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Isolation, identification, semi-synthesis of aziditaxel derivatives and their biological evaluation

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Two new taxoids (**5** and **6**) were obtained by isolating impurities in aziditaxel, and their structures were characterized based on data analysis of ^{1}H NMR, ^{13}C NMR, HPLC-MS, and through comparison with literature. In order to test their cytotoxicities against human nonsmall lung cancer cell lines (A549), sufficient amounts of compounds **5** and **6** were obtained by semi-synthesis and both of them showed equipotent cytotoxiesty compared with taxol, docetaxel, and aziditaxel.

Keywords: taxol; docetaxel; aziditaxel; semi-synthesis

1. Introduction

Cancer is one of lethal diseases for human being leading to mass mortality all over the world [1,2]. Paclitaxel (**1**) and docetaxel (**2**) are among the most widely used chemotherapeutic drugs against ovarian, breast, and lung cancers, as well as Kaposi's sarcoma [3–5]. Their action mechanism lies on binding to the tubulin subunit, accelerating the polymerization, inhibiting their depolymerization, and leading to apoptosis finally [6]. Though paclitaxel and docetaxel have gained great success in clinical practice, they still have many drawbacks including low availability in the nature, poor water solubility, and especially severe multidrug resistance (MDR). MDR to paclitaxel and docetaxel has been one of the major causes in terms of chemotherapy failure. Aziditaxel (**4**) is one of new taxoids which was obtained through semi-synthesis [7] from cephalomannine (**3**) and it is effective to the MDR of ovarian carcinoma [8] (Figure 1).

By the method of HPLC we found that there were two main impurities in aziditaxel and their retention times were 41.062 and 44.961 min, respectively, in our HPLC condition. We isolated them and named them as 41m (**5**) and 45m (**6**). We also identified their structures (Figure 2) based on data analysis of ^{1}H NMR, ^{13}C NMR, HPLC-MS, and through comparison with literature [9]. In order to further determine their structures and test their anti-tumor activities, we synthesized sufficient 41m and 45m.

2. Chemical synthesis of compounds 41m and 45m

The synthesis of compound **5** is illustrated in Scheme 1 [10,11]. 7-TES-baccatin III was first reacted with *N*-isovaleryl-β-lactam **7** through the Ojima–Holton coupling protocol in the presence of

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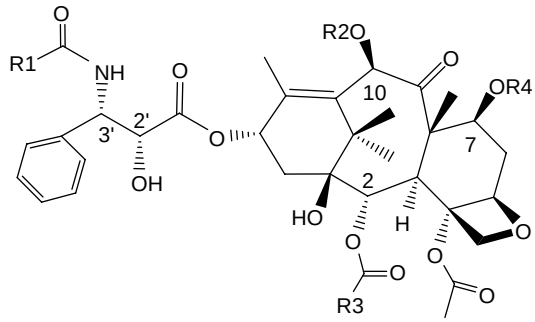
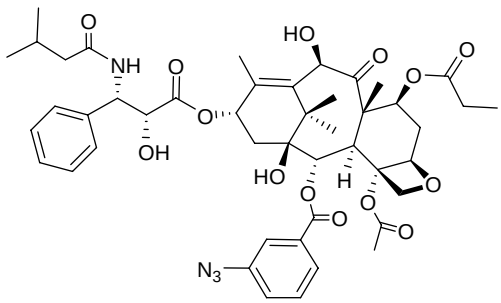


1 R1 = Ph, R2 = Ac, R3 = Ph, R4 = H
2 R1 = t-Buo, R2 = H, R3 = Ph, R4 = H
3 R1 = Tigloyl, R2 = Ac, R3 = Ph, R4 = H
4 R1 = Tigloyl, R2 = H, R3 = *m*-N_3-Ph, R4 = Propionyl

Figure 1. Structures of compounds **1**–**4**.

bis(trimethyl-silyl) amine lithium salt (LHMDS) in THF, to afford the corresponding taxoid **8**. The benzoyl in **8** was removed by hydrolysis with benzyltrimethylammonium hydroxide (Triton B) in CH_2Cl_2 to afford **9**. The 2-OH in **9** was esterized with 3-azidobenzoic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in toluene to afford **10**. Deprotection of silyl ether groups of **10** at C-2′ and C-7 was realized by HF–pyridine in the solvent of pyridine and acetonitrile (1:1) to afford **11**. After the hydroxyl group at C-2′ position was selectively protected as a TBS ester, the acetyl at C-10 was removed by 85% hydrazine hydrate in ethanol at 0°C to afford dihydroxyl compound **13**. The 10-hydroxyl group of **13** was selectively protected by TMS using bis(trimethylsilyl)-trifluoroacetamide (BSTFA) in THF, with catalytic amounts of LHMDS. The 7-hydroxyl group of **14** was reacted with propionic anhydride, in the presence of triethylamine as acid trapping agent and DMAP as catalyst. Finally, the silyl groups of TMS and TBS in **15** were removed by HF–pyridine in pyridine and acetonitrile at room temperature to furnish compound **5**.

The synthesis of compound **6**, which was prepared from cephalomannine (**3**), is illustrated in Scheme 2 [10–13]. The hydroxyl groups of cephalomannine at the



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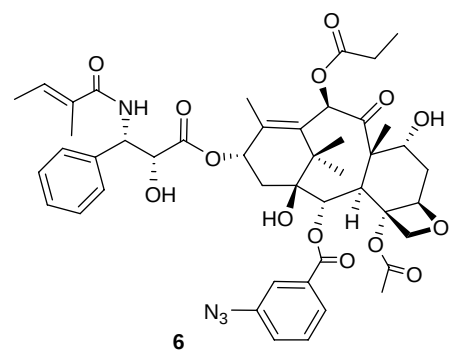

