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# Synthetic Study toward Ecteinascidin 743: Concise Construction of the Diazabicyclo[3.3.1]nonane Skeleton and Assembly of the Pentacyclic Core

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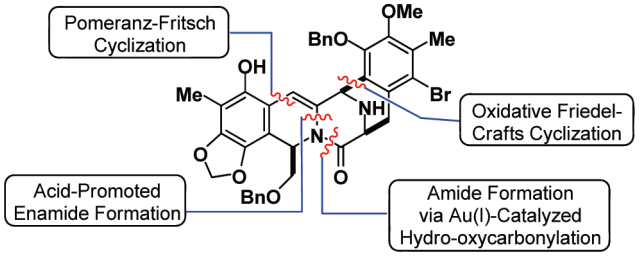


Synthesis of the pentacyclic core of ecteinascidin 743 is described. This synthesis features concise construction of the diazabicyclo[3.3.1]nonane skeleton using gold(I)-catalyzed one-pot keto amide formation, acid-promoted enamide formation, and oxidative Friedel−Crafts cyclization as the key steps.

Tetrahydroisoquinoline alkaloids, which comprise a large family of biologically active natural products, have received considerable attention due to their potent biological activities and structural diversity.[1] In particular, ecteinascidin 743 (Et-743, **1**; Figure 1), which was isolated from the Caribbean tunicate *Ecteinascidia turbinate*,[2] possesses potent cytotoxic activities against several tumor cell lines, several rodent tumors, and human tumor xenografts in vitro.[3,4] It was

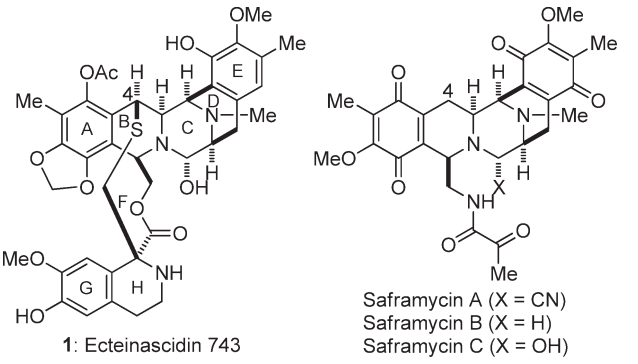


**FIGURE 1.** Ecteinascidin 743 and saframycins.

recently approved and sold as Yondelis for use in Europe, Russia, and South Korea for the treatment of advanced soft tissue sarcoma. It is also undergoing clinical trials for breast, prostate, and pediatric sarcomas. The antiproliferative activity of Et-743 is greater than that of paclitaxel, camptothecin, mitomycin C, and cisplatin. Et-743 is structurally similar to the saframycin family.[1] A significant difference is that the C-4 carbon of Et-743 possesses a higher oxidation state than that in saframycins. Its remarkable biological activity, the scarcity of the natural product from tunicates, and its complex molecular structure render Et-743 an attractive target for synthesis. To date, three total syntheses have been accomplished by the groups of Corey,[5] Fukuyama,[6] and Zhu,[7] and the groups of Danishefsky[8] and Williams[9] have each developed formal total syntheses. A semisynthesis from cyanosafracin B has also been developed by Cuevas, Manzanares, and co-workers at PharmaMar.[10] Additionally, other synthetic approaches have been reported by several research groups.[11] We describe here a concise alternative approach to the diazabicyclo[3.3.1]nonane skeleton and assembly of the core (ABCDE ring system) that can be applied to the synthesis of Et-743.

