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

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Abstract-To develop non-prodrugs of taxoids possessing satisfactory stability \textit{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\textsuperscript{®}),\textsuperscript{1} which was originally isolated from Pacific yew \textit{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\textsuperscript{®}),\textsuperscript{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\textsuperscript{®} EL or Tween\textsuperscript{®} 80.

\textbf{Figure 1}

\[ \text{Paclitaxel (1: } R^1 = \text{Ph, } R^2 = \text{Ac), Docetaxel (2: } R^1 = \text{t-BuO, } R^2 = \text{H)} \]
These detergents frequently cause untoward hypersensitivity reactions (hypotension, bronchospasm, urticaria etc.), and patients receiving these drugs should be premedicated. 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. 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-\textit{O}-sec-aminoethyl docetaxel analogs, 10-\textit{C}-amino propyl docetaxel analogs and 10-\textit{C}-carboxypropyl docetaxel analogs. Among these analogs, 10-\textit{O}-(2-morpholinoethyl)docetaxel (3) and 10-\textit{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. On the other hand, 10-\textit{C}-aminoalkyldocetaxel analog (5) and 10-\textit{C}-carboxypropyl docetaxel 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-\textit{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-\textit{O}-sec-aminoethyl docetaxel analogs, 10-\textit{C}-alkyldocetaxel analogs with a secondary amino group at the end of the 10-\textit{C}-alkyl side chain were designed. Furthermore, to examine the influence of the length of the 10-\textit{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-\textit{C}-sec-aminoalkyldocetaxel analogs, with from one to three alkyl carbon bonds.

![Structural formula of docetaxel analogs](image)

**Table 1. Cytotoxicity of Water Soluble Docetaxel Analogs**

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R</th>
<th>Cytotoxic activity GI_{50} (ng/mL)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P388</td>
</tr>
<tr>
<td>Docetaxel (2)</td>
<td>—</td>
<td>—</td>
<td>6.74</td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>—\text{O}</td>
<td>24.1</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>—\text{S}</td>
<td>2.90</td>
</tr>
<tr>
<td>5</td>
<td>CH₂</td>
<td>NH₂</td>
<td>1520</td>
</tr>
<tr>
<td>6</td>
<td>CH₂</td>
<td>COOH</td>
<td>1870</td>
</tr>
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</table>

^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-morpholinopropyl docetaxel (12) was synthesized from 10-deacetoxy-10-hydroxypropyl-7-O-TES baccatin III (7) using protected [alpha]-phenylisoserine (10) 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 gave 10-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-Bu4NI, THF, 0 °C, 2) NaIO4, MeOH-H2O, 0 °C (84%); b) K2CO3, 1,2-dichlorobenzene, 170 °C (37%, net. 76%); c) 15, NaH, THF, 0 °C (91%); d) 1) OsO4, NMO, acetone-H2O, rt, 2) NaIO4, MeOH-H2O (84%).
The reaction of 10-deacetoxy-7-O-TES-10-tosyloxypropylbaccatin III (8) with MeSNa followed by oxidation with NaIO₄ gave the sulfoxide (13) in high yield. The sulfoxide (13) was heated with K₂CO₃ to give olefin (14). A phenylisoserine side chain was introduced into the baccatin moiety using the β-lactam to give 16 in high yield. Oxidation of 16 with OsO₄ followed by cleavage with NaIO₄ gave the aldehyde (17) in high yield. Finally, compound (17) was subjected to reductive amination with various sec-amines followed by standard desilylation to give the 10-C-sec-aminoethyl-10-deoxydocetaxel analogs (18a-h, Table 2).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Compound</th>
<th>R</th>
<th>yield (%)</th>
<th>method*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18a</td>
<td>-N[O]</td>
<td>91</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>18b</td>
<td>-N[S]</td>
<td>52</td>
<td>b</td>
</tr>
<tr>
<td>3</td>
<td>18c</td>
<td>-N'</td>
<td>65</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>18d</td>
<td>-N[O]</td>
<td>39</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>18e</td>
<td>-N[OME]</td>
<td>39</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>18f</td>
<td>-N[O]</td>
<td>26</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>18g</td>
<td>-N[O]</td>
<td>59</td>
<td>b</td>
</tr>
<tr>
<td>8</td>
<td>18h</td>
<td>-N[O]</td>
<td>83</td>
<td>b</td>
</tr>
</tbody>
</table>

*: method a: 1) amine, 5% Pd-C in MeOH under H₂ gas, 2) HF-Py. method b: 1) amine, NaBH₃CN, AcOH, 2) HF-Py.