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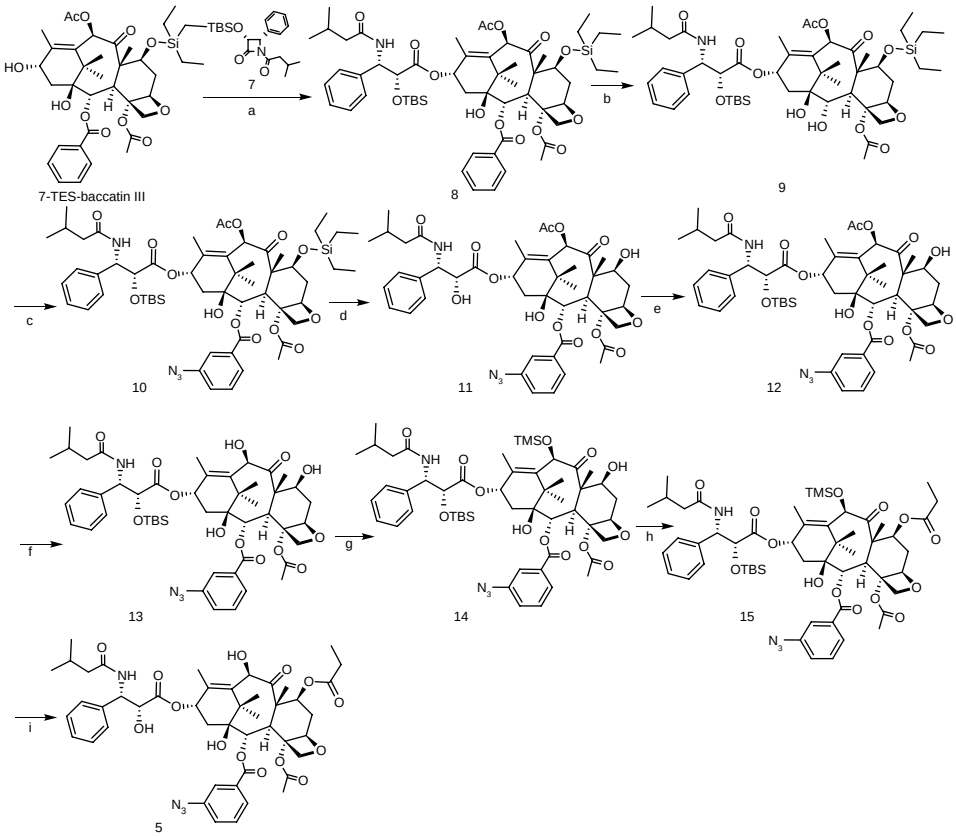
Figure 2. Structures of compounds **5** and **6**.

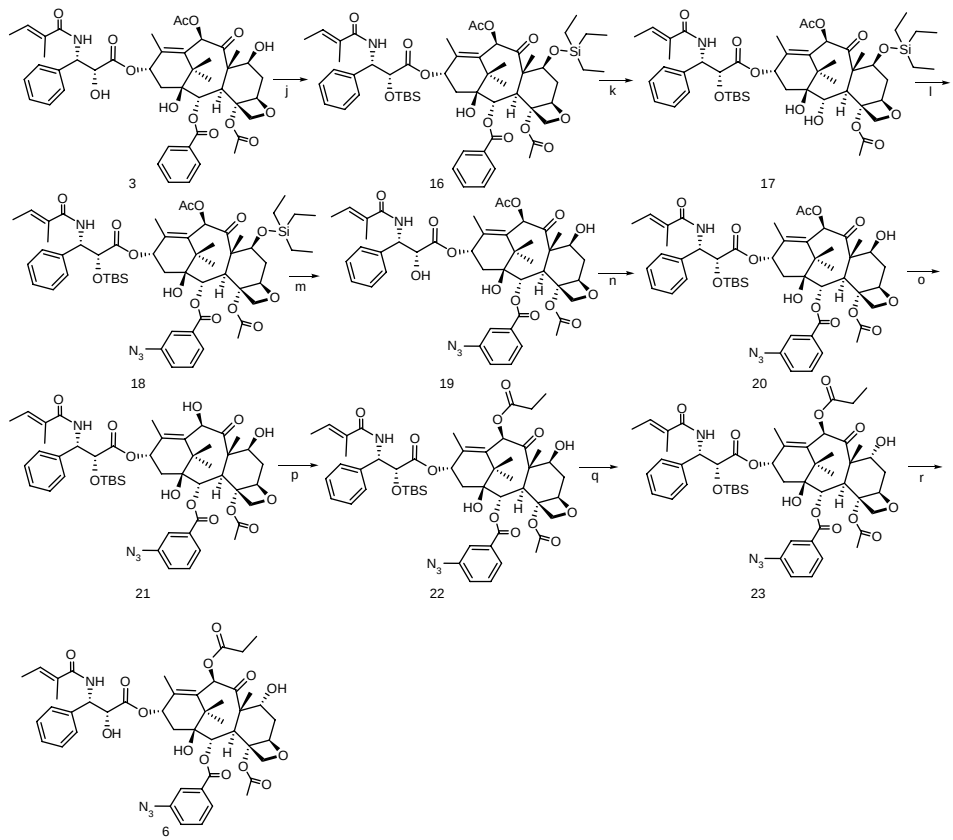


Scheme 1. Synthesis of compound **5**. Reagents and conditions: (a) LHMDS, THF, −40°C; (b) Triton B, CH_2Cl_2, −30°C; (c) DCC, DMAP, 3-azidobenzoic acid, toluene, 70°C; (d) HF, pyridine, CH_3CN, 25°C; (e) TBSCl, imidazole, DMF, 40°C; (f) $NH_2NH_2.H_2O$, C_2H_5OH, 0°C; (g) BSTFA, LHMDS, THF, −20°C; (h) propionic anhydride, triethylamine, DMAP, THF, 25°C; and (i) HF, pyridine, CH_3CN, 25°C.

positions of 2′ and 7 were protected, respectively, by TBS and TES when subsequently treated with t-butyldimethylchlorosilane (TBSCl) and then triethylchlorosilane (TESCl) in DMF to afford **16**. The follow-up synthesis steps k–o were almost as same as the synthesis steps b–f (Scheme 1), respectively, until the intermediate **21** was obtained. The hydroxyl group of **21** at the position of C-10 was selectively acylated by propionic anhydride catalyzed by anhydrous $CeCl_3$ to afford **22**. The role of $CeCl_3$ should be the catalyst of the acylation at the C-10 hydroxyl group. Then the hydroxyl group of **22** at the position of C-7 became epimerized through retroaldol–aldol reaction [12,13] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford **23**. At last, the silyl groups of TBS were removed by HF–pyridine in pyridine and acetonitrile and the target compound **6** was afforded (Scheme 2).

3. Results and discussion

During the isolation of impurities in aziditaxel, two taxoids were characterized as the main impurities. First, we identified the structures of the two compounds based on spectroscopic data (^{1}H NMR, ^{13}C NMR, and MS). Then we synthesized those compounds and characterized them



Scheme 2. Synthesis of compound **6**. Reagents and conditions: (j) TBSCl, imidazole, then TESCl, imidazole, DMF, 40°C; (k) Triton B, CH_2Cl_2, −30°C; (l) DCC, DMAP, 3-azidobenzoic acid, toluene, 70°C; (m) HF, pyridine, CH_3CN, 25°C; (n) TBSCl, imidazole, DMF, 40°C; (o) $NH_2NH_2.H_2O$, C_2H_5OH, 0°C; (p) propionic anhydride, $CeCl_3$, THF, 25°C; (q) DBU, toluene, 70°C; and (r) HF, pyridine, CH_3CN, 25°C.

by the comparison of the spectra of ^1H NMR, ^{13}C NMR, and MS with those of isolated impurities. Since we obtained sufficient amounts of 41m and 45m, we could test their *in vitro* anti-tumor activities, and found that their cytotoxicities against human nonsmall lung cancer cell lines were equipotent compared with those of taxol, docetaxel, and aziditaxel (Table 1). Their activities against other tumor cells will be further tested.

In conclusion, two new taxoids were found by isolation of impurities in aziditaxel and they also showed strong cytotoxic activity, which suggested that the activities or toxicities of any impurity cannot be ignored.

