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Synthesis of Natural Ecteinascidins (ET-729, ET-745, ET-759B, ET-736, ET-637, ET-594) from Cyanosafracin B

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The semisynthetic process initially described for the synthesis of **1** (ET-743) has been extended to the preparation of other natural ecteinascidins. For the synthesis of **2** (ET-729) a demethylation of a *N*-Me intermediate was carried out by a selective oxidation with MCPBA. Other natural ecteinascidins (ET-745, ET-759B, ET-736, ET-637, ET-594) were accessible from key intermediate **25**. The described methodologies allow for the preparation of a wide variety of ecteinascidins by procedures that can be easily scaled up.

Introduction

The ecteinascidins are marine natural products isolated from the caribbean tunicate *Ecteinascidia turbinata*[1] (see Figure 1). The chemical structure of the ecteinascidins is formed by two fused tetrahydroisoquinoline rings linked to a 10-member lactone bridge through a benzylic sulfide linkage. Most ecteinascidins have an additional tetrahydroisoquinoline or tetrahydro-β-carboline ring attached to the rest of the structure through a spiro ring. Their potent antiproliferative activity against a variety of tumor cells, the scarce availability from natural sources, and the unique mechanism of action[2] have made them attractive candidates for development as anticancer agents and very attractive synthetic targets.

The precedents to the synthesis of ecteinascidin **1** (ET-743), the lead compound that is currently in Phase II clinical trials in Europe and the United States[3] for ovarian, endometrium, and breast cancer and that has already shown efficacy in soft tissue sarcomas in three pivotal phase II trials, are to be found in synthetic work leading to related molecules such as saframycins, safracins, and renieramycins[4] (see Figure 2). These antimicrobial compounds isolated from bacterial sources or marine sponges[5] have the same pentacyclic skeleton as the ecteinascidins but one or two of the aromatic rings contain a different oxidation pattern, resulting in mono- or bis-quinone structures.

To date, two total syntheses of **1** (ET-743) have been reported by Corey et al.[6] and Fukuyama et al.[7] We have recently reported a semisynthesis of **1** (ET-743)[8] more suitable for large-scale preparation starting from cyanosafracin B, an antibiotic of bacterial origin, available through fermentation of the bacteria *Pseudomonas fluorescens*.[9]

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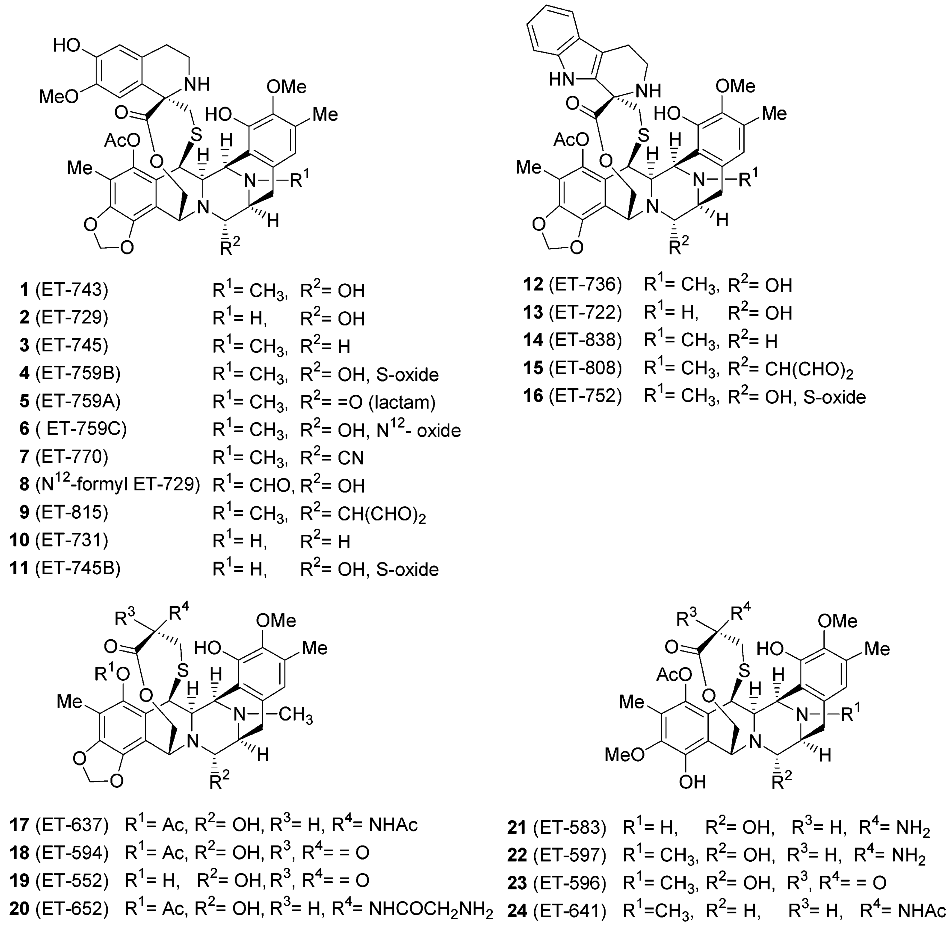

FIGURE 1. Ecteinascidins isolated from the caribbean tunicate *Ecteinascidia turbinata.*

The semisynthetic approach provides access not only to **1** (ET-743) but also to other natural members of the ecteinascidins family. To extend the scope of the semisynthetic route, we report herein syntheses of **2** (ET-729), **3** (ET-745), **4** (ET-759B), **12** (ET-736), **17** (ET-637), and **18** (ET-594) using the key intermediate **25**[10] as shown in the retrosynthetic analysis outlined in Scheme 1. As it was previously described in the semisynthesis of **1** (ET-743), we envisaged formation of **25** using different protection and deprotection reactions of the functional groups of cyanosafracin B, cleavage of the amide bond by Edman degradation, and transformation of the amino group into the primary alcohol.[8] The synthesis of other ecteinascidins was accomplished from readily available intermediate **25**.

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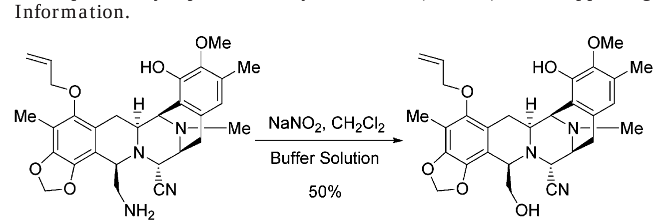
(10) Compound **25** was obtained from compound **49**, an intermediate in the previously reported semisynthesis of **1** (ET-743).[8] See Supporting Information.



