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Biosynthesis of the mC$_7$N unit of Acarbose and Validamycin A

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Acarbose, known as an á-glucosidase inhibitor and a clinically useful drug for the treatment of type II insulin-independent diabetes, is isolated from the fermentation broth of *Actinoplanes* sp. And validamycin A is widely used in the Far East for the treatment of sheath blight disease of rice plant, is isolated from the *Streptomyces hygroscopicus* var. *limoneus*. Acarbose consists of an unsaturated aminocyclitol (valienamine), a deoxyhexose, and a maltose. Validamycin A contains two aminocyclitols (valienamine and validamine), and a glucose. The valienamine and related amino-cyclitols could be considered aliphatic analogues of the mC$_7$N unit, a biosynthetically unique structural element, which is found in many secondary metabolites such as ansamycins and mitomycins. The mC$_7$N unit in those metabolites is synthesized via a branch of the shikimate pathway, whereas feeding experiments with stable isotope-labeled precursors have demonstrated that mC$_7$N unit of acarbose and validamycin A is derived from the pentose phosphate pathway. And it was predicted that either sedoheptulose 7-phosphate or its C-5 epimer *ido*-heptulose 7-phosphate is a proximate precursor of the mC$_7$N unit of those metabolites.

To study the biosynthetic pathway leading to the mC$_7$N unit of acarbose and validamycin A, a number of potential precursors labeled with ^{3}H, ^{2}H, and ^{13}C were synthesized and fed to cultures. The results from the feeding experiments for acarbose demonstrated that the cyclitols such as valienone, valienamine, valiolone, valiolamine, and 1-*epi*-valienol having the same strereochemistry at C-2 as the valienamine moiety were not plausible intermediates in acarbose biosynthesis. Furthermore, 2-*epi*-valiolone, which has the same stereochemistry as the open-chain precursor, sedoheptulose 7-phosphate identified as an intermediate, was also not incorporated. Interestingly, 2-*epi*-5-*epi*-valiolone, C-5 epimer of 2-*epi*-valiolone, was incorporated efficiently into valienamine moiety of acarbose. But, 2-*epi*-valienone, dehydrate form of 2-*epi*-5-*epi*-valiolone was not incorporated. The results suggest that 2-*epi*-5-*epi*-valiolone is the initial cyclization product of sedoheptulose 7-phosphate and converted to the mC$_7$N moiety of acarbose without the intervention of other free cyclitol intermediates.

The results from the feeding experiments for validamycin A demonstrated that 2-*epi*-5-*epi*-valiolone is also the first cyclic intermediate. In contrast to acarbose, the validamycin A formation involves a series of free intermediates such as 5-*epi*-valiolone, valienone, and validone. But very low incorporation of 2-*epi*-valiolone suggests that epimerization at C-2 of 2-*epi*-5-*epi*-valiolone occurs to produce 5-*epi*-valiolone, followed by dehydration of 5-*epi*-valiolone to be valienone which is a proximate intermediate of the two cyclitols, valienamine and validamine of validamycin A.