4. Experimental

4.1. General experimental procedures

Optical rotations were measured on a PerkinElmer Polarimeter 341LC (PerkinElmer, Waltham, MA, USA) using 10 cm cells and the sodium D line (589 nm) at 20°C and concentration indicated. NMR spectra were determined with Mercury 300, 400 MHz or INOVA 500 MHz spectrometers (Varian Medical Systems, Inc., Palo Alto, CA, USA) in $CDCl_3$. J and δ values are given in Hz and ppm,

Table 1. Cytotoxicity against human nonsmall lung cancer cell (A549).

Compounds	Taxol	Docetaxel	Aziditaxel	**5**	**6**
IC50/M	$(1.12 \pm 0.32) \times 10^{-8}$	$(3.16 \pm 0.96) \times 10^{-9}$	$(1.37 \pm 0.37) \times 10^{-8}$	$(8.94 \pm 2.99) \times 10^{-9}$	$(7.30 \pm 2.46) \times 10^{-9}$

respectively. Mass spectra (ESI-MS) were recorded on an Agilent LC–MSD-Trap-SL instrument (Agilent Technologies, Santa Clara, CA, USA). All chemicals other than solvents were obtained from Aldrich Chemical Co. and used without further purification. All reactions were monitored by TLC (silica gel, GF254) with UV light and H_2SO_4–anisaldehyde spray visualization. Column chromatography was conducted over silica gel 60 (200–300 mesh), (Qingdao Haiyang Chemical Co., Qingdao, China).

4.2. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-7-O-(triethylsilyl)-taxol (8)

7-*O*-Triethylsilyl-10-deacetylbacctin III (137 mg, 0.207 mmol) was dissolved in 6.8 ml THF, then 1.0 M solution of LHMDS in THF (0.415 ml, 0.415 mmol) was added under N_2 atmosphere at −40°C. The mixture was stirred for 10 min at this temperature. β-Lactam **7** (150 mg, 0.415 mmol) was added to the mixture, then the mixture was stirred for another 60 min at −40°C. Saturated aqueous NH_4Cl was added and the aqueous layer was extracted with EtOAc. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 5:1) to afford **8** (186 mg, 84.7% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, $J = 7.2$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.51 (t, $J = 7.2$ Hz, 2H), 7.42–7.21 (m, 5H), 6.47 (s, 1H), 6.32 (d, $J = 9.0$ Hz, 1H), 6.25 (t, $J = 8.7$ Hz, 1H), 5.72 (d, $J = 6.9$ Hz, 1H), 5.58 (d, $J = 9.0$ Hz, 1H), 4.96 (d, $J = 8.1$ Hz, 1H), 4.57 (d, $J = 2.1$ Hz, 1H), 4.48 (dd, $J = 10.5$, 6.6 Hz, 1H), 4.33 (d, $J = 8.4$ Hz, 1H), 4.21 (d, $J = 8.4$ Hz, 1H), 3.85 (d, $J = 6.9$ Hz, 1H), 2.55 (s, 3H), 2.61–2.47 (m, overlapped 1H), 2.39 (dd, $J = 15.1$, 9.7 Hz, 1H), 2.19 (s, 3H), 2.16–2.08 (m, 3H), 2.02 (s, 3H), 2.07–1.99 (m, 2H), 1.71

(s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.01–0.83 (m, 15H), 0.78 (s, 9H), 0.58 (q, $J = 7.8$ Hz, 6H), −0.09 (s, 3H), −0.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 171.9, 171.4, 170.1, 169.3, 167.1, 140.2, 138.5, 133.6, 133.6, 130.2, 129.2, 128.7, 128.6, 127.8, 126.4, 84.2, 81.2, 78.8, 77.1, 76.6, 75.2, 74.9, 72.2, 71.4, 58.4, 55.1, 46.6, 45.8, 43.4, 37.2, 35.5, 26.5, 26.1, 25.5, 23.1, 22.4, 22.3, 21.5, 20.9, 18.2, 14.2, 10.1, 6.7, 5.3, −5.4, −5.9; ESI-MS: *m/z* 1062.5 $[M + H]^+$.

4.3. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-7-O-(triethylsilyl)-taxol (9)

To a solution of **8** (824 mg, 0.776 mmol) in 27 ml CH_2Cl_2 was added 40% solution of Triton B in CH_3OH (0.68 ml, 1.552 mmol) at −30°C and the solution was stirred for 3 h. Then the reaction was quenched by addition of aqueous NH_4Cl, and the aqueous solution was extracted by CH_2Cl_2. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 2:1) to afford **9** (570 mg, 76.8% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.29 (m, 3H), 7.15 (d, $J = 7.2$ Hz, 2H), 6.35 (d, $J = 9.0$ Hz, 1H), 6.30 (s, 1H), 6.24 (t, $J = 8.7$ Hz, 1H), 5.46 (d, $J = 9.0$ Hz, 1H), 4.41 (s, 1H), 4.31 (d, $J = 11.4$ Hz, 1H), 4.22 (d, $J = 9.3$ Hz, 1H), 4.12 (d, $J = 6.6$ Hz, 1H), 3.95 (dd, $J = 11.4$, 3.3 Hz, 1H), 3.68 (d, $J = 11.4$ Hz, 1H), 3.29 (d, $J = 6.3$ Hz, 1H), 2.63 (dd, $J = 14.4$, 9.3 Hz, 1H), 2.32 (s, 3H), 2.15 (s, 3H), 2.28–2.01 (m, 4H), 2.14 (s, 3H), 1.89 (s, 3H), 1.92–1.80 (m, 2H), 1.26 (s, 3H), 1.25 (s, 3H), 1.08 (s, 3H), 0.91 (m, 15H), 0.73 (s, 9H), 0.53 (q, $J = 7.8$ Hz, 6H), −0.16 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 172.0, 171.5, 171.3, 169.2, 139.4, 138.5, 136.4, 128.5, 127.8, 126.2, 95.0, 85.8, 76.2, 75.4, 75.0, 72.0, 71.3, 70.8, 70.5, 55.4, 55.0, 50.5, 45.8, 43.4, 36.6, 35.2, 26.1, 25.4, 25.1, 22.8, 22.3, 22.2, 21.6, 20.7, 18.1, 15.4, 14.3, 6.7, 4.9, −5.4, −5.9; ESI-MS: *m/z* 958.6 $[M + H]^+$; 980.5 $[M + Na]^+$.

