Butitaxel Analogues: Synthesis and Structure−Activity Relationships

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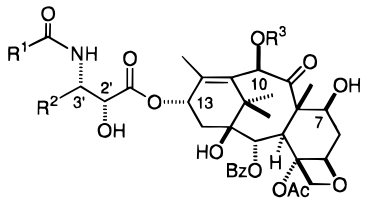
N-Acyl analogues **8**, **9**, and **12**−**26** of butitaxel (**3**) were prepared in one or two steps from amines **5** and **6** through Schotten−Baumann acylation. Seventeen novel analogues, consisting of aliphatic carbamates, alicyclic amides, and heteroaromatic amides, were synthesized. They were evaluated for their *in vitro* ability to stimulate the formation of microtubules, their cytotoxicity toward B16 melanoma cells, and their solubility in water. The most potent analogue found in this study was *N*-debenzoyl-*N*-(2-thenoyl)butitaxel (**20**), possessing ca. 2-fold better tubulin assembly properties and cytotoxic activity against B16 melanoma cells than paclitaxel. Compound **20** was ca. 25 times more water soluble than paclitaxel.

The structurally and biologically unique diterpenoid paclitaxel (**1**)[1] has been approved by the Food and Drug Administration for the treatment of metastatic ovarian cancer and breast cancer.[2] In addition, paclitaxel has shown promise for the therapy of lung cancer, head and neck cancer, and esophageal carcinomas.[2] Docetaxel (**2**), a semisynthetic analogue of paclitaxel,[3] is currently in clinical trials and awaiting FDA approval.[2] Docetaxel has shown slightly better activity when compared to paclitaxel in an *in vitro* microtubule assembly assay and several *in vivo* tumor models.[4] The demonstrated clinical activity along with a unique mechanism of action[5] has made paclitaxel a target of extensive research directed toward the preparation of second-generation analogues with outstanding biological properties and improved drug delivery profiles.[6] Extensive structure−activity studies have included modifications on both the C13 side chain and the diterpene skeleton of paclitaxel.[3,7−13]



1 $R^1 = R^2 =$ Ph, $R^3 =$ Ac (paclitaxel)
2 $R^1 =$ *tert*-BuO, $R^2 =$ Ph, $R^3 =$ H (docetaxel)
3 $R^1 =$ Ph, $R^2 =$ *tert*-Bu, $R^3 =$ H (butitaxel)
4 $R^1 =$ *tert*-BuO, $R^2 =$ *tert*-Bu, $R^3 =$ H

We[14,15] and others[16,17] have recently reported that the 3′-phenyl group of paclitaxel can be replaced by aliphatic moieties to provide taxanes with significant *in vitro* cytotoxicity. Among the analogues prepared, butitaxel (**3**) and *N*-(*tert*-butoxycarbonyl)-*N*-debenzoylbutitaxel (**4**) possess excellent cytotoxicity and improved water solubility compared to the parent compound paclitaxel.[15] Inspired by the interesting activity profile and solubility data of these initial analogues, we decided to explore the structure−activity relationship profile of these derivatives in more detail. We are now reporting on the synthesis, biological activity, and aqueous solubility of novel *N*-acyl analogues of butitaxel. This report supplements our earlier disclosure by focusing on side chains containing carbo- and heterocyclic moieties.

Compounds **8**−**26** (Table 1) were synthesized according to the sequences shown in Scheme 1. The key intermediates for their synthesis, the amines **5** and **6**, were prepared from L-*tert*-leucine and 10-deacetylbaccatin III as described by us previously.[15] When amine **5** was used in the reaction, treatment with chloroformates or acid chlorides under Schotten−Baumann conditions[18] was followed by removal of the Troc protection of the C7 and C10 alcohols with zinc and acetic acid to give the corresponding *N*-substituted taxanes. Employing amine **6** as the starting material in the Schotten−Baumann acylation allows for the one-step synthesis of the desired analogues.[18] All of the novel derivatives prepared for this study were characterized by ^{1}H NMR, ^{13}C NMR, and MS and showed satisfactory purity by HPLC analysis (>90%). The new taxanes were evaluated for biological activity in a microtubule assembly assay and for their cytotoxicity against B16 melanoma cells (Table 1). In addition, they were subjected to aqueous solubility studies (Table 2) to allow comparison with paclitaxel and docetaxel.

Our earlier investigation had revealed that various aliphatic 3′-carbamate derivatives of butitaxel possessed slightly better or similar efficacy compared to paclitaxel when tested for their ability to cause the polymerization of tubulin and their cytotoxicity toward B16 melanoma cells.[15] We therefore decided to synthesize and evaluate (Table 1) additional aliphatic carbamates as well as amides containing open chain, alicyclic, and heteroaromatic groups at the 3′-nitrogen.

First, we investigated the influence of aliphatic chain length of the carbamate moiety on tubulin assembly properties and cytotoxicity against B16 melanoma cells. Since we had found that the butoxycarbonyl analogue **10** of butitaxel was more active in both assays than its

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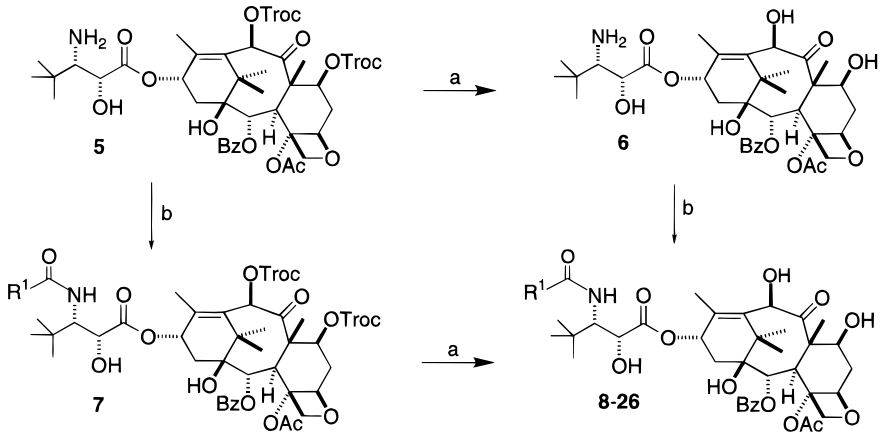
Scheme 1[a]



[a] (a) Zn dust, AcOH−MeOH, 60 °C, 2 h, 65%; (b) R^1COCl, EtOAc, aq $NaHCO_3$, room temperature, 20 min. For R^1, see Table 1.

