Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 4315–4323

BIOORGANIC & MEDICINAL CHEMISTRY

The Discovery of BMS-275183: An Orally Efficacious Novel Taxane

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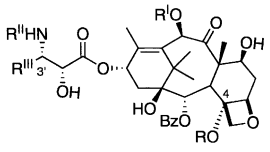
Received 12 March 2003; revised 16 July 2003; accepted 25 July 2003

Abstract—The evolution of **2**, a C-4-methylcarbonate analogue of paclitaxel with minimal oral bioavailability and oral efficacy, into its C-3′-*t*-butyl-3′-*N*-*t*-butyloxycarbonyl analogue (**15i**), a novel taxane with oral efficacy in preclinical models that is comparable to iv administered paclitaxel, is described.

Introduction

Paclitaxel (**1**), the diterpenoid natural product isolated from *Taxus brevifolia* in 1971 by Wani and Wall[1] is the active constituent of the antitumor drug Taxol®. It is a schedule dependent drug whose benefits are obtained through prolonged tumor exposure times.[2] Recently, clinical utility has been demonstrated using repetitive, once-weekly, administrations of moderate (less than maximally tolerated) doses of paclitaxel.[3] An oral taxane would be ideal for such protracted regimens, providing a compliant and cost-effective way of accomplishing an extended duration of exposure. Unfortunately, the oral bioavailability (%F) of paclitaxel is very low[4] and it does not show oral efficacy in preclinical models.[5] This is not surprising when the molecule is viewed in terms of features that are considered predictive of ADME properties.[6,7] Its molecular weight of 854 gm/mole is high, and it carries 15 heteroatoms that can function as H-bond acceptors. Paclitaxel possesses poor aqueous solubility and is subject to efflux mediated by P-gycloprotein (P-gp).[8] In spite of these limitations, recent efforts to identify an orally active taxane have been encouraging. A water-soluble prodrug of a paclitaxel analogue has shown oral efficacy in preclinical in vivo models.[5] Presumably, the improved solubility provides higher drug/prodrug concentrations in the gastrointestinal tract and thereby improves passive absorption. Co-administration of paclitaxel with P-gp blockers[9] such as cyclosporin A have been found to significantly increase the oral bioavailability of paclitaxel. Analogues of 14β-hydroxy-10-deacetylbaccatin show increased efficacy against cancer cell lines that overexpress P-gp and have been reported to exhibit good oral bioavailability and in vivo efficacy.[10] It was suggested that these analogues show better oral absorption because they are no longer good substrates for P-gp mediated efflux in the gastrointestinal tract.



1 R = Ac, R^{I} = Ac, R^{II} = Bz, R^{III} = Ph
2 R = CO_2Me, R^{I} = Ac, R^{II} = Bz, R^{III} = Ph
3 R = Ac, R^{I} = H, R^{II} = Boc, R^{III} = Ph
4 R = Ac, R^{I} = H, R^{II} = Boc, R^{III} = *t*-Bu

Our approach to identifying an orally active taxane was largely empirical. It took advantage of our extensive

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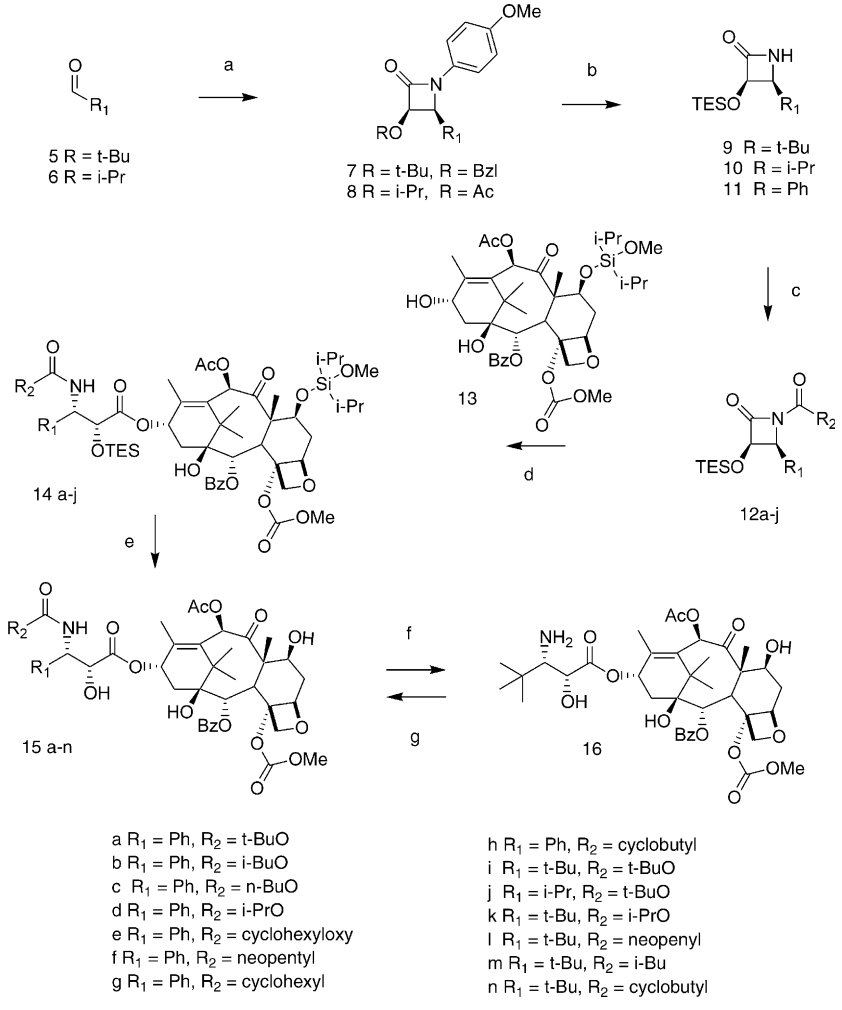
doi:10.1016/S0968-0896(03)00495-4

research experience in the taxane area and the availability of a large inventory of novel analogues that were generated during previous programs to identify second generation taxanes for clinical development. Representative members of that analogue inventory were screened in a mouse oral exposure assay[11] and this provided us with promising leads for an oral analogue program as well as insights into structural features that affect the oral absorption of taxane analogues. One such insight was that more than one structural modification to paclitaxel would probably be required to achieve an acceptable oral bioavailability (%F > 20). A promising lead that emerged was the C-4-methyl carbonate analogue of paclitaxel (**2**), a compound which had already demonstrated excellent in vivo efficacy when administered iv and is currently in clinical trials.[12] It was selected as a starting point in our quest for an orally bioavailable analogue with an in vivo oral efficacy profile that is at least equivalent to iv dosed paclitaxel in preclinical models. This paper[13] describes the highlights of that work, an effort that led to the discovery of BMS-275183 (**15i**), an orally bioavailable and efficacious novel taxane that is currently in Phase I clinical trials.