4.4. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-7-O-(triethylsilyl)-taxol (10)

3-Azidobenzoic acid (485 mg, 2.975 mmol), DCC (644 mg, 3.124 mmol), and DMAP (7 mg, 0.060 mmol) were dissolved in 11.4 ml toluene. The mixture was stirred for 30 min at room temperature and **9** was added. Then the reaction mixture was stirred for 72 h. The reaction mixture was filtered and washed by ethyl ether. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 5:1) to afford **10** (562 mg, 85.7% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 7.8$ Hz, 1H), 7.80 (s, 1H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.39–7.26 (m, 5H), 7.20–7.24 (m, 1H), 6.45 (s, 1H), 6.31 (d, $J = 9.0$ Hz, 1H), 6.18 (t, $J = 8.7$ Hz, 1H), 5.69 (d, $J = 6.9$ Hz, 1H), 5.54 (d, $J = 9.0$ Hz, 1H), 4.95 (d, $J = 8.4$ Hz, 1H), 4.52 (s, 1H), 4.46 (dd, $J = 10.5$, 6.6 Hz, 1H), 4.32 (d, $J = 8.4$ Hz, 1H), 4.18 (d, $J = 8.4$ Hz, 1H), 3.84 (d, $J = 6.9$ Hz, 1H), 2.61–2.46 (m, overlapped, 1H), 2.52 (s, 3H), 2.37 (dd, $J = 15.3$, 9.6 Hz, 1H), 2.23–2.10 (m, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.96–1.85 (m, 2H), 1.68 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.93 (t, $J = 7.8$ Hz, 9H), 0.87 (d, $J = 5.1$ Hz, 6H), 0.77 (s, 9H), 0.57 (q, $J = 7.8$ Hz, 6H), −0.11 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 171.9, 171.4, 170.0, 169.2, 166.0, 140.7, 140.3, 138.5, 133.6, 131.0, 130.2, 128.5, 127.8, 126.8, 126.5, 124.2, 120.1, 84.2, 81.2, 78.7, 76.4, 75.3, 75.1, 74.9, 72.1, 71.6, 58.3, 55.1, 46.5, 45.8, 43.3, 37.2, 35.4, 26.4, 26.0, 25.5, 23.0, 22.4, 22.3, 21.4, 20.8, 18.1, 14.2, 10.0, 6.7, 5.2, −5.4, −5.8; ESI-MS: *m/z* 1103.5 $[M + H]^+$; 1125.5 $[M + Na]^+$.

4.5. 3′N-Debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-taxol (11)

To a solution of **10** (562 mg, 0.510 mmol) in 4.1 ml pyridine and 15.5 ml acetonitrile was added dropwise 40% solution of HF in water (2.4 ml) at 0°C. The mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted by EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 1:1) to afford **11** (413 mg, 92.6% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, $J = 7.8$ Hz, 1H), 7.78 (s, 1H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.42–7.27 (m, 5H), 7.21–7.24 (m, 1H), 6.31 (d, $J = 9.0$ Hz, 1H), 6.27 (s, 1H), 6.14 (t, $J = 9.0$ Hz, 1H), 5.66 (d, $J = 6.9$ Hz, 1H), 5.53 (d, $J = 9.0$ Hz, 1H), 4.92 (d, $J = 8.7$ Hz, 1H), 4.63 (s, 1H), 4.38 (dd, $J = 10.5$, 6.6 Hz, 1H), 4.28 (d, $J = 8.4$ Hz, 1H), 4.16 (d, $J = 8.4$ Hz, 1H), 3.78 (d, $J = 6.9$ Hz, 2H), 2.61–2.47 (m, 2H), 2.30 (s, 3H), 2.28–2.19 (m, 1H), 2.22 (s, 3H), 2.00–1.96 (m, 2H), 1.89–1.78 (m, 2H), 1.81 (s, 3H), 1.66 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 0.88 (d, $J = 5.1$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 173.0, 172.4, 171.2, 170.2, 165.8, 142.0, 140.6, 138.1, 133.0, 130.9, 130.2, 128.9, 128.2, 127.0, 126.8, 124.3, 120.0, 84.4, 81.1, 78.7, 76.3, 75.5, 75.4, 72.9, 72.4, 72.0, 58.5, 54.6, 45.8, 45.5, 43.2, 35.6, 34.7, 26.7, 26.1, 22.6, 22.3, 22.3, 21.8, 20.8, 14.7, 9.5; ESI-MS: *m/z* 875.4 $[M + H]^+$.

4.6. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-taxol (12)

To a solution of **11** (413 mg, 0.472 mmol) and imidazole (193 mg, 2.832 mol) in 4.0 ml DMF was added TBSCl (391 mg, 2.596 mmol) at room temperature. The mixture was stirred for 4 h at 40°C and then diluted with EtOAc. The reaction mixture was then washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 3:1) to afford **12** (442 mg, 94.7% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, $J = 7.8$ Hz, 1H), 7.84 (s, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.45–7.28 (m, 5H), 7.24–7.21 (m, 1H), 6.36 (d, $J = 8.7$ Hz 1H), 6.34 (s, 1H), 6.14 (t, $J = 9.0$ Hz, 1H), 5.72 (d, $J = 7.2$ Hz, 1H), 5.59 (d, $J = 8.7$ Hz, 1H), 5.02 (d, $J = 8.1$ Hz, 1H), 4.55 (d, $J = 1.8$ Hz, 1H), 4.47 (dd, $J = 10.5$, 6.6 Hz, 1H), 4.37 (d, $J = 8.4$ Hz, 1H), 4.23 (d, $J = 8.4$ Hz, 1H), 3.87 (d, $J = 7.2$ Hz, 1H), 2.63–2.49 (m, overlapped, 2H), 2.55 (s, 3H), 2.42 (dd, $J = 15.3$, 9.6 Hz, 1H), 2.30–2.13 (m, 2H), 2.26 (s, 3H), 2.10–2.01 (m, 1H), 1.99–1.85 (m, 1H), 1.93 (s, 3H), 1.71 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H), 0.93 (d, $J = 5.1$ Hz, 6H), 0.82 (s, 9H), −0.08 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 171.9, 171.4, 171.2, 170.0, 166.0, 142.6, 140.7, 138.4, 132.8, 130.9, 130.2, 128.6, 127.9, 126.8, 126.5, 124.3, 120.1, 84.4, 81.2, 79.0, 76.4, 75.3, 75.1, 74.9, 72.1, 71.6, 58.5, 55.1, 45.8, 45.4, 43.2, 35.7, 35.5, 29.2, 26.6, 26.0, 25.5, 23.0, 22.4, 22.3, 22.2, 20.8, 14.9, 9.5, −5.5, −5.8; ESI-MS: *m/z* 989.5 $[M + H]^+$; 1011.5 $[M + Na]^+$.

4.7. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-10-deacetyl-taxol (13)

To a solution of **12** (442 mg, 0.447 mmol) in 8.8 ml ethanol was added dropwise 85% hydrazine hydrate (0.174 ml, 3.075 mmol) at 0°C and the mixture was stirred for 12 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel

(petroleum ether:EtOAc = 2:1) to afford **13** (387 mg, 91.5% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.41–7.24 (m, 5H), 7.24–7.21 (m, 1H), 6.40 (d, J = 9.0 Hz, 1H), 6.19 (t, J = 8.7 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 5.51 (d, J = 9.0 Hz, 1H), 5.19 (s, 1H), 4.94 (d, J = 9.0 Hz, 1H), 4.51 (s, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.23 (m, 1H), 4.19 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 6.9 Hz, 1H), 2.50 (s, 3H), 2.50 (m, overlapped 1H), 2.35 (dd, J = 15.0, 9.6 Hz, 1H), 2.19 (d, J = 6.6 Hz, 2H), 2.12–1.99 (m, 2H), 1.97–1.89 (m, 1H), 1.89 (s, 3H), 1.68 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 0.90 (d, J = 5.1 Hz, 6H), 0.78 (s, 9H), −0.10 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 172.1, 171.3, 169. 9, 165.7, 140.6, 138.5, 138.4, 135.7, 131.0, 130.2, 128.5, 127.8, 126.7, 126.4, 124.2, 120.0, 84.2, 81.1, 78.5, 77.2, 76.4, 75.4, 75.0, 74.3, 71.7, 57.5, 55.0, 46.2, 45.8, 43.1, 36.6, 35.8, 26.2, 26.0, 25.4, 22.9, 22.3, 22.2, 20.9, 18.1, 14.2, 9.8, −5.4, −5.8; ESI-MS: *m/z* 969.5 $[M + Na]^+$.

