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Silicate Esters of Paclitaxel and Docetaxel: Synthesis, Hydrophobicity, Hydrolytic Stability, Cytotoxicity, and Prodrug Potential

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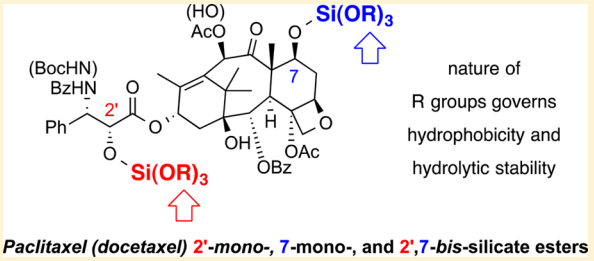
Supporting Information

ABSTRACT: We report here the synthesis and selected properties of various silicate ester derivatives (tetraalkoxysilanes) of the taxanes paclitaxel (PTX) and docetaxel (DTX) [i.e., PTX-OSi(OR)$_3$ and DTX-OSi(OR)$_3$]. Both the hydrophobicity and hydrolytic lability of these silicates can be (independently) controlled by choice of the alkyl group (R). The synthesis, structural characterization, hydrolytic reactivity, and in vitro cytotoxicity against the MDA-MB-231 breast cancer cell line of most of these derivatives are described. We envision that the greater hydrophobicity of these silicates (vis-à-vis PTX or DTX itself) should be advantageous from the perspective of preparation of stable aqueous dispersions of amphiphilic block-copolymer-based nanoparticle formulations.



Paclitaxel (docetaxel) **2'-*mono*-, 7-mono-, and 2',7-*bis*-silicate esters**

INTRODUCTION

Paclitaxel (PTX) is a potent antimitotic antitumor compound. It is the active agent in front-line chemotherapeutic drugs used for treatment of a variety of cancers.[1,2] Because it is only minimally water-soluble, PTX is administered to humans as a drug formulation that is formed by its solubilization with an emulsifier [a 1:1 (v/v) mixture of polyethoxylated castor oil and absolute ethanol], with human serum albumin, or with PEG-PLA. These formulations comprise a significant advance in chemotherapeutics, but the drug loading is relatively low (1.1, 10, and 16.7 wt % PTX, respectively). In the case of the first, significant undesirable side effects of the emulsifier are experienced by some patients. Similarly, the closely related taxane docetaxel (DTX) is administered as an ethanolic suspension of 4% wt/vol DTX in polysorbate 80.

Because these taxanes are such effective cytotoxins, new conceptual and practical strategies for improving the administration of PTX and DTX remain desirable. In particular, drug delivery vehicles containing higher drug loading levels than currently in the front-line drug formulations mentioned above have the potential to be quite advantageous. Accordingly, we envision that proper matching of the physicochemical properties of a taxane derivative with a suitable polymer-based drug carrier might allow for formulation of an effective nanoparticle drug delivery entity. One potentially attractive strategy is the incorporation of drugs into block copolymer (BCP) based nanoparticles (NPs) by rapid co-precipitation of the drug and the BCP in a process known as flash nanoprecipitation (FNP).[3,4] This can provide NPs with dimensions attractive from a drug delivery perspective and that are highly loaded (to ≥50 wt %) with the small molecule drug agent. FNP has been used to prepare NPs comprising PTX and various BCPs, in particular, the biocompatible poly(ethylene glycol)-*b*-poly(ester) amphiphilic block polymer PEG-PCL, PEG-PLA, or PEG-PLGA [where the poly(ester) is poly(caprolactone), poly(lactic acid), or poly(lactic/glycolic acid), respectively].[5,6] However, the resulting aqueous dispersions of these PTX-loaded NPs were kinetically unstable; the PTX exited the hydrophobic core of the particle and crystallized in the exterior in a matter of minutes, presumably via the mechanism of Ostwald ripening.[7,8] We envision that this undesirable process could be arrested by use of a modified taxane derivative that is *more* hydrophobic than the parent drug molecule. Moreover, if that derivative is susceptible to reversion back to the parent taxane, say by simple hydrolysis, then it could serve as a taxane prodrug.

We hypothesized that silicate esters, tetraalkoxysilanes [(RO)$_4$Si], comprise a class of derivatives that meet these requirements. The concept is portrayed in Figure 1. A parent

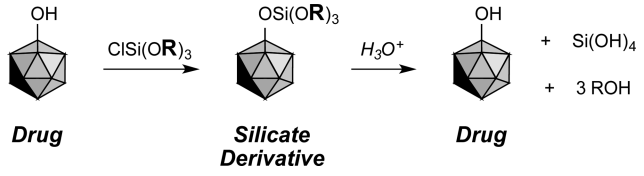


Figure 1. Potential silicate prodrug strategy. Modification of a hydroxyl group in the drug with a trialkoxychlorosilane generates the (labile) silicate derivative, which following administration undergoes hydrolysis to return the free drug along with benign alcohol and orthosilicic acid byproducts.

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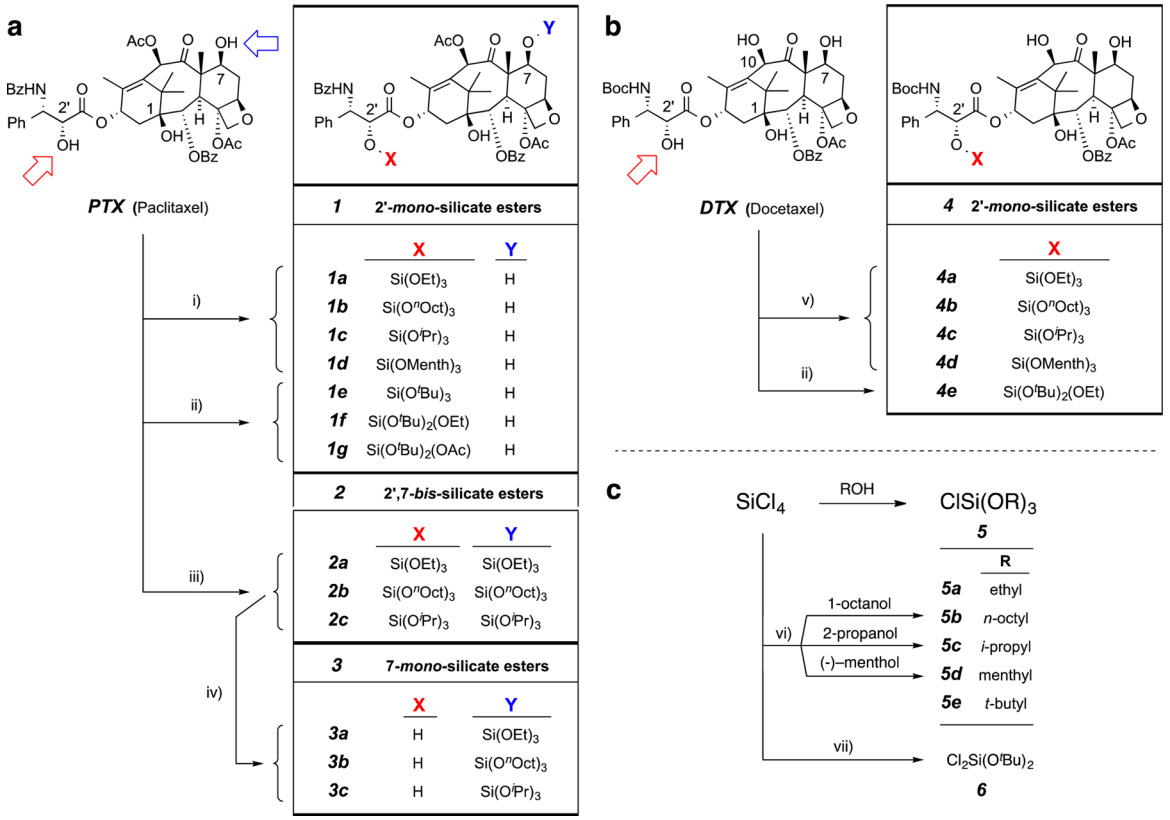
Scheme 1. Synthesis of Silicate Ester Derivatives of (a) PTX (1a–g, 2a–c, and 3a,b) and (b) DTX (4a–e) and of (c) the Necessary Chlorosilane Derivatizing Agents (5 and 6)[a]



[a]Conditions: (i) $SiCl(OR)_3$ (**5a–d**), NEt_3 (for **1a–c**) or py (for **1d**), THF; (ii) $SiCl_2(O^tBu)_2$ (**6**), py, THF; then EtOH (for **1f** or **4e**) or AcOH (for **1g**); (iii) $SiCl(OR)_3$ (**5a–c**), py, THF; (iv) acetone, water, TFA (90/9/1, v/v/v); (v) $SiCl(OR)_3$ (**5a–d**), *n*-$BuNMe_2$ (for **4a–c**) or py (for **4d**), THF; (vi) alcohol, rt, pentane; (vii) *t*-BuOH (2.1 equiv), py, THF. Yields of chromatographed taxane silicates: **1a** (91%); **1b** (81%); **1c** (65%); **1d** (62%); **1e** (18%); **1f** (84%); **1g** (66%); **2a** (85%); **2b** (77%); **2c** (67%); **3a** (91%, brsm); **3b** (66%, brsm); **3c** (77%, brsm); **4a** (65%); **4b** (64%); **4c** (85%); **4d** (44%); **4e** (60%). brsm = based on recovered starting material.

drug molecule containing a reactive hydroxyl group is converted to its tetraalkoxysilane (the silicate derivative) by reaction with a trialkoxychlorosilane[9] derivatizing agent.[10] Eventual hydrolytic cleavage returns the parent drug. Note that a number of studies imply that orthosilicic acid [$Si(OH)_4$], the ultimate stoichiometric byproduct of silicate ester cleavage, does not pose any significant toxicity issues.[11−13] The nature of the three auxiliary R groups in the silicate prodrug (Figure 1) would provide considerable flexibility in allowing for adjustment of the degree of hydrophobicity as well as the hydrolytic stability of the derivative. DeSimone and co-workers recently described a construct that capitalized on the second of these features: alteration of steric hindrance at silicon to impact hydrolysis and drug release.[14] They used nanoparticles derived from nanoparticle-bound dialkoxydialkylsilanes (or silaketals) having the formulation of polyacrylate−$OSi(R_2)O$−drug (where drug is camptothecin, dasatinib, or gemcitabine) and demonstrated that the steric bulk of the alkyl groups (R = ethyl, isopropyl, or *tert*-butyl) altered the hydrolysis rate, thereby allowing for controlled release rates of the drug from its carrier.

Numerous prodrugs and derivatives of PTX and DTX have been explored, in part with an eye toward identification of a bioactive agent that might no longer require the use of any formulation agent.[15] The vast majority of these efforts have centered on increasing the hydro*philicity* of the parent taxane with the intent of improving its solubility parameter (e.g., phosphates,[16,17] amino acid conjugates,[18] succinates,[19] and sugar conjugates[20]). In contrast, the use of PTX prodrugs that are *more hydrophobic* than PTX itself (e.g., cholesteryl carbonate,[21] phospholipid,[22] or fatty acid ester[23−25] derivatives) has been explored somewhat. The motivating hypothesis was that these derivatives could be more efficiently loaded into the hydrophobic regions of the various nanocarrier encapsulating vehicles that are water dispersible.[26,27] Notably, a PTX docosahexaenoate (DHA) ester conjugate[28] has been studied in a phase III clinical trial.[29]

We report here on the chemistry and initial in vitro cytotoxicity properties of a series of taxane silicate derivatives. In particular, the synthesis, hydrolysis rates, and IC_{50} values of a family of hydrophobic PTX- and DTX-silicate esters [taxane-$Si(OR)_3$] bearing various R groups differing in their degree of hydrophobicity and steric bulk (cf. **1**−**3** and **4**, respectively) are described. These constitute a set of promising agents for loading into nanoparticle formulations[30] potentially useful in drug delivery studies.

RESULTS AND DISCUSSION

To achieve taxane silicate ester synthesis, we took advantage of the known differences in reactivity of the free hydroxyl groups in PTX or DTX (Scheme 1). For example, the relative rates of derivatization of the three hydroxyl groups in PTX is C2′ > C7 > C1,[15,31] which principally reflects the relative steric hindrance

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Table 1. Hydrophobicity Indicators for the Silicate Esters 1−4

substrate	2′ alkyl	7 alkyl	retention time t_R (min),[a] C18 (ODS)	calcd octanol/water partition coefficient (cLogP)[b]	calcd aqueous solubility (cLogS [36] converted to mg/L)
PTX			10.5	3.20	5.56
1a	Et	na[c]	13.8	4.96	2.66
1b	*n*-Oct	na	22.1	7.74	0.24
1c	*i*-Pr	na	15.4	5.60	1.57
1d	menthyl	na	24.5	7.37	0.25
1f	$(t\text{-Bu})_2$/Et	na	16.1	5.81	0.94
PTX-$SiEt_3$			15.4	5.40	1.06
2a	Et	Et	16.6	6.31	1.70
2b	*n*-Oct	*n*-Oct	*d*	8.59	0.13
2c	*i*-Pr	*i*-Pr	18.9	6.84	0.87
3a	na	Et	14.6	5.05	2.33
3b	na	*n*-Oct	24.6	7.84	0.22
3c	na	*i*-Pr	16.4	5.64	1.44
DTX			10.9	2.83	12.72
4a	Et	na	14.1	4.05	6.84
4b	*n*-Oct	na	22.4	7.34	0.32
4c	*i*-Pr	na	15.9	4.99	3.78
4d	menthyl	na	26.1	7.02	0.29
4e	$(t\text{-Bu})_2$/Et	na	16.4	5.29	2.58

[a]Each retention time was determined by gradient elution from LC/MS on an (octadecyl)silyl (ODS, C18) column [5 μm, 4.6 (i.d.) × 150 mm] using a flow rate of 1 mL/min. Gradient elution was 56/44% methanol/water to 98/2% methanol/water (15 mM NH_4OAc) over 15 min followed by an appropriate final hold time. [b]aLogP [37] data shown here; see Supporting Information (Table S1) for the values from these additional empirical predictors of cLogP: AC logP, KOWWIN, miLogP, XLOGP3; the trends among the values from any of these methods are very similar for all of the predictors. [c]na: not applicable. [d]Not observed; elution time of >60 min.

