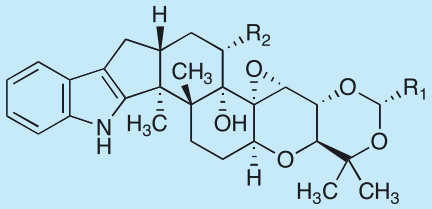
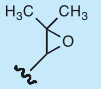
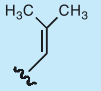
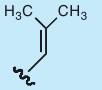
Terpendole

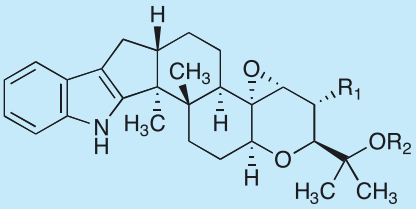
1. Discovery, producing organism and structures[1-6)]

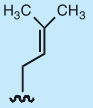
Terpendoles were isolated from the culture broth of the fungal strain FO-2546 and found to be inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). The taxonomic study of the producing organism led us to establish a new genus of *Albophoma yamanashiensis*[1, 2)]. [See "*Albophoma yamanashiensis*" (p. 386)].

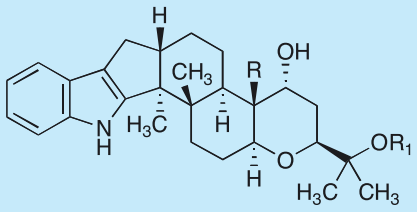
Terpendoles have a common indoloditerpene moiety. Structurally related known compounds, paspaline[3)] and emindole SB[4)], were also produced and isolated from the same strain. The relative stereostructures were determined by NOE experiments and X-ray crystallographic analysis of terpendoles D and E[5,6)].



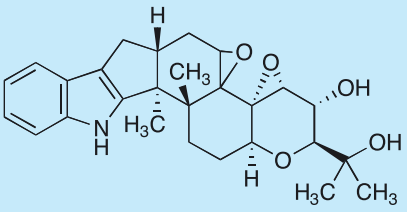
	R_1	R_2
Terpendole A		H
Terpendole C		H
Terpendole M		OH



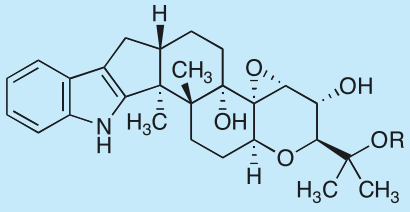
	R_1	R_2
Terpendole B	H	H
Terpendole D	OH	

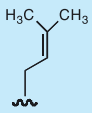


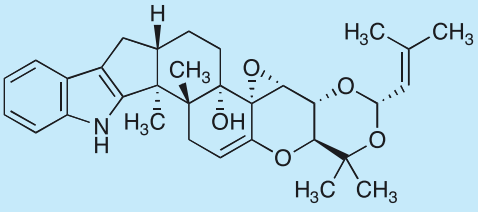
	R
Terpendole E	CH_3
Terpendole F	CH_2OH
Terpendole G	CHO



