Communication

Total Synthesis of Ecteinascidin 743

Fumiki Kawagishi, Tatsuya Toma, Tomohiko Inui, Satoshi Yokoshima, and Tohru Fukuyama

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Total Synthesis of Ecteinascidin 743

Fumiki Kawagishi,[†,‡] Tatsuya Toma,[†] Tomohiko Inui,[†] Satoshi Yokoshima,[‡] Tohru Fukuyama*[,‡]

[†]Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[‡]Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

Supporting Information Placeholder

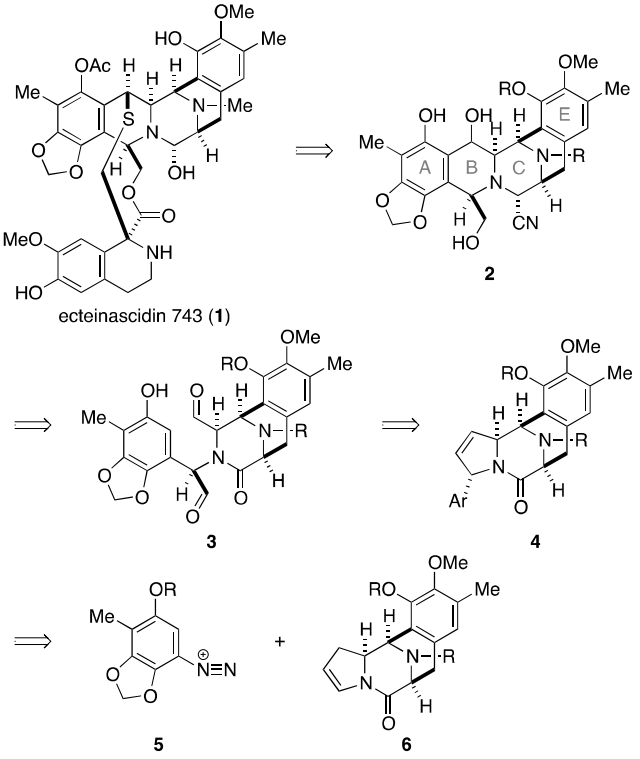
ABSTRACT: A straightforward synthesis of ecteinascidin 743 was accomplished from readily available L-glutamic acid as a single chiral source. Our novel synthesis features a concise and convergent approach for construction of the B-ring, consisting of a sequence of a stereoselective Heck reaction between a diazonium salt and an enamide, oxidative cleavage of the resulting alkene and intramolecular *ortho* substitution of the phenol by an aldehyde.

Ecteinascidin 743 (**1**, Scheme 1), a tetrahydroisoquinoline alkaloid, was isolated from the Caribbean tunicate *Ecteinascidia turbinata* by Rinehart and coworkers.[1] This alkaloid attracted strong interest as a potential anticancer agent due to its combination of strong cytostatic properties and antitumor activity[2,3] and has recently been approved for the treatment of soft tissue sarcoma and ovarian cancer. However, only minute quantities of ecteinascidin 743 are available from the marine sources. While several total syntheses have been reported to date,[4,5] they are not amenable to scale up for manufacturing purposes. Ecteinascidin 743 is currently provided by a long-step semisynthesis from cyanosafracin B.[6] There is, however, an urgent need for more efficient synthesis of the natural product from readily available chemicals due to the increasing demand. Since our first-generation total synthesis was reported in 2002,[4b] we have made continued efforts to establish a practical synthetic pathway that could meet the demand for ecteinascidin 743. Herein we disclose an interim report of our novel approach for the robust synthesis of ecteinascidin 743.

