Chemistry of Ecteinascidins. Part 2.[1] Preparation of 6′-*O*-Acyl Derivatives of Stable Ecteinascidin and Evaluation of Cytotoxicity

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A large amount of stable ecteinascidin 770 (1b) was isolated from the Thai tunicate, *Ecteinascidia thurstoni*, which was pretreated with potassium cyanide in buffer solution (pH 7), along with a minor metabolite, ecteinascidin 786 (1c). A number of 6′-*O*-acyl derivatives 3—19 and three diacetyl derivatives 2a—c of the stable 1b were prepared and evaluated for activity against human tumor cell lines HCT116, QG56, and DU145. Nitrogen-containing heterocyclic ester derivatives such as 12, 13, and 16—19 showed similar *in vitro* cytotoxicity to 1b, whereas the other derivatives were less cytotoxic than 1b. Furthermore, we discovered that the *N*-indole-3-carbonyl derivative of ecteinascidin 770 (22) has higher cytotoxicity than 1b.

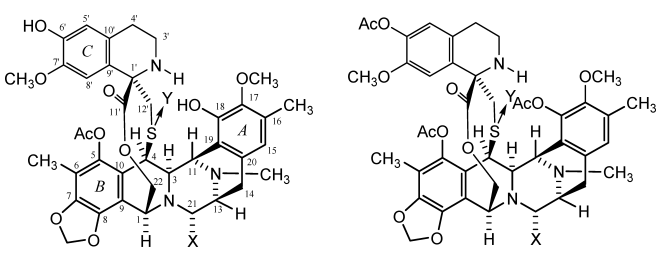
Key words ecteinascidin 770; acyl derivative; cytotoxicity; *Ecteinascidia thurstoni*

Ecteinascidin 743 (**1a**)[2] is an exceedingly potent and rare marine-derived antitumor compound isolated from the Caribbean tunicate *Ecteinascidia turbinata*,[3] and is currently being studied in phase II/III clinical trials for ovarian, breast, endometrial, prostate, and pediatric cancers.[4] Its novel structure, combined with meager availability from nature and unique mechanism of action, has made **1a** a very attractive and important synthetic target. The first complete synthetic route to **1a** was accomplished by Corey and coworkers,[5,6] and this strategy has subsequently enabled its large-scale preparation.[7,8] In addition, two independent groups, Fukuyama *et al.*[9] and Zhu *et al.*,[10] were able to design synthetic routes to **1a**. Ecteinascidin 743 is the first of a new class of DNA binding agents having a complex transcription-targeted mechanism of action. Although the detailed molecular mechanism of action remains unclear, **1a** was reported to induce the DNA-sequence-selective alkylation of guanine *N*2 in a minor groove of duplex DNA.[11] Interestingly, the *C*-subunit, which is perpendicular to the combined *AB*-subunit, is responsible for the propeller-like character of pentacyclic natural products, such as saframycins and renieramycins,[12] both of which are fairly flat molecules. It was postulated that this bending structure of **1a** disrupts DNA-protein binding and may be responsible for the enhanced biological activities of ecteinascidins.[13,14] We succeeded in isolating the stable ecteinascidin 770 (**1b**) along with ecteinascidin 786 (**1c**) from the Thai tunicate, *Ecteinascidia thurstoni*, which was pretreated with potassium cyanide in buffer solution.[1] The availability of **1b** enabled us to prepare ecteinascidin analogs having increased antitumor activity and broadened spectrum. In this work, we focused on the conversion of **1b** into corresponding aromatic ester derivatives **3**—**19** along with diacetates **2a**—**c**.

Results and Discussion

According to the procedure for the acetylation of **1a** to the corresponding acetate in a published patent,[15] we treated **1b** with acetic anhydride in pyridine to give **2b** in 82% yield (Fig. 1). Oxidation of **1b** with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane gave ecteinascidin 786 (**1c**) in 92% yield.[16] Treatment of **1c** with acetic anhydride in pyridine afforded **2c** in 78% yield. Compound **2a** was obtained by reacting **2b** with $AgNO_3$ in 41% yield, along with the recovery of **2b** in 46% yield. In the primary screening for *in vitro* cytotoxicity, three human solid tumor cell lines (HCT116 colon carcinoma, QG56 lung carcinoma, and DU145 prostate carcinoma) were used. As shown in Table 1, diacetyl derivatives **2a**—**c** possessed low cytotoxicity relative to **1b**. Oxidation of the sulfide group of ecteinascidins resulted in dramatically diminished cytotoxicity.

Next, we examined the transformation of **1b** into the corresponding aromatic ester derivatives. In contrast with the acetylation of **1b** as above, treatment of **1b** with benzoyl chloride and a catalytic amount of 4-dimethylaminopyridine (DMAP) in pyridine afforded mainly monoacylated compound **3** in 88% yield (Fig. 2). In addition, fourteen monoacyl derivatives (**4**—**17**) of **1b**, including substituted benzoyl, pyridinoyl, naphthoyl, and quinolinoyl, were obtained in a similar manner in 66—99% yields. No isoquinolinoyl derivatives **18** and **19** were obtained from **1b** with the corresponding acid chloride in the same manner; however, these com-



ecteinascidins
743 (**1a**): X = OH, Y = none
770 (**1b**): X = CN, Y = none
786 (**1c**): X = CN, Y = O

2a: X = OH, Y = none
2b: X = CN, Y = none
2c: X = CN, Y = O

Fig. 1. Structure of Ecteinascidin Natural Marine Products and Their Diacetates

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pounds were obtained by treating **1b** with corresponding mixed anhydrides **20a** and **20b**, in 65% and 85% yields, respectively.[17] All compounds were characterized by IR, mass, and NMR measurements.

The assignment of acyl substituents at C-6′ in the *C*-subunit of monoacyl derivatives **3**—**19** was made by NMR analysis. Prior to the determination of aromatic ester orientation for **1b**, all proton and carbon signals of **2b** were assigned using H–H, H–C COSY, and a series of ^{1}H detected two-dimensional heteronuclear multiple-bond correlation (HMBC) experiments, as shown in Table 2. The signal of aromatic C-6′ carbon was shifted upfield, whereas the signals of C-5′, C-7′, and C-9′ carbons were shifted downfield compared with those of **1b**. In the *A*-subunit, the signals of C-15 and C-19 carbons were shifted downfield compared with that of **1b**. The ^{13}C-NMR spectral data of the mononitrobenzoyl derivative **4** and **1b** revealed three major differences. The signals of C-5′, C-7′ and C-9′ quaternary carbons of **4** were shifted downfield to δ 122.3 ppm, δ 148.3 ppm, and δ 133.2 ppm compared with those of **1b** (δ 114.2 ppm, δ 144.7 ppm, and δ 125.8 ppm, respectively). On the other hand, the signal of C-6′ carbon of **4** was shifted upfield to δ 138.6 ppm compared with that of **1b** (δ 144.6 ppm). The above information revealed 6′-*O*-acylation in **4**. Furthermore, the 18-OH proton signal of **4** at δ 5.76 ppm showed long-range correlations with C-17 (δ 143.1 ppm), C-18 (δ 147.9 ppm), and C-19 (δ 118.2 ppm). Together, these data confirmed that the free OH group at C-18 in **4** might be oriented. The cytotoxicites of **4**—**6** that possessed a nitro group on the benzene ring, and those of **10** and **11** that possessed a methoxy group on the benzene ring, were similar to that of **1b** against all the cell lines investigated. On the other hand, **7**—**9** and **14**—**15**, which possessed, respectively, a bromo group on the benzene ring and a naphthoyl group, showed significantly decreased cytotoxicity. This reduction of cytotoxicity might be due to steric hindrance. It is noteworthy that nitrogen-containing heterocycles **12**, **13**, **16**—**19** had high cytotoxicity. Thus, we were interested in the preparation of other esters such as **21** (Fig. 3). However, numerous efforts aimed at transforming of **1b** into **21** were unsuccessful, and only starting material **1b**

Table 1. Cytotoxicity of Ecteinascidin 770 Acylated Compounds to Various Cancer Cell Lines (IC_{50} nM)[a]

Compound	HCT116	QG56	DU145
2a	1.4	8.3	4.4
2b	1.3	9.5	4.4
2c	160	220	200
3	0.68	3.2	1.1
4	0.26	0.96	0.37
5	0.49	3.3	1.6
6	1.9	7.1	2.7
7	15	36	16
8	7.1	39	11
9	4.2	19	7.6
10	0.31	1.7	0.62
11	0.62	3.6	1.1
12	0.20	1.0	0.51
13	0.15	0.87	0.48
14	13	36	24
15	6.3	24	12
16	0.41	2.4	0.95
17	2.1	9.5	4.5
18	0.64	1.9	0.83
19	0.62	2.1	1.5
22	0.07	0.53	0.37
1b (ecteinascidin 770)	0.40	1.8	0.66

a) HCT116=human colon carcinoma; QG56=human lung carcinoma; DU145=human prostate carcinoma.