Table 2. Relative Rates of Hydrolysis[a] of the PTX (1−3) or DTX (4) Silicates[b]

	at C2′				at C7			
silicate	2′-silicate alkyl	$t_{1/2}$ (min)	k_{obs} (10^{-6} s^{-1})	~k_{rel}	7-silicate alkyl	$t_{1/2}$ (min)	k_{obs} (10^{-6} s^{-1})	~k_{rel}
1a	Et	3.7	3100 ± 900	18000	na			
1b	*n*-Oct	12	960 ± 40	5600	na			
1c	*i*-Pr	120	97 ± 6	570	na			
1d[c]	menthyl	69000	0.17 ± 0.002	1.0	na			
1f[c]	$(t\text{-Bu})_2$/Et	12000	0.96 ± 0.1	5.6	na			
1g[c]	$(t\text{-Bu})_2$/Ac[d]	35	330 ± 20	1900	na			
2a	Et	4.6	2500 ± 100	15000	Et	33	350 ± 20	2100
2b	*n*-Oct	18	640 ± 10	3800	*n*-Oct	200	58 ± 4	340
2c	*i*-Pr	130	89 ± 5	520	*i*-Pr	1500	7.8 ± 2	46
3a	na[e]				Et	30	380 ± 10	2200
3b	na				*n*-Oct	150	77 ± 5	450
3c	na				*i*-Pr	1700	6.7 ± 2	39
4a	Et	11	1100 ± 100	6500	na			
4b	*n*-Oct	26	440 ± 40	2600	na			
4c	*i*-Pr	260	45 ± 5	260	na			
4d[c]	menthyl	78900	0.15 ± 0.02	0.88	na			
4e[c]	$(t\text{-Bu})_2$/Et	13600	0.85 ± 0.09	5.0	na			

[a]Each silicate in a solution of acetone-d_6/D_2O/CF_3CO_2H (volume ratio of 90:9:1) at a concentration of ~0.01 M was kept at ~22 °C and the reaction progress monitored periodically and continuously by ^1H NMR spectroscopy. [b]The k_{rel} values are benchmarked relative to that of the PTX-trimenthyloxy derivative **1d**, the PTX-silicate having the slowest observed rate of hydrolysis. [c]NMR analysis suggested the presence of steady-state levels (typically ≤10%) of intermediate, partially cleaved silicates [i.e., $(RO)_{4-n}Si(OH)_n$, where n = 1−3], which underwent further clean conversion of the fully hydrolyzed alcohols, including the taxane. [d]Acetyl (CH_3CO), which is part of an acetoxy substituent on the silicate oxygen atom. [e]na: not applicable.

among the three. Similarly, the C2′ hydroxyl group in DTX is the most reactive. Selective monosilylation at C2′ in PTX to give **1a−c** was best achieved when triethylamine was used as the base to promote reaction with the appropriate chlorosilane reagent (**5a−c**). The preparation of the requisite chlorosilanes **5b**,[32] **5c**,[33] **5d**,[34] and **6**[35] is indicated in Scheme 1 (panel c); **5a** and **5e** are commercially available. Use of the hindered tertiary alkylamine rather than pyridine showed greater selectivity for C2′-monosilicate ester production with minimal formation of the C2′,C7-bis-silicate esters. In the case of the hindered trimenthyloxychlorosilane reagent (**1d**), the second silylation at C7 was very slow. Accordingly, we experienced little difficulty in using the less selective catalyst pyridine for the preparation of trimenthyl silicate derivatives. The mixed, *tert*-butoxy-contain-

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ing silicates **1f–h** were prepared using an excess of the bulky electrophile $(t\text{-BuO})_2SiCl_2$ (**6**) and pyridine as the base. As with the menthyl-containing reagent **1d**, we again did not observe competitive reaction at C7. Addition of an excess of ethanol (for **1f**) or acetic acid (for **1g**) to substitute the second chloride (as well as consume the excess **6** still present) allowed isolation of the mixed silicates **1f,g**, respectively, albeit in overall modest to low yields. On one occasion a small amount of the tri(*tert*)butyl silicate **1e** was isolated from an experiment using an in situ generated (and less pristine) lot of the chlorosilane reagent **6**. Attempts to prepare **1e** using a commercial sample of $(t\text{-BuO})_3SiCl$ (**5e**) and pyridine, even at elevated temperatures, gave no evidence of reaction. We presume that **1e** was produced by way of the intermediate PTX-Si(O-*t*-Bu)$_2$Cl followed by subsequent reaction with *t*-BuOH.

The PTX C2′,C7-bis-silicate esters **2a–c** were best prepared using the less hindered pyridine as the base and a larger excess (3–4 equiv) of the $(RO)_3SiCl$ **5a–c**. The C7-monosilicate **3a–c** derivatives of PTX were accessed by selective hydrolytic cleavage [trifluoroacetic acid (TFA), H_2O, acetone] of the more labile C2′-silicate ester present in the bis-derivatives **2a–c**, respectively.

Similarly, the DTX 2′-monosilicate esters **4a–e** (Scheme 1, panel b) were prepared. In these experiments we chose to use a different tertiary amine, *N*,*N*-dimethyl-1-butanamine, and as we conjectured, it showed comparably good C2′ vs C7 selectivity as triethylamine but a faster reaction rate under otherwise identical conditions.

The relative hydrophobicities of the silicate esters were assessed in several ways. Qualitatively, we observed the expected trend that the silicates with greasier alkyl groups traveled faster on silica gel during thin layer and preparative chromatographic experiments. A more quantitative measure of this same trend was observed from measurement of the retention times on a reversed-phase HPLC column (Table 1, column 4). In addition, two empirical indicators of hydrophobicity show similar trends: (i) calculated octanol/water partition coefficients (cLogP values, Table 1, column 5) and (ii) calculated aqueous solubilities (Table 1, column 6).

We anticipated that these silicates would also differ in their hydrolytic lability given the differences in steric bulk at the silicon atom of the silicate esters across the series. We explored this question by devising a ^{1}H NMR spectroscopy based method[38] to establish the relative rates of chemical hydrolysis of the derivatives (Table 2). By design, these silicate esters were sufficiently highly hydrophobic to render them only marginally soluble in buffered aqueous solutions. To get meaningful fundamental understanding of the hydrolytic lability under acidic conditions, we deemed it essential to identify a common set of conditions under which each of the silicates would be fully soluble; that is, homogeneity is paramount. We determined that a 10:1 (v/v) ratio of acetone/water would solubilize all of these silicates at concentrations suitable for NMR analysis. We then established that use of 1% TFA in this solvent mixture (measured pH of 1.2) at ambient temperature led to rates of silicate ester cleavage that could be conveniently monitored spectroscopically. The change in intensity over time of the chemical shifts of H2′, H3′, H7 and/or the OC*H* resonances in the R groups as the silicates were cleaved to release PTX and ROH was monitored. For all silicates not containing a menthyloxy or *tert*-butoxy moiety (Table 2, footnote [c]), we saw no evidence for partially hydrolyzed silanol intermediates [i.e., $(RO)_nSi(OH)_{4-n}$]. This suggests that the initial hydrolysis event (i.e., cleavage of the first Si–OR bond) is the rate-limiting step and that the initially formed monohydroxysilane then degrades, sequentially but faster, to release all of its alcohol moieties, including the free drug.

The relative rates of hydrolysis (k_{rel}) of **1–4**, normalized to the least reactive silicate, the PTX-menthyloxysilicate **1d**, are shown in Table 2. As anticipated, increase in steric bulk of the silicate near the silicon center slows its hydrolysis rate. The k_{rel} values differ by >2000 between the extremes of the triethyl PTX-silicate **1a** vs the hindered trimenthyl silicate ester **1d**. The hydrolysis rates for the triethyl vs trioctyl silicates **1a** vs **1b** (for PTX) or **4a** vs **4b** were similar (difference in k_{rel} of ∼3), which shows that the hydrophobicity of the silicate can be significantly altered with only a small accompanying change in the relative hydrolysis rate. PTX-silicates at the more hindered C7-position hydrolyzed approximately 7–15 times more slowly than those at C2′. Moreover, (i) the rate difference for cleavage of silicates at these two sites increased slightly as the bulk of the alkyl groups increased in the series of ethyl to *n*-octyl to isopropyl and (ii) the trends were the same whether comparing the differences at C7 vs C2′ for both the monosilicates (**1a** vs **3a**, **1b** vs **3b**, and **1c** vs **3c**) and those same sites within each of the bis-silicates **2a–c**.

Cytotoxicity of the PTX-silicates **1–3** and DTX-silicates **4** was examined against MDA-MB-231 cells (Table 3). We used this as a model cell line representing triple negative breast cancer, a malignancy for which taxanes are used as front-line agents. Silicates having faster rates of hydrolysis (Table 2) tend to show cytotoxicities similar to those of the parent taxane. This suggests that the silicate esters are hydrolyzed back to PTX or DTX either in the culture medium or inside the cell during the course of the assay.

Table 3. Cytotoxicity (IC_{50}) of PTX, PTX-silicates (1–3), DTX, and DTX-silicates (4) in MDA-MB-231 Cells[a]

PTX compd	IC_{50} (nM)[b]	DTX compd	IC_{50} (nM)[b]
PTX	5.6	DTX	1.0
1a	8.3	**4a**	2.5
1b	7.0	**4b**	9.7
1c	4.2	**4c**	0.2
1d	590	**4d**	720
1f	260	**4e**	430
2a	12		
2b	280		
2c	1600		
3a	18		
3b	290		
3c	260		
PTX-2′-$SiEt_3$ [39]	220		

[a]Cell viability was measured after 72 h. [b]The reported data are the median values for the distribution of IC_{50} values falling within the 95% confidence interval.

CONCLUSIONS

A new class of potential prodrug (silicate esters) is reported. The strategy provides the ability to control both the hydrophobicity and the hydrolysis rate of these drug derivatives. Each of these features provides a mechanism through which drug encapsulation and release properties into and from nanoparticles can likely be tuned. We have determined relative rates of hydrolysis of these silicates via

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^{1}H NMR spectroscopic analysis. Cytotoxicity studies were performed against the MDA-MB-231 cell line. Silicates **1a**−**c**, **2a**, **3a**, and **4a**−**c** all showed IC_{50} values similar to that of their parent taxane, suggesting hydrolysis in the culture medium and/or inside the cell. The IC_{50} values spanned a range of ~10^3 for each of the PTX and DTX family of taxanes. Certain of these silicates are being further evaluated here for their ability to form small, stable, block-copolymer-based nanoparticles as potential drug-delivery constructs.

EXPERIMENTAL SECTION

Chemistry. General Methods. Triethylamine and pyridine were purified by distillation over CaH_2. *N*,*N*-Dimethyl-1-butanamine was stored over 3 Å molecular sieves. The known tri-*n*-octyloxychlorosilane,[32] triisopropoxychlorosilane,[33] trimenthyloxychlorosilane,[34] and di-*tert*-butoxydichlorosilane[35] were synthesized from silicon tetrachloride and *n*-octanol, isopropanol, (−)-menthol, and *tert*-butanol (the liquids, each dried over activated 3 Å molecular sieves overnight), respectively. Tetrahydrofuran was dried by being passed through an activated alumina column. Ethanol (anhydrous) was further dried by storing overnight over activated 3 Å molecular sieves. Ethyl acetate (EtOAc, ACS grade) and hexanes (ACS grade) were used as received. The acetone-d_6 and chloroform-*d* were dried over activated 3 Å molecular sieves overnight. D_2O was used as received.

All thin layer chromatography (TLC) data were collected on glass- or plastic-backed plates coated with F-254 indicator. Visualization was done by UV light and/or staining with phosphomolybdic acid (PMA). Medium pressure liquid chromatography (MPLC) purifications were performed using columns dry-packed with approximately 25−35 μm silica gel. The MPLC apparatus was pressurized with a dual piston HPLC pump. Compound detection was performed by using a UV absorbance detector at 254 nm and a differential refractometer in series. Each silicate ester was purified by MPLC, under conditions that achieved effective separation of starting taxane, monosilicate, and bis-silicate esters, shortly before being used in the cytotoxicity study. Each compound whose cytotoxicity is reported in Table 3 was purified in this fashion, at which point it was shown to be of >95% purity by HPLC analysis in a C18- or C8-reversed phase column.

^{1}H NMR spectra were taken on a 500 MHz (^{1}H) instrument. All ^{1}H characterization spectra were taken in $CDCl_3$, and chemical shifts (δ) are referenced to tetramethylsilane at δ = 0.00. All ^{13}C NMR characterization spectra were taken in $CDCl_3$ on either a 125 MHz (^{13}C) or a 75 MHz (^{13}C) instrument and referenced to $CHCl_3$ at δ = 77.23. The following abbreviations are used to describe the NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), br (broad), and app (apparent). Coupling constants (*J*) are reported in Hz. High resolution mass spectra were collected on an ESI-TOF instrument using poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG) as an internal standard. Infrared spectra were recorded using an FT-IR instrument. All samples were collected in attenuated total reflectance (ATR) mode as thin films on a germanium window. Melting point data were collected on a hot stage and are uncorrected.

