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Structure–Activity Relationship Study of Taxoids for Their Ability to Activate Murine Macrophages as well as Inhibit the Growth of Macrophage-like Cells

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Abstract—A series of new taxoids modified at the C-3′, C-3′*N*, C-10, C-2 and C-7 positions has been designed, synthesized and evaluated for their potency to induce NO and TNF production by peritoneal murine macrophages (Mϕ) from LPS-responsive C3H/HeN and LPS-hyporesponsive C3H/HeJ strains and human blood cells, and for their ability to inhibit the growth of Mϕ-like cell lines J774.1 and J7.DEF3. The SAR-study has shown that the nature of the substituents at these positions have critical effect on the induction of TNF and NO production by Mϕ. Positions C-3′ and C-10 are the most flexible and an intriguing effect of the length of the substituents at the C-10 position is observed for taxoids bearing a straight chain alkanoyl moiety. An aromatic group at the C-3′*N* and C-2 positions is required for the activity, while only hydroxyl or acetyl substituents seem to be tolerated at the C-7 position. The natural stereochemistry in the C-13 isoserine side chain of the taxoids is an absolute requirement for macrophage activation. It has also been clearly shown that there is no correlation between the ability of the taxoids to induce TNF/NO production in C3H/HeN Mϕ and the cytotoxicity against Mϕ-like cells.

Introduction

Taxol® (paclitaxel), a complex diterpene isolated from the bark of *Taxus brevifolia*,[1] is currently considered one of the most important drugs in cancer chemotherapy (Fig. 1). Paclitaxel has been approved by the FDA for treatment of various human tumors such as metastatic breast cancer, advanced ovarian cancer, and Kaposi's sarcoma.[2–4] Paclitaxel is currently undergoing clinical trials worldwide for the treatment of other cancers (e.g., lung, head and neck, prostate, and cervical cancers) as well as in combination with other anticancer agents. Paclitaxel's antimitotic activity is due to its ability to bind to the β-subunit of tubulin and cause tubulin polymerization.[5,6] As a result, stable bundles of microtubules are formed within cells and mitosis is blocked at the metaphase/anaphase transition step.

It has been shown that paclitaxel can mimic several biological activities of bacterial lipopolysaccharides (LPS).[7–11] In fact, paclitaxel induces the expression of the same six cytokine genes which are expressed by LPS, in particular that of the mediator Tumor Necrosis Factor α (TNF-α). Like LPS, paclitaxel decreases the surface expression of the TNF-α receptor; it causes tyrosine phosphorylation of microtubule-associated protein kinases; and it enhances γ-interferon induction of NO synthase and the secretion of NO.

These effects are observed only in LPS-responsive C3H/HeN murine macrophages (Mϕ), bearing the *Lps*^{n} gene, but not in LPS-hyporesponsive C3H/HeJ Mϕ, bearing the mutated allelic form *Lps*^{d} of the gene, suggesting the existence of a common signalling pathway for both paclitaxel and LPS.[7–9] Ding and co-workers have shown that like paclitaxel, LPS is capable of binding to the β-subunit of tubulin, as well as to microtubule-associated proteins (MAPs).[12] Since paclitaxel can equally block cell proliferation of C3H/HeN and C3H/HeJ bone marrow cells in vitro, the β-subunit of tubulin does not

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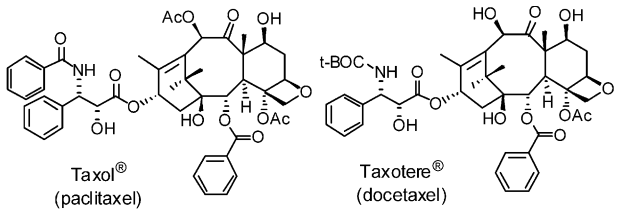


Figure 1. Taxol® (paclitaxel) and Taxotere® (docetaxel).

seem to be the cellular target shared by paclitaxel and LPS. At the same time, the LPS-like activity of paclitaxel appears to be totally unrelated to its microtubule assembly and cytotoxic properties. In this context, Burkhart et al. reported a SAR study of paclitaxel analogues on macrophage activation.[13]

It has been shown that Taxotere® (docetaxel), a potent semisynthetic analogue of paclitaxel, fails to stimulate TNF-α and NO production by Mϕ and to decrease the expression of TNF-R (Fig. 1).[14] This observation suggested that the structural requirements among taxoids for macrophage activation and for inhibition of cell proliferation might be totally different. Since docetaxel structurally differs from paclitaxel for the substituents at the C-10 and C-3′*N* positions, we have investigated and communicated the effect of the C-3′ and the C-3′*N* substituents and/or the acetyl group at the C-10 position, as well as the importance of the stereochemistry of the C-13 side chain on macrophage activation.[15,16] We have also communicated the effects of the substituents at the C-2 and C-7 positions on macrophage activation.[17] We describe here a full account of our study on the design, syntheses, characterization, and SAR study of new taxoids for their ability to activate murine macrophage as well as their cytotoxicity.

Results and Discussion

Syntheses of taxoids

The 'β-lactam synthon method',[18–20] developed in these laboratories, was successfully applied to the syntheses of taxoids. Enantiomerically pure (3*R*,4*S*)-3-TIPSO-4-phenylazetidin-2-one (**4a**) and its enantiomer (3*S*,4*R*)-3-TIPSO-4-phenylazetidin-2-one (**4b**) (TIPS = triisopropylsilyl) were prepared through chiral ester enolate-imine cyclocondensation in high yield using (−)-*trans*-2-phenylcyclohexanol and (+)-*trans*-2-phenylcyclohexanol,[21] respectively. Introduction of a benzoyl or a *tert*-butoxycarbonyl (*t*-Boc) moiety to **4a** and **4b** provided the C-13 phenylisoserine side-chain precursors for paclitaxel, *epi*-paclitaxel, and 10-acetyldocetaxel, that is *N*-acyl-β-lactams **5a**, **5b**, and **6** (Scheme 1). The β-lactam **5b** having (3*S*,4*R*) stereochemistry at the C-3 and C-4 positions was prepared for the synthesis of taxoids with unnatural configurations at the C-13 side chain (i.e., *epi*-taxoids).

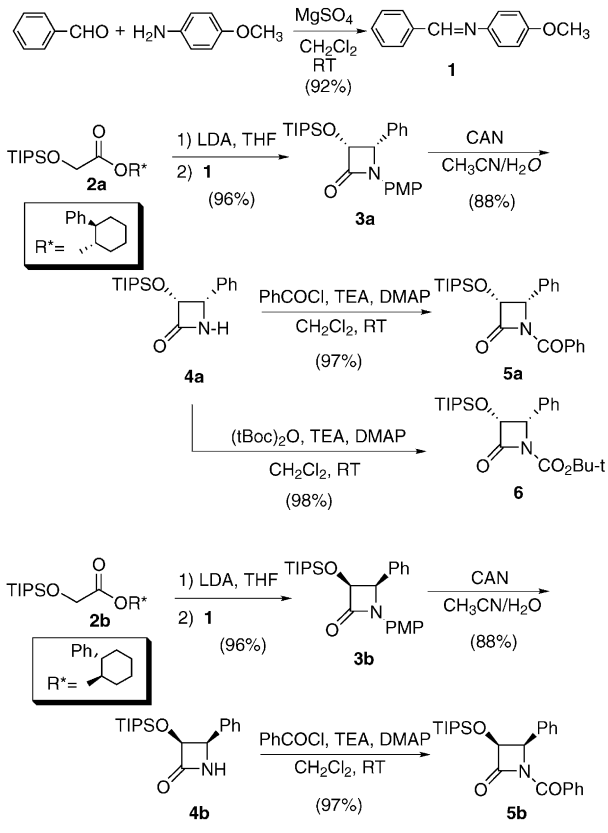
β-Lactams **10a** and **10b**, bearing a 2-methylprop-1-enyl moiety at the C-4 position and a benzoyl or a *t*-Boc group at the *N*-1 position, respectively, were prepared following the procedure reported by these laboratories (Scheme 2).[22–24]

Several 7-TES-protected baccatins (TES = triethylsilyl) modified at the C-10 position have been synthesized starting from 10-deacetylbaccatin III (DAB), following the literature methods with minor modifications (Scheme 3).[25,26] DAB was first protected at the C-7 hydroxyl group as a TES ether.[27] Then, the C-10 position was modified using various acid chlorides in the presence of lithium hexamethyldisilazide (LiHMDS) as the base to give baccatins **12a–j**.[25,26]

Taxoid **13a**, modified at the C-3′ position,[28] and taxoid **13b**, modified at both the C-3′ and C-3′*N* positions,[29] were obtained by coupling 7-TES-DAB with β-lactams **10a** and **10b**, respectively, using LiHMDS as the base, followed by deprotection with HF/pyridine (Scheme 4).

The C-3′*N*-modified paclitaxel analogues (**17a–q**) were prepared by acylation of 3′-*N*-debenzoylpaclitaxel (**16**) with various acid chlorides under the standard Schotten–Baumann conditions in good to excellent yields (Scheme 5, Table 1). 3′-*N*-Debenzoylpaclitaxel (**16**) was prepared through removal of the *t*-Boc group from 10-acetyldocetaxel (**14**), which was prepared in accordance with the literature method[30–32] with minor modification by coupling 7-TES-DAB with **6** followed by deprotection with HF/pyridine (Scheme 5).

As Scheme 6 shows, C-10 modified baccatins **12a**,**b**, **12d–g** and **12i**,**j** were coupled with β-lactam **5a** to afford,

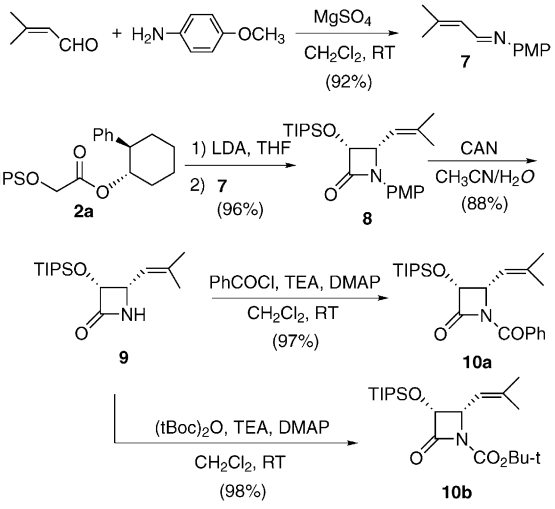


Scheme 1.

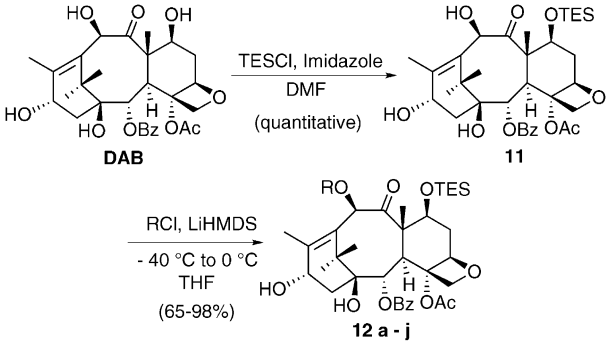
upon deprotection with HF-pyridine, taxoids **18a**,**b**, **18d–g** and **18i**,**j** that bear an *N*-benzoylphenylisoserine with natural stereochemistry, (2′*R*,3′*S*), as the C-13 side chain. In the same manner, baccatins **12c**,**d** were coupled with both β-lactams **5a** and **5b** to give taxoids **18c**,**d** and **18c′**,**d′**, while baccatin **12h** was coupled only with β-lactam **5b** to give taxoid **18h′**. Taxoids **18c′**, **18d′**, and **18h′** bear a paclitaxel side chain with unnatural stereochemistry, (2′*S*,3′*R*), at the C-13 position. Results are summarized in Table 2.

Hydrogenation of taxoid **18f**, bearing a crotonyl group, over palladium on carbon (Pd/C) in methanol afforded taxoid **18k** with a butanoyl substituent at the C-10 position in 98% yield (Scheme 7).

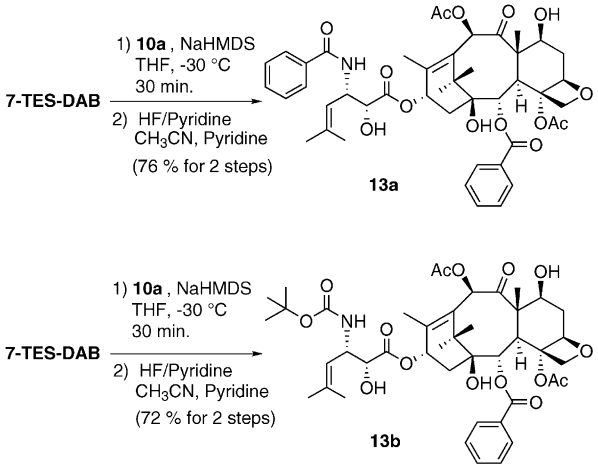
Two different approaches were used for the preparation of the C-2 modified paclitaxel analogues. The first method (Scheme 8) involved the oxidation of the C-13 hydroxyl group of 7-TES-DAB (**11**) by using tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) to afford 13-oxo-7-TES-DAB **19** in 98% yield.[33,34] Acetylation of the C-10 hydroxyl group with acetic anhydride provided 13-oxo-7-TES-baccatin III (**20**) in 95% yield. Treatment of **20** with Red-Al, that is sodium bis(2-methoxyethoxy)-aluminum hydride, led to the removal of the benzoyl substituent at the C-2 position, affording diol **21** in 75% yield. Modification of the C-2 position by either DCC-DMAP coupling with 3,3-dimethylacrylic acid or acetylation using acetic anhydride afforded baccatins **22a** and **22b** in good yields. The $NaBH_4$ reduction of the C-13 position gave the C-2 modified baccatins **23a** and **23b**.[29] Coupling of these intermediates with β-lactam **5a**, followed by deprotection with HF/pyridine afforded the taxoids **24a** and **24b**.



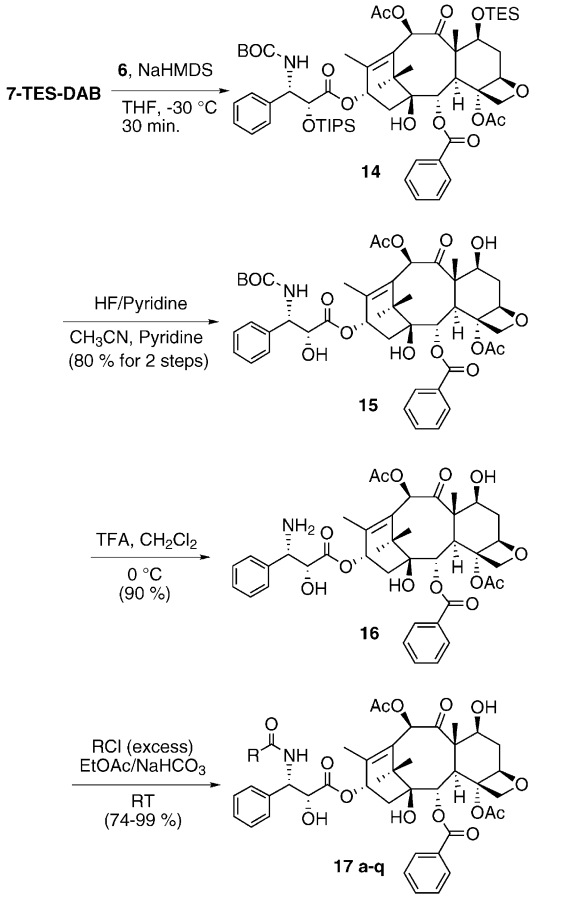
Scheme 2.



Scheme 3.

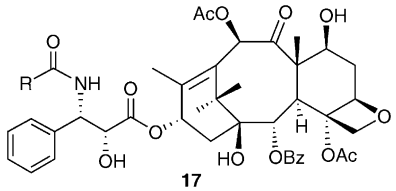


Scheme 4.

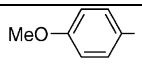
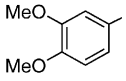
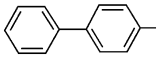
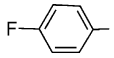
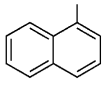
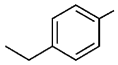
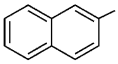
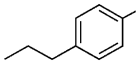
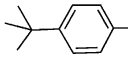
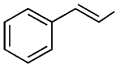
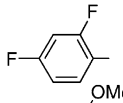
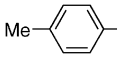
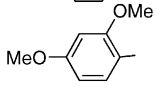
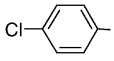


Scheme 5.

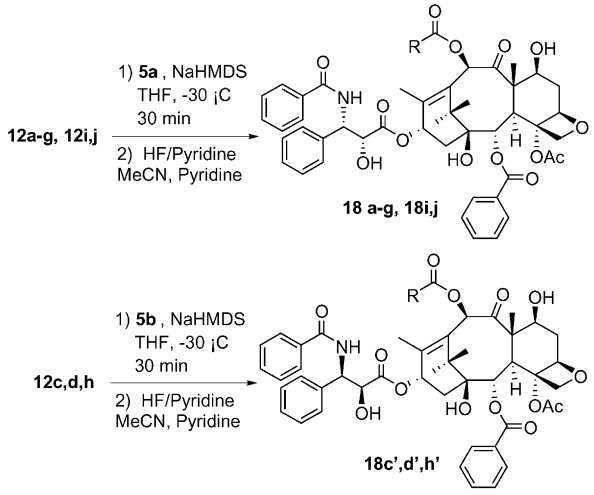
Table 1. Synthesis of taxoids **17**



17

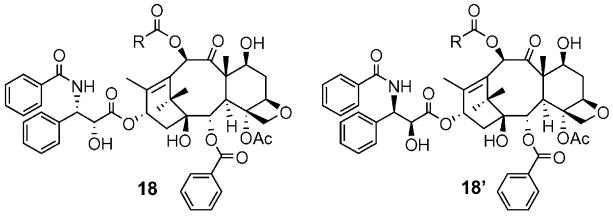
Taxoid		Yield (%)	Taxoid		Yield (%)
17a		74	**17j**		96
17b		82	**17k**		78
17c		77	**17l**		95
17d		90	**17m**		95
17e		99	**17n**		95
17f		83	**17o**		87
17g		78	**17p**		88
17h		89	**17q**		97
17i		81			

The second approach to the synthesis of the C-2 modified analogues (Schemes 9 and 10) involved Tri-TES-DAB 25 as a key intermediate, which was obtained in 95% yield by reacting DAB with an excess of TES-Cl.[35] Baccatin **25** was treated with Red-Al to remove the benzoyl group at the C-2 position, affording diol **26** in 95% yield. Esterification of **26** at the C-2 position by DCC-DMAP coupling using various carboxylic acids yielded baccatins **27a**,**b** in good yields. The three TES-protecting groups were removed by treatment with HF/pyridine, leading to tetraols **28a**,**b** (Scheme 9).



Scheme 6.