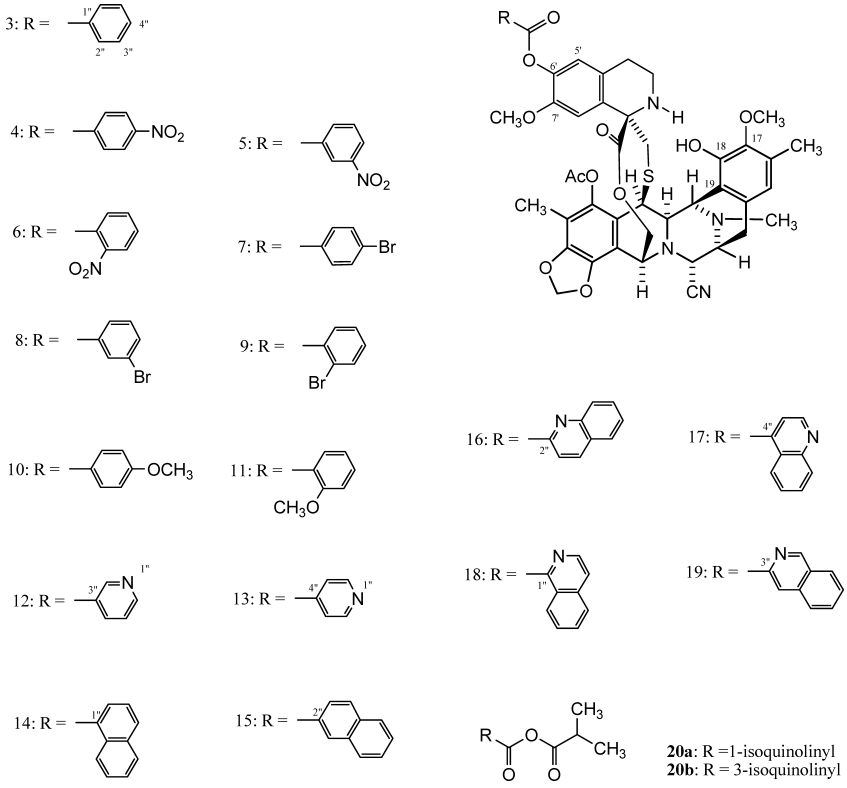
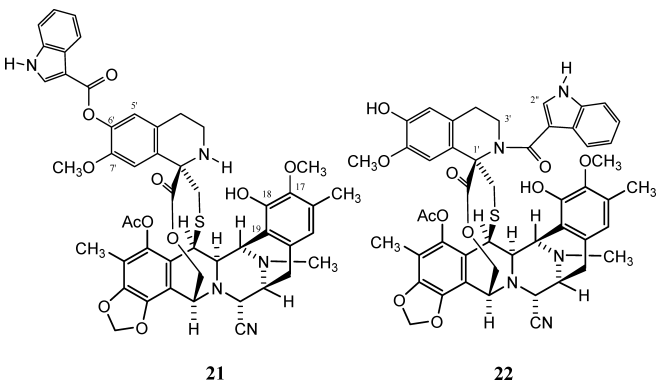


Fig. 2. 6′-*O*-Acyl Derivatives of the Ecteinascidin

Table 2. NMR Data for Core Structures of **1b**, **2b**, **4**, and **22** in $CDCl_3$

Position	**2b**		**4**		**22**		**1b**	
	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C
1	4.34 s	61.1	4.35 s	61.1	4.36 s	60.7	4.32 s	61.2
3	3.52 d (4.6)	59.6	3.53 d (4.6)	59.6	3.50 d (4.9)	61.1	3.51 d (4.9)	59.7
4	4.44 br s	42.1	4.59 br s	42.0	4.62 br s	41.8	4.57 br s	41.9
5		141.3		141.4		141.4		141.4
6		113.6		113.5		113.3		113.4
7		145.6		145.4		145.7		145.3
8		140.4		140.1		141.3		140.2
9		113.9		114.0		113.7		114.1
10		120.8		121.0		122.4		121.2
11	3.83 d (4.6)	55.8	4.29 d (3.7)	54.7	4.20 dd (5.0, 1.4)	54.9	4.28 dd (4.9, 1.2)	54.8
13	3.46 dt (4.9, 2.8)	54.4	3.43 br t	54.6	3.35 br t	54.9	3.41 br t	54.7
14	2.99 d (4.9)	24.0	2.96 d (6.1)	24.2	2.85 d (6.1)	24.9	2.91 d (7.6)	24.2
15	6.95 s	127.3	6.61 s	120.7	5.41 s	121.4	6.60 s	120.7
16		130.6		129.4		129.0		129.4
17		143.8		143.1		142.7		143.1
18		148.0		147.9		147.0		147.9
19		124.3		118.2		117.3		118.4
20		131.5		130.8		129.7		130.8
21	4.18 d (2.8)	59.2	4.19 d (2.7)	59.6	4.19 d (2.7)	59.8	4.18 d (2.8)	59.6
22	5.02 d (11.3)	60.1	5.04 d (11.6)	60.2	4.62 d (11.3)	60.3	5.01 d (11.6)	60.1
	4.12 dd (11.3, 2.2)		4.14 dd (11.6, 2.2)		4.54 dd (11.3, 1.8)		4.12 dd (11.6, 2.0)	
1′		65.0		64.9		70.2		64.9
3′	3.12 m	39.6	3.15 m	39.5	4.00 m	38.5	3.11 m	39.7
	2.83 m		2.83 m		2.49 m		2.79 m	
4′	2.65 m	28.5	2.67 m	29.6	2.49 m	29.7	2.60 m	28.8
	2.49 m		2.52 m		2.28 m		2.42 dt (15.9, 3.4)	
5′	6.62 s	122.6	6.75 s	122.3	6.40 m	113.7	6.46 s	114.2
6′		138.6		138.6		144.7		144.6
7′		148.5		148.3		144.6		144.7
8′	6.54 s	111.6	6.64 s	111.9	6.48 s	110.5	6.44 s	109.9
9′		132.3		133.2		127.5		125.8
10′		128.7		128.8		127.6		129.2
11′		172.0		172.0		170.6		172.6
12′	2.33 br d	42.4	2.34 br d	42.3	3.94 d (11.3)	46.6	2.35 br d	42.3
	2.24 br d		2.21 br d		3.47 br d		2.15 br d	
OCHO	6.04 s	102.0	6.02 d (0.9)	101.9	6.09 d (1.5)	101.9	6.04 d (1.2)	102.0
	5.98 s		5.96 d (0.9)		5.99 d (1.5)		5.97 d (1.2)	
21-CN		117.8		118.0		118.3		118.7
NCH_3	2.16 s	41.5	2.21 s	41.6	2.09 s	41.6	2.19 s	41.6
6-CH_3	2.04 s	9.6	2.03 s	9.7	2.05 s	9.8	2.04 s	9.7
16-CH_3	2.33 s	15.8	2.33 s	15.8	1.14 s	14.2	2.32 s	15.8
17-OCH_3	3.72 s	60.1	3.80 s	60.3	3.57 s	59.8	3.78 s	60.4
7′-OCH_3	3.56 s	55.6	3.55 s	55.2	3.71 s	55.3	3.60	55.2
5-OCO$\underline{C}H_3$	2.30 s	20.2	2.27 s	20.4	2.30 s	20.4	2.26 s	20.4
5-O$\underline{C}OCH_3$		167.9		168.2		168.2		168.2
18-OH			5.76 br s		5.61 br s		5.77 br s	
6′-OH					5.41 s		5.59 s	



21 **22**

Fig. 3. Structure of Compound **21** and **22**

was recovered.

Finally, we prepared *N*-indole-3-carbonyl derivative **22**. Coupling of **1b** with indole-3-carboxylic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) provided amide **22** in 65% yield. The major differences in the ^{13}C-NMR spectral data between **22** and **1b** were the downfield shifts of the signals of carbons adjacent to the nitrogen atom in the *C*-subunit, namely, from δ 64.9 ppm (C-1′) and δ 42.3 ppm (C-12′) for **1b** to δ 70.2 ppm and δ 46.6 ppm for **22**, respectively. The characteristic upfield shifts of the *A*-subunit protons of **22** at δ 5.41 ppm (15-H), δ 3.37 ppm (17-OCH_3), and δ 1.14 ppm (16-CH_3) confirmed that these protons lie in the ring current of the indole ring (see Table 2). This compound showed very high cytotoxicity to the three human tumor cell lines *in vitro*. Further evaluation of **22** and synthetic efforts

aimed at other analogs related to **22** are under way.[18)]

Experimental

Optical rotations were recorded on a Horiba-SEPA polarimeter. IR spectra were measured on a Shimadzu FT-IR 8200PC spectrophotometer. ^{1}H-, ^{13}C-NMR, COSY, HMBC, and NOESY spectra were recorded on a JEOL JNM-LA-500 FT-NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C, and on a JEOL JNM-EX 270 spectrometer at 270 MHz for ^{1}H and 67.5 MHz for ^{13}C, using TMS as internal standard. The chemical shifts are given in δ (ppm) and coupling constants, in Hz. Mass spectra were recorded on a JMS 700 instrument with a direct inlet system operating at 70 eV. All reactions were conducted under argon atmosphere. Dry solvents and reagents were obtained using standard preparations. Removal of solvent was accomplished with a rotary evaporator and finally under high vacuum. Column chromatography was performed with silica gel 60 (Merck).

Extraction and Isolation *Ecteinascidia thurstoni* was collected by scuba divers at the east coast of Phuket Island at a depth of 1—5 m in four separate sampling periods from October 2002 to June 2003, and the combined animals were frozen until used. The frozen-animals (totally 136.4 kg, wet weight) were homogenized and phosphate buffer solution was added until the pH reached 7. Then, 10% potassium cyanide solution was added very slowly to the suspension, and the mixture was stirred for 5 h and extracted with methanol. After performing usual extraction and purification 1.426 g and 435.5 mg of ecteinascidins 770 (**1b**) and 786 (**1c**) were obtained, respectively.