4.8. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-10-deacetyl-10-O-(trimethylsilyl)-taxol (14)

To a solution of **13** (387 mg, 0.409 mmol) in 15.5 ml THF were added bis(trimethylsilyl) trifluoro-acetamide (0.543 ml, 4.090 mmol) and 1.0 M solution of LHMDS in THF (0.041 ml, 0.041 mmol) at −20°C under nitrogen atmosphere and the mixture was stirred for 10 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 4:1) to afford **14** (344 mg, 82.6% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.42–7.27 (m, 5H), 7.24–7.21 (m, 1H), 6.45 (d, J = 9.0 Hz, 1H), 6.45 (m, overlapped 1H), 6.16 (t, J = 9.0 Hz, 1H), 5.70 (d, J = 7.2 Hz, 1H), 5.53 (d, J = 9.0 Hz, 1H), 5.22 (s, 1H), 4.97 (d, J = 8.4 Hz, 1H), 4.51 (s, 1H), 4.33 (d, J = 8.4 Hz, 1H), 4.21 (d, J = 8.4 Hz, 1H), 4.21 (m, overlapped, 1H), 3.95 (d, J = 7.2 Hz, 1H), 2.70–2.58 (m, 1H), 2.51 (s, 3H), 2.38 (dd, J = 15.0, 9.6 Hz, 1H), 2.26–2.15 (m, 2H), 2.11 (m, 1H), 2.07–1.95 (m, 1H), 1.93–1.77 (m, 1H), 1.93 (s, 3H), 1.75 (s, 3H), 1.27 (s, 6H), 0.90 (d, J = 5.1 Hz, 6H), 0.79 (s, 9H), 0.17 (s, 9H), −0.11 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 172.2, 171.7, 169.9, 166.0, 140.7, 138.4, 137.4, 135.3, 131.0, 130.2, 128.6, 127.9, 126.8, 126.5, 124.3, 120.0, 84.3, 81.3, 78.8, 75.6, 75.2, 75.2, 72.0, 71.9, 71.8, 57.5, 55.2, 46.6, 45.8, 43.2, 37.0, 35.6, 26.2, 26.1, 25.5, 23.1, 22.4, 22.3, 20.9, 18.2, 14.0, 10.0, 0.5, −5.5, −5.8; ESI-MS: *m/z* 1041.4 $[M + Na]^+$.

4.9. 2′-O-(t-Butyldimethylsilyl)-3′N-debenzoyl-3′N-isovaleryl-2- debenzoyl-2-m-N_3-benzoyl-7-propionyl-10-deacetyl-10-O-(trimethylsilyl)-taxol (15) and 3′N-debenzoyl-3′N-isovaleryl-2-debenzoyl-2-m-N_3-benzoyl-7-propionyl-10-deacetyl-taxol (5)

(a) To a solution of **14** (344 mg, 0.337 mmol), triethylamine (0.328 ml, 2.359 mmol), and DMAP (4 mg, 0.034 mmol) in 7.0 ml THF was added propionic anhydride (0.206 ml, 2.022 mmol) at 0°C and the mixture was stirred for 12 h at room temperature. Then the reaction mixture was diluted by EtOAc, washed by 2 M aqueous HCl, aqueous $NaHCO_3$, aqueous NaCl and dried by anhydrous Na_2SO_4. After filtration and removal of EtOAc *in vacuo*, we obtained the residue (359 mg). The residue was subjected to silyl ether deprotection without purification.

(b) The above residue (359 mg) was dissolved in 2.6 ml pyridine and 9.8 ml acetonitrile, and to this solution 40% aqueous HF (1.5 ml) was added. The reaction was stirred for 12 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous solution was extracted by EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 1:1) to afford **5** (237 mg, 79.1% yield for steps (a) and (b)) as a white solid. $[\alpha]_D^{20}$ −55.3 (*c* 0.010, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 1H), 7.79 (s, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.43–7.30 (m, 5H), 7.24 (dd, J = 7.5, 1.5 Hz, 1H), 6.28 (d, J = 9.0 Hz, 1H), 6.14 (t, J = 8.5 Hz, 1H), 5.67 (d, J = 7.0 Hz, 1H), 5.56 (dd, J = 9.0, 2.0 Hz, 1H), 5.47 (dd, J = 10.5, 7.5 Hz, 1H), 5.30 (s, 1H), 4.93 (d, J = 8.5 Hz, 1H), 4.65 (dd, J = 5.0, 2.0 Hz, 1H), 4.33 (d, J = 8.5 Hz, 1H), 4.21 (d, J = 8.5 Hz, 1H), 3.99 (d, J = 7.0 Hz, 1H), 3.98 (s, 1H), 3.56 (d, J = 5.0 Hz, 1H), 2.52 (ddd, J = 14.5, 9.5, 7.5 Hz, 1H), 2.35–2.29 (m, overlapped, 2H), 2.33 (s, 3H), 2.25 (q, J = 7.5 Hz, 2H), 2.09–1.99 (m, 3H), 1.96–1.88 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.21 (s, 3H), 1.10(s, 3H), 1.09 (s, 3H), 1.09 (3H, J = 7.5 Hz, 3H), 0.90 (d, J = 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 173.2, 172.7, 172.2, 170.2, 165.8, 140.8, 138.7, 138.2, 135.7, 130.9, 130.2, 128.9, 128.2, 127.0, 126.8, 124.4, 120.1, 83.8, 80.8, 78.6, 76.5, 75.1, 74.5, 73.0, 72.5, 71.4, 56.4, 54.5, 46.1, 45.9, 43.0, 35.9, 33.4, 27.6, 26.3, 26.2, 22.5, 22.4, 22.4, 20.5, 14.2, 10.9, 9.1; ESI-MS: *m/z* 889.1 $[M + H]^+$; 911.4 $[M + Na]^+$.

