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Total Synthesis of Ecteinascidin 743

Atsushi Endo, Arata Yanagisawa, Masanao Abe, Shigemitsu Tohma, Toshiyuki Kan, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, The Japan Science and Technology Cooperation (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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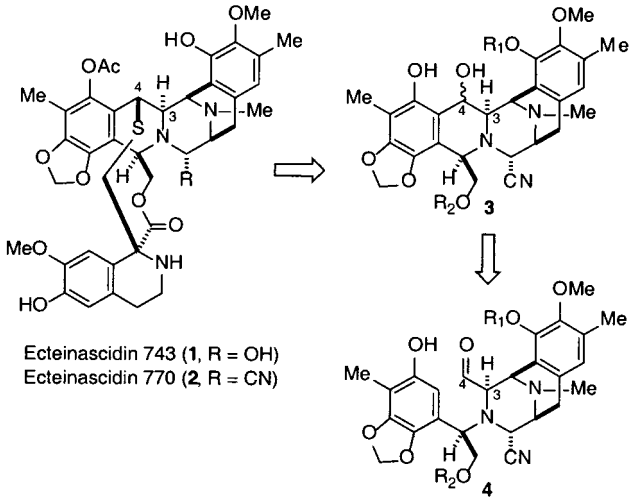
Ecteinascidin 743[1] (Et 743, **1**) is an extremely potent antitumor agent isolated from a marine tunicate, *Ecteinascidia turbinata*. Et 743 is currently undergoing phase II clinical trials and also attracting considerable attention owing to its unique mechanism of action.[2] The novelty of its structure, the remarkable biological activities, and its natural scarcity make it an attractive target for total synthesis.[3] To date, Corey and co-workers have reported the only total synthesis of **1**,[3a] which has recently been applied to the semisynthesis of **1** from cyanosafracin B by chemists at Pharma Mar.[3b] We describe herein the efficient total synthesis of **1** that would potentially lead to the development of a practical synthesis of this important compound and its analogues.

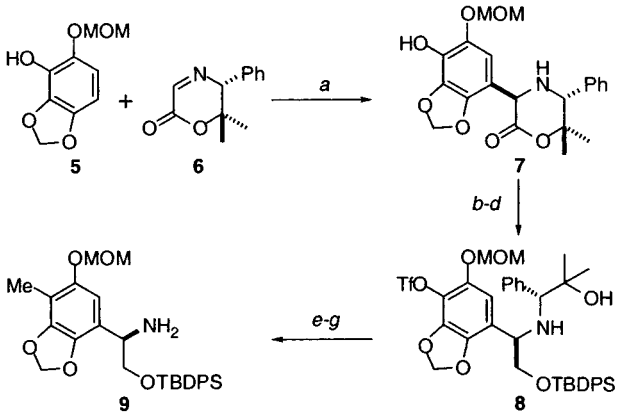
Scheme 1



The heart of our synthetic plan is illustrated in Scheme 1. The pentacyclic benzyl alcohol **3** was designed as the key intermediate in our strategy. The tricyclic aldehyde **4** was envisaged as an appropriate platform for the preparation of **3**, since the intramolecular *ortho* substitution of the phenol by the aldehyde would give the requisite oxidation state at the C-4 position, which is essential for constructing the unique ten-membered cyclic sulfide.

