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Synthesis and Biological Evaluation of C-3′NH/C-10 and C-2/C-10 Modified Paclitaxel Analogues

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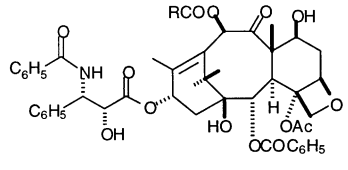
Abstract—Concurrent modifications on the C-3′NH/C-10, and C-2/C-10 positions on paclitaxel were carried out as a way of investigating possible synergistic effects. The biological activities of these analogues were evaluated in both a microtubule assembly assay and human ovarian cancer (A2780) and prostate cancer (PC3) cytotoxicity assay. In some cases the doubly modified analogues were more active than would have been predicted based on the activity of the singly modified analogues, indicating probable synergistic effects.

Introduction

The complex natural product paclitaxel (Taxol®; 1), first isolated from *Taxus brevifolia*,[1] is a member of a large family of taxane diterpenoids.[2] Paclitaxel has excellent clinical activity against ovarian and breast cancers, and shows promising results in the treatment of lung, skin and head and neck cancers.[3] The structure–activity relationships (SAR) of paclitaxel have been extensively studied, and it is well known that key modifications at certain positions may result in significant differences in its activity.[4] Knowledge of the SAR of paclitaxel will help in the design and synthesis of new analogues, with improved physical, chemical and biological properties. It is already well known that the C-13 side chain with a free hydroxyl group at the C-2′ position, the ester groups at C-2 and C-4, the oxetane ring, and the rigid taxane ring system are all important for activity. Modifications in the northern hemisphere of the molecule, consisting of C-6–C-12, do not usually result in drastic changes in activity, but modifications in the southern hemisphere, consisting of carbons 1-5 and 14, including the oxetane ring, have dramatic effects on paclitaxel's anticancer activity. The oxetane ring, for example, is one of the four structural features regarded as essential for biological activity, and has been of great interest to many researchers.[5]

Many derivatives of paclitaxel have been reported, some of which have been found to be more, and some less potent than paclitaxel. Most of the SAR studies reported to date have focused primarily on modifications at only one position and their effects on activity, although several have involved in manipulations at more than one site.[6] The questions of interest in this study were 'How would the activity be affected if paclitaxel was simultaneously modified at more than one site? Would the simultaneous modification of two groups that are known to increase paclitaxel's activity when used singly result in analogues that are more active than either singly modified analogue? Would the increase in activity be merely additive, or would there be a synergistic effect?' In order to answer these questions, we prepared various paclitaxel analogues with modifications at the C-3′NH/C-10, and C-2/C-10 positions.



1 Paclitaxel (Taxol™)

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Synthesis

Previous SAR studies on the effects of modifications at the C-3′ nitrogen showed that analogues without a C-3′-*N*-acyl group are significantly less active than paclitaxel.[7] It is also known that aliphatic and heteroaromatic *N*-acyl analogues are slightly more active than paclitaxel.[8] Therefore, an aliphatic, a heteroaromatic and a heteroaliphatic group were selected to be substituted for the phenyl ring of the benzoyl group at the C-3′-NH position.

In order to evaluate the biological activity of paclitaxel analogues modified at more than one site, it was logically necessary to compare their activities with those of the corresponding monosubstituted analogues. The C-3′-NH and C-10 monosubstituted paclitaxel analogues **2**–**8** were thus prepared according to literature procedures (Fig. 1).[9]

The doubly modified C-3′-NH/C-10 analogues **17**–**28** were prepared by the Holton-Ojima β-lactam synthon method[10] using appropriately modified baccatin III analogues and β-lactams as starting materials. The baccatin III analogues **10**–**13** were prepared from the available

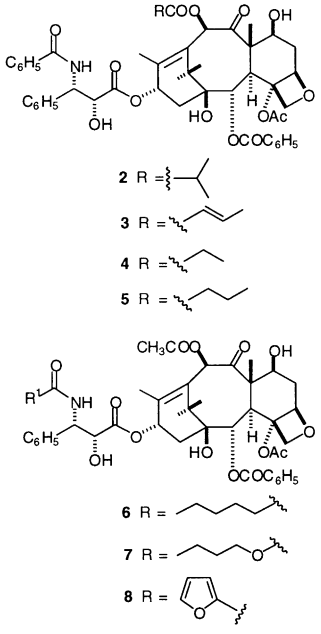
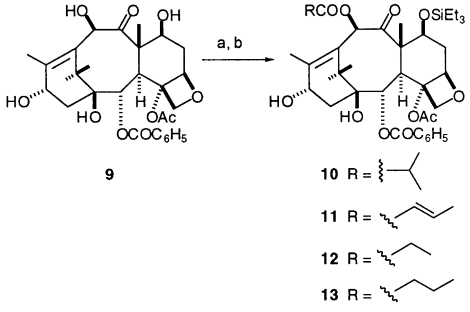


Figure 1. Mono-modified paclitaxel analogues.



Scheme 1. (a) RCOOCOR, $CeCl_3$, THF, rt, 4 h, 95–100%; (b) $SiEt_3Cl$ (5 equiv), Im., DMF, 0 °C, 3 h, 90–95%.

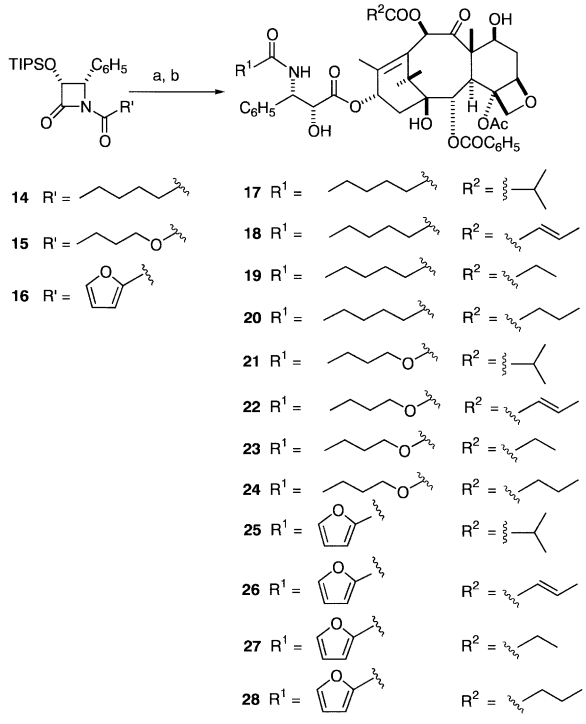
10-deacetylbaccatin III (10-DAB, **9**) by selective acylation at C-10 by Holton's procedure[11] (Scheme 1).

The β-lactams **14**–**16** were prepared by previously described methods,[12,13] and the baccatin III analogues **10**–**13** were coupled with them in the presence of NaH. The coupled products were finally deprotected with HF-pyridine to give the desired C-3′NH/C-10 modified paclitaxel analogues **17**–**28** in good yield (Scheme 2).

The design of the selected C-2/C-10 modified analogues and choice of the groups to be introduced to these compounds followed a careful study of the reported SAR information of paclitaxel. To maximize the probability of synthesizing a more potent analogue, *m*-azido and *m*-chloro benzoyl groups were selected to replace the benzoyl group at the C-2 position, since these groups are known to increase paclitaxel's activity.[14] At the same time, four different groups with different sizes were explored for the C-10 position.

As before, the synthesis started from the easily accessible natural product 10-DAB (**9**). Selective acylation of the C-10 hydroxyl group as previously described followed by protection of the C-7 and C-13 hydroxyl groups yielded the four baccatins **29**–**32**. Selective removal of the C-2 benzoyl group with Red-Al, followed by carbodiimide-based reesterification with either *m*-azido or *m*-chlorobenzoic acid in the presence of EDC, and finally removal of the silyl protecting groups with HF-pyridine gave the baccatin analogues **33**–**40** (Scheme 3).

In order to convert these new baccatin analogues to paclitaxel derivatives, the C-7 hydroxyl groups were



Scheme 2. (a) NaH, THF, rt, 4 h, 85–96%; (b) HF-pyridine, THF, rt, 24 h, 85–95%.

reprotected to give analogues **41–48**, which were coupled with the appropriate β-lactam derivative to give the protected paclitaxel analogues. Simultaneous removal of the silyl protecting groups with HF/pyridine furnished the new paclitaxel analogues **49–56**, modified at the C-2 and C-10 positions (Scheme 4).

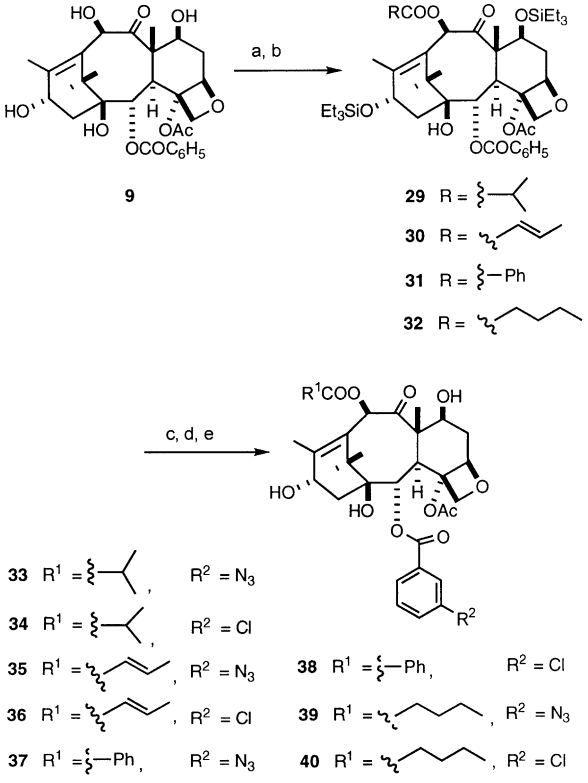
Biological Results and Discussion

Cytotoxicity values were obtained for most of the compounds in two different cell lines; the A2780 human ovarian cancer and the PC3 cell lines. Compounds **2–5** showed increased cytotoxicity as compared with paclitaxel (**1**) in both cell lines, while only compound **8** showed a diminished cytotoxic activity in both cell lines. Interestingly, only analogues **2** and **6** showed greater activity than paclitaxel in the microtubule assembly assay (Table 1).