2′-*O*-[(Triethoxy)silyl]paclitaxel (1a). Paclitaxel (55.3 mg, 0.0648 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Triethylamine (20 μL, 0.130 mmol, 2.0 equiv) was added by Wiretrol. Triethoxychlorosilane (**5a**) (25 μL, 0.0127 mmol, 2.0 equiv) was then added, and a white precipitate was immediately observed. The culture tube was sealed, and the suspension was allowed to stir for 1 h at room temperature. The reaction slurry was diluted with a mixture of hexanes/EtOAc (1:1) and filtered through a short plug of Celite to remove the triethylammonium salt. The filtrate was concentrated under reduced pressure, and the residue was redissolved in a mixture of hexanes/EtOAc (1:1). Chromatography (SiO_2, 1:1 hexanes/EtOAc) via MPLC yielded the title compound as a white, crystalline solid (59.6 mg, 0.0587 mmol, 90.6%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.5, 1.4 Hz, 2H, $C2O_2C$-*o*-Ph), 7.78 (dd, *J* = 8.5, 1.3 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, *J* = 7.5, 1.2 Hz, 1H, $C2O_2C$-*p*-Ph), 7.56−7.46 (m, 3H, $C2O_2C$-*m*-Ph and C3′NHCO-*p*-Ph), 7.43−7.36 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.29 (tt, *J* = 6.5, 2.2 Hz, 1H, C3′-*p*-Ph), 7.19 (d, *J* = 8.6 Hz, 1H, C3′NH), 6.28 (s, 1H, H10), 6.24 (br dd, *J* = 9, 9 Hz, 1H, H13), 5.72 (dd, *J* = 8.5, 3.2 Hz, 1H, H3′), 5.68 (d, *J* = 7.1 Hz, 1H, H2), 4.97 (dd, *J* = 9.4, 2.0 Hz, 1H, H5), 4.96 (d, *J* = 3.3 Hz, 1H, H2′), 4.43 (ddd, *J* = 10.9, 6.4, 4.5 Hz, 1H, H7), 4.32 (d, *J* = 8.5 Hz, 1H, H20α), 4.20 (d, *J* = 8.5 Hz, 1H, H20β), 3.80 (d, *J* = 7.2 Hz, 1H, H3), 3.71 [q, *J* = 7.0 Hz, 6H, C2′OSi(OCH_2CH_3)$_3$], 2.56 (ddd, *J* = 14.7, 9.6, 6.5 Hz, 1H, H6α), 2.45 (s, 3H, C4OAc), 2.44 (br s, 1H, C7OH), 2.32 (dd, *J* = 15.4, 9.4, Hz, 1H, H14α), 2.24 (s, 3H, C10OAc), 2.08 (dd, *J* = 15.2, 8.8 Hz, 1H, H14β), 1.90 (d, *J* = 1.2 Hz, 3H, $C18H_3$), 1.89 (ddd, *J* = 14.5, 11.0, 2.4 Hz, 1H, H6β), 1.68 (s, 3H, $C19H_3$), 1.64 (br s, 1H, C1OH), 1.24 (s, 3H, $C17H_3$), 1.15 [t, *J* = 7.0 Hz, 9H, C2′OSi(OCH_2CH_3)$_3$], and 1.13 (s, 3H, $C16H_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 171.6, 171.0, 170.1, 167.3, 167.2, 143.0, 138.2, 134.2, 133.9, 132.9, 132.0, 130.4, 129.3, 128.9 (×2), 128.8, 128.2, 127.3, 126.8, 84.6, 81.2, 79.3, 76.7, 75.8, 75.3, 75.1, 72.3, 71.5, 59.7, 58.7, 55.6, 45.7, 43.4, 35.7, 35.6, 27.0, 23.0, 22.4, 21.1, 18.2, 14.9, and 9.8. HRMS (ESI) calcd for $C_{53}H_{65}NNaO_{17}Si$ $[M + Na]^+$ 1038.3914, found 1038.3942. IR (thin film) 3500 (br), 2977, 2898, 1744, 1730, 1636, 1580, 1540, 1487, 1452, 1371, 1314, 1268, 1240, 1170, 1145, 1078, 1025, 978, 908, 854, 797, and 710 cm^{-1}. Mp = 131−134 °C. TLC R_f (1:1 hexanes/EtOAc) = 0.45.

2′-*O*-[(Tri-*n*-octyloxy)silyl]paclitaxel (1b). Paclitaxel (76.0 mg, 0.0890 mmol, 1.0 equiv) was dissolved in dry THF (1.5 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Triethylamine (60 μL, 0.430 mmol, 4.8 equiv) was added by Wiretrol. A 1.67:1 mixture of tri-*n*-octyloxychlorosilane (**5b**)[32]/tetra-*n*-octyloxysilane (0.200 mg, 0.257 mmol, 2.9 equiv of tri-*n*-octyloxychlorosilane) was added, and a white precipitate was immediately observed. The culture tube was capped, and the suspension was allowed to stir for 22 h at room temperature. The reaction slurry was diluted with a mixture of hexanes/EtOAc (1:1), the slurry filtered through a short plug of Celite to remove the triethylammonium salt, the filtrate concentrated under reduced pressure, and the residue redissolved in a mixture of hexanes/EtOAc (2:1). Chromatography (SiO_2, 2:1 hexanes/EtOAc) via MPLC yielded the title compound as a white, crystalline solid (91.5 mg, 0.0721 mmol, 81.0%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.5, 1.5 Hz, 2H, $C2O_2C$-*o*-Ph), 7.77 (dd, *J* = 8.5, 1.4 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, *J* = 7.4, 1.3 Hz, 1H, $C2O_2C$-*p*-Ph), 7.55−7.46 (m, 3H, $C2O_2C$-*m*-Ph and C3′NHCO-*p*-Ph), 7.43−7.35 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.28 (tt, *J* = 6.9, 1.7 Hz, 1H, C3′-*p*-Ph), 7.19 (d, *J* = 8.6 Hz, 1H, C3′NH), 6.28 (s, 1H, H10), 6.25 (br dd, *J* = 9, 9 Hz, 1H, H13), 5.72 (dd, *J* = 8.6, 3.2 Hz, 1H, H3′), 5.68 (d, *J* = 7.1 Hz, 1H, H2), 4.97 (dd, *J* = 9.8, 2.1 Hz, 1H, H5), 4.96 (d, *J* = 3.2 Hz, 1H, H2′), 4.44 (ddd, *J* = 10.9, 6.7, 4.2 Hz, 1H, H7), 4.31 (d, *J* = 8.4 Hz, 1H, H20α), 4.20 (d, *J* = 8.3 Hz, 1H, H20β), 3.80 (d, *J* = 7.1 Hz, 1H, H3), 3.61 {t, *J* = 6.8 Hz, 6H, C2′OSi[$OCH_2(CH_2)_6CH_3$]$_3$}, 2.56 (ddd, *J* = 14.8, 9.6, 6.6 Hz, 1H, H6α), 2.47 (d, *J* = 4.1 Hz, 1H, C7OH), 2.44 (s, 3H, C4OAc), 2.32 (dd, *J* = 15.4, 9.4 Hz, 1H, H14α), 2.24 (s, 3H, C10OAc), 2.07 (dd, *J* = 15.4, 8.8 Hz, 1H, H14β), 1.89 (d, *J* = 1.4 Hz, 3H, $C18H_3$), 1.89 (m, 1H, H6β), 1.68 (s, 3H, $C19H_3$), 1.65 (br s, 1H, C1OH), 1.48 [tt, *J* = 6.9, 6.9 Hz, 6H, C2′OSi($OCH_2CH_2(CH_2)_5CH_3$)$_3$], 1.32−1.22 {m, 33H, C2′OSi[$OCH_2CH_2(CH_2)_5CH_3$]$_3$ and $C17H_3$}, 1.13 (s, 3H, $C16H_3$), and 0.88 {t, *J* = 6.9 Hz, 9H, C2′OSi-[$OCH_2CH_2(CH_2)_5CH_3$]$_3$}. ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 171.5, 170.9, 170.1, 167.2, 167.2, 143.0, 138.3, 134.3, 133.9, 132.9, 132.0, 130.4, 129.3, 128.9 (x2), 128.8, 128.1, 127.3, 126.8, 84.7, 81.2, 79.3, 76.6, 75.8, 75.3, 74.9, 72.4, 71.4, 64.1, 58.7, 55.5, 45.7, 43.4, 35.8, 35.7, 32.4, 32.0, 29.54, 29.52, 27.0, 25.8, 23.0, 22.9, 22.4, 21.1, 14.9, 14.3, and 9.8. HRMS (ESI) calcd for $C_{71}H_{101}NNaO_{17}Si$ $[M + Na]^+$ 1290.6731; found 1290.6749. IR (thin film) 2926, 2855, 1730, 1665, 1643, 1602, 1581, 1518, 1484, 1453, 1371, 1312, 1271, 1240, 1174, 1094, 1025, 985, 926, 907, 851, 801, 777, and 711 cm^{-1}. Mp = 60−63 °C. TLC R_f (3:1 hexanes/EtOAc) = 0.15.

2′-*O*-[(Triisopropoxy)silyl]paclitaxel (1c). Paclitaxel (38.8 mg, 0.0454 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an

oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Triethylamine (25 μL, 0.179 mmol, 3.9 equiv) was added by Wiretrol. A 2.9:1 mixture of triisopropoxychlorosilane (**5c**)[33]/tetraisopropoxysilane (0.155 mg, 0.132 mmol, 2.9 equiv of triisopropoxychlorosilane) was added. The culture tube was capped, and a white precipitate was observed within minutes. The suspension was stirred at room temperature for 48 h, and the cloudy, heterogeneous reaction mixture was noted to be slightly yellowed. The suspension was diluted with a mixture of hexanes/EtOAc (1:1), the slurry filtered through a short plug of Celite to remove the triethylammonium salt, the filtrate concentrated under reduced pressure, and the residue redissolved in a mixture of hexanes/EtOAc (1:1). Chromatography (SiO_2, 1:1 hexanes/ethyl acetate) via MPLC yielded the title compound as a white, crystalline solid (31.1 mg, 0.0294 mmol, 64.7%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.5, 1.4 Hz, 2H, C2O_2C-*o*-Ph), 7.79 (dd, J = 8.4, 1.3 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, J = 7.6, 1.3 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.55−7.47 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.44−7.35 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.27 (tt, J = 7.0, 1.7 Hz, 1H, C3′-*p*-Ph), 7.17 (d, J = 8.5 Hz, 1H, C3′NH), 6.28 (s, 1H, H10), 6.19 (br dd, J = 9, 9 Hz, 1H, H13), 5.69 (dd, J = 8.5, 3.6 Hz, 1H, H3′), 5.68 (d, J = 6.7 Hz, 1H, H2), 4.98 (d, J = 3.6 Hz, 1H, H2′), 4.96 (dd, J = 9.7, 2.4 Hz, 1H, H5), 4.44 (ddd, J = 10.9, 6.6, 4.1 Hz, 1H, H7), 4.31 (d, J = 8.4 Hz, 1H, H20α), 4.20 (d, J = 8.4 Hz, 1H, H20β), 4.13 {sept, J = 6.1 Hz, 3H, C2′OSi[OC*H*$(CH_3)_2]_3$}, 3.80 (d, J = 7.1 Hz, 1H, H3), 2.56 (ddd, J = 14.8, 9.8, 6.6 Hz, 1H, H6α), 2.47 (d, J = 4.1 Hz, 1H, C7OH), 2.42 (s, 3H, C4OAc), 2.29 (dd, J = 15.4, 9.4 Hz, 1H, H14α), 2.24 (s, 3H, C10OAc), 2.06 (dd, J = 15.4, 8.9 Hz, 1H, H14β), 1.91 (d, J = 1.4 Hz, 3H, C18H_3), 1.88 (ddd, J = 14.3, 11.0, 2.4 Hz, 1H, H6β), 1.76 (br s, 1H, C1OH), 1.68 (s, 3H, C19H_3), 1.23 (s, 3H, C17H_3), 1.15 {d, J = 6.1 Hz, 9H, C2′OSi[OCH$(CH_3)_a(CH_3)_b]_3$}, 1.12 {d, J = 6.1 Hz, 9H, C2′OSi[OCH$(CH_3)_a(CH_3)_b]_3$}, and 1.12 (s, 3H, C16H_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 171.5, 171.1, 170.1, 167.3, 167.2, 143.1, 138.3, 134.4, 133.9, 132.9, 131.9, 130.4, 129.4, 128.9 (x2), 128.8, 128.1, 127.3, 127.0, 84.7, 81.2, 79.3, 76.7, 75.9, 75.3, 74.9, 72.3, 71.5, 66.7, 58.7, 55.8, 45.7, 43.4, 35.8, 35.7, 27.0, 25.44, 25.42, 23.0, 22.4, 21.1, 15.2, and 9.8. HRMS (ESI) calcd for $C_{56}H_{71}NNaO_{17}Si$ $[M + Na]^+$ 1080.4383; found 1080.4380. IR (thin film) 3500 (br), 2974, 2934, 1729, 1666, 1603, 1583, 1515, 1485, 1452, 1371, 1313, 1269, 1241, 1174, 1114, 1052, 985, 897, 850, 800, 773, and 712 cm^{-1}. Mp = 126−129 °C. TLC R_f (1:1 hexanes/EtOAc) = 0.45.

