Enantioselective Total Synthesis of Ecteinascidin 743

E. J. Corey,* David Y. Gin, and Robert S. Kania

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

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Described herein is the first total synthesis of ecteinascidin 743 (**1**),[1] an exceedingly potent and rare marine-derived antitumor agent which is slated for clinical trials when adequate quantities become available.[2,3] The synthesis is enantio- and stereocontrolled, convergent and short (Scheme 1).

The α,β-unsaturated malonic ester **2**, prepared as a mixture of *E* and *Z* isomers from 2-(benzyloxy)-3-methyl-4,5-(methylenedioxy)benzaldehyde[4a] and allyl 2,2-dimethoxyethyl malonate[4b] (2 equiv of piperidine and 4 equiv of acetic acid in C_6H_6 or C_7H_8 at 23 °C for 18 h; 99%), was subjected to selective allyl ester cleavage ($Et_3N-HCOOH$, catalytic $Pd(PPh_3)_4$, 23 °C, 4 h; 94% yield), Curtius rearrangement (1.2 equiv of $(PhO)_2P(O)N_3$, 4 equiv of Et_3N, in C_7H_8 containing 4 Å molecular sieves at 70 °C for 2 h), and reaction of the intermediate isocyanate with benzyl alcohol at 23 °C for 1 h to form **3** stereospecifically (93% yield).[5] Hydrogenation of **3** at 3 atm with $Rh[(COD)(R,R)\text{-DIPAMP}]^+BF_4^-$ as catalyst at 23 °C for 16 h afforded **4** in 97% yield and 96% ee.[6] Acetal cleavage of **4** (10 equiv $BF_3{\cdot}Et_2O$ and 10 equiv of H_2O in CH_2Cl_2 at 0 °C for 10 min), isolation, and exposure of the resulting aldehyde to $BF_3{\cdot}Et_2O$ (17 equiv) and 4 Å molecular sieves in CH_2Cl_2 at 23 °C for 18 h gave the bridged lactone **5** in 73% yield.[7] Hydrogenolysis of **5** (1 atm H_2, 10% Pd/C, EtOAc, 23 °C, 6 h) produced the free amino phenol **6** in 100% yield. The protected α-amino ester **7** was synthesized by an analogous route, starting with 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzaldehyde and methyl hydrogen malonate, and then reduced (2 equiv of diisobutylaluminum hydride in CH_2Cl_2 at −78 °C for 1 h) to give the chiral aldehyde **8** (>90% yield).

The next stage of the synthesis, which involved the combination of the building blocks **6** and **8** and subsequent elaboration to construct the key monobridged pentacyclic intermediate **10**, commenced with the reaction of **6** and **8** in HOAc containing 25 equiv of KCN at 23 °C for 18 h to give a coupled phenolic α-amino nitrile (61%) and subsequent *O*-allylation to give allyl ether **9** in 87% yield (2 equiv of Cs_2CO_3 and 5 equiv of allyl bromide in DMF at 23 °C for 1 h). Treatment of **9** with 1.2 equiv of diisobutylaluminum hydride in toluene at −78 °C for 5 h effected the selective conversion of the lactone function to a lactol which was desilylated by exposure to excess $KF{\cdot}2H_2O$ in CH_3OH at 23 °C for 20 min and cyclized to pentacycle **10** by internal Mannich bisannulation with 20 equiv of CH_3SO_3H in CH_2Cl_2 in the presence of 3 Å molecular sieves at 23 °C for 5 h (55% overall from **9**). Selective trifluoromethanesulfonation of the least hindered phenolic hydroxyl (5 equiv of Tf_2NPh, Et_3N, 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 at 23 °C for 6 h; 72% yield) was followed by (1) selective silylation of the primary hydroxyl (excess *tert*-butyldiphenylsilyl chloride−DMAP in CH_2Cl_2 at 23 °C for 13 h; 89%), (2) protection of the remaining phenolic group as the methoxymethyl ether ($MeOCH_2Br$ and *i*-Pr_2NEt in CH_2Cl_2 at 23 °C for 20 min; 92%), (3) double deallylation (Bu_3SnH, catalytic $Cl_2Pd(PPh_3)_2$, excess HOAc in CH_2Cl_2 at 23 °C for 15 min; 100%), (4) reductive *N*-methylation (excess Formalin, $NaBH_3CN$, HOAc in CH_3CN at 23 °C for 30 min; 95%), and (5) replacement of CF_3SO_3 by CH_3 (excess Me_4Sn, $Cl_2Pd(Ph_3P)_2$, LiCl, DMF, 80 °C, 2 h) to give **11** in 83% yield. Oxidation of the phenol **11** with 1.1 equiv of $(PhSeO)_2O$ in CH_2Cl_2 at 23 °C for 15 min effected position-selective angular hydroxylation to yield after desilylation (2 equiv of Bu_4NF in THF at 23 °C for 10 min) the dihydroxy dienone **12** (75% from **11**).

