# Synthesis, Conformational Analysis, and Biological Evaluation of Heteroaromatic Taxanes

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The asymmetric syntheses of heteroaromatic 3-[(*tert*-butyldimethylsilyl)oxy]-2-azetidinones **12**−**16** via chiral ester enolate−imine cyclocondensation chemistry are described. The azetidinones contain heteroaromatic moieties which, in certain cases, contribute to a decrease in enantioselectivity due to possible alternate coordinations in the transition states. The (3*R*,4*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-4-heteroaryl-2-azetidinones were subsequently converted to the heteroaromatic taxanes **31**−**36** and **43**−**45**. Conformational analyses of the 3′-(2-pyridyl) analogue **31** and 3′-(2-furyl) analogue **43** indicate they have solution conformational preferences virtually identical to paclitaxel and docetaxel. Heteroaromatic *N*-acyl paclitaxel analogues **47**−**51** were prepared from *N*-debenzoylpaclitaxel via Schotten−Baumann acylation. The majority of the 14 analogues displayed good to excellent activity in a microtubule assembly assay in comparison to paclitaxel. The analogues were also tested for cytotoxicity against B16 melanoma cells. 3′-Dephenyl-3′-(2-pyridyl)-paclitaxel (**31**), 3′-dephenyl-3′-(2-furyl)paclitaxel (**34**), *N*-BOC-3′-dephenyl-3′-(2-furyl)paclitaxel (**43**), 3′-dephenyl-3′-(2-furyl)-*N*-(hexanoyl)paclitaxel (**44**), and *N*-debenzoyl-*N*-(3-furoyl)paclitaxel (**51**) were found to be more cytotoxic than paclitaxel against this cell line. 3′-Dephenyl-3′-(4-pyridyl)paclitaxel (**33**) and *N*-debenzoyl-*N*-(2-furoyl)paclitaxel (**50**) displayed cytotoxicity against B16 melanoma cells similar to paclitaxel.

The antitumor agent paclitaxel (Figure 1, **1**) was isolated in 1971 from the bark of the pacific yew.[1] Paclitaxel's utility for the treatment of cisplatin refractory ovarian cancer, metastatic breast cancer, head and neck cancer, and lung cancer[2] as well as its complex structure have made it an exciting target for synthetic[3−5] and semisynthetic studies.[6−8] Paclitaxel also possesses a unique mechanism of action in which this agent promotes the polymerization and subsequent stabilization of cellular microtubules.[9,10] Intense studies on the paclitaxel framework and its diterpene moiety have been performed to attempt to identify the paclitaxel pharmacophore.[7,8,11−14]

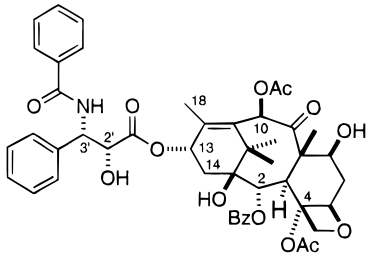


**Figure 1.** Paclitaxel (**1**).

Structure−activity relationship studies have shown that the C13 *N*-benzoyl-3′-phenylisoserine side chain of paclitaxel is crucial for the molecule to elicit its biological activity.[1] Also of importance is the stereochemistry at the C2′ and C3′ stereogenic centers, with the most active diastereoisomer being that which is found in the natural product.[15] In our continuing studies on the asymmetric

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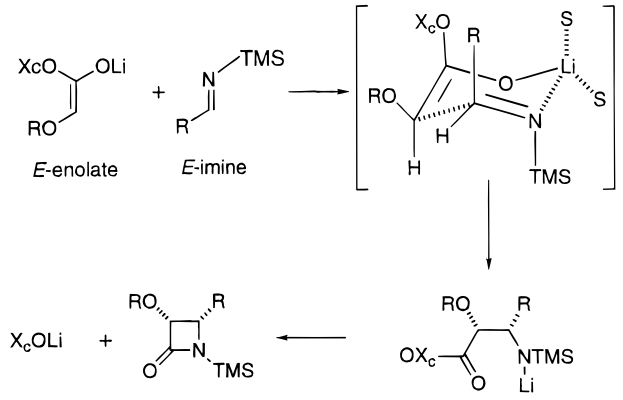


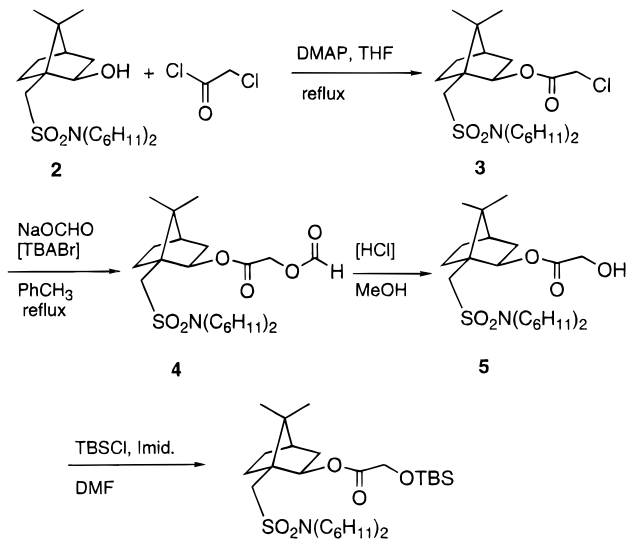

**Figure 2.** Proposed mechanism for the formation of *cis*-β-lactams in the ester enolate−imine cyclocondensation reaction.

synthesis of β-amino acids and their conversion to the phenylisoserine moiety of paclitaxel,[16−21] we now report on the asymmetric synthesis of a series of *cis*-3-[(*tert*-butyldimethylsilyl)oxy]-4-heteroaromatic-2-azetidinones and their application to the synthesis of novel taxanes.[22] Conformational analyses of two representative heteroaromatic analogues indicated that they have solution conformational preferences virtually identical to paclitaxel and docetaxel. We are also detailing the synthesis and biological evaluation of novel *N*-debenzoyl-*N*-heteroaroylpaclitaxel analogues from *N*-debenzoyl-paclitaxel via Schotten−Baumann acylation.

## Chemistry and Discussion

The chiral ester enolate−imine cyclocondensation reaction has proven to be a useful approach to the asymmetric synthesis of functionalized 2-azetidinones and β-amino acids.[23−28] Remote stereocontrol in this reaction can be invoked by a chiral alcohol moiety of an achiral ester, which can afford excellent stereoselectivity (Figure 2). This chemistry also results in the recovery of the intact chiral auxiliary as the final cyclization, after the generation of the stereogenic centers, results in displacement of the auxiliary. The ester enolate−imine cyclocondensation reaction proves to be quite versatile for the synthesis of *cis*-2-azetidinones via control of the imine and enolate geometries which can be rationalized through a six-membered chairlike transition state (Figure 2). (*E*)-enolates and (*E*)-imines react to form cis products while (*Z*)-enolates and (*E*)-imines (not shown) typically react to form mixtures of cis and trans products.[25]

**Scheme 1**




We have shown that paclitaxel's *N*-benzoyl-3-phenylisoserine side chain, an α-hydroxy β-amino acid, can be derived through this chemistry.[17,21] The α-hydroxyl moiety of the starting glycolate affords a handle to control enolate geometry,[29−31] and the use of trimethylsilyl imines afford (*E*)-aza-aldehyde equivalents.[25,32] We herein fully report on our chemistry leading to the synthesis of optically active *cis*-3-[(*tert*-butyldimethylsilyl)oxy]-4-pyridyl- and *cis*-3-[(*tert*-butyldimethylsilyl)oxy]-4-furyl-2-azetidinones which were further transformed into heterocyclic taxanes.[22]

The asymmetric syntheses of the targeted 4-heteroaryl-2-azetidinone intermediates were initiated by the synthesis of the appropriately functionalized chiral glycolate **6** (Scheme 1), which is utilized in the asymmetric ester enolate−imine cyclocondensation.[17] Acylation of Oppolzer's chiral auxiliary[33] **2** was accomplished with chloroacetyl chloride and (*N*,*N*-dimethylamino)pyridine (Scheme 1). Nucleophilic displacement of the halide of **3** with sodium formate gave **4** quantitatively. Treatment of **4** with methanolic HCl afforded the free carbinol **5** in quantitative yield. The free hydroxyl group was then protected as the *tert*-butyldimethylsilyl ether **6**.

The addition of a bulky protecting group to the α-position of the ester functionality allows for the selective formation of the (*E*)-enolate as intramolecular coordination by the counterion to the lone electron pairs of the ether oxygen is prevented by the steric demand of the protecting group.[29−31] The sterically demanding TBS functionality is also important to achieve high enantioselectivity in the β-lactam formation.[17] Deprotonation of the chiral ester **6** with LDA at −78 °C was followed by the addition of heterocyclic imines **7**−**11** (Scheme 2).

The imines were synthesized following chemistry developed by Hart[34] and used as crude products since

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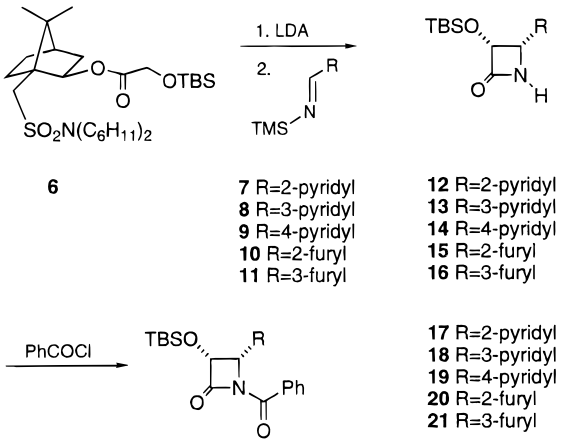
**Scheme 2**




**6**

**7** R=2-pyridyl
**8** R=3-pyridyl
**9** R=4-pyridyl
**10** R=2-furyl
**11** R=3-furyl

**12** R=2-pyridyl
**13** R=3-pyridyl
**14** R=4-pyridyl
**15** R=2-furyl
**16** R=3-furyl

**17** R=2-pyridyl
**18** R=3-pyridyl
**19** R=4-pyridyl
**20** R=2-furyl
**21** R=3-furyl

**Table 1. Optical Rotations, Enantiomeric Excesses (ee), HPLC Retention Times, and Flow Rates (DIACEL CHIRACEL OD-H Chiral Column) of Azetidinones 12−16 in Comparison to *cis*-3-[(*tert*-Butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone (R = phenyl)**


major minor

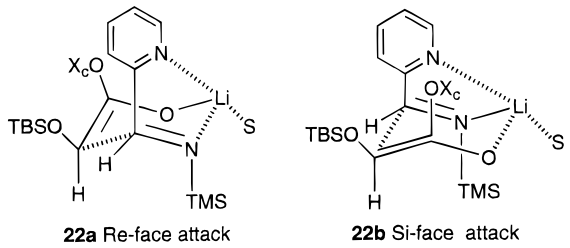
| R | optical rotation $[\alpha]_D$ | ee (%) | $t_R$ of major enantiomer (min) | $t_R$ of minor enantiomer (min) | flow rate (mL/min) |
|---|---|---|---|---|---|
| phenyl | +56 | 93 | 20.7 | 19.2 | 0.7 |
| 2-pyridyl (**12**) | +86 | 44 | 22.3 | 30.7 | 1.4 |
| 3-pyridyl (**13**) | +26 | 31 | 24.2 | 35.8 | 1.3 |
| 4-pyridyl (**14**) | +96 | 95 | 23.0 | 14.0 | 1.3 |
| 2-furyl (**15**)[a] | +30 | 92 | 18.7 | 17.2 | 1.0 |
| 3-furyl (**16**) | +21 | 36 | 13.8 | 12.0 | 1.4 |

[a] Cis isomer.

attempts to purify them by vacuum distillation led to intense polymerization. The syntheses of the 4-heteroaryl-2-azetidinones **12**−**16** were accomplished in good yields (Scheme 2) but with varying asymmetric induction (Table 1).

*β*-Lactams **14** and **15** were produced in excellent enantiomeric excesses (92 and 95%, respectively). The remainder of the 2-azetidinones were isolated in good yields but low ee's, and surprisingly, azetidinone **15** was isolated in a 14:1 cis:trans ratio.[35] The heteroaryl substituents on **12**, **13**, **15**, and **16** are functionalities that contain additional accessible coordination sites. The lone pairs of electrons available for coordination of the 2-furyl, 3-furyl, 2-pyridyl, and 3-pyridyl moieties are situated such that chelation[36,37] possibly occurs with the lithium counterion in the ester enolate−imine cyclocondensation transition state (Figure 3, **22a** and **22b**).

This additional coordination could strain and disrupt the transition state by enhancing a disfavorable 1,3-diaxial interaction with the chiral auxiliary or by significantly distorting the ordered transition state (Figure 3), allowing for the cyclocondensation to also occur through a competing open transition state where facial selectivity is compromised. This phenomenon is not




**22a** Re-face attack **22b** Si-face attack

**Figure 3.** Coordinated transition states leading to cis products.

observed with the 4-pyridyl, as the lone electron pair in this compound is not oriented properly for coordination. Also supporting this hypothesis is the formation of the trans isomer of **15**, which presumably forms through an open transition state.

A multiple coordinated polymeric system could be an alternate cause for the decreases in enantioselectivity, but the fact that the 4-pyridyl-2-azetidinone, which has an additional coordination site, is formed in excellent enantiomeric purity seems to disfavor this alternate hypothesis.

The absolute stereochemistry of azetidinones **12**−**16** was assigned by comparing the signs of their optical rotations to the known 4-phenyl analogue, (3*R*,4*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone (Table 1).[21] It is of interest to note that the retention times of the major and minor enantiomer of the 2-azetidinones on the chiral HPLC column varied (Table 1). In the case of the 2-pyridyl- and 3-pyridylazetidinones **12** and **13**, the minor enantiomer had the longer retention time, whereas the other analogues showed longer retention times for the major isomer.

Azetidinones **12**−**16** were converted to their electrophilic imides **17**−**21** via acylation with benzoyl chloride and catalytic amounts of DMAP (Scheme 2). *N*-Benzoyl-2-azetidinones **17**−**21** were then reacted with the sodium alkoxide[35] of 7-*O*-(triethylsilyl)baccatin III (**25**) to afford the disilyltaxanes **26**−**30** (Scheme 3).

Due to the poor enantioselectivity in the synthesis of azetidinones **13** and **16**, compounds **27** and **30** were isolated as a 2:1 and 3:1 mixture of diastereomers, respectively. However, in the synthesis of 3′-(2-pyridyl)-taxane **26** from *β*-lactam **12** (44% ee), the reaction proceeded with kinetic resolution to afford a single stereoisomer. Interestingly, reaction of *N*-benzoyl-2-azetidinone **19** with 7-*O*-(triethylsilyl)baccatin III resulted in the formation of the desired product **28a** and an elimination side product **28b** (Scheme 4).