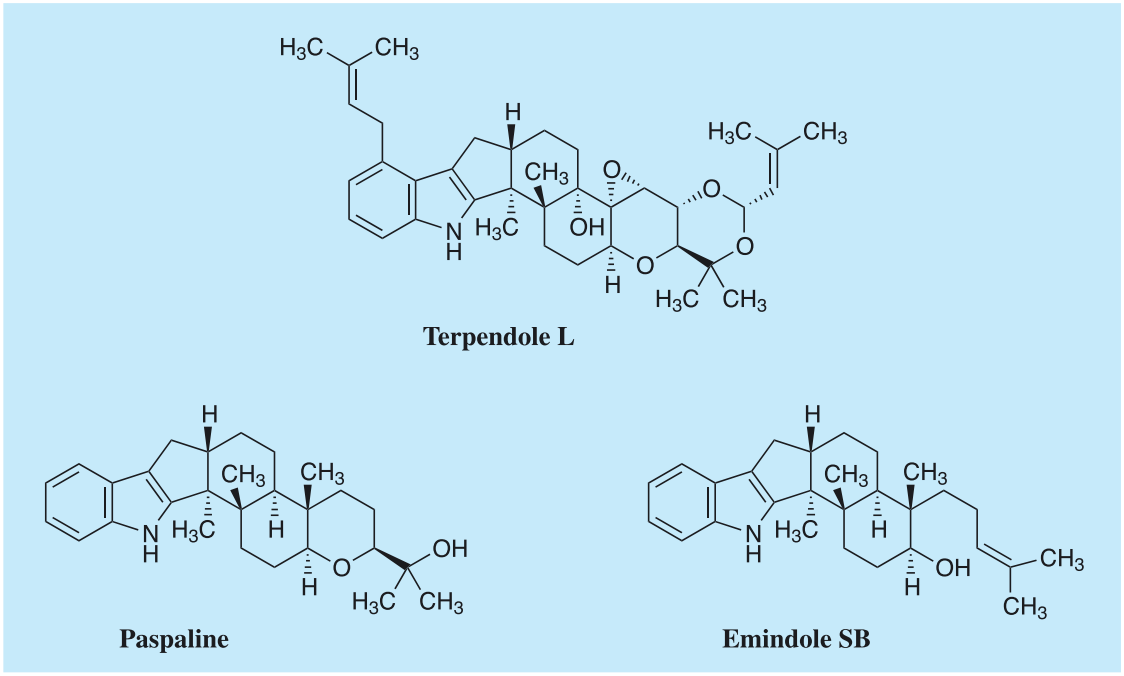
Terpendole H



	R
Terpendole I	H
Terpendole J	



Terpendole K



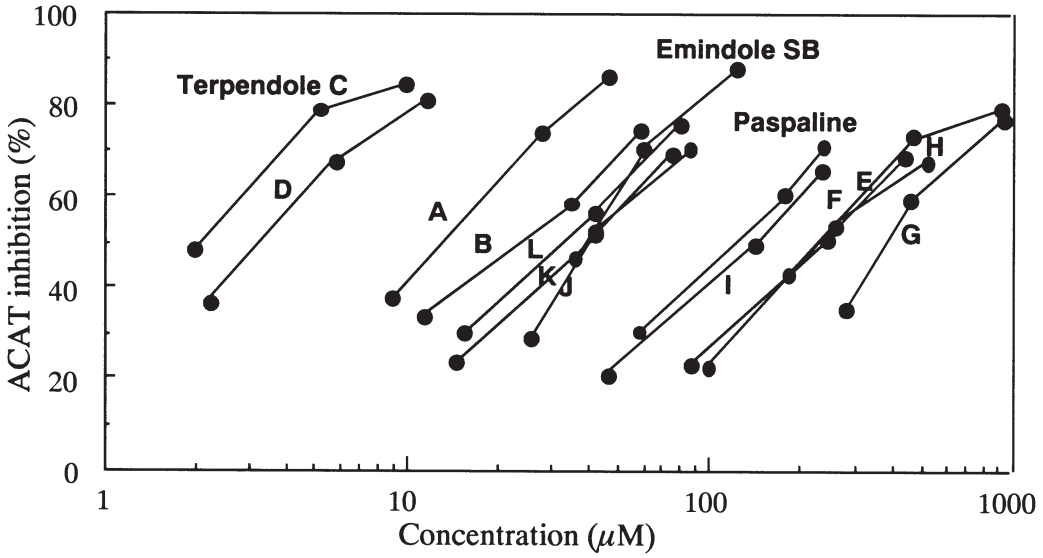
2. Physical data (Terpendole A)[3]

White powder. $C_{32}H_{41}NO_6$; mol wt 535.29. Sol. in MeOH, EtOAc, $CHCl_3$, DMSO. Insol. in H_2O, hexane.

3. Biological activity[2,6-8]

1) Enzyme assay for ACAT inhibition

ACAT inhibitory activity [See also "Purpactin" (p. 279)] was tested in an enzyme assay using rat liver microsomes. An additional prenyl residue at the diterpene moiety is responsible for potent ACAT inhibiton.



Compound		IC_{50} (μM)	Compound	IC_{50} (μM)
Terpendole	A	15.1	Terpendole H	230
	B	26.8	I	145
	C	2.10	J	38.8
	D	3.20	K	38.0
	E	228	L	32.4
	F	221	Paspaline	134
	G	388	Emindole SB	41.0

2) Cell assay[2)]
ACAT inhibitory activity was evaluated in a cell assay using J774 macrophages. Cytotoxicity (CD_{50}) was also determined to evaluate the specificity. Among the terpendoles tested, terpendole D was the most potent ACAT inhibitor (IC_{50}) and had the highest specificity.

Compound	J774 (μM)		Specificity (CD_{50} / IC_{50})
	IC_{50}	CD_{50}	
Terpendole A	0.29	> 23.4	> 81
B	1.80	> 29.7	>17
C	0.46	> 24.1	> 52
D	0.048	> 24.8	> 520
Paspaline	2.85	29.0	10
Emindole SB	6.48	16.0	2.5

3) Tremorgenic activity of terpendole C[7)]
Some indoloditerpenes were reported to be tremorgens. Terpendole C was found to have tremorgenic activity in mice. It was faster acting and produced more intense tremors than the same dose of paxilline[8)]. It is still unclear as to whether or not other terpendoles show tremorgenic activity.

4) Inhibition of motor activation of mitotic kinesin Eg 5 by terpendole E[9)]
Terpendole E was recognized as a specific M phase inhibitor. The compound inhibited both motor and microtubule-stimulated human Eg 5 ATPase activity.

4. Biosynthesis[10)]
The biosynthetic gene cluster for terpendol was identified and the biosynthetic pathway was proposed by Motoyama *et al*.

5. References

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4. J. P. Springer *et al*., *Tetrahedron Lett*. **21**, 231-234 (1980)
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7. [659] S. C. Munday-Finch *et al*., *J. Agricult. Food Chem*. **45**, 199-204 (1997)
8. R. J. Cole *et al*., *Can. J. Microbiol*. **20**, 1159-1162 (1974)
9. J. Nakazawa *et al., Chem. Biol*. **10**, 131-137 (2003)
10. T. Motoyama *et al., Chem. Biol*. **19**, 1611-1619 (2012)