

## Total Synthesis of Ecteinascidin 743

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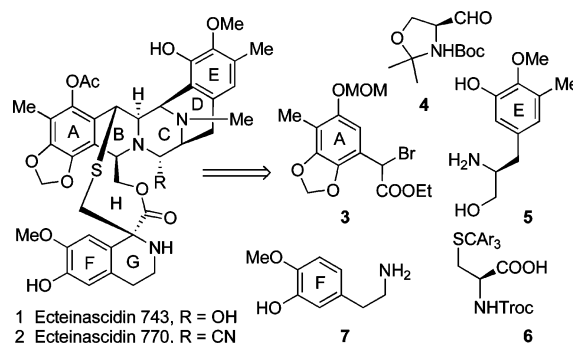
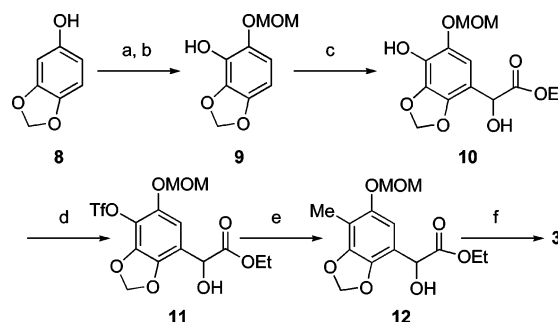
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Ecteinascidin 743 (Et 743, **1**, Scheme 1), isolated from the Caribbean tunicate *Ecteina scidia turbinata*,<sup>1</sup> possesses potent cytotoxic activity against a variety of tumor cell lines in vitro and against several rodent tumors and human tumor xenografts in vivo. It is currently in phase II/III clinical trials in Europe and in the United States for ovarian, endometrium, and breast cancer as well as several types of sarcoma.<sup>2</sup> The antiproliferative activity of Et 743 is greater than that of Taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etoposide by 1–3 orders of magnitude. The complexity of molecular architecture, the remarkable biological activities, and the restricted natural availability (1.0 g from about 1.0 ton of tunicate) made it an attractive synthetic target for total synthesis.<sup>3</sup> To date, two total syntheses have been accomplished by Corey et al.<sup>4</sup> and Fukuyama et al.<sup>5</sup> A semisynthesis from cyanosafraicin B has been developed by Cuevas, Manzanares, and co-workers at PharmaMar.<sup>6</sup> In addition, other synthetic approaches have been reported from a number of research groups.<sup>7</sup> We report herein a highly convergent total synthesis of **1** that would potentially be amenable to large-scale production of this important antitumor agent. As shown in Scheme 1, Et 743 is retrosynthetically disconnected into five building blocks (**3** to **7**) of almost equal size.

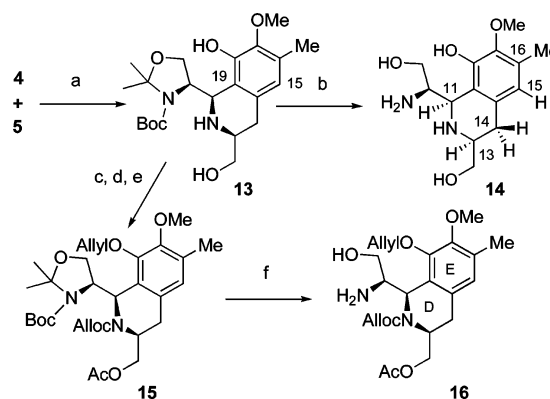
Synthesis of  $\alpha$ -bromo- $\alpha$ -aryl substituted ethyl acetate **3** is depicted in Scheme 2. Masking the hydroxyl group of sesamol **8** by MOMCl followed by a sequence of regioselective lithiation/boration/oxidation according to Fukuyama<sup>5b</sup> afforded phenol **9**. Friedel–Crafts reaction of **9** with ethyl glyoxalate under the conditions we developed recently for the Pictet–Spengler reaction (LiCl, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)/toluene = 1:4, room temperature, rt)<sup>8</sup> furnished  $\alpha$ -hydroxy ester **10** in excellent yield. Triflation of **10** with triflic anhydride under classic conditions provided a complex reaction mixture. However, using 4-nitrophenyltriflate as sulfonylating agent developed in this laboratory,<sup>9</sup> we found that chemoselective trifluoromethanesulfonylation of phenol **10** proceeded smoothly to afford triflate **11**. Palladium-catalyzed Suzuki–Miyaura cross-coupling<sup>10</sup> between **11** and trimethyl boroxine provided **12** in 93% yield. Treatment of benzyl alcohol **12** with thionyl bromide in the presence of benzotriazole<sup>11</sup> afforded the corresponding benzyl bromide **3** in excellent yield.