4.10. 2′-O-(t-Butyldimethylsilyl)-7-O-(triethylsilyl)-cephalomannine (16)

To a solution of cephalomannine (5.157 g, 6.2 mmol) and imidazole (3.377 g, 49.6 mmol) in 51 ml DMF was added TBSCl (6.540 g, 43.4 mmol) at room temperature. After the mixture was stirred for 4 h at 40°C, TESCl (2.602 ml, 15.5 mmol) and imidazole (1.266 g, 18.6 mmol) were added. The mixture was stirred for another 1 h at the same temperature and diluted with EtOAc. The solution was washed successively with water and brine and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 5:1) to afford **16** (6.370 g, 96.9% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.25–7.28 (3H, m), 6.65 (d, J = 8.7 Hz, 1H), 6.45 (s, 1H), 6.45 (overlapped, 1H), 6.25 (t, J = 8.7 Hz, 1H), 5.70 (d, J = 7.2 Hz, 1H), 5.58 (d, J = 9.0 Hz, 1H), 4.94 (d, J = 9.0 Hz, 1H), 4.59 (d, J = 1.8 Hz, 1H), 4.47 (dd, J = 10.8, 6.9 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 7.2 Hz, 1H), 2.54 (s, 3H), 2.51–2.63 (m, 1H), 2.37 (dd, J = 9.3, 12.3 Hz,1H), 2.17 (3H, s), 2.12 (dd, J = 8.8, 15.2 Hz,1H), 2.04 (s, 3H), 1.91 (m, 1H), 1.81 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H), 1.70 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 0.93 (t, J = 8.1 Hz, 9H), 0.78 (s, 9H), 0.54–0.61 (q, J = 8.1 Hz, 6H), −0.05 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 171.4, 170.2, 169.3, 168.6, 167.1, 140.3, 138.5, 133.6, 131.5, 130.2, 129.2, 128.7, 128.6, 128.4, 127.7, 126.5, 126.4, 84.2, 81.1, 78.9, 77.3, 76.6, 75.0, 74.9, 72.2, 71.3, 58.4, 55.2, 46.6, 43.3, 37.2, 35.5, 26.6, 25.5, 23.1, 21.5, 20.8, 18.1, 14.2, 14.0, 12.3, 10.1, 6.7, 5.3, −5.3, −5.9; ESI-MS: *m/z* 1060.6 $[M + H]^+$; 1082.7 $[M + Na]^+$.

4.11. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-7-O-(triethylsilyl)-cephalomannine (17)

To a solution of **16** (6.370 g, 6.009 mmol) in 210 ml CH_2Cl_2 was added 40% solution of Triton B in CH_3OH (5.1 ml, 12.018 mmol) at −30°C and the solution was stirred for 3 h. Then the reaction was quenched by aqueous NH_4Cl, and the aqueous solution was extracted by CH_2Cl_2. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 2:1) to afford **17** (3.667 g, 63.9% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.30 (5H, m), 6.65 (d, J = 9.0 Hz, 1H), 6.48 (q, J = 7.8 Hz, 1H), 6.31 (s, 1H), 6.25 (t, J = 9.0 Hz, 1H), 5.49 (d, J = 9.0 Hz, 1H), 4.47 (d, J = 1.2 Hz, 1H), 4.34 (d, J = 11.4 Hz, 1H), 4.25 (t, J = 9.3 Hz, 1H), 4.13 (dd, J = 6.9 Hz, 1H), 3.88 (dd, J = 11.4, 3.9 Hz, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.26 (d, J = 6.6 Hz, 1H), 2.64 (dd, J = 14.7, 9.3 Hz, 1H), 2.38 (s, 3H), 2.20 (dd, J = 14.7, 9.3 Hz, 1H), 1.91 (m, 2H), 1.90 (s, 3H), 1.88 (s, 3H), 1.78 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.11 (s, 3H), 0.93 (t, J = 8.1 Hz, 9H), 0.78 (9H, s), 0.56 (q, J = 7.8 Hz, 6H), −0.07 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 171.9, 171.4, 169.3, 168.6, 139.7, 138.7, 136.4, 131.6, 131.5, 128.6, 127.8, 126.3, 95.2, 85.7, 76.6, 75.5, 75.1, 71.9, 71.3, 70.9, 70.5, 55.5, 55.2, 50.6, 43.5, 36.2, 35.1, 25.5, 25.2, 23.0, 21.7, 20.8, 18.1, 15.9, 14. 5, 14.1, 12.4, 6.8, 5.0, −5.2, −5.9; ESI-MS: *m/z* 956.6 $[M + H]^+$; 978.7 $[M + Na]^+$.

4.12. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-2-m-N_3-benzoyl-7-O-(triethylsilyl)-cephalomannine (18)

3-Azidobenzoic acid (4.564 g, 28 mmol), DCC (5.974 g, 29 mmol), and DMAP (0.122 g, 1 mmol) were dissolved in 60 ml toluene. The mixture was stirred for 30 min at room temperature and **17** (3.667 g, 3.838 mmol) was added. Then the reaction mixture was stirred for 72 h. The reaction mixture was filtered and washed by diethyl ether. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 5:1) to afford **18** (3.491 g, 82.6% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.80 (m, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.31–7.40 (m, 5H), 7.22–7.25 (m, 1H), 6.66 (d, J = 8.7 Hz, 1H), 6.48 (s, 1H), 6.44 (q, overlapped, 1H), 6.20 (t, J = 8.7 Hz, 1H), 5.70 (d, J = 7.2 Hz, 1H), 5.57 (dd, J = 8.7, 1.5 Hz, 1H), 4.96 (d, J = 8.1 Hz, 1H), 4.56 (d, J = 1.5 Hz, 1H), 4.47 (dd, J = 10.5, 6.6 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 3.84 (d, J = 7.2 Hz, 1H), 2.53 (s, 3H), 2.54–2.50 (m, overlapped, 1H), 2.40–2.34 (m, 1H), 2.18 (s, 3H), 2.22–2.15 (m, 1H), 2.01 (s, 3H), 1.94–1.87 (m, 1H), 1.81 (s, 3H), 1.72 (d, J = 7.2 Hz, 3H), 1.70 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.78 (s, 9H), 0.54–0.61 (q, J = 7.8 Hz, 6H), −0.05 (s, 3H), −0.31 (s, 3H); ^{13}C NMR (100 MHz) δ 201.7, 171.5, 170.1, 169.3, 168.7, 166.1, 140.7, 140.4, 138.6, 133.6, 131.5, 131.4, 131.0, 130.3, 128.6, 127.8, 126.8, 126.5, 124.3, 120.2, 84.3, 81.2, 78.8, 76.7, 75.4, 75.0, 74.9, 72.2, 71.5, 58.4, 55.2, 46.6, 43.3, 37.2, 35.5, 26.5, 25.5, 23.1, 21.5, 20.8, 18.1, 14.2, 14.0, 12.3, 10.1, 6.7, 5.3, −5.3, −5.9; ESI-MS: *m/z* 1101.7 $[M + H]^+$; 1123.8 $[M + Na]^+$.