Analogue Synthesis

Compounds **15a**–**15h** are analogues of **2** that have different *N*-acyl groups at the C-3′ position. Their preparation (Scheme 1) entailed, *N*-acylation of the chiral azetidinone (**11**)[14] with the appropriate acylating agent, base-promoted reaction[15] of the resulting *N*-acylated azetidinones, **12a** to **12h**, with the C-4-carbamate intermediate **13** that is derived from 10-desacetyl baccatin III,[12b] and the final removal of the silyl protecting groups. Preparation of the C-3′-*t*-butyl and C-3′-*i*-propyl analogues, **15i** and **15j**, used the racemic azetidinones, **7** and **8**, that were generated by the Staudinger reaction of the imines derived from trimethylacetaldehyde (**5**) and isobutyraldehyde (**6**) with benzyloxyacetyl chloride and acetoxyacetyl chloride respectively. Oxidative removal of the *N*-*p*-methoxyphenyl groups of **7** and **8** was followed by replacement of the respective benzyl and acetyl groups with the triethylsilyl group to give **9** and **10**. After conversion to their *N*-Boc derivatives, excess racemic **12i** and **12j** was allowed to react with **13** under basic conditions. Removal of the silyl protecting groups from the resulting mixtures of C-2′, C-3′ diastereomers followed by chromatography afforded the major iso-



Scheme 1. (a) *p*-Anisidine, DCM then benzyloxacetylchloride or acetoxyacetylchloride, TEA, DCM, −78 °C to rt; (b) $Ce(NH_4)_2(NO_3)_6$, aq CH_3CN, then H_2, Pd/C, EtOH or K_2CO_3 in MeOH, then TESCI, imidazole (2 equiv), DMF; (c) R_2COCl or $(Boc)_2O$, DIPEA (1.2 equiv), DMAP (0.2 equiv), DCM, 0 °C to rt; (d) **13**, LiHMDS (1.3 equiv), THF; (e) $(HF)_3TEA$ (4 equiv), THF, rt; (f) TFA, DCM; (g) R_2COCl (1.5 equiv), aq $NaHCO_3$, DCM.

mers, **15i** and **15j**, that possessed the natural configuration of substituents at the C-2′ and C-3′ positions. The observed diastereoselectivity is well known for the base-promoted reaction of racemic azetidinones with the C-13-hydroxy group of baccatin derivatives.[14a,16] Compounds **15k** to **15n** are analogues of **15i** that have different C-3′-*N*-acyl groups. They were prepared by first removing the Boc group from **15i** by treatment with TFA and then *N*-acylating the resulting C-3′-amino group using Schotten–Baumann conditions. The latter chemistry is analogous to that which had been used by Georg and coworkers[17] to efficiently generate C-3′-*N*-acyl analogues of paclitaxel.

Results and Discussion

One of several interesting leads that emerged form our oral exposure screen was the C-4-methyl carbonate analogue **2**. It is as potent against the HCT-116, human colon carcinoma, cell line as paclitaxel and slightly more potent in a tubulin polymerization assay (Table 1). More importantly, it exhibits significant efficacy advantages in preclinical in vivo models.[12] Because of its excellent in vivo efficacy, it was considered a prime candidate for optimization in the oral taxane program. It is about 40 times more soluble than paclitaxel[18] and exhibits about 50-fold higher drug plasma levels than paclitaxel in the mouse oral exposure screen. Initial studies with amorphous samples of **2** suggested that it might possess a significant oral bioavailability advantage over paclitaxel but definitive studies with crystalline material demonstrated that it possessed minimal (4%) oral bioavailability in the rat. It lacked oral efficacy in mice verses sc implanted murine neoplasms. For example, when it was administered orally at its maximum tolerated dose (MTD) to mice in the paclitaxel-sensitive M109 Madison murine lung carcinoma model (Table 1), it was found to be more than 2-fold less active than iv administered paclitaxel. Since the program objective was to identify an orally bioavailable taxane that showed comparable or superior efficacy to iv dosed paclitaxel, modifications of the C-3′-phenyl and/or the C-3′-*N*-acyl groups of **2** were explored in an effort to enhance oral bioavailability and efficacy. A systematic screening protocol and decision tier was used to determine which analogues would be advanced. All compounds were initially evaluated in a tubulin polymerization assay and their in vitro cytotoxicity against HCT 116, a human colon tumor cell line that is sensitive to paclitaxel, and HCT 116/VM26, a human colon cell line that is resistant to paclitaxel due to a MDR phenotype overexpressing gp 170, were determined. They were screened for oral exposure in the mouse and those compounds that showed higher drug plasma levels than **2** were evaluated for oral efficacy in the M109 murine lung tumor model. The compounds that showed a log cell kill (LCK) ratio of between 0.8 and 1.2 for the orally dosed analogue versus iv dosed paclitaxel were considered comparable in efficacy to iv dosed paclitaxel in this model and were advanced to the next evaluation tier. Here, their cytotoxicity against A2780, a paclitaxel sensitive human ovarian cancer cell line, and an A2780 cell line that is resistant to paclitaxel due to mutated β-tubulin, were determined together with their oral bioavailability in the rat and oral in vivo efficacy in an A2780, human ovarian carcinoma, tumor xenograft model. The choice of candidates for final preclinical evaluation was based on their performance in this evaluation tier.

A group of C-3′-*N*-alkoxycarbonyl analogues was initially surveyed. Previous SAR studies suggested that the

Table 1. In vitro and preliminary in vivo profile of potential orally-active taxane analogues

	R_1	R_2	Tubulin[a]	HCT-116[b] (nM)	R/S ratio[c]	Mouse oral absorption (ng/mL)[d]	PO/SC M109[e]
1	Phenyl	Phenyl	1.0	4.0	114	84	0.02 (160)
2	Phenyl	Phenyl	0.4	2.3	68	3935	0.4 (32)
15a	Phenyl	*t*-Butoxy	nd	0.33	22	15,626	0.6 (15)[f]
15b	Phenyl	*i*-Butoxy	0.8	2.9	9.9	5718	0.3 (70)
15c	Phenyl	*n*-Butoxy	0.9	1.3	24	6641	0.9 (50)
15d	Phenyl	*i*-Propoxy	1.0	0.62	65	9479	0.1 (13)
15e	Phenyl	Cyclohexyloxy	1.0	0.79	13	10,950	0.7 (25)
15f	Phenyl	Neopentyl	0.9	3.6	24	7877	1.3 (50)
15g	Phenyl	Cyclohexyl	0.4	0.40	76	1759	nd
15h	Phenyl	Cyclobutyl	0.7	0.85	87	5443	1.0 (160)
15i	*t*-Butyl	*t*-Butoxy	0.4	1.8	3.9	7636	0.8 (25)
15j	*i*-Propyl	*t*-Butoxy	0.9	0.53	7.1	7205	0.9 (12)
15k	*t*-Butyl	*i*-Propoxy	0.9	2.6	14	14,656	0.4 (15)
15l	*t*-Butyl	Neopentyl	0.9	14	84	8087	1.0 (160)
15n	*t*-Butyl	*i*-Butyl	0.6	6.1	6	16,853	0.6 (100)
15m	*t*-Butyl	Cyclobutyl	0.8	7.0	>17	18,223	1.1 (60)

[a]Concentration of test compound to give a change of 0.01 OD/h expressed as a ratio to the concentration of paclitaxel.
[b]IC_{50} for HCT-116, human colon tumor, cell line sensitive to paclitaxel.
[c]Ratio of IC_{50} for HCT-116 multi-drug resistant (MDR) cell line/IC_{50} for HCT-116 sensitive cell line. The resistant HCT-116 cell line was established by exposing cells to VM-26 and establishing a cell line resistant to these drugs.
[d]Mouse plasma concentration of the analogue 1 h after oral dosing at 100 mg/kg in 10:10:80 Cremophor EL/ethanol/water.
[e]Madison Murine Lung Carcinoma, M109, tumors implanted sc. The analogue was given orally every day for 5 days beginning 4 days after implantation and paclitaxel given iv on the same schedule. Values presented are a ratio of the log cell kill (LCK) for the analogue (optimum dose in mg/kg/administration)/LCK for iv dosed paclitaxel. Log cell kill is defined as LCK = (T−C/TVDT)/3.32. T−C refers to the difference in days for the tumor to reach target size for the treated versus the control group. TVDT is the tumor volume doubling time. All compounds were administered as solutions in Cremophor EL/ethanol/water mixtures except **15h** for which a Tween 80/water vehicle was used.
[f]This result was confirmed when this study was repeated.

