 203 (24), 189 (35), 85 (23), 71 (49), 55 (17), 43 (75). X-Ray crystallographic analysis: unit-cell dimensions; $a=13.51$, $b=20.1$, $c=8.21$: crystal system: orthorhombic: linear absorption coefficient; 6.59 cm^{-1} (Cu κ-alpha): diffractometer used; Mac Science MXC18 (direct method, Montecalro-Multan):

radiation; Cu κ-alpha (lambda = 1.54): unique reflections; 212: residuals (*R*); 0.032.

Heteroscyphone B (**4**). Mp 211.5–214°; $[\alpha]_D$ +17.1 (*c* 0.80); UV: λ_{max} (log ε): 236 (4.11). IR ν_{max}^{KBr} cm^{-1}: 3440, 3200, 2950, 1740, 1620, 1360, 1240, 1030, 1010. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 392.2195, $C_{22}H_{32}O_6$ requires 392.2199. EI-MS *m/z* (rel. int.): 392 $[M]^+$ (3), 374 (5), 321 (100), 279 (32), 262 (54), 216 (64), 201 (52), 189 (25), 173 (20), 159 (16), 135 (49), 123 (23), 109 (14), 95 (15), 83 (29), 71 (22), 55 (12), 43 (35). Anal. calcd for: $C_{22}H_{32}C_6$: C; 66.43, H; 8.13; found: C; 67.32, H; 8.22.

Heteroscyphone C (**5**). Mp 72–74°; $[\alpha]_D$ −21.4 (*c* 0.76). UV: λ_{max} (log ε): 237 (4.04). IR: ν_{max}^{KBr} cm^{-1}: 3500, 3350, 2920, 1730, 1440 1660, 1620, 1380, 1240, 1080, 1040, 920, 840, 800, 740. CD: Δε 329 nm − 1.72, Δε 259 nm + 0.63. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 376.2222, $C_{22}H_{32}O_5$ requires 376.2250. EI-MS *m/z* (rel. int.): 376 $[M]^+$ (3), 333 (2), 316 (8), 305 (87), 263 (100), 246 (59), 231 (19), 217 (6), 203 (14), 189 (24), 175 (9), 161 (13), 135 (18), 123 (27), 109 (14), 95 (13), 83 (19), 71 (10), 55 (9), 43 (25).

Heteroscyphone D (**6**). Mp 138–140.5°: $[\alpha]_D$ −13.8 (*c* 0.55). UV: λ_{max} (log ε): 234.5 (4.05). IR ν_{max}^{KBr} cm^{-1}: 3500, 3350, 2980, 2950, 1740, 1660, 1230, 1060,.1030, 930 840. CD: Δε 333 nm −1.29 (MeOH). ^1H and ^{13}C NMR Tables 1 and 2). HRMS: found: 390.2012, $C_{22}H_{30}O_6$ ($C_{22}H_{32}O_7$–H_2O) requires 390.2042. EI-MS *m/z* (rel. int.): 408 $[M]^+$ (0.3), 390 (4), 337 (63), 319 (84), 295 (11), 277 (100), 259 (19), 249 (11), 232 (21), 199 (23), 189 (14), 175 (22), 165 (14), 149 (13), 135 (57), 123 (32), 109 (18), 95 (27), 83 (31), 71 (24), 55 (13), 43 (52).

Heteroscyphol (**7**). Oil: $[\alpha]_D$ − 37.5 (*c* 0.55). UV: λ_{max} (log ε): 232 (4.59). FT-IR ν_{max} cm^{-1}: 3400, 2920, 1610, 1450, 1380, 990, 900, 760. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 288.2458, $C_{20}H_{32}O$ requires 288.2463. EI-MS *m/z* (rel. int.): 288 $[M]^+$ (0.3), 191 (43), 175 (15), 161 (3), 147 (2), 135 (9), 121 (22), 107 (42), 95 (100), 81 (11), 69 (7), 55 (9), 41 (8).

Plagiochiline L (**8**). Mp 158–161°; $[\alpha]_D$ + 9.6 (*c* 0.63). UV: λ_{max} (log ε): 207.5 (3.71), 235 (3.99). FT-IR ν_{max} cm^{-1}: 2930, 2820, 1780, 1680, 1630, 1430, 1370, 1300, 1220, 1180, 1080, 1060, 960, 910. CD: Δε 271 nm − 0.53. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 306.1494, $C_{17}H_{22}O_5$ requires 306.1427. EI-MS *m/z* (rel. int.): 306 $[M]^+$ (8), 246 (72), 228 (35), 203 (100), 185 (30), 175 (27), 163 (19), 147 (22), 131 (16), 122 (20), 107 (19), 91 (23), 82 (26), 69 (21), 43 (94).

