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PREPARATION OF BIOLOGICALLY ACTIVE SUBSTANCES AND ANIMAL AND MICROBIAL METABOLITES FROM MENTHOLS, CINEOLES AND KAURANES

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Key Word Index—*Cryptomeria japonica*; Taxodiaceae; *l*-menthol; *l*-menthyl acetate; iso-menthol; neo-menthol; 1,4-cineole; 1,8-cineole; *ent*-kaurene; hydroxylated menthols, cineoles and kauranes; *meta*-chloroperbenzoic acid; dry ozonization; plant growth inhibitor; mosquito repellent; animal and microbial metabolites; mono- and diterpenoids

Abstract—Six monoterpenoids, *l*-menthol, *l*-menthyl acetate, iso-menthol, neo-menthol, 1,4-cineole and 1,8-cineole and one diterpene hydrocarbon, *ent*-kaurene were oxidized by *meta*-chloroperbenzoic acid or dry ozone to give various hydroxylated products and their structures elucidated by NMR spectroscopy. Some hydroxylated menthols showed plant growth inhibitory and strong mosquito repellent activity. Among the hydroxylated cineoles, microbial and animal metabolites of cineoles were included. From *ent*-kauranes, a plant growth inhibitory diterpene alcohol, (−)-16α-hydroxy kaurane was obtained along with 16α-kauran-13α-ol.

INTRODUCTION

Monoterpenoids are widespread in the plant kingdom as essential oils and used as perfumes, drugs, paint plasticizers and starting materials for organic synthesis and so on. In order to obtain biologically active compounds, various biological hydroxylations of terpenoids and steroids have been carried out by using micro-organisms, plant tissue cultures and mammals. In previous papers [1–6], we reported that *meta*-chloroperbenzoic acid (MCPBA) was a useful oxidising reagent to introduce a hydroxyl group at non-activated carbon atoms of sesqui-, di- and triterpenoids. Application of this oxidation method to aromatic hydrocarbons and phenolic compounds led to the preparation of 1,4- and 1,2-quinones in good yield [7]. In this paper, we report the structures and biological activities of oxidation products of several monoterpenoids and kaurane-type diterpenoids obtained by MCPBA treatment and dry ozonization.

RESULTS AND DISCUSSION

MCPBA oxidation of menthols **1**, **7**, **12** *and* **20**

Menthols **1**, **7**, **12**, and **20** in chloroform were oxidized by MCPBA (1.2–2.2 eq) under reflux for 20–24 hr. The resulting products, after removal of the excess MCPBA and *meta*-chlorobenzoic acid, were chromatographed on silica gel, Sephadex LH-20, or a combination of silica gel chromatography and HPLC to give each oxidation product (Table 1). From *l*-menthol (**1**) the compounds obtained were *l*-menthone (**2**), mentholactone (**3**), and three hydroxylated menthols (**4**–**6**). The spectral data of **3** showed the presence of an ester carbonyl group (δ 175.0; and 1720 cm^{-1}), three secondary methyls (δ 0.97, 0.98, 1.04) and a methine group δ 84.8, *d*) bearing an ester oxygen, indicating **3** to be 3,4-*seco*-*l*-mentholactone which might be formed from **2** by Baeyer–Villiger oxidation. The presence of the secondary and tertiary hydroxyl groups in compounds **4**–**6** was confirmed by their IR, ^{13}C NMR and mass spectra (Table 2). Compound **4** contained in its ^1H NMR spectrum the signals of three secondary methyls and one methine proton (δ 2.08, *septet*, $J=7$ Hz) shifted at the lower field. These data suggested that **4** was 4β-hydroxy-*l*-menthol. This assumption was further supported as follows. *trans*- and *cis*-Diols have been obtained from (1*R*,4*R*)-4-hydroxymenthone by lithium aluminium hydride reduction [8]. The spectral data of **4** were consistent with those of the *cis*-isomer. The structure of **5** was directly confirmed to be 8-hydroxy-*l*-menthol by the presence of one doublet at δ 0.92 (3H, $J=7$ Hz) and one singlet signal at δ 1.22 (6H) as well as the base peak at *m/z* 59 $[(Me)_2COH]^+$. The ^1H NMR spectrum of **6** contained the signals of two secondary methyls (δ 0.98, 1.03) and one tertiary methyl group (δ 1.43) resonated in the lower field, indicating that **6** might be 1-hydroxy-*l*-menthol. This was further confirmed by the identical melting point and specific optical rotation values of the known 1α-hydroxy-*l*-menthol (**6**) [9]. As the hydroxyl group at C-3 of *l*-menthol was oxidized to give *l*-menthone (**2**), followed by Baeyer–Villiger oxidation to afford 3,4-secolactone (**3**), the yield of the hydroxylated products was low.

Next, the secondary hydroxyl group of **1** was protected by an acetyl group and the *l*-menthyl acetate (**7**) was oxidized by MCPBA to furnish four hydroxylated products (**8**–**11**). Neither ketone nor lactonized products were obtained from compound **7**. The structures of **8** and **9** were easily established by the presence of the septet signal (δ 1.82, H-8) in the ^1H NMR spectrum of **8** and two tertiary methyls (δ 1.14, 1.16), one secondary methyl group (δ 0.91, $J=7$ Hz) and *m/z* 59 (base peak) in the ^1H NMR and mass spectra, respectively, of **9**. The structures of **10** and **11** were determined to be 1-hydroxy-*l*-menthyl acetates by

Table 1. Oxidation products of menthols, cineoles and kauranes produced by MCPBA treatment*

Starting material (g)	Product	Isolated yield (%)	MCPBA (eq)	Reaction time (hr)
l-Menthol (**1**) (8.0)	**2**	14.5	2.2	20
	3	39.3		
	4	6.6		
	5	25.6		
	6	4.2		
l-Menthyl acetate (**7**) (5.0)	**8**	10.8	1.2	24
	9	25.1		
	10	32.4		
	11	21.6		
Iso-menthol (**12**) (8.0)	**13**	2.4	2.2	20
	14	52.4		
	15	6.4		
	16	14.2		
	17	4.4		
	19	11.6		
Neo-menthol (**20**) (5.0)	**2**	5.8	1.2	24
	3	70.5		
	21	13.3		
	22	13.3		
1,4-Cineole (**23**) (13)	**24**	31.3	1.2	20
	25	3.4		
	26	2.9		
	27	8.5		
1,8-Cineole (**31**) (3.0)	**32**	1.8	1.2	20
	33	7.2		
	34	18.1		
	35	10.9		
Kauranes (**37**) (2.0)	**38**	20.0	2.0	6
	39	2.0		

* The starting materials were oxidized by MCPBA under reflux at 65–75°.

their ^1H and ^{13}C NMR spectra. The stereostructures of each compound were further established by difference NOE examinations. Compound **10** showed the NOE between H-3 and the isopropyl methyls, on the other hand, compound **11** indicated the NOEs between H-3 and H_3-7 and between H-3 and the isopropyl methyls. Thus, the structures of **10** and **11** were 1α-hydroxy-*l*-menthyl acetate and its C-1 isomer, respectively. Iso-menthol (**12**) was treated in the same manner as described above to give iso-menthone (**13**), iso-mentholactone (**14**) and four hydroxylated products (**15**–**17**, **19**). The structure of 3,4-*seco*-iso-mentholactone (**14**) was confirmed by the