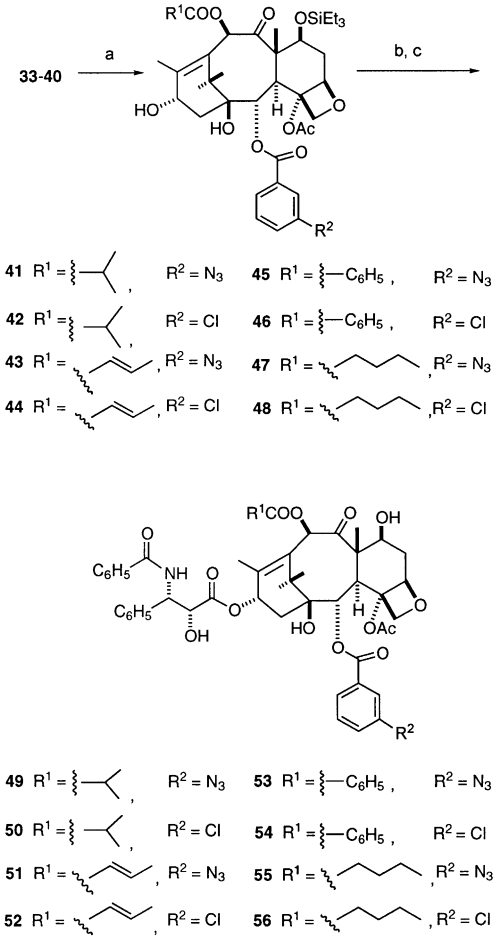
Several of the C-3′NH/C-10 modified compounds showed increased activity in both cytotoxicity assays as compared with paclitaxel, while other compounds had better tubulin assembly activity (Table 2). However, compounds **25**, **27**, and **28** were the only compounds of this group that showed increased activity when compared to paclitaxel in all three of the assays. This disconnect between improved cytotoxicity and tubulin assembly activity is not unprecedented, but it is nevertheless unusual; in the case of the 2-acyl analogues of paclitaxel, for example, a reasonably good correlation between cytotoxicity and tubulin assembly activity was observed.[14]

In the cytotoxicity test of the C-2/C-10 modified compounds using the A2780 human ovarian cancer cell line compounds **49** and **50** both showed significantly increased activity. However, compounds **49** and **53** were the only compounds that showed increased activity when compared to paclitaxel in the microtubule assembly assay and the PC3 cytotoxicity assay, and compound **49** was the only compound with increased activity in all three assays (Table 3).

Although compound **49** showed improved activity relative to paclitaxel in both cytotoxicity assays and the tubulin assembly assay, this improvement is not significantly greater than would have been expected from the C-2 substituent alone. Thus Kingston and collaborators have shown that 2-(*m*-azidobenzoyl)taxol has increased cytotoxicity in the A2780 cell line compared with paclitaxel by a factor of 5.6.[14] The improvement in activity of compound **49** in the A2780 cell line is of comparable magnitude to this value, suggesting that the effect of the C-10 substituent is not significant. The activities of compounds **51–56**, which are less than those expected for the C-2 substituents alone, indicate that the



Scheme 3. (a) RCOOCOR, $CeCl_3$, THF, rt, 4 h, 95–100%; (b) $SiEt_3Cl$, Im., DMF, rt, 5 h, 95–100%; (c) Red-Al, THF, 0 °C, 15 min, 85–90%; (d) *m*-R^2-$C_6H_4CO_2H$, EDC, DMAP, 55 °C, 4 h, 80–90%; (e) HF-pyridine, THF, rt, 24 h, 85–95%.



Scheme 4. (a) Et_3SiCl, DMF, 0 °C, 3 h, 90–95%; (b) β-lactam 14 (R = Ph), NaH, THF, rt, 4 h, 85–95%; (c) HF-pyridine, THF, rt, 24 h, 85–95%.

Table 1. Biological evaluation of the singly modified paclitaxel analogues **2–8**

Compd	PC3 cytotoxicity (IC_{50}, μg/mL)	A2780 cytotoxicity (IC_{50}, μg/mL)	Microtubule assembly activity (I_{50}, μM)
1	0.07	0.02	0.44±0.19
2	0.05	<0.001	0.14±0.06
3	0.05	0.005	0.54±0.07
4	0.04	<0.001	0.71±0.17
5	0.04	<0.001	0.67±0.28
6	0.05	0.07, 0.13, 0.19	0.11±0.04
7	ND	0.05, 0.04	3.78±1.55
8	1.9	14.1, 14.9, 16.3	2.0±0.48

ND, not determined.

Table 2. Biological evaluation of C-3′N/C-10 modified Taxol analogues

Compd	PC3 cytotoxicity (IC_{50}, μg/mL)	A2780 cytotoxicity (IC_{50}, μg/mL)	Microtubule assembly activity (I_{50}, μM)
17	0.25, 0.3	<0.00122	1.20±0.31
18	0.14, 0.13	0.01, 0.002	0.08±0.036
19	0.04	0.04, 0.002	0.65±0.31
20	0.19, 0.3	<0.001	0.14±0.06
21	1.3, 1	0.007±0.005	2.03±0.17
22	0.5	0.022, 0.03	4.85±2.44
23	0.05	<0.001	1.63±0.44
24	0.2	0.06, 0.02	4.99±2.32
25	0.04	0.001±0.001	0.07±0.02
26	0.35	0.02±0.01, 0.42	1.10±0.52
27	0.04	0.004, 0.05	0.49±0.08
28	0.03	0.002±0.001	0.36±0.13
1	0.07	0.02	0.55±0.10

Table 3. Biological evaluation of C-2/C-10 modified Taxol analogues

Compd	PC3 cytotoxicity (IC_{50}, μg/mL)	A2780 cytotoxicity (IC_{50}, μg/mL)	Microtubule assembly activity (I_{50}, μM)
49	0.05	0.014, <0.00122	0.32±0.15
50	0.4	0.007, 0.08	1.50±0.45
51	0.4, 0.4	2.2	2.47±1.02
52	0.3	0.24, 0.22	1.09±0.33
53	0.055, 0.045	0.17, 0.15	0.29±0.002
54	0.3	0.17, 0.2	1.08±0.34
55	0.1, 0.09	0.07, 0.14	3.90±0.49
56	0.4	0.19, 0.17	0.78±0.17
1	0.07	0.02	0.55±0.1

Table 4. Evidence for positive synergistic effect[a]

Compd	R_1	R_2	PC3 cytotoxicity (IC_{50}, μg/mL)	A2780 cytotoxicity (IC_{50}, μg/mL)	Microtubule assembly activity (I_{50}, μM)
1	Ph	Me	0.07	0.02	0.55±0.1
4	Ph	Et	0.04	<0.00122	N/A
5	Ph	Pr	0.04	<0.00122	5.70±1.07
8	2-Furyl	Me	1.9	14.1, 14.9	2.10±0.29
27	2-Furyl	Et	0.04	0.004	0.49±0.08
28	2-Furyl	Pr	0.03	0.002±0.001	0.36±0.13

[a]PTX, paclitaxel.

C-10 substituent has *reduced* their activity as compared with the corresponding C-10 acetyl analogues.

Given the available data, it was of interest to attempt to evaluate whether any synergistic effects were observed. A comparison of selected data for the C-3′NH/C-10 analogues is shown in Table 4.

These data indicate that replacement of the C-10 acetyl group with C-10 propanoyl or butanoyl groups (**4** and **5**) results in a significant increase in cytotoxicity to the A2780 cell line, while replacement of the C-3′-N benzoyl group with a 2-furoyl group gave a product (**8**) with significantly *decreased* cytotoxicity and microtubule assembly activity. Interestingly, replacement of *both* the C-3′N benzoyl group with a 2-furoyl group and the C-10 acetate with a butanoate (**27**) gave a product with improved cytotoxicity and *also improved microtubule assembly activity*. This improvement in the microtubule assembly activity would not have been predicted, and indicates a probable positive synergistic effect.

Conclusion

In conclusion, a series of analogues of paclitaxel have been synthesized modified at the C-3′-NH, C-2 and C-10 positions. It appears that simultaneously modifying two substituents on the paclitaxel system produces effects on the bioactivity of paclitaxel which are not simply the sum of the effects of the individual modifications. The reasons for this complex situation are not currently understood, and additional studies in this area are needed.

Experimental

General methods

Chemicals were obtained from Aldrich Chemical Co. and were used without further purification, unless otherwise noted. All anhydrous reactions were performed in oven-dried glassware under argon. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. All reactions were monitored by E. Merck analytical thin-layer chromatography (TLC) plates (silica gel 60 GF, aluminum back) and analyzed with 254 nm UV light and/or vanillin/sulfuric acid spray and/or phosphomolybdic acid/ethanol spray. Silica gel for column chromatography was purchased from E. Merck (230–400 mesh). Preparative thin layer chromatography (PTLC) plates (silica gel 60 GF) were purchased from Analtech. ^{1}H and; ^{13}C NMR spectra were obtained in $CDCl_3$ or CD_3OD on Varian Unity 400 spectrometer (operating at 399.951 MHz for ^{1}H and 100.578 MHz for ^{13}C) and were assigned by comparison of chemical shifts and coupling constants with those of related compounds. Chemical shifts were reported as δ-values relative to tetramethylsilane (TMS) as internal reference, and coupling constants were reported in Hertz. HRFAB and LRFAB mass spectra were obtained at the Nebraska Center for Mass Spectrometry, University of Nebraska and in the Department of Chemistry at Virginia Polytechnic Institute and State University. The phrase 'worked-up in the usual way' refers to diluting the reaction mixture with an excess amount of organic solvent, washing with water and brine, drying over anhydrous sodium sulfate and evaporating the solvent in vacuo unless otherwise noted. The known intermediates were prepared following the procedures that are reported in the literature, and NMR data of these compounds were identical to those in literature.