(1) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
(2) (a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S. *J. Nat. Prod.* **1990**, *53*, 771. (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. (c) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456.
(3) (a) Sakai, R.; Jares-Erijiman, E. A.; Manzanares, I.; Silva Elipe, M. V.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017. (b) Takebayashi, Y.; Pourquier, P.; Zimonjic, D. B.; Nakayama, K.; Emmert, S.; Ueda, T.; Urasaki, Y.; Kanzaki, A.; Akiyama, S.; Popescu, N.; Kraemer, K. H.; Pommier, Y. *Nature Med.* **2001**, *7*, 961. (c) Zewai-Foote, M.; Li, V.-S.; Kohn, H.; Bearss, D.; Guzman, M.; Hurley, L. H. *Chem. Biol.* **2001**, *8*, 1033.
(4) (a) Rinehart, K. L. *Med. Drug. Rev.* **2000**, 1. (b) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545.
(5) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993.
(6) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.
(7) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87.
(8) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1754.
(9) Fishlock, D.; Williams, R. M. *J. Org. Chem.* **2008**, *73*, 9594.
(10) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545.
(11) (a) Saito, N.; Kamayachi, H.; Tachi, M.; Kubo, A. *Heterocycles* **1999**, *51*, 9. (b) Saito, N.; Tachi, M.; Seki, R.; Kamayachi, H.; Kubo, A. *Chem. Pharm.Bull.* **2000**, *48*, 1549. (c) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43. (d) Paolis, M. D.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, 2896. (e) Tang, Y.-F.; Liu, Z.-Z.; Chen, S.-Z. *Tetrahedron Lett.* **2003**, *44*, 7091. (f) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397. (g) González, J. F.; Salazar, L.; Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447. (h) Aubry, S.; Pellet-Rostaing, S.; Fenet, B.; Lemaire, M. *Tetrahedron Lett.* **2006**, *47*, 1319. (i) Ceballos, P. A.; Péres, M.; Cuevas, C.; Francesch, A.; Manzanares, I.; Echavarren, A. M. *Eur. J. Org. Chem.* **2006**, 1926. (j) Chandrasekhar, S.; Reddy, N. R.; Rao, Y. S. *Tetrahedron* **2006**, *62*, 12098. (k) Vincent, G.; Lane, J. W.; Williams, R. M. *Tetrahedron Lett.* **2007**, *48*, 3719. (l) Chang, Y.-A.; Sun, T.-H.; Chiang, M. Y.; Lu, P.-J.; Huang, Y.-T.; Liang, L.-C.; Ong, C. W. *Tetrahedron* **2007**, *63*, 8781.



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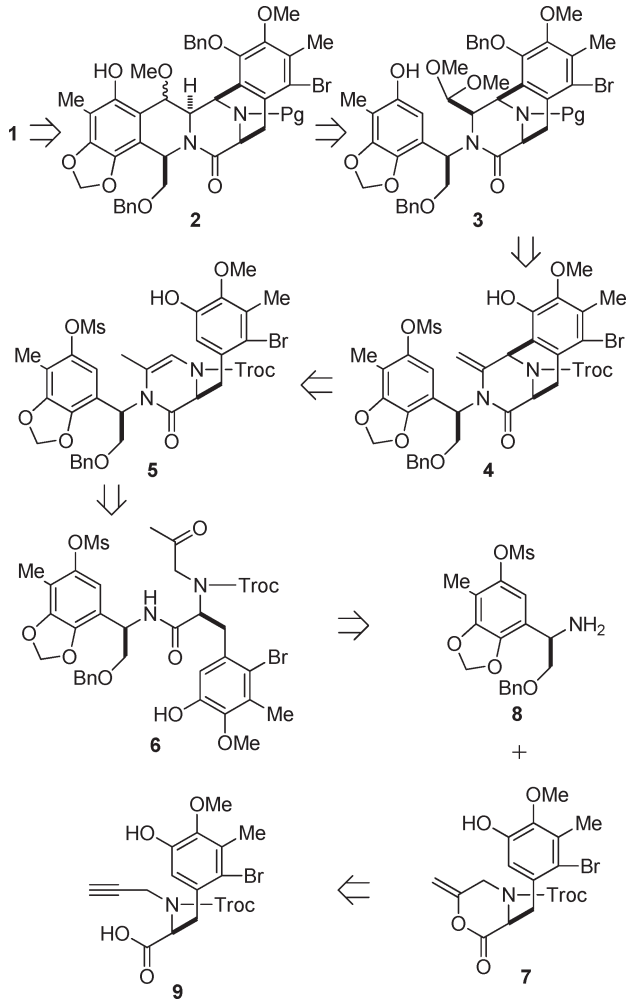
**SCHEME 1. Retrosynthesis**

