The Effect of the Aromatic Rings of Taxol on Biological Activity and Solution Conformation: Synthesis and Evaluation of Saturated Taxol and Taxotere Analogues

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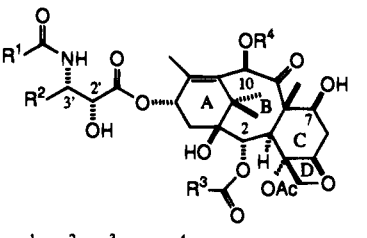
The synthesis and biological evaluation of novel cyclohexyl analogues of taxol and taxotere are detailed. 2-(Cyclohexylcarbonyl)-2-debenzoylbaccatin III (**6**) was prepared from baccatin III by hydrogenation. Subsequent coupling of **6** with *N*-*t*-BOC-3-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone (**7**), followed by removal of the protecting groups, afforded 2-(cyclohexylcarbonyl)-2-debenzoyltaxotere (**9**). In a similar synthetic sequence, 3′-cyclohexyl-3′-dephenyltaxol (**14**) was prepared from *N*-benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-cyclohexyl-2-azetidinone (**12**) and (triethylsilyl)baccatin III. The taxol analogue **15**, in which all three taxol phenyl groups are substituted by a cyclohexyl moiety, was synthesized in one step from taxol via hydrogenation. All three analogues (**9**, **14**, and **15**) exhibited strong activity in the microtubule assembly assay and cytotoxicity comparable to taxol against B16 melanoma cells. It was also shown that **9**, like taxol and taxotere, has an extended side chain in chloroform, but in DMSO/water mixtures preferentially adopts a different conformation in which the 2-(cyclohexylcarbonyl), 3′-phenyl, and 4-acetyl groups cluster. However, this behavior does not appear to occur for 3′-cyclohexyl analogues **14** and **15**, in which the side chain conformation remains extended independent of solvent. These results suggest the aromaticity of the 3′-phenyl ring significantly stabilizes the clustered conformation.

Taxol (**1**, paclitaxel), a complex natural product isolated[1] from the bark of *Taxus brevifolia* and other yew species,[2-7] has recently gained FDA approval for the treatment of cisplatin refractory ovarian cancer and metastatic breast cancer.[8-10] It has also shown exciting antitumor activity against lung cancer[11] and head and neck cancer.[12] Studies have revealed that taxol has a unique mechanism of action, blocking cell replication by promoting the assembly of unusually stable microtubules.[13,14]

The interesting biological activities of taxol have stimulated efforts in many laboratories, aimed at understanding structure–activity relationships of taxol analogues.[5,15-17] Most analogues synthesized to date are modified at the C-13 side chain of taxol.[5,15-17] These taxol side chain analogues can be prepared semisynthetically, utilizing the readily available diterpene 10-deacetylbaccatin III[18] and synthetic phenylisoserine analogues.[16,19] The C-13 *N*-benzoyl-3-phenylisoserine moiety is essential for biological activity.[1] Extensive structure–activity studies have revealed that the C-3′ *N*-benzoyl group can be replaced by a number of other acyl groups without loss of bioactivity.[5,15-17] The C-2′ hydroxyl group[20] and the natural stereochemistry in the A-ring side chain[21] are of importance for high activity. Deletion of the 3′-phenyl group of taxol resulted in a derivative with greatly reduced cytotoxicity.[22] A few taxol analogues, possessing a methyl group in place of the 3′-phenyl group have been synthesized.[21] None of these derivatives showed significant microtubule assembly properties.[21] Structure–activity studies at the 2-benzoyl moiety of taxol have not been extensive. However, recent results demonstrated the importance of the 2-benzoate group for bioactivity since it was found that 2-des(benzoyloxy)taxol is an inactive compound.[23] Replacement of the 2-benzoyl group by meta-substituted benzoyl groups has provided the most active taxol analogues prepared to date.[24]

As part of continuing structure–activity relationship (SAR) studies in our laboratory[25-31] and in light of our recent findings[32] that a number of active taxol analogues adopt similar hydrophobically clustered conformations in an aqueous environment,[33] we have synthesized several representative bioisosteric taxol analogues to further probe the taxol pharmacophore. In particular we were interested to find out whether the replacement of the 3′-phenyl group and/or the 2-benzoate group, implicated to be part of the hydrophobic cluster, with cyclohexyl groups would influence biological activity and conformational properties.



1 $R^1 = R^2 = R^3 = Ph$; $R^4 = Ac$ (taxol)
2 $R^1 = O^tBu$; $R^2 = R^3 = Ph$; $R^4 = H$ (taxotere)
3 $R^1 = O^tBu$; $R^2 = R^3 = Ph$; $R^4 = Ac$
9 $R^1 = O^tBu$; $R^2 = Ph$; $R^3 = C_6H_{11}$; $R^4 = Ac$
14 $R^1 = R^3 = Ph$; $R^2 = C_6H_{11}$; $R^4 = Ac$
15 $R^1 = R^2 = R^3 = C_6H_{11}$; $R^4 = Ac$

Chemistry

Our first target was 10-acetyl-2-(cyclohexylcarbonyl)-2-debenzoyltaxotere (**9**), a derivative of the potent semisynthetic taxane taxotere (**2**, docetaxel).[34] The taxotere analogue was selected to facilitate the NMR analysis of hydrophobic clustering by removing the