3′-*N*-*t*-butoxycarbonyl analogue **15a** might have improved oral bioavailability and, like docetaxel (**3**), which also has a C-3′-*N*-*t*-butyloxycarbonyl group, exhibit more potent cytotoxicity than paclitaxel **1**.[2] Indeed, **15a** showed an impressive increase in oral exposure in the mouse screen as well as subsequent oral bioavailaibility studies in rats. It was 7-fold more cytotoxic than **2** against the paclitaxel-sensitive HCT-116 cell line but continued to show reduced potency against the paclitaxel-resistant cell line (*R*/*S* ratio of 22) indicating that the 3′-*N*-*t*-butoxycarbonyl group does not significantly reduce susceptibility to MDR based resistance. Unfortunately, **15a** did not show oral efficacy comparable to iv administered paclitaxel in the M109 tumor model and therefore a number of additional 3′-*N*-alkoxycarbonyl analogues, **15b**–**15e,** were prepared to see if it would be possible to modulate the cytotoxicity and thereby achieve improved oral efficacy. These analogues exhibited drug plasma levels that were lower than **15a** but still higher than **2** in the oral exposure screen and their cytotoxicity against the HCT-116 cell line was 2–9-fold less than **15a**. Of these compounds, only **15f**, an analogue that was comparable to paclitaxel in cytotoxicity against the HCT-116 cell line, showed oral efficacy comparable to iv dosed paclitaxel in the M109 model. It, together with **15a** and **15e**, was advanced to the next evaluation tier. Even thought the latter two compounds did not show oral efficacy comparable to iv paclitaxel in the M109 model, it was felt that they deserved evaluation in other in vivo tumor models because exhibited such high oral exposure in the mouse screen.

The effect of replacing the *N*-benzoyl group at C-3′ in **2** with aliphatic *N*-acyl groups isosteric to the carbamates was examined to see if this would attenuate potency and improved efficacy (Table 1). The neopentanoyl (**15f**) and cyclobutanoyl (**15h**), analogues were less cytotoxic than **15a** against the HCT-116 cell line while the cyclohexanoyl analogue (**15g**) was comparable. Only the former two compounds showed drug plasma levels that were higher than **2** in the oral exposure screen and both were found to be as active as iv dosed paclitaxel when dosed orally in the M109 model.

Further exploration of the C-3′-carbamates included analogues where the phenyl group at the 3′ position was replaced by a *t*-butyl or *i*-propyl group. This choice was based on a report that **4**, the C-3′-*t*-butyl analogue of docetaxel, is about 5 times more water-soluble than docetaxel (**3**) and performs similarly in tubulin polymerization and cytotoxicity assays.[19] It was thought that this modification in our C-4-methyl carbamate series may further improve solubility and thereby increase oral absorption. Although the drug plasma levels for the C-3′-*t*-butyl (**15i**) and C-3′-*i*-propyl (**15j**) analogues were only found to be about half that seen for the C-3′-phenyl analogue (**15a**) in the mouse screen, subsequent studies showed respectable oral bioavailability for **15i** in three species. Both compounds were found to be less cytotoxic against the HCT-116 cell line than **15a** but they did exhibit reduced cross resistance against the paclitaxel-resistant HCT-116 cell line. This suggests that replacement of the C-3′-phenyl group of the C-3′-methylcarbonate (**15a**) with small aliphatic groups reduces susceptibility to P-gp mediated efflux and this is in agreement with data that has been reported by Ojima and coworkers for C-3′-alkyl analogues derived from 14β-hydroxy-10-deacetyl baccatin.[10a] There the C-3′-alkyl analogues also performed better against cell lines expressing MDR than their C-3′-phenyl counterparts. In any event, both **15i** and **15j** performed comparably to **15a** in the M109 model in spite of their weaker cytotoxicity and lower oral exposure. The C-3′-*N*-*i*-propoxycarbonyl analogue (**15k**) of **15i** was prepared and it showed a two-fold increase in oral exposure in the mouse. Although, it was comparable in cytotoxic against the HCT-116 cell line, it showed poor oral efficacy in the M109 model. Lastly some aliphatic C-3′-*N*-acyl analogues of **15i** were prepared. The C-3′-*N*-neopentanoyl analogue (**15l**) is isosteric to **15i** and shows reduced cytotoxicity but similar oral exposure. It was found to be comparable to iv administered paclitaxel in the M109 model but this required a six-fold higher dose than for **15i**. The C-3′-*N*-isobutanoyl (**15n**) and C-3′-*N*-cyclobutanoyl (**15m**) analogues both showed higher oral exposure but only the latter showed efficacy comparable to iv dosed paclitaxel in the M109 model.

Those analogues that performed as well as iv administered paclitaxel in the M109 tumor model were then evaluated in A2780, human ovarian carcenoma, xenograft models (Table 2). In vitro all of these compounds except for **15l** and **15m**, two of the C-3′-*t*-butyl analogues, were as cytotoxic as paclitaxel. Against paclitaxel-resistant A2780, a subline which is resistant to paclitaxel due to altered tubulin, the C-3′-*N*-*t*-butyloxycarbonyl analogues carrying the C-3′-*t*-butyl (**15i**) and the C-3′-*i*-propyl (**15j**) groups performed best, showing only a 4 to 6-fold drop in potency. In vivo, in the A2780 xenograft model, the latter two compounds continued to perform well and showed a LCK of greater than or equal to 3. The 3′-phenyl analogues, **15c**, **15f** and **15h**, performed at least as well although higher doses were required to achieve this effect. Of these compounds, the C-3′-*t*-butyl analogue (**15i**) showed the highest oral bioavailability in the rat. Its solubility in 10:10:80 Cremophor El/ethanol/water was 16.5 mg/mL; just a little more than that observed for **2** in this medium. Taken all together, **15i** showed good oral efficacy in two tumor models, good oral bioavailability, and potency against cell lines resistant to paclitaxel due to MDR and altered tubulin. It was therefore moved forward for additional preclinical evaluation[20] and emerged from those studies as a clinical candidate for an orally active taxane.