Table 1. *In Vitro* Biological Evaluation of *N*-Modified Butitaxel Analogues

		$ED_{50}/ED_{50(paclitaxel)}$	
compound	R^1	microtubule assembly assay[a]	B16 melanoma cytotoxicity[b]
1, paclitaxel		1.0	1.0
2, docetaxel[14]		0.45	0.41
3, butitaxel[15]	Ph	1.8	7.5
4[15]	*tert*-butoxy	0.38	0.40
8	ethoxy	1.4	3.4
9	propoxy	1.7	1.5
10[15]	butoxy	0.86	2.1
11[15]	hexyloxy	2.3	12
12	isopropoxy	0.84	1.2
13	cyclopropyl	0.95	2.1
14	cyclobutyl	0.67	3.0
15	cyclopentyl	1.5	1.4
16	1-ethylpropyl	1.7	26
17	cyclohexyl	1.5	3.8
18	2-furyl	1.5	2.1
19	3-furyl	1.6	2.3
20	2-thienyl	0.42	0.53
21	3-thienyl	0.85	1.2
22	5-methyl-2-thienyl	2.4	32
23	3-methyl-2-thienyl	1.4	1.3
24	2-thienyl-2-ethenyl	2.7	2.7
25	2-thienylmethyl	1.9	3.3
26	1-methyl-2-pyrrolyl	0.96	1.2

[a] ED_{50} is the concentration which causes polymerization of 50% of the tubulin present in 15 min at 37 °C. [b] ED_{50} refers to the concentration which produces 50% inhibition of proliferation after 40 h incubation.

hexyloxy derivative **11**,[15] we prepared and tested the two lower homologues, the ethoxycarbonyl and propoxycarbonyl derivatives **8** and **9**. Both carbamates were less potent in the tubulin assembly assay than the corresponding butoxy analogue **10** and paclitaxel. However, the propoxy derivative **9** was found to be slightly more cytotoxic ($ED_{50}/ED_{50(paclitaxel)} = 1.5$) than the butoxy analogue **10** ($ED_{50}/ED_{50(paclitaxel)} = 2.1$). Thus, the most cytotoxic carbamates in this series of compounds are the propoxy and butoxy analogues **9** and **10**. The cytotoxic potencies of the higher and lower homologues **11** and **8** were clearly decreased. The results obtained for ethoxy derivative **8**, good microtubule assembly properties and reduced cytotoxicity against B16 melanoma cells, are similar to the findings for the 9-dihydropaclitaxel analogue of **8**.[19] Branching of the aliphatic side chain provided the isopropoxy analogue **12**, which is similar to paclitaxel in both assays, thus possessing slightly better properties than the corresponding *n*-propoxy derivative **9**. Similar microtubule assembly data and B16 melanoma cell cytotoxicity were reported for the related *N*-(isopropoxycarbonyl)-9-dihydropaclitaxel analogue of **12**.[19]

Next, we investigated alicyclic amides **13**−**15** and **17**. All compounds displayed tubulin assembly properties similar to paclitaxel. However, they showed reduced cytotoxicity toward B16 melanoma cells. The almost 4-fold reduced cytotoxicity of cyclohexanecarboxamide **17** is somewhat surprising since a related 3′-cyclohexylpaclitaxel analogue was only 1.6-fold less active than paclitaxel against B16 melanoma cell growth.[14] The most cytotoxic alicyclic amide in this series was cyclopentylcarbonyl derivative **15** ($ED_{50}/ED_{50(paclitaxel)} = 1.4$). To further probe the potential of this analogue, we prepared its open chain derivative, 2-ethylbutyric amide **16**. We found that **16** had similar activity in the tubulin assay but showed greatly decreased cytotoxicity against B16 melanoma cells, demonstrating that the cyclic structure of **15** is of significant importance for its B16 melanoma cell cytotoxicity.

The excellent cytotoxicity reported for *N*-furoylpaclitaxel analogues prompted us to investigate heteroaromatic *N*-acyl derivatives in the butitaxel series.[20] 2-Furamide **18** and 3-furamide **19** both showed activity similar to paclitaxel in the tubulin assay but only one-half of the cytotoxicity of paclitaxel. This is different from the trends observed in the paclitaxel series, in which the 3-furamide was 2 times as cytotoxic relative to paclitaxel and the 2-furamide derivative.[21] Bioisosteric replacement of the oxygen in the furyl moiety with sulfur provided 2-thenoyl analogue **20** which was the most active compound prepared in this study. 2-Thenoyl derivative **20** was more active than paclitaxel in both the microtubule assembly assay ($ED_{50}/ED_{50(paclitaxel)} = 0.42$) and the B16 melanoma cell cytotoxicity assay ($ED_{50}/ED_{50(paclitaxel)} = 0.53$). Encouraged by the activity of this compound, we decided to extend our study to substituted thienyl derivatives. Most of the thienyl analogues **21**−**25** showed activity slightly less than or similar to paclitaxel, with the exception of 5-methyl-2-thenoyl analogue **22**, which was found to be about 2 times less active in the microtubule assembly assay and 32 times less cytotoxic than the parent. None of the analogues, however, was as active as the original 2-thenoyl compound **20**. It is of interest to note that

Table 2. Water Solubility of Butitaxel Analogues

compound	R^1	water solubility (μg/mL)	analogue solubility/ paclitaxel solubility
1, paclitaxel		0.30	1
2, docetaxel		5.0−6.0	17−20
3, butitaxel[15]	Ph	2.8	9.3
4[15]	*tert*-butoxy	28−33	93−110
8	ethoxy	9.7	32
10[15]	butoxy	27−29	90−97
12	isopropoxy	0.50	1.7
13	cyclopropyl	33−45	120−150
14	cyclobutyl	24	80
17	cyclohexyl	45	150
18	2-furyl	22	73
20	2-thienyl	6.8−8.4	23−28
21	3-thienyl	4.7	16
22	5-methyl-2-thienyl	4.0	13
24	2-thienyl-2-ethenyl	1.0	3
25	2-thienylmethyl	6.7	23
26	1-methyl-2-pyrrolyl	0.5	1.8

the introduction of a 5-methyl group at the 2-thenoyl moiety (compound **22**) reduced cytotoxicity greatly, whereas a methyl group at position 3 provided a very cytotoxic analogue (**23**). The final heteroaroyl derivative prepared was the 1-methyl-2-pyrrolyl analogue **26** which showed activity similar to paclitaxel in both assays.

