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Rational design and efficient synthesis of a fluorescent-labeled jasmonate

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ABSTRACT

A fluorescent-labeled jasmonate was rationally designed based on examination of the model of interaction between the jasmonate and its receptor. An efficient synthetic route has been developed for this molecule. The biological activity of this fluorescent probe was retained which was similar to that of the methyl jasmonate as examined by root growth inhibition bioassay. This fluorescent probe will greatly facilitate biological studies of jasmonates through fluorescent imaging.

Jasmonic acid (JA) and its derivatives, collectively referred to as jasmonates, occur widespread in plants and some lower eukaryotes.[1] Jasmonates originate from oxidation of linolenic acid and share notable structural and functional similarities with prostaglandins in animals.[2] They are of general biological importance, not only regulating plant growth and development but also mediating environmental stress responses of plants through reprograming of gene expression.[3] Recently several studies indicated that jasmonates were promising in cancer treatment which induced apoptosis in various cancer cell lines including breast, prostate, melanoma, and leukemia.[4] Significant anti-inflammatory activity was also found for jasmonate analogues that exhibited enhanced activity than natural anti-inflammatory prostaglandins.[5] These results have provoked much research interest in jasmonates as a class of versatile bioactive molecules either in plant or animal kingdom.

To elucidate biological mechanisms of jasmonates on molecular basis a way to visualize the molecules is highly desirable. Fluorescent probes have been established as the most powerful way to monitor the events in proteomics, functional genomics, and cell biology studies.[6] Although a few labeled jasmonates have been designed,[7] a fluorescent-labeled jasmonate is still not available. One fluorescent probe at hand will undoubtedly facilitate the biological studies. Inspired by this notion, we initiated the development of fluorescent-labeled jasmonates retaining biological activities. Herein we described a rational design and efficient synthesis of a fluorescent-labeled jasmonate.

To design a fluorescent-labeled biomolecule a few requirements should be fulfilled. First the fluorescent group does not interfere with the biological activity. Second the fluorescent group can be easily introduced. Coumarin 343[8] was carefully chosen as fluorescent carrier due to its biocompatibility, high quantum yield, ease of handling, and stability. Next we needed to decide where and how to install the fluorescent group to maintain integrity of the biological activity. According to known studies, the aliphatic side chain of JA is important to keep its biological activities and derivatization of the carboxyl group does not severely interfere with the activities.[7b] The endogenous amino acid conjugate of JA, jasmonoyl-L-isoleucine (JA-Ile)[9] represents an active jasmonate derivative. Scrutinizing the model of interaction between JA-Ile and its receptor COI1[7b] revealed the carboxyl group of isoleucine moiety is far away from the active site. Therefore modification of the carboxyl group of JA-Ile has more chance to realize an active form of fluorescent probe of JA. To best mimic JA-Ile and keep a reasonable space for the fluorescent group from the jasmonate moiety, L-lysine was selected as the link chain with an additional advantage of synthetic simplicity.[10] Taken all of the factors together, a possibly bioactive fluorescent probe of jasmonates was designed (Fig. 1).

The synthetic study was commenced with the synthesis of the fluorescent coumarin 343 (**6**) (Scheme 1). Although the preparation of coumarin 343 is known in the literature,[11] it is far from straightforward always requiring multiple protection and deprotection operations. To eliminate the employment of protecting groups, we started from commercially available 3-aminophenol. Following

