

## Practical synthesis of DOPA derivative for biosynthetic production of potent antitumor natural products, saframycins and ecteinascidin 743

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# Practical Synthesis of DOPA Derivative for Biosynthetic Production of Potent Antitumor Natural Products, Saframycins and Ecteinascin 743

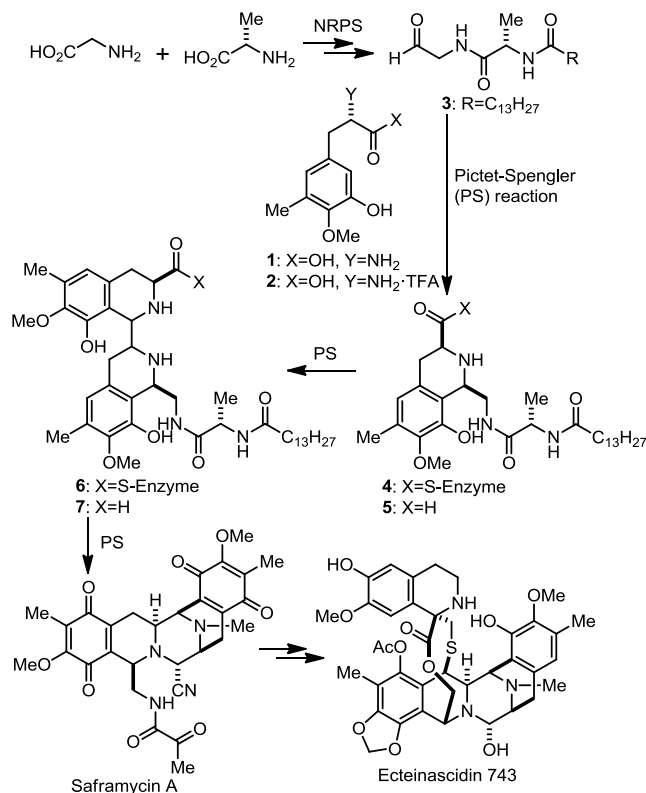
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**Abstract** A practical synthetic route of DOPA derivative **2**, which should be useful for direct biosynthetic production of potent antitumor natural products, saframycins and ecteinascin 743 was established. The developed strategy features i) easy-to-handle reactions without special care upon both dryness and inert atmosphere, and ii) the facile HPLC-free purification of **2** via recrystallization enabling scalable synthesis of **2**.

**Introduction** Saframycins (SMs), produced by *Streptomyces* and various soil bacteria as well as marine vertebrates such as ascidians and sponges, are potent antitumor antibiotics [1]. In particular, a highly potent SM analog, ecteinascin 743 [2] (ET-743), has recently been in use as an anticancer drug against soft-tissue sarcoma [3]. ETs share the central pentacyclic tetrahydroisoquinoline core with SMs, except for the oxidation state of their terminal rings and the additional ten-membered lactone bridge found in ET-743. Due to the short supply from natural resources, the production of ET-743 should depend on a semi-synthesis including 21 synthetic steps [4]. In order to facilitate the direct biosynthetic production of SMs including ETs, unremitting bioinformatic analyses were carried out, and it was found that SMs are biosynthesized from L-alanine, glycine and two molecules of 3,4-dihydroxyphenylalanine (DOPA) derivative **1** [5] through dual Pictet-Spengler (PS) mechanism [6] (Scheme 1). Briefly, tetrahydroisoquinoline core is constructed by the following three steps; i) Schiff base is formed between DOPA derivative **1** and dipeptidic aldehyde **3**, generated from glycine and L-alanine by the aid of non-ribosomal polypeptide synthetases (NRPSs); ii) PS cyclization occurs to give **4**; and iii) enzymatic region is reductively eliminated to afford aldehyde **5**, which is involved in the same sequence to furnish SMs and ETs through intermediates **6** and **7**. Thus, to develop an engineered perpetual SM-producing system, we cloned necessary biosynthetic gene clusters for SMs and expressed them in model creatures, however, it was unsuccessful to detect the production of SMs even by mass spectrometric analysis [7]. We envisaged that one of the reasons would be insufficient amount of endogenous non-natural amino acid **1**, and if **2** were fed from outside the system, enough supply of SMs would be realized. Herein, we report practical and scalable synthesis of amino acid **2** to tolerate the feeding experiments.

**Results and Discussion** Synthesis of DOPA derivative **2** commenced with *N*-*t*-butoxycarbonyl (*N*-Boc) tyrosine **8** according to the Schmidt's report [8], one of the most expeditious and easy-to-handle methods to date [9] (Scheme 2). Aldehyde **9** was prepared by Reimer-Tiemann formylation [10a] and the subsequent esterification of *N*-Boc tyrosine **8** as reported previously [8,10b]. Although we attempted the



**Scheme 1.** Hypothetical Biosynthesis of Saframycin A and Ecteinascin 743.

conversion of **9** into iodobenzene **10** by the action of I<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>, the reaction could not be reproduced even in refluxing ethanol. Hence, we decided to set a robust and reproducible route for the two-steps-introduction of iodine as follows; (i) NaBH<sub>4</sub> reduction of aldehyde **9** into the corresponding alcohol [9a], and (ii) iodination of the resulting alcohol with I<sub>2</sub>/H<sub>2</sub>O<sub>2</sub> combination. As a result, probably due to the fact that electron-withdrawing formyl group was converted to electron-donating hydroxymethyl group, electrophilic iodination proceeded smoothly to afford **11** in good yield (69% for two steps).

Our next task was to oxidize alcohol **11** into Schmidt's intermediate **10** with MnO<sub>2</sub> under argon atmosphere, however, our endeavor was wasteful only to observe the decomposition of substrate **11**. We postulated that *o*-hydroxybenzaldehyde structure of **10** would be unstable even to mild heterogeneous oxidant under inert atmosphere, therefore, methylation of phenolic hydroxy group was first performed. After selective methylation of **11** using methyl iodide and potassium carbonate



132.4, 130.9, 127.2, 61.9, 57.1, 37.3, 24.8, 16.2 ppm; IR (KBr) 3431, 2989, 2361, 2341, 1695, 1610, 1481, 1396, 1265, 1220, 1139, 1011, 897, 807  $\text{cm}^{-1}$

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