To improve olefination from 7 to 14, we examined oxidative olefination of selenide (Scheme 3). 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.
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-Remeix reaction. Subsequent hydrogenation of the aldehyde (20) with NaBH₄ 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).
Reagents and conditions: a) 1) TESCl, imidazole, DMF, 2) OsO₄, NMO, MeOH-THF-H₂O, 3) NaIO₄, MeOH-THF-H₂O (54%); b) NaBH₄, MeOH (96%); c) o-nitrophenylseleno cyanide, n-tributylphosphine, THF (92%); d) m-chloroperbenzoic acid, CH₂Cl₂ (79%); e) 1) OsO₄, NMO, MeOH-THF-H₂O, 2) NaIO₄, MeOH-THF-H₂O (96%); f) morpholine, NaBH₄CN, 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, PC-6/VP) in vitro were examined (Table 3).

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

<table>
<thead>
<tr>
<th>n</th>
<th>R</th>
<th>P388</th>
<th>PC-6</th>
<th>PC-12</th>
<th>SBC-3</th>
<th>SBC-3/ADM10</th>
<th>PC-6/VCR29-9</th>
<th>PC-6/VP1-1</th>
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<tr>
<td>2</td>
<td>—</td>
<td>6.7</td>
<td>1.1</td>
<td>53.4</td>
<td>0.5</td>
<td>280</td>
<td>135</td>
<td>820</td>
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<tr>
<td>12</td>
<td>3</td>
<td>20.6</td>
<td>5.5</td>
<td>432</td>
<td>19.5</td>
<td>&gt;1000</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>18a</td>
<td>2</td>
<td>3.1</td>
<td>0.6</td>
<td>13.5</td>
<td>1.1</td>
<td>51.6</td>
<td>76.3</td>
<td>779</td>
</tr>
<tr>
<td>18b</td>
<td>2</td>
<td>3.1</td>
<td>4.8</td>
<td>32.9</td>
<td>3.0</td>
<td>262</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>18c</td>
<td>2</td>
<td>17.3</td>
<td>1.2</td>
<td>299</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>18d</td>
<td>2</td>
<td>3.8</td>
<td>1.4</td>
<td>193.5</td>
<td>3.0</td>
<td>441</td>
<td>NT</td>
<td>NT</td>
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<tr>
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<td>2</td>
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<td>2.0</td>
<td>293</td>
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<td>755</td>
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<td>NT</td>
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<tr>
<td>18f</td>
<td>2</td>
<td>11.2</td>
<td>1.8</td>
<td>414</td>
<td>7.2</td>
<td>1003</td>
<td>NT</td>
<td>NT</td>
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<tr>
<td>18g</td>
<td>2</td>
<td>3.6</td>
<td>2.7</td>
<td>91.2</td>
<td>NT*</td>
<td>NT</td>
<td>916</td>
<td>&gt;1000</td>
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<tr>
<td>18h</td>
<td>2</td>
<td>1.1</td>
<td>1.3</td>
<td>5.6</td>
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<td>NT</td>
<td>79.6</td>
<td>676</td>
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<tr>
<td>29</td>
<td>1</td>
<td>1.2</td>
<td>1.2</td>
<td>3.3</td>
<td>NT</td>
<td>NT</td>
<td>62.0</td>
<td>220</td>
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</table>

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)].*: 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. 1H-NMR spectra were taken at 400 MHz with a JEOL JNM-EX400 spectrometer; all values are reported in ppm (δ) downfield from (CH3)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).