Synthesis of the D–E fragment **16** is shown in Scheme 3. Condensation of Garner's aldehyde (S)-**4**<sup>12</sup> with L-3-hydroxy-4-methoxy-5-methyl phenylalanol (**5**), which was prepared from 3-methyl catechol in eight steps,<sup>13</sup> provided under optimized conditions (AcOH, CH<sub>2</sub>Cl<sub>2</sub>/CF<sub>3</sub>CH<sub>2</sub>OH, molecular sieves 3 Å) the desired tetrahydroisoquinoline **13** in 84% yield as the only isolable product at the expense of other regio- (C-19 vs C-15, Et 743 numbering) and diastereoisomers.<sup>14,15</sup> The NOEs observed between protons H15/C<sub>16</sub>-Me, H15/H14, H13/H11 of compound **14** supported both the regio- and stereochemistry assigned for compound **13**. Interestingly, the stereochemistry at C<sub>11</sub> was controlled solely by the absolute configuration of amino alcohol **5** since condensation of **5** and (R)-**4** gave also the C<sub>11</sub>–C<sub>13</sub> cis diastereoisomer in excellent yield. It seems reasonable to assume that, under this circum-

Scheme 1

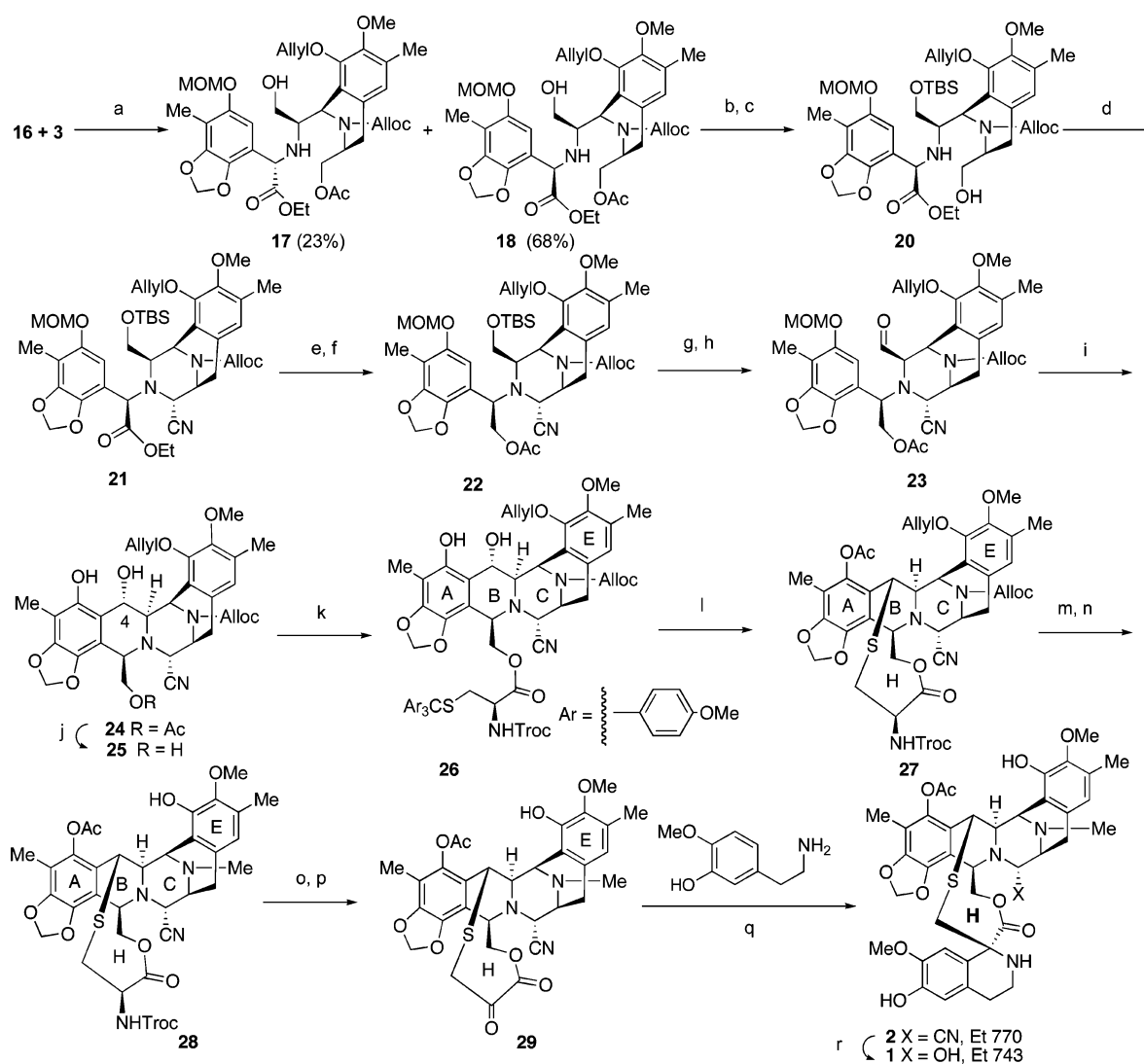
Scheme 2<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) MOMCl, NaH, Et<sub>2</sub>O/DMF, 0 °C to rt, 96%; (b) *n*-BuLi, B(OMe)<sub>3</sub>, THF then AcOH, H<sub>2</sub>O<sub>2</sub>, 0 °C to rt, 95%; (c) LiCl, 3 Å molecular sieves, HFIP/toluene, ethyl glyoxalate, rt, 97%; (d) 4-nitrophenyltriflate, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 94%; (e) trimethyl boroxine, K<sub>3</sub>PO<sub>4</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, dioxane, reflux, 93%; (f) SOBr<sub>2</sub>, benzotriazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 91%.