Table 2. Synthesis of taxoids **18** and **18′**



18 **18'**

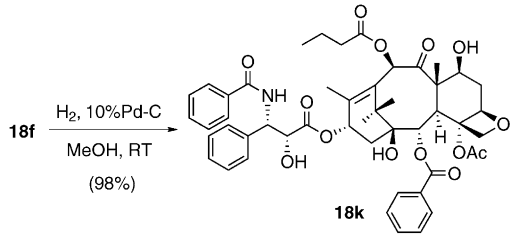
Taxoid	R	Two-step yield (%)
18a	CH_3CH_2CO	54
18b	$CH_3(CH_2)_4CO$	50
18c	$CH_3(CH_2)_{10}CO$	48
18c′		47
18d	$CH_3(CH_2)_{12}CO$	49
18d′		45
18e	Cyclohexanoyl	52
18f	$CH_3CH{=}CHCO$	48
18g	PhCO	46
18h	$PhCH_2CO$	40
18i	$(CH_3)_2N{-}CO$	55
18j	Morpholine	55

Selective protection of the C-7 position with TES-Cl and acetylation of the C-10 position gave **30a**,**b**, which were coupled with β-lactam **5a** and/or **5b**. The resulting coupling products afforded, upon deprotection with HF/pyridine, taxoids **31a**,**b** and **31a′**,**b′** (Scheme 10). The second approach to the preparation of the C-2 modified taxoids (Schemes 9 and 10) was preferable over the first one (Scheme 8) in the case of the cinnamoyl group since the $NaBH_4$ reduction of the C-13 keto intermediate **22c** (R = –CH = CH–Ph) resulted in the partial reduction of the double bond of this particular moiety.

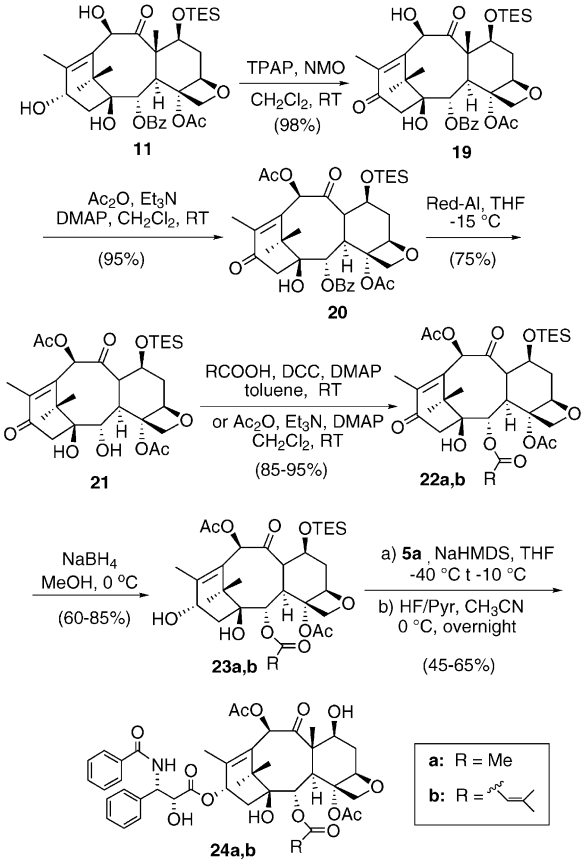
Taxoids **24b**, **31a**,**b** and **31a′** were subjected to hydrogenation over 10% Pd/C in MeOH, to afford the corresponding taxoids **32**, **33a**,**b** and **33a′**, bearing saturated alkanoate groups at the C-2 position, in near-quantitative yield (Scheme 11).

Taxoid **35**, bearing a cyclohexanoyl group at the C-2 position, was synthesized through the coupling of β-lactam **5a** with 2-debenzoyl-2-cyclohexanecabonyl-7-TES-baccatin (**34**), which was prepared by the method reported by Boge et al.,[36] followed by deprotection using HF/pyridine (Scheme 12).

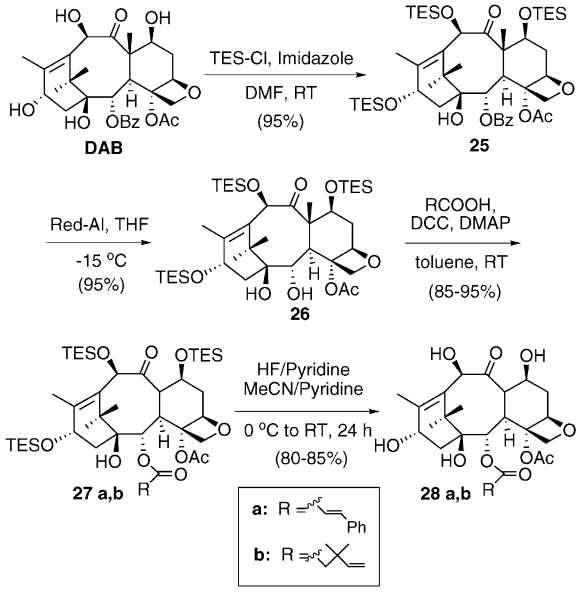
Scheme 13 illustrates the synthesis of the C-7 modified taxoids **38** and **41**. 7-TES-DAB was coupled with β-lactams **5a** and **5b** in the presence of NaHMDS as the base to give coupling products **36** and **39**, respectively (Scheme 13). The TES protecting group at the C-7 position was selectively removed by treatment with 0.1N HCl in EtOH, giving **37** and **40**. Under these reaction conditions, the TIPS protecting group at the C-2′ position



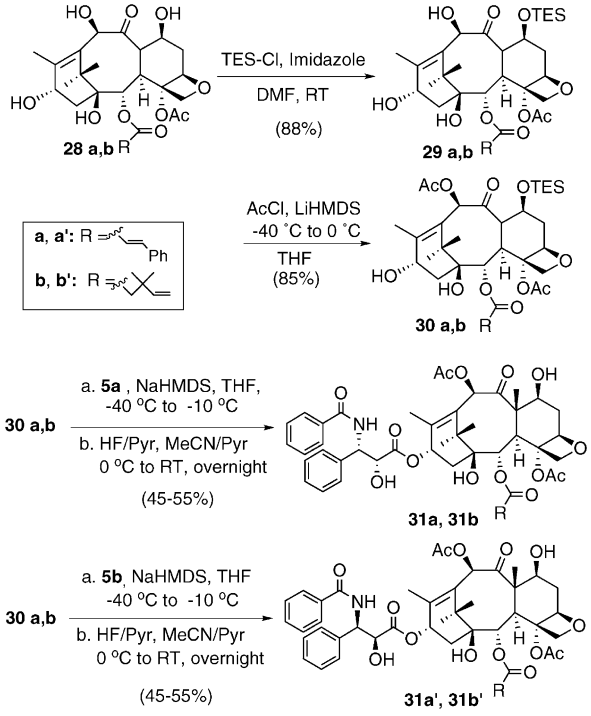
Scheme 7.



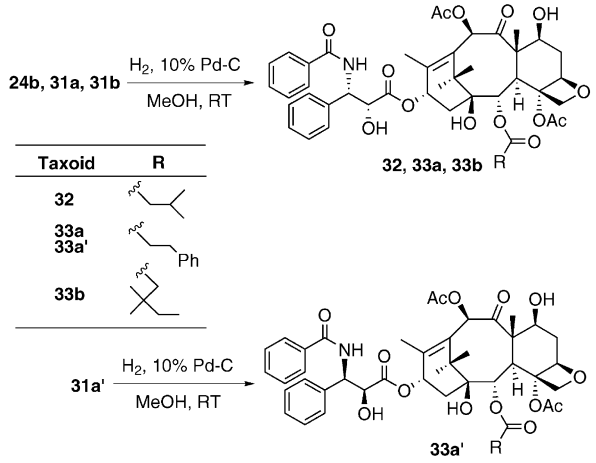
Scheme 8.



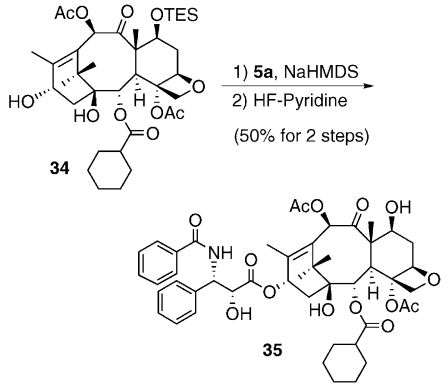
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

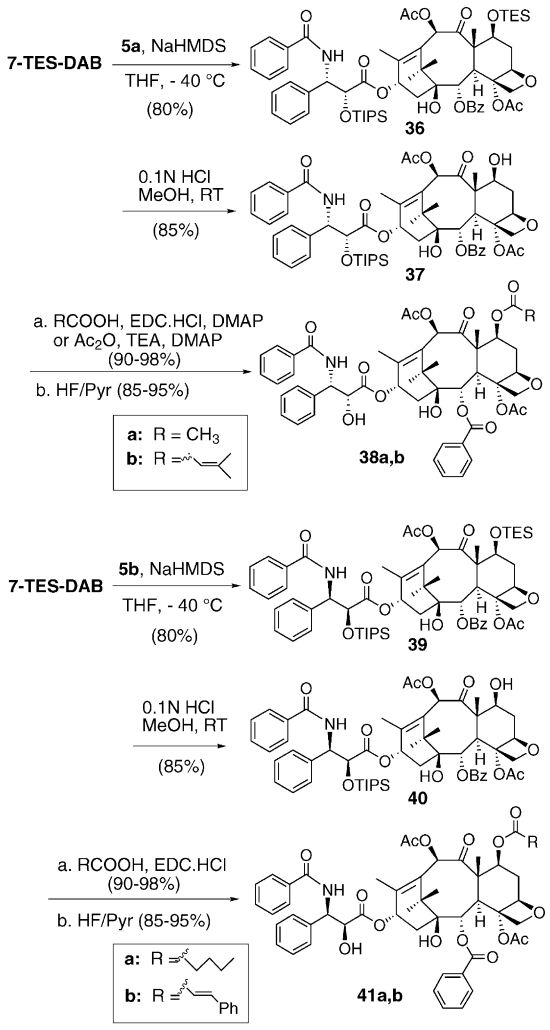
was not removed. 2′-TIPS-taxoids **37** and **40** were then modified at the C-7 position by reaction with acetic anhydride, triethylamine (TEA) and DMAP or with various carboxylic acids in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC·HCl) and DMAP. Deprotection of the C-2′ position with HF/pyridine afforded taxoids **38a**,**b** and **41a**,**b**. As Scheme 14 shows, taxoid **38c** was prepared in 96% yield by hydrogenation of **38b** over 10% Pd/C in MeOH.

Biological activity of taxoids

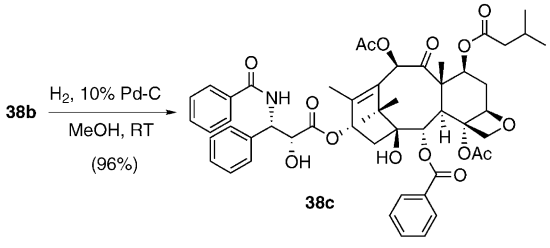
Paclitaxel and its analogues were evaluated for their potency to induce NO and TNF production by peritoneal Mϕ from LPS-responsive C3H/HeN strains, and for their cytotoxicity to inhibit the growth of Mϕ-like cell lines J774.1 and J7.DEF3. The results are shown in Tables 3–7.

NO and TNF production by peritoneal Mϕ stimulated by taxoids. A series of paclitaxel analogues (**13a**,**b**, **15**, **17a**–**g**), modified at the C-3′ and C-3′*N* positions and/or at the C-10 position, was evaluated for their ability to induce NO and TNF production by LPS-responsive C3H/HeN peritoneal Mϕ (Table 3).

This SAR study shows that the benzoylamino group at the C-3′ position of paclitaxel is an extremely crucial site



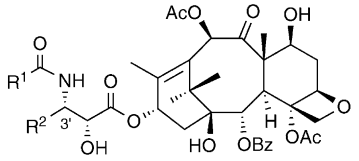
Scheme 13.

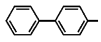
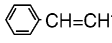


Scheme 14.

for the activation of macrophages, while a phenyl group at the C-3′ position is not strictly required for the activity. This is clearly represented by the cases of taxoids **13a** and **13b**, both bearing a 2-methylpropenyl moiety at the C-3′ position. While taxoid **13a**, having a benzoyl group at the C3′-*N* position, retains the activity, taxoid **13b** carrying a *t*-Boc group at the same position is totally inactive. The acetyl moiety at the C-10 position was also found to have a certain effect on macrophage activation. For example, 10-acetyldocetaxel (**15**) was found to induce the production of both TNF and NO by Mϕ, albeit at much lower levels as compared to paclitaxel, while docetaxel is totally inactive, as reported by Manthey et al.[8] A good

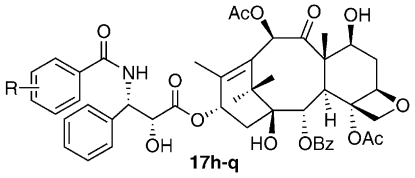
Table 3. Biological activities of taxoids **13**, **15**, and **17a–g**



Taxoid	R^1	R^2	Macrophage activation		Cytotoxicity (IC_{50}, nM)[b]	
			NO	TNF	J774.1	J7.DEF3
Paclitaxel			+ + + +[a]	+ + + +	33	30
13a		$CH{=}C(CH_3)_2$	+ + +	+ + +	0.042	0.061
13b	$(CH_3)_3CO$	$CH{=}C(CH_3)_2$	–	–	0.045	0.088
15	$(CH_3)_3CO$		+	+	5.8	7.3
17a			+	+ +	2.0	16
17b			–	–	5.0	200
17c			–	–	49	140
17d			+ + + +	+ + + +	67	370
17e			+	–	21	55
17f			+ + +	+ + +	77	48
17g			–	–	30	77

[a]The minimal concentration of compounds to induce 4 μM of formation or 20 U/mL of TNF secretion which were semiquantitatively estimated from those dose–response curves from three independent experiments for NO formation and two independent experiments as follows: + + + +: Š3.8 μM, + + +: > 7.5 μM, + +: > 15 μM or compounds which induced less but significant amounts of NO formation (1–4 μM) or TNF secretion (10–20 U/mL) at any concentration, –: > 30 μM.
[b]The concentration of compounds which inhibited 50% (IC_{50}) of the growth of J774.1 cells and J7.DEF3 cells, after 72 h incubation with compounds. The data represent the mean values of three independent experiments.

Table 4. Potency of taxoids **17h–q** to induce NO/TNF production

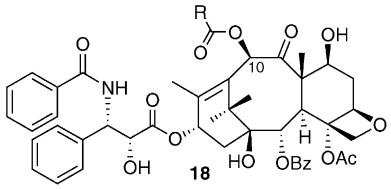


17h-q

Taxoid	R	Macrophage activation C3H/He Mϕ		Cytotoxicity (IC_{50}, nM)[b]	
		NO	TNF	J774.1	J7.DEF3
Paclitaxel	H[a]	+ + + +	+ + + +	33	30
17h	4-CH_3	+ + + + +	+ + + + +	17	15
17i	4-Cl	+ + + +	+ + + + +	30	26
17j	4-CH_3O	+ + + +	+ + + +	59	37
17k	3,4-$(CH_3O)_2$	+ +	+ +	62	58
17l	4-F	+ + + +	+ + + + +	21	17
17m	4-CH_3CH_2	+ + +	+ + + +	15	14
17n	4-$CH_3CH_2CH_2$	+	–	18	17
17o	4-Bu-*t*	–	–	24	25
17p	2,4-F_2	+ + + +	+ + + +	26	25
17q	2,4-$(CH_3O)_2$	–	–	76	83

[a]The minimal concentration of compounds to induce 4 μM of formation or 20 U/mL of TNF secretion which were semiquantitatively estimated from those dose–response curves from three independent experiments for NO formation and two independent experiments as follows: + + + +:, Š3.8 μM, + + +: □ 7.5 μM, + +: □ 15 μM or compounds which induced less but significant amounts of NO formation (1–4 μM) or TNF secretion (10–20 U/mL) at any concentration, –: > 30 μM.
[b]The concentration of compounds which inhibited 50% (IC_{50}) of the growth of J774.1 cells and J7.DEF3 cells, after 72 h incubation with compounds. The data represent the mean values of three independent experiments.

Table 5. Potency of taxoids **18** to induce NO/TNF production

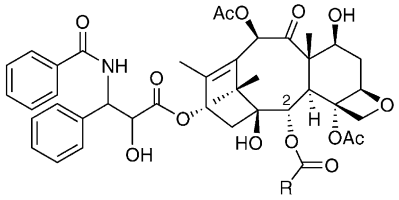


18

Taxoid	R	Macrophage activation C3H/He Mϕ		Cytotoxicity (IC_{50}, nM)[b]	
		NO	TNF	J774.1	J7.DEF3
Paclitaxel	CH_3[a]	+ + + +	+ + + + +	33	30
18a	CH_2CH_3	+ +	+ + +	39	37
18k	$(CH_2)_2CH_3$	+	+ +	43	36
18b	$(CH_2)_4CH_3$	+ + + +	+ + + + + +	35	32
18c	$(CH_2)_{10}CH_3$	+ + + + +	+ + + + + +	622	443
18d	$(CH_2)_{12}CH_3$	+	+	> 1000	> 1000
18e	Cyclohexyl	–	–	41	35
18f	$CH=CHCH_3$	–	+ + +	15	28
18g	Ph	+ + +	+ + + + +	26	32
18i	$N(CH_3)_2$	–	–	27	30
18j	N-morpholine	–	–	41	45
18c′	$(CH_2)_{10}CH_3$	–	–	> 1000	> 1000
18d′	$(CH_2)_{12}CH_3$	–	–	> 1000	> 1000
18h′	CH_2Ph	–	–	> 1000	> 1000

[a]Symbols + + + + + + to + + indicate the minimal concentration of taxoids to induce significant amounts of NO (> 4 μM) or TNF (> 20 U/mL): + + + + + + < 0.9 μM, + + + + + < 1.9 μM, + + + + < 3.8 μM, + + + < 7.5 μM, + + < 15 μM, + < 30 μM or compound which induce less but significant amount of NO (1–4 mM) or TNF (10–20 U/mL); –indicates the potency of taxoids to induce no significant NO (< 1 μM) or TNF (< 10 U/mL).
[b]The concentration of taxoids to inhibit 50% (IC_{50}) of growth of J774.1 cells and J7.DEF3 cells at 72 h of incubation. The data represent the mean values of three independent experiments.

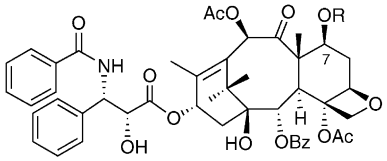
Table 6. Potency of taxoids **24**, **31**–**33**, **35** to induce NO/TNF production



Taxoid	R	Macrophage activation C3H/He Mϕ		Cytotoxicity (IC^{50}, nM)[b]	
		NO	TNF	J774.1	J7.DEF3
Paclitaxel	Ph[a]	+ + + +	+ + + + +	33	30
24a	CH_3	–	–	> 1000	> 1000
24b	$(CH_3)_2C=CH^-$	–	–	394	393
31a	Ph-CH=CH$^-$	–	–	> 1000	> 1000
31b	$CH_2=CHC(CH_3)_2CH_2$	+	+	509	508
32	$(CH_3)_2CHCH_2^-$	–	–	> 1000	> 1000
33a	Ph-CH_2CH_2	–	–	> 1000	> 1000
33b	$CH_3CH_2C(CH_3)_2CH_2$	–	+	508	512
35	Cyclohexyl	–	–	339	448
31a′	Ph–CH=CH$^-$	–	–	> 1000	> 1000
31b′	$CH_2=CHC(CH_3)_2CH_2$	–	–	> 1000	> 1000
33a′	Ph–CH_2CH_2	–	–	> 1000	> 1000

[a]Symbols + + + + + to + + indicate the minimal concentration of taxoids to induce significant amounts of NO (> 4 μM) or TNF (> 20 U/mL): + + + + + < 1.9 μM, + + + + < 3.8 μM, + + + < 7.5 μM, + + < 15 μM, + < 30 μM, or compound which induce less but significant amount of NO (1–4 mM) or TNF (10–20 U/mL); –indicates the potency of taxoids to induce no significant NO (< 1 μM) or TNF (< 10 U/mL).
[b]The concentration of taxoids to inhibit 50% (IC_{50}) of growth of J774.1 cells and J7.DEF3 cells at 72 h of incubation. The data represent the mean values of three independent experiments.