[10R]-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 MgSO4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (3% MeOH/CHCl3) to give compound (8) (360 mg, quant.) as a colorless oil; 1H-NMR (CDCl3) 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/CHCl₃) to give compound (9) (74 mg, 82%) as a colorless oil; \(^1\)H-NMR (CDCl₃) \(\delta\): 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-tet-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. NaHCO₃ and brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by TLC (3% MeOH/CHCl₃) to give compound (11) (12 mg, 20%) as a colorless oil; \(^1\)H-NMR (CDCl₃) \(\delta\): 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-tet-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 CHCl₃, washed with sat. NaHCO₃ and brine, dried over anhydrous MgSO₄ 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/CHCl₃) and freeze-dried to give compound (12) (5 mg, 54%) as a white solid; \([\alpha]_D^{24} -69.8^\circ\) (c = 0.12, CHCl₃); IR (KBr): 3455, 2980, 1980, 1716, 1608 (cm\(^{-1}\)); \(^1\)H-NMR (CDCl₃) \(\delta 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\(_2\)O\(_{14}\)\(\cdot\)1.5H\(_2\)O; 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\(_2\)O (50% w/v, 2.3 mL, 16.4 mmol) and \(n\)-Bu\(_4\)NI (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\(_2\)O 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\(_2\)O (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\(_2\)O 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, 1716, 1608 (cm\(^{-1}\)); \(^1\)H-NMR (CDCl₃) \(\delta 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), 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, 1H), 4.97\ (d, 1H, J = 7 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\(_2\)CO\(_3\) (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; \([\alpha]_D^{24} -55.8^\circ\) (c = 0.50, CHCl₃); IR (KBr): 3475, 2970, 1720 (cm\(^{-1}\)); \(^1\)H-NMR (CDCl₃) \(\delta 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$_9$Si: 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$_4$Cl, 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$_3$) $\delta$ 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, 1H, $J = 7$ 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, 5H), 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$_2$O (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$_2$S$_2$O$_3$, and extracted with ethyl acetate. The combined organic phase was washed with brine and dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The residue was dissolved in THF/H$_2$O (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$_2$O, 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$_3$) $\delta$ 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 C₅₇H₈₃NO₁₄Si · H₂O: 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 H₂ 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. NaHCO₃, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by TLC (6% MeOH/CHCl₃) and freeze-dried from dioxane to give compound (18a) (7 mg, 91%) as a colorless powder; [α]D²⁴ -55.8° (c = 0.15, CHCl₃); IR (KBr): 3455, 2974, 1982, 1716, 1610 (cm⁻¹); ¹H-NMR (CDCl₃) 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 C₄₉H₆₄N₂O₁₄ · H₂O: 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 NaBH₃CN (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. NaHCO₃, extracted with ethyl acetate, and dried over anhydrous MgSO₄. After removal of the solvent, the residue was purified by TLC (5% acetone/CHCl₃). 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. NaHCO₃, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by TLC (3% MeOH/CHCl₃) and freeze-dried from dioxane to give compound (18b) (8 mg, 52%) as a colorless powder; [α]D° -59.5° (c = 0.1, CHCl₃); IR (KBr): 3448, 2976, 1982, 1714, 1608 (cm⁻¹); ¹H-NMR (CDCl₃) 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), 4.28 (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⁺);

[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-dimethyamine and removal of the protecting group with hydrogen fluoride pyridine complex. 18c was attained as a colorless powder (65%); ¹H-NMR (CDCl₃) 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: 903 (MH⁺); HR-MS Calcd for C₄₇H₆₃N₂O₁₃: 903.4643. Found: 903.4656.

[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%); ¹H-NMR (CDCl₃) 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 (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: 903 (MH⁺); HR-MS Calcd for C₅₀H₆₇N₂O₁₃: 903.4656. Found: 903.4656.