49 **25**

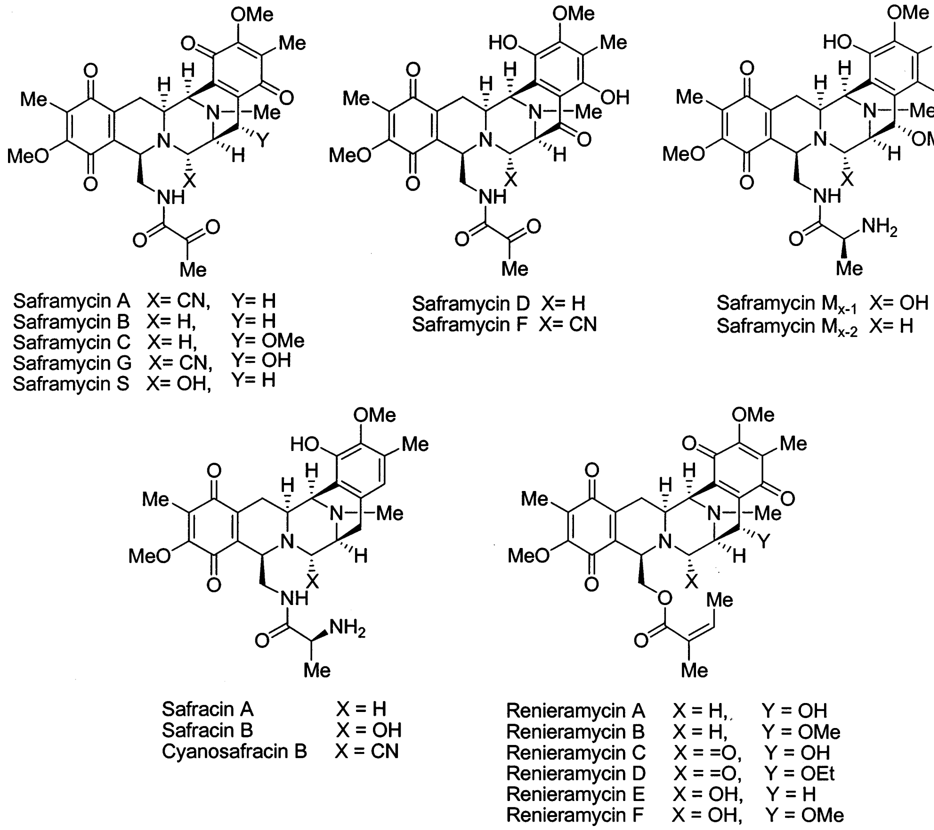
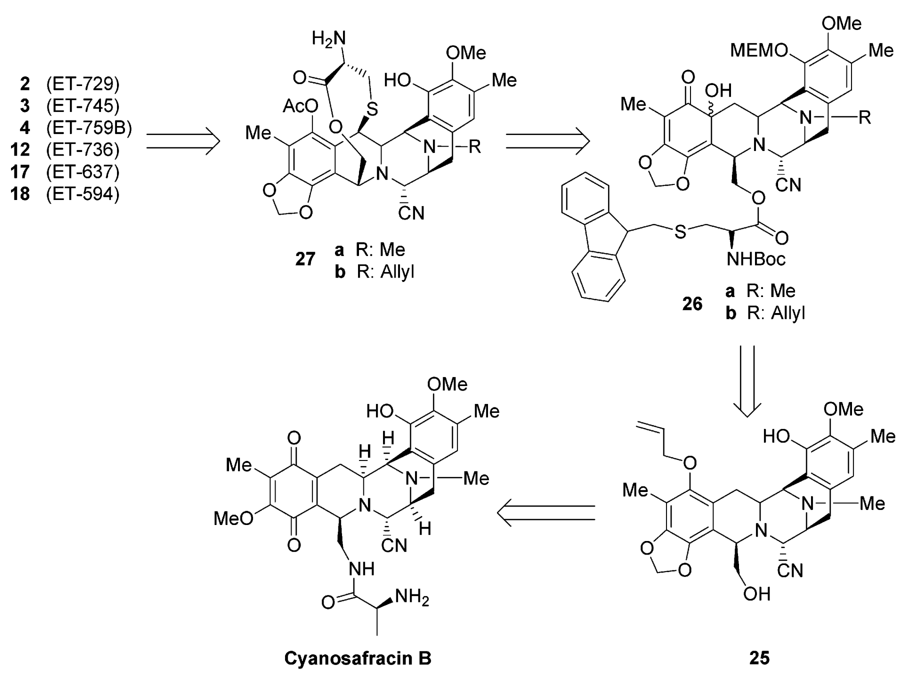


FIGURE 2. Structures of saframycins, safracins, and renieramycins.