Conversion of 1b into 1c Ecteinascidin 770 (**1b**, 30.8 mg, 0.04 mmol) was dissolved in dichloromethane (3.0 ml), and *m*-CPBA (80%, 9.5 mg, 0.044 mmol, 1.1 eq) was added slowly to the solution. After stirring at 0 °C for 30 min, the mixture was diluted with water (30 ml) and extracted with dichloromethane (20 ml×3). The combined extracts were washed successively with 5% $NaHCO_3$ solution and water, dried, and concentrated *in vacuo* to give a residue. Chromatography on a silica gel column with hexane–ethyl acetate (1 : 3) as the eluent solvent gave **1c** (29.0 mg, 92%) as a solid, which was identical in all respects with the authentic sample.[1)]

Diacetylecteinascidin 770 (2b) Acetic anhydride (4.7 μl, 0.05 mmol) was added to a stirred solution of **1b** (7.7 mg, 0.01 mmol) and DMAP (0.6 mg, 0.005 mmol) in pyridine (1.0 ml) at 0 °C, and the resulting solution was stirred for 4 h at 25 °C. After the solvent was removed *in vacuo*, the residue was diluted with water (10 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a solid (10.7 mg). Chromatography on a silica gel column with hexane–ethyl acetate (4 : 1) as eluent gave **2b** (7.3 mg, 82%) as a pale yellow solid. ^{1}H-NMR δ: 6.95 (1H, s, 15-H), 6.62 (1H, s, 5′-H), 6.54 (1H, s, 8′-H), 6.04 and 5.98 (each 1H, s, OCHO), 5.02 (1H, d, J=11.3 Hz, 22-H), 4.44 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.18 (1H, d, J=2.8 Hz, 21-H), 4.12 (1H, dd, J=11.3, 2.2 Hz, 22-H), 3.83 (1H, d, J=4.6 Hz, 11-H), 3.72 (3H, s, 17-OCH$_3$), 3.56 (3H, s, 7′-OCH$_3$), 3.52 (1H, d, J=4.6 Hz, 3-H), 3.46 (1H, dt, J=4.9, 2.8 Hz 13-H), 3.12 (1H, m, 3′-H), 2.99 (2H, d, J=4.9 Hz, 14-H$_2$), 2.83 (1H, m, 3′-H), 2.65 (1H, m, 4′-H), 2.49 (1H, m, 4′-H), 2.37 (3H, s, OCOCH$_3$), 2.33 (1H, br, 12′-H)*, 2.33 (3H, s, 16-CH$_3$), 2.30 (3H, s, OCOCH$_3$), 2.24 (3H, s, OCOCH$_3$), 2.24 (1H, m, 12′-H)*, 2.16 (3H, s, NCH$_3$), 2.04 (3H, s, 6-CH$_3$) (* the signals overlapped with the methyl signals). ^{13}C-NMR δ: 172.0 (11′-CO), 169.0 (s, OCOCH$_3$), 168.4 (s, OCOCH$_3$), 167.9 (s, OCOCH$_3$), 148.5 (C-7′), 148.0 (C-18), 145.6 (C-7), 143.8 (C-17), 141.3 (C-5), 140.4 (C-8), 138.6 (C-6′), 132.3 (C-9′), 131.5 (C-20), 130.6 (C-16), 128.7 (C-10′), 127.3 (C-15), 124.3 (C-19), 122.6 (C-5′), 120.8 (C-10), 117.8 (21-CN), 113.9 (C-9), 113.6 (C-6), 111.6 (C-8′), 102.0 (OCH$_2$O), 65.0 (C-1′), 61.1 (C-1), 60.1 (C-22), 60.1 (17-OCH$_3$), 59.6 (C-3), 59.2 (C-21), 55.8 (C-11), 55.0 (7′-OCH$_3$), 54.4 (C-13), 42.4 (C-12′), 42.1 (C-4), 41.5 (NCH$_3$), 39.6 (C-3′), 28.5 (C-4′), 24.0 (C-14), 20.6 (OCOCH$_3$), 20.6 (OCOCH$_3$), 20.2 (OCOCH$_3$), 15.8 (16-CH$_3$), 9.6 (6-CH$_3$). IR (KBr) cm^{-1}: 3855, 2932, 2816, 1767, 1618, 1433, 1371, 1560, 1514, 1321, 1263, 1198, 1088, 1028. HR-FAB-MS m/z 855.2913 [M+H]$^+$ (Calcd for $C_{44}H_{47}N_4O_{12}S$, 855.2911). FAB-MS (Glycerol) m/z 855 [(M+H)$^+$]. $[\alpha]_D^{19}$ −37.6° (c=0.56, $CHCl_3$).

Diacetylecteinascidin 786 (2c) Using the same procedure as that described above, ecteinascidin 786 (**1c**, 7.9 mg, 0.01 mmol) was acetylated to give **2c** (6.8 mg, 78%) as a pale yellow solid. ^{1}H-NMR δ: 6.93 (1H, s, 15-H), 6.65 (1H, s, 5′-H), 6.45 (1H, s, 8′-H), 6.08 and 6.02 (each 1H, s, OCHO), 4.92 (1H, d, J=11.9 Hz, 22-H), 4.42 (1H, s, 1-H), 4.26 (1H, dd, J=11.9, 2.2 Hz, 22-H), 4.20 (1H, dd, J=4.9, 1.2 Hz, 11-H), 4.16 (1H, d, J=2.6 Hz, 21-H), 4.02 (1H, br s, 4-H), 3.84 (3H, s, 17-OCH$_3$), 3.68 (1H, m, 3-H), 3.56 (3H, s, 7′-OCH$_3$), 3.50 (1H, m, 13-H), 3.07 (2H, d, J=5.3 Hz, 14-H$_2$), 3.01 (1H, br t, 3′-H), 2.80 (1H, m, 3′-H), 2.74 (1H, m, 4′-H), 2.51 (1H, m, 4′-H), 2.38 (3H, s, OCOCH$_3$), 2.33 (1H, br, 12′-H)*, 2.33 (3H, s, 16-CH$_3$), 2.28 (3H, s, OCOCH$_3$), 2.26 (3H, s, OCOCH$_3$), 2.24 (1H, m, 12′-H)*, 2.17 (3H, s, NCH$_3$), 2.09 (3H, s, 6-CH$_3$) (* the signal overlapped with the methyl signal). IR (KBr) cm^{-1}: 2928, 2855, 1767, 1448, 1369, 1261, 1198, 1088, 1028. HR-FAB-MS m/z 871.2852 [M+H]$^+$ (Calcd for $C_{44}H_{47}N_4O_{13}S$, 871.2860). FAB-MS (Glycerol) m/z 871 [(M+H)$^+$]. $[\alpha]_D^{20}$ −97.3° (c=0.16, $CHCl_3$).

Diacetylecteinascidin 743 (2a) Compound **2b** (9.0 mg, 0.011 mmol) was dissolved in a mixture of acetonitrile and water [3 : 2 (v/v), 3.5 ml], and silver nitrate (42.7 mg, 0.25 mmol, 23.8 eq) was added.. The suspension was stirred at 40 °C for 19 h. The reaction mixture was filtered and the precipitate was washed carefully with chloroform (30 ml). The combined filtrates were concentrated *in vacuo* to give a residue. This residue was diluted with water (10 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated *in vacuo* to give a residue (11.6 mg). The residue was purified by silica gel column chromatography with hexane–ethyl acetate (3 : 7) as eluent to give **2a** (3.5 mg, 0.041 mmol, 41%) as a pale yellow solid. Further elution with ethyl acetate as eluent afforded the starting material (**1b**, 4.1 mg, 46%). Compound **2a** ($[\alpha]_D$ −47.9° (c=0.16, $CHCl_3$)) was fairly stable, and thus only ^{1}H-NMR and MS spectral data were obtained. ^{1}H-NMR δ: 6.98 (1H, s, 15-H), 6.61 (1H, s, 5′-H), 6.54 (1, s, 8′-H), 6.02 and 5.95 (each 1H, d, J=1.0 Hz, OCHO), 5.14 (1H, d, J=11.2 Hz, 22-H), 4.88 (1H, br s, 1-H), 4.54 (1H, br s, 21-H), 4.45 (1H, br s, 4-H), 4.36 (1H, dd, J=4.9, 1.2 Hz, 11-H), 4.04 (1H, dd, J=11.5, 2.2 Hz, 22-H), 3.79 (3H, s, 17-OCH$_3$), 3.55 (3H, s, 7′-OCH$_3$), 3.52 (1H, m, 3-H), 3.13 (1H, m, 13-H), 2.98 (2H, d, J=5.3 Hz, 14-H$_2$), 2.85 (1H, br t, 3′-H), 2.60 (1H, m, 3′-H), 2.52 (1H, m, 4′-H), 2.44 (1H, m, 4′-H), 2.38 (3H, s, 16-CH$_3$), 2.34 (3H, s, OCOCH$_3$), 2.34 (1H, br, 12′-H)*, 2.30 (3H, s, NCH$_3$), 2.24 (3H, s, OCOCH$_3$), 2.24 (1H, m, 12′-H)*, 2.03 (3H, s, 6-CH$_3$) (* the signals overlapped with the methyl signals). IR (KBr) cm^{-1}: 2926, 2855, 1744, 1431, 1369, 1261, 1196, 1030. HR-FAB-MS m/z 828.2800 [M+H−H$_2$O]$^+$ (Calcd for $C_{43}H_{46}N_3O_{12}S$, 828.2802). FAB-MS (Glycerol) m/z 828 [(M+H−H$_2$O)$^+$].

General Procedure for the Preparation of Compounds 3—17 Compound **1b** (7.7 mg, 0.01 mmol) and DMAP (0.6 mg) were dissolved in pyridine (1 ml), and equimolar quantity of various acid chlorides (0.01 mmol) was added to this mixture at 0 °C. The reaction mixture was stirred at 25 °C for 4—12 h. After the solvent was removed *in vacuo*, the residue was diluted with water (10 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated *in vacuo* to give a solid. This residue was purified by silica gel column chromatography using appropriate eluent to give the purified product.