2′-[(Trimenthyloxy)silyl]paclitaxel (1d). Paclitaxel (95.0 mg, 0.111 mmol, 1.0 equiv) was dissolved in dry THF (8.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (100 μL, 1.24 mmol, 11.2 equiv) was added by Wiretrol. Trimenthyloxychlorosilane (**5d**),[34] judged to contain 90% of the chlorosilane (579.1 mg, 0.986 mmol, 8.9 equiv) by ^{1}H NMR analysis, was added by Wiretrol. The culture tube was capped, and the suspension was allowed to stir for 12 h at 45 °C. The THF was removed by evaporation under reduced pressure. The solid residue was triturated with a mixture of hexanes/EtOAc (3:1), and the resulting slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 3:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (94.2 mg, 0.069 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.3, 1.3 Hz 2H, O_2C-*o*-Ph, 7.77 (dd, J = 8.1, 1.0 Hz, 2H, C3′NHCO-*o*-Ph), 7.60 (tt, J = 7.4, 1.3 Hz, 1H, C2O_2C-*p*-Ph), 7.53−7.47 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.43−7.36 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.30 (tt, J = 7.0, 1.6 Hz, 1H, C3′-*p*-Ph), 7.11 (d, J = 8.5 Hz, 1H, C3′NH), 6.28 (s, 1H, H10), 6.22 (ddq, J = 10.3, 9.3, 1.4 Hz, 1H, H13), 5.72 (dd, J = 8.5, 3.5 Hz, 1H, H3′), 5.68 (d, J = 7.1 Hz, 1H, H2), 5.10 (d, J = 3.5 Hz, 1H, H2′), 4.97 (dd, J = 9.6, 2.3 Hz, 1H, H5), 4.45 (ddd, J = 10.8, 6.7, 4.1 Hz, 1H, H7), 4.30 (dd, J = 8.6, 0.9 Hz, 1H, H20α), 4.20 (d, J = 8.5, 1.1 Hz, 1H, H20β), 3.80 (d, J = 7.1 Hz, 1H, H3), 3.64 (ddd, J = 10.6, 10.6, 4.3 Hz, 3H, $H1_{menth}$), 2.57 (ddd, J = 14.8, 9.8, 6.6 Hz, 1H, H6α), 2.48 (d, J = 4.1 Hz, 1H, C7OH), 2.39 (s, 3H, C4OAc), 2.30 (dd, J = 15.3, 9.5 Hz, 1H, H14α), 2.25 (s, 3H, C10OAc), 2.20 (dsep, J = 2.6, 7.0 Hz, 3H, $H7_{menth}$), 2.12 (dd, J = 15.9, 9.0 Hz, 1H, H14β), 1.92−1.86 (m, 4H, $H6eq_{menth}$ and H6β), 1.88 (d, J = 1.3 Hz, 3H, H18 =CCH_3), 1.80 (s, 1H, C1OH), 1.68 (s, 3H, H19 O=CCCH_3), 1.61 (m, 3H, $H4eq_{menth}$), 1.58 (dddd, J = 13.0, 3.0, 3.0, 3.0 Hz, $H3eq_{menth}$), 1.28−1.24 (m, 6H, $H5_{menth}$), 1.25 (s, 3H, C(Me)C16H_3), 1.16−1.10 (dddd, 3H, J = 11.2, 11.2, 2.8, 2.8 Hz $H2_{menth}$), 1.14 [s, 3H, C(Me)C17H_3], 0.92 (ddd, J = 12, 12, 12 Hz, 3H, $H6ax_{menth}$), 0.91−0.85 (m, 3H, $H3ax_{menth}$), 0.87 (d, 9H, J = 7.1 Hz, $H8_{menth}$), 0.83 (d, J = 6.6 Hz, 9H, $H10_{menth}$), 0.83−0.77 (dddd, J = 12.3, 12.3, 12.3, 3.0 Hz, 3H, $H4ax_{menth}$), and 0.74 (d, J = 6.9 Hz, 9H, $H9_{menth}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 171.6, 170.7, 170.0, 167.2, 167.1, 143.2, 138.1, 134.2, 133.8, 132.6, 132.0, 130.4, 129.3, 129.0, 128.9, 128.8, 128.1, 127.3, 126.9, 84.7, 81.1, 79.3, 76.7, 75.8, 75.3, 74.5, 74.2, 71.4 ($C1_{menth}$), 71.36, 58.7, 55.5, 49.7 ($C2_{menth}$), 45.6, 45.0 ($C7_{menth}$), 43.4, 35.9, 35.7, 34.5 ($C5_{menth}$), 31.7 ($C6_{menth}$), 27.0, 25.4 ($C3_{menth}$), 22.9 ($C4_{menth}$), 22.7, 22.5 ($C8_{menth}$), 22.4, 21.4 ($C9_{menth}$), 21.1, 15.8 ($C10_{menth}$), 15.1, and 9.8. HRMS (ESI) calcd for $C_{67}H_{103}NNaO_{17}Si$ $[M + Na]^+$ 1368.7206; found 1368.7275. IR (thin film) 3443, 2953, 2925, 2870, 1762, 1718, 1496, 1452, 1368, 1316, 1274, 1245, 1162, 1108, 1083, 1070, 1052, 1026, 987, 890, 765, and 751 cm^{-1}. Mp = 115−118.5 °C. TLC R_f (9:1 hexanes/EtOAc) = 0.20.

2′-*O*-[(Tri-*tert*-butoxy)silyl]paclitaxel (1e). Paclitaxel (PTX, 49.8 mg, 0.0583 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube with a Teflon-lined cap and magnetic stir bar. In a separate oven-dried culture tube fitted with a Teflon-lined cap, $SiCl_4$ (0.40 mL, 2.6 mmol), pyridine (0.84 mL, 10.4 mmol), *tert*-butanol (0.73 mL, 7.6 mmol), and THF (∼10 mL) were combined, and the mixture was stirred for 24 h. A 1 mL aliquot of this silylating reagent mixture was added to the tube containing PTX. The culture tube was capped, and the solution was allowed to stir at room temperature overnight. To the resulting suspension, additional pyridine (50 μL, 0.62 mmol, 13 equiv) and glacial acetic acid (50 μL, 0.87 mmol, 24 equiv) were added. The mixture was allowed to stir for an additional 48 h at room temperature. The reaction suspension was diluted with EtOAc. The slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was redissolved in a mixture of hexanes/EtOAc (2:1). Chromatography (SiO_2, 2:1 hexanes/EtOAc) via MPLC yielded **1e** (11.2 mg, 0.0107 mmol, 18.4%). Material collected from two later eluting fractions gave mass spectral evidence for the chloride PTX-Si(O-*t*-Bu)$_2$Cl (23.0 mg, 0.0212 mmol, 36.3%) and the silanol PTX-Si(O-*t*-Bu)$_2$OH (8.6 mg, 0.0078 mmol, 13.4%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.8, 1.7 Hz, 2H, C2O_2C-*o*-Ph), 7.78 (dd, J = 8.8, 1.8 Hz, 2H, C3′NHCO-*o*-Ph), 7.61 (tt, J = 7.3, 1.2 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.56−7.34 (m, 9H, C2O_2C-*m*-Ph, C3′NHCO-*p*-Ph, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.30−7.24 (m, 1H, C3′-*p*-Ph), 7.05 (d, J = 8.5 Hz, 1H, C3′NH), 6.29 (s, 1H, H10), 6.17 (br dd, J = 9, 9 Hz, 1H, H13), 5.74−5.66 (m, 2H, H2 and H3′), 5.16 (d, J = 2.9 Hz, 1H, H2′), 4.97 (dd, J = 9.2, 2.3 Hz, 1H, H5), 4.45 (app br dd, J = 11, 6 Hz, 1H, H7), 4.31 (d, J = 8.4 Hz, 1H, H20α), 4.20 (d, J = 8.6 Hz, 1H, H20β), 3.80 (d, J = 7.0 Hz, 1H, H3), 2.57 (ddd, J = 15.2, 9.9, 6.7 Hz, 1H, H6α), 2.47 (br d, J = 4 Hz, 1H, C7OH), 2.42 (s, 3H, C4OAc), 2.32 (dd, J = 15.9, 9.6, Hz, 1H, H14α), 2.25 (s, 3H, C10OAc), 2.17 (br dd, J = 14, 5 Hz, 1H, H14β), 1.93 (br d, J = 1 Hz, 3H, C18H_3), 1.89 (br m, 1H, H6β), 1.78 (br s, 1H, C1OH), 1.68 (s, 3H, C19H_3), 1.24 {overlapping s, 27H, C2′OSi[OC$(CH_3)_3]_3$ and s, 3H, C17H_3}, and 1.13 (s, 3H, C16H_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 171.6, 171.1, 170.1, 167.4, 167.2, 143.2, 138.3, 134.5, 133.9, 132.8, 131.9, 130.4, 129.4, 128.97, 128.95, 128.8, 128.0, 127.3, 126.9, 84.7, 81.2, 79.3, 76.7, 75.9, 75.3, 74.2, 73.9, 72.4, 71.4, 58.7, 55.5, 45.7, 43.4, 36.0, 35.7, 31.4, 27.0, 23.0, 22.4, 21.1, 15.3, and 9.8. IR (thin film) 3500 (br), 2973, 2929, 1729, 1670, 1511, 1483, 1452, 1389, 1367, 1268, 1242, 1183, 1124, 1069, 1025, 985, 835, 800, 758, and 711 cm^{-1}. HRMS (ESI) calcd for $C_{59}H_{77}NNaO_{17}Si$ $[M + Na]^+$ 1122.4853; found 1122.4901. Mp = 134−138 °C.

2′-*O*-[(Di-*tert*-butoxy)(ethoxy)silyl]paclitaxel (1f). Paclitaxel (49.3 mg, 0.0577 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (0.12 mL, 1.48 mmol, 26 equiv) was added

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by syringe. A distilled sample of di-*tert*-butoxydichlorosilane (**6**)[35] (0.349 mg, 1.42 mmol, 25 equiv) was added by Wiretrol. The culture tube was sealed, and the solution was allowed to stir at room temperature. A small amount of a white precipitate was observed after ~30 min, and the reaction mixture was noted to be cloudy and heterogeneous after stirring for 6 h. To this suspension, additional pyridine (0.47 mL, 5.81 mmol, 100 equiv) and anhydrous ethanol (dried overnight over 3 Å molecular sieves, 0.68 mL, 11.7 mmol, 200 equiv) were added. The mixture was allowed to stir for an additional 1 h at room temperature. The suspension was diluted with a mixture of hexanes/EtOAc (1:1). The slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was redissolved in a mixture of hexanes/EtOAc (2:1). Chromatography (SiO_2, 2:1 hexanes/EtOAc) via MPLC yielded the title compound as a white, crystalline solid (52.0 mg, 0.0485 mmol, 84.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.5, 1.4 Hz, 2H, C2O_2C-*o*-Ph), 7.79 (dd, J = 8.4, 1.4 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, J = 7.4, 1.3 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.56−7.46 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.45−7.33 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.30−7.22 (m, 1H, C3′-*p*-Ph), 7.15 (d, J = 8.4 Hz, 1H, C3′NH), 6.28 (s, 1H, H10), 6.18 (br dd, J = 9, 9 Hz, 1H, H13), 5.68 (d, J = 7.2 Hz, 1H, H2), 5.66 (dd, J = 8.3, 3.6 Hz, 1H, H3′), 5.01 (d, J = 3.6 Hz, 1H, H2′), 4.97 (dd, J = 9.7, 2.3 Hz, 1H, H5), 4.44 (ddd, J = 10.8, 6.6, 4.1 Hz, 1H, H7), 4.31 (d, J = 8.4 Hz, 1H, H20α), 4.19 (d, J = 8.4 Hz, 1H, H20β), 3.79 (d, J = 7.0 Hz, 1H, H3), 3.64 (q, J = 7.0 Hz, 2H, C2′OSiOCH_2CH$_3$), 2.56 (ddd, J = 14.8, 9.7, 6.6 Hz, 1H, H6α), 2.45 (d, J = 4.1 Hz, 1H, C7OH), 2.41 (s, 3H, C4OAc), 2.28 (dd, J = 15.4, 9.4, Hz, 1H, H14α), 2.24 (s, 3H, C10OAc), 2.05 (dd, J = 15.3, 9.0 Hz, 1H, H14β), 1.90 (d, J = 1.4 Hz, 3H, C18H$_3$), 1.88 (ddd, J = 14.4, 11.1, 2.5 Hz, 1H, H6β), 1.68 (s, 4H, C1OH and C19H$_3$), 1.26 (s, 9H, C2′OSiOC(CH_3)$_2$], 1.25 (s, 9H, C2′OSiOC(CH_3)$_2$], 1.23 (s, 3H, C17H$_3$), and 1.13 (overlapping t, J = 7.0 Hz, 3H, C2′OSiCH$_2$CH_3 and s, 3H, C16H$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 171.5, 171.0, 170.0, 167.3, 167.2, 143.1, 138.4, 134.4, 133.9, 132.8, 131.9, 130.4, 129.4, 128.90, 128.89, 128.8, 128.1, 127.3, 127.0, 84.7, 81.2, 79.3, 76.6, 75.9, 75.3, 74.9, 73.99, 73.98, 72.3, 71.4, 59.3, 58.7, 55.8, 45.7, 43.4, 35.8, 35.7, 31.41, 31.38, 27.0, 22.9, 22.3, 21.1, 18.2, 15.1, and 9.8. IR (thin film) 3500 (br), 2976, 2936, 1726, 1665, 1603, 1582, 1514, 1485, 1452, 1389, 1368, 1312, 1270, 1242, 1179, 1128, 1069, 1025, 981, 909, 853, 821, 800, 775, 733, and 711 cm^{-1}. HRMS (ESI) calcd for $C_{57}H_{73}NNaO_{17}Si$ [M + Na]$^+$ 1094.4540; found 1094.4579. Mp = 130−134 °C. TLC R_f (2:1 hexanes/EtOAc) = 0.2.

