STUDIES TOWARD THE TOTAL SYNTHESIS OF NAHUOIC ACID A

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Nahuoic acid A (1) (Fig. 1) is a highly hydroxylated marine polyketide that was isolated in 2013 by Andersen and co-workers from a culture of *Streptomyces* sp. found in tropical marine sediments. Nahuoic acid A (1) was the first selective *S*-adenosylmethionine (SAM)-competitive inhibitor of the lysine methyl transferase SETD8 ever to be identified [1,2]. So far, only one total synthesis of a nahuoic acid family member, i. e. nahuoic acid C (3), has been successfully completed by Smith and co-workers [3].

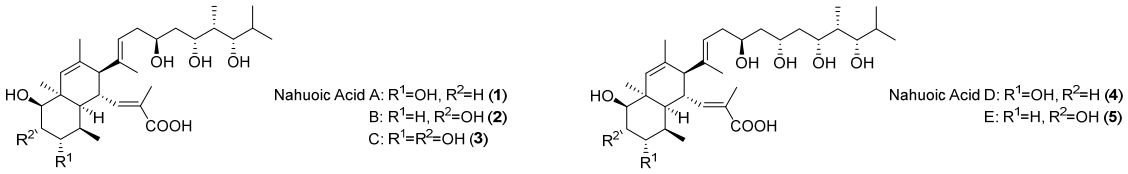
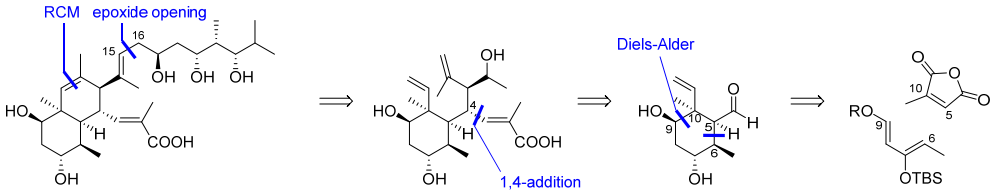


Figure 1: Structure of the nahuoic acids A-E (**1**-**5**).

Our strategy (Scheme 1) toward 1 envisions its final assembly by a late stage epoxide opening to form the C15-C16 bond. The *cis*-decalin core is planned to be accessed by ring closing olefin metathesis (RCM) of triene 6, in which the C4 side chain should be installed in a stereoselective, substrate-controlled 1,4-addition. The stereochemistry of the four contiguous stereocenters at C5, C6, C9, C10 was foreseen to be installed in an *endo*-selective Diels-Alder reaction of diene 8 and citraconic anhydride.



Scheme 1: Retrosynthetic approach to nahuoic acid A (**1**).

Our work so far has led to the development of an efficient, stereoselective route for the synthesis of the intermediate aldehyde 7. This contribution will discuss the chemistry involved in the preparation of 7 together with our ongoing efforts on the further elaboration of 7 *en route* to nahuoic acid A (1).

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[1] D. E. Williams, D. S. Dalisay, F. Li, J. Amphlett, W. Maneerat, M. A. Garcia Chavez, Y. A. Wang, T. Matainaho, W. Yu, P. J. Brown, C. H. Arrowsmith, M. Vedadi, R. J. Andersen, *Org. Lett.*, **2013**, 15, 414-417.

[2] D. E. Williams, F. Izard, S. Arnould, D. S. Dalisay, C. Tantapakul, W. Maneerat, T. Matainaho, E.Julien, R. J. Andersen, *J. Org. Chem.*, **2016**, 81, 1324-1332.

[3] Q. Liu, Y. Deng, A. B. Smith III, *J. Am. Chem. Soc.*, **2017**, 139, 13668-13671.