The enamide **28b**, generated under base catalysis, may have been a product of deprotonation of the C3′ amide functionality (**28c**, Scheme 4) which could then in turn have catalyzed the intramolecular deprotonation of H3′ and initiated the antiperiplanar elimination cascade which led to the formation of the energetically favored highly conjugated enamide **28b**. One also cannot rule out the possibility of direct deprotonation at C3′ (**28a**, Scheme 4), although no C3-epimerized products were detected. The formation of the enamide **28b** is evident by $^1$H NMR by the loss of the signal of the (*tert*-butyldimethylsilyl)oxy functionality. In addition, the $^1$H NMR of the enamide is devoid of a doublet resonance at 5.70 ppm which corresponds to the 3′-phenylisoserine proton. The new olefinic 2′ side chain proton is now deshielded; the $^1$H NMR resonance shifts from 4.71 ppm to 5.44 ppm, and the multiplicity changes from a doublet to a singlet. The amide proton of **28b**, intensely involved

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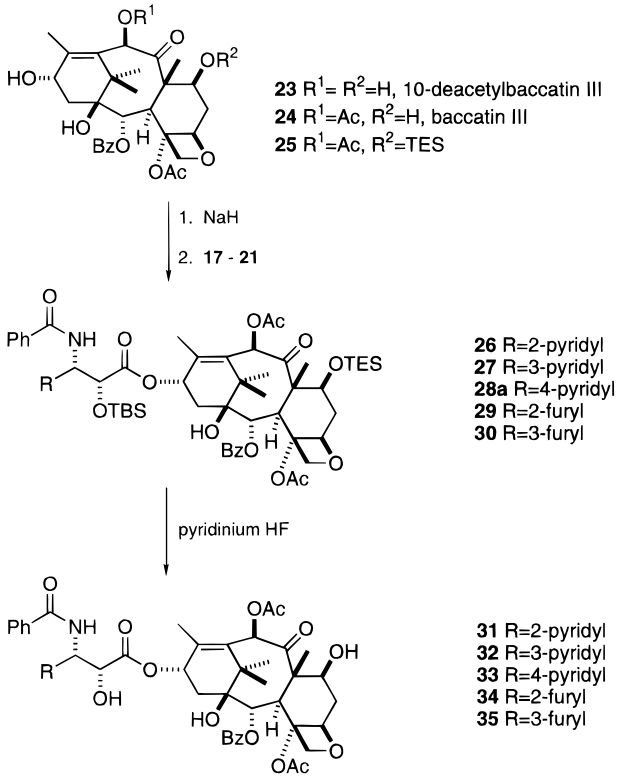
**Scheme 3**

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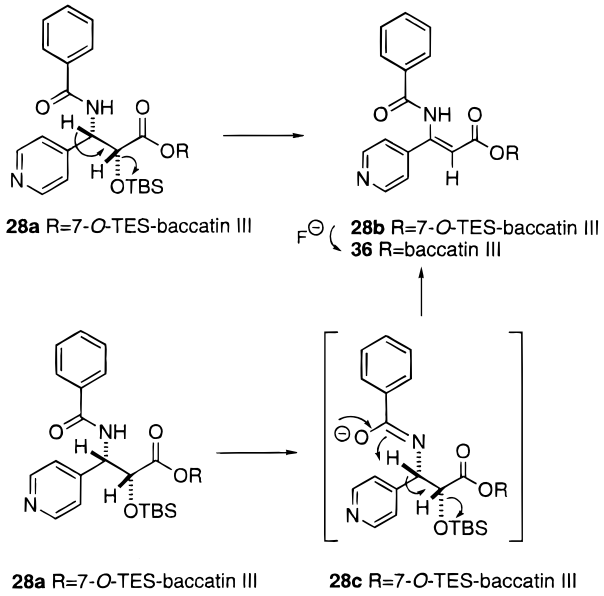


in a six-membered hydrogen bond with the C1′ carbonyl oxygen, resonates at 11.72 ppm. The *Z*-configuration at the double bond was assigned through NOE studies in which irradiation at H2′ (5.44 ppm) results in an NOE enhancement at the pyridyl protons and irradiation at the amide proton at 11.72 ppm causes NOE enhancement of the ortho benzamide protons only. It was found that the ratios of enamide **28b** to desired product **28a** (60%: 20%) could be altered to disfavor the production of the enamide by limiting the quantity of base utilized in the reaction. A decreased amount of NaH (10 equiv) produced the 4-pyridyltaxane **28a** in 80% yield and enamide **28b** in 10%. The protected heterocyclic taxanes **26**−**30** were then converted to their corresponding free taxanes **31**−**36** via fluoride-mediated deprotection (Schemes 3 and 4).

Biological evaluation of these heteroaromatic taxanes revealed that the 3′-(2-furyl)paclitaxel analogues **34** was about three times more cytotoxic against B16 melanoma cells than paclitaxel (Table 3). We therefore decided to prepare analogues of **34**, in the hope to increase its potency even further. Since docetaxel and taxol C were reported to be more cytotoxic than paclitaxel,[15,38] we prepared the corresponding 3′-furyl analogues **43** and **44** (Scheme 5). In addition, we prepared *N*-decanoyl analogue **45** to test whether an increase in lipophilicity might increase cytotoxicity in this series of compounds.

The synthesis of taxanes **43**−**45** started with the acylation of 2-azetidinone **15** (Scheme 5). The first step in the synthesis of analogue **43** was the formation of the *N*-*tert*-butoxycarbonyl derivative of **15** to form **37** in high yield. The activated 2-azetidinone was then treated with the sodium alkoxide of 7-*O*-(triethylsilyl)baccatin III to give protected taxane **40**. Desilylation promoted by pyridinium hydrofluoride afforded heteroaromatic docetaxel analogue **43**. Following along the same synthetic route with the exception of the acylating agents used, heteroaromatic side chain analogues **44** and **45** were assembled. For the synthesis of the furyl analogue of taxol C **44**, the acylating agent was caproyl chloride, and for the synthesis of furyl taxane **45** the acylating agent was decanoyl chloride. Base-mediated coupling and fluoride-assisted deprotection produced the target compounds **44** and **45**.

Previously, we[39] and others[40−42] have noted that in polar solvents, a "hydrophobically collapsed" conformation of paclitaxel and docetaxel becomes populated in which the 2-benzoyl, 3′-phenyl, and 4-acetyl groups are proximate. The size of $J_{2',3'}$ also increases in polar solvents, indicating increasing population of rotamers with a large torsion angle. A recent X-ray structure of paclitaxel shows these same features.[43] In the case of the 3′-heterocycle analogues, the aromatic rings show chemical shift changes (Table 2) and new NOE's in DMSO/water analogous to those seen for paclitaxel and docetaxel, showing the presence of this same conformation (Figures 4 and 5). Since the protons on the pyridyl ring are now nonequivalent, it is possible to ascertain that, in **31**, the pyridyl nitrogen prefers to face "up" away from the 4-acetyl and the interior of the hydrophobic cluster (Figure 4). The 3″-pyridyl proton has the largest NOE's to the 4-acetyl methyl, which is "down;" also, the 6″-pyridyl proton has a small NOE to the 14-proton assigned as $\beta$ by its large NOE to H13, which is "up." The 4″-pyridyl proton lacks this NOE. The 5″-pyridyl proton (corresponding to *para* for the 3′-phenyl) shows the largest NOE's to the 2-benzoyl ring, with those from 4″ and 6″ being of approximately equal size. The NOE's involving 2′, 3′, and the 4-acetyl to the 2-benzoyl and 3′-(2″-pyridyl) groups are also illustrated in Figure 4. Although there are some overlapping peaks in the

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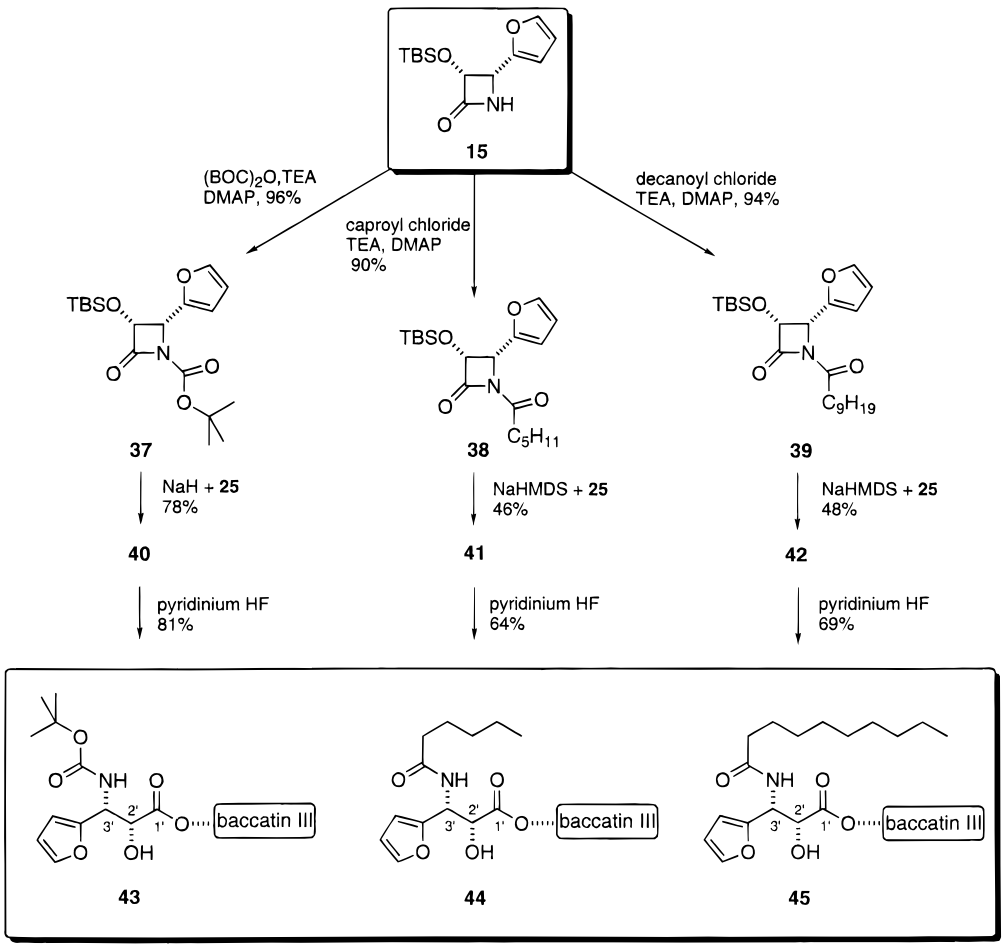
**Scheme 5**




spectrum, there are no unambiguous NOE's to the *N*-benzoyl group from any of these others. This is consistent with our earlier observation that there are no NOE's of this type in paclitaxel or docetaxel[39] and molecular dynamics results indicating this group has no preferred orientation in solution.[40]

Analogue **43** appears to have the same "up" orientation of the heteroatom, away from the 4-acetyl (Figure 5). Furyl proton 3″ has a significantly stronger NOE to the 4-acetyl whereas the 4″ proton on the furyl ring has a significantly stronger NOE to the 2-benzoyl ortho proton. Additional NOE's between these rings are expected from this conformer, but because of overlap between the 5″-furyl and 2-benzoyl meta protons, they cannot be observed. The 3″ and 4″ protons of the furan ring, which are coincidentally isochronous in $CDCl_3$, show a separation of about 0.2 ppm in DMSO/water. This chemical shift change evidently results from the new proximity to the 2-benzoyl ring in the polar solvent. In the $CDCl_3$ spectra of compounds **15** (free NH) and **20**, to which a benzoyl group has been added adjacent to the 2-furyl ring, virtually identical shift changes are observed.

These compounds thus display solution conformational preferences like all other active taxanes with 3′-aromatic substituents which have been reported to date.[20] However, we have noted that highly active 3′-cyclohexyl analogs do not adopt this conformation.[20,44]

The syntheses of the *N*-acyl heterocyclic taxanes **47**−**51** were achieved through a common intermediate, *N*-debenzoylpaclitaxel (**46**, Scheme 6).[45,46] This intermediate can be derived through removal of the *N*-BOC or the *N*-CBZ group of *N*-BOC- or *N*-CBZ-*N*-debenzoylpaclitaxel.[45,46] Acylation of this intermediate under Schotten−Baumann conditions[47] with the appropriate heteroaromatic acid chlorides afforded taxanes **47**−**51**.

## Biological Evaluation

The heteroaromatic taxanes were evaluated for their ability to promote assembly of tubulin into microtubules and for their cytotoxicity against B16 melanoma cells (Table 3). The majority of the heteroaromatic analogues, with the exception of **36**, **45, 47,** and **49**, displayed a better or similar ability to promote polymerization of microtubules than the parent paclitaxel (**1**). The evaluation of the 3′-heteroaryl analogues **31**−**35** revealed that the 2-pyridyl and the 2-furyl analogues **31** and **34** were more cytotoxic against B16 melanoma cell cells than paclitaxel. Although the 3-pyridyl and the 3-furyl analogues **32** and **35** were quite active in the tubulin assembly assay, their cytotoxicity against B16 melanoma cells was reduced in comparison to paclitaxel. Their diminished cytotoxicity may be partly due to the fact that they were tested as diastereomeric mixtures. It is interesting to note that the 4-pyridyl analogue **33** has

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(45) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1825−1830.

(46) Dasgupta, D.; Park, H.; Harriman, G. C. B.; Georg, G. I.; Himes, R. H. *J. Med. Chem.* **1994**, *37*, 2976−2980.

(47) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335−338.

