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Design and synthesis of de novo cytotoxic alkaloids by mimicking the bioactive conformation of palitaxel

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ABSTRACT

Novel paclitaxel-mimicking alkaloids were designed and synthesized based on a bioactive conformation of paclitaxel, that is, REDOR-Taxol. The alkaloid **2** bearing a 5-7-6 tricyclic scaffold mimics REDOR-Taxol best among the compounds designed and was found to be the most potent compound against several drug-sensitive and drug-resistant human cancer cell lines. MD simulation study on the paclitaxel mimics **1** and **2** as well as REDOR-Taxol bound to the 1JFF tubulin structure was quite informative to evaluate the level of mimicking. The MD simulation study clearly distinguishes the 5-6-6 and 5-7-6 tricyclic scaffolds, and also shows substantial difference in the conformational stability of the tubulin-bound structures between **2** and REDOR-Taxol. The latter may account for the large difference in potency, and provides critical information for possible improvement in the future design of paclitaxel mimics.

1. Introduction

Cancer is the first leading cause of death for people under the age of 85 in the US.[1,2] Paclitaxel (Taxol®) and docetaxel (Taxotere®) currently serve as the most widely used drugs in the fight against cancer among a variety of chemotherapeutic agents (Fig. 1).[3,4] The drugs bind to the β-tubulin subunit, accelerate the polymerization of tubulin and stabilize the resultant microtubules, which leads to apoptosis through cell-signaling cascade.[5,6] New generation taxoids with much higher activities have been developed through structure-activity relationship (SAR) studies.[7–11]

Since the paclitaxel structure is highly complex, especially its baccatin component, it would be exciting if we can design and develop paclitaxel mimics with much simpler structure, retaining potent anticancer activity.[12,13] Thus, some pioneering efforts along this line have been made by a couple of research groups. In 2004, Ojima and coworkers reported four paclitaxel mimics with an indolizidine alkaloid scaffold based on their pharmacophore model (Fig. 2).[14] Two hydroxyl groups were designed to mimic the C2 and C13 hydroxyl groups (atom–atom distance and dihedral angle) of the baccatin III skeleton. Their mimics showed substantially reduced but still good cytotoxicity (IC_{50} = single–double digit μM) against human breast cancer cell lines, but did not promote tubulin polymerization at the concentrations examined.[14] In 2005, Génard, Gérrite and coworkers synthesized eight steroidal compounds bearing the phenylisoerine and benzoate side-chains to mimic the "T-form" docetaxel (Fig. 2).[15] Their mimics only showed four orders of magnitude lower activity than docetaxel and did not show any inhibitory activity for microtubule disassembly.[15] Unexpectedly, however, two compounds showed inhibitory activity for microtubule assembly.[15] In 2006, Kingston and coworkers reported five macrocyclic paclitaxel-mimics (Fig. 2) based on a highly potent conformationally restrained macrocyclic paclitaxel analog, which was designed to mimic the T-Taxol structure.[16,17] Their mimics showed fairly good cytotoxicity (IC_{50} = 11–18 μM) against a human ovarian cancer cell line A2780 as well as weak, but recognizable activity in promoting tubulin polymerization and stabilizing

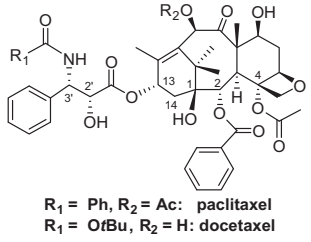

Figure 1. Paclitaxel and docetaxel.

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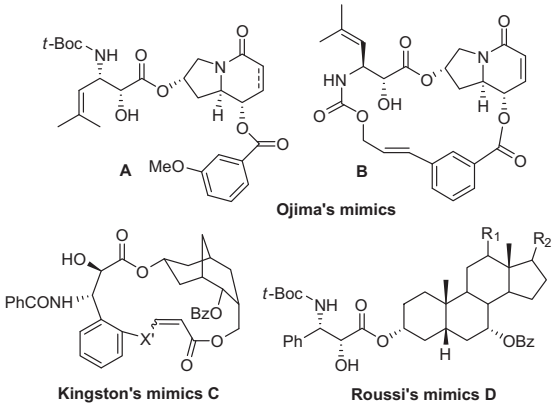


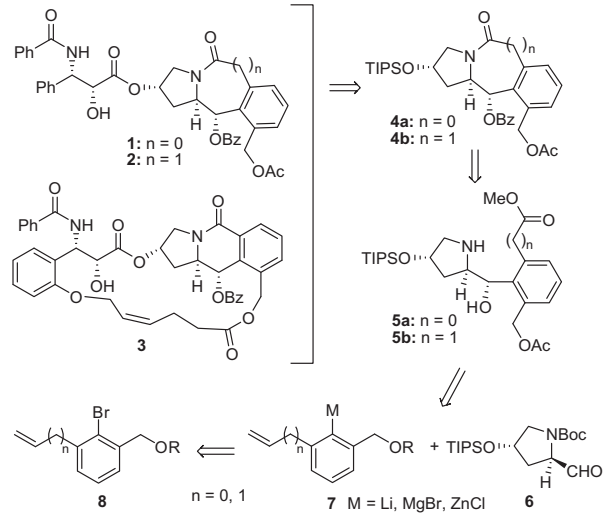
Figure 2. Previously reported paclixel mimics.

microtubules.[16,17] We report here the design, synthesis and biological evaluation of novel paclitaxel mimics, bearing tricyclic alkaloid scaffolds, mimicking the REDOR-Taxol[13,18,19] structure.

2. Design and synthesis of novel paclitaxel mimics

We set out to design novel paclitaxel mimics through molecular modeling analysis of tricyclic alkaloid skeletons by adding an acetoxymethylbenzene moiety to the previously reported indolizidine scaffold, mentioned above. The acetoxymethyl moiety was intended to mimic the acetoxy group of paclitaxel at the C4 position. The molecular design and analysis of the novel paclitaxel mimics were carried out using the REDOR-Taxol structure,[13,18,19] which was proposed based on the analysis of the tubulin-bound bioactive conformation of paclitaxel. The REDOR-Taxol structure has been successfully used for the design and synthesis of highly active conformationally rigidified macrocyclic taxoids.[13,18]

First, the designed tricyclic alkaloids with an *N*-benzoylphenylisoserine side chain were analyzed by molecular mechanics (MM) energy-minimization (InsightII 2000) at the binding site of paclitaxel in β-tubulin (1TUB[20]). The binding structures were compared with the REDOR-Taxol structure and the ones showing good overlays were selected. Mimics **1** and **2** have three ester groups in the tricyclic ring systems to mimic the C2, C4 and C13 groups of the baccatin III skeleton. Macrocyclic mimic **3** was also designed to rigidify the *N*-benzoylphenylisoserine and acetoxy moieties. These three mimics showed good overlay with the REDOR-Taxol structure in the 1TUB β-tubulin, as illustrated in Fig. 3.



Scheme 1. Retrosynthesis of paclitaxel-mimicking alkaloids **1**–**3**.

3. Synthesis of paclitaxel-mimicking alkaloids

As Scheme 1 shows, the retrosynthetic analysis indicates that (i) compounds **1** and **2** can be obtained by introducing the phenylisoserine moiety to the tricyclic alkaloid scaffold **4**, and (ii) compound **3** can be synthesized by introducing two olefinic side chains to **4** followed by ring-closing metathesis (RCM). Tricyclic alkaloid scaffold **4** can be prepared by the coupling reaction of lithium or Grignard species **7** with protected enantiopure prolinal **6**, followed by lactamization and acylations.