Ecteinascidin 770 6′-*O*-Benzoate (**3**): Yield 88%, ^{1}H-NMR δ: 8.14 (2H, d, J=8.4 Hz, 2″-, 6″-H), 7.60 (1H, t, J=8.4 Hz, 4″-H), 7.47 (2H, t, J=8.4 Hz, 3″-, 5″-H), 6.73 (1H, s, 5′-H), 6.60 (1H, s, 8′-H), 6.48 (1, s, 15-H), 6.03, 5.97 (each 1H, br s, OCHO), 5.73 (1H, br s, 18-OH), 5.03 (1H, d, J=11.6 Hz, 22-H), 4.58 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.29 (1H, d, J=3.7 Hz, 11-H), 4.18 (1H, d, J=2.7 Hz, 21-H), 4.11 (1H, dd, J=11.6, 2.2 Hz, 22-H), 3.79 (3H, s, 17-OCH$_3$), 3.55 (3H, s, 7′-OCH$_3$), 3.55 (1H, d, J=4.6 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.14 (1H, m, 3′-H), 2.95 (2H, d, J=6.1 Hz, 14-H$_2$), 2.84 (1H, m, 3′-H), 2.64 (1H, m, 4′-H), 2.54 (1H, m, 4′-H), 2.33 (1H, br, 12′-H), 2.33 (3H, s, 16-CH$_3$), 2.28 (3H, s, OCOCH$_3$), 2.21 (3H, s, NCH$_3$), 2.21 (1H, br, 12-H), 2.03 (3H, s, 6-CH$_3$). IR (KBr) cm^{-1}: 3753, 2932, 2855, 2810, 1744, 1620, 1508, 1431, 1371, 1263, 1026. HR-FAB-MS m/z 875.2964 [M+H]$^+$ (Calcd for $C_{47}H_{47}N_4O_{11}S$, 875.2962). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) m/z 875 [(M+H)$^+$]. $[\alpha]_D^{22}$ −20.2° (c=0.33, $CHCl_3$).

Ecteinascidin 770 6′-*O*-4″-Nitrobenzoate (**4**): Yield 95%, ^{1}H-NMR δ: 8.31 (4H, s, Ar-H), 6.75 (1H, s, 5′-H), 6.64 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.02, 5.96 (each 1H, d, J=0.9 Hz, OCHO), 5.76 (1H, br s, 18-OH), 5.04 (1H, d, J=11.6 Hz, 22-H), 4.59 (1H, br s, 4-H), 4.35 (1H, br s, 1-H), 4.29 (1H, d, J=3.7 Hz, 11-H), 4.19 (1H, d, J=2.7 Hz, 21-H), 4.14 (1H, dd, J=11.6, 2.2 Hz, 22-H), 3.80 (3H, s, 17-OCH$_3$), 3.55 (3H, s, 7′-OCH$_3$), 3.53 (1H, d, J=4.6 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.15 (1H, m, 3′-H), 2.96 (2H, d, J=6.1 Hz, 14-H$_2$), 2.83 (1H, m, 3′-H), 2.67 (1H, m, 4′-H), 2.52 (1H, m, 4′-H), 2.34 (1H, br d, 12′-H), 2.33 (3H, s, 16-CH$_3$), 2.27 (3H, s, OCOCH$_3$), 2.21 (3H, s, NCH$_3$), 2.21 (1H, br d, 12-H), 2.03 (3H, s, 6-CH$_3$). ^{13}C-NMR δ: 172.0 (11′-CO), 168.2 (OCOCH$_3$), 162.8 (OCOPh), 150.8 (C-4″), 148.3 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.1 (C-17), 141.4 (C-5), 140.1 (C-8), 138.3 (C-6′), 134.7 (C-1″), 133.2 (C-9′), 131.3 (C-2″), 131.3 (C-6″), 130.8 (C-20), 129.4 (C-16), 128.8 (C-10′), 123.6 (C-3″), 123.6 (C-5″), 122.3 (C-5′), 121.0 (C-10), 120.7 (C-15), 118.2 (C-19), 118.0 (21-CN), 114.0 (C-9), 113.5 (C-

6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9 (C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.2 (C-22), 59.6 (C-21), 59.6 (C-3), 55.2 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 42.3 (C-12′), 42.0 (C-4), 41.6 (NCH_3), 39.5 (C-3′), 29.6 (C-4′), 24.2 (C-14), 20.4 ($OCOCH_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2930, 2810, 1746, 1589, 1529, 1508, 1431, 1350, 1319, 1028. HR-FAB-MS *m/z* 920.2824 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_5O_{13}S$, 920.2812). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 920 $[(M+H)^+]$. $[\alpha]_D^{20}$ −28.8° (*c*=0.68, $CHCl_3$).

Ecteinascidin 770 6′-*O*-3″-Nitrobenzoate (**5**): Yield 66%, ^{1}H-NMR δ: 8.96 (1H, t, *J*=1.8 Hz, 2″-H), 8.45 (2H, dd, *J*=8.1, 1.8 Hz, 3″-, 4″-H), 7.69 (1H, t, *J*=8.1 Hz, 5″-H), 6.75 (1H, s, 5′-H), 6.63 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.03 and 5.97 (each 1H, br s, OCHO), 5.73 (1H, br s, 18-OH), 5.04 (1H, d, *J*=11.6 Hz, 22-H), 4.59 (1H, br s, 4-H), 4.35 (1H, br s, 1-H), 4.29 (1H, d, *J*=3.7 Hz, 11-H), 4.19 (1H, d, *J*=2.7 Hz, 21-H), 4.12 (1H, dd, *J*=11.6, 2.2 Hz, 22-H), 3.81 (3H, s, 17-OCH_3), 3.55 (3H, s, 7′-OCH_3), 3.55 (1H, d, *J*=4.6 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.15 (1H, m, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.84 (1H, m, 3′-H), 2.65 (1H, m, 4′-H), 2.55 (1H, m, 4′-H), 2.34 (1H, br, 12′-H), 2.34 (3H, s, 16-CH_3), 2.29 (3H, s, $OCOCH_3$), 2.22 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.04 (3H, s, 6-CH_3). IR (KBr) cm^{-1}. 2933, 2810, 1747, 1618, 1587, 1535, 1512, 1452, 1352, 1192. HR-FAB-MS *m/z* 920.2831 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_5O_{13}S$, 920.2812). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 920 $[(M+H)^+]$. $[\alpha]_D^{20}$ −18.5° (*c*=0.21, $CHCl_3$).

Ecteinascidin 770 6′-*O*-2″-Nitrobenzoate (**6**): Yield 83%, ^{1}H-NMR δ: 7.92 (1H, d, *J*=8.9 Hz, 3″-H), 7.88 (1H, d, *J*=7.4 Hz, 6″-H), 7.72 (2H, m, 4″-, 5″-H), 6.93 (1H, s, 5′-H), 6.60 (1H, s, 8′-H), 6.50 (1H, s, 15-H), 6.08 and 6.00 (each 1H, br s, OCHO), 5.82 (1H, s, 18-OH), 5.04 (1H, d, *J*=11.6 Hz, 22-H), 4.67 (1H, br s, 4-H), 4.32 (1H, d, *J*=4.6 Hz, 1-H), 4.24 (1H, dd, *J*=11.6, 2.2 Hz, 22-H), 4.20 (1H, d, *J*=3.7 Hz, 11-H), 4.17 (1H, d, *J*=2.7 Hz, 21-H), 3.96 (3H, s, 17-OCH_3), 3.61 (3H, s, 7′-OCH_3), 3.56 (1H, d, *J*=4.2 Hz, 3-H), 3.44 (1H, br t, 13-H), 2.96 (1H, m, 3′-H), 2.92 (2H, d, *J*=6.1 Hz, 14-H_2), 2.84 (1H, m, 3′-H), 2.65 (1H, m, 4′-H), 2.55 (1H, m, 4′-H), 2.44 (3H, s, 16-CH_3), 2.34 (1H, br, 12′-H), 2.33 (3H, s, $OCOCH_3$), 2.24 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.05 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2928, 2855, 2757, 1535, 1508, 1458, 1350, 1194, 1088, 1028. HR-FAB-MS *m/z* 920.2811 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_5O_{13}S$, 920.2812). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 920 $[(M+H)^+]$. $[\alpha]_D^{19}$ −17.8° (*c*=0.15, $CHCl_3$).