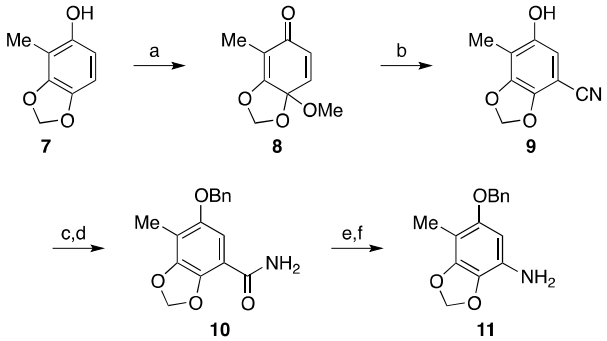
As shown in our retrosynthesis in Scheme 1, the ten-membered cyclic sulfide in **1** would be generated according to our published strategy[4b] from alcohol **2,** a key intermediate with the pentacyclic core structure. Construction of the B-ring could be achieved via an intramolecular *ortho* substitution of the phenol with an aldehyde. Intermediate **3** bearing two aldehyde moieties would be derived from dihydropyrrole **4**. Given the aryl group on the less hindered side, stereoselective introduction of the aryl group in **4** would be achieved via a Heck reaction between diazonium salt **5** and enamide **6**.[7]

Our synthesis commenced with preparation of amine **11** as the precursor for diazonium salt **5** (Scheme 2). Oxidation of known phenol **7**[5e,8] with $PhI(OAc)_2$ in methanol gave dienone **8**, which was treated with sodium cyanide to afford nitrile **9**. After benzylation of the phenolic hydroxy group, the resulting nitrile was hydrolyzed to furnish carboxamide **10**. Hofmann rearrangement followed by hydrolysis afforded amine **11**.

Scheme 1. Retrosynthesis



Scheme 2

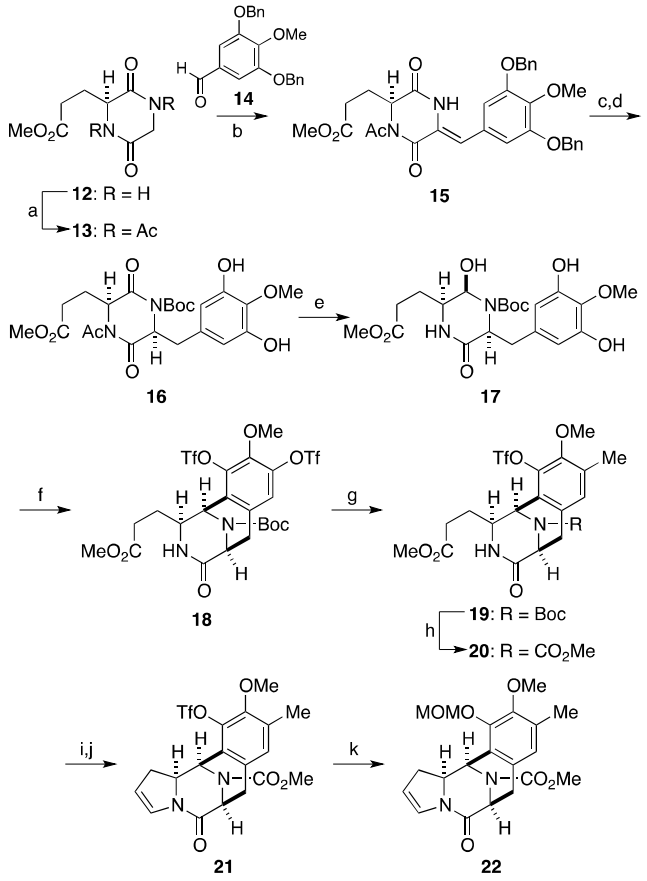


Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 0 °C; (b) NaCN, DMF-H_2O, 0 °C to rt, 37% (2 steps); (c) BnBr, K_2CO_3,

DMF, rt; (d) aq H_2O_2, K_2CO_3, DMSO, rt; (e) $PhI(OAc)_2$, KOH, MeOH, 0 °C; (f) LiOH, EtOH-H_2O, reflux, 83% (4 steps).

