HETEROCYCLES, Vol. 53, No12, 2000, pp. 2719 - 2737, Received, 1st September, 2000

SYNTHESIS AND ANTITUMOR ACTIVITY OF NON-PRODRUG WATER-SOLUBLE TAXOID: 10-*C*-AMINOALKYLARED DOCETAXEL ANALOGS

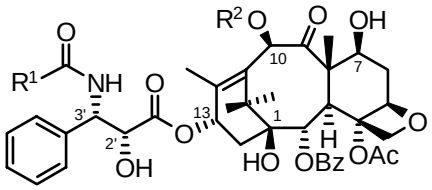
Shin Iimura, Satoru Ohsuki, Jun Chiba, Kouichi Uoto, Michio Iwahana, Hirofumi Terasawa, and Tsunehiko Soga*

New Product Research Laboratories IV, Daiichi Pharmaceutical Co., Ltd., 1-16-13, Kitakasai, Edogawa, Tokyo 134-8630, Japan

Abstract-To develop non-prodrugs of taxoids possessing satisfactory stability *in vivo*, high water solubility and potent antitumor activity, we prepared several 10-*C*-sec-aminoalkylated docetaxel analogs and evaluated their cytotoxicity against mouse leukemia and human tumor cell lines. These analogs were synthesized from a 10-deacetoxy-10-*C*-formylethyl baccatin derivative. Among these analogs, the 10-*C*-morpholinoethyl and 10-*C*-morpholinomethyl analogs exhibited cytotoxicity comparable or superior to that of docetaxel.

Paclitaxel (**1**, Taxol®),[1] which was originally isolated from Pacific yew *Taxus brevifolia*, has been used clinically for the treatment of ovarian and breast cancers, and has shown significant beneficial effects. On the other hand, docetaxel (**2**, Taxotere®),[2] a semisynthetic analog of paclitaxel, has been used most often for the treatment of breast and lung cancers. These two drugs are currently considered to be the most important drugs in cancer chemotherapy. However, their low water solubility requires that they should be co-injected with a detergent, Cremophor® EL or Tween® 80.

Figure 1



Paclitaxel (1: R^1 = Ph, R^2 = Ac), Docetaxel (2: R^1 = *t*-BuO, R^2 = H)

These detergents frequently cause untoward hypersensitivity reactions (hypotension, bronchospasm, urticaria etc.), and patients receiving these drugs should be premedicated.[3] To solve the problem of low water solubility, several research groups have synthesized and evaluated water-soluble taxoids such as esterase- or phosphatase-cleavable prodrugs.[4] However, these prodrugs are liable to exhibit variable efficacy because of variations in the enzymatic activity of patients. To resolve these problems, we have already described the synthesis of 10-*O*-*sec*-aminoethyldocetaxel analogs,[5] 10-*C*- aminopropyldocetaxel analogs and 10-*C*-carboxypropyldocetaxel analogs.[6] Among these analogs, 10-*O*-(2-morpholinoethyl)docetaxel (**3)** and 10-*O*-(2-thiomorpholinoethyl)docetaxel (**4**) exhibited cytotoxicity comparable or superior to that of docetaxel (**2**). In addition, the methanesulfonic acid salt of one of these analogs showed good water solubility.[5] On the other hand, 10-*C*-aminoalkyldocetaxel analog (**5**) and 10-*C*-carboxypropyldocetaxel analog (**6**) exhibited considerably lower activity than docetaxel (**2**) (Table 1). It was hypothesized that this decrease of activity was because of the presence of a functional group, in the end of the 10-*C* alkyl group, that may serve as hydrogen bond donor. On the basis of this hypothesis and the relationships between structures and activities of 10-*O*-*sec*-aminoethyldocetaxel analogs, 10-*C*-alkyldocetaxel analogs with a secondary amino group at the end of the 10-*C*-alkyl side chain were designed. Furthermore, to examine the influence of the length of the 10-*C* alkyl chain within a homologous series on the cytotoxic activity, the chain length was varied from one to three. Here we report the synthesis and cytotoxicity of 10-*C*-*sec*-aminoalkyldocetaxel analogs, with from one to three alkyl carbon bonds.

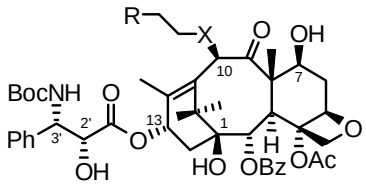


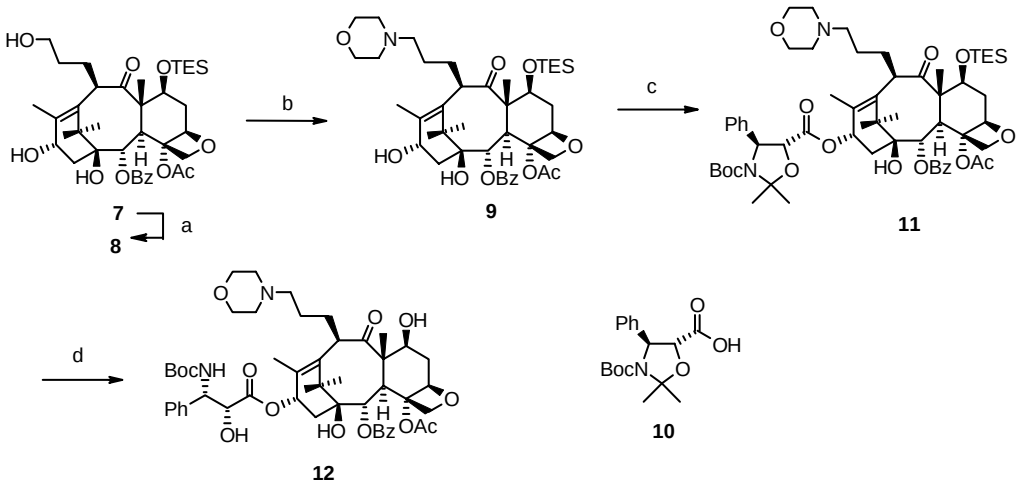
Table 1. Cytotoxicity of Water Soluble Docetaxel Analogs

Compound	X	R	Cytotoxic activity GI_{50} (ng/mL)[a]		
			P388	PC-6	PC-12
Docetaxel (**2**)	—	—	6.74	1.13	53.4
3	O		24.1	4.79	215
4	O		2.90	2.54	65.4
5	CH_2	NH_2	1520	236	6820
6	CH_2	COOH	1870	934	>10000

a) Concentration that inhibited the growth of cells by 50% on 72 h continuous exposure for three cell lines [mouse leukemia (P388), human lung cancer cell lines (PC-6, PC-12)].

Chemistry: 10-Deoxy-10-morpholinopropyldocetaxel (**12)** was synthesized from10-deacetoxy-10-hydroxypropyl-7-*O*-TES baccatin III (**7)**[6] using protected β-phenylisoserine (**10)**[7] as an ester side chain precursor (Scheme 1). Tosylation of the primary hydroxyl group in **7** and substitution with morpholine gave the 10-*C*-morpholinopropyl analog (**9)** in 82% yield. Succeeding introduction of the phenylisoserine side chain and the removal of protective groups gave10-deoxy-10-*C*-(3-morpholinopropyl) docetaxel (**12)**.

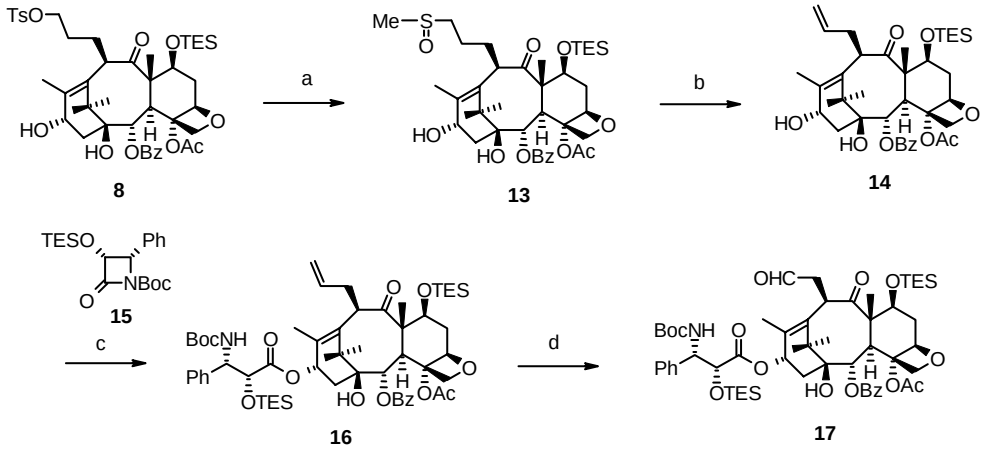
Scheme 1



Reagents and conditions: a) TsCl, triethylamine, dichloromethane, 0 °C; b) morpholine, MeOH, reflux (82% from **7**); c) **10**, dicyclohexylcarbodiimide, *N*,*N*-dimethylaminopyridine, dichloromethane (20%); d) 1) formic acid, rt; 2) *tert*-butoxycarbonyl anhydride, THF (54% from **11**).

