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Syntheses and bioactivities of macrocyclic paclitaxel bis-lactones

Changhui Liu,[a] Jennifer K. Schilling,[a] Rudravajhala Ravindra,[b] Susan Bane[b] and David G. I. Kingston[a,*]

[a]*Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA*
[b]*Department of Chemistry, State University of New York, Binghamton, NY 13902, USA*

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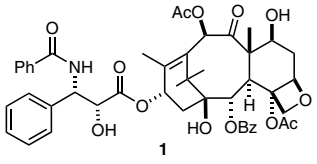
Abstract—Five macrocyclic paclitaxel bis-lactones and their corresponding open chain taxoids were synthesized as models of the tubulin-binding conformation of paclitaxel. Macrocyclic lactones with a 19–21-membered ring underwent isomerization to form smaller rings. The lactones were evaluated for cytotoxicity and tubulin-polymerization ability. All five macrocyclic paclitaxel lactones were active, but less so than paclitaxel, while the rearranged macrocyclic lactones and the corresponding open-chain taxoids were much less active or inactive.

1. Introduction

Paclitaxel (Taxol®, **1**) is currently one of the world's most successful anticancer drugs, and it is used for the treatment of breast, ovarian, and other cancers.[1]



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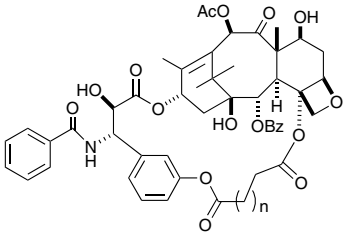
Its anticancer activity comes primarily from its ability to bind to microtubules and prevent them from undergoing depolymerization,[2] leading ultimately to apoptosis. The exact nature of the paclitaxel–tubulin interaction is thus of great interest. It is known that paclitaxel binds preferentially to the β-tubulin unit of the mictrotubule,[3,4] and it is probable that it binds to this β-tubulin unit in a specific binding conformation or in a few closely related conformations. Several studies have attempted to elucidate the nature of this bioactive conformation. Three models have been proposed for it, based primarily on NMR data, but also including the electron crystallographic coordinates of polymerized β-tubulin.[5] Studies based on solid state NMR spectroscopy led to the determination of specific internuclear distances for tubulin-bound paclitaxel,[6,7] while solution NMR studies led to the identification of three major conformers; a 'non-polar' form,[8,9] a 'polar' form,[10] and a 'T-taxol' form.[11] The 'T-taxol' conformation is consistent with the solid state NMR studies referred to above, and it docks well into a hydrophobic cleft identified in β-tubulin.[12]

In order to test these hypotheses, various conformationally restricted paclitaxel analogs have been made, including analogs with conformationally restricted side chains[13,14] and analogs with bridged linkages from the C-3′ phenyl to the C-2 phenyl with both shorter[15] and longer[16,17] linkers. More recently, a series of macrocyclic docetaxel analogs was prepared with the bridge from the C-3′ nitrogen to the C-2 oxygen.[18] Our group has also prepared two macrocyclic paclitaxel analogs tethered from the C-4 position to the side chain C-3′ through ring closing metathesis (RCM) to test the T-taxol hypothesis.[19] None of these conformationally restricted paclitaxel analogs had comparable tubulin assembly activity to paclitaxel, and the cytotoxicities of even the best analogs were significantly lower than that of paclitaxel.



2a n = 1
2b n = 2
2c n = 3
2d n = 4
2e n = 5

Keywords: Taxol; Tubulin; Cytotoxicity; Paclitaxel.
* Corresponding author. Tel.: +1 5402316570; fax: +1 5402313255; e-mail: dkingston@vt.edu

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In the proposed T-taxol conformation, the distances between the two C-13 side chain terminal phenyl rings and the C-2 phenyl group are approximately 9–10 Å, and it is not possible to design a short conformationally directing tether between these centers. However, the C-4 acetate methyl is quite close to one edge of the C-3′ phenyl moiety in this conformer, indicating a possible conformational control. A variety of positional isomers and C3′–C4 linkers were modeled as T-Taxol mimics. From them, we designed and synthesized the analogs **2a**–**e** linked between the C-3′-phenyl group and the C-4 position through macrocyclic lactonization. A part of the motivation for this study was to compare the lactonization route to macrocycle formation with the Grubbs' olefin metathesis route used earlier,[19] from the perspective of both synthetic utility and activity of the final products.

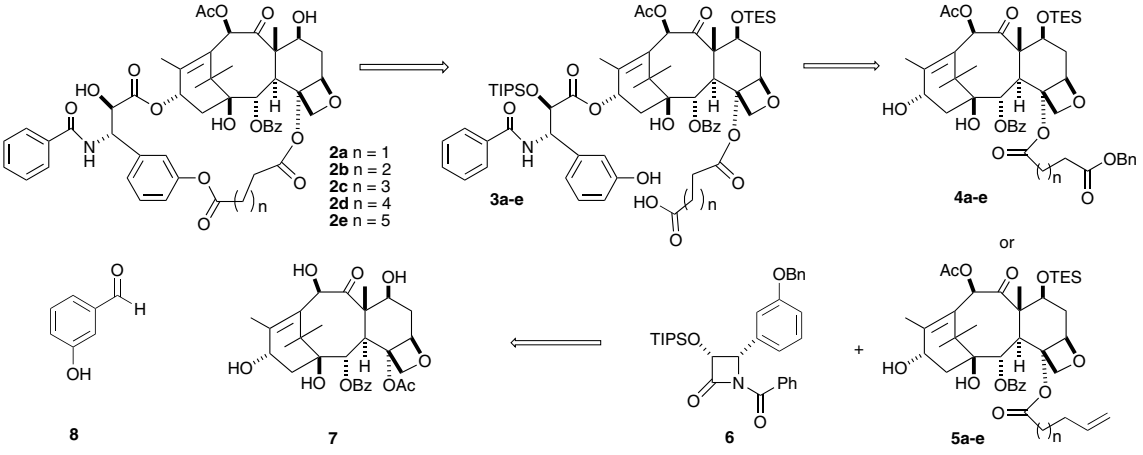
2. Synthesis

Our retrosynthetic analysis of the macrocyclic paclitaxel lactones **2a**–**e** is shown in Scheme 1. Compounds **2a**–**e** could be prepared by lactonization of the hydroxyacids **3a**–**e**, which could be prepared from the two key fragments **4a**–**e** and the β-lactam **6**; an alternate route would involve the alkenyl derivatives **5a**–**e**. Compounds **4a**–**e** can be synthesized through known C-4 deacetylation and reacylation procedures[20] from commercially available 10-deacetylbaccatin III (**7**, 10-DAB), while **6** could be synthesized through standard β-lactam synthesis[21] from 3-hydroxybenzaldehyde (**8**).

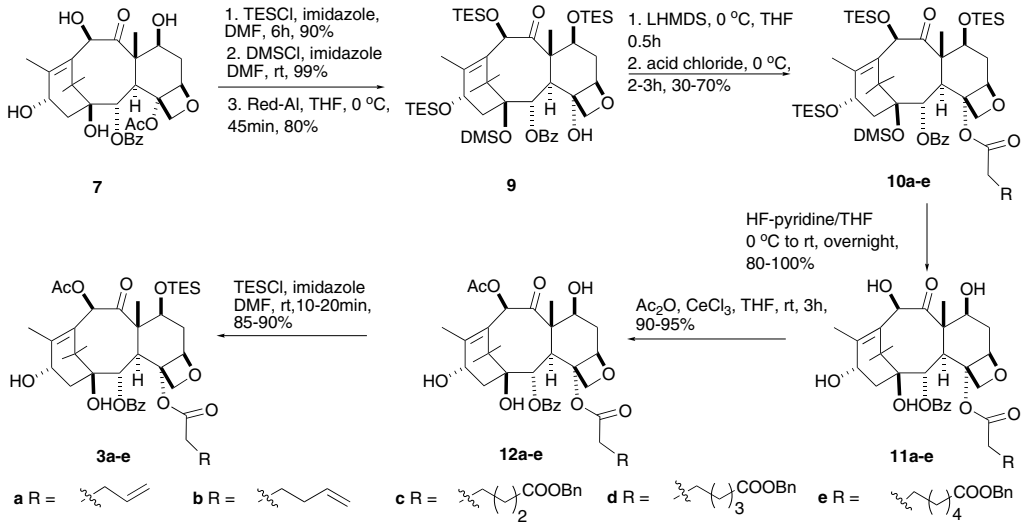
Compounds **3a**–**e** were prepared from 10-DAB (**7**) as shown in Scheme 2. The 4-deacetyl 10-DAB analog **9** was made through reported procedures.[20] Reacylation at the C-4 position was first tried using 3-benzyloxylcarbonylpropanoyl chloride.[22] Unfortunately, this reaction gave a very low yield and we thus used 4-pentenoyl chloride to make compound **10a** as previously described.[19] We planned to use an oxidative cleavage reaction to convert the terminal double bond into the carboxyl group necessary for macrolactonization, and compound **10b** was prepared in the same way as **10a**. The carboxylic acids with a terminal double bond were not commercially available for the longer chain derivatives **10c**–**e**, but the corresponding α,ω-dicarboxylic acids were available. It was found that acylation using 7-benzyloxylcarbonylheptanoyl chloride worked well, but the product **10e** and the starting material could not be separated. It was possible however to separate pure product after desilylation with HF-pyridine, and the desired product (**11e**) was isolated in good yield. Compounds **11c** and **11d** were made using the same procedures as for **11e**. After selective acetylation at the C-10 position and selective silylation at the C-7 position, the fully protected baccatin analogs (**3a**–**e**) were ready for coupling with the β-lactam.

The synthesis of β-lactam (+)-**6** was achieved as shown in Scheme 3. The commercially available aldehyde **8** was first protected as its benzyl ether. The resulting aldehyde was reacted with *p*-anisidine to form the imine, which subsequently reacted with a ketene generated from acetoxyacetyl chloride to give the racemic β-lactam (**15**). This lactam was then subjected to an enzymatic resolution using lipase to generate (+)-**15** in 48% yield. A basic deacetylation followed by silyl reprotection afforded TIPS protected **17** in good yield. Oxidative deprotection of the PMP group using cerium(IV) ammonium nitrate (CAN) gave **18**, which was then treated with benzoyl chloride to generate the desired β-lactam **6**.The coupling between C-4 modified baccatin derivatives (**3a**–**e**) and (+)-β-lactam (**6**) was performed using standard coupling conditions.[23] In Scheme 4, baccatin derivatives **3a** or **3b** were first treated with NaH in anhydrous THF at 0 °C for 5 min, and then the β-lactam **6** was added. The reaction generally gave 50–60% yields of the desired products **19** and **20**. The oxidative cleavages of terminal alkenes were carried out using Sharpless conditions[24] to produce two carboxylic acids (**21** and **22**). After hydrogenolysis, the desired hydroxyl acids (**23** and **24**) were obtained in 75–80% yield.

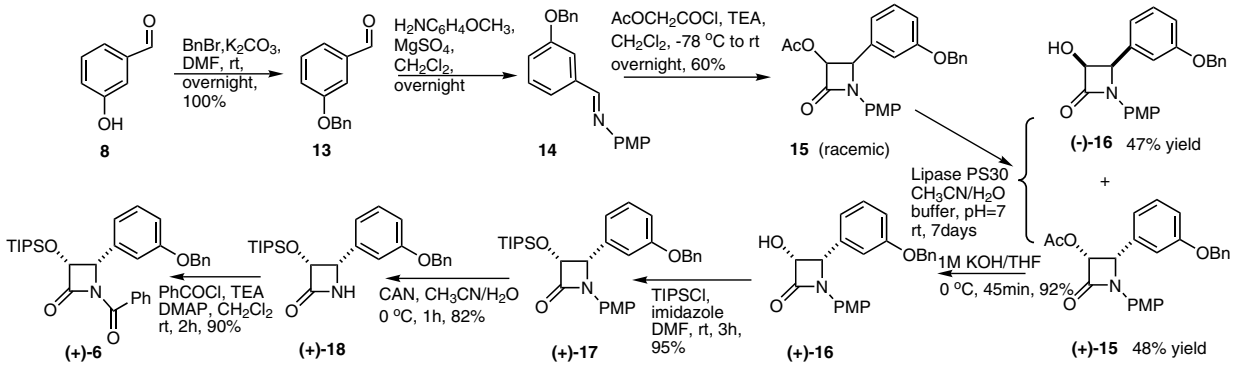
The coupling reaction to prepare compounds **28**–**30** was performed using LHMDS as base, since the NaH condi-



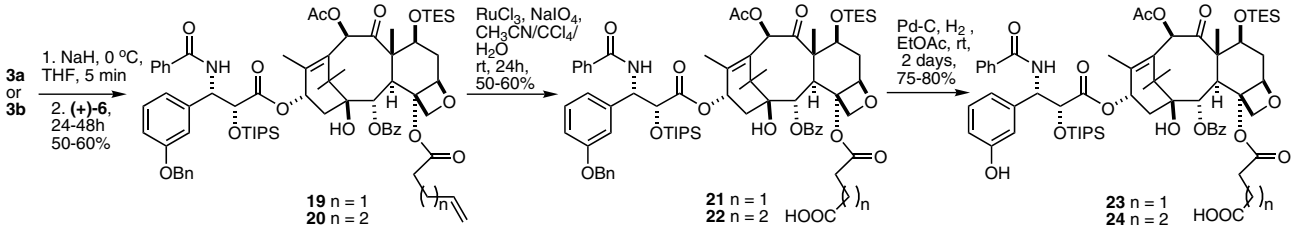
Scheme 1. Retrosynthetic analysis of macrocyclic paclitaxel lactone.



Scheme 2. Synthesis of the baccatin III core (**3a**–**e**).



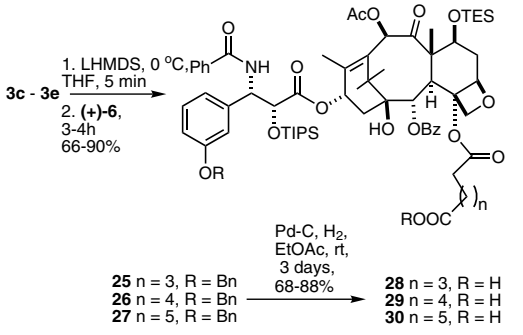
Scheme 3. Synthesis of (+)-β-lactam **6**.



