

Asymmetric Synthesis of Dienomycin C

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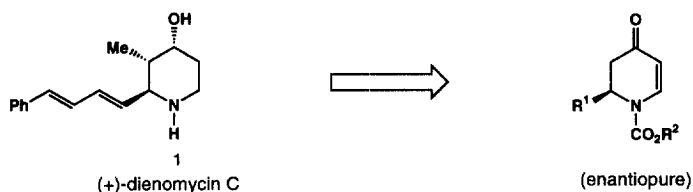
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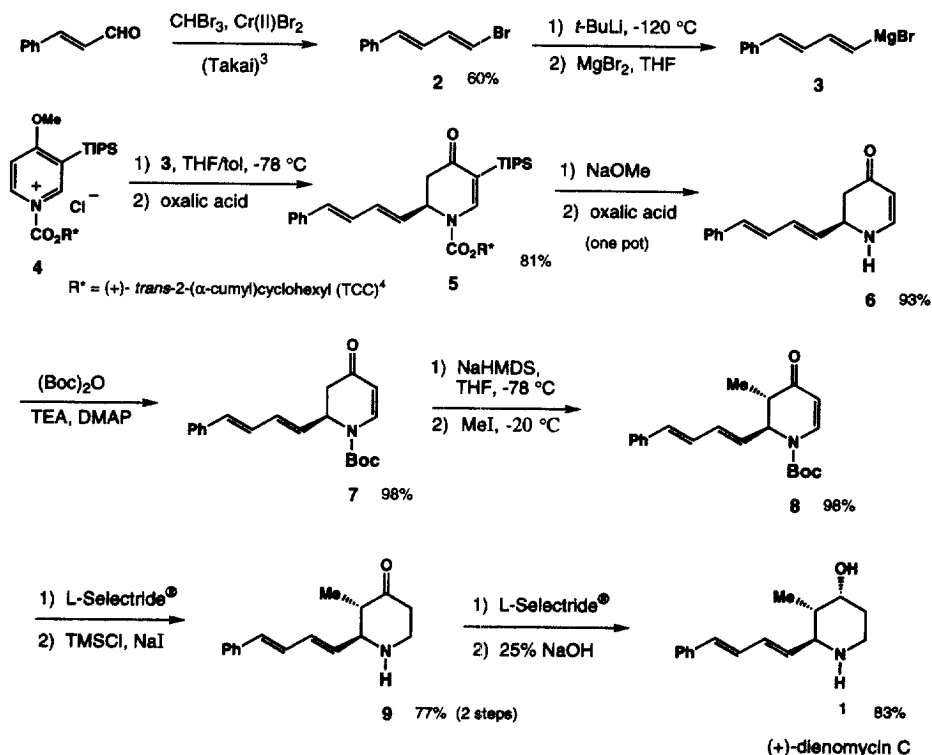
Abstract: The first asymmetric synthesis of dienomycin C was accomplished in seven steps and 46% overall yield. © 1998 Elsevier Science Ltd. All rights reserved.

Dienomycin C (**1**), an alkaloid isolated from the *Streptomyces* strain MC67-C1 by Umezawa and coworkers has been found to exhibit antibiotic activity against some strains of *Mycobacteria*.¹ Dienomycin C and its derivatives were the first examples of microbial metabolites containing piperidine or phenylbutadiene structural units. A racemic synthesis of **1** has been reported by Troin and coworkers.² Herein we report the first asymmetric synthesis of the alkaloid using an enantiopure 2,3-dihydro-4-pyridone as a chiral building block.



The synthetic plan called for the preparation of known (*E,E*)-1-bromo-4-phenylbutadiene (**2**) and its conversion to Grignard reagent **3**. Vinyl bromide **2** was prepared from *trans*-cinnamaldehyde using the Takai olefination³ (*E/Z* = 7/1). Several attempts to form the vinyl Grignard by direct metalation using magnesium metal were unsuccessful. A two-step method involving lithium-halogen exchange with *t*-BuLi, followed by addition of anhydrous MgBr₂ in THF, gave the desired organometallic **3**. Addition of **3** to chiral 1-acylpyridinium salt **4**, formed in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and the chloroformate of (+)-TCC⁴, provided the crude dihydropyridone **5** in quantitative yield and 86% de. Purification by radial PLC (silica gel, EtOAc/hexanes) afforded an 81% yield of pure **5**. Hydrolysis with NaOMe/MeOH followed by aqueous oxalic acid provided dihydropyridone **6** in 93% yield, and the chiral auxiliary ((-)-TCC) was recovered in 95% yield. Acylation of **6** with Boc-anhydride gave a 98% yield of enantiopure carbamate **7**. Enolate formation using NaHMDS in THF and methylation with methyl iodide provided a near quantitative yield of *trans*-dihydropyridone **8**. Conjugate reduction with L-Selectride[®] and removal of the Boc group using in situ formed TMSI gave a 77% yield of piperidone **9**. Finally, stereoselective reduction with L-Selectride[®] according to Troin's procedure² gave enantiopure dienomycin C

(83%, mp 129.5 - 130.5 °C, $[\alpha]_D^{23} + 82.1$ (c 0.03, CHCl₃); [lit.¹ mp 130-131 °C, $[\alpha]_{589}^{20} + 85$ (c 1.0, MeOH)]. The spectral properties of (+)-**1** were in agreement with reported data.¹ The natural product was constructed enantioselectively from **4** in seven steps and 46% overall yield. Syntheses of other piperidine-containing alkaloids using this strategy are under study in our laboratories.



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References and Notes.

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- (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) (+)- and (-)-TCC alcohols are available from Aldrich Chemical Company.