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ASYMMETRIC SYNTHESIS OF THE ANTICOCCIDIAL ANTIBIOTIC DIOLMYCIN A1. DETERMINATION OF ABSOLUTE STEREOCHEMISTRY

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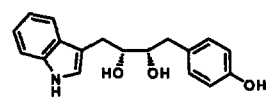
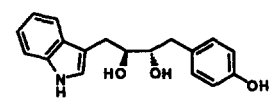
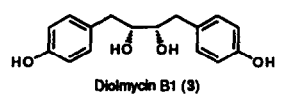
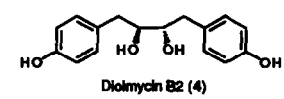
Abstract: An asymmetric total synthesis of diolmycin A1 (1), a recently discovered anticoccidial antibiotic, has been achieved in six steps from 2-(4-hydroxyphenyl)ethanol. The natural product comprises an unusual ca. 4:1 mixture of enantiomers; the synthesis defined the (11*R*,12*S*) absolute configuration of the predominant (-) antipode.

Our search for new anticoccidial agents recently led to the isolation of diolmycins A1, A2, B1, and B2 (1-4) from a fermentation broth of *Streptomyces* sp. WK-2955.[1] Diolmycin A1 proved most active in vitro, inhibiting the growth of *Eimeria tenella* in BHK-21 host cells at a concentration of 0.02 μg/ml.[1] The structures of 1-4 were initially deduced via extensive spectroscopic analysis, and a total synthesis of the racemate confirmed the presence of an erythro vicinal diol moiety in 1.[2] However, the absolute configurations of 1, 2, and 4 remained unknown. Herein we describe a concise asymmetric construction of diolmycin A1 (1) as well as the elucidation of the natural absolute stereochemistry.


Diolmycin A1 (1)

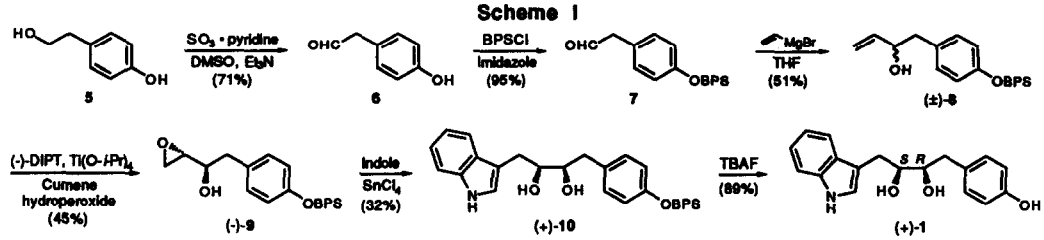

Diolmycin A2 (2)


Diolmycin B1 (3)


Diolmycin B2 (4)

As our point of departure, Doering-Parikh oxidation[3] of 2-(4-hydroxyphenyl)ethanol (5) (pyridine•SO_3, DMSO, Et_3N) furnished hydroxy aldehyde 6[4] (Scheme I), which in turn was protected as the corresponding *t*-butyldiphenylsilyl (BPS) ether 7[4] (67% yield overall). Addition of vinylmagnesium bromide afforded the racemic allylic alcohol 8[4] in 51% yield. Kinetic resolution of (±)-8 via Sharpless asymmetric epoxidation[5] [1.2 equiv (-)-DIPT, 1 equiv Ti(O-*i*-Pr)$_4$, 0.5 equiv cumene hydroperoxide, CH_2Cl_2, -20 °C, 2 days] then gave the desired epoxy alcohol (-)-9[4] in 45% yield (90% of theory) and >90%

Scheme I



ee, as determined by NMR analysis of the derived (+)-MTPA ester.[6]

Stereospecific alkylation of indole (2 equiv) with epoxide (-)-**9** (1.4 equiv $SnCl_4$, CCl_4, 0 °C)[7] afforded the (11*S*,12*R*) diol (+)-**10**[4] in 32% yield. Finally, removal of the BPS group (TBAF) generated (+)-diolmycin A1 (89%). The synthetic material[4] was identical with natural **1** in all respects (TLC, ^1H and ^{13}C NMR, IR, HRMS, UV) except optical rotation (synthetic (+)-**1**: $[\alpha]_D^{25}$ +11.8° (*c* 1.0, methanol); natural (-)-**1**:[1] $[\alpha]_D^{25}$ -8° (*c* 0.1, methanol)). The synthesis established that the absolute configurations of (+)- and (-)-diolmycin A1 are (11*S*,12*R*) and (11*R*,12*S*), respectively.

We next analyzed racemic diolmycin A1 [(±)-**1**], synthetic (+)-**1**, and natural (-)-**1** via HPLC with a scalemic stationary phase (Figure 1).[8] Interestingly, the natural material comprised an *ca.* 4:1 mixture of the (-) and (+) enantiomers;[9] the antipodes were separated and individually characterized. The enantiomeric purity of synthetic (+)-**1** proved to be 94% ee.

Use of (+)-DIPT for asymmetric epoxidation of (±)-**8** subsequently furnish the natural (-) enantiomer of **1** ($[\alpha]_D^{27}$ -12.0° (*c* 1.0, methanol)). HPLC analysis revealed an enantiomeric purity of 96% ee.[8]

In summary, we have prepared (+)- and (-)-diolmycin A1 (**1**) in sufficient quantities to permit more detailed biological evaluation. Further studies of the diolmycins are in progress.

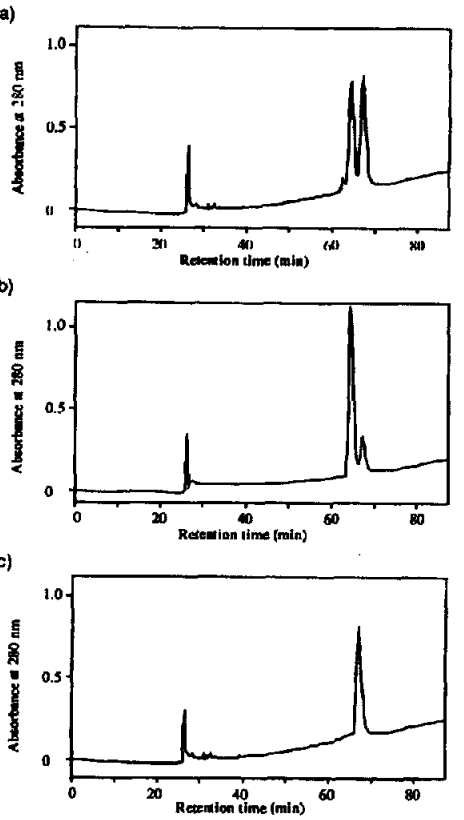


Figure 1. HPLC analysis of diolmycin A1 (**1**) employing a scalemic stationary phase. (a) Synthetic (±)-**1**. (b) Natural (-)-**1**. (c) Synthetic (+)-**1**.

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References and Notes

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4. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 270-MHz ^1H NMR, and 67.5-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. In addition, **6-8**, (-)-**9**, (+)-**10**, (+)-**1** and (-)-**1** gave satisfactory C and H combustion analysis.
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8. Waters Opti-Pak XC 3.9 x 300 mm column; 60-min linear gradient, *n*-hexane to 1:1 *n*-hexane/*i*-propanol; 0.5 mL/min flow rate; UV detection at 280 nm.
9. Similarly, natural limatulone is produced as a mixture of (+), (-), and meso stereoisomers: Takikawa, H.; Mori, K.; Kido, M. *34th Symposium on the Chemistry of Natural Products, Symposium Papers;* Tokyo, 1992; p 707.

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