General procedure for the coupling of the baccatin III derivatives (10–13) with the β-lactams (14–16). Synthesis of the silyl protected paclitaxel derivatives. To a stirred solution of the baccatin derivative (**10–13**) (0.04 mmol) in THF (2 mL) at 0 °C was added NaH (2 mmol). The mixture was stirred for 15 min, and then β-lactam (**14–16**; 0.08 mmol) was introduced. The reaction mixture was allowed to come to room temperature and further stirred for 4 h. The reaction mixture was cooled down to 0 °C, quenched with acetic acid, and diluted with EtOAc, washed with dil. NaOH solution (0.1 N) and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (30% EtOAc/hexane) and the desired product was isolated in 85–95% yield.

Synthesis of the paclitaxel derivatives 17–28; general procedure for removal of the silyl protecting groups. To a stirred solution of every 10 mg of the of protected paclitaxel derivative THF (0.5 mL) was added 0.15 mL of pyridine at 0 °C, stirred for 5 min where 0.15 mL of HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight for 24 h. The reaction mixture was then diluted with EtOAc, washed with satd aq $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (60% EtOAc/hexane) and the desired product was isolated in 85–95% yield.

3′-*N*-Debenzoyl-3′-*N*-hexanoyl-10-deacetyl-10-isopropanoylpaclitaxel (17). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.52–7.33 (m, 7H), 6.26 (s, 1H), 6.19 (t, 1H), 6.16 (d, J = 8.8 Hz, 1H), 5.67 (d, J = 7.2 Hz, 1H), 5.56 (d, J = 9.2 Hz, 1H), 4.93 (d, J = 8 Hz, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 3.80 (d, J = 7.2 Hz, 1H), 3.44 (d, J = 5.2 Hz, 1H), 2.73 (m, 1H), 2.54 (m, 1H), 2.51 (s, 1H), 2.34 (s, 3H), 2.29 (m, 1H), 2.21 (t, 2H), 1.82 (s, 3H), 1.76 (s, 1H), 1.67 (s, 3H), 1.58 (s, 6H), 1.31 (d, 3H), 1.26 (d, 3H), 1.24–1.15 (m, 6H), 0.84 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 177.20, 172.84, 170.23, 167.00, 141.85, 138.06, 133.71, 133.27, 130.22, 129.09, 128.97, 128.27, 126.96, 84.42, 81.12, 79.04, 76.47, 75.19, 74.94, 73.13, 72.41, 72.22, 58.61, 54.51, 45.60, 43.20, 36.59, 35.55, 34.04, 31.30, 26.83, 25.36, 22.61, 19.19, 18.62, 14.81, 13.84, 9.54. HRFABMS m/z calculated for $C_{48}H_{62}NO_{14}$ $(M+H)^+$ 876.4170, found 876.4099, Δ 8.1 ppm. LRFABMS m/z found 876.5.

3′-*N*-Debenzoyl-3′-*N*-hexanoyl-10-deacetyl-10-(2-butene)-oylpaclitaxel (18). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40–7.30 (m,

5H), 7.10 (m, 1H), 6.34 (s, 1H), 6.23 (d, NH, 1H), 6.21 (t, 1H), 5.99 (d, $J=15.6$ Hz, 1H), 5.67 (d, $J=7.2$ Hz, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.42 (m, 1H), 4.28 (d, $J=8.8$ Hz, 1H), 4.18 (d, $J=8.8$ Hz, 1H), 3.80 (d, $J=7.2$ Hz, 1H), 3.51 (d, $J=5.6$ Hz, 1H), 2.64 (d, 1H), 2.53 (m, 1H), 2.34 (s, 3H), 2.30 (t, 2H), 2.18 (t, 2H), 1.94 (d, 3H), 1.91 (s, 1H), 1.85 (dt, 1H), 1.81 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.27 (s, 3H), 1.25–1.20 (m, 5H), 1.16 (s, 3H), 0.83 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.75, 173.00, 172.80, 170.23, 166.95, 166.23, 147.26, 142.06, 138.05, 133.68, 133.26, 130.20, 129.13, 128.95, 128.68, 128.26, 126.95, 121.59, 84.43, 81.13, 78.98, 76.48, 75.28, 74.98, 73.11, 72.41, 72.24, 58.59, 54.51, 45.58, 43.20, 36.58, 35.63, 35.55, 31.29, 26.87, 25.35, 22.59, 22.28, 21.99, 18.23, 14.81, 13.84, 9.52. HRFABMS m/z calculated for $C_{47}H_{60}NO_{14}$ $(M+H)^+$ 874.4017, found 874.4013, Δ 3.5 ppm. LRFABMS m/z found 874.2.

3′-*N*-Debenzoyl-3′-*N*-hexanoyl-10-deacetyl-10-propanoylpaclitaxel (19). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40–7.30 (m, 5H), 6.29 (s, 1H), 6.23 (d, NH, 1H), 6.21 (t, 1H), 5.67 (d, $J=7.2$, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.28 (d, $J=8.8$ Hz, 1H), 4.18 (d, $J=8.8$ Hz, 1H), 3.78 (d, $J=7.2$ Hz, 1H), 3.52 (d, $J=5.6$ Hz, 1H), 2.61–2.44 (m, 4H), 2.33 (s, 3H), 2.30 (t, 2H), 2.18 (t, 2H), 1.93 (s, 1H), 1.88 (dt, 1H), 1.81 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.25–1.22 (m, 11H), 1.14 (s, 3H), 0.83 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.73, 174.62, 173.03, 172.84, 170.23, 166.93, 141.89, 138.05, 133.68, 133.22, 130.20, 129.12, 128.95, 128.68, 128.26, 126.94, 84.40, 81.11, 78.94, 76.47, 75.36, 74.95, 73.11, 72.40, 72.18, 58.57, 54.52, 45.58, 43.20, 36.58, 35.63, 31.28, 27.55, 26.79, 25.35, 22.59, 22.28, 21.90, 14.79, 13.84, 9.55, 9.00. HRFABMS m/z calculated for $C_{47}H_{60}NO_{14}$ $(M+H)^+$ 862.4014, found 862.4013, Δ 2.3 ppm. LRFABMS m/z found 862.2.

3′-*N*-Debenzoyl-3′-*N*-hexanoyl-10-deacetyl-10-butanoylpaclitaxel (20). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40–7.33 (m, 5H), 6.28 (s, 1H), 6.22 (d, NH, 1H), 6.21 (t, 1H), 5.67 (d, $J=7.2$ Hz, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.28 (d, $J=8.8$ Hz, 1H), 4.18 (d, $J=8.8$ Hz, 1H), 3.78 (d, $J=7.2$ Hz, 1H), 3.51 (d, $J=5.2$ Hz, 1H), 2.58–2.40 (m, 4H), 2.34 (s, 3H), 2.29 (t, 2H), 2.18 (t, 2H), 1.90 (s, 1H), 1.84 (dt, 1H), 1.81 (s, 3H), 1.73 (m, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.25 (s, 3H), 1.22 (m, 5H), 1.14 (s, 3H), 1.02 (t, 3H), 0.83 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 173.85, 172.84, 170.23, 166.94, 141.90, 138.05, 133.68, 133.26, 130.20, 129.12, 128.96, 128.68, 128.26, 126.95, 84.41, 81.11, 78.96, 76.47, 75.30, 74.95, 73.11, 72.40, 72.19, 58.57, 54.51, 45.57, 43.19, 36.58, 36.07, 35.63, 35.54, 31.29, 26.81, 25.35, 22.59, 22.28, 21.93, 18.41, 14.79, 13.84, 13.65, 9.55. HRFABMS m/z calculated for $C_{48}H_{62}NO_{14}$ $(M+H)^+$ 876.4170, found 876.4170, Δ 0 ppm. LRFABMS m/z found 876.3.

3′-*N*-Debenzoyl-3′-*N*-butoxycarbonyl-10-deacetyl-10-isopropanoylpaclitaxel (21). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.60 (t, 1H), 7.51–7.32 (m, 7H), 6.26 (s, 1H), 6.25 (t, 1H), 5.66 (d, $J=7.2$ Hz, 1H), 5.52 (d, $J=9.2$ Hz, 1H), 5.30 (d, 1H), 4.94 (d, $J=8$ Hz, 1H), 4.64 (s, 1H), 4.41 (m, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.13 (d, $J=8.4$ Hz, 1H), 3.80 (d, $J=7.2$ Hz, 1H), 2.73 (m, 1H), 2.54 (m, 2H), 2.36 (s, 3H), 2.23 (m, 1H), 1.87 (t, 2H), 1.83 (s, 3H), 1.72 (d, 1H), 1.67 (s, 3H), 1.63 (d, 2H), 1.48 (m, 2H), 1.32 (d, 3H), 1.26 (d, 3H), 1.25–1.15 (m, 6H), 0.84 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.63, 197.00, 193.84, 177.20, 170.31, 133.73, 130.20, 129.07, 128.90, 128.68, 128.21, 126.73, 84.42, 79.17, 76.47, 75.17, 72.22, 65.36, 58.59, 45.65, 43.17, 35.55, 34.04, 30.88, 26.86, 22.60, 19.19, 18.62, 14.85, 13.62, 9.56. HRFABMS m/z calculated for $C_{47}H_{60}NO_{15}$ $(M+H)^+$ 878.3963, found 878.3975, Δ 1.2 ppm. LRFABMS m/z found 878.4.