SCHEME 1. Retrosynthetic Analysis of 2, 3, 4, 12, 17, and 18

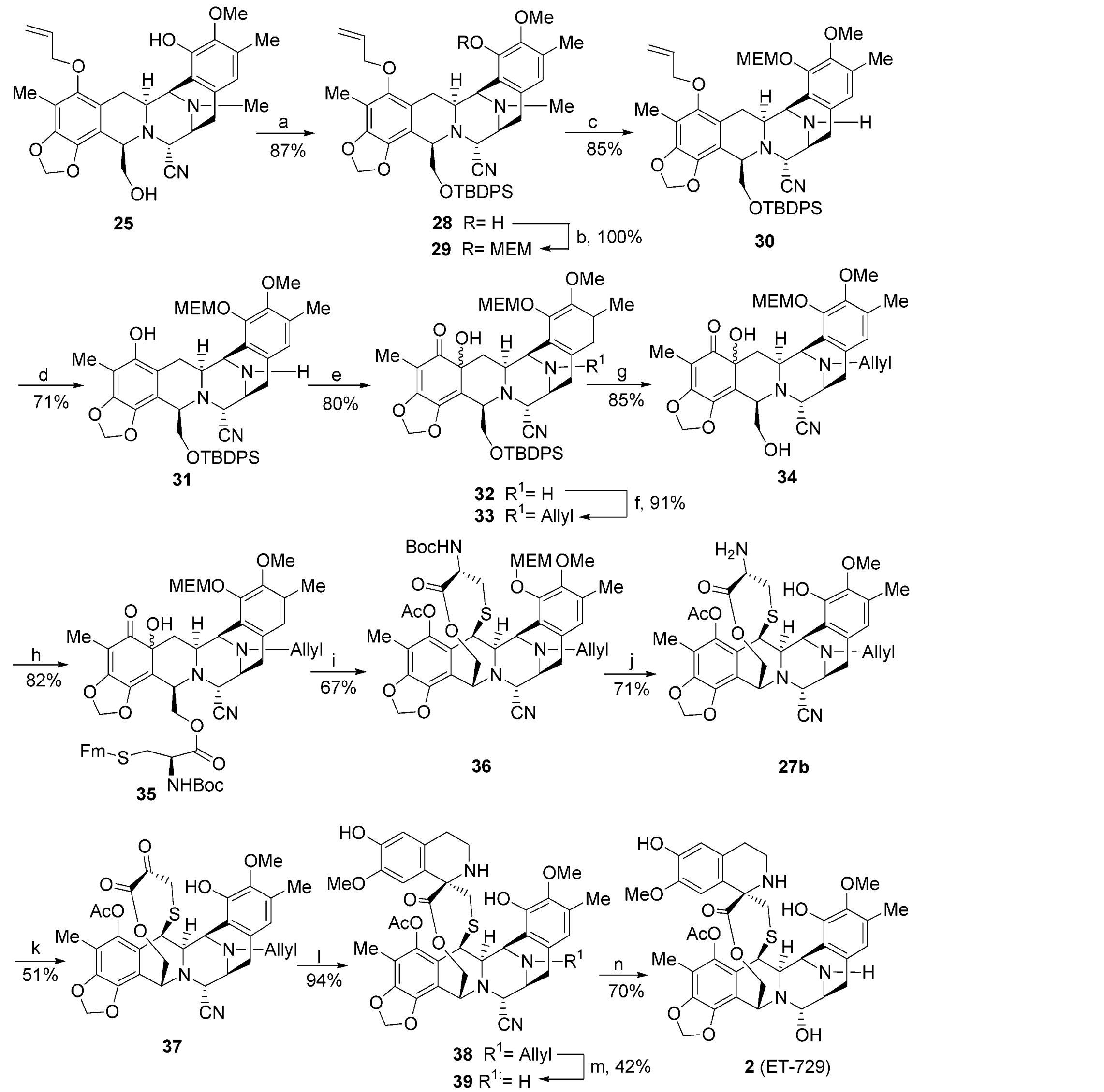


Results and Discussion

Synthesis of 2 (ET-729). The most relevant structural difference of **2** (ET-729) with other members of the family is the absence of *N*-methyl group in the bridgehead nitrogen of the fused tetrahydroisoquinoline unit. Therefore, the synthesis of **2** (ET-729) requires a demethylation reaction of the bridgehead nitrogen of the synthetic intermediate used, which is the key step of the synthetic plan (Scheme 2).

According to Scheme 2, silylation of the primary alcohol of intermediate **25** under standard conditions and protection of the phenol with MEMCl in THF, using NaH as base, furnished **29** in 87% yield. All attempts to accomplish the critical *N*-demethylation of the tertiary

SCHEME 2. Synthesis of 2 (ET-729)[a]



[a] Conditions: (a) TBDPSCl, imidazole, DMAP, DMF; (b) MEMCl, NaH, THF; (c) MCPBA, TEA, TFAA, CH_2Cl_2; (d) $HSnBu_3$, AcOH, $(PPh_3)_2PdCl_2$, CH_2Cl_2; (e) $(PhSeO)_2O$, CH_2Cl_2; (f) Cs_2CO_3, AllylBr, DMF; (g) TBAF, THF; (h) L-cysteine derivative, EDC·HCl, DMAP, DIPEA, CH_2Cl_2; (i) DMSO; Tf_2O, DIPEA, *t*-BuOH, *tert*-butyltetramethyl guanidine, Ac_2O, CH_2Cl_2; (j) *p*-TsOH, $CHCl_3$; (k) *N*-methylpyridinium-4-carboxaldehyde iodide, DBU, oxalic acid; (l) 3-hydroxy-4-methoxyphenylethylamine, silica gel, EtOH; (m) $HSnBu_3$, $(PPh_3)_2PdCl_2$, AcOH, CH_2Cl_2; (n) $AgNO_3$, CH_3CN-H_2O.

amine under different conditions described in the literature such us I_2/CaO,[11] vinyl chloroformate,[12] *tert*-butyl hydroperoxide/$RuCl_2(PPh_3)_2$,[13] or $RuCl_3/H_2O_2$[14] led to undesired products or unaltered starting material. By contrast demethylation in CH_2Cl_2 with MCPBA, TEA, and TFAA[15] afforded **30** in 85% yield. With compound **30** in hand, deprotection of the allyl group, oxidation of the phenol, and subsequent protection with allyl bromide of the bridgehead amine furnished **33**, which was submitted to desilylation under standard conditions to give **34** in 68% yield. Next, esterification of the resulting alcohol with *(R)*-*N*-[(*tert*-butoxy)carbonyl-*S*-(9-fluorenylmethyl)]cysteine and subsequent cyclization gave the 10-membered lactone bridge intermediate **36** via formation of the exo quinone methide followed by nucleophilic addition of the deprotected cysteine and further acetylation of the phenoxide ion. Simultaneous removal of the Boc and MEM protecting groups with *p*-TsOH in $CHCl_3$ afforded compound **27b** in 71% yield. Next, transamination and introduction of the dopamine moiety by Pictet–Spengler reaction gave intermediate **38** in excellent yield. Deprotection of the allyl protecting group and replacement of CN by OH with $AgNO_3$ in a mixture of CH_3CN-H_2O gave **2** (ET-729) in high yield, which had identical data upon comparison with that of a natural sample.

