

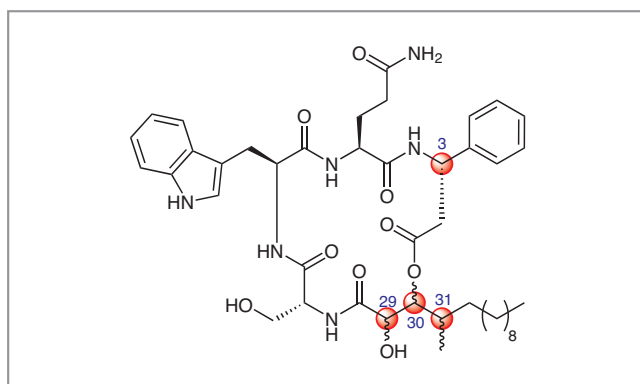
# Cyclodepsipeptide Alveolaride C: Total Synthesis and Structural Assignment

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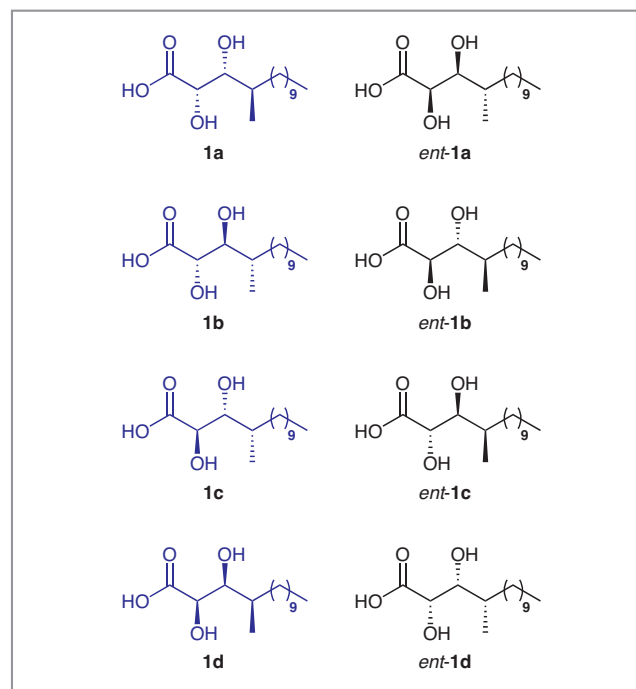
Alveolarides are a class of agriculturally important cyclodepsipeptides, which were isolated from cultures of the fungus *Microascus alveolaris* in 2018 by researchers at Dow AgroSciences (DAS) in the USA who partially elucidated the structures of alveolarides A–C (*J. Nat. Prod.* **2018**, *81*, 10–15). These are 17-membered macrocyclic compounds having the rarely found 2,3-dihydroxy-4-methyltetradecanoic acid (DHMTDA) as the common nonpeptide unit. The stereochemistry of asymmetric centers on the DHMTDA segment remained unassigned. The group of Professor Rajib Kumar Goswami at the Indian Association for the Cultivation of Science (Jadavpur, India) has targeted alveolaride C (Figure 1) with the intention of solving the mystery of its structural assignment using total synthesis as the key tool. Professor Goswami remarked: “There are three asymmetric centers in the DHMTDA fragment of alveolaride C, whose configuration is unknown, giving rise to the possibility of eight configurational isomers (Figure 2); finding the actual structure of alveolaride C was quite challenging.”

A convergent synthetic route was adopted by Professor Goswami and his co-workers. To narrow down the search for structural possibilities, four isomers (**1a–d**) (Figure 2) of the DHMTDA fragment were synthesized initially and their data were compared with the reported data. “The data of isomer **1d** matched nicely with the reported one,” explained Professor Goswami. He continued: “However, isomer *ent-1d* was also taken into account, as no specific rotational value of the

