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Design and synthesis of simplified taxol analogs based on the T-Taxol bioactive conformation

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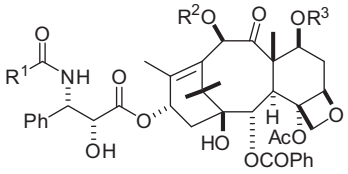
ABSTRACT

A series of compounds designed to adopt a conformation similar to the tubulin-binding T-Taxol conformation of the anticancer drug paclitaxel has been synthesized. Both the internally bridged analogs **37–39**, **41** and the open-chain analogs **27–29** and 4**3** were prepared. The bridged analogs **37–39** and **41** were synthesized by Grubbs' metatheses of compounds **30**–**32** and **33**, which, in turn, were prepared by coupling β-lactams **24–26** with alcohols **22** and **23**. Both the bridged and the open-chain analogs showed moderate to good cytotoxicity.

1. Introduction

The clinically important naturally occurring anticancer agent paclitaxel (Taxol®) (**1a**) was first isolated in the 1960's by Wall and Wani, and its structure was published in 1971.[1] After a difficult and lengthy development period[2] it was approved in 1992 by the US Food and Drug Administration (FDA) for the treatment of ovarian cancer and in 1994 for treatment of breast cancer. The drug, together with its semisynthetic analog docetaxel (**1b**),[3] have become two of the most important and widely used anticancer drugs for treatment of breast[4] and ovarian cancers.[5] Their superior biological activities have spurred extensive studies on the chemistry and structure–activity relationships of the taxanes, and virtually every position of the molecule has been modified.[6] Numerous synthetic analogs with better activities and pharmacokinetic properties have been developed and some promising analogs have entered clinical trials.[7] However, none of the analogs other than docetaxel (**1b**)[8] and cabazitaxel (**1c**)[9] have yet been approved for clinical use by the Food and Drug Administration.



1a R^1 = Ph, R^2 = Ac, R^3 = H
1b R^1 = $(CH_3)_3CO$, R^2 = R^3 = H
1c R^1 = $(CH_3)_3CO$, R^2 = R^3 = CH_3

Paclitaxel exerts its anticancer activity by binding to the protein tubulin and promoting its polymerization to microtubules.[10] The disruption of the normal tubulin-microtubule dynamics leads to abnormal cell division followed by apoptosis.[11] The interaction of paclitaxel with tubulin has been studied intensively by several methods, including photoaffinity labeling,[12] fluorescence spectroscopy[13] and electron crystallography.[14] While these studies provided crucial information on the nature of the paclitaxel–tubulin interaction, only the latter has been able to furnish details of the actual binding conformation of paclitaxel.

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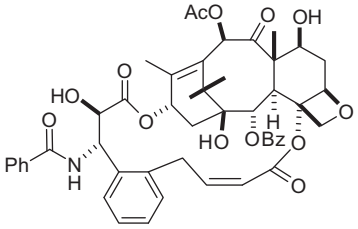
Early investigations of the conformation of paclitaxel in solution led to the identification of both 'polar'[15] and 'non-polar'[16] conformations, based on NMR studies of paclitaxel in polar and non-polar solvents, respectively. Later NMR studies using the NAMFIS analysis identified the T-Taxol conformation as a third solution-phase conformation,[17] and this was proposed to be the tubulin-binding conformation by Snyder and coworkers based on computational studies and data obtained from the electron density map of paclitaxel-bound tubulin from the electron crystallography studies.[18] The validity of the T-Taxol model was then established experimentally by the determination of intramolecular distances in tubulin-bound paclitaxel by REDOR NMR experiments[19] and by the synthesis of constrained paclitaxel analogs such as **2**. This compound adopts the T-Taxol conformation and is significantly more active than paclitaxel in both cytotoxicity and tubulin polymerization assays.[20] Analog **2**, in its 3-D representation, thus defines the required conformation for the effective binding of paclitaxel analogs to tubulin.



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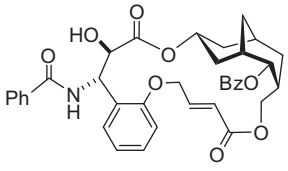
The synthesis of paclitaxel is a challenging task, and although several outstanding total syntheses have been published,[21] none of them are scaleable to economical commercial production. The synthesis of structurally simplified paclitaxel analogs with retained or even improved activities is thus an attractive goal. Although several attempts toward this goal have been reported,[22] the analogs resulting from these studies were either inactive or significantly less active than paclitaxel.



3

Our group has previously designed and synthesized the simplified paclitaxel analog (**3**) where a 2.2.1-bicyclononane moiety was used as a structurally simpler surrogate of the baccatin core.[23] The logic behind this design was that the northern hemisphere of the paclitaxel structure is less crucial to its bioactivity based on its known SAR,[6a] and that a structure with the T-Taxol pharmacophore could be achieved by installation of the paclitaxel side chain to a simple bridged bicyclic skeleton and subsequent constraint of the conformation by a suitable bridge. The resulting compound **3** showed moderate activity in assays for antiproliferative activity.

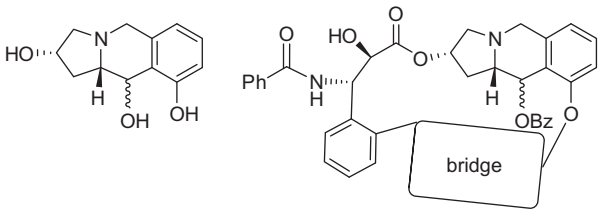


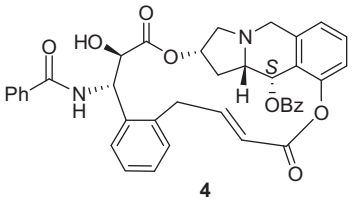
Figure 1. General structure of second generation tricyclic core (left) and T-Taxol mimics (right).

However, it was found to be highly insoluble in water, which made its biological evaluation very difficult, and it had only modest tubulin assembly activity.[23]

In this second approach to the objective of developing a new generation of water-soluble simplified paclitaxel analogs, an aza-tricyclic moiety (Fig. 1, left) was designed to mimic the baccatin core of paclitaxel, based on an earlier bicyclic analog prepared by Ojima.[22a] The basic tertiary nitrogen was anticipated to increase water-solubility, and the aza-tricyclic moiety is functionalized with three hydroxyl groups where the key side chains can be attached. The final construct (Fig. 1, right) can be constrained to the T-Taxol conformation by selection of an appropriate length for the bridge linking the side chain and the tricyclic core. This new core bears three stereogenic centers which can lead to eight possible stereoisomers. The availability of various hydroxyprolines as starting materials allows for control of two of these three centers.

A computer modeling study was performed to determine which of the eight possible isomers best serves as the optimal replacement of the baccatin structure. Thus, a conformational search was carried out for each of the eight isomers using the MMFF force field embedded in Maestro,[24] and subsequently each of the eight global minima was fitted with analog side chains and various bridges. Each such structure was then geometry optimized and Glide docked[25] into the paclitaxel binding site on tubulin. Individual dockings returned a variety of poses (i.e. binding modes). Those that best mimicked the shape and extension of **2** were selected and evaluated with the independent MM-GBSA scoring function.[26] Figure 2 shows the two most favorable binding structures (**4** and **5**) together with the active analog **2** in a 3-D representation of the tubulin binding site. Compounds **4** and **5** are derived from two different stereoisomers of the aza-tricyclic moiety, with *S*- and *R*-configurations at C-10, respectively.

Encouraged by these results we elected to prepare analogs arising from both stereoisomers and with different bridge lengths for comparison. For easier synthetic manipulation, the bridged structure was modified to that of **6**, containing an ether linkage rather than the ester linkage of compounds **4** and **5**. After the synthetic part of this work had been completed, Ojima reported the synthesis and biological evaluation of a similar series of compounds, albeit with longer bridges and other variations.[22b] The present work can be viewed as an extension of this parallel study.



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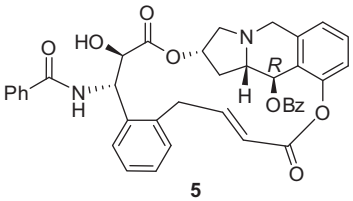

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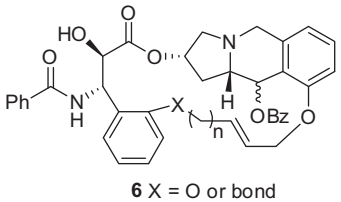


6 X = O or bond
n = 1-3

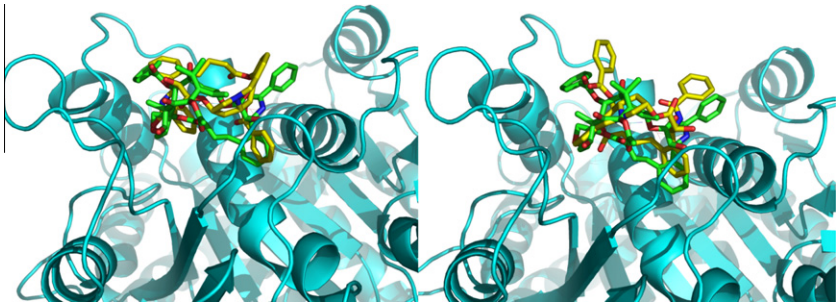


Figure 2. Left: low energy poses of compounds of **4** (in green) and **2** (in yellow) in the paclitaxel tubulin binding site. Right: low energy poses of compounds **5** (in green) and **2** (in yellow) in the paclitaxel tubulin binding site.

2. Results and discussion

The retro-synthetic analysis of compounds of general structure **6** is shown in Scheme 1. The synthesis of the simplified analogs started with the construction of the aza-tricyclic core from *cis*-4-hydroxyproline derivative **7** and aldehyde **8**, followed by its coupling with the β-lactam forms of the side chain derivatives to furnish the side chains and finally Grubbs' metatheses to furnish the bridges.

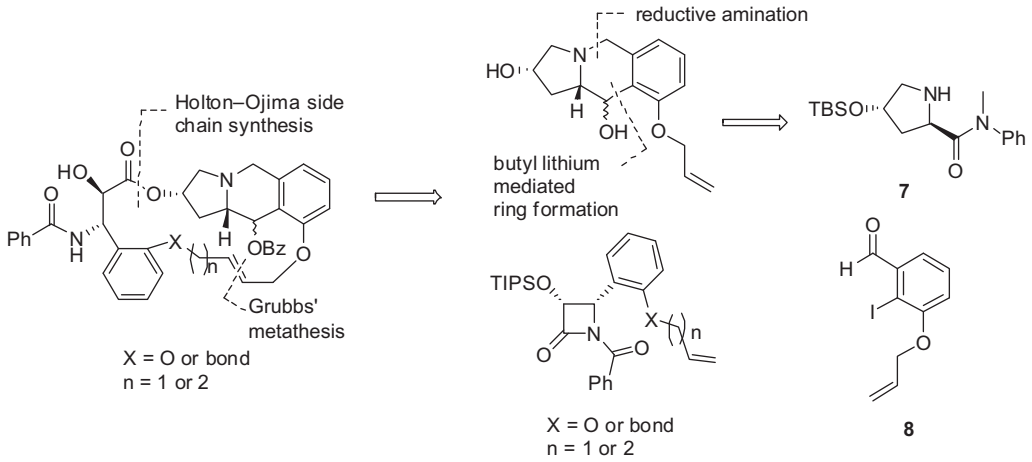
The *cis*-4-hydroxyproline derivative **7** was synthesized from commercially available *trans*-4-hydroxy-L-proline in nine straightforward steps with high yields (Scheme 2). The amino acid was protected as its carbamate and methyl ester derivative **9**,[27] followed by a Mitsunobu reaction, which successfully inverted the stereochemistry at C-4.[28] The resulting ester **10** was hydrolyzed and reprotected as its TBS ether **11** with an overall yield of 63% in five steps. Compound **11** was hydrolyzed to acid **12**, which was converted to amide **14** in two steps. The Boc protecting group was selectively removed with $ZnBr_2$ to produce **7** in 95% yield.

Aldehyde **8** was synthesized from 3-methoxybenzyl alcohol in four steps (Scheme 3). Commercially available 3-methoxybenzyl alcohol was treated with butyl lithium and iodine to afford compound **15**,[29] which was oxidized with Jones' reagent. The resulting aldehyde **16** was treated with boron tribromide to cleave the methyl ether and then combined with allyl bromide in the presence of base to generate compound **8**.

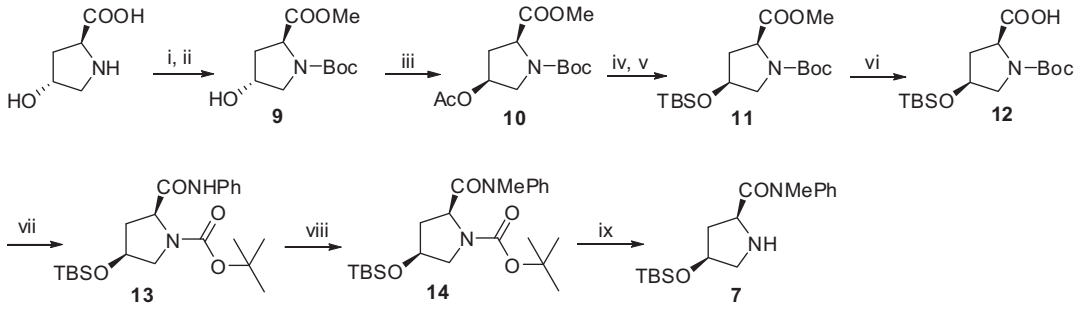
Reductive amination between compounds **7** and **8** with sodium triacetoxyborohydride went smoothly, generating compound **18** (Scheme 4). Cyclization of **18** mediated with *n*-BuLi afforded the key aza-tricyclic intermediate **19**. This compound was found to be unstable on a silica gel column, and so it was reduced directly with sodium borohydride to afford **20** as the only stereoisomer in an overall yield of 42% for three steps. The stereoselectivity was conceivably driven by the bulky TBS protecting group. The absolute stereochemistry of **20** was determined by X-ray crystallography of compound **21** (Fig. 3), which was prepared by acylation of the newly generated hydroxyl group followed by deprotection of the silyl ether. As expected, reduction of **19** after deprotection of the large protecting group produced the epimeric diol **22** as the major product, together with lesser amounts of diol **23** (**22**:**23** = 3:2). The absolute stereochemistry of the former was also determined by X-ray crystallography (Fig. 3).

