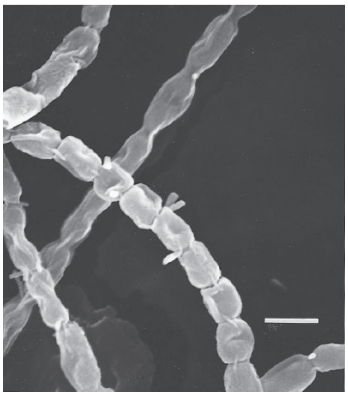
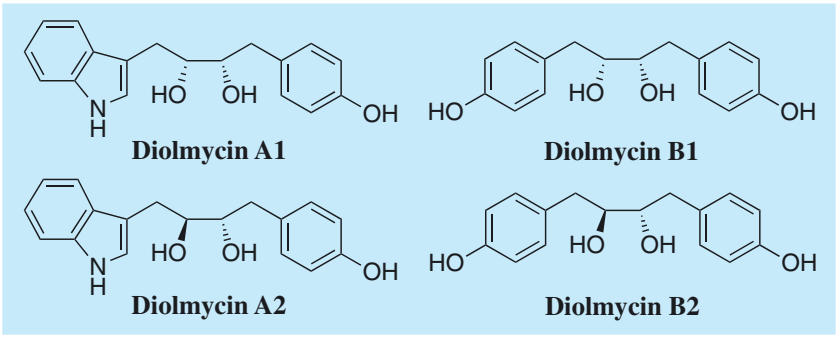
Diolmycin

1. Discovery, producing organism and structures[1,2)]

Diolmycins were isolated from the culture broth of the actinomycete strain WK-2955 and identified as anticoccidial compounds.



Streptomyces sp. WK-2955



2. Physical data (Diolmycin A1)[1)]

Colorless powder. $C_{18}H_{19}NO_3$; mol wt 297.14. Sol. in MeOH, DMSO. Insol. in $CHCl_3$.

3. Biological activity[1)]

1) Anticoccidial activity

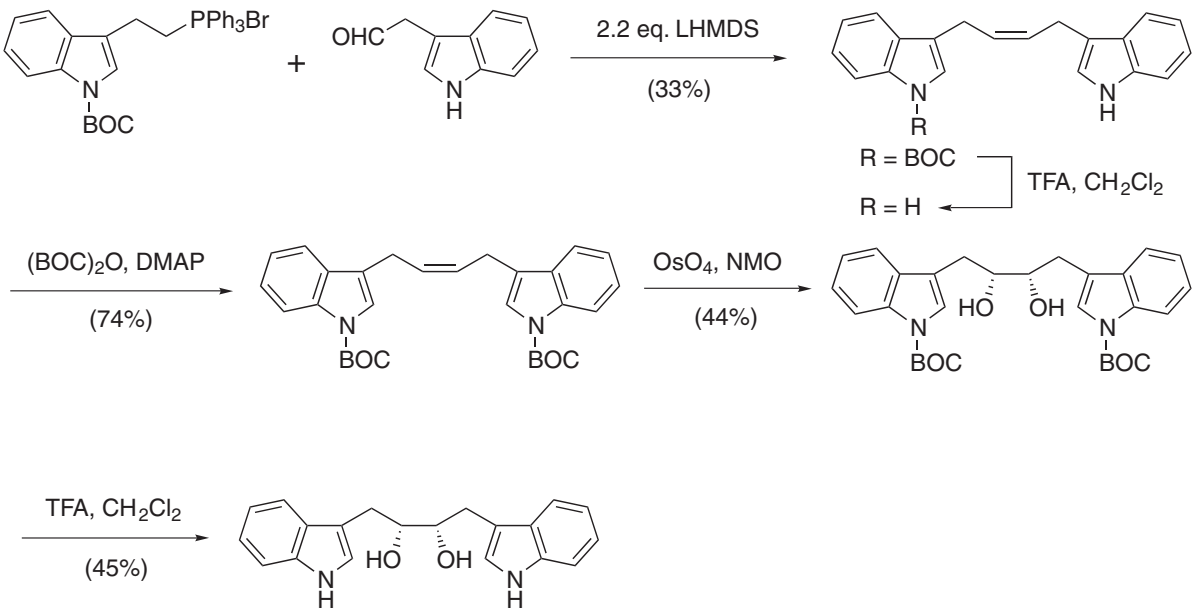
Diolmycins inhibited growth of monensin-resistant *Eimeria tenella* in an *in vitro* assay system using BHK cells as a host.