Scheme 3<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) AcOH, CH<sub>2</sub>Cl<sub>2</sub>/CF<sub>3</sub>CH<sub>2</sub>OH (7:1), 3 Å molecular sieves, rt, 20 h, 84%; (b) 6 N HCl, in MeOH, rt, 95%; (c) AllocCl, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h, 88%; (d) AllylBr, Cs<sub>2</sub>CO<sub>3</sub>, DMF, rt, 3 h, 86%; (e) Ac<sub>2</sub>O, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, 92%; (f) TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 72%.

stance, both C<sub>11</sub> and C<sub>13</sub> substituents adopted pseudoequatorial positions leading to the observed cis selectivity after ring closure.

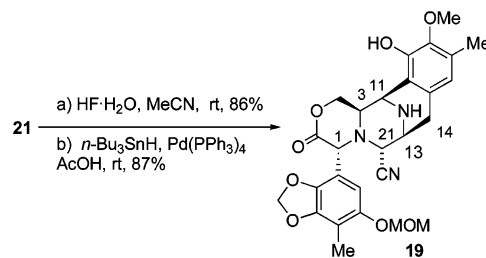
Scheme 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) TEA, MeCN, 0 °C, 91%; (b) TBSCl, imidazole, DMF, rt, 97%; (c) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 94%; (d) Dess–Martin reagent, rt, then TMSCN, ZnCl<sub>2</sub>, rt, 78%; (e) LiBH<sub>4</sub>, MeOH, THF, 0 °C, 80%; (f) Ac<sub>2</sub>O, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 92%; (g) HF·H<sub>2</sub>O, MeCN, rt, 91%; (h) Dess–Martin reagent, rt, 93%; (i) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 95%; (j) K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 96%; (k) EDCI, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 95%; (l) TFA, TFE, rt, then Ac<sub>2</sub>O, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 77%; (m) *n*-Bu<sub>3</sub>SnH, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 87%; (n) NaBH<sub>3</sub>CN, AcOH, HCHO, rt, 96%; (o) AcOH, Zn, rt, 92%; (p) 4-formyl-1-methylpyridinium benzenesulfonate, DBU, saturated aqueous oxalic acid, DMF–CH<sub>2</sub>Cl<sub>2</sub>, rt, 53%; (q) NaOAc, EtOH, rt, 97%; (r) AgNO<sub>3</sub>, MeCN–H<sub>2</sub>O, rt, 92%.

This experimentally simple, yet highly efficient, synthesis of the D–E fragment is one of the key steps in our efforts toward the development of a practical synthesis of Et 743. Masking the secondary amine of **13** as *N*-allyloxycarbamate followed by chemoselective allylation of the phenol and acetylation of the remaining primary alcohol provided compound **15**. Simultaneous removal of *N*-Boc and isopropylidene protective groups was realized under acidic conditions (TFA, rt) to afford amino alcohol **16** in 72% yield.

The accomplishment of the total synthesis of Et 743 is described in Scheme 4, starting from the assembly of two segments, **3** and **16**. After much experimentation varying the solvents (MeCN, trifluoroethanol, THF), bases (TEA, pyridine, DBU, Ag<sub>2</sub>O), and temperatures (from –45 °C to rt), the coupling of **3** and **16** (1:1 ratio) was realized in MeCN in the presence of triethylamine (2.0 equiv) at 0 °C. Under these conditions, two coupled products **18** and **17** were isolated in 68 and 23% yield, respectively. The observed diastereoselectivity in the *N*-alkylation of racemic bromide **3** could be tentatively explained by a S<sub>N</sub>1 mechanism via an *ortho*-quinone methide intermediate.<sup>16</sup> The absolute configuration of the

Scheme 5



newly created chiral center of the major stereoisomer was determined to be *R* by its transformation to the corresponding lactone (cf. Scheme 5, *vide infra*).

