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Synthesis of Ecteinascidin ET-743 and Phthalascidin Pt-650 from Cyanosafracin B

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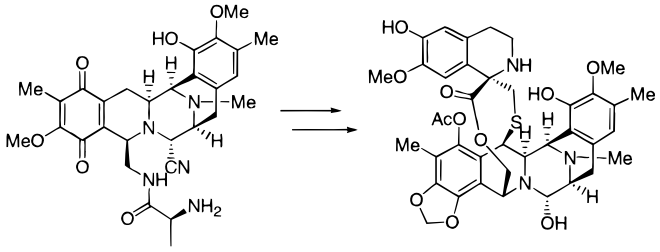
ABSTRACT



An efficient new process is described for the synthesis of ecteinascidin ET-743 (1) and phthalascidin (2), starting from readily available cyanosafracin B (3).

Ecteinascidin (ET)-743 (**1**) is a highly promising, exceedingly potent new antitumor agent isolated from the marine tunicate *Ecteinascidia turbinata*[1] which is currently in Phase II clinical trials in Europe and the United States.[2] The novel structure of ET-743, the lack of availability from the natural source, and the unique mechanism of action[3] maks the drug a very attractive synthetic target. The first total synthesis of

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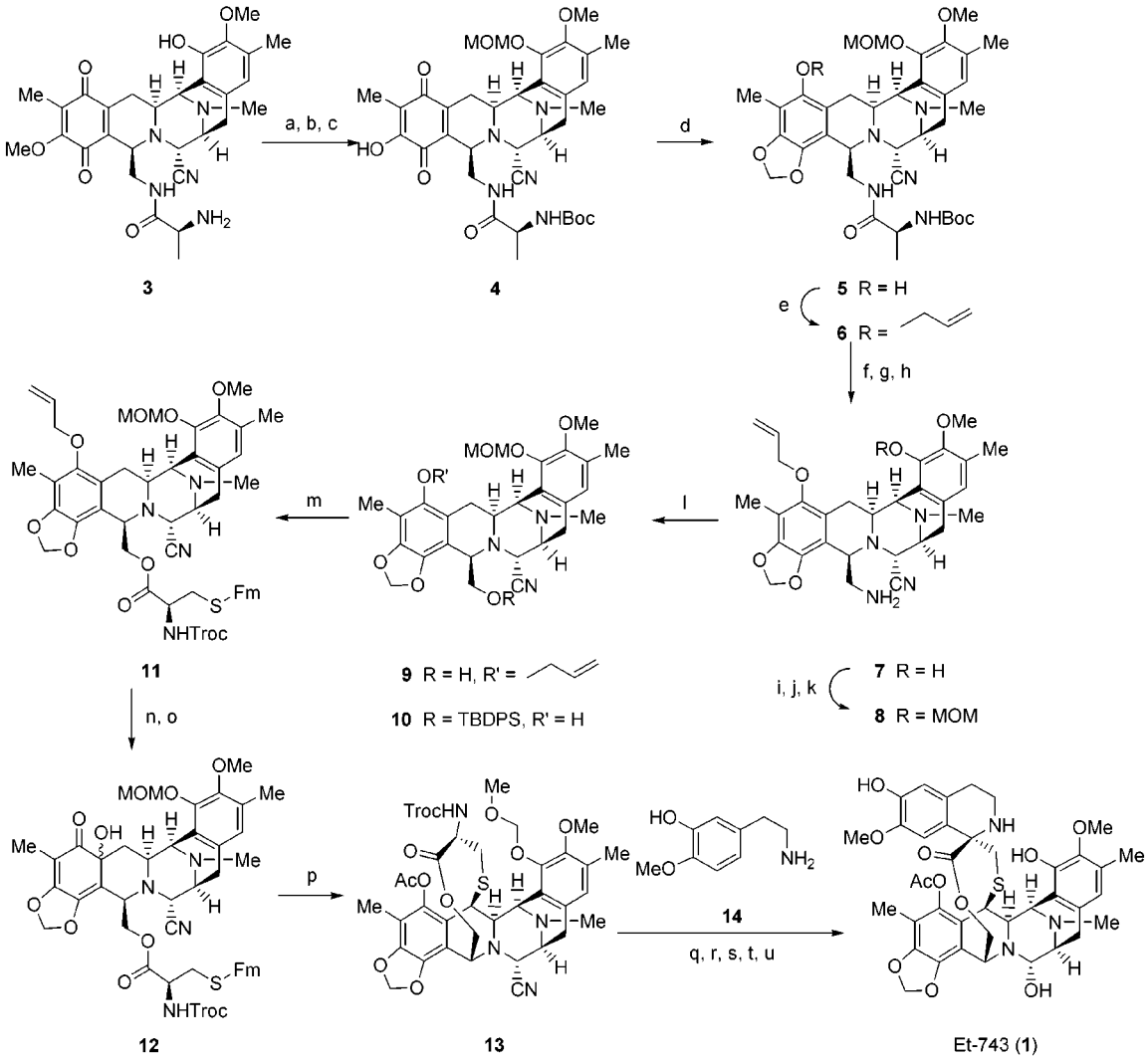
Scheme 1[a]