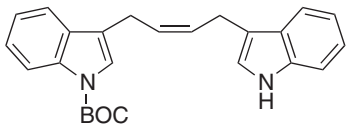
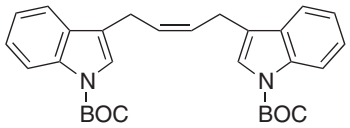
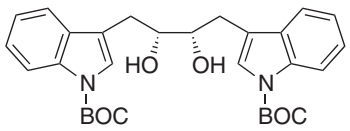
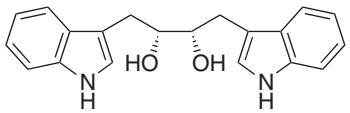
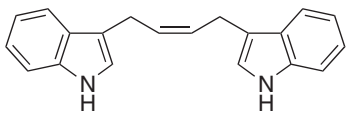
Compound	Minimum effective concentration (μg/ml)		Specificity (C/A)
	Anticoccidial activity (A)[a]	Cytotoxicity (C)[b]	
Diolmycin A1	0.02	0.2	10
Diolmycin A2	0.2	2.0	10
Diolmycin B1	20	NT[c]	—
Diolmycin B2	20	NT[c]	—

[a] No mature shizonts were observed in the cells at the indicated drug concentration or higher.
[b] No BHK-21 cells were observed at the indicated drug concentration or higher.
[c] NT : Not tested at a concentration higher than 20 μg/ml.

4. Synthesis of diolmycin analogs[2,3)]

Racemic diolmycin A1 and its analogs were synthesized *via* a stereoselective Wittig reaction followed by osmium oxidation.



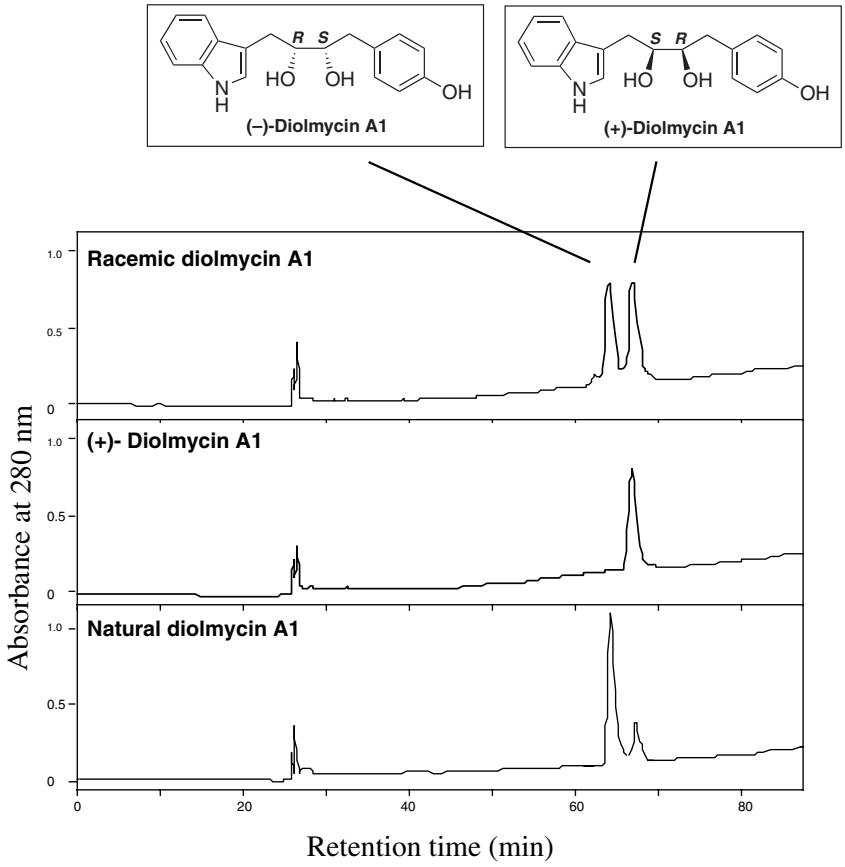
Compound	Minimum effective concentration (μg/ml)		Specificity C/A
	Anticoccidal activity (A)[a]	Cytotoxicity (C)[b]	
	0.5	10	20
	10	50	5
	—[c]	5.0	—
	—[c]	0.05	—
	0.5	10	20

[a] No mature shizonts were observed in the cells at the indicated drug concentration or higher.
[b] No BHK-21 cells were observed at the indicated drug concentration or higher.
[c] NT : Not tested at a concentration higher than 20 μg/ml.

5. Absolute configuration of diolmycin A[4,5)]

An asymmetric total synthesis of diolmycin A1 was achieved in six steps using 2-(4-hydroxyphenyl) ethanol as a starting material, and established that the absolute configurations of (+)- and (-)-diolmycin A1 were (11*S*, 12*R*) and (11*R*, 12*S*), respectively. HPLC analysis using a chiral column revealed the natural diolmycin A1 was comprised of a 4:1 mixture of (–) and (+) enantiomers.

The total synthesis of diolmycin A2 using a Yb(III) trifluoromethanesulfonate-catalyzed high pressure reaction was reported by Kotsuki *et al*., and showed the absolute configuration of (+)-diolmycin A2 was (11*S*, 12*S*) (See Appendix-I).



6. References

1. [501] N. Tabata *et al*., *J. Antibiot*. **46**, 756-761 (1993)
2. [502] N. Tabata *et al*., *J. Antibiot*. **46**, 762-769 (1993)
3. [509] T. Sunazuka *et al*., *J. Antibiot*. **46**, 1178-1180 (1993)
4. [519] T. Sunazuka *et al*., *Tetrahedron Lett*. **34**, 6659-6660 (1993)
5. H. Kotsuki *et al*., *Tetrahedron Lett*. **37**, 3727-3730 (1996)