The aqueous solubility of all the active compounds was measured (Table 2) and compared with that of paclitaxel using the method described earlier.[15] It was found that most of the active compounds in the butitaxel series were more water soluble than the parent compound paclitaxel. Although this improved solubility is not sufficient for these analogues to be formulated without a surfactant, it should allow their formulation with a wider variety of surfactants in order to avoid vehicle-related side effects.[6]

Summary

It can be concluded from this study that modifications at the *N*-acyl group of butitaxel are tolerated well in many cases, as had been observed for paclitaxel previously.[6] In addition to several analogues that showed paclitaxel-like activity, we identified 2-thenoyl analogue **20** as a derivative possessing about 2-fold increased potency compared to paclitaxel in both assays. Most of the analogues demonstrated slightly better water solubility than paclitaxel. Further evaluation of these derivatives is in progress in our laboratory.

Experimental Section

General. For general synthetic procedures, see ref 22. For a description of the biological assays, see refs 15 and 23. For the preparation of butitaxel (**3**), *N*-(*tert*-butoxycarbonyl)-*N*-debenzoylbutitaxel (**4**), amines **5** and **6**, and carbamates **10** and **12** and the conditions of the solubility studies, see ref 15.

General Procedure for the *N*-Acylation of 5 and 6. Method A: The chloroformate or acid chloride (1.2 equiv) was added dropwise to a solution of amine **5** or **6** (0.2 mmol) in ethyl acetate (7 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and water (10 mL). The mixture was stirred at 24 °C for 30 min and extracted with ethyl acetate (2 × 30 mL). The organic extracts were washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography over silica gel using ethyl acetate/hexane (1:3) as the eluent to provide the *N*-acylated product.

General Procedure for the Removal of the [(2,2,2-Trichloroethyl)oxy]carbonyl (Troc) Protecting Groups. Method B: A mixture of either amine **5** or **7** (0.3 mmol), zinc dust (0.3 g), methanol (8 mL), and acetic acid (8 mL) was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and filtered. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate (15 mL). The heterogeneous mixture was washed with aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent followed by flash column chromatography over silica gel (CH_2Cl_2/MeOH, 20:1) gave the 7,10-deprotected product.

***N*-Debenzoyl-*N*-(ethoxycarbonyl)butitaxel (8).** Amine **5** (0.045 g, 0.043 mmol) was reacted with ethyl chloroformate (0.011 mL, 0.11 mmol, 2.6 equiv) according to the procedure described in method A to give a carbamate that was deprotected as discussed in method B to give (0.015 g, 45% overall) as a solid: mp 168−171 °C dec; R_f 0.40 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.11 (t, J = 6.9 Hz, 3H), 1.24 (s, 3H), 1.25 (s, 3H), 1.74 (s, 3H), 1.85 (s, 1H), 1.90 (s, 3H), 2.20 (m, 1H), 2.27 (m, 2H), 2.44 (s, 3H), 2.58 (m, 1H), 3.39 (s, 1H), 3.86 (d, J = 10.3 Hz, 1H), 3.90 (d, J = 6.9 Hz, 1H), 3.95 (q, J = 6.9 Hz, 2H), 4.20 (d, J = 8.3 Hz, 1H), 4.26 (m, 1H), 4.30 (d, J = 8.3 Hz, 1H), 4.58 (s, 1H), 4.94 (d, J = 8.0 Hz, 1H), 5.13 (d, J = 10.3 Hz, 1H), 5.21 (s, 1H), 5.67 (d, J = 6.9 Hz, 1H), 6.23 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 8.13 (d, J = 7.3 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 174.4, 170.5, 167.0, 156.5, 138.6, 135.7, 133.6, 130.3, 129.2, 128.7, 84.2, 81.0, 79.0, 74.9, 74.5, 72.7, 72.0, 70.6, 61.1, 60.0, 57.6, 46.4, 43.1, 36.9, 35.9, 35.3, 29.7, 27.4, 26.5, 22.8, 21.0, 14.5, 14.3, 10.0; HRMS (FAB) m/z calcd for $C_{39}H_{54}NO_{14}$ 760.3544, found 760.3558; MS (FAB) m/z 760 $(M + H)^+$, 742, 527, 509, 345, 327, 234; $[\alpha]^{20}_D$ −36.4° (c = 1.24, $CHCl_3$).

***N*-Debenzoyl-*N*-(propoxycarbonyl)butitaxel (9).** Amine **5** (0.10 g, 0.096 mmol) was reacted with propyl chloroformate (0.015 g, 0.13 mmol, 1.3 equiv) according to the procedure described in method A to give a carbamate (0.08 g), which was deprotected as discussed in method B to give **9** (0.04 g, 49% overall yield) as a white solid: mp 155−157 °C; R_f 0.49 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, J = 7.4 Hz, 3H), 1.04 (s, 9H), 1.11 (s, 3H), 1.22 (s, 3H), 1.74 (s, 3H), 1.87 (m, 1H), 1.89 (s, 3H), 2.22 (m, 2H), 2.43 (s, 3H), 2.57 (m, 1H), 3.35 (bs, 1H), 3.85 (m, 4H), 4.20 (d, J = 8.3 Hz, 1H), 4.28 (d, J = 9.2 Hz, 2H), 4.58 (d, J = 4.9 Hz, 1H), 4.94 (d, J = 8.4 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 5.21 (s, 1H), 5.65 (d, J = 6.8 Hz, 1H), 6.21 (t, J = 8.9 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 8.12 (d, J = 7.4 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.4, 170.4, 167.0, 156.6, 138.6, 135.7, 133.6, 130.3, 129.2, 128.7, 84.2, 81.0, 79.0, 74.9, 74.5, 72.7, 72.0, 70.6, 66.7, 59.7, 57.6, 46.4, 43.1, 36.9, 35.8, 35.3, 27.4, 26.5, 22.8, 22.3, 21.0, 14.3, 10.0, 9.9; HRMS (FAB) m/z calcd for $C_{40}H_{56}NO_{14}$ 774.3701, found 774.3703; MS (FAB) m/z 774 $(M + H)^+$, 756, 527, 509, 387, 345, 327, 248; $[\alpha]^{20}_D$ −34.0° (c = 1.41, $CDCl_3$).