**Table 2. $^1$H NMR Data for Paclitaxel (1) and Paclitaxel Analogues 31−47[a]**

| protons at | 1 | 31 | 31[b] | 32[c] | 33 | 34 | 34[b] | 35[c] | 36 | 43 | 43[d] | 44 | 45 | 46 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C-2 | 5.67 (d, 7.0) | 5.67 (d, 6.8) | 5.52 (d, 6.9) | 5.67 (d, 6.8) | 5.63 (d, 7.0) | 5.67 (d, 7.2) | 5.52 (d, 7.2) | 5.67 (d, 7.2 | 5.66 (d, 6.9) | 5.66 (d, 6.9) | 5.51 (d, 6.8) | 5.64−5.68 (m)[e] | 5.64−5.68 (m)[e] | 5.67 (d, 6.8) |
| C-2′ | 4.78 (d, 2.6) | 4.82 (d, 3.3) | 4.94 (d, 5.9) | 5.68 and 5.78 (d, 2.4) | 4.79 (d, 2.2) | 4.81 (d, 2.1) | 4.76 (d, 6.6) | 4.59 and 4.67 (d, 1.5) | 5.42 (s) | 4.70 (d, 1.8) | under HDO | 4.71 (d, 1.8) | 4.71 (d, 2.4) | 4.82 (d, 3.3) |
| C-3 | 3.77 (d, 7.0) | 3.83 (d, 6.6) | 3.74 (d, 6.3) | 3.79 and 3.85 (d, 6.3) | 3.76 (d, 6.8) | 3.81 (d, 6.9) | 3.75 (d, 6.9) | 2.80 (s, 7.1) | 3.83 (d, 6.9( | 3.80 (d, 7.2) | 3.71 (d, 6.3) | 3.80 (d, 6.9) | 3.80 (d, 6.9) | 3.83 (d, 6.6) |
| C-3′ | 5.76 (dd, 2.0, 9.0) | 5.92 (dd, 2.9, 9.4) | 5.68 (d, 5.9) | 5.81 and 5.85 (dd, 2.4, 8.7) | 5.79 (d, 9.3) | 5.87 (dd, 2.4, 9.3) | 5.64 (d, 6.6) | 5.72 (dd, 1.5, 9.0) | | 5.23−5.34 (m)[e] | 5.09 (m) | 5.64−5.68 (m)[e] | 5.64−5.68 (m)[e] | 5.92 (dd, 2.9, 9.4) |
| C-4 OAc | 2.36 (s) | 2.48 (s) | 2.37 (s) | 2.41 (s) | 2.37 (s) | 2.42 (s) | 2.34 (s) | 2.38 (s) | 2.31 (s) | 2.39 (s) | 2.31 (s) | 2.37 (s) | 2.37 (s) | 2.48 (s) |
| C-5 | 4.92 (d, 8.0) | 4.99 (d, 7.5) | 5.02 (d, 7.8) | 4.95 and 4.97 (d, 7.8) | 4.91 (dd, 1.5, 7.8) | 4.95 (d, 7.8) | 5.03 (d, 7.8) | 4.94 (d, 7.5) | 4.96 (d, 8.7) | 4.94 (d, 7.8) | 5.04 (d, 7.8) | 4.94 (dd, 1.8, 9.3) | 4.93 (d, 8.1) | 4.99 (d, 7.5) |
| C-6a | 1.85 (m) | 1.89 (m) | 1.75 (m) | 1.86 (m) | 1.85 (m) | 1.90 (m) | 1.71 (m) | 1.89 (m) | 1.87 (m) | 1.87 (m) | 1.74 (m) | 1.88 (m) | 1.86 (m) | 1.89 (m) |
| C-6b | 2.49 (m) | 2.56 (m) | 2.46 (m) | 2.56 (m) | 2.52 (m) | 2.55 (m) | 2.45 (m) | 2.55 (m) | 2.58 (m) | 2.53 (m) | 2.43 (m) | 2.54 (m) | 2.54 (m) | 2.56 (m) |
| C-7 | 4.36 (m) | 4.44 (dd, 3.4, 14.0) | 4.18 (dd, 3.4, 14.0) | 4.38 and 4.46 (dd, 7.1, 11.1) | 4.35 (dd, 6.8, 10.8) | 4.41 (m) | 4.18 (m) | 4.40 (m) | 4.44 (dd, 6.3, 10.8) | 4.41 (dd, 6.6, 10.8) | 4.15 (dd, 6.6, 10.8) | 4.41 (m) | 4.40 (m) | 4.44 (dd, 3.4, 14.0) |
| C-10 | 6.26 (s) | 6.28 (s) | 6.36 (s) | 6.26 (m) | 6.19−6.23 (m)[e] | 6.26 (s) | 6.36 (s) | 6.27 and 6.29 (s) | 6.30 (s) | 6.30 (m) | 6.38 (m) | 6.28 (s) | 6.28 (s) | 6.28 (s) |
| C-10 OAc | 2.22 (s) | 2.24 (s) | 2.18 (s) | 2.24 (s) | 2.20 (s) | 2.23 (s) | 2.18 (s) | 2.22 (s) | 2.23 (s) | 2.23 (s) | 2.18 (s) | 2.23 (s) | 2.23 (s) | 2.24 (s) |
| C-13 | 6.20 (bt, 9.0) | 6.19 (bt, 8.4) | 6.06 (bt, 8.4) | 6.26 (m) | 6.19−6.23 (m)[e] | 6.23 (bt, 9.0) | 6.08 (bt, 9.0) | 6.22 (m) | 6.23 (bt, 9.3) | 6.22 (bt, 9.0) | 6.03 (m) | 6.21 (bt, 9.0) | 6.20 (bt, 9.0) | 6.19 (bt, 8.4) |
| C-14 | 2.28 (m) | 2.28 (m) | 2.09 (m) | 2.32 (m) | 2.18 (m) | 2.39 (m) | 2.14 (m) | 2.37 (m) | 2.24 (m) | 2.33 (m) | 2.17 (m) | 2.35 (m) | 2.36 (m) | 2.28 (m) |
| C-16 | 1.21 (s) | 1.23 (s) | 1.11 (s) | 1.23 (s) | 1.19 (s) | 1.23 (s) | 1.11 (s) | 1.23 (s) | 1.26 (s) | 1.24 (s) | 1.09 (s) | 1.23 (m) | 1.14−1.25 (m)[e] | 1.23 (s) |
| C-17 | 1.13 (s) | 1.13 (s) | 1.10 (s) | 1.15 (s) | 1.11 (s) | 1.14 (s) | 1.10 (bs) | 1.14 (s) | 1.15 (s) | 1.13 (s) | 1.09 (s) | 1.15 (s) | 1.14−1.25 (m)[e] | 1.13 (bs) |
| C-18 | 1.77 (s) | 1.84 (s) | 1.89 (s) | 1.78 (s) | 1.76 (s) | 1.85 (s) | 1.86 (s) | 1.83 (s) | 1.96 (s) | 1.87 (s) | 1.87 (s) | 1.86 (s) | 1.86 (s) | 1.84 (s) |
| C-19 | 1.67 (s) | 1.68 (s) | 1.58 (s) | 1.69 (s) | 1.65 (s) | 1.68 (s) | 1.58 (s) | 1.68 (s) | 1.67 (s) | 1.66 (s) | 1.56 (s) | 1.67 (s) | 1.67 (s) | 1.68 (s) |
| C-20 | 4.22 (ABq, 8.0, 31.0) | 4.24 (ABq, 8.3, 44.9) | 4.11 (ABq, 8.1, 44.9) | 4.21 and 4.25 (ABq, 8.3, 36.1) | 4.22 (ABq, 8.3, 48.0) | 4.25 (ABq, 8.4, 34.8) | 4.12 (ABq, 8.4, 34.8) | 4.25 (ABq, 8.4, 34.8) | 4.22 (ABq, 8.4, 49.0) | 4.22 (ABq, 8.4, 42.3) | 4.09 (ABq, 8.4, 42.3) | 4.24 (ABq, 8.7, 33.3) | 4.23 (ABq, 8.4, 33.0) | 4.24 (ABq, 8.3, 44.9) |
| NH | 7.22 (d, 9.0) | 7.43-7.64 (m) | | 7.10 and 7.14, (d, 8.9) | 7.19 (d, 9.1) | 6.84 (d, 9.3) | | 6.66 and 6.71 (d, 9.0) | 11.72 (s) | 5.23−5.34 (m)[e] | | 6.08 (d, 9.3) | 6.09 (d, 9.3) | 7.43−7.64 (m)[e] |
| aromatics | *o*-PhCO$_2$ | Ar and pyr | *o*-PhCO$_2$ | Ar and pyr | Ar and pyr | Ar and fur | *o*-PhCO$_2$ | Ar and fur | Ar and pyr | *o*-PhCO$_2$ | *o*-PhCO$_2$ | *o*-PhCO$_2$ | *o*-PhCO$_2$ | Ar and pyr |
| | 8.11 (d, 7.2) | 7.43−7.64 (m) | 8.07 | 7.33−7.65 (m)[e] | 7.35−7.60 (m)[e] | 7.37−7.62 (m)[e] | 8.08 | 7.35−7.72 (m)[e] | 7.46−7.61 (m)[e] | 8.09 (d, 7.5) | 8.08 | 8.10 (d, 7.5) | 8.00 (d, 7.5) | 7.43−7.64 (m)[e] |
| | *m*-PhCO$_2$ | 7.71−7.78 (m) | *m*-PhCO$_2$ | 7.60 and 7.61 (t, 7.4) | 7.73 (d, 7.2) | 7.73 (d, 7.5) | *m*-PhCO$_2$ | 8.04 and 8.13 (d, 7.2) | 7.77 (t, 7.5) | *m*-PhCO$_2$ | *m*-PhCO$_2$ | *m*-PhCO$_2$ | *m*-PhCO$_2$ | 7.71−7.78 (m)[e] |
| | 7.49 (t, 7.2) | 7.86 (d, 7.4) | 7.66 | 7.72 and 7.73 (d, 7.2) | 8.09 (d, 7.3) | 8.14 (d, 7.5) | 7.64 | | 7.97 (d, 7.2) | 7.47 (t, 7.5) | 7.65 | 7.48 (t, 7.2) | 7.48 (t, 7.2) | 7.86 (d, 7.4) |
| | *p*-PhCO$_2$ | 8.10 (d, 7.3) | *p*-PhCO$_2$ | 7.89 (m) | | | *p*-PhCO$_2$ | fur | 8.07 (d, 7.4) | *p*-PhCO$_2$ | *p*-PhCO$_2$ | *p*-PhCO$_2$ | *p*-PhCO$_2$ | 8.10 (d, 7.3) |
| | 7.59 (5, 7.2) | | 7.76 | 8.04 and 8.13 (d, 7.2) | pyr | fur | 7.75 | 6.51 and 6.58 (t, 0.9) | | 7.59 (t, 7.5) | 7.75 | 7.59 (t, 7.2) | 7.59 (t, 7.5) | |
| | | pyr | | | 8.57 (bs) | 6.39 (d, 0.9) | | | pyr | | | | | pyr |
| | *o*-ArCONH | 7.30 (dd, 5.3, 7.6) | *o*-ArCONH | pyr | | | *o*-ArCONH | | 7.36 (d, 4.6) | fur-3 | fur-3 | fur-3 | fur-3 | 7.30 (d, 5.3, 7.6) |
| | 7.72 (d, 7.2) | 8.53 (bd, 4.0) | 7.93 | 8.76 and 8.88 (d, 2.0) | | | 7.88 | | 8.69−8.78 (bs) | 6.30 (m) | 6.36 | 6.31 (d, 3.3) | 6.31 (d, 3.0) | 8.53 (bd, 4.0) |
| | *m*-ArCONH | | *m*-ArCONH | 8.57−8.60 (m)[e] | | | *m*-ArCONH | | | fur-4 | fur-4 | fur-4 | fur-4 | |
| | 7.36 (d, 7.2) | | 7.55 | | | | 7.53 | | | 6.36 (m) | 6.50 (dd, 1.8, 3.3) | 6.38 (dd, 1.8, 3.3) | 6.37 (dd, 1.8, 3.0) | |
| | *p*-ArCONH | | *p*-ArCONH | pyr | | | *p*-ArCONH | | | fur-5 | fur-5 | fur-5 | fur-5 | |
| | 7.46 (t, 7.2) | | 7.64 | 8.76 and 8.88 (d, 2.0) | | | 7.63 | | | 7.40 (d, 0.9) | 7.40 (d, 0.9) | 7.41 (d, 1.2) | 7.41 (bs) | |
| | | | | 8.57−8.60 (m)[e] | | | | | | | | | | |
| | *o*-Ar | | pyr-3 | | | | fur-3 | | | | | | | |
| | 7.45 (d, 7.2) | | 7.51 | | | | 6.44 | | | | | | | |
| | *m*-Ar | | pyr-4 | | | | fur-4 | | | | | | | |
| | 7.39 (t, 7.2) | | 7.91 | | | | 6.50 | | | | | | | |
| | *p*-Ar | | pyr-5 | | | | fur-5 | | | | | | | |
| | 7.32 (t, 7.2) | | 7.35 | | | | 7.65 | | | | | | | |
| | | | pyr-6 | | | | | | | | | | | |
| | | | 8.62 | | | | | | | | | | | |
| other | | | | | | | | | | *tert*-butyloxy | *tert*-butyloxy | hexanoyl | decanoyl | |
| | | | | | | | | | | 1.33 (s) | 1.38 (s) | (H2″−H6″) | (H2″−H10″) | |
| | | | | | | | | | | | | H6″ | H10″ | |
| | | | | | | | | | | | | 0.83 (m) | 0.85 (t, 6.6) | |
| | | | | | | | | | | | | H5″ and H4″ | H4″−H9″ | |
| | | | | | | | | | | | | 1.21−1.25 (m)[e] | 1.14−1.25 (m)[e] | |
| | | | | | | | | | | | | H3″ | H3″ | |
| | | | | | | | | | | | | 2.20 (m) | 2.19 (m) | |
| | | | | | | | | | | | | H2″ | H2″ | |
| | | | | | | | | | | | | 2.36 (m) | 2.36 (m) | |

[a] Multiplicities and coupling constants in Hz are given in parentheses. If the coupling constants in the DMSO spectra were identical to the ones in the $CDCl_3$ spectra, they are not listed again. The spectrum of **1** and the spectra in DMSO/$D_2O$ were recorded at 500 MHz; all other data were obtained at 300 MHz. [b] DMSO/$D_2O$ at rt. [c] Mixture of diastereomers. [d] DMSO/$D_2O$ at −20 °C. [e] Overlapping peaks.

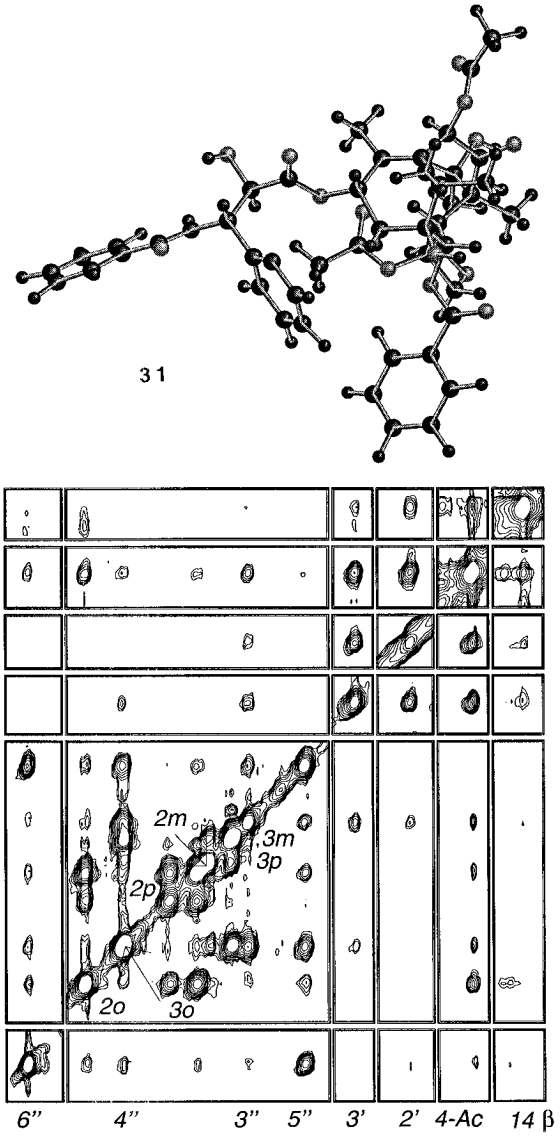



**Figure 4.** Structure of **31** and tile plots of low-temperature NOESY spectra of **31** taken in DMSO/$D_2O$, illustrating correlations between the 2-benzoyl, 4-acetyl, and side chain protons. The NOE's indicate that a conformation like the one pictured (derived from a recent X-ray structure of paclitaxel)[43] is significantly populated in polar solvents. The 4″- and 3′-benzamide ortho signals overlap. The intense 18-methyl signal appears just upfield of 14$\beta$, producing some NOE's visible in the figure.

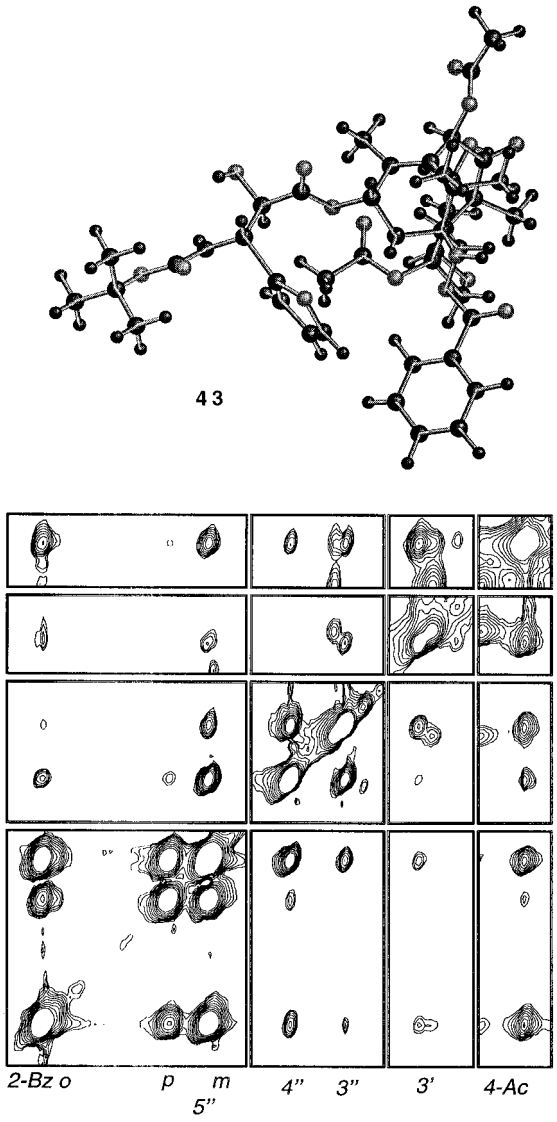



**Figure 5.** Structure of **43** and tile plots of low-temperature NOESY spectra of **43** taken in DMSO/$D_2O$, illustrating correlations between the 2-benzoyl, 4-acetyl, and side chain protons. The NOE's indicate that a conformation like the one pictured (derived from a recent X-ray structure of paclitaxel)[43] is significantly populated in polar solvents. The 5″- and 2-benzoyl meta signals overlap. The 2′ signal was lost under the HOD line and is not shown. The spectrum also shows some doubled signals (most notably 3′) owing to slow cis−trans isomerism around the BOC group.

cytotoxicity comparable to paclitaxel. These results indicate that cellular uptake and/or metabolic fate may be influenced by the exact spatial orientation of the heteroatom in the 3′-aryl moiety of the 3-arylisoserine side chain. The enamide **36** proved to be virtually inactive in both assays. This is not surprising as taxanes devoid of the 2′-hydroxyl or taxanes with protected 2′-hydroxyl positions exhibit poor biological activities.[15,48]

Replacement of the *N*-benzoyl group in **34** with a BOC group provided docetaxel analogue **43**, a compound that was approximately five times more potent in the microtubule assembly assay than paclitaxel and **34**. However, no further improvement of cytotoxicity against B16 melanoma was seen due to the introduction of the *N*-BOC group. The cytotoxicity of **43** was similar to **34**. The *N*-hexanoyl analogue **44** showed reduced activity in the microtubule assembly assay compared to paclitaxel and compound **34** but was about twice as cytotoxic as paclitaxel. The *N*-decanoylpaclitaxel analogue **45** displayed reduced activity in both assays compared to paclitaxel, indicating that introduction of an *N*-decanoyl side chain is detrimental to activity.