Table 2. ^{13}C NMR chemical shifts of menthols, cineoles and their oxidation products*

C	**1**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**16**	**17**	**19**
1	31.8	31.0	31.4	70.3	31.5	30.9	31.3	70.8	70.9	26.2	25.7	28.2	71.2	71.5
2	45.2	39.4	44.6	50.1	41.1	35.5	41.0	44.5	44.4	40.2	36.9	41.6	43.9	48.2
3	71.4	71.1	72.8	68.0	73.9	74.5	76.1	72.0	72.1	68.1	69.2	68.8	69.6	68.6
4	50.2	75.1	53.2	51.1	47.2	74.5	51.6	46.9	46.5	49.8	75.1	54.6	48.5	50.1
5	23.2	29.1	27.0	19.9	23.7	27.9	27.1	19.3	20.2	19.6	27.8	22.2	18.9	19.0
6	34.7	27.4	34.6	39.4	34.5	28.9	34.3	37.7	38.5	30.6	29.5	31.4	37.7	38.5
7	22.3	22.0	22.0	32.2	22.1†	21.8	21.7	31.3	27.0	18.2	20.5	18.3	29.0	31.6
8	25.7	33.3	74.9	26.3	26.5	34.2	73.0	26.3	26.1	27.6	30.0	75.0	25.9	25.8
9	16.1	16.4	23.7	16.8	16.5	16.4	26.0	16.5	17.2	20.0	15.9	23.8	21.2	16.2
10	21.1	17.8	29.8	21.5	20.8†	17.6	28.5	20.7	20.9	21.1	16.7	29.9	21.2	21.0
C=O					170.0	170.2	169.9	170.7	170.3					
Me CO					21.1†	21.1	21.7	21.3	21.3					

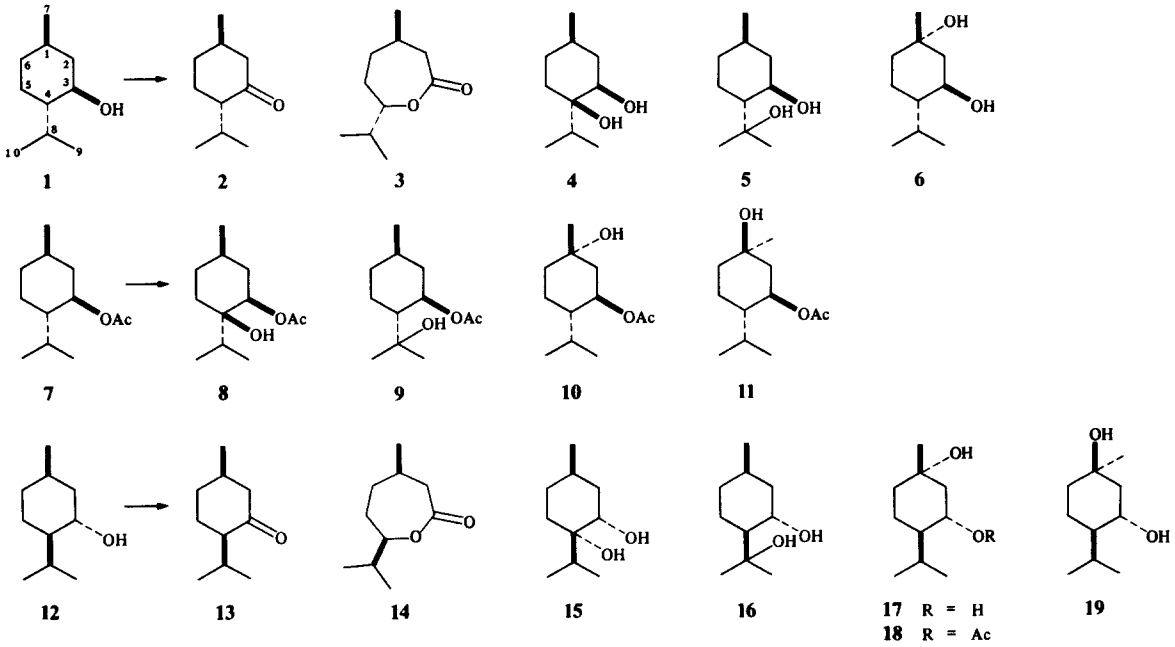
* Compounds were measured in $CDCl_3$ solution, TMS as internal standard.

† Assignments may be interchangeable.

presence of the molecular ion at *m/z* 170, an ester carbonyl (δ 174.2; 1720 cm^{-1}), a methine group (δ 4.02, *m*, H-4; δ 84.7 *d*, C-4) bearing an ester oxygen and an activated methylene group (δ 2.55, 1H, *dd*, $J = 14$, 5.6 Hz; 2.89, *dd*, $J = 14$, 2.4 Hz). From IR, ^{13}C NMR and mass spectra (Table 2), the other four compounds were confirmed to have one tertiary and one secondary hydroxyl group. By comparison of ^{1}H NMR spectra with those of **8** and **9**, the structures of **15** and **16** were easily determined to be 4α-hydroxy-iso-menthol and 8-hydroxy-iso-menthol, respectively. The remaining two compounds **17** and **19** were suggested to be the stereoisomers of 1-hydroxylated isomenthols. Each structure was established by the difference NOE data. Compound **17** showed NOEs between H-3 and H_3-7 and between H-3 and the isopropyl methyls. On the other hand, compound **19** showed an NOE only between H-3 and the isopropyl methyls. Acetylation of **17** gave a mono acetate (**18**), whose spectral data were identical to those of **11**, however, the sign of the specific optical rotation of **18** was opposite to that of **11**. Thus, **17** and **19** were established as 1α-hydroxy-iso-menthol and 1β-hydroxy-iso-menthol, respectively. By choosing appropriate substrates, both enantiomers (**11** and **18**) were obtained. Neo-menthol (**20**) was oxidized by MCPBA to give menthone (**2**), 3,4-secomentholactone (**3**) and two hydroxylated products (**21** and **22**). The structure of **21** was established to be 1α-hydroxy-neo-menthol by the presence of two secondary methyls (δ 0.94, 0.95, *d*, $J = 6.5$ Hz), one tertiary methyl (δ 1.20) and one proton (δ 4.16, H-3) on a carbon bearing a hydroxyl group and by the assignments of the ^{13}C NMR spectrum (Table 2). Compound **22** contained the signals of two tertiary methyls (δ 1.23, 1.36), one secondary methyl (δ 0.88) and one proton (δ 4.41, H-3) on a carbon bearing a hydroxyl group, indicating that **22** was 8-hydroxy-neo-menthol.