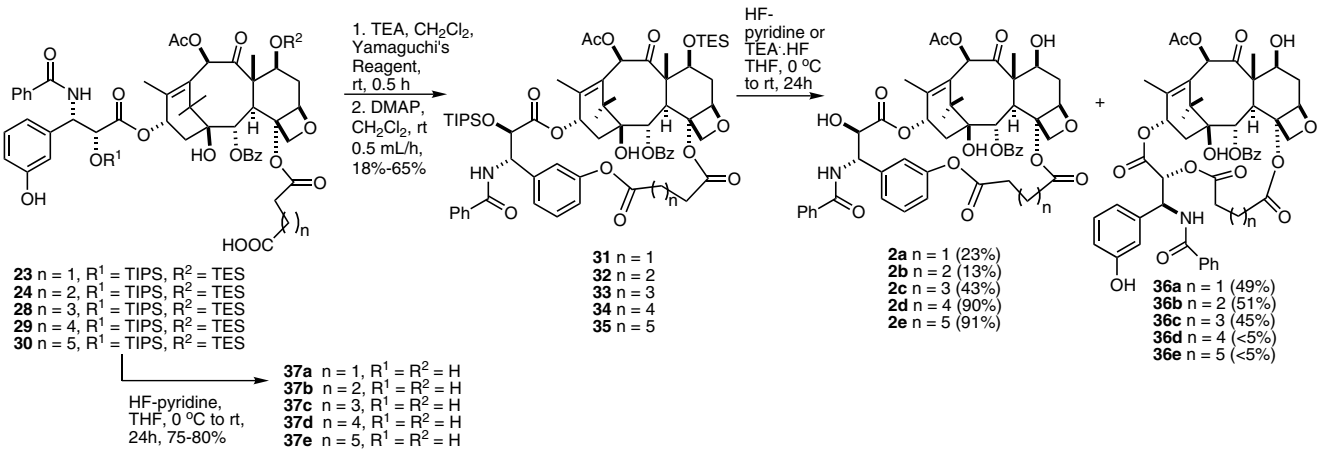
Scheme 4. Synthesis of the hydroxy acids **23**–**24**.

tions gave only complex mixtures. The resulting three paclitaxel analogs (**25**–**27**) were then converted into hydroxyacids **28**–**30** by hydrogenolysis (Scheme 5).

With five hydroxyacids in hand, we investigated the best conditions for macrocyclic lactonization, and the Yamaguchi lactonization strategy was found to work the best. In general, macrolactonization proceeded well and gave the desired products in 18–65% yields. As expected, the yield of the macrolactonization reaction was sensitive to ring size, with yields of 25% for **31**, 18% for **32**, and 31–65% for **33**–**35**. These results



Scheme 5. Synthesis of the hydroxy acids **26**–**28**.



Scheme 6. Syntheses of the macrocyclic paclitaxel lactones.

suggested that **31** and **32** might have larger ring strain than **33**–**35**.

Surprisingly, desilylation of **31**–**35** under HF-pyridine or HF-TEA conditions gave two series of products (**2a**–**e** and **36a**–**e**) with the same composition as determined by HRFABMS. The NMR analysis of these two series of products showed that **2a**–**e** were the desired products, while **36a**–**e** were rearranged products with a bridge from C-4 to C-2′, because the chemical shift of C-2′ proton was shifted down field dramatically to suggest an ester at this position, while the *ortho* protons at the C-3′ phenyl ring was shifted up field to support a free hydroxyl group on the phenyl ring (Scheme 6).

The ratio between these two series of products varied with the ring size. In the formation of **2a** and **2b**, the major products were actually **36a** and **36b**, which suggests that the ring strain of **2a** and **2b** is quite large. This is consistent with the fact that **31** and **32**, the precursors of **2a** and **2b**, gave lower yields of macrocycles than precursors **33**–**35**. On the other hand, compounds **2d** and **2e** were the dominant products, and only trace amounts of **36d** and **36e** could be found by TLC. Compound **36c** was somewhere in between, with **2c** and **36c** formed in comparable yields.

In order to have a better understanding of the bioactivities for these macrocyclic paclitaxel analogs, we also prepared a series of the corresponding open chain analogs **37a**–**e** by desilylation of **23**–**24** and **28**–**30**.

3. Biological results and discussion

The biological activities of paclitaxel and of the macrocyclic paclitaxel analogs **2a**–**e**, **36a**–**c**, and the open chain compounds **37a**–**e** were evaluated in the A2780 ovarian cancer cell line, and six compounds were also tested for their tubulin-assembly ability (Table 1).

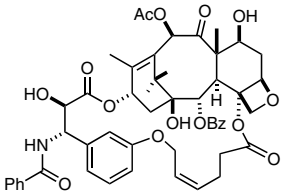
Two major conclusions emerge from these data. In the first place, it is significant that all the bridged compounds are more cytotoxic than their corresponding open-chain analogs. Bridging can thus be seen as a way of minimizing unfavorable interactions between the side chains and tubulin. The second conclusion is that all the bridged analogs were less active than paclitaxel itself. The most active compound in both the A2780 assay and the tubulin-assembly assay was compound **2e**, which has a C-4 to C-3′-phenyl chain of 10 heavy atoms. This contrasts with the results from our study of *ortho* bridged derivatives described in more detail below, where compounds with only five heavy atoms provided the greatest activity.[25] The three rearranged macrocyclic paclitaxel analogs **36a**–**c** and all five open chain paclitaxel analogs were essentially inactive.

Table 1. Cytotoxicity and tubulin-assembly ability of compounds **2a**–**e**, **34a**–**c**, **35a**–**e**

Compound	A2780 IC_{50} (μM)	Tubulin assembly IC_{50} (μM)
Paclitaxel (**1**)	0.024	0.5
2a	18	ND
2b	5.2	ND
2c	>21	>30
2d	10	2.2
2e	4.2	1.3
36a	>21	ND
36b	20	ND
36c	21	>30
37a	>21	ND
37b	>21	ND
37c	18	ND
37d	>21	>15
37e	>21	20.6

One reason that none of the macrocyclic paclitaxel lactones were as active as paclitaxel may be that the lactones are not stable, and can rearrange to the corresponding inactive macrocyclics (**36a**–**c**). This is supported by the fact that the moderately stable compound **2c** (IC_{50} > 21 μM) was less active than cycloalkene **38**, which has a similar length chain between C-4 and the C-3′-phenyl; compound **38** had an IC_{50} value of 1.23 μM in the A2780 assay.[19] Both compounds have the same ring size, and it seems unlikely that the chemical difference between a monolactone and a bis-lactone

could account for this activity difference. It is thus possible that the instability of the lactone **2c** with respect to its inactive isomer **36c** accounts for this difference, although *Z*-geometry of the double bond might also be a factor. If the instability of the lactone is the reason for the reduced activity of **2c**, then the relatively good activity of lactone **2b** is surprising, since this is less stable than **2c**. The relatively good activity of the stable analog **2e** is also significant, and again supports the hypothesis that bridged compounds provide an extra measure of tubulin-binding affinity.



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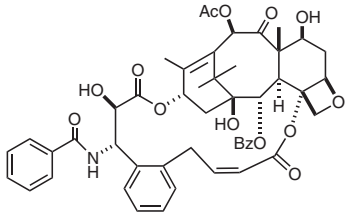
Since the completion of this work we have prepared a series of stable bridged analogs linked through the *ortho* position on the C-3′ phenyl group to C-4, as shown for compound **39**. Several related bridged analogs of this type have been made, and some of them have turned out to have superior activity in several assays.[25] These results support the importance of the T-conformation for the tubulin-binding activity of paclitaxel. A macrocyclic paclitaxel lactone with the same bridge tether would presumably also have good activity, but the problem of isomerization to an inactive lactone makes this a less attractive type of derivative for future work.



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4. Experimental

4.1. Materials and instruments

Chemicals were obtained from Aldrich Chemical Co. and were used without further purification. All solvents were of reagent grade or HPLC grade. THF was distilled over sodium/benzophenone, and CH_2Cl_2 was distilled over calcium hydride. All ^1H NMR spectral data were obtained in $CDCl_3$, CD_3OD, or $(CD_3)_2CO$ on Varian Unity 400 or Varian Inova 400 spectrometer (operating at 399.951 MHz for ^1H and 100.578 MHz for ^{13}C). Mass spectra were obtained at Analytical Service in the Department of Chemistry (HRFABMS) Virginia Tech.

4.2. General procedure for acylation of 4-deacetylbaccatins at C-4

To a solution of 1-DMS-7,10,13-triTES-4-deacetyl-10-deacetylbaccatin III **9**[20] (610 mg, 0.676 mmol) in dried THF (5.5 mL) at 0 °C was added 1 M LHMDS (0.81 mL, 0.81 mmol). The solution was stirred for 0.5 h before 5-hexenoyl chloride (0.879 mmol in 0.5 mL THF) was added. The reaction mixture was allowed to stir at 0 °C for 2.5 h, and then quenched with saturated NH_4Cl. After diluted with EtOAc, the organic phase was washed with water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (30% EtOAc/hexane) to give **10b** as a colorless gum (350 mg, 67%) and recovered **9** (140 mg, 23%). Compounds **10a**[19] and **10c–d** were prepared similarly.

4.2.1. 1-DMSO-7,10,13-triTES-4-deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III (10b). ^1H NMR (400 MHz, $CDCl_3$) δ: −0.28 (3H, d, J = 2.8 Hz), 0.08 (3H, d, J = 2.8 Hz), 0.57–0.78 (18H, overlapped), 0.96–1.09 (27H, overlapped), 1.13 (3H, s), 1.21 (3H, s), 1.60 (1H, s), 1.68 (3H, s), 1.86–1.98 (3H, overlapped), 1.99 (3H, d, J = 1.2 Hz), 2.19–2.40 (4H, overlapped), 2.49–2.70 (3H, overlapped), 3.85 (1H, d, J = 6.9 Hz), 4.24 (1H, d, J = 8.3 Hz), 4.27 (1H, d, J = 8.3 Hz), 4.41 (1H, dd, J = 10.6, 6.6 Hz), 4.91 (1H, dd, J = 9.6, 2.0 Hz), 4.99 (1H, t, J = 8.4 Hz), 5.08–5.17 (2H, overlapped), 5.18 (1H, s), 5.74 (1H, d, J = 6.9 Hz), 5.84–5.95 (1H, m), 7.44–7.50 (2H, m, Ar), 7.56–7.62 (1H, m, Ar), 8.11–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.2, 0.6, 5.0, 5.4, 6.2, 7.1, 7.2, 10.6, 14.6, 21.7, 24.7, 27.6, 33.5, 35.2, 37.6, 39.5, 44.3, 46.8, 58.4, 68.6, 72.9, 75.9, 76.1, 76.9, 81.2, 82.3, 84.4, 115.9, 128.5, 130.3, 130.7, 133.3, 136.2, 137.6, 138.8, 165.5, 172.3, 205.7; HRFABMS m/z 1021.5504 [M+H$^+$]; calcd for $C_{53}H_{90}O_{10}Si_4Na$, 1021.5509.

4.3. General procedures for deprotection of silyl groups

To a solution of 1-DMS-7,10,13-triTES-4-deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III **10b** (350 mg, 0.34 mmol) in dried THF (10 mL) was added anhydrous pyridine (2.0 mL), then the solution was cooled to 0 °C, and HF–pyridine (2.0 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was diluted with EtOAc (100 mL), and the organic phase was washed with sodium bicarbonate, water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (60% EtOAc/hexane) to give **11b** as a colorless gum (184 mg, 88%). Compounds **11a**[19] and **11c–e** were prepared similarly.

4.3.1. 4-Deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III (11b). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08 (6H, s), 1.73 (3H, s), 1.78–1.90 (3H, m, overlapped), 2.05 (3H, s), 2.15–2.43 (6H, overlapped), 2.53–2.70 (3H, overlapped), 3.98 (1H, d, J = 7.1 Hz), 4.18 (1H, d, J = 8.3 Hz), 4.25–4.36 (3H, overlapped), 4.70–4.87 (1H, m), 4.94 (1H, dd, J = 9.3, 1.5 Hz), 5.05–5.15 (2H, overlapped), 5.26

(1H, s), 5.61 (1H, d, $J = 7.1$ Hz), 5.81–5.92 (1H, m), 7.45–7.52 (2H, m, Ar), 7.58–7.64 (1H, m, Ar), 8.08–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 15.2, 19.9, 23.8, 26.8, 33.2, 34.7, 37.0, 38.9, 42.8, 47.2, 57.8, 67.8, 72.1, 75.0, 75.1, 76.8, 79.0, 80.8, 84.5, 115.7, 128.7, 129.5, 130.2, 133.8, 134.7, 137.8, 167.2, 173.3, 211.7; HRFABMS *m/z* 599.2886 [M+H$^+$]; calcd for $C_{33}H_{43}O_{10}$, 599.2856.

4.3.2. 4-Deacetyl-4-(5-benzyloxylcarbonylpentanoyl)-10-deacetylbaccatin III (11c). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (6H, s), 1.69–1.90 (9H, overlapped), 2.04 (3H, d, $J = 1.0$ Hz), 2.17–2.33 (3H, overlapped), 2.41–2.64 (4H, overlapped), 2.68–2.88 (2H, overlapped), 3.99 (1H, d, $J = 7.1$ Hz), 4.19 (1H, d, $J = 8.5$ Hz), 4.27–4.36 (3H, overlapped), 4.81 (1H, m), 4.96 (1H, dd, $J = 9.3$, 1.6 Hz), 5.16 (2H, s), 5.27 (1H, d, $J = 1.7$ Hz), 5.64 (1H, d, $J = 7.1$ Hz), 7.32–7.42 (5H, m, Ar, overlapped), 7.46–7.53 (2H, m, Ar), 7.58–7.65 (1H, m, Ar), 8.10–8.15 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.8, 15.1, 19.8, 23.5, 24.2, 26.7, 33.8, 34.4, 36.9, 38.8, 42.6, 47.1, 57.7, 66.5, 67.6, 72.0, 74.9, 75.0, 76.6, 78.9, 80.7, 84.4, 128.2, 128.4, 128.6, 128.7, 129.4, 130.1, 133.6, 134.5, 135.8, 142.8, 167.1, 172.8, 173.7, 211.7; HRFABMS *m/z* 721.3218 [M+H$^+$]; calcd for $C_{40}H_{49}O_{12}$, 721.3224.