In the *N*-heteroaroyl series, the two furoyl analogues **50** and **51** displayed very good cytotoxicity. Taxane **51** showed approximately 2-fold greater activity than paclitaxel in both assays. Analogue **50** was slightly more active in the microtubule assembly assay and as cytotoxic as paclitaxel against B16 melanoma cell proliferation. None of the pyridinecarboxylic acid derivatives **47**−**49** demonstrated significant activity to inhibit B16 melanoma cell proliferation. The picolinoyl analogue **47** was about five times less active than taxol and the two other analogues **48** and **49** showed greatly decreased toxicity.

In summary, the most cytotoxic analogues prepared in this study were the 3′-(2-pyridyl) analogue **31**, the 3′-

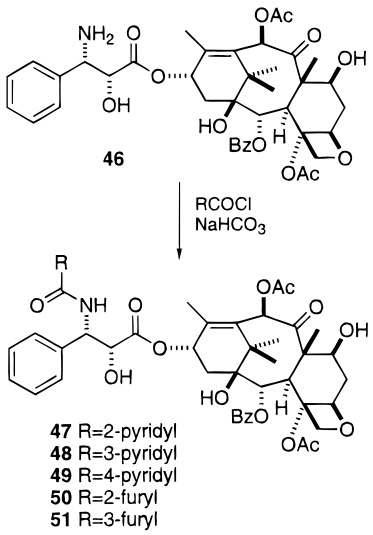
(48) Kant, J.; Huang, S.; Wong, H.; Fairchild, C.; Vyas, D.; Farina, V. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2471−2474.

**Table 3. Biological Evaluation of Heteroaryl Taxanes**

| compd no. | compd name | microtubule assembly[a] $ED_{50}/ED_{50(paclitaxel)}$ | B16 melanoma[b] $ED_{50}/ED_{50(paclitaxel)}$ |
|---|---|---|---|
| **1** | paclitaxel | 1 | 1 |
| **31** | 3′-dephenyl-3′-(2-pyridyl)paclitaxel | 0.7 | 0.8 |
| **32**[c] | 3′-dephenyl-3′-(3-pyridyl)paclitaxel | 0.5 | 27 |
| **33** | 3′-dephenyl-3′-(4-pyridyl)paclitaxel | 0.4 | 1.3 |
| **34** | 3′-dephenyl-3′-(2-furyl)paclitaxel | 0.9 | 0.3 |
| **35**[d] | 3′-dephenyl-3′-(3-furyl)paclitaxel | 0.9 | 3.3 |
| **36** | baccatin III 13-*O*-[(*Z*)-3-amino-*N*-benzoyl-3-(4-pyridyl)acrylate] | 14 | >36 |
| **43** | *N*-BOC-*N*-debenzoyl-3′-dephenyl-3′-(2-furyl)paclitaxel | 0.20 | 0.41 |
| **44** | *N*-debenzoyl-3′-dephenyl-3′-(2-furyl)-*N*-(hexanoyl)paclitaxel | 1.6 | 0.50 |
| **45** | *N*-debenzoyl-3′-dephenyl-3′-(2-furyl)-*N*-(decanoyl)paclitaxel | 2.1 | 2.6 |
| **47** | *N*-debenzoyl-*N*-(picolinoyl)paclitaxel | 3.5 | 4.6 |
| **48** | *N*-debenzoyl-*N*-(nicotinoyl)paclitaxel | 0.6 | 26 |
| **49** | *N*-debenzoyl-*N*-(isonicotinoyl)paclitaxel | 2.0 | >36 |
| **50** | *N*-debenzoyl-*N*-(2-furoyl)paclitaxel | 0.8 | 1.0 |
| **51** | *N*-debenzoyl-*N*-(3-furoyl)paclitaxel | 0.4 | 0.5 |

[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. [c] Assayed as a 2:1 diastereomeric mixture. [d] Assayed as a 3:1 diastereomeric mixture.

**Scheme 6**




(4-pyridyl) analogue **33**, the 3′-(2-furyl) analogues **34**, **43**, and **44**, and the *N*-(2-furoyl) and *N*-(3-furoyl) derivatives **50** and **51**, all of which displayed either better or similar cytotoxic activity against B16 melanoma cells compared to paclitaxel. Thus, the replacement of the 3′-phenyl and the *N*-benzoyl moiety of paclitaxel by select heteroaromatic moieties provided highly cytotoxic novel paclitaxel analogues.

## Experimental Procedures

**General.** For general synthetic procedures, see refs 49 and 50. All starting materials and reagents are commercially available with the exception of 3-furoyl chloride and picolinoyl chloride which were prepared from the corresponding commercially available acids by treatment with cyanuric chloride.[51] HPLC analyses for the determination of the enantiomeric excesses of the described 2-azetidinones were performed on a Waters Model 481 LC spectrometer detector set at 254 nm equipped with a Waters 740 Data Module integrator using a chiral column (DIACEL CHIRACEL OD-H) utilizing a 20:1 hexane/2-propanol mobile phase with a flow rate of 0.7−1.4 mL/min (Table 1). For a description of the biological assays, see refs 52 and 53.

All spectra in DMSO/$D_2O$ were acquired on a Bruker AM-500 operating at 500.14 MHz for $^1H$. 1D and COSY spectra were acquired at room temperature; phase sensitive (TPPI) NOESY spectra were acquired in a dedicated $^1H$ probe at −20 °C in 75% DMSO/25% $D_2O$ with a taxane concentration of 2−5 mg/mL. Typical NOESY conditions were as follows: sweep width 4000 Hz, 2K data points in $t_2$, 2 s delay, 0.26 s acquisition time with sequential quadrature sampling, $t_{mix}$ 200 ms, 256 blocks with four dummy scans and 80 scans per block. 2D files were transferred to a Silicon Graphics Indigo workstation for processing and plotting using Felix 2.30 (Biosym, San Diego, CA). A 1024 point squared sinebell window function was used prior to transforming the data taken in $t_2$; the $t_1$ data was linear predicted to 512 points, multiplied by a 512 point squared sinebell window, and zero-filled to 1K points prior to transformation to give a final matrix size of 1K × 1K complex points. All crosspeaks were of the same sign as the diagonal; only positive contours are presented in the figures as there were no negative features except $t_1$ streaks.

**2-*O*-(Chloroacetyl)-10-(dicyclohexylsulfamoyl)-D-isoborneol (3).** To a cold (0 °C) stirring solution of 10-(dicyclohexylsulfamoyl)-D-isoborneol (2.50 g, 6.30 mmol) in anhydrous THF (20 mL) were added DMAP (0.880 g, 2.52 mmol) and over a period of 2 min dropwise chloroacetyl chloride (0.753 mL, 9.45 mmol). The ice bath was removed, and the solution was refluxed for 18 h. Since TLC (20% EtOAc/hexane) indicated remaining starting material, the reaction was cooled to rt, additional chloroacetyl chloride (0.251 mL, 3.15 mmol) was added, and stirring at reflux temperature was continued until the disappearance of the starting material by TLC (20% EtOAc/hexane). The reaction was then cooled to rt, carefully quenched with a saturated solution of $NaHCO_3$ (20 mL), extracted with ether, and dried over anhydrous $MgSO_4$. Isobornyl chloroacetate (**3**) was isolated in quantitative yield as white crystals after purification by silica gel flash chromatography eluting with 20% EtOAc/hexane: mp 136 °C; $[\alpha]_D$ −38 ($c$ = 0.59, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (s, 3H), 0.99 (s, 3H), 1.03−2.02 (m, 27H), 2.94 ($q_{ab}$, $J$ = 189.3, 13.2 Hz, 2H), 3.18−3.28 (m, 2H), 4.04 (s, 2H), 5.03 (dd, $J$ = 8.4, 3.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.4, 20.8, 25.7, 26.9, 27.4, 30.7, 33.1, 33.4, 39.6, 41.5, 44.9, 49.6, 50.1, 54.1, 57.9, 80.6, 166.0. Anal. Calcd for $C_{24}H_{40}ClNO_4S$: C, 60.86; H, 8.52; N, 2.96. Found: C, 60.48; H, 8.49; N, 2.58.

**10-(Dicyclohexylsulfamoyl)-2-*O*-[(formyloxy)acetyl]-D-isoborneol (4).** To a solution of **3** (2.99 g, 6.31 mmol) in toluene (20 mL) were added sodium formate (0.858 g, 12.6 mmol) and tetrabutylammonium bromide (0.010 g, 0.032 mmol). The reaction was heated to reflux for 12 h or until the disappearance of **3** by TLC (25% EtOAc/hexane). After

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being cooled to rt the suspension was filtered, and the filtrate was diluted with water, extracted with ether, and dried over anhydrous $MgSO_4$. (Formyloxy)acetate **4** was isolated as white crystals in quantitative yield after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: mp 170 °C; $[\alpha]_D$ −38 ($c$ = 0.88, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (s, 3H), 0.94 (s, 3H), 1.00−2.02 (m, 27H), 2.90 ($q_{ab}$, $J$ = 161.4, 13.2 Hz, 2H), 3.18−3.28 (m, 2H), 4.66 ($q_{ab}$, $J$ = 22.2, 15.3 Hz, 2H), 5.05 (dd, $J$ = 7.8, 2.7 Hz, 1H), 8.10 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.4, 20.8, 25.6, 26.9, 27.4, 30.7, 33.2, 39.6, 44.9, 49.6, 50.0, 54.2, 57.9, 80.2, 160.2, 165.9. Anal. Calcd for $C_{25}H_{41}NO_6S$: C, 62.08; H, 8.55; N, 2.90. Found: C, 61.68; H, 8.90; N, 2.50.

**10-(Dicyclohexylsulfamoyl)-2-*O*-(hydroxyacetyl)-D-isoborneol (5).** (Formyloxy)acetate **4** (3.05 g, 6.31 mmol) was dissolved in MeOH (20 mL) and after addition of five drops of concentrated HCl stirred for 10 min. The volatiles were removed under reduced pressure, and glycolate **5** was isolated in quantitative yield as white crystals after purification by silica gel flash chromatography eluting with 20% EtOAc/hexane: mp 165 °C; $[\alpha]_D$ −45 ($c$ = 0.65, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.86 (s, 3H), 0.95 (s, 3H), 1.00−2.05 (m, 27H), 2.47 (br s, 1H), 2.90 ($q_{ab}$, $J$ = 156.9, 13.5 Hz, 2H), 3.15−3.26 (m, 2H), 4.10 (dd, $J$ = 5.7, 3.0 Hz, 2H), 5.06 (dd, $J$ = 7.8, 2.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 20.4, 20.8, 25.6, 26.9, 27.4, 30.7, 33.2, 33.3, 39.8, 44.9, 49.6, 50.0, 54.2, 58.0, 61.2, 80.2, 172.3. Anal. Calcd for $C_{24}H_{41}NO_5S$: C, 63.26; H, 9.08; N, 3.08. Found: C, 62.88; H, 8.83; N, 2.90.

**2-*O*-[[(*tert*-Butyldimethylsilyl)oxy]acetyl]-10-(dicyclohexylsulfamoyl)-D-isoborneol (6).** To a stirring solution of **5** (2.88 g, 6.31 mmol) in methylene chloride (20 mL) under argon were added triethylamine (1.756 mL, 12.62 mmol), DMAP (0.003 g, 0.03 mmol), and *tert*-butyldimethylsilyl chloride (1.143 g, 7.570 mmol). This mixture was stirred for 2 h at rt, quenched with water (30 mL), extracted with methylene chloride, and subsequently dried over anhydrous $MgSO_4$. Compound **6** was isolated in 98% yield as white crystals after purification by silica gel flash chromatography eluting with 10% EtOAc/hexane: mp 112 °C; $[\alpha]_D$ −37 ($c$ = 0.83, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.71 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.88 (s, 9H), 0.95 (s, 3H), 1.02−2.02 (m, 27H), 2.89 ($q_{ab}$, $J$ = 170.7, 13.2 Hz, 2H), 3.14−3.24 (m, 2H), 4.19 (s, 2H), 4.97 (dd, $J$ = 8.7, 2.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.2, −4.8, 18.8, 20.5, 20.8, 25.6, 26.2, 27.4, 30.6, 33.2, 33.4, 40.0, 44.9, 49.5, 49.9, 54.1, 58.0, 79.4, 170.7. Anal. Calcd for $C_{30}H_{55}NO_5SSi$: C, 63.23; H, 9.74; N, 2.46. Found: C, 63.00; H, 0.10; N, 2.30.

**General Procedure for the Synthesis of Aldimines 7−11.** To a cold (0 °C) solution of hexamethyldisilazane (4.0 mmoles) in anhydrous THF under an argon atmosphere was added 2.5 M *n*-butyllithium (3.6 mmoles) dropwise. The reaction was stirred at 0 °C for 0.5 h. The reaction was cooled further to −78 °C, and a THF solution of aldehyde (4.0 mmol in 2 mL THF) was added dropwise to the lithiated HMDS. The reaction was stirred at −78 °C for 0.5 h and then warmed to rt. Excess solvent was removed under reduced pressure at 35 °C. The imines were utilized crude in the ester enolate−imine cyclocondensation reactions.

***N*-(Trimethylsilyl)picolinaldimine (7)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.30 (s, 9H), 7.32 (ddd, $J$ = 7.4, 4.9, 1.4 Hz, 1H), 7.74 (dt, $J$ = 7.9, 2 Hz, 1H), 7.99 (dd, $J$ = 4.8, 1.1 Hz, 1H), 8.65 (dd, $J$ = 4.9, 1.1 Hz, 1H), 9.02 (s, 1H).

***N*-(Trimethylsilyl)nicotinaldimine (8)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.25 (s, 9H), 7.36 (q, $J$ = 7.8, 4.8 Hz, 1H), 8.16 (dt, $J$ = 6.0, 1.8 Hz, 1H), 8.67 (dd, $J$ = 4.9, 1.7 Hz, 1H), 8.93 (d, $J$ = 1.9 Hz, 1H), 8.99 (s, 1H).

