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New synthetic route to access (±) salinosporamide A via an oxazolone-mediated ene-type reaction

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ABSTRACT

We report herein a racemic key intermediate in the synthesis of salinosporamide A via a *tert*-alkyl amino hydroxy carboxylic ester produced in an ene-type reaction of an oxazolone with an enol ether.

Cultivation and characterization of salinosporamide A (**1**, Fig. 1) by Fenical et al. in 2003[1] have led to many syntheses of the natural product and structurally related analogues.[2–16] The natural product, as well as some analogues, has been shown to inhibit the 26S proteasome, which is an emerging area in anticancer therapy.[17–19] The structure of salinosporamide A comprises a bicylic core, composed of a pyrrolidinone and a β-lactone, which is critical for its biological activity[1,20] and is similar to the biologically active terrestrial microbial product omuralide (**2**).[21] Many of the structural features necessary for activity of compounds in this class have been identified through structure-activity relationships, natural product analogues (e.g., **3** and **4**, Fig. 1), and X-ray crystallography.[12,22] Even though many elegant syntheses[2–16] have been reported of this intriguing class of proteasome inhibitors, its potential clinical relevance warrants the development of new approaches that may provide access to additional candidates.

Recently, we reported the diastereoselective synthesis of *tert*-alkyl amino hydroxy carboxylic esters by means of a sequential ene-type reaction of oxazolones with enol ethers followed by hydride reduction (Fig. 2).[23,24] This new reaction allowed the construction of compounds with high diversity depending on the nature of the oxazolone and enol ether used.[25]

The functionalities surrounding the quaternary stereocenter formed in this reaction are also represented at the C4 center in salinosporamide A (Fig. 1). To the best of our knowledge, this center has never been constructed via an oxazolone intermediate and may be a useful means to incorporate a wide range of diversities into the pyrrolidinone skeleton. The total synthesis of salinosporamide A by Corey and co-workers involves the construction of pivotal intermediate **5**, which undergoes cyclization via a Baylis–Hillman-aldol reaction to give the core pyrrolidinone scaffold.[16] This key intermediate could be readily accessed using our chemistry after a few functional group modifications. Due to the skeletal diversity afforded by the use of various enol ethers in the aforementioned ene-type reaction, this could potentially serve as a

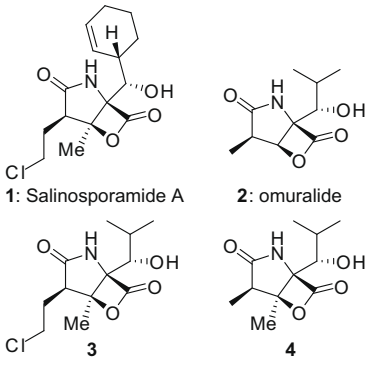

Figure 1. Natural proteasome inhibitors and their synthetic analogues.

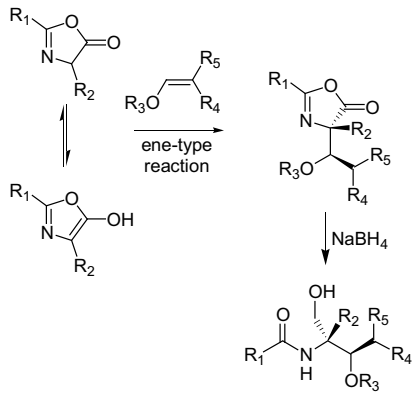

Figure 2. Intermolecular ene-type reaction utilizing oxazolones and enol ethers followed by reduction.

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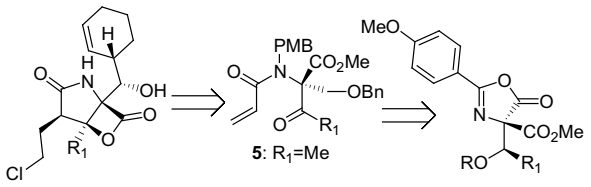
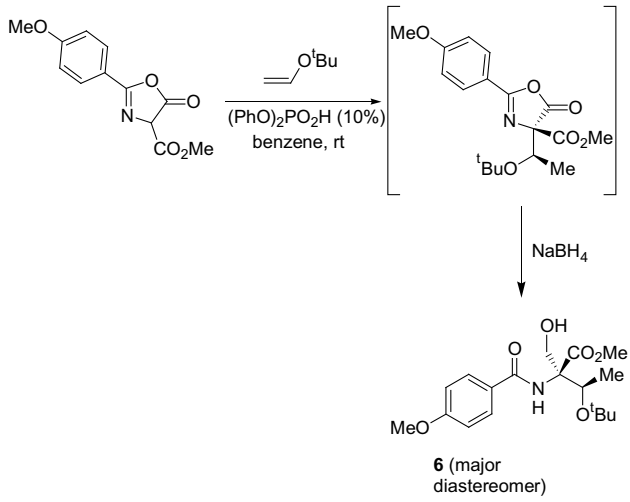


Scheme 1. Strategy for the synthesis of **5** and analogues of **1**.

strategy for the synthesis of C3 analogues of **1** (Scheme 1). We sought Corey's intermediate **5**,[16] then, as our target to demonstrate the utility of quaternary centers produced via oxazolones in the synthesis of natural products.