4.3.3. 4-Deacetyl-4-(6-benzyloxylcarbonylhexanoyl)-10-deacetylbaccatin III (11d). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (6H, s), 1.34–1.51 (2H, m), 1.63–1.76 (7H, overlapped), 1.77–1.87 (2H, overlapped), 2.01 (3H, d, $J = 1.0$ Hz), 2.12–2.30 (2H, overlapped), 2.37–2.45 (3H, overlapped), 2.46–2.59 (2H, overlapped), 2.61–2.70 (1H, m), 2.77 (1H, d, $J = 4.8$ Hz), 3.94 (1H, d, $J = 7.1$ Hz), 4.15 (1H, d, $J = 8.3$ Hz), 4.23–4.33 (3H, overlapped), 4.76 (1H, m), 4.91 (1H, dd, $J = 9.3$, 1.5 Hz), 5.11 (2H, s), 5.23 (1H, d, $J = 1.5$ Hz), 5.59 (1H, d, $J = 7.1$ Hz), 7.28–7.40 (5H, m, Ar, overlapped), 7.42–7.49 (2H, m, Ar), 7.54–7.60 (1H, m, Ar), 8.06–8.11 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.1, 15.3, 20.1, 23.9, 24.7, 26.9, 28.5, 34.2, 34.8, 37.0, 39.0, 42.8, 47.2, 57.9, 66.6, 67.7, 72.2, 75.2, 76.8, 79.1, 80.8, 84.6, 128.4, 128.5, 128.8, 129.6, 130.3, 133.9, 134.6, 136.0, 143.2, 167.2, 173.3, 174.2, 211.9; HRFABMS *m/z* 735.3356 [M+H$^+$]; calcd for $C_{41}H_{51}O_{12}$, 735.3381.

4.3.4. 4-Deacetyl-4-(7-benzyloxylcarbonylheptanoyl)-10-deacetylbaccatin III (11e). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (6H, s), 1.36–1.50 (4H, overlapped), 1.65–1.78 (7H, overlapped), 1.79–1.85 (1H, m), 1.91 (1H, s), 2.05 (3H, s), 2.17–2.32 (2H, overlapped), 2.41 (2H, t, $J = 7.3$ Hz), 2.49–2.71 (4H, overlapped), 2.88 (1H, m), 3.98 (1H, d, $J = 7.1$ Hz), 4.18 (1H, d, $J = 8.3$ Hz), 4.26–4.38 (3H, overlapped), 4.82 (1H, m), 4.94 (1H, dd, $J = 9.4$, 1.5 Hz), 5.13 (2H, s), 5.27 (1H, s), 5.62 (1H, d, $J = 7.1$ Hz), 7.30–7.41 (5H, m, Ar, overlapped), 7.45–7.51 (2H, m, Ar), 7.57–7.63 (1H, m, Ar), 8.09–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.8, 15.0, 19.9, 23.9, 24.5, 26.7, 28.5, 28.6, 34.1, 34.9, 36.8, 38.9, 42.6, 47.0, 57.7, 66.3, 67.5, 72.0, 74.9, 75.0, 76.6, 78.9, 80.6, 84.5, 128.2, 128.3, 128.6, 129.5, 130.1, 133.6, 134.4, 135.9, 143.0, 167.0, 173.2, 174.1, 211.7; HRFABMS *m/z* 749.3574 [M+H$^+$]; calcd for $C_{42}H_{53}O_{12}$, 749.3537.

4.4. General procedure for selective acetylation of 10-DAB derivatives at C-10

To a solution of 4-deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III **11b** (226 mg, 0.38 mmol) in dried THF (3.5 mL) was added $CeCl_3$ (10 mg, cat.), and then acetic anhydride (0.55 mL, 5.7 mmol) was added. After stirring at room temperature for 3 h, the reaction mixture was diluted with EtOAc (50 mL), and then washed with saturated $NaHCO_3$, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (50% EtOAc/hexane) to give **12b** as colorless gum (230 mg, 95%). Compounds **12a**[19] and **12c**–**e** were prepared in similar procedure.

4.4.1. 4-Deacetyl-4-(5-hexenoyl)baccatin III (12b). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (3H, s), 1.05 (3H, s), 1.74–1.84 (3H, overlapped), 1.94–2.00 (4H, overlapped), 2.09–2.29 (7H, overlapped), 2.45–2.82 (5H, overlapped), 3.82 (1H, d, $J = 7.0$ Hz), 4.11 (1H, d, $J = 8.3$ Hz), 4.24 (1H, d, $J = 8.3$ Hz), 4.44 (1H, dd, $J = 10.2$, 7.3 Hz), 4.75–4.84 (1H, m), 4.89 (1H, dd, $J = 9.4$, 1.2 Hz), 4.98–5.09 (2H, overlapped), 5.56 (1H, d, $J = 7.0$ Hz), 5.75–5.87 (1H, m), 6.27 (1H, s), 7.38–7.46 (2H, m, Ar), 7.52–7.60 (1H, m, Ar), 8.01–8.08 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 15.6, 20.0, 21.0, 23.6, 26.9, 33.1, 34.5, 35.6, 39.0, 42.7, 46.2, 58.6, 67.6, 72.3, 75.0, 76.4, 76.5, 79.0, 80.6, 84.7, 115.5, 128.7, 129.4, 130.1, 131.3, 133.7, 137.8, 147.1, 166.9, 171.5, 173.0, 204.4; HRFABMS *m/z* 641.2967 [M+H$^+$]; calcd for $C_{35}H_{45}O_{11}$, 641.2962.

4.4.2. 4-Deacetyl-4-(5-benzyloxylcarbonylpentanoyl)-baccatin III (12c). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (6H, s), 1.69 (3H, s), 1.72–1.92 (6H, overlapped), 2.03 (3H, br s), 2.20–2.36 (5H, overlapped), 2.40–2.77 (6H, overlapped), 2.90 (1H, br s), 3.88 (1H, d, $J = 7.1$ Hz), 4.17 (1H, d, $J = 8.4$ Hz), 4.31 (1H, d, $J = 8.4$ Hz), 4.51 (1H, m), 4.84 (1H, m), 4.96 (1H, d, $J = 9.2$ Hz), 5.15 (2H, s), 5.64 (1H, d, $J = 7.1$ Hz), 6.33 (1H, s), 7.32–7.42 (5H, m, Ar, overlapped), 7.46–7.54 (2H, m, Ar), 7.58–7.65 (1H, m, Ar), 8.09–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 15.6, 20.9, 21.0, 23.5, 24.2, 27.0, 33.8, 34.4, 35.6, 38.7, 42.7, 46.3, 58.7, 66.5, 67.7, 72.3, 75.0, 76.3, 76.4, 79.1, 80.7, 84.6, 128.2, 128.4, 128.6, 128.7, 129.4, 130.1, 131.5, 133.7, 135.8, 146.9, 167.1, 171.4, 172.7, 173.7, 204.3; HRFABMS *m/z* 763.3360 [M+H$^+$]; calcd for $C_{42}H_{51}O_{13}$, 763.3330.

4.4.3. 4-Deacetyl-4-(6-benzyloxylcarbonylhexanoyl)baccatin III (12d). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, s), 1.11 (3H, s), 1.38–1.52 (2H, m), 1.68 (3H, s), 1.69–1.81 (4H, overlapped), 1.82–1.90 (1H, m), 1.93 (1H, s), 2.03 (3H, d, $J = 1.0$ Hz), 2.20–2.35 (5H, overlapped), 2.43 (2H, t, $J = 7.5$ Hz), 2.50–2.61 (2H, overlapped), 2.63–2.74 (2H, overlapped), 3.00 (1H, d, $J = 5.0$ Hz), 3.87 (1H, d, $J = 7.1$ Hz), 4.17 (1H, d, $J = 8.4$ Hz), 4.30 (1H, d, $J = 8.4$ Hz), 4.50 (1H,

m), 4.83 (1H, m), 4.95 (1H, dd, $J = 9.5$, 1.6 Hz), 5.14 (2H, s), 5.63 (1H, d, $J = 7.1$ Hz), 6.33 (1H, s), 7.32–7.42 (5H, m, Ar, overlapped), 7.45–7.51 (2H, m, Ar), 7.57–7.63 (1H, m, Ar), 8.08–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 9.5, 15.5, 20.9, 21.1, 23.6, 24.5, 26.9, 28.2, 34.0, 34.5, 35.6, 38.9, 42.7, 46.2, 58.6, 66.3, 67.6, 72.3, 75.1, 76.3, 76.4, 79.1, 80.6, 84.6, 128.2, 128.3, 128.6, 129.4, 130.1, 131.4, 133.6, 135.9, 147.0, 167.0, 171.4, 173.0, 173.9, 204.3; HRFABMS *m/z* 777.3447 [M+H$^+$]; calcd for $C_{43}H_{53}O_{13}$, 777.3486.

4.4.4. 4-Deacetyl-4-(7-benzyloxylcarbonylheptanoyl)-baccatin III (12e). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 (3H, s), 1.09 (3H, s), 1.33–1.45 (4H, overlapped), 1.62–1.75 (7H, overlapped), 1.78–1.88 (2H, overlapped), 2.01 (3H, s), 2.16–2.33 (5H, overlapped), 2.35–2.41 (2H, m), 2.45–2.68 (4H, overlapped), 2.88 (1H, m), 2.96 (1H, br s), 3.84 (1H, d, $J = 7.0$ Hz), 4.13 (1H, d, $J = 8.3$ Hz), 4.27 (1H, d, $J = 8.3$ Hz), 4.48 (1H, m), 4.82 (1H, m), 4.92 (1H, dd, $J = 9.5$, 1.6 Hz), 5.10 (2H, s), 5.60 (1H, d, $J = 7.0$ Hz), 6.30 (1H, s), 7.27–7.37 (5H, m, Ar, overlapped), 7.41–7.48 (2H, m, Ar), 7.54–7.60 (1H, m, Ar), 8.05–8.11 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 15.7, 21.1, 21.3, 23.9, 24.7, 27.1, 28.6, 28.7, 34.3, 34.9, 35.8, 39.1, 42.9, 46.4, 58.8, 66.5, 67.8, 72.5, 75.3, 76.5, 76.6, 79.3, 80.8, 84.9, 128.4, 128.5, 128.8, 129.6, 130.3, 131.5, 133.8, 136.1, 147.3, 167.2, 171.6, 173.3, 174.3, 204.5; HRFABMS *m/z* 791.3688 [M+H$^+$]; calcd for $C_{44}H_{55}O_{13}$, 791.3643.

4.5. General procedure for selective silylation of baccatin III derivatives at C-7

To a solution of 4-deacetyl-4-(5-hexenoyl)baccatin III**12b** (230 mg, 0.36 mmol) in anhydrous DMF (2 mL) was added imidazole (144 mg, 2.2 mmol) and TESCl (180 μL, 1.1 mmol). The reaction mixture was stirring for 10 min, and then diluted with EtOAc (50 mL). The organic phase was washed with water, brine, and dried with sodium sulfate. After concentrated in vacuum, the residue was applied to PTLC (30% EtOAc/hexane) to give **3b** as colorless gum (241 mg, 89%). Compounds **3a**[19] and **3c**–**e** were prepared in similar procedures.

4.5.1. 4-Deacetyl-4-(5-hexenoyl)-7-TES-baccatin III (3b). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.52 (6H, m), 0.93 (9H, t, $J = 7.9$ Hz), 1.03 (3H, s), 1.19 (3H, s), 1.68 (3H, s), 1.74 (1H, s), 1.82–1.91 (3H, overlapped), 2.15–2.33 (8H, overlapped), 2.50–2.62 (3H, overlapped), 3.88 (1H, d, $J = 7.0$ Hz), 4.15 (1H, d, $J = 8.3$ Hz), 4.30 (1H, d, $J = 8.3$ Hz), 4.50 (1H, dd, $J = 10.5$, 6.7 Hz), 4.77–4.85 (1H, m), 4.92 (1H, dd, $J = 9.4$, 1.4 Hz), 5.04–5.14 (2H, overlapped), 5.63 (1H, d, $J = 7.0$ Hz), 5.80–5.92 (1H, m), 6.46 (1H, s), 7.44–7.50 (2H, m, Ar), 7.58–7.64 (1H, m, Ar), 8.09–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.4, 6.8, 10.0, 15.0, 20.2, 21.1, 23.9, 26.9, 33.3, 34.9, 37.4, 38.5, 42.9, 47.4, 58.8, 68.0, 72.4, 74.9, 75.9, 76.7, 78.8, 80.8, 84.5, 115.7, 128.7, 129.5, 130.2, 132.6, 133.7, 137.8, 144.3, 167.1, 169.5, 173.0, 202.5; HRFABMS *m/z* 755.3873 [M+H$^+$]; calcd for $C_{41}H_{59}O_{11}Si$, 755.3827.

4.5.2. 4-Deacetyl-4-(5-benzyloxylcarbonylpentanoyl)-7-TES-baccatin III (3c). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.66 (6H, m), 0.95 (9H, t, $J = 7.8$ Hz), 1.06 (3H, s), 1.21 (3H, s), 1.70 (3H, s), 1.72 (1H, s), 1.74–1.93 (6H, overlapped), 2.17 (3H, d, $J = 1.1$ Hz), 2.20 (3H, s), 2.21–2.34 (2H, overlapped), 2.42–2.73 (6H, overlapped), 3.88 (1H, d, $J = 7.0$ Hz), 4.16 (1H, d, $J = 8.4$ Hz), 4.31 (1H, d, $J = 8.4$ Hz), 4.52 (1H, dd, $J = 10.4$, 6.7 Hz), 4.80 (1H, m), 4.94 (1H, dd, $J = 9.5$, 1.6 Hz), 5.16 (2H, s), 5.65 (1H, d, $J = 7.0$ Hz), 6.48 (1H, s), 7.32–7.48 (5H, m, Ar, overlapped), 7.46–7.52 (2H, m, Ar), 7.57–7.64 (1H, m, Ar), 8.10–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.7, 10.0, 14.9, 20.2, 21.0, 23.6, 24.3, 26.8, 33.8, 34.7, 37.2, 38.4, 42.8, 47.4, 58.7, 66.4, 67.7, 72.3, 74.8, 75.8, 76.5, 78.8, 80.7, 84.3, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.4, 133.6, 135.8, 144.4, 167.1, 169.4, 172.5, 173.6, 202.3; HRFABMS *m/z* 877.4147 [M+H$^+$]; calcd for $C_{48}H_{65}O_{13}Si$, 877.4194.