Ecteinascidin 770 6′-*O*-4″-Bromobenzoate (**7**): Yield 97%, ^{1}H-NMR δ: 7.99 (2H, d, *J*=8.5 Hz, 2″-, 6″-H), 7.61 (2H, d, *J*=8.5 Hz, 3″-, 5″-H), 6.73 (1H, s, 5′-H), 6.61 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.03 and 5.97 (each 1H, s, OCHO), 5.73 (1H, br s, 18-OH), 5.04 (1H, d, *J*=11.6 Hz, 22-H), 4.59 (1H, br s, 4-H), 4.35 (1H, br s, 1-H), 4.29 (1H, d, *J*=4.6 Hz, 11-H), 4.19 (1H, d, *J*=2.4 Hz, 21-H), 4.12 (1H, dd, *J*=11.6, 2.2 Hz, 22-H), 3.81 (3H, s, 17-OCH_3), 3.55 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.9 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.15 (1H, m, 3′-H), 2.96 (2H, d, *J*=6.1 Hz, 14-H_2), 2.84 (1H, m, 3′-H), 2.65 (1H, m, 4′-H), 2.55 (1H, m, 4′-H), 2.34 (1H, br, 12′-H), 2.34 (3H, s, 16-CH_3), 2.29 (3H, s, $OCOCH_3$), 2.22 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.04 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.0 (11′-<u>C</u>O), 168.1 (O<u>C</u>OCH$_3$), 164.0 (O<u>C</u>OPh), 147.9 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.2 (C-17), 141.4 (C-5), 140.1 (C-8), 138.3 (C-6′), 132.8 (C-9′), 131.8 (C-3″), 131.8 (C-5″), 131.7 (C-6″), 131.7 (C-2″), 131.4 (C-1″), 130.8 (C-20), 129.4 (C-10′), 128.7 (C-16), 128.2 (C-4″), 122.5 (C-5′), 120.8 (C-10), 120.6 (C-15), 118.1 (C-19), 118.0 (21-CN), 113.9 (C-9), 113.5 (C-6), 111.8 (C-8′), 101.9 (OCH_2O), 65.0 (C-1′), 61.1 (C-1), 60.4 (17-OCH_3), 60.2 (C-22), 59.6 (C-21), 59.6 (C-3), 55.2 (7′-OCH_3), 54.6 (C-11), 54.6 (C-13), 42.0 (C-12′), 42.0 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 29.6 (C-4′), 24.1 (C-14), 20.4 (OCO<u>C</u>H$_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2930, 2855, 2810, 1744, 1591, 1508, 1431, 1369, 1011. HR-FAB-MS *m/z* 953.2057 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_4O_{11}BrS$, 953.2067). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 955 $[(M+2+H)^+]$, 953 $[(M+H)^+]$. $[\alpha]_D^{19}$ −30.9° (*c*=0.75, $CHCl_3$).

Ecteinascidin 770 6′-*O*-3″-Bromobenzoate (**8**): Yield 84%, ^{1}H-NMR δ: 8.27 (1H, t, *J*=2.0 Hz, 2″-H), 8.06 (1H, d, *J*=8.1 Hz, 6″-H), 7.73 (1H, dd, *J*=8.1, 2.0 Hz, 4″-H), 7.35 (1H, t, *J*=8.1 Hz, 5″-H), 6.75 (1H, s, 5′-H), 6.63 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.02 and 5.97 (each 1H, br s, OCHO), 5.73 (1H, br s, 18-OH), 5.03 (1H, d, *J*=11.2 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.33 (1H, br s, 1-H), 4.29 (1H, d, *J*=5.3 Hz, 11-H), 4.19 (1H, d, *J*=2.7 Hz, 21-H), 4.13 (1H, dd, *J*=11.2, 2.2 Hz, 22-H), 3.80 (3H, s, 17-OCH_3), 3.55 (3H, s, 7′-OCH_3), 3.51 (1H, d, *J*=5.3 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.13 (1H, m, 3′-H), 2.96 (2H, d, *J*=6.1 Hz, 14-H_2), 2.83 (1H, m, 3′-H), 2.66 (1H, m, 4′-H), 2.55 (1H, m, 4′-H), 2.34 (1H, br, 12′-H), 2.33 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.03 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2963, 2926, 2853, 1746, 1261, 1024. HR-FAB-MS *m/z* 953.2018 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_4O_{11}BrS$, 953.2067). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 955 $[(M+2+H)^+]$, 953 $[(M+H)^+]$. $[\alpha]_D^{21}$ −17.9° (*c*=0.14, $CHCl_3$).

Ecteinascidin 770 6′-*O*-2″-Bromobenzoate (**9**): Yield 74%, ^{1}H-NMR δ: 8.00 (1H, m, 6″-H), 7.70 (1H, m, 3″-H), 7.38 (2H, m, 3″-, 4″-H), 6.77 (1H, s, 5′-H), 6.63 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.03 and 5.97 (each 1H, br s, OCHO), 5.73 (1H, s, 18-OH), 5.03 (1H, d, *J*=11.6 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.29 (1H, d, *J*=4.8 Hz, 11-H), 4.19 (1H, d, *J*=2.8 Hz, 21-H), 4.12 (1H, dd, *J*=11.6, 2.4 Hz, 22-H), 3.80 (3H, s, 17-OCH_3), 3.58 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=5.0 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.14 (1H, m, 3′-H), 2.96 (2H, d, *J*=6.1 Hz, 14-H_2), 2.82 (1H, m, 3′-H), 2.68 (1H, m, 4′-H), 2.52 (1H, m, 4′-H), 2.33 (1H, br, 12′-H), 2.33 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.23 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.04 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2966, 1751, 1589, 1508, 1431, 1369, 1261, 1240, 1024. HR-FAB-MS *m/z* 953.2080 $[M+H]^+$ (Calcd for $C_{47}H_{46}N_4O_{11}BrS$, 953.2067). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 955 $[(M+2+H)^+]$, 953 $[(M+H)^+]$. $[\alpha]_D^{21}$ −44.9° (*c*=0.17, $CHCl_3$).

Ecteinascidin 770 6′-*O*-4″-Methoxybenzoate (**10**): Yield 67%, ^{1}H-NMR δ: 8.09 (2H, d, *J*=8.6 Hz, 2″-, 6″-H), 6.95 (2H, d, *J*=8.6 Hz, 3″-, 5″-H), 6.72 (1H, s, 5′-H), 6.60 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.03 and 5.97 (each 1H, br s, OCHO), 5.72 (1H, s, 18-OH), 5.03 (1H, d, *J*=11.6 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.33 (1H, br s, 1-H), 4.28 (1H, d, d, *J*=4.8 Hz, 11-H), 4.18 (1H, d, *J*=2.8 Hz, 21-H), 4.12 (1H, dd, *J*=11.6, 2.4 Hz, 22-H), 3.87 (3H, s, 4″-OCH_3), 3.80 (3H, s, 17-OCH_3), 3.55 (3H, s, 7′-OCH_3), 3.55 (1H, d, *J*=5.0 Hz, 3-H), 3.42 (1H, br t, 13-H), 3.14 (1H, m, 3′-H), 2.94 (2H, d, *J*=6.1 Hz, 14-H_2), 2.82 (1H, m, 3′-H), 2.65 (1H, m, 4′-H), 2.51 (1H, m, 4′-H), 2.33 (1H, br, 12′-H), 2.32 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.03 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2928, 2855, 2812, 1740, 1607, 1582, 1514, 1462, 1421, 1371, 1028. HR-FAB-MS *m/z* 905.3058 $[M+H]^+$ (Calcd for $C_{48}H_{49}N_4O_{12}S$, 905.3068). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 905 $[(M+H)^+]$. $[\alpha]_D^{20}$ −34.8° (*c*=0.27, $CHCl_3$).

Ecteinascidin 770 6′-*O*-2″-Methoxybenzoate (**11**): Yield 72%, ^{1}H-NMR δ: 7.98 (1H, dd, *J*=8.2, 1.5 Hz, 6″-H), 7.51 (1H, dt, *J*=8.2, 1.5 Hz, 4″-H), 7.00 (2H, t, *J*=8.2 Hz, 3″-, 5″-H), 6.73 (1H, s, 5′-H), 6.60 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.03 and 5.97 (each 1H, br s, OCHO), 5.73 (1H, s, 18-OH), 5.03 (1H, d, *J*=11.3 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.33 (1H, br s, 1-H) , 4.28 (1H, d, *J*=4.8 Hz, 11-H), 4.18 (1H, d, *J*=2.4 Hz, 21-H), 4.12 (1H, dd, *J*=11.6, 2.4 Hz, 22-H), 3.89 (3H, s, 4″-OCH_3), 3.81 (3H, s, 17-OCH_3), 3.55 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.6 Hz, 3-H), 3.42 (1H, br t, 13-H), 3.14 (1H, m, 3′-H), 2.94 (2H, d, *J*=6.1 Hz, 14-H_2), 2.82 (1H, m, 3′-H), 2.66 (1H, m, 4′-H), 2.51 (1H, m, 4′-H), 2.34 (1H, br, 12′-H), 2.32 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.21 (1H, br, 12-H), 2.03 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.0 (11′-<u>C</u>O), 168.0 (O<u>C</u>OCH$_3$), 163.7 (O<u>C</u>OPh), 159.9 (C-2″), 148.7 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.1 (C-17), 141.4 (C-5), 140.1 (C-8), 138.3 (C-6′), 135.0 (C-4″), 132.8 (C-9′), 132.4 (C-6″), 130.8 (C-20), 129.2 (C-10′), 128.6 (C-16), 122.8 (C-5′), 120.8 (C-10), 120.6 (C-15), 120.2 (C-1″), 120.2 (C-5″), 118.1 (C-19), 118.0 (21-CN), 113.9 (C-9), 113.5 (C-6), 112.3 (C-3″), 111.6 (C-8′), 101.9 (OCH_2O), 65.0 (C-1′), 61.1 (C-1), 60.4 (17-OCH_3), 60.2 (C-22), 59.5 (C-21), 59.5 (C-3), 56.0 (7′-OCH_3), 56.0 (2″-OCH_3), 55.3 (C-11), 54.6 (C-13), 42.3 (C-12′), 42.0 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.7 (C-4′), 24.2 (C-14), 20.4 (OCO*C*H$_3$), 15.9 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 3506, 2934, 2854, 2810, 1747, 1659, 1601, 1491, 1437, 1371, 1028. HR-FAB-MS *m/z* 905.3074 $[M+H]^+$. (Calcd for $C_{48}H_{49}N_4O_{12}S$, 905.3068). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 905 $[(M+H)^+]$. $[\alpha]_D^{19}$ −48.2° (*c*=0.85, $CHCl_3$).