2′-*O*-(Di-*tert*-butoxyacetoxysilyl)paclitaxel (1g). Paclitaxel (33.5 mg, 0.0392 mmol, 1.0 equiv) was dissolved in THF (1.0 mL, dried by distillation from sodium/benzophenone) in an oven-dried culture tube with a Teflon-lined cap and magnetic stir bar. Pyridine (50 μL, 0.618 mmol, 16 equiv) was added by Wiretrol. A distilled sample of di-*tert*-butoxydichlorosilane (**6**)[35] (0.0524 mg, 0.214 mmol, 5.5 equiv) was added by Wiretrol. The culture tube was sealed, and the solution was allowed to stir at room temperature for 24 h. The reaction mixture was noted to be cloudy and heterogeneous after stirring overnight. To the suspension, pyridine was again added (50 μL, 0.618 mmol, 16 equiv). Immediately afterward, glacial acetic acid (50 μL, 0.873 mmol, 22 equiv) was added. The mixture was allowed to stir for an additional 24 h at room temperature. The reaction suspension was diluted with EtOAc, the slurry filtered through a short plug of Celite to remove the pyridinium salt, the filtrate concentrated under reduced pressure, and the residue redissolved in a mixture of hexanes/EtOAc (2:1). Purification (SiO_2, 2:1 hexanes/EtOAc) using MPLC yielded the title compound (28.0 mg, 0.0258 mmol, 65.8%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.5, 1.4 Hz, 2H, C2O_2C-*o*-Ph), 7.81 (dd, J = 8.5, 1.4 Hz, 2H, C3′NHCO-*o*-Ph), 7.63 (tt, J = 7.4, 1.3 Hz, 1H, C2O_2C-*p*-Ph), 7.54 (t, J = 7.9 Hz, 2H, C2O_2C-*m*-Ph), 7.48 (tt, J = 7.4, 1.9 Hz, 1H, C3′NHCO-*p*-Ph), 7.43−7.34 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.30−7.21 (m, 2H, C3′-*p*-Ph and C3′NH), 6.28 (s, 1H, H10), 6.13 (br dd, J = 9, 9 Hz, 1H, H13), 5.69 (dd, J = 8.5, 3.9 Hz, 1H, H3′), 5.66 (d, J = 7.2 Hz, 1H, H2), 5.19 (d, J = 4.0 Hz, 1H, H2′), 4.96 (dd, J = 9.6, 2.1 Hz, 1H, H5), 4.44 (ddd, J = 10.8, 6.4, 4.3 Hz, 1H, H7), 4.31 (d, J = 8.4 Hz, 1H, H20α), 4.20 (d, J = 8.3 Hz, 1H, H20β), 3.79 (d, J = 7.0 Hz, 1H, H3), 2.56 (ddd, J = 14.9, 9.9, 6.6 Hz, 1H, H6α), 2.45 (overlapping m, 1H, C7OH and s, 3H, C4OAc), 2.30−2.18 (overlapping m, 1H, H14α and s, 3H, C10OAc), 1.97−1.84 (m, 8H, H14β, C18H$_3$, SiOAc, and H6β), 1.67 (s, 3H, C19H$_3$), 1.61 (s, 1H, C1OH), 1.30 (s, 9H, C2′OSiOC-(CH_3)$_2$], 1.26 (s, 9H, C2′OSiOC(CH_3)$_2$], 1.22 (s, 3H, C17H$_3$), and 1.12 (s, 3H, C16H$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 171.6, 170.9, 170.3, 170.2, 167.2, 167.1, 143.2, 138.2, 134.4, 133.9, 132.7, 131.8, 130.4, 129.4, 128.92, 128.85, 128.7, 128.1, 127.4, 127.1, 84.7, 81.1, 79.3, 76.6, 75.9, 75.4, 75.31, 75.27 (×2), 72.3, 71.6, 58.7, 56.1, 45.7, 43.3, 35.70, 35.68, 31.34, 31.32, 26.9, 23.1, 22.9, 22.4, 21.1, 15.2, and 9.8. HRMS (ESI) calcd for $C_{57}H_{71}NNaO_{18}Si$ [M + Na]$^+$ 1108.4333; found 1108.4360.

2′,7-Di-*O*-(triethoxysilyl)paclitaxel (2a). Paclitaxel (58.0 mg, 0.0679 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and a stir bar. Pyridine (25 μL, 0.309 mmol, 4.5 equiv) was added by Wiretrol. Triethoxychlorosilane (**5a**) (50 μL, 0.255 mmol, 3.8 equiv) was added, and a white precipitate was immediately observed. The suspension was allowed to stir for 2 h at room temperature and then diluted with hexanes/EtOAc (1:1). The slurry was filtered through a short plug of Celite to remove the pyridinium salt, and the filtrate was concentrated under reduced pressure. The residue was purified by MPLC (SiO_2, 2:1 hexanes/EtOAc) to yield **2a** as a white crystalline solid (68.0 mg, 0.058 mmol, 85%). If necessary, residual EtOAc was removed by storage under high vacuum for ≥24 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.5, 1.5 Hz, 2H, C2O_2C-*o*-Ph), 7.78 (dd, J = 8.5, 1.5 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, J = 7.5, 1.0 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.54−7.46 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.44−7.36 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.29 (tt, J = 7.0, 1.5 Hz, 1H, C3′-*p*-Ph), 7.20 (d, J = 8.5 Hz, 1H, C3′NH), 6.58 (s, 1H, H10), 6.18 (br dd, J = 9, 9 Hz, 1H, H13), 5.72 (dd, J = 8.5, 3.0 Hz, 1H, H3′), 5.71 (d, J = 6.5 Hz, 1H, H2), 4.98 (d, J = 3.0 Hz, 1H, 2′H), 4.96 (dd, J = 10.0, 2.0 Hz, 1H, H5), 4.62 (dd, J = 10.5, 6.7 Hz, 1H, H7), 4.31 (d, J = 8.5 Hz, 1H, H20α), 4.20 (d, J = 8.5 Hz, 1H, H20β), 3.85 (d, J = 7.0 Hz, 1H, H3), 3.76 [q, J = 7.0 Hz, 6H, C7OSi-(OCH_2CH$_3$)$_3$], 3.71 [q, J = 7.0 Hz, 6H, C2′OSi(OCH_2CH$_3$)$_3$], 2.66 (ddd, J = 14.5, 9.5, 6.5 Hz, 1H, H6α), 2.45 (s, 3H, C4OAc), 2.33 (dd, J = 15.4, 9.4 Hz, 1H, H14α), 2.15 (s, 3H, C10OAc), 2.08 (d, J = 1.5 Hz, 3H, C18H$_3$), 2.07 (dd, J = 15.1, 9.0 Hz, 1H, H14β), 1.96 (ddd, J = 14.5, 10.8, 2.2 Hz, 1H, H6β), 1.73 (s, 3H, C19H$_3$), 1.65 (br s, 1H, C1OH), 1.23 (s, 3H, C17H$_3$), 1.19 [t, J = 7.0 Hz, 9H, C7OSi(OCH$_2$CH_3)$_3$], 1.17 (s, 3H, C16H$_3$), and 1.15 [t, J = 7.0 Hz, 9H, C2′OSi(OCH$_2$CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.6, 171.0, 169.8, 169.0, 167.3, 167.2, 141.0, 138.2, 134.3, 133.9, 133.3, 132.0, 130.4, 129.4, 128.9, 128.8, 128.7, 128.1, 127.3, 126.8, 84.5, 81.2, 78.9, 76.7, 75.9, 75.02, 74.99, 72.1, 71.6, 59.7, 59.5, 58.3, 55.5, 46.9, 43.4, 36.5, 35.5, 26.7, 23.0, 21.4, 21.0, 18.0 (×2), 14.2, and 10.4. HRMS (ESI) calcd for $C_{59}H_{79}NNaO_{20}Si_2$ [M + Na]$^+$ 1200.4626, found 1200.4631. IR (thin film) 3500 (br), 2976, 2928, 2896, 1744, 1725, 1644, 1603, 1580, 1541, 1486, 1451, 1370, 1314, 1268, 1238, 1169, 1098, 1080, 1027, 969, 891, 842, 795, and 708 cm^{-1}. Mp = 121−123 °C. TLC R_f (2:1 hexanes/EtOAc) = 0.4.

2′,7-Di-*O*-(Tri-*n*-octyloxysilyl)paclitaxel (2b). Paclitaxel (57.8 mg, 0.0677 mmol, 1.0 equiv) was dissolved in dry THF (1.5 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (25 μL, 0.309 mmol, 4.6 equiv) was added by Wiretrol. A 1.67:1 mixture of tri-*n*-octyloxychlorosilane (**5b**)[32]/tetra-*n*-octyloxysilane (0.155 mg, 0.199 mmol, 2.9 equiv of tri-*n*-octyloxychlorosilane) was added, and formation of a white precipitate was immediately observed. The culture tube was capped, and the suspension was allowed to stir for 5 h at room temperature. The reaction mixture was diluted with a mixture of hexanes/EtOAc (1:1), and the slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 9:1 hexanes/EtOAc) to yield **2b** as a colorless viscous glass (88.1 mg, 0.0523 mmol, 77.3%). Additional elution with hexanes/EtOAc (2:1) yielded **1b** (1.7 mg, 0.0013 mmol, 2.0%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.6, 1.4 Hz, 2H, C2O_2C-*o*-Ph), 7.78 (dd, J = 8.6, 1.5 Hz, 2H, C3′NHCO-*o*-Ph), 7.60

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(tt, J = 7.4, 1.2 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.54−7.46 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.44−7.35 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.28 (tt, J = 7.2, 1.3 Hz, 1H, C3′-*p*-Ph), 7.22 (d, J = 8.7 Hz, 1H, C3′NH), 6.55 (s, 1H, H10), 6.23 (br dd, J = 10, 9 Hz, 1H, H13), 5.74 (dd, J = 8.6, 3.0 Hz, 1H, H3′), 5.70 (d, J = 7.1 Hz, 1H, H2), 4.99 (d, J = 3.0 Hz, 1H, 2′H), 4.94 (dd, J = 9.7, 1.9 Hz, 1H, H5), 4.61 (dd, J = 10.6, 6.8 Hz, 1H, H7), 4.31 (d, J = 8.4 Hz, 1H, H20α), 4.20 (d, J = 8.4 Hz, 1H, H20β), 3.86 (d, J = 7.0 Hz, 1H, H3), 3.67 {t, J = 6.7 Hz, 6H, C7OSi[OCH_2(CH_2)$_6$CH_3]$_3$}, 3.61 {t, J = 6.7 Hz, 6H, C2′OSi[OCH_2(CH_2)$_6$CH_3]$_3$}, 2.65 (ddd, J = 14.7, 9.7, 6.8 Hz, 1H, H6α), 2.45 (s, 3H, C4OAc), 2.33 (dd, J = 15.3, 9.4 Hz, 1H, H14α) 2.13 (s, 3H, C10OAc), 2.06 (d, J = 1.2 Hz, 3H, C18H$_3$), 2.09−2.02 (m, 1H, H14β), 1.96 (ddd, J = 14.5, 10.8, 2.2 Hz, 1H, H6β), 1.73 (s, 3H, C19H$_3$), 1.66 (br s, 1H, C1OH), 1.56−1.44 {m, 12H, C2′OSi[OCH$_2$CH_2(CH$_2$)$_5$CH$_3$]$_3$ and C7OSi-[OCH$_2$CH_2(CH$_2$)$_5$CH$_3$]$_3$}, 1.34−1.21 {m, 63H, C17H$_3$, C2′OSi-[OCH$_2$CH$_2$(CH_2)$_5$CH$_3$]$_3$, and C7OSi[OCH$_2$CH$_2$(CH_2)$_5$CH$_3$]$_3$}, 1.17 (s, 3H, C16H$_3$), and 0.88 {overlapping t's, J = 6.8 Hz, 18H, C2′OSi[OCH$_2$CH$_2$(CH$_2$)$_5$CH_3]$_3$ and C7OSi-[OCH$_2$CH$_2$(CH$_2$)$_5$CH_3]$_3$}. ^{13}C NMR (75 MHz, CDCl$_3$): δ 202.4, 170.9, 169.8, 168.7, 167.3, 167.2, 140.9, 138.3, 134.3, 133.8, 133.3, 131.9, 130.4, 129.4, 128.91, 128.89, 128.8, 128.1, 127.3, 126.8, 84.6, 81.2, 79.0, 76.8, 75.8, 75.1, 74.9, 72.0, 71.5, 64.1, 63.9, 58.3, 55.5, 46.8, 43.5, 36.6, 35.6, 32.5, 32.4, 32.1, 32.0, 29.6, 29.63, 29.60, 29.57, 26.7, 25.92, 25.89, 23.0, 22.91, 22.90, 21.6, 21.1, 14.3 (×2), 14.1, and 10.4. HRMS (ESI) calcd for $C_{95}H_{151}NNaO_{20}Si_2$ [M + Na]$^+$ 1705.0260; found 1705.0228. IR (thin film) 3500 (br), 2927, 2856, 1741, 1728, 1634, 1580, 1545, 1456, 1371, 1315, 1270, 1239, 1174, 1095, 1028, 989, 968, 924, 893, 843, 779, and 709 cm^{-1}. TLC R_f (3:1 hexanes/EtOAc) = 0.55.

2′,7-Di-*O*-(triisopropoxysilyl)paclitaxel (2c). Paclitaxel (30.1 mg, 0.0352 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (15 μL, 0.185 mmol, 5.3 equiv) was added by Wiretrol. A 3.5:1 mixture of triisopropoxychlorosilane (**5c**)[33]/tetraisopropoxysilane (0.0424 mg, 0.134 mmol, 2.9 equiv of triisopropoxychlorosilane) was added. The culture tube was capped, and a white precipitate was observed within minutes. The suspension was stirred at room temperature for 18 h, and the mixture was filtered through a short plug of Celite to remove the triethylammonium salt. The filtrate was concentrated under reduced pressure, and the residue was redissolved in a mixture of hexanes/EtOAc (2:1). Purification by MPLC (SiO$_2$, 2:1 hexanes/ethyl acetate) yielded the title compound as a white, crystalline solid (29.8 mg, 0.0236 mmol, 67.0%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.12 (dd, J = 8.5, 1.5 Hz, 2H, C2O_2C-*o*-Ph), 7.80 (dd, J = 8.4, 1.5 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, J = 7.4, 1.7 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.55−7.46 (m, 3H, C2O_2C-*m*-Ph and C3′NHCO-*p*-Ph), 7.43−7.34 (m, 6H, C3′-*o*-Ph, C3′-*m*-Ph, and C3′NHCO-*m*-Ph), 7.29−7.24 (m, 1H, C3′-*p*-Ph), 7.17 (d, J = 8.4 Hz, 1H, C3′NH), 6.53 (s, 1H, H10), 6.14 (br dd, J = 9, 9 Hz, 1H, H13), 5.70 (d, J = 7.3 Hz, 1H, H2), 5.67 (dd, J = 8.4, 3.6 Hz, 1H, H3′), 5.00 (d, J = 3.6 Hz, 1H, H2′), 4.96 (dd, J = 9.4, 2.0 Hz, 1H, H5), 4.61 (dd, J = 10.7, 6.7, Hz, 1H, H7), 4.31 (d, J = 8.8 Hz, 1H, H20α), 4.19 (d, J = 8.6 Hz, 1H, H20β), 4.13 and 4.12 {overlapping septs, J = 6.2 Hz, 6H, C2′OSi[OCH(CH$_3$)$_2$]$_3$ and C7OSi[OCH(CH$_3$)$_2$]$_3$}, 3.85 (d, J = 7.4 Hz, 1H, H3), 2.68 (ddd, J = 14.7, 9.7, 6.8 Hz, 1H, H6α), 2.41 (s, 3H, C4OAc), 2.30 (dd, J = 15.1, 9.3 Hz, 1H, H14α), 2.14 (s, 3H, C10OAc), 2.10 (d, J = 1.2 Hz, 3H, C18H$_3$), 2.03 (dd, J = 15.7, 9.5 Hz, 1H, H14β), 1.95 (ddd, J = 14.6, 10.9, 2.2 Hz, 1H, H6β), 1.72 (s, 3H, C19H$_3$), 1.61 (br s, 1H, C1OH), 1.23 (m, 3H, C17H$_3$), and 1.18−1.10 {m, 39H, C2′OSi[OCH(CH$_3$)$_a$(CH_3)$_b$]$_3$}, C2′OSi[OCH-(CH_3)$_a$(CH$_3$)$_b$]$_3$, C7OSi[OCH(CH$_3$)$_a$(CH_3)$_b$]$_3$}, C7OSi[OCH-(CH_3)$_a$(CH$_3$)$_b$]$_3$, and C16H$_3$}. ^{13}C NMR (125 MHz, CDCl$_3$): δ 202.6, 171.1, 169.6, 168.9, 167.3, 167.2, 141.2, 138.4, 134.4, 133.8, 133.3, 131.9, 130.4, 129.5, 128.9 (×2), 128.8, 128.1, 127.3, 127.0, 84.6, 81.2, 80.0, 76.8, 75.9, 75.2, 74.9, 72.3, 71.7, 66.6, 66.2, 58.3, 55.9, 46.8, 43.5, 36.7, 35.5, 26.8, 25.5, 25.42, 25.41, 25.38, 23.0, 21.5, 21.1, 14.7, and 10.5. HRMS (ESI) calcd for $C_{65}H_{91}NNaO_{20}Si_2$ [M + Na]$^+$ 1284.5565, found 1284.5563. IR (thin film) 3500 (br), 2973, 2933, 1725, 1671, 1603, 1582, 1512, 1484, 1452, 1371, 1313, 1267, 1238, 1173, 1116, 1047, 989, 893, 839, 767, and 711. Mp = 108−113 °C. TLC R_f (2:1 hexanes/EtOAc) = 0.55.