4.5.3. 4-Deacetyl-4-(6-benzyloxylcarbonylhexanoyl)-7-TES-baccatin III (3d). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.53–0.68 (6H, m), 0.95 (9H, t, $J = 7.7$ Hz), 1.05 (3H, s), 1.20 (3H, s), 1.39–1.55 (2H, m), 1.70 (3H, s), 1.71–1.93 (6H, overlapped), 2.18 (3H, s), 2.19 (3H, s), 2.20–2.34 (2H, overlapped), 2.44 (2H, t, $J = 7.2$ Hz), 2.50–2.70 (3H, overlapped), 2.73 (1H, d, $J = 5.0$ Hz), 3.88 (1H, d, $J = 7.0$ Hz), 4.16 (1H, d, $J = 8.3$ Hz), 4.30 (1H, d, $J = 8.3$ Hz), 4.52 (1H, dd, $J = 10.3$, 6.7 Hz), 4.79 (1H, m), 4.93 (1H, d, $J = 9.2$ Hz), 5.14 (2H, s), 5.64 (1H, d, $J = 7.0$ Hz), 6.48 (1H, s), 7.31–7.42 (5H, m, Ar, overlapped), 7.44–7.51 (2H, m, Ar), 7.56–7.63 (1H, m, Ar), 8.10–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.8, 10.0, 14.9, 20.2, 21.0, 23.8, 24.5, 26.8, 28.4, 34.0, 34.9, 37.3, 38.5, 42.8, 47.3, 58.6, 66.3, 67.7, 72.3, 74.9, 75.9, 76.6, 78.8, 80.7, 84.4, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.3, 133.6, 135.9, 144.5, 167.0, 169.4, 172.8, 173.8, 202.4; HRFABMS *m/z* 891.4338 [M+H$^+$]; calcd for $C_{49}H_{67}O_{13}Si$, 891.4351.

4.5.4. 4-Deacetyl-4-(7-benzyloxylcarbonylheptanoyl)-7-TES-baccatin III (3e). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.66 (6H, m), 0.95 (9H, t, $J = 7.8$ Hz), 1.06 (3H, s), 1.21 (3H, s), 1.38–1.50 (4H, overlapped), 1.67–1.82 (8H, overlapped), 1.84–1.93 (2H, overlapped), 2.20 (6H, s), 2.21–2.36 (2H, overlapped), 2.42 (2H, t, $J = 7.3$ Hz), 2.51–2.71 (4H, overlapped), 3.89 (1H, d, $J = 7.0$ Hz), 4.16 (1H, d, $J = 8.3$ Hz), 4.31 (1H, d, $J = 8.3$ Hz), 4.53 (1H, dd, $J = 10.4$, 6.8 Hz), 4.82 (1H, m), 4.94 (1H, dd, $J = 9.6$, 1.3 Hz), 5.14 (2H, s), 5.65 (1H, d, $J = 7.0$ Hz), 6.49 (1H, s), 7.31–7.42 (5H, m, Ar, overlapped), 7.45–7.51 (2H, m, Ar), 7.58–7.64 (1H, m, Ar), 8.11–8.17 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.8, 10.0, 14.9, 20.2, 21.0, 24.0, 24.5, 26.8, 28.5, 34.1, 35.2, 37.3, 38.5, 42.8, 47.3, 58.7, 66.3, 67.7, 72.3, 74.9, 75.9, 76.6, 78.8, 80.6, 84.4, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.4, 133.6, 135.9, 144.5, 167.1, 169.4, 173.0, 173.9, 202.4; HRFABMS *m/z* 905.4471 [M+H$^+$]; calcd for $C_{50}H_{69}O_{13}Si$, 905.4507.

4.6. Preparation of racemic β-lactam (15)

To a solution of *m*-benzyloxylbenzaldehyde (**13**) (21.2 g, 0.10 mol) in anhydrous DCM (250 mL) was added *p*-anisidine (14.8 g, 0.12 mol) and anhydrous $MgSO_4$ (12.0 g, 0.1 mol). After stirring at room temperature for overnight, the resulting imine **14** solution was filtrated and used directly. The filtrate was cooled to −78 °C, and then triethylamine (40.47 g, 0.4 mol) and acetyloxyacetyl chloride (17.75 g, 0.13 mol) were added. The reaction mixture was then allowed to warm up slowly to room temperature. After stirring for overnight, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography (30% EtOAc/hexane) to give **15** as slightly yellow solid (25.1 g, 60%).

4.6.1. Cis-2-(3-(benzyloxy)phenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (15). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69 (3H, s), 3.76 (3H, s), 5.02 (2H, ABq, J = 12.0 Hz), 5.29 (1H, d, J = 4.8 Hz), 5.94 (1H, d, J = 4.8 Hz), 6.78–6.83 (2H, m, Ar), 6.87–6.97 (3H, m, Ar, overlapped), 7.23–7.41 (8H, m, Ar, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$): 20.1, 55.6, 61.6, 70.2, 76.5, 114.4, 114.6, 115.6, 119.0, 120.8, 127.7, 128.2, 128.8, 129.9, 130.5, 134.2, 136.8, 156.8, 159.0, 161.5, 169.5; HRFABMS *m*/*z* 418.1644 [M+H$^+$]; calcd for $C_{25}H_{24}NO_5$, 418.1654.

4.6.2. Resolution of β-lactam 15. To a solution of racemic β-lactam (**15**) (1.0 g, 2.4 mmol) in CH_3CN (5 mL) and phosphate buffer (45 mL) was added Lipase PS 30 (1.0 g). The reaction mixture was allowed to stir for 7 days, and then extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30–50% EtOAc/hexane) to give (+)-lactam acetate **15** (476 mg, 48%) and deacetylated (−)-lactam **16** (465 mg, 47%) both as white solids.

4.7. Preparation of (+)-β-lactam 16

To a solution of (+)-lactam acetate **15** (1.05 g, 2.5 mmol) in THF (100 mL) was added 1 M KOH (100 mL) at 0 °C. The reaction mixture was allowed to stir for 45 min, and then extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with saturated NH_4Cl, water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (50% EtOAc/hexane) to give (+)-β-lactam **16** as white solid (900 mg, 92%).

4.7.1. (3*R*,4*S*)-4-(3-(Benzyloxy)phenyl)-3-hydroxy-1-(4-methoxyphenyl)azetidin-2-one (16). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 3.74 (3H, s), 5.03 (1H, d, J = 7.7 Hz), 5.09 (2H, ABq, J = 11.8 Hz), 5.26 (1H, dd, J = 7.7, 5.2 Hz), 5.30 (1H, d, J = 5.2 Hz), 6.83–6.88 (2H, m, Ar), 6.95–7.00 (2H, m, Ar), 7.03–7.05 (1H, m, Ar), 7.27–7.39 (6H, m, Ar, overlapped), 7.42–7.47 (2H, m, Ar); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ: 54.9, 62.5, 69.7, 78.1, 114.2, 114.4, 114.9, 118.5, 120.7, 127.8, 127.9, 128.6, 129.6, 131.6, 137.0, 137.6, 156.4, 159.2, 165.9; HRFABMS *m*/*z* 376.1539 [M+H$^+$]; calcd for $C_{23}H_{22}NO_4$, 376.1549.

4.8. Preparation of (+)-O-TIPS-β-lactam 17

To a solution of (+)-β-lactam **16** (900 mg, 2.4 mmol) in DMF (5 mL) was added imidazole (653 mg, 9.6 mmol) and TIPSCl (924 mg, 4.8 mmol). The reaction mixture was allowed to stir for 3 h, and then quenched with water. The resulting mixture was added EtOAc (150 mL). The combined organic phase was washed with water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30% EtOAc/hexane) to give (+)-O-TIPS-β-lactam **17** as white solid (1.21 g, 95%).

4.8.1. (3*R*,4*S*)-4-(3-(Benzyloxy)phenyl)-1-(4-methoxyphenyl)-3-TIPS-azetidin-2-one (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98–1.14 (21H, overlapped), 3.78 (3H, s), 5.00–5.08 (3H, overlapped), 5.09 (1H, d, J = 4.9 Hz), 6.78–6.84 (2H, m, Ar, overlapped), 6.95–7.06 (3H, m, Ar, overlapped), 7.27–7.45 (8H, m, Ar, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.8, 17.6, 17.7, 56.3, 63.2, 70.0, 77.9, 114.3, 114.8, 114.9, 118.7,121.1, 127.5, 127.9, 128.6, 129.3, 131.0, 135.9, 137.0, 156.2, 165.6; HRFABMS *m*/*z* 532.2887 [M+H$^+$]; calcd for $C_{32}H_{42}NO_4Si$, 532.2883.

4.9. Preparation of (+)-β-lactam 18

To a solution of (+)-β-lactam **17** (1.21 g, 2.3 mmol) in CH_3CN (50 mL) was added CAN reagent (3.53 g in 30 mL H_2O) at 0 °C dropwise in 15 min. The reaction mixture was allowed to stir for another 30 min, and then extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with saturated $Na_2S_2O_4$, water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30% EtOAc/hexane) to give (+)-β-lactam **18** as a yellowish solid (922 mg, 96%).

4.9.1. (3*R*,4*S*)-4-(3-(Benzyloxy)phenyl)-3-TIPS-azetidin-2-one (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89–1.05 (21H, overlapped), 4.80 (1H, d, J = 4.7 Hz), 5.08 (2H, ABq, J = 12.4 Hz), 5.18 (1H, dd, J = 4.7, 2.7 Hz), 6.37 (1H, br s), 6.91–6.98 (2H, m, Ar), 7.00–7.03 (1H, m, Ar), 7.24–7.30 (2H, m, Ar), 7.32–7.48 (4H, m, Ar, overlapped); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.6, 17.5, 17.6, 59.5, 70.0, 80.0, 114.6, 114.8, 120.9, 127.4, 127.9, 128.6, 129.0, 137.0, 138.0, 158.7, 169.9; HRFABMS *m*/*z* 426.2467 [M+H$^+$]; calcd for $C_{25}H_{36}NO_3Si$, 426.2464.

4.10. Preparation of (+)-β-lactam 6

To a solution of (+)-β-lactam **18** (922 mg, 2.2 mmol) in anhydrous DCM (5 mL) was added TEA (658 mg, 6.5 mmol), benzoyl chloride (365 mg, 2.6 mmol) and DAMP (50 mg, cat.). The reaction mixture was allowed to stir for 2 h, and then diluted with EtOAc (150 mL). The combined organic phase was washed with saturated $NaHCO_3$, water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue

was purified by column chromatography (20% EtOAc/hexane) to give (+)-β-lactam **6** as a white solid (900 mg, 90%).

4.10.1. (3*R*,4*S*)-1-Benzoyl-4-(3-(benzyloxy)phenyl)-3-TIPS-azetidin-2-one (6). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96–1.10 (21H, overlapped), 5.10 (2H, ABq, J = 11.9 Hz), 5.28 (1H, d, J = 6.1 Hz), 5.45 (1H, d, J = 6.1 Hz), 6.95–7.00 (1H, m, Ar), 7.04–7.10 (2H, m, Ar), 7.28–7.70 (9H, m, Ar, overlapped), 8.07–8.12 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.7, 17.5, 17.6, 61.1, 70.1, 76.7, 114.7, 114.9, 121.0, 127.4, 128.0, 128.2, 128.6, 129.3, 129.9, 132.1, 133.4, 135.5, 137.1, 158.8, 165.4, 166.3; HRFABMS *m*/*z* 529.2638 [M+H$^+$]; calcd for $C_{32}H_{39}NO_4Si$, 529.2648.

4.11. General procedure for coupling of baccatin and the β-lactam

To a solution of 4-deacetyl-4-(4-pentenoyl)-7-TES-baccatin III **3a** (55 mg, 0.074 mmol) in dried THF (3.6 mL) at 0 °C was added NaH (40 mg, 1.67 mmol) and the solution was stirred for 5 min. (+)-β-Lactam **6** (75 mg, 0.15 mmol in 0.8 mL THF) was then added and the reaction was allowed to stir at room temperature for 24 h. The reaction mixture was quenched with saturated NH_4Cl and diluted with EtOAc (30 mL), and then washed with water, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuo, and the residue was applied to PTLC (20% EtOAc/hexane) to give paclitaxel derivative **19** (50 mg, 57%). Compounds **20**, **25**, **26**, and **27** were prepared by similar procedures, except that the last three used LHMDS (1.2 equiv) as base and the reaction only ran for 3–4 h.

4.11.1. 4-Deacetyl-4-(4-pentenoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (19). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.57–0.70 (6H, m), 0.94–1.07 (30H, overlapped), 1.21 (3H, s), 1.26 (3H, s), 1.73 (3H, s), 1.87–1.97 (1H, m), 2.07 (3H, d, J = 1.3 Hz), 2.11–2.25 (2H, overlapped), 2.20 (3H, s), 2.38–2.75 (5H, overlapped), 3.03–3.12 (1H, m), 3.87 (1H, d, J = 7.0 Hz), 4.24 (1H, d, J = 8.4 Hz), 4.34 (1H, d, J = 8.4 Hz), 4.51 (1H, dd, J = 10.6, 6.7 Hz), 4.89–4.94 (2H, overlapped), 5.03–5.07 (1H, m), 5.10 (2H, s), 5.11–5.17 (1H, m), 5.69 (1H, d, J = 8.9 Hz), 5.73 (1H, d, J = 7.0 Hz), 5.81–5.92 (1H, m), 6.20 (1H, dt, J = 9.1, 1.3 Hz), 6.47 (1H, s), 6.90–7.03 (3H, m, Ar, overlapped), 7.11 (1H, d, J = 8.9 Hz), 7.30–7.65 (12H, m, Ar, overlapped), 7.74–7.78 (2H, m, Ar), 8.17–8.21 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.5, 6.9, 10.3, 12.7, 14.4, 18.0, 18.1, 21.0, 21.7, 26.7, 29.9, 35.7, 36.0, 37.4, 43.5, 46.9, 56.1, 58.6, 70.2, 72.1, 72.4, 75.1, 75.2, 75.7, 76.7, 79.0, 81.4, 84.6, 113.3, 114.6, 117.0, 119.1, 127.1, 127.5, 128.2, 128.8, 128.9, 129.0, 129.5, 129.9, 130.4, 131.9, 133.7, 133.8, 134.1, 135.9, 137.0, 140.2, 140.4, 159.4, 167.1, 169.5, 172.0, 172.1, 201.9; HRFABMS *m*/*z* 1292.6179 [M+Na$^+$]; calcd for $C_{72}H_{95}NO_{15}Si_2Na$, 1292.6138.