Ecteinascidin 770 6′-*O*-Nicotinate (**12**): Yield 76%, ^{1}H-NMR δ: 9.29 (1H, dd, *J*=2.2, 0.6 Hz, 2″-H), 8.80 (1H, dd, *J*=4.9, 1.8 Hz, 6″-H), 8.34 (1H, ddd, *J*=7.9, 2.2, 1.8 Hz, 4″-H), 7.40 (1H, ddd, *J*=7.9, 4.9, 0.6 Hz, 5″-H), 6.72 (1H, s, 5′-H), 6.63 (1H, s, 8′-H), 6.59 (1, s, 15-H), 5.99 and 5.94 (each 1H, d, *J*=1.2 Hz, OCHO), 5.77 (1H, br s, 18-OH), 5.01 (1H, d, *J*=11.3 Hz, 22-H), 4.56 (1H, br s, 4-H), 4.32 (1H, br s, 1-H), 4.27 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.16 (1H, d, *J*=2.4 Hz, 21-H), 4.11 (1H, dd, *J*=11.6, 2.4 Hz, 22-H), 3.78 (3H, s, 17-OCH_3), 3.53 (3H, s, 7′-OCH_3), 3.49 (1H, d, *J*=2.7 Hz, 3-H), 3.39 (1H, br t, 13-H), 3.12 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.92 (2H, d, *J*=6.1 Hz, 14-H_2), 2.84 (1H, ddd, *J*=11.6, 5.5, 3.4 Hz, 3′-H), 2.64 (1H, ddd, *J*=15.9, 10.1, 5.5 Hz, 4′-H), 2.50 (1H, ddd, *J*=15.9, 3.7, 3.4 Hz, 4′-H), 2.34 (1H, d, *J*=14.6 Hz, 12′-H), 2.31 (3H, s, 16-CH_3), 2.26 (3H, s, $OCOCH_3$), 2.18 (3H, s, NCH_3), 2.14 (1H, d, *J*=14.6 Hz, 12′-H), 2.01 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.1 (11′-<u>C</u>O), 168.1 (5-O<u>C</u>OCH$_3$), 163.3 (O<u>C</u>OAr), 153.8 (C-6″), 151.5 (C-2″), 148.5 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.2 (C-17), 141.4 (C-5), 140.1 (C-8), 138.3 (C-6′), 137.6 (C-4″), 133.0 (C-9′), 130.8 (C-20), 129.3 (C-16), 128.8 (C-10′), 125.4 (C-3″), 123.4 (C-5″), 122.4 (C-5′), 121.1 (C-10), 120.7 (C-15), 118.2 (21-CN), 118.1 (C-19), 114.0 (C-9), 113.4 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9

(C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.2 (C-22), 59.7 (C-21), 59.6 (C-3), 55.2 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 42.4 (C-12′), 41.9 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.7 (C-4′), 24.2 (C-14), 20.4 ($OCO\underline{C}H_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2922, 2808, 1744, 1618, 1591, 1508, 1431, 1369, 1194, 1024. HR-FAB-MS *m/z* 876.2911 $[M+H]^+$ (Calcd for $C_{46}H_{46}N_5O_{11}S$, 876.2914). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 876 $[(M+H)^+]$. $[\alpha]_D^{20}$ −33.7° (*c*=0.45, $CHCl_3$).

Ecteinascidin 770 6′-*O*-Isonicotinate (**13**): Yield 85%, ^{1}H-NMR δ: 8.80 (2H, dd, *J*=4.5, 1.5 Hz, 2″-H), 7.92 (2H, dd, *J*=4.5, 1.5 Hz, 3″-H), 6.72 (1H, s, 5′-H), 6.62 (1H, s, 8′-H), 6.59 (1, s, 15-H), 5.99 and 5.94 (each 1H, d, *J*=0.9 Hz, OCHO), 5.77 (1H, br s, 18-OH), 5.01 (1H, d, *J*=11.3 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.32 (1H, br s, 1-H), 4.27 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.17 (1H, d, *J*=2.7 Hz, 21-H), 4.11 (1H, dd, *J*=11.6, 2.4 Hz, 22-H), 3.78 (3H, s, 17-OCH_3), 3.53 (3H, s, 7′-OCH_3), 3.50 (1H, d, *J*=4.9 Hz, 3-H), 3.40 (1H, br t, 13-H), 3.12 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.93 (2H, d, *J*=6.1 Hz, 14-H_2), 2.80 (1H, ddd, *J*=11.6, 5.5, 3.4 Hz, 3′-H), 2.64 (1H, ddd, *J*=15.9, 10.1, 5.5 Hz, 4′-H), 2.50 (1H, ddd, *J*=15.9, 3.7, 3.4 Hz, 4′-H), 2.34 (1H, d, *J*=14.6 Hz, 12′-H), 2.31 (3H, s, 16-CH_3), 2.26 (3H, s, $OCOCH_3$), 2.19 (3H, s, NCH_3), 2.14 (1H, d, *J*=14.6 Hz, 12′-H), 2.01 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.1 (11′-$\underline{C}O$), 168.1 (5-$O\underline{C}OCH_3$), 163.2 ($O\underline{C}OAr$), 150.7 (C-2″), 150.7 (C-6″), 148.3 (C-7′), 147.8 (C-18), 145.3 (C-7), 143.1 (C-17), 141.3 (C-5), 140.1 (C-8), 138.3 (C-6′), 136.6 (C-4″), 133.2 (C-9′), 130.8 (C-20), 129.3 (C-16), 128.9 (C-10′), 123.3 (C-3″), 123.3 (C-5″), 122.3 (C-5′), 121.1 (C-10), 120.7 (C-15), 118.2 (21-CN), 118.1 (C-19), 114.0 (C-9), 113.4 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9 (C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.2 (C-22), 59.7 (C-21), 59.6 (C-3), 55.2 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 42.3 (C-12′), 41.9 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.7 (C-4′), 24.2 (C-14), 20.4 ($OCO\underline{C}H_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 3315, 2934, 2810, 1747, 1589, 1560, 1508, 1410, 1369, 1005. HR-FAB-MS *m/z* 876.2921 $[M+H]^+$ (Calcd for $C_{46}H_{46}N_5O_{11}S$, 876.2914). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 876 $[(M+H)^+]$. $[\alpha]_D^{20}$ −38.7° (*c*=0.45, $CHCl_3$).

Ecteinascidin 770 6′-*O*-1″-Naphthoate (**14**): Yield 96%, ^{1}H-NMR δ: 8.94 (1H, d, *J*=8.3 Hz, 8″-H), 8.37 (1H, dd, *J*=7.3, 1.3 Hz, 2″-H), 8.06 (1H, d, *J*=8.1 Hz, 4″-H), 7.89 (1H, dd, *J*=7.9, 1.5 Hz, 5″-H), 7.61 (1H, m, 7″-H), 7.58 (1H, m, 6″-H), 7.55 (1H, dd, *J*=8.1, 7.3 Hz, 3″-H), 6.79 (1H, s, 5′-H), 6.65 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.02 and 6.00 (each 1H, d, *J*=1.0 Hz, OCHO), 5.76 (1H, br s, 18-OH), 5.00 (1H, d, *J*=11.4 Hz, 22-H), 4.57 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.28 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.19 (1H, d, *J*=2.3 Hz, 21-H), 4.13 (1H, dd, *J*=11.5, 2.3 Hz, 22-H), 3.79 (3H, s, 17-OCH_3), 3.58 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.4 Hz, 3-H), 3.42 (1H, br t, 13-H), 3.15 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.94 (2H, d, *J*=6.1 Hz, 14-H_2), 2.85 (1H, m, 3′-H), 2.70 (1H, m, 4′-H), 2.54 (1H, m, 4′-H), 2.34 (1H, d, *J*=14.6 Hz, 12′-H), 2.33 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.20 (3H, s, NCH_3), 2.20 (1H, signals overlapped with NCH_3, 12′-H), 2.03 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2922, 2810, 1744, 1620, 1508, 1431, 1369, 1013. HR-FAB-MS *m/z* 925.3128 $[M+H]^+$ (Calcd for $C_{51}H_{49}N_4O_{11}S$, 925.3118). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 925 $[(M+H)^+]$. $[\alpha]_D^{20}$ −55.4° (*c*=0.17, $CHCl_3$).

Ecteinascidin 770 6′-*O*-2″-Naphthoate (**15**): Yield 94%, ^{1}H-NMR δ: 8.73 (1H, br s, 1”-H), 8.11 (1H, dd, *J*=8.6, 1.5 Hz, 8″-H), 7.97 (1H, d, *J*=7.9 Hz, 4″-H), 7.91 (1H, d, *J*=8.6 Hz, 5″-H), 7.89 (1H, d, *J*=7.9 Hz, 3″-H), 7.61 (1H, dt, *J*=8.6, 1.5 Hz, 6″-H), 7.54 (1H, dt, *J*=8.6, 0.9 Hz, 7″-H), 6.79 (1H, s, 5′-H), 6.64 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.03, 5.96 (each 1H, s, OCHO), 5.76 (1H, br s, 18-OH), 5.04 (1H, d, *J*=11.6 Hz, 22-H), 4.58 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.30 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.20 (1H, d, *J*=2.3 Hz, 21-H), 4.14 (1H, dd, *J*=11.5, 2.3 Hz, 22-H), 3.80 (3H, s, 17-OCH_3), 3.56 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.3 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.17 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.85 (1H, m, 3′-H), 2.69 (1H, m, 4′-H), 2.54 (1H, m, 4′-H), 2.34 (1H, d, *J*=14.6 Hz, 12′-H), 2.34 (3H, s, 16-CH_3), 2.29 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.20 (1H, signals overlapped with NCH_3, 12′-H), 2.04 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.1 (11′-$\underline{C}O$), 168.1 (5-$O\underline{C}OCH_3$), 164.8 ($O\underline{C}OAr$), 148.7 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.1 (C-17), 140.4 (C-5), 140.1 (C-8), 139.0 (C-6′), 135.8 (C-10″), 132.5 (C-9′), 132.5 (C-9″), 132.0 (C-1″), 130.8 (C-20), 129.5 (C-8″), 129.3 (C-16), 128.8 (C-10′), 128.5 (C-6″), 128.3 (C-2″, C-4″), 127.8 (C-5″), 126.7 (C-7″), 125.6 (C-3″), 122.6 (C-5′), 121.1 (C-10), 120.7 (C-15), 118.1 (21-CN), 118.1 (C-19), 114.0 (C-9), 113.4 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9 (C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.2 (C-22), 59.6 (C-21), 59.6 (C-3), 55.3 (7′-OCH_3), 54.6 (C-11), 54.6 (C-13), 41.6 (C-12′), 41.6 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.9 (C-4′), 24.2 (C-14), 20.4 ($OCO\underline{C}H_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2922, 2855, 2810, 1744, 1589, 1508, 1439, 1369, 1030. HR-FAB-MS *m/z* 925.3125 $[M+H]^+$ (Calcd for $C_{51}H_{49}N_4O_{11}S$, 925.3118). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 925 $[(M+H)^+]$. $[\alpha]_D^{20}$ −22.6° (*c*=0.62, $CHCl_3$).