Table 7. Potency of taxoids **38** and **41** to induce NO/TNF production



Taxoid	R	Macrophage activation C3H/He Mϕ		Cytotoxicity (IC_{50}, nM)[b]	
		NO	TNF	J774.1	J7.DEF3
Paclitaxel	H[a]	+ + + +	+ + + + +	33	30
38a	CH_3CO	+ + + +	+ + + + +	39	42
38b	$(CH_3)_2C{=}CHCO$	–	–	44	45
38c	$(CH_3)_2CHCH_2CO$	–	–	34	35
41a	$CH_3(CH_2)_3CO$	–	–	> 1000	> 1000
41b	Ph–CH=CH–CO	–	–	> 1000	> 1000

[a]Symbols + + + + + to + + indicate the minimal concentration of taxoids to induce significant amounts of NO (> 4 μM) or TNF (> 20 U/mL): + + + + + < 1.9 μM, + + + + < 3.8 μM, + + + < 7.5 μM, + + < 15 μM, + < 30 μM or compound which induce less but significant amount of NO (1–4 mM) or TNF (10–20 U/mL); –indicates the potency of taxoids to induce no significant NO (< 1 mM) or TNF (< 10 U/mL).
[b]The concentration of taxoids to inhibit 50% (IC_{50}) of growth of J774.1 cells and J7.DEF3 cells at 72 h of incubation. The data represent the mean values of three independent experiments.

correlation was observed, in general, between the production of TNF and that of NO by macrophages.

Since the benzoylamino group at the C-3′ position was proved to be an extremely important site for macrophage activation, a second series of paclitaxel analogues (**17h–q**) was designed and synthesized with modifications at this position in order to study the effect of modified benzoyl groups on the activity (Table 4).

In this series, taxoids **17h** and **17i**, bearing a 4-methylbenzoyl and a 4-chlorobenzoyl group at the C3′-*N* position, respectively, were found to be the most active ones, showing activity higher than that of paclitaxel. The presence of a longer or bulkier alkyl moiety than an ethyl group at the *para* position of the benzoyl group turned out not to be tolerated. When the methyl group was substituted by an *n*-propyl group (**17n**) or a *t*-butyl group (**17o**), the activity dropped dramatically.

Taxoid **17j**, bearing a methoxy group at the *para* position of the benzoyl group, was found to be much more active than taxoid **17k**, having two methoxy groups at the *para* and *meta* positions. On the other hand, taxoid **17q**, bearing two methoxy groups at the *ortho* and *para* positions, was found to be totally inactive. These findings seem to indicate that both the bulkiness and the electronic nature of the substituents on the C3′-*N* benzoyl group have significant effects on the activity. Regarding taxoid **17q**, the absence of coplanarity between the benzene ring and the amide carbonyl group due to the presence of an additional methoxy group at the *ortho* position, might be responsible for the loss of activity.

In order to study the effect of the nature of the substituents at the C-10, C-2 and C-7 positions on macrophage activation, as well as that of the stereochemistry of the C-13 side chain of paclitaxel, three other series of taxoids were prepared and their activity evaluated (Tables 5–7). Among these three positions examined, the C-10 position appeared to be more flexible than other positions, tolerating a greater diversity of functional groups (Table 5).

In the series of taxoids bearing an alkanoyl moiety at the C-10 position, a clear effect of the length of the alkyl chain on the activity was observed. While paclitaxel bearing an acetyl group at this position was significantly active, taxoids **18a** and **18k**, bearing an *n*-propanoyl and an *n*-butanoyl group respectively, showed a progressively decreased ability to induce both NO and TNF productions as compared to paclitaxel. On the other hand, when the length of the *n*-alkanoyl group at the C-10 position was further increased to **6** or even **12** carbons, the resulting taxoids **18b** and **18c** were found to be more active than paclitaxel.

These interesting results seem to suggest that a superior activity can be achieved by introducing hydrophobic alkyl moieties at this particular position of the baccatin core. It should be noted that the bacterial lipopolysaccharides (LPS), the principal activating factors of macrophages, are characterized in their complex structure by the presence of many fatty acid moieties and it is, in fact, the acylation pattern (i.e., number, nature and distribution of fatty acids) of lipid A (the endotoxic principle of LPS) that determines the ability of LPS to activate macrophages and other cells and to induce mediators release.[37] Taxoid **18c**, bearing a dodecanoyl group at the C-10 position, is the most active compound among the taxoids tested so far and thus represents the first example of a structural correlation between a taxoid and LPS. It is worth mentioning that the release of TNF by **18c** does not require an induction period in contrast with paclitaxel. The minimum inducing dose for paclitaxel is 1.9 μM, whereas that of taxoid **18c** is 0.9 μM.

On the other hand, when the alkyl chain length of the alkanoyl moiety at the C-10 position is increased to **14** carbons, the activity drops again. Analogue **18d**, bearing a tetradecanoyl group at the C-10 position, showed only a very weak ability to induce NO and TNF production. This result may indicate that there is a limit in the hydrophobicity or the size of the substituent that can be tolerated, which would be related to cell-bioavailability of taxoid **18d**.

The activity of analogue **18g**, having a benzoyl group at the C-10 position, was found to be similar to that of paclitaxel. It was found that taxoid **18f**, bearing an acryloyl moiety at the same position, was able to induce the production of TNF only, but not that of NO. Substituents such as cyclohexanoyl (**18e**), *N*,*N*-dimethylcarbamoyl (**18i**) and morpholine-*N*-carbonyl (**18j**) were not tolerated and totally suppressed the activity.

An important and interesting finding in terms of SAR study comes from the comparison of the activities of analogues **18c** and **18c′**, both bearing a dodecanoyl moiety at the C-10 position, but having different stereochemistry in the C-13 side chain. Taxoid **18c** with the natural stereochemistry was found to be more active than paclitaxel. On the contrary, analogue **18c′** having the unnatural stereochemistry in the C-13 side chain was totally inactive. This result, together with the fact that all the analogues having the unnatural stereochemistry in the C-13 side chain resulted in the total loss of activity, confirms the absolute requirement of the natural stereochemistry, that is (2′*R*,3′*S*), in the C-13 side chain for Mϕ activation.

The C-2 position was found to be much more sensitive to the nature of the substituents introduced as compared to the C-10 position (Table 6). Among the C-2 modified taxoids examined, only **31b** and **33b** showed a very weak activity. All the other C-2 modified taxoids were totally inactive. These findings appear to indicate that an aromatic substituent at the C-2 position and a long chain alkanoyl/alkenoyl group (with a number of carbons higher than 4, but less than 14) at the C-10 position are essential for taxoids to be highly active.

The effect of the nature of the substituent at the C-7 position was also evaluated (Table 7). This position does not seem to tolerate any of the alkanoyl or alkenoyl moieties that are bulkier than acetyl group. Thus, only taxoid **38a** maintains the same level of activity as paclitaxel.

All taxoids were also examined for their activity against LPS-hyporesponsive C3H/HeJ Mϕ. None of the taxoids tested (with the exception of taxoid **33b**) induced any detectable NO/TNF production by C3H/HeJ Mϕ, even when these taxoids induced significant levels of NO/TNF production by C3H/HeN Mϕ. This result indicates that paclitaxel and its analogues can mimic LPS effects on a genetic basis. Taxoid **33b**, bearing a 3,3-dimethylpentanoyl group at the C-2 position, was found to be the only exception, which can induce TNF production by both C3H/HeN Mϕ and C3H/HeJ Mϕ supplemented with IFN-γ, albeit weakly. On the other hand, taxoid **33b** could not induce any detectable NO production. The C-2 modified taxoid **33b** represents the first example of taxoid that can induce TNF production in C3H/HeJ Mϕ. This might indicate that a unique mechanism of action different from that of LPS and paclitaxel and/or a different intracellular target might be involved.

Growth inhibition of murine Mϕ-like cell lines by paclitaxel and its analogues. The cytotoxicity of taxoids to inhibit the growth of murine Mϕ-like cell lines J774.1 and J7.DEF3 was also evaluated (Tables 3–7). All the taxoids bearing a C-13 side chain with the unnatural stereochemistry, that is (2′*S*,3′*R*), were found to be totally inactive, which confirms the crucial importance of the (2′*R*,3′*S*) configuration at the C-13 side chain of paclitaxel and taxoids for their cytoxicity.

Most of the other taxoids were found to inhibit the growth of both cell lines J774.1 and J7.DEF3 almost equally, with different levels of activity depending on the nature of the substituents that were introduced at the C-10, C-2 or C-7 position. The cytotoxicity data indicate that the anti-proliferative ability of these taxoids against J774.1 and J7.DEF3 cells is independent of their ability to induce NO/TNF production by murine macrophages. This proves again that the mechanisms involved in cytotoxicity and macrophage activation are not related to one another, and that the structural requirements for the induction of NO/TNF production are different from those for the inhibition of tumor growth.

Conclusion

A series of new taxoids has been designed and synthesized for the SAR study on their potency for murine macrophage activation. It has been found that the aromatic acyl substituent at the C3′-*N* position plays an extremely important role in the activation of macrophages by paclitaxel and its congeners, while an aromatic moiety at the C-3′ position is not strictly required for the activity. It has also been shown that the nature of the substituents at the C-10, C-2 and C-7 positions have critical effects on the induction of TNF and NO production by Mϕ, and the C-10 position is the most tolerant of the three.

An intriguing effect of the chain length of the *n*-alkanoyl substituent at the C-10 position is observed, that is taxoids **18c** and **18d**, bearing an hexanoyl and a dodecanoyl moiety, respectively, exhibited activity superior to that of paclitaxel. Taxoid **18d** is the most active taxoid so far in this macrophage activation study, with a minimal inducing dose much lower than the one required for paclitaxel, which also represents the first example of a structural correlation between a taxoid and LPS. An aromatic acyl moiety at the C-2 position is required for the activity, while only hydroxyl or acetyl substituents seem to be tolerated at the C-7 position. The natural stereochemistry in the C-13 side chain amino acid moiety of the taxoids is an absolute requirement for the activity.

A good correlation between TNF and NO production is generally observed, while there is no correlation between the TNF/NO inducibility in C3H/HeN Mϕ and cytotoxicity against Mϕ-like cells. None of the taxoids stimulated TNF/NO production by C3H/HeJ Mϕ, with the exception of analogue 33b, bearing a 3,3-dimethylpentanoyl group at the C-2 position.

Experimental

General methods

Melting points were measured with Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured using a Varian Gemini 2300 spectrometer using tetramethylsilane as the internal standard. Thin layer chromatography was performed on Merk DC-alufolien with Kieselgel 60F-254. Column chromatography was carried out on silica gel 60 (230–400 mesh ASTM, Merck).

Materials

The chemicals were purchased from Aldrich Co. and Sigma and purified by standard methods. Solvents were freshly distilled: tetrahydrofuran under nitrogen in the presence of benzophenone and sodium, dichloromethane under nitrogen over CaH_2. (3*R*,4*S*)-3-Triisopropylsilyloxy-4-phenylazetidin-2-one (**4a**),[22] (3*R*,4*S*)-1-*tert*-butoxycarbonyl-3-triisopropylsilyloxy-4-phenylazetidin-2-one (**6**),[23,24] (3*R*,4*S*)-3-triisopropylsilyloxy-4-(2-methylprop-1-enyl)azetidin-2-one (**9**),[26] 7-triethylsilyl-10-deacetylbaccatin III (**11**),[27] 7-triethylsilylbaccatin III (**12a**),[27] 7-triethylsilyl-10-propanoyl-10-deacetylbaccatin III (**12b**),[26] 7-triethylsilyl-10-*n*-hexanoyl-10-deacetylbaccatin III (**12c**),[26] 7-triethylsilyl-10-cyclohexanoyl-10-deacetylbaccatin III (**12f**),[26] 7-triethylsilyl-10-(*E*-but-2-enoyl)-10-deacetylbaccatin III (**12g**),[26] 7-triethylsilyl-10-dimethylcarbamoyl-10-deacetylbaccatin III (**12j**),[26] 7-triethylsilyl-10-(4-morpholine-*N*-carbonyl)-10-deacetylbaccatin III (**12k**),[26] 10-acetyl-3′-dephenyl-3′-(2-methyl-2-propenyl)docetaxel (**13b**),[26] 3′-*N*-debenzoylpaclitaxel (**16**),[30–32] 3′-*N*-debenzoyl-3′*N*-(4-fluorobenzoyl)-paclitaxel (**17l**),[30] 7-triethylsilyl-13-oxo-10-deacetyl baccatin III (**19**),[38] 2-debenzoyl-7-triethylsilyl-13-oxobaccatin III (**21**),[38] 2-debenzoyl-2-(3-methylbut-2-enoyl)-7-triethylsilyl-13-oxobaccatin III (**22b**),[38] 2-debenzoyl-2-(3-methylbut-2-enoyl)-7-triethylsilylbaccatin III (**23b**),[38] 7,10,13-tris(triethylsilyl)-10-deacetylbaccatin III (**25**),[35] 2-debenzoyl-2-cyclohexanecarbonyl-7-triethylsilylbaccatin III (**34**)[36] were prepared by literature methods.

(3*S*,4*R*)-3-Triisopropylsilyloxy-4-phenylazetidin-2-one (4b). To a stirring solution of 1.00 g (2.35 mmol) of β-lactams **3b** in 100 mL of acetonitrile and 20 mL of water at −10 °C, was added dropwise a solution of 4.33 g (7.66 mmol) of cerium (IV) ammonium nitrite (CAN) in 80 mL of water. After stirring the for 2 h, the reaction was quenched with a saturated aqueous solution of Na_2SO_3 and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous solution of Na_2SO_3 and brine, dried over magnesium sulfate and concentrated in vacuo. Chromatography on silica gel (hexane/EtOAc = 6:1) of the crude product afforded 670 mg (88% yield) of pure **4b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85–0.88 (m, 21H), 4.78 (d, J = 4.5 Hz, 1H), 5.15 (dd, J = 4.5 Hz, 2.6 Hz, 1H), 6.70 (br s, 1H), 7.32 (m, 5H).

(3*S*,4*R*)-1-Benzoyl-3-triisopropylsilyloxy-4-phenylazetidin-2-one (5b). To a solution of 228 mg (0.71 mmol) of 3-triisopropylsilyloxy-4-phenyl-azetidin-2-one **4b**, 0.2 mL (1.21 mmol) of triethylamine (TEA), and a catalytic amount of dimethylaminopyridine (DMAP) in 10 mL of methylene chloride, was added 0.09 mL (0.78 mmol) of benzoyl chloride. The reaction mixture was stirred at room temperature overnight, quenched with a saturated aqueous solution of ammonium chloride and extracted with methylene chloride. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified via chromatography on silica gel (hexane/EtOAc = 8:1) to yield pure product **5b** in 97% yield as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91–0.93 (m, 21H), 5.25 (d, J = 6.3, 1H), 5.44 (d, J = 6.3 Hz, 1H), 7.33-7.41 (m, 5H), 7.45 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H).

(3*R*,4*S*)-1-Benzoyl-3-triisopropylsilyloxy-4-(2-methylprop-1-enyl)azetidin-2-one (10a). To a solution of 200 mg (0.673 mmol) of **9**, 5 mg of DMAP, and 1.00 mL (5 equiv) of triethylamine in 8 mL of dichloromethane, was added 0.086 mL (0.74 mmol) of benzoyl chloride. The reaction mixture was stirred for 3 h at room temperature. The organic layer was washed several times with brine, dried over Na_2CO_3 and concentrated. The crude oil was purified by chromatography on silica gel (hexane/EtOAc = 5:1) to yield 313 mg (quantitative yield) of **10a** as a clear, colorless oil: $[\alpha]_D^{20}$ +108.6 (c 0.35, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3020, 2865, 1793, 1718, 1675, 1508, 1293; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (bs, 21H), 1.82 (bs, 3H), 1.89 (s, 3H), 5.07 (bs, 1H), 5.09 (dd, J = 14.6, 5.8 Hz, 1H), 7.44 (t, 2H), 7.55 (t, 1H), 7.98 (d, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.8, 17.5, 17.6, 26.1, 56.0, 76.3, 117.9, 128.0, 129.8, 132.4, 133.1, 140.5, 165.4, 166.4. Anal. calcd for $C_{23}H_{36}NO_3Si$: C, 68.61; H, 9.01; N, 3.48. Found: C, 68.45; H, 8.94; N, 3.43.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-triisoproylsilyloxy-4-(2-methyl-1-propenyl)-2-azetidinone (10b). To a solution of 421 mg (1.41 mmol) of **9**, 0.92 mL (7.07 mmol) of triethylamine, and a catalytic amount of dimethylaminopyridine (DMAP) in 10 mL of CH_2Cl_2, was added dropwise at room temperature 381 mg (1.55 mmol) of di-*tert*-butyl dicarbonate in 10 mL CH_2Cl_2. The mixture was stirred for 2 h and the reaction was quenched with saturated NH_4Cl. The reaction mixture was diluted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography on silica gel (hexane/EtOAc = 4:1) to give 458 mg (82% yield) of I0b as colorless oil: $[\alpha]_D^{20}$ −7.61 (*c* 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–1.10 (m, 21H), 1.51 (s, 9H), 1.75 (s, 3H), 1.78 (s, 3H), 4.74 (dd, J = 9.8, 5.7 Hz,

1H), 4.96 (d, $J=5.7$ Hz, 1H), 5.27 (bd, $J=9.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.5, 18.2, 26.0, 28.0, 56.8, 77.3, 82.8, 118.4, 139.5, 148.1, 166.3.

General procedure for the acylation at C-10 position

To a solution of 7-TES-10-deacetylbaccatin III[27] (11, 70 mg, 0.11 mmol) in 3 mL of THF was added LiHMDS (1 M in THF, 0.13 mL, 0.132 mmol) at −40 °C. After stirring the solution for 5 min at this temperature, acyl chloride or *N,N*-dialkylcarbonyl chloride (0.132 mmol) was added dropwise. The solution was allowed to warm to 0 °C. The reaction was quenched with 20 mL of saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (hexane/EtOAc = 2:1) afforded products **12a**–**j** as white solids.

7-Triethylsilyl-10-dodecanoyl-10-deacetylbaccatin III (12c). Yield 95%; mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (q, $J=7.8$ Hz, 6H), 0.85–0.97 (m, 12H), 1.06 (s, 3H), 1.18 (bs, 18H), 1.64–1.69 (m, 6H), 1.86 (dt, 1H), 2.24 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 2.38–2.50 (m, 3H), 3.87 (d, $J=7.0$ Hz, 1H), 4.13 (d, $J=8.3$ Hz, 1H), 4.29 (d, $J=8.3$ Hz, 1H), 4.48 (dd, $J=6.7$ Hz, 10.3 Hz, 1H), 4.81 (t, $J=7.9$ Hz, 1H), 4.95 (d, $J=8.4$ Hz, 1H), 5.62 (d, $J=7.0$ Hz, 1H), 6.46 (s, 1H), 7.49 (t, $J=7.4$ Hz, 2H), 7.59 (t, $J=7.4$ Hz, 1H), 8.09 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.13, 6.62, 9.81, 13.96, 14.79, 19.98, 22.53, 22.55, 24.89, 26.68, 29.00, 29.16, 29.21, 29.33, 29.48, 31.79, 34.24, 37.15, 38.19, 42.67, 47.18, 58.59, 67.91, 72.31, 74.73, 75.49, 76.50, 78.73, 80.85, 83.23, 128.65, 129.48, 130.16, 132.90, 133.67, 143.93, 167.24, 170.86, 172.29, 202.41.