3′-*N*-Debenzoyl-3′-*N*-butoxycarbonyl-10-deacetyl-10-but-2-enoylpaclitaxel (22). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40--7.30 (m, 5H), 7.10 (m, 1H), 6.34 (s, 1H), 6.26 (t, 1H), 5.99 (d, $J=15.6$ Hz, 1H), 5.66 (dd, 1H), 5.56 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.43 (m, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.18 (d, $J=8.4$ Hz, 1H), 3.94 (d, 1H), 3.93 (m, 1H), 3.80 (d, $J=7.2$ Hz, 1H), 3.40 (d, $J=5.2$ Hz, 1H), 2.66 (d, 1H), 2.54 (m, 1H), 2.36 (s, 3H), 2.24 (m, 1H), 1.95 (d, 3H), 1.88 (dt, 1H), 1.82 (s, 3H), 1.79 (s, 1H), 1.67 (s, 6H), 1.48 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H), 0.82 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.72, 173.00, 172.80, 170.32, 167.03, 166.23, 147.29, 133.71, 130.20, 129.07, 128.88, 128.66, 128.19, 126.73, 121.58, 84.44, 81.14, 79.17, 76.47, 75.26, 74.97, 72.23, 65.34, 58.59, 45.62, 43.16, 35.54, 30.87, 26.91, 22.57, 18.84, 18.22, 14.83, 13.60, 9.52. HRFABMS m/z calculated for $C_{47}H_{58}NO_{15}$ $(M+H)^+$ 876.3806, found 876.3806 LRFABMS m/z found 876.1.

3′-*N*-Debenzoyl-3′-*N*-butoxycarbonyl-10-deacetyl-10-propanoylpaclitaxel (23). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40–7.30 (m, 5H), 6.29 (s, 1H), 6.26 (t, 1H), 5.66 (d, 1H), 5.54 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.41 (m, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.4$ Hz, 1H), 3.95 (d, 1H), 3.94 (m, 1H), 3.80 (d, $J=7.2$ Hz, 1H), 3.37 (d, $J=5.2$ Hz, 1H), 2.60–2.44 (m, 4H), 2.36 (s, 3H), 2.24 (m, 2H), 1.88 (dt, 1H), 1.83 (s, 3H), 1.77 (s, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.48 (m, 2H), 1.27 (s, 3H), 1.23 (t, 3H), 1.14 (s, 3H), 0.82 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.69, 174.61, 172.80, 170.31, 167.03, 166.23, 133.71, 130.16, 130.19, 129.08, 128.89, 128.66, 128.19, 126.73, 84.40, 79.14, 76.47, 75.34, 74.94, 72.19, 65.35, 58.57, 45.62, 43.16, 35.52, 30.87, 27.54, 26.83, 22.58, 18.85, 14.83, 13.61, 9.55, 9.00. HRFABMS m/z calculated for $C_{46}H_{58}NO_{15}$ $(M+H)^+$ 864.3806, found 864.3806 LRFABMS m/z found 864.1.

3′-*N*-Debenzoyl-3′-*N*-butoxycarbonyl-10-deacetyl-10-butanoylpaclitaxel (24). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40–7.30 (m, 5H), 6.29 (s, 1H), 6.26 (t, 1H), 5.66 (d, 1H), 5.54 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.41 (m, 1H), 4.28 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.4$ Hz, 1H), 3.95 (d, 1H), 3.94 (m, 1H), 3.80 (d, $J=7.2$ Hz, 1H), 3.37 (d, $J=5.2$ Hz, 1H), 2.55–2.40 (m, 5H), 2.36 (s, 3H), 2.24

(m, 2H), 1.88 (dt, 1H), 1.83 (s, 3H), 1.72 (m, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.48 (m, 2H), 1.27 (s, 3H), 1.14 (s, 3H), 1.02 (t, 3H), 0.82 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.63, 173.83, 172.80, 170.30, 167.03, 166.23, 133.70, 133.20, 130.19, 129.07, 128.87, 128.66, 128.19, 126.71, 84.40, 81.12, 79.14, 76.46, 75.27, 74.94, 73.59, 72.18, 65.35, 58.57, 45.61, 43.16, 36.04, 35.53, 30.87, 26.84, 22.58, 18.83, 18.39, 14.83, 13.64, 13.60, 9.55. HRFABMS *m/z* calculated for $C_{47}H_{60}NO_{15}$ $(M+H)^+$ 878.3963, found 878.3962 Δ 3.0 ppm LRFABMS *m/z* found 878.2.

3′-*N*-Debenzoyl-3′-*N*-(2-furoyl)-10-deacetyl-10-isopropanoylpaclitaxel (25). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.53–7.33 (m, 8H), 7.16 (d, $J=9.2$, 1H, NH), 7.01 (d, $J=3.2$ Hz, 1H), 6.46 (m, 1H), 6.28 (s, 1H), 6.23 (t, 1H), 5.74 (d, $J=9.2$ Hz, 1H), 5.66 (d, $J=7.2$ Hz, 1H), 4.94 (d, $J=7.6$ Hz, 1H), 4.76 (s, 1H), 4.40 (m, 1H), 4.29 (d, $J=8.4$ Hz, 1H), 4.19 (d, $J=8.4$ Hz, 1H), 3.79 (d, $J=7.2$, 1H), 3.60 (bs, 1H), 2.54 (m, 2H), 2.52 (m, 2H), 2.37 (s, 3H), 1.85 (m, 1H), 1.83 (s, 1H), 1.80 (s, 3H), 1.67 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.94, 174.87, 172.67, 170.61, 167.2, 1650, 158.1, 147.36, 144.58, 142.09, 138.07, 133.98, 133.46, 130.46, 129.38, 129.23, 128.95, 127.26, 115.46, 111.58, 84.64, 81.39, 79.26, 75.59, 75.16, 73.57, 72.54, 72.44, 58.83, 54.55, 45.86, 43.38, 35.86, 27.78, 27.09, 22.84, 22.05, 15.06, 9.79, 9.23. HRFABMS *m/z* calculated for $C_{47}H_{54}NO_{15}$ $(M+H)^+$ 872.3493, found 872.3433, Δ 6 ppm. LRFABMS *m/z* found 872.3.

3′-*N*-debenzoyl-3′-*N*-(2-furoyl)-10-deacetyl-10-(2-butene)oylpaclitaxel (26). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 2H), 7.62 (tt, 1H), 7.53–7.32 (m, 8H), 7.16 (d, $J=8.8$ Hz, 1H, NH), 7.10 (m, 1H), 7.01 (d, $J=3.2$ Hz, 1H), 6.46 (m, 1H), 6.32 (s, 1H), 6.23 (t, 1H), 6.00 (d, $J=15.6$ Hz, 1H), 5.74 (d, $J=9.6$ Hz, 1H), 5.67 (d, $J=7.2$ Hz, 1H), 4.94 (d, $J=7.6$ Hz, 1H), 4.76 (s, 1H), 4.43 (m, 1H), 4.29 (d, $J=8.4$ Hz, 1H), 4.19 (d, $J=8.4$ Hz, 1H), 3.81 (d, $J=7.2$ Hz, 1H), 2.55 (m, 1H), 2.37 (s, 3H), 2.3 (m, 2H), 1.95 (d, 3H), 1.86 (m, 2H), 1.8 (s, 3H), 1.68 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.71, 172.37, 170.37, 167.01, 166.23, 157.81, 147.28, 144.31, 142.04, 137.83, 133.74, 133.26, 130.23, 129.13, 128.99, 128.71, 128.36, 127.03, 121.58, 115.18, 112.33, 84.44, 81.17, 79.11, 76.5, 75.27, 74.95, 73.37, 72.3, 58.64, 54.3, 45.61, 43.14, 35.63, 26.95, 22.61, 21.89, 18.23, 14.85, 9.51. HRFABMS *m/z* calculated for $C_{47}H_{51}NO_{15}Na$ $(M+Na)^+$ 892.3156, found 892.3153, Δ 0.3 ppm. LRFABMS *m/z* found $(M+Na)^+$ 892.

3′-*N*-Debenzoyl-3′-*N*-(2-furoyl)-10-deacetyl-10-propanoylpaclitaxel (27). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.18 (d, 2H), 7.62 (tt, 1H), 7.53–7.33 (m, 8H), 7.16 (d, $J=9.2$ Hz, 1H, NH), 7.01 (d, $J=3.6$ Hz, 1H), 6.46 (m, 1H), 6.27 (s, 1H), 6.23 (t, 1H), 5.72 (d, $J=8.4$ Hz, 1H), 5.66 (d, $J=7.2$ Hz, 1H), 4.93 (d, 1H), 4.76 (s, 1H), 4.4 (m, 1H), 4.29 (d, $J=8.4$ Hz, 1H), 4.19 (d, $J=8.4$ Hz, 1H), 3.79 (d, $J=7.2$ Hz, 1H), 2.53 (m, 1H), 2.47 (m, 2H), 2.36 (s, 3H), 2.28 (m, 2H), 1.87 (m, 2H), 1.79 (s, 3H), 1.67 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H), 1.01 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.94, 174.87, 172.67, 170.61, 167.2, 165.05, 158.1, 147.36, 144.58, 142.09, 138.07, 133.98, 130.46, 129.38, 128.95, 128.61, 127.26, 115.46, 112.58, 84.64, 81.39, 79.26, 75.59, 75.16, 73.57, 72.54, 58.83, 54.55, 45.86, 43.38, 35.86, 27.78, 27.09, 22.84, 22.05, 15.06, 9.79, 9.23. HRFABMS *m/z* calculated for $C_{46}H_{52}NO_{15}$ $(M+H)^+$ 858.3337, found 858.3380, Δ 5.1 ppm. LRFABMS *m/z* found 858.3.