***N*-Debenzoyl-*N*-(isopropoxycarbonyl)butitaxel (12).** Amine **6** (0.019 g, 0.028 mmol) was treated with isopropyl chloroformate (1 M solution in toluene, 0.036 mL, 0.036 mmol, 1.3 equiv) according to the procedure described in method A to give **12** (0.019 mg, 80%) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.11 and 1.15 (2s, 6H), 1.13 (s, 3H), 1.23 (s, 3H), 1.71(s, 3H), 1.90 (s, 3H), 2.28 (m, 2H), 2.43 (s, 3H), 2.58 (m, 1H), 3.30 (bs, 1H), 3.86 (d, J = 10 Hz, 1H), 3.89 (d, J = 6.9 Hz, 1H), 4.20 and 4.31 (2d, J = 8.3 Hz, 2H), 4.27 (m, 1H), 4.58 (bs, 1H), 4.71 (m, 1H), 4.95 (d, J = 8.1 Hz, 1H), 5.06 (d, J = 10.5 Hz, 1H), 5.21 (s, 1H), 5.67 (d, J = 7.2 Hz, 1H), 6.19 (t, J = 8.4 Hz, 1H), 7.49, 7.60, and 8.13 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.5, 170.4, 166.9, 156.1, 138.6, 135.7, 133.6, 130.2, 129.1, 128.6, 84.1, 81.0, 78.8, 74.9, 74.4, 72.8, 71.9, 70.5, 68.4, 59.8, 57.5, 46.3, 43.1, 36.9, 35.8, 35.2, 29.7, 27.3, 26.4, 22.7, 21.9, 21.0, 14.3, 9.9; HRMS (FAB) m/z calcd for $C_{40}H_{55}NO_{14}Li$ 780.3783, found 780.3751; MS (FAB) m/z 796 $(M + Na)^+$, 780 $(M + Li)^+$, 774 $(M + H)^+$, 756, 738, 549, 533, 509, 480, 449, 411, 387, 345; $[\alpha]^{20}_D$ −37.4° (c = 0.735, $CHCl_3$).

***N*-(Cyclopropylcarbonyl)-*N*-debenzoylbutitaxel (13).** Amine **6** (0.025 g, 0.036 mmol) was treated with cyclopropane-

carbonyl chloride (0.004 mL, 0.046 mmol, 1.3 equiv) according to the procedure described in method A to give **13** (0.017 g, 62%) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (m, 2H), 1.05 (s, 9H), 1.11 (s, 3H), 1.23 (s, 3H), 1.34 (m, 2H), 1.73 (s, 3H), 1.88 (s, 3H), 2.22 (m, 2H), 2.42 (s, 3H), 2.56 (m, 1H), 3.86 (d, J = 6.8 Hz, 1H), 4.17−4.31 (m, 4H), 4.59 (bs, 1H), 4.94 (d, J = 8.4 Hz, 1H), 5.20 (s, 1H), 5.67 (d, J = 7.2 Hz, 1H), 6.11 (t, J = 9.3 Hz, 1H), 7.49, 7.60, and 8.11 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.6, 173.6, 170.4, 166.8, 138.5, 135.8, 133.6, 130.3, 129.2, 128.6, 84.2, 81.0, 78.6, 74.9, 74.4, 72.9, 71.9, 70.5, 57.7, 57.5, 46.2, 43.1, 36.8, 35.8, 35.2, 27.4, 26.4, 22.7, 21.1, 14.6, 14.2, 9.9, 7.4, 1.4; HRMS (FAB) m/z calcd for $C_{40}H_{53}NO_{13}Li$ 762.3677, found 762.3652; MS (FAB) m/z 762 $(M + Li)^+$, 756 $(M + H)^+$, 677, 664, 604, 577, 551, 533, 523, 466, 460, 405, 397, 369, 341, 329, 320, 313, 289, 230, 154 (base peak), 136, 120, 107; $[\alpha]^{20}_D$ −39° (c = 0.80, $CHCl_3$).

***N*-(Cyclobutylcarbonyl)-*N*-debenzoylbutitaxel (14).** Amine **6** (0.019 g, 0.0276 mmol) was treated with cyclobutanecarbonyl chloride (0.004 g, 0.035 mmol, 1.3 equiv) according to the procedure described in method A to give **14** (0.017 g, 80%) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.11 (s, 3H), 1.23 (s, 3H), 1.25 (m, 2H), 1.74 (s, 3H), 1.88 (s, 3H), 2.10 (m, 4H), 2.30 (m, 2H), 2.44 (s, 3H), 2.58 (m, 1H), 2.97 (m, 1H), 3.36 (bs, 1H), 3.88 (d, J = 7.2 Hz, 1H), 4.16 (d, J = 10.2 Hz, 1H), 4.19 and 4.32 (2d, J = 8.3 Hz, 2H), 4.26 (m, 1H), 4.59 (bs, 1H), 4.95 (d, J = 8 Hz, 1H), 5.20 (s, 1H), 5.69 (d, J = 7.1 Hz, 1H), 5.75 (d, J = 10.2 Hz, 1H), 6.13 (t, J = 8.3 Hz, 1H), 7.51, 7.61, and 8.14 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.9, 174.7, 170.3, 166.8, 138.4, 135.8, 133.6, 130.3, 129.2, 128.7, 84.1, 81.0, 78.6, 74.8, 74.4, 73.0, 71.9, 70.3, 57.5, 57.2, 46.2, 43.2, 39.8, 36.9, 35.9, 35.0, 29.7, 27.4, 26.4, 25.5, 25.4, 22.8, 21.0, 18.2, 14.2, 9.9; HRMS (FAB) m/z calcd for $C_{41}H_{55}NO_{13}Li$ 776.3833, found 776.3867; MS (FAB) m/z 776 $(M + Li)^+$, 770 $(M + H)^+$, 752, 683, 663, 619, 551, 533, 466, 460, 443, 397, 379, 313, 289, 244, 226, 154, 136; $[\alpha]^{20}_D$ −40° (c = 0.75, $CHCl_3$).