[2'R,3'S]-13-O-(3-tert-Butoxycarbonylamino-3-phenylisoserinyl)-10-deacetoxy-10-[2-(4-N-methyl-1-piperadinyethyl)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$_3$) $\delta$ 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, 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$_3$O$_{13}$ : 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$_3$) $\delta$ 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$_2$, and 6-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, 1H, 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$_2$O$_{13}$ : 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$_3$) $\delta$ 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$_2$O$_{13}$ : 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); ¹H-NMR (CDCl₃) 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, 1H), 3.92 (d, 1H, J = 7 Hz), 4.00 (d, 1H, J = 9 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 C₅₁H₆₉N₂O₁₄: 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 N₂ 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/CHCl₃) to give 19 (80 mg, 73%) as a colorless solid; IR (KBr): 3508, 2884, 2340, 1970, 1710, 1454 (cm⁻¹); ¹H-NMR (CDCl₃) 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, 1H, 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 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 (CHCl₃/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. NH₄Cl, extracted with ethylacetate, washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was dissolved in THF/H₂O (17 mL, 13:4, v/v), and N-methylmorpholine N-oxide (168 mg, 1.44 mmol) and a catalytic amount of OsO₄ 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 MgSO₄, and concentrated under reduced
pressure. The residue was dissolved in THF/MeOH/H2O (12 mL, 1:1:1, v/v/v), and NaIO4 (773 mg, 2.8 mmol) was added. After stirring for 6 h at ambient temperature, the mixture was diluted with H2O, extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous MgSO4, 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; 1H-NMR (CDCl3) 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 NaBH4 (78 mg, 2.0 mmol) at 0 °C. Stirring was continued for 2 h at the same temperature. The mixture was diluted with CHCl3, poured into ice-water, extracted with CHCl3. The combined organic phase was washed with brine, dried over anhydrous MgSO4, 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; 1H-NMR (CDCl3) 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 N2 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; 1H-NMR (CDCl3) 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; ¹H-NMR (CDCl₃) 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), 9.17 (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-H₂O (1:1:1, v/v/v, 9 mL) were added N-methylmorpholine N-oxide (213 mg, 2.0 mmol) and a catalytic amount of OsO₄, and the reaction mixture was stirred for 18 h. Saturated Na₂S₂O₃ (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 MgSO₄, and concentrated under reduced pressure. The residue was dissolved in THF-MeOH-H₂O (1:1:1, v/v/v, 9 mL) and NaIO₄ (387 mg, 1.8 mmol) was added, and stirred for 13 h at ambient temperature. Saturated Na₂S₂O₃ (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 MgSO₄, 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; ¹H-NMR (CDCl₃) 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 = 9 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 23 (283 mg, 0.36 mmol) in THF-MeOH-H₂O (1:1:1, v/v/v, 9 mL) were added N-methylmorpholine N-oxide (213 mg, 2.0 mmol) and a catalytic amount of OsO₄, and the reaction mixture was stirred for 18 h. Saturated Na₂S₂O₃ (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 MgSO₄, 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; ¹H-NMR (CDCl₃) 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 = 9 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⁺).
NMR (CDCl₃) δ 0.58 (m, 6H), 0.68 (m, 6H), 0.96 (t, 9H, J = 8 Hz), 1.01 (s, 12H), 1.09 (s, 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. NaHCO₃, dried over anhydrous MgSO₄, 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. NaHCO₃ and extracted with CHCl₃ (50 mL x 3). The combined organic phase was washed with brine and dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was purified by TLC (5% MeOH/CHCl₃) to give 26 (5 mg, 35%) as a pale yellow oil; ¹H-NMR (CDCl₃) 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. NH₄Cl, extracted with CHCl₃ (50 mL x 3). The combined organic phase was washed with brine and dried over MgSO₄. After removal of the solvent under reduced pressure, the residue was purified by TLC (10% acetone/CHCl₃) to give 28 (3.7 mg, 49%) as a colorless oil; ¹H-NMR (CDCl₃) 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. NaHCO₃, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by TLC (8% MeOH/CHCl₃) and freeze-dried from dioxane to give compound (29) (2.9 mg, 100%) as a colorless powder; ¹H-NMR (CDCl₃) 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 C₄₈H₆₃N₂O₁₄ : 891.4279. Found, 891.4284.

REFERENCES AND NOTES

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 Adriamycin®. PC-6/VP1-1: PC-6 cell line which is resistant to Verapamil®.