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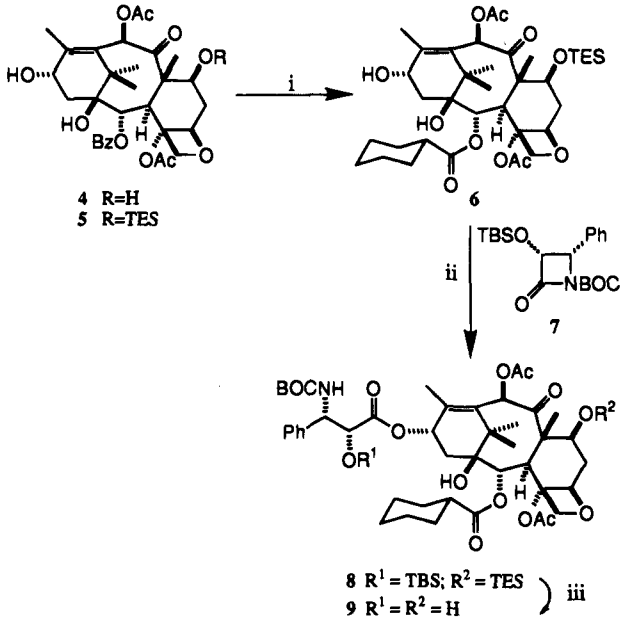
Scheme 1[a]



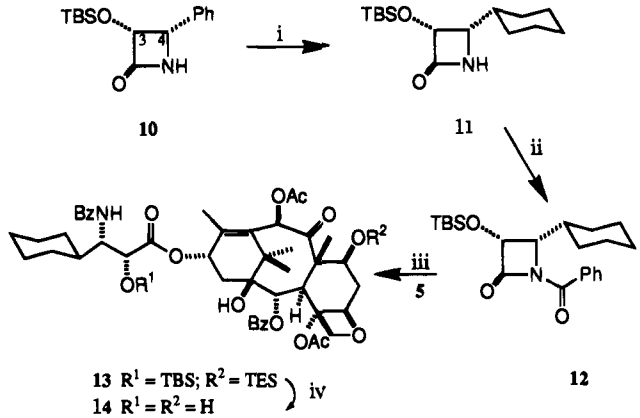
[a] (i) 3% Pt/C, H_2 (30 psi), EtOAc, 12 h, 91%; (ii) NaH, THF, 0 °C to room temperature, 1.5 h, 78%; (iii) pyridinium hydrofluoride, pyridine, 3 h, 84%.

interfering aromatic resonances of the nonparticipating benzamide moiety. The approach to the preparation of **9** was based on semisynthetic methodology developed in our laboratory (Scheme 1).[26,35]

The key diterpene intermediate **6** was obtained in two steps by protection of baccatin III (**4**) as the 7-triethylsilyl ether **5**[18] followed by hydrogenation over 3% platinum on carbon (Pt/C). The reduction of the 2-benzoyl ester proceeded in excellent yield to the 2-(cyclohexylcarbonyl)baccatin III derivative **6**.[36] This product is easily identified by the lack of aromatic resonance in the NMR spectra. Additionally, the reluctance of the bridgehead double bond to participate in reductive reactions is evident by the presence of the olefinic signals in the ^{13}C NMR spectrum. The alkoxide of **6**, generated by excess NaH,[37] was coupled with *N*-*t*-BOC-2-azetidinone **7** to provide 2′,7-bis(silyl) protected derivative **8** (Holton coupling). Subsequent removal of the silyl protecting groups with pyridinium hydrofluoride gave target compound **9**. This semisynthetic strategy represents a very efficient route to the 2-cyclohexylcarbonyl derivative **9**, greater than 75% isolated yields were achieved for each step of the reaction sequence.

The synthesis of the 3′-cyclohexyl analogue **14** started with enantioenriched β-lactam **10** (Scheme 2).[35] Hydrogenation of the phenyl moiety with 3% Pt/C was an effective means of introducing the cyclohexyl group even though the C4–N1 bond is benzylic and might be expected to undergo ring cleavage. Proof for hydrogenation over hydrogenolysis can be obtained from the ^1H NMR spectrum since H-4 is observed as a one-proton doublet of doublets ($J_{3,4}$ = 4.7 and $J_{4,cyclohexyl}$ = 9.1 Hz) at 3.29 ppm. Obviously, under these conditions, aromatic reduction proceeds faster than hydrogenolysis. Conversion of **11** to the *N*-benzoyl derivative **12** was achieved with benzoyl chloride, triethylamine, and catalytic DMAP. The two-step synthesis of **12** from **10** was nearly quantitative. The standard coupling reaction between *N*-acyl β-lactam **12** and 7-(triethylsilyl)-

Scheme 2[a]



[a] (i) 3% Pt/C, H_2 (55 psi), EtOAc, 12 h, quant.; (ii) benzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h, 96%; (iii) NaH, THF, 0 °C to 35 °C, 2 h, 71%; (iv) pyridinum hydrofluoride, pyridine, 2 h, 84%.