Dry ozonization of menthols **1**, **7**, **12** *and* **20**

Dry ozonization has been used to introduce a hydroxyl group at non-activated carbon atoms [10–15]. This method is convenient but very dangerous with the possi-



20	21	22	23	24	25	26	27	28	30	31	33	34	35
25.8	70.8	25.6	82.9	83.9	84.3	82.2	88.7	83.1	90.3	69.1	72.6	72.6	71.1
42.8	43.4	42.6	37.4	37.6	36.7†	49.8	76.6	37.2	76.8	31.7	71.1	70.5	42.8
67.6	68.6	68.1	33.2	32.0	29.8	76.0	45.2	33.9	41.6	23.0	34.6	35.4	64.9
48.2	47.9	48.5	89.6	91.9	90.1	92.1	85.7	87.5	85.0	33.1	34.3	33.5	40.4
24.2	20.0	20.3	33.2	32.0	36.2†	25.1	33.0	34.1	33.3	23.0	22.2	22.2	13.9
35.2	39.1	35.0	37.4	37.6	37.5	36.5	32.2	37.2	29.3	31.7	25.0	29.2	31.1
22.4	30.9	22.2	21.3	21.1	21.1	21.0	16.3	21.1†	19.2	27.4	24.1	23.2	27.1
29.1	29.0	73.3	33.1	71.5	39.8	26.4	32.5	37.8	33.1	73.0	73.5	74.0	73.4
20.8	20.6	28.9	18.2	25.4	66.0	16.8	18.1	66.6	17.6	28.8	28.6	28.3	28.4
21.2	21.0	28.9	18.2	25.4	13.0	18.1	18.1	13.2	17.9	28.8	29.1	29.1	29.1
								171.2					
								21.0†					

Table 3. Oxidation products of menthols and 1,4-cineole produced by dry ozonization*

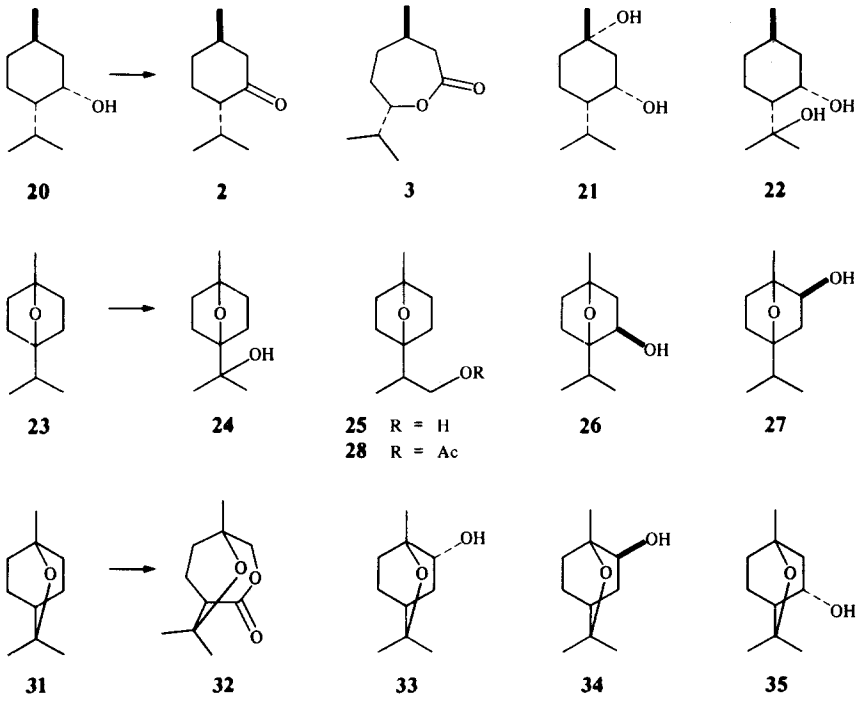
Starting material (g)	Product	Isolated yield (%)	Reaction time (hr)
l-Menthol (**1**) (1.57)	**2**	57.6	3
	5	16.1	
	6	4.0	
l-Menthyl acetate (**7**)	**9**	78.4	6
(1.47)	**10**	20.3	
Iso-menthol (**12**)	**13**	54.6	2
(3.50)	**16**	8.8	
	17	1.4	
Neo-menthol (**20**)	**2**	87.6	2
(3.50)	**21**	3.2	
	22	3.2	
1,4-Cineole (**23**) (3.0)	**24**	16.0	2

*Dry ozonization was carried out at −60 to −50°.

bility of explosion. In order to compare the utility of the oxidation reaction using MCPBA with that of dry ozonization, compounds **1**, **7**, **12** and **20** were oxidized by dry ozone. The ozonization was carried out by the modified method of Ourisson [16]. Ozone gas was passed from the upper part into the reaction column to increase the yield of the oxidation products which are shown in Table 3. The conversion of the substrates by dry ozonization was better than that using MCPBA. Except for menthyl acetate (**7**), the yield of hydroxylated products by MCPBA was somewhat better than that of dry ozonization. Neither 4-hydroxylated nor epimeric hydroxylated products were obtained by dry ozonization. 3-Keto products were obtained by dry ozonization as the major components. In the case of *l*-menthyl acetate (**7**), 1- and 8-hydroxylated compounds were the major products in dry ozonization.

MCPBA oxidation and dry ozonization of 1,4-*cineole* (**23**) *and* 1,8-*cineole* (**31**)