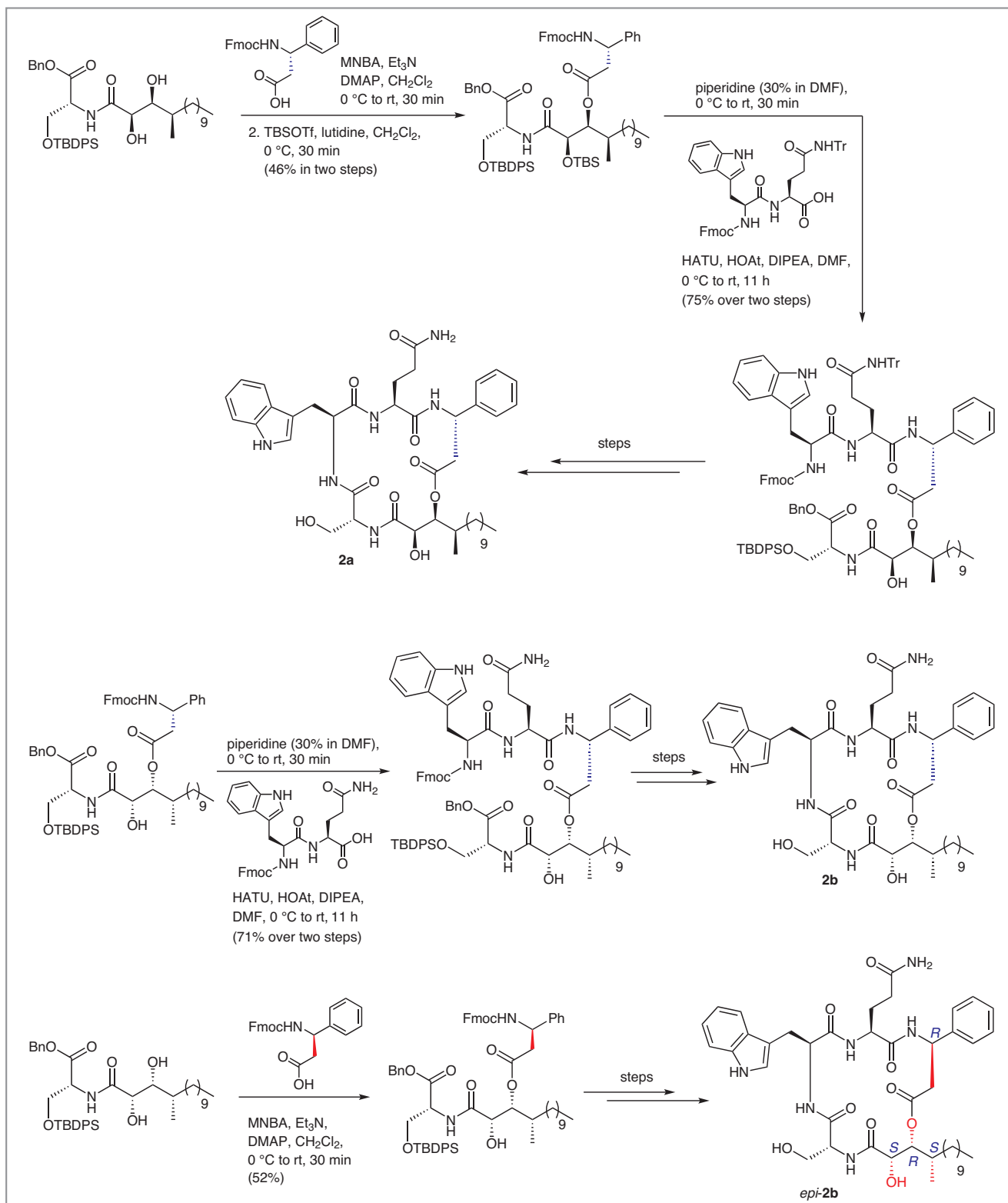
DHMTDA fragment was reported by the DAS team.” According to Professor Goswami, selective esterification of a  $\beta$ -hydroxyl group in the presence of a free  $\alpha$ -hydroxyl on the key D-serine-DHMTDA synthetic intermediate (first step in Scheme 1) was one of the crucial steps, which was likely possible due to the presence of hydrogen bonding between the  $\alpha$ -hydroxyl and the amide carbonyl. This possibility was conceived from the crystal structure of isomer *ent-1d*. “Two possible structures (**2a** and **2b**) of alveolaride C were synthesized from DHMTDA counterparts **1d** and *ent-1d* and their NMR spectroscopic data were compared with the reported data of the isolated alveolaride C,” said Professor Goswami. He continued: “The isomer **2b**, having 29*S*,30*R*,31*S* configuration of the DHMTDA unit, was close to the reported NMR data of isolated alveolaride C. However, a few noticeable discrepancies in the  $^1\text{H}$  NMR data were observed for the protons nearby the  $\beta$ -phenylalanine and the DHMTDA counterpart.” This observation led the group to



**Figure 1** Putative structure of alveolaride C



**Figure 2** Possible stereoisomers of DHMTDA (**1a–d** and *ent-1a–d*)



**Scheme 1** Total synthesis of alveolaride C and two of its diastereoisomers

reconsider the absolute configuration of the  $\beta$ -phenylalanine fragment. Thus, the group synthesized the C-3 epimer (*epi-2b*) of the compound **2b** which turned out to be in complete accordance with the data of the isolated natural product.

“The structural riddle of alveolaride C was solved successfully,” said Prof Goswami. “The absolute stereochemistry of three undetermined centres on the DHMTDA segment was established unambiguously as 29*S*,30*R*,31*S*. The stereochemistry of the  $\beta$ -phenylalanine unit was revised from *S* to *R*.” Professor Goswami concluded: “This synthetic study was crucial for determining the unassigned stereocenters common to all the members of this family and also a very important stepping-stone for the total synthesis of other members of this family.”

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