The last three rings of ecteinascidin 743, the 10-membered lactone bridge and the spiro tetrahydroisoquinoline subunit, were then added in the final stage of the synthesis of **1** by a novel sequence of reactions. The primary hydroxyl function of **12** was esterified with (*S*)-*N*-((allyloxy)carbonyl)-*S*-(9-fluorenylmethyl)cysteine using 5 equiv of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 5 equiv of DMAP in CH_2Cl_2 at 23 °C for 30 min to form **13** (91%). Compound **13** was then transformed in one flask to the bridged lactone in 79% overall yield by the following operations: (1) reaction of **13** with the *in situ*-generated Swern reagent from excess triflic anhydride and DMSO at −40 °C for 30 min,[8a] (2) addition of *i*-Pr_2NEt and warming to 0 °C for 30 min to form the exendo quinone methide,[8b] (3) quenching with *tert*-butyl alcohol (to destroy excess Swern reagent), (4) addition of excess *N*-*tert*-butyl-*N*′,*N*′,*N*″,*N*″-tetramethylguanidine[9] to convert the 9-fluorenylmethyl thiolether to the thiolate ion and to promote nucleophilic addition of sulfur to the quinone methide to generate the 10-membered lactone bridge, and (5) addition of excess Ac_2O to acetylate the resulting phenoxide group. The *N*-((allyloxy)carbonyl) group of **14** was cleaved (excess Bu_3SnH, HOAc, and catalytic $Cl_2Pd(PPh_3)_2$ in CH_2Cl_2 at 23 °C for 5 min; 84%), and the resulting α-amino lactone was oxidized to the corresponding α-keto lactone by transamination with the methiodide of pyridine-4-carboxaldehyde, 1,8-diazabicyclo[6.4.0]undec-7-ene (DBU), and DMF in CH_2Cl_2 at 23 °C for 40 min to give **15** (70%). Reaction of **15** with 2-[3-hydroxy-

(1) The pioneering research in this area is due to Prof. Kenneth L. Rinehart and his group, see: (a) Rinehart, K. L.; Shield, L. S. In *Topics in Pharmaceutical Sciences*; Breimer, D. D., Crommelin, D. J. A., Midha, K. K., Eds.; Amsterdam Medical Press: Noordwijk, The Netherlands, 1989; pp 613. (b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J., Jr.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. *J. Nat. Prod.* **1990**, *53*, 771. (c) Rinehart, K. L.; Sakai, R.; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.* **1990**, *62*, 1277. (d) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. (e) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508. (f) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456.

(2) *Science* **1994**, *266*, 1324.

(3) The current clinical plan calls for the administration of three 0.5 mg doses of **1** per patient; personal communication from Dr. Glynn Faircloth, PharmaMar USA, Cambridge, MA.