4.13. 2-Debenzoyl-2-m-N_3-benzoyl-cephalomannine (19)

To a solution of **18** (3.491 g, 3.170 mmol) in 80.4 ml pyridine and acetonitrile was added dropwise 40% solution of HF in water (46.8 ml) at 0°C. The mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous

solution was extracted by EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 1:1) to afford **19** (2.449 g, 88.5% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 7.8$ Hz, 1H), 7.80 (m, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.31–7.40 (5m, H), 7.22–7.25 (m, 1H), 6.46 (d, $J = 8.7$ Hz, 1H), 6.42 (q, overlapped, 1H), 6.27 (s, 1H), 6.17 (t, $J = 8.7$ Hz, 1H), 5.65 (d, $J = 6.9$ Hz, 1H), 5.58 (dd, $J = 2.7$, 8.7 Hz, 1H), 4.94 (d, $J = 8.1$ Hz, 1H), 4.68 (s, 1H), 4.39 (dd, $J = 10.8$, 6.6 Hz, 1H), 4.30 (d, $J = 8.4$ Hz, 1 Hz), 4.16 (d, $J = 8.4$ Hz, 1H), 3.79 (d, $J = 6.9$ Hz, 1H), 2.54–2.49 (m, 1H), 2.32 (s, 3H), 2.30–2.23 (m, 1H), 2.24 (s, 3H), 2.08–2.01 (m, 1H), 1.82–1.92 (m, 1H), 1.80 (s, 6H), 1.72 (d, $J = 6.9$ Hz, 3H), 1.67 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz) δ 203.6, 172.8, 171.2, 170.3, 169.1, 165.9, 142.2, 140.7, 138.2, 133.0, 131.8, 131.2, 130.9, 130.2, 128.9, 128.2, 127.0, 126.8, 124.3, 120.2, 84.4, 81.0, 78.9, 76.4, 75.5, 75.4, 73.1, 72.3, 72.1, 58.5, 54.9, 45.5, 43.1, 35.6, 35.5, 26.8, 22.6, 21.8, 20.8, 14.8, 14.0, 12.4, 9.5; ESI-MS: *m/z* 873.5 $[M + H]^+$; 895.5 $[M + Na]^+$.

4.14. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-2-m-N_3-benzoyl-cephalomannine (20)

To a solution of **19** (2.449 g, 2.806 mmol) and imidazole in 25 ml DMF was added TBSCl (2.537 g, 16.836 mmol) at room temperature. The mixture was stirred for 4 h at 40°C and then diluted with EtOAc. The reaction mixture was then washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 3:1) to afford **20** (2.520 g, 91.0% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, $J = 7.8$ Hz, 1H), 7.83 (m, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.40–7.29 (m, 5H), 7.21–7.25 (m, 1H), 6.67 (d, $J = 9.0$ Hz, 1H), 6.43 (q, $J = 7.2$ Hz, 1H), 6.30 (s, 1H), 6.22 (t, $J = 9.0$ Hz, 1H), 5.69 (d, $J = 7.2$ Hz, 1H), 5.56 (d, $J = 9.0$ Hz, 1H), 4.99 (d, $J = 8.4$ Hz, 1H), 4.54 (d, $J = 1.8$ Hz, 1H), 4.43 (dd, $J = 10.2$, 6.9 Hz, 1H), 4.33 (d, $J = 8.1$ Hz, 1H), 4.20 (d, $J = 8.1$ Hz, 1H), 3.83 (d, $J = 7.2$ Hz, 1H), 2.59–2.52 (m, 1H), 2.52 (s, 3H), 2.42–2.34 (m, 1H), 2.24 (s, 3H), 2.04–2.01 (m, 1H), 1.89–1.94 (m, 1H), 1.90 (s, 3H), 1.81 (s, 3H), 1.72 (d, $J = 7.2$ Hz, 3H), 1.68 (s, Me-19, 3H), 1.28 (s, 3H), 1.15 (s, 3H), 0.80 (s, 9H), −0.08 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (100 MHz) δ 203.7, 171.4, 171.2, 170.0, 168.5, 166.0, 142.6, 140.7, 138.5, 132.8, 131.5, 130.9, 130.3, 128.7, 128.6, 127.8, 126.8, 126.4, 124.3, 120.1, 84.4, 81.1, 79.0, 76.4, 75.5, 75.4, 75.1, 72.0, 71.5, 58.5, 55.2, 45.4, 43.2, 35.7, 35.5, 33.9, 26.7, 25.5, 24.9, 23.0, 22.2, 20.8, 18.1, 14.9, 14.0, 12.3, 9.6, −5.4, −5.8; ESI-MS: *m/z* 987.6 $[M + H]^+$; 1009.6 $[M + Na]^+$.

4.15. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-2-m-N_3-benzoyl-10-deacetyl-cephalomannine (21)

To a solution of **20** (2.520 g, 2.553 mmol) in ethanol was added dropwise 85% hydrazine hydrate (4.978 ml, 88 mmol) at 0°C and the mixture was stirred for 12 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 2:1) to afford **21** (2.150 g, 89.1% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, $J = 7.8$ Hz, 1H), 7.82 (m, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.38–7.28 (m, 5H), 7.22–7.25 (m, 1H), 6.67 (d, $J = 9.0$ Hz, 1H), 6.41 (q, $J = 6.9$ Hz, 1H),

6.24 (t, $J = 8.7$ Hz, 1H), 5.70 (d, $J = 7.2$ Hz, 1H), 5.54 (d, $J = 9.0$ Hz, 1H), 5.20 (s, 1H), 4.98 (d, $J = 8.4$ Hz, 1H), 4.54 (s, 1H), 4.35 (d, $J = 8.4$ Hz, 1H), 4.27 (dd, $J = 10.8$, 6.6 Hz, 1H), 4.21 (d, $J = 8.4$ Hz, 1H), 3.95 (d, $J = 7.2$ Hz, 1H), 2.57–2.65 (m, 1H), 2.53 (s, 3H), 2.39–2.32 (m, 1H), 2.19–2.12 (m, 1H), 1.83–1.90 (m, 1H), 1.93 (s, 3H), 1.81 (s, 3H), 1.76 (s, 3H), 1.72 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 3H), 1.13 (s, 3H). 0.80 (s, 9H), −0.05 (s, 3H), −0.31 (s, 3H); ^{13}C NMR (100 MHz) δ 211.4, 171.3, 170.1, 168.7, 166.0, 140.8, 138.8, 138.6, 135.6, 131.6, 131.4, 131.0, 130.3, 128.6, 127.8, 126.8, 126.5, 124.3, 120.1, 84.2, 81.1, 78.8, 76.5, 75.4, 75.0, 74.4, 71.8, 71.5, 57.7, 55.2, 46.2, 43.1, 36.9, 35.9, 26.3, 25.5, 23.0, 21.0, 18.1, 14.3, 14.0, 12.3, 9.9, −5.3, −5.9; ESI-MS: *m/z* 945.5 $[M + H]^+$; 967.5 $[M + Na]^+$.