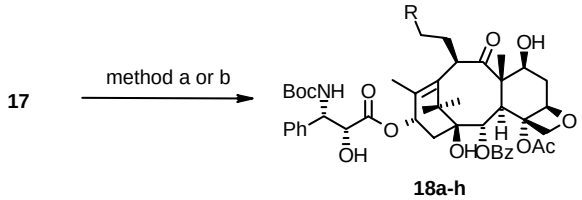
Synthesis of *sec*-aminoethyl analogs (**18a-h**) is described in Scheme 2 and Table 2. The key intermediate **(17)** for the synthesis of 10-*C*-aminoethyl analogs was synthesized from **8** (Scheme 2).

Scheme 2



Reagents and conditions: a) 1) 50% aq. MeSNa (w/v), *n*-Bu_4NI, THF, 0 °C, 2) $NaIO_4$, MeOH-H_2O, 0 °C (84%); b) K_2CO_3, 1,2-dichlorobenzene, 170 °C (37%, net. 76%); c) **15**, NaH, THF, 0 °C (91%); d) 1) OsO_4, NMO, acetone-H_2O, rt, 2) $NaIO_4$, MeOH-H_2O (84%).

The reaction of 10-deacetoxy-7-*O*-TES-10-tosyloxypropylbaccatin III (**8**) with MeSNa followed by oxidation with $NaIO_4$ gave the sulfoxide (**13)** in high yield. The sulfoxide (**13**) was heated with K_2CO_3 to give olefin (**14)**. A phenylisoserine side chain was introduced into the baccatin moiety using the *β*-lactam to give **16** in high yield.[8] Oxidation of **16** with OsO_4 followed by cleavage with $NaIO_4$ gave the aldehyde (**17**) in high yield. Finally, compound (**17**) was subjected to reductive amination[9] with various *sec*-amines followed by standard desilylation to give the 10-*C*-*sec*-aminoethyl-10-deoxydocetaxel analogs (**18a-h**, Table 2).



18a-h

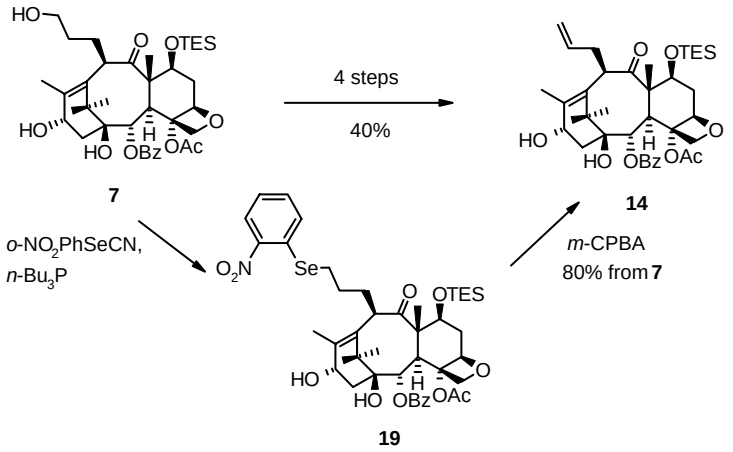
Table 2. Synthesis of Aminoethyl Analogs by Reductive Amination.

entry	Compound	R	yield (%)	method*
1	**18a**		91	a
2	**18b**		52	b
3	**18c**		65	a
4	**18d**		39	a
5	**18e**		39	a
6	**18f**		26	a
7	**18g**		59	b
8	**18h**		83	b

*: method a: 1) amine, 5% Pd-C in MeOH under H_2 gas, 2) HF-Py. method b: 1) amine, $NaBH_3CN$, AcOH, 2) HF-Py.

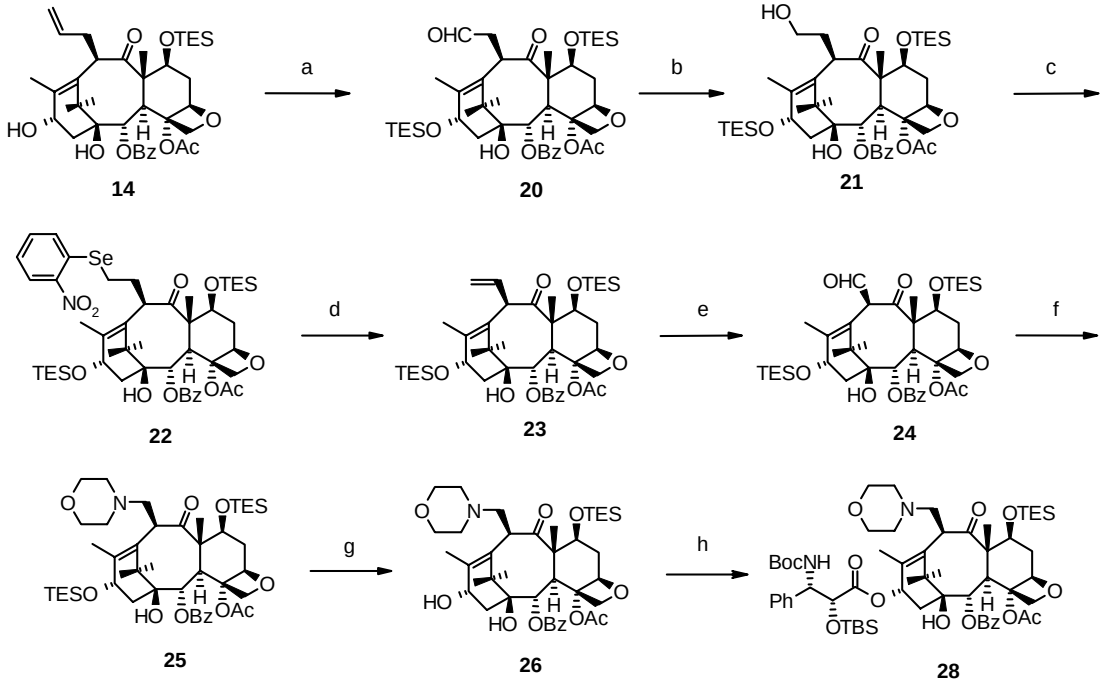
To improve olefination from **7** to **14**, we examined oxidative olefination of selenide (Scheme 3)[10]. An *o*-nitrophenylselenyl group was introduced at the end of the 10-*C* alkyl group using *o*-nitrophenylselenyl cyanide with *n*-tributylphosphine. The resulting selenide (**19)** was oxidized with *m*-chloroperbenzoic acid to give the desired **14** in high yield. This method improved the yield, and reduced the number of reaction steps required.

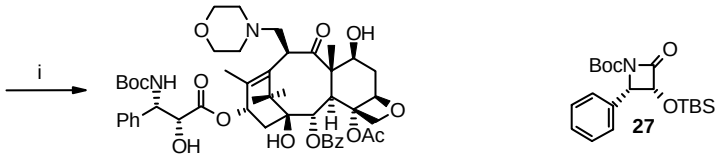
Scheme 3



Synthesis of *sec*-aminomethyl analog (**29**) is described in Scheme 4. The hydroxy group at position 13 of **14** was protected with a TES group, and the resulting olefin was transformed to the aldehyde by Johnson-Remeiux reaction.[11] Succeeding hydrogenation of the aldehyde (**20**) with $NaBH_4$ and the subsequent terminal olefination described above gave 10-*C*-vinyl intermediate (**23)**. Reductive amination of **24**, removal of 7-*O*- and 13-*O*-TES, and re-introduction of TES to 7-hydroxy group afforded **26**. Finally, introduction of a phenylisoserine side chain to 13-hydroxy group and removal of the protecting groups, 2'-*O*-TBDMS and 7-*O*-TES, by hydrogen fluoride pyridine complex gave the desired 10-deoxy-10-*C*-morpholinomethyldocetaxel (**29)** (Scheme 4).

Scheme 4





Reagents and conditions: a) 1) TESCl, imidazole, DMF, 2) OsO_4, NMO, MeOH-THF-H_2O, 3) $NaIO_4$,MeOH-THF-H_2O (54%); b) $NaBH_4$, MeOH (96%); c) *o*-nitrophenylseleno cyanide, *n*-tributylphosphine, THF (92%); d) *m*-chloroperbenzoic acid, CH_2Cl_2 (79%); e) 1) OsO_4, NMO, MeOH-THF-H_2O, 2) $NaIO_4$, MeOH-THF-H_2O (96%); f) morpholine, $NaBH_3CN$, AcOH, EtOH (82%); g) 1) hydrogen fluoride pyridine complex, Py, 2) TESCl, imidazole, DMF (32%); h) **27**, NaHMDS, THF (49%); i) hydrogen fluoride pyridine complex, Py (100%).