Synthesis of Other Natural Ecteinascidins. The

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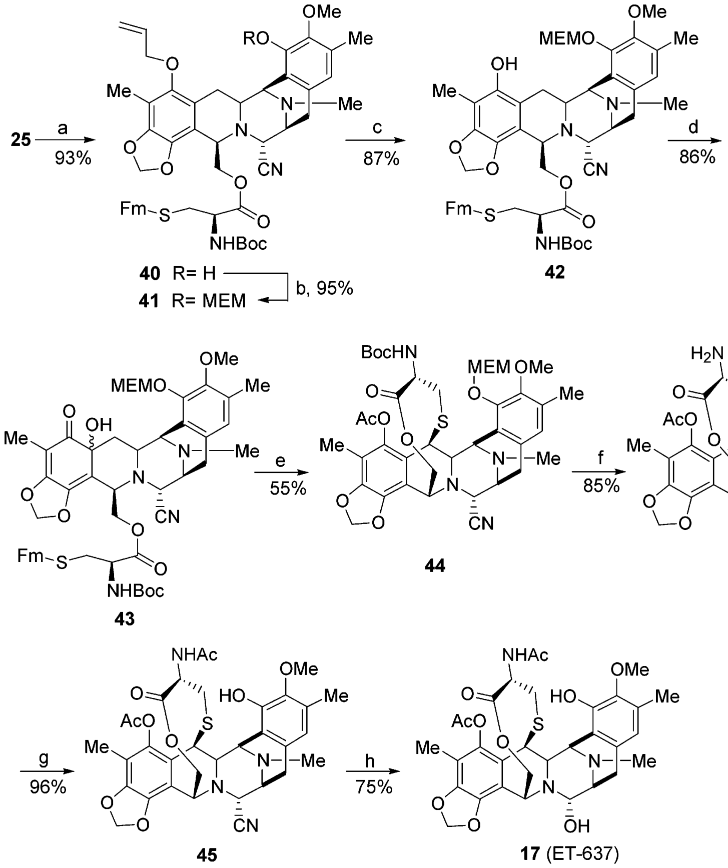
SCHEME 3. Synthesis of 17 (ET-637)[a]



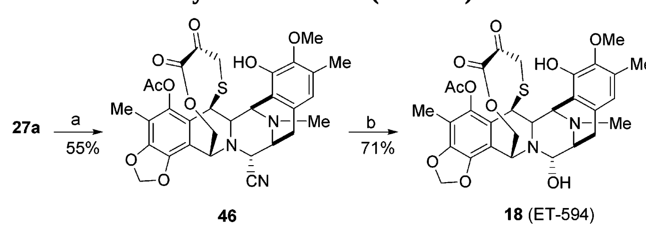
[a] Conditions: (a) L-cysteine derivative, EDC·HCl, DMAP, DIPEA, CH_2Cl_2; (b) MEMCl, NaH, THF; (c) $HSnBu_3$, AcOH, $(PPh_3)_2PdCl_2$, CH_2Cl_2; (d) $(PhSeO)_2O$, CH_2Cl_2; (e) DMSO; Tf_2O, DIPEA, *t*-BuOH, *tert*-butyltetramethyl guanidine, Ac_2O, CH_2Cl_2; (f) *p*-TsOH, $CHCl_3$; (g) Ac_2O, CH_2Cl_2; (h) CuCl, THF−H_2O.

synthesis of other natural ecteinascidins that retain the *N*-Me group can be achieved from the common intermediate **27a**. From this compound the preparation of **17** (ET-637) and **18** (ET-594) involves two additional steps while four steps produce **3** (ET-745) and **4** (ET-759B). For the synthesis of **12** (ET-736) the tryptamine moiety needs to be introduced to give the tetrahydro β-carboline ring.

Following the synthetic route (Scheme 3), we first prepared the common intermediate **27a** by esterification of **25** with protected L-cysteine to obtain **40** in 93% yield. Protection of the phenol with MEMCl and deprotection of the allyl group gave compound **42**, which was then oxidized to **43** in good yield. Cyclization of **43** under the conditions developed by Corey[6] furnished **44**. Treatment of **44** with acid to effect simultaneous deprotection of the Boc and MEM groups gave intermediate **27a** in excellent yield. With compound **27a** in hand, **17** (ET-637) was obtained in 72% yield by acetylation with Ac_2O without base to avoid protection of the free phenol. Substitution of the CN group by OH was better performed in this case with CuCl in a mixture of THF−H_2O since the reaction failed when carried out under the standard conditions with $AgNO_3$.

Ecteinascidin **18** (ET-594) was obtained from **27a** by transamination reaction with the pyridiniumcarboxaldehyde iodide, DBU, and oxalic acid to give **46**, followed by replacement of CN by OH under the same conditions used to prepare **17** (ET-637) (Scheme 4).

SCHEME 4. Synthesis of 18 (ET-594)[a]



[a] Conditions: (a) *N*-methylpyridinium-4-carboxaldehyde iodide, DBU, oxalic acid; (b) CuCl, THF−H_2O.

For the synthesis of **4** (ET-759B) (Scheme 5), we followed the same sequence that we defined previously for the synthesis of ET-743. We introduced the dopamine residue through a Pictet−Spengler reaction to give **7** (ET-770), followed by oxidation of the sulfide with MCPBA to give compound **47** as single isomer in 90% yield. The synthesis of **4** (ET-759B) was finally completed by treatment of **47** with $AgNO_3$. The reduction of **1** (ET-743) with sodium cyanoborohydride proceeded smoothly to give **3** (ET-745) in 77% yield.

Finally, to synthesize **12** (ET-736) we introduced the tetrahydro-β-carboline ring into compound **46** under milder conditions than those usually employed for Pictet−Spengler reaction.[16] Thus, treatment of **46** with the

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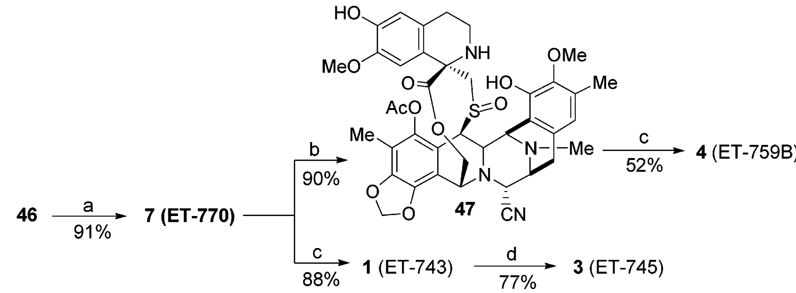
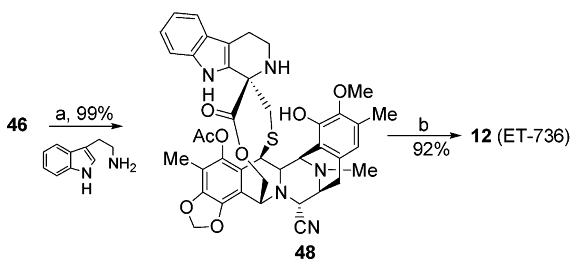
SCHEME 5. Synthesis of 4 (ET-759B) and 3 (ET-745)[a]



[a] Conditions: (a) 3-hydroxy-4-metoxyphenethylamine, silica gel, EtOH; (b) MCPBA, CH_2Cl_2; (c) $AgNO_3$, CH_3CN-H_2O; (d) $NaCNBH_3$, AcOH, CH_3CN.