Experimental

General experimental methods

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer and chemical shifts reported in ppm downfield from a TMS standard. ^{13}C NMR spectra were recorded on the same instrument at 75.5 MHz. High resolution mass spectral analysis was performed on a Kratos MS50RF spectrometer in the FAB mode

Table 2. Oral bioavailability, in vitro potency and oral efficacy of taxane analogues in human ovarian carcinoma (A2780) xenograft models

	Rat oral F[a] (%)	Cytotoxicity versus A2780		Oral efficacy versus sc A2780	
		Analogue/paclitaxel ratio[b]	*R*/*S* ratio[c]	LCK (cures/treated)	Oral dose[d]
15a	44	0.2	17	0.9 (0/8)	32
15c	18	0.9	29	7.0 (1/8)	100
15e	10	0.5	15	1.5 (0/8)	55
15f	30	1.4	32	3.8 (0/8)	100
15h	nd	1.0	15	4.1 (0/8)	140
15i	52	1.6	3.5	4.4 (0/8)	65
15j	36	0.7	6.1	3.0 (1/8)	28
15l	51	10	>7.2	1.8 (0/8)	36
15m	34	6.7	11	2.1 (0/8)	120

[a]Determined using an oral dose of 40 mg/kg and an iv dose of 10 mg/kg of amorphous samples of the analogue with 10:10:80 Cremophor EL/ethanol/water as the vehicle.
[b]Ratio of IC_{50} for the analogue/IC_{50} for paclitaxel versus A2780 cells.
[c]Ratio of IC_{50} versus paclitaxel resistant A2780 cells/IC_{50} versus A2780 cells.
[d]Optimal or maximally tolerated dose in mg/kg/administration given q2dx5 (every 2nd day for five treatments) except for 15 h where the indicated dose was an LD_{50}.

using *m*-nitrobenzyl alcohol as the matrix. Column chromatography was performed using silica gel 60 (200–400 mesh). Unless otherwise noted, materials were obtained from commercial sources and used without further purification. Detailed descriptions of the in vitro assays and the in vivo tumor models have been published.[20]

4-Deacetyl-3′-*N*-debenzoyl-4-*N*-neopentylcarbonyl-*O*-methoxycarbonyl-3′-paclitaxel (15f). *tert*-Butylacetyl chloride (1.17 mL, 1.2 equiv) was added to a solution of (3R,4S)-4-phenyl-3-triethylsilyloxy-azetidin-2-one (**11**, 1.94 g, 7 mmol), DIPEA (1.46 mL, 1.2 equiv), and DMAP (171 mg, 0.2 equiv) in dry DCM (40 mL) at 0 °C. After 3 h, the reaction was diluted with DCM (100 mL) and washed successively with aq HCl (1.0 M, 40 mL), saturated aq $NaHCO_3$ solution (40 mL) and brine (40 mL). After drying with Na_2SO_4, the solvent was removed and the residue was chromatorgraphed on silica gel (step gradient elution with 0–5% ethyl acetate in hexane) to (3*R*,4*S*)-1-neopentylcarbonyl-4-phenyl-3-triethylsilyloxy-azetidin-2-one (**10f**, 2.51 g, 96%) as an oil: H NMR[1] ($CDCl_3$): 0.18–0.62 (m, 15e), 0.87 (s, 9H), 2.43 (d, 1H, $J=13.8$ Hz), 2.62 (d, 1H, $J=13.8$ Hz), 4.90 (d, 1H, $J=5.7$ Hz), 4.95 (d, 1H, $J=6$ Hz), 7.05–7.17 (m, 5H).

A solution of **10f** (525 mg, 1.4 equiv) and 4-deacetyl-7-[bisisopropyl(methoxy)]silyloxy-4-*O*-methoxycarbonyl-baccatin (**13**, 523 mg, 0.700 mmole) in dry THF (15 mL) was cooled to −50 °C and a solution of LiHMDSA (0.84 mL, 1.2 equiv, 1.0 M in THF) was added with stirring. After 40 min, the reaction was allowed to warm to 0 °C. After 1.5 h, this was quenched with a saturated aq solution of NH_4Cl and extracted with EtOAc. The organic phase was washed with a saturated aq solution of NH_4Cl, water, brine and dried (Na_2SO_4). Removal of the solvents followed by silica gel column chromatography (gradient elution with mixtures of 0–20% EtOAc in hexane) afforded 3′-*N*-neopentyloxycarbonyl-7-[bisisopropyl(methoxy)]silyloxy-4-deacetyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-2′-triethylsilyloxy-paclitaxel (**14f**, 274 mg, 54%). This was taken directly and treated with triethylamine trihydrofluoride (0.161 mL, 4 equiv) in dry THF (6 mL) and left stirring at RT overnight. After neutralization with saturated aq $NaHCO_3$ solution, the reaction was extracted with EtOAc. The organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvents followed by silica gel column chromatography (gradient elution with mixtures of 20–50% EtOAc in hexane) afforded 151 mg (71%) of the title compound: ^{1}H NMR ($CDCl_3$): δ 0.96–2.58 [32H, including 0.96 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.66 (s, 3H), 1.84 (s, 3H), 2.23 (s, 3H)], 3.58 (br s, 1H), 3.77 (s, 3H), 3.80 (d, 1H, $J=5.5$ Hz), 4.19 (d, 1H, $J=8.3$ Hz), 4.33 (d, 1H, $J=8.7$ Hz), 4.36 (m, 1H), 4.65 (d, 1H, $J=2.0$ Hz), 4.95 (d, 1H, $J=8.5$ Hz), 5.58 (dd, 1H, $J=2.3$, 8.8 Hz), 5.69 (d, 1H, $J=7.0$ Hz), 6.11 (d, 1H, $J=8.9$ Hz), 6.16 (m, 1H), 6.27 (s, 1H), 7.29–8.12 (m, 10H); ^{13}C NMR ($CDCl_3$) : δ 9.7, 15.0, 21.0, 26.9, 29.8, 31.0, 35.5, 35.9, 43.2, 45.9, 50.6, 54.7, 56.0, 58.4, 72.1, 72.5, 73.1, 75.0, 75.7, 76.1, 79.0, 83.1, 84.2, 127.3, 128.3, 128.8, 129.0, 129.2, 130.3, 133.4, 133.8, 138.8, 142.4, 153.4, 167.1, 171.4, 171.5, 173.2, 196.2, 203.65; LRMS (ESI) 864 [$(M+H)^+$]; HRMS (ESI): calcd for $C_{46}H_{57}NO_{15}+H$: 864.3801, found: 864.3790.

3′-N-*t*-Butoxycarbonyl-4-deacetyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15a). Following the same procedure with di-*t*-butyl-dicarbonate gave the title compound: ^{1}H NMR ($CDCl_3$) δ 1.03–2.59 [30H, including 1.14 (s, 3H), 1.27 (s, 3H), 1.32 (s, 9H), 1.71 (s, 3H), 1.87 (s, 3H), 2.24 (s, 3H)], 3.40 (d, 1H, $J=5.1$ Hz), 3.85–3.81 (m, 4H), 4.15 (d, 1H, $J=8.8$ Hz), 4.34 (d, 1H, $J=8.8$ Hz), 4.40 (m, 1H), 4.63 (d, 1H, $J=3.9$ Hz), 4,97 (d, 1H, $J=7.7$ Hz), 5.32 (m, 2H), 5.68 (d, 1H, $J=6.9$ Hz), 6.19 (m, 1H), 6.27 (s, 1H), 7.61–7.26 (m, 8H) 8.13–8.10 (m, 2H); LRMS (ESI) 864 [$(M-H)^-$].