The known β-lactams **24–26** were prepared following the literature procedures.[30] They were coupled with alcohol **21** to generate open-chain analogs **27–29** in good yields (Scheme 5). The subsequent ring closing metatheses of these alkenes with Grubbs' 2nd generation catalyst failed to bring about the desired bridged products, even though several different catalysts and conditions were evaluated. Examination of the 3-D structure of a low energy conformer of compound **28** (Fig. 4) suggested that the benzoyl group interposing between the two olefins could be responsible for the low reactivity. Thus, an alternate synthesis was developed allowing introduction of the benzoyl group after alkene metathesis.

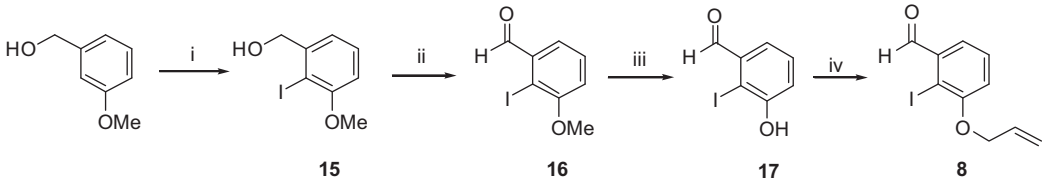
Alkenes **30–32** were prepared by coupling alcohol **23** with β-lactams **24–26**, respectively, and **33** was synthesized from alcohol **22** and β-lactam **26** in good yield. Pleasingly, the ring closing metathesis of alkene **30** gave the desired bridged product, but only in trace amounts. Since it has been reported that some nitrogen containing compounds, especially amines, are poor substrates for Grubbs' ruthenium catalysts,[31] we surmised that the low yield



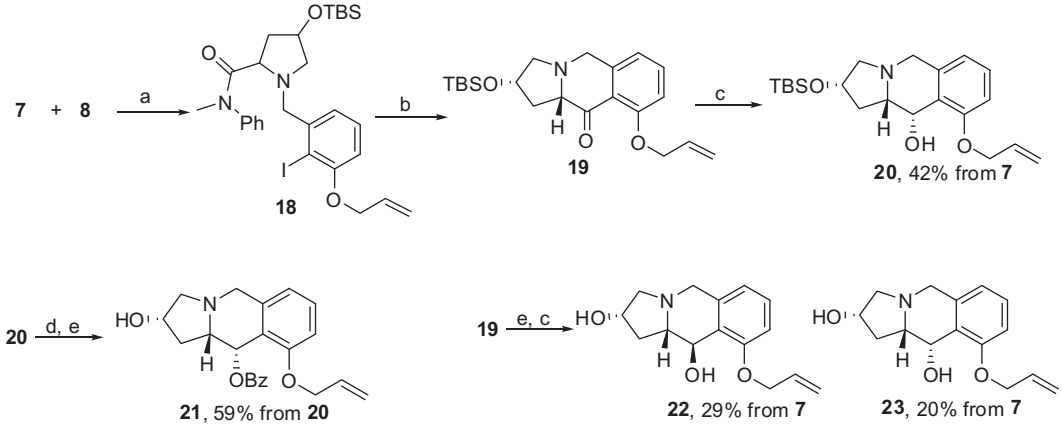
Scheme 1. Retro-synthesis of simplified paclitaxel analogs.



Scheme 2. Synthesis of intermediate **7**. Reagents and conditions: (i) aqueous NaOH, di-*tert*-butyl dicarbonate, THF/H_2O, overnight; (ii) Cs_2CO_3, MeI, DMF, overnight; (iii) AcOH, PPh_3, DIAD, THF, overnight; (iv) K_2CO_3, MeOH, 1 h; (v) TBSCl, imidazole, DMF, 16 h, 63% for five steps; (vi) aqeous LiOH, MeOH, 45 °C, 6 h, 95%; (vii) TEA, $ClCOOCH_3$, 0 °C, TFH, 1 h; aniline, THF, 1 h, 79%; (viii) NaH, MeI, DMF, 93%; (ix) $ZnBr_2$, CH_2Cl_2, 95%.



Scheme 3. Synthesis of compound **8**. Reagents and conditions: (i) *n*-BuLi, I_2, hexane/ether, −78 °C, 57%; (ii) Jones reagent, acetone/water; (iii) BBr_3, CH_2Cl_2, 41% for two steps; (iv) allyl bromide, K_2CO_3, DMF, 96%.



Scheme 4. Synthesis of alcohols **21**–**23**. Reagents and conditions: (a) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (b) BuLi, THF, −78 °C; (c) $NaBH_4$, MeOH; (d) LiHMDS, PhCOCl, THF; (e) HF·pyridine, THF.

was due to the presence of the tertiary amine in **30**. To overcome this problem, compound **30** was protonated with 10-camphorsulfonic acid before the addition of the Grubbs' catalyst, and the yield of the metathesis reaction was found to be greatly improved. The resulting macrocyclic compound was benzoylated and deprotected to afford the target analog **37** with an overall yield of 61% in three steps from **30**. Compound **38** with a shorter bridge was prepared from alkene **31** by similar procedures, although the overall yield was much lower.

In the case of compound **32**, the metathesis reaction suffered from very poor yield (7% for 2 steps), affording the bridged analog **39**. Interestingly, the C-2 epimeric alkene **33** reacted smoothly under the same ring closing metathesis conditions to deliver 5-atom bridged **41** in 33% overall yield from compound **33**. The different reactivities of **32** and **33** were probably due to the opposite orientation of the free hydroxyl groups. The corresponding open-chain analog **43** was synthesized in two steps from **33**.

3. Biological evaluation

The open-chain analogs **27–29**, **43** and bridged analogs **37–39**, **41** were evaluated for their antiproliferative activities against the A2780 cell line. The results are summarized in Table 1. The simplified analogs were cytotoxic, but over 300-fold less cytotoxic than paclitaxel. The bridged analogs (**37**–**39**) exhibited slightly better activity than their open-chain counterparts **27–29**. Compound **41** was significantly more active (4-fold) than the open-chain analog **43**.

The analogs were also evaluated for tubulin assembly or disassembly activity with pure α,β-tubulin. Relatively high concentrations of ligand are required for this type of assay,[32] so the solubility of each molecule as a function of analog concentration and DMSO concentration was first assessed. The limit of solubility of these molecules in 10% DMSO in buffer is about 60 μM. The combination of weak activity and low solubility severely complicates

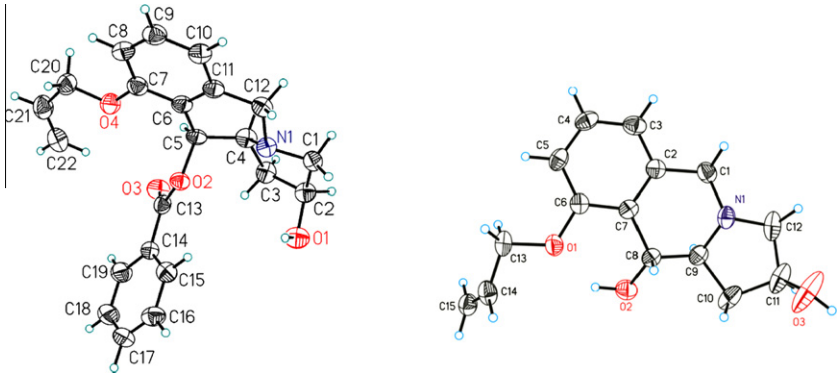
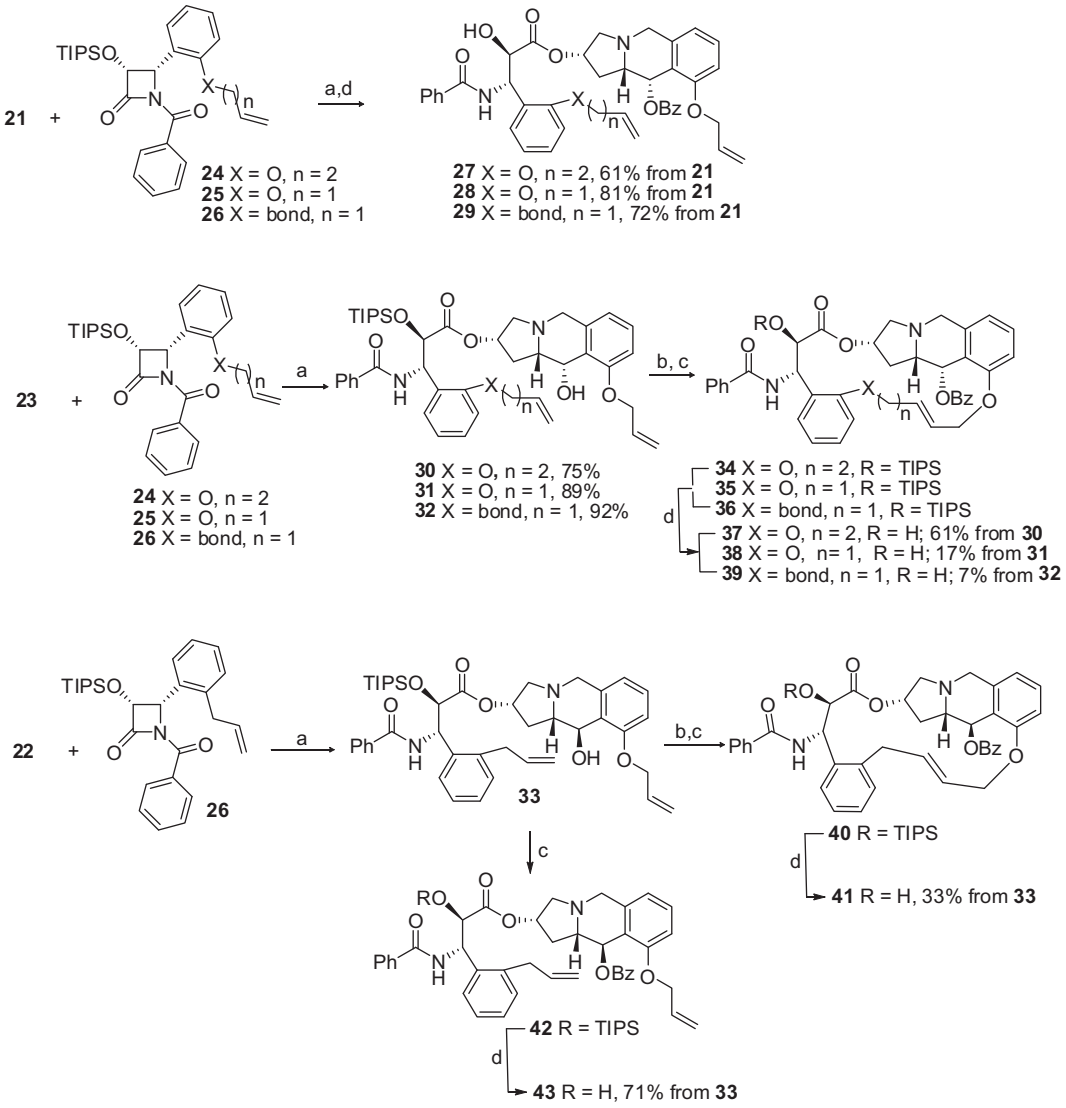


Figure 3. Anisotropic displacement ellipsoid drawing of the X-ray crystal structures of **21** (left) and **22** (right).



Scheme 5. Synthesis of open-chain and bridged paclitaxel analogs. Reagents and conditions: (a) NaH, THF, 0 °C, 76–92%; (b) 10-camphorsulfonic acid, CH_2Cl_2, 40 °C; Grubbs' 2nd generation catalyst, CH_2Cl_2, 40 °C; (c) LiHMDS, benzoyl chloride, −78 °C, THF; (d) HF·Py, THF, 0 °C to rt.

measuring the effect of the molecules on tubulin assembly. A number of experimental conditions to assess polymerization were evaluated, two of which are described.

Figure 5 illustrates a microtubule disassembly assay. In this assay, the ability of a ligand to stabilize microtubules against cold-induced depolymerization is assessed. Tubulin is polymerized in the presence and absence of the ligand by raising the temperature of the solutions to 37 °C. The concentration of microtubules is proportional to the amount of light scattered, assessed as the change in the optical density of the sample at 350 nm. For each

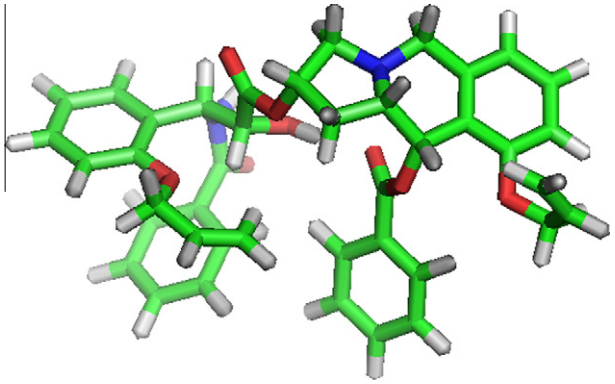


Figure 4. 3-D structure of **28** optimized with PM3 method in Spartan.