Table 1. *In Vitro* Biological Data[26]

analog	microtubule assembly[a]	B16 melanoma[a]
1 (taxol)	1	1
2 (taxotere)	0.45	0.41
3[29]	0.55	0.23
9	0.67	1.1
14	0.29	0.91
15	0.47	1.6

[a] $ED_{50}/ED_{50(taxol)}$.

baccatin III (**5**) afforded **13** and after deprotection the 3′-cyclohexyl target **14**.

The novel tricyclohexyltaxol analogue **15** was obtained in a single step by hydrogenation (H_2, 55 psi, 24 h) of taxol over 3% Pt/C. As was noted previously, hydrogenation of the aromatic rings was very efficient (quantitative yield), and no complication was observed due to benzylic hydrogenolysis.

Biological Evaluation and Discussion

The results of the microtubule assembly and B16 melanoma cytotoxicity assays for **9**, **14**, and **15** are provided in Table 1. All of the derivatives prepared displayed better microtubule assembly and similar B16 cytotoxicity compared to taxol. These results clearly show, in particular analogue **15**, that none of the aromatic moieties is essential for bioactivity.

The results of the biological assays for the C-3′ analogues **14** and **15** are similar to results obtained by Li[38] and Ojima[39] for related taxol analogues. The biological activities for 2-cyclohexyl derivatives **9** and **15** are in good agreement with data reported by Ojima for similar derivatives.[39] However, the results from our laboratory and the data from the Ojima group are different from the findings by Chen *et al.*[40] In their study 2-(cyclohexylcarbonyl)-2-debenzoyltaxol exhibited virtually no activity in the microtubule polymerization assay and was not cytotoxic against HCT116 cancer cells,[40] whereas in the Ojima study the same compound (2-(cyclohexylcarbonyl)-2-debenzoyltaxol) had significant microtubule disassembly properties.[39] The higher activity of our analogues **9** and **15** (Table 1) in comparison to 2-(cyclohexylcarbonyl)-2-debenzoyltaxol in the microtubule assembly assay and against B16 melanoma cells can probably be traced to their *N*-acyl substituents. For example, taxotere (**2**, Table 1), possessing an *N*-BOC

moiety, is about twice as active as taxol in the microtubule assembly assay and more than 3 times as cytotoxic against B16 melanoma cells than taxol (**1**).

On the basis of our data we must disagree with the conclusion by Chen *et al.*[40] that aromatic interactions between the 2-benzoate of taxol and tubulin are important for microtubule activity. If a specific protein–taxol interaction is important for activity, it must be at least in part lipophilic in nature, since 2-benzoyl and 2-cyclohexylcarbonyl derivatives are active compounds.

While these three compounds unambiguously demonstrate that aromaticity is not required at any position for biologically active taxanes, we were also interested in the effect of saturating the aromatic rings on the conformational preferences of these compounds in solution. Recently we presented direct NMR evidence (NOE's, chemical shift perturbations) for a hydrophobically clustered conformation of taxol and taxotere, involving close approach of the 2-benzoyl, 3′-phenyl, and 4-acetyl groups favored in polar solvents.[33] In agreement with other groups,[41,42] we believe this conformation is in fast exchange with a side chain-extended conformation very similar to the solid state structure of taxotere.[43] Other highly active analogs also show this conformation, whereas several inactive compounds do not.[32] Although the conformation of taxanes bound to microtubules is unknown, it has been observed in other conformationally flexible bioactive molecules that the conformation favored in water often is very similar to the bound-state structure.[44,45] Since the arrangement of the aromatic rings in this conformation is expected to be energetically favorable,[46] contributing to its stability, we wanted to investigate if it was still favored in the highly active saturated ring analogs described here. The results bear at least indirectly on the question of whether this conformation is required for recognition by microtubules, i.e., it is "preorganized" for microtubule binding.

The experimental techniques used to assess solvent-dependent conformational changes in these compounds were the same as described previously: comparisons of chemical shifts in $CDCl_3$ and 75% DMSO/25% D_2O (assignments being made on the basis of COSY and HMQC data), changes in $^3J_{2',3'}$ which reflect rotamer populations around this bond (the extended conformation being *gauche* and the clustered conformation *trans*)[41] and NOESY experiments in DMSO/D_2O which give optimal results at low temperature.[33]