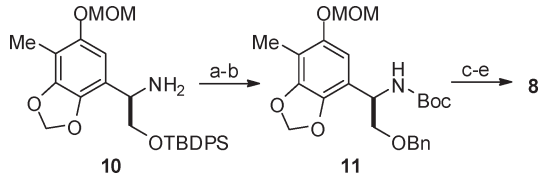


Our retrosynthesis of Et-743 is illustrated in Scheme 1. We envisioned that Pomeranz−Fritsch-type cyclization of appropriately protected dimethyl acetal **3** would afford the desired synthetic intermediate **2,** which has all of the requisite functionalities for the pentacyclic core of Et-743. The acetal **3** could be obtained from *exo*-enamide **4** through a sequence of hydroxylation, oxidation, and acetalization according to Fukuyama's method.[6] The key intermediate **4**, which bears a diazabicyclo[3.3.1]nonane system, is derived from *endo*-enamide **5** by the oxidative Friedel−Crafts-type cyclization developed in our group for the synthesis of saframycin B.[12] By the acid-promoted intramolecular condensation of the amide and ketone moieties, the desired enamide **5** would be prepared from keto amide **6**. The requisite product **6** can be transformed from (*R*)-phenylglycinol derivative **8** and cyclic enol ester **7**, which is easily prepared by a 6-*exo*-*dig* cyclization of alkynoic acid **9**.

The synthesis of (*R*)-phenylglycinol derivative **8** was achieved as described in Scheme 2. The one-pot *N*-Boc protection and desilylation of *O*-TBDPS amine **10**, prepared by the reported procedure,[6] was followed by regioselective benzylation to give the desired product **11**. To switch the protecting group from the

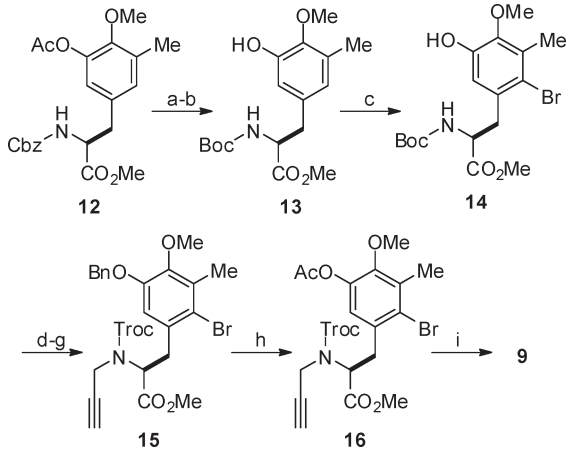
(12) Obika, S.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2008**, *73*, 5206.

**SCHEME 2. Synthesis of Phenylglycinol Derivative 8**[a]



[a]Conditions: (a) (i) $Boc_2O$, THF, (ii) TBAF, two steps 75%; (b) NaH, BnBr, TBAI, DMF/THF, 78%; (c) (i) 4 M HCl aq, MeOH/dioxane, (ii) $Boc_2O$, $CH_2Cl_2$/satd $NaHCO_3$ aq; (d) MsCl, DIPEA, $CH_2Cl_2$; (e) TFA, anisole, $CH_2Cl_2$, 4 steps 99%.

**SCHEME 3. Synthesis of Phenylalanine Derivative 9**[a]



[a]Conditions: (a) $K_2CO_3$, MeOH; (b) $H_2$, Pd/C, $Boc_2O$, MeOH, two steps 85%; (c) NBS, MeCN, 88%; (d) BnBr, $K_2CO_3$, TBAI, DMF, 92%; (e) AcCl, MeOH (3 M HCl), $CH_2Cl_2$; (f) propargyl bromide, LiOH·$H_2O$, MS4A, DMF, two steps 81%; (g) TrocCl, $CH_2Cl_2$/$NaHCO_3$ aq, 93%; (h) AcBr, $SnBr_2$, $CH_2Cl_2$, 94%; (i) LiOH, MeOH/$H_2O$/THF.

MOM ether to the mesylate, we converted **11** into amine **8** in good yield by the usual protection and deprotection protocol.