[a] Reagents: (a) Boc_2O, EtOH, 23 °C, 23 h, 81%; (b) MOMBr, *i*-Pr_2NEt, DMAP, CH_3CN, 40 °C, 6 h, 83%; (c) NaOH 1 M, MeOH, 20 °C, 2.5 h, 68%; (d) H_2, 10% Pd/C, 23 °C, 2 h; $ClBrCH_2$, Cs_2CO_3, DMF, 110 °C, 2.5 h; (e) allyl bromide, Cs_2CO_3, DMF, 23 °C, 3 h, 56% for two steps; (f) TFA, CH_2Cl_2, 23 °C, 4 h, 95%; (g) phenyl isothiocyanate, CH_2Cl_2, 23 °C, 3 h, 87%; (h) HCl/dioxane 4.3M, 23 °C, 1 h, 82%; (i) TrocCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 98%; (j) MOMBr, *i*-Pr_2NEt, DMAP, CH_3CN, 40 °C, 6 h, 88%; (k) Zn, AcOH aq, 23 °C, 7 h, 83%; (l) $NaNO_2$, AcOH, THF, H_2O, 0 °C, 3 h, 50%; (m) (*S*)-*N*-[(trichloroethoxy)carbonyl]-*S*-(9-fluorenylmethyl)cysteine, EDC·HCl, DMAP, CH_2Cl_2, 23 °C, 2 h, 95%; (n) Bu_3SnH, $(PPh_3)_2PdCl_2$, AcOH, CH_2Cl_2, 23 °C, 15 min, 90%; (o) $(PhSeO)_2O$, CH_2Cl_2, −10 °C, 15 min, 91%; (p) DMSO, Tf_2O, CH_2Cl_2, −40 °C, 35 min; *i*-Pr_2NEt, 0 °C, 45 min; *t*-BuOH, 0 °C, 5 min; $(CH_3N)_2C{=}N$-*t*-Bu, 23 °C, 40 min; Ac_2O, 23 °C, 1 h, 58%; (q) TMSCl, NaI, CH_2Cl_2, CH_3CN, 23 °C, 30 min; (r) Zn, AcOH aq, 70 °C, 6 h, 77% for two steps; (s) [*N*-methylpyridinium-4-carboxaldehyde]$^+I^-$, DBU, $(CO_2H)_2$, 23 °C, 4 h, 57%; (t) **14**, silica gel, EtOH, 23 °C, 12 h, 90%; (u) $AgNO_3$, CH_3CN, H_2O, 23 °C, 16 h, 90%.