We next focused on construction of the enamide unit (Scheme 3). L-glutamic acid, chosen as an inexpensive, readily available, and reliable chiral source, was converted to *N*,*N'*-diacetylated diketopiperazine **13**.[9] Perkin condensation of **13** with aldehyde **14** proceeded stereoselectively to give **15**. After introduction of a Boc group at the lactam, cleavage of the benzyl group and stereoselective reduction of the double bond were simultaneously carried out to furnish **16**. Hydrazinolysis of the acetyl group in **16** followed by selective reduction of the imide carbonyl group with sodium borohydride afforded **17**. Upon treatment of **17** with TFA, the *N*-acyliminium ion-mediated cyclization reaction proceeded smoothly, and subjection of the product to $PhNTf_2$ under basic conditions afforded bis-triflate **18** in 88% yield. Suzuki-Miyaura coupling of **18** with trimethylboroxine took place selectively at the less hindered triflate to produce **19** in 92% yield. After the Boc group was switched to a methoxycarbonyl group, partial reduction of the ester moiety in **20** with L-Selectride® and subsequent dehydration of the resulting hemiaminal under acidic conditions afforded enamide **21**. The Tf group was replaced with a MOM group in a one-pot process to afford **22**.

Scheme 3

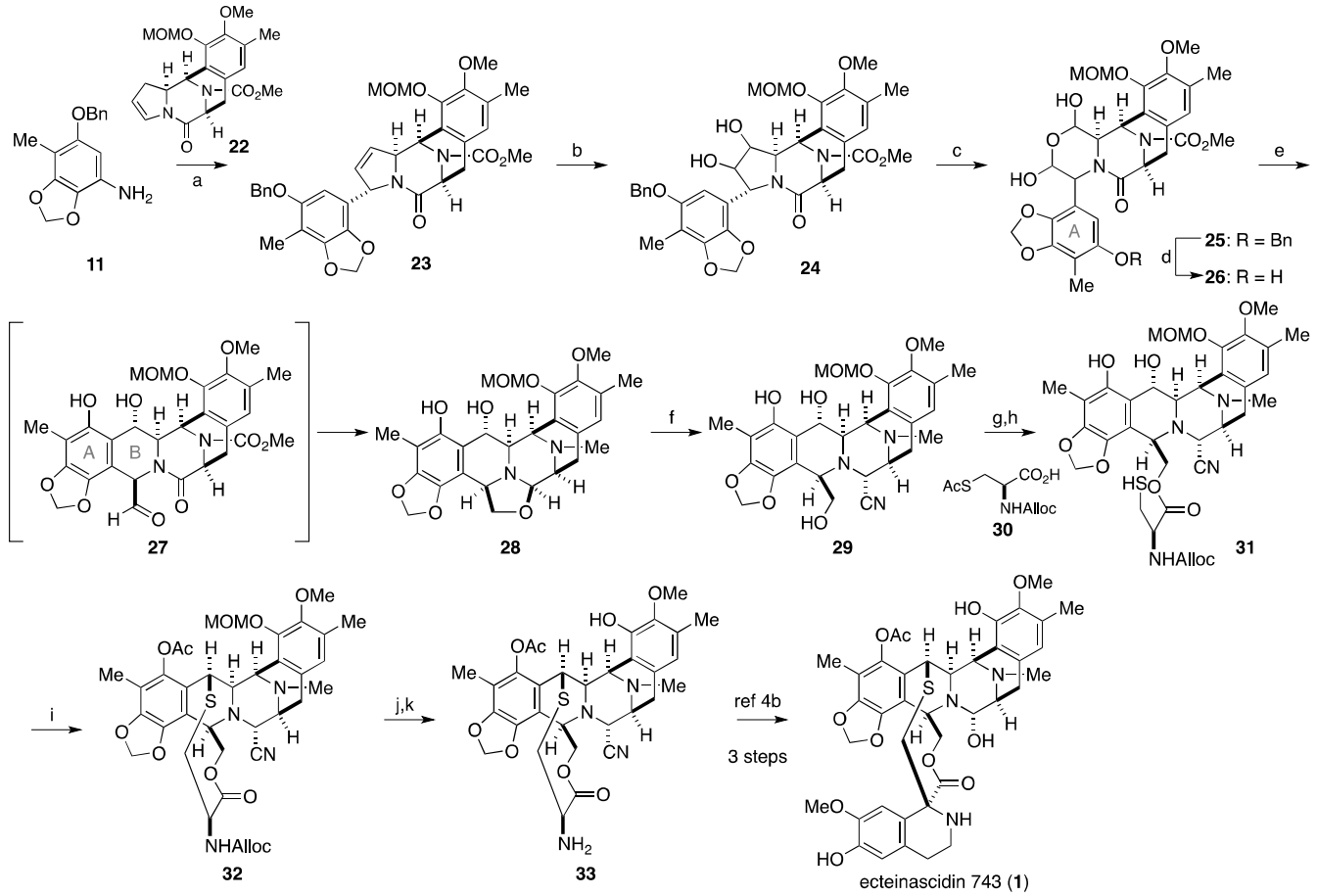


Reagents and conditions: (a) Ac_2O, 130 °C, 80%; (b) **14**, *t*-BuOK, THF, –78 to 0 °C; DBU, 0 °C; (c) Boc_2O, DMAP, THF, rt, quant (2 steps); (d) H_2 (750 psi), Pd/C, EtOAc, rt; (e) $H_2NNH_2 \cdot H_2O$, THF, rt; evaporation; $NaBH_4$, MeOH, 0 °C, 57% (2 steps); (f) TFA, CF_3CH_2OH, rt; evaporation; $PhNTf_2$, DMAP, Cs_2CO_3, MeCN, rt, 88%; (g) trimethylboroxine, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, 100 °C, 92%; (h) HCl, EtOAc, rt; $ClCO_2Me$, $NaHCO_3$, H_2O, 0 °C, 91%; (i) L-Selectride®, THF, –42 °C; (j) CSA, toluene, reflux, 55% (2 steps); (k) aq KOH, 1,4-dioxane, rt; MOMCl, 0 °C, 95%.