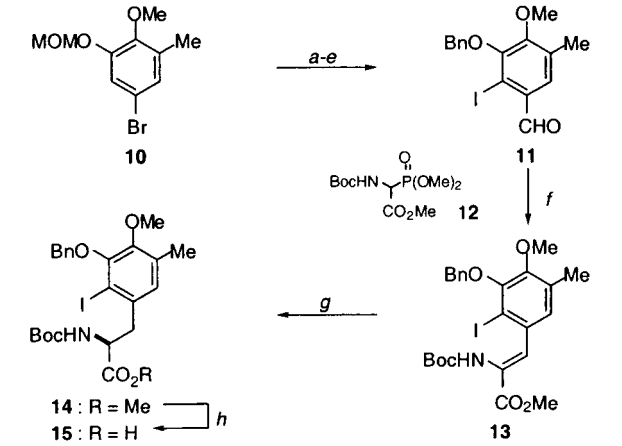
Synthesis of the left segment **9**, a highly functionalized (*R*)-phenylglycinol derivative, involves a Mannich-type reaction of phenol **5** with the chiral template **6**[4] developed recently in our laboratories (Scheme 2). Thus, regio- and stereoselective coupling of phenol **5**[5] with iminolactone **6** proceeded smoothly under acidic conditions at −10 °C to give the desired adduct **7** as a single product (89%). Conversion of the phenol to the triflate, reductive ring opening of the lactone, and subsequent silylation of the primary alcohol furnished **8**. Introduction of the methyl group onto the aromatic ring was achieved by Pd-catalyzed cross-coupling reaction with MeZnCl (97%).[6] Oxidative cleavage of the amino alcohol moiety was effected with $Pb(OAc)_4$, and the resultant imine was converted to the desired amine **9** by treatment with NH_2OH.

Scheme 2[a]



[a] Reagents and conditions: (a) TFA, CH_2Cl_2, −10 °C (89%); (b) Tf_2O, pyridine, CH_2Cl_2, 0 °C (90%); (c) $NaBH_4$, MeOH, 0 °C (85%); (d) TBDPSCl, imidazole, DMF, room temperature (91%); (e) MeZnCl, $PdCl_2$(dppf) (3 mol %), THF, reflux (97%); (f) $Pb(OAc)_4$, CH_3CN, 0 °C; (g) NH_2OH·HCl, NaOAc, EtOH, room temperature (89% in 2 steps).

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −60 °C; DMF (79%); (b) $HC(OMe)_3$, cat. CSA, MeOH, room temperature (94%); (c) *n*-BuLi, Et_2O, 0 °C to room temperature; I_2; (d) concentrated HCl, THF, room temperature (72% in 2 steps); (e) BnBr, K_2CO_3, CH_3CN, reflux (98%); (f) **12**, TMG, CH_2Cl_2, room temperature (93%); (g) Rh[(COD)-(*S*,*S*)-Et-DuPHOS]$^+$OTf$^-$, H_2 (500 psi), EtOAc, 50 °C (99%, 94% ee); (h) LiOH, MeOH−H_2O−THF, 0 °C to room temperature (quant).

The right segment **15**, (*S*)-iodophenylalanine derivative, was synthesized from commercially available 3-methylcatechol by employing DuPHOS-mediated asymmetric hydrogenation (Scheme 3).[7] The previously reported bromide **10**[3j,8] was converted to the

* To whom correspondence should be addressed. E-mail: fukuyama@mol.f.u-tokyo.ac.jp.