Ecteinascidin 770 6′-*O*-2″-Quinolinecarboxylate (**16**): Yield 99%, ^{1}H-NMR δ: 8.34 (1H, d, *J*=8.4 Hz, 4″-H), 8.33 (1H, d, *J*=8.3 Hz, 8″-H), 8.25 (1H, d, *J*=8.4 Hz, 3″-H), 7.90 (1H, d, *J*=8.1 Hz, 5″-H), 7.80 (1H, dd, *J*=8.3, 7.7 Hz, 7″-H), 7.67 (1H, dd, *J*=8.1, 7.7 Hz, 6″-H), 6.86 (1H, s, 5′-H), 6.61 (1H, s, 8′-H), 6.60 (1H, s, 15-H), 6.03 and 5.97 (each 1H, s, OCHO), 5.76 (1H, br s, 18-OH), 5.05 (1H, d, *J*=11.2 Hz, 22-H), 4.58 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.30 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.20 (1H, d, *J*=2.6 Hz, 21-H), 4.12 (1H, dd, *J*=11.5, 2.3 Hz, 22-H), 3.82 (3H, s, 17-OCH_3), 3.56 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.4 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.17 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.88 (1H, m, 3′-H), 2.73 (1H, m, 4′-H), 2.60 (1H, *m,* 4′-H), 2.36 (1H, d, *J*=14.6 Hz, 12′-H), 2.36 (3H, s, 16-CH_3), 2.30 (3H, s, $OCOCH_3$), 2.22 (3H, s, NCH_3), 2.20 (1H, signals overlapped with NCH_3, 12′-H), 2.03 (3H, s, 6-CH_3). IR (KBr) cm^{-1}: 2934, 2810, 1744, 1659, 1589, 1508, 1431, 1317, 1028. HR-FAB-MS *m/z* 926.3079 $[M+H]^+$ (Calcd for $C_{50}H_{48}N_4O_{11}S$, 926.3021). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 926 $[(M+H)^+]$. $[\alpha]_D^{21}$ −21.0° (*c*=0.17, $CHCl_3$).

Ecteinascidin 770 6′-*O*-4″-Quinolinecarboxylate (**17**): Yield 96%, ^{1}H-NMR δ: 9.07 (1H, d, *J*=4.6 Hz, 2″-H), 8.80 (1H, dd, *J*=8.5, 1.5 Hz, 8″-H), 8.19 (1H, dd, *J*=8.5, 0.6 Hz, 5″-H), 8.07 (1H, d, *J*=4.3 Hz, 3″-H), 7.79 (1H, ddd, *J*=8.5, 7.0, 1.5 Hz, 7″-H), 7.65 (1H, ddd, *J*=8.5, 7.0, 1.5 Hz, 6″-H), 6.82 (1H, s, 5′-H), 6.67 (1H, s, 8′-H), 6.66 (1H, s, 15-H), 6.03 and 5.97 (each 1H, d, *J*=0.9 Hz, OCHO), 5.76 (1H, br s, 18-OH), 5.05 (1H, d, *J*=11.3 Hz, 22-H), 4.58 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.30 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.20 (1H, d, *J*=2.7 Hz, 21-H), 4.12 (1H, dd, *J*=11.5, 2.3 Hz, 22-H), 3.82 (3H, s, 17-OCH_3), 3.56 (3H, s, 7′-OCH_3), 3.54 (1H, d, *J*=4.6 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.17 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.88 (1H, m, 3′-H), 2.73 (1H, m, 4′-H), 2.60 (1H, ddd, m, 4′-H), 2.36 (1H, d, *J*=14.6 Hz, 12′-H), 2.34 (3H, s, 16-CH_3), 2.30 (3H, s, $OCOCH_3$), 2.22 (3H, s, NCH_3), 2.20 (1H, signals overlapped with NCH_3, 12′-H), 2.03 (3H, s, 6-CH_3). ^{13}C-NMR δ: 168.1 (11′-$\underline{C}O$), 167.7 (5-$O\underline{C}OCH_3$), 164.2 ($O\underline{C}OAr$), 149.8 (C-2″), 149.1 (C-9″), 148.5 (C-7′), 147.9 (C-18), 145.4 (C-7), 143.2 (C-17), 141.4 (C-5), 140.1 (C-8), 138.5 (C-6′), 134.0 (C-4″), 132.5 (C-9′), 130.8 (C-20), 130.0 (C-7″), 129.8 (C-6″), 129.5 (C-16), 128.8 (C-10′), 128.4 (C-5″), 125.6 (C-8″), 125.2 (C-10″), 122.8 (C-3″), 122.5 (C-5′), 121.0 (C-10), 120.6 (C-15), 118.1 (21-CN), 118.0 (C-19), 113.9 (C-9), 113.5 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 68.1 (C-1′), 61.1 (C-1), 60.4 (17-OCH_3), 60.2 (C-22), 59.6 (C-21), 59.6 (C-3), 56.2 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 41.8 (C-12′), 41.6 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.9 (C-4′), 24.1 (C-14), 20.4 ($OCO\underline{C}H_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2928, 2855, 2810, 1747, 1535, 1508, 1431, 1369, 1263, 1028. HR-FAB-MS *m/z* 926.3079 $[M+H]^+$ (Calcd for $C_{50}H_{48}N_4O_{11}S$, 926.3021). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 926 $[(M+H)^+]$. $[\alpha]_D^{20}$ −25.3° (*c*=0.17, $CHCl_3$).

Preparation of Compounds 18 and 19 (Typical Procedure) A mixture of 1-isoquinolinecarboxylic acid (173.0 mg, 1.0 mmol) and anhydrous K_2CO_3 (138.2 mg, 1.0 ml) in dichloromethane (2 ml) was stirred for 10 min. Isopropyl chloroformate (116 μl, 1.0 mmol) was added dropwise over 5 min, and the mixture was stirred overnight at room temperature. After the reaction mixture was filtered, the precipitate was washed with dichloromethane (30 ml×3). The combined filtrates were concentrated *in vacuo* to give an anhydride (**21a**), which was immediately used in the next step with the general procedure as above.

Ecteinascidin 770 6′-*O*-1″-Isoquinolinecarboxylate (**18**): Yield 65%, ^{1}H-NMR δ: 8.86 (1H, d, *J*=8.5 Hz, 8″-H), 8.67 (1H, d, *J*=5.5 Hz, 3″-H), 7.90 (1H, d, *J*=8.2 Hz, 5″-H), 7.86 (1H, d, *J*=5.5 Hz, 4″-H), 7.74 (1H, dt, *J*=8.5, 1.1 Hz, 7″-H), 7.68 (1H, dt, *J*=8.5, 1.4 Hz, 6″-H), 6.78 (1H, s, 5′-H), 6.68 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.04 and 5.97 (each 1H, d, *J*=1.2 Hz, OCHO), 5.81 (1H, br s, 18-OH), 5.05 (1H, d, *J*=11.6 Hz, 22-H), 4.58 (1H, br s, 4-H), 4.35 (1H, br s, 1-H), 4.29 (1H, dd, *J*=4.9, 1.2 Hz, 11-H), 4.20 (1H, d, *J*=2.7 Hz, 21-H), 4.14 (1H, dd, *J*=11.6, 2.1 Hz, 22-H), 3.80 (3H, s, 17-OCH_3), 3.62 (3H, s, 7′-OCH_3), 3.53 (1H, d, *J*=4.3 Hz, 3-H), 3.43 (1H, br t, 13-H), 3.17 (1H, ddd, *J*=11.6, 10.1, 3.7 Hz, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.83 (1H, m, 3′-H), 2.69 (1H, ddd, *J*=16.1, 10.0, 6.1 Hz, 4′-H), 2.55 (1H, dt, *J*=15.9, 3.7 Hz, 4′-H), 2.47 (1H, d, *J*=14.6 Hz, 12′-H), 2.34 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.20 (1H, signals overlapped with NCH_3, 12′-H), 2.05 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.2 (11′-$\underline{C}O$), 168.1 (5-$O\underline{C}OCH_3$), 163.9 ($O\underline{C}OAr$), 148.5 (C-7′), 147.9 (C-18), 147.8 (C-3″), 145.4 (C-7), 143.1 (C-17), 141.8 (C-3″), 141.4 (C-5), 140.1 (C-8), 138.8 (C-6′), 137.0 (C-10″), 133.0 (C-9′), 130.8 (C-20), 130.5 (C-7″), 129.3 (C-16), 128.9 (C-10′), 128.8 (C-6″), 127.2 (C-9″), 127.1 (C-5″), 126.4 (C-8″), 124.4 (C-4″), 122.6 (C-5′), 121.1 (C-10), 120.7 (C-15),

118.2 (21-CN), 118.1 (C-19), 114.1 (C-9), 114.1 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9 (C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.2 (C-22), 59.7 (C-21), 59.6 (C-3), 55.3 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 42.3 (C-12′), 41.9 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.7 (C-4′), 24.2 (C-14), 20.4 ($OCOCH_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2910, 2808, 1744, 1659, 1585, 1508, 1431, 1005. HR-FAB-MS *m/z* 926.3083 $[M+H]^+$ (Calcd for $C_{50}H_{48}N_5O_{11}S$, 926.3021). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 926 $[(M+H)^+]$. $[\alpha]_D^{22}$ −36.1° (*c*=0.43, $CHCl_3$).