7-*O*-(Triethoxysilyl)paclitaxel (3a). Bis(triethoxy)silicate ester **2a** (99.5 mg, 0.0845 mmol, 1.0 equiv) was dissolved in acetone-d_6 (1.8 mL, dried over 3 Å molecular sieves) in an NMR sample tube. A 9:1 mixture of D$_2$O/TFA was added (200 μL), and the reaction progress was monitored by ^{1}H NMR spectroscopy. After 8 min at 21.4 °C, the mixture was transferred into saturated aqueous NaHCO$_3$ (2 mL). This mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by MPLC (SiO$_2$, 2:1 hexanes/EtOAc) to provide recovered starting material **2a** (27.3 mg, 0.0232 mmol, 27.4%). Additional elution in 1:1 hexanes/EtOAc gave the title compound as a white, crystalline solid [56.9 mg, 0.0560 mmol, 66.3% (91.4% brsm)]. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.12 (dd, J = 8.5, 1.3 Hz, 2H, C2O_2C-*o*-Ph), 7.75 (dd, J = 8.5, 1.4 Hz, 2H, C3′NHCO-*o*-Ph), 7.61 (tt, J = 7.5, 1.2 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.53−7.46 (m, 5H, C2O_2C-*m*-Ph, C3′NHCO-*p*-Ph, and C3′-*o*-Ph,), 7.43−7.37 (m, 4H, C3′-*m*-Ph and C3′NHCO-*m*-Ph), 7.34 (tt, J = 7.3, 1.2 Hz, 1H, C3′-*p*-Ph), 7.09 (d, J = 9.0 Hz, 1H, C3′NH), 6.56 (s, 1H, H10), 6.18 (br dd, J = 9, 9 Hz, 1H, H13), 5.80 (dd, J = 6.9, 2.5 Hz, 1H, H3′), 5.69 (d, J = 6.9 Hz, 1H, H2), 4.93 (dd, J = 9.6, 1.7 Hz, 1H, H5), 4.78 (dd, J = 4.9, 2.7 Hz, 1H, 2′H), 4.57 (dd, J = 10.5, 6.9 Hz, 1H, H7), 4.30 (d, J = 8.4 Hz, 1H, H20α), 4.19 (dd, J = 8.3, 0.9 Hz, 1H, H20β), 3.83 (d, J = 6.9 Hz, 1H, H3), 3.76 [q, J = 7.0 Hz, 6H, C7OSi(OCH_2CH$_3$)$_3$], 3.69 (br s, 1H, C2′OH), 2.65 (ddd, J = 14.7, 9.7, 6.9 Hz, 1H, H6α), 2.37 (s, 3H, C4OAc), 2.35−2.25 (m, 2H, H14α and H14β), 2.15 (s, 3H, C10OAc), 1.95 (ddd, J =14.6, 10.7, 2.1 Hz, 1H, H6β), 1.93 (d, J = 1.3 Hz, 3H, C18H$_3$), 1.76 (br s, 1H, C1OH), 1.73 (s, 3H, C19H$_3$), 1.23 (s, 3H, C17H$_3$), 1.19 [t, J = 7.0 Hz, 9H, C7OSi(OCH$_2$CH_3)$_3$], and 1.16 (s, 3H, C16H$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 202.4, 172.6, 170.4, 169.0, 167.2, 167.1, 140.1, 138.2, 133.9, 133.8, 132.1, 130.3, 129.4, 129.1, 128.89, 128.87, 128.5, 127.3, 127.24, 127.23, 84.4, 81.5, 78.8, 76.8, 76.1, 74.8, 73.4, 72.5, 72.1, 59.5, 58.6, 55.0, 47.0, 43.4, 36.7, 35.6, 26.8, 22.9, 21.1, 21.0, 18.2, 14.5, and 10.3. HRMS (ESI) calcd for $C_{53}H_{65}NNaO_{17}Si$ [M + Na]$^+$ 1038.3914, found 1038.3914. IR (thin film) 3500 (br), 2975, 2898, 1724, 1653, 1602, 1580, 1515, 1485, 1451, 1394, 1370, 1314, 1266, 1240, 1172, 1079, 1025, 969, 913, 888, 839, 797, and 712 cm^{-1}. Mp = 141−146 °C. TLC R_f (1:1 hexanes/EtOAc) = 0.5.

7-*O*-(Tri-*n*-octyloxysilyl)paclitaxel (3b). Bis(trioctyloxy)silicate ester **2b** (88.1 mg, 0.0523 mmol, 1.0 equiv) was dissolved in acetone-d_6 (1.8 mL, dried over 3 Å molecular sieves) in an NMR tube. A 9:1 mixture of D$_2$O/TFA was added (200 μL), and the solution became white and cloudy. Upon vigorous mixing for 30 s, the mixture became homogeneous and transparent. The hydrolysis progress was monitored by ^{1}H NMR spectroscopy. After 30 min at room temperature, the solution was transferred into saturated aqueous NaHCO$_3$ (2 mL). This mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by MPLC (SiO$_2$, 3:1 hexanes/EtOAc) to provide recovered **2b** (12.9 mg, 0.0076 mmol, 27.4%). Additional elution in 2:1 hexanes/EtOAc gave the title compound as a crystalline solid [37.3 mg, 0.0294 mmol, 56.2% (65.7% brsm)]. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.12 (dd, J = 8.5, 1.3 Hz, 2H, C2O_2C-*o*-Ph), 7.75 (dd, J = 8.5, 1.4 Hz, 2H, C3′NHCO-*o*-Ph), 7.61 (tt, J = 7.4, 1.3 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.53−7.47 (m, 5H, C2O_2C-*m*-Ph, C3′NHCO-*p*-Ph, and C3′-*o*-Ph,), 7.43−7.38 (m, 4H, C3′-*m*-Ph and C3′NHCO-*m*-Ph), 7.34 (tt, J = 7.2, 1.3 Hz, 1H, C3′-*p*-Ph), 7.06 (d, J = 9.0 Hz, 1H, C3′NH), 6.53 (s, 1H, H10), 6.17 (br dd, J = 9, 9 Hz, 1H, H13), 5.81 (dd, J = 6.8, 2.4 Hz, 1H, H3′), 5.68 (d, J = 6.9 Hz, 1H, H2), 4.92 (dd, J = 9.6, 1.8 Hz, 1H, H5), 4.78 (dd, J = 4.8, 2.6 Hz, 1H, 2′H), 4.56 (dd, J = 10.5, 6.7 Hz, 1H, H7), 4.29 (d, J = 8.3 Hz, 1H, H20α), 4.19 (d, J = 8.5 Hz, 1H, H20β), 3.83 (d, J = 7.0 Hz, 1H, H3), 3.66 {t, J = 6.7 Hz, 6H, C7OSi[OCH_2(CH$_2$)$_6$CH$_3$]$_3$}, 3.60 (d, J = 4.9 Hz, 1H, C2′OH), 2.64 (ddd, J = 14.7, 9.7, 6.9 Hz, 1H, H6α), 2.37 (s, 3H, C4OAc), 2.34−2.27 (m, 2H, H14α and H14β), 2.14 (s, 3H, C10OAc), 1.97−1.90 (m, 4H, H6β and C18H$_3$), 1.74−1.70 (m, 4H, C1OH and C19H$_3$), 1.52 {tt, J = 6.8, 6.8 Hz, 6H, C7OSi[OCH$_2$CH_2(CH$_2$)$_5$CH$_3$]$_3$}, 1.34−1.22 {m, 33H, C17H$_3$ and

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C7OSi[$OCH_2CH_2(CH_2)_5CH_3]_3$}, 1.16 (s, 3H, C16H_3), and 0.88 {t, J = 6.8 Hz, 9H, C7OSi[$OCH_2CH_2(CH_2)_5CH_3]_3$}. ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.2, 172.7, 170.3, 168.8, 167.2, 167.0, 140.0, 138.3, 133.93, 133.89, 132.1, 130.4, 129.4, 129.1, 128.9 (x3), 128.5, 127.3, 127.2, 84.5, 81.5, 78.8, 76.8, 76.0, 74.9, 72.5, 72.3, 71.7, 63.9, 58.6, 54.9, 47.0, 43.4, 36.6, 35.6, 32.5, 32.1, 29.62, 29.57, 26.8, 25.9, 22.91, 22.88, 21.1, 21.0, 14.5, 14.3, and 10.3. HRMS (ESI) calcd for $C_{71}H_{101}NNaO_{17}Si$ $[M + Na]^+$ 1290.6731; found 1290.6738. IR (thin film) 3500 (br), 2926, 2855, 1732, 1710, 1673, 1602, 1582, 1452, 1396, 1370, 1317, 1281, 1269, 1241, 1179, 1093, 1025, 988, 968, 890, 844, 809, and 712 cm^{-1}. Mp = 69−73 °C. TLC R_f (2:1 hexanes/EtOAc) = 0.4.

7-*O*-(Tri-*n*-octyloxysilyl)paclitaxel (3c). Bis-silicate ester **2b** (102.3 mg, 0.081 mmol, 1.0 equiv) was dissolved in acetone-d_6 (1.35 mL, dried over 3 Å molecular sieves). A 9:1 mixture of D_2O/TFA was added (150 μL), and the solution became white and cloudy. Upon being shaken for ∼30 s, the mixture became homogeneous and transparent. The hydrolysis progress was monitored by ^{1}H NMR spectroscopy. After 18 h at room temperature, the solution was transferred into saturated aqueous $NaHCO_3$ (3 mL). This mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by MPLC (SiO_2, 1:1 hexanes/EtOAc) to provide recovered **2c** (35.8 mg, 0.028 mmol, 35%) and the title compound as a crystalline solid [43.3 mg, 0.041 mmol, 50.5% (77% brsm)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.4, 1.3 Hz, 2H, C2O_2C-*o*-Ph), 7.75 (dd, J = 8.5, 1.3 Hz, 2H, C3′NHCO-*o*-Ph), 7.62 (tt, J = 7.0, 1.3 Hz, 1H, C2O_2C-*p*-Ph, 1H), 7.53−7.49 (m, 5H, C2O_2C-*m*-Ph, C3′NHCO-*p*-Ph, and C3′-*o*-Ph,), 7.43−7.39 (m, 4H, C3′-*m*-Ph and C3′NHCO-*m*-Ph), 7.34 (tt, J = 7.3, 1.2 Hz, 1H, C3′-*p*-Ph), 7.05 (d, J = 9.0 Hz, 1H, C3′NH), 6.50 (s, 1H, H10), 6.19 (ddq, J = 9.1, 9.1, 1.4 Hz, 1H, H13), 5.80 (dd, J = 9.0, 2.4 Hz, 1H, H3′), 5.68 (d, J = 7.0 Hz, 1H, H2), 4.94 (dd, J = 9.6, 1.9 Hz, 1H, H5), 4.81 (d, J = 2.6 Hz, 1H, H2′), 4.57 (dd, J = 6.8, 10.5 Hz, 1H, H7), 4.30 (d, J = 8.4 Hz, 1H, H20α), 4.19 (d, J = 8.5 Hz, 1H, H20β), 4.11 {sept, J = 6.1 Hz, 3H, C7OSi[OCH(CH_3)$_2$]$_3$}, 3.83 (d, J = 7.0 Hz, 1H, H3), 3.60 (br s, 1H, C2′OH), 2.67 (ddd, J = 14.8, 9.8, 6.9 Hz, 1H, H6α), 2.37 (s, 3H, C4OAc), 2.36−2.25 (m, 2H, H14α and H14β), 2.14 (s, 3H, C10OAc), 1.96 (d, J = 1.5 Hz, C18H_3), 1.95−1.91 (ddd, J 14.7, 10.6, 2.1 Hz, 1H, H6β), 1.73 (s, 3H, C19H_3), 1.65 (br s, 1H, C1OH), 1.24 (s, C17H_3), 1.160 (s, 3H, C16H_3), 1.160, {d, J = 6.1, 9H, C7OSi[OCH(CH_3)$_3$]}, and 1.15 {d, J = 6.1 Hz, 9H C7OSi-[OCH(C′H_3)$_3$]}. ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.5, 172.7, 170.3, 168.9, 167.2, 167.1, 140.3, 138.2, 133.92, 133.80, 132.1, 130.4, 129.4, 129.2 (2x), 128.9 (2×), 128.5, 127.3, 127.2, 84.5, 81.5, 78.8, 76.8, 76.0, 74.9, 73.3, 72.6, 72.4, 66.3 {SiOCH(CH_3)$_2$}, 58.5, 54.9, 47.0, 43.4, 36.8, 35.6, 26.9, 25.5 {SiOCH(CH_3)$_2$}, 25.4 {SiOCH-(C′H_3)$_2$}, 22.9, 21.1, 21.0, 14.8, and 10.4. HRMS (ESI) calcd for $C_{56}H_{71}NNaO_{17}Si$ $[M + Na]^+$ 1080.4383; found 1080.4393. IR (thin film) (br) 3448, 3067, 3026, 2972, 2934, 2898, 1724, 1662, 1602, 1581, 1485, 1452, 1370, 1315, 1289, 1269, 1239, 1174, 1136, 1113, 1048, 987, 969, 949, 892, 838, 803, and 775 cm^{-1}. Mp = 134.5−136 °C. TLC R_f (1:1 hexanes/EtOAc) = 0.40.