Results (Biological Activity) and Discussion: Cytotoxicities of the 10-*C-sec*-aminoalkyl-10-deoxydocetaxel analogs against 7 cell lines (P388, PC-6, PC-12, SBC-3, SBC-3/ADM, PC-6/VCR29-9,[11] PC-6/VP)[12] *in vitro* were examined (Table 3).

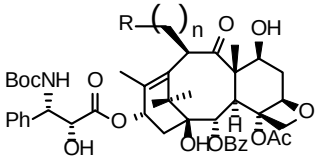


Table 3. Cytotoxicity of 10-*C-sec*-Aminoalkylated Docetaxel Analogs.

	n	R	Cytotoxic activity GI_{50} (ng/mL)[a]						
			P388	PC-6	PC-12	SBC-3	SBC-3/ADM10	PC-6/VCR29-9	PC-6/ VP1-1
2	—	—	6.7	1.1	53.4	0.5	280	135	820
12	3		20.6	5.5	432	19.5	>1000	NT	NT
18a	2		3.1	0.6	13.5	1.1	51.6	76.3	779
18b	2		3.1	4.8	32.9	3.0	262	NT	NT
18c	2		17.3	1.2	299	NT	NT	NT	NT
18d	2		3.8	1.4	193.5	3.0	441	NT	NT
18e	2		5.8	2.0	293	5.2	755	NT	NT
18f	2		11.2	1.8	414	7.2	1003	NT	NT
18g	2		3.6	2.7	91.2	NT*	NT	916	>1000
18h	2		1.1	1.3	5.6	NT	NT	79.6	676
29	1		1.2	1.2	3.3	NT	NT	62.0	220

a) Concentration that inhibited the growth of cells by 50% on 72 h continuous exposure for the seven cell lines [mouse leukemia (P388), human lung cancer cell lines (PC-6, PC-12, SBC-3), and resistant cancer cell lines (PC-6/ VCR29-9, SBC-3/ADM10, PC-6/VP1-1)].[13] *: NT: not tested.

Cytotoxicity of **12**, which has a morpholinopropyl group at the *C*-10 position, was improved compared

with 10-*C*-aminopropyldocetaxel (**5**), but the activity was lower than that of docetaxel. However, some *sec*-aminoethyl analogs showed potent activity similar to that of docetaxel against four cancer cell lines and three resistant cancer cell lines. Morpholinoethyl analogs, (**18a**) and (**18h**), showed the strongest activity among the *sec*-aminoethyl analogs. Comparison of the activities of **18a-h** clarified two things. Firstly, there is spatial margin around 10-*C* position. Secondly, electronic and conformational factors affected the activity. The morpholinomethyl analog (**29**) showed the most potent activity among these aminoalkyl analogs. This result indicated that the chain length of the aminoalkyl group greatly influences the potency of activity. In comparison of the 10-*O*-morpholinoethyl analog (**3**) with **12**, the cytotoxicity of the ether type was slightly stronger than that of the alkyl type. Shortening of the chain length markedly improved the cytotoxicity (compare activities of **2** vs. **18a**, and **18a** vs. **29**). This result indicated that the alkyl type is superior to the ether type, because shortening of the 10-*O*-aminoalkyl chain has a limitation.

In conclusion, several 10-*C*-*sec*-aminoalkyl-10-deoxydocetaxel analogs exhibited cytotoxicity comparable or superior to that of docetaxel (**2**). Further investigation into the *in vivo* antitumor activities of these analogs are currently underway in our laboratory and will be reported in the near future.

EXPERIMENTAL

General Procedures: All melting points were found using a Yanaco PM-S3 or MP-500D apparatus and we are not corrected. IR spectra were obtained on a Hitachi 270-300 IR spectrophotometer. Ms spectra were recorded on a JEOL JMS-HX-100, AX505W, JMS-D300 or JMS-700 spectrometer. ^{1}H-NMR spectra were taken at 400 MHz with a JEOL JNM-EX400 spectrometer; all values are reported in ppm (δ) downfield from $(CH_3)_4Si$. Elemental analyses were performed on a Heraeus CHN-O-Rapid or a Perkin-Elmer 2400CHN instrument. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Merck silica gel (230-400 mesh) was used for column chromatography. Thin layer chromatography (TLC) was performed using silica gel (150A 1.0 mm thickness; PLK5F Whatman).

[10*R*]-10-Deacetoxy-(3-*p*-toluenesulfonyloxypropyl)-7-*O*-triethylsilylbaccatin III (8)

To a stirred solution of **7** (300 mg, 0.428 mmol) in dichloromethane (10 mL) were added *p*-toluenesulfonyl chloride (245 mg, 1.28 mmol), triethylamine (130 mg, 1.28 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine at 0 °C. Stirring was continued for 18 h at ambient temperature. The mixture was poured into ice-water and extracted with chloroform. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (3% MeOH/$CHCl_3$) to give compound (**8**) (360 mg, quant.) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.52 (m, 6H), 0.92 (t, 9H, *J* = 8 Hz), 1.00 (s, 3H), 1.04 (s, 3H), 1.60 (s, 3H), 1.92 (s, 3H), 2.28 (s, 3H), 2.46 (s, 3H), 3.73—3.77 (m, 1H), 4.00—4.10 (m, 3H), 4.15 (d, 1H, *J* = 8

Hz), 4.29 (d, 1H, *J* = 8 Hz), 4.49—4.55 (m, 1H), 4.80—4.88 (br, 1H), 4.95 (d, 1H, *J* = 10 Hz), 5.57 (d, 1H, *J* = 7 Hz), 7.36 (d, 2H, *J* = 8 Hz), 7.47 (t, 2H, *J* = 7 Hz), 7.60 (t, 1H, *J* = 7 Hz), 8.10 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 856 (MH^+).

10-Deacetoxy-10-(3-morpholinopropyl)-7-*O*-triethylsilylbaccatin III (9)

To a stirred solution of **8** (100 mg, 0.117 mmol) in MeOH (2 mL) was added morpholine (51 mg, 0.59 mmol) at ambient temperature. The mixture was refluxed for 5 h. The solvent was removed under reduced pressure, and the residue was purified by TLC (10% MeOH/$CHCl_3$) to give compound (**9**) (74 mg, 82%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.50—0.61 (m, 6H), 0.95 (t, 9H, *J* = 8 Hz), 1.04 (s, 3H), 1.11 (s, 3H), 1.45—2.51 (m, 23H), 3.72 (t, 4H, *J* = 5 Hz), 3.81 (dd, 1H, *J* = 9 Hz, 5 Hz), 4.05 (d, 1H, *J* = 7 Hz), 4.16 (d, 1H, *J* = 8 Hz), 4.29 (d, 1H, *J* = 8 Hz), 4.54 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.80—4.85 (m, 1H), 4.96 (d, 1H, *J* = 8 Hz), 5.59 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.59 (t, 1H, *J* = 8 Hz), 8.10 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 770 (MH^+).

[2'*R*,3'*S*]-13-*O*-(*N*-*tert*-Butoxycarbonyl-*N*,*O*-isopropylidene-3-phenylisoserinyl)-10-deacetoxy-10-(3-morpholinopropyl)-7-*O*-triethylsilylbaccatin III (11)

To a stirred solution of **9** (43.5 mg, 0.057 mmol) and **10** (36.3 mg, 0.113 mmol) in toluene (2 mL) was added dicyclohexylcarbodiimide (23 mg, 0.113 mmol) at 0 °C. Stirring was continued for 15 min at the same temperature, then *N*,*N*-dimethylaminopyridine (7 mg) was added to the reaction at ambient temperature. Stirring was continued for 3 h. The mixture was diluted with ethyl acetate, washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by TLC (3% MeOH/$CHCl_3$) to give compound (**11**) (12 mg, 20%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.48 (m, 6H), 0.93 (t, 9H, *J* = 8 Hz), 1.05—1.50 (m, 5H), 1.13 (s, 3H), 1.20 (s, 3H), 1.59 (s, 3H), 1.67 (s, 9H), 1.77—1.98 (m, 2H), 1.77 (s, 3H), 1.79 (s, 3H), 1.82 (s, 3H), 2.08—2.16 (m, 3H), 2.30—2.48 (m, 5H), 3.70—3.80 (m, 5H), 3.92 (d, 1H, *J* = 7 Hz), 4.06 (d, 1H, *J* = 7 Hz), 4.11 (d, 1H, *J* = 8 Hz), 4.23 (d, 1H, *J* = 8 Hz), 4.44—4.50 (m, 1H), 4.47 (m, 1H), 4.88 (d, 1H, *J* = 8 Hz), 5.04 (br, 1H), 5.62 (d, 1H, *J* = 7 Hz), 6.24 (t, 1H, *J* = 8 Hz), 7.30—7.41 (m, 5H), 7.50 (t, 2H, *J* = 7 Hz), 7.63 (t, 1H, *J* = 7 Hz), 8.05 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 1073 (MH^+).