***N*-(Cyclopentylcarbonyl)-*N*-debenzoylbutitaxel (15).** Amine **5** (0.10 g, 0.096 mmol) on treatment with cyclopentanecarbonyl chloride (0.017 g, 0.13 mmol, 1.3 equiv) according to the procedure described in method A gave an amide (0.04 g) that was deprotected as described in method B to yield **15** (0.01 g, 13% overall yield) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.24 (s, 3H), 1.13 (s, 3H), 1.48−1.74 (m, 9H), 1.75 (s, 3H), 1.90 (s, 3H), 2.20−2.40 (m, 2H), 2.44 (s, 3H), 2.48−2.62 (m, 2H), 3.23 (d, J = 4.4 Hz, 1H), 3.88 (d, J = 6.8 Hz, 1H), 4.20 (m, 3H), 4.31 (d, J = 8.4 Hz, 1H), 4.58 (d, J = 3.4 Hz, 1H), 4.95 (d, J = 7.8 Hz, 1H), 5.19 (s, 1H), 5.69 (d, J = 7.3 Hz, 1H), 5.78 (d, J = 10.3 Hz, 1H), 6.14 (t, J = 9.0 Hz, 1H), 7.50 (t, J = 7.1 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 8.13 (d, J = 7.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.6, 176.0, 174.8, 170.3, 166.9, 138.5, 135.8, 133.6, 130.3, 129.2, 128.7, 84.1, 81.0, 78.7, 77.2, 74.9, 74.5, 73.1, 72.0, 70.4, 57.6, 57.2, 46.3, 45.9, 43.2, 37.0, 36.0, 35.1, 30.6, 30.5, 27.4, 26.4, 25.8, 25.7, 22.8, 21.1, 14.2, 10.0; HRMS (FAB) m/z calcd for $C_{42}H_{58}NO_{13}$ 784.3908, found 784.3870; MS (FAB) m/z 784 $(M + H)^+$, 307, 258, 185; $[\alpha]^{20}_D$ −41° (c = 0.70, $CHCl_3$).

***N*-Debenzoyl-*N*-(2-ethylbutyryl)butitaxel (16).** Amine **6** (0.02 g, 0.09 mmol) was treated with 2-ethylbutyryl chloride (0.006 g, 0.108 mmol, 1.2 equiv) according to the procedure described in method A to give **16** (0.017 g, 75%) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H), 1.06 (s, 9H), 1.11 (s, 3H), 1.21 (s, 3H), 1.48 (m, 4H), 1.73 (s, 3H), 1.83 (m, 1H), 1.88 (s, 3H), 2.02 (m, 1H), 2.30 (m, 2H), 2.42 (s, 3H), 2.57 (m, 1H), 3.36 (d, J = 3.9 Hz, 1H), 3.86 (d, J = 6.9 Hz, 1H), 4.20−4.30 (m, 4H), 4.59 (d, J = 3.9 Hz, 1H), 4.94 (d, J = 8.7 Hz, 1H), 5.20 (s, 1H), 5.68 (d, J = 6.9 Hz, 1H), 5.84 (d, J = 10.2 Hz, 1H), 6.11 (t, J = 8.8 Hz, 1H), 7.50, 7.61, and 8.12 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 175.6, 174.9, 170.1, 166.8, 138.5, 135.8, 133.6, 130.2, 129.2, 128.7, 84.1, 81.0, 78.6, 74.9, 74.4, 73.2, 71.9, 70.3, 57.5, 57.2, 51.5, 46.2, 43.2, 36.9, 35.8, 35.1, 27.5, 26.3, 25.6, 25.4, 22.8, 21.1, 14.1, 12.2, 11.9, 9.9; HRMS (FAB) m/z calcd for $C_{42}H_{60}NO_{13}$ 786.4065, found 786.4089; MS (FAB) m/z 808 $(M+Na)^+$, 786 $(M + H)^+$, 770, 527, 509, 327, 311, 260; $[\alpha]^{20}_D$ −44° (c = 0.67, $CHCl_3$).

***N*-(Cyclohexylcarbonyl)-*N*-(debenzoyl)butitaxel (17).** Amine **6** (0.04 g, 0.058 mmol) was treated with cyclohexanecarbonyl chloride (0.01 mL, 0.075 mmol, 1.3 equiv) according to the procedure described in method A to give **17** (0.037 g, 80%) as amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.12 (s, 3H), 1.23 (s, 3H), 1.34 (m, 2H), 1.6−1.8 (m, 6H), 1.74 (s, 3H), 1.88 (s, 3H), 2.30 (m, 2H), 2.42 (s, 3H), 2.58 (m, 1H), 3.87 (d, J = 6.8 Hz, 1H), 4.14 (d, J = 10.2 Hz, 1H), 4.23−4.32 (m, 3H), 4.58 (bs, 1H), 4.95 (d, J = 7.7 Hz, 1H), 5.19 (s, 1H), 5.70 (d, J = 6.8 Hz, 1H), 5.84 (d, J = 10 Hz, 1H), 6.09 (t, J = 9.2 Hz, 1H), 7.50, 7.61 and 8.13 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 176.1, 174.8, 170.2, 166.7, 138.4, 135.8, 133.5, 130.2, 129.3, 128.7, 84.2, 81.1, 78.5, 74.9, 74.4, 73.2, 71.8, 70.3, 57.5, 56.9, 46.2, 45.6, 43.2, 36.8, 35.8, 35.0, 29.9, 29.5, 27.4, 26.4, 25.6, 25.5, 22.7, 21.1, 14.1, 9.9; HRMS (FAB) m/z calcd for $C_{43}H_{59}NO_{13}Li$ 804.4146, found 804.4108; MS (FAB) m/z 821 $(M+Na)^+$, 804 $(M + Li)^+$, 798, 784, 758, 707, 604, 551, 533, 523, 466, 443, 425, 397, 369, 329, 313, 289, 278, 272, 254, 226; $[\alpha]^{20}_D$ −37° (c = 0.66, $CHCl_3$).