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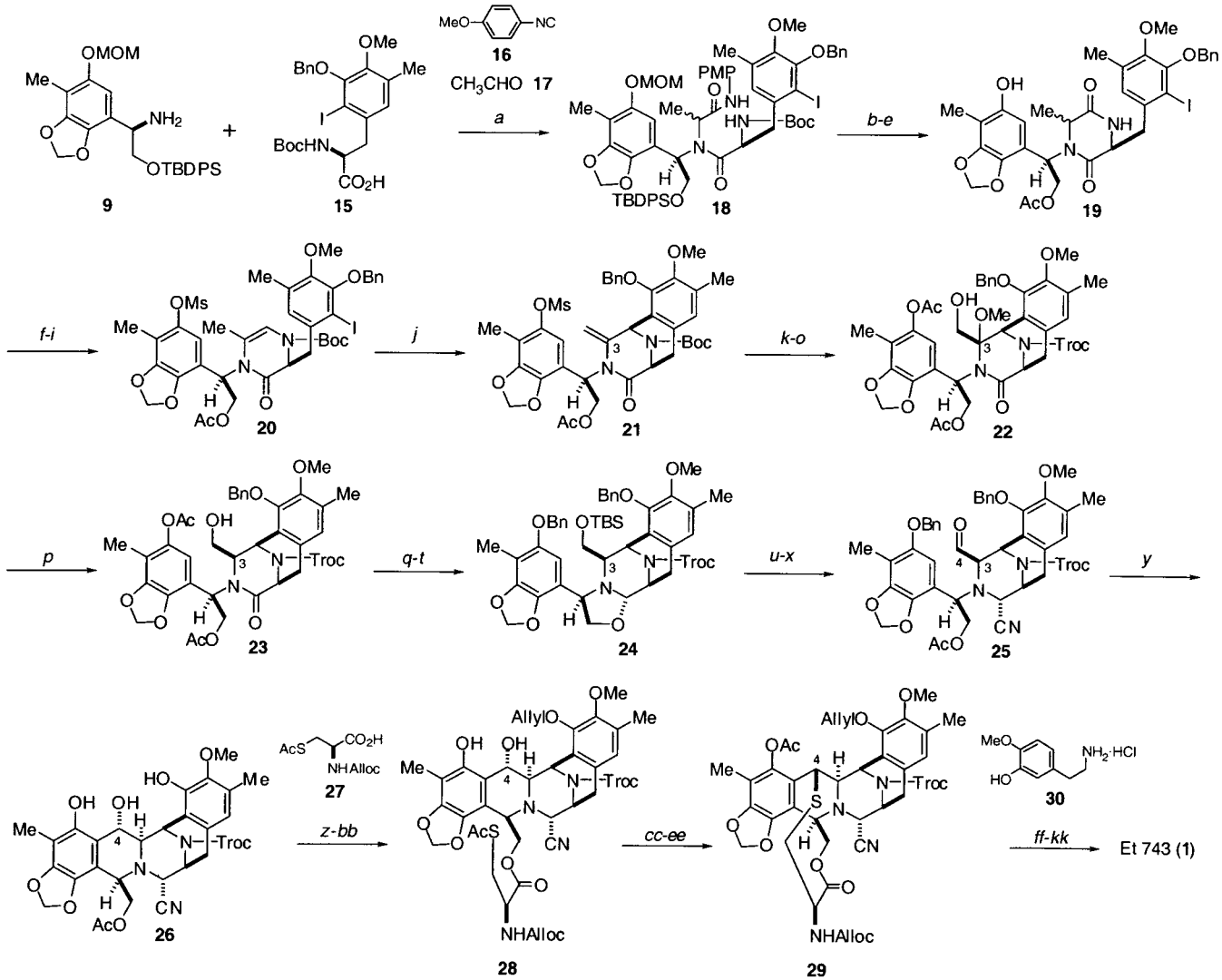
Scheme 4[a]