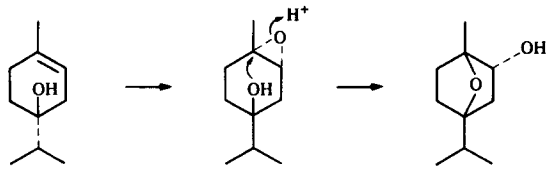
1,4-Cineole (**23**) is the major monoterpenoid of lime peel and 1,8-cineol (**31**) is obtained from several *Eucalyptus* species and *Curcuma* leaves. Both compounds are commercially available. To compare the reaction of MCPBA and dry ozone with saturated monoterpene alcohols and monoterpene ethers, 1,4-cineole (**23**) and 1,8-cineole (**31**) were oxidized by MCPBA and dry ozone. From compound **23**, four hydroxylated products (**24**–**27**) were obtained as shown in Table 1. All the oxidative compounds contained a hydroxyl group which was confirmed by IR, ^{1}H NMR , ^{13}C NMR and mass spectra (Table 2). The structure of of **24** was established by the presence of a quaternary carbon (δ71.5, *s*) bearing a tertiary hydroxyl group and three tertiary methyl groups as well as a base peak at *m/z* 59 has the mass spectrum. In the ^{1}H NMR spectrum of **25**, one of the secondary methyl signals disappeared and a signal of a hydroxyl methyl group (δ 3.49, *dd*, J = 11.0, 4.5 Hz; 3.72, *dd*, J = 11.0, 9.5 Hz; δ 66.0, *t*) appeared, indicating that **25** was 9-hydroxy-1,4-cineole, whose spectral data were identical to those of optically active 9-hydroxy-1,4-cineole obtained from the metabolites of rabbits after administration of 1,4-cineole (**23**) [17]. The ^{1}H NMR spectrum of **26** contained the signals of one tertiary and two secondary methyl groups and a proton (δ 3.90, *dd*, J = 7.0, 4.0 Hz) on a carbon bearing a hydroxyl group, indicating that **26** might be 2- or 3-hydroxylated 1,4-cineole. The position of the hydroxyl group at C-3 was confirmed by the presence of the NOE between H-3 and H-8. The stereochemistry at C-3 of **26** was also established as follows. It is known that 3-exo- and 5-exo-protons are long range coupled to each other [18]. The proton at C-3 of **26** appeared as a double doublet, showing that the orientation of the hydroxyl group at C-3 was β-exo. The IR and ^{1}H NMR spectral data of **27** contained the signals of one tertiary, two secondary methyls and a secondary hydroxyl group. Compound **27** showed the NOE between H_3-7 and one proton at δ 3.75, indicating that the newly introduced hydroxyl group was located at C-2. The orientation of the hydroxyl group at C-2 was confirmed to be 2-exo by the coupling constant (J = 7.0, 2.0 Hz) of H-2. The above assumption was further supported by the following results. Oxidation of 4-terpineol (**29**) with MCPBA gave 2-endo-hydroxy-1,4-cineole (**30**) [19], whose ^{1}H NMR spectral data, particularly, the signal of H-2 (δ 3.83, *br d*, J = 8 Hz) were different from that of **27**. By MCPBA oxidation of 1,4-cineole, the primary hydroxylated compound has been obtained. Interestingly, **24** and **25** have been obtained from the metabolites of rabbits, after oral administration of 1,4-cineol [17]. When 1,4-cineole was treated with dry ozone, only the 8-hydroxylated product (**24**) was obtained in low yield. MCPBA oxidation of 1,8-cineole (**31**) resulted in the isolation of four oxidation products (**32**–**35**). The molecular formula, $C_{10}H_{16}O_3$, of **32** was confirmed by high resolution mass spectral data. The IR spectrum contained the intense absorption band at 1725 cm^{-1}, assignable to the ester group. The ^{1}H NMR spectrum contained three tertiary methyls and a methylene group bearing an ester oxygen. The geminal protons of the methylene group appeared at δ 4.03 and 4.18 as a doublet (J = 12.0 Hz) and a double doublet (J = 12.0, 1.5 Hz), respectively. From this splitting pattern, the structure of **32** was easily determined to be 1,8-cineole-3,2-olide. Compounds **33**, **34** and **35** were confirmed to be the secondary alcohols by their spectral data.



20 **2** **3** **21** **22**

23 **24** **25** R = H, **28** R = Ac **26** **27**

31 **32** **33** **34** **35**

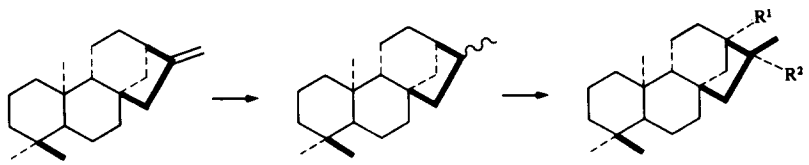


29 **30**

The secondary hydroxylated 1,8-cineole has already been obtained from the metabolites of 1,8-cineole produced by microorganisms [18, 20]. The spectral data of three oxidation products (**33**, **34** and **35**) were identical to those of 2-endo-hydroxy-1,8-cineole, 2-exo-hydroxy-1,8-cineole and 3-endo-hydroxy-1, 8-cineole, respectively. 1,8-Cineole (**31**) possesses a tertiary carbon atom at C-4; however, no hydroxylation occurred at this position. Thus, the microbial metabolites of 1,8-cineole were directly obtained by MCPBA oxidation of 1,8-cineole. When 1,8-cineole was treated in dry ozone, complex mixtures were obtained and their structures remain to be clarified. On the basis of the above results, it is obvious that MCPBA oxidation produces not only lactonization but also introduction of a hydroxyl group at various non-activated carbon atoms of cineoles.

MCPBA oxidation of ent-*kauranes* (**37**)

ent-Kaurane-type diterpenoids are widespread not only in higher plants but also in spore-forming plants and some of them exhibit interesting biological activities such as antitumour [21, 22], plant growth inhibitory [23] and a sweet taste [24]. These active compounds possess hydroxyl groups in their molecules. (−)-16α-Hydroxykaurane (**38**) isolated from the liverworts *Anthelia julacea* and *A. juratzkana* [25] shows plant growth inhibitory activity against cress root [23]. In order to obtain **38**, the naturally abundant (−)-kaurene (**36**) was chosen as the starting material. The Japanese *Cryptomeria japonica* is one of the important conifer trees used for making furniture and wooden houses and its leaves contain *ca* 80% of (−)-kaurene (**36**), however, the leaves are not used in Japan. Extraction of the leaves with *n*-hexane gave a characteristic fragrant green oil which was chromatographed on silica gel to afford a large amount of (−)-kaurene (**36**). This diterpene hydrocarbon was hydrogenated in the presence of Pd-C to give kaurane mixtures (**37**) (5:1 in GC) followed by MCPBA oxidation without further purification to afford two hydroxylated products (**38** and **39**). The physical constants and spectral data of **38** were identical to those of (−)-16α-hydroxykaurane [25, 26]. Compound **39** contained a



36 **37** **38** R^1 = H, R^2 = OH
39 R^1 = OH, R^2 = H

tertiary hydroxyl group (3600, 3430 cm^{-1}; δ 79.8, *s*) indicating that a newly introduced hydroxyl group might be located at C-5, C-9 or C-13 of the kaurane. By comparison of the ^1H NMR spectral data of **39** with those of **38**, the structure of **39** was suggested to be a 13α-hydroxylated product. In fact, the spectral data of **39** were consistent with those of (16α)-kauran-13α-ol, which was derived from lindokaurenoside C isolated from the fern, *Lindsaea chienii* [27]. By the present reaction, (−)-16α-hydroxykaurane (**38**), a plant growth inhibitor, has been obtained from (−)-kaurene (**36**), along with **39** which is similar to steviol, the aglycone of the sweet-tasting diterpenoid, stevioside.