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[3-(morpholinopropyl)]baccatin III (12)

Compound **(11)** (10 mg, 10 μmol) was dissolved in formic acid (2 mL) and the mixture was stirred for 30 min at ambient temperature. The mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$, washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (2 mL) and $(Boc)_2O$ (15 mg, 0.069 mmol) was added. Stirring was continued for 18 h. The mixture was concentrated under reduced pressure,

and the residue was purified by TLC (3% MeOH/$CHCl_3$) and freeze-dried to give compound (**12**) (5 mg, 54%) as a white solid; $[\alpha]_D^{24}$ -69.8° (c = 0.12, $CHCl_3$); IR (KBr): 3455, 2980, 1980, 1716, 1608 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 0.48—0.56 (m, 6H), 0.93 (t, 9H, *J* = 8 Hz), 1.05—1.50 (m, 5H), 1.13 (s, 3H), 1.20 (s, 3H), 1.59 (s, 3H), 1.67 (s, 9H), 1.77—1.98 (m, 2H), 1.78 (s, 3H), 1.79 (s, 3H), 1.82 (s, 3H), 2.08—2.16 (m, 3H), 2.30—2.48 (m, 5H), 3.70—3.80 (m, 5H), 3.92 (d, 1H, *J* = 7 Hz), 4.06 (d, 1H, *J* = 7 Hz), 4.11 (d, 1H, *J* = 8 Hz), 4.23 (d, 1H, *J* = 8 Hz), 4.44—4.50 (m, 1H), 4.47 (m, 1H), 4.88 (d, 1H, *J* = 8 Hz), 5.04 (br, 1H), 5.62 (d, 1H, *J* = 7 Hz), 6.24 (t, 1H, *J* = 7 Hz), 7.30—7.41 (m, 5H), 7.50 (t, 2H, *J* = 7 Hz), 7.63 (t, 1H, *J* = 7 Hz), 8 05 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 919 (MH^+); *Anal.* Calcd for $C_{50}H_{66}N_2O_{14}$ · $1.5H_2O$; C, 63.48; H, 7.35; N, 2.96. Found: C, 63.21; H, 7.22; N, 2.90.

10-Deacetoxy-10-(3-methanesulfinylpropyl)-7-*O*-triethylsilylbaccatin III (13)

To a cooled and stirred solution of **8** (425 mg, 0.50 mmol) in THF (5 mL) were added NaSMe solution in H_2O (50% w/v, 2.3 mL, 16.4 mmol) and *n*-Bu_4NI (127 mg, 0.34 mmol). Stirring was continued for 6 h at ambient temperature. The mixture was diluted with ethyl acetate (100 mL), washed with H_2O and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel ($CHCl_3$/*n*-hexane/acetone, 14:5:1) to give 10-deacetyl-10-(3-methylthiopropyl)-7-*O*-triethylsilylbaccatin III (332 mg). The compound was dissolved in MeOH (7 mL) and was added to a solution of $NaIO_4$ (150 mg, 0.70 mmol) in H_2O (3.5 mL) at 0 °C. Stirring was continued for 2 h at 0 °C. The mixture was diluted with ethyl acetate (100 mL), washed with H_2O and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by TLC (6% MeOH/$CHCl_3$) to give compound (**13**) (312 mg, 84%) as a colorless oil; IR (KBr): 3455, 2980, 1980, 1716, 1608 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 0.55 (m, 6H), 0.95 (t, 9H, *J* = 8 Hz), 1.06, 1.08, 1.10 and 1.11 (each s, total 6H), 1.63 (s, 3H), 1.98 (s, 3H), 2.29 (s, 3H), 1.70—2.35 (m, 6H), 2.50 (m, 1H), 2.59 (s, 3H), 2.60—2.90 (m, 3H), 3.86 (dd, 1H, *J* = 10 Hz, 5 Hz), 4.04 (d, 1H, *J* = 7 Hz), 4.16 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 8 Hz), 4.55 (dd, 1H, *J* = 10 Hz, 6 Hz), 4.85 (br, 1 H), 4.97 (d, 1H, *J* = 8 Hz), 5.60 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 7 Hz), 8.11 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 747 (MH^+).

10-Allyl-10-deacetoxy-7-*O*-triethylsilylbaccatin III (14)

To a stirred solution of **13** (294 mg, 0.39 mmol) in *o*-dichlorobenzene (20 mL) was added Na_2CO_3 (42 mg, 0.39 mmol). The mixture was refluxed for 4 h. The insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by TLC ($CHCl_3$/*n*-hexane/acetone, 7:2:1) and freeze-dried to give compound (**14**) (100 mg, 37%) as a colorless powder; $[\alpha]_D^{24}$ -55.8° (c = 0.50, $CHCl_3$); IR (KBr): 3475, 2970, 1980, 1720 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 0.57 (m, 6H), 0.96 (t, 9H, *J*= 8 Hz), 1.13 (s, 3H), 1.18 (s, 3H), 1.63 (s, 3H), 1.89 (m, 1H), 1.93 (d, 3H, *J* = 1 Hz), 2.15—2.35 (m, 2H),

2.29 (s, 3H), 2.40—2.60 (m, 2H), 2.80 (m, 1H), 3.90 (dd, 1H, *J* = 10 Hz, 4 Hz), 4.05 (d, 1H, *J* = 7 Hz), 4.17 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 8 Hz), 4.54 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.85 (br, 1H), 4.96 (dd, 1H, *J* = 10 Hz, 2 Hz), 5.01 (d, 1H, *J* = 10 Hz), 5.09 (d, 1H, *J* = 16 Hz), 5.61 (d, 1H, *J* = 7 Hz), 5.79 (ddt, *J* = 16 Hz, 10 Hz, 7 Hz, 1H), 7.47 (t, 2H, *J* = 7 Hz), 7.60 (t, 1H, *J* = 7 Hz), 8.11 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 683 (MH^+); *Anal.* Calcd for $C_{38}H_{54}O_9Si$: C, 66.83; H, 7.97. Found: C, 66.85; H, 8.05.

[2'*R*,3'*S*]-10-Allyl-13-*O*-(3-*tert*-butoxycarbonylamino-2-*O*-triethylsilyl-3-phenylisoserinyl)-10-deacetoxy-7-*O*-triethylsilylbaccatin III (16)

To a stirred suspension of NaH (100 mg, 2.5 mmol, 60% oil suspension) in THF (1.5 mL) were added **14** (100 mg, 0.15 mmol) and **15** (110 mg, 0.29 mmol) in THF (1.5 mL) at 0 °C. Stirring was continued for 2 h at 0 °C. The mixture was poured into sat. NH_4Cl, and extracted with ethyl acetate. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by TLC ($CHCl_3$/*n*-hexane/acetone, 10:9:1) to give compound (**16**) (141 mg, 91%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.38 (m, 6H), 0.57 (m, 6H), 0.78 (t, 9H, *J* = 8 Hz), 0.96 (m, 9H), 1.16 (s, 3H), 1.25 (s, 3H), 1.30 (s, 9H), 1.64 (s, 3H), 1.76 (s, 3H), 1.91 (m, 1H), 2.13 (m, 1H), 2.38 (m, 1H), 2.45—2.55 (m, 1H), 2.48 (m, 1H), 2.52 (s, 3H), 2.84 (m, 1H), 3.84 (dd, 1H, *J* = 10 Hz, 4 Hz), 3.99 (d, 1 H, *J* = 7 Hz), 4.21 (d, 1H, *J* = 8 Hz), 4.31 (d, 1H, *J* = 8 Hz), 4.52 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.54 (br, 1H), 4.96 (dd, 1H, *J* = 10 Hz, 2 Hz), 5.04 (d, 1H, *J* = 10 Hz), 5.10 (d, 1H, *J* = 17 Hz), 5.39 (br, 1H), 5.49 (br, 1H), 5.67 (d, 1H, *J* = 7 Hz), 5.78 (m, 1H), 6.26 (t, 1H, *J* = 9 Hz), 7.20—7.40 (m, 5 H), 7.48 (t, 2H, *J* = 7 Hz), 7.58 (t, 1H, *J* = 7 Hz), 8.12 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 1061 (MH^+).