ET-743 was accomplished by Corey and co-workers[4] by using a multistep enantiocontrolled process. Later Corey and Schreiber and co-workers found a synthetic analogue of ET-743 (**2**, phthalascidin, Pt-650)[5] with essentially the same in vitro activity as ET-743. More recently an improvement of

(6) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993.
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(8) Ikeda, Y.; Idemoto, H.; Hirayama, F.; Yamamoto, K.; Iwao, K.; Asao, T.; Munakata, T. *J. Antibiot.* **1983**, *36*, 1279.
(9) General methods to cleave methyl ethers of quinone systems use Lewis acids or mineral acids, conditions not compatible with BOC and MOM groups. See, for example: Hoire, T.; Kobayashi, T.; Kawamura, Y.; Yoshida, I.; Tominaga, H.; Yamashita, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2033.
(10) (a) Castillo, P.; Rodríguez-Ubis, J. C. *Synthesis* **1986**, 839. (b) Zelle, R. E.; McClellan, W. J. *Tetrahedron Lett.* **1991**, *32*, 2461.
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(12) (a) Wiberg, K. B.; österle, C. G. *J. Org. Chem.* **1999**, *64*, 7756. (b) Wiberg, K. B.; österle, C. G. *J. Org. Chem.* **1999**, *64*, 7763. (c) Wiberg, K. B.; Shobe, D. S. *J. Org. Chem.* **1999**, *64*, 7768.
(13) The TROC protecting group is compatible with the existing allyl and MOM groups.
(14) For synthetic methods of imide derivatives, see: (a) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352; *Tetrahedron Lett.* **1994**, *35*, 665. (b) Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2975. (c) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567. (d) Braish, T. F.; Fox, D. E. *Synlett* **1992**, 979.

the original synthesis has been described on the basis of a more efficient preparation of a key pentacyclic intermediate (Figure 1).[6]

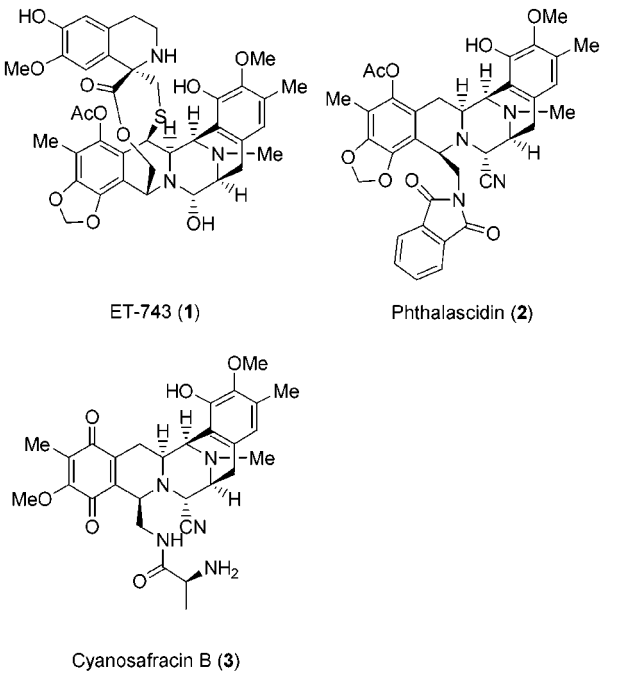


Figure 1.