SCHEME 6. Synthesis of 12 (ET-736)[a]



[a] Conditions: (a) AcOH; (b) $AgNO_3$, CH_3CN-H_2O.

tryptamine in acetic acid as solvent provided compound **48** in good yield, which was transformed into **12** (ET-736) by reaction with $AgNO_3$ (Scheme 6).

In summary we have demonstrated that the semisynthetic process developed to synthesize **1** (ET-743) is a versatile methodology that allows the preparation of a large number of natural ecteinascidins. Particularly significant is the smooth demethylation of the intermediate **29** that could allow the preparation of a wide variety of new *N*-derivatives of the ectainascidins difficult to obtain from the natural source.

Experimental Section

General Methods. Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD at 300 and 75 MHz, respectively. All air- and water-sensitive reactions were performed in flame-dried glassware under a positive pressure of argon. Analytical thin-layer chromatography was performed on silica gel 60 plates. Silica gel chromatography was performed with the indicated solvents on silica gel (type 60A, 170−400 mesh).

Compound 30. To a solution of intermediate **29** (2.51 g, 0.003 mol) in anhydrous CH_2Cl_2 (25 mL, 0.12 M) at −20 °C under Argon atmosphere was added *m*-CPBA (1.33 g, 0.006 mol). The solution was warmed to −10 °C and stirred for 25 min. TEA (4.14 mL, 0.03 mol) was added and the reaction mixture was warmed to 0 °C. Finally TFAA (6.29 mL, 0.045 mol) was added dropwise and the solution was stirred at 0 °C for 30 min. After this time water was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography (eluent mixtures of ethyl acetate/hexane in gradient from 1:4 to 6:1 and final washing with methanol) to afford intermediate **30** (2.1 g, 85%) as a yellow solid. R_f 0.19 (ethyl acetate/hexane 1:1). Mp 92−94 °C. IR (KBr, cm^{-1}) 3560, 2890, 1690, 1410, 1100. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 6.3 Hz, 2H), 7.45−7.28 (m, 8H), 6.70 (s, 1H), 6.14−6.02 (m, 1H), 5.81 (d, J = 1.2 Hz, 1H), 5.67 (d, J = 1.2 Hz, 1H), 5.43−5.35 (m, 2H), 5.26 (m, 2H), 5.03 (br s, 1H), 4.73 (br s, 1H), 4.68 (m, 1H), 4.22−4.09 (m, 3H), 3.81 (br s, 2H), 3.73 (s, 3H), 3.61 (dd, J = 2.2, 10.0 Hz, 1H), 3.53 (br s, 4H), 3.46−3.28 (m, 2H), 3.34 (s, 3H), 2.97 (d, J = 17.8 Hz, 1H), 2.25 (s, 3H), 2.11 (s, 3H), 1.95 (dd, J = 11.7, 15.4 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.13, 148.8, 147.1, 144.9, 139.4, 135.9, 135.6, 133.9, 133.6, 133.2, 132.5, 130.1, 130.0, 128.7, 127.9, 127.8, 125.6, 120.9, 119.8, 117.7, 113.9, 111.8, 101.4, 98.4, 74.5, 71.8, 70.0, 68.6, 60.7, 60.1, 59.2, 55.3, 50.1, 48.4, 30.2, 27.0, 26.0, 25.3, 21.3, 19.2, 16.2, 14.4, 9.5. MS (EI+) calcd for $C_{48}H_{57}N_3O_8Si$ (M + H) 832.4, found 832.3.

Compound 39. To a solution of intermediate **38** (30 mg, 0.038 mmol), $(PPh_3)_2PdCl_2$ (3 mg, 0.003 mmol), and acetic acid (11 mL, 0.188 mmol) in anhydrous CH_2Cl_2 (1 mL, 0.04 M) at 23 °C was added dropwise $HSnBu_3$ (36 mL, 0.13 mmol). The reaction mixture was stirred at 23 °C for 20 min. Then, the reaction mixture was poured onto a chromatography column (eluent mixtures of CH_2Cl_2/methanol with a gradient from 100/0 to 30:1) to afford intermediate **39** (12 mg, 42%) as a pale yellow solid. Some starting material (17 mg) was recovered contaminated with traces of tin byproducts. R_f 0.22 (CH_2Cl_2/methanol 20:1). Mp 186−188 °C. IR (KBr, cm^{-1}) 3420, 1740, 1520, 1450, 1210. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 6.06 (d, J = 1.2 Hz, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.03 (d, J = 11.5 Hz, 1H), 4.57 (br s, 1H), 4.50 (d, J = 5.1 Hz, 1H), 4.34 (s, 1H), 4.20 (d, J = 2.4 Hz, 1H), 4.12 (dd, J = 2.2, 11.5 Hz, 1H), 3.85 (d, J = 9.0 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.52 (d, J = 4.6 Hz, 1H), 3.15−2.95 (m, 3H), 2.77 (m, 1H), 2.60 (m, 1H), 2.46 (m, 1H), 2.35 (d, J = 14.9 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.15 (d, J = 14.9 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.1, 145.9, 145.6, 144.8, 144.5, 143.0, 141.6, 140.4, 131.5, 129.8, 129.4, 125.8, 124.6, 121.6, 121.3, 118.3, 114.33, 114.2, 109.9, 102.1, 64.8, 61.5, 60.7, 60.2, 59.2, 59.0, 55.4, 48.8, 47.9, 42.1, 39.9, 29.0, 28.3, 20. 7, 16.0, 10.0. MS (EI+) calcd for $C_{39}H_{40}N_4O_{10}S$ (M + H) 757.2, found 757.3.

