Generation of Mid-sized Alkaloidal Scaffolds Exhibiting Potent Anti-Cancer Activities: Systematic Diversification of Macrocyclic Framework of Ecteinascidins

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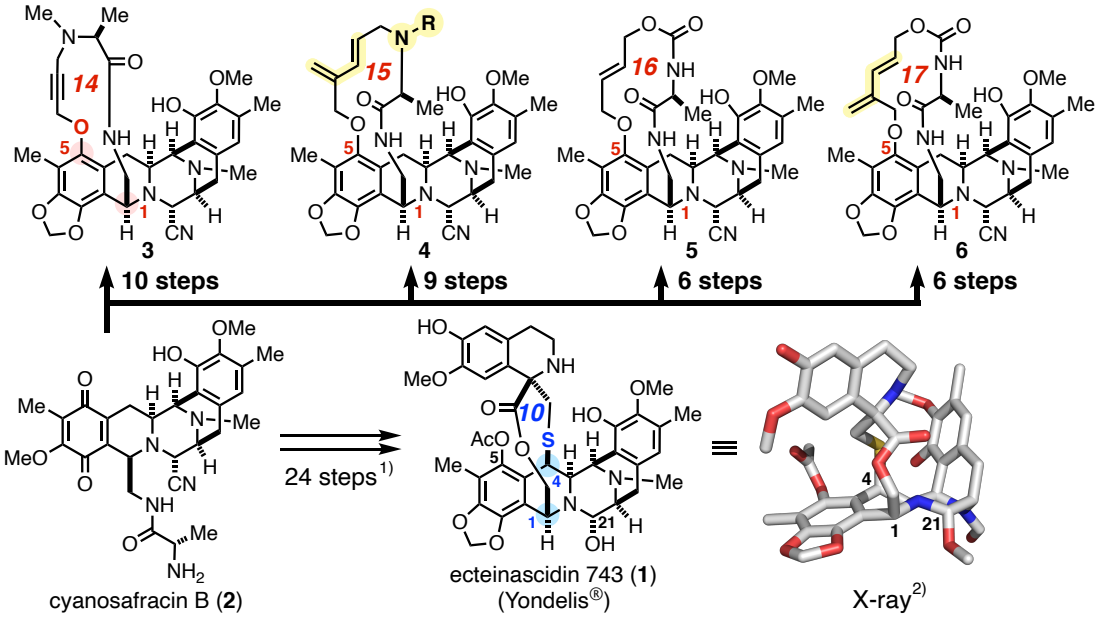
Ecteinascidin 743 (**1**) exhibits potent anticancer activity and is clinically approved for the chemotherapy for sarcoma. The highly functionalized marine-derived alkaloid **1** has a 10-membered macrolactone ring bridged on the hexacyclic core scaffold at C1 and C4 positions. In this study, we conceived macrocycle formation at C5 in place of the C4 position to gain concise and flexible access to the novel alkaloidal scaffolds with DNA binding ability. We are developing a semi-synthetic process starting from cyanosafracin B (**2**), allowing systematic diversification of the macrocyclic frameworks ranging from 14 to 17 membered rings.

Semi-synthesis of **3** bearing a 14-membered ring was achieved via Cu(I)-catalyzed three-component coupling reaction as a key step for macrocyclization. Then, 15- and 17-membered macrocycles (**4**, **6**) with a conjugated diene moiety were efficiently synthesized by employing ring-closing enyne metathesis reactions in 9 and 6 steps from **2**, respectively. The 16-membered macrocycle **5** with an olefinic double bond was also generated in 6 steps from **2** via a ring-closing metathesis reaction. DNA alkylating ability, potent growth inhibitory activity against various cancer cell lines, and further extension of semi-synthetic process will be presented.



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