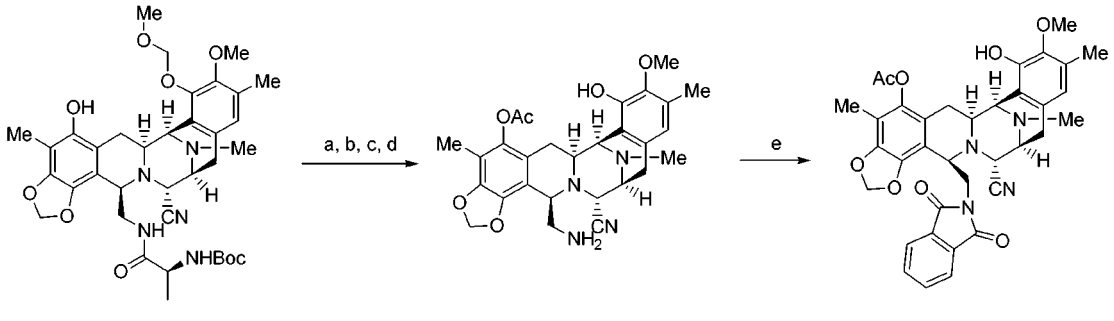
Described herein is a new synthesis of ET-743 (**1**) and Pt-650 (**2**) starting from cyanosafracin B (**3**).[7] Safracin B is an antibiotic of bacterial origin, available through fermentation of the bacteria *Pseudomonas fluorescens*.[8] Optimization of the fermentation process has allowed for the synthesis of cyano derivative (**3**) on a kilogram scale, providing a robust, sophisticated, and cheap starting material for the synthesis of ecteinascidin compounds.

The synthesis of Et-743 (**1**) from cyanosafracin B (**3**) is outlined in Scheme 1. The amino and phenol groups of **3** were protected as the BOC and MOM derivatives, respectively, and the methoxy-*p*-quinone was hydrolyzed with NaOH in $H_2O-MeOH$ to give **4**.[9] Quinone **4** was reduced (1 atm of H_2, Pd/C) to give an unstable hydroquinone, which was immediately treated with bromochloromethane and Cs_2CO_3 in DMF[10] to yield **5**. Alkylation of the remaining phenol gave fully protected **6**. After deprotection of the MOM and BOC groups, cleavage of the amide was accomplished by an Edman degradation by forming first the thiourea with excess phenyl isothiocyanate, followed by treatment with HCl in 1,4-dioxane to give **7**.[11] Conversion of primary amine of **7** to the alcohol required the protection of the E ring phenol as the MOM ether. Thus, temporary protection of the primary amine as the TROC carbamate, followed by reaction with MOMBr and *i*-Pr_2NEt, and removal of the TROC with Zn/HOAc gave rise to **8**. The critical substitution of the amino by an alcohol function was best performed by treatment with $NaNO_2$/HOAc yielding **9**,[12] a key intermediate. Silylation of the primary alcohol and removal of the allyl protecting group furnishs **10**, an intermediate in the total synthesis of **1** by Corey, thus concluding the formal synthesis of the natural product. We nevertheless completed the synthesis from **9** in nine additional steps as shown in Scheme 1. Salient features of this end-game operation are the early removal of the MOM group with TMSI and the use of TROC protection for the amino function of the (*S*)-cysteine derivative,[13] which was efficiently removed by Zn/HOAc.

The synthesis of phthalascidin (**2**) from **5** is outlined in Scheme 2. Acetylation of **5** followed by cleavage of N-BOC and Edman degradation of the alanine side chain afforded **15** which was allowed to react with phthalic anhydride and carbonyldiimidazole[14] to give **2**.

In summary, we have developed an efficient synthesis of ecteinascidin ET-743 (**1**) and phthalascidin (**2**) from readily available cyanosafracin B (**3**) that allows for the preparation

Scheme 2[a]



[a]Reagents: (a) AcCl, Pyridine, CH_2Cl_2, 0 °C, 1 h, quantitative; (b) TFA, CH_2Cl_2, 23 °C, 4 h, 60%; (c) Phenyl isothiocyanate, CH_2Cl_2, 23 °C, 3 h, 63%; (d) HCl/Dioxane 5.3 M, 23 °C, 1 h, 87%; (e) Pht_2O, CDI, CH_2Cl_2, 23 °C, 24 h, 93%.

of multigram amounts of these potent antitumor agents. The availability of derivatives such as **7**, **8**, **9**, **10**, and **15** bearing reactive primary amino or alcohol functionalities should allow for the preparation of a wide range of active analogues of the ecteinascidins.

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Supporting Information Available: Experimental procedures and compound characterization data for transformations described in Schemes 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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