7-Triethylsilyl-10-tetradecanoyl-10-deacetylbaccatin III (12d). Yield 98%; mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (q, $J=7.8$ Hz, 6H), 0.85–0.97 (m, 12H), 1.02 (s, 3H), 1.19 (s, 3H), 1.24–1.29 (m, 21H), 1.64–1.69 (m, 6H), 1.86 (dt, 1H), 2.21 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 2.38–2.53 (m, 3H), 3.87 (d, $J=7.0$ Hz, 1H), 4.13 (d, $J=8.3$ Hz, 1H), 4.29 (d, $J=8.3$ Hz, 1H), 4.48 (dd, $J=6.7$ Hz, 10.3 Hz, 1H), 4.82 (t, $J=7.9$ Hz, 1H), 4.95 (d, $J=8.4$ Hz, 1H), 5.62 (d, $J=7.0$ Hz, 1H), 6.46 (s, 1H), 7.49 (t, $J=7.4$ Hz, 2H), 7.59 (t, $J=7.4$ Hz, 1H), 8.09 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.15, 6.64, 9.82, 13.98, 14.80, 19.99, 22.55, 22.57, 24.91, 26.70, 29.01, 29.18, 29.24, 29.35, 29.51, 29.53, 29.54, 29.57, 31.81, 34.25, 37.16, 38.19, 42.68, 47.19, 58.60, 67.93, 72.32, 74.73, 75.49, 76.51, 78.74, 80.88, 84.23, 128.66, 129.49, 130.17, 132.93, 133.68, 143.91, 167.25, 170.87, 172.30, 202.41.

7-Triethylsilyl-10-benzoyl-10-deacetylbaccatin III (12g). Yield 90%; mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.574 (m, 6H), 0.89 (m, 9H), 1.06 (s, 3H), 1.21 (s, 3H), 1.67 (s, 3H), 2.03 (s, 3H), 2.29 (s, 3H), 2.51 (m, 1H), 4.01 (d, $J=6.9$ Hz, 1H), 4.13 (d, $J=8.4$ Hz, 1H), 4.27 (d, $J=8.4$ Hz, 1H), 4.46 (dd, $J=6.7$ Hz, 10.2 Hz, 1H), 4.76 (t, 1H), 4.96 (d, $J=9.0$ Hz, 1H), 5.61 (d, $J=6.9$ Hz, 1H), 6.45 (s, 1H), 7.26–7.32 (m, 5H), 7.46 (t, $J=7.4$ Hz, 2H), 7.59 (t, $J=7.4$ Hz, 1H), 8.11 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.24, 6.71, 9.24, 9.98, 14.94, 22.63, 27.60, 37.25, 38.34, 42.78, 58.61, 67.82, 72.33, 74.75, 75.51, 76.57, 77.03, 77.52, 78.77, 80.89, 84.26, 128.41, 128.53, 129.45, 129.76, 130.02, 130.58, 133.39, 133.57, 143.96, 167.82, 170.74, 174.55, 202.33.

7-Triethylsilyl-10-phenylacetyl-10-deacetylbaccatin III (12h). Yield 80%; mp 151–153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.57 (m, 6H), 0.89 (m, 9H), 1.06 (s, 3H), 1.21 (s, 3H), 1.67 (s, 3H), 2.03 (s, 3H), 2.29 (s, 3H), 2.51 (m, 1H), 3.76 (s, 2H), 4.01 (d, $J=6.9$ Hz, 1H), 4.13 (d, $J=8.4$ Hz, 1H), 4.27 (d, $J=8.4$ Hz, 1H), 4.46 (dd, $J=6.7$ Hz, 10.2 Hz, 1H), 4.76 (t, 1H), 4.96 (d, $J=9.0$ Hz, 1H), 5.61 (d, $J=6.9$ Hz, 1H), 6.45 (s, 1H), 7.26–7.32 (m, 5H), 7.46 (t, $J=7.4$ Hz, 2H), 7.59 (t, $J=7.4$ Hz, 1H), 8.11 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.20, 6.75, 9.21, 9.98, 14.93, 22.65, 27.60, 37.27, 38.29, 40.76, 42.79, 58.65, 67.87, 72.33, 74.75, 75.61, 76.57, 77.12, 77.52, 78.80, 80.88, 84.26, 128.39, 128.55, 129.42, 129.76, 130.08, 130.60, 133.39, 133.53, 143.93, 167.81, 170.74, 174.48, 202.30.

3′-Dephenyl-3′-(2-methyl-1-propenyl)paclitaxel (13a). To a mixture of 200 mg (0.285 mmol) of 7-TES-baccatin and 172 mg (0.428 mmol) of **10a** in 9 mL of THF was added 0.37 mL of NaHMDS (1.0 M in THF) at −30 °C. After 35 min, the reaction was quenched by addition of 10 mL of aqueous NH_4Cl. The aqueous layer was extracted with 2×50 mL portions of EtOAc, dried over $MgSO_4$, filtered and concentrated. The crude residue was subjected to silica gel chromatography (hexane/EtOAc = 1:1) to afford a white solid (233 mg, 64%). A solution of this material (150 mg) was dissolved in 8 mL of pyridine and 4 mL of CH_3CN, and treated with 1 mL of HF-pyridine (70% wt solution) at 62 °C and stirred for 3 h. The reaction was quenched with 15 mL of water, extracted with EtOAc (2×50 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by chromatography on silica gel (hexane/EtOAc = 1:1) afforded 85 mg (76% yield) of **13a** as a white film: mp 144–146 °C; $[\alpha]_D^{20}$ −60.87 (*c* 0.23, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (bs, 3H), 1.21 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.79 (s, 3H), 1.86 (s, 3H), 2.15 (m, 1H), 2.20 (s, 3H), 2.36 (s, 3H), 2.41 (m, 2H), 2.51 (m, 1H), 3.80 (d, $J=6.9$ Hz, 1H), 4.19 (d, $J=8.4$ Hz, 1H), 4.27 (d, $J=8.4$ Hz, 1H), 4.35 (m, 2H), 4.93 (d, $J=8.6$ Hz, 1H), 5.27 (bt, $J=6.4$ Hz, 1H), 5.46 (d, $J=8.7$ Hz, 1H), 5.67 (d, $J=7.0$ Hz, 1H), 6.16 (bt, $J=8.3$ Hz, 1H), 6.28 (s, 1H), 6.69 (bd, $J=8.3$ Hz, 1H), 7.32 (t, $J=7.4$ Hz, 2H), 7.44 (t, $J=7.4$ Hz, 3H), 7.58 (t, $J=7.4$ Hz, 1H), 7.68 (d, $J=7.4$ Hz, 2H), 8.09 (d, $J=7.4$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6, 14.2, 14.9, 18.6, 20.8, 21.8, 22.4, 25.8, 26.7, 35.7, 35.8, 43.2, 45.7, 50.7, 58.5, 72.0, 73.4, 75.1, 75.6, 76.5, 78.8, 81.0, 84.4, 120.2, 127.0, 128.6, 129.4, 130.1, 131.8, 133.1, 133.6, 133.8, 139.0, 142.1, 166.7, 167.3, 170.3, 171.2, 172.96, 203.7. Anal. calcd for $C_{45}H_{51}NO_{14}$: C, 65.13; H, 6.19; N, 1.69. Found: C, 65.00; H, 5.93; N, 1.64.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-acetyldocetaxel (13b). This compound was synthesized in the same manner as that described for the synthesis of **13a**.

13b. White solid: mp 157–160 °C; $[\alpha]_D^{20}$ −76.3 (*c* 0.76, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3528, 2976, 1734, 1718, 1676, 1369, 1243, 1168, 1070; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.26 (s, 3H), 1.36 (s, 9H), 1.68 (s, 3H), 1.77 (bs, 6H), 1.90 (bs, 4H), 2.25 (s, 3H), 2.36 (s, 3H), 2.39 (bs, 1H), 2.53 (m, 2H), 3.44 (d, *J* = 6.7 Hz, 1H), 3.82 (d, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 4.31 (d, *J* = 8.5 Hz, 1H), 4.24 (m, 1H), 4.43 (m, 1H), 4.78 (dq, *J* = 8.5, 2.6 Hz, 1H), 4.83 (bs, 1H), 4.96 (d, *J* = 8.1 Hz, 1H), 5.32 (d, *J* = 8.3 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 6.17 (t, *J* = 8.6 Hz, 1H), 6.31 (s, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6, 14.9, 18.5, 20.8, 22.4, 25.7, 26.6, 28.2, 35.6, 43.2, 45.7, 51.6, 58.5, 72.1, 72.2, 73.8, 75.1, 75.6, 76.4, 79.1, 79.9, 81.0, 84.4, 120.7, 128.6, 129.3, 130.1, 132.8, 133.6, 137.7, 145.6, 155.5, 166.9, 170.1, 171.2, 173.7, 203.7. Anal. calcd for $C_{43}H_{57}NO_{15}$: C, 62.38; H, 6.94; N, 1.69. Found: C, 62.47; H, 6.71; N 1.60.

General procedure for the preparation of 3′-*N*-debenzoyl-3′-*N*-acylpaclitaxel (17a–q)

To a solution of 3′-*N*-debenzoylpaclitaxel[30–32] (**16**, 20 mg, 0.031 mmol) in a mixture of ethyl acetate (1.5 mL) and saturated aq $NaHCO_3$ (1.5 mL) was added an acyl chloride (excess). After stirring at room temperature for 20 min, the reaction mixture was diluted with EtOAc. The aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed in vacuo. Purification of the crude product by chromatography on silica gel (hexane/EtOAc = 1:1.5) afforded 3′-*N*-debenzoyl-3′-*N*-acylpaclitaxel **17a–q** as a white solid in good to high yield. Paclitaxel analogues **17h**, **17i**, and **17j** have been reported, but without any characterization data.[30–32] Thus, the data for these analogues are reported here.

3′-*N*-Debenzoyl-3′-(2-thiophenecarbonyl)paclitaxel (17a). Yield 74%; mp 135–136 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.79 (m, 5H), 2.23 (s, 3H), 2.29 (m, 2H), 2.31 (s, 3H), 2.36 (m, 2H), 2.49 (m, 1H), 3.67 (s, 1H), 3.78 (d, *J* = 6.75 Hz, 1H), 4.22 (dd, 2H), 4.38 (m, 1H), 4.75 (s, 1H), 4.92 (d, *J* = 8.7 Hz, 1H), 5.65 (d, *J* = 7.0 Hz, 1H), 5.74 (d, *J* = 8.7 Hz, 1H), 6.27 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.30–7.59 (m, 8H), 7.62 (m, 1H), 8.12 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 14.8, 14.9, 21.0, 22.1, 23.2, 26.8, 29.5, 35.6, 43.7, 45.8, 54.3, 58.5, 72.1, 72.5, 73.6, 74.9, 75.5, 78.9, 82.4, 84.4, 127.0, 127.1, 128.7, 128.9, 130.2, 132.6, 133.2, 134.2, 137.5, 142.5, 144.8, 157.4, 167.7, 171.2, 172.5, 173.2, 203.0. Anal. calcd for $C_{45}H_{49}NO_{14}S$: C, 62.85; H, 5.74. Found: C, 62.86; H, 6.00.

3′-*N*-Debenzoyl-3′-*N*-(2-furancarbonyl)paclitaxel (17b). Yield 82%; mp 167–168 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.79 (m, 5H), 1.88 (m, 1H), 2.25 (m, 2H), 2.31 (s, 3H), 2.38 (s, 3H), 2.49 (m, 1H), 3.78 (d, *J* = 6.7 Hz, 1H), 4.22 (dd, 2H), 4.38 (m, 1H), 4.75 (s, 1H), 4.92 (d, *J* = 8.7 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 5.72 (d, *J* = 8.7 Hz, 1H), 6.27 (m, 2H), 7.01 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.38–7.59 (m, 8H), 7.62 (m, 1H), 8.12 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 14.8, 14.9, 21.0, 22.1, 23.2, 26.8, 29.5, 35.6, 43.7, 45.8, 54.3, 58.5, 72.1, 72.5, 73.6, 74.9, 75.5, 78.9, 82.4, 84.4, 127.0, 127.1, 128.7, 128.9, 130.2, 132.6, 133.2, 134.2, 137.5, 142.5, 144.8, 157.4, 167.7, 171.2, 172.5, 173.2, 203.0. Anal. calcd for $C_{45}H_{49}NO_{15}$: C, 64.05; H, 5.85. Found: C, 64.27; H, 6.00.

3′-*N*-Debenzoyl-3′-*N*-(4-phenylbenzoyl)paclitaxel (17c). Yield 77%; mp 169–170 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.79 (m, 5H), 2.22 (s, 3H), 2,31 (m, 2H), 2.38 (s, 3H), 2.49 (m, 1H), 3.72 (s, 1H), 3.78 (d, *J* = 6.7 Hz, 1H), 4.24 (dd, 2H), 4.38 (m, 1H), 4.79 (s, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 5.80 (d, *J* = 8.8 Hz, 1H), 6.20 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.10–7.60 (m, 15H), 7.80 (d, *J* = 7.2 Hz, 2H), 8.12 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.58, 14.8, 21.0, 22.1, 22.6, 26.8, 28.0, 29.8, 35.6, 43.7, 45.8, 55.3, 58.5, 72.1, 72.5, 73.6, 74.9, 75.5, 78.9, 82.4, 84.4, 127.1, 127.2, 127.4, 127.6, 128.1, 128.3, 128.7, 128.9, 129.0, 129.2, 130.2, 132.6, 133.2, 133.7, 137.6, 139.5, 142.5, 144.8, 167.4, 167.7, 170.6, 171.8, 173.2, 203.4. Anal. calcd for $C_{53}H_{55}NO_{14}$: C, 68.45; H, 5.96. Found: C, 68.21; H, 6.07.

3′-*N*-Debenzoyl-3′-*N*-(1-naphthoyl)paclitaxel (17d). Yield 90%; mp 175–176 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.84 (m, 5H), 2.24 (s, 3H), 2.31 (m, 2H), 2.45 (s, 3H), 2.49 (m, 1H), 3.62 (m, 1H), 3.80 (d, *J* = 6.7 Hz, 1H), 4.24 (dd, 2H), 4.39 (m, 1H), 4.79 (s, 1H), 4.93 (d, *J* = 8.7 Hz, 1H), 5.68 (d, *J* = 7.0 Hz, 1H), 5.87 (d, *J* = 8.7 Hz, 1H), 6.30 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.10–7.50 (m, 12H), 7.86 (m, 2H), 8.08 (d, *J* = 7.2 Hz, 2H). 8.20 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.0, 15.7, 22.0, 23.0, 23.8, 27.5, 30.3, 35.6, 35.9, 44.3, 45.8, 55.3, 58.5, 72.5, 73.6, 74.9, 75.5, 77.1, 79.3, 80.4, 85.2, 125.1, 125.5, 125.7, 127.6, 128.2, 128.3, 128.9, 129.0, 129.2, 129.5, 129.8, 130.2, 132.6, 133.2, 133.7, 135.6, 137.5, 143.4 167.4, 170.6, 170.8, 171.8, 173.8, 204.7. Anal. calcd for $C_{51}H_{53}NO_{14}$: C, 67.76; H, 5.91. Found: C, 67.78; H, 6.06.

3′-*N*-Debenzoyl-3′-*N*-(2-naphthoyl)paclitaxel (17e). Yield 99%; mp 173–174 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.79 (m, 5H), 2.22 (s, 3H), 2.31 (m, 2H), 2.38 (s, 3H), 2.49 (m, 1H), 3.72 (s, 1H), 3.78 (d, *J* = 6.7 Hz, 1H), 4.24 (dd, 2H), 4.38 (m, 1H), 4.79 (s, 1H), 4.83 (d, *J* = 8.75 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 5.82 (d, *J* = 8.7 Hz, 1H), 6.27 (m, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.10–7.51 (m, 10H), 7.80 (m, 4H), 8.14 (d, *J* = 7.2 Hz, 2H). 8.24 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.58, 14.8, 14.9, 21.0, 22.1, 22.6, 26.8, 28.0, 29.8, 35.6, 43.7, 45.8, 55.3, 58.5, 72.1, 72.5, 73.6, 74.9, 75.5, 78.9, 82.4, 84.4, 123.1, 126.8, 127.0, 127.6, 127.8, 127.9, 128.1, 128.3, 128.7, 128.9, 129.0, 129.2, 130.2, 132.6, 133.2, 133.7, 135.6, 137.5, 142.5, 144.8, 167.4, 167.7, 170.6, 171.8, 173.2, 204.4. Anal. calcd for $C_{50}H_{52}NO_{14}$: C, 67.76; H, 5.91. Found: C, 67.54; H, 6.02.

3′-*N*-Debenzoyl-3′-*N*-phenyacetylpaclitaxel (17f). Yield 83%; mp 141–142 °C; ^1H NMR (250 MHz, $CDCl_3$) δ

1.14 (s, 3H), 1.24 (s, 3H), 1.68 (s, 3H), 1.77 (s, 3H), 1.92 (m, 1H), 2.24 (m, 5H), 2.33 (s, 3H), 2.51 (m, 1H), 3.53 (s, 3H), 3.73 (d, $J=6.7$ Hz, 1H), 4.24 (dd, 2H), 4.39 (m, 1H), 4.92 (d, $J=7.0$ Hz, 1H), 5.58 (m, 1H), 5.65 (d, $J=7.5$ Hz, 1H), 6.14 (t, $J=7.0$ Hz, 1H), 6.25 (s, 1H), 6.36 (d, $J=8.7$ Hz, 1H), 7.11–7.42 (m, 10H), 7.51 (t, $J=7.2$ Hz, 2H), 7.62 (t, $J=7.2$ Hz, 1H), 8.10 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.0, 15.3, 22.0, 23.0, 23.8, 27.5, 35.9, 36.0, 42.1, 44.5, 44.7, 45.8, 55.0, 58.7, 73.5, 73.6, 74.0, 75.5, 76.5, 77.1, 79.7, 82.6, 127.8, 128.2, 128.5, 129.0, 129.1, 129.2, 129.5, 129.8, 130.0, 130.8, 134.2, 134.9, 135.2, 138.5, 143.7, 167.4, 170.6, 171.2, 172.8, 173.8, 204.8. Anal. calcd for $C_{48}H_{53}NO_{14}$: C, 66.42; H, 6.15. Found: C, 66.56; H, 5.96.

3′-*N*-Debenzoyl-3′-*N*-cinnamoylpaclitaxel (17g). Yield 78%; mp 149–150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.24 (s, 3H), 1.69 (s, 3H), 1.84 (m, 4H), 2.23 (s, 3H), 2.31 (m, 2H), 2.39 (s, 3H), 2.51 (m, 1H), 3.75 (m, 1H), 3.80 (d, $J=6.7$ Hz, 1H), 4.24 (dd, 2H), 4.39 (m, 1H), 4.75 (s, 1H), 4.94 (d, $J=7.0$ Hz, 1H), 5.70 (m, 1H), 6.26 (m, 2H), 6.38 (d, $J=8.7$ Hz, 1H), 6.48 (d, $J=7.2$ Hz, 1H), 6.52 (d, $J=8.8$ Hz, 1H), 7.30–7.62 (m, 14H), 8.16 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.0, 15.7, 22.0, 23.0, 23.8, 27.5, 35.9, 36.0, 44.3, 45.8, 55.3, 58.5, 73.5, 73.6, 74.0, 75.5, 77.1, 77.6, 79.7, 85.2, 95.6, 120.4, 127.8, 128.2, 128.7, 129.0, 129.2, 129.5, 129.8, 131.2, 132.0, 134.2, 134.9, 135.2, 138.5, 143.4, 143.7, 167.4, 170.6, 171.2, 172.8, 173.8, 204.8. Anal. calcd for $C_{49}H_{53}NO_{14}$: C, 66.88; H, 6.07. Found: C, 66.85; H, 6.02.