4.16. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-2-m-N_3-benzoyl-10-deacetyl-10-propionyl-cephalo-manine (22)

To a solution of **21** (972 mg, 1.028 mmol) and propionic anhydride (0.795 ml, 6.168 mmol) in 24.3 ml THF was added $CeCl_3$ (25 mg, 0.103 mmol) and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with EtOAc, washed by saturated aqueous Na_2CO_3 and brine, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 3:1) to afford **22** (950 mg, 92.3% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J = 7.8$ Hz, 1H), 7.82 (m, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.42–7.27 (m, 5H), 7.22 (m, 1H), 6.67 (d, $J = 9.0$ Hz, 1H), 6.42 (q, $J = 6.9$ Hz, 1H), 6.30 (1H, s), 6.20 (t, $J = 8.7$ Hz, 1H), 5.69 (d, $J = 7.2$ Hz, 1H), 5.56 (d, $J = 9.0$ Hz, 1H), 4.99 (d, $J = 8.7$ Hz, 1H), 4.54 (d, $J = 1.8$ Hz, 1H), 4.44 (dd, $J = 10.8$, 6.6 Hz, 1H), 4.34 (d, $J = 8.4$ Hz, 1H), 4.20 (d, $J = 8.4$ Hz, 1H), 3.83 (d, $J = 7.2$ Hz, 1H), 2.65–2.57 (m, 1H), 2.55 (s, 3H), 2.57–2.47 (q, overlapped, 2H), 2.38 (m, 1H), 2.24 (m, 1H), 1.83–1.90 (m, 1H), 1.89 (s, 3H), 1.80 (s, 3H), 1.72 (d, $J = 6.9$ Hz, 3H), 1.68 (3H, s), 1.19 (t, $J = 4.5$ Hz, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 0.79 (s, 9H), −0.08 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 174.6, 171.5, 170.0, 168.7, 165.9, 142.5, 140.7, 138.4, 132.9, 131.6, 131.4, 130.9, 130.3, 128.6, 127.9, 126.8, 126.4, 124.4, 120.1, 84.5, 81.1, 79.0, 76.4, 75.5, 75.3, 75.0, 72.1, 71.6, 58.4, 55.2, 45.4, 43.2, 35.7, 35.5, 27.5, 26.7, 25.5, 23.0, 22.3, 18.1, 14.9, 14.0, 12.3, 9.6, 9.0, −5.4, −5.8; ESI-MS: *m/z* 1001.5 $[M + H]^+$; 1024.5 $[M + Na]^+$.

4.17. 2′-O-(t-Butyldimethylsilyl)-2-debenzoyl-2-m-N_3-benzoyl-7-epi-10-deacetyl-10-propionyl-cephalomannine (23)

To a solution of **22** (703 mg, 0.701 mmol) in 14.0 ml toluene was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.121 ml, 14.2 mmol) and the mixture was stirred for 2.5 h at 0°C. The reaction mixture was diluted by EtOAc, washed by 2 M aqueous HCl and brine, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether:EtOAc = 5:1) to afford **23** (446 mg, 63.5% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, $J = 7.8$ Hz, 1H), 7.84 (m, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.43–7.23 (m, 5H), 7.22–7.24 (m, 1H), 6.84 (s, 1H), 6.68 (d, $J = 9.0$ Hz, 1H), 6.40 (q, $J = 6.9$ Hz, 1H), 6.22 (t, $J = 8.7$ Hz, 1H), 5.77 (d, $J = 7.5$ Hz, 1H), 5.61 (d, $J = 9.0$ Hz, 1H), 4.96 (dd, $J = 8.7$, 3.6 Hz, 1H), 4.69 (d, $J = 11.7$ Hz, 1H), 4.55 (d, $J = 1.8$ Hz, 1H), 4.43 (s, 2H), 3.94 (d, $J = 7.5$ Hz, 1H), 3.72 (d, $J = 11.5$ Hz, 1H), 2.59 (s, 3H), 2.51 (q, $J = 7.5$ Hz, 2H), 2.48–2.28 (m, 2H), 2.28–2.17 (m, 2H), 1.88 (s, 3H), 1.79 (s, 3H), 1.72

(d, $J = 6.9$ Hz, 3H), 1.67 (s, 3H), 1.25–1.20 (t, $J = 7.5$ Hz, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 0.79 (s, 9H), −0.07 (s, 3H), −0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 172.7, 172.0, 171.2, 168.8, 166.0, 140.7, 140.1, 138.4, 133.1, 131.5, 131.4, 131.0, 130.3, 128.6, 127.8, 126.8, 126.4, 124.2, 120.1, 82.7, 82.2, 79.0, 77.9, 77.5, 75.8, 75.7, 75.1, 71.2, 57.5, 55.1, 42.7, 40.2, 36.1, 35.3, 27.5, 25.8, 25.4, 22.8, 21.5, 18.1, 16.3, 14.8, 14.0, 12.3, 9.1, −5.4, −5.9; ESI-MS: *m/z* 1001.5 $[M + H]^+$; 1024.5 $[M + Na]^+$.

4.18. 2-Debenzoyl-2-m-N_3-benzoyl-7-epi-10-deacetyl-10-propionyl-cephalomannine (6)

To a solution of **23** (696 mg, 0.695 mmol) in 5.0 ml pyridine and 17.4 ml acetonitrile was added dropwise 40% solution of HF in water (2.7 ml) at 0°C. The mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous solution was extracted by EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 3:1) to afford **6** (510 mg, 82.7% yield) as a white solid. $[\alpha]_D^{20}$ − 23.2 (*c* 0.009, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, $J = 7.5$ Hz, 1H), 7.82 (m, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.40–7.32 (m, 5H), 7.27–7.23 (m, 1H), 6.81 (s, 1H), 6.55 (d, $J = 9.0$ Hz, 1H), 6.38 (q, $J = 6.9$ Hz, 1H), 6.17 (t, $J = 8.4$ Hz, 1H), 5.74 (d, $J = 7.5$ Hz, 1H), 5.59 (dd, $J = 9.0$, 2.4 Hz, 1H), 4.90 (dd, $J = 3.3$, 8.4 Hz, 1H), 4.70 (d, $J = 2.4$ Hz, 1H), 4.65 (d, $J = 11.6$ Hz, 1H), 4.36 (s, 2H), 3.91 (d, $J = 7.5$ Hz, 1H), 3.74 (d, $J = 5.1$ Hz, 1H), 3.68 (dd, $J = 11.7$, 3.0 Hz, 1H), 2.52 (q, $J = 8.4$ Hz, 2H), 2.45 (s, 3H), 2.27–2.35 (m, 4H), 1.77 (s, 6H), 2.12 (s, 6H), 1.70 (d, $J = 6.9$ Hz, 3H), 1.65 (s, 3H), 1.22 (t, $J = 8.4$ Hz, 3H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 172.7, 172.6, 172.2, 169.0, 166.1, 140.7, 139.8, 138.2, 133.2, 131.7, 131.3, 131.0, 130.2, 128.9, 128.1, 126.9, 126.8, 124.2, 120.1, 82.7, 82.0, 79.0, 77.9, 77.4, 75.7, 75.6, 73.1, 72.0, 57.5, 54.8, 42.6, 40.2, 36.0, 35.2, 27.5, 25.9, 22.5, 21.3, 16.1, 14. 7, 13.9, 12.4, 9.1; ESI-MS: *m/z* 887.4 $[M + H]^+$.

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