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-2-*O*-triethylsilyl-3-phenylisoserinyl)-10-deacetoxy-10-formylmethyl-7-*O*-triethylsilylbaccatin III (17)

To a stirred solution of **16** (141 mg, 0.13 mmol) in THF/H_2O (3.6 mL, 5:1, v/v) were added *N*-methylmorpholine *N*-oxide (24 mg, 0.20 mmol) and a catalytic amount of OsO_4. Stirring was continued for 2 h at ambient temperature. The mixture was poured into 10% $Na_2S_2O_3$, and extracted with ethyl acetate. The combined organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in THF/H_2O (12 mL, 1:1, v/v) and $NaIO_4$ (150 mg, 0.70 mmol) was added . After stirring for 24 h at ambient temperature, the mixture was poured into H_2O, and extracted with ethyl acetate. The combined organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by TLC ($CHCl_3$/*n*-hexane/acetone, 14:5:1) and freeze-dried from dioxane to give compound (**17**) (119 mg, 84%) as a colorless powder; $[\alpha]_D^{24}$ -25.0° (c = 0.55, $CHCl_3$); IR (KBr): 3452, 2960, 1755, 1720 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 0.39 (m, 6H), 0.57 (m, 6H), 0.78 (t, 9H, *J* = 8 Hz), 0.94 (t, 9H, *J* = 8 Hz), 1.13 (s, 3H), 1.24 (s, 3H), 1.29 (s, 9H), 1.66 (s, 3H), 1.88 (s, 3H), 1.92 (m,

1H), 2.15 (m, 1H), 2.38 (m, 1H), 2.45—2.62 (m, 2H), 2.53 (s, 3H), 3.59 (dd, 1H, *J* = 17 Hz, 6 Hz), 4.00 (d, 1H, *J* = 7 Hz), 4.20 (d, 1H, *J* = 8 Hz), 4.32 (d, 1H, *J* = 8 Hz), 4.49 (t, 1H, *J* = 6 Hz), 4.54 (br, 1H), 4.59 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.97 (dd, 1H, *J* = 10 Hz, 2 Hz), 5.29 (br, 1H), 5.48 (br, 1H), 5.68 (d, 1H, *J* = 7 Hz), 6.21 (t, 1H, *J* = 10 Hz), 7.22—7.37 (m, 5H), 7.48 (t, 2H, *J* = 7 Hz), 7.58 (t, 1H, *J* = 7 Hz), 8.12 (d, 2H, *J* = 7 Hz), 9 79 (s, 1H); MS (FAB) *m/z*: 1063 (MH^+); *Anal.* Calcd for $C_{57}H_{83}NO_{14}Si \cdot H_2O$: C, 63.36; H, 7.93; N, 1.30. Found: C, 63.27; H, 7.82; N, 1.22.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-(2-morpholinoethyl)baccatin III (18a)

To a stirred solution of **17** (9 mg, 8.5 μmol) in MeOH (1.0 mL) were added morpholine (10 μL, 0.083 mmol) and 10% Pd on carbon (25 mg, 50% w/w, wet). Stirring was continued for 3 h under H_2 gas at ambient temperature. The insoluble material was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in pyridine (1 mL), and hydrogen fluoride pyridine complex (0.2 mL, 0.14 mmol) was added at 0 °C. The reaction was stirred for 12 h at ambient temperature. The mixture was diluted with ethyl acetate and was washed with water and sat. $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by TLC (6% MeOH/$CHCl_3$) and freeze-dried from dioxane to give compound (**18a**) (7 mg, 91%) as a colorless powder; $[\alpha]_D^{24}$ -55.8° (c = 0.15, $CHCl_3$); IR (KBr): 3455, 2974, 1982, 1716, 1610 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.21 (s, 3H), 1.39 (s, 9H), 1.45—1.55 (m, 1H), 1.62 (s, 3H), 1.70—1.95 (m, 2H), 1.78 (s, 3H), 2.38 (s, 3H), 2.15—2.75 (m, 9H), 3.68 (m, 4H), 3.94 (d, 1H, *J* = 7 Hz), 4.01 (dd, 1H, *J* = 9 Hz, 2 Hz), 4.19 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 8 Hz), 4.44 (dd, 1H, *J* = 11 Hz, 6 Hz), 4.60 (br, 1H), 5.00 (dd, 1H, *J* = 10 Hz, 2 Hz), 5.27 (d, 1H, *J* = 9 Hz), 5 37 (d, 1H, *J* = 9 Hz), 5.64 (d, 1H, *J* = 7 Hz), 6.17 (d, 1H, *J* = 9 Hz), 7.32—7.44 (m, 5H), 7.50 (t, 2H, *J* = 7 Hz), 7.61 (t, 1H, *J* = 7 Hz), 8.11 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 905 (MH^+); *Anal.* Calcd for $C_{49}H_{64}N_2O_{14} \cdot H_2O$: C, 63.76; H, 7.20; N, 3.03. Found: C, 63.47; H, 7.32; N, 2.92.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-(2-thiomorpholinoethyl)baccatin III (18b)

To a stirred solution of **17** (17 mg, 16 μmol) in EtOH (1.0 mL) were added thiomorpholine (16 μL, 0.16 mmol), AcOH (9.2 μl, 0.16 mmol) and $NaBH_3CN$ (10 mg, 0.16 mmol). Stirring was continued for 1.5 h at ambient temperature. The mixture was diluted with ethyl acetate, poured into sat. $NaHCO_3$, extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by TLC (5% acetone/$CHCl_3$). The purified compound was dissolved in pyridine (1 mL), and hydrogen fluoride pyridine complex (0.2 mL, 0.14 mmol) was added at 0 °C. The reaction was stirred for 18 h at ambient temperature. The mixture was diluted with ethyl acetate, washed with water

and sat. $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by TLC (3% MeOH/$CHCl_3$) and freeze-dried from dioxane to give compound (**18b**) (8 mg, 52%) as a colorless powder; $[\alpha]_D^{24}$ -59.5° (c = 0.1, $CHCl_3$); IR (KBr): 3448, 2976, 1982, 1714, 1608(cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.21 (s, 3H), 1.32 (s, 9H), 1.62 (s, 3H), 1.78 (s, 3H), 1.87 (m, 1H), 2.19 (m, 1H), 2.36 (m, 5H), 2.37 (s, 3H), 2.49 (m, 1H), 2.68 (m, 6H), 2.78 (m, 2H), 3.94 (d, 1H, *J* = 7 Hz), 4.19 (d, 1H, *J* = 8 Hz), 4.29 (d, 1H, *J* = 8 Hz), 4.42 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.60 (s, 1H), 4.98 (d, 1H, *J* = 8 Hz), 5.24 (d, 1H, *J* = 9 Hz), 5.36 (d, 1H, *J* = 9 Hz), 5.62 (d, 1H, *J* = 6 Hz), 6.17 (t, 1H, *J* = 9 Hz), 7.31—7.37 (m, 5H), 7.47 (t, 2H, *J* = 7 Hz), 7.61 (t, 1H, *J* = 7 Hz), 8.11 (d, 2H, *J* = 7 Hz); MS (FAB) *m/z*: 921 (MH^+); *Anal.* Calcd for $C_{49}H_{64}N_2O_{13}S \cdot 2H_2O$: C, 61.49; H, 7.16; N, 2.93. Found: C, 61.20; H, 6.99; N, 2.63.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-(2-*N*,*N*-dimethylaminoethyl)baccatin III (18c) was prepared by a method similar to that described for preparation of **18a** by reaction of aldehyde (**17**) with *N, N*-dimethylamine and removal of the protecting group with hydrogen fluoride pyridine complex. **18c** was attained as a colorless powder (65%); ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.36 (S, 9H), 1.61 (m, 1H), 1.65 (s, 3H), 1.70 (m, 3H), 1.82 (m, 1H), 2.04 (s, 6H), 2.15 (m, 1H), 2.32 (s, 3H), 2.38—2.53 (m, 3H), 2.78 (dd, *J* = 14 Hz, 9 Hz, 1H), 3.33 (br s, 4H), 3.58 (m, 1H), 3.80 (d, *J* = 7 Hz, 1H), 4.16 (dd, *J* = 9 Hz, 1 Hz, 1H), 4.28—4.30 (m, 2H), 4.57 (d, *J* = 3 Hz), 4.90 (t, *J* = 8 Hz, 1H), 5.24 (m, 1H), 5.67 (d, *J* = 7 Hz, 1H), 5.97 (m, 1H), 7.40 (m, 3H), 7.47 (m, 2H), 7.58 (m, 1H), 8.03 (m, 1H), 8.06 (m, 1H); MS (FAB) *m/z*: 863 (MH^+); HR-MS Calcd for $C_{47}H_{63}N_2O_{13}$: 863.4330. Found: 863.4371.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-(2-piperidinylethyl)baccatin III (18d) was prepared by a method similar to that described for preparation of **18a** by reaction of aldehyde (**17**) with piperidine and removal of the protecting group with hydrogen fluoride pyridine complex. **18d** was attained as a colorless powder (39%); ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.36 (S, 9H), 1.42—1.50 (m, 6H), 1.61 (m, 1H), 1.65 (s, 3H), 1.70 (m, 3H), 1.82 (m, 1H), 2.22 (m, 2H), 2.30 (m, 2H), 2.32 (s, 3H), 2.38—2.53 (m, 5H), 2.78 (dd, *J* = 14 Hz, 9 Hz, 1H), 3.33 (brs, 4H), 3.58 (m, 1H), 3.80 (d, *J* = 7 Hz, 1H), 4.16 (dd, *J* = 9 Hz, 1 Hz, 1H), 4.28—4.30 (m, 2H), 4.57 (d, *J* = 3 Hz), 4.90 (t, *J* = 8 Hz, 1H), 5.24 (m, 1H), 5.67 (d, *J* = 7 Hz, 1H), 5.97 (m, 1H), 7.40 (m, 3H), 7.47 (m, 2H), 7.58 (m, 1H), 8.03 (m, 1H), 8.06 (m, 1H); MS (FAB) *m/z*: 903 (MH^+); HR-MS Calcd for $C_{50}H_{67}N_2O_{13}$: 903.4643. Found: 903.4656.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[2-(4-*N*-methyl-1-piperadinyl)ethyl]baccatin III (18e) was prepared by a method similar to that described for preparation of **18a** by reaction of aldehyde (**17**) with *N*-methylpiperazine and removal of the protecting group with