With the requisite units in hand, we next investigated construction of the B-ring (Scheme 4). After treatment of amine **11** with *tert*-butyl nitrite and $BF_3 \cdot OEt_2$,[10] the resulting diazonium salt was reacted with enamide **22** in the presence of a palladium catalyst to perform the crucial Heck reaction. As expected, the reaction occurred exclusively from the less hindered face of the enamide to produce coupling product **23** with the desired stereo- and regiochemistry. It should be noted that this crucial intermolecular Heck reaction was carried out on a multi-gram scale in an excellent yield. An osmium-mediated dihydroxylation of the resulting, highly hindered double bond in **23** was accomplished by using $K_3[Fe(CN)_6]$ as a co-oxidant in the presence of quinuclidine and methanesulfonamide.[11,12,13] Oxidative cleavage of the resulting 1,2-diol with H_5IO_6 formed a dialdehyde, which underwent facile hydration to afford **25**. Although partial epimerization occurred during the oxidative cleavage of the diol, the crude product could be purified by recrystallization from methanol to give **25** as a single diastereomer.[14] Hydrogenolysis of the benzyl ether in **25** gave phenol **26**. Heating **26** in *m*-xylene promoted liberation of the dialdehyde, which was trapped intramolecularly by the electron-rich A-ring moiety to furnish **27**.[15] Subsequent reduction of **27** with Red-Al® afforded **28** in 76% yield over the 2 steps. Treatment of **28** with KCN in acetic acid induced cleavage of the oxazolidine ring, forming aminonitrile **29**.