3′-*N*-Debenzoyl-3′-*N*-(4-methylbenzoyl)paclitaxel (17h). Yield 89%; mp 142–143 °C; $[\alpha]_D^{20}$ −43.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.22 (s, 6H), 1.67 (s, 3H), 1.78 (s, 3H), 1.88 (m, 1H), 2.22 (s, 3H), 2.29 (m, 2H), 2.35 (s, 3H), 2.37 (s, 3H), 2.54 (m, 1H), 3.78 (d, $J=7.0$ Hz, 1H), 3.88 (s, 3H), 4.24 (dd, 2H), 4.36 (dd, $J_1=8.2$ Hz, $J_2=7.0$ Hz, 1H), 4.77 (d, $J=2.2$ Hz, 1H), 4.92 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.76 (dd, $J_1=8.7$ Hz, $J_2=2.2$ Hz, 1H), 6.20 (m, 2H), 7.00 (d, $J=8.7$ Hz, 1H), 7.15–7.69 (m, 12H), 8.11 (d, $J=7.2$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.8, 20.9, 21.6, 22.6, 26.8, 29.6, 35.6, 43.1, 45.5, 55.0, 56.5, 72.2, 73.3, 74.9, 75.5, 76.5, 79.0, 81.1, 84.4, 120.0, 127.3, 128.3, 128.7, 129.0, 129.1, 129.3, 130.2, 133.1, 133.7, 138.0, 142.0, 143.5, 166.9, 170.4, 171.8, 172.7, 203.6. Anal. calcd for $C_{48}H_{53}NO_{14}$: C, 66.42; H, 6.15; N, 1.61 Found: C, 66.45, H, 6.11; N, 1.59.

3′-*N*-Debenzoyl-3′-*N*-(4-chlorobenzoyl)paclitaxel (17i). Yield 81%; mp 159–160 °C; $[\alpha]_D^{20}$ −48.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 1.84 (m, 1H), 2.23 (s, 3H), 2.30 (m, 2H), 2.36 (s, 3H), 2.56 (m, 1H), 3.78 (d, $J=7.0$ Hz, 1H), 4.22 (dd, 2H), 4.38 (dd, $J_1=8.2$ Hz, $J_2=7.0$ Hz, 1H), 4.77 (d, $J=2.2$ Hz, 1H), 4.93 (d, $J=8.7$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.76 (dd, $J_1=8.7$ Hz, $J_2=2.2$ Hz, 1H), 6.21 (m, 2H), 6.28 (s, 1H), 7.02 (d, $J=8.7$ Hz, 1H), 7.20–7.90 (m, 12H), 8.12 (d, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.5, 14.8, 20.8, 21.7, 22.6, 26.8, 35.6, 43.2, 45.6, 55.0, 58.6, 72.2, 72.3, 73.1, 74.8, 75.5, 76.5, 79.0, 81.5, 84.3, 127.0, 128.5, 128.7, 128.9, 129.0, 130.0, 133.2, 133.7, 137.8, 141.9, 165.9, 167.0, 170.4, 171.3, 172.7, 203.6. Anal. calcd for $C_{47}H_{50}ClNO_{14}$: C, 63.55; H, 5.96; N, 1.58 Found: C, 63.56, H, 6.01; N, 1.53.

3′-*N*-Debenzoyl-3′-*N*-(4-methoxybenzoyl)paclitaxel (17j). Yield 96%; mp 158–159 °C; $[\alpha]_D^{20}$ −42.2 (c 0.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.92 (m, 1H), 2.23 (s, 3H), 2.30 (m, 2H), 2.37 (s, 3H), 2.54 (m, 1H), 3.81 (m, 3H), 4.23 (dd, 2H), 4.38 (dd, $J_1=8.2$ Hz, $J_2=7.0$ Hz, 1H), 4.77 (d, $J=2.5$ Hz, 1H), 4.93 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.76 (dd, J1 = 8.7 Hz, J2 = 2.4 Hz, 1H), 6.20 (m, 2H), 6.84–6.95 (m, 3H), 7.25–7.77 (m, 8H), 7.95 (d, $J=8.7$ Hz, 2H), 8.11 (d, $J=7.2$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6, 14.8, 20.8, 21.8, 22.6, 26.8, 35.7, 43.1, 45.6, 54.1, 54.4, 58.6, 72.2, 72.3, 73.3, 74.9, 75.5, 76.5, 79.0, 81.6, 84.4, 113.6, 113.9, 125.7, 127.0, 128.3, 128.7, 128.9, 129.0, 130.2, 132.2, 133.1, 133.7, 136.1, 142.0, 166.9, 170.4, 171.3, 172.7, 203.6. Anal. calcd for $C_{48}H_{53}NO_{15}$: C, 65.22; H, 6.04; N, 1.58 Found: C, 65.32, H, 6.01; N, 1.51.

3′-*N*-Debenzoyl-3′-*N*-(3,4-dimethoxybenzoyl)paclitaxel (17k). Yield 78%; mp 148–149 °C; $[\alpha]_D^{20}$ −36.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.26 (s, 3H), 1.67 (s, 3H), 1.86 (s, 3H), 1.90 (m, 1H), 2.22 (s, 3H), 2.35 (m, 2H), 2.42 (s, 3H), 2.54 (m, 1H), 3.64 (s, 3H), 3.69 (d, $J=7.0$ Hz, 1H), 3.88 (s, 3H), 4.24 (dd, 2H), 4.40 (dd, $J_1=8.2$ Hz, $J_2=7.0$, 1H), 4.80 (d, $J=2.2$ Hz, 1H), 4.93 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.81 (dd, $J_1=8.7$ Hz, $J_2=2.2$ Hz, 1H), 6.23 (m, 2H), 6.81 (d, $J=8.2$ Hz, 1H), 6.96 (d, $J=8.7$ Hz, 1H), 7.25–7.66 (m, 10H), 8.16 (d, $J=7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.6, 14.8, 20.8, 21.8, 22.7, 25.8, 35.5, 43.1, 45.5, 54.8, 55.7, 56.0, 56.5, 72.2, 72.3, 73.3, 74.9, 75.5, 76.5, 79.1, 81.0, 84.4, 110.0, 110.8, 119.2, 126.1, 126.9, 128.2, 128.7, 129.0, 129.1, 130.2, 133.1, 133.7, 138.0, 142.0, 149.1, 152.1, 167.0, 170.4, 171.3, 172.7, 203.6. Anal. calcd for $C_{49}H_{55}NO_{16}$: C, 69.26; H, 6.48; N, 1.65 Found: C, 69.38, H, 6.54; N, 1.58.

3′-*N*-Debenzoyl-3′-*N*-(4-ethylbenzoyl)paclitaxel (17m). Yield 95%; mp 146–147 °C; $[\alpha]_D^{20}$ −45.3 (*c* 0.75, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.24 (m, 6H), 1.68 (s, 3H), 1.79 (s, 3H), 1.84 (m, 1H), 2.23 (s, 3H), 2.30 (m, 2H), 2.38 (s, 3H), 2.64 (m, 3H), 3.78 (d, $J=5.7$ Hz, 1H), 4.24 (dd, 2H), 4.40 (dd, $J_1=8.2$ Hz, $J_2=5.2$ Hz, 1H), 4.77 (d, $J=2.2$ Hz, 1H), 4.94 (d, $J=6.5$ Hz, 1H), 5.66 (d, $J=6.0$ Hz, 1H), 5.76 (dd, $J_1=7.5$ Hz, $J_2=2.2$ Hz, 1H), 6.22 (m, 2H), 6.97 (d, $J=7.0$ Hz, 1H), 7.20–7.67 (m, 12H), 8.11 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.4, 14.7, 20.7, 21.7, 22.5, 26.7, 28.6, 35.5, 35.6, 43.0, 45.5, 54.9, 58.5, 72.1, 72.2, 73.2, 74.9, 75.5, 78.9, 81.0, 84.3, 99.9, 126.9, 127.0, 128.0, 128.2, 128.9, 129.1, 130.1, 130.9, 133.0, 133.6, 133.9, 138.0, 148.7, 166.9, 170.3, 171.3, 172.6, 203.6. Anal. calcd for $C_{49}H_{55}NO_{14}$: C, 66.74; H, 6.24; N, 1.59 Found: C, 66.75, H, 6.30; N, 1.55.

3′-*N*-Debenzoyl-3′-*N*-(4-propylbenzoyl)paclitaxel (17n). Yield 95%; mp 145–146 °C; $[\alpha]_D^{20}$ −41.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 6H),

1.59 (m, 2H), 1.67 (s, 3H), 1.78 (s, 3H), 1.90 (m, 1H), 2.22 (m, 3H), 2.33 (m, 2H), 2.37 (s, 3H), 2.56 (m, 4H), 3.78 (d, $J=6.7$, 1H), 4.29 (dd, 2H), 4.39 (dd, $J_1=8.2$ Hz, $J_2=7.0$ Hz, 1H), 4.77 (d, $J=2.6$ Hz, 1H), 4.93 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=6.5$ Hz, 1H), 5.76 (dd, $J_1=8.7$ Hz, $J_2=2.2$ Hz, 1H), 6.23 (m, 2H), 6.97 (d, $J=8.7$ Hz, 1H), 7.16–7.67 (m, 12H), 8.12 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.1, 15.2, 21.3, 22.2, 23.1, 24.7, 27.3, 30.1, 36.0, 36.1, 38.3, 43.6, 46.1, 55.5, 59.1, 72.7, 73.7, 75.4, 76.0, 79.5, 81.6, 84.8, 127.5, 127.6, 127.8, 128.7, 129.1, 129.2, 129.4, 129.6, 130.7, 131.5, 132.7, 133.6, 134.1, 134.7, 137.0, 138.5, 142.5, 143.6, 147.6, 167.4, 169.8, 171.7, 173.2, 204.1. Anal. calcd for $C_{50}H_{57}NO_{14}$: C, 67.04; H, 6.37; N, 1.56. Found: C, 66.97, H, 6.37; N, 1.63.

3′-*N*-Debenzoyl-3′-*N*-(4-*t*-butylbenzoyl)paclitaxel (17o). Yield 87%; mp 149–150 °C; $[\alpha]_D^{20}$ −37.9 (*c* 0.95, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.23–1.33 (m, 12H), 1.68 (s, 3H), 1.79 (s, 3H), 1.82 (m, 1H), 2.23 (s, 3H), 2.35 (m, 2H), 2.38 (s, 3H), 2.46 (m, 1H), 3.79 (m, 1H), 4.24 (dd, 2H), 4.40 (dd, $J_1=8.2$ Hz, $J_2=7.0$, 1H), 4.78 (d, $J=2.2$, 1H), 4.94 (d, $J=8.0$ Hz, 1H), 5.66 (d, $J=7.0$ Hz, 1H), 5.78 (dd, $J_1=8.75$ Hz, $J_2=2.2$ Hz, 1H), 6.22 (m, 2H), 7.00 (d, $J=7.5$ Hz, 1H), 7.26–7.74 (m, 12H), 8.11 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.4, 14.7, 20.7, 21.7, 22.5, 26.7, 30.9, 35.5, 43.1, 45.5, 54.8, 58.5, 72.1, 72.2, 73.1, 74.8, 75.4, 78.9, 81.0, 84.3, 125.5, 126.8, 126.9, 128.1, 128.6, 128.9, 130.1, 133.6, 133.9, 138.0, 141.9, 166.9, 170.3, 172.6, 176.6, 203.6. Anal. calcd for $C_{51}H_{59}NO_{14}$: C, 67.32; H, 6.49; N, 1.54. Found: C, 67.35, H, 6.53; N, 1.52.

3′-*N*-Debenzoyl-3′-*N*-(2,4-difluorobenzoyl)paclitaxel (17p). Yield 88%; mp 140–151 °C $[\alpha]_D^{20}$ −54.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.84 (m, 1H), 2.23 (s, 3H), 2.35 (m, 2H), 2.38 (s, 3H), 2.50 (m, 1H), 3.78 (d, $J=7.2$ Hz, 1H), 4.24 (dd, 2H), 4.38 (dd, $J_1=8.2$ Hz, $J_2=7.0$ Hz, 1H), 4.73 (d, $J=2.2$ Hz, 1H), 4.94 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.81 (d, $J=8.7$ Hz, 1H), 6.24 (m, 2H), 6.87 (m, 2H), 7.33–7.64 (m, 8H), 7.97 (dd, $J_1=12.2$ Hz, $J_2=8.7$ Hz, 1H), 8.11 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.4, 14.7, 20.7, 21.7, 22.5, 26.7, 30.9, 35.5, 43.1, 45.5, 54.8, 58.5, 72.1, 72.2, 73.1, 74.8, 75.4, 78.9, 81.0, 84.3, 125.5, 126.8, 126.9, 128.1, 128.6, 128.9, 130.1, 133.6, 133.9, 138.0, 141.9, 166.9, 170.3, 172.6, 176.6, 203.6. Anal. calcd for $C_{47}H_{49}NO_{14}$: C, 63.44; H, 5.51; N, 1.57. Found: C, 63.39, H, 5.54; N, 1.56.

3′-*N*-Debenzoyl-3′-*N*-(2,4-dimethoxybenzoyl)paclitaxel (17q). Yield 97%; mp 160–161 °C; $[\alpha]_D^{20}$ −39.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.22 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.82 (m, 1H), 2.22 (s, 3H), 2.35 (m, 2H), 2.41 (s, 3H), 2.49 (m, 1H), 3.79 (m, 1H), 3.81 (s, 3H), 3.95 (s, 3H), 4.24 (dd, 2H), 4.40 (dd, $J_1=8.2$ Hz, $J_2=7.0$, 1H), 4.71 (d, $J=2.2$, 1H), 4.94 (d, $J=8.0$ Hz, 1H), 5.65 (d, $J=7.0$ Hz, 1H), 5.75 (dd, $J_1=8.7$ Hz, $J_2=2.2$, 1H), 6.19 (t, $J=7.0$ Hz, 1H), 6.25 (s, 1H), 6.47 (m, 2H), 7.25–7.64 (m, 9H), 8.03 (m, 1H), 8.11 (d, $J=7.2$ Hz, 2H), 8.70 (d, $J=7.2$ Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.4, 14.6, 20.7, 21.7, 22.5, 26.7, 35.5, 35.6, 43.0, 45.5, 55.4, 55.5, 56.0, 58.4, 71.9, 72.0, 73.9, 74.9, 75.5, 76.3, 78.9, 81.0, 84.3, 98.5, 105.3, 114.2, 126.9, 127.9, 128.6, 128.7, 129.0, 129.1, 130.1, 132.8, 133.6, 133.9, 138.4, 142.2, 159.1, 164.1, 165.1, 166.8, 170.3, 172.3, 203.6. Anal. calcd for $C_{49}H_{55}NO_{16}$: C, 69.26; H, 6.48; N, 1.65 Found: C, 69.31, H, 6.43; N, 1.63.

General procedure for the coupling of modified baccatin 12, 23 or 34 with β-lactam 5 or 6 and deprotection to give taxoids 18, 24, 31, and 37

To a mixture of 0.04 mmol of modified baccatins **12**, **23** or **34** and **28** mg (0.066 mmol) of **5** or **6** in 3 mL of THF was added NaHMDS or LiHMDS (1.0 M in THF, 0.08 mL, 0.068 mmol) at −40 °C. After 30 min the reaction was quenched with 10 mL of saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with EtOAc (2×25 mL), dried over magnesium sulfate filtered and concentrated. Purification of the crude product by chromatography on silica gel (hexane/EtOAc = 1:1) afforded a mixture of the coupling products and unreacted β-lactam, which was dissolved in 1.5 mL of pyridine and 1.5 mL of acetonitrile. 0.5 mL of HF/pyridine (70% wt solution) at 0 °C was added and the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with 10 mL of saturated aqueous solution of copper sulfate. The aqueous layer was extracted ethyl acetate (with 3×30 mL). The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered and concentrated. Purification of the crude product by chromatography on silica gel (hexane/EtOAc = 2:1) afforded the desired taxoid **18**, **24**, **31**, and **37** as a white solid.

10-Propanoyl-10-deacetylpaclitaxel (18a). Yield 54%; mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.20–1.25 (m, 6H), 1.68 (s, 3H), 1.79 (s, 3H), 1.86 (m, 1H), 2.19 (s, 3H), 2.25 (s, 2H), 2.38 (s, 3H), 2.48 (m, 3H), 3.60 (br s, 1H), 3.81 (d, $J=6.9$ Hz, 1H), 4.19 (d, $J=8.1$ Hz, 1H), 4.30 (d, $J=8.1$ Hz, 1H), 4.43 (dd, 1H), 4.79 (d, $J=2$ Hz, 1H), 4.94 (d, $J=9.2$ Hz, 1H), 5.67 (d, $J=6.9$ Hz, 1H), 5.79 (dd, $J=8.7$, 2.0 Hz, 1H), 6.23 (t, $J=9.3$, 1H), 6.29 (s, 1H), 6.97 (d, $J=8.7$, 1H), 7.32–7.53 (m, 10H), 7.43 (t, $J=7.4$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 8.08 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.88, 9.43, 14.73, 21.71, 22.54, 26.77, 27.46, 35.53, 35.61, 43.11, 45.58, 54.97, 58.60, 72.22, 72.39, 73.19, 74.94, 75.36, 76.58, 79.07, 81.18, 84.43, 128.13, 128.47, 128.79, 128.82, 129.13, 129.23, 130.13, 130.31, 132.07, 133.37, 133.71, 133.83, 138.08, 141.96, 167.17, 170.53, 172.88, 174.80, 203.93; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{48}H_{53}NO_{14}{\bullet}H^+$: 868.3465. Found: 868.3551.

10-*n*-Hexanoyl-10-deacetylpaclitaxel (18b). Yield 50%; mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.23 (s, 3H), 1.32–1.39 (m, 4H), 1.68–1.73 (m, 5H), 1.78 (s, 3H), 1.82–1.91 (m, 1H), 2.01 (s, 3H), 2.17–2.30 (m, 5H), 2.38–2.50 (m, 3H), 3.80 (d, $J=7.0$ Hz, 1H), 4.19 (d, $J=8.3$ Hz, 1H), 4.29 (d, $J=8.3$ Hz, 1H), 4.41 (dd, $J=6.7$ Hz, 10.3 Hz, 1H), 4.79 (t, $J=2.7$ Hz, 1H), 4.94 (d, $J=8.4$ Hz, 1H), 5.60 (d, $J=7.0$ Hz, 1H), 5.81

(dd, $J=8.7$, 2.7, 1H), 6.21 (t, 1H), 6.25 (s, 1H), 6.98 (d, $J=8.7$, 1H), 7.42–7.51 (m, 10H), 7.58 (t, $J=7.4$ Hz, 2H), 7.73 (t, $J=7.4$ Hz, 1H), 8.11 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.43, 13.78, 14.71, 22.16, 24.38, 26.79, 31.12, 34.05, 35.50, 43.10, 45.55, 54.97, 58.59, 72.22, 72.40, 73.18, 74.94, 75.27, 76.58, 79.68, 81.18, 84.44, 127.13, 128.46, 128.79, 128.82, 129.13, 129.23, 130.30, 132.07, 133.42, 133.71, 133.81, 138.08, 141.94, 167.17, 170.53, 172.88, 174.98, 203.85; HRMS (FAB, DCM/NBA) m/z calcd for $C_{51}H_{59}NO_{14}\cdot H^+$: 910.3935. Found: 910.3981.