Plagiochiline M (**9**). Mp 94–96°; $[\alpha]_D$ +9.7 (*c* 0.76). UV: λ_{max} (log ε): 204.5 (3.49), 237.5 (3.81). IR ν_{max}^{KBr} cm^{-1}: 2950, 1760, 1710, 1630, 1630, 1440, 1370, 1300, 1240, 1180, 1080, 960, 910, 770, 620, 410. CD: Δε 252 nm −0.40. ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 320.1616, $C_{18}H_{24}O_5$ requires 320.1624. EI-MS *m/z* (rel. int.): 320 $[M]^+$ (73), 277 (11), 260 (64), 245 (28), 231 (77), 217 (96), 203 (47), 185 (37), 175 (27), 147 (27), 109 (26), 91 (38), 82 (40), 69 (23), 43 (100).

(+)-5,8-*Dihydroxycalamenene* (**11**). Oil; $[\alpha]_D$ +45.6 (*c* 0.31). UV: λ_{max} (log ε): 214 (4.20), 275.7 (3.33). FT-IR ν_{max} cm^{-1}: 3450, 2960, 2870, 1710, 1630, 1500, 1470, 1300, 1230, 1040, 930, 890, 800, 570, 470, 450. CD: Δε 295 nm −0.85, CD: Δε 245 nm −0.65. ^1H NMR (Table 1). HRMS: found: 234.1597, $C_{15}H_{22}O_2$ requires 234.1619. EI-MS *m/z* (rel. int.): 234 $[M]^+$ (20), 191 (100), 173 (22), 145 (7), 115 (2), 91 (2). ^{13}C NMR (100 MHz): δ15.6 (*q*), 19.3 (*t*), 19.6 (*q*), 21.1 (*q*), 22.1 (*q*), 27.0 (*t*), 27.1 (*d*), 33.1 (*d*), 42.6 (*d*), 120.7 (*s*), 123.0 (*d*), 127.1 (*s*), 132.2 (*s*), 139.3 (*s*), 141.1 (*s*).

Acetylation of 13-*epi-neoverrucosan*-5β,20-*diol* (**1**). Compound **1** (20 mg) was acetylated with Ac_2O (2 ml) and pyridine (2 ml) for 34 hr at room temp. Work-up as usual afforded a diacetate (**13**) (16 mg): mp 220–221.5°. ^1H NMR (Table 1). HRMS: 390.2743, $C_{24}H_{38}O_4$ requires 390.2770. EI-MS *m/z* (rel. int.): 390 $[M]^+$ (40), 347 (6), 330 (60), 317 (39), 288 (21), 270 (32), 257 (100), 227 (62), 217 (14), 203 (21), 189 (37), 147 (25), 133 (33), 119 (39), 105 (38), 95 (32), 81 (29), 69 (24), 55 (18), 41 (15).

Tosylation of 13-*epi-neoverrucosan*-5β,20-*diol* (**1**). To **1** (21 mg) in pyridine (2 ml) was added *p*-TsCl (80 mg) and the mixt. allowed to stand for 48 hr. Work-up as usual gave a mono tosylate (**14**) (7 mg) as an oil: $[\alpha]_D$ + 21.4 (*c* 0.86); UV λ_{max} (log ε): 225.5 (3.99); IR ν_{max}^{Neat} cm^{-1}: 3400, 2940, 2970, 2870, 1600, 1460, 1180, 950, 820, 840, 660. ^1H NMR (Table 1).

Reduction of tosylate (**14**). To the mono tosylate (**14**) (5 mg) in HMPA (2 ml) was added NaI (29 mg) and Zn (48 mg) and the mixt. stirred for 14 hr at 105°. The reaction mixt., after filtration, was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over $MgSO_4$ and the solvent was evapd to give the residue which was chromatographed on silica gel (*n*-hexane–EtOAc gradient) to furnish a mono alcohol (2 mg) whose spectral data were identical to those of authentic 13-epi-neoverrucosane-5β-ol (**2**).

Oxidation of heteroscyphone A (**3**). To the soln of **3** (40 mg) in dry CH_2Cl_2 (10 ml) was added PCC–Al_2O_3 (244 mg) and the mixt. stirred for 20 hr at room temp. The reaction mixt. was filtered through a short column packed with silica gel using EtOAc as a solvent and the filtrate, after removal of solvent, was chromatographed on silica gel to give **15** (36.3 mg); mp 197–198°; $[\alpha]_D$ +14.5 (*c* 0.41); IR ν_{max}^{KBr} cm^{-1}: 3250, 2930, 1760, 1720, 1360, 1280, 1230, 1020. CD: Δε 257 nm + 0.92; CD: Δε 315 nm −1.57; ^1H and ^{13}C NMR (Tables 1 and 2). HRMS: found: 406.1988, $C_{22}H_{30}O_7$ requires 406.1992. EI-MS *m/z* (rel. int.): 406 $[M]^+$ (39), 391 (32), 363 (47), 346 (14), 335 (20), 295 (10), 276 (61), 258 (14), 247 (25), 234 (38), 189 (22), 166 (49), 148 (38), 135 (24), 111 (32), 95 (21), 79 (16), 71 (48), 55 (23), 43 (100).