Plant growth inhibitory activity of p-*menthane derivatives*

Recently, Nishimura *et al.* [28] found that *p*-menthane-3,8-diols, for example, 8-hydroxy-neomenthol (**22**), isolated from *Eucalyptus citriodra* showed potent germination inhibitory activity against lettuce seeds. The growth regulatory activity of menthols and their oxidation products (**1**–**12**, **14**–**17**, **19**–**22**) were tested against the second coleoptile and root of rice in husk. Compounds (**1**, **4**, **8**, **10**, **12**, **19** and **22**) showed more than 50% growth inhibition of the second coleoptile of rice in husk at a concentration of 250 ppm (Table 4). The orders of inhibitory activity of the compounds are **12** > **19** > **4** > **8** = **11** = **22** > **1**. Among *l*-menthol (**1**) and its oxidation products, 8-hydroxy-*l*-menthol (**5**) indicated the strongest inhibitory activity against growth of the rice root. Compound **22** obtained from *Eucalyptus* species [28], and from *neo*-menthol (**20**) by MCPBA oxidation or dry ozonization did not show the strongest inhibitory activity against the second coleopitle of rice in husk. Inagaki *et al.* [29] reported that *iso*-menthol (**12**) exhibited the strongest inhibition against growth of the second coleoptile of several higher plants. The present results support the above fact. It is known that some *p*-menthane derivatives possess mosquito repellent activity [30]. The *p*-menthane diols, lactones and ketones obtained from each substrate by MCPBA and the commercial mosquito repellent drug, *N*,*N*-diethyl-*m*-toluamide (DEET) were tested against the mosquito adult, *Aedes albopictus*. As shown in Tables 5–8, 8-hydroxy-*l*-menthol (**5**) showed potent repellent activity. A 1.0% ethanol solution of **5** and of DEET showed repellent activity for 8 and 6 hr, respectively. With a 0.5% solution, compound **5** and DEET showed repellent effects for 7 and 4 hr, respectively. In a 0.1% solution, both compounds were ineffective. The cream containing 0.5% of **5** and that containing 0.5% of DEET had no lasting repellent activity effects. From these results, compound **5** showed a greater repellent activity than the commercial DEET against mosquito adults.

As described above, MCPBA oxidation is very advantageous to obtain various hydroxylated compounds from natural or non-natural terpenoids and the work-up is very simple. Among the resulting products, some biologically active compounds and both enantiomers of *p*-menthane diols are included. Application of this method to different monoterpenoids and related compounds could lead to the preparation of compounds with different biological activity compared to the starting materials.

Table 4. Plant growth inhibitory activity of menthols and their oxidation products against rice seeds [31]

	Sample concentration					
	62.5 ppm		125 ppm		250 ppmm	
Compound	C*	R†	C	R	C	R
1	76%‡	70%	84%	163%	48%	18%
2	82	112	124	71	76	112
3	88	88	56	21	82	20
4	88	68	64	88	39	100
5	80	41	140	71	88	15
6	92	67	104	94	104	53
7					74	
8					44	
9					91	
10					43	
11					87	
12					29	
14					76	
15					73	
16					83	
17					66	
19					31	
20					76	
21					104	
22					44	

* Second coleoptile

† Root elongation

‡ Growth expressed as a percentage of the control. The second coleoptile and root length of grown plant were measured and the average values calculated.

EXPERIMENTAL

Mps: uncorr. The solvents used for spectral measurements were TMS–$CDCl_3$ [^1H NMR (400 MHz); ^{13}C NMR (100 MHz) unless other wise stated] and $CHCl_3$ (IR and $[\alpha]_D$) unless otherwise stated. TLC: precoated silica gel (0.25 mm) F_{254}, *n*-hexane–EtOAc (4:1) or C_6H_6–EtOAc (4:1). Spots were visualized by spraying with 30% H_2SO_4 and then heating at 120°. GC: 10% SE-30 or 15% PEG-20M, 2 m × 2 mm glass column, temp. programme from 50 to 260° at 5°/min, injector temp. 260°, N_2 30 ml/min. GC/MS: 70 eV, 1% SE-30, 1 m × 2 mm, temp. programme from 50 to 270° at 5°/min, injector temp. 270°, He 30 ml/min.

MCPBA oxidation. Each substrate (Table 1) was dissolved in $CHCl_3$ (25 ml) and then MCPBA (1.2–2.0 eq) was added to the $CHCl_3$ soln. The reaction mixture was refluxed for 6–24 hr at 65–75°. The resulting product was filtered to remove excess MCPBA and *m*-chlorobenzoic acid and the filtrate was successively washed with 5% Na_2SO_3, 5% $NaHCO_3$ and satd NaCl and dried over Na_2SO_4. The residue, after removal of the solvent, was chromatographed on silica gel using a *n*-hexane–EtOAc gradient or on Sephadex LH-20 using CH_2Cl_2–*n*-hexane (4:1) to afford pure oxidized compounds. The residue from *neo*-menthol was directly purified by HPLC (μ-Bondapack C_{18}; MeOH–H_2O, 1:1; flow rate 1.5 ml/min) to give **2**, **3**, **21** and **22**. The oxidized residue from (−)-kauranes (**37**) was also directly purified by HPLC [μ-Porasil; *n*-hexane–EtOAc, 199:1; flow rate 2 ml/min].

Dry ozonization. To silica gel (70 g) dried to 160° for 3 hr was added each substrate (Table 3) dissolved in EtOAc or CH_2Cl_2 (200 ml). The silica gel impregnated with the substrate, after the solvent was completely removed *in vacuo*, was packed into Pyrex glass column (5 × 11 cm) and this column was cooled at −60°

Table 5. Mosquito repellent activity of compound **5** (1.0% EtOH solution)

Sample	3 hr	6 hr	7 hr	8 hr
Control	1* 2	3	3	6 10
5	0 0 0 0	0 0 0 0	0 0 0 0	0 1 2 1
DEET†	0 0 0 0	0 0 0 0	0 1 0 0	2 1 3 2

* The number of blood sucking mosquito.
† *N,N*-diethyl-*m*-toluamide.

Table 6. Mosquito repellent activity of compound **5** (0.5% EtOH solution)

Sample	2 hr	5 hr	7 hr	8 hr
Control	3 5	1 6	4	4 5
5	0 0 0 0	0 0 0 0	0 0 0 0	1 2 3 2
DEET	0 0 0 0	3 3 3 2	4 3	1 2 2 3

Table 7. Mosquito repellent activity of compound **5** (0.1% EtOH solution)

Sample	0.5 hr	2 hr
Control	2 4 4	0 0 2 3
5	0 0 0 0	1 2 1 3
DEET	0 0 0 0	0 1 1 2

Table 8. Mosquito repellent activity of compound **5** (applied as a cream containing 0.5% of **5**)

Sample	1 hr	5 hr
Control	2 3	1 1
5	0 0 0 0	0 1 2 3
DEET	0 0 0 0	0 0 1 1

to −50° [16] and then ozone was passed from the upper part of the reaction column for 2–6 hr at the same temp. as described above. The column was allowed to stand until the temp. of the cooling pot reached room temp and the oxidation products were eluted with EtOAc or CH_2Cl_2 as in CC. The eluant was concd *in vacuo* to give the residue which was chromatographed on silica gel to afford pure compounds.

Bioassay. Plant growth inhibitory activity was measured using a modified method of ref. [31] in which Me_2CO instead of MeOH was used to dissolve the test samples. 0.1, 0.5 and 1.0% EtOH solns were prepared of the *p*-menthane derivatives obtained from each menthol and of *N,N*-diethyl-*m*-toluamide (DEET). Also creams were made containing 0.5% of each oxidation product and of DEET. Each preparation was painted onto individual mice (30 g weight, 300 mg substance/mouse) which were then fixed into folded wire-netting (18 × 13 cm, 12 mesh). Then the mouse in netting was put into a mosquito (*Aedes albopictus*) raising cage (30 × 30 × 30 cm) and the number of blood sucking mosquito counted every 1 min. As a control, only EtOH or the cream (300 mg/mouse) was painted onto the mouse and then the mouse was treated in the same manner as described above.