4.11.2. 4-Deacetyl-4-(5-hexenoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (20). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.51–0.72 (6H, m), 0.93–1.03 (30H, overlapped), 1.20 (3H, s), 1.25 (3H, s), 1.74 (3H, s), 1.77 (1H, s), 1.84–2.04 (3H, overlapped), 2.08 (3H, d, J = 1.0 Hz), 2.10–2.22 (6H, overlapped), 2.38–2.47 (1H, m), 2.52–2.69 (2H, overlapped), 2.95–3.04 (1H, m), 3.87 (1H, d, J = 7.0 Hz), 4.25 (1H, d, J = 8.3 Hz), 4.34 (1H, d, J = 8.3 Hz), 4.53 (1H, dd, J = 10.6, 6.6 Hz), 4.90–4.96 (2H, overlapped), 4.99–5.05 (2H, overlapped), 5.10 (2H, s), 5.67–5.83 (3H, overlapped), 6.21 (1H, t, J = 9.1 Hz), 6.50 (1H, s), 6.90–7.12 (4H, overlapped), 7.30–7.65 (12H, m, Ar, overlapped), 7.73–7.79 (2H, m, Ar), 8.16–8.21 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.8, 10.1, 12.6, 14.3, 17.8, 17.9, 20.9, 21.6, 25.0, 26.6, 32.8, 35.4, 35.8, 37.3, 43.4, 46.8, 55.9, 58.4, 70.1, 71.9, 72.2, 74.9, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 115.8, 118.9, 127.0, 127.4, 128.0, 128.5, 128.6, 128.7, 129.3, 129.7, 130.3, 131.7, 133.5, 133.6, 134.0, 136.8, 137.1, 140.1, 140.3, 159.3, 166.8, 167.0, 169.3, 171.9, 172.5, 201.8; HRFABMS *m*/*z* 1306.6212 [M+Na$^+$]; calcd for $C_{73}H_{97}NO_{15}Si_2Na$, 1306.6294.

4.11.3. 4-Deacetyl-4-(5-benzyloxycarbonylpentanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (25). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.52–0.67 (6H, m), 0.90–1.01 (30H, overlapped), 1.18 (3H, s), 1.22 (3H, s), 1.60–1.74 (5H, overlapped), 1.75–1.95 (4H, overlapped), 2.05 (3H, d, J = 1.1 Hz), 2.09–2.20 (4H, overlapped), 2.48–2.64 (2H, overlapped), 2.95–3.04 (1H, m), 3.83 (1H, d, J = 7.2 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.29 (1H, d, J = 8.4 Hz), 4.49 (1H, dd, J = 10.5, 6.5 Hz), 4.87 (1H, dd, J = 9.5, 1.6 Hz), 4.91 (1H, d, J = 1.6 Hz), 5.05 (2H, s), 5.06 (2H, s), 5.65–5.72 (2H, overlapped), 6.20 (1H, t, J = 9.3 Hz), 6.46 (1H, s), 6.87 (1H, dd, J = 8.2, 2.4 Hz), 6.94–7.01 (2H, overlapped), 7.06 (1H, d, J = 8.9 Hz), 7.26–7.42 (13H, m, Ar, overlapped), 7.44–7.59 (4H, overlapped), 7.70–7.75 (2H, m, Ar), 8.13–8.18 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.5, 7.0, 10.4, 12.8, 14.4, 18.0, 18.1, 21.1, 21.9, 24.4, 25.5, 26.8, 33.8, 36.0, 36.1, 37.5, 43.6, 47.0, 56.1, 58.6, 66.4, 70.3, 71.9, 72.5, 75.1, 75.2, 75.7, 76.7, 79.1, 81.4, 84.7, 113.3, 114.6, 119.0, 127.2, 127.6, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.5, 130.1, 130.5, 132.0, 133.7, 133.8, 134.2, 136.1, 137.0, 140.2, 140.4, 159.5, 167.1, 167.2, 169.6, 172.0, 172.6, 172.9, 202.0; HRFABMS *m*/*z* 1428.6735 [M+Na$^+$]; calcd for $C_{80}H_{103}NO_{17}Si_2Na$, 1428.6662.

4.11.4. 4-Deacetyl-4-(6-benzyloxylcarbonylhexanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (26). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.57–0.71 (6H, m), 0.96–1.06 (30H, overlapped), 1.22 (3H, s), 1.27 (3H, s), 1.30–1.44 (2H, m), 1.57–1.71 (2H, m), 1.76 (3H, s), 1.77–2.00 (4H, overlapped), 2.10 (3H, d, J = 1.1 Hz), 2.15–2.24 (4H, overlapped), 2.27 (2H, t, J = 7.6 Hz), 2.39–2.48 (1H, m), 2.53–2.68 (2H, overlapped), 2.98–3.07 (1H, m), 3.89 (1H, d, J = 7.1 Hz), 4.27 (1H, d, J = 8.4 Hz), 4.34 (1H, d, J = 8.4 Hz), 4.55 (1H, dd, J = 10.4, 6.6 Hz), 4.91 (1H, dd, J = 9.5, 1.6 Hz), 4.97 (1H, d, J = 1.6 Hz), 5.10 (2H, s), 5.12 (2H, s), 5.72–5.77 (2H, overlapped), 6.25 (1H, t, J = 9.1 Hz), 6.52 (1H, s), 6.92 (1H, dd, J = 8.3, 2.4 Hz), 7.00–7.07 (2H, overlapped), 7.11 (1H, d,

J = 8.9 Hz), 7.30–7.46 (13H, m, Ar, overlapped), 7.49–7.63 (4H, overlapped), 7.75–7.80 (2H, m, Ar), 8.17–8.23 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.4, 6.8, 10.2, 12.6, 14.2, 17.8, 17.9, 20.9, 21.7, 24.5, 25.5, 26.6, 28.6, 33.9, 35.9, 36.1, 37.3, 43.4, 46.8, 55.9, 58.5, 66.1, 70.1, 71.8, 72.3, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 118.9, 127.0, 127.4, 128.0, 128.1, 128.2, 128.5, 128.6, 128.7, 129.4, 129.8, 130.3, 131.8, 133.6, 134.0, 136.1, 136.9, 140.1, 140.2, 159.3, 166.8, 167.0, 169.3, 171.8, 172.6, 173.1, 201.7; HRFABMS *m/z* 1419.6912 [M$^+$]; calcd for $C_{81}H_{105}NO_{17}Si_2$, 1419.6921.

4.11.5. 4-Deacetyl-4-(7-benzyloxylcarbonylheptanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (27). Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.71 (6H, m), 0.95–1.05 (30H, overlapped), 1.21 (3H, s), 1.26 (3H, s), 1.28–1.38 (4H, overlapped), 1.52–1.62 (2H, m), 1.75 (3H, s), 1.76–2.00 (4H, overlapped), 2.09 (3H, d, J = 1.1 Hz), 2.14–2.24 (4H, overlapped), 2.29 (2H, t, J = 7.6 Hz), 2.39–2.48 (1H, m), 2.53–2.65 (2H, overlapped), 2.96–3.06 (1H, m), 3.88 (1H, d, J = 7.2 Hz), 4.26 (1H, d, J = 8.4 Hz), 4.33 (1H, d, J = 8.4 Hz), 4.54 (1H, dd, J = 10.5, 6.7 Hz), 4.91 (1H, dd, J = 9.5, 1.6 Hz), 4.96 (1H, d, J = 1.6 Hz), 5.09 (2H, s), 5.13 (2H, s), 5.70–5.76 (2H, overlapped), 6.24 (1H, t, J = 9.1 Hz), 6.51 (1H, s), 6.91 (1H, dd, J = 8.3, 2.4 Hz), 6.99–7.06 (2H, overlapped), 7.10 (1H, d, J = 8.9 Hz), 7.31–7.48 (13H, m, Ar, overlapped), 7.49–7.65 (4H, overlapped), 7.74–7.79 (2H, m, Ar), 8.18–8.23 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.4, 6.8, 10.2, 12.6, 14.2, 17.8, 17.9, 20.9, 21.7, 24.7, 25.8, 26.6, 28.7, 28.8, 34.1, 35.9, 36.3, 37.3, 43.4, 46.8, 55.9, 58.5, 66.1, 70.1, 71.8, 72.3, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 118.9, 127.0, 127.3, 128.0, 128.1, 128.2, 128.5, 128.6, 128.7, 129.4, 129.7, 130.3, 131.7, 133.5, 133.6, 134.0, 136.1, 136.9, 140.1, 140.2, 159.3, 166.8, 167.0, 169.3, 171.8, 172.7, 173.3, 201.7; HRFABMS *m/z* 1434.7103 [M+H$^+$]; calcd for $C_{81}H_{105}NO_{17}Si_2$, 1434.7156.

4.12. General procedure for oxidative cleavage of double bond to carboxylic acid

To a solution of 4-deacetyl-4-(4-pentenoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel **19** (44 mg, 0.035 mmol) in $H_2O/CH_3CN/CCl_4$ (0.9 mL/0.6 mL/0.6 mL) was added $RuCl_3$ (1 mg, cat.) and $NaIO_4$ (75 mg, 0.35 mmol). After stirring for 24 h, the reaction mixture was quenched with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with water, brine, and dried with sodium sulfate. After concentrated in vacuum, the residue was applied to PTLC (35% EtOAc/hexane) to give **21** as colorless gum (25.9 mg, 58%). Compound **22** was prepared by a similar procedure.

4.12.1. 4-Deacetyl-4-(3-carboxypropanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (21). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.55–0.65 (6H, m), 0.90–1.03 (30H, overlapped), 1.20 (3H, s), 1.24 (3H, s), 1.72 (3H, s), 1.85–1.94 (1H, m), 2.05 (3H, d, J = 1.2 Hz), 2.09–2.22 (5H, overlapped), 2.33–2.41 (1H, m), 2.48–2.58 (1H, m), 2.82–2.96 (3H, overlapped), 3.09–3.18 (1H, m), 3.85 (1H, d, J = 7.1 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.30 (1H, d, J = 8.4 Hz), 4.50 (1H, dd, J = 10.6, 6.6 Hz), 4.91 (1H, d, J = 1.9 Hz), 4.97 (1H, dd, J = 9.5, 1.7 Hz), 5.07 (2H, s), 5.69 (1H, d, J = 8.8 Hz), 5.73 (1H, d, J = 7.1 Hz), 6.23 (1H, t, J = 9.1 Hz), 6.47 (1H, s), 6.89–7.01 (3H, m, Ar, overlapped), 7.14 (1H, d, J = 8.9 Hz), 7.29–7.61 (12H, m, Ar, overlapped), 7.73–7.77 (2H, m, Ar), 8.11–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 5.3, 6.8, 10.2, 12.5, 14.1, 17.8, 17.9, 20.9, 21.8, 26.6, 29.0, 30.9, 35.9, 37.2, 43.4, 46.7, 56.0, 58.5, 70.1, 71.9, 72.2, 74.9, 75.0, 75.5, 76.5, 78.9, 81.7, 84.1, 113.4, 114.3, 118.7, 120.1, 127.0, 127.4, 128.1, 128.6, 128.8, 129.2, 129.9, 130.2, 131.9, 133.6, 133.7, 136.7, 139.9, 140.2, 155.1, 159.2, 167.0, 167.2, 169.3, 171.0, 171.7, 174.5, 201.7; HRFABMS *m/z* 1310.5851 [M+Na$^+$]; calcd for $C_{71}H_{93}NO_{17}Si_2Na$, 1310.5880.

4.12.2. 4-Deacetyl-4-(4-carboxybutanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel (22). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 0.52–0.66 (6H, m), 0.94 (9H, t, J = 7.9 Hz), 0.97–1.07 (21H, overlapped), 1.13 (3H, s), 1.19 (3H, s), 1.68 (3H, s), 1.77–1.86 (1H, m), 1.96 (3H, br s), 2.06–2.23 (6H, overlapped), 2.29–2.48 (3H, overlapped), 2.51–2.61 (1H, m), 2.70–2.80 (1H, m), 2.94–3.04 (1H, m), 3.84 (1H, d, J = 7.1 Hz), 4.20 (1H, d, J = 8.3 Hz), 4.23 (1H, d, J = 8.3 Hz), 4.53 (1H, dd, J = 10.4, 6.7 Hz), 4.94–5.00 (2H, overlapped), 5.11 (2H, ABq, J = 12.3 Hz), 5.65–5.72 (2H, overlapped), 6.11 (1H, t, J = 9.2 Hz), 6.47 (1H, s), 6.92–6.98 (1H, m, Ar), 7.08–7.15 (2H, m, overlapped), 7.24–7.63 (12H, m, Ar, overlapped), 7.73–7.79 (2H, m, Ar), 8.12–8.18 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 6.3, 7.2, 10.7, 13.8, 15.0, 18.5, 18.6, 20.8, 22.0, 22.4, 27.0, 34.0, 36.5, 36.8, 38.3, 44.7, 48.0, 57.9, 59.7, 71.1, 73.3, 73.8, 76.1, 76.4, 77.0, 77.5, 78.9, 82.4, 85.6, 115.2, 115.8, 120.8, 128.3, 128.5, 128.9, 129.5, 129.7, 129.8, 131.1, 131.2, 131.3, 133.0, 134.5, 135.2, 135.5, 138.6, 140.8, 141.4, 160.6, 167.6, 170.1, 170.8, 173.5, 173.6, 176.3, 204.2; HRFABMS *m/z* 1324.6067 [M+Na$^+$]; calcd for $C_{72}H_{95}NO_{17}Si_2Na$, 1324.6036.

4.13. General procedure for deprotection of benzyl group using hydrogenolysis

To a solution of 4-deacetyl-4-(3-carboxypropanoyl)-3′-desphenyl-3′-(*m*-benzyloxyphenyl)-7-TES-2′-TIPS-paclitaxel **21** (33 mg, 0.026 mmol) in EtOAc (10 mL) was added 10% Pd–C (10 mg, cat.). The mixture was hydrogenated at 30 psi at room temperature for 48 h. The reaction mixture was filtered, and the organic phase was concentrated in vacuum. The residue was purified by preparative TLC (70% EtOAc/hexane) to give **23** as colorless gum (22.5 mg, 73%). Compounds **24**, **28**, **29**, and **30** were prepared by similar procedures.