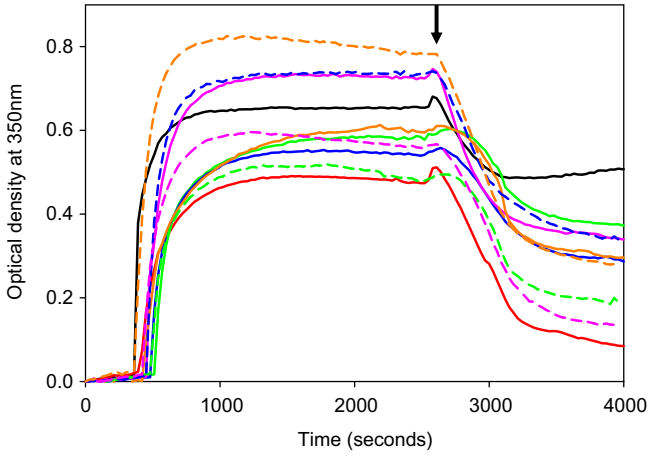


Figure 5. Tubulin assembly was monitored by optical density at 350 nm at 37 °C as described under Section 5. At the time indicated by the arrow the temperature was decreased to 4 °C to monitor temperature induced disassembly. Taxol: solid black line. DMSO only (no ligand): solid red line. Open chain compounds (solid lines): **27** (green), **28** (blue), **29** (pink), **43** (orange). Bridged compounds (dashed lines): **37** (green), **38** (blue), **39** (pink), **41** (orange). The concentration of Taxol was 15 μM. The concentration of all synthetic ligands was 60 μM. The concentration of tubulin was 15 μM.

sample, after a steady state is reached the temperature of the cell holder is dropped to 4 °C (arrow, Fig. 5). In the absence of a stabilizing ligand, microtubules are completely disassembled after the sample is cooled (solid red curve in Fig. 5). A stabilizing ligand such as paclitaxel increases the concentration of microtubules formed at 37 °C (solid black curve, Fig. 5) and prevents complete disassembly at 4 °C. A new steady state of microtubule polymers is established in the paclitaxel-containing sample.

The activity of the open chain and bridged analogs were similar to paclitaxel in this assay. Some of the analogs appeared to increase the concentration of microtubules and provide some protection against cold-induced depolymerization, as judged by the higher plateau values at 37 and 4 °C relative to the control.

It was noted that ligand solutions that contain undissolved material scatter light in the same wavelength range as microtubules. We suspect this to be due to the aggregation of the highly hydrophobic simplified taxanes.[33] Such clusters not only inhibit proteins in vitro at micromolar concentrations, but also appear to promote partial protein unfolding.[34] Therefore the light scattering assay cannot distinguish between a solution containing partially perturbed microtubules and one in which an insoluble and possibly aggregated taxane analog is also present. Also, since the depolymerization assay involves changing the temperature of the solution, this may also affect the solubility of the ligand. Multiple parameters of the assay were changed in attempts to verify the apparent effect of the analogs on microtubule assembly, but the results of all experiments were ambiguous.

An alternative method for monitoring tubulin assembly is to observe the fluorescence of DAPI (4′,6-diamidino-2-phenylindole), which increases as tubulin polymerizes.[35] Light scattering from insoluble material is therefore not directly observed in this detection method. Again, a number of parameters were varied. Figure 6 shows the results of one of these experiments. The assay conditions were adjusted such that the tubulin concentration was just slightly below the critical concentration of the protein, so no significant polymerization is observed in the control (compare red curve to black curve in Fig. 6). In contrast to the light scattering results, none of the analogs showed activity in the fluorescence assays.

These experiments illustrate that great care must be taken to assess molecules that may be weakly active in microtubule assembly assays. Conclusions based on just one or two measurements

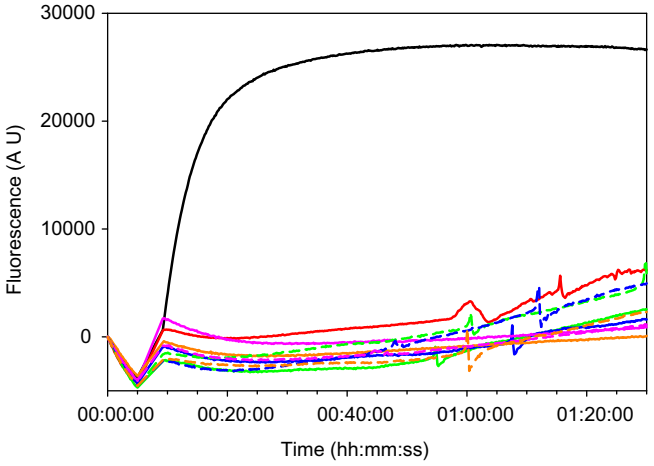


Figure 6. Tubulin assembly was monitored by the fluorescence of microtubule-bound DAPI as a function of time at 37 °C using a SynergyMx multi-mode microplate reader as described under Section 5. Taxol (final concentration 8 μM) or test compound (final concentration 60 μM) in DMSO (final concentration 10% v/v) was added to initiate polymerization in solutions containing 8 μM tubulin and 10 μM DAPI. Taxol: solid black line. DMSO only (no ligand): solid red line. Open chain compounds (solid lines): **27** (green), **28** (blue), **29** (pink), **43** (orange). Bridged compounds (dashed lines): **37** (green), **38** (blue), **39** (pink), **41** (orange).

may incorrectly attribute microtubule assembly activity to poorly soluble and potentially aggregated small molecules, especially when using light scattering methods. Such an outcome might likewise have influenced recent measurements on a related series of truncated taxanes with cytotoxic activities similar to those reported here (IC_{50} 6 to >20 μM).[22b,33] Unless parallel microtubule

Table 1
Antiproliferative activities (IC_{50}, μM)[a] of paclitaxel and the simplified paclitaxel analogs

Compound#	**37**	**27**	**38**	**28**	**39**	**29**	**41**	**43**	Paclitaxel
A2780[b]	4.5 ± 0.7	5.8 ± 0.5	4.1 ± 0.4	8.3 ± 0.7	4.0 ± 1.5	4.7 ± 0.6	5.1 ± 0.7	23.8 ± 5.2	0.015 ± 0.001

[a] The concentration at which the compound inhibits 50% of the cell growth.
[b] Human ovarian cancer cell line.

assembly measurements are carried out, however, a direct comparison cannot be made.

4. Conclusions

The simplified paclitaxel analogs **27–29**, **37–39**, **41** and **43** containing an aza-tricyclic moiety have been designed and synthesized. The bridged analogs **37–39** designed to adopt the T-Taxol conformation show only very slightly better activities compared to their open-chain counterparts in the cytotoxicity assay. However, their low solubility and putative aggregation precluded confirmation of microtubule activity in assays using pure tubulin. The lack of activity relative to paclitaxel in the cells can, in part, be attributed to the complex conformational profile of the macrocyclic rings relative to the parent molecule and to its bridged analogs and, perhaps, in part to micelle-like small molecule clusters formed both in solution and in cells. These problems are not insurmountable, and the synthesis of analogs with modified structures that can better mimic the T-Taxol conformation based on modeling studies may yet be achieved by suitable synthetic design.

5. Experimental section

5.1. Chemistry

5.1.1. General experimental methods

The following standard conditions apply unless otherwise stated. All reactions were performed under argon or nitrogen in oven-dried glassware using dry solvents and standard syringe techniques. Tetrahydrofuran (THF) was distilled from the sodium benzophenone ketyl radical ion. Dichloromethane was distilled from calcium hydride. All reagents were of commercial quality and used as received. After workup, partitioned organic layers were washed with water and brine and dried over sodium sulfate (Na_2SO_4). Reaction progress was monitored using aluminum-backed thin layer chromatography (TLC) plates pre-coated with silica UV254. Purification of products by column chromatography was conducted using a column filled with Silica Gel 60 (220–240 mesh) using eluting solvent systems as indicated. Purification by preparative thin layer chromatography (PTLC) was performed using glass-backed plates pre-coated with silica UV254. HPLC was conducted on Shimadzu SCL-10AVP system using a column purchased from Phenomenex (Luna 5μ C18 (2) 25 × 4.6 mm). ^1H and ^{13}C NMR spectra were recorded on a 400 MHz (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer or a 500 MHz (500 MHz for ^1H and 126 MHz for ^{13}C) spectrometer in $CDCl_3$. All chemical shifts (δ) were referenced to the solvent peaks of $CDCl_3$ (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). Optical rotation was measured on a polarimeter operating at the sodium D-line.

5.1.2. (2*S*,4*R*)-*N*-Boc-4-hydroxy-proline methyl ester (9)

A solution of *trans*-4-hydroxy-L-proline (5.24 g, 40 mmol) in THF (50 mL) and water (25 mL) was treated with aqueous NaOH (10%, 17 mL) and di-*tert*-butyl dicarbonate (13.1 g, 60 mmol, 1.5 equiv). The mixture was stirred overnight at room temperature. THF was evaporated under reduced pressure. The aqueous solution was adjusted to pH 2 with 10% aqueous $NaHSO_4$ solution and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed, dried and concentrated to yield the crude product, which was used in the next step without further purification.

To a solution of the above mentioned crude product in DMF (180 mL) at room temperature was added Cs_2CO_3 (18.5 g, 56.8 mmol). After the mixture was stirred for 15 min, MeI (4.05 mL, 59.4 mmol) was added dropwise. The resulting mixture was then stirred overnight and filtered through a short column packed with Celite®. The filtrate was concentrated under reduced pressure and the residue was partitioned between saturated aqueous $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The aqueous phase was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed, dried and concentrated. Column chromatography (50% EtOAc in hexanes) afforded the title compound as a yellowish oil (9.5 g, 97% for two steps). $[\alpha]_D^{23}$ −69.4 (*c* 1.3, MeOH); ^1H NMR (400 MHz) δ 4.48 (s, 1H), 4.44 (t, *J* = 7.7 Hz, 0.4H), 4.38 (t, *J* = 8.0 Hz, 0.6H), 3.72 (d, *J* = 4.7 Hz, 3H), 3.61 (dt, *J* = 15.6, 7.8 Hz, 1H), 3.55 (d, *J* = 11.7 Hz, 0.6H), 3.44 (d, *J* = 11.3 Hz, 0.4H), 2.28 (m, 1.6H), 2.16 (s, 0.4H), 2.11–2.00 (m, 1H), 1.75 (s, 0.6H), 1.42 (m, 9H); ^{13}C NMR (126 MHz) δ 173.73, 173.51, 154.61, 154.05, 80.47, 80.38, 77.36, 77.31, 77.11, 76.85, 70.31, 69.57, 57.98, 57.55, 54.84, 54.78, 52.35, 52.14, 39.21, 38.56, 28.46, 28.33, 0.07; HRMS (ESI) calcd for $C_{11}H_{20}NO_5$ *m/z* 246.1341 ($[M+H]^+$), found *m/z* 246.1333.

5.1.3. (2*S*,4*S*)-*N*-Boc-4-acetoxy-proline methyl ester (10)

To a solution of **9** (9.5 g, 38.7 mmol), triphenyl phosphine (21 g, 80 mmol, 2.1 equiv) and acetic acid (4.6 mL, 80 mmol, 2.1 equiv) in THF was added diisopropyl azodicarboxylate (DIAD) dropwise (15.8 mL, 80 mmol, 2.1 equiv) at 0 °C. The resulting mixture was warmed up to rt and stirred overnight. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (1:2 EtOAc–hexanes) to yield **10** as a colorless oil (9.7 g, 87%). $[\alpha]_D^{23}$ −18.4 (*c* 1.1, MeOH); ^1H NMR (500 MHz) δ 5.23–5.17 (m, 1H), 4.48 (d, *J* = 9.0 Hz, 0.5H), 4.36 (d, *J* = 9.2 Hz, 0.5H), 3.75–3.66 (m, 4H), 3.57 (d, *J* = 12.4 Hz, 0.5H), 3.49 (d, *J* = 12.4 Hz, 0.5H), 2.43 (m, 1H), 2.31–2.20 (m, 1H), 1.98 (s, 3H), 1.41 (m, 9H); ^{13}C NMR (126 MHz) δ 172.63, 172.28, 170.50, 170.33, 154.18, 80.40, 72.94, 71.79, 62.63, 57.81, 57.43, 52.32, 52.16, 51.82, 36.37, 35.43, 28.44, 28.33; HRMS (ESI) calcd for $C_{13}H_{21}NNaO_6$ *m/z* 310.1267.1341 ($[M+Na]^+$), found *m/z* 310.1263.

5.1.4. (2*S*,4*S*)-*N*-Boc-4-(*tert*-butyldimethylsilyloxy)prolinemethyl ester (11)

To a solution of **10** (9.7 g, 33.8 mmol**)** in methanol (250 mL) was added K_2CO_3 (5.5 g, 36 mmol, 1.07 equiv). The mixture was stirred for 1 h at rt and filtered. The solvent was evaporated in vacuo and the residue purified by column chromatography (1:1 EtOAc–hexanes) to yield (2*S*,4*S*)-*N*-Boc-4-hydroxy-proline methyl ester as a colorless oil (6.5 g, 78%): $[\alpha]_D^{23}$ −64.1 (*c* 0.5, MeOH); ^1H NMR (500 MHz) δ 4.29–4.24 (m, 7H), 3.75 (s, 1H), 3.77 (s, 2H), 3.66 (d, *J* = 12.0 Hz, 0.5H), 3.59 (d, *J* = 12.0 Hz, 0.5H), 3.51 (m, 1.5 H), 3.29 (d, *J* = 9.5 Hz, 0.5H), 2.40–2.17 (m, 1H), 2.11–2.03 (m, 1H), 1.44 (s, 2.5H), 1.39 (s, 6.5H); ^{13}C NMR (126 MHz) δ 175.80, 175.50, 154.55, 153.77, 80.52, 71.36, 70.32, 60.48, 57.95, 57.76, 56.02, 55.43, 52.87, 52.58, 38.62, 37.79, 28.43, 28.32, 22.02, 21.12, 14.26; HRMS (ESI) calcd for $C_{11}H_{20}NO_5$ *m/z* 246.1341 ($[M+H]^+$), found *m/z* 246.1325.