3′-*N*-Debenzoyl-3′-*N*-(2-furoyl)-10-deacetyl-10-butanoylpaclitaxel (28). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.18 (d, 2H), 7.62 (tt, 1H), 7.53–7.33 (m, 8H), 7.16 (d, $J=9.2$ Hz, 1H, NH), 7.01 (d, $J=3.6$ Hz, 1H), 6.46 (m, 1H), 6.27 (s, 1H), 6.23 (t, 1H), 5.72 (d, $J=8.4$ Hz, 1H), 5.66 (d, $J=7.2$ Hz, 1H), 4.93 (d, 1H), 4.76 (s, 1H), 4.4 (m, 1H), 4.29 (d, $J=8.4$ Hz, 1H), 4.19 (d, $J=8.4$ Hz, 1H), 3.79 (d, $J=7.2$ Hz, 1H), 2.53 (m, 1H), 2.47 (m, 2H), 2.36 (s, 3H), 2.28 (m, 2H), 1.87 (m, 2H), 1.79 (s, 3H), 1.73 (m, 2H), 1.67 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H), 1.01 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.64, 201.42, 198.87, 181.29, 173.85, 172.43, 170.36, 166.94, 157.86, 151.81, 147.6, 147.1, 144.35, 141.98, 141.83, 138.67, 137.82, 133.73, 133.27, 130.22, 122.15, 128.99, 128.36, 127.02, 115.22, 112.34, 84.4, 81.15, 79.01, 75.3, 74.92, 73.32, 72.31, 58.58, 54.31, 45.6, 43.14, 36.06, 35.64, 33.48, 26.86, 22.6, 21.85, 20.41, 18.4, 14.81, 13.64, 9.55. HRFABMS *m/z* calculated for $C_{47}H_{54}NO_{15}$ $(M+H)^+$ 872.3493, found 872.3508, Δ 1.5 ppm. LRFABMS *m/z* found 872.3.

Synthesis of the baccatin derivatives 33–40; general procedure for esterification of the C-2 hydroxyl group of 7,13-di(triethylsilyl)baccatin III derivatives. To a stirred suspension of either *m*-azido- or *m*-chlorobenzoic acid in anhydrous toluene (2 mL for every 30 mg of acid) was added EDC (1-[3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride) (1 equiv) at room temperature and the reaction mixture was stirred for 15 min. DMAP [4-(dimethylamino)pyridine] (catalytic amount) was then added and the reaction mixture was stirred for another 5 min. The 2-debenzoyl baccatin derivative (1/15 equiv) was then introduced at room temperature and the reaction mixture was warmed up to 55 °C and further stirred for 24 h. The reaction mixture was cooled down to room temperature, diluted with EtOAc, washed with water, satd aq $NaHCO_3$ solution and worked up in the usual way. Finally the crude product was applied on a PTLC place (10% EtOAc/hexane) and the desired products was isolated in 80–90% yield.

General procedure for removal of the triethylsilyl protecting groups. To a stirred solution of the baccatin derivative in THF was added pyridine at 0 °C, stirred for 5 min where HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight for 24 h. The reaction mixture was then diluted with EtOAc, washed with satd aq $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/hexane) and the desired products was isolated in 85–95% yield. For every 10 mg of the baccatin derivative 0.5 mL THF, 0.15 mL of pyridine and 0.15 mL of HF-pyridine was used.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoylbaccatin III (33). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.78 (s, 1H), 7.46 (t, 1H), 7.24 (dd, 1H), 6.30 (s, 1H), 5.6 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 7.6 Hz, 1H), 4.88 (t, 1H), 4.46 (m, 1H), 4.3 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 8.4 Hz, 1H), 3.89 (d, J = 7.2 Hz, 1H), 2.73 (m, 1H), 2.56 (m, 1H), 2.29 (d, 2H), 2.27 (s, 3H), 2.04 (s, 3H), 1.86 (m, 1H), 1.65 (s, 3H), 1.61 (bs, 1H), 1.32 (d, 3H), 1.25 (d, 3H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.09, 177.21, 170.67, 166.06, 146.27, 140.76, 131.82, 131.05, 130.11, 126.62, 124.24, 120.05, 84.49, 80.71, 79.07, 75.79, 75.3, 72.3, 67.85, 58.66, 46.1, 42.64, 38.55, 35.52, 34.03, 26.95, 22.58, 20.86, 19.16, 18.62, 15.71, 9.37. HRFABMS m/z calculated for $C_{33}H_{42}N_3O_{11}$ $(M+H)^+$ 656.2819, found 656.2843, Δ 3.6 ppm LRFABMS m/z found 656.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoylbaccatin III (34). ^{1}H NMR (CD_3OD, 399.951 MHz) δ 8.13 (s, 1H), 8.03 (d, 1H), 7.65 (d, 1H), 7.52 (t, 1H), 6.49 (s, 1H), 5.6 (d, J = 8 Hz, 1H), 5.03 (d, J = 10 Hz, 1H), 4.85 (t, 1H), 4.38 (m, 1H), 4.17 (q, 2H), 3.93 (d, J = 7.2 Hz, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.38 (d, 1H), 2.34 (d, 1H), 2.28 (s, 3H), 2.07 (s, 3H), 1.79 (m, 1H), 1.64 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (CD_3OD, 100.578 MHz) δ 205.54, 177.19, 171.88, 166.20, 147.5, 135.64, 134.33, 133.53, 132.8, 131.36, 130.98, 129.37, 85.85, 81.97, 79.33, 77.32, 76.79, 72.48, 68.07, 59.27, 43.97, 40.49, 37.52, 35.29, 27.17, 22.66, 21.59, 19.42, 19.36, 15.49, 10.30. HRFABMS m/z calculated for $C_{33}H_{42}ClO_{11}$ $(M+H)^+$ 649.2416, found 649.2390, Δ 4.0 ppm. LRFABMS m/z found 649.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-but-2-enoylbaccatin III (35). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.88 (dt, 1H), 7.78 (t, 1H), 7.47 (t, 1H), 7.23 (d, 1H), 7.15 (m, 1H), 6.38 (s, 1H), 6.00 (d, J = 15.6 Hz, 1H), 5.61 (d, J = 7.2 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), 4.89 (t, 1H), 4.48 (m, 1H), 4.30 (d, J = 8 Hz, 1H), 4.13 (d, J = 8 Hz, 1H), 3.9 (d, J = 7.6 Hz, 1H), 2.68 (bs, 1H), 2.57 (m, 1H), 2.29 (d, 2H), 2.28 (s, 3H), 2.18 (bs, 1H), 2.05 (s, 3H), 1.94 (d, J = 6.8 Hz, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.17, 170.68, 166.3, 166.08, 147.06, 146.5, 140.78, 131.82, 131.07, 130.12, 126.64, 124.24, 121.7, 120.06, 84.51, 80.74, 79.10, 75.89, 75.35, 72.36, 67.9, 58.7, 46.07, 42.65,38.53, 35.53, 29.68, 27.02, 22.59, 20.95, 18.21, 15.60, 9.35. HRFABMS m/z calculated for $C_{33}H_{40}N_3O_{11}$ $(M+H)^+$ 654.2663, found 654.2666, Δ 0.3 ppm. LRFABMS m/z found 654.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-but-2-enoylbaccatin III (36). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (t, 1H), 7.98 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.1 (m, 1H), 6.38 (s, 1H), 6.00 (d, J = 15.6 Hz, 1H), 5.85 (d, J = 6.8 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), 4.88 (t, 1H), 4.48 (m, 1H), 4.28 (d, J = 8.4 Hz, 1H), 4.12 (d, J = 8.4 Hz, 1H), 3.89 (d, J = 6.8 Hz, 1H), 2.57 (m, 1H), 2.28 (s, 3H), 2.26 (m, 2H), 2.05 (s, 3H), 1.93 (d, J = 6.8 Hz, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.12, 170.55, 166.29, 165.63, 147.07, 146.49, 134.71, 133.60, 131.75, 131.11, 130.15, 129.97, 128.23, 121.68, 84.45, 80.71, 79.2, 76.25, 75.87, 75.35, 72.4, 67.87, 58.61, 46.10, 42.61, 38.52, 35.51, 26.99, 22.46, 20.98, 18.21, 15.59, 9.33. HRFABMS m/z calculated for $C_{33}H_{40}ClO_{11}$ $(M+H)^+$ 647.2259, found 647.2233, Δ 4.1 ppm. LRFABMS m/z found 647.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoylbaccatin III (37). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.10 (s, 1H), 8.08 (d, 1H), 7.88 (dt, 1H), 7.79 (t, 1H), 7.61 (tt, 1H), 7.47 (m, 3H), 7.23 (dd, 1H), 6.58 (s, 1H), 5.65 (d, J = 6.8 Hz, 1H), 5.02 (d, J = 7.6 Hz, 1H), 4.92 (t, 1H), 4.55 (m, 1H), 4.32 (d, J = 8 Hz, 1H), 4.15 (d, J = 8 Hz, 1H), 3.95 (d, J = 6.8 Hz, 1H), 2.61 (m, 2H), 2.33 (d, 2H), 2.29 (s, 3H), 2.1 (s, 3H), 1.89 (m, 1H), 1.68 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.93, 170.71, 166.43, 166.08, 146.72, 140.78, 133.61, 131.70, 131.05, 130.12, 129.94, 129.18, 128.50, 126.64, 124.26, 120.07, 84.5, 80.72, 79.10, 76.55, 76.33, 75.34, 72.34, 67.88, 58.73, 46.19, 42.71, 38.58, 35.63, 27.14, 22.59, 21.12, 15.66, 9.39. HRFABMS m/z calculated for $C_{36}H_{40}N_3O_{11}$ $(M+H)^+$ 690.2663, found 690.2669, Δ 0.6 ppm. LRFABMS m/z found 690.2.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoylbaccatin III (38). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 1H), 8.08 (s, 2H), 7.98 (d, 1H), 7.62 (m, 2H), 7.48 (m, 3H), 6.58 (s, 1H), 5.61 (d, J = 7.2 Hz, 1H), 5.03 (d, J = 8.8 Hz, 1H), 4.91 (t, 1H), 4.55 (m, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.4, 1H), 3.95 (d, J = 7.2 Hz, 1H), 2.6 (m, 1H), 2.32 (d, 2H), 2.30 (s, 3H), 2.10 (s, 3H), 1.88 (m, 1H), 1.68 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.88, 170.57, 166.43, 165.63, 146.73, 134.72, 133.61, 131.63, 131.11, 130.16, 129.99, 129.93, 129.17, 128.5, 128.24, 84.44, 80.72, 79.2, 76.53, 76.26, 75.36, 72.38, 67.85, 58.65, 46.24, 42.68, 38.58, 35.65, 27.12, 22.46, 21.16, 15.65, 14.16, 9.39. HRFABMS m/z calculated for $C_{36}H_{40}ClO_{11}$ $(M+H)^+$ 683.2259, found 683.2267, Δ 1.1 ppm. LRFABMS m/z found 683.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoylbaccatin III (39). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.86 (d, 1H), 7.77 (s, 1H), 7.45 (t, 1H), 7.24 (dd, 1H), 6.31 (s, 1H), 5.59 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 7.6 Hz, 1H), 4.87 (t, 1H), 4.46 (m, 1H), 4.29 (d, J = 8 Hz, 1H), 4.12 (d, J = 8 Hz, 1H), 3.87 (d, J = 7.2 Hz, 1H), 2.53 (m, 1H), 2.28 (m, 2H), 2.28 (d, 2H), 2.27 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.36 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.11, 174.06, 170.64, 166.03, 146.43, 140.75, 131.74, 131.05, 130.09, 126.6, 124.22, 120.04, 84.48, 80.67, 79.03, 76.31, 75.9, 75.33, 72.28, 67.79, 58.62, 46.06, 42.61, 38.58, 35.49, 33.9, 26.92, 26.86, 22.55, 22.17, 20.87, 15.55, 13.69, 9.36. HRFABMS m/z calculated for $C_{34}H_{44}N_3O_{11}$ $(M+H)^+$ 670.2976, found 670.2994, Δ 2.6 ppm. LRFABMS m/z found 670.3.