4-Deacetyl-3′-*N*-debenzoyl-3′-*N*-isobutoxycarbonyl-4-*O*-methoxycarbonyl-paclitaxel (15b). Following the same procedure with isobutylchloroformate gave the title compound: ^{1}H NMR ($CDCl_3$) δ 0.80–2.61 [m, 28H including: 1.16 (s, 3H), 1.26 (s, 3H), 1.70 (s, 3H), 1.88 (s, 3H), 2.26 (s, 3H)], 3.46 (br s, 1H), 3.75 (m, 2H), 3.98 (m, 4H), 4.20 (d, 1H, $J=8.6$ Hz), 4.36 (d, 1H, $J=8.5$ Hz), 4.40 (m, 1H), 4.68 (br s, 1H), 4.96 (d, 1H, $J=7.8$ Hz), 5.35 (d, 1H, $J=9.2$ Hz), 5.53 (d, 1H, $J=9.4$ Hz), 5.71

(d, 1H, $J=7.0$ Hz), 6.24 (m, 1H), 6.29 (s, 1H), 7.31–8.12 (m, 10H); LRMS (ESI) 866 [$(M+H)^+$].

N-*n*-Butoxycarbonyl-4-deacetyl-3′-*N*-debenzoyl-3′-4-*O*-methoxycarbonyl-paclitaxel (15c). Following the same procedure with *n*-butyl chloroformate gave title compound: ^{1}H NMR ($CDCl_3$) δ 0.83–2.59 [30H, including 1.14 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.86 (s, 3H), 2.24 (s, 3H)], 3.42 (d, 1H, $J=4.1$ Hz), 3.83 (s, 3H), 4.15 (d, 1H, $J=8.6$ Hz), 4.34 (d, 1H, $J=8.6$ Hz), 4.34 (m, 1H), 4.63 (brs, 1H), 4.97 (d, 1H, $J=7.0$ Hz), 5.41 (m, 2H), 5.69 (d, 1H, $J=7.0$ Hz), 6.27 (m, 1H), 6.27 (s, 1H), 7.62–7.29 (m, 10H) 8.11 (d, 2H, $J=7.4$ Hz). Anal. calcd For $C_{45}H_{55}NO_{16}$: C, 62.42; H, 6.40; N, 1.62. Found: C, 62.28; H, 6.45; N, 1.55.

4-Deacetyl-3′-*N*-debenzoyl-3′-*N*-isopropoxycarbonyl-4-*O*-methoxycarbonyl-paclitaxel (15d). Following the same procedure with *i*-propyl chloroformate gave the title compound: ^{1}H NMR ($CDCl_3$) δ 1.03–2.58 [m, 26H including: 1.24 (s, 3H), 1.66 (s, 3H), 1.84 (s, 3H), 2.28 (s, 3H)], 3.44 (br s, 1H), 3.82 (s, 3H), 3.84 (m, 1H), 4.17 (d, 1H, $J=8.6$ Hz), 4.33 (d, 1H, $J=8.5$ Hz), 4.38 (m, 1H), 4.64 (m, 1H), 4.77 (sept, 1H, $J=6.2$ Hz), 4.96 (d, 1H, $J=7.8$ Hz), 5.38 (m, 2H), 5.69 (d, 1H, $J=7.1$ Hz), 6.20 (m, 1H), 6.37 (s, 1H), 7.28–8.32 (m, 10H); LRMS (ESI) 852 [$(M+H)^+$].

3′-*N*-Cyclohexyloxycarbonyl-4-deacetyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15e). A mixture of cyclohexanol (12.68 mL, 120 mole) and pyridine (10.68 mL, 1.1 equiv) was added dropwise to a solution of triphosgene (11.87, 0.33 equiv) in anhydrous diethyl ether (100 mL) at −78 °C. After 1 h, the reaction was removed from the bath and after a further 1.5 h, aq HCl (1.0 N, 110 mL) was added. The organic phase was separated and washed with brine (60 mL) and dried (Na_2SO_4). Removal of the solvent followed by distillation afforded cyclohexyl chloroformate (14.2 gm, bp 41 to 42 °C at 4 mm Hg): ^{1}H NMR ($CDCl_3$) δ 1.08–1.80 (m, 10H), 4.65 (m, 1H). Following the above procedure with cyclohexyl chloroformate gave the title compound: ^{1}H NMR ($CDCl_3$) δ 1.15–2.60 [m, 31H including: 1.15 (s, 3H), 1.26 (s, 3H), 1.68 (s, 3H), 1.85 (s, 3H), 2.26 (s, 3H)], 3.48 (br s, 1H), 3.86 (m, 4H), 4.18 (d, 1H, $J=8.6$ Hz), 4.40 (m, 3H), 4.68. (br s, 1H), 4.99 (d, 1H, $J=7.9$ Hz), 5.36 (d, 1H, $J=8.9$ Hz), 5.49 (d, 1H, $J=9.4$ Hz), 5.70 (d, 1H, $J=7.1$ Hz), 6.23 (m, 1H), 6.29 (s, 1H), 7.30–8.16 (m, 10H); LRMS (ESI) 892 [$(M+H)^+$].

3′-*N*-Cyclohexylcarbony-4-deacetyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15g). Following the same procedure with cyclohexanecarbonyl chloride gave the title compound: ^{1}H NMR ($CDCl_3+D_2O$) δ 1.17–2.60 [m, 49H including: 1.17 (s, 3H), 1.27 (s, 3H), 1.69 (s, 3H), 1.95 (s, 3H), 2.26 (s, 3H)], 3.77 (s, 3H), 3.84 (d, 1H, $J=7.0$ Hz), 4.23 (d, 1H, $J=8.5$ Hz), 4.35 (d, 1H, $J=8.0$ Hz), 4.39 (m, 1H), 4.70 (d, 1H, $J=2.1$ Hz), 4.98 (d, 1H, $J=7.6$ Hz), 5.60 (m, 1H), 5.74 (d, 1H, $J=7.0$ Hz), 6.16 (m, 1H), 6.29 (s, 1H), 7.33–8.16 (m, 10H); LRMS (ESI) 876 [$(M+H)^+$].

3′-*N*-Cyclobutyl-4-deacetyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15h). Following the same procedure with cyclobutanecarbonyl chloride gave the title compound: ^{1}H NMR ($CDCl_3$) δ 1.14–2.53 [m, 27H including: 1.14 (s, 3H), 1.25 (s, 3H), 1.67 (s, 3H), 1.84 (s, 3H), 2.24 (s, 3H)], 3.01 (m, 1H), 3.56 (br s, 1H), 3.81 (s, 3H), 3.82 (m, 1H), 4.20 (d, 1H, $J=8.4$ Hz), 4.34 (d, 1H, $J=8.5$ Hz), 4.37 (m, 1H), 4.68 (d, 1H, $J=2.3$ Hz), 4.96 (d, 1H, $J=8.6$ Hz), 5.58 (dd, 1H, $J=2.4$, 9.0 Hz), 5.70 (d, 1H, $J=7.0$ Hz), 6.16 (m, 2H), 6.27 (s, 1H), 7.29–8.14 (m, 10H); LRMS (ESI) 848 [$(M+H)^+$].