The product obtained above (6.5 g, 26.5 mmol), *tert*-butyldimethylsilyl chloride (9.6 g, 63.6 mmol, 2.4 equiv) and imidazole (9.0 g, 132.5 mmol, 5 equiv) were stirred in DMF (50 mL) overnight at rt. The reaction mixture was diluted with EtOAc (100 mL), washed with water (10 mL × 2) and brine (10 mL × 2), dried with anhydrous Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (1:4 EtOAc–hexanes) yielded **11** as a colorless oil (8.8 g, 93%). $[\alpha]_D^{23}$ −35.0 (*c* 0.7, MeOH); ^1H NMR (500 MHz) δ 4.43–4.21 (m, 2H), 3.67 (s, 3H), 3.60 (dd, *J* = 11.1, 5.4 Hz, 0.63H), 3.54 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.30 (dd, *J* = 11.1, 3.6 Hz, 0.63 H), 3.25 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.33–2.16 (m, 1H), 2.09–2.02 (m, 1H), 1.44 (s, 3H), 1.39 (s, 6H), 0.83 (s, 3H), 0.82 (s, 6H), 0.04–-0.02 (m, 6H); ^{13}C NMR (126 MHz) δ 172.95, 172.51, 154.44, 153.93, 79.96, 70.73, 69.80, 57.84, 57.44, 54.82, 54.25, 52.10, 51.96, 39.63, 38.81, 28.50, 28.38, 25.68, 25.66, 17.96, −4.88, −4.98; HRMS

(ESI) calcd for $C_{17}H_{34}NO_5Si$ *m/z* 360.2206 ([M+H]$^+$), found *m/z* 360.2199.

5.1.5. (2*S*,4*S*)-*tert*-Butyl 4-(*tert*-butyldimethylsilyloxy)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (13)

To a solution of **11** (8.8 g, 24.5 mmol) in methanol (45 mL) was added aqueous lithium hydroxide (2.5 M, 15 mL). The mixture was stirred for 6 h at 45 °C. The solution was adjusted to pH 3 with 3 M HCl solution and extracted with EtOAc (30 mL × 3). The organic solution was dried and concentrated at reduced pressure. Column chromatography (5% MeOH in CH_2Cl_2) afforded the carboxylic acid **12** as a colorless oil (5.8 g, 77%).

To a stirred solution of the acid (5.8 g, 16.8 mmol) and triethylamine (2.6 mL, 18.5 mmol) in THF (60 mL) at 0 °C was added methyl chloroformate (1.4 mL, 18.5 mmol, 1.1 equiv) dropwise. After stirring for 1 h at 0 °C, aniline (1.7 mL, 18.5 mmol, 1.1 equiv) was added. The resulting mixture was stirred for 1 h at 0 °C, 16 h at rt and then 3 h under reflux. The reaction was cooled to rt and diluted with EtOAc (100 mL). The organic solution was washed, dried and concentrated to produce the crude product, which was purified by column chromatography (1:6 EtOAc–hexanes) to yield compound **13** as a colorless oil (5.5 g, 78%). $[\alpha]_D^{23}$ −32.8 (*c* 0.7, MeOH); ^{1}H NMR (500 MHz) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 6.9 Hz, 1H), 4.38 (m, 2H), 3.70–3.26 (br s, 2H), 2.27 (br s, 2H), 1.42 (br s, 9H), 0.76 (br s, 9H); ^{13}C NMR (126 MHz) δ 170.99, 155.15, 128.96, 124.07, 119.52, 81.24, 70.70, 61.41, 56.39, 39.65, 28.40, 25.67, 18.10, −4.85; HRMS (ESI) calcd for $C_{22}H_{37}N_2O_4Si$ *m/z* 421.2523 ([M+H]$^+$), found *m/z* 421.2516.

5.1.6. (2*S*,4*S*)-*tert*-Butyl 4-(*tert*-butyldimethylsilyloxy)-2-(*N*-methyl-*N*-phenylcarbamoyl)-pyrrolidine-1-carboxylate (14)

To a solution of **13** (5.4 g, 12.8 mmol) in DMF (75 mL) was added NaH (3.1 g, 60%, dispersed in mineral oil, 77.5 mmol, 6.6 equiv) at 0 °C and the resulting mixture was stirred at the same temperature for 1 h, followed by the slow addition of MeI (4.8 mL, 76.6 mmol, 6 equiv). The reaction was stirred for another 15 min at 0 °C and quenched by adding cold water. The aqueous phase was extracted with EtOAc (50 mL × 3) and the combined organic phase was washed, dried and concentrated. The crude product was purified with column chromatography (1:4 EtOAc–hexanes) to afford **14** as a crystalline solid (5.2 g, 93%). $[\alpha]_D^{23}$ −22.1 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz) δ 7.52–7.28 (m, 5H), 7.21 (d, *J* = 8.5 Hz, 1H), 4.22–3.99 (m, 2H), 3.78–3.58 (m, 1H), 3.26 (s, 3H), 3.23–3.16 (m, 1H), 2.06–1.91 (m, 1H), 1.89–1.69 (m, 1H); ^{13}C NMR (126 MHz) δ 171.88, 154.16, 153.59, 143.50, 143.19, 129.86, 129.76, 128.62, 128.17, 127.99, 127.85, 127.75, 125.72, 124.81, 79.89, 79.51, 69.55, 68.91, 55.66, 55.30, 53.38, 52.81, 39.52, 38.52, 37.88, 37.82, 28.59, 28.54, 25.69, 17.91, 17.89, −4.82, −4.83, −4.86, −4.95; HRMS (ESI) calcd for $C_{23}H_{39}N_2O_4Si$ *m/z* 435.2679 ([M+H]$^+$), found *m/z* 435.2714.

5.1.7. (2*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-methyl-*N*-phenyl pyrrolidine-2-carboxamide (7)

To a cold solution (0 °C) of **14** (0.94 g, 2.2 mmol) in CH_2Cl_2 (100 mL) was added $ZnBr_2$ (2.43 g, 10.8 mmol, 4.9 equiv) and the resulting suspension was warmed up to rt and stirred overnight. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (40 mL × 3) and the combined organic phase was dried and concentrated. The crude product was purified by column chromatography (50% EtOAc in hexanes, then 10% methanol in CH_2Cl_2) to yield compound **7** as a colorless oil (0.69 g, 93%). $[\alpha]_D^{23}$ −46.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.40 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 4.14 (br, 1H), 3.48 (t, *J* = 8.1 Hz, 1H), 3.27 (s, 3H), 2.92 (d, *J* = 11.6 Hz, 1H), 2.74 (s, 2H), 2.58 (dd, *J* = 11.6, 4.3 Hz, 1H), 1.78–1.67 (m, 1H), 1.59–1.46 (m, 1H), 0.84 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (126 MHz) δ 173.40, 129.80, 128.08, 127.89, 73.39, 58.25, 56.39, 41.37, 37.85, 25.84, 18.02, −4.70, −4.72; HRMS (ESI) calcd for $C_{18}H_{31}N_2O_2Si$ *m/z* 335.2155 ([M+H]$^+$), found *m/z* 335.2193.

5.1.8. 2-Iodo-3-methoxybenzaldehyde (16)

To a stirred solution of (2-iodo-3-methoxyphenyl)methanol (**15**)[29] (1.05 g, 4.0 mmol) in acetone (16 mL) at 0 °C was added Jones' reagent (1.5 mL) dropwise. The resulting yellow solution was stirred at 0 °C for 10 min. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ether (20 mL × 3) and the resulting organic solution was dried and concentrated to afford crude **16** as a yellow solid (0.9 g). This was used in the next step without further purification. ^{1}H NMR (500 MHz) δ 10.18 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (126 MHz) δ 196.61, 158.37, 136.81, 129.58, 122.38, 116.11, 94.01, 56.93.

5.1.9. 3-Hydroxy-2-iodobenzaldehyde (17)

To a cooled solution (0 °C) of **16** (0.86 g, 3.3 mmol) in CH_2Cl_2 (30 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (8.2 mL, 8.2 mmol, 2.5 equiv) dropwise. The resulting solution was brought to rt and stirred for 4 h. The reaction was stopped by adding cold water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL × 3) and the combined organic phase was washed, dried and concentrated. The crude product was purified by column chromatography (1:4 EtOAc–hexanes) to give compound **17** as a crystalline solid (0.40 g, 49%). ^{1}H NMR (500 MHz) δ 10.03 (s, 1H), 7.45 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.26 (dd, *J* = 8.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz) δ 194.69, 155.56, 135.79, 130.01, 124.13, 120.83, 100.00.

5.1.10. 3-(Allyloxy)-2-iodobenzaldehyde (8)

A solution of **17** (0.38 g, 1.5 mmol) in DMF (10 mL) was treated with K_2CO_3 (0.63 g, 4.5 mmol, 3 equiv) and allybromide (0.15 mL, 1.7 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at rt. Water (5 mL) and ether (15 mL) were added to the reaction mixture and the aqueous phase was extracted with ether (15 mL × 2). The combined ether layers was dried and concentrated. The residue was purified by column chromatography (1:9 EtOAc–hexanes) to afford compound **8** as a colorless oil (0.42 g, 96%). ^{1}H NMR (400 MHz) δ 10.20 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.16–6.00 (m, 1H), 5.56 (d, *J* = 17.2 Hz, 1H), 5.36 (d, *J* = 10.6 Hz, 1H), 4.65 (s, 2H); ^{13}C NMR (126 MHz) δ 196.66, 157.39, 136.88, 132.13, 129.47, 122.58, 118.21, 117.65, 94.67, 70.32.

5.1.11. (2*S*,4*S*)-1-(3-(Allyloxy)-2-iodobenzyl)-4-(*tert*-butyldimethylsilyloxy)-*N*-methyl-*N*-phenyl-pyrrolidine-2-carboxamide (18)

A mixture of **8** (0.60 g, 2.1 mmol) and **7** (0.70 g, 2.1 mmol, 1 equiv) in 1,2-dichloroethane (15 mL) was treated with $NaBH(OAc)_3$ (0.62 g, 2.9 mmol, 1.4 equiv). The resulting solution was stirred at rt overnight followed by the addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL × 2) and the combined organic phase was dried and concentrated in vacuo. The residue was purified by column chromatography (11% isopropanol in hexanes) to afford **18** as a colorless oil (1.1 g, 87%). $[\alpha]_D^{23}$ −49.4 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz) δ 7.34 (m, 3H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.8 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.17–6.02 (m, 1H), 5.57 (ddd, *J* = 17.2, 3.2, 1.4 Hz, 1H), 5.33 (ddd, *J* = 10.4 Hz, 4.1, 1.5 Hz, 1H), 4.62 (dt, *J* = 4.7, 1.6 Hz, 1H), 4.32–4.18 (m, 1H), 3.88 (d, *J* = 14.5 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.45 (t, *J* = 7.1 Hz, 1H),

3.27 (s, 3H), 3.17 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.73–2.65 (m, 1H), 2.18–2.08 (m, 1H), 2.00–1.89 (m, 1H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (126 MHz) δ 173.26, 156.98, 143.57, 132.84, 129.77, 129.34, 128.81, 127.83, 127.57, 123.07, 121.14, 118.19, 117.73, 117.59, 111.64, 111.00, 92.64, 70.63, 70.02, 69.78, 61.31, 60.93, 60.28, 40.06, 37.79, 25.91, 18.12, 1.10, 0.08, −4.66, −4.67, −4.69, −4.70; HRMS (ESI) calcd for $C_{28}H_{40}IN_2O_3Si$ *m/z* 607.1853 ([M+H]$^+$), found *m/z* 607.1883.

5.1.12. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-hydroxy-2-(*tert*-butyldimethylsilyloxy)-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline (20)

A solution of **18** (150 mg, 0.25 mmol) in THF (10 mL) was cooled to −78 °C and a 2.5 M solution of *n*-BuLi in hexanes (0.1 mL, 0.25 mmol) was added over 10 min. The resulting yellow solution was stirred for 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (10 mL × 2) and the combined organic phase was dried and concentrated to afford the crude ketone **19**. This was used in the next step without further purification.

Crude ketone **19** from the previous step was dissolved in MeOH (5 mL) and the resulting solution was treated with $NaBH_4$ (38 mg, 1 mmol). After stirring for 1 h at rt, saturated aqueous $NaHCO_3$ (5 mL) was added carefully to quench the unreacted hydride. To the resulting solution was added ether (20 mL). The aqueous phase was extracted with ether (20 mL × 2) and the combined organic phase was washed, dried and concentrated. The residue was purified by preparative thin layer chromatography (PTLC) (1:3 EtOAc–hexanes) to yield **20** as a colorless oil (53 mg, 57% for two steps). $[\alpha]_D^{23}$ +13.7 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz) δ 7.16 (t, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.08 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H), 5.43 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.26 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.86 (dd, *J* = 9.7, 1.7 Hz, 1H), 4.66 (ddt, *J* = 12.9, 5.0, 1.6 Hz, 1H), 4.55 (ddt, *J* = 13.0, 5.3, 1.5 Hz, 1H), 4.45–4.38 (m, 1H), 4.10 (d, *J* = 14.9 Hz, 1H), 3.32 (d, *J* = 14.8 Hz, 1H), 3.16 (d, *J* = 9.7 Hz, 1H), 2.62 (d, *J* = 9.9 Hz, 1H), 2.48–2.40 (m, 2H), 2.26–2.15 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz) δ 157.14, 136.70, 133.48, 128.40, 127.18, 118.89, 117.44, 109.68, 70.55, 69.06, 64.84, 64.00, 61.87, 55.62, 36.49, 26.02, 18.26, −4.52, −4.70; HRMS (ESI) calcd for $C_{21}H_{34}NO_3Si$ *m/z* 376.2364 ([M+H]$^+$), found *m/z* 376.2308.