4.13.1. 4-Deacetyl-4-(3-carboxypropanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel (23). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.50–0.65 (6H, m), 0.90–0.98 (30H, overlapped), 1.16 (3H, s), 1.22 (3H, s), 1.70 (3H, s), 1.86–1.96 (1H, m), 2.02 (3H, d,

J = 1.0 Hz), 2.07–2.20 (4H, overlapped), 2.31–2.41 (1H, m), 2.46–2.57 (1H, m), 2.75–3.00 (3H, overlapped), 3.11–3.20 (1H, m), 3.85 (1H, d, J = 6.9 Hz), 4.24 (1H, d, J = 8.5 Hz), 4.34 (1H, d, J = 8.5 Hz), 4.47 (1H, dd, J = 10.6, 6.6 Hz), 4.88 (1H, dd, J = 9.5, 1.5 Hz) 4.94 (1H, d, J = 1.7 Hz), 5.62 (1H, d, J = 9.1 Hz), 5.74 (1H, d, J = 6.9 Hz), 6.14 (1H, t, J = 9.2 Hz), 6.45 (1H, s), 6.69–6.86 (3H, m, Ar, overlapped), 7.08–7.19 (2H, overlapped), 7.32–7.39 (2H, m, Ar), 7.45–7.60 (4H, m, Ar, overlapped), 7.65–7.71 (2H, m, Ar), 8.10–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.5, 7.0, 10.4, 12.7, 14.4, 18.0, 21.1, 21.9, 26.6, 29.9, 31.3, 35.9, 37.4, 43.6, 46.8, 56.6, 58.7, 72.3, 72.4, 75.2, 75.6, 78.8, 82.0, 84.7, 113.5, 115.4, 117.8, 127.2, 129.0, 129.1, 129.4, 130.1, 130.4, 132.3, 133.6, 133.8, 133.9, 139.2, 140.5, 157.2, 167.3, 168.1, 169.6, 171.5, 172.3, 175.5, 201.9; HRFABMS m/z 1220.5438 [M+Na$^+$]; calcd for $C_{64}H_{87}NO_{17}Si_2Na$, 1220.5410.

4.13.2. 4-Deacetyl-4-(4-carboxybutanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel (24). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 0.53–0.67 (6H, m), 0.91–1.06 (30H, overlapped), 1.13 (3H, s), 1.18 (3H, s), 1.67 (3H, s), 1.78–1.87 (1H, m), 1.98 (3H, br s), 2.00–2.20 (6H, overlapped), 2.25–2.50 (3H, overlapped), 2.52–2.63 (1H, m), 2.68–2.79 (1H, m), 2.92–3.04 (1H, m), 3.84 (1H, d, J = 7.0 Hz), 4.17–4.26 (2H, overlapped), 4.54 (1H, dd, J = 10.4, 6.7 Hz), 4.95–5.01 (2H, overlapped), 5.62 (1H, d, J = 3.4 Hz), 5.67 (1H, d, J = 7.0 Hz), 6.08 (1H, t, J = 9.3 Hz), 6.47 (1H, s), 6.71–6.77 (1H, m, Ar), 6.93–7.00 (2H, m, Ar), 7.21–7.27 (1H, m, Ar), 7.41–7.68 (6H, m, Ar, overlapped), 7.77–7.83 (2H, m, Ar), 8.12–8.18 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 5.1, 6.1, 9.6, 12.7, 13.9, 17.3, 17.4, 19.6, 21.2, 21.7, 25.8, 35.0, 35.5, 35.6, 37.2, 43.6, 46.8, 57.0, 58.5, 72.1, 72.7, 75.0, 75.3, 75.9, 76.4, 77.7, 81.1, 84.6, 114.1, 115.1, 118.1, 127.1, 128.5, 128.7, 129.8, 130.0, 130.1, 131.8, 133.4, 134.0, 134.5, 139.4, 140.3, 158.0, 165.7, 166.5, 168.9, 169.7, 172.6, 172.7, 203.2; HRFABMS m/z 1212.5789 [M+H$^+$]; calcd for $C_{65}H_{90}NO_{17}Si_2$, 1212.5747.

4.13.3. 4-Deacetyl-4-(5-carboxypentanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel (27). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 0.57–0.72 (6H, m), 0.99 (9H, t, J = 7.9 Hz), 1.02–1.10 (21H, overlapped), 1.17 (3H, s), 1.23 (3H, s), 1.72 (3H, s), 1.73–1.99 (5H, overlapped), 2.01 (3H, br s), 2.14–2.26 (4H, overlapped), 2.33–2.50 (3H, overlapped), 2.56–2.66 (1H, m), 2.69–2.79 (1H, m), 2.96–3.06 (1H, m), 3.90 (1H, d, J = 7.1 Hz), 4.26 (2H, ABq, J = 8.3 Hz), 4.58 (1H, dd, J = 10.5, 6.8 Hz), 4.98 (1H, d, J = 9.2 Hz)5.02 (1H, d, J = 3.0 Hz), 5.68–5.76 (2H, overlapped), 6.17 (1H, t, J = 9.1 Hz), 6.51 (1H, s), 6.80 (1H, dd, J = 8.1, 2.3 Hz), 6.94–6.97 (1H, m, Ar), 7.00 (1H, d, J = 7.8 Hz), 7.30 (1H, t, J = 8.1 Hz), 7.45–7.73 (6H, m, Ar, overlapped), 7.79–7.84 (2H, m, Ar), 8.17–8.23 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.1, 24.9, 25.6, 33.1, 35.5, 35.7, 37.0, 43.4, 46.6, 56.3, 58.3, 71.9, 72.5, 74.8, 75.1, 75.5, 76.1, 77.6, 80.9, 84.4, 114.0, 114.7, 117.8, 126.9, 128.3, 128.4, 129.6, 129.9, 130.0, 131.6, 133.2, 133.9, 134.2, 139.3, 140.1, 157.7, 166.3, 168.6, 169.5, 172.2, 172.6, 202.9; HRFABMS m/z 1226.5916 [M+H$^+$]; calcd for $C_{66}H_{90}NO_{17}Si_2$, 1226.5904.

4.13.4. 4-Deacetyl-4-(6-carboxyhexanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel (29). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 0.57–0.72 (6H, m), 0.99 (9H, t, J = 8.1 Hz), 1.01–1.10 (21H, overlapped), 1.18 (3H, s), 1.23 (3H, s), 1.42–1.53 (2H, m), 1.61–1.75 (5H, overlapped), 1.80–1.98 (3H, overlapped), 2.03 (3H, d, J = 1.0 Hz), 2.18 (3H, s), 2.21–2.31 (3H, overlapped), 2.43–2.51 (1H, m), 2.57–2.77 (2H, overlapped), 2.94–3.03 (1H, m), 3.90 (1H, d, J = 7.2 Hz), 4.25 (2H, br s), 4.58 (1H, dd, J = 10.5, 6.7 Hz), 4.96 (1H, dd, J = 9.7, 1.6 Hz), 5.03 (1H, d, J = 2.7 Hz), 5.69–5.74 (2H, overlapped), 6.18 (1H, t, J = 9.1 Hz), 6.51 (1H, s), 6.82 (1H, dd, J = 8.1, 2.1 Hz), 6.94–6.97 (1H, m, Ar), 7.01 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 8.1 Hz), 7.45–7.70 (6H, m, Ar, overlapped), 7.78–7.83 (2H, m, Ar), 8.17–8.22 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3 OD) δ: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.4, 25.1, 25.6, 28.3, 33.2, 35.5, 35.7, 37.0, 43.4, 46.6, 56.2, 58.3, 71.9, 72.5, 74.8, 75.1, 75.5, 76.2, 77.6, 80.9, 84.4, 114.0, 114.6, 117.7, 126.8, 128.3, 128.4, 129.6, 129.9, 130.0, 131.6, 133.2, 133.9, 134.2, 139.4, 140.0, 157.8, 166.3, 168.6, 169.5, 172.2, 172.7, 175.9, 202.9; HRFABMS m/z 1262.5826 [M+Na$^+$]; calcd for $C_{67}H_{93}NO_{17}Si_2Na$, 1262.5880.

4.13.5. 4-Deacetyl-4-(7-carboxyheptanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel (30). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 0.57–0.72 (6H, m), 0.99 (9H, t, J = 8.1 Hz), 1.02–1.10 (21H, overlapped), 1.18 (3H, s), 1.22 (3H, s), 1.34–1.51 (4H, overlapped), 1.52–1.65 (2H, m), 1.72 (3H, s), 1.79–1.95 (3H, overlapped), 2.03 (3H, d, J = 1.0 Hz), 2.18 (3H, s), 2.19–2.30 (3H, overlapped), 2.44–2.53 (1H, m), 2.56–2.76 (2H, overlapped), 2.94–3.04 (1H, m), 3.91 (1H, d, J = 7.2 Hz), 4.25 (2H, ABq, J = 8.6 Hz), 4.59 (1H, dd, J = 10.4, 6.6 Hz), 4.95 (1H, dd, J = 9.5, 1.7 Hz), 5.04 (1H, d, J = 2.5 Hz), 5.69–5.75 (2H, overlapped), 6.19 (1H, t, J = 9.1 Hz), 6.52 (1H, s), 7.78–6.85 (1H, m, Ar), 6.93–6.98 (1H, m, Ar), 7.00 (1H, d, J = 7.6 Hz), 7.28 (1H, t, J = 8.2 Hz), 7.45–7.62 (5H, m, Ar, overlapped), 7.65–7.71 (1H, m, Ar), 7.78–7.83 (2H, m, Ar), 8.17–8.22 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.4, 25.3, 25.6, 28.5, 33.4, 35.5, 35.9, 37.0, 43.4, 46.6, 56.1, 56.2, 58.4, 71.9, 72.4, 74.9, 75.1, 75.5, 76.2, 77.7, 80.9, 84.5, 114.0, 114.6, 117.7, 126.8, 128.4, 129.5, 129.9, 130.0, 131.6, 133.2, 133.9, 134.3, 139.4, 139.5, 140.0, 157.8, 166.3, 168.6, 169.5, 172.2, 172.9, 176.1, 202.9; HRFABMS m/z 1276.5984 [M+Na$^+$]; calcd for $C_{68}H_{95}NO_{17}Si_2Na$, 1276.6037.

4.14. General procedures for macrolactonization

To a solution of compound 4-deacetyl-4-(3-carboxypropanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-7-TES-2′-TIPS-paclitaxel **23** (20.4 mg, 0.017 mmol) in anhydrous DCM (1.5 mL) was added 2,4,6-trichlorobenzoyl chloride (7.9 μL, 0.051 mmol). After stirring for 30 min, the reaction mixture was transferred into a syringe. Very slow addition of this mixture through

syringe pump to a flask with DMAP (6.4 mg, 0.051 mmol) in DCM (8.5 mL) under stirring. The addition rate was set to be 0.5 mL/h. After addition was over, the mixture was kept stirring for another hour. The reaction mixture was diluted with DCM (20 mL), and then washed with 0.1 N HCl (3 × 20 mL), saturated $NaHCO_3$, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (30% EtOAc/hexane) to give **31** as colorless gum (5.1 mg, 25%). Compounds **32**–**35** were prepared in similar procedures.

4.14.1. Macrocyclic taxoid 31. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.50–0.60 (6H, m), 0.92 (9H, t, J = 7.8 Hz), 1.13–1.27 (27H, overlapped), 1.29 (3H, s), 1.62–1.71 (5H, overlapped), 1.81–1.90 (1H, m), 2.16 (3H, s), 2.39–2.48 (1H, m), 2.75–3.15 (4H, overlapped), 3.39 (1H, d, J = 7.8 Hz), 4.15 (1H, d, J = 8.5 Hz), 4.23 (1H, d, J = 8.5 Hz), 4.39 (1H, dd, J = 10.6, 6.5 Hz), 4.77–4.82 (2H, overlapped), 5.63 (1H, d, J = 7.8 Hz), 5.72 (1H, br s), 5.94 (1H, br t, J = 8.7 Hz), 6.24 (1H, s), 7.13–7.20 (2H, overlapped), 7.32–7.37 (1H, m, Ar), 7.46–7.80 (8H, m, Ar, overlapped), 7.89–7.95 (2H, m, Ar), 8.02–8.07 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.5, 6.9, 11.0, 12.5, 18.2, 21.1, 28.1, 29.2, 30.5, 36.4, 36.7, 36.98, 36.99, 37.01, 43.5, 47.2, 58.1, 72.1, 73.8, 74.5, 75.9, 76.4, 77.3, 82.0, 84.7, 120.5, 127.4, 128.8, 129.0, 129.5, 130.2, 130.5, 132.3, 132.9, 133.7, 134.09, 134.12, 141.0, 146.3, 152.0, 162.7, 166.6, 167.4, 169.4, 170.6, 201.4; HRFABMS m/z 1202.5312 [M+Na$^+$]; calcd for $C_{64}H_{85}NO_{16}Si_2Na$, 1202.5305.

4.14.2. Macrocyclic taxoid 32. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.54–0.68 (6H, m), 0.93–1.12 (30H, overlapped), 1.26 (3H, s), 1.28 (3H, s), 1.65 (3H, s), 1.75 (3H, s), 1.81 (1H, s), 1.81–2.11 (3H, overlapped), 2.21 (3H, s), 2.23–2.90 (7H, overlapped), 3.79 (1H, br s), 4.27 (1H, d, J = 8.3 Hz), 4.39 (1H, d, J = 8.3 Hz), 4.51 (1H, dd, J = 10.6, 6.5 Hz), 4.78 (1H, br s), 4.87 (1H, d, J = 9.2 Hz), 5.45 (1H, br s), 5.76 (1H, d, J = 7.4 Hz), 6.16 (1H, t, J = 9.2 Hz), 6.46 (1H, s), 7.13 (1H, d, J = 8.0 Hz), 7.22 (1H, d, J = 7.8 Hz), 7.38–7.71 (8H, m, Ar, overlapped), 7.88 (2H, d, J = 7.8 Hz), 8.15 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.7, 10.4, 12.4, 17.8, 17.9, 20.8, 22.8, 25.1, 26.9, 29.7, 32.6, 36.2, 37.1, 43.4, 47.0, 56.3, 58.3, 68.2, 69.6, 72.2, 74.8, 75.1, 76.5, 81.9, 84.7, 120.1, 120.3, 122.2, 127.1, 128.7, 128.8, 129.2, 130.1, 130.4, 131.9, 133.6, 133.9, 140.1, 140.3, 149.4, 153.0, 166.3, 167.0, 169.3, 171.7, 172.2, 175.2, 201.9; HRFABMS m/z 1216.5433 [M+Na$^+$]; calcd for $C_{65}H_{87}NO_{16}Si_2Na$, 1216.5461.