In the case of **9**, the available evidence suggests the population of the clustered conformation is increasing in polar media. $J_{2',3'}$ increases substantially with the change in solvent, from virtually unresolved in $CDCl_3$ to 5.9 Hz in DMSO/D_2O (a typical value for a number of active analogs from our laboratory; in the case of taxol, the values are 2.7 Hz and 7.0 Hz, respectively). With taxol and taxotere, both the 2-benzoyl and 3′-phenyl showed significant relative chemical shift perturbations with the change in solvent (distinct from small systematic changes that affect all protons more or less equally), attributed to their mutual proximity in the clustered conformation. Since the 2-benzoyl ring is now saturated, no such changes are expected for the 3′-phenyl shifts, and none are observed. The cyclohexyl region of the spectrum is complex, since all 11 protons are inequivalent. In the COSY spectrum, the large couplings of the proton at C-1 to two upfield axial protons is readily identified, which must be 2_{ax} and 6_{ax}. The axial–equatorial couplings between geminal pairs are also prominent, completing the assignments of 2 and 6. Of the three remaining axial–equatorial pairs, two are very similar (3 and 5), and the unique pair is 4. Identical assignments are derived from proton–carbon correlations in the HMQC spectrum, with C-1 at δ 42.6, C-2 and 6 at δ 28.4 and 28.2, C-3 and 5 at δ 25.0 and 25.2, and C-4 at δ 25.5. With these assignments made, it can be seen that there are significant relative changes in the chemical shifts of the 2-cyclohexylcarbonyl ring for both 2 (or 6) and 3 (or 5) protons (see Table 2). These are equivalent to the ortho and meta protons which in taxol and taxotere showed NOE's to the 3′-phenyl ring. In the NOESY spectrum of **9**, NOE's are observed between the 3′-phenyl signals and axial 3 or 5 protons at δ 1.33. A weaker NOE to the equatorial 3 or 5 protons at δ 1.77 may also be present but is partially obscured by the 18-methyl signal. When the solvent-dependent shifts of other protons in **9** are compared with those of taxol, it can be seen that the magnitude and direction of these shifts are quite similar (see Table 2). Taken together, these results imply a population of the clustered conformation similar to other active analogs in which there is a 2-benzoyl group.

In the case of **14**, the same analysis suggests the clustered conformation is not nearly as populated in the more polar solvent. There is only a minimal increase in $J_{2',3'}$ (2.2 Hz in DMSO/D_2O). Either the 2 or the 6 protons in the 3′-cyclohexyl ring undergo a modest relative chemical shift change (ca. δ 0.05). (The peak assignments were made as previously described for **9**.) In taxol and taxotere, it was the para proton on the 3′-phenyl ring that showed the most chemical shift perturbation, and the meta and para which have NOE's to the 2-benzoyl protons. In the low-temperature NOESY experiment, there are weak crosspeaks to the 2-benzoyl ortho protons in this region (δ 1.08 and 1.59). However, these crosspeaks coincide with the shifts of the 16/17 and 19 methyl groups, respectively, at low temperature, and these probably do not originate from the cyclohexyl group. The population of a clustered conformation is therefore likely lower than for the compounds where there is an aromatic ring at the 3′-position (e.g., taxol, taxotere), and the involvement of the 2 proton rather than the 3 or 4 proton of the cyclohexyl suggests that if present, its geometry is somewhat different than the aromatic analogs. There is almost no solvent dependence of the 2′ and 3′ chemical shifts in **14** (or **15**), as is observed for **9** and for taxol. This observation suggests those particular upfield shifts result from shielding of the 2′ and 3′ protons by the 3′-phenyl ring when it is in the clustered conformation.

The extensive overlap of the cyclohexyl region in **15** precludes a complete analysis of this region, but the behavior of $J_{2',3'}$ is very similar to **14**. An overlay of the HOHAHA spectrum of **15** (which shows all connectivities originating within each cyclohexyl ring) with the NOESY did not show any NOE's which could be unambiguously attributed to contacts between the 2- and 3′-rings, although their presence could not be conclusively ruled out. The same conclusions drawn for **14** apply to **15**, although more tentatively.

The aromaticity of the 3′-ring does appear to be a

Table 2. Solvent Dependent ^1H NMR Spectral Data for Taxol and Cyclohexyl Analogues **9**, **14**, and **15**[a]

	taxol		**9**		**14**		**15**	
proton	$CDCl_3$	DMSO/D_2O	$CDCl_3$	DMSO/D_2O	$CDCl_3$	DMSO/D_2O	$CDCl_3$	DMSO/D_2O
2	5.67	5.48	5.43	5.23	5.68	5.54	5.44	5.28
3	3.79	3.66	3.68	3.52	3.79	3.75	3.63	3.58
5	4.94	5.00	4.95	4.96	4.98	5.05	4.97	5.02
6	2.54, 1.88	2.41, 1.75	2.54, 1.87	2.41, 1.72	2.57, 1.89	2.45, 1.76	2.55, 1.80	2.41, 1.73
7	4.40	4.14	4.36	4.12	4.44	4.16	4.37	4.14
10	6.27	6.33	6.17	6.33	6.26	6.35	6.24	6.33
13	6.23	5.96	6.17	5.86	6.20	5.94	6.09	5.77
14	2.35, 2.28	1.92, 1.71	2.24, 2.15	1.79, 1.69	2.40, 2.33	2.35, 2.26	n.d.	2.26, 2.10
16	1.14	1.08	1.15	1.06	1.13	1.08	1.07	1.09
17	1.24	1.08	1.00	1.03	1.21	1.10	1.23	1.03
18	1.79	1.82	1.72	1.81	1.84	1.86	1.83	1.86
19	1.68	1.82	1.55	1.51	1.68	1.58	1.63	1.53
20	4.30, 4.19	4.00, 3.93	4.46, 4.14	4.35, 4.02	4.34, 4.19	4.18, 4.12	4.48, 4.37	4.40, 4.05
2′	4.78	4.64	4.57	4.37	4.61	4.59	4.45	4.40
3′	5.78	5.41	5.21	4.92	4.28	4.24	3.99	3.89
NH	7.01	–	5.35	–	6.30	–	5.57	7.50
4-Ac	2.38	2.27	2.17	2.15	2.50	2.47	2.33	2.27
10-Ac	2.23	2.18	2.16	2.14	2.22	2.17	2.23	2.16
2-ring								
1	–	–	2.29	2.29	–	–	nd	nd
2,6	8.13	8.03	2.00, 1.43 1.88, 1.50	1.94, 1.34 1.90, 1.35	8.17	8.12	nd	nd
3,5	7.51	7.69	1.78, 1.29 1.78, 1.36	1.80, 1.32 1.80, 1.32	7.52	7.64	nd	nd
4	7.61	7.80	1.65, 1.24	1.68, 1.23	7.62	7.74	nd	nd
3′-ring								
1	–	–	–	–	1.81	1.78	nd	nd
2,6	7.48	7.46	7.41	7.41	1.99, 1.08 1.09, 1.06	1.92, 1.04 1.77, 1.05	nd	nd
3,5	7.42	7.46	7.32	7.32	1.73, 1.19 1.79, 1.24	1.73, 1.21 1.67, 1.19	nd	nd
4	7.35	7.24	7.30	7.30	1.85, 1.32	1.81, 1.27	nd	nd
3′-NHBz								
o-	7.74	7.91	–	–	7.76	7.66	nd	nd
m-	7.40	7.60	–	–	7.48	7.37	nd	nd
p-	7.35	7.24	–	–	7.57	7.43	nd	nd