hydrogen fluoride pyridine complex. **18e** was attained as a colorless powder (39%); ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.36 (S, 9H), 1.58 (m, 1H), 1.65 (s, 3H), 1.70 (s, 3H), 1.78 (m, 1H), 2.23 (s, 3H), 2.32 (s, 3H), 2.35—2.53 (m, 12H), 2.78 (dd, *J* = 14 Hz, 9 Hz, 1H), 3.33 (br, 4H), 3.58 (m, 1H), 3.80 (d, *J* = 7 Hz, 1H), 4.16 (dd, *J* = 9 Hz, 1 Hz, 1H), 4.28—4.30 (m, 2H), 4.57 (d, *J* = 3 Hz), 4.90 (t, *J* = 8 Hz, 1H), 5.24 (m, 1H), 5.67 (d, *J* = 7 Hz, 1H), 5.97 (m, 1H), 7.40 (m, 3H), 7.47 (m, 2H), 7.58 (m, 1H), 8.03 (m, 1H), 8.06 (m, 1H); MS (FAB) *m/z*: 918 (MH^+); HR-MS Calcd for $C_{50}H_{68}N_3O_{13}$: 918.4752. Found, 918.4747.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[2-(1-pyrrolidinyl)ethyl]baccatin III (18f) was prepared by a method similar to that described for preparation of **18a** by reaction of aldehyde (**17**) with pyrrolidine and removal of the protecting group with hydrogen fluoride pyridine complex. **18f** was attained as a colorless powder (26%); ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H, 17-Me), 1.11 (s, 3H, Me), 1.36 (S, 9H, *t*-Butyl), 1.61 (m, 1H, 10-CH_2), 1.65 (s, 3H, 19-Me), 1.70 (s, 3H, 18-Me), 1.72 (m, 2H, CH_2-pyrrolidine), 1.81 (m, 3H, CH_2-pyrrolidine and 10-CH_2), 2.32 (s, 3H, acetyl), 2.38 (m, 1H, 6-CH_2), 2.45—2.59 (m, 8H, 14-CH_2, CH_2-pyrrolidine, 10-CH_2, and6-CH_2), 2.78 (dd, *J* = 14 Hz, 9 Hz, 1H, 14-CH_2), 3.33 (brs, 4H, 1-OH, 7-OH, 2'-OH, and 3'-NH), 3.58 (m, 1H,10-CH), 3.80 (d, *J* = 7 Hz, 1H, 3-CH), 4.16 (dd, *J* = 9 Hz, 1 Hz, 1H, 20-CH_2), 4.28—4.30 (m, 2H, 7-CH and 20-CH_2), 4.57 (d, *J* = 3 Hz, 2'-CH), 4.90 (t, *J* = 8 Hz, 1H, 5-CH), 5.24 (m, 1H, 3'-CH), 5.67 (d, *J* = 7 Hz,1H,2-CH), 5.97 (m, 1H, 13-CH), 7.40 (m, 3H, 3'-Ph), 7.47 (m, 2H, 2'-Bz), 7.58 (m, 1H, 2'-Bz), 8.03 (m, 1H, 2'-Bz), 8.06 (m, 1H, 2'-Bz); MS (FAB) *m/z*: 889 (MH^+); HR-MS Calcd for $C_{49}H_{65}N_2O_{13}$: 889.4487. Found, 889.4506.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[2-(1-homopiperidinyl)ethyl]baccatin III (18g) was prepared by a method similar to that described for preparation of **18b** by reaction of aldehyde (**17**) with homopiperidine and removal of the protecting group with hydrogen fluoride pyridine complex. **18g** was attained as a colorless powder (59%); IR (KBr): 3668, 2936, 1962, 1714, 1606 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.12 (s, 3H), 1.32 (brs, 9H), 1.62 (s, 3H), 1.68 (m, 6H), 1.87 (m, 5H), 1.88 (s, 3H), 2.20 (m, 1H), 2.30 (m, 2H), 2.37 (s, 3H), 2.49 (m, 1H), 2.60 (m, 1H), 2.90—3.10 (br, 6H), 3.52 (m, 1H), 3.95 (d, 1H, *J* = 7 Hz), 4.19 (d, 1H, *J* = 9 Hz), 4.23 (m, 1H), 4.28 (d, 1H, *J* = 9 Hz), 4.51 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.60 (s, 1H), 4.96 (d, 1H, *J* = 8 Hz), 5.26 (m, 1H), 5.42 (m, 1H), 5.62 (d, 1H, *J* = 7 Hz), 6.17 (m, 1H), 7.31—7.38 (m, 5H), 7.49 (t, 2H, *J* = 8 Hz), 7.61 (t, 1H, *J* = 8 Hz), 8.13 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 915 (MH^+); HR-MS Calcd for $C_{51}H_{69}N_2O_{13}$: 917.4800. Found, 917.4835.

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[2-(2,6-*cis*-dimethyl-4-morpholyl)ethyl]baccatin III (18h) was prepared by a method similar to that described for

preparation of **18b** by reaction of aldehyde (**17**) with 2,6-*cis*-dimethylmorpholine and removal of the protecting group with hydrogen fluoride pyridine complex. **18h** was attained as a colorless powder (83%); IR (KBr): 3448, 2936, 2348, 1714, 1604 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.16 (d, 1H, *J* = 7 Hz), 1.21 (s, 3H), 1.32 (s, 9H), 1.62 (s, 3H), 1.78 (m, 6H), 1.87 (m, 1H), 2.15—2.35 (m, 7H), 2.37 (m, 7H), 2.49 (m, 1H), 2.60 (m, 1H), 2.72—2.90 (m, 2H), 3.62 (m, 2H), 3.92 (d, 1H, *J* = 7 Hz), 4.00 (d, 1H, *J* = 7 Hz), 4.19 (d, 1H, *J* = 9 Hz), 4.29 (d, 1H, *J* = 9 Hz), 4.42 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.60 (s, 1H), 5.00 (d, 1H, *J* = 8 Hz), 5.28 (m, 1H), 5.38 (d, 1H, *J* = 9 Hz), 5.62 (d, 1H, *J* = 6 Hz), 6.18 (m, 1H), 7.31—7.42 (m, 5H), 7.49 (t, 2H, *J* = 8 Hz), 7.61 (t, 1H, *J* = 8 Hz), 8.11 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 933 (MH^+); HR-MS Calcd for $C_{51}H_{69}N_2O_{14}$: 933.4749. Found, 933.4758.

10-Deacetoxy-10-[2-(*o*-nitrophenylselenyl)ethyl]-7-*O*-triethylsilylbaccatin III (19)

To a stirred solution of **7** (87 mg, 0.12 mmol) and *o*-nitrophenylselenocyanate (34 mg, 0.15 mmol) in THF (2 mL) was added *n*-tributylphosphine (37 μL, 0.15 mmol) at 0 °C under N_2 gas. Stirring was continued for 2 h at ambient temperature. After removal of the solvent under reduced pressure, the residue was purified by TLC (3% MeOH/$CHCl_3$) to give **19** (80 mg, 73%) as a colorless solid; IR (KBr): 3508, 2884, 2340, 1970, 1710, 1454 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 0.52 (m, 6H), 0.94 (t, 9H, *J* = 8 Hz), 1.02 (s, 3H), 1.11 (s, 3H), 1.62 (s, 3H), 1.70—1.90 (m, 5H), 1.94 (s, 3H), 2.20—30 (m, 2H), 2.28 (s, 3H), 2.49 (m, 1H), 2.90—3.05 (m, 2H), 3.82 (m, 1H), 4.03 (d, 1H, *J* = 7 Hz), 4.16 (d, 1H, *J* = 9 Hz), 4.28 (d, 1H, *J* = 9 Hz), 4.52 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.82 (m, 1H), 4.96 (d, 1H, *J* = 9 Hz), 5.59 (d, 1H, *J* = 6 Hz), 7.32 (m, 1H), 7.46 (t, 2H, *J* = 8 Hz), 7.53 (d, 2H, *J* = 4 Hz), 7.59 (t, 1H, *J* = 8 Hz), 8.10 (m, 2H), 8.29 (d, 1H, *J* = 8 Hz); MS (FAB) *m/z*: 886 (MH^+).