Miyashita reaction [10] *of* **3**. To $(PhSe)_2$ (36 mg) in EtOH (3 ml) was added $NaBH_4$ (12.8 mg) and the mixt. stirred for 20 min at room temp. and then one drop of $MeCO_2H$ was added at 0°, followed by **2** (19.8 mg) and the mixt. stirred for 15 min at room temp. in an Ar stream. The reaction mixt. was extracted with EtOAc, washed with NaCl and dried over Na_2SO_4, filtered and the solvent evapd to afford **3** (12 mg), the spectral data of which were identical to those of the natural heteroscyphone B.

Oxidation of heteroscyphone B (**4**). To the soln of **4** (37.1 mg) in dry CH_2Cl_2 (10 ml) was added PCC–Al_2O_3

(243.4 mg) and the mixt. stirred for 20 hr at room temp. The reaction mixt. was treated as described above to give **16** (18.8 mg) as crystals; mp 181–183°; $[\alpha]_D$ +23.1 (*c* 0.14). UV: λ_{max} (log ε): 239.5 (3.97). IR ν_{max}^{KBr} cm^{-1}: 3450, 2950, 1760, 1670, 1240, 1040. CD: $\Delta\varepsilon$ 329 nm −2.39, $\Delta\varepsilon$ 263 nm +0.76; ^1H NMR (Table 1). HRMS: found: 390.2032, $C_{22}H_{32}O_6$ requires 390.2042. EI-MS *m/z* (rel. int.): 390 $[M]^+$ (53), 375 (100), 357 (58), 348 (20), 320 (35), 277 (65), 261 (55), 242 (16), 233 (30), 217 (24), 199 (19), 95 (19), 83 (41), 71 (32), 43 (50).

Oxidation of heteroscyphol (**7**). Compound **7** (40 mg) in dry CH_2Cl_2 (10 ml) was treated with PCC–Al_2O_3 (244 mg) in the same manner as described above to give **7** (4 mg) as an oil. $[\alpha]_D$ −55.7 (*c* 0.29). UV: λ_{max} (log ε): 268 (4.62), 204.5 (4.35). IR ν_{max}^{Neat} cm^{-1}: 2930, 1730, 1670, 1580, 1460, 1380, 1040, 450. CD: $\Delta\varepsilon$ 300 nm +0.19. EI-MS *m/z* (rel. int.): 286 $[M]^+$ (8), 236 (2), 223 (3), 207 (4), 191 (41), 175 (17), 163 (4), 149 (23), 135 (14), 121 (23), 107 (43), 95 (100), 81 (16), 69 (12), 55 (12), 43 (20).

Methylation of **8** *with diazomethane.* To **8** (29.7 mg) in Et_2O (2 ml) was added CH_2N_2–Et_2O (5 ml) at 0° and the mixt. allowed to stand for 15 min. The reaction mixt. was purified by CC on silica gel using *n*-hexane–EtOAc (9:1) as eluent to give a methyl ester (28.6 mg) whose spectral data were identical to those of natural plagiochiline M (**9**).

Reduction of **8**. To $(COCl)_2$ (0.5 ml) in DMF (0.2 ml) was added **8** (9.2 mg) in THF (3 ml), then $NaBH_4$ (33.1 mg) in DMF (3 ml) was added at −78° and the mixt. then allowed to stand for 2 hr at −20°. The reaction mixt. was washed with 1 N HCl, 5% $NaHCO_3$, satd NaCl successively and dried over $MgSO_4$, filtered and evapd to give a residue which was acetylated with Ac_2O (1 ml) and pyridine (1 ml) for 4 hr with stirring. Work-up as usual gave a diacetate (2 mg), the spectral data of which were identical to those of plagiochiline C (**10**) [1].

Formation of (1S, 4R)*-calamenene-5,8-quinone* (**20**). Compound **11** (209 mg) was purified by CC on silica gel using an EtOAc–$CHCl_3$ gradient. A pale yellow material and **11** were obtained and each compound was isolated by prep. TLC to give **11** (96 mg) and (1*S*,4*R*)-calamenene-5,8-quinone (**20**) (13 mg) as oil: $[\alpha]_D$ +237.2 (*c* 0.55). UV: λ_{max} (log ε): 212.5 (3.98). FT-IR ν_{max} cm^{-1}: 3400, 2950, 2930, 2860, 1680, 1660, 1650, 1590, 1450, 1400, 1260, 1040, 900, 720. EI-MS *m/z* (rel. int.): 234 $[M]^+$ (3), 204 (24), 191 (17), 161 (100), 147 (9), 133 (6), 105 (7), 91 (8), 77 (4), 41 (5).

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