Preliminary study indicated that the coupling reaction of **7** with **6** was very sensitive to the bulkiness of the groups at the 2 and 6 positions of **7**, and only small groups were tolerated in this coupling. After screening of various 2,6-substituents, bromobenzene **8a** with a vinyl group serving as a hydroxymethyl synthon was selected for the synthesis of **4a** via **5a** ($n = 0$) (Scheme 2). An aryllithium species **7a** ($n = 0$; R = Li) was generated by treating **8a** ($n = 0$; R = H) with 2.2 equivalents of *n*-BuLi. The coupling of **7a** with **6** in the presence of HMPA afforded the desired product **9a** in 81% yield, and the subsequent acetylation of hydroxyl groups gave **10a** in 97% yield. Since the diastereomers of **9a** and **10a** were not separable by HPLC analysis, the determination of diastereomer ratio (d.r.) had to wait after lactamization. The vinyl moiety of **10a** was subjected to ozonolysis, oxidization, esterification, *N*-deprotection and lactamization to afford the desired 5-6-6 tricyclic

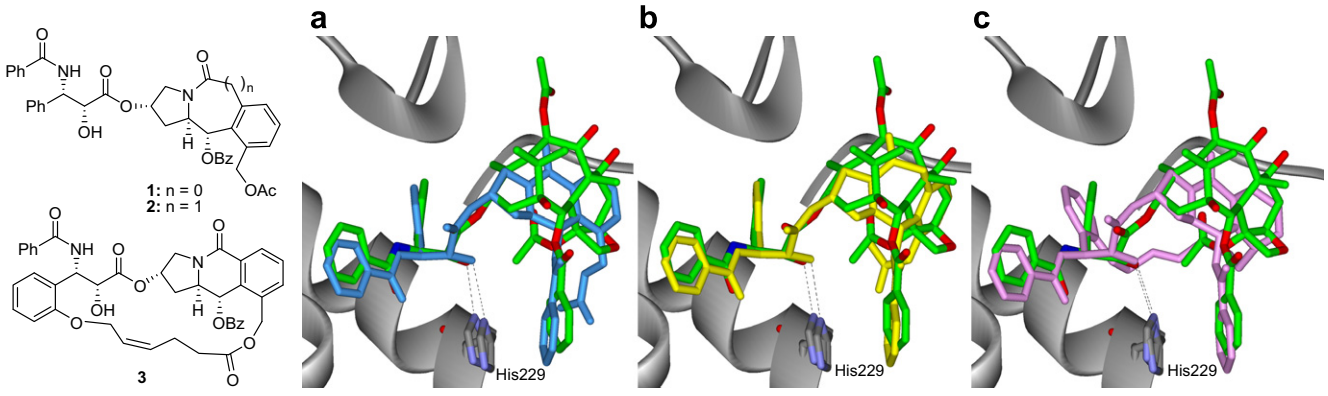
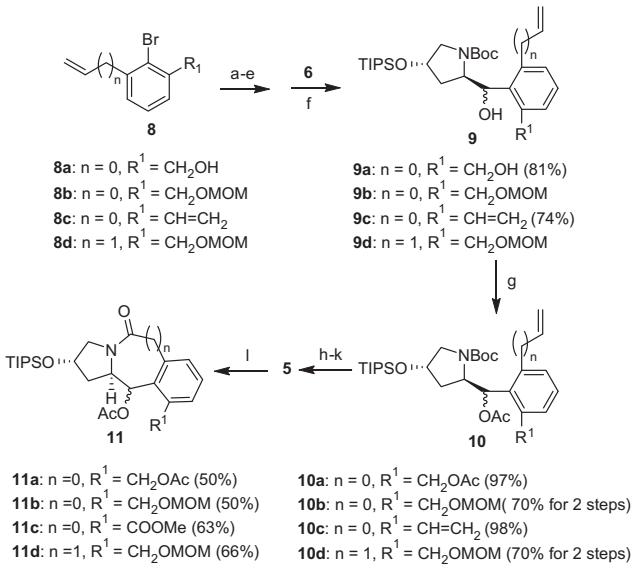


Figure 3. Overlays of **1** (cyan) (a), **2** (yellow) (b), **3** (magenta) (c), and REDOR-Taxol (green) in the 1TUB β-tubulin.



Scheme 2. Synthesis of tricyclic alkaloid scaffold **11**. Reagents and conditions: (a)–(f) see Table 1; (g) Ac_2O (1.5–3.0 equiv), Et_3N (2.5–5.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C to rt, overnight; (h) O_3, CH_2Cl_2, −78 °C; Me_2S, rt, 3 h; (i) $NaClO_2$ (8 equiv), NaH_2PO_4 (8 equiv), acetone, H_2O, rt, 40 min; (j) CH_2N_2, ether, rt, 10 min; (k) CF_3COOH, anisole (0.3 equiv), CH_2Cl_2, 0 °C to rt, 1 h; (l) $NaHCO_3$, H_2O, EtOAc, rt, overnight.

scaffold **11a** in 50% yield for 5 steps. Diastereomers, **11a**-α and **11a**-β, were separated by column chromatography. It was found that the d.r. was 2:1 with the undesirable diastereomer **11a**-β as the major product (Table 1, entry 1) although the Garner model[14,21] predicted that **11a**-α should be the major product. The stereochemistry of the acetoxy group in **11a**-α as well as **11a**-β was unambiguously assigned by NOE analysis.

In the hope of possible improvement of diastereoselectivity in the coupling reaction of **8** with **6**, **8b** and **8c** were employed under different coupling conditions (Scheme 2). Results are summarized in Table 1. Bromo(vinyl)benzene **8b** with a MOM-protected hydroxymethyl group reacted with **6** to give **10b** via **9b** in good yield (70% for 2 steps), and **10b** was subjected to the same protocol as that for **10a** to afford **11b** in 50% overall yield for five steps.[22] The d.r. was found to be 3:4 in favor of **11b**-β (entry 2). Next, **8b** was successfully converted to potentially more selective Grignard species (entry 3) and zinc species (entry 4) by standard procedures.[23,24] However, the attempted coupling reaction did not yield any desired product.

2,6-Divinylbromobenzene **8c**, bearing no oxygen to coordinate to lithium, was converted to the corresponding aryllithium species[25] and subjected to the coupling reaction with **6** to afford the product **9c** in 74% yield. The desired product **11c** ($R^1 = CO_2Me$) was obtained in good yield via **10c**, using the same 6-step protocol as that for **9a**. The d.r. was 1:1. The coupling reaction using the Grignard species generated from **8c** afforded **9c** in 74% yield, which was converted to **11c** with a 3:2 d.r. in favor of the desirable **11c**-α (entry 6).