5.1.13. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-benzoyloxy-2-hydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (21)

To a cooled (0 °C) solution of **20** (55 mg, 0.15 mmol) in THF (6 mL) was added slowly a 1.0 M solution of LiHMDS in THF (0.22 mL, 0.22 mmol, 1.5 equiv) and the resulting solution was stirred for 10 min at 0 °C. Benzoyl chloride (0.034 mL, 0.30 mmol, 2 equiv) was added to the mixture in one portion and the reaction was stirred for 4 h at the same temperature. Saturated aqueous $NaHCO_3$ (5 mL) was added. Usual workup afforded the crude product as a brown gum. The above crude product was dissolved in 5 mL THF and cooled to 0 °C. To this solution was added HF (0.15 mL, 70% in pyridine) and warmed up to rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (20 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (3:1 EtOAc–hexanes) to yield compound **21** (32 mg, 59% for two steps) as a white solid. $[\alpha]_D^{23}$ +50.9 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz) δ 8.01 (m, 2H), 7.49 (m, 1H), 7.41–7.33 (m, 2H), 7.26 (m, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 5.87–5.72 (m, 1H), 5.20 (m, 1H), 5.08 (m, 1H), 4.49–4.36 (m, 2H), 4.23 (m, 2H), 3.40 (d, *J* = 14.8 Hz, 1H), 3.21 (d, *J* = 9.8 Hz, 1H), 2.62 (t, *J* = 8.4 Hz, 1H), 2.49–2.34 (m, 2H), 1.81–1.66 (m, 1H); ^{13}C NMR (126 MHz) δ 166.48, 157.71, 138.01, 132.78, 130.56, 129.91, 129.41, 128.27, 122.03, 118.82, 117.38, 109.52, 100.87, 69.98, 68.93, 65.09, 63.58, 63.17, 55.05, 36.59; HRMS (ESI) calcd for $C_{22}H_{24}NO_4$ *m/z* 366.1705 ([M+H]$^+$), found *m/z* 366.1729.

5.1.14. (2*S*,10*R*,10a*S*)-9-Allyloxy-2,10-dihydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (22) and (2*S*,10*S*,10a*S*)-9-allyloxy-2,10-dihydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinoline (23)

A solution of **18** (470 mg, 0.77 mmol) in THF (15 mL) was cooled to −78 °C and a 2.5 M solution of *n*-BuLi in hexanes (0.34 mL, 0.85 mmol) was added over 10 min. The resulting yellow solution was stirred for 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (8 mL). The aqueous phase was extracted with EtOAc (20 mL × 2). The combined organic layers were dried and concentrated to afford the crude ketone. A solution of this ketone in THF (8 mL) was cooled to 0 °C and treated with HF (0.3 mL, 70% in pyridine). The reaction mixture was warmed up to rt and stirred overnight. Saturated aqueous $NaHCO_3$ (15 mL) was added carefully to quench the unreacted HF and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic solution was washed, dried and concentrated to afford the crude product containing the deprotected ketone as an orange oil. To a stirred solution of this crude product in methanol (5 mL) was added $NaBH_4$ (117 mg, 3.1 mmol) in portions. After stirring for 1 h at rt saturated aqueous $NaHCO_3$ (15 mL) was added slowly and the resulting solution was extracted with diethyl ether (20 mL × 3). The combined ether layers were dried and concentrated. The resulting crude product was purified by a short silica gel column and eluted first with hexanes–EtOAc = 1: 2 (50 mL) and then CH_2Cl_2–MeOH = 9: 1 (50 mL). The second eluate was concentrated to give a diastereomeric mixture of **22** and **23**. The mixture was further separated by a short column packed with reversed phase silica gel C-18 (40% methanol in water) to afford **22** (59 mg, 29% for 3 steps) and **23** (40 mg, 20% for 3 steps) as white crystalline solids. Compound **22**: $[\alpha]_D^{23}$ +100.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.15 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.06 (qd, *J* = 10.6, 5.3 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.90 (d, *J* = 8.7 Hz, 1H), 4.61 (d, *J* = 5.1 Hz, 2H), 4.36 (t, *J* = 4.7 Hz, 1H), 4.20 (s, 1H), 3.97 (d, *J* = 14.4 Hz, 1H), 3.39 (d, *J* = 14.4 Hz, 1H), 3.13 (d, *J* = 10.0 Hz, 1H), 2.79 (dt, *J* = 14.9, 7.6 Hz, 1H), 2.41 (dd, *J* = 10.0, 4.9 Hz, 1H), 2.30 (q, *J* = 8.3 Hz, 1H), 1.76 (dd, *J* = 13.5, 8.5 Hz, 1H); ^{13}C NMR (126 MHz) δ 157.18, 137.07, 132.59, 128.13, 126.73, 119.56, 118.64, 110.00, 72.45, 70.35, 69.20, 65.85, 63.89, 55.54, 41.60; HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ *m/z* 262.1443 ([M+H]$^+$), found *m/z* 262.1423. **23**: $[\alpha]_D^{23}$ +63.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 6.09 (ddt, *J* = 17.2, 10.2, 5.1 Hz, 1H), 5.46 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.29 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.82 (s, 1H), 4.64 (dd, *J* = 12.9, 4.8 Hz, 1H), 4.56 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 3.37 (d, *J* = 14.9 Hz, 1H), 3.06 (d, *J* = 14.8 Hz, 1H), 2.95 (d, *J* = 10.1 Hz, 1H), 2.37–2.22 (m, 3H), 2.22–2.16 (m, 1H); ^{13}C NMR (126 MHz) δ 157.25, 136.35, 133.26, 128.49, 126.34, 119.24, 117.57, 109.53, 77.36, 77.11, 76.86, 69.93, 68.98, 65.12, 64.18, 61.80, 54.84, 36.04; HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ *m/z* 262.1443 ([M+H]$^+$), found *m/z* 262.1424.

5.1.15. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-benzoyloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-(2-(allyloxy)phenyl)-propanoate (28)

To a stirred suspension of NaH (100 mg, 60%, dispersed in mineral oil, 2.5 mmol, 25 equiv) in THF (1 mL) at 0 °C was added a solution of **21** (36.5 mg, 0.1 mmol, 1 equiv) in THF (1 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **25**[32a] (75 mg, 0.16 mmol, 1.6 equiv) in THF (1 mL). The reaction was allowed to warm up gradually to rt

overnight and quenched by careful addition of excess aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 2:1) yielded a colorless oil (82 mg, 97%). $[\alpha]_D^{23}$ −16.6 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz) δ 8.06 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.88–7.83 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39–7.33 (m, 3H), 7.32–7.21 (m, 4H), 7.17–7.12 (m, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.74–6.67 (m, 2H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 3.2 Hz, 1H), 5.88–5.68 (m, 3H), 5.37 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.25–5.20 (m, 1H), 5.18 (ddd, *J* = 17.3, 3.1, 1.6 Hz, 1H), 5.09–5.03 (m, 2H), 4.87 (d, *J* = 2.7 Hz, 1H), 4.41 (qd, *J* = 12.7, 5.2 Hz, 2H), 4.32 (dt, *J* = 4.7, 1.3 Hz, 2H), 3.87 (d, *J* = 15.0 Hz, 1H), 3.23–3.14 (m, 2H), 2.62–2.48 (m, 2H), 2.45–2.36 (m, 1H), 1.95–1.86 (m, 1H), 0.93–0.82 (m, 3H), 0.80–0.69 (m, 18H); ^{13}C NMR (125 MHz) δ 172.55, 166.61, 166.38, 157.56, 155.71, 137.64, 134.58, 132.71, 132.70, 131.39, 130.67, 130.08, 129.43, 128.82, 128.55, 128.26, 127.98, 127.24, 121.54, 120.64, 118.81, 117.38, 111.65, 109.41, 77.29, 73.54, 72.96, 68.90, 68.59, 64.89, 63.59, 61.31, 55.19, 53.80, 32.44, 17.71, 17.67, 12.16; HRMS (ESI) calcd for $C_{50}H_{61}N_2O_8Si$ *m/z* 845.4197 ([M+H]$^+$), found *m/z* 845.4203.

A solution of the compound obtained above (18 mg, 0.038 mmol) in THF (5 mL) was cooled to 0 °C with an ice bath and treated with HF pyridine (0.15 mL, 70%). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (20 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (50% EtOAc in hexanes) to yield compound **28** (11.5 mg, 84%) as a white solid. $[\alpha]_D^{23}$ −47.8 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz) δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.49–7.32 (m, 6H), 7.25–7.16 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 2.9 Hz, 1H), 5.85–5.67 (m, 2H), 5.52 (dd, *J* = 9.0, 6.8 Hz, 1H), 5.28 (m, 2H), 5.20–5.12 (m, 2H), 5.05 (d, *J* = 10.4 Hz, 2H), 4.52 (br s, 1H), 4.38 (ddd, *J* = 35.2, 12.6, 5.1 Hz, 2H), 4.19–4.08 (m, 2H), 3.99 (dd, *J* = 12.6, 4.8 Hz, 1H), 3.33 (d, *J* = 11.5 Hz, 1H), 3.26 (d, *J* = 15.1 Hz, 1H), 2.56–2.40 (m, 2H), 2.23–2.10 (m, 1H); ^{13}C NMR (126 MHz) δ 173.07, 167.39, 166.28, 157.54, 156.19, 137.37, 134.30, 132.84, 132.65, 132.52, 131.60, 130.63, 130.20, 129.68, 129.54, 129.31, 128.53, 128.30, 127.14, 125.22, 121.40, 121.19, 118.78, 118.18, 117.39, 112.06, 109.49, 73.87, 73.20, 68.89, 68.64, 64.81, 63.79, 61.22, 55.78, 55.32, 32.38; HRMS (ESI) calcd for $C_{41}H_{41}N_2O_8$ *m/z* 689.2863 ([M+H]$^+$), found *m/z* 689.2858.

5.1.16. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-benzoyloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-(2-(but-3-enyloxy)phenyl)-propanoate (27)

To a stirred suspension of NaH (79 mg, 60%, dispersed in mineral oil, 2.0 mmol, 27 equiv) in THF (2.5 mL) at 0 °C was added slowly a solution of **21** (27 mg, 0.074 mmol) in THF (2.5 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **24**[32a] (61 mg, 0.12 mmol, 1.7 equiv) in THF (2.5 mL). The reaction was allowed to warm up gradually to rt overnight and quenched by careful addition of excess aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 2:1) yielded a colorless oil (44 mg, 72%). $[\alpha]_D^{23}$ −27.4 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43–7.13 (m, 8H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 2H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 3.0 Hz, 1H), 5.86–5.67 (m, 3H), 5.29–4.94 (m, 5H), 4.88 (d, *J* = 2.6 Hz, 1H), 4.41 (ddd, *J* = 27.5, 12.6, 5.0 Hz, 2H), 3.85 (ddd, *J* = 23.5, 17.9, 12.2 Hz, 3H), 3.22–3.11 (m, 2H), 2.63–2.46 (m, 2H), 2.45–2.27 (m, 2H), 1.96–1.86 (m, 1H), 1.01–0.60 (m, 21H); ^{13}C NMR (125 MHz) δ 172.53, 166.73, 166.37, 157.54, 156.00, 137.69, 134.62, 134.58, 132.70, 131.38, 130.68, 130.06, 129.41, 128.85, 128.52, 128.25, 127.91, 127.30, 126.39, 121.56, 120.42, 118.81, 117.37, 117.35, 111.07, 109.38, 73.59, 72.89, 68.89, 67.17, 64.88, 63.55, 61.27, 55.13, 53.92, 33.52, 32.43, 17.71, 17.66, 12.16; HRMS (ESI) calcd for $C_{51}H_{63}N_2O_8Si$ *m/z* 859.4354 ([M+H]$^+$), found *m/z* 859.4358.

A solution of the above product (8 mg, 0.009 mmol) in THF (3 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (20 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (1:1 EtOAc–hexanes) to yield compound **27** (5.5 mg, 85%) as an amorphous solid. $[\alpha]_D^{23}$ −31.8 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz) δ 8.10–8.05 (m, 2H), 7.75–7.67 (m, 2H), 7.54–7.48 (m, 1H), 7.48–7.42 (m, 1H), 7.41–7.33 (m, 5H), 7.24–7.14 (m, 2H), 7.07 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.84–6.79 (m, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.82–5.60 (m, 2H), 5.47 (dd, *J* = 9.1, 6.9 Hz, 1H), 5.15 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.07–4.96 (m, 3H), 4.90 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.50 (m, 1H), 4.44–4.29 (m, 2H), 4.11 (m, 2H), 3.72 (ddd, *J* = 9.0, 7.4, 5.8 Hz, 1H), 3.52–3.32 (m, 2H), 3.29 (d, *J* = 11.5 Hz, 1H), 3.24 (d, *J* = 14.9 Hz, 1H), 2.53–2.38 (m, 2H), 2.32–2.18 (m, 2H), 2.17–2.05 (m, 1H); ^{13}C NMR (126 MHz) δ 173.08, 167.91, 166.23, 157.53, 156.58, 137.39, 134.47, 134.35, 132.85, 132.64, 131.59, 130.62, 130.18, 129.80, 129.54, 129.46, 128.48, 128.31, 127.29, 124.94, 121.37, 121.04, 118.79, 117.88, 117.39, 111.62, 109.48, 74.03, 73.01, 68.87, 66.77, 64.80, 63.78, 61.21, 56.39, 55.34, 33.68, 32.36, 29.78; HRMS (ESI) calcd for $C_{42}H_{43}N_2O_8$ *m/z* 703.3014 ([M+H]$^+$), found *m/z* 703.3027.