2-Debenzoyl-2-*m*-cholorobenzoyl-10-deacetyl-10-pentanoylbaccatin III (40). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.09 (s, 1H), 7.96 (d, 1H), 7.56 (dd, 1H), 7.4 (t, 1H), 6.30 (s, 1H), 5.55 (d, J = 6.8 Hz, 1H), 4.98 (d, J = 8 Hz, 1H), 4.86 (t, 1H), 4.45 (m, 1H), 4.27 (d, J = 8.4 Hz, 1H),

4.11 (d, $J=8.4$ Hz, 1H), 3.86 (d, $J=6.8$ Hz, 1H), 2.53 (m, 2H), 2.48 (m, 2H), 2.27 (d, 2H), 2.26 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.42 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.33, 174.33, 170.77, 165.84, 146.72, 134.96, 133.83, 131.92, 131.38, 130.39, 130.22, 128.46, 84.68, 80.90, 79.39, 76.5, 76.16, 75.62, 72.59, 68.01, 58.8, 46.36, 42.84, 38.87, 35.76, 34.16, 27.17, 27.12, 22.68, 22.43, 21.17, 15.81, 13.96, 9.62. HRFABMS m/z calculated for $C_{34}H_{44}ClO_{11}$ $(M+H)^+$ 663.2572, found 663.2541, Δ 4.6 ppm. LRFABMS m/z found 663.2.

General procedure for the selective triethylsilylation of the C-7 hydroxyl of the baccatin III derivatives 33–40. Synthesis of the baccatin derivatives 41–48. To a stirred solution of the baccatin derivative (**33–40**) (0.02 mmol) in DMF (0.5 mL) was added imidazole (0.06 mmol) and the reaction mixture was cooled down to 0 °C. 0.022 mmol of chlorotriethylsilane was then introduced and the reaction mixture was stirred at this temperature for 3–4 h. The reaction mixture was allowed to come to room temperature, diluted with 5% $NaHCO_3$ in MeOH, stirred for 15 min where further diluted with EtOAc, washed with satd aq $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (30% EtOAc/hexane) and the desired product was isolated in 90–95% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoyl-7-triethylsilylbaccatin III (41). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.79 (s, 1H), 7.46 (t, 1H), 7.26 (dd, 1H), 6.45 (s, 1H), 5.61 (d, $J=6.8$ Hz, 1H), 4.97 (d, $J=8$ Hz, 1H), 4.83 (t, 1H), 4.49 (m, 1H), 4.30 (d, $J=8.4$ Hz, 1H), 4.12 (d, $J=8.4$ Hz, 1H), 3.9 (d, $J=6.8$ Hz, 1H), 2.71 (m, 1H), 2.55 (m, 1H), 2.28 (s, 3H), 2.26 (d, 2H), 2.21 (s, 3H), 1.87 (m, 1H), 1.67 (s, 3H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.92 (t, 9H), 0.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.19, 175.28, 170.79, 166.15, 143.92, 140.74, 132.69, 131.13, 130.09, 126.66, 124.21, 120.07, 84.26, 80.81, 78.77, 76.43, 75.35, 75.13, 72.28, 67.9, 58.61, 47.23, 42.72, 38.17, 37.19, 34.13, 26.78, 22.70, 20.06, 19.06, 18.89, 14.96, 9.91, 6.77, 5.25. LRFABMS m/z calculated for $(M+H)^+$ $C_{39}H_{56}N_3O_{11}Si$ 770.3684, found 770.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoyl-7-triethylsilylbaccatin III (42). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 7.97 (d, 1H), 7.57 (d, 1H), 7.41 (t, 1H),6.44 (s, 1H), 5.58 (d, $J=7.2$ Hz, 1H), 4.97 (d, $J=8.8$ Hz, 1H), 4.81 (t, 1H), 4.47 (m, 1H), 4.27 (d, $J=8$ Hz, 1H), 4.11 (d, $J=8$ Hz, 1H), 3.88 (d, $J=6.8$ Hz, 1H), 2.69 (m, 1H), 2.52 (m, 1H), 2.28 (s, 3H), 2.25 (d, 2H), 2.20 (s, 3H), 1.87 (m, 1H), 1.66 (s, 3H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.91 (t, 9H), 0.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.17, 175.28, 170.63, 165.67, 143.95, 134.68, 133.54, 132.58, 131.17, 130.16, 129.93, 128.23, 84.18, 80.76, 78.87, 76.34, 75.33, 75.13, 72.31, 67.84, 58.53, 47.26, 42.66, 38.17, 37.16, 34.12, 26.73, 22.52, 20.08, 19.05, 18.87, 14.94, 9.89, 6.76, 5.23. LRFABMS m/z calculated for $(M+H)^+$ $C_{39}H_{56}ClO_{11}Si$ 763.3280, found 763.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-but-2-enoyl-7-triethylsilylbaccatin III (43). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.88 (d, 1H), 7.80 (s, 1H), 7.46 (t, 1H), 7.22 (d, 1H), 7.08 (m, 1H), 6.50 (s, 1H), 5.98 (d, $J=15.6$ Hz, 1H), 5.63 (d, $J=6.8$ Hz, 1H), 4.97 (d, $J=8$ Hz, 1H), 4.83 (t, 1H), 4.5 (m, 1H), 4.3 (d, $J=8.4$ Hz, 1H), 4.13 (d, $J=8.4$ Hz, 1H), 3.9 (d, $J=7.2$ Hz, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.13 (s, 3H), 1.90 (d, $J=6.8$ Hz, 3H), 1.87 (m, 1H), 1.64(s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.91 (t, 9H), 0.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.21, 170.81, 166.16, 164.71, 145.73, 143.95, 140.75, 132.7, 131.14, 130.09, 126.67, 124.21, 122.29, 120.09, 84.28, 80.31, 78.77, 76.44, 75.5, 75.15, 72.32, 67.93, 58.65, 47.26, 42.75, 38.18, 37.22, 26.76, 22.71, 20.11, 18.15, 14.96, 9.9, 6.74, 5.25. LRFABMS m/z calculated for $(M+H)^+$ $C_{39}H_{54}N_3O_{11}Si$ 768.3528, found 768.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-but-2-enoyl-7-triethylsilylbaccatin III (44). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (s, 1H), 7.97 (d, 1H), 7.57 (d, 1H), 7.42 (t, 1H), 7.07 (m, 1H), 6.50 (s, 1H), 5.98 (d, $J=15.6$ Hz, 1H), 5.57 (d, $J=6.8$ Hz, 1H), 4.98 (d, $J=7.6$ Hz, 1H), 4.82 (t, 1H), 4.49 (m, 1H), 4.28 (d, $J=8$ Hz, 1H), 4.12 (d, $J=8$ Hz, 1H), 3.90 (d, $J=7.2$ Hz, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 2.22 (s, 3H), 1.90 (d, $J=7.2$ Hz, 3H), 1.84 (m, 1H), 1.68 (s, 3H), 1.21 (s, 3H), 1.02 (s, 3H), 0.92 (t, 9H), 0.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.17, 170.67, 165.69, 164.7, 145.73, 143.94, 134.69, 133.55, 132.63, 131.19, 130.19, 129.93, 128.25, 122.27, 84.21, 80.80, 78.88, 76.36, 75.48, 75.14, 72.36, 67.9, 58.58, 47.29, 42.7, 38.16, 37.2, 26.74, 22.56, 20.13, 18.14, 14.94, 9.89, 6.74, 5.24. LRFABMS m/z calculated for $(M+H)^+$ $C_{39}H_{54}ClO_{11}Si$ 761.3124, found 761.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoyl-7-triethylsilylbaccatin III (45). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.15 (s, 1H), 8.13 (d, 1H), 7.89 (dt, 1H), 7.79 (t, 1H), 7.59 (tt, 1H), 7.46 (m, 3H), 7.22 (d, 1H), 6.69 (s, 1H), 5.68 (d, $J=7.2$ Hz, 1H), 4.99 (d, $J=8$ Hz, 1H), 4.85 (t, 1H), 4.57 (m, 1H), 4.32 (d, $J=8$ Hz, 1H), 4.15 (d, $J=8$ Hz, 1H), 3.96 (d, $J=7.2$ Hz, 1H), 2.5 (m, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.27 (s, 3H), 1.89 (m, 1H), 1.71 (s, 3H), 1.32 (s, 3H), 1.18 (m, 1H), 1.04 (s, 3H), 0.89 (t, 9H), 0.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.08, 170.82, 166.15, 165.02, 144.39, 140.75, 133.16, 132.58, 131.13, 130.09,129.88, 129.81, 128.49, 126.66, 124.22, 122.09, 84.29, 80.83, 78.80, 76.43, 76.19, 75.17, 72.38, 67.93, 58.70, 47.29, 42.8, 38.25, 37.22, 26.83, 22.71, 20.35, 15.07, 9.92, 6.72, 5.27. LRFABMS m/z calculated for $(M+H)^+$ $C_{42}H_{54}N_3O_{11}Si$ 804.3528, found 804.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoyl-7-triethylsilylbaccatin III (46). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.15 (s, 1H), 8.13 (d, 2H), 7.97 (d, 1H), 7.56 (d, 2H), 7.44 (m, 3H), 6.69 (s, 1H), 5.64 (d, $J=6.8$ Hz, 1H), 5.0 (d, $J=7.6$ Hz, 1H), 4.84 (t, 1H), 4.56 (m, 1H), 4.30 (d, $J=8.4$ Hz, 1H), 4.14 (d, $J=8.4$ Hz, 1H), 3.95 (d, $J=7.6$ Hz, 1H), 2.55 (m, 1H), 2.31 (s, 3H), 2.26 (m, 1H), 2.25 (s, 3H), 2.04 (s, 1H), 1.87 (m, 1H), 1.71 (s, 3H), 1.31 (s, 3H), 1.11 (s, 3H), 1.01 (t, 9H), 0.58 (m,