(4) (a) Prepared from 3,4-(methylenedioxy)phenyl methoxymethyl ether by the sequence: (1) lithiation at C-2 (3 equiv of BuLi, 3 equiv of tetramethylethylene diamine in hexane at 0 °C for 4 h) and reaction with CH_3I (6 equiv at −78 → 23 °C over 15 min) to afford exclusively the 2-methyl derivative (87%); (2) ortho lithiation (2 equiv of BuLi in THF at −30 °C for 13 h) and subsequent formylation with 4 equiv of DMF (64% yield); (3) cleavage of the $MeOCH_2$ protecting group (0.55 equiv of CH_3SO_3H in CH_2Cl_2 at 0 °C; (4) treatment of the resulting 3-methyl-4,5-(methylenedioxy)salicylaldehyde with 1.5 equiv of NaH in DMF at 0 °C for 5 min and 2 equiv of benzyl bromide at 23 °C for 40 min (86% overall). (b) Prepared from the monoallyl ester of malonic acid by conversion to the mixed anhydride with BOP chloride (Aldrich) and reaction with 2,2-dimethoxyethanol.

(5) This step, which involves isomerization possibly of the intermediate isocyanate, represents a generally useful process for the stereospecific synthesis of such compounds.

(6) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, FL, 1985; Vol. 5, p 71.

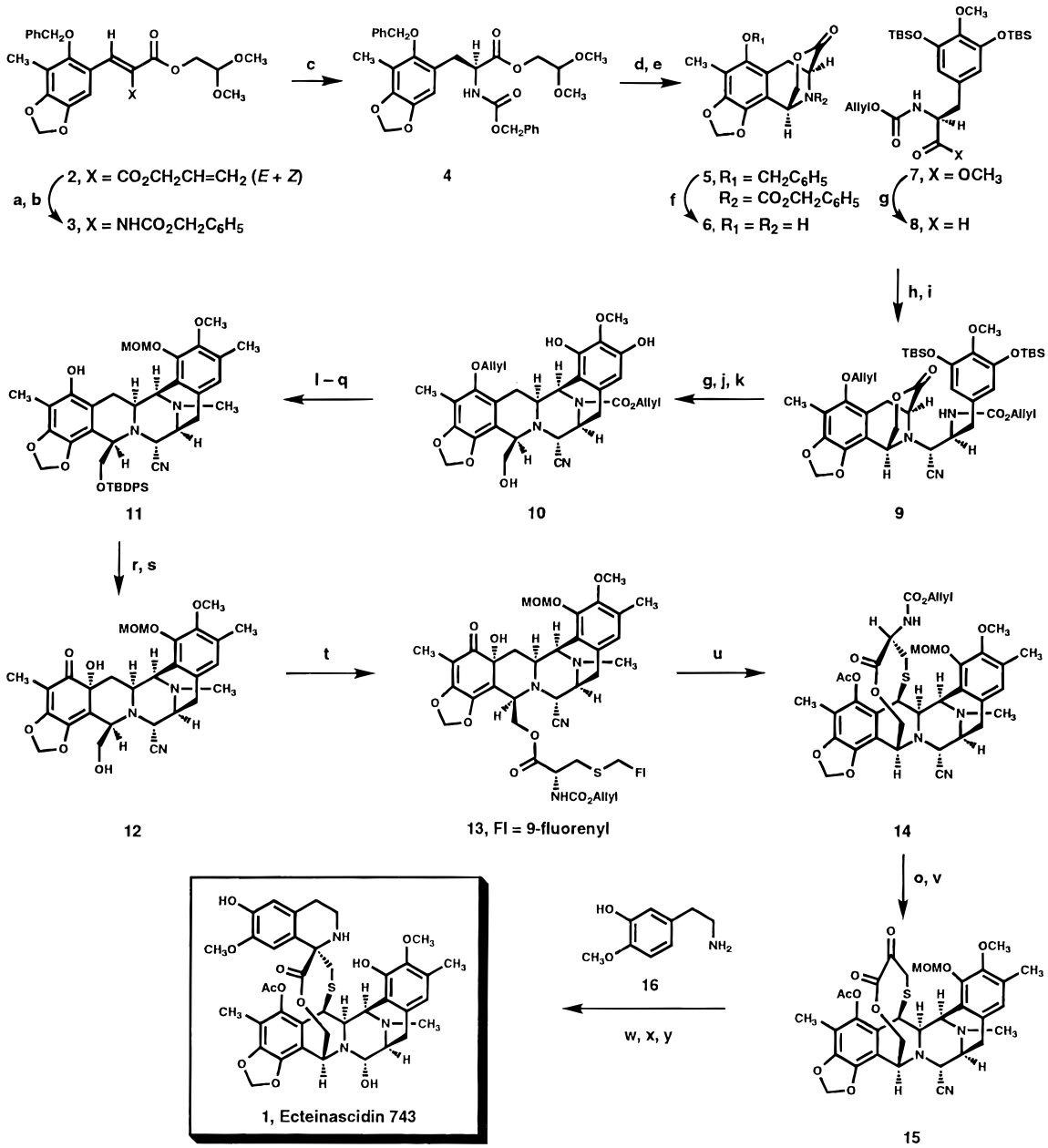
(7) The conversion **4** → **5** demonstrates a method for control of stereochemistry in the tetrahydroisoquinoline series.