10-Dodecanoyl-10-deacetylpaclitaxel (18c). Yield 48%; mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.26 (m, 18H), 1.59–1.72 (m, 9H), 1.86 (m, 1H), 2.04 (s, 3H), 2.20 (s, 3H), 2.45–2.61 (m, 3H), 3.59 (br s, 1H), 3.86 (d, $J=6.9$ Hz, 1H), 4.15 (d, $J=8.1$ Hz, 1H), 4.28 (d, $J=8.1$ Hz, 1H), 4.45 (dd, 1H), 4.65 (d, $J=2$ Hz, 1H), 4.96 (d, $J=9.2$ Hz, 1H), 5.66 (d, $J=6.9$ Hz, 1H), 5.79 (dd, $J=8.7$, 2.0 Hz, 1H), 6.18 (t, $J=9.3$, 1H), 6.31 (s, 1H), 6.93 (d, $J=8.7$, 1H), 7.32–7.53 (m, 10H), 7.43 (t, $J=7.4$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 8.08 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.37, 13.99, 15.15, 21.49, 22.51, 22.57, 24.68, 26.67, 29.00, 29.15, 29.24, 29.34, 29.50, 31.82, 34.05,35.46, 36.01, 42.97, 45.70, 55.35, 58.59, 72.23, 72.60, 73.57, 74.90, 75.30, 76.42, 79.33, 81.18, 84.50, 127.16, 127.32, 128.57, 128.76, 128.80, 129.22, 130.13, 132.07, 133.07, 133.04, 133.88, 138.75, 142.31, 167.14, 167.35, 169.69, 172.65, 174.12, 203.92; HRMS (FAB, DCM/NBA) m/z calcd for $C_{57}H_{71}NO_{14}\cdot H^+$: 994.4874. Found: 994.4954.

10-Dodecanoyl-10-deacetyl-*epi*-paclitaxel (18c′). Yield 47%; mp 123–124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3H), 1.24 (s, 3H), 1.25 (m, 18H), 1.59–1.72 (m, 9H), 1.85 (m, 1H), 2.01 (s, 3H), 2.20 (s, 3H), 2.45–2.61 (m, 3H), 3.61 (br s, 1H), 3.84 (d, $J=6.9$ Hz, 1H), 4.17 (d, $J=8.2$ Hz, 1H), 4.28 (d, $J=8.2$ Hz, 1H), 4.44 (dd, 1H), 4.70 (d, $J=2$ Hz, 1H), 4.98 (d, $J=9.2$ Hz, 1H), 5.67 (d, $J=6.9$ Hz, 1H), 5.81 (dd, $J=8.7$, 2.0 Hz, 1H), 6.18 (t, $J=9.3$, 1H), 6.35 (s, 1H), 6.89 (d, $J=8.7$, 1H), 7.32–7.55 (m, 10H), 7.42 (t, $J=7.4$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 8.06 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.35, 13.98, 15.17, 21.49, 22.53, 22.56, 24.68, 26.67, 29.07, 29.16, 29.24, 29.37, 29.51, 31.83, 34.05, 35.44, 36.01, 42.97, 45.68, 55.36, 58.59, 72.27, 72.62, 73.57, 74.91, 75.30, 76.42, 79.33, 81.18, 84.50, 127.16, 127.32, 128.57, 128.76, 128.80, 129.22, 130.15, 132.06, 133.07, 133.10, 133.82, 138.71, 142.32, 167.15, 167.35, 169.69, 172.65, 174.16, 203.92; HRMS (FAB, DCM/NBA) m/z calcd for $C_{57}H_{71}NO_{14}\cdot H^+$: 994.4874. Found: 994.4921.

10-Tetradecanoyl-10-deacetylpaclitaxel (18d). Yield 49%; mp 117–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.26 (m, 22H), 1.58–1.75 (m, 9H), 1.86 (m, 1H), 2.04 (s, 3H), 2.20 (s, 3H), 2.45–2.61 (m, 3H), 3.61 (br s, 1H), 3.86 (d, $J=6.9$ Hz, 1H), 4.15 (d, $J=8.1$ Hz, 1H), 4.28 (d, $J=8.1$ Hz, 1H), 4.46 (dd, 1H), 4.65 (d, $J=2$ Hz, 1H), 4.96 (d, $J=9.2$ Hz, 1H), 5.65 (d, $J=6.9$ Hz, 1H), 5.74 (dd, $J=8.7$, 2.0 Hz, 1H), 6.17 (t, $J=9.3$, 1H), 6.31 (s, 1H), 6.93 (d, $J=8.7$, 1H), 7.32–7.53 (m, 10H), 7.43 (t, $J=7.4$ Hz, 2H), 7.56 (t, $J=7.4$ Hz, 1H), 8.08 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.38, 14.00, 15.15, 21.49, 22.52, 22.58, 24.69, 26.67, 29.02, 29.16, 29.27, 29.36, 29.54, 29.56, 29.60, 31.83, 34.06, 35.47, 36.02, 42.99, 45.73, 55.37, 58.60, 72.23, 72.58, 73.57, 74.91, 75.31, 76.43, 79.32, 81.19, 84.50, 127.17, 127.32, 128.57, 128.76, 128.81, 129.23, 130.13, 132.08, 133.04, 133.88, 138.75, 142.31, 167.14, 167.37, 169.71, 172.66, 174.13, 203.92; HRMS (FAB, DCM/NBA) m/z calcd for $C_{59}H_{75}NO_{14}\cdot H^+$: 1022.5187. Found: 1022.5270.

10-Tetradecanoyl-10-deacetyl-*epi*-paclitaxel (18d′). Yield 45%; mp 118–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 3H), 1.24 (s, 3H), 1.27 (m, 22H), 1.58–1.77 (m, 9H), 1.85 (m, 1H), 2.14 (s, 3H), 2.22 (s, 3H), 2.47–2.61 (m, 3H), 3.60 (br s, 1H), 3.85 (d, $J=6.9$ Hz, 1H), 4.14 (d, $J=8.1$ Hz, 1H), 4.28 (d, $J=8.1$ Hz, 1H), 4.45 (dd, 1H), 4.67 (d, $J=2$ Hz, 1H), 4.96 (d, $J=9.1$ Hz, 1H), 5.63 (d, $J=6.9$ Hz, 1H), 5.78 (dd, $J=8.7$, 2.0 Hz, 1H), 6.18 (t, $J=9.2$, 1H), 6.33 (s, 1H), 6.94 (d, $J=8.7$, 1H), 7.35–7.54 (m, 10H), 7.43 (t, $J=7.4$ Hz, 2H), 7.57 (t, $J=7.4$ Hz, 1H), 8.09 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.39, 14.12, 15.16, 21.49, 22.56, 22.61, 24.70, 26.67, 29.04, 29.17, 29.29, 29.34, 29.54, 29.56, 29.65, 31.81, 34.06, 35.51, 36.02, 43.04, 45.73, 55.36, 58.60, 72.28, 72.59, 73.57, 74.91, 75.33, 76.43, 79.32, 81.20, 84.53, 127.19, 127.37, 128.63, 128.76, 128.83, 129.23, 130.12, 132.09, 133.08, 133.90, 138.77, 142.42, 167.14, 167.39, 169.76, 172.66, 174.12, 203.92; HRMS (FAB, DCM/NBA) m/z calcd for $C_{59}H_{75}NO_{14}\cdot H^+$: 1022.5187. Found: 1022.5266.

10-Cyclohexanoyl-10-deacetylpaclitaxel (18e). Yield 52%; mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.24 (s, 3H), 1.23–1.52 (m, 6H), 1.67 (s, 3H), 1.73–2.00 (m, 6H), 2.16 (s, 3H), 2.24 (br s, 4H), 2.36–2.54 (m, 2H), 3.80 (d, $J=6.9$ Hz, 1H), 4.18 (d, $J=8.2$ Hz, 1H), 4.30 (d, $J=8.2$ Hz, 1H), 4.46 (dd, $J=6.7$ Hz, 10.2 Hz, 1H), 4.78 (d, $J=2.7$ Hz, 1H), 4.94 (d, $J=8.7$ Hz, 1H), 5.67 (d, $J=6.9$ Hz, 1H), 5.80 (dd, $J=8.7$, 2.7, 1H), 6.26 (m, 2H), 7.37–7.50 (m, 10H), 7.64 (t, $J=7.4$ Hz, 2H), 7.73 (t, $J=7.4$ Hz, 1H), 8.11 (d, $J=7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.42, 14.69, 21.80, 22.53, 25.14, 25.35, 25.61, 26.81, 28.55, 29.17, 35.48, 35.61, 42.91, 43.11, 45.58, 54.95, 58.59, 72.23, 72.40, 73.18, 74.95, 75.09, 76.55, 79.35, 81.18, 84.45, 127.13, 128.46, 128.79, 128.82, 129.12, 129.23, 130.30, 132.06, 132.06, 133.46, 133.72, 133.81, 138.08, 141.83, 167.17, 170.51, 170.89, 176.31, 203.89; HRMS (FAB, DCM/NBA) m/z calcd for $C_{52}H_{59}NO_{14}\cdot H^+$: 922.3935. Found: 922.4019.

10-*Trans*-crotonoyl-10-deacetylpaclitaxel (18f). Yield 48%; mp 145–147 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 3H), 1.23 (br s, 6H), 1.68 (s, 3H), 1.80 (m, 1H), 1.88 (d, 3H), 2.19 (s, 2H), 2.20 (s, 3H), 2.26 (s, 3H), 2.51 (m, 3H), 3.52 (br s, 1H), 3.87 (d, $J=6.8$ Hz, 1H), 4.08 (d, $J=8.2$ Hz, 1H), 4.26 (d, $J=8.2$ Hz, 1H), 4.45 (dd, $J=6.7$ Hz, 9.9 Hz, 1H), 4.80 (t, 1H), 4.92 (d, $J=9.7$ Hz, 1H), 5.61 (d, $J=6.8$ Hz, 1H), 5.92 (d, $J=15$ Hz, 1H), 6.01 (dd, $J=9.9$, 6.0 Hz, 1H), 6.23 (t, 3H), 6.32 (s, 1H), 6.97 (d, $J=6.0$, 1H), 7.37–7.51 (m, 10H), 7.59 (m, 1H),

7.61 (t, 2H), 7.73 (t, 1H), 8.12 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.04, 14.72, 18.12, 21.81, 22.53, 26.85, 35.51, 35.61, 40.69, 43.10, 45.57, 54.97, 58.62, 72.27, 72.37, 76.50, 73.21, 74.97, 75.27, 79.10, 81.19, 84.46, 121.69, 127.13, 128.46, 128.79, 128.82, 129.12, 129.23, 130.31, 130.30, 132.06, 133.40, 133.82, 138.06, 142.12, 147.38, 166.37, 167.18, 170.53, 172.84, 203.94; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{49}H_{53}NO_{14}\cdot H^+$: 880.3465. Found: 880.3544.

10-Benzoyl-10-deacetylpaclitaxel (18g). Yield 46%; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 1.33 (s, 3H), 1.71 (s, 3H), 1.81 (dt, 1H), 1.83 (s, 3H), 2.21 (m, 2H), 2.40 (s, 3H), 2.38–2.60 (m, 2H), 3.56 (br s, 1H), 3.87 (d, J = 6.9 Hz, 1H), 4.21 (d, J = 8.4 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.49 (dd, J = 6.7 Hz, 10.2 Hz, 1H), 4.80 (d, J = 2.7, 1H), 4.97 (d, J = 9.0 Hz, 1H), 5.72 (d, J = 6.9 Hz, 1H), 5.79 (dd, J = 9.0, 2.7, 1H), 6.27 (t, 1H), 6.54 (s, 1H), 7.00 (d, J = 9.0, 1H), 7.24–7.88 (m, 16H), 8.05 (d, 2H), 8.16 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.42, 13.99, 15.12, 21.21, 22.50, 26.44, 35.56, 35.94, 40.86, 42.91, 45.78, 55.34, 58.60, 72.09, 72.54, 73.56, 74.85, 75.85, 76.40, 79.25, 81.16, 84.44, 127.16, 127.31, 128.62, 128.76, 128.81, 129.23, 129.69, 130.31, 130.12, 132.10, 132.80, 133.88, 138.73, 142.29, 167.14, 167.36, 169.71, 171.77, 172.64, 203.51; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{52}H_{53}NO_{14}\cdot H^+$: 916.3465. Found: 916.3478.

10-Phenylacetyl-10-deacetyl-*epi*-paclitaxel (18 h′). Yield 40%; mp 159–161 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.81 (dt, 1H), 2.02 (s, 3H), 2.21 (m, 2H), 2.19 (s, 3H), 2.38–2.60 (m, 3H), 3.60 (br s, 1H), 3.82 (s, 2H), 3.84 (d, J = 6.9 Hz, 1H), 4.15 (d, J = 8.4 Hz, 1H), 4.27 (d, J = 8.4 Hz, 1H), 4.45 (dd, J = 6.7 Hz, 10.2 Hz, 1H), 4.64 (d, J = 2.7, 1H), 4.95 (d, J = 9.0 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.76 (dd, J = 9.0, 2.7, 1H), 6.15 (t, 1H), 6.33 (s, 1H), 6.92 (d, J = 9.0, 1H), 7.24–7.63 (m, 16H), 7.74 (d, 2H), 8.04 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.42, 13.99, 15.12, 21.21, 22.50, 26.44, 35.56, 35.94, 40.86, 42.91, 45.78, 55.34, 58.60, 72.09, 72.54, 73.56, 74.85, 75.85, 76.40, 79.25, 81.16, 84.44, 127.16, 127.31, 128.62, 128.76, 128.81, 129.23, 129.69, 130.31, 130.12, 132.10, 132.80, 133.88, 138.73, 142.29, 167.14, 167.36, 169.71, 171.77, 172.64, 203.51; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{53}H_{55}NO_{14}\cdot H^+$: 930.3622. Found: 930.3699.

10-*N*,*N*-Dimethylcarbamoyl-10-deacetylpaclitaxel (18i). Yield 55%; mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.81 (dt, 1H), 1.89 (s, 3H), 2.21 (m, 2H), 2.38 (s, 3H), 2.49 (m, 1H), 2.95 (s, 3H), 3.04 (s, 3H), 3.79 (d, J = 6.9 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.43 (dd, J = 6.7 Hz, 10.2 Hz, 1H), 4.78 (d, J = 2.7, 1H), 4.94 (d, J = 9.0 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 5.80 (dd, J = 9.0, 2.7, 1H), 6.22 (m, 2H), 7.02 (d, J = 9.0, 1H), 7.34–7.55 (m, 10H), 7.59 (t, 2H), 7.73 (t, 1H), 8.13 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.68, 15.26, 22.51, 22.97, 27.39, 35.79, 36.09, 36.39, 37.00, 43.10, 45.54, 45.97, 55.40, 60.97, 73.83, 73.93, 74.66, 76.40, 77.49, 77.58, 80.61, 80.67, 84.08, 121.69, 127.13, 128.46, 128.79, 128.82, 129.12, 129.23, 130.31, 130.30, 132.06, 133.40, 133.82, 138.06, 142.12, 147.38, 166.37, 167.18, 170.53, 172.84, 206.25; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{48}H_{54}N_2O_{14}\cdot H^+$: 883.3574. Found: 883.3562.

10-(4-Morpholine-*N*-carbonyl)-10-deacetylpaclitaxel (18j). Yield 55%; mp 177–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 3H), 1.22 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.83 (s, 3H), 2.04 (s, 3H), 2.24 (m, 2H), 2.38 (s, 3H), 2.43–2.55 (m, 1H), 3.40–3.75 (m, 8H), 3.80 (d, J = 6.9 Hz, 1H), 4.11 (d, J = 8.3 Hz, 1H), 4.28 (d, J = 8.3 Hz, 1H), 4.45 (dd, J = 6.7 Hz, 10.2 Hz, 1H), 4.79 (d, J = 2.4 Hz, 1H), 4.95 (d, J = 8.9 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 5.80 (dd, J = 8.7, 2.4 Hz, 1H), 6.27 (m, 2H), 7.35–7.51 (m, 10H), 7.58 (t, J = 7.4 Hz, 2H), 7.73 (t, J = 7.4 Hz, 1H), 8.12 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.28, 14.85, 22.20, 22.53, 26.98, 35.36, 35.64, 43.07, 45.52, 54.97, 58.55, 72.38, 72.47, 73.18, 74.99, 76.29, 79.12, 82.19, 84.56, 127.11, 127.13, 128.45, 128.78, 128.81, 129.12, 129.21, 130.30, 132.06, 132.32, 133.71, 133.82, 138.09, 142.78, 155.09, 167.17, 170.51, 170.48, 172.88, 205.51; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{50}H_{56}N_2O_{14}\cdot H^+$: 925.3680. Found: 925.3794.

General procedure for the hydrogenation reactions

A solution of taxoids **18f**, **24b**, **31a**,**b**, **31a′** or **40b** in methanol was subjected to hydrogenation in the presence of 10% Pd/C (30–50% by weight of starting material) at ambient temperature and pressure for 24 h. The solution was filtered through a pad of Celite to remove the catalyst and concentrated in vacuo. The crude products were purified by chromatography on silica gel (hexane/EtOAc = 1:1 or 1:2) to afford final taxoid **18k**, **32**, **33a**,**b**, **33a′** or **40c** as a white solid.

10-Butanoyl-10-deacetylpaclitaxel (18k). Yield 95%; mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J = 7.2 Hz, 3H), 1.41 (s, 3H), 1.24 (s, 3H), 1.68 (s, 3H), 1.70–1.77 (m, 4H), 1.79 (s, 3H), 1.82–2.00 (m, 1H), 2.28–2.33 (m, 1H), 2.39 (s, 3H), 2.35–2.53 (m, 2H), 3.80 (d, J = 6.9 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.42 (dd, 1H), 4.78 (d, J = 2.7 Hz, 1H), 4.95 (d, J = 9.6 Hz, 1H), 5.67 (d, J = 7.2 Hz, 1H), 5.79 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 6.25 (m, 2H), 6.96 (d, J = 8.7 Hz, 1H), 7.26–7.75 (m, 8H), 8.12 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.89, 10.43, 14.70, 21.61, 22.54, 26.77, 28.46, 34.76, 35.53, 35.64, 43.11, 46.54, 54.97, 58.60, 72.22, 72.40, 73.19, 75.74, 75.98, 76.61, 80.28, 81.18, 84.43, 128.13, 128.47, 128.79, 128.82, 129.13, 129.23, 130.13, 130.31, 132.07, 133.37, 133.71, 133.83, 138.08, 141.96, 167.17, 170.53, 172.88, 174.80, 203.93; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{49}H_{55}NO_{14}\cdot H^+$: 882.3622. Found: 882.3702.