Table 1
Diastereoselectivity of the coupling of **8** with **6**

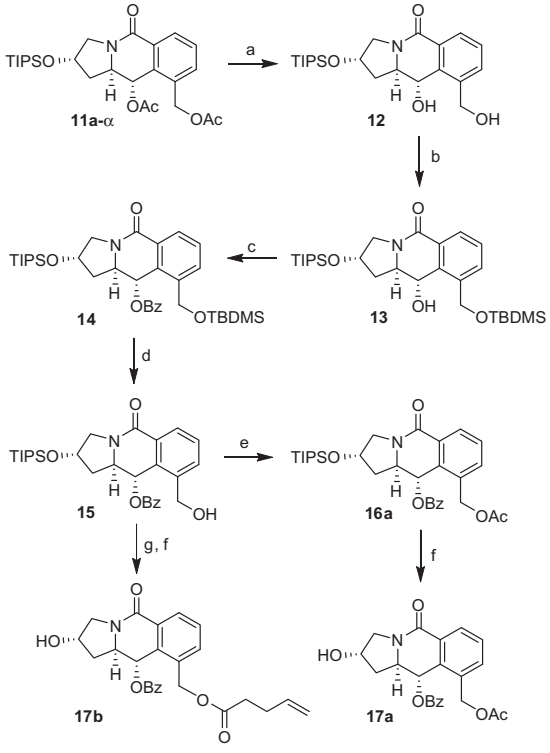
Entry	Substrate	Conditions	**11**-α:**11**-β
1	**8a**	a, b, f	1:2
2	**8b**	c, b, f	3:4
3	**8b**	d, f	NA
4	**8b**	c, e, b, f	NA
5	**8c**	c, b, f	1:1
6	**8c**	d, f	3:2
7	**8d**	c, b, f	1:10

Reagents and conditions: (a) *n*-BuLi (2.2 equiv), THF, −78 °C, 1 h; (b) HMPA, −78 °C, 1 h (c) *n*-BuLi (1.1 equiv), THF, −78 °C, 1 h; (d) Mg (1.2 equiv), $BrCH_2CH_2Br$, THF, reflux, 2 h; (e) $ZnCl_2$ (0.5 equiv), THF, 0 °C, 1 h; (f) **6** (1.0 equiv), −78 °C to rt, overnight. NA = not applicable.

The 5-7-6 tricyclic scaffold **11d** was synthesized in a similar manner from **8d** ($n = 1$, $R^1 = CH_2O$-MOM) (Scheme 2). The coupling of the aryllithium species generated from **8d** with **6** gave **9c** in 74% yield. The subsequent acetylation afforded **10d** in 96% yield, which was converted to the 5-7-6 tricylclic scaffold **11d** in 66% overall yield through the same 5-step protocol as that for **10a** (Scheme 2). The d.r. was substantially increased to 10:1, but in favor of **11d**-β. Since this stereochemistry can be inverted through the Mitsunobu reaction, further optimization of the coupling conditions was not pursued.

Enantiopure tricyclic scaffold **11a**-α was converted to the coupling-ready 5-6-6 tricyclic scaffolds **17a** and **17b** as illustrated in Scheme 3. Basic hydrolysis of the two acetate groups of **11a**-α gave **12** in high yield, and the subsequent selective protection of the primary alcohol of **12** with TBDMSCl in the presence of imidazole proceeded with very high selectivity, affording **13** in 99% yield.[26] Acylation of the secondary alcohol of **13** using 6 equivalents of benzoyl chloride gave **14** in quantitative yield. Acidic deprotection of TBDMS group afforded **15** in 95% yield.[27] Acylation of the primary alcohol of **15** with acetic anhydride gave **16a** and the subsequent deprotection of the TIPS group with HF/pyridine afforded **17a** quantitatively. In the same manner, the acylation of **15** with 4-pentenoyl chloride, Et_3N, DMAP followed by deprotection with HF/pyridine gave **17b** in quantitative yield.

For the synthesis of enantiopure 5-7-6 tricyclic scaffold **17c**, **11d**-β was deacetylated to give **18** first, and then, **18** was subjected



Scheme 3. Synthesis of tricyclic scaffolds **17a** and **17b**. Reagents and conditions: (a) K_2CO_3 (2.5 equiv), MeOH, H_2O, rt, 30 min (84%); (b) TBDMSCl (1.5 equiv), Imidazole (4.0 equiv), DMF, rt, 30 min (99%); (c) BzCl (6.0 equiv), Et_3N (8.0 equiv), DMAP (0.05 equiv), CH_2Cl_2, rt, overnight (100%); (d) 0.1 N HCl, EtOH, rt, 2.5 h (95%); (e) Ac_2O (2.0 equiv), Et_3N (4.0 equiv), DMAP (0.03 equiv), CH_2Cl_2, rt, overnight (100%); (f) HF/Py, CH_3CN, Py, rt, overnight (100%); (g) 4-pentenoyl chloride (2 equiv), Et_3N (4 equiv), DMAP (0.03 equiv), CH_2Cl_2, rt, 1.5 h (100%).

to the Mitsunobu reaction with benzoic acid in the presence of DIAD and PPh_3 (Scheme 4). The conversion of this reaction was only 35% in refluxing THF for 3 days. Nevertheless, the desired α-benzoate **19** was obtained in 63% yield (based on 35% conversion) for 2 steps, after deprotection of the MOM group. Acetylation and the subsequent deprotection of the TIPS group with HF/pyridine gave coupling-ready **17c** in high yield. The inversion of configuration at the chiral center bearing the benzoate moiety was confirmed by NOE analysis.

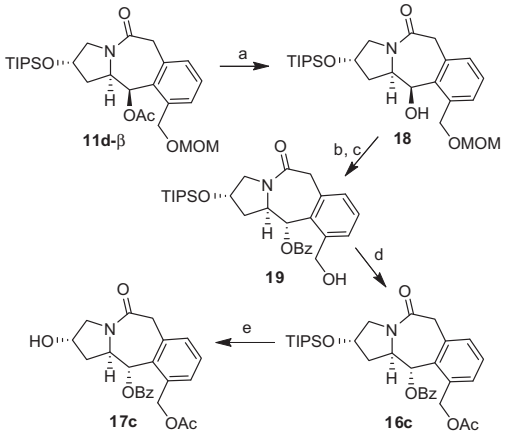
Tricyclic scaffolds **17a** and **17c** were coupled with oxazolidine acid **20a** (R^2 = H), which was prepared by the literature method,[28,29] in the presence of EDC and DMAP in CH_2Cl_2 to give **21a** and **21b**. Deprotection of **21a** and **21b** with *p*-toluenesulfonic acid (*p*-TsOH) in methanol afforded the designed paclitaxel-mimicking alkaloids **1** and **2** in good yields (Scheme 5).

For the synthesis of the macrocyclic paclitaxel-mimicking alkaloid **3**, **20b** was coupled with **17b**, followed by deprotection to give the final precursor, diene **22** in high yield in the same manner as that described above. Finally, **22** was subjected to ring-closing metathesis (RCM) using the first-generation Grubbs catalyst. The reaction was very slow and not completed after 2 days in refluxing dichloromethane. Nevertheless, the designed paclitaxel mimic **3** was obtained in 60% yield.