[a] Reagents and conditions: (a) MeOH, reflux (90%); (b) TBAF, THF, room temperature (89%); (c) Ac_2O, pyridine, DMAP, room temperature (93%); (d) TFA, anisole, CH_2Cl_2, room temperature; (e) EtOAc, reflux (87% in 2 steps); (f) MsCl, Py, CH_2Cl_2, 0 °C (91%); (g) $(Boc)_2O$, DMAP, CH_3CN, room temperature (97%); (h) $NaBH_4$, H_2SO_4, EtOH−CH_2Cl_2, 0 °C; (i) CSA, quinoline, toluene, reflux (88% in 2 steps); (j) $Pd_2(dba)_3$ (5 mol %), P(*o*-tol)$_3$ (20 mol %), TEA, CH_3CN, reflux (83%); (k) NaOH, MeOH−H_2O, reflux; (l) Ac_2O, pyridine, DMAP, room temperature (93% in 2 steps); (m) TFA, CH_2Cl_2, room temperature; (n) TrocCl, aq. $NaHCO_3$−CH_2Cl_2, room temperature (74% in 2 steps); (o) dimethyldioxirane, MeOH−acetone, 0 °C; cat. CSA (90%); (p) $NaBH_3CN$, TFA−THF, 0 °C (94%); (q) TBSCl, imidazole, DMF, room temperature (92%); (r) guanidinium nitrate, NaOMe, MeOH−CH_2Cl_2, 40 °C (85%); (s) BnBr, K_2CO_3, CH_3CN, reflux (91%); (t) Red-Al, THF, 0 °C (82%); (u) TMSCN, BF_3·OEt_2, CH_2Cl_2, 0 °C (73%); (v) Ac_2O, pyridine, DMAP, room temperature (92%); (w) HF, CH_3CN, room temperature (quant); (x) Dess−Martin periodinane, CH_2Cl_2, room temperature (92%); (y) Pd−C, H_2, THF, room temperature (84%); (z) allyl bromide, *i*-Pr_2NEt, CH_2Cl_2, reflux (89%); (aa) K_2CO_3, MeOH, room temperature (99%); (bb) **27**, WSCD·HCl, DMAP, CH_2Cl_2, room temperature (94%); (cc) NH_2NH_2, CH_3CN, room temperature (98%); (dd) TFA, CF_3CH_2OH, room temperature; (ee) Ac_2O, pyridine, DMAP, room temperature (71% in 2 steps); (ff) Zn, AcOH, Et_2O, room temperature (92%); (gg) HCHO, AcOH, $NaBH_3CN$, MeOH, room temperature (96%); (hh) $Pd(PPh_3)_2Cl_2$, AcOH, *n*-Bu_3SnH, CH_2Cl_2, room temperature (89%); (ii) 4-formyl-1-methylpyridinium benzenesulfonate, DMF−CH_2Cl_2, room temperature; DBU; citric acid (54%); (jj) **30**, NaOAc, EtOH, room temperature (96%); (kk) $AgNO_3$, CH_3CN−H_2O, room temperature (93%).

benzaldehyde by halogen−lithium exchange and subsequent treatment with DMF. Regioselective introduction of the iodo substituent was next achieved by directed ortho-lithiation[9] of the corresponding dimethylacetal followed by quenching with I_2. Simultaneous cleavage of the MOM ether and the dimethylacetal and subsequent benzylation of the phenol afforded the iodobenzaldehyde **11**, which was then subjected to Horner−Emmons reaction with the phosphonate **12**[10] to give the (*Z*)-dehydrophenylalanine derivative **13**. Catalytic asymmetric hydrogenation of **13** proceeded smoothly in the presence of Rh[(COD)-(*S*,*S*)-Et-DuPHOS]$^+$OTf$^-$ (1.5 mol %) under an atmosphere of hydrogen (500 psi) to afford the aminoester **14** without appreciable loss of the aromatic iodide (99%, 94% ee). Finally, basic hydrolysis of the methyl ester gave the desired carboxylic acid **15**.

These two segments, **9** and **15**, were incorporated into the diketopiperazine **19** by means of the powerful Ugi's four-component condensation reaction (Scheme 4).[11] A mixture of amine **9**, carboxylic acid **15**, *p*-methoxyphenyl isocyanide (**16**),[12] and acetaldehyde (**17**) was heated in MeOH to afford the dipeptide **18** in 90% yield, which implies that all the carbon atoms needed for the pentacyclic key intermediate **3** were efficiently assembled in a single step. After switching from the TBDPS ether to the acetate, simultaneous cleavage of the Boc group and the MOM ether gave the aminophenol, which cyclized to afford **19** upon gentle heating in EtOAc. As in our total synthesis of saframycins,[13] acyliminium ion-mediated cyclization was extensively studied to construct the bicyclo[3.3.1] system without success. It was therefore extremely gratifying to find that the intramolecular Heck reaction[14] of the

cyclic enamide **20** proceeded under mild conditions to give the tricyclic nucleus as in **21** that constitutes the right half of **1**. Thus, **19** was converted to the key intermediate **20** by a four-step sequence involving mesylation of the phenol, introduction of a Boc group onto the lactam nitrogen, partial reduction of the ring carbonyl with $NaBH_4$, and dehydration of the resultant hemiaminal derivative by treatment with CSA and quinoline. The crucial Heck reaction of **20** was performed in the presence of 5 mol % of $Pd_2(dba)_3$ and 20 mol % of P(*o*-tol)$_3$ to afford the desired tricycle **21** in 83%.