Having established an efficient and robust synthetic route toward the pentacyclic core skeleton of the target molecule, we then undertook a study to construct the ten-membered cyclic sulfide. Condensation of the primary hydroxy group in **29** with cysteine derivative **30**[4b] followed by selective cleavage of the *S*-acetyl group with hydrazine furnished thiol **31** in good yield. Upon treatment of **31** with TFA, the cyclic sulfide formation occurred presumably via the generation of an *ortho* quinone methide to give, after acetylation of the phenolic hydroxy group, compound **32** in 55% yield. Sequential cleavage of the MOM and Alloc protecting groups furnished **33**, which was identical to the intermediate of our previous synthesis, and was converted into ecteinascidin 743 (**1**) via the published 3-step sequence.[4b]

Scheme 4



Reagents and condition: (a) $BF_3{\cdot}OEt_2$, *t*-BuONO, THF, –15 to 0 °C; **22**, $Pd_2(dba)_3$, NaOAc, MeCN-THF, 0 °C to rt; (b) OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, quinuclidine·HCl, $MeSO_2NH_2$, *t*-BuOH, H_2O, rt, 93% (2 steps); (c) H_5IO_6, THF, 0 °C, 87%; (d) H_2, Pd/C, MeOH, rt; (e) *m*-xylene, 120 °C; Red-Al®, –42 to 60 °C, 76% (2 steps); (f) KCN, AcOH, rt, 98%; (g) **30**, EDCI·HCl, DMAP, CH_2Cl_2, rt, 92%; (h) $H_2NNH_2{\cdot}H_2O$, MeCN, rt, 85%; (i) TFA, CF_3CH_2OH, 25 °C; toluene, evaporation; Ac_2O, pyridine, rt, 55%; (j) TFA, CH_2Cl_2, rt, 64%; (k) $(Ph_3P)_2PdCl_2$, AcOH, *n*-Bu_3SnH, CH_2Cl_2, rt, 95%.

In conclusion, a straightforward synthesis of ecteinascidin 743 has been accomplished in 28 steps and 1.1% overall yield from readily available L-glutamic acid as a single chiral source. Our novel synthesis features a concise and convergent approach for construction of the B-ring, consisting of a sequence of a stereoselective Heck reaction between a diazonium salt and an enamide, oxidative cleavage of the resulting alkene and intramolecular *ortho* substitution of the phenol by an aldehyde. Other highlights of the synthesis include a straightforward method to access a functionalized diketopiperazine by Perkin condensation, facile construction of the bicyclo[3.3.1] system by an *N*-acyliminium ion-mediated cyclization, and a regioselective Suzuki-Miyaura coupling. We are currently exploring a more practical synthetic route that could be applied on a manufacturing scale to supply ecteinascidin 743 for clinical use.

ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* fukuyama@ps.nagoya-u.ac.jp

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REFERENCES

(1) (a) Holt, T. G. Ph.D. Dissertation, University of Illinois, Urbana-Champaign **1986**. (b) 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. (d) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H. J. *Proc. Natl. Acad. Sci.* **1992**, *89*, 11456. (d) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; Mcconnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508. (e) Sakai, R.; Jares-Erijman, E. A.; Manzanares, I.; Elipe, M. V. S.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017.