***N*-Debenzoyl-*N*-(2-furoyl)butitaxel (18).** Amine **5** (0.080 g, 0.077 mmol) was treated with 2-furoyl chloride (0.01 mL, 0.10 mmol, 1.3 equiv) according to the procedure described in method A to give an amide which was deprotected as discussed in method B to give **18** (0.030 g, 50% overall yield) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 9H), 1.17 (s, 3H), 1.73 (s, 3H), 1.82 (s, 3H), 2.26 (m, 2H), 2.46 (s, 3H), 2.58 (m, 1H), 3.61 (bs, 1H), 3.86 (d, J = 6.8 Hz, 1H), 4.26 (m, 3H), 4.35 (d, J = 10.6 Hz, 1H), 4.67 (bs, 1H), 4.94 (d, J = 8.8 Hz, 1H), 5.19 (s, 1H), 5.66 (d, J = 6.8 Hz, 1H), 6.15 (t, J = 8.8 Hz, 1H), 6.43 (s, 1H), 6.79 (d, J = 10.3 Hz, 1H), 6.96 (d, J = 3.3 Hz, 1H), 7.43 (s, 1H), 7.52, 7.67, and 8.15 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.3, 174.0, 170.4, 166.8, 158.0, 147.2, 144.1, 138.3, 135.8, 133.6, 130.2, 129.3, 128.6, 114.9, 112.3, 84.2, 81.1, 78.7, 74.8, 74.4, 72.7, 71.9, 70.5, 57.5, 57.3, 46.3, 43.0, 36.8, 35.9, 35.4, 29.7, 27.4, 26.5, 22.8, 20.9, 14.2, 9.9; HRMS (FAB) m/z calcd for $C_{41}H_{51}NO_{14}Li$ 788.3470, found 788.3468; MS (FAB) m/z 804 $(M + Na)^+$, 782 $(M + H)^+$, 764, 746, 682, 549, 527, 509, 491, 387, 345, 327; $[\alpha]^{20}_D$ +16.4° (c = 0.795, $CHCl_3$).

***N*-Debenzoyl-*N*-(3-furoyl)butitaxel (19).** Amine **5** (0.045 g, 0.043 mmol) was treated with 3-furoyl chloride (0.011 g, 0.86 mmol, 2 equiv) according to the procedure described in method A followed by deprotection as discussed in method B to give **19** (0.015 g, 45% overall) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (bs, 12H), 1.19 (s, 3H), 1.75 (s, 3H), 1.84 (s, 3H), 2.28 (m, 2H), 2.48 (s, 3H), 2.59 (m, 1H), 3.88 (d, J = 7.2 Hz, 1H), 4.22 (bd, J = 8.28 Hz, 2H), 4.24 (d, J = 8.4 Hz, 1H), 4.39 (d, J = 10.3 Hz, 1H), 4.66 (s, 1H), 4.94 (d, J = 8.3 Hz, 1H), 5.17 (s, 1H), 5.67 (d, J = 7.2 Hz, 1H), 6.19 (m, 2H), 6.52 (s, 1H), 7.38 (s, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.61 (t, J = 7.23 Hz, 1H), 7.81 (s, 1H), 8.16 (d, J = 7.1 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.1, 170.5, 166.9, 162.1, 144.8, 143.9, 138.3, 135.9, 133.7, 130.3, 129.2, 128.7, 122.1, 108.1, 84.1, 81.1, 78.8, 77.3, 77.2, 76.8, 76.4, 74.8, 74.4, 72.7, 72.0, 70.5, 57.6, 57.3, 46.3, 43.1, 37.0, 35.9, 35.4, 27.4, 26.5, 22.8, 20.9, 14.3, 9.9; MS (FAB) m/z 804 $(M + Na)^+$, 782 $(M + H)^+$, 764, 748, 551, 523; $[\alpha]^{20}_D$ −0.73° (c = 0.33, $CHCl_3$).

***N*-Debenzoyl-*N*-(2-thenoyl)butitaxel (20).** Amine **5** (0.40 g, 0.39 mmol) was treated with 2-thiophenecarbonyl chloride (0.048 mL, 0.46 mmol, 1.2 equiv) according to method A to give an amide (0.42 g, 95%) that was deprotected as described in method B to provide **20** (0.19 g, 67% overall yield) as white crystals: mp 214 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 1.11 (s, 3H), 1.12 (s, 9H), 1.14 (s, 3H), 1.69 (s, 3H), 1.85 (s, 3H), 2.20 (m, 2H), 2.40 (m, 1H), 2.48 (s, 3H), 3.87 (d, J = 7.3 Hz, 1H), 4.21 (m, 3H), 4.37 (bs, 1H), 4.73 (bs, 1H), 5.01 (d, J = 8.8 Hz, 1H), 5.24 (s, 1H), 5.66 (d, J = 7 Hz, 1H), 6.13 (t, J = 9 Hz, 1H), 7.11, 7.55, 7.63, 7.71, and 8.15 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 211.0, 174.2, 170.3, 166.5, 162.3, 138.2, 138.0, 136.0, 133.3, 130.4, 130.1, 129.6, 128.5, 128.3, 127.7, 84.4, 81.2, 77.9, 74.9, 74.2, 72.8, 71.4, 70.5, 58.3, 58.2, 57.5, 46.1, 43.2, 36.4, 35.7, 35.5, 27.3, 26.6, 26.3, 22.7, 21.0, 13.8, 9.8; HRMS (FAB) m/z calcd for $C_{41}H_{51}NO_{13}SLi$ 804.3241, found 804.3279; MS (FAB) m/z 820 $(M + Na)^+$, 798 $(M + H)^+$,

780, 762, 700, 617, 549, 527, 509, 491, 480, 449, 429, 405, 399, 387, 378, 369, 327, 307, 272, 254, 226; $[\alpha]^{20}_D$ +11.2° (*c* = 0.365, MeOH).