[a] Experimental conditions: 500 MHz at room temperature in $CDCl_3$ or 75% DMSO/25% D_2O.

significant driving force in the formation of the clustered conformation, with the 2-ring having much less effect. The bound state conformation of taxanes must still be addressed experimentally, but the concept of "preorganization" of the side chain in the clustered conformation is weakened by the fact that the population of this conformer in the highly active **14** appears to be low.

Experimental Procedures[47]

General Procedure for the Coupling of 2-Azetidinones and Baccatin III Derivatives. The 2-azetidinone (1.5 equiv) and the baccatin III derivatives (0.025 mmol) were dissolved in THF (2 mL) at 0 °C. NaH (60% mineral oil dispersion, 50 equiv) was added in one portion. The reaction stirred at 0 °C for 5 min then at 25–35 °C for 1.5–2 h. The excess NaH was decomposed by addition of aqueous AcOH (ca. 30% v/v). The reaction mixture was extracted between Et_2O and saturated aqueous $NaHCO_3$, followed by drying (Na_2SO_4), filtration of the desiccant, and evaporation of the organic fractions. Final purification of the crude residue was achieved by flash column chromatography (silica; 4:1 hexane–EtOAc).

10-*O*-Acetyl-2′-*O*-(*tert*-butyldimethylsilyl)-2-*O*-(cyclohexylcarbonyl)-2-debenzoyl-7-*O*-(triethylsilyl)taxotere (8). Obtained from baccatin III derivative **6** and 2-azetidinone **7**, as an amorphous solid, in 78% yield: $[\alpha]_D$ −44.6° (c = 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ −0.34 (s, 3H, $SiCH_3$), −0.12 (s, 3H, $SiCH_3$), 0.5–0.62 (m, 6H, $Si(CH_2CH_3)_3$), 0.73 (s, 9H, $SiC(CH_3)_3$), 0.91 (t, J = 8.1 Hz, 9H, $Si(CH_2CH_3)_3$), 1.15 (s, 3H, H17), 1.19 (s, 3H, H16), 1.20–2.35 (m, 14H, cyclohexyl, H6 and H14), 1.41 (s, 9H, $OC(CH_3)_3$), 1.64 (s, 3H, H19), 1.95 (s, 3H, H18), 2.16 (s, 3H, 10-OAc), 2.45 (s, 3H, 4-OAc), 2.48–2.58 (m, 1H, H6), 3.70 (d, J = 7.2 Hz, 1H, H3), 4.16 (d, J = 7.8 Hz, 1H, H20), 4.40–4.55 (m, 3H, H2′, H7 and H20), 4.96 (d, J = 7.9 Hz, 1H, H5), 5.24 (bd, J = 8.8 Hz, 1H, NH), 5.38–5.50 (m, 2H, H2 and H3′), 6.23 (bt, J = 9.3 Hz, 1H, H13), 6.42 (s, 1H, H10), 7.20–7.38 (m, 5H, Har); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.9 ($SiCH_3$), −5.4 ($SiCH_3$), 5.2, 6.7 ($Si(CH_2CH_3)_3$), 10.0 (C19), 14.2 (C18), 18.1 ($SiC(CH_3)_3$), 20.9 (10-OAc), 21.4 (C17), 23.0 (4-OAc), 25.1, 25.5, 25.7, 26.5, 28.4, 29.3, 43.3, 43.5 (cyclohexyl, C16 and C15), 25.4 ($SiC(CH_3)_3$) 28.2 ($OC(CH_3)_3$), 34.8, 37.2 (C6 and C14), 46.4 (C3), 56.8 (C3′), 58.3 (C8), 71.3, 72.1 (C7 and C13), 74.3, 74.9, 75.5 (C2′, C2 and C10), 76.5 (C20), 79.0 (C1), 80.8 (C4), 84.3 (C5), 126.4, 127.7, 128.4, 128.5, 139.0 (Car), 133.3 (C11), 140.6 (C12), 152.2 (3′-$NHCO_2C(CH_3)_3$), 169.2, 170.0, 171.5 (4-, 10-OAc and 2-$OCOC_6H_{11}$), 201.8 (C9); HRMS (FAB) m/z calcd for $C_{57}H_{89}LiNO_{15}Si_2$ (M + Li): 1090.5793, found 1090.5739.