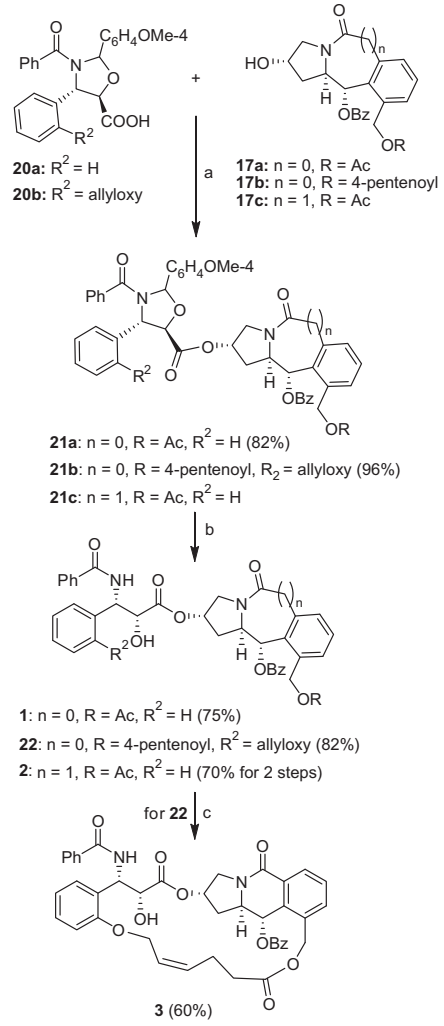
In order to examine the difference between the tricyclic alkaloid scaffolds and the bicyclic alkaloid scaffold that we reported previously,[14] paclitaxel mimic **24** was also synthesized through coupling of **23**[14] with oxazolidine carboxylic acid **20a** in the same manner as that described above (Scheme 6).

4. Biological activity of novel paclitaxel mimics

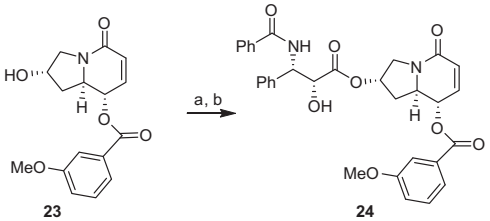
Novel paclitaxel mimics, thus obtained, were evaluated for their cytotoxicities against drug-sensitive and drug-resistant human cancer cell lines and compared with those of previously reported paclitaxel mimics. Results are summarized in Table 2. As Table 2 shows, paclitaxel-mimic **2** bearing the 5-7-6 tricyclic scaffold is the most potent among the novel paclitaxel-mimicking alkaloids synthesized, exhibiting a single micromolar IC_{50} values against drug-sensitive human breast cancer cell lines, MCF7-S, LCC6-WT, human ovarian cancer cell line, A2780, and human pancreatic cancer cell line, CFPAC-1 in spite of its drastically simplified structure (entry 6). The macrocyclic mimic **3**, bearing a 5-6-6 tricyclic scaffold, is the least potent among the newly synthesized paclitaxel-mimicking alkaloids. Nevertheless, mimic **3** shows IC_{50} value (14.8 μM), comparable to Kingston's mimics (IC_{50} = 11.3–20 μM)[14,17] against A2780 ovarian cancer cell line (entry 7). The polycyclic alkaloid scaffold structures have critical effect on the potency of the mimics (entries 5, 6 and 8), that is, the potency increases in the order, **24** (5-6 bicyclic) < **1** (5-6-6 tricyclic) < **2** (5-7-6 tricyclic), wherein **2** is substantially more potent than **1**. Mimics **1** and **2** also possess an acetoxy group, mimicking the acetoxy group at the C4 position of paclitaxel, which might be contributing to better potency than



Scheme 4. Synthesis of tricyclic scaffold **17c**. Reagents and conditions: (a) K_2CO_3 (2.5 equiv), MeOH, H_2O, rt, 30 min (81%); (b) DIAD (1.1 equiv), PhCOOH (1.2 equiv), PPh_3 (1.1 equiv), THF, reflux, 3 days; (c) anisole, CF_3COOH, CH_2Cl_2, rt, 2 h (63% for 2 steps); (d) Ac_2O (2 equiv), Et_3N (3 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C-rt, overnight (88%); (e) HF/Py, CH_3CN, Py, rt, overnight (86%).



Scheme 5. Synthesis of paclitaxel mimics **1**-**3**. Reagents and conditions: (a) **20** (1.5 equiv), EDC (2 equiv), DMAP (0.5 equiv), CH_2Cl_2, rt, overnight; (b) *p*-TSA (0.2 equiv), MeOH, rt, 10 h; (c) $Cl_2Ru(=CHPh)(PCy_3)_2$ (0.2 equiv), CH_2Cl_2, reflux, 2 days.



Scheme 6. Reagents and conditions: (a) **20a** (1.5 equiv), EDC (2 equiv), DMAP (0.5 equiv), CH_2Cl_2, rt, overnight; (b) *p*-TSA (0.2 equiv), MeOH, rt, 10 h, (76% for two steps).

Table 2
In vitro cytotoxicities of paclitaxel mimics (IC_{50}, μM)[a]

Entry	Compounds	MCF7-S[b]	NCI/ADR[c]	LCC6-WT[d]	LCC6-MDR[e]	A2780[f]	CFPAC-1[g]
1	Paclitaxel	0.0020 ± 0.0002	0.410 ± 0.045	0.0030 ± 0.0003	0.379 ± 0.022	0.020 ± 0.002	0.047 ± 0.007
2	Mimic A[h]	5.70 ± 0.26	8.70 ± 0.18	6.68 ± 0.17	10.00 ± 0.56	N.D.	N.D.
3	Mimic B[h]	8.10 ± 0.22	13.0 ± 0.6	10.5 ± 0.8	>20	N.D.	N.D.
4	Mimic C[i]	N.A.	N.A.	N.A.	N.A.	10.9 ± 1.5–20 ± 2	N.A.
5	**1**	39.6 ± 4.0	>100	36.3 ± 3.5	>100	7.80 ± 0.13	>100
6	**2**	8.31 ± 0.75	41.5 ± 4.5	4.93 ± 0.39	16.8 ± 1.9	3.81 ± 0.33	6.16 ± 0.71
7	**3**	>100	>100	>100	>100	14.8 ± 1.5	>100
8	**24**	45.9 ± 0.40	>100	42.8 ± 0.26	>100	N.D.	>100

[a] Concentration of compound which inhibits 50% (IC_{50}, μM) of the growth of human tumor cell line after 72 h drug exposure.
[b] MCF7-S: human breast carcinoma cell line (Pgp^-).
[c] NCI/ADR: multi-drug resistant human ovarian carcinoma cell line (Pgp^+).
[d] LCC6-WT: human breast carcinoma cell line (Pgp^-).
[e] LCC6-MDR: mdr1 transduced cell line (Pgp^+).
[f] A2780: human ovarian carcinoma cell line.
[g] CFPAC-1: human pancreatic carcinoma cell line.
[h] Ref. 14.
[i] Ref. 17.

24. Based on the overlay, **2** is better mimicking paclitaxel than **1** for this acetoxyl group.

The results also show clear difference between *N*-benzoylphenylisoserine, that is, paclitaxel's C13 side chain, and *N*-*t*-Boc-3-(2-methylprop-2-enyl)isoserine, a C13 side chain of second- and third-generation taxoids,[10] with regard to their effect on the potency of paclitaxel mimics (entries 2 and 8), that is, the potencies of mimic **A** is one order of magnitude higher than those of **24**, wherein the only difference is the structure of the isoserine side chain.