***N*-Debenzoyl-*N*-(3-thenoyl)butitaxel (21)**. Amine **6** (0.020 g, 0.029 mmol) was reacted with 3-thiophenecarbonyl chloride (0.008 mL, 0.058 mmol, 2.0 equiv) as described in method A to give **21** (0.017 g, 74%) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (bs, 12H), 1.15 (s, 3H), 1.61 (s, 3H), 1.80 (s, 3H), 2.22 (m, 2H), 2.46 (s, 3H), 2.54 (m, 1H), 3.57 (bs, 1H), 3.85 (d, *J* = 6.8 Hz, 1H), 4.18−4.30 (m, 3H), 4.38 (d, *J* = 10.2 Hz, 1H), 4.64 (bs, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 5.16 (s, 1H), 5.64 (d, *J* = 7.0 Hz, 1H), 6.15 (t, *J* = 9.0 Hz, 1H), 6.39 (d, *J* = 10 Hz, 1H), 7.25 (bs , 2H), 7.49−8.14 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.1, 170.5, 166.9, 162.6, 138.4, 136.9, 135.8, 133.7, 130.3, 129.2, 128.7, 128.4, 126.7, 125.9, 84.1, 81.0, 78.8, 74.8, 74.4, 72.6, 71.9, 70.5, 57.6, 46.3, 43.0, 36.9, 35.9, 35.5, 27.5, 26.5, 22.8, 20.9, 14.3, 9.9; HRMS (FAB) *m*/*z* calcd for $C_{41}H_{51}NO_{13}SLi$ 804.3241, found 804.3267; MS (FAB) *m*/*z* 820 $(M + Na)^+$, 804 $(M + Li)^+$, 780, 533, 509, 447, 377, 313, 272, 226, 176, 154; $[\alpha]^{20}_D$ +4.5° (*c* = 0.58, $CHCl_3$).

***N*-Debenzoyl-*N*-(5-methyl-2-thenoyl)butitaxel (22)**. Amine **5** (0.10 g, 0.096 mmol) was treated with 5-methyl-2-thiophenecarbonyl chloride (0.02 g, 0.13 mmol, 1.3 equiv) as described in method A to give an amide that was deprotected as described in method B to provide **22** (0.04 g, 52% overall yield) as a white solid: mp 192−194 °C dec; R_f 0.52 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 1.11 (s, 3H), 1.12 (s, 9H), 1.16 (s, 3H), 1.70 (s, 3H), 1.87 (s, 3H), 2.21 (m, 1H), 2.41 (m, 3H), 2.47 (s, 3H), 2.48 (s, 3H), 3.88 (d, *J* = 7.1 Hz, 1H), 4.19 (m, 1H), 4.22 (s, 2H), 4.35 (d, *J* = 1.7 Hz, 1H), 4.73 (d, *J* = 1.6 Hz, 1H), 5.02 (d, *J* = 8.1 Hz, 1H), 5.25 (s, 1H), 5.67 (d, *J* = 7.3 Hz, 1H), 6.13 (t, *J* = 9.2 Hz, 1H), 6.80 (d, *J* = 2.7 Hz, 1H), 7.51 (d, *J* = 3.8 Hz, 1H), 7.56 (t, *J* = 9.6 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 8.16 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (300 MHz, CD_3OD) δ 212.7, 177.1, 173.3, 169.3, 165.9, 148.9, 141.0, 139.3, 138.5, 136.0, 133.0, 132.8, 131.8, 131.3, 129.0, 87.5, 83.9, 80.7, 79.2, 78.0, 77.2, 74.7, 74.2, 73.7, 61.3, 60.4, 46.2, 39.1, 38.5, 38.4, 29.6, 28.7, 25.0, 23.5, 17.0, 15.9, 12.1; HRMS (FAB) calcd for $C_{42}H_{54}NO_{13}S$ 812.3316, found 812.3322; MS (FAB) *m*/*z* 812 $(M + H)^+$, 549, 308, 286, 240, 133, 125; $[\alpha]^{20}_D$ −42° (*c* = 0.65, MeOH).

***N*-Debenzoyl-*N*-(3-methyl-2-thenoyl)butitaxel (23)**. Amine **5** (0.10 g, 0.096 mmol) on reaction with 3-methyl-2-thiophenecarbonyl chloride (0.019 g, 0.12 mmol) according to procedure A gave an amide (0.093 g) that was deprotected following method B to provide **23** (0.041 g, 32% overall yield) as a white amorphous solid: R_f 0.61 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 1.15 (s, 9H), 1.21 (s, 3H), 1.71 (s, 3H), 1.80 (m, 1H), 1.89 (s, 3H), 2.02 (s, 3H), 2.31 (m, 1H), 2.35 (m, 1H), 2.41 (m, 1H), 2.46 (s, 3H), 2.49 (s, 3H), 3.90 (d, *J* = 7.0 Hz, 1H), 4.23 (s, 2H), 4.24 (m, 1H), 4.36 (s, 1H), 4.74 (s, 1H), 5.28 (s, 1H), 5.02 (d, *J* = 9.3 Hz, 1H), 5.69 (d, *J* = 7.0 Hz, 1H), 6.17 (t, *J* = 9.3 Hz, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 7.45 (d, *J* = 5.0 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 6.7 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (300 MHz, CD_3OD) δ 212.8, 177.2, 173.2, 169.3, 167.3, 143.1, 141.1, 139.3, 136.1, 134.3, 133.0, 132.8, 131.3, 130.1, 87.5, 84.0, 80.9, 80.7, 79.2, 78.1, 77.2, 75.0, 74.2, 73.3, 61.5, 60.4, 52.0, 46.2, 39.1, 38.5, 38.1, 30.0, 29.6, 29.5, 28.7, 25.0, 23.5, 17.4, 16.0, 12.1; HRMS (FAB) calcd for $C_{42}H_{54}NO_{13}S$ 812.3316, found 812.3338; MS (FAB) *m*/*z* 812 $(M + H)^+$, 549, 527, 509, 387, 345, 327, 308, 286, 268, 240; $[\alpha]^{20}_D$ +1.5° (*c* = 1.3, MeOH).