5.1.17. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-benzoyloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-(2-allylphenyl)-propanoate (29)

To a stirred suspension of NaH (41 mg, 60%, dispersed in mineral oil, 1.0 mmol, 25 equiv) in THF (1.5 mL) at 0 °C was added slowly a solution of **21** (15 mg, 0.041 mmol) in THF (1.5 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **3.37**[32a] (28.5 mg, 0.062 mmol, 1.5 equiv) in THF (1.5 mL). The reaction was allowed to warm up gradually to rt overnight and quenched by careful addition of excess aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 2:1) yielded a colorless oil (28 mg, 83%). $[\alpha]_D^{23}$ −24.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.36 (m, 3H), 7.28 (m, 3H), 7.25–7.22 (m, 1H), 7.20–7.10 (m, 2H), 7.10–7.02 (m, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 5.82–5.71 (m, 2H), 5.62 (t, *J* = 8.1 Hz, 1H), 5.32–5.25 (m, 2H), 5.18 (d, *J* = 17.3 Hz, 1H), 5.06 (d, *J* = 9.8 Hz, 1H), 4.54 (s, 1H), 4.42 (qd, *J* = 12.7, 5.2 Hz, 2H), 3.90 (d, *J* = 15.0 Hz, 1H), 3.40 (dd, *J* = 15.9, 5.6 Hz, 1H), 3.30–3.11 (m, 3H), 2.65–2.44 (m, 3H), 2.10–1.96 (m, 1H), 0.83–0.63 (m, 21H); ^{13}C NMR (126 MHz) δ 172.37, 166.60, 166.45, 137.55, 137.02, 136.97, 136.28, 136.26, 132.75, 132.69, 131.50, 131.49, 130.56, 130.30, 130.07, 129.45, 128.58, 128.24, 127.83, 127.24, 126.89, 126.22, 121.48, 118.81, 117.40, 116.49, 109.45, 74.65, 73.48, 68.91, 64.81, 63.77, 61.52, 55.14, 53.63, 36.53, 32.50, 29.78, 17.70, 17.66, 12.20; HRMS (ESI) calcd for $C_{50}H_{61}N_2O_7Si$ *m/z* 829.4248 ([M+H]$^+$), found *m/z* 829.4196.

A solution of the above compound (5 mg, 0.006 mmol) in THF (3 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reac-

tion was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (1:1 EtOAc–hexanes) to yield compound **29** (3.5 mg, 87%) as a colorless oil. $[\alpha]_D^{23}$ −16.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.47–7.42 (m, 1H), 7.39 (m, 2H), 7.34 (m, 2H), 7.31–7.22 (m, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.12–7.05 (m, 2H), 6.76–6.68 (m, 3H), 6.54 (d, *J* = 2.8 Hz, 1H), 5.83–5.64 (m, 3H), 5.27 (t, *J* = 8.6 Hz, 1H), 5.18 (d, *J* = 17.3 Hz, 1H), 5.06 (d, *J* = 10.6 Hz, 1H), 4.85–4.77 (m, 2H), 4.48–4.32 (m, 3H), 4.15 (d, *J* = 14.9 Hz, 1H), 3.43 (d, *J* = 11.6 Hz, 1H), 3.31 (d, *J* = 14.8 Hz, 1H), 3.26 (m, 2H), 2.68–2.47 (m, 3H), 1.95 (m, 1H).^{13}C NMR (126 MHz) δ 173.09, 166.84, 166.49, 157.60, 138.03, 137.36, 137.08, 136.47, 134.14, 132.77, 132.69, 131.68, 130.47, 130.43, 130.02, 129.54, 128.61, 128.18, 128.16, 127.16, 126.89, 126.76, 121.55, 118.78, 117.45, 116.33, 109.54, 77.35, 77.09, 76.84, 74.78, 72.90, 68.93, 64.70, 63.94, 61.01, 55.28, 51.55, 36.91, 29.78; HRMS (ESI) calcd for $C_{41}H_{41}N_2O_7$ *m/z* 673.2914 ([M+H]$^+$), found *m/z* 673.2878.

5.1.18. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-hydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-triisopropylsilyloxy-3′-(2-(but-3-enyloxy)phenyl)-propanoate (30)

A solution of **23** (12 mg, 0.046 mmol, 1 equiv) in THF (1.5 mL) was added into a stirred cold (0 °C) suspension of NaH (52.3 mg, 60%, dispersed in mineral oil, 1.3 mmol, 28 equiv) in THF (1.5 mL) at and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **24** (22.7 mg, 0.046 mmol, 1.0 equiv) in THF (1.5 mL) and the reaction was allowed to continue for 20 min at 0 °C. Aqueous $NaHCO_3$ (5 mL) was added and the aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 3:1) yielded compound **30** as a colorless oil (26 mg, 75%). $[\alpha]_D^{23}$ −15.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.89–7.83 (m, 2H), 7.44–7.28 (m, 4H), 7.23–7.14 (m, 3H), 6.88–6.81 (m, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.14–5.95 (m, 2H), 5.83 (dd, *J* = 8.5, 1.4 Hz, 1H), 5.43 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.30–5.18 (m, 3H), 5.08 (dd, *J* = 13.4, 3.2 Hz, 1H), 4.97 (d, *J* = 1.9 Hz, 1H), 4.86 (s, 1H), 4.70–4.53 (m, 2H), 4.13–4.03 (m, 2H), 3.85 (d, *J* = 15.1 Hz, 1H), 3.26–3.14 (m, 2H), 2.73–2.56 (m, 2H), 2.53 (dd, *J* = 11.2, 6.1 Hz, 1H), 2.42 (tdd, *J* = 16.6, 10.2, 6.6 Hz, 2H), 2.30 (ddd, *J* = 12.2, 8.0, 6.0 Hz, 1H), 0.96–0.81 (m, 21H); ^{13}C NMR (126 MHz) δ 172.47, 166.40, 157.09, 155.96, 136.13, 134.96, 134.60, 133.41, 131.50, 128.79, 128.65, 128.54, 127.59, 127.07, 126.66, 120.39, 118.92, 117.52, 117.25, 111.07, 109.81, 73.77, 73.55, 69.10, 67.47, 64.58, 61.51, 61.48, 55.37, 53.04, 33.77, 31.72, 17.83, 17.83, 17.82, 17.76, 12.31; HRMS (ESI) calcd for $C_{44}H_{59}N_2O_7Si$ *m/z* 755.4092 ([M+H]$^+$), found *m/z* 755.4101.

5.1.19. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-hydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-triisopropylsilyloxy-3′-(2-(allyloxy)phenyl)-propanoate (31)

A solution of **23** (11.4 mg, 0.044 mmol) in THF (1.5 mL) was added into a stirred cold (0 °C) suspension of NaH (42 mg, 60%, dispersed in mineral oil, 1.05 mmol, 24 equiv) in THF (1.5 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **25** (22 mg, 0.046 mmol, 1.04 equiv) in THF (1.5 mL) and the reaction was allowed to continue for 20 min at 0 °C. Aqueous $NaHCO_3$ (5 mL) was added into the reaction mixture and the aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 3:1) yielded compound **31** as a yellowish oil (29 mg, 89%). $[\alpha]_D^{23}$ −14.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.87–7.83 (m, 2H), 7.39 (dt, *J* = 2.4, 1.8 Hz, 1H), 7.34 (dd, *J* = 8.1, 6.4 Hz, 3H), 7.19 (dt, *J* = 16.0, 4.8 Hz, 3H), 6.89–6.83 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.18–6.03 (m, 2H), 5.89–5.82 (m, 1H), 5.57–5.51 (m, 1H), 5.48–5.40 (m, 1H), 5.35–5.20 (m, 4H), 4.98 (d, *J* = 2.0 Hz, 1H), 4.89–4.83 (m, 1H), 4.68 (ddt, *J* = 13.1, 4.9, 1.5 Hz, 1H), 4.63–4.53 (m, 3H), 3.86 (d, *J* = 15.0 Hz, 1H), 3.25–3.15 (m, 2H), 2.53 (dd, *J* = 11.3, 6.1 Hz, 1H), 2.48–2.36 (m, 2H), 2.33–2.26 (m, 1H), 2.21 (d, *J* = *J* = 9.8 Hz, 1H), 0.95–0.81 (m, 21H); ^{13}C NMR (126 MHz) δ 172.48, 166.35, 157.09, 155.72, 136.13, 134.56, 133.40, 133.09, 131.50, 128.79, 128.65, 128.56, 127.74, 127.06, 126.86, 126.63, 120.62, 118.93, 117.55, 117.53, 111.66, 109.83, 73.83, 73.57, 69.10, 68.92, 64.57, 61.51, 61.50, 55.40, 53.07, 31.68, 17.82, 17.81, 17.76, 12.31; HRMS (ESI) calcd for $C_{43}H_{57}N_2O_7Si$ *m/z* 741.3935 ([M+H]$^+$), found *m/z* 741.3915.

5.1.20. (2*S*,10*S*,10a*S*)-9-Allyloxy-10-hydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-triisopropylsilyloxy-3′-(2-allylphenyl)-propanoate (32)

A solution of **23** (18 mg, 0.069 mmol) in THF (1.5 mL) was added into a stirred cold (0 °C) suspension of NaH (66 mg, 60%, dispersed in mineral oil, 1.65 mmol, 24 equiv) in THF (1.5 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **26** (33.6 mg, 0.072 mmol, 1.05 equiv) in THF (1.5 mL) and the reaction was allowed to continue for 20 min at 0 °C. Aqueous $NaHCO_3$ (5 mL) was added into the reaction mixture and the aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 3:1) yielded compound **32** as a yellowish oil (46 mg, 92%). $[\alpha]_D^{23}$ −14.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.87–7.80 (m, 2H), 7.46–7.35 (m, 3H), 7.35–7.27 (m, 3H), 7.22–7.10 (m, 4H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.62 (t, *J* = 9.9 Hz, 1H), 6.15–5.98 (m, 2H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.47–5.41 (m, 1H), 5.32–5.26 (m, 2H), 5.22–5.16 (m, 1H), 5.16–5.12 (m, 1H), 4.88 (d, *J* = 4.2 Hz, 1H), 4.72–4.64 (m, 2H), 4.58 (m, 1H), 3.87 (d, *J* = 15.0 Hz, 1H), 3.74–3.53 (m, 2H), 3.27–3.14 (m, 2H), 2.52 (m, 2H), 2.38 (m, 2H), 0.99–0.83 (m, 21H); ^{13}C NMR (126 MHz) δ 172.29, 166.26, 157.11, 137.15, 137.10, 136.82, 136.14, 134.31, 133.36, 131.57, 130.36, 128.74, 128.66, 128.60, 127.90, 127.13, 127.02, 126.96, 126.50, 126.26, 124.89, 118.95, 117.61, 116.67, 109.80, 74.79, 74.16, 69.10, 64.60, 61.52, 55.34, 53.27, 36.76, 31.69, 17.83, 17.79, 17.75, 12.46, 12.36, 0.08; HRMS (ESI) calcd for $C_{43}H_{57}N_2O_6Si$ *m/z* 725.3986 ([M+H]$^+$), found *m/z* 725.3967.

5.1.21. (2*S*,10*R*,10a*S*)-9-Allyloxy-10-hydroxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-triisopropylsilyloxy-3′-(2-allylphenyl)-propanoate (33)

A solution of **22** (24 mg, 0.092 mmol) in THF (1.5 mL) was added into a stirred cold (0 °C) suspension of NaH (44 mg, 60%, dispersed in mineral oil, 1.1 mmol, 12 equiv) in THF (1.5 mL) and the resulting mixture was stirred for 10 min at 0 °C. To this mixture was added a solution of **26** (43 mg, 0.093 mmol, 1.01 equiv) in THF (1.5 mL) and the reaction was allowed to continue for 20 min at 0 °C. Aqueous $NaHCO_3$ (5 mL) was added into the reaction mixture and the aqueous phase was extracted with EtOAc (10 mL × 3) and the combined organic phase was dried and concentrated. Purification by PTLC (hexanes–EtOAc = 3:1) yielded compound **33** as a yellowish oil (49 mg, 73%). $[\alpha]_D^{23}$ −8.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.84–7.76 (m, 2H), 7.39–7.34 (m, 2H), 7.31–7.26 (m, 3H), 7.23–7.07 (m, 4H), 6.75 (dd, *J* = 10.6, 6.1 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.14–5.99 (m, 2H), 5.79 (d, *J* = 8.0 Hz, 1H), 5.48–5.41 (m, 1H), 5.37–5.28 (m, 2H), 5.19 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.11 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.89 (d, *J* = 8.5 Hz, 1H), 4.70–4.57 (m, 3H), 4.16 (s, 1H), 3.74 (d, *J* = 14.5 Hz, 1H), 3.70–3.54 (m, 2H), 3.29 (d, *J* = 14.4 Hz, 1H), 3.16 (d, *J* = 11.2 Hz, 1H), 2.90–2.78 (m, 1H), 2.52 (dd, *J* = 11.1, 5.8 Hz, 1H), 2.31 (dd, *J* = 16.0, 8.7 Hz, 1H),

2.00–1.90 (m, 1H), 1.01–0.82 (m, 21H); ^{13}C NMR (126 MHz) δ 172.07, 166.33, 137.12, 137.04, 136.93, 136.71, 134.34, 132.64, 131.45, 130.22, 128.66, 128.55, 127.99, 127.90, 127.11, 127.06, 126.97, 126.62, 126.28, 119.59, 118.61, 116.72, 109.87, 74.80, 74.12, 72.07, 69.20, 65.65, 61.13, 55.28, 53.31, 37.51, 36.84, 17.83, 17.82, 17.80, 17.79, 12.38; HRMS (ESI) calcd for $C_{43}H_{57}N_2O_6Si$ *m/z* 725.3922 ([M+H]$^+$), found *m/z* 725.3986.

5.1.22. Protected macrocyclic paclitaxel mimic 34

To a stirred solution of **30** (20 mg, 0.026 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was added D-(−)-10-camphorsulphonic acid (18.5 mg, 0.079 mmol, 3 equiv) and the mixture was refluxed for 1 h. The reaction mixture was cooled to rt and Grubbs 2nd generation catalyst (2.2 mg, 10 mol %) in CH_2Cl_2 (5 mL) was added slowly. The resulting solution was heated to reflux and continued stirring for 2 h. The resulting light brown solution was washed with 1 N aqueous NaOH (3 mL × 2), dried with anhydrous Na_2SO_4 and concentrated under vacuum to yield a dark brown residue. The crude product was purified by PTLC (hexanes–EtOAc = 2:1) and the spot with a R_f = 0.3 was collected (15.5 mg, with minor impurities) and used in the next step without further purification.