***N*-(Trimethylsilyl)isonicotinaldimine (9)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.27 (s, 9H), 7.65 (d, $J$ = 6.0 Hz, 2H), 8.73 (d, $J$ = 5.9 Hz, 2H), 8.94 (s, 1H).

***N*-(Trimethylsilyl)-2-furaldimine (10)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.25 (s, 9H), 6.50 (dd, $J$ = 3.3, 1.8 Hz, 1H), 6.82 (dd, $J$ = 3.3, 0.6 Hz, 1H), 7.51−7.52 (m, 1H), 8.75 (s, 1H).

***N*-(Trimethylsilyl)-3-furaldimine (11)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.20 (s, 9H), 6.81 (d, $J$ = 1.5 Hz, 1H), 7.38 (s, 1H), 7.76 (s, 1H), 8.87 (s, 1H).

**General Procedure for the Synthesis of (3*R*,4*S*)-4-Aryl-3-[(*tert*-butyldimethylsilyl)oxy]-2-azetidinones.** To a cold (−78 °C) stirred solution of diisopropylamine (0.32 mL, 2.25 mmol) in anhydrous THF (1 mL) was added 2.5 M *n*-butyllithium (0.78 mL, 1.95 mmol) dropwise. The reaction was stirred at −78 °C for 0.5 h. Ester **6** (0.92 mg, 1.62 mmol) in THF (2 mL) was then added to the cold LDA solution dropwise. The reaction was stirred at −78 °C for 2 h. Imine (2.25 mmol) in THF (2 mL) was added dropwise to the cold enolate solution. The reaction was stirred at −78 °C for 3 h and then rt overnight. The reaction was quenched by the addition of a saturated aqueous $NH_4Cl$ solution (1 mL). The reaction mixture was extracted with ether (3 × 20 mL) and subsequently dried over anhydrous $MgSO_4$.

**(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-pyridyl)-2-azetidinone (12).** Azetidinone **12** was isolated as a viscous colorless oil in 59% yield and 44% ee after purification by silica gel flash chromatography eluting with EtOAc: $[\alpha]_D$ +86 ($c$ = 2.5, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.20 (s, 3H), −0.01 (s, 3H), 0.56 (s, 9H), 4.91 (d, $J$ = 4.8 Hz, 1H), 5.07 (q, $J$ = 4.8, 2.9 Hz, 1H), 7.13−7.17 (m, 1H), 7.36 (br s, 1H), 7.39 (d, $J$ = 7.9 Hz, 1H), 7.64 (dt, $J$ = 7.8, 1.6 Hz, 1H), 8.48 (d, $J$ = 3.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.6, −5.1, 17.6, 25.1, 60.1, 79.8, 122.2, 122.6, 135.9, 148.6, 156.9, 170.0. Anal. Calcd for $C_{14}H_{22}N_2O_2Si$: C, 60.39; H, 7.96; N, 10.06. Found: C, 60.43; H, 8.32; N, 9.85.

**(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(3-pyridyl)-2-azetidinone (13).** Azetidinone **13** was isolated in 58% yield and 31% ee as a white powder after purification by silica gel flash chromatography eluting with EtOAc: mp 76−78 °C; $[\alpha]_D$ +26 ($c$ = 1.6, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.15 (s, 3H), −0.03 (s, 3H), 0.62 (s, 9H), 4.83 (d, $J$ = 4.5 Hz, 1H), 5.07 (q, $J$ = 4.6, 2.8 Hz, 1H), 7.00 (br s, 1H), 7.29 (ps t, $J$ = 7.4 Hz, 1H), 7.67 (dd, $J$ = 7.9, 1.7 Hz, 1H), 8.49 (s, 1H), 8.51 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.6, −5.0, 17.6, 25.1, 56.6, 79.4, 122.8, 132.3, 135.6, 149.1, 169.7. Anal. Calcd for $C_{14}H_{22}N_2O_2Si$: C, 60.39; H, 7.96; N, 10.06. Found: C, 60.79; H, 8.10; N, 9.80.

**(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(4-pyridyl)-2-azetidinone (14).** Azetidinone **14** was isolated in 74% yield and 95% ee as a white powder after purification by silica gel flash chromatography eluting with EtOAc: mp 174−176 °C; $[\alpha]_D$ +96 ($c$ = 1.2, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.11 (s, 3H), −0.04 (s, 3H), 0.62 (s, 9H), 4.79 (d, $J$ = 4.8 Hz, 1H), 5.09 (dd, $J$ = 4.8, 2.9 Hz, 1H), 6.80−6.88 (br s, 1H), 7.21 (d, $J$ = 6.0 Hz, 2H), 8.57 (d, $J$ = 5.9 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.4, −4.9, 17.7, 26.2, 58.0, 79.8, 122.7, 145.7, 149.4, 169.3. Anal. Calcd for $C_{14}H_{22}N_2O_2Si$: C, 60.39; H, 7.96; N, 10.06. Found: C, 60.21; H, 8.00; N, 9.82.

**(3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-furyl)-2-azetidinone (15a).** Azetidinone **15a** was isolated as a white solid in 86% yield and 92% ee, along with 6% of the corresponding trans isomer **15b** (15:1, cis:trans), after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: mp 78 °C; $[\alpha]_D$ +30 ($c$ = 0.9, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.20 (s, 3H), 0.50 (s, 3H), 0.76 (s, 9H), 4.80 (d, $J$ = 4.5 Hz, 1H), 5.05 (dd, $J$ = 4.5, 2.4 Hz, 1H), 6.04 (br s, 1H), 6.36 (m, 2H), 7.39 (d, $J$ = 0.9 Hz, 1H). Anal. Calcd for $C_{13}H_{21}NO_3Si$: C, 58.40; H, 7.92; N, 5.24. Found: C, 58.12; H, 8.20; N, 5.01.

***trans*-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-furyl)-2-azetidinone (15b)**: yellow oil; $[\alpha]_D$ +44.7 ($c$ = 1.33, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.03 (s, 3H), 0.07 (s, 3H), 0.84 (s, 9H), 4.47 (d, $J$ = 1.8 Hz, 1H), 4.85 (t, $J$ = 1.8 Hz, 1H), 6.31−6.36 (m, 2H), 7.39 (d, $J$ = 1.2 Hz, 1H).

**(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(3-furyl)-2-azetidinone (16).** Azetidinone **16** was isolated as a white solid in 55% yield and 36% ee after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: mp 116 °C; $[\alpha]_D$ +21 ($c$ = 0.95, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.05 (s, 3H), 0.90 (s, 3H), 0.78 (s, 9H), 4.72 (d, $J$ = 4.5 Hz, 1H), 5.00 (dd, $J$ = 4.5, 2.4 Hz, 1H), 6.13 (br s, 1H), 6.43 (d, $J$ = 0.9 Hz, 1H), 7.39−7.41 (m, 2H). Anal. Calcd for $C_{13}H_{21}NO_3Si$: C, 58.40; H, 7.92; N, 5.24. Found: C, 58.46; H, 8.32; N, 5.04.

**General Procedure for the Synthesis of *N*-Benzoyl-2-azetidinones 17−21.** To a cold (0 °C) stirred solution of $\beta$-lactam (50 mg, 0.18 mmol), triethylamine (1 mL, excess), and DMAP (2 mg, catalytic) in anhydrous $CH_2Cl_2$ was added

benzoyl chloride (0.03 mL, 0.27 mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 min, quenched with brine, extracted with $CH_2Cl_2$ (3 × 15 mL), and dried over anhydrous $MgSO_4$.

**(3*R*,4*S*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(2-pyridyl)-2-azetidinone (17).** *N*-Benzoyl-2-azetidinone **17** was isolated as a colorless oil in 85% yield after purification via silica gel flash chromatography eluting with 25% EtOAc/hexane: $[\alpha]_D$ +98.0 ($c$ = 1.33, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.08 (s, 3H), 0.10 (s, 3H), 0.65 (s, 9H), 5.21 (d, $J$ = 6.3 Hz, 1H), 5.55 (d, $J$ = 6.2 Hz, 1H), 7.23 (dd, $J$ = 7.3, 4.9 Hz, 1H), 7.32 (d, $J$ = 7.8 Hz, 1H), 7.49 (t, $J$ = 7.2 Hz, 2H), 7.61 (t, $J$ = 7.3 Hz, 1H), 7.68 (dt, $J$ = 7.7, 1.7 Hz, 1H), 8.07 (d, $J$ = 7.3 Hz, 2H), 8.61 (d, $J$ = 4.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.1, −4.5, 18.2, 25.6, 62.0, 76.9, 122.2, 123.3, 128.6, 130.3, 132.3, 133.8, 136.5, 149.7, 154.6, 165.2, 166.8; HRMS $m/z$ calcd or $C_{21}H_{26}N_2O_3Si$ ($M^+$ + H) 382.1713, found 382.1708.

**(3*R*,4*S*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(3-pyridyl)-2-azetidinone (18).** *N*-Benzoyl-2-azetidinone **18** was isolated in 79% yield as a colorless glass after purification by silica gel flash chromatography eluting with 20% EtOAc/hexane: $[\alpha]_D$ +92 ($c$ = 0.68, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.090 (s, 3H), −0.093 (s, 3H), 0.69 (s, 9H), 5.16 (d, $J$ = 5.9 Hz, 1H), 5.43 (d, $J$ = 6.2 Hz, 1H), 7.31 (dd, $J$ = 8.0, 4.8 Hz, 1H), 7.48 (t, $J$ = 8.2 Hz, 2H), 7.59 (t, $J$ = 8.3 Hz, 1H), 7.68 (d, $J$ = 7.9 Hz, 1H), 8.02 (d, $J$ = 8.3 Hz, 2H), 8.58 (d, $J$ = 4.8 Hz, 1H), 8.65 (s, 1H,); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.5, −5.0, 17.8, 25.2, 58.3, 76.2, 123.0, 126.2, 128.2, 128.3, 129.7, 129.8, 131.5, 133.6, 135.5, 149.4, 164.4, 166.1; EI HRMS $m/z$ calcd for $C_{21}H_{26}N_2O_3Si$ ($M^+$ + H) 382.1713, found 382.1712.

**(3*R*,4*S*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(4-pyridyl)-2-azetidinone (19).** *N*-Benzoyl-2-azetidinone **19** was isolated in 52% yield as a light yellow oil after purification by silica gel flash chromatography eluting with 20% EtOAc/hexane: $[\alpha]_D$ +88.9 ($c$ = 0.875, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.05 (s, 3H), 0.10 (s, 3H), 0.69 (s, 9H), 5.17 (d, $J$ = 6.2 Hz, 1H), 5.39 (d, $J$ = 6.2 Hz, 1H), 7.26 (dd, $J$ = 4.5, 1.6 Hz, 2H), 7.51 (t, $J$ = 7.3 Hz, 2H), 7.63 (tt, $J$ = 7.4, 1.3 Hz, 1H), 8.06 (dd, $J$ = 7.1, 1.5 Hz, 2H), 8.62 (dd, $J$ = 4.4, 1.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.4, −4.9, 17.8, 25.2, 59.4, 76.2, 122.7, 128.3, 129.9, 131.4, 133.7, 143.1, 149.6, 164.2, 166.1; EI HRMS $m/z$ calcd for $C_{21}H_{26}N_2O_3Si$ ($M^+$ + H) 382.1713, found 382.1712.

**(3*R*,4*R*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(2-furyl)-2-azetidinone (20).** *N*-Benzoyl-2-azetidinone **20** was isolated as a transparent oil in 86% yield after purification by silica gel flash chromatography eluting with 10% EtOAc/hexane: $[\alpha]_D$ +82 ($c$ = 0.61, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.05 (s, 3H), 0.12 (s, 3H), 0.80 (s, 9H), 5.11 (d, $J$ = 6.0 Hz, 1H), 5.43 (d, $J$ = 6.0 Hz, 1H), 6.36 (dd, $J$ = 3.3, 1.8 Hz, 1H), 6.42 (d, $J$ = 3.3 Hz, 1H), 7.41−7.48 (m, 3H), 7.54−7.60 (m, 1H), 7.97−8.00 (m, 2H). Anal. Calcd for $C_{20}H_{25}NO_4Si$: C, 64.66; H, 6.79; N, 3.77. Found: C, 64.56; H, 6.81; N, 3.60.

**(3*R*,4*S*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(3-furyl)-2-azetidinone (21).** *N*-Benzoyl-2-azetidinone **21** was isolated as a transparent oil in 88% yield after purification by silica gel flash chromatography eluting with 10% EtOAc/hexane: $[\alpha]_D$ +27 ($c$ = 0.76, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.02 (s, 3H), 0.15 (s, 3H), 0.85 (s, 9H), 5.10 (d, $J$ = 6.3 Hz, 1H), 5.37 (d, $J$ = 6.0 Hz, 1H), 6.49 (s, 1H), 7.39−7.47 (m, 3H), 7.54−7.59 (m, 2H), 7.95 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.0, −4.3, 18.0, 26.2, 54.5, 76.8, 110.4, 118.9, 127.8, 130.0, 134.1, 142.2, 143.2, 165.4, 166.6. Anal. Calcd for $C_{20}H_{25}NO_4Si$: C, 64.66; H, 6.79; N, 3.77. Found: C, 64.60; H, 6.89; N, 3.50.

**7-*O*-(Triethylsilyl)baccatin III (25).**[54] To a stirring solution of baccatin III (0.150 g, 0.256 mmol) in pyridine (10 mL) was added dropwise at 0 °C triethylsilyl chloride (0.857 mL, 5.12 mmol). The reaction mixture was stirred at rt for 12 h, quenched with water and extracted with methylene chloride (3 × 50 mL). The combined organic layer was washed with 1 N HCl (3 × 10 mL) and brine (3 × 10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Protected baccatin III **25** was isolated as a white solid in 71% yield after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.52−0.60 (m, 6H), 0.91 (t, $J$ = 7.8 Hz, 9H), 1.02 (s, 3H), 1.19 (s, 3H), 1.59 (s, 3H), 1.84 (s, 3H), 2.19 (s, 3H), 2.30 (s, 3H), 3.87 (d, $J$ = 7.2 Hz, 1H), 4.21 ($q_{ab}$, $J$ = 49.2, 8.1 Hz, 2H), 4.48 (dd, $J$ = 10.5, 6.6 Hz, 1H), 4.82 (t, $J$ = 7.8 Hz, 1H), 4.94 (d, $J$ = 7.8 Hz, 1H), 5.62 (d, $J$ = 6.9 Hz, 1H), 6.44 (s, 1H), 7.46 (t, $J$ = 7.2 Hz, 2H), 7.59 (t, $J$ = 7.2 Hz, 1H), 8.09 (t, $J$ = 7.2 Hz, 2H).

**General Procedure for the Acylation of 7-*O*-(Triethylsilyl)baccatin III with Sodium Hydride as the Base.** To a cold (0 °C) stirred solution of **24** (0.20 mg, 0.029 mmol) and $\beta$-lactam (0.038 mmol) in anhydrous THF (1 mL) was added NaH (47 mg, 1.45 mmol, 60% dispersion) at once. The reaction was stirred at 0 °C for 0.5 h and then warmed to 30 °C. The reaction was stirred at 30 °C for 3 h or until the disappearance of **24** was evident by TLC (35% EtOAc/hexane). The reaction mixture was cooled back down to 0 °C and carefully quenched by the dropwise addition of acetic acid (1 mL). The reaction mixture was extracted with ether and subsequently dried over anhydrous $MgSO_4$. Pure coupled products **26**−**30** were obtained via silica gel flash chromatography.

