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Study on the Total Synthesis of Ecteinascidin 743 and Its Analogues--Construction of A Pentacyclic Intermediate

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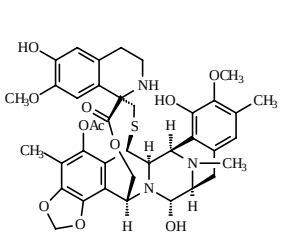
Abstract: A concise and efficient synthesis of the pentacyclic intermediate **1**, as a simple model compound of Ecteinascidin 743 and its analogues, is described.

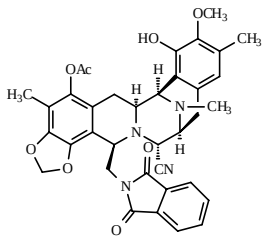
Keywords: Pentacyclic intermediate, ecteinascidin 743, L-dopa.

Ecteinascidin 743(Et 743) is an exceedingly potent antitumor agent isolated from the marine tunicate *Ecteinascidia turbinata*. As its structurally simplified version, phthalascidin, was found to retain the cytotoxicity of the natural product. Their novel structures, impressive biological activities and difficult availabilities conspire to render them attractive targets for total synthesis. E. J Corey and co-workers completed the total synthesis of Et 743 and phthalascidin in a delicate way[1,2]. Our research is to develop a new approach to synthesize some structurally simplified analogues of Et 743, from which we hope to find new antitumor drug candidates. Here we report the synthesis of a pentacyclic intermediate **1**, as a simple model compound of Et 743.

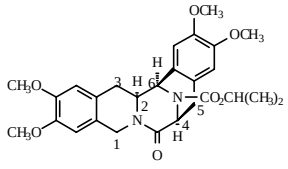
Scheme 1



Et 743



Phthalascidin



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As seen in the **Scheme 1**, compound **1** possesses a bis-isoquinoline skeleton, which not only is the core structure of Et 743 and phthalascidin, but also features another family

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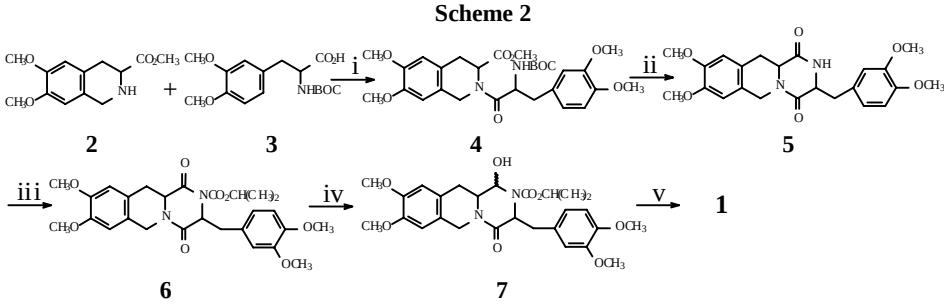
of natural product saframycins. Different from the common way of constructing this typical skeleton in the synthesis of saframycins[3], the synthetic strategy employed is outlined below (**Scheme 1**).

Scheme 2



Reagents and conditions: (i) BOP-Cl,Et_3N,CH_2Cl_2,25°C,4 h,80%; (ii) CF_3CO_2H/CH_2Cl_2,25°C,4 h, 86 %; (iii) $ClCO_2CH(CH_3)_2$,DMAP,Et_3N,CH_2Cl_2,25°C,6 h,80 %; (iv) Li(tert-BuO)$_3$AlH,THF,0°C, 2 h, 90 %; (v) HCO_2H,60°C, 3 h,65 %.

In this route, both of the two building blocks **2** and **3** were prepared from L-dopa according to the literature method[4]. Coupling of **2** and **3** *via* amide bond was accomplished through the action of bis-(2-oxo-3-oxa-zolidinyl) phesphinic chloride (BOP-Cl) in 80% yield. **4** was treated with TFA in CH_2Cl_2 to afford the cyclized compound **5**, which was then converted to the compound **6** in 80% yield. **6** was reduced with an excess amount of Li(tert-BuO)$_3$AlH in THF to provide the diastereomeric mixtures of the alcohol **7**, which, on treatment with formic acid at 60°C, afforded the desired pentacyclic compound **1**[5].

In summary, we developed a simple and efficient way of constructing the core skeleton of Et 743 and its analogues. The study on the total synthesis of Et 743 and its analogues is in progress based on this pathway.

References and Notes

1. E. J. Martinez, T. Owa *et al*., *Proc. Natl. Acad. Sci. USA*, **1999**, *96*, 3496.
2. E. J Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.*, **1996**, *118*, 9202.
3. A. Kubo, N. Saito *et al*., *J. Org. Chem*., **1988**, *53*, 4295.
4. R. T. Dean, H. Rapoport, *J. Org. Chem*., **1978**, *43* (21), 4183.
5. Data of compound **1**: ^{1}H NMR (300MHz, $CDCl_3$, δppm): 6.66 (s, 2H Ar-H), 6.63 (s, 1H, Ar-H), 6.62 (s, 1H, Ar-H), 5.33 (d, 1H, J=2.5Hz, H-6), 5.12 (d, 1H, J=5.5Hz, H-4), 4.95 (m, 1H, J=6.0Hz, NCH), 4.57 (d, 1H, J=17.5Hz, H-1), 4.47 (d, 1H, J=17.5Hz, H-1), 4.04 (dd, 1H, J=2.5Hz, 12Hz, H-2), 3.97-3.85 (m, 12H, 4×OCH_3), 3.23-3.12 (m, 2H, H-5), 2.87 (d, 1H, J=14Hz, H-3), 2.55 (dd, 1H, J=12, 14Hz, H-3), 1.25 (d, 3H, J=6.0Hz, CH(CH_3)), 1.24 (d, 3H, J=6.0Hz, CH(CH_3)); ^{13}C-NMR (125MHz, $CDCl_3$, δ ppm): 168.7, 153.6, 149.3, 148.3, 148.0, 147.2, 126.8, 26.2, 123.6, 122.6, 112.2, 112.0, 110.9, 109.7, 69.8, 58.2, 58.0, 56.5, 56.2, 56.0, 53.3, 52.2, 45.1, 33.5, 32.2, 22.3, 22.3; IR (KBr,cm^{-1}): 1697 (C=O): 1651 (C=O); FABMS (m/z): 497 (M+1).

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