2-Debenzoyl-2-acetyl-7-triethylsilyl-13-oxo-baccatin III (22a). Oxo-baccatin **21**[38] (55 mg, 0.093 mmol) and DMAP (6 mg, 0.046 mmol) were dissolved in 4 mL of methylene chloride. Triethylamine (28 mg, 0.279 mmol) and acetic anhydride (19 mg, 0.186 mmol) were added dropwise and the reaction mixure was stirred at room temperature for 5 h. The reaction was quenched with 10 mL of saturated aqueous solution of ammonium chloride

and extracted with 2×30 mL of methylene chloride dried over magnesium sulfate filtered and concentrated in vacuo. Chromatography on silica gel (hexane/EtOAc = 1:1) afforded 72 mg (95%) of **22a** as a clear film: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.56 (q, J = 7.8 Hz, 6H), 0.90 (t, J = 7.8 Hz, 9H), 1.15 (s, 3H), 1.19 (s, 3H), 1.59 (s, 3H), 1.81–1.87 (m, 1H), 2.06 (s, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 2.20 (s, 3H), 2.27–2.54 (m, 1H), 2.53 (d, J = 20.1 Hz, 1H), 2.76 (d, J = 20.1 Hz, 1H), 3.77 (d, J = 6.3 Hz, 1H), 4.16 (d, J = 8.4 Hz, 1H), 4.40–4.49 (m, 2H), 4.90 (d, J = 7.8 Hz, 1H), 5.38 (d, J = 6.3 Hz, 1H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.09, 6.56, 9.39, 13.40, 17.91, 20.70, 21.18, 21.50, 32.91, 37.05, 42.08, 43.35, 46.06, 59.37, 72.14, 72.53, 76.03, 76.18, 76.50, 78.22, 80.21, 84.06, 140.39, 152.92, 169.02, 170.41, 172.02, 198.59, 200.46; HRMS (FAB, DCM/NBA) m/z calcd for $C_{31}H_{46}O_{11}Si{\cdot}H^+$: 637.3031. Found: 637.3026.

General procedure for the preparation of taxoids 23a and 23b

7-TES-13-oxo-baccatin **22a** or **22b**[38] (50 mg, 0.084 mmol) were dissolved in 4 mL of methanol and 1 mL of THF, and $NaBH_4$ (100 mg, 2.0 mmol) was added in small portions at 0 °C. The reaction mixture was stirred for 5 h. Addition of more $NaBH_4$ was necessary for the reduction of **22b** and in this case the solution was warmed up to room temperature. The reaction was quenched with 10 mL of saturated aqueous solution of ammonium chloride and stirred for 5 min. The aqueous layer was extracted with 2×30 mL of ethyl acetate, dried over magnesium sulfate, filtered and concentrated. Chromatography on silica gel (hexane/EtOAc = 1:2) afforded taxoid **23a** or **23b**[38] as a white film.

2-Debenzoyl-2-acetyl-7-triethylsilylbaccatin III (23a). Yield 97%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.48–0.51 (m, 6H), 0.84 (t, J = 7.8 Hz, 9H), 1.01 (s, 3H), 1.13 (s, 3H), 1.61 (s, 3H), 1.57–1.60 (m, 1H), 2.08–2.12 (m, 1H), 2.07 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.41–2.56 (m, 1H), 3.73 (d, J = 6.3 Hz, 1H), 4.17 (d, J = 8.4 Hz, 1H), 4.41–4.48 (m, 2H), 4.79 (bt, 1H), 4.93 (d, J = 9.3 Hz, 1H), 5.33 (d, J = 6.6 Hz, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.12, 6.59, 9.74, 14.78, 19.81, 20.81, 21.36, 22.52, 26.72, 37.11, 37.83, 42.71, 47.12, 58.60, 67.88, 72.25, 74.29, 75.77, 76.57, 78.49, 80.56, 84.38, 132.69, 144.16, 169.48, 171.08, 172.23, 202.43; HRMS (FAB, DCM/NBA) m/z calcd for $C_{31}H_{48}O_{11}Si{\cdot}H^+$: 639.3142. Found: 639.3196.

2-Debenzoyl-2-acetylpaclitaxel (24a). Yield 50%; mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 3H), 1.22 (s, 3H), 1.62 (s, 3H), 1.57–1.60 (m, 1H), 1.76 (s, 3H), 1.19–2.00 (m, 1H), 2.04 (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 2.23–2.58 (m, 2H), 3.51 (d, 1H), 3.67 (d, J = 6.3 Hz, 1H), 4.21 (d, J = 8.4 Hz, 1H), 4.36 (m, 1H), 4.48 (d, J = 8.4 Hz, 1H), 4.75 (d, 1H), 4.94 (d, J = 9.3 Hz, 1H), 5.39 (d, J = 6.6 Hz, 1H), 5.72 (m, 1H), 6.18 (m, 1H), 6.23 (s, 1H), 6.93 (m, 1H), 7.34–7.56 (m, 8H), 7.78 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.34, 14.71, 20.72, 21.38, 21.46, 22.53, 26.79, 35.16, 35.44, 43.09, 45.48, 54.95, 58.56, 72.08, 72.64, 72.79, 74.47, 75.55, 76.55, 78.76, 80.88, 84.54, 127.13, 127.19, 128.46, 128.83, 129.11, 132.10, 133.29, 138.17, 142.13, 167.27, 170.46, 171.39, 172.04, 173.08, 203.86; HRMS (FAB, DCM/NBA) m/z calcd for $C_{42}H_{49}NO_{14}{\cdot}H^+$: 792.3152. Found: 792.3256.

2-Debenzoyl-2-(3-methylbut-2-enoyl)paclitaxel (24b). Yield 49%; mp 165–167 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (s, 3H), 1.23 (s, 3H), 1.63 (s, 3H), 1.57–1.60 (m, 1H), 1.76 (s, 3H), 1.19–2.00 (m, 1H), 1.97 (s, 3H), 2.20 (s, 3H), 2.22 (s, 3H), 2.25 (s. 3H), 2.23–2.58 (m, 2H), 3.51 (bs, 1H), 3.68 (d, 1H), 4.18 (d, J = 6.3 Hz, 1H), 4.21 (d, J = 8.4 Hz, 1H), 4.36 (dd, 1H), 4.44 (d, J = 8.4 Hz, 1H), 4.75 (d, 1H), 4.94 (d, J = 9.3 Hz, 1H), 5.44 (d, J = 6.6 Hz, 1H), 5.70–5.75 (m, 2H), 6.19 (m, 1H), 6.23 (s, 1H), 6.96 (m, 1H), 7.34–7.56 (m, 8H), 7.78 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.44, 14.72, 20.54, 20.74, 21.51, 22.59, 26.82, 27.64, 35.48, 35.54, 43.18, 45.69, 54.91, 58.63, 72.12, 72.74, 72.86, 73.22, 75.62, 76.58, 78.58, 80.99, 84.50, 115.28, 127.14, 127.19, 128.45, 128.45, 128.82, 129.10, 132.08, 133.51, 138.80, 138.21, 141.97, 160.75, 167.26, 170.53, 171.42, 173.03, 203.99; HRMS (FAB, DCM/NBA) m/z calcd for $C_{45}H_{53}NO_{14}{\cdot}H^+$: 832.3465. Found: 832.3472.

7,10,13-Tris(triethylsilyl)-2-debenzoyl-10-deacetylbaccatin III (26). To a solution of 7,10,13-tris(triethylsilyl)-10-deacetylbaccatin III (**25**) (375 mg, 0.423 mmol) in dry THF (20 mL) at −10 °C was added dropwise a solution of Red-Al in toluene (0.317 mL, 65% wt), and the reaction mixture was stirred for 20 min at −10 °C. The reaction was quenched with aqueous saturated ammonium chloride solution (20 mL), and the aqueous layer was extracted with ethyl acetate (50 mL×3). The combined extracts were then dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 1:5) to afford **26** as a white solid (95% yield): mp 68–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.57 (m, 18H), 0.94 (m, 27H), 1.11 (s, 3H), 1.16 (s, 3H), 1.55 (s, 3H), 1.87 (m, 1H), 1.88 (s, 3H), 1.94 (m, 1H), 2.00 (m, 1H), 2.12 (s, 3H), 2.47 (m, 1H), 3.42 (d, J = 6.6 Hz, 1H), 3.80 (d, J = 6.6 Hz, 1H), 4.31 (dd, J = 10.4, 6.5 Hz, 1H), 4.50 (d, J = 9.0 Hz, 1H), 4.57 (d, J = 9.1 Hz, 1H), 4.63 (s, 1H), 4.89 (d, J = 8.3 Hz, 1H), 4.91 (m, 1H), 5.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.7, 5.1, 5.8, 6.7, 6.8, 10.5, 14.4, 20.5, 22.3, 37.3, 40.3, 42.5, 58.1, 65.0, 66.3, 72.6, 74.6, 75.7, 77.9, 78.5, 81.9, 83.7, 126.8, 127.4, 128.4, 135.9, 138.9, 169.6, 206.3; HRMS (FAB, DCM/NBA) m/z calcd for C40H74O9Si3·H+: 783.4719. Found: 783.4726.

2-Debenzoyl-2-cinnamoylpaclitaxel (31a). Yield 48%; mp 167–169 °C; ^{1}H NMR (CDCl3, 300 MHz) δ 1.12 (s, 3H), 1.24(s, 3H), 1.66 (s, 3H), 1.79 (s, 3H), 1.8 (m, 2H), 2.23 (s, 3H), 2.35 (s, 3H), 2.45 (m, 1H), 2.55 (m, 1H), 3.51 (d, J = 4.5 Hz, 1H), 3.75 (d, J = 6.9 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 4.39 (m, 1H), 4.47 (d, J = 8.4 Hz, 1H), 4.79 (m, 1H), 4.95 (d, J = 8.1 Hz, 1H), 5.54 (d, J = 6.9 Hz, 1H), 5.79 (dd, J = 1.8 Hz, J = 8.7 Hz, 1H), 6.26 (m, 2H), 6.45 (d, J = 15.9 Hz, 1H), 6.96 (d, J = 9 Hz, 1H), 7.35 (m, 11H), 7.62 (m, 2H), 7.73 (m, 2H), 7.83 (d, J = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.50, 15.29, 20.81, 21.51, 22.69, 26.77, 35.58, 36.06,

45.88, 55.41, 58.62, 72.18, 72.69, 73.60, 74.45, 75.57, 79.22, 81.12, 84.55, 116.97, 127.09, 127.22, 128.34, 128.49, 128.71, 129.03, 129.13, 130.98, 131.54, 131.98, 133.86, 142.32, 147.11, 167.27, 169.58, 170.46, 171.39, 173.0, 203.86; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{49}H_{53}NO_{14}\cdot H^+$: 880.3465. Found: 880.3547.

2-Debenzoyl-2-cinnamoyl-*epi*-paclitaxel (31a′). Yield 47%; mp 166–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 3H), 1.21 (s, 3H), 1.67 (s, 3H), 1.57–1.63 (m, 1H), 1.19–2.02 (m, 1H), 2.04 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 2.23–2.59 (m, 2H), 3.80 (d, *J* = 6.2 Hz, 1H), 4.20 (d, *J* = 8.3 Hz, 1H), 4.46 (m, 1H), 4.64 (d, *J* = 8.3 Hz, 1H), 4.98 (d, *J* = 9.3 Hz, 1H), 5.51 (d, *J* = 6.6 Hz, 1H), 5.76 (d, *J* = 8.5 Hz, 1H), 6.16 (t, *J* = 8 Hz, 1H), 6.32 (s, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.92 (d, *J* = 9 Hz, 1H), 7.34–7.65 (m, 13H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.85 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.48, 15.29, 20.83, 21.51, 22.70, 26.79, 35.58, 36.04, 45.88, 55.42, 58.65, 72.19, 72.68, 73.60, 74.47, 75.57, 76.55, 79.19, 81.12, 84.48, 116.89, 127.07, 127.29, 128.36, 128.50, 128.74, 129.09, 129.19, 131.15, 131.52, 131.96, 133.88, 142.33, 147.22, 167.27, 169.59, 170.54, 171.39, 173.0, 203.92; HRMS (FAB, DCM/NBA) *m*/z calcd for $C_{49}H_{53}NO_{14}\cdot H^+$: 880.465. Found: 880.3451.

2-Debenzoyl-2-(3,3-dimethyl-pent-4-enoyl)paclitaxel (31b). Yield 50%; mp 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 3H), 1.18 (s, 6H), 1.21 (s, 3H), 1.60 (s, 3H), 1.57–1.60 (m, 1H), 1.74 (s, 3H), 1.91–2.00 (m, 1H), 2.09–2.19 (m, 2H), 2.21 (s, 3H), 2.26 (s, 3H), 2.33–2.61 (m, 2H), 3.58 (bs, 1H), 3.65 (d, *J* = 6.9 Hz, 1H), 4.19 (d, *J* = 8.1 Hz, 1H), 4.33 (dd, 1H), 4.48 (d, *J* = 8.1 Hz, 1H), 4.76 (s, 1H), 4.93 (d, *J* = 8.4 Hz, 1H), 5.02 (m, 2H), 5.38 (d, *J* = 6.6 Hz, 1H), 5.74 (d, *J* = 6.9 Hz, 1H), 5.97 (dd, *J* = 10.8 Hz, 1H), 6.18 (m, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.32–7.56 (m, 8H), 7.77 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.29, 15.15, 20.67, 21.31, 22.48, 26.55, 26.73, 27.12, 35.45, 36.04, 36.19, 42.95, 45.76, 47.33, 55.31, 58.58, 72.13, 72.63, 73.54, 74.19, 75.52, 77.20, 78.88, 80.83, 84.63, 111.51, 127.15, 127.28, 128.56, 128.81, 129.21, 132.08, 132.87, 133.88, 138.75, 142.34, 146.92, 167.30, 169.75, 171.33, 172.61, 172.65, 203.90; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{47}H_{57}NO_{14}\cdot H^+$: 860.3778. Found: 860.3791.

2-Debenzoyl-2-(3,3-dimethyl-pent-4-enoyl)-*epi*-paclitaxel (31b′). Yield 48%; mp 173–175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 3H), 1.19 (s, 6H), 1.23 (s, 3H), 1.61 (s, 3H), 1.57–1.61 (m, 1H), 1.75 (s, 3H), 1.91–2.02 (m, 1H), 2.09–2.19 (m, 2H), 2.21 (s, 3H), 2.26 (s, 3H), 2.35–2.67 (m, 2H), 3.59 (bs, 1H), 3.65 (d, *J* = 6.9 Hz, 1H), 4.19 (d, *J* = 8.1 Hz, 1H), 4.36 (dd, 1H), 4.47 (d, *J* = 8.1 Hz, 1H), 4.75 (s, 1H), 4.93 (d, *J* = 8.3 Hz, 1H), 5.01 (m, 2H), 5.36 (d, *J* = 6.6 Hz, 1H), 5.75 (d, *J* = 6.9 Hz, 1H), 5.98 (dd, *J* = 10.8 Hz, 1H), 6.19 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 1H), 7.31–7.58 (m, 8H), 7.76 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.32, 15.22, 20.67, 21.33, 22.49, 26.53, 26.74, 27.13, 35.48, 36.04, 36.23, 42.97, 45.76, 47.31, 54.31, 57.58, 72.13, 71.63, 73.67, 74.25, 75.53, 77.21, 78.83, 80.83, 84.64, 112.51, 127.15, 127.31, 128.58, 128.85, 129.26, 133.14, 132.92, 133.89, 138.80, 142.32, 146.91, 167.31, 169.78, 171.29, 172.64, 172.66, 203.95; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{47}H_{57}NO_{14}\cdot H^+$: 860.3778. Found: 860.3798.

2-Debenzoyl-2-(3-methylbutanoyl)paclitaxel (32). Yield 97%; mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (d, *J* = 1.8 Hz, 3H), 1.01 (d, *J* = 1.8 Hz, 3H), 1.08 (s, 3H), 1.22 (s, 3H), 1.62 (s, 3H), 1.75 (s, 3H), 1.82–2.00 (m, 1H), 2.02–2.21 (m, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 2.35–2.53 (m, 2H), 3.47 (bs, 1H), 3.67 (d, *J* = 6.6 Hz, 1H), 4.19 (d, *J* = 7.2 Hz, 1H), 4.45 (m, 1H), 4.48 (d, *J* = 8.1 Hz, 1H), 4.75 (bs, 1H), 4.95 (d, *J* = 9.0 Hz, 1H), 5.40 (d, *J* = 6.9 Hz, 1H), 5.73 (d, *J* = 6.6 Hz, 1H), 6.20 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.34–7.53 (m, 8H), 7.77 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.44, 14.72, 20.54, 20.74, 21.51, 22.59, 26.82, 27.64, 35.48, 35.54, 43.18, 45.69, 54.91, 58.63, 72.12, 72.74, 72.86, 73.22, 75.62, 76.58, 78.58, 80.99, 84.50, 115.28, 127.14, 127.19, 128.45, 128.45, 128.82, 129.10, 132.08, 133.51, 138.80, 138.21, 141.97, 160.75, 167.26, 170.53, 171.42, 173.03, 203.99; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{45}H_{55}NO_{14}\cdot H^+$: 834.3622. Found: 834.3699.

2-Debenzoyl-2-(3-phenylpropanoyl)paclitaxel (33a). Yield 97%; mp 163–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 3H), 1.20 (s, 3H), 1.60 (s, 3H), 1.75 (s, 3H), 1.77–1.99 (m, 1H), 2.02–2.17 (m, 1H), 2.22 (s, 6H), 2.46–2.80 (m, 4H), 2.98 (t, 2H), 3.48 (bs, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 4.03 (d, *J* = 8.1 Hz, 1H), 4.26 (d, *J* = 8.1 Hz, 1H), 4.34 (dd, 1H), 4.74 (d, 1H), 4.91 (d, *J* = 8.1 Hz, 1H), 5.41 (d, *J* = 6.6 Hz, 1H), 5.73 (d, 1H), 6.16 (t, 1H), 6.22 (s, 1H), 6.93 (d, 1H), 7.34–7.56 (m, 10H), 7.76 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.31, 14.71, 20.72, 21.48, 22.50, 26.75, 30.43, 35.28, 35.43, 36.27, 43.04, 45.43, 54.93, 58.55, 72.08, 72.55, 72.84, 74.53, 75.53, 76.41, 78.68, 80.82, 84.45, 126.62, 127.11, 127.17, 128.45, 128.74, 128.43, 129.10, 132.08, 133.23, 133.80, 138.14, 140.21, 142.07, 167.23, 170.43, 171.39, 173.01, 173.77, 203.84; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{49}H_{55}NO_{14}\cdot H^+$: 882.3622. Found: 882.3702.

2-Debenzoyl-2-(3-phenylpropanoyl)-*epi*-paclitaxel (33a′). Yield 98%; mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 3H), 1.19 (s, 3H), 1.61 (s, 3H), 1.75 (s, 3H), 1.77–1.99 (m, 1H), 2.01–2.17 (m, 1H), 2.21 (s, 6H), 2.47–2.82 (m, 4H), 2.99 (t, 2H), 3.46 (bs, 1H), 3.64 (d, *J* = 6.6 Hz, 1H), 4.02 (d, *J* = 8.1 Hz, 1H), 4.27 (d, *J* = 8.1 Hz, 1H), 4.33 (dd, 1H), 4.73 (d, 1H), 4.94 (d, *J* = 8.1 Hz, 1H), 5.42 (d, *J* = 6.6 Hz, 1H), 5.72 (d, 1H), 6.15 (t, 1H), 6.22 (s, 1H), 6.92 (d, 1H), 7.35–7.55 (m, 10H), 7.75 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.33, 14.69, 20.78, 21.52, 23.22, 26.35, 31.42, 34.78, 35.49, 36.45, 43.31, 45.77, 54.92, 58.54, 72.23, 72.75, 72.87, 74.66, 75.73, 76.39, 79.68, 80.83, 84.46, 126.81, 127.21, 127.29, 128.47, 128.94, 129.08, 129.41, 132.18, 133.29, 133.79, 138.12, 141.35, 143.09, 167.53, 171.44, 171.75, 173.09, 173.70, 203.94; HRMS (FAB, DCM/NBA) *m*/*z* calcd for $C_{49}H_{55}NO_{14}\cdot H^+$: 882.3622. Found: 882.3644.