**2-*O*-(*tert*-Butyldimethylsilyl)-3′-dephenyl-3′-(2-pyridyl)-7-*O*-(triethylsilyl)paclitaxel (26).** Taxane **26** was isolated as a white powder in 86% yield after purification through silica gel flash chromatography eluting with 50% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.32 (s, 3H), 0.05 (s, 3H), 0.57−0.62 (m, 6H), 0.74 (s, 9H), 0.93 (t, $J$ = 7.7 Hz, 9H), 1.17 (s, 3H), 1.22 (s, 3H), 1.64 (s, 3H), 1.70 (s, 3H,), 1.83−1.98 (m, 1H), 2.10−2.22 (m, 1H), 2.17 (s, 3H), 2.35−2.48 (m, 1H), 2.50−2.59 (m, 1H), 2.61 (s, 3H), 3.85 (d, $J$ = 7.2 Hz, 1H), 4.25 ($q_{ab}$, $J$ = 37.6, 8.3 Hz, 2H), 4.49 (dd, $J$ = 10.6, 6.45 Hz, 1H), 4.96 (d, $J$ = 8.1 Hz, 1H), 5.30 (d, $J$ = 1.9 Hz, 1H), 5.68−5.75 (m, 2H), 6.24 (t, $J$ = 9.8 Hz, 1H), 6.47 (s, 1H), 7.20−7.32 (m, 4H), 7.42−7.61 (m, 7H), 7.67 (dt, $J$ = 7.7, 1.7 Hz, 1H).

**2-*O*-(*tert*-Butyldimethylsilyl)-3′-dephenyl-3′-(3-pyridyl)-7-*O*-(triethylsilyl)paclitaxel (27).** Taxane **27** was isolated as a 2:1 diastereomeric mixture in 74% yield after purification by silica gel flash chromatography eluting with 30% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.22 and −0.18 (s, 3H), −0.01 and 0.05 (s, 3H), 0.55−0.70 (m, 6H), 0.85 and 0.88 (s, 9H), 0.59−1.00 (m, 9H), 1.20 (s, 3H), 1.25 and 1.29 (s, 3H), 1.72 and 1.82 (s, 3H), 1.88−2.00 (m, 1H), 2.08 and 2.13 (s, 3H), 2.10−2.25 (m, 1H), 2.18 and 2.20 (s, 3H), 2.30−2.48 (m, 1H), 2.32 and 2.59 (s, 3H), 2.50−2.61 (m, 1H), 3.86 and 3.90 (d, $J$ = 7.4 Hz, 1H), 4.29 and 4.27 ($q_{ab}$, $J$ = 40.4, 8.3 Hz, 2H), 4.47−4.53 (m, 1H), 4.55 and 4.67 (d, $J$ = 1.6 Hz, 1H), 4.88 (b d, $J$ = 7.4 Hz, 1H), 5.70−5.79 (m, 2H), 6.25 and 6.28 (t, $J$ = 9.3 Hz, 1H), 6.48 and 6.49 (s, 1H), 7.15 (d, $J$ = 9.0 Hz, 1H), 7.30−7.88 (m, 10H), 8.10 and 8.17 (d, $J$ = 7.6 Hz, 2H), 8.61 (d, $J$ = 4.4 Hz, 1H), 8.68 and 8.80 (d, $J$ = 2.0 Hz, 1H).

**2-*O*-(*tert*-Butyldimethylsilyl)-3′-dephenyl-3′-(4-pyridyl)-7-*O*-(triethylsilyl)paclitaxel (28a).** Taxane **28a** was isolated in 60% yield as a white powder along with 20% of elimination product **28b** after purification via silica gel flash chromatography eluting with 50% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.25 (s, 3H), 0.04 (s, 3H), 0.58−0.62 (m, 2H), 0.79 (s, 9H), 0.89−0.96 (m, 3H), 1.18 (s, 3H), 1.22 (s, 3H), 1.71 (s, 3H), 1.88−1.96 (m, 1H), 2.02−2.14 (m, 1H), 2.05 (s, 3H), 2.18 (s, 3H), 2.31−2.41 (m, 1H), 2.51−2.58 (m, 1H), 2.55 (s, 3H), 3.83 (d, $J$ = 6.8 Hz, 1H), 4.26 ($q_{ab}$, $J$ = 36.5, 8.7 Hz, 2H), 4.48 (dd, $J$ = 10.4, 6.4 Hz, 1H), 4.71 (d, $J$ = 1.9 Hz, 1H), 4.95 (dd, $J$ = 7.6, 1.9 Hz, 1H), 5.69−5.73 (m, 2H), 6.28 (t, $J$ = 8.4 Hz, 1H), 6.45 (s, 1H), 7.07 (d, $J$ = 8.5 Hz, 1H), 7.30 (d, $J$ = 6.0 Hz, 2H), 7.40−7.63 (m, 6H), 7.74 (d, $J$ = 7.1 Hz, 2H), 8.13 (d, $J$ = 7.0 Hz, 2H), 8.66 (d, $J$ = 6.0 Hz, 2H).

**7-*O*-(Triethylsilyl)baccatin III 13-*O*-[(*Z*)-3-amino-*N*-benzoyl-3-(4-pyridyl)acrylate] (28b)**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.59 (q, $J$ = 6.9 Hz, 6H), 0.88−0.95 (m, 9H), 1.21 (s, 3H), 1.25 (s, 3H), 1.69 (s, 3H), 1.81-1.92 (m, 1H), 2.10−2.38 (m, 2H), 2.11 (s, 3H), 2.18 (s, 3H), 2.33 (s, 3H), 2.46-2.60 (m, 1H), 3.85 (d, $J$ = 6.8 Hz, 1H), 4.23 ($q_{ab}$, $J$ = 50.0, 8.3 Hz, 2H), 4.48 (dd, $J$ = 10.3, 6.8 Hz, 1H), 4.96 (d, $J$ = 8.8 Hz, 1H), 5.44 (s, 1H), 5.68 (d, $J$ = 6.8 Hz, 1H), 6.20 (b t, $J$ = 7.9 Hz, 1H), 6.47 (s, 1H), 7.33−7.61 (m, 8H), 7.97 (d, $J$ = 7.1 Hz, 1H), 8.07

(54) Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.

(d, $J$ = 7.3 Hz, 1H), 8.71 (b d, $J$ = 4.4 Hz, 1H), 11.72 (s, 1H); MS $m/z$ calcd for $C_{52}H_{62}O_{12}Si$ ($M^+$ + H) 951, found 951.

**2-*O*-(*tert*-Butyldimethylsilyl)-3′-dephenyl-3′-(2-furyl)-7-*O*-(triethylsilyl)paclitaxel (29).** Protected taxane **29** was isolated as an amorphous solid in 80% yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.19 (s, 3H), 0.08 (s, 3H), 0.50−0.61 (m, 6H), 0.81 (s, 9H), 0.91 (t, $J$ = 7.7 Hz, 9H), 1.15 (s, 3H), 1.22 (s, 3H), 1.68 (s, 3H), 1.84−1.94 (m, 1H), 2.02 (s, 3H), 2.10−2.19 (m, 2H), 2.15 (s, 3H), 2.36−2.44 (m, 1H), 2.53 (s, 3H), 3.83 (d, $J$ = 6.9 Hz, 1H), 4.29 ($q_{ab}$, $J$ = 37.2, 8.4 Hz, 2H), 4.46 (dd, $J$ = 10.5, 6.6 Hz, 1H), 4.86 (d, $J$ = 1.8 Hz, 1H), 4.94 (d, $J$ = 8.1 Hz, 1H), 5.68 (d, $J$ = 6.9 Hz, 1H), 5.79 (d, $J$ = 9.3 Hz, 1H), 6.17−6.22 (m, 2H), 6.34−6.35 (m, 1H), 6.44 (s, 1H), 6.89 (d, $J$ = 9.0 Hz, 1H), 7.39−7.61 (m, 7H), 7.71−7.73 (m, 2H), 8.16 (d, $J$ = 7.2 Hz, 2H).

**2-*O*-(*tert*-Butyldimethylsilyl)-3′-dephenyl-3′-(3-furyl)-7-*O*-(triethylsilyl)paclitaxel (30).** Silylated taxane **30** was isolated in 72% yield as a 3:1 inseparable mixture of diastereomers after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.04 and −0.01 (s, 3H), 0.08 and 0.10 (s, 3H), 0.50−0.66 (m, 6H), 0.86−0.97 (m, 9H), 0.88 and 0.92 (s, 9H), 1.16 (s, 3H), 1.21 and 1.25 (s, 3H), 1.67 and 1.68 (s, 3H), 1.84−2.06 (m, 1H), 1.99 (s, 3H), 2.14 and 2.16 (s, 3H), 2.25−2.41 (m, 2H), 2.48 (s, 3H), 2.48−2.58 (m, 1H), 3.82 (d, $J$ = 6.9 Hz, 1H), 4.23 and 4.25 ($q_{ab}$, $J$ = 34.2, 8.4 Hz, 2H), 4.43−4.48 (m, 1H), 4.53 and 4.60 (d, $J$ = 2.1 Hz, 1H), 4.93 (b d, $J$ = 8.1 Hz, 1H), 5.64−5.70 (m, 2H), 6.13 and 6.20 (t, $J$ = 9.0 Hz, 1H), 6.38 (s, 1H), 6.43 and 6.45 (s, 1H), 6.82 and 7.00 (d, $J$ = 9.0 Hz, 1H), 7.35−7.62 (m, 8H), 7.69 and 7.75 (d, $J$ = 6.9 Hz, 2H), 8.05 and 8.11 (d, $J$ = 7.2 Hz, 2H).

**General Procedure for the Deprotection of Taxanes 31−35.** Silylated taxanes (20 mg, 0.019 mmol) in anhydrous pyridine (1 mL) were placed in a nalgene reaction vessel. To the solution was added pyridinium HF (0.25 mL, excess). The reaction vessel was then sealed and allowed to stir at rt for 3 h. The reaction mixture was carefully quenched by pouring the reaction mixture into a saturated $NaHCO_3$ solution, extracted with EtOAc (3 × 10 mL), and dried over anhydrous $MgSO_4$.

**3′-Dephenyl-3′-(2-pyridyl)paclitaxel (31).** Taxane **31** was isolated as a white powder in 90% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: $[\alpha]_D$ −30.2 ($c$ = 0.215, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.83−1.94 (m, 1H), 1.84 (s, 3H), 2.20−2.36 (m, 2H), 2.24 (s, 3H), 2.48 (s, 3H), 2.50−2.62 (m, 1H), 3.83 (d, $J$ = 6.6 Hz, 1H), 4.24 ($q_{ab}$, $J$ = 44.9, 8.3 Hz, 2H), 4.44 (dd, $J$ = 14.0, 3.4 Hz, 1H), 4.82 (d, $J$ = 3.3 Hz, 1H), 4.99 (d, $J$ = 7.5 Hz, 1H), 5.67 (d, $J$ = 6.8 Hz, 1H), 5.92 (dd, $J$ = 9.4, 2.9 Hz, 1H), 6.19 (b t, $J$ = 8.4 Hz, 1H), 6.28 (s, 1H), 7.30 (dd, $J$ = 7.6, 5.3 Hz, 1H), 7.43−7.64 (m, 8H), 7.71−7.78 (m, 2H), 7.86 (d, $J$ = 7.4 Hz, 2H), 8.10 (d, $J$ = 7.3 Hz, 2H), 8.53 (b d, $J$ = 4.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 9.5, 14.8, 20.8, 21.8, 22.2, 26.7, 29.7, 35.6, 35.7, 43.1, 45.7, 54.6, 58.6, 71.2, 72.2, 73.5, 75.0, 75.6, 76.4, 79.3, 80.8, 84.4, 122.5, 123.3, 127.1, 128.7, 128.7, 129.1, 130.1, 132.1, 132.8, 133.7, 137.9, 142.5, 148.2, 167.1, 170.6, 171.3, 173.3, 203.8; FAB HRMS $m/z$ calcd for $C_{46}H_{51}N_2O_{14}$ ($M^+$ + H) 855.3340, found 855.3369.

**3′-Dephenyl-3′-(3-pyridyl)paclitaxel (32).** Taxane **32** (an inseparable 2:1 mixture of diastereomers) was isolated in 90% yield after purification by silica gel flash chromatography eluting with EtOAc: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, 3H), 1.23 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 1.81−1.91 (m, 1H), 2.03 (s, 1H), 2.24 (s, 3H), 2.27−2.36 (m, 2H), 2.41 (s, 3H), 2.49−2.64 (m, 1H), 3.79 and 3.85 (d, $J$ = 6.8 Hz, 1H), 4.25 and 4.21 ($q_{ab}$, $J$ = 36.1, 8.3 Hz, 2H), 4.38 and 4.46 (dd, $J$ = 11.1, 7.1 Hz, 1H), 4.68 and 4.78 (d, $J$ = 2.4 Hz, 1H), 4.95 and 4.97 (d, $J$ = 7.8 Hz, 1H), 5.67 (d, $J$ = 6.8 Hz, 1H), 5.81 and 5.85 (dd, $J$ = 2.4, 8.7 Hz, 1H), 6.21−6.31 (m, 2H), 7.10 and 7.14 (d, $J$ = 8.9 Hz, 1H), 7.33−7.65 (m, 8H), 7.60 and 7.61 (t, $J$ = 7.4 Hz, 1H), 7.72 and 7.73 (d, $J$ = 7.2 Hz, 2H), 7.85−7.93 (m, 1H), 8.04 and 8.13 (d, $J$ = 7.2 Hz, 2H), 8.57−8.60 (m, 1H), 8.76 and 8.88 (d, $J$ = 2.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 9.49, 9.54, 14.9, 20.78, 20.83, 21.6, 22.6, 26.9, 29.7, 35.6, 35.7, 43.2, 45.7, 52.9, 58.6, 72.2, 72.5, 72.8, 74.8, 75.5, 76.5, 78.9, 81.3, 84.3, 123.7, 127.0, 127.1, 128.7, 128.8, 129.1, 130.0, 130.1, 132.2, 133.2, 128.7, 129.1, 130.0, 130.1, 132.2, 133.2, 133.4, 133.8, 134.1, 135.2, 141.5, 148.6, 149.4, 166.9, 167.0, 170.4, 171.1, 172.1, 203.5; FAB HRMS $m/z$ calcd for $C_{46}H_{51}N_2O_{14}$ ($M^+$ + H) 855.3340, found 855.3356.

**3′-Dephenyl-3′-(4-pyridyl)paclitaxel (33).** Taxane **33** was isolated in 89% yield after purification via silica gel flash chromatography eluting with 2% MeOH/$CH_2Cl_2$: $[\alpha]_D$ −40 ($c$ = 0.6, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.11 (s, 3H), 1.19 (s, 3H), 1.65 (s, 3H), 1.76 (s, 3H), 1.80−1.89 (m, 1H), 2.12−2.32 (m, 2H), 2.20 (s, 3H), 2.37 (s, 3H), 2.46−2.58 (m, 1H), 3.76 (d, $J$ = 6.8 Hz, 1H), 4.22 ($q_{ab}$, $J$ = 48, 8.3 Hz, 2H), 4.35 (dd, $J$ = 10.7, 6.8 Hz, 1H), 4.79 (d, $J$ = 2.2 Hz, 1H), 4.91 (dd, $J$ = 7.8, 1.5 Hz, 1H), 5.63 (d, $J$ = 7.0 Hz, 1H), 5.79 (d, $J$ = 9.3 Hz, 1H), 6.19−6.23 (m, 2H), 7.19 (d, $J$ = 9.1 Hz, 1H), 7.35−7.60 (m, 8H), 7.73 (d, $J$ = 7.2 Hz, 2H), 8.09 (d, $J$ = 7.3 Hz, 2H), 8.57 (br s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.6, 14.9, 20.8, 21.7, 22.6, 26.9, 29.7, 35.6, 36.7, 43.2, 45.7, 54.0, 58.6, 72.2, 72.4, 72.6, 74.8, 75.5, 79.0, 81.3, 84.3, 122.3, 127.1, 128.7, 128.8, 129.1, 130.2, 132.3, 133.0, 133.5, 133.8, 141.5, 148.1, 149.6, 167.96, 167.01, 170.5, 171.2, 171.9, 203.5; FAB HRMS $m/z$ calcd for $C_{46}H_{51}N_2O_{13}$ ($M^+$ + H) 855.3335, found 855.3340.