(2) (a) Pommier, Y.; Kohlhagen, G.; Bailly, C.; Waring, M.; Mazumder, A.; Kohn, K. W. *Biochemistry* **1996**, *35*, 13303. (b) Moore, B. M.; Seaman, F. C.; Hurley, L. H. *J. Am. Chem. Soc.* **1997**, *119*, 5475. (c) Moore, B. M.; Seaman, F. C.; Wheelhouse, R. T.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 9975. (d) Moore, B. M.; Seaman, F. C.; Wheelhouse, R. T.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 2490. (e) Seaman, F. C.; Hurley, L. H. *J. Am. Chem. Soc.* **1998**, *120*, 13028. (f) Zewail-Foote, M.; Hurley, L. H. *J. Med. Chem.* **1999**, *42*, 2493. (g) Garcia-Nieto, R.; Manzanares, I.; Cuevas, C.; Gago, F. *J. Med. Chem.* **2000**, *43*, 4367. (h) Garcia-Nieto, R.; Manzanares, I.; Cuevas, C.; Gago, F. *J. Am. Chem. Soc.* **2000**, *122*, 7172. (i) Zewail-Foote, M.; Hurley, L. H. *J. Am. Chem. Soc.* **2001**, *123*, 6485. (j) Marco, E.; Garcia-Nieto, R.; Mendieta, J.; Manzanares, I.; Cuevas, C.; Gago, F. *J. Med. Chem.* **2002**, *45*, 871. (k) Marco, E.; David-Cordonnier, M.-H.; Bailly, C.; Cuevas, C.; Gago, F. *J. Med. Chem.* **2006**, *49*, 6925.

(3) (a) Gajate, C.; An, F. Y.; Mollinedo, F. *J. Biol. Chem.* **2002**, *277*, 41580. (b) Minuzzo, M.; Ceribelli, M.; Pitarque-Marti, M.; Borrelli, S.; Erba, E.; diSilvio, A.; D'Incalci, M.; Mantovani, R. *Mol. Pharmacol.* **2005**, *68*, 1496.

(4) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552. (c) Chen, J. C.; Chen, X. C.; Bois-Choussy, M.; Zhu, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 87. (d) Zheng, S. P.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 1754. (e) Fishlock, D.; Williams, R. M. *J. Org. Chem.* **2008**, *73*, 9594. (f) Imai, T.; Nakata, H.; Yokoshima, S.; Fukuyama, T. *Synthesis* **2012**, *44*, 2743.

(5) For syntheteic studies toward ecteinascidin 743, see: (a) Endo, A.; Kan, T.; Fukuyama, T. *Synlett* **1999**, *1999*, 1103. (b) Zhou, B. S.; Guo, J. S.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43. (c) De Paolis, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, 2896. (d) De Paolis, M.; Chen, X. C.; Zhu, J. P. *Synlett* **2004**, *2004*, 729. (e) Chen, X. C.; Chen, J. C.; De Paolis, M.; Zhu, J. P. *J. Org. Chem.* **2005**, *70*, 4397. (f) Chen, X.; Chen, J.; Zhu, J. *Synthesis* **2006**, *2006*, 4081. (g) Enomoto, T.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2010**, *75*, 4876.

(6) (a) Cuevas, C.; Perez, M.; Martin, M.; Chicharro, J.; Fernandez-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; De La Calle, F.; Garcia, J.; Polanco, C.; Rodriguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545. (b) Menchaca, R.; Martínez, V.; Rodríguez, A.; Rodríguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem.* **2003**, *68*, 8859.

(7) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305.

(8) Hussain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023.

(9) Weigl, M.; Wünsch, B. *Tetrahedron* **2002**, *58*, 1173.

(10) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572.

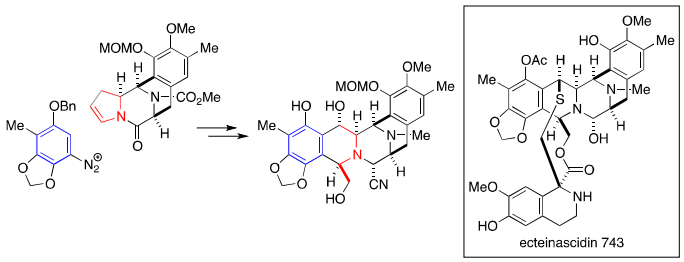
(11) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.

(12) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768.

(13) While diol **24** was obtained as a single diastereomer, we could not determine the stereochemistry.

(14) Without recrystallization at this stage, construction of the B-ring was difficult to reproduce.

(15) This aldehyde could be isolated as a 5:1 mixture of the isomers.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