The synthesis of alkynoic acid **9**, a highly functionalized (*S*)-bromophenylalanine derivative, is depicted in Scheme 3. Starting from Cbz-carbamate **12**, which was synthesized by Zhu's method,[13] we removed the acetyl group, and subsequent conversion of the Cbz moiety to the Boc group afforded phenol **13**, which was then subjected to regioselective bromination with *N*-bromosuccinimide (NBS) to give bromide **14** in 88% yield. After the hydroxyl group of **14** was masked with benzyl bromide, successive deprotection of the Boc group, *N*-propargylation,[14] and *N*-Troc protection provided alkynyl ester **15** in 69% yield in four steps. Conversion of the benzyl ether to the acetate and simultaneous hydrolysis of the methyl ester and acetate moieties furnished the desired alkynoic acid **9**, which was used for the next reaction without any purification.

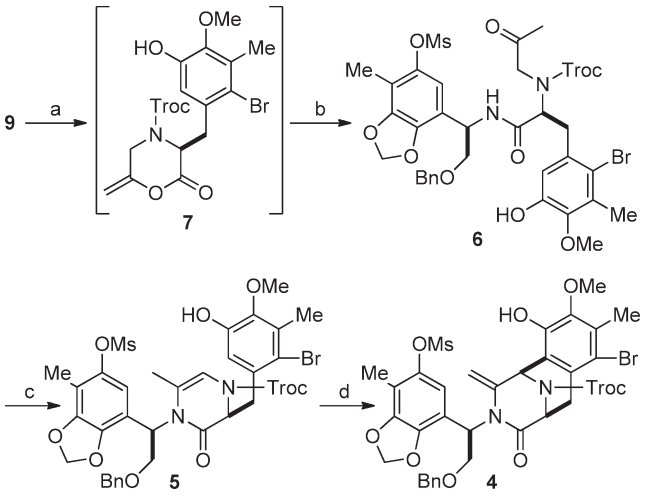
At this stage, two requisite fragments **8** and **9** were incorporated into keto amide **6** by means of a one-pot sequence, which consisted of the gold(I)-catalyzed 6-*exo*-*dig* intramolecular hydro-oxycarbonylation of **9**[15] and a coupling reaction

(13) Demoulin, N.; Zhu, J. *Synlett* **2009**, 466.

(14) Cho, J. H.; Kim, B. M. *Tetrahedron Lett.* **2002**, *43*, 1273.

(15) (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517. (c) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273. (d) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.

**SCHEME 4. Construction of Diazabicyclo[3.3.1]nonane system**[a]



[a]Conditions: (a) $AuCl(PPh_3)$ (1 mol %)/$AgNTf_2$ (1 mol %), $CH_2Cl_2$; (b) **8**, $CH_2Cl_2$, three steps, 80% based on **16**; (c) anhydrous TsOH, $MgSO_4$, toluene, 75%; (d) see Table 1.

of the resulting enol ester **7** with amine **8** (Scheme 4). In fact, treatment of alkynoic acid **9** with a dichloromethane solution of 1 mol % of $AuCl(PPh)_3/AgNTf_2$ followed by the addition of **8** led to the formation of keto amide **6** in 80% yield.

Condensation is an elementary organic transformation.[16] However, to the best of our knowledge, intramolecular condensation between an amide and a ketone has rarely been applied to the synthesis of a highly functionalized enamide.[17] Indeed, the intramolecular condensation of **6** resulted in formation of the desired enamide **5** in low yields due to recovery or decomposition of the starting material under a variety of Lewis acidic conditions [$TiCl_4-Et_3N$,[17d] $HfCl_4\cdot(THF)_2$,[18] $BF_3\cdot OEt_2$, $Zn(OTf)_2$]. Therefore, various Brønsted acids were next examined for use in intramolecular condensation. After many experiments under a variety of reaction conditions, we finally found that the use of anhydrous TsOH (1.0 equiv) and $MgSO_4$ (50 equiv) in toluene at 90 °C improved the yield to give the desired product **5** in 75% yield.