Ecteinascidin 770 6′-*O*-3″-Isoquinolinecarboxylate (**19**): This compound was prepared as described above but using anhydride (**21b**) in 85% yield, ^{1}H-NMR δ: 9.38 (1H, s, 1″-H), 8.69 (1H, s, 4″-H), 8.08 (1H, d, *J*=7.9 Hz, 5″-H), 8.00 (1H, d, *J*=7.9 Hz, 8″-H), 7.80 (1H, dt, *J*=7.9, 1.2 Hz, 6″-H), 7.70 (1H, dt, *J*=7.9, 0.6 Hz, 7″-H), 6.82 (1H, s, 5′-H), 6.64 (1H, s, 8′-H), 6.61 (1H, s, 15-H), 6.02 and 5.96 (each 1H, d, *J*=1.2 Hz, OCHO), 5.75 (1H, br s, 18-OH), 5.04 (1H, d, *J*=11.3 Hz, 22-H), 4.56 (1H, br s, 4-H), 4.34 (1H, br s, 1-H), 4.28 (1H, dd, *J*=4.9, 0.9 Hz, 11-H), 4.20 (1H, d, *J*=2.7 Hz, 21-H), 4.14 (1H, dd, *J*=11.6, 2.1 Hz, 22-H), 3.80 (3H, s, 17-OCH_3), 3.56 (3H, s, 7′-OCH_3), 3.52 (1H, d, *J*=4.6 Hz, 3-H), 3.42 (1H, br t, 13-H), 3.16 (1H, dt, *J*=10.9, 3.7 Hz, 3′-H), 2.95 (2H, d, *J*=6.1 Hz, 14-H_2), 2.82 (1H, ddd, *J*=11.3, 5.2, 3.7 Hz, 3′-H), 2.67 (1H, ddd, *J*=15.9, 9.8, 5.2 Hz, 4′-H), 2.54 (1H, dt, *J*=15.9, 3.7 Hz, 4′-H), 2.39 (1H, d, *J*=14.3 Hz, 12′-H), 2.34 (3H, s, 16-CH_3), 2.28 (3H, s, $OCOCH_3$), 2.21 (3H, s, NCH_3), 2.22 (1H, signals overlapped with NCH_3, 12′-H), 2.04 (3H, s, 6-CH_3). ^{13}C-NMR δ: 172.2 (11′-CO), 168.1 (5-O<u>C</u>OCH$_3$), 163.7 (O<u>C</u>OAr), 152.9 (C-1″), 148.6 (C-7′), 147.8 (C-18), 145.4 (C-7), 143.1 (C-17), 141.3 (C-5), 140.8 (C-3″), 140.1 (C-8), 138.9 (C-6′), 135.4 (C-10″), 132.8 (C-9′), 131.2 (C-6″), 130.8 (C-20), 130.1 (C-7″), 129.8 (C-9″), 129.3 (C-16), 128.7 (C-10′), 128.1 (C-8″), 127.7 (C-5″), 125.0 (C-4″), 122.6 (C-5′), 121.1 (C-10), 120.7 (C-15), 118.2 (21-CN), 118.1 (C-19), 114.0 (C-9), 113.6 (C-6), 111.9 (C-8′), 101.9 (OCH_2O), 64.9 (C-1′), 61.1 (C-1), 60.3 (17-OCH_3), 60.1 (C-22), 59.7 (C-21), 59.6 (C-3), 55.2 (7′-OCH_3), 54.7 (C-11), 54.6 (C-13), 42.2 (C-12′), 41.9 (C-4), 41.6 (NCH_3), 39.6 (C-3′), 28.7 (C-4′), 24.2 (C-14), 20.4 ($OCO\underline{C}H_3$), 15.8 (16-CH_3), 9.7 (6-CH_3). IR (KBr) cm^{-1}: 2932, 2808, 1744, 1618, 1587, 1508, 1433, 1369, 1005. HR-FAB-MS *m/z* 926.3081 $[M+H]^+$ (Calcd for $C_{50}H_{48}N_5O_{11}S$, 926.3021). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 926 $[(M+H)^+]$. $[\alpha]_D^{21}$ −35.6° (*c*=0.45, $CHCl_3$).

N-3″-Indolecarboxylecteinascidin 770 (**22**): Indole-3-carboxylic acid (16.1 mg, 0.1 mmol) was added to a solution of **1b** (15.4 mg, 0.02 mmol) and 0.2 M dichloromethane solution of DCC (0.5 ml) in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 3 d, and the solvent was removed *in vacuo*. The residue was subjected to chromatography with hexane–ethyl acetate (1 : 1) as the eluent to give **22** (11.8 mg, 65%) as a solid. ^{1}H-NMR δ: 8.62 (1H, br s, NH), 8.06 (1H, d, *J*=7.9 Hz, 4″-H), 7.68 (1H, d, *J*=2.7 Hz, 2″-H), 7.64 (1H, d, *J*=7.9 Hz, 7″-H), 7.38 (1H, ddd, *J*=7.9, 7.0, 0.9 Hz, 5″-H or 6″-H), 7.27 (1H, ddd, *J*=7.9, 7.0, 1.2 Hz, 5″-H or 6″-H), 6.48 (1H, s, 8′-H), 6.40 (1H, s, 5′-H), 6.09 and 5.99 (each 1H, d, *J*=1.5 Hz, OCHO), 5.61 (1H, s, 18-OH), 5.41 (2H, br, 15-H, 6′-OH), 4.62 (1H, d, *J*=11.3 Hz, 22-H), 4.62 (1H, signals overlapped with 22-H, 4-H), 4.54 (1H, dd, *J*=11.3, 1.8 Hz, 22-H), 4.36 (1H, br s, 1-H), 4.20 (1H, dd, *J*=5.0, 1.4 Hz, 11-H), 4.19 (1H, d, *J*=2.7 Hz, 21-H), 4.00 (1H, ddd, *J*=14.3, 5.8, 2.4 Hz, 3′-H), 3.94 (1H, d, *J*=14.8 Hz, 12′-H), 3.71 (3H, s, 7′-OCH_3), 3.57 (3H, s, 17-OCH_3), 3.50 (1H, d, *J*=4.9 Hz, 3-H), 3.47 (1H, m, 12′-H), 3.35 (1H, br t, 13-H), 2.85 (2H, d, *J*=6.1 Hz, 14-H_2), 2.49 (2H, m, 3′-H, 4′-H), 2.30 (3H, s, $OCOCH_3$), 2.28 (1H, *J*=16.8, 8.2, 3.3 Hz, 4′-H), 2.09 (3H, s, NCH_3), 2.05 (3H, s, 6-CH_3), 1.14 (3H, s, 16-CH_3). ^{13}C-NMR δ: 170.6 (11′-CO), 168.2 (5-O<u>C</u>OCH$_3$), 164.1 (N<u>C</u>OAr), 147.0 (C-18), 145.4 (C-7), 144.7 (C-6′), 144.6 (C-7′), 142.7 (C-17), 141.4 (C-5), 141.3 (C-8), 135.7 (C-8″), 129.7 (C-20), 129.3 (C-2″), 129.0 (C-16), 127.6 (C-10′), 127.5 (C-9′). 125.0 (C-9″), 122.9 (C-6″), 122.6 (C-4″), 122.4 (C-10), 121.4 (C-15), 121.3 (C-5″), 118.3 (21-CN), 117.3 (C-19), 114.7 (C-3″), 113.7 (C-5′), 113.7 (C-9), 113.3 (C-6), 111.4 (C-7″), 110.5 (C-8′), 101.9 (OCH_2O), 70.2 (C-1′), 61.1 (C-3), 60.7 (C-1), 60.3 (C-22), 59.8 (17-OCH_3), 59.8 (C-21), 55.3 (7′-OCH_3), 54.9 (C-11), 54.9 (C-13), 46.6 (C-12′), 41.8 (C-4), 41.6 (NCH_3), 38.5 (C-3′), 29.7 (C-4′), 24.9 (C-14), 20.4 ($OCO\underline{C}H_3$), 14.2 (16-CH_3), 9.8 (6-CH_3). IR (KBr) cm^{-1}: 3358, 2926, 2853, 2810, 1751, 1595, 1508, 1431, 1375, 1171, 1028. HR-FAB-MS *m/z* 914.3063 $[M+H]^+$ (Calcd for $C_{49}H_{48}N_5O_{11}S$, 914.3071). FAB-MS (Dithiothreitol : Thioglycerol=1 : 1) *m/z* 914 $[(M+H)^+]$. $[\alpha]_D^{20}$ +18.5° (*c*=0.26, $CHCl_3$).

Biological Assay A single-cell suspension (2×10^3 cells/well) was added to serially diluted test compounds in a microplate. The cells were then cultured for 4 d. Cell growth was enumerated with a cell counting kit (DOJINDO, Osaka, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with untreated control.

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