Compound **20** has all the requisite functionalities to build the polycyclic ring system of Et 743. The sequence of construction that we adopted in the present synthesis involved the formation of C-ring, B-ring, and then H-ring. Ring C was constructed onto the D–E segment as follows. Masking of the primary hydroxyl group of **18** as TBS ether and hydrolysis of the acetate under mild basic

conditions afforded compound **20**. Oxidation of the hydroxyl group using Dess–Martin reagent<sup>17</sup> followed by zinc chloride-catalyzed Strecker reaction provided amino nitrile **21** as one single stereoisomer, thus accomplishing the construction of the bicyclo[3.3.1] system with high efficacy.

The configuration of **21** was determined as follows. Treatment of an acetonitrile solution of **21** with HF·H<sub>2</sub>O effected a sequential O-desilylation and in situ lactonization leading to, after removal of *N*-Alloc and *O*-allyl protective groups, the rigid tetracyclic compound **19** (Scheme 5). The characteristic NOEs observed between H1/H21 and H21/H14 (Et 743 numbering) indicated that the configuration of **19**, hence that of **21**, is (1*R*,3*R*,11*R*,13*S*,21*R*).

With the absolute configuration of **21** being assigned, the synthesis was pursued by installation of ring B with a correct oxidation state at C<sub>4</sub> (Scheme 4). Reduction of the ester function and subsequent acetylation of the resulting primary alcohol afforded compound **22**. O-Desilylation followed by Dess–Martin oxidation of the C<sub>4</sub> hydroxyl group afforded aldehyde **23**. The Pomerantz–Fritsch-type cyclization<sup>7d,e,18</sup> of **23** took place smoothly under acidic conditions (TFA in dichloromethane) to afford the A–B–C–D–E polyheterocycle **24** with concomitant removal of the phenolic MOM-protecting group. Although of no consequence, the cyclization is highly stereoselective (*dr* > 20/1) and the configuration at C<sub>4</sub> of the major isomer was tentatively assigned as *S* based on the coupling constant (compound **25**: *J*<sub>H3–H4</sub> = 10.1 Hz) and in analogy to the work done by Fukuyama and co-workers.<sup>5b</sup> Saponification of **24** followed by coupling of the resulting alcohol **25** with (*R*)-*N*-Troc-(*S*-4,4',4''-trimethoxytrityl) Cys (**6**) under standard conditions afforded compound **26** in 94% yield. With the hexacyclic compound **26** in hand, a one-pot S-deprotection/cyclization to the 1,4-bridged 10-membered ring via formation of C–S bond was sought next.<sup>5b,7f,8</sup> Gratifyingly, by simply dissolving **26** in TFE containing 1% of TFA, the bridged macrocycle **27** was produced in 77% isolated yield after masking the phenol as the corresponding acetate. In this operationally simple experiment, a complex reaction sequence involving *S*-trityl deprotection, 1,4-β elimination leading to *ortho*-quinone methide and macrocyclization via an intramolecular Michael addition occurred in a highly ordered manner, to accomplish the key C–S bond-forming process. Simultaneous removal of *N*-Alloc and *O*-allyl functions under Guibé's conditions,<sup>19</sup> followed by reductive N-methylation, provided the key intermediate **28** in excellent overall yield.

Following Corey's protocol, compound **28** was converted to Et 743 in four steps. Removal of the *N*-Troc protective group under reductive conditions<sup>20</sup> afforded the corresponding amino ester that was oxidized to ketoester **29**. Pictet–Spengler reaction of **29** with 3-hydroxy-4-methoxyphenethylamine afforded ecteinascidin 770 (**2**) in 97% yield.<sup>1f</sup> Finally, treatment of Et 770 (**2**) with AgNO<sub>3</sub> in MeCN/H<sub>2</sub>O provided ecteinascidin 743 (**1**) in 92% yield. Synthetic Et 770 and Et 743 exhibited physical, spectroscopic, and spectrometric characteristics (<sup>1</sup>H, <sup>13</sup>C NMR, IR, [α]<sub>D</sub>, and HRMS) identical to those reported for the natural products.

In conclusion, a total synthesis of ecteinascidin 743 (**1**) has been achieved in 31 steps in the longest linear sequence and 1.7% overall yield from 3-methyl catechol (23 steps and 3% overall yield from the point of assembly). Notable features of our convergent approach include: (a) Rapid construction of D–E segment by highly diastereoselective Pictet–Spengler condensation of Garner's aldehyde **4** with substituted phenylalanol **5**, (b) diastereoselective *N*-alkylation of racemic benzyl bromide **3** by enantiomerically pure amino alcohol **16**, and (c) one-pot deprotection/cyclization of the *S*-protected precursor **26** leading to a 1,4-bridged 10-membered ring.

The synthesis is straightforward without using sophisticated reaction conditions and should potentially be amenable to large-scale production.

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**Supporting Information Available:** Experimental procedures and product characterization for all compounds synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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