The resistance factor, that is, R-factor = IC_{50} (drug-resistant cell line)/IC_{50} (drug-sensitive cell line), is an excellent indicator for the sensitivity of cytotoxic agents against MDR phenotype (P-glycoprotein overexpression, Pgp+). The R-factors of paclitaxel for the MCF-7 versus NCI/ADR and LCC6-WT versus LCC6-ADR are 205 and 126, respectively (entry 1). In contrast, the R-factors of **2** for the same pair of cell lines are 5.0 and 3.4, respectively (entry 6), whereas those of **A** are 1.5 for both pairs of cell lines (entry 2). Accordingly, mimics **2** and **A** are significantly less affected by the P-glycoprotein efflux pump and the use of non-aromatic isoserine side chain is found to be beneficial to further increase the potency against MDR cancer cell lines.

For the binding of mimics **2** to microtubules, a preliminary study has been done through competitive displacement of Flutax-2[30] using TR-NOESY analysis.[31] The critical concentration of tubulin required for microtubule assembly was determined to be 3.7 μM, while DMSO (vehicle) was 3.3 μM. This might suggest that mimic **2** inhibits tubulin polymerization through low affinity interaction. Due to low water solubility of mimic **2**, accurate binding constant has not been determined. Nevertheless, the result observed for Flutax-2 displacement indicates that the binding constant (Kb) would be in 50–100 μM range. Unexpected inhibitory activity was also observed for a T-Taxol mimic (mimic D, Fig. 2).[15] These results may imply that there are compounds, which interact with the paclitaxel binding site in β-tubulin, but destabilize tubulin nucleates/oligomers. The study on the binding ability of mimic **2** to tubulin will be reported elsewhere.

5. Molecular modeling analysis

When we first designed paclitaxel mimics **1**, **2** and **3**, the REDOR-Taxol structure in the 1TUB[20] tubulin was employed, as shown in Figure 3. Since then, the REDOR-Taxol structure was refined using the higher-resolution 1JFF[32] β-tubulin.[18,19] Accordingly, we performed molecular modeling as well as molecular dynamics (MD) studies on the mimics **1** and **2** in comparison with the REDOR-Taxol structure in the 1JFF tubulin. The overlay of the energy minimized structures of **1** and **2** in the 1JFF tubulin, using the InsightII 2000 program (CVFF force field), with the REDOR-Taxol-1JFF structure is shown in Figure 4.

The critical H-bond between the phenylisoserine moiety's C2′–OH of **1** (1.8 Å) or **2** (2.1 Å) and His229 was very stable during the energy minimization. As Figure 5 shows, the three structures have very good matching for the 3′-phenyl, 3′*N*-benzoyl, and 2-benzoate groups, as well as even the 4-acetoxyl group, although the oxetane and the northern part of the baccatin structure are missing. Nevertheless, **1** and **2** only exhibit much lower potency than paclitaxel. To obtain some insight into this observation, we carried out the MD simulations of **1** and **2** in 1JFF using the Macromodel program (MMFF94 force field[33]) and compared their conformational stability with that of REDOR-Taxol-1JFF. In the MD simulations, all atoms farther than 10 Å from the binding site were fixed, following our previously reported protocol,[19] and the stability of the C2′–OH···N(His229) H-bond was monitored during the whole simulation in each case. The overlays of 200 snapshots for each (sampled every 0.25 ps) of the conformations of **1**, **2** and paclitaxel are shown in Figure 5.

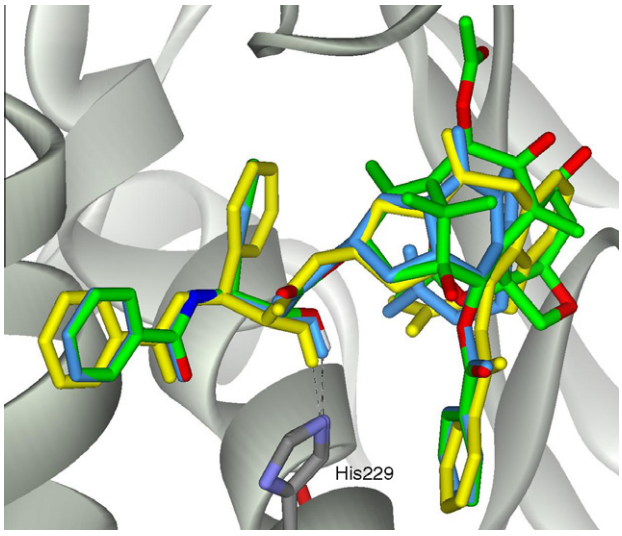


Figure 4. Overlay of paclitaxel (REDOR-Taxol-1JFF) (green), **1** (cyan) and **2** (yellow) in 1JFF.

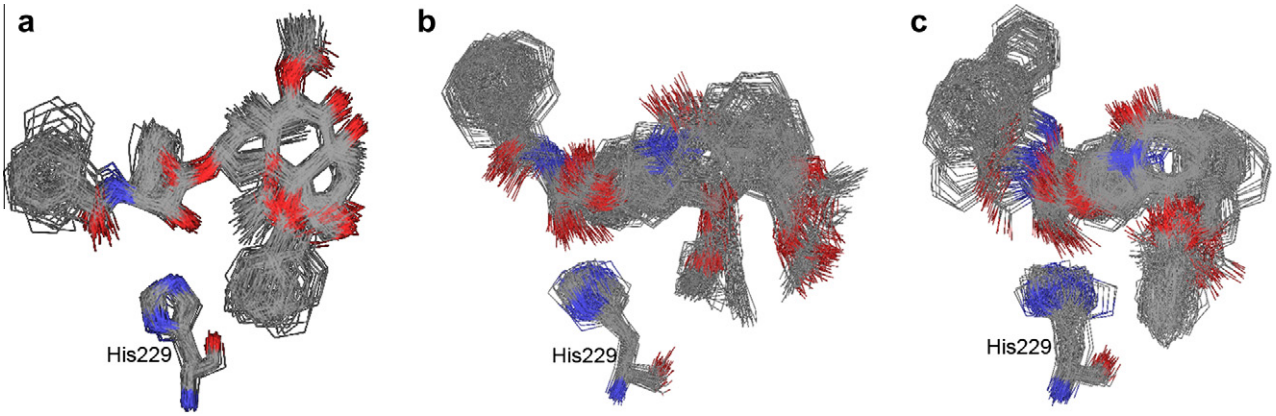


Figure 5. MD simulation of paclitaxel (REDOR-Taxol-1JFF) (a), **1** (b) and **2** (c) in 1JFF (50 ps).

As Figure 5 shows, the critical C2′–OH···N(His229) H-bond is stable in all three cases (average distance: 2.1 ± 0.4 Å for **1**; 2.3 ± 0.7 Å for **2**; 2.0 ± 0.2 Å for REDOR-Taxol-1JFF). However, the conformation of **1** is very flexible, that is, unstable (Fig. 5b), and substantially deviates from that of REDOR-Taxol (Fig. 5a), especially the phenyl moiety as well as the acetoxy group, which is supposed to mimic the same group at the C4 position of paclitaxel. As Figure 5c indicates, **2** mimics REDOR-Taxol much better than **1**, but the 3′-phenyl and 3′*N*-benzoyl groups, especially the latter, move around in a wide range, showing conformational instability. The MD simulation analysis may indicate that the conformational instability of the paclitaxel mimics needs to be addressed to improve their potency, besides structural over-simplification.