(±)-*cis*-3-benzyloxy-4-*tert*-butyl-1-*p*-methoxyphenyl-azetidinone (7). Trimethylacetaldehyde (**5**, 20.3 mL, 1.25 equiv) was added to a strirred suspension of *p*-anisidine (18.4 g, 0.150 mole) and anhydrous Na_2SO_4 (150 g) in anhydrous DCM (250 mL) at rt. After 2 h, this was filtered and the solid was wash with additional anhydrous DCM. The solvent was removed from the filtrate and the crystalline residue was dissolved in anhydrous DCM (750 mL) and placed under a nitrogen atmosphere. TEA (48.0 mL, 2.3 equiv) was added and the reaction was cooled to −78 °C. Benzyloxyacetyl chloride (27.2 mL 1.15 equiv) was added dropwise and then the reaction was allowed to warm to rt. After 24 h, this was washed twice with aq HCl (0.5 M), sat. aqueous $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on a silica gel column (gradient elution with 20% DCM in hexane containing 0–20% EtOAc) to afford **7** (46.9 g, 92%): ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.81 (s, 3H), 4.15 (d, 1H, $J=5.5$ Hz), 4.77 (d, 1H, $J=11.9$ Hz), 4.81 (d, 1H, $J=5.5$ Hz), 5.03 (d, 1H, $J=11.9$ Hz) 6.87–7.43 (m, 9 Hz); LRMS (ESI) 340 ([$M+H]^+$).

(±)-*cis*-4-*tert*-Butyl-3-triethylsilyloxy-azetidin-2-one (9). A solution of ceric ammonium nitrate (60.4 g, 3.6 equiv) in 900 mL of water was added over 1 h to a well stirred solution of **7** (10.38 g, 30.6 mmole) in acetonitrile (600 mL) in an ice bath. This was extracted twice with EtOAc and the combined organic extracts were washed twice with satd aqueous $NaHCO_3$ solution, 20% aqueous $NaHSO_3$ solution, satd aqueous $NaHCO_3$ solution and brine. After being dried (Na_2SO_4), the solvents were removed and the residue was chromatographed on a silica gel column (gradient elution with 10 to 40% EtOAc in hexane) to afford 5.64 g of crude (±)-*cis*-3-benzyloxy-4-*tert*-butyl-azetidin-2-one: ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H), 3.51 (d, 1H, $J=5.2$ Hz), 4.71 (m, 2H), 4.96 (d, 1H, $J=11.9$ Hz) 6.10 (brs, 1H), 7.35 (m, 5H). A suspension of this material (5.54 g, 23.8 mmole) and 2.5 g of 10% Pd on charcoal in absolute EtOH (100 mL) was hydrogenated (34 psi, Parr apparatus) for 23 h. A further 2 g of the Pd catalyst was added and the hydrogenation was continued for a further 17 h at 50 psi. Removal of the catalyst followed by the solvent left crude (±)-*cis*-4-(*tert*-butyl)-3-hydroxy-azetidin-2-one: ^{1}H NMR ($CDCl_3$ + 1 drop DO) δ 1.05 (s, 9H), 3.48 (d, 1H, $J=5.0$ Hz), 4.98 (d, 1H, $J=5.0$ Hz). This was dissolved in dry DMF (40 mL) and imidazole (3.24 g, 2 equiv) and triethylsilyl chloride (4.0 mL, 1 equiv) were added. After 10 min, the reaction was partitioned between water and a mixture of EtOAc and hexane (1:1). The organic phase was washed with water (twice), brine and then dried (Na_2SO_4). The solvents were removed and the

residue was chromatographed on a silica gel column (gradient elution with 20–25% EtOAc in hexane) to give **9** (3.86 g, 49%): ^{1}H NMR (CDCl3) δ 0.70 (m, 6H), 0.98 (m, 18H), 3.39 (d, 1H, $J=5.0$ Hz), 4.88 (dd, 1H, $J=2.1$, 5.0 Hz), 6.08 (brs, 1H).

(±)-*cis*-4-*tert*-Butyl-1-*tert*-butyloxycarbonyl-3-triethylsilyloxy-azetidin-2-one (12i). A solution of **9** (2.04 g, 7.92 mmole), diisopropylethylamine (1.66 mL, 1.2 equiv), di-*tert*-butyl dicarbonate (1.90 g, 1.1 equiv) and *p*-dimethylaminopyridine (194 mg, 0.2 equiv) in dry DCM (24 mL) was left stirring at rt for 3 h. The reaction was diluted with DCM, washed with brine and dried (Na_2SO_4). Removal of the solvent followed by silica gel column chromatography (gradient elution with 0–20% EtOAc in hexane) gave **12i** (2.71 gm, 96%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 6H), 1.00 (m, 9H), 1.09 (s, 9H), 1.53 (s, 9H), 3.90 (d, 1H, $J=6.5$ Hz), 4.93 (d, 1H, $J=6.5$ Hz).

(±)-*cis*-3-Acetoxy-4-isopropyl-1-*p*-methoxybenzyl-azetidin-2-one (8). Isobutyraldehyde (**6**, 4.62 mL, 1.25 equiv) was added to a strirred suspension of *p*-anisidine (5.00 g, 40.7 mmole) and anhydrous Na_2SO_4 (25 g) in anhydrous DCM (80 mL) at rt. After 1 h, this was filtered and the solid was wash with additional anhydrous DCM. The solvent was removed from the filtrate and the residue was dissolved in anhydrous DCM (200 mL) and placed under a nitrogen atmosphere. Triethylamine (13.1 mL, 2.3 equiv) was added and the reaction was cooled to −78 °C. Acetoxyacetyl chloride (5.00 mL 1.15 equiv) was added dropwise and the reaction was allowed to warm to rt. After 20 h, this was washed twice with 0.5 M HCl, satd aqueous $NaHCO_3$ solution, brine and dried (Na_2SO_4), the solvent was removed and the residue was chromatographed on a silica gel column (gradient elution with 20–30% EtOAc in hexane) to afford **8** as a solid (7.15 g, 63%): ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 3H, $J=7.0$ Hz),1.02 (d, 3H, $J=7.0$ Hz), 2.20 (s, 3H), 3.82 (s, 3H), 4.24 (t, 1H, $J=5.6$ Hz), 6.06 (d, 1H, $J=5.3$ Hz), 6.88–7.38 (m, 4H).

(±)-*cis*-4-Isopropyl-3-triethylsilyloxy-azetidin-2-one (10). A solution of ceric ammonium nitrate (51.3 g, 3.6 equiv) in 750 mL of water was added to a well stirred solution of the azetidinone (7.20 g, 26.0 mmole) in acetonitrile (500 mL) in an ice bath over 1 h. The reaction was then extracted twice with EtOAc and the combined organic extracts were washed twice with satd aqueous $NaHCO_3$ solution, 20% aqueous $NaHSO_3$ solution, satd aqueous $NaHCO_3$ solution and brine. After being dried (Na_2SO_4), the solvents were removed to leave 4.26 g of crude (±)-cis-3-acetoxy-4-*iso*-propyl-azetidin-2-one: ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 3H, $J=6.6$ Hz), 0.99 (d, 3H, $J=6.6$ Hz), 1.89 (m, 1H), 2.17 (s, 3H), 3.52 (dd, 1H, $J=4.8$, 9.0 Hz), 5.96 (dd, 1H, $J=2.5$, 4.6 Hz), 6.38 (br s, 1H), LRMS (negative ESI) 170 [$(M-H)^-$]. A suspension of this material (4.26 g, 24.9 mmole) and K_2CO_3 (102 mg, 0.03 equiv) in MeOH (40 mL) was stirred at rt for 1.5 h. The reaction was neutralized with Amberlite IR-20. Filtration followed by removal of the solvent left crude (±)-*cis*-3-hydroxy-4-*iso*-propyl-azetidin-2-one. This was dissolved in dry DMF (40 mL) and imidazole (3.39 g, 2 equiv) and triethylsilyl chloride (4.19 mL, 1 equiv) were added. After 10 min, the reaction was partitioned between water and a mixture of EtOAc and hexane (1:1). The organic phase was washed twice with water, brine and then dried (Na_2SO_4). The solvents were removed and the residue was chromatographed on a silica gel column (gradient elution with 25–35% EtOAc in hexane) to give **10** (4.63 g, 77%): ^{1}H NMR ($CDCl_3$) δ 0.65–1.03 (m, 21H), 1.93 (m, 1H), 3.29 (dd, 1H, $J=4.8$, 9.1 Hz), 4.87 (dd, 1H, $J=2.8$, 4.7 Hz), 6.05 (br s, 1H).