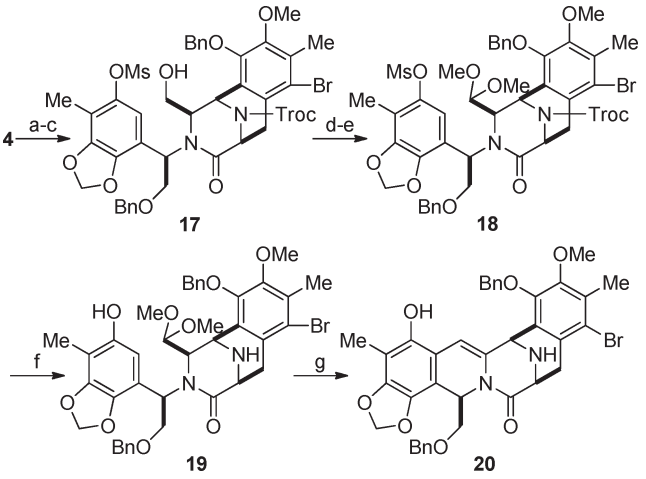
The next challenge in the synthesis is the construction of the diazabicyclo[3.3.1]nonane system. For this purpose, we explored the oxidative Friedel–Crafts cyclization of phenolic enamides such as **5**. We first examined the reaction of nonbrominated compound of **5**, which provided the product that was exclusively cyclized at the para position of the phenol ring, not at the desired ortho position, due to the high reactivity of the para position. We then synthesized the corresponding bromide **5** to suppress the undesired cyclization. In fact, treatment of enamide **5** with an acetonitrile solution of NBS[12] gave the desired tricyclic product **4** in 31% yield (Table 1, entry 1). The promising result with NBS prompted us to optimize the reaction conditions. As a result, we found that the addition of dehydrating agents such as $MgSO_4$ and activated MS 3A improved the reaction efficiency (entries 2 and 3). Moreover, while the reaction of **5** with AcNHBr or *N*-bromosaccharin did not give good results, the use of trimethylphenylammonium tribromide and MS 3A significantly increased the yield of **4** (entries 4–6). On the basis of these studies, it appears that MS 3A acts not only as a dehydrating agent but also as an acid scavenger.

**TABLE 1. Investigation of Oxidative Friedel–Crafts Cyclization**

| entry | conditions[a] | yield[b] (%) |
|---|---|---|
| 1 | NBS (0.95 equiv) | 31 |
| 2 | NBS (0.95 equiv), $MgSO_4$ (30 equiv) | 36 |
| 3 | NBS (0.95 equiv), MS 3A | 56 |
| 4 | AcNHBr (0.95 equiv), MS 3A | 55 |
| 5 | *N*-bromosaccharin (0.95 equiv), MS 3A | 17 |
| 6 | $PhNMe_3\cdot Br_3$ (0.95 equiv), MS 3A | 70 |

[a]Reactions were carried out at room temperature for 15 min and then at 60 °C for 1 h. [b]Isolated yields of **4**

**SCHEME 5. Assembly of the Pentacyclic Core of Et-743**[a]



[a]Conditions: (a) BnBr, $K_2CO_3$, KI, DMF, 91%; (b) (i) DMDO, MeOH/acetone, (ii) CSA; (c) $NaBH_3CN$, TFA/THF, three steps, 86%; (d) Dess–Martin periodinane, $CH_2Cl_2$; (e) PTSA, $(MeO)_3CH$/MeOH, two steps, 60%; (f) TMSOK, MeCN, 75%; (g) 5 M HCl, dioxane/$H_2O$, 82%.

Our final goal was to reach the ABCDE ring system of Et-743. Toward this end, after the hydroxyl group of **4** was subjected to benzylation, it was subsequently transformed to alcohol **17** by epoxidation with dimethyldioxirane, ring-opening with MeOH, and reduction with $NaBH_3CN$ according to Fukuyama's total synthesis (Scheme 5).[6] Subsequently, alcohol **17** was oxidized to the corresponding aldehyde with Dess–Martin periodinane,[19] which was followed by acetalization to give dimethyl acetal **18** in 60% yield. To elaborate B ring formation by Pomeranz–Fritsch cyclization, both the mesyl and *N*-Troc groups of **18** were cleaved by reaction with TMSOK,[20] and treatment of the resulting product **19** with

(16) (a) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; p 1129. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 335. (c) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.