2-Debenzoyl-2-(3,3-dimethylpentanoyl)paclitaxel (33b). Yield 96%; mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 1.8 Hz, 3H), 1.00 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H), 1.22 (s, 3H), 1.34–1.50 (m, 2H), 1.61

(s, 3H), 1.74 (s, 3H), 1.87–1.93 (m, 1H), 2.18–2.27 (m, 1H), 2.22 (s, 3H), 2.24 (s, 3H), 2.46–2.80 (m, 2H), 3.52 (bs, 1H), 3.68 (d, $J=6.6$ Hz, 1H), 4.18 (d, $J=8.1$ Hz, 1H), 4.34 (dd, 1H), 4.52 (d, $J=7.8$ Hz, 1H), 4.74 (bs, 1H), 4.95 (d, $J=8.1$ Hz, 1H), 5.37 (d, $J=6.9$ Hz, 1H), 5.74 (dd, 1H), 6.17 (t, 1H), 6.23 (s, 1H), 6.97 (d, 1H), 7.34–7.56 (m, 8H), 7.77 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.46, 9.45, 14.86, 20.83, 21.26, 21.47, 22.58, 26.79, 26.97, 27.07, 33.71, 34.08, 35.12, 35.58, 43.27, 45.74, 45.94, 54.99, 58.63, 72.19, 72.46, 73.11, 73.90, 75.55, 77.21, 78.91, 80.87, 84.51, 127.05, 127.08, 128.34, 128.71, 128.98, 131.96, 133.12, 133.70, 138.05, 141.94, 166.86, 170.38, 171.24, 172.61, 173.56, 203.62; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{47}H_{59}NO_{14}\cdot H^+$: 862.3935. Found: 862.4011.

2-Debenzoyl-2-cyclohexanoylpaclitaxel (35). Yield 50%; mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 3H), 1.21 (s, 3H), 1.63 (s, 3H), 1.20–1.60 (m, 13H), 1.74 (s, 3H), 2.22 (s, 3H), 2.26 (s. 3H), 2.23–2.58 (m, 2H), 3.65 (d, $J=7.3$ Hz, 1H), 4.16 (d, $J=8.0$ Hz, 1H), 4.35 (bs, 1H), 4.46 (d, 1H), 4.74 (d, 1H), 4.75 (d, 1H), 4.94 (d, $J=8.1$ Hz, 1H), 5.42 (d, $J=7.3$ Hz, 1H), 5.73 (dd, 1H), 6.17 (t, 1H), 6.22 (s, 1H), 6.99 (d, 1H), 7.34–7.56 (m, 8H), 7.78 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.34, 14.70, 20.72, 21.50, 22.46, 25.05, 25.47, 25.59, 26.78, 28.35, 29.29, 35.10, 35.49, 43.05, 45.48, 45.41, 55.05, 58.60, 72.14, 72.34, 73.21, 74.22, 75.53, 76.55, 79.07, 80.91, 84.52, 127.13, 127.14, 128.43, 128.81, 129.08, 132.08, 133.17, 138.11, 142.08, 171.39, 172.89, 177.24, 203.87; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{47}H_{57}NO_{14}\cdot H^+$: 860.3778. Found: 860.3771.

Preparation of 2′-triisopropylsilyl-7-triethylsilylpaclitaxel (36) and 2′-triisopropylsilyl-7-triethylsilyl-*epi*-paclitaxel (39). To a solution of 7-TES-baccatin III (48 mg, 0.068 mmol) and β-lactam **5a** or **5b** (44 mg, 0.103 mmol) in dry THF (2 mL) was added dropwise LiHMDS (0.103 mmol) at −40 °C with stirring. After stirring 1 h the reaction was quenched with saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate, then the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc = 4:1) afforded **36** or **39** as a white solid.

2′-Triisopropylsilyl-7-triethylsilylpaclitaxel (36). Yield 70%, based on 83% conversion; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.59 (m, 6H), 0.92 (m, 30H), 1.17 (s, 3H), 1.21 (s, 3H), 1.70 (s, 3H), 1.90 (m, 1H), 2.04 (s, 3H), 2,17 (s, 3H), 2.28–2.49 (m, 3H), 2.54 (s, 3H), 3.83 (d, $J=7.0$ Hz, 1H), 4.20 (d, $J=8.4$ Hz, 1H), 4.30 (d, $J=8.4$ Hz, 1H), 4.48 (m, 1H), 4.93 (m, 2H), 5.71 (m, 2H), 6.22 (t, $J=8.8$ Hz, 1H), 6.45 (s, 1H), 7.11 (d, $J=8.8$ Hz, 1H), 7.29–7.61 (m, 11H), 7.74 (d, $J=7.1$ Hz, 2H), 8.13 (d, $J=7.1$ Hz, 2H); ^{13}C NMR (CDCl3, 75 MHz) δ 5.28, 6.72, 10.10, 12.54, 14.22, 17.77, 17.83, 20.83, 21.48, 23.01, 26.51, 35.69, 37.18, 43.29, 46.68, 55.94, 58.38, 71.64, 72.20, 74.89, 74.96, 75.64, 76.55, 78.81, 81.14, 84.23, 126.33, 126.89, 127.91, 128.69, 129.21, 130.01, 130.21, 131.72, 133.56, 133.98, 138.24, 140.15, 166.78, 167.00, 169.27, 170.03, 171.70, 201.66.

Preparation of 2′-triisopropylsilylpaclitaxel (37) and 2′-triisopropylsilyl-*epi*-paclitaxel (40). 7-TES-2′-TIPS-paclitaxel (**36**) or 7-TES-2′-TIPS-*epi*-paclitaxel (**39**) (44 mg, 0.039 mmol) and 0.1 N HCl in ethanol (2 mL) was stirred at room temperature for 18 h, then the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Purification by chromatography on silica gel (hexane/EtOAc = 2:1) gave 2′-TIPS-paclitaxel (**37**) or gave 2′-TIPS-*epi*-paclitaxel (**40**) as a white solid.

2′-Triisopropylsilylpaclitaxel (37). Yield 75%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (m, 21H), 1.13 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.89 (m, 1H), 1.92 (s, 3H), 2,17 (m, 1H), 2.22 (s, 3H), 2.35–2.49 (m, 2H), 2.53 (s, 3H), 3.83 (d, $J=6.9$ Hz, 1H), 4.22 (d, $J=8.4$ Hz, 1H), 4.31 (d, $J=8.4$ Hz, 1H), 4.43 (m, 1H), 4.94 (m, 2H), 5.70 (t, $J=7.5$ Hz, 2H), 6.25 (m, 2H), 7.11 (d, $J=9.0$ Hz, 1H), 7.30–7.59 (m, 11H), 7.74 (d, $J=7.2$ Hz, 2H), 8.18 (d, $J=7.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.61, 12.51, 14.90, 17.75, 17.80, 20.80, 22.32, 22.92, 26.74, 35.52, 35.94, 43.20, 45.47, 55.92, 58.47, 71.61, 72.08, 75.05, 75.52, 75.67, 76.55, 79.11, 81.11, 84.43, 126.30, 126.89, 127.98, 128.69, 128.75, 129.13, 130.21, 131.21, 132.83, 133.59, 133.95, 138.21, 142.45, 166.82, 166.95, 170.02, 171.26, 171.62, 203.72.

7-Acetylpaclitaxel (38a). 2′-TIPS-paclitaxel (37, 38 mg, 0.038 mmol) and DMAP (2 mg, 0.009 mmol) were dissolved in 3 mL of methylene chloride. Triethylamine (12 mg, 0.114 mmol) and acetic anhydride (5 mg, 0.046 mmol) were added dropwise and the reaction mixure was stirred at room temperature for 5 h. The reaction was quenched with 10 mL of saturated aqueous solution of ammonium chloride and extracted with 2×30 mL of methylene chloride dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica gel (hexane/EtOAc = 1:1) afforded the product of as a clear film (95%), which was dissolved in 1.5 mL of pyridine and 1.5 mL of acetonitrile. 0.5 mL of HF/pyridine (70% wt solution) at 0 °C was added and the reaction mixture was allowed to warm up to room temperature and stir overnight. The reaction was quenched with 10 mL of saturated aqueous solution of copper sulfate. The aqueous layer was extracted with 3×30 mL of ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica gel (hexane/EtOAc = 2:1) afforded 7-acetylpaclitaxel (**38a**) as a white solid (89%): mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 3H), 1.19 (s, 3H), 1.80 (s, 6H), 1.95 (m, 1H), 2.03 (s, 3H), 2.16 (s, 3H), 2.31 (d, 2H), 2.37 (s, 3H), 2.56–2.62 (m, 1H), 3.90 (d, $J=6.6$ Hz, 1H), 4.16 (d, $J=8.4$ Hz, 1H), 4.30 (d, $J=8.4$ Hz, 1H), 4.79 (d, $J=2.7$ Hz, 1H), 4.93 (d, $J=8.1$ Hz, 1H), 5.53 (dd, $J=6.9$ Hz, 10.5 Hz, 1H), 5.66 (d, $J=6.9$ Hz, 1H), 5.80 (dd, $J=8.7$ Hz, 2.7 Hz, 1H), 6.17 (t, 1H), 6.22 (s, 1H), 7.13 (d, $J=8.7$ Hz, 1H), 7.33–7.50 (m, 10H), 7.61 (t, 1H), 7.76 (d, 2H), 8.11 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.64, 14.49, 20.61, 20.97, 20.43, 26.44, 33.33, 35.45, 43.14, 43.15, 46.99, 54.85, 56.11, 71.35, 72.05, 73.24,

74.27, 75.30, 76.42, 78.47, 81.09, 83.92, 127.13, 126.17, 128.36, 128.77, 128.80, 129.03, 129.15, 130.24, 131.99, 133.04, 133.78, 133.86, 138.14, 140.43, 167.02, 167.08, 169.06, 170.52, 170.60, 172.51, 202.84; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{49}H_{53}NO_{15}\cdot H^+$: 896.3414. Found: 896.3468.

General procedure for the acylation at the C-7 position and deprotection

2′-TIPS-paclitaxel (**37**) or 2′-TIPS-*epi*-paclitaxel (**40**) (30 mg, 0.03 mmol), DMAP, (37 mg, 0.30 mmol), EDC.HCl (58 mg, 0.30 mmol), and various carboxylic acids (0.15 mmol) were dissolved in 2 mL of methylene chloride and stirred at room temperature. The reaction was quenched with 10 mL of saturated aqueous solution of sodium bicarbonate and extracted with 2×30 mL of ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica gel (hexane/EtOAc = 1:2) afforded the products as clear films, which were dissolved in 1.5 mL of pyridine and 1.5 mL of acetonitrile. 0.5 mL of HF/pyridine (70% wt solution) at 0 °C was added and the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with 10 mL of saturated aqueous solution of copper sulfate. The aqueous layer was extracted with 3×30 mL of ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica gel (hexane/EtOAc = 1:1) afforded the final product **38b** or **41a**,**b** as a white solid.

7-(3-Methylbut-2-enoyl)paclitaxel (38b). Yield 88%; mp 167–169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.19 (s, 3H), 1.83 (s, 3H), 1.87 (s, 3H), 1.88 (s, 3H), 1.95 (m, 1H), 2.12 (s, 3H), 2.16 (s, 3H), 2.31 (d, 2H), 2.37 (s, 3H), 2.56–2.62 (m, 1H), 3.94 (d, J = 6.6 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 2.7 Hz, 1H), 4.94 (d, J = 8.1 Hz, 1H), 5.57 (m, 2H), 5.67 (d, J = 6.9 Hz, 1H), 5.81 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 6.17 (t, 1H), 6.31 (s, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.33–7.50 (m, 10H), 7.62 (t, 1H), 7.77 (d, 2H), 8.11 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.92, 14.70, 20.41, 20.74, 22.57, 26.56, 27.42, 30.91, 33.60, 35.55, 43.22, 47.07, 54.83, 56.36, 70.72, 72.15, 73.30, 74.39, 75.18, 76.55, 78.51, 81.19, 84.03, 115.94, 127.07, 128.28, 128.71, 128.96, 130.16, 131.92, 133.19, 133.76, 138.11, 140.14, 156.81, 166.02, 166.88, 168.55, 170.31, 172.31, 202.09; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{52}H_{57}NO_{15}\cdot H^+$: 936.3727. Found: 936.3808.

7-(3-Methylbutanoyl)paclitaxel (38c). Yield 96%; mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.17 (s, 3H), 1.20 (s, 3H), 1.81 (s, 3H), 1.83 (s, 3H), 1.98–2.07 (m, 1H), 2.15 (s, 3H), 2.22–2.29 (m, 4H), 2.37 (s, 3H), 2.56–2.62 (m, 1H), 3.91 (d, J = 6.6 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 2.7 Hz, 1H), 4.93 (d, J = 8.1 Hz, 1H), 5.56 (m, 2H), 5.67 (d, J = 6.9 Hz, 1H), 5.81 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 6.17 (t, 1H), 6.24 (s, 1H), 7.09 (d, J = 8.7 Hz, 1H), 7.33–7.50 (m, 10H), 7.62 (t, 1H), 7.77 (d, 2H), 8.11 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.69, 14.52, 20.62, 22.21, 22.28, 22.45, 25.43, 26.46, 33.42, 35.55, 43.05, 43.16, 46.96, 55.78, 56.19, 71.07, 72.15, 73.22, 74.29, 75.25, 76.57, 78.46, 81.12, 83.92, 127.12, 127.17, 128.41, 128.81, 129.81, 129.07, 129.15, 130.25, 132.03, 133.12, 133.88, 138.13, 140.39, 166.95, 167.06, 168.96, 170.51, 170.65, 172.51, 202.14; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{52}H_{59}NO_{15}\cdot H^+$: 938.3884. Found: 938.3963.

2′-Triisopropylsilyl-7-triethylsilyl-*epi*-paclitaxel (39). Yield 72%, based on 85% conversion; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (m, 6H), 0.91 (m, 30H), 1.18 (s, 3H), 1.22 (s, 3H), 1.70 (s, 3H), 1.91 (m, 1H), 2.03 (s, 3H), 2.17 (s, 3H), 2.28–2.50 (m, 3H), 2.54 (s, 3H), 3.82 (d, J = 7.0 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 4.30 (d, J = 8.4 Hz, 1H), 4.49 (m, 1H), 4.92 (m, 2H), 5.71 (m, 2H), 6.23 (t, J = 8.8 Hz, 1H), 6.46 (s, 1H), 7.11 (d, J = 8.8 Hz, 1H), 7.27–7.60 (m, 11H), 7.74 (d, J = 7.1 Hz, 2H), 8.12 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.29, 6.70, 10.09, 12.51, 14.24, 17.78, 17.84, 20.79, 21.48, 23.11, 26.54, 35.72, 37.22, 43.30, 46.71, 55.93, 58.36, 71.66, 72.28, 74.73, 75.05, 75.69, 78.79, 81.17, 84.23, 126.44, 126.87, 127.91, 128.71, 129.23, 131.01, 131.21, 131.78, 133.64, 134.22, 138.31, 140.08, 166.67, 167.07, 168.29, 170.00, 170.13, 171.76, 202.28.

2′-Triisopropylsilyl-*epi*-paclitaxel (40). Yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (m, 21H), 1.12 (s, 3H), 1.21 (s, 3H), 1.67 (s, 3H), 1.88 (m, 1H), 1.92 (s, 3H), 2.18 (m, 1H), 2.21 (s, 3H), 2.34–2.50 (m, 2H), 2.54 (s, 3H), 3.82 (d, J = 6.9 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.42 (m, 1H), 4.93 (m, 2H), 5.69 (t, J = 7.5 Hz, 2H), 6.24 (m, 2H), 7.12 (d, J = 9.0 Hz, 1H), 7.29–7.59 (m, 11H), 7.73 (d, J = 7.2 Hz, 2H), 8.19 (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.72, 12.58, 14.88, 17.65, 17.77, 20.81, 22.32, 22.94, 26.79, 35.53, 35.94, 43.14, 45.49, 55.88, 58.57, 71.64, 72.18, 75.25, 75.52, 75.69, 76.55, 79.15, 82.17, 84.55, 126.20, 126.88, 127.95, 128.63, 128.69, 129.34, 130.32, 131.49, 132.89, 133.76, 134.11, 138.22, 142.46, 167.52, 166.88, 170.82, 171.29, 172.62, 203.86.

7-Pentanoyl-*epi*-paclitaxel (41a). Yield 95%; mp 154–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 0 7.2 Hz, 3H) 1.16 (s, 3H), 1.19 (s, 3H), 1.30 (m, J = 7.2 Hz, 2H), 1.51–1.63 (m, 4H), 1.80 (s, 3H), 2.07 (s, 3H), 2.15 (s, 3H), 2.17 (s, 3H), 2.21–2.43 (m, 2H), 2.58–2.64 (m, 1H), 3.96 (d, J = 6.6 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.63 (d, J = 2.7 Hz, 1H), 4.94 (d, J = 8.1 Hz, 1H), 5.58 (dd, J = 6.9 Hz, 10.5 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 5.72 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 6.08 (t, 1H), 6.29 (s, 1H), 6.89 (d, J = 8.7 Hz, 1H), 7.36–7.50 (m, 10H), 7.61 (t, 1H), 7.76 (d, 2H), 8.05 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.82, 13.74, 14.96, 20.71, 22.17, 22.51, 26.42, 26.60, 33.41, 33.84, 36.06, 43.13, 47.10, 55.95, 71.12, 72.42, 74.00, 74.37, 75.15, 76.55, 78.47, 80.97, 84.00, 127.10, 127.28, 128.55, 128.68, 129.19, 130.04, 131.95, 132.56, 133.80, 136.87, 140.71, 167.02, 167.08, 169.06, 170.52, 170.60, 172.51, 202.06; HRMS (FAB, DCM/A) *m/z* calcd for $C_{51}H_{57}NO_{15}\cdot H+$: 924.3727. Found: 924.3778.

7-Cinnamoyl-*epi*-paclitaxel (41b). Yield 94%; mp 160–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.20 (s, 3H), 1.80 (m, 2H), 1.88 (s, 3H), 2.07 (s, 3H), 2.10 (s, 3H), 2.20 (s, 3H), 2.36–2.44 (m, 1H), 2.64–2.28 (m, 1H), 4.02 (d, J = 6.6 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.64 (d, J = 2.7 Hz, 1H), 4.98 (d, J = 8.1 Hz, 1H), 5.67–5.75 (m, 3H), 6.09 (t, 1H), 6.37 (d, J = 14.1, 1H), 6.40 (s, 1H), 6.89 (d, J = 8.7 Hz, 1H), 7.35–7.64 (m, 12H), 7.76 (d, 2H), 8.06 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.94, 14.75, 20.12, 20.72, 22.57, 26.56, 27.42, 33.60, 35.58, 43.22, 54.83, 56.41, 70.82, 72.63, 74.36, 75.52, 75.18, 76.55, 78.52, 81.98, 84.83, 116.95, 128.07, 128.38, 128.43, 128.68, 128.86, 129.77, 130.53, 131.11, 131.92, 133.22, 133.74, 134.21, 138.21, 141.15, 158.51, 166.45, 166.68, 167.54, 171.32, 174.36, 202.19; HRMS (FAB, DCM/NBA) m/z calcd for $C_{56}H_{57}NO_{15}\cdot H^+$: 984.3727. Found: 984.3833.

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