7-*O*-(Triethylsilyl)baccatin III 13-*O*-[(2*R*,3*S*)-*N*-Benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-3-cyclohexylisoserinate] (13). Obtained from baccatin III derivative **5** and 2-azetidinone **12**, as an amorphous solid, in 71% yield: $[\alpha]_D$ -25.7° (c = 1.73, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.52–0.64 (m, 6H, $Si(CH_2CH_3)_3$), 0.92 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.98 (s, 9H, $SiC(CH_3)_3$), 1.13 (s, 3H, H17), 1.03–1.32 (m, 5H, cyclohexyl), 1.20 (s, 3H, H16), 1.58–1.96 (m, 7H, cyclohexyl and H6), 1.69 (s, 3H, H19), 2.01 (s, 3H, H18), 2.10–2.20 (m, 1H, H14), 2.15 (s, 3H, 10-OAc), 2.30–2.42 (m, 1H, H14), 2.46–2.56 (m, 1H, H6), 2.48 (s, 3H, 4-OAc), 3.80 (d, J = 6.8 Hz, 1H, H3), 4.21 (d, J = 8.4 Hz, 1H, H20), 4.25–4.36 (m, 2H, H20 and H3′), 4.45 (dd, J = 6.7, 10.4 Hz, 1H, H7), 4.63 (d, J = 1.5 Hz, 1H, H2′), 4.95 (d, J = 8.1 Hz, 1H, H5), 5.70 (d, J = 6.8 Hz, 1H, H2), 6.10 (bt, J = 9.0 Hz, 1H, H13), 6.29 (d, J = 10.0 Hz, 1H, NH), 6.44 (s, 1H, H10), 7.34–7.66 (m, 8H, Har), 8.15 (d, J = 7.1 Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.4 ($SiCH_3$), 5.3 and 6.7 ($Si(CH_2CH_3)_3$), 10.1 (C19), 14.2 (C18), 18.3 ($SiC(CH_3)_3$), 20.8 (10-OAc), 21.5 (C17), 23.1 (4-OAc), 25.8 ($SiC(CH_3)_3$), 26.0, 26.1, 26.2, 26.5, 29.8, 30.3, 39.1 (cyclohexyl and C16), 35.5, 37.2 (C6 and C14), 43.3 (C15), 46.5 (C3), 56.7 (C3′),

58.4 (C8), 71.0, 71.3 (C7 and C13), 72.2 (C2'), 74.9, 75.0 (C2 and C10), 76.6 (C20), 78.6 (C1), 81.1 (C4), 84.2 (C5), 126.7, 128.5, 128.6, 128.7, 129.3, 130.3, 131.4, 134.7 (Car), 133.5 (C11), 140.4 (C12), 166.9 (2-OBz), 167.5 (3'-NHBz), 169.3 (4-OAc), 170.1 (10-OAc), 172.6 (C1'), 201.8 (C9); HRMS (FAB) m/z calcd for $C_{59}H_{86}NO_{14}Si_2$ (M + 1) 1088.5587, found 1088.5594.

General Procedure for Deprotection of 2',7-Di-*O*-silyl Taxanes. The protected intermediate (0.02–0.03 mmol) was dissolved in cold (0 °C) pyridine (0.5 mL) and pyridinium hydrofluoride (0.5 mL) was added dropwise. The reaction mixture was stirred until the reaction was deemed complete by TLC (2–3 h). The excess reagent was decomposed with saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2, and the organic fraction was collected. The organic layer was washed with cold (0 °C) 3 N HCl, dried (Na_2SO_4), filtered, and evaporated. The target taxane was obtained by flash column chromatography (silica; 2:1 hexane–EtOAc) of the crude residue.