In summary, novel paclitaxel-mimicking alkaloids were synthesized based on the computational design, mimicking the REDOR-Taxol structure. The alkaloid **2** bearing a 5-7-6 tricyclic scaffold mimics REDOR-Taxol best among the compounds designed and was found to be the most potent compound against several drug-sensitive and drug-resistant human cancer cell lines. An MD simulation study on the paclitaxel mimics **1** and **2** as well as REDOR-Taxol in the 1JFF tubulin was quite informative to evaluate the level of mimicking, as compared to static energy minimized structures of these mimics. For example, the MD simulation study clearly distinguishes the difference between the 5-6-6 and 5-7-6 tricyclic scaffolds, and also substantial difference in the conformational stability of the tubulin-bound structures between **2** and REDOR-Taxol. The latter may account for the large difference in potency, and provides critical information for possible improvement in the future design of paclitaxel mimics. The comparison of potency with the previously reported paclitaxel mimics has disclosed a considerable enhancement in potency by introducing non-aromatic isoserine side chain, especially against MDR cancer cell lines. Thus, it is anticipated that the paclitaxel mimics, combining 5-7-6 tricyclic scaffolds and a non-aromatic isoserine side chains, would be considerably more potent than the mimics **2** and **A**, exhibiting IC_{50} values less than 1 μM against several cancer cell lines examined in this study. Further studies along this line are actively in progress in these laboratories.

6. Experimental

6.1. Chemistry

6.1.1. General methods

^1H and ^{13}C NMR spectra were measured on a Varian 300, 400, 500 or 600 MHz NMR spectrometer. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Specific optical rotations were measured on a Perkin–Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried out on silica gel 60 (Merck; 230–400 mesh ASTM). Purity was determined with a Waters HPLC assembly consisting of dual Waters 515 HPLC pumps, a PC workstation running Millennium 32, and a Waters 996 PDA detector, using a Phenomenex Curosil-B column, employing CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min. High-resolution mass spectra were obtained at the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL.

6.1.2. Materials

The chemicals were purchased from Aldrich–Sigma Co. and used as received or purified before use by standard methods. Tetrahydrofuran (THF) was freshly distilled from sodium metal and benzophenone. Dichloromethane was distilled immediately prior to use under nitrogen from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was distilled over 4A molecular sieves under reduced pressure. 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) was uses as received. The preparation of **8a**–**d** is described in the Supplementary data.

6.1.3. (3*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-5-[hydroxy(2-ethenyl-6-hydroxymethylphenyl)methyl]-3-triisopropylsiloxy-pyrrolidine (9a)

Aryl bromide **8a** (94 mg, 0.44 mmol) was desolved in dry THF (4 mL) under N_2 and 2.5 M *n*-BuLi in hexane (0.39 mL, 0.97 mmol) was added at −78 °C. The resulting solution was stirred for 1 h. Then, HMPA (0.09 mL) was added and the solution was stirred for 1 h. To this solution, a solution of aldehyde **6** (127 mg, 0.34 mmol) in dry THF (2.8 mL) was added dropwise. The resulting mixture was allowed to slowly warm up to room temperature with stirring overnight. Then, the reaction was quenched with a saturated NH_4Cl solution (20 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc = 8:1–4:1) as eluent to give **9a** (139 mg, 81% yield) as white solid: mp 38–40 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (m, 21H), 1.32–1.44 (m, 9H), 1.74 (m, 1H), 2.19 (m, 1H), 3.34 (m, 1H), 3.67 (m, 1H), 4.31 (m, 1H), 4.58 (m, 1H), 4.76 (m, 1H), 4.96 (m, 1H), 5.10 (m, 1H), 5.42 (m, 2H), 7.03 (m, 1H), 7.28 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.8, 18.5, 28.9, 39.4, 56.5, 57.1, 65.5, 70.9, 80.2, 81.3, 116.5, 117.7, 127.4, 127.7, 131.2, 136.5, 136.8, 140.2, 158.7. HRMS calcd. for $C_{28}H_{47}NO_5SiNa^+$ 528.3121, found 528.3116 (Δ = −1.0 ppm).

6.1.4. 1-(*tert*-Butoxycarbonyl)-2-[(2,6-diethenylphenyl)-hydroxymethyl]-4-triisopropylsiloxypyrrolidine (9c)

A mixture of **8c** (257 mg, 1.22 mmol) and Mg turnings (35 mg, 1.47 mmol) in THF (12 mL) was added 1 drop of 1,2-dibromoethane and the mixture was heated at reflux for 2 h. Then, the resulting Grignard reagent solution was cooled to room temperature. Aldehyde **6** (226 mg, 0.61 mmol) was dissolved in THF (7 mL) and cooled down to −78 °C. The Grignard reagent generated above (1.22 mmol, 2.0 equiv) was added to the aldehyde solution by cannula and the reaction mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (17:1) as the eluent to afford **9c** (227 mg, 74% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (m, 21H), 1.32–1.44 (m, 9H), 1.74 (m, 1H), 2.19 (m, 1H), 3.31 (m, 1H), 3.57 (m, 1H), 3.85 (m, 1H), 4.51 (m, 1H), 4.98 (m, 1H), 5.12 (m, 2H), 5.41 (m, 2H), 6.96–7.74 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.0, 18.0, 28.2, 36.8, 39.6, 55.6, 63.8, 70.0, 74.1, 81.0, 114.9, 127.4, 127.9, 128.1, 136.5, 136.4, 137.9, 158.8. HRMS calcd. for $C_{29}H_{46}NO_4SiH^+$ 502.3353, found 502.3373 (Δ = 4.0 ppm).

6.1.5. (3*S*,5*R*)-5-[Acetoxy(2-acetoxymethyl-6-ethenyl-phenyl) methyl]-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxypyrrolidine (10a)

To a solution of **9a** (134 mg, 0.26 mmol) and DMAP (4.8 mg, 0.06 mmol) in CH_2Cl_2 (2.0 mL) was added triethylamine (0.41 mL, 1.4 mmol) and acetic anhydride (0.27 mL, 0.84 mmol) at 0 °C. The reaction mixture was stirred overnight, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford a liquid residue. The residue was purified by silica gel column chromatography on silica gel using hexanes/EtOAc (8:1) as the eluent to afford **10a** (150 mg, 97% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (m, 21H), 1.28–1.43 (m, 9H), 1.70 (m, 1H), 2.06–2.10 (m, 7H), 3.40 (m, 1H), 3.62 (m,1H), 4.57 (m, 1H), 4.79 (m, 1H), 5.31 (m, 3H), 5.54 (m, 2H), 6.03 (m, 1H), 7.17–7.52 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.1, 17.9, 20.9, 28.0, 28.4, 38.3, 55.0, 58.5, 64.3, 71.0, 73.9, 79.5, 116.6, 128.2, 128.7, 129.9, 132.3, 134.2, 136.5, 139.4, 154.6, 170.3, 170.7. HRMS calcd. for $C_{32}H_{51}NO_7SiNa^+$ 612.3333, found 612.3329 (Δ = −0.6 ppm).