(±)-*cis*-1-*tert*-Butyloxycarbonyl-4-*iso*-propyl-3-triethylsilyloxy-azetidin-2-one (12j). A solution of **10** (1.05 g, 4.32 mmole), diisopropylethyl amine (0.90 mL, 1.2 equiv), di-*tert*-butyl dicarbonate (1.04 g, 1.1 equiv) and p-dimethylaminopyridine (106 mg, 0.2 equiv) in dry DCM (10 mL) was left stirring at rt for 30 min. The reaction was diluted with DCM, washed with brine and dried (Na_2SO_4). Removal of the solvent followed by silica gel column chromatography (gradient elution with 10–20% EtOAc in hexane) afforded 1.31 g (88%) of **12b** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.66–1.07 (m, 21H), 1.53 (s, 9H), 2.15 (m, 1H), 3.87 (t, 1H, $J=6.4$ Hz), 4.88 (d, 1H, $J=6.1$ Hz); LRMS (ESI) 344 [$(M+H)]^+$.

3′-*tert*-Butyl-3′-*N*-*tert*-Butyloxycarbonyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15i). A solution of **12i** (2.71 g, 5 equiv) and 4-deacetyl-7-[bisisopropyl(methoxy)]silyloxy-4-methoxycarbonyl-baccatin (**13**, 1.13 g, 1.52 mmole) in dry THF (100 mL) under nitrogen was cooled to −50 °C and a solution of LiHMDSA (1.97 mL, 1.3 equiv, 1.0 M in THF) was added. After 5 min this was transferred to a bath that was maintained at −35 to −30 °C for 20 h and then −25 °C for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with a mixture of EtOAc and hexane (1:1). The organic extracts were washed with brine and dried (Na_2SO_4). The solvents were removed and the residue was chromatographed (radial chromatography; 6-mm silica gel plate; gradient elution with 5–20% EtOAc in hexane) to afford **14a** (1.55 g) as a mixture of 2′,3′-diastereomers. This was dissolved in dry THF (60 mL) and triethylamine trihydrofluoride (0.92 mL 4 equiv) were added. After 22 h at rt, the reaction was neutralized with saturated aq $NaHCO_3$ solution and then extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and the solvents were removed. The residue was chromatographed (radial chromatography; 2 mm silica gel plate; gradient elution with 10–50% EtOAc in hexane) to afford (in order of elution): 210 mg (18%) of 2′*S*,3′*R*-3′-*tert*-butyl-3-′*N*-*tert*-butyloxycarbonyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel {^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.13 (s, 3H), 1.20 (s, 3H), 1.37 (s, 9H), 1.65 (s, 1H), 1.66 (s, 3H), 1.84–1.93 (m, 2H), 2.17 (s, 3H), 2.25 (s, 3H), 2.55 (m, 3H), 3.00 (d, 1H, $J=6.5$ Hz), 3.74 (d, 1H, $J=10.8$ Hz), 3.79 (d, 1H, $J=6.9$ Hz), 3.92 (s, 3H), 4.16 (d, 1H, $J=8.5$ Hz), 4.33 (d, 1H, $J=8.5$ Hz), 4.42 (m, 1H), 4.54 (d, 1H, $J=6.5$ Hz) 4.87 (d, 1H, $J=10.6$ Hz), 5.01 (d, 1H, $J=7.7$ Hz), 5.68 (d, 1H, $J=7.0$ Hz), 5.76 (m, 1H), 6.32 (s, 1H), 7.44–8.05 (m, 5H);. LRMS

(ESI) 846 [(M + H)$^+$]} and the 2′*R*,3′*S* isomer **15i** (668 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.33 (s, 9H), 1.66 (s, 4H), 2.23 (s, 3H), 2.38–2.59 (m, 4H), 3.11 (d, 1H, *J* = 5.8 Hz), 3.77 (d, 1H, *J* = 11.1 Hz), 3.82 (d, 1H, *J* = 7.0 Hz), 3.96 (s, 3H), 4.20 (d, 1H, *J* = 8.6 Hz), 4.33 (d, 1H, *J* = 8.6 Hz), 4.39 (m, 1H), 4.53 (d, 1H, *J* = 5.4 Hz) 4.88 (d, 1H, *J* = 10.6 Hz), 4.98 (d, 1H, *J* = 7.9 Hz), 5.69 (d, 1H, *J* = 7.1 Hz), 6.03 (m, 1H), 6.28 (s, 1H), 7.40–8.11 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8, 14.3, 15.0, 21.0, 21.2, 22.3, 26.9, 27.5, 28.4, 35.1, 35.5, 35.9, 43.4, 45.9, 55.9, 58.4, 60.1, 60.5, 70.4, 72.1, 73.7, 75.2, 75.8, 76.2, 79.2, 79.6, 83.1, 84.3, 128.8, 129.3, 130.4, 133.1, 133.8, 143.0, 153.5, 155.9, 167.1, 171.3, 171.5, 175.4, 203.8; LRMS (ESI) 846 [(M + H)$^+$]; HRMS (ESI): calcd for $C_{43}H_{58}NO_{16}$: 844.3755, found: 844.3780.

3′-*N*-*tert*-Butyloxycarbonyl-4-deacetyl-3′-*N*-debenzoyl-3′-dephenyl-3′-isopropyl-4-*O*-methoxycarbonyl-paclitaxel (15j). Following the above procedure with **12j** afforded **15j**: ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.03 (d, 3H, *J* = 6.7 Hz), 1.09 (d, 3H, *J* = 6.7 Hz), 1.14 (s, 3H), 1.24 (s, 3H), 1.31 (s, 9H), 1.66 (m, 3H), 1.83–2.02 (m, 5H), 2.24 (s, 3H), 2.25–2.59 (m, 3H), 3.68 (dd, 1H, *J* = 2.0, 9.2 Hz), 3.82 (d, 1H, *J* = 6.9 Hz), 3.98 (s, 3H), 4.19 (d, 1H, *J* = 8.6 Hz), 4.34 (d, 1H, *J* = 8.6 Hz), 4.39 (m, 1H), 4.43 (d, 1H, *J* = 2.0 Hz) 4.82 (br s, 1H), 4.98 (d, 1H, *J* = 7.8 Hz), 5.69 (d, 1H, *J* = 7.0 Hz), 6.11 (m, 1H), 6.28 (s, 1H), 7.45–8.12 (m, 5H); LRMS (ESI) 832 [(M + H)$^+$].