Compound 2 (ET-729). To a solution of intermediate **39** (12 mg, 0.016 mmol) in MeCN (0.66 mL) and water (0.44 mL, 0.015 M, final concentration) at 23 °C was added $AgNO_3$ (81 mg, 0.47 mmol). The reaction mixture was stirred at 23 °C for 23 h protected from light. The reaction was diluted with CH_2Cl_2, a saturated solution of $NaHCO_3$, and a saturated solution of sodium chloride. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. The crude was purified by flash chromatography (eluent CH_2Cl_2/methanol in gradient from 100/0 to 3:1) to afford the final product **2** (ET-729) (8.3 mg, 70%) as a white solid. R_f 0.07 (CH_2Cl_2/methanol 95:5). $[\alpha]^{22}_D$ −51.6 (*c* 0.1, CH_2Cl_2). Mp 179−181 °C. IR (KBr, cm^{-1}) 3650, 1720, 1650, 1420, 1200. ^{1}H NMR (300 MHz, CD_3OD) δ 6.59 (s, 1H), 6.44 (s, 1H), 6.40 (s, 1H), 6.13 (s, 1H), 6.02 (s, 1H), 5.20 (d, J = 11.2 Hz, 1H), 4.73 (s, 1H), 4.58 (d, J = 4.9 Hz, 2H), 4.26 (d, J = 2.4 Hz, 1H), 4.13 (dd, $J = 2.2$, 11.5 Hz, 1H), 3.80 (br d, $J = 8.5$ Hz, 1H), 3.73 (s, 3H), 3.67 (d, $J = 4.6$ Hz, 1H), 3.59 (s, 3H), 3.22−3.02 (m, 3H), 2.78 (m, 1H), 2.59 (m, 1H), 2.42 (m, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 2.05 (m, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 173.5, 170.3, 148.1, 147.0, 146.9, 146.9, 145.0, 142.7, 141.9, 132.0, 129.3, 125.8, 122.8, 122.4, 121.4, 116.3, 115.9, 111.6, 103.5, 90.9, 65.5, 61.8, 60.4, 58.2, 57.2, 55.8, 47.3, 43.1, 40.7, 28.8, 27.8, 20.5, 16.1, 9.4. MS (EI+) calcd for $C_{38}H_{41}N_3O_{11}S$ (M + H) 748.2, found 748.1.

Compound 45. To a solution of compound **27a**[8] (520.8 mg, 0,84 mmol) in CH_2Cl_2 (17 mL, 0.05M) at 23 °C was added acetic anhydride (0.08 mL, 0.88 mmol). The reaction was stirred for 30 min and then quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. The crude was purified by flash chromatography (hexane/EtOAc, 1:2, 2:5, 1:3) affording pure compound **45** in 96% yield. R_f 0.2 (Hexane/ethyl acetate 2:3). Mp 205−207 °C. IR (KBr, cm^{-1}) 3360, 1720, 1450, 1200. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.09 (d, $J = 1.3$ Hz, 1H), 6.00 (d, $J = 1.3$ Hz, 1H), 5.78 (s, 1H), 5.52 (br d, $J = 9.0$ Hz, 1H), 5.02 (d, $J = 11.8$ Hz, 1H), 4.58 (ddd, $J = 4.3$, 6.4, 9.0 Hz, 1H), 4.53 (br s, 1H), 4.27−4.25 (m, 2H), 4.19−4.15 (m, 2H), 3.77 (s, 3H), 3.44−3.43 (m, 2H), 2.92−2.90 (m, 2H), 2.36−2.02 (m, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 168.8, 168.4, 148.1, 145.8, 143.1, 141.0, 140.3, 130.7, 129.9, 129.0, 120.3, 119.0, 117.9, 113.5, 102.0, 61.3, 60.3, 60.2, 59.3, 58.9, 54.7, 54.5, 51.9, 41.8, 41.4, 32.4, 23.7, 22.8, 20.4, 16.0, 9.5. MS (EI+) calcd for $C_{33}H_{36}N_4O_9S$ (M + H) 665.2, found 665.2.

Compound 17 (ET-637). To a solution of 1 equiv of **45** (512 mg) in THF/H_2O 4:1 (0.03M) at 23 °C was added 10 equiv of CuCl. The reaction was stirred for 24 h protected from light. After this time, the reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with CH_2Cl_2, and washed twice with saturated aqueous solutions of $NaHCO_3$ and NH_4Cl. The aqueous layers were extracted with CH_2Cl_2, and the organic layers were dried over Na_2SO_4. Flash chromatography (CH_2Cl_2/MeOH 50:1, 35:1, 20:1, 15:1, 10:1, 7:1) yielded pure compound **17** (ET-637) (75%). R_f 0.28 (CH_2Cl_2:MeOH 30:1). $[\alpha]^{22}_D$ −13.6 (*c* 0.1, CH_2Cl_2). Mp 151−153 °C. IR (KBr, cm^{-1}) 3400, 1750, 1650, 1190. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.07 (d, $J = 1.5$ Hz, 1H), 5.96 (d, $J = 1.5$ Hz, 1H), 5.79 (br s, 1H), 5.60 (br d, $J = 8.7$ Hz, 1H), 5.15 (d, $J = 10.2$ Hz, 1H), 4.77 (s, 1H), 4.56 (m, 1H), 4.46−4.43 (m, 2H), 4.15 (d, $J = 3.3$ Hz, 1H), 4.09 (dd, $J = 2.1$, 11.4 Hz, 1H), 3.77 (s, 3H), 3.49−3.47 (m, 1H), 3.23−3.20 (m, 1H), 2.91−2.76 (m, 2H), 2.31−2.11 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 168.8, 168.5, 148.0, 145.6, 143.0, 141.0, 140.7, 131.5, 128.8, 120.9, 120.6, 118.9, 115.2, 112.7, 101.8, 81.5, 61.6, 60.2, 57.7, 57.4, 55.9, 55.0, 52.1, 52.0, 41.3, 32.4, 23.6, 22.9, 20.5, 16.1, 9.5. MS (EI+) calcd for $C_{32}H_{37}N_3O_{10}S$ (M − H_2O + H) 638.2, found 638.1.