6.1.6. (3*S*,5*R*)-2-[Acetoxy(2-methoxymethoxymethyl-6-ethenyl-phenyl)methyl]-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-pyrrolidine (10b)

Colorless oil; 70% yield for 2 steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (m, 21H), 1.28–1.43 (m, 9H), 2.06–2.10 (m, 5H), 3.40 (m, 4H), 3.59 (m, 1H), 4.57 (m, 2H), 4.79 (m, 4H), 5.28 (d, J = 10.8 Hz, 1H), 5.51 (d, J = 17.6, 1H), 6.02–6.22 (m, 1H), 7.17–7.52 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.1, 17.9, 20.9, 28.0, 28.4, 38.3, 54.7, 55.0, 58.6, 66.6, 70.2, 72.7, 79.7, 95.4, 116.0, 127.2, 127.5, 128.9, 129.1, 133.5, 136.4, 136.8, 137.0, 138.6, 154.4, 169.5. HRMS calcd. for $C_{32}H_{53}NO_7SiH^+$ 592.3670, found 592.3663 (Δ = −1.2 ppm)

6.1.7. (3*S*,5*R*)-5-[Acetoxy(2,6-diethenylphenyl)methyl]-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxypyrrolidine (10c)

Colorless oil; 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 21H), 1.28–1.47 (m, 9H), 1.66 (m, 1H), 1.90–2.10 (m, 4H), 3.48 (m, 2H), 4.43 (m, 1H), 4.79 (m, 1H), 5.23 (m, 2H), 5.47 (m, 2H), 6.43 (m, 1H), 7.27–7.74 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.7, 18.5, 21.1, 28.7, 37.5, 55.5, 59.4, 71.5, 73.9, 79.4, 116.6, 128.2, 128.7, 129.5, 132.8, 137.4, 139.4, 155.8, 169.4. HRMS calcd. for $C_{31}H_{48}NO_5SiH^+$ 544.3458, found 544.3472 (Δ = 2.6 ppm).

6.1.8. (3*S*,5*R*)-5-[Acetoxy(2-allyl-6-methoxymethoxymethyl-phenyl)methyl]-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-pyrrolidine (10d)

Colorless oil; 70% yield for 2 steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (m, 21H), 1.28–1.43 (m, 9H), 1.66 (m, 1H), 2.05 (m, 4H), 3.42 (s, 3H), 3.65 (m, 4H), 4.70 (m, 6H), 5.05 (m, 2H), 5.97 (m, 1H), 6.10 (m, 1H), 7.11–7.31 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.8, 21.0, 27.7, 37.6, 38.4, 55.2, 58.6, 66.9, 70.7, 72.5, 73.4, 79.7, 95.4, 115.9, 127.7, 128.1, 130.3, 133.5, 134.1, 137.1, 139.2, 154.5, 169.6. ^{1}HRMS calcd. for $C_{33}H_{55}NO_7SiH^+$ 606.3826, found 606.3832 (Δ = 1.0 ppm).

6.1.9. (2*S*,10*S*/*R*,10a*R*)-10-Acetoxy-9-acetoxymethyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (11a)

Nitrogen gas was bubbled into a solution of **10a** (167 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) at −78 °C for 3 min. Then, O_3 gas was bubbled into the solution till the color of the solution turned blue (8 min), and N_2 was bubbled into the solution for another 3 min until the blue color disappeared. Dimethyl sulfide (0.1 mL, 1.4 mmol) was added to the solution and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 3 h. The solvents were removed in vacuo and the resulting crude aldehyde was used in the next step without further purification.

Sodium chlorite (200 mg, 2.24 mmol) was added to a solution of the aldehyde obtained (~0.28 mmol) and sodium phosphate (monobasic) (350 mg, 2.24 mmol) in acetone/water (1:1, 2.4 mL). The reaction mixture was stirred at room temperature for 1 h and quenched with ethyl acetate (60 mL). The organic layer was washed with hydrochloric acid (1N, 10 mL), $Na_2S_2O_3$ (10%, 10 mL × 2), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting crude acid was used in the next step without further purification.

A solution of potassium hydroxide (4 g) in water (8 mL) and ethanol (32 mL) was added to a solution of diazald® (4 g) in ether (60 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and distilled to afford a yellow ether solution. The diazomethane solution in ether was added to the solution of the acid obtained (~0.28 mmol) in ether (12 mL) until the yellow color did not disappear. The mixture was stirred for 10 min and the reaction was quenched with acetic acid. The solvents were removed in vacuo and the resulting crude methyl ester was used in the next step without further purification.

To a solution of crude ester obtained (~0.28 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added trifluoroacetic acid (1.5 mL). The mixture was stirred at 0 °C for 30 min and room temperature for 30 min. The solvent and the acid were removed under reduced pressure and the residue was used in next step without further purification.

To a solution of the residue in ethyl acetate (14 mL) was added saturated aqueous sodium bicarbonate (14 mL). The mixture was stirred vigorously overnight and the reaction was quenched with ethyl acetate (50 mL). The reaction mixture was washed with water (10 mL) saturated aqueous ammonium chloride (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (3:1–2:1) as the eluent to afford **11a**-**α** and **11a**-**β** (1:2) in 50% yield for 5 steps.

6.1.9.1. (2*S*,10*S*,10a*R*)-10-Acetoxy-9-acetoxymethyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (11a-α). Colorless oil; 17% for 5 steps; $[\alpha]_D^{22}$ −80.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 21H), 2.05 (s, 3H), 2.06 (m, 2H), 2.21 (s, 3H), 3.80 (d, J = 3.2 Hz, 2H), 4.15 (td, J = 10.8, 5.6 Hz, 1H), 4.61 (s, 1H), 5.09 (d, J = 12.8 Hz, 1H), 5.33 (d,

J = 12.8 Hz, 1H), 6.38 (d, J = 12.8, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H), 8.15 (dd, J = 7.6, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.2, 18.2, 20.8, 21.1, 42.2, 55.3, 58.9, 65.8, 69.5, 73.1, 128.6, 129.2, 130.8, 132.9, 134.2, 135.5, 162.3, 170.4, 171.1. HRMS calcd. for $C_{26}H_{39}NO_6SiH^+$ 490.2625, found 490.2621 (Δ = −0.8 ppm).

6.1.9.2. (2*S*,10*R*,10a*R*)-10-Acetoxy-9-acetoxymethyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (11a-β). Colorless oil; 33% yield for five steps; $[\alpha]_D^{22}$ −137 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 21H), 1.83 (td, J = 12.4, 4.0 Hz, 1H), 2.02 (s, 3H), 2.07 (s, 3H), 2.13 (ddd, J = 18.4, 7.2, 4.8 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.80 (dd, J = 12.8, 4.4, 1H), 4.31 (ddd, J = 10.8, 5.6, 2.4 Hz, 1H), 4.66 (t, J = 3.6 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.28 (d, J = 12.8 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 7.55 (m, 2H), 8.18 (dd, J = 7.2, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.0, 17.9, 20.8, 20.9, 37.8, 54.6, 57.5, 63.1, 63.7, 69.5, 128.5, 129.8, 131.5, 133.5, 133.8, 162.0, 170.0, 170.4. HRMS calcd. for $C_{26}H_{39}NO_6SiH^+$ 490.2625, found 490.2618 (Δ = −1.4 ppm).