The next challenge in the synthesis is the construction of the pentacyclic framework via elaboration of the tricyclic aldehyde such as **4** while controlling the stereochemistry at the C-3 position. After switching the protecting groups of the amine and the phenol of **21** to the corresponding *N*-Troc-*O*-Ac compound, the enamide was oxidized with dimethyldioxirane[15] in MeOH−acetone to generate an acid-sensitive epoxide, which, without isolation, was immediately treated with CSA to afford methoxyalcohol **22** (90%) as a single isomer. The subsequent acyliminium ion-mediated reduction under acidic conditions occurred from the less hindered *exo*-face of the molecule to afford alcohol **23** as a single product with the correct stereochemistry (94%). Conversion of **23** to the oxazolidine **24** was achieved in a four-step sequence involving silylation of the alcohol, cleavages of the two acetyl groups,[16] selective benzylation of the phenolic hydroxyl group, and partial reduction of the lactam carbonyl with Red-Al with concomitant formation of the oxazolidine ring. Cleavage of the oxazolidine **24** with TMSCN and $BF_3{\cdot}OEt_2$ afforded the aminonitrile as a single stereoisomer, which was subsequently converted to aldehyde **25** by a sequence involving acetylation of the regenerated hydroxyl group, cleavage of the TBS ether, and oxidation of the resultant alcohol with Dess−Martin periodinane.[17] As expected from our earlier model studies, hydrogenolysis of the benzyl ethers **25** invoked a spontaneous cyclization, giving the desired pentacycle **26**, a synthetic equivalent of **3**, in 84% yield. Having succeeded in obtaining the key intermediate **26** with the correct oxidation state at the C-4 position, we then turned our attention to the formation of the ten-membered sulfide ring. Selective allylation of the phenols, cleavage of the acetyl group, and condensation of the resultant alcohol with L-cysteine derivative **27** furnished ester **28**. Chemoselective hydrazinolysis of the thioacetate gave the thiol, which, upon exposure to TFA in 2,2,2-trifluoroethanol under high dilution conditions (0.009 M), smoothly underwent cyclization to give the ten-membered sulfide. Subsequent acetylation of the resultant phenol gave **29** (71% in 2 steps).

With the desired ten-membered sulfide **29** in hand, all that is necessary to complete the total synthesis of **1** is the construction of the last tetrahydroisoquinoline moiety. Cleavage of the Troc group followed by reductive alkylation afforded *N*-methyl amine, whose Alloc group and allyl ether were simultaneously cleaved with palladium catalyst to give the aminophenol. According to the protocol reported by Corey,[3a] biomimetic transamination reaction[18] afforded the known α-ketolactone,[3b] and subsequent Pictet−Spengler reaction with amine **30** furnished ecteinascidin 770 (**2**).[19] Finally, generation of the labile hemiaminal from the aminonitrile was effected by treatment with $AgNO_3$ in CH_3CN-H_2O to give ecteinascidin 743 (**1**), which gave spectral data (^{1}H NMR, ^{13}C NMR, IR, and HR MS) in full agreement with those of the natural product.

In conclusion, an enantioselective total synthesis of ecteinascidin 743 (**1**) has been accomplished. Our synthesis features Ugi's four-component condensation reaction for a ready access to diketopiperazine **19**, the intramolecular Heck reaction of the cyclic enamide **20** to give tricycle **21**, phenol−aldehyde cyclization to construct the pentacyclic key intermediate **26**, and acid-induced ten-membered sulfide formation. Further modifications of the present route to establish a truly practical synthesis of **1** and its analogues are currently underway in our laboratories.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Bromide **10** was prepared from commercially available 3-methylcatechol in 5 steps: (i) TsCl, TEA, CH_2Cl_2, 0 °C (83%); (ii) Br_2, AcOH, CH_2Cl_2, room temperature (97%); (iii) MeI, K_2CO_3, acetone, reflux (96%); (iv) NaOH, EtOH−H_2O, reflux (97%); (v) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C (97%). For experimental details, see the Supporting Information.

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