**3′-Dephenyl-3′-(2-furyl)paclitaxel (34).** Taxane **34** was isolated as a white solid in 79% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: $[\alpha]_D$ −42 ($c$ = 0.21, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.14 (s, 3H), 1.23 (s, 3H,), 1.68 (s, 3H,), 1.81−1.92 (m, 1H), 1.85 (s, 3H), 2.23 (s, 3H), 2.31−2.46 (m, 2H), 2.42 (s, 3H), 2.44−2.68 (m, 1H), 3.47 (d, $J$ = 5.4 Hz, 1H), 3.81 (d, $J$ = 6.9 Hz, 1H), 4.25 ($q_{ab}$, $J$ = 34.8, 8.4 Hz, 2H), 4.37−4.44 (m, 1H), 4.81 (d, $J$ = 2.1 Hz, 1H), 4.95 (d, $J$ = 7.8 Hz, 1H), 5.67 (d, $J$ = 7.2 Hz, 1H), 5.87 (dd, $J$ = 9.3, 2.4 Hz, 1H), 6.23 (b t, $J$ = 9.0 Hz, 1H), 6.26 (s, 1H), 6.39 (d, $J$ = 0.9 Hz, 2H), 6.84 (d, $J$ = 9.3 Hz, 1H), 7.37−7.62 (m, 7H), 7.73 (d, $J$ = 7.5 Hz, 2H), 8.14 (d, $J$ = 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.0, 15.3, 21.3, 22.2, 23.0, 27.3, 36.0, 43.6, 46.0, 50.6, 59.1, 72.2, 72.6, 72.9, 75.4, 76.0, 76.8, 79.4, 81.5, 84.9, 108.4, 111.2, 127.5, 129.1, 129.7, 130.7, 132.7, 133.8, 134.2, 142.7, 143.3, 151.2, 167.4, 170.9, 171.8, 172.8, 204.1; FAB HRMS $m/z$ calcd for $C_{45}H_{49}NO_{15}Na$ ($M^+$ + Na) 866.3000, found 866.3030.

**3′-Dephenyl-3′-(3-furyl)paclitaxel (35).** The mixture of the two diastereomers of deprotected taxane **33** was isolated as a white solid in 59% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.14 (s, 3H), 1.23 (s, 3H,), 1.68 (s, 3H), 1.83 (s, 3H), 1.86−1.92 (m, 1H), 2.03 (s, 1H), 2.22 (s, 3H), 2.34−2.39 (m, 2H), 2.38 (s, 3H), 2.49−2.62 (m, 1H), 3.57 (d, $J$ = 4.8 Hz, 1H), 3.80 (d, $J$ = 7.2 Hz, 1H), 4.25 ($q_{ab}$, $J$ = 34.8, 8.4 Hz, 2H), 4.36−4.43 (m, 1H), 4.59 and 4.67 (d, $J$ = 1.5 Hz, 1H), 4.94 (d, $J$ = 7.5 Hz, 1H), 5.67 (d, $J$ = 7.2 Hz, 1H), 5.72 (dd, $J$ = 9.0, 1.5 Hz, 1H), 6.14−6.29 (m, 1H), 6.27 and 6.29 (s, 1H), 6.51 and 6.58 (t, $J$ = 0.9 Hz, 1H), 6.66 and 6.71 (d, $J$ = 9.0 Hz, 1H), 7.35−7.72 (m, 10H), 8.04 and 8.13 (d, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.0, 15.3, 22.0, 22.2, 22.9, 27.3, 36.1, 43.8, 46.1, 48.5, 59.2, 72.7, 72.8, 73.1, 75.4, 76.0, 76.8, 77.0, 79.4, 81.7, 84.8, 110.0, 110.1, 123.4, 127.4, 129.1, 129.7, 130.4, 130.6, 132.4, 133.8, 139.2, 140.9, 142.3, 144.1, 167.2, 167.3, 170.9, 171.5, 173.1, 204.1; FAB HRMS $m/z$ calcd for $C_{45}H_{49}NO_{15}Li$ ($M^+$ + Li) 850.3262, found 850.3288.

**Baccatin III 13-*O*-[(*Z*)-3-Amino-*N*-benzoyl-3-(4-pyridyl)acrylate] (36).** Enamide **36** was isolated quantitatively by silica gel flash chromatography eluting with 80% EtOAc/hexane. Taxane **36** was isolated in a 10:1 *Z*:*E* mixture. Major isomer: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, 3H), 1.26 (s, 3H), 1.67 (s, 3H), 1.82−1.91 (m, 1H), 1.96 (s, 3H), 2.20−2.37 (m, 2H), 2.23 (s, 3H), 2.31 (s, 3H), 2.50−2.65 (m, 1H), 3.83 (d, $J$ = 6.9 Hz, 1H), 4.22 ($q_{ab}$, $J$ = 49, 8.4 Hz, 2H), 4.44 (dd, $J$ = 10.8, 6.3 Hz, 1H), 4.96 (d, $J$ = 8.7 Hz, 1H), 5.42 (s, 1H), 5.66 (d, $J$ = 6.9 Hz, 1H), 6.23 (t, $J$ = 9.6 Hz, 1H), 6.30 (s, 1H), 7.36 (d, $J$ = 4.6 Hz, 2H), 7.46−7.61 (m, 5H), 7.77 (t, $J$ = 7.5 Hz, 1H), 7.97 (d, $J$ = 7.2 Hz, 2H), 8.07 (d, $J$ = 7.4, 2H,), 8.69−8.78 (br s, 2H), 11.72 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.5, 15.3, 20.8, 21.5, 22.7, 26.8, 29.7, 35.6, 35.9, 43.1, 46.3, 58.7, 59.2, 70.4, 72.2, 74.9, 75.6, 76.4, 79.3, 80.8, 81.1, 84.3, 101.1, 121.3, 127.0, 127.8, 128.7, 129.1, 129.2, 130.0, 133.2, 133.8, 142.4, 149.7, 154.4, 164.9, 166.7, 167.9, 171.2, 171.9, 203.6; FAB HRMS $m/z$ calcd for $C_{46}H_{49}N_2O_{13}$ ($M^+$ + H) 837.3235, found 837.3249.

**(3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-4-(2-furyl)-2-azetidinone (37).** To a stirring solution of (3*R*,4*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-4-(2-furyl)-2-azetidinone (**15**, 0.426 g, 0.160 mmol) in THF (10 mL) were added at rt triethylamine (0.111 mL, 0.800 mmol), DMAP (0.004 g, 0.03 mmol), and $(BOC)_2O$ (0.110 mL, 0.480 mmol). After being stirred for 10 min, the reaction mixture was diluted with ether, quenched with water, extracted with ether (3 × 20 mL), washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. 2-Azetidinone **37** was isolated as a white solid in 96% yield after purification by silica gel flash chromatography eluting with 5% EtOAc/hexane: mp 51−52 °C; $[\alpha]_D$ +53.6 (*c* = 1.09, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.06 (s, 3H), 0.08 (s, 3H), 0.78 (s, 9H), 1.41 (s, 9H), 5.01 (d, *J* = 5.7 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 5.36 (d, *J* = 1.2 Hz, 2H), 7.40 (t, *J* = 3.0, 1.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −4.6, −4.6, 18.3, 25.7, 27.9, 28.3, 56.3, 83.9, 110.1, 110.9, 143.1, 148.1, 148.4, 166.0. Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.83; H, 7.96; N, 3.81. Found: C, 58.68; H, 8.10; N, 4.00.

**(3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-furyl)-1-hexanoyl-2-azetidinone (38).** 2-Azetidinone **38** was prepared according to the general procedure by acylation of **15** (0.040 g, 0.15 mmol) with hexanoyl chloride (0.032 mL, 0.22 mmol) and isolated as a transparent oil in 90% yield after purification by silica gel flash chromatography eluting with 5% EtOAc/hexane: $[\alpha]_D$ +42 (*c* = 1.1, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.08 (s, 3H), 0.10 (s, 3H), 0.75 (s, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 1.25−1.33 (m, 4H), 1.59−1.66 (m, 2H), 2.62−2.81 (m, 2H), 5.05 (d, *J* = 5.7 Hz, 1H), 5.16 (d, *J* = 5.7 Hz, 1H), 6.33 (s, 2H), 7.37 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.0, −4.6, 14.3, 18.3, 22.7, 24.1, 25.7, 31.6, 37.2, 55.0, 77.0, 110.2, 110.9, 143.2, 147.9, 166.4, 177.7; HRMS *m*/*z* calcd for $C_{19}H_{32}NO_4Si$ 366.2100, found 366.2108.

**(3*R*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-decanoyl-4-(2-furyl)-2-azetidinone (39).** 2-Azetidinone **39** was prepared according to the general procedure by acylation of **15** (0.040 g, 0.15 mmol) with decanoyl chloride (0.047 mL, 0.22 mmol) and isolated as a transparent oil in 94% yield after purification by silica gel flash chromatography eluting with 5% EtOAc/hexane: $[\alpha]_D$ +28.5 (*c* = 1.05, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.08 (s, 3H), 0.10 (s, 3H), 0.73 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 1.23−1.33 (m, 12H), 1.58−1.68 (m, 2H), 2.61−2.81 (m, 2H), 5.05 (d, 5.7 Hz, 1H), 5.16 (d, 5.7 Hz, 1H), 6.31−6.34 (m, 2H), 7.37 (t, *J* = 1.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ −5.0, −4.6, 14.5, 18.3, 23.1, 24.5, 25.7, 29.4, 29.6, 29.7, 29.8, 32.3, 37.2, 55.0, 71.4, 77.0, 110.2, 110.9, 143.2, 147.9, 166.4, 171.7; HRMS *m*/*z* calcd for $C_{23}H_{40}NO_4Si$ 422.2726, found 422.2748.

***N*-(*tert*-Butoxycarbonyl)-2′-*O*-(*tert*-butyldimethylsilyl)-*N*-debenzoyl-3′-dephenyl-3′-(2-furyl)-7-*O*-(triethylsilyl)paclitaxel (40).** Protected taxane **40** was prepared according to the general procedure (NaH as the base) by coupling of protected baccatin III **25** (0.036 g, 0.051 mmol) with **37** (0.028 g, 0.076 mmol) and isolated as a transparent solid in 78% yield after purification by silica gel flash chromatography eluting with 5% EtOAc/hexane: mp 132 °C; $[\alpha]_D$ −41.4 (*c* = 1.01, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.16 (s, 3H), 0.03 (s, 3H), 0.52−0.60 (m, 6H), 0.77 (s, 9H), 0.91 (t, *J* = 7.8 Hz, 9H), 1.19 (s, 3H), 1.22 (s, 3H), 1.32 (s, 9H), 1.68 (s, 3H), 1.85−1.94 (m, 1H), 2.01 (s, 3H), 2.16 (s, 3H), 2.30−2.43 (m, 2H), 2.45−2.62 (m, 1H), 2.48 (s, 3H), 3.84 (d, *J* = 6.9 Hz, 1H), 4.23 ($q_{ab}$, *J* = 38.1, 8.4 Hz, 2H), 4.46 (dd, *J* = 10.5, 6.9 Hz, 1H), 4.73 (d, *J* = 1.5 Hz, 1H), 4.93 (d, *J* = 8.4 Hz, 1H), 5.22−5.36 (m, 2H), 5.67 (d, *J* = 6.9 Hz, 1H), 6.20−6.26 (m, 2H), 6.32−6.34 (m, 1H), 6.45 (s, 1H), 7.35 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H).

**General Procedure for the Sodium Bis(trimethylsilyl)amide-Promoted Acylation of 7-*O*-(Triethylsilyl)-baccatin III for the Formation of Compounds 41 and 42.** To a cold (−41 °C) solution of 7-*O*-(triethylsilyl)baccatin III (0.025 g, 0.036 mmol) and *N*-acyl-2-azetidinone (0.054 mmol) in anhydrous THF (1 mL) was added dropwise a 1 M THF solution of sodium bis(trimethylsilyl)amide (0.54 mL). The reaction was stirred at −41 °C for 10 min or until the disappearance of **24** by TLC (35% EtOAc/hexane), warmed to 0 °C, carefully quenched by the dropwise addition of a saturated ammonium chloride solution (5 mL), extracted with ether, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure.

**2′-*O*-(*tert*-Butyldimethylsilyl)-*N*-debenzoyl-3′-dephenyl-3′-(2-furyl)-*N*-hexanoyl-7-*O*-(triethylsilyl)paclitaxel (41).** Protected taxane **41** was prepared according to the general procedure by coupling of protected baccatin III **25** (0.036 g, 0.051 mmol) with **38** (0.037 g, 0.10 mmol) and isolated as a transparent oil in 46% yield after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.16 (s, 3H), 0.01 (s, 3H), 0.51−0.59 (m, 6H), 0.79 (s, 9H), 0.79−0.93 (m, 12H), 1.20 (s, 3H), 1.22−1.25 (m, 7H), 1.54−1.68 (m, 2H), 1.68 (s, 3H), 1.84−1.93 (m, 2H), 2.10−2.24 (m, 2H), 2.16 (s, 3H), 2.32−2.41 (m, 2H), 2.48 (s, 3H), 2.48−2.56 (m, 1H), 3.82 (d, *J* = 6.9 Hz, 1H), 4.24 ($q_{ab}$, *J* = 34.8, 8.4 Hz, 2H), 4.45 (dd, *J* = 10.5, 6.6 Hz, 1H), 4.76 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 8.1 Hz, 1H), 5.62−5.70 (m, 2H), 6.12−6.22 (m, 3H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.44 (s, 1H), 7.36 (d, *J* = 1.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 8.07−8.10 (m, 2H).

**2′-*O*-(*tert*-Butyldimethylsilyl)-*N*-debenzoyl-*N*-decanoyl-3′-dephenyl-3′-(2-furyl)-7-*O*-(triethylsilyl)paclitaxel (42).** Protected taxane **42** was prepared according to the general procedure from protected baccatin III (0.035 g, 0.050 mmol) and **39** (0.042 g, 0.10 mmol) and isolated as a transparent oil in 48% yield after purification by silica gel flash chromatography eluting with 25% EtOAc/hexane: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.16 (s, 3H), 0.01 (s, 3H), 0.51−0.59 (m, 6H), 0.79 (s, 9H), 0.81−0.94 (m, 12H), 1.15−1.30 (m, 18H), 1.50−1.60 (m, 2H), 1.68 (s, 3H), 1.81−1.94 (m, 1H), 2.00 (s, 3H), 2.07−2.23 (m, 2H), 2.16 (s, 3H), 2.31−2.41 (m, 2H), 2.47−2.58 (m, 1H), 2.47 (s, 3H), 3.82 (d, *J* = 6.9 Hz, 1H), 4.23 ($q_{ab}$, *J* = 33.6, 8.1 Hz, 2H), 4.45 (dd, *J* = 10.5, 6.9 Hz, 1H), 4.75 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 8.1 Hz, 1H), 5.61−5.70 (m, 2H), 6.12−6.21 (m, 3H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.44 (s, 1H), 7.34 (bs, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 6.9 Hz, 2H).