4.14.3. Macrocyclic taxoid 33. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.67 (6H, m), 0.93–1.05 (30H, overlapped), 1.25 (3H, s), 1.26 (3H, s), 1.68–1.80 (5H, overlapped), 1.84–2.13 (6H, overlapped), 2.15–2.31 (7H, overlapped), 2.41–2.87 (6H, overlapped), 3.90 (1H, d, J = 7.3 Hz), 4.28 (1H, d, J = 8.3 Hz), 4.34 (1H, d, J = 8.4 Hz), 4.50 (1H, dd, J = 10.6, 6.5 Hz), 4.76–4.83 (2H, overlapped), 5.53 (1H, d, J = 8.0 Hz), 5.76 (1H, d, J = 7.3 Hz), 6.13 (1H, t, J = 9.1 Hz), 6.50 (1H, s), 7.03–7.12 (2H, m, overlapped), 7.17–7.22 (1H, m, Ar), 7.40 (2H, t, J = 7.8 Hz), 7.47–7.692 (6H, m, Ar, overlapped), 7.85–7.91 (2H, m, Ar), 8.14–8.20 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.7, 10.2, 12.4, 14.0, 17.7, 17.8, 20.9, 21.9, 25.3, 26.7, 27.0, 35.1, 36.1, 36.3, 37.3, 43.4, 47.1, 56.4, 58.5, 71.8, 72.2, 74.9, 75.0, 76.8, 79.0, 81.9, 84.9, 120.1, 120.3, 122.3, 127.1, 128.7, 128.8, 129.3, 130.1, 130.2, 131.9, 133.4, 133.8, 134.0, 140.3, 141.4, 151.7, 166.9, 167.3, 169.3, 171.7, 172.5, 173.1, 201.5; HRFABMS m/z 1230.5566 [M+Na$^+$]; calcd for $C_{66}H_{89}NO_{16}Si_2Na$, 1230.5618.

4.14.4. Macrocyclic taxoid 34. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.67 (6H, m), 0.92–1.02 (30H, overlapped), 1.23 (3H, s), 1.26 (3H, s), 1.66–1.80 (5H, overlapped), 1.89–2.11 (9H, overlapped), 2.20 (3H, s), 2.25–2.34 (1H, m), 2.41–2.49 (1H, m), 2.51–2.79 (4H, overlapped), 2.81–2.91 (1H, m), 3.86 (1H, d, J = 7.1 Hz), 4.26 (1H, d, J = 8.5 Hz), 4.37 (1H, d, J = 8.5 Hz), 4.52 (1H, dd, J = 10.5, 6.6 Hz), 4.85 (1H, d, J = 1.0 Hz), 4.89 (1H, dd, J = 9.6, 1.8 Hz), 5.61 (1H, d, J = 8.4 Hz), 5.77 (1H, d, J = 7.1 Hz), 6.10 (1H, t, J = 9.3 Hz), 6.49 (1H, s), 6.98–7.03 (1H, m, Ar), 7.17 (1H, dd, J = 8.0, 1.8 Hz), 7.21–7.25 (1H, m, Ar), 7.29 (1H, d, J = 8.4 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.47–7.69 (6H, m, Ar, overlapped), 7.83–7.88 (2H, m, Ar), 8.14–8.19 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.3, 6.7, 10.2, 12.5, 14.0, 17.7, 17.9, 20.8, 21.8, 24.8, 24.9, 26.7, 28.2, 34.5, 35.8, 35.9, 37.2, 43.4, 46.7, 56.3, 58.4, 72.2, 72.6, 74.9, 75.0, 76.2, 76.5, 78.8, 81.4, 84.6, 119.6, 121.8, 123.2, 127.0, 128.7, 128.8, 129.3, 129.9, 130.1, 131.9, 133.6, 133.7, 134.0, 140.2, 140.6, 151.3, 166.9, 167.4, 169.3, 171.9, 172.3, 201.6; HRFABMS m/z 1244.5759 [M+Na$^+$]; calcd for $C_{67}H_{91}NO_{16}Si_2Na$, 1244.5774.

4.14.5. Macrocyclic taxoid 35. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.51–0.64 (6H, m), 0.88–0.98 (30H, overlapped), 1.16 (3H, s), 1.22 (3H, s), 1.60–2.10 (16H, overlapped), 2.16 (3H, s), 2.21–2.30 (1H, m), 2.34–2.74 (5H, overlapped), 2.78–2.88 (1H, m), 3.87 (1H, d, J = 7.0 Hz), 4.22 (1H, d, J = 8.5 Hz), 4.33 (1H, d, J = 8.5 Hz), 4.48 (1H, dd, J = 10.5, 6.6 Hz), 4.80–4.87 (2H, overlapped), 5.59 (1H, d, J = 8.7 Hz), 5.72 (1H, d, J = 7.0 Hz), 6.03 (1H, t, J = 9.0 Hz), 6.47 (1H, s), 7.00–7.08 (2H, m, Ar, overlapped), 7.16–7.24 (2H, m, Ar, overlapped), 7.35–7.67 (7H, m, Ar, overlapped), 7.77–7.83 (2H, m, Ar), 8.10–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.5, 6.9, 10.3, 12.7, 14.4, 18.0, 18.1, 21.1, 21.6, 25.0, 26.7, 27.0, 28.8, 29.5, 34.6, 35.8, 37.2, 37.4, 43.6, 46.8, 56.6, 58.7, 72.4, 73.1, 75.0, 75.3, 75.9, 76.8, 78.7, 81.4, 84.8, 119.7, 122.0, 124.0, 127.2, 128.9, 129.0, 129.5, 130.1, 130.4, 132.1, 133.9, 134.2, 140.3, 140.5, 151.2, 167.1, 167.4, 169.5, 172.3, 172.4, 172.9, 202.0; HRFABMS m/z 1236.6061 [M+H$^+$]; calcd for $C_{68}H_{94}NO_{16}Si_2$, 1236.6111.

4.15. General procedures for desilylation

To a solution of macrocyclic taxoid **31** (6.0 mg, 0.005 mmol) in dried THF (1.0 mL) was added anhydrous pyridine (0.2 mL), then the solution was cooled to 0 °C, and HF–pyridine (0.2 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was

diluted with EtOAc (20 mL), and the organic phase was washed with sodium bicarbonate, water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give **2a** (1.2 mg, 26%) and **36a** (2.3 mg, 49%) both as colorless gums. Compounds **37a**–**e** were prepared similarly from compounds **23**, **24**, and **28**–**30**, while compounds **2b**, **36b**, **2c**, **36c**, **2d**, and **2e** were prepared from compounds **32**–**35** by using HF–TEA instead of HF–pyridine in THF as solvent.

4.15.1. Macrocyclic taxoid 2a. ^{1}H NMR (400 MHz, $CDCl_3$)δ: 1.12 (3H, s), 1.29 (3H, s), 1.35 (3H, br s), 1.62–1.69 (1H, m), 1.69 (3H, s), 1.84–1.92 (1H, m), 2.25 (3H, s), 2.47–2.69 (3H, overlapped), 2.83–3.05 (4H, overlapped), 3.48 (1H, d, J = 7.4 Hz), 3.79 (1H, br s), 4.18 (1H, d, J = 8.3 Hz), 4.25 (1H, d, J = 8.3 Hz), 4.35 (1H, m), 4.53 (1H, br s), 4.83 (1H, dd, J = 9.3, 1.8 Hz), 5.47 (1H, m), 5.65 (1H, d, J = 7.4 Hz), 6.12 (1H, s), 6.15 (1H, t, J = 9.3 Hz), 7.15–7.32 (3H, overlapped), 7.39–7.62 (7H, m, Ar, overlapped), 7.68–7.75 (1H, m, Ar), 7.87–7.91 (2H, m, Ar), 8.00–8.04 (2H, m, Ar); HRFABMS m/z 910.3317 [M+H$^+$]; calcd for $C_{49}H_{52}NO_{16}$, 910.3286.

4.15.2. Macrocyclic taxoid 36a. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (3H, s), 1.20 (3H, s), 1.39 (3H, d, J = 1.0 Hz), 1.69 (1H, s), 1.71 (3H, s), 1.88–1.96 (1H, m), 2.01–2.08 (1H, m), 2.13–2.21 (1H, m), 2.25 (3H, s), 2.46–2.56 (2H, overlapped), 2.70–2.79 (2H, overlapped), 3.07–3.24 (2H, overlapped), 3.85 (1H, d, J = 7.6 Hz), 4.24 (1H, d, J = 8.6 Hz), 4.28 (1H, d, J = 8.6 Hz), 4.34 (1H, m), 4.78 (1H, dd, J = 9.7, 1.8 Hz), 5.52 (1H, d, J = 3.0 Hz), 5.61 (1H, d, J = 7.6 Hz), 5.94 (1H, dd, J = 9.3, 3.0 Hz), 6.14 (1H, s), 6.21 (1H, t, J = 8.9 Hz), 6.79–6.84 (1H, m, Ar), 6.98–7.03 (2H, overlapped), 7.24–7.28 (1H, m, Ar), 7.49–7.68 (7H, m, Ar, overlapped), 7.88–7.94 (2H, m, Ar), 8.11–8.16 (2H, m, Ar); HRFABMS m/z 910.3295 [M+H$^+$]; calcd for $C_{49}H_{52}NO_{16}$, 910.3286.

4.15.3. 4-Deacetyl-4-(3-carboxypropanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-paclitaxel (37a). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.16 (3H, s), 1.18 (3H, s), 1.67 (3H, s), 1.73–1.85 (2H, overlapped), 1.90 (3H, s), 2.06–2.15 (1H, m), 2.16–2.24 (4H, overlapped), 2.42–2.53 (1H, m), 2.60–2.84 (2H, overlapped), 2.86–2.97 (1H, m), 3.81 (1H, d, J = 7.3 Hz), 4.20 (2H, ABq, J = 8.6 Hz), 4.35 (1H, dd, J = 10.9, 6.6 Hz), 4.68 (1H, d, J = 7.3 Hz), 5.06 (1H, d, J = 9.1 Hz), 5.43 (1H, d, J = 7.3 Hz), 5.65 (1H, d, J = 7.3 Hz), 6.08 (1H, t, J = 9.1 Hz), 6.45 (1H, s), 6.69 (1H, dd, J = 8.2, 2.5 Hz), 6.93 (1H, d, J = 7.7 Hz), 7.02 (1H, m, Ar), 7.22 (1H, t, J = 7.9 Hz), 7.47–7.73 (6H, m, Ar, overlapped), 7.95–8.00 (2H, m, Ar), 8.10–8.15 (2H, m, Ar); HRFABMS m/z 928.3373 [M+H$^+$]; calcd for $C_{49}H_{54}NO_{17}$, 928.3392.

4.15.4. Macrocyclic taxoid 2b. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, s), 1.35 (3H, s), 1.73 (3H, s), 1.79 (3H, s), 1.80 (3H, s), 1.85–1.98 (2H, overlapped), 2.11–2.26 (2H, overlapped), 2.27 (3H, s), 2.42–2.82 (6H, overlapped), 2.85–2.94 (1H, m), 3.68 (1H, d, J = 7.4 Hz), 3.89 (1H, d, J = 7.0 Hz), 4.25 (1H, d, J = 8.5 Hz), 4.34 (1H, d, J = 8.5 Hz), 4.42 (1H, m), 4.64 (1H, br t, J = 6.5 Hz), 4.89 (1H, dd, J = 9.5, 1.8 Hz), 5.64 (1H, dd, J = 7.8, 6.1 Hz), 5.72 (1H, d, J = 7.4 Hz), 6.22 (1H, t, J = 9.0 Hz), 6.24 (1H, s), 7.02–7.08 (1H, m, Ar), 7.14–7.21 (2H, overlapped), 7.28–7.34 (1H, m, Ar), 7.42–7.73 (7H, m, Ar, overlapped), 7.82–7.87 (2H, m, Ar), 8.12–8.17 (2H, m, Ar); HRFABMS m/z 924.3463 [M+H$^+$]; calcd for $C_{50}H_{54}NO_{16}$, 924.3443.

4.15.5. Macrocyclic taxoid 36b. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, s), 1.29 (3H, s), 1.40 (3H, d, J = 1.3 Hz), 1.68 (1H, s), 1.82 (3H, s), 1.85–2.16 (4H, overlapped), 2.26 (3H, s), 2.27–2.40 (1H, m), 2.48–2.81 (5H, overlapped), 2.91–3.00 (1H, m), 3.58 (1H, d, J = 7.1 Hz), 4.16 (1H, d, J = 8.5 Hz), 4.31 (1H, d, J = 8.5 Hz), 4.39 (1H, m), 4.98 (1H, dd, J = 9.6, 1.7 Hz), 5.66 (1H, d, J = 7.1 Hz), 5.87 (1H, dd, J = 9.4, 3.5 Hz), 6.01 (1H, d, J = 3.5 Hz), 6.10 (1H, br s), 6.14 (1H, s), 6.42 (1H, dt, J = 9.1, 1.3 Hz), 6.77–6.81 (1H, m, Ar), 6.90–6.94 (1H, m, Ar), 6.96–6.99 (1H, m, Ar), 7.23 (1H, t, J = 7.9 Hz), 7.50–7.69 (7H, m, Ar, overlapped), 7.87–7.92 (2H, m, Ar), 8.05–8.09 (2H, m, Ar); HRFABMS m/z 924.3410 [M+H$^+$]; calcd for $C_{50}H_{54}NO_{16}$, 924.3443.