The product (5 mg) after the ring-closing metathesis was dissolved in dry THF (1 mL) and cooled to −78 °C, followed by slow addition of lithium bis(trimethylsilyl)amide solution in THF (1 M, 21 μL, 3 equiv). The resulting mixture was stirred at −78 °C for 10 min before the addition of benzoyl chloride (3.2 μL, 4 equiv) in one portion. The reaction was allowed to continue for another 3 h at −78 °C before the addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting solution was extracted with EtOAc (20 mL × 3), washed with brine and dried. The crude product was purified with PTLC (5% MeOH in CH_2Cl_2) to yield **34** (5 mg, 70% from **30**) as a colorless oil. $[\alpha]_D^{23}$ −27.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.61–7.42 (m, 6H), 7.22–7.10 (m, 3H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.91–6.83 (m, 2H), 6.80–6.72 (m, 2H), 6.09 (d, *J* = 7.0 Hz, 1H), 5.92–5.78 (m, 2H), 5.57–5.45 (m, 1H), 5.35–5.25 (m, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 4.42 (dd, *J* = 12.8, 7.9 Hz, 1H), 4.27 (dd, *J* = 12.7, 5.3 Hz, 1H), 3.98 (m, 1H), 3.90–3.74 (m, 3H), 3.59 (d, *J* = 15.2 Hz, 1H), 3.14–3.07 (m, 1H), 2.57–2.48 (m, 1H), 2.43 (m, 1H), 2.34 (m, 1H), 2.08 (m, 2H), 0.91–0.75 (m, 21H); ^{13}C NMR (126 MHz) δ 171.63, 166.70, 166.41, 155.80, 155.67, 138.04, 136.25, 134.85, 133.55, 133.13, 131.61, 130.17, 128.79, 128.58, 127.55, 127.41, 127.09, 126.95, 126.71, 124.66, 122.52, 120.71, 111.57, 73.71, 73.12, 72.04, 70.26, 68.15, 58.43, 56.04, 52.34, 51.17, 33.79, 32.83, 29.78, 17.68, 17.65, 12.27, 1.10, 1.09; HRMS (ESI) calcd for $C_{49}H_{59}N_2O_8Si$ *m/z* 831.4041 ([M+H]$^+$), found *m/z* 831.4054.

5.1.23. Macrocyclic paclitaxel mimic 37

A solution of compound **34** (6 mg, 0.007 mmol) in THF (2 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (1:1 EtOAc–hexanes) to yield compound **37** (4.3 mg, 88%) as a colorless oil. $[\alpha]_D^{23}$ +20.2 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz) δ 8.27 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.78–7.71 (m, 2H), 7.60–7.54 (m, 3H), 7.52–7.48 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.31 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.28–7.21 (m, 4H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 6.0 Hz, 1H), 5.96 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.81–5.68 (m, 1H), 5.38 (dt, *J* = 15.6, 5.7 Hz, 1H), 5.17 (dq, *J* = 10.1, 5.0 Hz, 1H), 4.63 (d, *J* = 4.2 Hz, 1H), 4.40 (dd, *J* = 13.8, 5.5 Hz, 1H), 4.31 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.82–3.70 (m, 2H), 3.66 (d, *J* = 14.9 Hz, 1H), 3.49–3.38 (m, 3H), 2.89–2.76 (m, 1H), 2.44 (dt, *J* = 15.0, 7.7 Hz, 1H), 2.37–2.19 (m, 3H), 2.14 (ddd, *J* = 13.4, 6.5, 4.1 Hz, 1H); ^{13}C NMR (126 MHz) δ 172.05, 167.69, 166.66, 156.44, 156.40, 134.24, 133.17, 132.50, 131.88, 130.36, 130.19, 129.33, 128.77, 128.67, 127.37, 127.26, 127.15, 126.65, 126.55, 123.91, 120.88, 118.76, 112.45, 74.27, 71.04, 68.83, 68.52, 60.51, 57.93, 52.65, 51.23, 33.28, 32.57, 29.78; HRMS (ESI) calcd for $C_{40}H_{39}N_2O_8$ *m/z* 675.2706 ([M+H]$^+$), found *m/z* 675.2696.

5.1.24. Protected macrocyclic paclitaxel mimic 35

To a stirred solution of **31** (21 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was added D-(−)-10-camphorsulphonic acid (19.7 mg, 0.085 mmol, 3 equiv) and the mixture was stirred under reflux for 1 h. The reaction was cooled to rt and Grubbs 2nd generation catalyst (2.4 mg, 10 mol %) in CH_2Cl_2 (5 mL) was added slowly in 10 minutes. The resulting solution was heated to reflux and continued stirring for 2 h. The resulting light brown solution was washed with 1 N aqueous NaOH (3 mL × 2), dried with anhydrous Na_2SO_4 and concentrated under vacuum to yield a dark brown residue. The crude product was purified by PTLC (hexanes–EtOAc = 2:1) and the spot with a R_f = 0.35 was collected as the product (7 mg, with minor impurities) and used in the next step without further purification. Also collected was the unreacted starting material (5 mg).

The product (7 mg) from last step was completely dried and dissolved in dry THF (1 mL). The resulting solution was cooled to −78 °C, followed by slow addition of lithium bis(trimethylsilyl)amide solution in THF (1 M, 39 μL, 4 equiv). The reaction mixture was stirred at −78 °C for 10 min before the addition of benzoyl chloride (7.3 μL, 8 equiv) in one portion. The reaction was allowed to continue for another 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (5 mL). To the resulting mixture was added EtOAc (20 mL). The organic solution was separated and the aqueous was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine and dried. The crude product was purified with PTLC (hexanes–EtOAc = 6:5) to yield **35** (3.4 mg, 19% for two steps from **31**) as a colorless oil. $[\alpha]_D^{23}$ −34.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.24–8.17 (m, 2H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.62–7.48 (m, 4H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.24–7.20 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 6.08 (d, *J* = 7.1 Hz, 1H), 5.87–5.79 (m, 2H), 5.74 (dt, *J* = 16.4, 3.3 Hz, 1H), 5.30 (p, *J* = 7.8 Hz, 1H), 4.63–4.45 (m, 4H), 4.10 (dt, *J* = 16.3, 2.4 Hz, 1H), 4.02–3.92 (m, 2H), 3.60 (d, *J* = 15.2 Hz, 1H), 3.31 (dd, *J* = 9.4, 6.9 Hz, 1H), 2.69–2.55 (m, 1H), 2.16–1.94 (m, 2H), 0.87–0.76 (m, 21H); ^{13}C NMR (126 MHz) δ 171.52, 166.84, 166.64, 155.68, 155.41, 138.75, 134.62, 132.98, 131.63, 130.53, 130.04, 128.79, 128.76, 128.57, 127.70, 127.48, 127.14, 126.10, 121.01, 120.87, 120.46, 112.33, 112.03, 77.29, 73.38, 72.65, 70.94, 69.11, 65.24, 59.11, 57.14, 51.51, 51.12, 43.06, 34.30, 17.74, 17.73, 17.72, 17.70, 12.29, 0.08, 0.08, 0.07, 0.06, 0.06, 0.05; HRMS (ESI) calcd for $C_{48}H_{57}N_2O_8Si$ *m/z* 817.3884 ([M+H]$^+$), found *m/z* 817.3815.

5.1.25. Macrocyclic paclitaxel mimic 38

A solution of compound **35** (3 mg, 0.004 mmol) in THF (2 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (1:1 EtOAc–hexanes) to yield the compound **38** (2.3 mg, 88%) as a colorless oil. $[\alpha]_D^{23}$ −27.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.35–8.28 (m, 2H), 7.79–7.73 (m, 2H), 7.57–7.38 (m, 7H), 7.25–7.22 (m, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.70 (t, *J* = 8.6 Hz, 2H), 6.14 (d,

J = 7.2 Hz, 1H), 6.07 (d, J = 9.1 Hz, 1H), 5.96–5.86 (m, 1H), 5.80 (d, J = 16.1 Hz, 1H), 5.36–5.26 (m, 1H), 4.62–4.45 (m, 3H), 4.33 (d, J = 1.3 Hz, 1H), 4.16–4.06 (m, 2H), 3.96 (m, 1H), 3.62 (d, J = 15.2 Hz, 1H), 3.24 (dd, J = 9.2, 6.5 Hz, 1H), 2.71–2.63 (m, 1H), 2.27 (dt, J = 14.3, 8.1 Hz, 1H), 2.22–2.17 (m, 1H); ^{13}C NMR (126 MHz) δ 173.03, 166.96, 166.45, 155.70, 155.33, 134.55, 132.86, 131.66, 130.65, 130.24, 129.16, 128.65, 128.48, 128.21, 127.95, 127.35, 127.24, 127.19, 126.42, 121.28, 121.14, 120.30, 112.91, 112.20, 74.00, 72.25, 70.46, 68.30, 66.14, 59.10, 56.62, 51.20, 48.91, 34.17; HRMS (ESI) calcd for $C_{39}H_{37}N_2O_8$ m/z 661.2550 ([M+H]$^+$), found m/z 661.2485.

5.1.26. Protected macrocyclic paclitaxel mimic 36

To a stirred solution of **32** (25 mg, 0.034 mmol, 1 equiv) in CH_2Cl_2 (25 mL) was added D-(−)-10-camphorsulphonic acid (24 mg, 0.103 mmol, 3 equiv) and the mixture was stirred under reflux for 1 h. The reaction was cooled to rt and Grubbs 2nd generation catalyst (1.5 mg, 5 mol %) in CH_2Cl_2 (5 mL) was added slowly in 10 minutes. The resulting solution was heated to reflux and continued overnight. The resulting light brown solution was washed with 1 N aqueous NaOH (3 mL × 2), dried with anhydrous Na_2SO_4 and concentrated under vacuum to yield a dark brown residue. The crude product was purified by PTLC (hexanes–EtOAc = 3:1) and the spot with a R_f = 0.3 was collected as the product (3.3 mg, with minor impurities) and used in the next step without further purification. Also collected was the unreacted starting material (10 mg).

The product (3.3 mg) from last step was completely dried and dissolved in dry THF (1 mL). The resulting solution was cooled to −78 °C, followed by slow addition of lithium bis(trimethylsilyl)amide solution in THF (1 M, 19 μL, 4 equiv). The reaction mixture was stirred at −78 °C for 10 min before the addition of benzoyl chloride (4.4 μL, 8 equiv) in one portion. The reaction was allowed to continue for another 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (5 mL). To the resulting mixture was added EtOAc (20 mL). The organic solution was separated and the aqueous was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine and dried. The crude product was purified with PTLC (hexanes–EtOAc = 1:1) to yield **36** (1.5 mg, 9% for two steps from **32**) as a colorless oil. $[\alpha]_D^{23}$ +11.0 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.30–8.26 (m, 2H), 7.83–7.79 (m, 2H), 7.59–7.46 (m, 4H), 7.46–7.40 (m, 2H), 7.39–7.35 (m, 1H), 7.19–7.07 (m, 4H), 7.01 (dd, J = 7.2, 1.7 Hz, 1H), 6.78–6.74 (m, 2H), 6.05 (d, J = 7.4 Hz, 1H), 5.95–5.88 (m, 1H), 5.83–5.75 (m, 1H), 5.65 (dd, J = 8.1, 1.7 Hz, 1H), 5.30–5.21 (m, 1H), 4.52 (dd, J = 13.7, 6.6 Hz, 1H), 4.33 (d, J = 1.9 Hz, 1H), 4.19 (dd, J = 14.3, 4.1 Hz, 1H), 4.05–3.94 (m, 2H), 3.61 (d, J = 15.4 Hz, 1H), 3.46 (d, J = 7.0 Hz, 2H), 3.20 (dd, J = 10.1, 5.8 Hz, 1H), 2.62–2.53 (m, 1H), 2.28 (dd, J = 9.8, 7.1 Hz, 1H), 2.10 (m, 1H), 1.08–0.79 (m, 21H); ^{13}C NMR (126 MHz) δ 171.30, 166.87, 166.51, 155.35, 137.58, 137.23, 135.02, 134.67, 133.10, 132.93, 131.58, 130.45, 130.25, 129.95, 129.87, 128.73, 128.61, 128.15, 127.64, 127.26, 127.04, 126.96, 126.49, 126.43, 123.37, 120.63, 117.31, 74.61, 73.39, 70.23, 68.48, 59.30, 57.28, 52.37, 51.53, 35.72, 31.68, 17.86, 17.82, 12.40; HRMS (ESI) calcd for $C_{48}H_{57}N_2O_7Si$ m/z 801.3935 ([M+H]$^+$), found m/z 801.3917.

5.1.27. Macrocyclic paclitaxel mimic 39

A solution of compound **36** (1.5 mg, 0.002 mmol) in THF (2 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (75% EtOAc in hexanes) to yield compound **39** (1 mg, 83%) as a colorless oil. $[\alpha]_D^{23}$ +42.5 (c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.19 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 14.8 Hz, 1H), 7.63 (dt, J = 9.0, 4.5 Hz, 3H), 7.52 (t, J = 7.7 Hz, 2H), 7.49–7.42 (m, 1H), 7.37 (t, J = 7.7 Hz, 2H), 7.13–7.07 (m, 1H), 6.89 (s, 1H), 6.65 (s, 1H), 6.48–6.39 (m, 2H), 6.19 (d, J = 4.5 Hz, 1H), 5.90–5.76 (m, 1H), 5.59–5.50 (m, 1H), 5.39 (d, J = 9.2 Hz, 1H), 4.86 (s, 1H), 4.39 (dd, J = 14.3, 7.3 Hz, 1H), 4.08 (d, J = 6.7 Hz, 1H), 4.01 (d, J = 14.2 Hz, 1H), 3.89 (s, 1H), 3.72–3.44 (m, 3H), 3.21 (d, J = 14.8 Hz, 2H), 2.99 (s, 1H), 2.51 (s, 2H); HRMS (ESI) calcd for $C_{39}H_{37}N_2O_7$ m/z 645.2595 ([M+H]$^+$), found m/z 645.2570.