2′-*O*-(Triethoxysilyl)docetaxel (4a). Docetaxel (75.0 mg, 0.0930 mmol, 1.0 equiv) was dissolved in dry THF (2.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. *N*,*N*-Dimethylbutylamine (35 μL, 0.250 mmol, 2.7 equiv) was added by Wiretrol. Triethoxychlorosilane (**5a**) (50 μL, 50.6 mg, 0.255 mmol, 2.7 equiv) was added. The culture tube was sealed, and the suspension was allowed to stir for 2 h at room temperature. A white precipitate was observed immediately upon the addition of the chlorosilane to the reaction mixture. The THF was removed by evaporation under reduced pressure, and the solid residue was triturated with a mixture of hexanes/EtOAc (1:1), and the resulting slurry was filtered through a short plug of Celite to remove the ammonium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 1:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (58.1 mg, 0.060 mmol, 64.5%). ^{1}H NMR (500 MHz, $CDCl_3$, some resonances were broadened presumably because of the presence of NBoc rotamers): δ 8.10 (d, J = 7.9 Hz 2H, O_2C-*o*-Ph), 7.60 (t, J = 7.2 Hz, 1H, O_2C-*p*-Ph), 7.50 (t, J = 7.9 Hz, 2H, O_2C-*m*-Ph), 7.36 (t, 2H, J = 8.0 Hz, C3′-*m*-Ph), 7.33 (d, 2H, J = 7.2 Hz, C3′-*o*-Ph), 7.25 (t, J = 6.5 Hz 1H, C3′-*p*-Ph), 6.27 (br m, 1H, H13), 5.67 (d, J = 7.3 Hz, 1H, H2), 5.62 (d, J = 8.9 Hz, 1H, H3′), 5.28 (br s, 1H, NH), 5.21 (s, 1H, H10), 4.96 (dd, J = 9.9, 1.9 Hz, 1H, H5), 4.81 (br s, 1H, H2′), 4.31 (d, J = 8.6 Hz, 1H, H20α), 4.25 (br dd, J = 11.6, 7.2, Hz, 1H, H7), 4.22 (d, J = 1.5 Hz, 1H, C10OH), 4.19 (d, J = 8.6 Hz 1H, H20β), 3.92 (d, J = 6.9 Hz, 1H, H3), 3.66 {br q, J = 6.7, 5.8 Hz, 6H, C2′OSi[OCH_2CH_3]$_3$}, 2.58 (ddd, J = 14.0, 9.9, 6.4 Hz, 1H, α), 2.44 (s, 3H, C4OAc), 2.29 (br m, 1H, 14α), 2.11 (br m, 1H, 1β), 1.93 (s, 3H, =CCH_3), 1.85 (ddd, J = 14.6, 11.5, 2.8 Hz 1H, β), 1.74 (s, 3H, O=CCCH_3), 1.71 (s, 1H, C1OH), 1.32 (br s, 9H, *t*Boc), 1.25 {s, C(Me)C16H_3}, 1.12 [t, J = 7.0 Hz, 9H, C2′OSi(OCH_2CH_3)$_3$], and 1.11 (s, 3H, C(Me)C17H_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.6 (C9), 170.7 (C1′), 170.0 (C21), 167.1 (C2−OCOBz), 155.4 (C3′-NHCO), 139.3 (C3′-*ipso*-Ph), 138.6 (C12), 135.4 (C11), 133.7 (OBz-*p*), 130.2 (OBz-*i*), 129.2 (OBz-*o*), 128.7 (OBz-*m*), 128.5 (2 × C3′-*o*-Ph), 127.6 (C3′-*m*-Ph), 126.5 (C3′-*p*-Ph), 84.2 (C5), 80.9 ($OCMe_3$), 79.9 (C1), 79.0 (C4), 76.6 (C20), 75.2 (C2), 75.0 (C10), 74.5 (C2′), 71.9 (C13), 71.2 (C7), 59.4 (3x C2′OSiOCH_2CH_3), 57.5 (C8), 56.3 (C3′), 46.4 (C3), 43.1 (C15), 36.9 (C6), 35.6 (C14), 28.2 [C3′-NHCOC(CH_3)], 26.4 (C16), 22.7 (C22), 21.0 (C17), 18.0 (SiOCH_2CH_3), 14.1 (C18), and 9.9 (C19). HRMS (ESI) calcd for $C_{49}H_{67}NNaO_{17}Si$ $[M + Na]^+$ 992.4070; found 992.4083. IR (thin film) 3443, 2977, 2930, 2897, 2368, 1756, 1712, 1495, 1453, 1392, 1367, 1314, 1271, 1244, 1166, 1105, 1081, 1025, 983, 915, 88, 798, 786, and 758 cm^{-1}. Mp = 117−119 °C. TLC R_f (1:1 hexanes/EtOAc) = 0.42.

2′-*O*-(Tri-*n*-octyloxysilyl)docetaxel (4b). Docetaxel (36.4 mg, 0.0450 mmol, 1.0 equiv) was dissolved in dry THF (2.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. *N*,*N*-Dimethylbutylamine (35 μL, 0.250 mmol, 5.5 equiv) was added by Wiretrol. Tri-*n*-octyloxychlorosilane (**5b**)[32] (containing ∼20% of tetra-*n*-octyloxysilane; 50 μL, estimated to contain 32.0 mg, 0.071 mmol, 1.6 equiv of the tri-*n*-octyloxychlorosilane) was added. The culture tube was sealed, and the suspension was allowed to stir for 3 h at room temperature. A white precipitate was observed to grow over the first 30 min of the reaction period. The THF was removed by evaporation under reduced pressure. The solid residue was triturated with a mixture of hexanes/EtOAc (2:1), and the resulting slurry was filtered through a short plug of Celite to remove the ammonium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 2:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (35.1 mg, 0.0287 mmol, 63.7%). ^{1}H NMR (500 MHz, $CDCl_3$, some resonances were broadened presumably because of the presence of NBoc rotamers): δ 8.12 (d, J = 7.9 Hz 2H, O_2C-*o*-Ph), 7.60 (t, J = 7.3 Hz, 1H, O_2C-*p*-Ph), 7.50 (t, J = 7.8 Hz, 2H, O_2C-*m*- Ph), 7.35 (t, 2H, J = 7.9 Hz, C3′-*m*-Ph), 7.32 (d, 2H, J = 6.9 Hz, C3′-*o*-Ph), 7.25 (t, J = 6.8 Hz 1H, C3′-*p*-Ph), 6.28 (br dd, J = 9, 9 Hz, 1H, H13), 5.69 (d, J = 7.1 Hz, 1H, H2), 5.62 (d, J = 9 Hz H3′), 5.28 (br s, 1H, NH), 5.20 (s, 1H, H10), 4.96 (dd, J = 9.6, 1.8 Hz, 1H, H5), 4.81 (br s, 1H, H2′), 4.32 (d, J = 8.5 Hz, 1H, H20α), 4.25 (br dd, J = 10.2, 7.0, Hz, 1H, H7), 4.20 (d, J = 8.1 Hz, 1H, H20β), 4.19 (br s, 1H, C10OH), 3.93 (d, J = 7.1 Hz, 1H, H3), 3.56 {t, J = 6.5 Hz, 6H, C2′OSi[OCH_2(CH_2)$_6CH_3]_3$}, 2.59 (ddd, J = 15.8, 9.5, 6.5 Hz, 1H, H6α), 2.43 (s, 3H, C4OAc), 2.29 (br m, 1H, H14α), 2.12 (br m, 1H, H14β), 1.93 (s, 3H, =CCH_3), 1.85 (ddd, J = 13.9, 11.6, 2.2 Hz 1H, H6β), 1.75 (s, 3H, O=CCCH_3), 1.65 (d, 1H, J = 2.6, C1OH), 1.46 {br pent, J = 6.4 Hz, 6H, C2′OSi[$OCH_2CH_2(CH_2)_5CH_3]_3$}, 1.32 (br s, 9H, *t*-Boc), 1.31−1.24 {m, 33H, C2′OSi[$OCH_2CH_2(CH_2)_5CH_3]_3$}, and C(Me)-C16H_3}, 1.12 (s, 3H, C(Me)C17H_3), and 0.89 {t, J = 6.7 Hz, 9H, C2′OSi[$OCH_2CH_2(CH_2)_5CH_3]_3$}. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9, 170.8, 170.1, 167.3, 155.3, 139.6, 138.9, 135.5, 133.8, 130.4, 129.4, 128.9 128.7, 127.8, 126.7, 84.4, 81.1, 80.0, 79.2, 77.6, 76.8, 75.2, 74.7, 72.1, 71.3, 64.0, 57.7, 56.3, 46.6, 43.3, 37.2, 35.9, 32.4, 32.1, 29.6, 29.5, 28.4, 26.5, 25.8, 22.93, 22.90, 21.2, 14.4, 14.3, and 10.2. HRMS (ESI) calcd for $C_{67}H_{103}NNaO_{17}Si$ $[M + Na]^+$ 1244.6887; found 1244.6954. IR (thin film) 3454, 3382, 2926, 2855, 1755, 1737, 1713, 1699, 1495, 1454, 1367, 1272, 1245, 1165, 1095, 1025, 987, 946, 943, 920, 888, 865, 824, 800, and 778 cm^{-1}. Mp = 54−58 °C. TLC R_f (3:1 hexanes/EtOAc) = 0.13.

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2′-*O*-(Triisopropoxysilyl)docetaxel (4c). Docetaxel (40.0 mg, 0.0490 mmol, 1.0 equiv) was dissolved in dry THF (2.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. *N*,*N*-Dimethylbutylamine (50 μL, 0.357 mmol, 7.3 equiv) was added by Wiretrol. Triisopropoxychlorosilane (**5c**)[33] (containing ∼80% of triisopropoxychlorosilane; 50 μL, estimated to contain 42.0 mg, 0.175 mmol, 3.8 equiv of the triisopropoxychlorosilane) was added. The culture tube was capped, and the suspension was allowed to stir for 5 h at room temperature. A white precipitate was observed to grow over 3 h of the reaction. The THF was removed by evaporation under reduced pressure, and the solid residue was triturated with a mixture of hexanes/EtOAc (2.4:1). The resulting slurry was filtered through a short plug of Celite to remove the ammonium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 2.4:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (31.2 mg, 0.0308 mmol, 62.8%). ^{1}H NMR (500 MHz, $CDCl_3$, some resonances were broadened presumably because of the presence of NBoc rotamers): δ 8.10 (d, *J* = 7.6 Hz 2H, O_2C-*o*-Ph), 7.62 (t, *J* = 7.4 Hz, 1H, O_2C-*p*-Ph), 7.51 (t, *J* = 7.8 Hz, 2H, O_2C-*m*-Ph), 7.35 (t, 2H, *J* = 8.0 Hz, C3′-*m*-Ph), 7.32 (d, 2H, *J* = 6.9 Hz, C3′-*o*-Ph), 7.23 (t, *J* = 6.6 Hz 1H, C3′-*p*-Ph), 6.21 (br m, 1H, H13), 5.69 (d, *J* = 9 Hz, 1H, H3′), 5.68 (d, *J* = 7.0 Hz, H2), 5.21 (br s, 1H, NH), 5.20 (s, 1H, H10), 4.96 (dd, *J* = 9.6, 2.1 Hz, 1H, H5), 4.81 (br s, 1H, H2′), 4.31 (d, *J* = 8.5 Hz, 1H, H20*α*), 4.25 (ddd, *J* = 11.3, 8.0, 7.0 Hz, 1H, H7), 4.19 (br s, 1H, C10OH), 4.18 (d, *J* = 8.6 Hz, 1H, H20*β*), 4.09 {br septet, *J* = 5.9 Hz, 3H, OSi[OC*H* $(CH_3)_2]_3$}, 3.91 (d, *J* = 7.1 Hz, 1H, H3), 2.60 (ddd, *J* = 14.4, 9.7, 6.5 Hz, 1H, H6*α*), 2.40 (s, 3H, C4OAc), 2.22 (br m, 1H, H14*α*), 2.05 (br m, 1H, H14*β*), 1.93 (s, 3H, =CCH_3), 1.84 (ddd, *J* = 14.1, 11.3, 2.5 Hz 1H, H6*β*), 1.75 (s, 3H, O=CCC19H_3), 1.60 (br s, 1H, C1OH), 1.46 (d, 1H, *J* = 8.0 Hz, C7OH), 1.33 (br s, 9H, *t*-Boc), 1.24 [s, 3H, C(Me)C16H_3], and 1.14−1.10 {m, 21H, C(Me)C17H_3 and OSi[OCH(CH_3)$_2$]$_3$}. ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.7, 170.7, 169.9, 167.1, 155.4, 139.5, 138.7, 135.2, 133.7, 130.2, 129.2, 128.7, 128.5, 127.6, 126.6, 84.2, 80.9, 79.0, 76.6, 75.1, 75.0, 74.5, 73.2, 71.9, 71.1, 66.3, 57.5, 56.7, 46.4, 43.1, 36.9, 35.6, 28.2, 26.3, 25.2, 22.7, 21.0, 14.4, and 10.0. HRMS (ESI) calcd for $C_{52}H_{73}NNaO_{17}Si$ $[M + Na]^+$ 1034.4540; found 1034.4545. IR (thin film) 3683, 2973, 2917, 2849, 2349, 1757, 1733, 1717, 1701, 1649, 1631, 1547, 1494, 1461, 1452, 1369, 1271, 1244, 1167, 1114, 1051, 986, 892, 846, and 778 cm^{-1}. Mp = 118.5−121 °C. TLC R_f (2.4:1 hexanes/EtOAc) = 0.10.