3′-*tert*-Butyl-3′-N-cyclobutanecarbonyl-4-deacetyl-3′-dephenyl-3′-N-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (15m). Trifluoroacetic acid (15 mL) was added to a solution of **15i** (2.30 g, 2.72 mmole) in dry DCM (15 mL) at 0 °C. After 1.5 h, this was diluted with DCM (100 mL) and poured into a 0 °C solution of $NaHCO_3$ in water (150 mL). The organic phase was separated and the solvent was removed. The crude 3′-*tert*-butyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-4-*O*-methoxycarbonyl-paclitaxel (**16**) was dissolved in DCM (15 mL) and a saturated solution of $NaHCO_3$ (15 mL) was added. Cyclobutane carbonyl chloride (0.46 mL, 1.5 equiv) was added with vigorous stirring. After 20 min, this was diluted with ethyl acetate and the organic phase was separated and dried (Na_2SO_4). Purification by preparative reverse phase chromatography (step gradient elution with 20–60% acetonitrile in water) afforded **15m** (1.47 g, 65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.66 (s, 3H), 1.88 (s, 3H), 1.92–1.76 (bm, 3H), 2.19–2.03 (bm, 4H), 2.23 (s, 3H), 2.58–2.36 (bm, 4H), 2.97 (p, *J* = 7.9 Hz, 1H), 3.30 (d, *J* = 5.1 Hz, 1H), 3.80 (d, *J* = 7.0 Hz, 1H), 3.98 (s, 3H), 4.14 (d, *J* = 10.2 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.40–4.32 (bm, 2H), 4.55 (dd, *J* = 1.1 Hz, *J* = 5.2 Hz, 1H), 4.98 (dd, *J* = 2.0 Hz, *J* = 9.5 Hz, 1H), 5.69 (m, 2H), 5.99 (dd, *J* = 7.8 Hz, *J* = 9.0 Hz, 1H), 6.27 (s, 1H), 7.48–7.43 (m, 2H), 7.62–7.55 (m, 1H), 8.08 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.72, 14.95, 18.29, 20.95, 22.12, 25.44, 26.85, 27.37, 35.47, 35.94, 39.91, 43.34, 45.74, 51.07, 56.03, 57.73, 58.36, 70.17, 72.06, 73.39, 74.94, 75.68, 76.09, 78.92, 83.21, 84.13, 128.72, 129.81, 130.22, 133.20, 133.74, 142.54, 153.21, 166.89, 171.46, 174.93, 174.99, 203.70; LRMS (ESI): 828.51 [(M + 1)+, 100%], 886.57 [(M + NH4 + ACN)+, 30%]; 826.48 [(M − 1)$^-$, 100%]. HRMS (ESI−): calcd for C43H56NO15: 826.3650; found: 826.3645.

3′-*tert*-Butyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-3′-*N*-isopropyloxycarbonyl-4-*O*-methoxycarbonyl-paclitaxel (15k). Following the above procedure with isopropylchloroformate afforded **15k**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 9H), 1.18–1.11 (m, 6H), 1.25 (s, 6H), 1.67 (s, 3H), 1.91 (s, 3H), 1.83–1.93 (m, 3H), 2.04 (s, 1H), 2.25 (s, 3H), 2.38 (d, *J* = 8.9 Hz, 2H), 2.50–2.60 (m, 2H), 3.23 (d, *J* = 4.8 Hz, 1H), 3.81–3.87 (bm, 2H), 3.99 (s, 3H), 4.21 (d, *J* = 8.6 Hz, 1H), 4.33–4.38 (bm, 2H), 4.57 (d, *J* = 3.9 Hz, 1H), 4.76 (m, 1H), 5.01 (m, 2H), 5.70 (d, *J* = 7.1 Hz, 1H), 6.06 (m, 1H), 6.29 (s, 1H), 7.44–7.49 (m, 2H), 7.55–7.62 (m, 1H), (8.09 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.79, 175.02, 171.53, 167.16, 156.39, 153.41, 142.85, 133.90, 133.27, 130.36, 128.85, 84.27, 83.35, 79.29, 77.45, 76.19, 75.80, 75.14, 73.38, 72.18, 70.44, 68.55, 60.47, 58.51, 56.13, 45.99, 43.43, 35.97, 35.58, 35.32, 27.47, 27.02, 26.97, 22.08, 21.25, 21.06, 15.06, 14.41, 14.32, 9.85; LRMS (ESI): 832.46 [(M + 1)$^+$, 100%]; 830.44 [(M − 1)$^-$, 100%]. HRMS (ESI−): calcd for $C_{42}H_{56}NO_{16}$: 830.3599; found: 830.3607.

3′-*tert*-Butyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-3′-*N*-neopentylcarbonyl-4-*O*-methoxycarbonyl-paclitaxel (15l). Following the above procedure with *tert*-butylacetyl chloride gave **15l**: ^{1}H NMR ($CDCl_2$ + D_2O) δ 1.00–2.56 [39H, including 1.00 (s, 9H), 1.11 (s, 9H), 1.16 (s, 3H), 1.26 (s, 3H),1.69 (s, 3H), 1.91 (s, 3H), 2.26 (s, 3H)], 3.83 (d, 1H, *J* = 7.1 Hz), 3.98 (s, 3H), 4.17 (d, 1H, *J* = 10.1 Hz), 4.26 (d, 1H, *J* = 8.8 Hz), 4.37 (m, 2H), 4.55 (s, 1H), 5.00 (d, 1H, *J* = 7.5 Hz), 5.73 (m, 2H), 6.02 (m, 1H), 6.29 (s, 1H), 7.45–8.13 (m, 5H); LRMS (ESI) 844 [(M + H)$^+$].

3′-*tert*-Butyl-4-deacetyl-3′-dephenyl-3′-*N*-debenzoyl-3′-*N*-isobutylcarbonyl-4-*O*-methoxycarbonyl-paclitaxel (15n). Following the above procedure with isobutylchloroformate gave **15n**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (dd, *J* = 2.5 Hz, *J* = 6.3 Hz, 6H), 1.08 (s, 9H), 1.15 (s, 3H), 1.25 (s, 3H), 1.68 (s, 3H), 1.90 (s, 3H), 2.07–2.00 (m, 3H), 2.25 (s, 3H), 2.45–2.39 (bm, 3H), 2.60–2.52 (bm, 2H), 3.28 (d, *J* = 5.2 Hz, 1H), 3.82 (d, *J* = 7.0 Hz, 1H), 3.99 (s, 3H), 4.43–4.13 (bm, 4H), 4.56 (dd, *J* = 0.87 Hz, *J* = 5.2 Hz, 1H), 5.00 (dd, *J* = 2.0 Hz, *J* = 9.5 Hz, 1H), 5.73 (d, *J* = 7.0 Hz, 1H), 5.79 (d, *J* = 10.1 Hz, 1H), 6.01 (m, 1H), 6.29 (s, 1H), 7.50–7.45 (m, 2H), 7.63–7.57 (m, 1H), 8.09 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.90, 13.88, 15.05, 21.09, 21.28, 22.38, 22.56, 26.26, 27.00, 27.54, 35.09, 35.59, 36.08, 45.81, 46.27, 56.11, 58.15, 58.44, 70.12, 72.16, 73.69, 75.12, 75.81, 76.24, 77.44, 78.95, 83.30, 84.29, 128.84, 129.48, 130.36, 133.37, 133.85, 142.55, 153.40, 166.94, 171.59, 172.61, 175.20, 203.81; LRMS (ESI): 830 [(M + H)$^+$].

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