(17) (a) Jirkovsky, I.; Noureldin, R. *J. Heterocycl. Chem.* **1980**, *17*, 449. (b) Fleitz, F.; Lyle, T. A.; Zheng, N.; Armstrong, J. D., III; Volante, R. P. *Synth. Commun.* **2000**, *30*, 3171. (c) Reiner, J. E.; Siev, D. V.; Araldi, G.-L.; Cui, J. J.; Ho, J. Z.; Reddy, K. M.; Mamedova, L.; Vu, P. H.; Lee, K.-S. S.; Minami, N. K.; Gibson, T. S.; Anderson, S. M.; Bradbury, A. E.; Nolan, T. G.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1203. (d) Liu, J.; Liang, F.; Liu, Q.; Li, B. *Synlett* **2007**, 156. (e) Yamazaki, Y.; Mori, Y.; Oda, A.; Okuno, Y.; Kiso, Y.; Hayashi, Y. *Tetrahedron* **2009**, *65*, 3688.

(18) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179.

(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(20) Mori, K.; Rikimaru, K.; Kan, T.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 3095.

excess aqueous HCl in 1,4-dioxane afforded the pentacyclic product **20** in 82% yield. Unfortunately, we could not obtain the desired product **2**, which bears a stereogenic center at C3, but we did achieve a concise synthesis of the important synthetic intermediate **20** for the total synthesis of Et-743.

In summary, we have developed an efficient route to pentacyclic segment **20** of Et-743. Our strategy features easy access to the diazabicyclo[3.3.1]nonane system by gold(I)-catalyzed one-pot keto amide formation, acid-promoted enamide formation, and oxidative Friedel−Crafts cyclization under newly developed conditions ($PhNMe_3 \cdot Br_3$, MS 3A, MeCN, room temperature, then 60 °C). Further research directed toward the total synthesis of Et-743 is in progress.

## Experimental Section

**Keto Amide 6.** To a solution of ester **16** (389 mg, 0.678 mmol) in a mixture of MeOH (9.2 mL), $H_2O$ (2.3 mL), and THF (2.3 mL) was added lithium hydroxide (73.1 mg, 3.05 mmol) at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was diluted with benzene and concentrated in vacuo. The residue was dissolved with $H_2O$, and to the resultant mixture was added a saturated aqueous $KHSO_4$ solution at 0 °C. The resultant suspension was extracted with AcOEt, and the combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford the corresponding carboxylic acid **9** as a colorless amorphous material, which was used in the next step without further purification. To a solution of carboxylic acid **9** in dichloromethane (1.5 mL) was added a mixture of $AuCl(PPh_3)$ (3.5 mg, 0.0071 mmol), $AgNTf_2$ (2.7 mg, 0.0070 mmol), and dichloromethane (0.5 mL) at room temperature. After being stirred at room temperature for 3.5 h, to the reaction mixture was added a solution of amine **8** (270 mg, 0.712 mmol) at room temperature, and the resultant mixture was additionally stirred for 22 h. After the reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution, the resultant mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 1.5/1 to 2/1) to afford amide **6** (484 mg, 80% in three steps) as a white amorphous material: $[\alpha]^{28}_D$ −37 ($c$ = 1.00, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 388 K) $\delta$ 8.85 (br, 1H), 8.36 (s, 1H), 7.32−7.27 (m, 2H), 7.27−7.22 (m, 3H), 6.84 (s, 1H), 6.71 (s, 1H), 6.04 (d, 1H, $J$ = 1.0 Hz), 5.99 (d, 1H, $J$ = 1.0 Hz), 5.17 (dd, 1H, $J$ = 13.9, 6.0 Hz), 4.73−4.56 (m, 3H), 4.50 (d, 1H, $J$ = 12.2 Hz), 4.47 (d, 1H, $J$ = 12.2 Hz), 4.26 (d, 1H, $J$ = 18.4 Hz), 3.92 (br, 1H), 3.74−3.65 (m, 2H), 3.69 (s, 3H), 3.30 (br, 1H), 3.29 (s, 3H), 3.05 (dd, 1H, $J$ = 14.4, 9.4 Hz), 2.26 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$, 388 K) $\delta$ 168.0, 152.9, 148.5, 146.0, 145.3, 142.4, 142.1, 137.9, 132.0, 130.9, 127.7, 126.92, 126.86, 118.5, 116.8, 115.3, 113.4, 113.2, 112.2, 101.5, 95.0, 74.5, 72.0, 70.7, 60.4, 59.3, 56.0, 47.7, 37.6, 35.2, 26.0, 16.2, 9.0; IR (ATR) $\nu$ 3370, 3305, 3027, 2940, 2869, 1727, 1680, 1091 cm$^{-1}$; MS (FAB$^+$) $m/z$ 895 $[M + H]^+$ (15), 815 (10), 488 (8), 391 (67), 149 (100); HRMS (FAB$^+$) calcd for $C_{35}H_{39}BrCl_3N_2O_{12}S$ $[M + H]^+$ 895.0473, found 895.0483.