4.15.6. 4-Deacetyl-4-(4-carboxybutanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-paclitaxel (37b). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.17 (3H, s), 1.18 (3H, s), 1.68 (3H, s), 1.69–1.87 (2H, overlapped), 1.91 (3H, br s), 2.05–2.18 (3H, overlapped), 2.20 (3H, s), 2.30–2.55 (3H, overlapped), 2.65 (2H, br t, J = 7.8 Hz), 3.83 (1H, d, J = 7.2 Hz), 4.20 (2H, br s), 4.37 (1H, dd, J = 10.9, 6.5 Hz), 4.69 (1H, d, J = 7.8 Hz), 4.96 (1H, d, J = 9.4 Hz), 5.43 (1H, d, J = 7.8 Hz), 5.65 (1H, d, J = 7.2 Hz), 6.05 (1H, t, J = 9.2 Hz), 6.46 (1H, s), 6.68 (1H, dd, J = 8.1, 2.3 Hz), 6.97 (1H, d, J = 7.6 Hz), 7.04–7.06 (1H, m, Ar), 7.24 (1H, t, J = 7.9 Hz), 7.48–7.74 (6H, m, Ar, overlapped), 7.99–8.04 (2H, m, Ar), 8.09–8.14 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 9.1, 13.2, 19.4, 21.1, 22.2, 25.5, 25.7, 34.8, 35.1, 36.1, 43.2, 46.5, 57.5, 57.8, 70.5, 70.9, 73.8, 74.9, 75.4, 76.1, 77.7, 80.8, 84.8, 114.0, 114.9, 118.5, 127.4, 128.1, 128.5, 129.4, 129.8, 129.9, 131.3, 133.2, 133.4, 134.2, 139.9, 140.9, 157.5, 166.3, 169.3, 169.9, 173.0, 173.2, 203.9; HRFABMS m/z 942.3602 [M+H$^+$]; calcd for $C_{50}H_{56}NO_{17}$, 942.3548.

4.15.7. Macrocyclic taxoid 2c. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (3H, s), 1.31 (3H, s), 1.72 (3H, s), 1.82 (1H, s), 1.86 (3H, d, J = 1.0 Hz), 1.87–2.25 (6H, overlapped), 2.27 (3H, s), 2.42–2.78 (6H, overlapped), 3.77 (1H, d, J = 7.1 Hz), 3.93 (1H, d, J = 6.8 Hz), 4.25 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 8.4 Hz), 4.40 (1H, m), 4.58 (1H, br t, J = 6.1 Hz), 4.82 (1H, dd, J = 9.6, 1.9 Hz), 5.64 (1H, dd, J = 7.9, 5.5 Hz), 5.71 (1H, d, J = 7.1 Hz), 6.20 (1H, t, J = 9.2 Hz), 6.29 (1H, s), 7.00 (1H, d, J = 7.9 Hz), 7.14–7.21 (2H, m, Ar, overlapped), 7.30–7.34 (1H, m, Ar), 7.41–7.72 (7H, m, Ar, overlapped), 7.80–7.87 (2H, m, Ar), 8.13–8.19 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 14.4, 20.8, 22.5, 25.1, 26.2, 27.1, 35.0, 35.6, 43.3, 45.8, 56.1, 58.6, 71.6, 72.2, 75.1, 75.5, 76.7, 79.2, 81.6, 84.9, 119.6, 121.2, 124.4, 127.2, 128.7, 128.8, 129.2, 130.2, 130.7, 132.1,

132.7, 133.5, 133.8, 139.8, 142.6, 151.6, 167.0, 168.2, 171.3, 172.4, 172.7, 203.5; HRFABMS *m/z* 938.3671 [M+H$^+$]; calcd for $C_{51}H_{56}NO_{16}$, 938.3599.

4.15.8. Macrocyclic taxoid 36c. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (3H, s), 1.30 (3H, s), 1.43 (3H, d, J = 1.1 Hz), 1.68 (3H, s), 1.81 (1H, s), 1.86–2.32 (9H, overlapped), 2.50–2.77 (6H, overlapped), 3.65 (1H, d, J = 7.2 Hz), 4.21 (1H, d, J = 8.6 Hz), 4.33 (1H, d, J = 8.6 Hz), 4.39 (1H, m), 4.93 (1H, dd, J = 9.5, 1.9 Hz), 5.66 (1H, d, J = 7.2 Hz), 5.84 (1H, d, J = 3.5 Hz), 5.94 (1H, dd, J = 9.5, 3.5 Hz), 6.14 (1H, s), 6.36 (1H, t, J = 9.1 Hz), 6.42 (1H, br s), 6.81–6.85 (1H, m, Ar), 6.94–6.98 (1H, m, Ar), 7.07–7.10 (1H, m, Ar), 7.24 (1H, t, J = 8.4 Hz), 7.48–7.68 (7H, m, Ar, overlapped), 7.88–7.93 (2H, m, Ar), 8.06–8.11 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.8, 13.9, 20.8, 22.6, 22.9, 23.0, 27.1, 32.6, 33.7, 35.4, 36.0, 43.2, 45.4, 53.5, 58.3, 71.8, 73.0, 74.2, 75.3, 75.4, 76.3, 79.6, 81.5, 84.5, 114.2, 115.8, 118.4, 127.1, 128.6, 128.9, 129.2, 130.0, 130.2, 132.3, 132.7, 133.3, 133.8, 138.4, 142.1, 156.5, 166.5, 167.0, 169.7, 171.3, 171.4, 172.4, 203.5; HRFABMS *m/z* 938.3608 [M+H$^+$]; calcd for $C_{51}H_{56}NO_{16}$, 938.3599.

4.15.9. 4-Deacetyl-4-(5-carboxypentanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-paclitaxel (37c). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.18 (3H, s), 1.20 (3H, s), 1.69 (3H, s), 1.70–2.04 (9H, overlapped), 2.20 (3H, s), 2.21–2.74 (6H, overlapped), 3.86 (1H, d, J = 7.2 Hz), 4.22 (2H, br s), 4.37 (1H, dd, J = 10.8, 6.6 Hz), 4.72 (1H, d, J = 5.8 Hz), 4.97 (1H, br d, J = 9.0 Hz), 5.54 (1H, d, J = 5.8 Hz), 5.68 (1H, d, J = 7.2 Hz), 6.17 (1H, t, J = 9.2 Hz), 6.48 (1H, s), 6.71–6.77 (1H, m, Ar), 6.96–7.02 (2H, m, Ar, overlapped), 7.27 (1H, t, J = 8.0 Hz), 7.46–7.74 (6H, m, Ar, overlapped), 7.89–7.95 (2H, m, Ar), 8.11–8.16 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 9.1, 13.2, 19.4, 21.1, 24.8, 24.9, 25.6, 35.1, 35.3, 36.1, 36.2, 43.2, 46.5, 56.5, 57.8, 70.8, 70.9, 73.3, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.2, 114.7, 118.2, 127.2, 128.1, 128.4, 129.4, 129.8, 130.0, 131.4, 133.2, 133.5, 134.3, 140.1, 140.8, 157.5, 166.3, 168.9, 169.9, 172.9, 173.2, 203.8; HRFABMS *m/z* 956.3688 [M+H$^+$]; calcd for $C_{51}H_{58}NO_{17}$, 956.3705.

4.15.10. Macrocyclic taxoid 2d. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (3H, s), 1.31 (3H, s), 1.68–1.75 (5H, overlapped), 1.85 (3H, s), 1.86–2.10 (6H, overlapped), 2.21–2.39 (5H, overlapped), 2.52–2.81 (6H, overlapped), 3.80 (1H, d, J = 7.2 Hz), 3.85 (1H, br s), 4.26 (1H, d, J = 8.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.45 (1H, m), 4.64 (1H, d, J = 2.6 Hz), 4.90 (1H, dd, J = 9.4, 1.7 Hz), 5.70–5.77 (2H, overlapped), 6.20 (1H, t, J = 9.1 Hz), 6.30 (1H, s), 7.10–7.20 (3H, m, Ar, overlapped), 7.33 (1H, d, J = 8.1 Hz), 7.43–7.50 (3H, m, Ar, overlapped), 7.52–7.60 (3H, m, Ar, overlapped), 7.63–7.70 (1H, m, Ar), 7.78–7.83 (2H, m, Ar), 8.12–8.18 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 14.4, 20.9, 22.5, 24.9, 25.2, 27.0, 28.3, 34.5, 35.6, 35.7, 35.9, 43.4, 45.6, 55.1, 58.5, 72.1, 72.5, 74.1, 75.1, 75.5, 76.5, 79.2, 81.5, 84.8, 120.1, 121.7, 123.7, 127.1, 128.7, 128.8, 129.2, 130.1, 130.4, 132.1, 133.0, 133.6, 133.8, 140.1, 142.3, 151.4, 166.9, 167.7, 171.3, 172.4, 172.5, 172.9, 203.6; HRFABMS *m/z* 952.3754 [M+H$^+$]; calcd for $C_{52}H_{58}NO_{16}$, 952.3756.

4.15.11. 4-Deacetyl-4-(6-carboxyhexanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-paclitaxel (37d). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.19 (3H, s), 1.21 (3H, s), 1.37–1.51 (2H, m), 1.62–1.75 (5H, overlapped), 1.76–1.90 (3H, overlapped), 1.95 (3H, d, J = 1.0 Hz), 2.02–2.11 (1H, m), 2.16–2.32 (6H, overlapped), 2.45–2.59 (2H, overlapped), 2.62–2.72 (1H, m), 3.86 (1H, d, J = 7.2 Hz), 4.22 (2H, br s), 4.37 (1H, dd, J = 10.8, 6.6 Hz), 4.74 (1H, d, J = 5.4 Hz), 4.95 (1H, d, J = 9.3 Hz), 5.58 (1H, d, J = 5.4 Hz), 5.68 (1H, d, J = 7.2 Hz), 6.20 (1H, t, J = 9.3 Hz), 6.48 (1H, s), 6.75–6.79 (1H, m, Ar), 6.97–7.02 (2H, m, Ar, overlapped), 7.27 (1H, t, J = 8.3 Hz), 7.46–7.52 (2H, m, Ar, overlapped), 7.54–7.59 (1H, m, Ar), 7.59–7.66 (2H, m, Ar), 7.67–7.74 (1H, m, Ar), 7.89–7.94 (2H, m, Ar), 8.12–8.18 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 9.1, 13.3, 19.4, 21.1, 24.8, 25.3, 25.6, 28.5, 34.9, 35.2, 36.1, 36.2, 43.2, 46.6, 56.2, 57.9, 70.9, 73.0, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.0, 114.6, 118.2, 127.2, 128.1, 128.4, 129.4, 129.8, 130.0, 131.4, 133.2, 133.4, 134.3, 140.2, 140.9, 157.6, 166.3, 169.5, 169.9, 173.0, 173.3, 174.1, 203.8; HRFABMS *m/z* 970.3882 [M+H$^+$]; calcd for $C_{52}H_{60}NO_{17}$, 970.3861.

4.15.12. Macrocyclic taxoid 2e. Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (3H, s), 1.28 (3H, s), 1.60–2.10 (16H, overlapped), 2.26 (3H, s), 2.30–2.64 (5H, overlapped), 2.70–2.87 (2H, overlapped), 3.79 (1H, d, J = 3.8 Hz), 3.88 (1H, J = 7.0 Hz), 4.26 (1H, d, J = 8.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.45 (1H, m), 4.67 (1H, br s), 4.87 (1H, dd, J = 9.4, 1.8 Hz), 5.70–5.77 (2H, overlapped), 6.21 (1H, t, J = 8.9 Hz), 6.32 (1H, s), 7.05–7.15 (3H, m, Ar, overlapped), 7.37–7.69 (8H, m, Ar, overlapped), 7.74–7.80 (2H, m, Ar), 8.13–8.19 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.6, 14.7, 20.9, 22.1, 24.9, 26.6, 26.9, 28.5, 29.2, 34.6, 35.6, 35.7, 36.3, 43.3, 45.6, 54.8, 58.6, 72.1, 72.8, 73.4, 75.0, 75.6, 76.5, 78.9, 81.3, 84.8, 120.2, 121.7, 124.1, 127.1, 127.7, 128.8, 129.2, 130.2, 130.3, 132.0, 133.1, 133.7, 133.8, 140.1, 142.1, 151.1, 166.9, 167.3, 171.3, 172.6, 172.9, 173.2, 203.6; HRFABMS *m/z* 966.3860 [M+H$^+$]; calcd for $C_{53}H_{60}NO_{16}$, 966.3912.

4.15.13. 4-Deacetyl-4-(7-carboxyheptanoyl)-3′-desphenyl-3′-(*m*-hydroxyphenyl)-paclitaxel (37e). Colorless gum; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.19 (3H, s), 1.21 (3H, s), 1.31–1.42 (4H, overlapped), 1.52–1.64 (2H, m), 1.70 (3H, s), 1.72–1.92 (3H, overlapped), 1.96 (3H, d, J = 1.1 Hz), 2.12–2.29 (6H, overlapped), 2.32–2.40 (1H, m), 2.46–2.60 (2H, overlapped), 2.68–2.77 (1H, m), 3.88 (1H, d, J = 7.1 Hz), 4.21 (1H, d, J = 8.3 Hz), 4.25 (1H, d, J = 8.3 Hz), 4.37 (1H, dd, J = 10.9, 6.5 Hz), 4.80 (1H, d, J = 4.4 Hz), 4.94 (1H, d, J = 9.6 Hz), 5.65 (1H, d, J = 4.4 Hz), 5.69 (1H, d, J = 7.1 Hz), 6.22 (1H, t, J = 9.1 Hz), 6.50 (1H, s), 6.76–6.81 (1H, m, Ar), 6.98–7.05 (2H, m, Ar, overlapped), 7.28 (1H, t, J = 8.0 Hz), 7.45–7.73 (6H, m, Ar, overlapped), 7.86–7.91 (2H, m, Ar), 8.14–8.20 (2H, m, Ar); ^{13}C NMR (100 MHz, CD_3OD) δ: 9.1, 13.3, 19.4, 21.0, 25.0, 25.1, 25.6, 28.4, 28.7, 35.3, 35.4, 35.5, 36.2, 43.3,

46.6, 55.7, 57.9, 70.9, 71.1, 72.8, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.1, 114.5, 118.1, 127.1, 128.2, 128.4, 129.4, 129.8, 130.0, 131.4, 133.2, 133.5, 134.3, 140.1, 140.8, 157.5, 166.3, 168.9, 169.9, 173.0, 173.3, 203.8; HRFABMS *m/z* 984.3974 [M+H$^+$]; calcd for $C_{53}H_{62}NO_{17}$, 984.4018.

4.16. Cytotoxicity bioassay

The A2780 ovarian cancer cell line assay was performed at Virginia Polytechnic Institute and State University as previously reported.[26]

4.17. Tubulin Assembly Bioassay

Tubulin polymerization bioassays were carried out as previously described.[27]

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