10-*O*-Acetyl-2-*O*-(cyclohexylcarbonyl)-2-debenzoyltaxotere (9). Obtained from **8**, as an amorphous solid, in 84% yield: $[\alpha]_D$ −52.8° (c = 0.54, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H, H17), 1.15 (s, 3H, H16), 1.20–2.40 (m, 14H, cyclohexyl, H6 and H14), 1.34 (s, 9H, $OC(CH_3)_3$), 1.55 (s, 3H, H19), 1.72 (s, 3H, H18), 2.16 and 2.17 (2 s, 6H, 4-OAc and 10-OAc), 2.43–2.60 (m, 1H, H6), 3.23 (b, 1H, OH), 3.58 (d, J = 6.7 Hz, 1H, H3), 4.09 (d, J = 8.2 Hz, 1H, H20), 4.29 (dd, J = 7.1, 10.9 Hz, 1H, H7), 4.39 (d, J = 8.2 Hz, 1H, H20), 4.51 (s, 1H, H2'), 4.88 (d, J = 7.7 Hz, 1H, H5), 5.11 (bd, J = 9.2 Hz, 1H, NH), 5.28 (d, J = 9.7 Hz, 1H, H3'), 5.35 (d, J = 6.8 Hz, 1H, H2), 6.09 (bt, J = 9.7 Hz, 1H, H13), 6.17 (s, 1H, H10), 7.22–7.38 (m, 5H, Har); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4 (C19), 14.9 (C18), 20.9 (10-OAc), 21.6 (C17), 22.6 (4-OAc), 25.1, 25.5, 25.6, 26.7, 28.3, 29.3 (cyclohexyl and C16), 28.2 ($OC(CH_3)_3$), 35.8, 35.4 (C6 and C14), 43.0, 43.4 (C15 and cyclohexyl), 45.3 (C3), 56.2 (C3'), 58.5C8, 72.1, 72.4 (C7 and C13), 73.6, 74.1 (C2' and C2), 75.5 (C10), 76.5 (C20), 78.6 (C1), 80.7 (C4), 84.4 (C5), 126.7, 128.1, 128.8, 138.1 (Car), 132.7 (C11), 142.3 (C12), 155.4 ($3'$-$NHCO_2C(CH_3)_3$), 170.2, 171.4 (10- and 4-OAc), 173.0 (2-COC_6H_{11}), 177.2 (C1'), 203.8 (C9); HRMS (FAB) m/z calcd for $C_{45}H_{62}NO_{15}$ (M + 1) 856.4119, found 856.4144.

Baccatin III 13-*O*-[(2*R*,3*S*)-*N*-Benzoyl-3-cyclohexylisoserinate] (14). Obtained from **13**, as an amorphous solid, in 84% yield: $[\alpha]_D$ −28.4° (c = 1.05, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.00–1.60 (m, 4H, cyclohexyl), 1.13 (s, 3H, H17), 1.21 (s, 3H, H16), 1.68 (s, 3H, H19), 1.70–2.04 (m, 8H, H6 and cyclohexyl), 1.84 (s, 3H, H18), 2.14–2.30 (m, 1H, H14), 2.22 (s, 3H, 10-OAc), 2.41 (dd, J = 9.4, 15.6 Hz, 1H, H14), 2.50 (s, 3H, 4-OAc), 2.52–2.63 (m, 1H, H6), 3.72 (b, 1H, OH), 3.79 (d, J = 6.8 Hz, 1H, H3), 4.19–4.34 (m, 3H, H20 × 2 and H3'), 4.41 (dd, J = 6.7, 10.7 Hz, 1H, H7), 4.61 (s, 1H, H2'), 4.97 (d, J = 8.7 Hz, 1H, H5), 5.68 (d, J = 6.8 Hz, 1H, H2), 6.20 (bt, J = 9.0 Hz, 1H, H13), 6.26 (s, 1H, H10), 6.32 (d, J = 9.7 Hz, 1H, NH), 7.32–7.42 (m, 2H, Har), 7.43–7.57 (m, 3H, Har), 7.58–7.70 (m, 3H, Har), 8.16 (d, J = 7.2 Hz, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (C19), 14.8 (C18), 20.9 (10-OAc), 22.1 (C17), 22.8 (4-OAc), 26.0, 26.2, 26.8, 30.1, 30.2, 38.9 (cyclohexyl and C16), 35.6, 35.7 (C6 and C14), 43.2 (C15), 45.5 (C3), 56.9 (C3'), 58.5 (C8), 70.3, 72.1, 72.4 (C2', C13 and C7), 75.0 (C2), 75.6 (C10), 76.5 (C20), 79.1 (C1), 81.0 (C4), 84.5 (C5), 126.9, 128.7, 128.8, 129.2, 130.3, 131.8, 132.9, 133.7, 133.9 (Car and C11), 142.3 (C12), 167.0 (2-OBz), 167.5 (3'-NHBz), 170.4 (4-OAc), 171.3 (10-OAc), 174.5 (C1'), 203.8 (C9); HRMS (FAB) m/z calcd for $C_{47}H_{58}NO_{14}$ (M + 1) 860.3857, found 860.3869.

2-*O*-(Cyclohexylcarbonyl)-2-debenzoyl-7-*O*-(triethylsilyl)baccatin III (6). 7-*O*-(Triethylsilyl)baccatin III (64 mg, 0.09 mmol) and 3% Pt/C (63 mg) were dissolved in EtOAc (10 mL) and shaken under H_2 (30 psi) for 12 h. The Pt/C was removed by filtration through Celite and the solvent evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 1:1 hexane–EtOAc) and gave the title compound in 91% yield (58 mg). The ^1H NMR spectrum was consistent with the previously prepared **6**.[36]

(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-cyclohexyl-2-azetidinone (11). A suspension of 2-azetidinone **10** (30 mg, 0.11 mmol) and 3% Pt/C (20 mg) in EtOAc (4 mL) was shaken under H_2 (55 psi) for 12 h. The Pt/C was removed by filtration through Celite and the solvent evaporated *in vacuo*. The title compound, as fine white needles, was isolated in quantitative yield (31 mg) without further purification: mp 118–119 °C; $[\alpha]_D$ +70.4° (c = 0.6, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.76–1.02 (m, 10H, cyclohexyl and $SiC(CH_3)_3$), 1.08–1.38 (m, 4H, cyclohexyl), 1.54–1.84 (m, 6H, cyclohexyl), 3.29 (dd, J = 4.7, 9.1 Hz, 1H, H4), 4.83 (dd, J = 2.9, 4.7 Hz, 1H, H3), 6.27 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 ($SiCH_3$), −4.5 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 25.4, 25.7, 26.4, 29.2, 29.7 and 37.4 (cyclohexyl), 60.0 (C3), 77.3 (C4), 169.9 (C2); HRMS (FAB) m/z calcd for $C_{15}H_{30}NO_2Si$ (M + 1) 284.2046, found 284.2044.