Plant material. Fresh leaves of *Cryptomeria japonica* were collected in Gotaki, Tokushima in October 1982 and the voucher specimen was deposited in the Herbarium of Institute of Pharmacognosy, Tokushima Bunri University.

Isolation of (−)-ent-*kaurene* (**36**). Fresh leaves (26.1 kg) were crushed mechanically and extracted with *n*-hexane for 2 weeks. A green fragrant viscous oil (422 g) was obtained after filtration and evaporation of the solvent. This oil (253 g) was chromatographed on silica gel using *n*-hexane to give the mixtures of mono-and diterpene hydrocarbons from the first fraction. A part of the mixture was distilled *in vacuo* (bp 130°/1 mm Hg) to afford (−)-*ent*-kaurene (23 g) (**36**), mp 50° (lit. 50° [32]); $[\alpha]_D$ -75.5° (*c* 3.0) (lit. -75.2° [32]); ^{1}H NMR (60 MHz) δ: 0.80, 0.85, 1.07 (each 3H, *s*), 4.70 (2H, *m*); MS *m/z*: 272 $[M]^+$.

Hydrogenation of compound **36**. Compound **36** (330 mg) in EtOAc (30 ml) was hydrogenated in the presence of 5% Pd-C (400 mg) for 5 hr. Work-up as usual gave viscous kaurane mixtures (355 mg) (**37**) (5:1 in GC). ^{1}H NMR δ: 0.80, 0.84, 1.01 (each 3H, *s*), 0.99 (3H, *d*, J = 7.0 Hz); MS *m/z*: 274 $[M]^+$.

Oxidation products from l-*menthol* (**1**) $[\alpha]_D$ −48.8° (lit −49.6° [33]). *l*-Menthone (**2**): The physical constants and spectral data were identical to those of an authentic sample. *l*-Mentholactone (**3**): oil; $[\alpha]_D$ -12.0° (*c* 0.8); IR ν_{max} cm^{-1}: 1720, 1285; ^{1}H NMR: δ 0.97, 0.98, 1.04 (each 3H, *d*, J = 7.0 Hz), 4.06 (1H, *dd*, J = 9.5, 4.5 Hz, H-4); ^{13}C NMR δ: 17.1, 18.5, 24.0 (each, *q*), 30.5, 33.4 (each, *d*), 31.0, 37.5, 42.6 (each *t*), 84.8 (*d*, C-4), 175.0 (*s*, C-3); MS *m/z*: 170 $[M]^+$, 127, 99, 81 (base), 69, 55, 43. 4β-Hydroxy-*l*-menthol (**4**): mp 71-72° (lit. 76° [8]); $[\alpha]_D$ + 7.6° (*c* 0.5) (lit. + 10.4° [8]); IR ν_{max}^{KBr} cm^{-1}: 3375; ^{1}H NMR: δ0.90, 0.93, 0.95 (each 3H, *d*, J = 7.0 Hz), 2.08 (1H, *sept.* J = 7.0, H-8), 3.66 (1H, *dd* J = 11.0, 5.0 Hz, H-3); ^{13}C NMR (22.6 MHz: δ see Table 2. MS *m/z*: 172·$[M]^+$, 154 $[M-H_2O]^+$, 129, 99, 55, 43 (base). 8-Hydroxy-*l*-menthol (**5**): mp 63° (lit. 58.5–60° [28]); $[\alpha]_D$ −10.6° (*c* 0.5) (lit. -11.0° [28]); ^{1}H NMR : δ 0.92 (3H, *d*, J = 7.0 Hz, C_1-Me), 1.22 [6H, *s*, C_8-$(Me)_2$], 3.72 (1H, *td*, J = 11, 4.5 Hz, H-3); HRMS: $[M-H_2O]^+$ (found 154.1354; calc. for $C_{10}H_{18}O$; 154.1358); ^{13}C NMR (22.6 MHz): see Table 3. MS *m/z*: 157 $[M-Me]^+$, 154, 139, 81, 59 (base). 1α-Hydroxy-*l*-menthol (**6**): mp 165° (lit. 165° [9]); $[\alpha]_D$ −39.8° (*c* 0.56) (lit. −33° [9]); IR ν_{max}^{KBr} cm^{-1}: 3380; ^{1}H NMR: δ0.85, 0.95 (each 3H, *d*, J = 7.0 Hz), 1.26 (3H, *s*, C_1-Me), 3.76 (1H, *td*, J = 11.0, 4.5 Hz, H-3); ^{13}C NMR (22.6 MHz): δ see Table 2. MS *m/z*: 154 $[M-H_2O]^+$, 139, 87, 71, 43 (base).

Oxidation products from l-*menthyl acetate* (**7**). 4β-Hydroxy-*l*-

menthyl acetate (**8**): oil; $[\alpha]_D$ −29.7° (*c* 0.5); IR ν_{max}^{liq} cm^{-1}: 3500, 1730, 1250; ^1H NMR : δ 0.84, 0.93, 0.94 (each 3H, *d*, *J* = 7.0 Hz), 1.82 (1H, *septet*, *J* = 7.0 Hz, H-8), 2.07 (3H, *s*), 4.90 (1H, *dd*, *J* = 11.0, 4.5 Hz, H-3); ^{13}C NMR (22.6 MHz): δ see Table 2. MS *m/z*: 171 $[M-MeCO]^+$, 96, 81, 59, 43 (base). 8-Hydroxy-*l*-menthyl acetate (**9**): oil; $[\alpha]_D$ −77.1° (*c* 0.36); IR ν_{max}^{liq} cm^{-1}: 3455, 1735, 1245; ^1H NMR :δ 0.91 (3H, *d*, *J* = 7.0 Hz), 1.14, 1.16 (each 3H, *s*), 2.07 (3H, *s*), 4.81 (1H, *td*, *J* = 11.0, 4.0 Hz, H-3); ^{13}C NMR (22.6 MHz) : δ see Table 2. MS *m/z*: 139 $[M-AcOH-H_2O]^+$, 96, 81, 59 (base), 43. 1α-Hydroxy-*l*-menthyl acetate (**10**): oil; $[\alpha]_D$ −65.4° (*c* 0.53); IR ν_{max} cm^{-1}: 3600, 3470, 1720, 1263; ^1H NMR: δ 0.80, 0.91 (each 3H, *d*, *J* = 7.0 Hz), 1.24 (3H, *s*, C_1-Me), 2.03 (3H, *s*), 2.37 (1H, *br s*, OH), 4.99 (1H, *td*, *J* = 11.0, 4.0 Hz, H-3); ^{13}C NMR: see Table 2. MS *m/z*: 154 $[M-AcOH]^+$, 139, 111, 43 (base). 1β-Hydroxy-*l*-menthyl acetate (**11**): oil; $[\alpha]_D$ −57.5° (*c* 0.85); IR ν_{max} cm^{-1}: 3600, 3450, 1720, 1250; ^1H NMR: δ 0.81, 0.93 (each 3H, *d*, *J* = 7.0 Hz), 1.26 (3H, *s*, H_3-7), 2.05 (3H, *s*), 4.82 (1H, *dt*, *J* = 10.0, 4.0 Hz, H-3); ^{13}C NMR: see Table 2. HRMS: $[M-AcOH]^+$ (found: 154.1350; calc. for $C_{10}H_{18}O$: 154.1358); MS *m/z*: 154 $[M-AcOH]^+$, 139, 111, 43 (base).