***N*-(*tert*-Butoxycarbonyl)-*N*-debenzoyl-3′-dephenyl-3′-(2-furyl)paclitaxel (43)**. Bis-silylated taxane **40** (0.040 g, 0.038 mmol) was deprotected according to the general procedure, and taxane **43** was isolated as a white solid in 81% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: mp 155−158 °C; $[\alpha]_D$ −79 (*c* = 0.67, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3H), 1.24 (s, 3H), 1.33 (s, 9H), 1.66 (s, 3H), 1.82−1.91 (m, 1H), 1.87 (s, 3H), 2.23 (s, 3H), 2.28−2.39 (m, 2H), 2.39 (s, 3H), 2.48−2.58 (m, 1H), 3.80 (d, *J* = 7.2 Hz, 1H), 4.22 ($q_{ab}$, *J* = 42.3, 8.4 Hz, 2H), 4.41 (dd, *J* = 10.8, 6.6 Hz, 1H), 4.70 (d, *J* = 1.8 Hz, 1H), 4.94 (d, *J* = 7.8 Hz, 1H), 5.23−5.34 (m, 2H,), 5.66 (d, *J* = 6.9 Hz, 1H), 6.22 (t, *J* = 9.0, 1H), 6.29−6.31 (m, 2H), 6.35−6.37 (m, 1H), 7.40 (d, *J* = 0.9 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.9, 15.3, 21.3, 22.2, 22.9, 23.0, 27.1, 28.5, 35.8, 35.9, 36.0, 43.6, 46.1, 52.1, 59.0, 72.2, 72.6, 72.9, 75.4, 75.5, 76.0, 79.4, 80.9, 81.4, 81.5, 81.6, 84.9, 107.9, 111.1, 129.5, 129.8, 130.7, 134.8, 135.0, 142.4, 142.7, 142.9, 151.9, 155.8, 167.6, 171.0, 171.5, 171.8, 173.2, 202.3; FAB HRMS *m*/*z* calcd for $C_{43}H_{53}NO_{16}Li$ 846.3524, found 846.3547.

***N*-Debenzoyl-3′-dephenyl-3′-(2-furyl)-*N*-hexanoylpaclitaxel (44).** Bis-silylated taxane **41** (0.020 g, 0.019 mmol) was deprotected according to the general procedure, and taxane **44** was isolated as an amorphous solid in 64% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: mp 136−139 °C; $[\alpha]_D$ −42 (*c* = 0.23, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.81−0.85 (m, 3H), 1.15 (s, 3H), 1.21−1.25 (m, 7H,), 1.67 (s, 3H), 1.83−1.92 (m, 1H), 1.86 (s, 3H), 2.16−2.23 (m, 2H), 2.23 (s, 3H), 2.28−2.44 (m, 4H), 2.37 (s, 3H), 2.49−2.59 (m, 1H), 3.33 (d, *J* = 5.1 Hz, 1H), 3.80 (d, *J* = 6.9 Hz, 1H), 4.24 ($q_{ab}$, *J* = 33.3, 8.7 Hz, 2H), 4.37−4.44 (m, 1H), 4.71 (d, *J* = 1.8 Hz, 1H), 4.94 (dd, *J* = 9.3, 1.8 Hz, 1H), 5.64−5.68 (m, 2H), 6.08 (d, *J* = 9.3 Hz, 1H), 6.21 (t, *J* = 9.0 Hz, 1H), 6.28 (s, 1H), 6.31 (d, *J* = 3.3 Hz, 1H), 6.38 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 9.6, 13.8, 14.9, 20.9, 21.9, 22.3, 22.5, 25.3, 26.8, 29.7, 31.2, 35.6, 36.4, 43.2, 45.6, 49.7, 58.6, 71.6, 72.2, 72.5, 75.0, 75.6, 76.5, 78.9, 81.1, 84.4, 107.7, 110.7,

128.7, 129.1, 130.2, 133.2, 133.7, 142.0, 142.6, 150.9, 167.0, 170.3, 171.3, 172.4, 173.1, 203.7; FAB HRMS *m/z* calcd for $C_{44}H_{56}NO_{15}$ 838.3650, found 838.3669.

***N*-Debenzoyl-*N*-decanoyl-3′-dephenyl-3′-(2-furyl)paclitaxel (45).** Bis-silylated taxane **42** (0.025 g, 0.022 mmol) was deprotected according to the general procedure and taxane **45** was isolated as a white solid in 69% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: mp 116−118 °C; $[\alpha]_D$ −88 (*c* = 0.28, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.85 (t, *J* = 6.6 Hz, 3H), 1.14−1.25 (m, 18H), 1.67 (s, 3H), 1.80−1.92 (m, 1H), 1.86 (s, 3H), 2.15−2.23 (m, 2H), 2.23 (s, 3H), 2.27−2.45 (m, 4H), 2.37 (s, 3H), 2.49−2.58 (m, 1H), 3.36 (d, *J* = 5.1 Hz, 1H), 3.79 (d, *J* = 6.9 Hz, 1H), 4.23 ($q_{ab}$, *J* = 33.0, 8.4 Hz, 2H), 4.37−4.43 (m, 1H), 4.71 (d, *J* = 2.4 Hz, 1H), 4.93 (d, *J* = 8.1 Hz, 1H), 5.64−5.68 (m, 2H), 6.09 (d, *J* = 9.3 Hz, 1H), 6.20 (t, *J* = 9.0 Hz, 1H), 6.28 (s, 1H), 6.31 (d, *J* = 3.0 Hz, 1H), 6.37 (dd, *J* = 3.0, 1.8 Hz, 1H), 7.41 (b s, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.0, 14.5, 15.2, 21.2, 22.3, 22.9, 23.0, 26.1, 27.2, 29.6, 29.7, 32.2, 36.0, 36.9, 43.6, 46.1, 50.1, 59.1, 72.1, 72.9, 75.4, 76.0, 79.4, 81.5, 84.9, 108.1, 111.2, 129.6, 130.6, 133.7, 134.1, 143.0, 151.4, 152.3, 154.0, 167.4, 170.7, 172.8, 173.3, 189.6, 204.1; FAB HRMS *m/z* calcd for $C_{48}H_{64}NO_{15}$ 894.4276, found 894.4305.

**General Schotten−Baumann Acylation Procedure for the Synthesis of 47−51.** To a stirring solution of **46** (20 mg, 0.033 mmol) in EtOAc (1 mL) and saturated $NaHCO_3$ solution (1 mL) was added acid chloride (1.5 equiv). The reaction mixture was vigorously stirred at rt for 15 min. The organic layer was separated and dried over anhydrous $MgSO_4$.

***N*-Debenzoyl-*N*-(picolinoyl)paclitaxel (47).** Taxane **47** was isolated as a white powder in 90% yield after purification by silica gel flash chromatography eluting with 50% EtOAc/hexane: $[\alpha]_D$ −30.2 (*c* = 0.215, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3H), 1.23 (s, 3H), 1.68 (s, 3H), 1.83−1.94 (m, 1H), 1.84 (s, 3H), 2.20−2.36 (m, 2H), 2.24 (s, 3H), 2.48 (s, 3H), 2.50−2.62 (m, 1H), 3.83 (d, *J* = 6.6 Hz, 1H), 4.24 ($q_{ab}$, *J* = 44.9, 8.3 Hz, 2H), 4.44 (dd, *J* = 14.0, 3.4 Hz, 1H), 4.82 (d, *J* = 3.3 Hz, 1H), 4.99 (d, *J* = 7.5 Hz, 1H), 5.67 (d, *J* = 6.8 Hz, 1H), 5.92 (dd, *J* = 9.4, 2.9 Hz, 1H), 6.19 (b t, *J* = 8.4 Hz, 1H), 6.28 (s, 1H), 7.30 (dd, *J* = 7.6, 5.3 Hz, 1H), 7.43−7.64 (m, 8H), 7.71−7.78 (m, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 8.10 (d, *J* = 7.3 Hz, 2H), 8.53 (b d, *J* = 4.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 9.5, 14.8, 20.8, 21.8, 22.2, 26.7, 29.7, 35.6, 35.7, 43.1, 45.7, 54.6, 58.6, 71.2, 72.2, 73.5, 75.0, 75.6, 76.4, 79.3, 80.8, 84.4, 122.5, 123.3, 127.1, 128.7, 128.7, 129.1, 130.1, 132.1, 132.8, 133.7, 137.9, 142.5, 148.2, 167.1, 170.6, 171.3, 173.3, 203.8; FAB HRMS *m/z* calcd for $C_{46}H_{51}N_2O_{14}$ ($M^+$ + H) 855.3340, found 855.3369.

***N*-Debenzoyl-*N*-(nicotinoyl)paclitaxel (48).** Taxane **48** was isolated in 79% yield as a colorless glass after purification by silica gel flash chromatography eluting with 2% MeOH/$CH_2Cl_2$: $[\alpha]_D$ −30 (*c* = 0.3, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 1.81−1.94 (m, 1H), 2.10−2.32 (m, 2H), 2.24 (s, 3H), 2.40 (s, 3H), 2.46−2.60 (m, 1H), 3.77 (d, *J* = 6.9 Hz, 1H), 4.24 ($q_{ab}$, *J* = 36.0, 8.0 Hz, 2H), 4.39 (dd, *J* = 10.9, 6.7 Hz, 1H), 4.81 (d, *J* = 3.5 Hz, 1H), 4.93 (dd, *J* = 9.1, 1.5 Hz, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 5.78 (dd, *J* = 8.0, 3.0 Hz, 1H), 6.22 (t, *J* = 7.9 Hz, 1H), 6.25 (s, 1H), 7.32−7.65 (m, 9H), 7.95 (br s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.31 (d, *J* = 7.0 Hz, 1H), 8.71−8.78 (m, 1H), 9.36−9.39 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.6, 14.2, 14.9, 20.9, 21.9, 22.7, 26.9, 29.7, 31.9, 35.6, 43.2, 45.6, 55.2, 58.6, 72.2, 72.3, 73.1, 74.9, 75.5, 77.2, 79.1, 81.2, 84.4, 127.1, 128.5, 128.7, 129.1, 129.15, 130.2, 133.3, 133.8, 137.6, 141.8, 164.7, 167.0, 170.4, 171.3, 172.6, 178.6, 203.2; FAB HRMS *m/z* calcd for $C_{46}H_{51}N_2O_{14}$ ($M^+$ + H) 855.3340, found 855.3339.

***N*-Debenzoyl-*N*-(isonicotinoyl)paclitaxel (49).** Taxane **49** was isolated as a white powder in 92% yield after purification by silica gel flash chromatography eluting with 2% MeOH/$CH_2Cl_2$: $[\alpha]_D$ −43 (*c* = 0.21, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3H), 1.22 (s, 3H), 1.67 (s, 3H), 1.76 (s, 3H), 1.83−1.93 (m, 1H), 2.17−2.31 (m, 2H), 2.22 (s, 3H), 2.36 (s, 3H), 2.47−2.58 (m, 1H), 3.77 (d, *J* = 6.9 Hz, 1H), 4.23 ($q_{ab}$, *J* = 35.4, 8.4 Hz, 2H), 4.37 (dd, *J* = 10.8, 6.6 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 7.8 Hz, 1H), 5.65 (d, *J* = 6.9 Hz, 1H), 5.76 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.22 (t, *J* = 8.7 Hz, 1H), 6.25 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.32−7.63 (m, 10H), 8.11 (d, *J* = 7.5 Hz, 2H), 8.68 (d, *J* = 5.7 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 9.5, 14.1, 14.9, 20.9, 21.7, 22.7, 26.9, 29.2, 29.7, 31.9, 35.5, 43.2, 45.6, 54.9, 58.6, 72.2, 72.5, 72.9, 74.9, 75.5, 76.5, 79.1, 81.2, 84.4, 120.8, 127.0, 128.6, 128.7, 129.1, 129.2, 130.2, 133.4, 133.8, 137.4, 141.0, 141.7, 150.7, 165.0, 167.0, 170.4, 171.3, 172.5, 203.5; FAB HRMS *m/z* calcd for $C_{46}H_{51}N_2O_{14}$ ($M^+$ + H) 855.3340, found 855.3343.

***N*-Debenzoyl-*N*-(2-furoyl)paclitaxel (50).** Taxane **50** was isolated as a white solid in 69% yield after purification by silica gel flash chromatography eluting with 30% EtOAc/hexane: $[\alpha]_D$ −30 (*c* = 0.7, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.12 (s, 3H), 1.22 (s, 3H), 1.68 (s, 3H), 1.75−1.92 (m, 1H), 1.79 (s, 3H), 2.20−2.38 (m, 2H), 2.24 (s, 3H), 2.39 (s, 3H), 2.44−2.49 (m, 1H), 3.53 (d, *J* = 5.3 Hz, 1H), 3.78 (d, *J* = 6.3 Hz, 1H), 4.23 ($q_{ab}$, *J* = 33.0, 8.4 Hz, 2H), 4.35−4.43 (m, 1H), 4.75 (dd, *J* = 5.1, 2.7 Hz, 1H), 4.93 (d, *J* = 8.1 Hz, 1H), 5.65 (d, *J* = 6.9 Hz, 1H), 5.72 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.19−6.27 (m, 1H), 6.25 (s, 1H), 6.46 (dd, *J* = 3.6, 1.8 Hz, 1H), 7.01 (d, *J* = 3.6 Hz, 1H), 7.13 (d, *J* = 9.3 Hz, 1H), 7.33−7.62 (m, 9H), 8.12 (d, *J* = 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.0, 15.2, 21.2, 22.2, 23.0, 27.3, 36.0, 36.1, 43.6, 46.1, 54.8, 59.1, 72.6, 72.7, 73.8, 75.4, 76.0, 79.5, 81.6, 84.8, 112.7, 115.6, 127.4, 128.8, 129.1, 129.4, 129.6, 130.6, 133.6, 134.2, 138.9, 142.8, 144.4, 158.4, 167.1, 170.3, 172.0, 203.1; FAB HRMS *m/z* calcd for $C_{45}H_{49}NO_{15}Na$ ($M^+$ + Na) 866.3000, found 866.3019.

***N*-Debenzoyl-*N*-(3-furoyl)paclitaxel (51).** Taxane **51** was isolated as a white solid in 71% yield after purification by silica gel flash chromatography eluting with 30% EtOAc/hexane: $[\alpha]_D$ −30 (*c* = 0.9, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.21 (s, 3H), 1.22 (s, 3H), 1.66 (s, 3H), 1.77−1.90 (m, 1H), 1.77 (s, 3H), 2.18−2.32 (m, 2H), 2.22 (s, 3H), 2.35 (s, 3H), 2.49−2.58 (m, 1H), 3.68 (br s, 1H), 3.77 (d, *J* = 6.9 Hz, 1H), 4.22 ($q_{ab}$, *J* = 32.4, 8.4 Hz, 2H), 4.35−4.40 (m, 1H), 4.75 (br s, 1H), 4.92 (d, *J* = 7.8 Hz, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 5.72 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.18−6.25 (m, 1H), 6.25 (s, 1H), 6.56−6.57 (m, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 7.29−7.63 (m, 9H), 7.86 (br s, 1H), 8.11 (d, *J* = 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.1, 14.9, 21.3, 23.1, 36.0, 43.6, 46.6, 47.0, 55.0, 59.0, 71.7, 73.6, 75.3, 76.5, 79.5, 81.6, 83.9, 122.2, 126.4, 128.1, 128.4, 129.5, 129.6, 130.2, 131.3, 133.6, 138.3, 142.4, 144.4, 145.5, 147.0, 162.6, 167.4, 170.8, 171.7, 173.0, 204.0; FAB HRMS *m/z* calcd for $C_{45}H_{50}NO_{15}$ ($M^+$ + H) 844.3180, found 844.3197.

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**Supporting Information Available:** Proton NMR spectra are provided for **10**, **11**, **17**−**19**, **26**, **27, 28a**, **29**−**31**, **31** expansion, **32**−**34**, **34** expansion in DMSO/$D_2O$, **35**, **36**, **38**−**43**, **43** COSY**, 43** COSY expansion, and **44**−**51**. Carbon NMR spectra are provided for **17**−**19**, **26**, **29**−**31, 31** expansion**, 32**−**35, 35** expansion**, 36**, **38**, **38** expansion**, 39**, **39** expansion, **43**−**45**, **45** expansion, **47**−**51**, and **51** expansion**.** HPLC analyses are provided for **34, 35, 43**−**45**, **50**, and **51** (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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