10-Allyl-10-deacetoxy-7-*O*-triethylsilylbaccatin III (14)

To a stirred solution of **19** (886 mg, 1.0 mmol) in THF (26 mL) was added a THF (2 mL) solution of *m*-chloroperbenzoic acid (181 mg, 1.05 mmol) at 0 °C. Stirring was continued for 3 h at ambient temperature. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel ($CHCl_3$/*n*-hexane/acetone, 7:3:0.3) to give **14** (556 mg, 81%) as a colorless powder.

10-Deacetoxy-10-formylmethyl-7-*O*-13-*O*-*bis*-triethylsilylbaccatin III (20)

To a stirred solution of **14** (368 mg, 0.54 mmol) in DMF (5 mL) were added imidazole (367 mg, 5.4 mmol) and triethylsilyl chloride (0.90 mL, 5.4 mmol) at ambient temperature. After 2 h, the mixture was poured into sat. NH_4Cl, extracted with ethylacetate,washedwithbrine,driedoveranhydrous$MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in THF/H_2O (17 mL, 13:4, v/v), and *N*-methylmorpholine *N*-oxide (168 mg, 1.44 mmol) and a catalytic amount of OsO_4 were added . Stirring was continued for 15 h at ambient temperature. The mixture was poured into brine, extracted with ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced

pressure. The residue was dissolved in THF/MeOH/H_2O (12 mL, 1:1:1, v/v/v), and $NaIO_4$ (773 mg, 2.8 mmol) was added . After stirring for 6 h at ambient temperature, the mixture was diluted with H_2O, extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 9:1) to give **20** (173 mg, 79%) as a colorless amorphous solid; ^{1}H-NMR ($CDCl_3$) δ 0.55 (m, 6H), 0.62 (m, 6H), 0.92 (t, 9H, *J* = 8 Hz), 1.0 (t, 9H, *J* = 8 Hz), 1.08 (s, 3H), 1.11 (s, 3H), 1.62 (s, 3H), 1.89 (m, 1H), 1.96 (d, 3H, *J* = 1 Hz), 2.10 (m, 1H), 2.22 (m, 1H), 2.29 (s, 3H), 2.48—2.60 (m, 3H), 3.46 (dq, 1H, *J* = 17 Hz, 6 Hz, 2 Hz), 3.98 (d, 1H, *J* = 7 Hz), 4.15 (d, 1H, *J* = 9 Hz), 4.29 (d, 1H, *J* = 9 Hz), 4.44 (dd, 1H, *J* = 7 Hz, 5 Hz), 4.59 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.86 (t, 1H, *J* = 8 Hz), 4.97 (d, 1H, *J* = 9 Hz), 5.60 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 8.08 (m, 2H), 9.77 (t, 1H, *J* = 2 Hz); MS (FAB) *m/z*: 799 (MH^+).

10-Deacetoxy-10-(2-hydroxyethyl)-7-*O*-13-*O*-*bis*-triethylsilylbaccatin III (21)

To a stirred solution of **20** (412 mg, 0.5 mmol) in MeOH (17 mL) was added $NaBH_4$ (78 mg, 2.0 mmol) at 0 °C. Stirring was continued for 2 h at the same temperature. The mixture was diluted with $CHCl_3$, poured into ice-water, extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 4:1) to give **21** (398 mg, 96%) as a colorless amorphous solid; ^{1}H-NMR ($CDCl_3$) δ 0.59 (m, 6H), 0.68 (m, 6H), 0.97 (t, 9H, *J* = 8 Hz), 1.01 (t, 9H, *J* = 8 Hz), 1.10 (s, 6H), 1.62 (s, 3H), 1.85 (m, 3H), 1.96 (s, 3H), 2.10 (m, 1H), 2.22 (m, 1H), 2.30 (s, 3H), 2.40—2.50 (m, 3H), 3.60 (br, 1H), 3.70 (br, 1H), 3.98 (m, 2H), 4.16 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 9 Hz), 4.58 (dd, 1H, *J* = 7 Hz, 5 Hz), 4.91 (t, 1H, *J* = 8 Hz), 4.99 (d, 1H, *J* = 9 Hz), 5.60 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 8.08 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 801 (MH^+).

10-Deacetoxy-10-[2-(*o*-nitrophenylselenyl)ethyl]-7-*O*-13-*O*-*bis*-triethylsilylbaccatin III (22)

To a stirred solution of **21** (398 mg, 0.5 mmol) and *o*-nitrophenylselenocyanate (135 mg, 0.6 mmol) in THF (8 mL) was added *n*-tributylphosphine (0.15 mL, 0.6 mmol) at 0 °C under N_2 gas. Stirring was continued for 2 h at ambient temperature. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 4:1) to give **22** (450 mg, 92%) as a colorless amorphous solid; ^{1}H-NMR ($CDCl_3$) δ 0.51 (m, 6H), 0.68 (m, 6H), 0.91 (m, 9H), 1.01 (m, 9H), 1.10 (s, 3H), 1.12 (s, 3H), 1.62 (s, 3H), 1.88 (m, 1H), 1.99 (s, 3H),2.10 (m, 2H), 2.23 (m, 1H), 2.29 (s, 3H), 2.50 (m, 1H), 2.61 (m, 1H), 2.83 (m, 1H), 2.94 (m, 1H), 3.92 (m, 2H), 4.15 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 9 Hz), 4.59 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.92 (m, 1H), 4.95 (d, 1H, *J* = 9 Hz), 5.60 (d, 1H, *J* = 7 Hz), 7.34 (t, 1H, *J* = 8 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.57 (m, 2H), 7.70 (d, 1H, *J* = 8 Hz), 8.09 (m, 2H), 8.31 (dd, *J* = 8 Hz, 1 Hz, 1H); MS (FAB) *m/z*: 986 (MH^+).

10-Deacetoxy-7-*O*-13-*O*-*bis*-triethylsilyl-10-vinylbaccatin III (23)

To a stirred solution of **22** (1.56 g, 1.58 mmol) in THF (45 mL) was added a THF (4 mL) solution of *m*-chloroperbenzoic acid (70%, 468 mg, 1.9 mmol) at 0 °C. Stirring was continued for 2 h at ambient temperature. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 9:1) to give **23** (1.05 g, 85%) as a colorless amorphous solid; ^{1}H-NMR ($CDCl_3$) δ 0.55 (m, 6H), 0.68 (m, 6H), 0.94 (m, 9H), 1.03 (m, 9H), 1.05 (s, 3H), 1.14 (s, 3H), 1.63 (s, 3H), 1.90 (m, 1H), 1.91 (d, 3H, *J* = 1 Hz), 2.11 (m, 1H), 2.25 (m, 1H), 2.30 (s, 3H), 2.46 (m, 1H), 4.02 (d, 1H, *J* = 7 Hz), 4.17 (d, 1H, *J* = 9 Hz), 4.30 (d, 1H, *J* = 9 Hz), 4.48 (d, 1H, *J* = 3 Hz), 4.52 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.96—5.06 (m, 3H), 5.23 (m, 1H), 5.60 (d, 1H, *J* = 7 Hz), 6.58 (m, 1H), 7.47 (t, 2H, *J* = 8 Hz), 7.59 (t, 1H, *J* = 8 Hz), 8.09 (m, 2H); MS (FAB) *m/z*: 783 (MH^+).