The starting material for our synthesis of **5** was obtained through our ene-type reaction/reduction protocol to yield amino



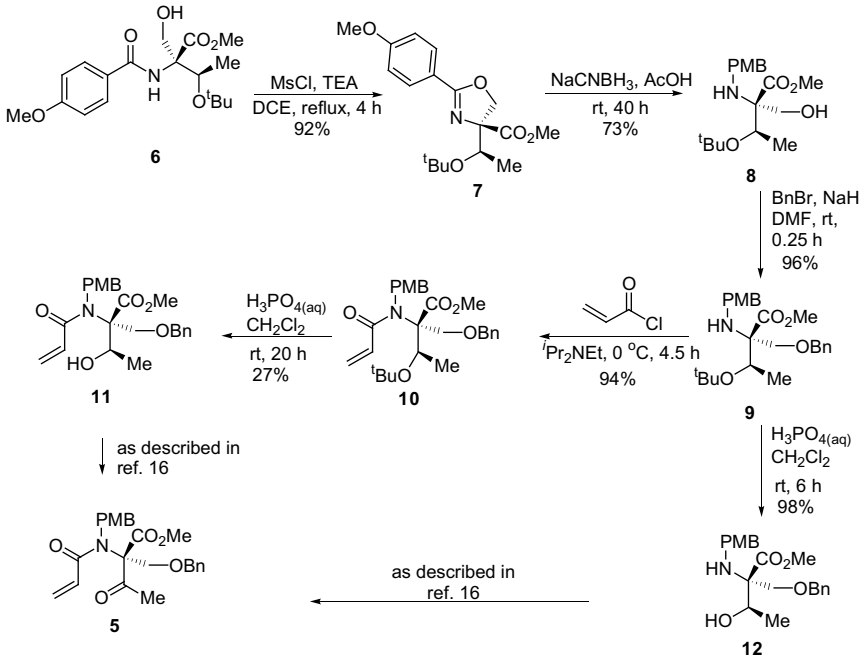
Scheme 2. Synthesis of **6** via an oxazolone-mediated ene-type reaction.

hydroxy carboxylic ester **6** as a 3:1 mixture of diastereomers in 88% yield (Scheme 2).[23] The synthesis of **5** was continued using only the major diastereomer as indicated in Scheme 3. However, it should be noted that both diastereomers could be used to complete the racemic synthesis of salinosporamide A due to the destruction of the second stereocenter during the oxidation of alcohol **11** (or **12**) (Scheme 3).

The synthesis of **5** continued with the reduction of the amide functionality present in the *tert*-alkyl amino hydroxy carboxylic ester **6**. This reduction was performed smoothly via dehydrative cyclization under basic conditions with MsCl followed by oxazoline reduction with sodium cyanoborohydride in acetic acid to afford amino alcohol **8** (Scheme 3). This transformation accomplished two goals in our synthesis: (1) the reduction of a stable amide in the presence of an ester, a feat we found to be unsuccessful under a variety of attempted conditions and (2) the protection of the amine as a PMB amine. The resultant primary alcohol was protected under basic conditions with benzyl bromide to give benzyl ether **9**, and acylation of the secondary amine with acrylyl chloride under Corey's conditions[16] gave amide **10** in 94% yield. Deprotection of the *tert*-butyl ether in **10** under acidic conditions proved to be problematic.

The reaction was often messy and low yielding, as treatment with TFA or aqueous phosphoric acid gave 25% and 27% yields, respectively, of alcohol **11** as a single diastereomer. Finally, oxidation of the free alcohol was performed using the reported procedure to cleanly afford racemic ketone **5**, the spectroscopic data of which matched with those of the known compound. The disappointing yields obtained from the deprotection of the *tert*-butyl ether prompted investigation into its removal in an earlier stage of the synthesis.

Access to **5** involved modification of alcohol **12** in the original synthesis, which could be accessed in our synthesis as well. Deprotection of the *tert*-butyl ether in compound **9** could be performed by treatment with aqueous phosphoric acid[26] to afford secondary alcohol **12** in near quantitative yield, thereby granting access to desired compound **5**.



Scheme 3. Synthesis of Corey's intermediate **5.**

In conclusion, we report a short racemic synthesis of an intermediate used in the synthesis of salinosporamide A starting from a *tert*-alkyl amino hydroxy carboxylic ester produced via an ene-type reaction.

Acknowledgments

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Supplementary data

Experimental procedures, IR, 1H, and 13C NMR data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.154.

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