6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.05, 170.69, 165.71, 165.35, 144.37, 134.71, 133.57, 133.17, 132.53, 131.19, 130.19, 129.96, 129.87, 129.81, 128.49, 128.26, 84.23, 80.81, 78.92, 76.17, 75.17, 72.42, 67.91, 58.64, 47.34, 42.76, 38.24, 27.20, 26.82, 22.56, 20.38, 15.06, 9.92, 6.72, 5.27. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{42}H_{54}ClO_{11}Si$ 797.3124, found 797.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoyl-7-triethylsilylbaccatin III (47). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.78 (s, 1H), 7.45 (t, 1H), 7.23 (m, 1H), 6.47 (s, 1H), 5.61 (d, $J=6.8$ Hz, 1H), 4.96 (d, $J=8$ Hz, 1H), 4.82 (t, 1H), 4.48 (m, 1H), 4.29 (d, $J=8$ Hz, 1H), 4.11 (d, $J=8$ Hz, 1H), 3.88 (d, $J=6.8$ Hz, 1H), 2.51 (m, 1H), 2.43 (m, 2H), 2.27 (s, 3H), 2.26 (d, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.63 (m, 2H), 1.4 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H), 0.92 (t, 9H), 0.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.19, 172.09, 170.76, 166.12, 143.94, 140.72, 132.67, 131.13, 130.06, 126.64, 124.18, 120.06, 84.24, 80.78, 78.72, 76.42, 75.45, 75.14, 72.28, 67.85, 58.61, 47.19, 42.7, 38.21, 37.18, 34.02, 27.04, 26.75, 22.67, 22.17, 20.04, 14.94, 13.69, 9.89, 6.74, 5.24. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{40}H_{58}N_3O_{11}Si$ 784.3841, found 784.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-pentanoyl-7-triethylsilylbaccatin III (48). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 7.97 (d, 1H), 7.56 (d, 1H), 7.41 (t, 1H), 6.47 (s, 1H), 5.57 (d, $J=7.2$ Hz, 1H), 4.96 (d, $J=7.6$ Hz, 1H), 4.81 (t, 1H), 4.48 (m, 1H), 4.27 (d, $J=7.6$ Hz, 1H), 4.11 (d, $J=7$. Hz6, 1H), 3.87 (d, $J=6.8$ Hz, 1H), 2.50 (m, 1H), 2.43 (m, 2H), 2.28 (s, 3H), 2.22 (m, 2H), 2.18 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.4 (m, 2H), 1.18 (s, 3H), 1.2 (s, 3H), 0.93 (s, 3H), 0.92 (t, 9H), 0.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.16, 172.08, 170.61, 165.64, 143.93, 134.67, 133.52, 132.6, 131.17, 130.15, 129.92, 128.21, 84.16, 80.74, 78.82, 76.34, 75.43, 75.14, 72.32, 67.81, 58.53, 47.23, 42.64, 38.19, 37.15, 34.01, 27.03, 26.72, 22.51, 22.16, 20.06, 14.91, 13.68, 9.88, 6.74, 5.23. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{40}H_{58}ClO_{11}Si$ 777.3437, found 777.4.

Synthesis of the paclitaxel derivatives 49–56. General procedure for the coupling of the baccatin III derivatives (41–48) with the β-lactam. To a stirred solution of the baccatin derivative (41–48) (0.04 mmol) in THF (2 mL) at 0 °C was added NaH (2 mmol). The mixture was stirred for 15 min, and then β-lactam (0.08 mmol) was introduced. The reaction mixture was allowed to come to room temperature and further stirred for 4 h. The reaction mixture was cooled down to 0 °C, quenched with acetic acid, and diluted with EtOAc, washed with dil. NaOH solution (0.1 N) and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (30% EtOAc/hexane) and the desired product was isolated in 90–95% yield.

General procedure for removal of the silyl protecting groups. All reactions were performed as described for the synthesis of baccatin III derivatives. For every 10 mg of the starting material 0.5 mL THF, 0.15 mL of pyridine and 0.15 mL of HF-pyridine was used and the desired products were isolated in 85–95% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoylpaclitaxel (49). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.91 (d, 1H), 7.82 (s, 1H), 7.71 (d, 2H), 7.51–7.23 (m, 10H), 6.90 (d, $J=8.8$ Hz, 1H, NH), 6.25 (s, 1H), 6.20 (t, 1H), 5.76 (d, $J=8.8$ Hz, 1H), 5.66 (d, $J=7.2$ Hz, 1H), 4.95 (d, $J=8.8$ Hz, 1H), 4.76 (m, 1H), 4.41 (m, 1H), 4.31 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.4$ Hz, 1H), 3.82 (d, $J=6.8$ Hz, 1H), 3.51 (d, $J=5.2$ Hz, 1H), 2.72 (m, 1H), 2.56 (m, 1H), 2.51 (d, 1H), 2.36 (s, 3H), 2.34 (m, 2H), 1.9 (m, 1H), 1.8 (s, 3H), 1.68 (s, 1H), 1.67 (s, 3H), 1.32(d, 3H), 1.24 (s, 3H), 1.22 (d, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.59, 177.19, 172.84, 170.34, 167.01, 166.03, 141.91, 140.78, 137.98, 133.63, 133.19, 131.95, 130.85, 130.24, 129.04, 128.68, 128.40, 127.11, 127.01, 126.82, 124.40, 120.13, 84.47, 81.13, 79.09, 76.40, 75.35, 75.17, 73.03, 72.47, 72.20, 58.59, 55.07, 45.59, 43.14, 35.65, 35.53, 34.03, 26.85, 22.68, 21.82, 19.19, 18.61, 14.84, 9.52. HRFABMS *m/z* calculated for $C_{49}H_{55}N_4O_{14}$ $(M+H)^+$ 923.3715, found 923.3752, Δ 4 ppm. LRFABMS *m/z* found 923.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoylpaclitaxel (50). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 8.01 (d, 1H), 7.72 (d, 2H), 7.58 (d, 1H), 7.53–7.32 (m, 9H), 6.97 (d, $J=8.8$ Hz, 1H, NH), 6.24 (s, 1H), 6.19 (t, 1H), 5.75 (dd, 1H), 5.61 (d, $J=6.8$ Hz, 1H), 4.95 (d, $J=8$ Hz, 1H), 4.76 (t, 1H), 4.38 (m, 1H), 4.27 (d, $J=8.4$ Hz, 1H), 4.15 (d, $J=8.4$ Hz, 1H), 3.80 (d, $J=7.6$ Hz, 1H), 3.64 (d, $J=5.2$ Hz, 1H), 2.72 (m, 1H), 2.55 (m, 1H), 2.52 (m, 1H), 2.35 (s, 3H), 2.30 (d, 2H), 1.86 (m, 1H), 1.78 (s, 3H), 1.74 (s, 1H), 1.66 (s, 3H), 1.31 (d, 3H), 1.24 (s, 3H), 1.22 (d, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.49, 177.16, 172.70, 170.25, 167.09, 165.55, 141.85, 137.7, 134.72, 133.67, 133.61, 133.12, 131.95, 130.95, 130.22, 130.12, 129.03, 128.66, 128.39, 127.10, 127.01, 84.39, 81.11, 79.1, 76.33, 75.32, 75.14, 73.18, 72.29, 72.22, 58.51, 55.18, 45.66, 43.08, 35.61, 35.54, 34.01, 26.79, 22.48, 21.76, 19.16, 18.59, 14.82, 9.4. HRFABMS *m/z* calculated for $C_{49}H_{55}ClNO_{14}$ $(M+H)^+$ 916.3311, found 916.3315, Δ 0.4 ppm. LRFABMS *m/z* found 916.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-but-2-enoylpaclitaxel (51). ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.91 (d, 1H), 7.82 (t, 1H), 7.71 (d, 2H), 7.52–7.23 (m, 10H), 7.10 (m, 1H), 6.91 (d, $J=8.8$ Hz, 1H, NH), 6.33 (s, 1H), 6.20 (t, 1H), 6.00 (d, $J=14.8$ Hz, 1H), 5.75 (d, $J=8.8$ Hz, 1H), 5.67 (d, $J=8.8$ Hz, 1H), 4.96 (d, $J=9.2$ Hz, 1H), 4.77 (m, 1H), 4.38 (m, 1H), 4.32 (d, $J=8$ Hz, 1H), 4.18 (d, $J=8$ Hz, 1H), 3.82 (d, $J=6.8$ Hz, 1H), 3.48 (d, $J=5.6$ Hz, 1H), 2.61 (d, 1H), 2.56 (m, 1H), 2.37 (s, 3H), 2.33 (d, 1H), 1.93 (d, 3H), 1.86 (m, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 195.74, 190.8, 186.66, 175.14, 172.79, 170.35, 168.67, 166.05, 147.34, 143.56, 142.16, 138.58, 137.95, 134.62, 133.62, 131.95, 130.24, 129.04, 128.41, 127.11, 126.82, 124.4, 121.55, 120.37, 84.48, 81.15, 79.14, 76.41, 75.25, 73.03, 72.25, 69.82, 58.61, 55.08, 45.55, 43.14, 35.64, 26.92, 22.67, 21.88, 18.93, 14.88, 9.49. HRFABMS *m/z* calculated for