10-Deacetoxy-10-formyl-7-*O*-13-*O*-*bis*-triethylsilylbaccatin III (24)

To a stirred solution of **23** (283 mg, 0.36 mmol) in THF-MeOH-H_2O (1:1:1, v/v/v, 9 mL) were added *N*-methylmorpholine *N*-oxide (213 mg, 2.0 mmol) and a catalytic amount of OsO_4, and the reaction mixture was stirred for 18 h. Saturated $Na_2S_2O_3$ (50 mL) was added to the mixture and stirred for 1 h. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in THF-MeOH-H_2O (1:1:1, v/v/v, 9 mL) and $NaIO_4$ (387 mg, 1.8 mmol) was added , and stirred for 13 h at ambient temperature. Saturated $Na_2S_2O_3$ (50 mL) was added to the mixture and stirred for 1 h. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 9:1) to give **24** (272 mg, 96%) as a colorless solid; ^{1}H-NMR ($CDCl_3$) δ 0.59 (m, 6H), 0.68 (m, 6H), 0.97 (t, 9H, *J* = 8 Hz), 1.02 (s, 12H), 1.20 (s, 3H), 1.64 (s, 3H), 1.87 (s, 3H), 1.92 (m, 1H), 2.14 (m, 1H), 2.21 (m, 1H), 2.29 (s, 3H), 2.52 (m, 1H), 3.89 (d, 1H, *J* = 7 Hz), 4.15 (d, 1H, *J* = 8 Hz), 4.30 (d, 1H, *J* = 8 Hz), 4.58 (dd, 1H, *J* = 11, 7 Hz), 4.66 (s, 1H), 4.97 (m, 2H), 5.61 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 8.09 (d, 2H, *J* = 8 Hz), 10.22 (s, 1H).; MS (FAB) *m/z*: 785 (MH^+).

10-Deacetoxy-10-morpholinomethyl-7-*O*-13-*O*-*bis*-triethylsilylbaccatin III (25)

To a stirred solution of **24** (219 mg, 0.28 mmol) in EtOH (6 mL) were added morpholine (243 μL, 2.8 mmol) and acetic acid (160 μl, 1.28 mmol) at ambient temperature. The mixture was stirred for 5 min at ambient temperature, then cooled to 0 ^oC. To the cooled solution was added $NaBH_3CN$ (175 mg, 2.8 mmol), and stirring was continued for 18 h at ambient temperature. The mixture was poured into sat. $NaHCO_3$, extracted with $CHCl_3$ (50 mL x 3). The combined organic phase was washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel ($CHCl_3$/acetone, 95: 5) to give **25** (204 mg, 85%) as a pale yellow oil; ^{1}H-

NMR ($CDCl_3$) δ 0.58 (m, 6H), 0.68 (m, 6H), 0.96 (t, 9H, *J* = 8 Hz), 1.01 (s, 12H), 1.09 (m, 3H), 1.17 (s, 3H), 1.60 (s, 3H), 1.88 (m, 1H), 2.00 (d, 3H, *J* = 1 Hz), 2.10 (m, 1H), 2.21 (m, 1H), 2.31 (s, 3H), 2.50 (m, 4H), 2.72 (dd, 1H, *J* = 14, 8 Hz), 3.10 (dd, 1H, *J* = 14, 4 Hz), 3.63 (m, 4H), 3.99 (d, 1H, *J* = 7 Hz), 4.07 (m, 1H), 4.15 (d, 1H, *J* = 8 Hz), 4.28 (d, 1H, *J* = 8 Hz), 4.55 (dd, 1H, *J* = 11, 6 Hz), 4.92 (m, 1H), 4.97 (m, 1H), 5.58 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 8.08 (m, 2H); MS (FAB) *m/z*: 856 (MH^+).

10-Deacetoxy-10-morpholinomethyl-7-*O*-triethylsilylbaccatin III (26)

To a stirred solution of **25** (18 mg, 0.02 mmol) in pyridine (1 mL) was added hydrogen fluoride pyridine complex (0.2 mL, 0.14 mmol) at 0 °C. The mixture was stirred for 12 h at ambient temperature. The mixture was diluted with ethyl acetate, washed with water and sat. $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in DMF (1 mL), and imidazole (5.7 mg, 0.08 mmol) and triethylsilyl chloride (0.014 mL, 0.08 mmol) were added at 0 °C. The reaction was stirred for 4 h at 0 °C. The mixture was poured into sat. $NaHCO_3$ and extracted with $CHCl_3$ (50 mL x 3). The combined organic phase was washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by TLC (5% MeOH/$CHCl_3$) to give **26** (5 mg, 35%) as a pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 0.59 (m, 6H), 0.98 (t, 9H, *J* = 8 Hz), 1.10 (s, 6H), 1.62 (s, 3H), 1.60 (s, 3H), 1.89 (m, 1H), 2.06 (s, 3H), 2.29 (s, 3H), 2.50 (m, 5H), 2.72 (dd, 1H, *J* = 14, 8 Hz), 3.14 (dd, 1H, *J* = 14, 4 Hz), 3.64 (m, 4H), 4.08 (d, 1H, *J* = 7 Hz), 4.11 (dd, 1H, *J* = 8, 4 Hz), 4.15 (d, 1H, *J* = 8 Hz), 4.29 (d, 1H, *J* = 8 Hz), 4.57 (dd, 1H, *J* = 11, 6 Hz), 4.83 (m, 1H), 4.96 (d, 1H, *J* = 8 Hz), 5.58 (d, 1H, *J* = 7 Hz), 7.47 (t, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 8 Hz), 8.10 (m, 2H); MS (FAB) *m/z*: 742 (MH^+).

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-2-*O*-*tert*-butyldimethylsilyl-3-phenylisoserinyl)-10-deacetoxy-10-morpholinomethyl-7-*O*-triethylsilylbaccatin III (28)

To a stirred solution of **26** (5 mg, 6.4 μmol) and *β*-lactam (**27**) (4 mg, 9.6 μmol) in THF (1 mL) was added NaHMDS (1.0 M in THF, 27 μL, 27 μmol) at -78 °C. The mixture was stirred for 15 min at the same temperature. The mixture was poured into sat. NH_4Cl, extracted with $CHCl_3$ (50 mL x 3). The combined organic phase was washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by TLC (10% acetone/$CHCl_3$) to give **28** (3.7 mg, 49%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ -0.32 (s, 3H), -0.12 (s, 3H), 0.58 (m, 6H), 0.75 (s, 9H), 0.95 (m, 9H), 1.12 (s, 3H), 1.28 (s, 3H), 1.31 (s, 9H), 1.62 (s, 3H), 1.85 (s, 3H), 1.90 (m, 1H), 2.11 (m, 1H), 2.40 (m, 1H), 2.50 (m, 6H), 2.52 (s, 3H), 2.62 (m, 1H), 3.20 (m, 1H), 3.64 (m, 4H), 4.00 (m, 2H), 4.19 (d, 1H, *J* = 9 Hz), 4.30 (d, 1H, *J* = 9 Hz), 4.52 (m, 1H), 4.55 (m, 1H), 4.96 (d, 1H, *J* = 8 Hz), 5.31 (m, 1H), 5.44 (m, 1H), 5.65 (d, 1H, *J* = 7 Hz), 6.25 (m, 1H), 7.28—7.39 (m, 5H), 7.48 (t, 2H, *J* = 8 Hz), 7.57 (m, 1H),8.11 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 1119 (MH^+).

[2'*R*,3'*S*]-13-*O*-(3-*tert*-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-morpholinomethylbaccatin III (29)

To a stirred solution of **28** (3.7 mg, 3 μmol) in pyridine (1 mL) was added hydrogen fluoride pyridine complex (0.2 mL) at 0 °C. The reaction was stirred for 12 h at ambient temperature. The mixture was diluted with ethyl acetate and extracted with ethyl acetate. The combined organic phase was washed with water and sat. $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by TLC (8% MeOH/$CHCl_3$) and freeze-dried from dioxane to give compound (**29**) (2.9 mg, 100%) as a colorless powder; ^{1}H-NMR ($CDCl_3$) δ 1.09 (s, 3H), 1.22 (s, 3H), 1.31 (s, 9H), 1.65 (s, 3H), 1.82 (s, 3H), 1.89 (m, 1H), 2.21 (m, 1H), 2.29 (s, 3H), 2.30 (m, 1H), 2.58 (m, 4H), 2.61 (m, 1H), 3.42 (m, 1H), 3.61 (m, 4H), 3.92 (d, 1H, *J* = 7 Hz), 4.20 (d, 1H, *J* = 9 Hz), 4.29 (d, 1H, *J* = 9 Hz), 4.38 (dd, 1H, *J* = 11 Hz, 7 Hz), 4.60 (s, 1H), 4.95 (d, 1H, *J* = 8 Hz), 5.24 (m, 1H), 5.36 (m, 1H), 5.62 (d, 1H, *J* = 7 Hz), 5.19 (m, 1H), 7.30—7.39 (m, 5H), 7.50 (t, 2H, *J* = 8 Hz), 7.61 (t, 1H, *J* = 8 Hz), 8.11 (d, 2H, *J* = 8 Hz); MS (FAB) *m/z*: 891 (MH^+); HR-MS Calcd for $C_{48}H_{63}N_2O_{14}$: 891.4279. Found,891.4284.

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12. PC-6/VCR29-9: PC-6 cell line which is resistant to Vincristine®. SBC-3/ADM10: SBC-3 cell line which is resistant to Adriamycine®. PC-6/VP1-1: PC-6 cell line which is resistant to Verapamil®.