5.1.28. (2*S*,10*R*,10a*S*)-9-Allyloxy-10-benzoyloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-triisopropylsilyloxy-3′-(2-allylphenyl)-propanoate (42)

A solution of **33** (8 mg, 0.011 mmol) in dry THF (2 mL) was cooled to −78 °C. To this solution was added slowly lithium bis(trimethylsilyl)amide solution in THF (1 M, 44 μL, 4 equiv). The reaction mixture was stirred at −78 °C for 10 min before the addition of benzoyl chloride (11 μL, 8 equiv) in one portion. The reaction was allowed to continue for another 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (5 mL). To the resulting mixture was added EtOAc (20 mL). The organic solution was separated and the aqueous was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine and dried. The crude product was purified with PTLC (hexanes–EtOAc = 4:1) to yield **42** (5.5 mg, 60%) as a colorless oil. $[\alpha]_D^{23}$ −20.9 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.99 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 7.9 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.38 (dd, J = 10.2, 4.9 Hz, 3H), 7.33 (t, J = 7.3 Hz, 1H), 7.28–7.17 (m, 8H), 7.16–7.09 (m, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.08 (ddt, J = 16.7, 10.2, 6.3 Hz, 1H), 5.79 (d, J = 8.0 Hz, 1H), 5.66 (ddt, J = 16.5, 10.7, 5.5 Hz, 1H), 5.27–5.14 (m, 3H), 5.07 (d, J = 17.3 Hz, 1H), 4.96 (d, J = 10.5 Hz, 1H), 4.67 (s, 1H), 4.36 (ddd, J = 60.8, 12.4, 5.4 Hz, 2H), 3.77–3.55 (m, 3H), 3.34 (d, J = 14.3 Hz, 1H), 3.14 (d, J = 11.3 Hz, 1H), 2.73–2.61 (m, 1H), 2.58–2.40 (m, 2H), 1.03–0.77 (m, 21H); ^{13}C NMR (126 MHz) δ 172.28, 166.37, 165.98, 157.69, 138.03, 137.13, 136.66, 134.29, 132.82, 132.67, 131.42, 130.87, 130.33, 130.16, 129.84, 128.74, 128.52, 128.43, 128.20, 127.91, 127.05, 126.96, 126.26, 122.76, 118.84, 117.61, 116.84, 110.04, 75.01, 73.73, 71.57, 69.12, 65.21, 60.98, 60.49, 54.94, 53.38, 36.91, 36.82, 21.13, 17.83, 17.80, 14.28, 12.40; HRMS (ESI) calcd for $C_{43}H_{57}N_2O_6Si$ m/z 829.4248 ([M+H]$^+$), found m/z 829.4201.

5.1.29. (2*S*,10*R*,10a*S*)-9-Allyloxy-10-benzoyloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-(2-allylphenyl)-propanoate (43)

A solution of compound **42** (3.3 mg, 0.004 mmol) in THF (3 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (50% EtOAc in hexanes) to yield compound **43** (2.4 mg, 89%) as a colorless oil. $[\alpha]_D^{23}$ +2.0 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.00 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.52 (dd, J = 11.5, 5.0 Hz, 2H), 7.39 (tt, J = 26.5, 7.8 Hz, 6H), 7.25–7.19 (m, 3H), 6.89 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 8.2 Hz, 1H), 6.06 (tt, J = 16.5, 6.2 Hz, 1H), 5.94 (dd, J = 8.6, 2.2 Hz, 1H), 5.64 (qd, J = 10.7, 5.5 Hz, 1H), 5.27 (t, J = 8.5 Hz, 1H), 5.17–5.01 (m, 3H), 4.95 (d, J = 10.5 Hz, 1H), 4.56 (d, J = 2.2 Hz, 1H), 4.34 (ddd, J = 17.9, 12.3, 5.1 Hz, 2H), 3.92 (d, J = 14.4 Hz, 1H), 3.69–3.53 (m, 2H), 3.46 (d, J = 14.3 Hz, 1H), 3.29 (d, J = 11.3 Hz, 1H), 2.80–2.67 (m, 1H), 2.62–2.50 (m, 2H), 2.33 (t, J = 7.5 Hz, 1H), 2.30–2.22 (m, 1H); ^{13}C NMR

(126 MHz) δ 172.94, 166.88, 165.99, 157.75, 138.21, 137.90, 137.08, 136.85, 134.15, 132.75, 132.72, 131.66, 130.81, 130.56, 129.85, 128.89, 128.61, 128.34, 128.23, 127.19, 126.95, 122.76, 118.80, 117.64, 116.71, 110.20, 74.90, 73.14, 71.65, 69.12, 65.39, 60.75, 55.23, 51.56, 37.25, 33.55, 32.01, 24.82, 22.78, 14.21, 0.08; HRMS (ESI) calcd for $C_{43}H_{57}N_2O_6Si$ *m/z* 673.2914 ([M+H]$^+$), found *m/z* 673.2876.

5.1.30. Protected macrocyclic paclitaxel mimic 40

To a solution of **33** (48 mg, 0.066 mmol) in CH_2Cl_2 (50 mL) was added D-(−)-10-camphorsulfonic acid (76.6 mg, 0.33 mmol, 5 equiv) and the mixture was stirred under reflux for 1 h. The reaction was cooled to rt and Grubbs 2nd generation catalyst (5.6 mg, 10 mol %) in CH_2Cl_2 (5 mL) was added slowly in 10 min. The resulting solution was heated to reflux and continued stirring overnight. The resulting light brown solution was washed with 1 N aqueous NaOH (3 mL × 2), dried with anhydrous Na_2SO_4 and concentrated under vacuum to yield a dark brown residue. The crude product was purified by PTLC (hexanes–EtOAc = 1:2) to yield the bridged compound with a R_f = 0.25 (16 mg) together with unreacted starting material (12 mg).

The product (8 mg, 0.012 mmol) from the previous step was completely dried and dissolved in dry THF (2 mL). The resulting solution was cooled to −78 °C, followed by slow addition of lithium bis(trimethylsilyl)amide solution in THF (1 M, 46 μL, 4 equiv). The reaction mixture was stirred at −78 °C for 10 min before the addition of benzoyl chloride (10.7 μL, 8 equiv) in one portion. The reaction was allowed to continue for another 3 h at −78 °C and quenched by adding saturated aqueous $NaHCO_3$ (5 mL). To the resulting mixture was added EtOAc (20 mL). The organic solution was separated and the aqueous was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine and dried. The crude product was purified with PTLC (hexanes–EtOAc = 1:2) to yield **40** (7.6 mg, 39% for two steps from **33**) as a colorless oil. $[\alpha]_D^{23}$ −11.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.55–7.46 (m, 2H), 7.41 (dt, *J* = 15.7, 7.7 Hz, 4H), 7.30 (dt, *J* = 16.7, 8.3 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.21–7.09 (m, 3H), 6.80 (t, *J* = 8.7 Hz, 2H), 6.62 (t, *J* = 11.8 Hz, 2H), 5.66 (d, *J* = 7.9 Hz, 1H), 5.37 (d, *J* = 15.9 Hz, 1H), 5.27 (t, *J* = 5.3 Hz, 1H), 4.74 (d, *J* = 14.3 Hz, 1H), 4.41–4.20 (m, 3H), 4.02 (dd, *J* = 16.5, 7.1 Hz, 1H), 3.75 (d, *J* = 15.8 Hz, 1H), 3.65–3.45 (m, 2H), 3.41 (dd, *J* = 11.5, 6.0 Hz, 1H), 2.73 (t, *J* = 15.8 Hz, 1H), 2.54 (dt, *J* = 14.5, 7.2 Hz, 1H), 2.44–2.32 (m, 1H), 0.89–0.61 (m, 21H); ^{13}C NMR (126 MHz) δ 171.75, 166.32, 166.28, 158.91, 138.05, 137.84, 137.19, 134.51, 132.78, 131.58, 131.32, 130.89, 130.69, 129.90, 129.58, 128.71, 128.30, 128.11, 127.78, 127.72, 127.08, 126.32, 123.60, 120.84, 114.37, 76.90, 74.50, 70.60, 67.83, 65.24, 57.75, 52.79, 50.23, 38.57, 34.81, 17.72, 17.69, 12.33; HRMS (ESI) calcd for $C_{48}H_{57}N_2O_7Si$ *m/z* 801.3935 ([M+H]$^+$), found *m/z* 801.3883.

5.1.31. Macrocyclic paclitaxel mimic 41

A solution of compound **40** (5.5 mg, 0.007 mmol) in THF (3 mL) was cooled to 0 °C with an ice bath and treated with HF (0.1 mL, 70% in pyridine). The ice bath was removed and the reaction was continued overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added slowly and the resulting solution was extracted with EtOAc (10 mL × 3). The EtOAc solution was washed, dried and concentrated. The crude product was purified by PTLC (3:1 EtOAc–hexanes) to yield compound **41** (3.5 mg, 85%) as a colorless oil. $[\alpha]_D^{23}$ +2.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 8.03–7.96 (m, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.57–7.50 (m, 1H), 7.45 (dd, *J* = 11.1, 3.8 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 4.0 Hz, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 6.0 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 5.4 Hz, 1H), 6.07–5.97 (m, 1H), 5.55 (dd, *J* = 15.6, 5.7 Hz, 2H), 5.36 (s, 1H), 4.55 (d, *J* = 5.3 Hz, 2H), 4.37 (d, *J* = 16.0 Hz, 1H), 4.28 (s, 1H), 3.77 (d, *J* = 15.8 Hz, 1H), 3.62 (dd, *J* = 14.6, 6.1 Hz, 2H), 3.49–3.31 (m, 2H), 2.86 (d, *J* = 11.6 Hz, 1H), 2.46 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.15 (d, *J* = 14.2 Hz, 1H); ^{13}C NMR (126 MHz) δ 172.46, 168.48, 166.92, 157.58, 137.43, 137.34, 134.03, 133.71, 133.12, 131.81, 130.61, 130.36, 129.88, 129.45, 128.60, 128.59, 128.40, 128.37, 127.39, 127.21, 126.36, 120.01, 114.46, 76.20, 72.89, 69.94, 68.15, 62.50, 58.17, 54.20, 51.21, 37.95, 36.09; HRMS (ESI) calcd for $C_{39}H_{37}N_2O_7$ *m/z* 645.2601 ([M+H]$^+$), found *m/z* 645.2573.

5.2. X-ray methods

5.2.1. X-ray of compound 22

A colorless prism (0.07 × 0.07 × 0.08 mm^3) was centered on the goniometer of an Oxford Diffraction Gemini A Ultra diffractometer operating with CuKα radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.[36] The Laue symmetry and systematic absences were consistent with the monoclinic space groups $P2_1$ and $P2_1/m$. As the substance was enantiomerically pure, the acentric space group $P2_1$ was chosen. The structure was solved by direct methods and refined using SHELXTL NT.[37] The asymmetric unit of the structure comprises two crystallographically independent molecules. The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms. A riding model was used for the aromatic and alkyl hydrogens. The hydrogen atom positions of the hydroxyl groups were located and refined independently. The absolute configuration was established from anomalous dispersion effects (Flack x = 0.0(2)). [Flack x = XXXX;[38] Hooft P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = 0.000; P3(false) = 0.000, *y* = −0.08(11)].[24,39]

5.2.2. X-ray of compound 23

A colorless rod (0.05 × 0.13 × 0.29 mm^3) was centered on the goniometer of an Oxford Diffraction Gemini A Ultra diffractometer operating with CuKα radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.[36] The Laue symmetry was consistent with the triclinic space groups *P*1 and *P*−1. As the substance was enantiomerically pure, the acentric space group *P*1 was chosen. The structure was solved by direct methods and refined using SHELXTL NT.[37] The asymmetric unit of the structure comprises two crystallographically independent molecules. The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms. A riding model was used for the alkyl hydrogens. The hydrogen atom positions of the hydroxyl groups were located and refined independently. The absolute configuration was established from anomalous dispersion effects [Flack x = 0.02(14)[38]; Hooft P2(true) = 1.000, P3(true) = 1.000, P3(rac-twin) = 0.000; P3(false) = 0.000, *y* = −0.05(5)].[24,39]

5.3. Biological experiments

5.3.1. Antiproliferative activities

Antiproliferative activity against the A2780 cell line was determined as described previously.[40]

5.3.2. Tubulin polymerization assays

5.3.2.1. Absorption. Tubulin assembly was monitored by measuring optical density at 350 nm using a Hewlett–Packard 8453 absorption spectrophotometer. Bovine brain tubulin (final concentration 15 μM) in PMEG buffer (100 mM Pipes, 1 mM $MgSO_4$, 2 mM EGTA, 1 mM GTP, pH 6.9) was equilibrated to 37 °C in the sample cell and a baseline was recorded. Taxol (final concen-

tration 15 μM) or test compound (final concentration 60 μM) in DMSO was added and optical density was monitored until a steady state was reached. At the time indicated by the arrow the temperature was decreased to 4 °C to monitor temperature induced disassembly. The control contained tubulin and DMSO but no ligand. The final concentration of DMSO was 10% (v/v) in all samples.

5.3.2.2. Fluorescence. Tubulin assembly was monitored by observing the increase in DAPI fluorescence as a function of time using SynergyMx multi- mode microplate reader (BioTek) (Software used: Gen 5). Bovine brain tubulin was incubated in PME buffer (100 mM Pipes, 1 mM $MgSO_4$, 2 mM EGTA, pH 6.9) containing excess GDP (final concentration 5 mM). Excess GDP was removed by rapid gel filtration into PMED buffer (PME buffer with 0.1 mM GDP). Samples containing tubulin (final concentration 8 μM) and 4′,6-diamidino-2-phenylindole (DAPI) (final concentration 10 μM) in PMED buffer was equilibrated to 37 °C in the 96-well black plate (Nunc). The excitation and emission wavelengths were set at 360 and 450 nm, respectively, and the fluorescence was recorded to obtain a baseline. Taxol (final concentration 8 μM) or test compound (final concentration 60 μM) in DMSO was added to initiate polymerization. Fluorescence was monitored until a steady state was reached. The control contained tubulin, DAPI, and DMSO but no ligand. The final concentration of DMSO was 10% (v/v) in all samples.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.10.010. These data include MOL files and InChiKeys of the most important compounds described in this article. CCDC 850019 and 850020 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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