$C_{49}H_{52}N_4O_{14}Na$ $(M+Na)^+$ 943.3378, found 943.3370, Δ 0.8 ppm. LRFABMS *m/z* found 943.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-but-2-enoylpaclitaxel (52). ^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (s, 1H), 8.02 (d, 1H), 7.72 (d, 2H), 7.59 (dt, 1H), 7.50–7.23 (m, 9H), 7.10 (m, 1H), 6.95 (d, $J=8.8$ Hz, 1H, NH), 6.32 (s, 1H), 6.2 (t, 1H), 5.98 (d, $J=15.6$ Hz, 1H), 5.75 (dd, 1H), 5.62 (d, $J=7.2$ Hz, 1H), 4.96 (d, $J=8$ Hz, 1H), 4.76 (m, 1H), 4.42 (m, 1H), 4.38 (d, $J=8.4$ Hz, 1H), 4.16 (d, $J=8.4$, 1H), 3.81 (d, $J=6.8$ Hz, 1H), 3.55 (d, $J=5.2$ Hz, 1H), 2.63 (d, 1H), 2.56 (m, 1H), 2.36 (s, 3H), 2.31 (d, 2H), 1.95 (d, 3H), 1.87 (m, 1H), 1.78 (s, 3H), 1.69 (s, 1H), 1.67 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.59, 172.65, 170.26, 167.00, 166.21, 165.61, 147.34, 142.13, 137.93, 134.74, 133.69, 133.60, 133.11, 131.95, 130.94, 130.22, 130.12, 129.05, 128.68, 128.42, 127.10, 127.01, 121.54, 84.42, 81.13, 79.18, 76.35, 75.34, 75.24, 73.19, 72.31, 58.57, 55.18, 45.62, 43.08, 35.61, 35.53, 36.89, 22.49, 21.83, 18.24, 14.88, 9.47. HRFABMS *m/z* calculated for $C_{49}H_{53}ClNO_{14}$ $(M+H)^+$ 914.3155, found 914.3143, Δ 1.2 ppm. LRFABMS *m/z* found 914.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoylpaclitaxel (53). ^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.08 (d, 2H), 7.93 (d, 1H), 7.83 (t, 1H), 7.71 (d, 2H), 7.62 (t, 1H), 7.52–7.23 (m, 12H), 6.92 (d, $J=8.8$ Hz, 1H, NH), 6.53 (s, 1H), 6.24 (t, 1H), 5.76 (d, $J=7.2$ Hz, 1H), 5.72 (d, $J=7.2$ Hz, 1H), 4.96 (d, $J=9.6$ Hz, 1H), 4.77 (m, 1H), 4.50 (m, 1H), 4.33 (d, $J=8.4$ Hz, 1H), 4.10 (d, $J=8.4$ Hz, 1H), 3.89 (d, $J=7.2$ Hz, 1H), 3.5 (d, $J=5.2$ Hz, 1H), 2.6 (d, 1H), 2.57 (m, 1H), 2.38 (s, 3H), 2.37 (d, 2H), 1.91 (m, 1H), 1.84 (s, 3H), 1.72 (s, 1H), 1.70 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.42, 172.79, 170.39, 167.00, 166.38, 166.05, 142.35, 140.78, 137.93, 133.71, 133.08, 131.95, 130.84, 130.25, 129.97, 128.68, 128.55, 128.42, 127.11, 126.82, 124.41, 120.14, 84.47, 81.14, 79.12, 76.41, 75.9, 75.36, 73.02, 72.24, 58.66, 55.1, 45.67. 43.21, 35.69, 27.27, 22.68, 22.03, 14.92, 9.53. HRFABMS *m/z* calculated for $C_{52}H_{53}N_4O_{14}$ $(M+H)^+$ 957.3558, found 957.3562, Δ 0.4 ppm. LRFABMS *m/z* found 957.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoylpaclitaxel (54). ^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.13 (s, 1H), 8.07 (d, 2H), 8.02 (d, 1H), 7.72 (d, 2H), 7.61–7.58 (m, 2H), 7.50–7.23 (m, 11H), 6.97 (d, $J=8.8$ Hz, 1H, NH), 6.52 (s, 1H), 6.22 (t, 1H), 5.78 (d, $J=7.6$ Hz, 1H), 5.66 (d, $J=6.8$ Hz, 1H), 4.97 (d, $J=9.2$ Hz, 1H), 4.77 (m, 1H), 4.48 (m, 1H), 4.30 (d, $J=8.4$ Hz, 1H), 4.17 (d, $J=8.4$ Hz, 1H), 3.87 (d, $J=7.2$ Hz, 1H), 3.59 (d, $J=5.6$ Hz, 1H), 2.63 (d, 1H), 2.59 (m, 1H), 2.37 (s, 3H), 2.34 (d, 2H), 1.90 (m, 1H), 1.82 (s, 3H), 1.76 (s, 1H), 1.69 (s, 3H), 1.65 (s, 1H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.34, 172.65, 170.3, 167.05, 166.37, 165.61, 142.31, 137.92, 134.75, 133.72, 133.6, 133.02, 131.95, 130.93, 130.24, 130.14, 129.97, 129.05, 129.06, 128.68, 128.55, 128.43, 128.39, 127.1, 84.41, 81.13, 79.18, 76.35, 75.89, 75.33, 73.19, 72.3, 58.61, 55.21, 45.75, 43.16, 35.66, 26.99, 22.49, 21.99, 14.93, 9.51. HRFABMS *m/z* calculated for $C_{52}H_{52}ClNO_{14}Na$ $(M+Na)^+$ 972.2975, found 972.2994, Δ 1.1 ppm. LRFABMS *m/z* found 972.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoylpaclitaxel (55). ^1H NMR ($CDCl_3$, 399.951 MHz) δ 7.92 (d, 1H), 7.81 (t, 1H), 7.71 (d, 2H), 7.51–7.23 (m, 10H), 6.92 (d, $J=8.8$ Hz, 1H, NH), 6.27 (s, 1H), 6.21 (t, 1H), 5.76 (d, $J=9.2$ Hz, 1H), 5.67 (d, $J=6.8$ Hz, 1H), 4.95 (d, $J=7.6$ Hz, 1H), 4.76 (m, 1H), 4.41 (m, 1H), 4.31 (d, $J=8$ Hz, 1H), 4.18 (d, $J=8$ Hz, 1H), 3.81 (d, $J=6.8$ Hz, 1H), 3.54 (d, $J=5.6$ Hz, 1H), 2.51 (m, 2H), 2.42 (m, 2H), 2.37 (s, 3H), 2.33 (d, 2H), 1.86 (m, 1H), 1.79 (s, 3H), 1.73 (s, 1H), 1.7 (m, 2H), 1.67 (s, 3H), 1.66 (s, 1H), 1.43 (m, 2H), 1.24 (s, 3H), 1.14 (s, 3H), 0.94 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.60, 174.02, 172.82, 170.35, 167.03, 166.02, 141.99, 140.77, 137.98, 133.62, 133.17, 131.95, 130.87, 130.24, 129.03, 128.68, 128.39, 127.11, 127.01, 126.82, 124.39, 120.13, 84.46, 81.12, 79.07, 76.40, 75.36, 73.03, 72.44, 72.19, 58.58, 55.09, 45.55, 43.13, 35.64, 35.51, 33.8, 26.87, 22.66, 21.81, 14.84, 13.71, 9.52. HRFABMS *m/z* calculated for $C_{50}H_{57}N_4O_{14}$ $(M+H)^+$ 937.3871, found 937.3843, Δ 3 ppm. LRFABMS *m/z* found 937.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-pentanoylpaclitaxel (56). ^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 8.01 (d, 1H), 7.71 (d, 2H), 7.57 (d, 1H), 7.53–7.25 (m, 9H), 6.98 (d, $J=8.8$ Hz, 1H, NH), 6.26 (s, 1H), 6.19 (t, 1H), 5.74 (d, $J=9.6$ Hz, 1H), 5.61 (d, $J=7.2$ Hz, 1H), 4.96 (d, $J=8.4$ Hz, 1H), 4.76 (m, 1H), 4.38 (m, 1H), 4.27 (d, $J=8$ Hz, 1H), 4.15 (d, $J=8$ Hz, 1H), 3.79 (d, $J=7.2$ Hz, 1H), 3.66 (d, $J=5.2$ Hz, 1H), 2.55 (m, 2H), 2.47 (m, 2H), 2.35 (s, 3H), 2.30 (d, 2H), 1.86 (m, 1H), 1.79 (s, 1H), 1.77 (s, 3H), 1.71 (m, 2H), 1.66 (s, 3H), 1.4 (m, 2H), 1.22 (s, 3H), 1.12 (s, 3H), 0.94 (t, 3H); ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.51, 173.99, 172.68, 170.25, 167.09, 165.55, 141.94, 137.96, 134.72, 133.67, 133.11, 131.94, 130.95, 130.11, 129.02, 128.65, 128.39, 127.01, 84.38, 81.1, 79.1, 76.34, 75.33, 75.25, 73.19, 72.27, 72.22, 58.11, 55.21, 45.62, 43.07, 35.61, 26.8, 22.47, 21.76, 14.83, 13.7, 9.49. HRFABMS *m/z* calculated for $C_{50}H_{57}ClNO_{14}$ $(M+H)^+$ 930.3468, found 930.3452, Δ 1.6 ppm. LRFABMS *m/z* found 930.3.

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