(8) (a) This step converts the tertiary hydroxyl group of **13** to the *O*-dimethylsulfonium derivative. The use of oxalyl chloride−DMSO as reagent is unsatisfactory due to interference by chloride in the subsequent steps of quinone methide formation and addition. (b) This step generates the quinone methide probably by cycloelimination of the Swern type oxosulfonium ylide intermediate.

(9) Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085.

S0002-7863(96)02480-8 CCC: $12.00

Scheme 1[a]



[a] Reagents: (a) Et_3N-HCO_2H, $Pd(PPh_3)_4$; (b) $(PhO)_2P(O)N_3$, Et_3N, 4 Å molecular sieves; 70 °C, BnOH; (c) Rh[(COD))-(*R*,*R*)-DiPAMP]$^+BF_4^-$, 3 atm of H_2; (d) $BF_3{\cdot}OEt_2$, H_2O; (e) $BF_3{\cdot}OEt_2$, 4 Å molecular sieves; (f) 10% Pd/C, H_2; (g) DIBAL, −78 °C; (h) HOAc, KCN; (i) allyl bromide, Cs_2CO_3; (j) $KF{\cdot}2H_2O$; (k) CH_3SO_3H, 3 Å molecular sieves; (l) Tf_2NPh, Et_3N, DMAP; (m) TBDPSCl, DMAP; (n) MOMBr, *i*-Pr_2NEt; (o) $PdCl_2(PPh_3)_2$, Bu_3SnH, HOAc; (p) CH_2O, $NaBH_3CN$, HOAc; (q) $PdCl_2(PPh_3)_2$, $SnMe_4$, LiCl, 80 °C; (r) $(PhSeO)_2O$; (s) TBAF; (t) Alloc-Cys(CH_2Fl)-OH, EDC·HCl, DMAP; (u) DMSO, Tf_2O, −40 °C; *i*-Pr_2NEt, 0 °C; *t*-BuOH, 0 °C; $(Me_2N)_2C{=}N$-*t*-Bu, 23 °C; Ac_2O, 23 °C; (v) [*N*-methylpyridinium-4-carboxaldehyde]$^+I^-$, DBU, $(CO_2H)_2$; (w) **16**, silica gel; (x) CF_3CO_2H, H_2O; (y) $AgNO_3$, H_2O.

4-methoxyphenyl]ethylamine (**16**) in EtOH in the presence of silica gel at 23 °C generated the spiro tetrahydroisoquinoline stereospecifically (82%) which was then subjected to methoxymethyl cleavage (4:1:1 $CF_3CO_2H-H_2O-THF$ at 23 °C for 9 h) and replacement of CN by HO ($AgNO_3$ in CH_3CN-H_2O at 23 °C for 11 h) to form in high yield ecteinascidin 743 (**1**), identical in all respects with an authentic sample.[10]

The synthetic approach reported herein provides access not only to **1** but also to a host of other members of the ecteinascidin family and analogs, as well as to related simpler structures such as the saframycins.[11]

(10) Obtained from Prof. K. L. Rinehart and PharmaMar USA.

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Supporting Information Available: Experimental procedures and spectral data (43 pages). See any current masthead page for ordering and Internet access instructions.

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(11) For previous work on the synthesis of the saframycins, see: (a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (b) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712. (c) Saito, N.; Yamauchi, R.; Nishioka, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391.