(3*R*,4*S*)-1-Benzoyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-cyclohexyl-2-azetidinone (12). 4-Cyclohexyl-2-azetidinone **11** (29 mg, 0.1 mmol), Et_3N (0.5 mL), and DMAP (2 mg, 0.16 equiv) were dissolved in cold (0 °C) CH_2Cl_2 (2 mL). Benzoyl chloride (0.02 mL, 1.5 equiv) was added and the mixture stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was washed with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The desiccant was filtered and the solvent evaporated *in vacuo*. Purification was achieved by flash column chromatography (silica, 19:1 hexane–EtOAc). The title compound was isolated in 96% yield (37 mg) as a transparent oil: $[\alpha]_D$ +244.7° (c = 1.65, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.18–1.34 (m, 5H, cyclohexyl), 1.60–2.0 (m, 6H, cyclohexyl), 4.23 (dd, J = 6.5, 6.7 Hz, 1H, H4), 4.92 (d, J = 6.5 Hz, 1H, H3), 7.43–7.50 (m, 2H, Har), 7.54-7.62 (m, 1H, Har), 7.90–7.96 (m, 2H, Har); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4 ($SiCH_3$), −4.6 ($SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 25.9, 26.1, 26.3, 29.5, 30.2, 37.8 (cyclohexyl), 61.2 (C3), 75.0 (C4), 128.0, 130.1, 132.5 and 133.3 (Car), 166.2 and 167.5 (C2 and NHCOPh); HRMS (FAB) m/z calcd for $C_{22}H_{34}NO_3Si$ (M + 1) 388.2308, found 388.2312.

2-*O*-(Cyclohexylcarbonyl)-2-debenzoylbaccatin III 13-*O*-[(2*R*,3*S*)-*N*-(cyclohexylcarbonyl)-3-cyclohexylisoserinate] (15). Taxol (15 mg, 0.017 mmol) and 3% Pt/C (20 mg) were dissolved in EtOAc (3 mL), and the mixture was shaken under H_2 (55 psi) for 24 h. The catalyst was removed by filtration through Celite and the solvent evaporated. The title compound, as an amorphous solid, was isolated in quantitative yield (15 mg) after flash chromatography (silica, 3:2 hexane–EtOAc) of the crude residue: $[\alpha]_D$ −59.7° (c = 0.43, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8–1.54 (m, 16H, cyclohexyl), 1.07 (s, 3H, H17), 1.23 (s, 3H, H16), 1.58–2.10 (m, 23H, H6, H14 and cyclohexyl), 1.63 (s, 3H, H19), 1.83 (s, 3H, H18), 2.16–2.38 (m, 3H, H14 and cyclohexyl), 2.23 (s, 3H, 10-OAc), 2.33 (s, 3H, 4-OAc), 2.50–2.60 (m, 1H, H6), 3.39 (b, 1H, OH), 3.63 (d, J = 6.8 Hz, 1H, H3), 3.99 (bt, J = 9.7 Hz, 1H, H3'), 4.17 (d, J = 7.8 Hz, 1H, H20), 4.37 (dd, J = 6.7, 10.7 Hz, 1H, H7), 4.42–4.48 (m, 2H, H20 and H2'), 4.97 (d, J = 7.8 Hz, 1H, H5), 5.44 (d, J = 7.2 Hz, 1H, H2), 5.57 (d, J = 9.7 Hz, 1H, NH), 6.09 (bt, J = 9.0 Hz, 1H, H13), 6.24 (s, 1H, H10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5 (C19), 14.8 (C18), 20.9 (10-OAc), 22.0 (C17), 22.7 (4-OAc), 25.1, 25.5, 25.6, 25.9, 26.1, 26.7, 28.4, 29.4, 29.8, 29.9, 30.0 (C16 and cyclohexyl), 35.1, 35.5 (C6 and C14), 43.2, 43.4, 45.3, 45.5 (C3, C15, and cyclohexyl), 55.7 (C3'), 58.5 (C8), 70.0, 72.1, 72.6 (C2', C7 and C13), 74.3 (C2), 75.6 (C10), 76.6 (C20), 79.0 (C1), 80.7 (C4), 84.5 (C5), 132.8 (C11), 142.4 (C12), 170.2 (2-$OCOC_6H_{11}$), 171.3 ($3'$-$NHCOC_6H_{11}$), 174.7 (4-OAc), 176.1 (10-OAc), 177.2 (C1'), 203.8 (C9); HRMS (FAB) m/z calcd for $C_{47}H_{70}NO_{14}$ (M + 1) 872.4796, found 872.4793.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for **8**, **9**, **11**, **12**, **13**, **14**, and **15** as well as NOESY

and expanded COSY spectra for **9** and **14** are provided (19 pages). Ordering information is given on any current masthead page.

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