Oxidation products from iso-*menthol* (**12**) $[\alpha]_D$ +20.0° (lit. +25.9° [33]). Isomentholactone (**14**): oil; $[\alpha]_D$ −18.5° (*c* 0.7); IR ν_{max} cm^{-1}: 1720, 1280; ^1H NMR: δ 0.98 (6H, *d*, *J* = 7.0 Hz), 1.05 (3H, *d*, *J* = 7 Hz), 2.55 (1H, *dd*, *J* = 14.0, 5.6 Hz, H-2a), 2.89 (1H, *dd*, *J* = 14.0, 2.4 Hz, H-2b), 4.02 (1H, *m*, 4-H); ^{13}C NMR (22.6 MHz): δ 17.3, 17.7, 18.5 (each *q*), 26.7, 33.3 (each *d*), 26.8, 34.2, 40.7 (each *t*), 84.7 (*d*, C-4), 174.2 (*s*, C-3); MS *m/z*: 170 $[M]^+$ (base), 153, 127, 81, 69. *iso*-Mentholactone (**13**): The spectral data of **13** were identical to those of an authentic sample. 4α-Hydroxy-iso-menthol (**15**): oil; $[\alpha]_D$ + 20.2° (*c* 0.5) (lit. + 22.6° [8]); IR ν_{max} cm^{-1}: 3450; ^1H NMR: δ 0.90, 0.91, 0.92 (each 3H, *d*, *J* = 7.0 Hz), 3.88 (1H, *dd*, *J* = 6.5, 6.5 Hz, H-3); ^{13}C NMR (22.6 MHz): see Table 2. HRMS: $[M]^+$ (found: 172.1382; calc. for $C_{10}H_{20}O_2$: 172.1463); MS *m/z*: 172 $[M]^+$; 129, 111, 99, 43 (base). 8-Hydroxy-10-menthol (**16**): mp 86–87°: $[\alpha]_D$ + 5.3° (*c* 0.73); IR ν_{max} cm^{-1}: 3290; ^1H NMR: δ 0.98 (3H, *d*, *J* = 7.0 Hz), 1.21, 1.25 (each 3H, *s*), 3.94 (1H, *td*, *J* = 11.0, 4.5 Hz, H-3); ^{13}C NMR (22.6 MHz): see Table 2. HRMS: $[M-H_2O]^+$ (found: 154.1351; calc. for $C_{10}H_{18}O$: 154.1358); MS *m/z*: 154 $[M-H_2O]^+$, 139, 96, 81, 59 (base). 1α-Hydroxy-*iso*-menthol (**17**): mp 75°; $[\alpha]_D$ + 31.3° (MeOH; *c* 0.46); IR ν_{max} cm^{-1}: 3300; ^1H NMR: δ 0.81, 0.86 (each 3H, *d*, *J* = 7.0 Hz), 1.12 (3H, *s*, H_3-7), 3.71 (1H, *m*, $W_{1/2}$ = 14 Hz, H-3); ^{13}C NMR (22.6 MHz): see Table 2. HRMS: $[M-H_2O]^+$ (found: 154.1359; calc. for $C_{10}H_{18}O$: 154.1358); MS *m/z*: 154 $[M-H_2O]^+$, 139, 111, 87, 43 (base). 1β-Hydroxy-*iso*-menthol (**19**): mp 121–123°; $[\alpha]_D$ + 48.3° (*c* 0.49 MeOH); IR ν_{max} cm^{-1}: 3375; ^1H NMR: δ 0.85, 0.96 (3H, *d*, *J* = 7.0 Hz), 1.27 (3H, *s*, H_3-7), 3.77 (1H, *dd*, *J* = 11.0, 4.5 Hz, H-3); ^{13}C NMR: see Table 2. HRMS: $[M-H_2O]^+$ (found 154.1350; calc. for $C_{10}H_{18}O$: 154.1358; MS *m/z*: 154 $[M-H_2O]^+$, 139, 111, 87 (base), 43.

Acetylation of compound **17**. Compound **17** (11 mg) was acetylated with Ac_2O–pyridine (each 0.5 ml) with stirring at room temp. for 2 hr. Work-up as usual gave a monoacetate (**18**) $[\alpha]_D$ + 57.6° (*c* 0.93), whose spectral data were identical to those of **11**, except for the sign of the specific optical rotation.

Oxidation products of neo-*menthol* (**20**) $[\alpha]_D$ +20.6° (lit. +20.7° [33]). 1-Hydroxy-*neo*-menthol (**21**): oil; $[\alpha]_D$ +18.6° (*c* 0.20) (lit. + 18.8° [91]); IR ν_{max} cm^{-1}: 3450; ^1H NMR: δ 0.94, 0.95 (each 3H, *d*, *J* = 6.5 Hz), 1.20 (3H, *s*, H_3-7), 3.22 (3H, *br s*, 2 × OH), 4.16 (1H, *m*, H-3), ^{13}C NMR (22.6 MHz): see Table 2. MS *m/z*: 172 $[M]^+$, 154, 111, 87 (base), 69, 55, 43. 8-Hydroxy-*neo*-menthol (**22**): mp 58–59° (lit. 57.5–59.5° [28]); $[\alpha]_D$ +16.6° (*c* 0.36) (lit. + 12.8° [28]); IR ν_{max} cm^{-1}: 3600, 3450, ^1H NMR: δ 0.88 (3H, *s*, H_3-7), 1.23, 1.36 (each 3H, *s*), 2.75, 3.06 (each *br s*, OH), 4.41 (1H, *m*, H-3); ^{13}C NMR (22.6 MHz): see Table 2. MS *m/z*: 154 $[M-H_2O]^+$, 139, 121, 96, 81 (base), 59, 43.