2′-(Trimenthyloxysilyloxy)docetaxel (4d). Docetaxel (50.5 mg, 0.063 mmol, 1.0 equiv) was dissolved in dry THF (1.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (35 μL, 0.45 mmol, 7.2 equiv) was added by Wiretrol. Trimenthyloxychlorosilane (**5d**)[34] (50 μL, 44 mg, 0.083 mmol, 1.3 equiv) was added. The culture tube was sealed, and the suspension was allowed to stir for 18 h at 45 °C. The THF was removed by evaporation under reduced pressure. The solid residue was triturated with a mixture of hexanes/EtOAc (2:1), and the resulting slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 2.3:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (36.0 mg, 0.028 mmol, 44%). ^{1}H NMR (500 MHz, $CDCl_3$, some resonances were broadened presumably because of the presence of NBoc rotamers): δ 8.11 (d, *J* = 7.5 Hz 2H, O_2C-*o*-Ph, 7.59 (t, *J* = 7.2 Hz, 1H, O_2C-*p*-Ph), 7.49 (t, *J* = 7.8 Hz, 2H, O_2C-*m*-Ph), 7.36 (t, 2H, *J* = 7.7 Hz, C3′-*m*-Ph), 7.33 (d, 2H, *J* = 7.2 Hz, C3′-*o*-Ph), 7.27 (t, *J* = 7.0 Hz 1H, C3′-*p*-Ph), 6.23 (br dd, *J* = 8.3, 8.4 Hz, 1H, H13), 5.70 (d, *J* = 7.1 Hz, 1H, H2), 5.50 (d, *J* = 9.3 Hz, 1H H3′), 5.24 (br d, *J* = 8.8 Hz 1H, NH), 5.22 (s, 1H, H10), 4.95 (dd, *J* = 9.5, 1.5 Hz, 1H, H5), 4.90 (br s, 1H, H2′), 4.31 (d, *J* = 8.5 Hz, 1H, H20*α*), 4.26 (br dd, *J* = 11.0, 7.2, Hz, 1H, H7), 4.21 (d, *J* = 7.1 Hz, 1H, H20*β*), 4.19 (br s, 1H, C10OH), 3.94 (dd, *J* = 7.6, 5.2 Hz, 1H, H3), 3.60 (dt, *J* = 10.2, 3.8 Hz, 3H, $H1_{menth}$), 2.60 (ddd, *J* = 14.5, 9.7, 6.6 Hz, 1H, H6*α*), 2.39 (s, 3H, C4OAc), 2.28 (br m, 1H, H14*α*), 2.21 (br m, 1H, H14*β*), 2.20 (dsep, *J* = 7.0, 2.1 Hz, 3H, $H7_{menth}$), 1.96 (s, 3H, H18 =CCH_3), 1.85 (m, 1H, H6*β*), 1.84 (m, 3H, $H6_{menth}$), 1.75 (s, 3H, H19 O=CCCH_3), 1.67 (s, 1H, C1OH), 1.58 (m, 6H, $H3_{menth}$ and $H4_{menth}$), 1.33 (br s, 9H, *t*Boc), 1.26−1.24 [m, 6H, $H5_{menth}$ and C(Me)C16H_3], 1.30 [s, 3H, C(Me)C17H_3], 1.11 (m, 3H, $H2_{menth}$), 0.93−0.86 (m, 6H, $H4_{menth}$ and $H6_{menth}$), 0.88 (br d, 9H, $H8_{menth}$), 0.87 (br d, 9H, $H9_{menth}$), 0.79 (m, 3H, $H3_{menth}$), and 0.73 (d, *J* = 6.9 Hz, 9H, $H10_{menth}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 170.8, 169.9, 167.3, 155.7, 139.9, 139.1, 135.3, 133.8, 130.4, 129.4, 128.9, 128.8, 127.7, 126.6, 84.4, 81.0, 79.9, 79.2, 76.8, 75.2, 74.8, 74.7, 73.9, 72.2, 71.4 ($C1_{menth}$), 57.7, 56.5 (br), 49.7 ($C2_{menth}$), 46.5, 45.0 ($C7_{menth}$), 43.3, 37.2, 36.0, 34.6 ($C5_{menth}$), 31.7 ($C6_{menth}$), 28.4, 26.5, 25.3 ($C3_{menth}$), 22.82, 22.78 ($C4_{menth}$), 22.5 ($C8_{menth}$), 21.5 ($C9_{menth}$), 21.3, 15.8 ($C10_{menth}$), 14.7, and 10.2 ppm. (assignments of resonances of the menthyl moieties deduced from ^{13}C NMR spectrum assignments of [$(MenthO)_3SiOH$].[34] HRMS (ESI) calcd for $C_{67}H_{103}NNaO_{17}Si$ $[M + Na]^+$ 1322.7357; found 1322.7351. IR (thin film) 3445, 2953, 2927, 2872, 2360, 2340, 1762, 1717, 1496, 1454, 1368, 1274, 1245, 1163, 1108, 1083, 1070, 1052, 986, and 889 cm^{-1}. Mp = 119−121 °C. TLC R_f (1.5:1 hexanes/EtOAc) = 0.30.

2′-(Di-*tert*-butoxyethoxysilyl)docetaxel (4e). Docetaxel (40.0 mg, 0.049 mmol, 1.0 equiv) was dissolved in dry THF (2.0 mL) in an oven-dried culture tube fitted with a Teflon-lined cap and magnetic stir bar. Pyridine (50 μL, 0.63 mmol, 12.8 equiv) was added by Wiretrol. Dichlorodi-*tert*-butoxysilane (**6**)[35] solution consisting of ∼90% of the dichlorosilane and ∼10% of the monochlorosilane (100 μL, 93 mg, 0.38 mmol, 7.8 equiv) was added. The culture tube was sealed, and the suspension was allowed to stir for 12 h at 30 °C. Absolute ethanol dried over 4 Å molecular sieves (50 μL, 0.85 mmol, 17.5 equiv) was added, and the reaction mixture continued to stir for another 3 h. The THF was removed by evaporation under reduced pressure. The solid residue was triturated with a mixture of hexanes/EtOAc (2:1), and the resulting slurry was filtered through a short plug of Celite to remove the pyridinium salt. The filtrate was concentrated under reduced pressure, and the residue was purified by MPLC (SiO_2, 2:1 hexanes/EtOAc) to yield the title compound as a white, crystalline solid (30.2 mg, 0.029 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$, some resonances were broadened presumably because of the presence of NBoc rotamers): δ 8.09 (d, *J* = 7.6 Hz 2H, O_2C-*o*-Ph, 7.63 (t, *J* = 6.8 Hz, 1H, O_2C-*p*-Ph), 7.52 (t, *J* = 7.5 Hz, 2H, O_2C-*m*-Ph), 7.43 (t, 2H, *J* = 8.0 Hz, C3′-*m*-Ph), 7.33 (br d, 2H, C3′-*o*-Ph), 7.20 (br t, 1H, C3′-*p*-Ph), 6.15 (br m, 1H, H13), 5.81 (d, *J* = 7.2 Hz, 1H, H2), 5.66 (d, *J* = 6.9 Hz, 1H H3′), 5.18 (s, 1H, H10), 5.14 (br s, 1H, NH), 4.94 (br dd, *J* = 9.5, 2.3 Hz, 1H, H5), 4.76 (br s, 1H, H2′), 4.30 (d, *J* = 8.4 Hz, 1H, H20*α*), 4.24 (br dd, *J* = 10.7, 6.4, Hz, 1H, H7), 4.18 (d, 1H, *J* = 9.5 Hz, C7OH), 4.17 (d, *J* = 8.5 Hz, 1H, H20*β*), 3.89 (br d, *J* = 7 Hz, 1H, H3), 3.67 [br q, 2H, C2′OSi(OCH_2CH$_3$)], 2.58 (ddd, *J* = 14.7, 9.7, 6.5 Hz, 1H, H6*α*), 2.43 (br d, 1H, C7OH), 2.35 (s, 3H, O=CCH_3), 2.12 (br m, 1H, H14*α*), 1.94 (very br m, 1H, H14*β*, chemical shift deduced from the COSY spectrum), 1.91 (br s, 3H, H18 =CCH_3), 1.83 (ddd, *J* = 13.8, 11.3, 2.0 Hz, 1H, H6*β*), 1.73 (s, 3H, H19 O=CCCH_3), 1.60 (br s, 2H C7OH and C1OH), 1.35 (br s, 9H, *t*-Boc), 1.29 (br s, 9H, C2′OSi[OC(CH_3)], 1.26 (br s, 9H, C2′OSi[OC(CH_3)′], 1.22 (s, 3H, C17H_3), 1.15 (br t, *J* = 6.8 Hz, 3H, C2′OSi[OCH$_2$CH_3]), and 1.10 (br s, 3H, C16H_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.9, 170.8, 170.1, 167.2, 155.7, 139.7, 139.0, 135.4, 133.9, 130.4, 129.9, 129.5, 128.9, 128.7, 127.0, 84.4, 81.0, 79.9, 79.1, 76.8, 75.2, 75.1, 74.7, 74.0, 72.1, 71.0, 57.7, 59.3, 57.4, 46.5, 43.2, 37.1, 35.7, 31.41, 31.40, 28.4, 26.5, 22.9, 21.2, 18.2, 14.6, and 10.2 ppm. HRMS (ESI) calcd for $C_{53}H_{75}NNaO_{17}Si$ $[M + Na]^+$ 1048.4696; found 1048.4695. IR (thin film) 3456, 2975, 2931, 1757, 1715, 1602, 1494, 1453, 1391, 1367, 1315, 1286, 1270, 1243, 1166, 1070, 1026, 986, 949, 915, 889, 870, 834, 782, 759, 730, and 650 cm^{-1}. Mp = 97−104 °C. TLC R_f (2:1 hexanes/EtOAc) = 0.50.

Silicate Ester Hydrolysis Rate Studies. The PTX-silicate (∼10 mg) was dissolved in 900 μL of acetone-d_6. To this homogeneous solution, 100 μL of a 9:1 v/v solution of D_2O/TFA was added, and the solution was vigorously mixed. ^{1}H NMR spectra were taken (16 or 32 transients) at 500 MHz at multiple time points (8−30) over the course of more than 3 half-lives for all but the slowest reacting silicates. The study was conducted at room temperature (22 °C ± 1.0 °C). The relative integration values were used to determine the extent of hydrolysis. Typically, resonances for the 2′- and/or 7-methine protons

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for the starting taxane silicate and the product free taxane (PTX or DTX) vs that of H5 (a remote proton whose chemical shift was invariant for the two species) were integrated in a baseline-corrected spectrum using MestRe-C or iNMR software. Data were plotted as growth or decay curves as ln[species observed] vs time. The slope of each linear correlation gave the reported k_{obs} value. The indicated errors are the observed standard deviation from three replications of the experiment. The $t_{1/2}$ values were calculated under the assumption that the process was pseudo-first-order. The k_{rel} data presented in Table 2 are the ratios of k_{obs} for each silicate divided by that for the most slowly hydrolyzed silicate (**1d**).

Biology. Cell Culture Cytotoxicity (IC_{50} Determination) Studies. MDA-MB-231 and MDA-MB-231 luciferase positive cells[40] were maintained independently in minimum essential medium (MEM) supplemented with 1% penicillan/streptomycin and 10% fetal bovine serum (FBS) at 37 °C in a humidified incubator. MDA-MB-231 cells were obtained from the American Type Culture Collection. MDA-MB-231 Luc+ cells were obtained from Caliper Life Sciences. For cytotoxicity studies, MDA-MB-231 cells were seeded at 8000 cells/well in a 96-well plate in 100 μL of MEM with 5% FBS. Taxane and taxane silicate stock solutions (10 mM) were prepared in DMSO. Each stock solution was serially diluted in MEM with 5% FBS, and an amount of 100 μL of the solutions was pipetted into the 96-well plate. Concentration ranges were from 1 to 10 000 nM for PTX-silicates and from 0.1 to 1000 for DTX-silicates. After 72 h, 30 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) bromide reagent was added to each well. Absorbance at 490 nm was monitored on a 96-well plate UV/vis detector at 60 min. Viable cells reduce the tetrazolium compound, and the absorbance (and the concentration) of the product correlates to the number of viable cells. IC_{50} values were determined by nonlinear regression analysis of log of concentration vs response data obtained from the MTT assay. The IC_{50} was interpolated from the resulting curves using Graphpad Prism, version 5.1.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for each silicate and a table of ancillary cLogP values. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

PTS, paclitaxel; DTX, docetaxel; BCP, block copolymer; NP, nanoparticle; FNP, flash nanoprecipitation; PEG, poly(ethylene glycol); PLA, poly(lactic acid); PCL, poly(caprolactone); PLGA, poly(lactic-*co*-glycolic acid); DHA, docosahexaenoate; TFA, trifluoroacetic acid; PPG, poly(propylene glycol); ACS, American Chemical Society; MPLC, medium pressure liquid chromatography; ATR, attenuated total reflectance; PMA, phosphomolybdic acid; MEM, minimum essential medium; FBS, fetal bovine serum; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

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