**Enamide 4.** To a mixture of enamide **5** (200 mg, 0.228 mmol), activated molecular sieves 3A (685 mg), and MeCN (9.0 mL) was added a solution of trimethylphenylammonium tribromide (77.7 mg, 0.207 mmol) in MeCN (2.4 mL) at room temperature. After being stirred at room temperature for 15 min, the reaction mixture was heated at 60 °C and additionally stirred for 1 h. To the reaction mixture was added an aqueous saturated $Na_2SO_3$ solution at 0 °C. The resultant mixture was extracted with AcOEt, and the combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (silica gel) (hexane/AcOEt = 1.5/1) to afford enamide **4** (139 mg, 70%) as a colorless foam: $[\alpha]^{22}_D$ +54 ($c$ = 1.25, $CHCl_3$); $^1$H NMR (500 MHz, DMSO-$d_6$, 388 K) $\delta$ 9.12 (br, 1H), 7.30−7.20 (m, 3H), 7.08 (d, 2H, $J$ = 7.0 Hz), 6.59 (s, 1H), 5.98 (dd, 1H, $J$ = 3.1, 2.6 Hz), 5.86 (d, 1H, $J$ = 1.0 Hz), 5.78 (dd, 1H, $J$ = 8.1, 6.2 Hz), 5.73 (dd, 1H, $J$ = 1.0 Hz), 5.05−5.01 (m, 1H), 4.92 (d, 1H, $J$ = 12.6 Hz), 4.84 (d, 1H, $J$ = 12.6 Hz), 4.83 (d, 1H, $J$ = 1.7 Hz), 4.52 (d, 1H, $J$ = 1.7 Hz), 4.32(d, 1H, $J$ = 12.5 Hz), 4.25 (d, 1H, $J$ = 12.5 Hz), 4.14 (dd, 1H, $J$ = 10.3, 6.2 Hz), 4.07 (dd, 1H, $J$ = 10.3, 8.1 Hz), 3.60 (s, 3H), 3.22 (s, 3H), 3.05- 3.03 (m, 2H), 2.23 (s, 3H), 2.08 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) mixture of carbamate rotamers $\delta$ 168.2, 167.8, 151.9, 151.3, 146.8, 145.2, 144.9, 144.24, 144.18, 143.1, 142.62, 142.58, 139.9, 137.7, 131.3, 128.5, 128.3, 128.1, 127.4, 127.3, 127.2, 119.5, 119.3, 117.6, 117.4, 116.3, 116.1, 113.71, 113.65, 113.3, 113.1, 101.71, 101.66, 96.3, 96.0, 95.1, 95.0, 75.11, 75.06, 72.86, 72.84, 67.8, 67.6, 61.2, 54.1, 53.6, 53.3, 52.6, 51.9, 50.9, 37.3, 34.3, 33.9, 29.6, 16.7, 9.8; IR (ATR) $\nu$ 3360, 3020, 2932, 1720, 1680, 1634, 1424, 1364 cm$^{-1}$; MS (FAB$^+$) $m/z$ 897 $[M + Na]^+$ (12), 875 $[M + H]^+$ (22), 797 (20), 769 (37), 91 (100); HRMS (FAB$^+$) calcd for $C_{35}H_{34}BrCl_3N_2O_{11}S$ $[M]^+$ 874.0132, found 874.0126.

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**Supporting Information Available:** Detailed experimental procedures and product characterization data for all new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.