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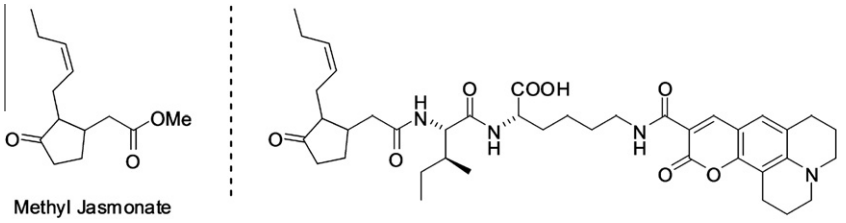
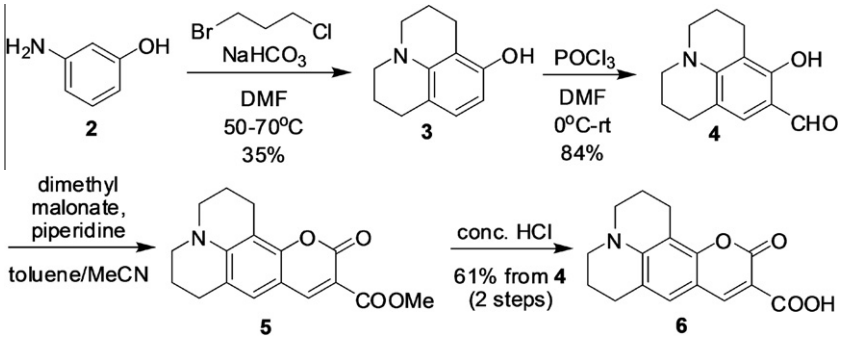
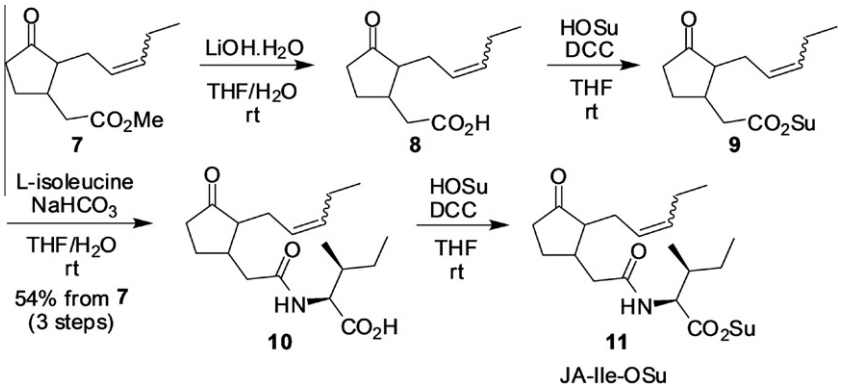


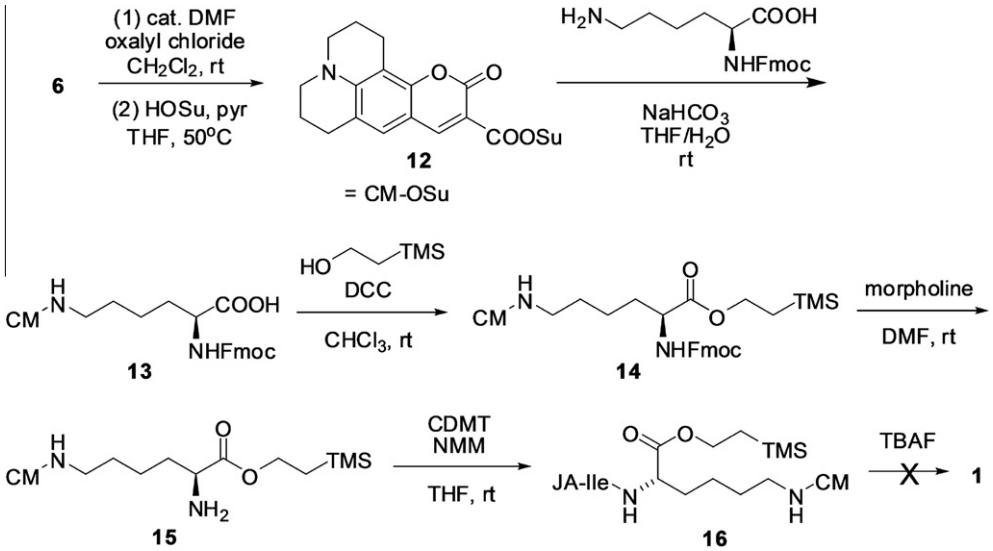
Figure 1. Designed bioactive fluorescent-labeled jasmonate.



Scheme 1. Synthesis of coumarin 343 (**6**).



Scheme 2. Synthesis of JA-Ile.



Scheme 3. Attempt to synthesis of the fluorescent-labeled jasmonate.