Oxidation products from 1,4-*cineole* (**23**). 8-Hydroxy-1,4-cineole (**24**): oil; IR ν_{max} cm^{-1}: 3580, 3445; ^1H NMR: δ 1.27 (6H, *s*, H_3-9, H_3-10), 1.45 (3H, *s*, H_3-7); ^{13}C NMR (22.6 MHz): see Table 2. HRMS: $[M]^+$ (found: 170.1250; calc. for $C_{10}H_{18}O_2$: 170.1307); MZ *m/z*: 170 $[M]^+$, 111, 59 (base). 9-Hydroxy-1, 4-cineole (**25**): oil; IR ν_{max} cm^{-1}: 3450; ^1H NMR: δ 0.87 (3H, *d*, *J* = 7 Hz, H_3-10), 1.44 (3H, *s*, H_3-7), 2.25 (1H, *m*, H-8), 3.49 (1H, *dd*, *J* = 11.0, 4.5 Hz, H-9a), 3.72 (1H, *dd*, *J* = 11, 9.5 Hz, H-9b); HRMS: $[M]^+$ (found: 170.1268; calc. for $C_{10}H_{18}O_2$: 170.1307); MS *m/z*: 170 $[M]^+$; 143, 111, 43 (base). Acetate (**28**) of **25**: oil; IR ν_{max} cm^{-1}: 1740, 1230, ^1H NMR: δ 1.04 (3H, *d*, *J* = 7.0 Hz, H_3-10), 1.44 (3H, *s*, H_3-7), 2.05 (3H, *s*), 2.30 (1H, *m*, H-8), 3.96 (1H, *dd*, *J* = 11.0, 5.0, H-9b), 4.22 (1H, *dd*, *J* = 11.0, 5.0, H-9b); ^{13}C NMR (22.6 MHz): see Table 2. MS *m/z*: 212 $[M-AcOH]^+$, 170, 152 (base), 137, 123, 109, 69, 43. 3-*exo*-Hydroxy-1,4-cineole (**26**): oil; IR ν_{max} cm^{-1}: 3445; ^1H NMR: δ 0.93, 1.01 (each 3H, *d*, *J* = 7.0 Hz, H_3-9, H_3-10), 1.46 (3H, *s*, H_3-7), 1.70 (1H, *ddd*, *J* = 13.0, 13.0, 4.0 Hz, H-2-*endo*), 2.19 (1H, *dd*, *J* = 13.0, 7.0 Hz, H-2-*exo*), 2.39 (1H, *septet*, *J* = 7.0 Hz, H-8), 3.90 (1H, *dd*, *J* = 7.0, 4.0 Hz, H-3); HRMS: $[M]^+$ (found: 170.1273; calc. for $C_{10}H_{18}O_2$: 170.1307); MS *m/z*: 170 $[M]^+$, 153, 87, 71, 43 (base). 2-*exo*-Hydroxy-1,4-cineole (**27**): mp 37–38°; IR ν_{max}^{KBr} cm^{-1}: 3450, 3300; ^1H NMR: δ 0.96, 0.97 (each 3H, *d*, *J* = 7.0 Hz, H_3-9, H_3-10), 1.42 (3H, *s*, H_3-7), 2.28 (1H, *br s*, OH), 3.75 (1H, *dd*, *J* = 7.0, 2.0 Hz, H-2); ^{13}C NMR (22.6 MHz): see Table 2. HRMS: $[M]^+$ (found: 170.1261; calc. for $C_{10}H_{18}O$: 170.1307); MS *m/z*: 170 $[M]^+$, 153, 112, 71, 43 (base).

MCPBA oxidation of 4-*terpineol* (**29**). To compound (**29**) (5.0 g) in $CHCl_3$ (15 ml) was added MCPBA (4.8 g) and the reaction mixture refluxed at 65–75° for 4 hr and then MCPBA (4.8 g) in $CHCl_3$ (5 ml) was added to the resulting soln which was further refluxed for 4 hr. The resulting products were treated in the same manner as described above and the residue was chromatographed on silica gel using a C_6H_6–EtOAc gradient to give 2-*endo*-hydroxy-1,4-cineole (**30**) [18] as an oil; IR ν_{max}^{liq} cm^{-1}: 3400; ^1H NMR: δ 0.87 (6H, *d*, *J* = 7.0 Hz, H_3-9, H_3-10), 1.33 (3H, *s*, H_3-7), 3.83 (1H, *br d*, *J* = 8.0 Hz, H-2); ^{13}C NMR (22.6 MHZ): see Table 2. MS *m/z*: 170 $[M]^+$, 153, 127, 122, 81, 71, 58, 43 (base).

Oxidation products from 1,8-*cineole* (**31**). 1,8-Cineole-3, 2-olide (**32**): oil; IR ν_{max} cm^{-1}: 1725, 1255; ^1H NMR: δ 1.16, 1.29, 1.36 (each, 3H, *s*), 4.03 (1H, *d*, *J* = 12.0 Hz, H-2-*endo*), 4.18 (1H, *dd*, *J* = 12.0, 1.5 Hz, H-2-*exo*); HRMS: $[M]^+$ (found: 180.1080; calc. for $C_{10}H_{16}O_2$: 180.1099); MS *m/z*: 184 $[M]^+$ 169, 153, 111, 55, 43 (base). 2-*endo*-Hydroxy-1,8-cineole (**33**): oil; IR ν_{max} cm^{-1}: 3600, 3450; ^1H NMR: δ 1.10, 1.20, 1.28 (each 3H, *s*), 2.51 (1H, *ddt*, *J* = 13.0, 10.0, 3.5 Hz, H-3-exo), 3.73 (1H, *ddd*, *J* = 10.0, 4.0, 1.5 Hz, H-2); ^{13}C NMR (100 MHz): see Table 2. MS *m/z*: 170 $[M]^+$, 126, 108 (base), 71, 43. 2-*exo*-Hydroxy-1,8-cineole (**34**) [20]: oil; IR ν_{max} cm^{-1}: 3560, 3450; ^1H NMR: δ 1.11, 1.27, 1.29 (each 3H, *s*), 3.50 (1H, *dd*, *J* = 9.0 Hz, H-2); ^{13}C NMR (22.6 MHz): see Table 2. MS *m/z*: 170 $[M]^+$ 170, 126, 108 (base), 71, 43, 3-*endo*-Hydroxy-1,8-cineole (**35**) [18]: oil; IR ν_{max} cm^{-1}: 3600, 3430; ^1H NMR: δ 1.08, 1.22, 1.30 (each 3H, *s*), 4.46 (1H, *br d*, *J* = 9 Hz, H-3); ^{13}C NMR (22.6 MHz): see Table 2. MS *m/z*: 170 $[M]^+$, 155, 108, 93, 69, 43 (base).

Oxidation products of ent-*kauranes* (**37**). (−)-*ent*-16α-Hydroxykaurane (**38**): mp 218–219° (lit. 217–218 [25, 26]); $[\alpha]_D$ -52.1° (*c* 0.39) (lit. -46° [25, 26]); ^1H NMR: δ 0.80, 0.84, 1.02 (each, 3H, *s*), 1.36 (3H, *s*, H_3-17); MS *m/z*: 272 $[M-H_2O]^+$, 257, 232, 217, 123 (base). (−)-16α-Kauran-13α-ol (**39**): mp 147° (lit. 147–148° [27]); $[\alpha]_D$-24.8 (*c* 0.10) (lit. −24.8° [27]); IR ν_{max}^{KBr} cm^{-1}: 3600, 3430; ^1H NMR: δ 0.79, 0.84, 0.99 (each 3H, *s*), 0.97 (3H, *d*, *J* = 6.8 Hz, H_3-17); ^{13}C NMR (100 MHz): δ 12.8, 17.6,

21.6, 33.6 (each *q*), 18.6, 19.6, 20.4, 33.5, 40.4, 42.1, 42.3, 47.7, 47.8 (each *t*), 29.7, 56.3 (each *d*), 33.3, 39.1, 43.3, 79.8 (each *s*); MS *m/z*: 290 $[M]^+$, 275, 257, 247 (basc), 137, 123.

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