Compound 18 (ET-594). To a solution of compound **46**[8] (100 mg, 0.16 mmol) in a mixture THF/H_2O (4.26 mL/ 1.06 mL, 0.03 M) at 23 °C was added CuCl (79.5 mg, 0.80 mmol). The reaction was protected from light and stirred for 24 h. The reaction was then diluted with CH_2Cl_2 and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was decanted and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, the organic layers were combined and dried over Na_2SO_4, and the solvent was eliminated under reduced pressure. The crude was purified by flash chromatography (eluent CH_2Cl_2/MeOH 60:1) to afford **18** (ET-594) (70 mg, 71%) as a yellow solid. R_f 0.44 (CH_2Cl_2/MeOH 60:1). $[\alpha]^{22}_D$ −44.7 (*c* 0.1, CH_3OH). Mp 188−190 °C. IR (KBr, cm^{-1}) 3450, 2950, 1720, 1650, 1420, 1150. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.49 (s, 1H), 6.07 (s, 1H), 6.05 (s, 1H), 5.98 (s, 1H), 5.94 (s, 1H), 5.71 (s, 2H), 5.18 (d, $J = 11.1$ Hz, 1H), 5.12 (d, $J = 11.7$ Hz, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 4.55−4.36 (m, 3H), 4.17−4.11 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H), 3.58 (d, $J = 4.8$ Hz, 1H), 3.47 (s, 4H), 3.19 (s, 2H), 3.07 (s, 3H), 2.87−2.54 (m, 6H), 2.31 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 2.18−2.05 (m, 2H), 2.15 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 170.2, 170.1, 168.9, 160.8, 148.0, 147.3, 146.3, 143.2, 143.1, 141.8, 141.3, 141.2, 141.0, 131.4, 131.3, 129.8, 129.6, 122.0, 121.9, 121.2, 121.0, 120.9, 117.9, 117.2, 115.5, 114.7, 102.2, 102.1, 102.0, 82.2, 81.8, 63.4, 60.5, 60.4, 58.1, 58.0, 57.9, 56.4, 56.2, 55.1, 55.0, 51.4, 41.6, 41.5, 37.0, 31.8, 29.9, 24.3, 24.0, 22.9, 20.7, 20.6, 20.5, 16.0, 15.9, 14.3, 9.9, 9.8. MS (EI+) calcd for $C_{30}H_{32}N_2O_{10}S$ (M − H_2O + H) 595.1, found 595.5.

Compound 47. To a solution of **7**[8] (ET-770) (45 mg, 0.058 mmol) in CH_2Cl_2 (3 mL, 0.03 M) at 0 °C was added *m*-CPBA (15.1 mg, 0.087 mmol). The reaction was stirred at 0 °C for 30 min. Then a saturated aqueous solution of $NaHCO_3$ was added and then the aqueous phase was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography (eluent: ethyl acetate/hexane 3:1) to afford compound **47** (45.6 mg, 90%). R_f 0.18 (ethyl acetate/hexane 2:1). Mp 190−192 °C. IR (KBr, cm^{-1}) 3300, 1680, 1520, 1450. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.51 (s, 1H), 6.47 (s, 1H), 6.19 (s, 1H), 6.05 (s, 1H), 6.00 (s, 1H), 4.66 (d, $J = 4.5$ Hz, 1H), 4.61 (d, $J = 11.7$ Hz, 1H), 4.30−4.28 (m, 1H), 4.19 (s, 1H), 4.07 (s, 1H), 3.82 (s, 1H), 3.73 (d, $J = 4.2$ Hz, 1H), 3.65 (d, $J = 15.0$ Hz, 1H), 3.60 (s, 3H), 3.43 (d, $J = 15.0$ Hz, 1H), 3.04−2.95 (m, 2H), 2.88−2.81 (m, 1H), 2.72−2.55 (m, 3H), 2.48−2.41 (m, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 169.2, 148.2, 146.8, 146.3, 145.1, 144.8, 142.3, 140.8, 130.8, 129.6, 129.5, 124.5, 122.6, 120.2, 120.0, 117.8, 114.6, 111.8, 109.5, 102.4, 70.9, 67.8, 61.8, 61.7, 60.9, 60.6, 60.0, 55.3, 54.9, 54.7, 41.9, 40.0, 29.9, 29.1, 25.0, 21.0, 16.2, 10.3. MS (EI+) calcd for $C_{40}H_{42}N_4O_{11}S$ (M + Na) 809.2, found 809.3.

Compound 4 (ET-759B). To a solution of compound **47** (45 mg, 0.057 mmol) in a mixture of CH_3CN/H_2O (6 mL/ 2 mL, 0.007 M) at 23 °C was added $AgNO_3$ (287.1 mg, 1.71 mmol). The reaction mixture was protected from light and stirred for 24 h. The reaction was then diluted with CH_2Cl_2 and quenched with a 1:1 mixture of saturated aqueous solutions of $NaHCO_3$ and brine. The aqueous phase was extracted with CH_2Cl_2, the organic layers were dried over Na_2SO_4, and the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography to afford **4** (ET-759B) (23.2 mg, 52%) as a pale yellow solid. Starting material (18.7 mg, 42%) was also recovered. R_f 0.36 (CH_2Cl_2/MeOH 8:0.5). $[\alpha]^{22}_D$ −148.3 (*c* 0.1, CH_2Cl_2). Mp 176−178 °C. IR (KBr, cm^{-1}) 3300, 1710, 1400, 1250, 1100. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 6.20 (s, 1H), 6.04 (s, 1H), 5.97 (s, 1H), 4.78 (s, 1H), 4.70 (d, $J = 10.8$ Hz, 1H), 4.55 (d, $J = 4.5$ Hz, 1H), 4.36 (d, $J = 3.3$ Hz, 1H), 4.21 (dd, $J = 1.8$, 10.8 Hz, 1H), 4.07−3.98 (m, 1H), 3.83 (s, 3H), 3.77 (d, $J = 4.5$ Hz, 1H), 3.69−3.63 (m, 1H), 3.61 (s, 3H), 3.46 (d, $J = 4.5$ Hz, 1H), 3.22 (d, $J = 7.5$ Hz, 1H), 3.06−2.82 (m, 4H), 2.66−2.43 (m, 4H), 2.31 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 169.3, 148.0, 146.9, 145.0, 144.7, 142.2, 141.0, 130.7, 130.1, 129.6, 124.9, 123.0, 120.9, 120.1, 114.6, 113.7, 109.5, 102.2, 82.9, 67.9, 63.1, 61.8, 60.5, 57.7, 57.6, 55.9, 55.3, 55.1, 41.7, 40.0, 29.9, 29.2, 24.7, 21.0, 16.1, 14.3, 10.2. MS (EI+) calcd for $C_{39}H_{43}N_3O_{12}S$ (M − H_2O + H) 760.8, found 760.2.