***N*-Debenzoyl-*N*-(2-thienylacryloyl)butitaxel (24)**. Amine **5** (0.10 g, 0.096 mmol) on reaction with 2-thienylacrylic acid chloride (0.022 g, 0.13 mmol, 1.3 equiv) according to procedure A gave an amide (0.09 g) that was deprotected as described in method B to give **24** (0.03 g, 40% overall yield) as a white solid: mp 203−205 °C dec; R_f 0.54 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.09 (s, 3H), 1.20 (s, 3H), 1.74 (s, 3H), 1.86 (s, 3H), 1.88 (m, 1H), 2.19 (m, 1H), 2.34 (m, 1H), 2.49 (s, 3H), 2.58 (m, 1H), 3.57 (s, 1H), 3.88 (d, *J* = 7.2 Hz, 1H), 4.24 (m, 2H), 4.32 (d, *J* = 10.2 Hz, 2H), 4.62 (d, *J* = 4.5 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H), 5.20 (s, 1H), 5.68 (d, *J* = 7.2 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 6.15 (d, *J* = 15.2 Hz, 1H), 6.19 (t, *J* = 9 Hz, 1H), 7.26 (s, 1H), 6.93 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.55 (d, *J* = 15.2 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), (8.20 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.9, 174.3, 170.6, 166.9, 165.4, 140.0, 139.7, 138.5, 135.7, 134.6, 133.7, 130.5, 130.4, 129.3, 128.8, 127.9, 127.5, 118.8, 84.2, 81.0, 78.9, 74.9, 74.4, 72.7, 71.9, 70.5, 57.7, 57.6, 46.3, 43.1, 36.9, 36.0, 35.4, 27.5, 26.5, 22.8, 32.2, 14.3, 10.0; HRMS (FAB) calcd for $C_{43}H_{54}NO_{13}S$ 824.3316, found 824.3341; MS (FAB) *m*/*z* 824 $(M + H)^+$, 595, 509, 406, 360, 298, 280, 252, 137; $[\alpha]^{20}_D$ +78.3° (*c* = 1.36, MeOH).

***N*-Debenzoyl-*N*-(2-thienylacetyl)butitaxel (25)**. Amine **5** (0.10 g, 0.096 mmol) was reacted with 2-thiopheneacetyl chloride (0.020 g, 0.13 mmol) according to procedure A to give an amide (0.07 g, 63%) that was deprotected following method B to give **25** (0.02 g, 26% overall yield) as a white solid: mp 160−162 °C; R_f 0.48 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.11 (s, 3H), 1.22 (s, 3H), 1.75 (s, 3H), 1.80 (m, 1H), 1.86 (s, 3H), 2.02 (m, 1H), 2.28 (m, 1H), 2.42 (s, 3H), 2.58 (m, 1H), 3.17 (d, *J* = 4.4 Hz, 1H), 3.70 (d, *J* = 2.1 Hz, 2H), 3.84 (d, *J* = 6.9 Hz, 1H), 4.24 (m, 3H), 4.31 (d, *J* = 8.3 Hz, 1H), 4.53 (d, *J* = 3.3 Hz, 1H), 4.92 (d, *J* = 7.7 Hz, 1H), 5.67 (d, *J* = 7.1 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 6.14 (t, *J* = 8.7 Hz, 1H), 6.93 (dd, *J* = 5.3, 3.4 Hz, 1H), 6.96 (d, *J* = 3.4 Hz, 1H), 7.17 (d, *J* = 5.3 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 174.4, 170.3, 169.4, 166.9, 138.3, 136.1, 135.9, 133.6, 130.4, 129.3, 128.7, 127.4, 125.6, 84.1, 81.0, 78.7, 74.9, 74.4, 72.9, 71.9, 70.3, 60.4, 57.5, 46.2, 43.1, 37.5, 36.9, 36.1, 35.1, 27.3, 26.5, 22.9, 21.1, 14.2, 10.0; HRMS (FAB) calcd for $C_{42}H_{54}NO_{13}S$ 812.3316, found 812.3304; MS (FAB) *m*/*z* 812 $(M + H)^+$, 286, 268, 240, 210, 184, 162, 149, 116, 105; $[\alpha]^{20}_D$ −31.5° (*c* = 1.01, $CHCl_3$).

***N*-Debenzoyl)-*N*-((1-methyl-2-pyrrolyl)carbonyl)butitaxel (26)**. Amine **5** (0.1 g, 0.096 mmol) was reacted with 1-methyl-2-pyrrolecarbonyl chloride (0.018 g, 0.13 mmol) according to procedure A to give an amide (0.055 g) that was deprotected following method B to give **26** (0.010 g, 13% overall yield) as a white solid: mp 194−195 °C dec; R_f 0.50 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 0.94 (s, 9H), 1.14 (s, 3H), 1.24 (s, 3H), 1.72 (s, 3H), 1.85 (m, 2H), 1.97 (s, 3H), 2.42 (s, 3H), 2.49 (m, 2H), 3.69 (s, 1H), 3.91 (d, *J* = 6.8 Hz, 1H), 4.23 (m, 3H), 4.61 (s, 1H), 5.02 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 1H), 5.67 (d, *J* = 7.3 Hz, 1H), 6.19 (t, *J* = 9.3 Hz, 1H), 7.09 (t, *J* = 4.2 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.60 (m, 2H), 7.72 (d, *J* = 4.9 Hz, 1H), 8.14 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (300 MHz, CD_3OD) δ 211.0, 176.7, 173.3, 141.3, 139.2, 136.0, 134.4, 134.3, 133.2, 132.8, 131.3, 129.8, 87.5, 84.0, 81.2, 79.23, 78.4, 77.2, 75.1, 74.2, 73.7, 66.6, 60.4, 49.4, 46.1, 39.1, 38.9, 38.2, 29.6, 28.8, 24.9, 23.6, 16.1, 12.2; HRMS (FAB) calcd for $C_{42}H_{55}N_2O_{13}$ 834.2829, found 834.2828; MS (FAB) *m*/*z* 834 $(M + H)^+$, 688, 549, 527, 509, 330, 262, 232, 206, 185, 162, 147, 115, 105; $[\alpha]^{20}_D$ −51.3° (*c* = 0.238, MeOH).

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