Compound 3 (ET-745). To a solution of **1**[8] (ET-743) (75 mg, 0.1 mmol) in acetonitrile (5 mL, 0.02 M) at 23 °C were added acetic acid (85 mL, 0.3 mmol) and $NaCNBH_3$ (166 mg, 2.65 mmol). The solution was stirred at 23 °C for 30 min. Then a saturated aqueous solution of $NaHCO_3$ was added and then aqueous phase was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and the solvent was eliminated under reduced pressure. The resulting crude was purified by flash column chromatography ($CHCl_3$/EtOAc/MeOH 49:49:2) to afford **3** (ET-745) (15.8 mg, 64%). R_f 0.17 ($CHCl_3$/EtOAc/MeOH 49:49:2). $[\alpha]^{22}_D$ −73.4 (*c* 0.1, CH_2Cl_2). Mp 219−221 °C. IR (KBr, cm^{-1}) 3400, 1750, 1680, 1200. ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.49 (s, 1H), 6.42 (s, 1H), 6.00 (d, J = 1.2 Hz, 1H), 5.95 (d, J = 1.2 Hz, 1H), 5.10 (d, J = 11.4 Hz, 1H), 4.50 (br s, 1H), 4.38 (d, J = 3.9 Hz, 1H), 4.09 (d, J = 9.3 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.38−3.21 (m, 3H), 3.17−2.81 (m, 5H), 2.71 (m, 1H), 2.52 (m, 2H), 2.41 (d, J = 13.8 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 2.12 (m, 1H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 168.19, 147.7, 144.8, 144.6, 144.50, 142.6, 141.0, 139.7, 131.6, 128.6, 126.1, 122.1, 120.5, 118.5, 115.4, 114.5, 112.6, 109.9, 101.4, 64.2, 64.0, 62.2, 60.8, 60.0, 55.0, 42.4, 41.7, 40.7, 39.3, 31.4, 29.5, 28.5, 25.4, 22.4, 20.3, 15.6, 13.9, 9.4. MS (EI+) calcd for $C_{39}H_{43}N_3O_{10}S$ (M + H) 746.3, found 746.2.

Compound 48. To a solution of 1 equiv (75 mg) of **46**[8] in acetic acid (1.5 mL) at room temperature was added tryptamine (3.5 equiv, 67.8 mg). The reaction mixture was stirred for 24 h and then the acetic acid was evaporated. $NaHCO_3$ saturated aqueous solution was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4. Flash chromatography afforded pure compound **48** (90 mg) in 99% yield. R_f 0.4 (hexane/ethyl acetate 2:3). Mp 215−217 °C. IR (KBr, cm^{-1}) 3650, 3400, 1710, 1520, 1200. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 6.9 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.66 (s, 1H), 6.22 (d, J = 1.2 Hz, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.79 (s, 1H), 5.08 (d, J = 11.7 Hz, 1H), 4.55 (s, 1H), 4.32 (s, 1H), 4.27 (d, J = 3.9 Hz, 1H), 4.21 (s, 1H), 4.19 (d, J = 11.7 Hz, 1H), 3.81 (s, 3H), 3.44−3.40 (m, 2H), 3.18−2.78 (m, 4H), 2.71−2.51 (m, 3H), 2.37 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 168.9, 148.2, 145.9, 143.2, 141.3, 140.5, 135.7, 130.8, 130.6, 129.5, 127.0, 122.2, 120.9, 120.8, 119.5, 118.6, 118.4, 113.8, 111.1, 110.5, 102.2, 62.5, 61.5, 60.8, 60.5, 59.7, 55.9, 54.8, 42.1, 41.7, 40.0, 39.5, 29.9, 24.0, 21.7, 20.8, 16.1, 9.9. MS (EI+) calcd for $C_{41}H_{41}N_5O_8S$ (M − H_2O + H) 763.8, found 764.2.

Compound 12 (ET-736). To a solution of 1 equiv (94 mg) of **48** in a mixture of CH_3CN/H_2O (3:2) (6.5 mL) was added $AgNO_3$ (30 equiv, 619 mg). The reaction mixture was protected from light and stirred for 24 h at 23 °C. The mixture was diluted with a 1:1 mixture of saturated aqueous solutions of brine and $NaHCO_3$ and stirred for 10 min. After dilution with CH_2Cl_2, the organic layer was separated and dried over Na_2SO_4. Purification by flash chromatography afforded pure compound **12** (ET-736) (85.4 mg) in 92% yield. R_f 0.5 (CH2Cl2:MeOH 8:1). $[\alpha]^{22}_D$ −19.3 (*c* 0.1, CH_2Cl_2). Mp 170−172 °C. IR (KBr, cm^{-1}) 3600, 1720, 1520, 1150, 1100. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.67 (s, 1H), 6.20 (d, J = 1.2 Hz, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.74 (s, 1H), 5.20 (d, J = 11.4 Hz, 1H), 4.82 (s, 1H), 4.34−4.38 (m, 3H), 4.16−4.10 (m, 2H), 3.81 (s, 3H), 3.49 (d, J = 4.5 Hz, 1H), 3.22−3.13 (m, 2H), 3.00 (d, J = 18.0 Hz, 1H), 2.88−2.79 (m, 2H), 2.71−2.52 (m, 3H), 2.37 (s, 3H), 2.28−2.24 (m, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 168.7, 147.8, 145.4, 142.8, 141.0, 140.6, 135.4, 131.2, 130.9, 129.0, 126.8, 121.8, 121.3, 120.9, 119.1, 118.3, 118.1, 115.5, 112.8, 110.8, 110.1, 101.7, 81.9, 62.3, 61.8, 60.2,57.6, 57.4, 55.8, 54.9, 42.1, 41.2, 39.7, 39.2, 31.5, 23.5, 22.6, 21.5, 20.5, 15.8, 14.0, 9.6. MS (EI^+) calcd for $C_{40}H_{42}N_4O_9S$ (M − H_2O + H) 737.8, found 737.2.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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