6.1.10. (2*S*,10*S*/*R*,10a*R*)-10-Acetoxy-9-methoxymethoxy-methyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]-isoquinolin-5-one (11b)

Colorless oil (α/β = 3:4 by ^{1}H NMR); 50% yield for 5 steps; 11bα: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 21H), 2.11 (m, 2H), 2.21 (s, 3H), 3.31 (s, 3H), 3.79 (m, 2H), 4.14 (td, J = 10.8, 5.6 Hz, 1H), 4.61 (m, 6H), 4.80 (d, J = 12.8 Hz, 1H), 6.32 (d, J = 10.4, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 8.10 (dd, J = 8.0, 1.6 Hz, 1H). HRMS calcd. for $C_{26}H_{41}NO_6SiH^+$ 492.2781, found 492.2775 (Δ = −1.2 ppm).

6.1.11. (2*S*,10*S*/*R*,10a*R*)-10-Acetoxy-9-methoxycarbonyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (11c)

Colorless oil (α/β = 3:2 by ^{1}H NMR); 63% yield for 5 steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (m, 21H), 1.89 (td, J = 12.8, 4.0, 0.5H), 1.98 (s, 1.5H), 2.16 (m, 2H), 3.77 (m, 2H), 3.84 (s, 1.5H), 3.92 (s, 1.5H), 4.07 (m, 0.5H), 4.30 (ddd, J = 11.2, 5.6, 2.4 Hz, 0.5H), 4.64 (m, 1H), 6.40 (d, J = 10.8, 0.5H), 6.74 (d, J = 2.4 Hz, 0.5H), 7.49 (t, J = 8.4 Hz, 0.5H), 7.58 (t, J = 7.6 Hz, 0.5H), 7.77 (dd, J = 8.0, 1.6 Hz, 0.5H), 8.04 (dd, J = 8.0, 1.6 Hz, 0.5 Hz), 8.24 (dd, J = 8.0, 1.6 Hz, 0.5H), 8.36 (dd, J = 7.6, 1.2 Hz, 0.5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.3, 12.5, 17.9, 20.6, 20.8, 38.2, 42.2, 52.4, 52.6, 54.7, 54.9, 57.6, 58.9, 64.6, 69.2, 69.5, 71.8, 128.3, 129.4, 130.1, 130.2, 130.3, 130.8, 131.7, 131.9, 132.9, 133.5, 134.9, 136.7, 161.5, 161.7, 166.9, 168.6, 169.7, 170.1. HRMS calcd. for $C_{26}H_{41}NO_6SiH^+$ 492.2781, found 492.2775 (Δ = −1.2 ppm).

6.1.11.1. (2*S*,11*S*,11a*R*)-11-Acetoxy-10-(methoxymethoxymethyl)-2-triisopropylsiloxy-2,3,11,11a-tetra-hydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepin-5(6H)-one (11d-α). Colorless oil; 63% yield for 5 steps; $[\alpha]_D^{22}$ −26 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (m, 21H), 1.99 (m, 2H), 2.07 (s, 3H), 3.36 (s, 3H), 3.46 (d, J = 13.2 Hz, 1H), 3.75 (d, J = 17.2 Hz, 1H), 3.98 (dd, J = 12.8, 5.6 Hz, 1H), 4.18 (dd, J = 10.8, 6.0 Hz, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.45 (t, J = 3.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 4.61 (dd, J = 12.8, 6.4 Hz, 2H), 5.05 (d, J = 11.6 Hz, 1H), 6.43 (s, 1H), 7.14 (dd, J = 6.0, 2.4 Hz, 1H), 7.25 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.9, 20.9, 40.9, 43.8, 55.4, 57.9, 59.8, 67.5, 68.9, 95.3, 128.9, 129.4, 131.2, 134.6, 135.6, 135.7, 167.5, 170.2. HRMS calcd. for $C_{27}H_{43}NO_6SiH^+$ 506.2938, found 506.2928 (Δ = −2.0 ppm).

6.1.11.2. (2*S*,11*R*,11a*R*)-11-Acetoxy-10-(methoxymethoxymethyl)-2-triisopropylsiloxy-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepin-5(6H)-one (11d-β). Colorless oil; 6% yield for 5 steps; $[\alpha]_D^{22}$ +62 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (m, 21H), 2.02 (dt, J = 13.6, 2.8 Hz, 1H), 2.06 (s, 3H), 2.26 (dd, J = 10.0, 4.0 Hz, 1H), 3.38 (s, 3H), 3.38 (d, J = 11.2 Hz, 1H), 3.47 (dd, J = 10.4, 3.6 Hz, 1H), 3.52 (d, J = 10.0 Hz, 1H), 4.36 (m, 2H), 4.46 (d, J = 10.0 Hz, 1H), 4.52 (d, J = 9.6 Hz, 1H), 4.65 (dd, J = 10.8, 5.2 Hz, 2H), 4.84 (d, J = 9.6 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 7.26 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.8, 21.1, 41.9, 42.7, 55.4, 55.9, 61.6, 67.3, 67.9 70.9, 95.6, 129.2, 129.3, 129.9, 131.9, 137.5, 137.6, 169.9, 170.6. HRMS calcd. for $C_{27}H_{43}NO_6SiH^+$ 506.2938, found 506.2928 (Δ = −2.0 ppm).

6.1.12. (2*S*,10*S*,10a*R*)-10-Hydroxy-9-hydroxymethyl-2-triisopropylsiloxy-2,3,10,10a-tetrahydro-1H-pyrrolo-[1,2-*b*]isoquinolin-5-one (12)

To a solution of **11a-α** (133 mg, 0.27 mmol) in methanol (10.9 mL) and water (5.5 mL) was added potassium carbonate (115 mg, 0.70 mmol). The mixture was stirred at room temperature for 35 min. Then, the reaction mixture was quenched with ethyl acetate (50 mL) and the organic layer was washed with saturated aqueous NH_4Cl solution (10 mL), water (10 mL × 2) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using 3% methanol in chloroform as the eluent to afford **12** as a white solid (92 mg, 84% yield): mp 153–155 °C; $[\alpha]_D^{22}$ −86 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 21H), 1.85 (ddd, J = 14.8, 10.8, 4.0 Hz, 1H), 2.48 (dd, J = 12.8, 5.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.72 (dd, J = 13.2, 4.4 Hz, 1H), 4.02 (td, J = 16.4, 5.2 Hz, 1H), 4.61 (t, J = 3.6 Hz, 1H), 4.71 (t, J = 12.4 Hz, 1H), 4.83 (m, 2H), 5.79 (br s, 1H), 7.22 (m, 2H), 7.78 (dd, J = 7.6, 3.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.9, 42.3, 55.3, 59.8, 65.1, 69.4, 73.3 127.5, 127.8, 129.5, 133.8, 137.3, 139.7, 162.9. HRMS: *m*/*e* calcd for $C_{22}H_{35}NO_4SiH^+$: 406.2414, found: 406.2411 (Δ = −0.6 ppm).

6.1.13. (2*S*,10*S*,10a*R*)-9-(*tert*-Butyldimethylsiloxymethyl)-10-hydroxy-2-triisopropylsiloxy-2,3,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]isoquinolin-5-one (13)

To a solution of **12** (90 mg, 0.22 mmol) and imidazole (60 mg, 0.88 mmol) in dry DMF (0.6 mL) was added *t*-butyldimethylsilyl chloride (0.29 mmol in 1.2 mL DMF) dropwise via syringe at 0 °C. The reaction mixture was stirred for 35 min at room temperature and quenched with saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with EtOAc (20 mL × 3), washed with water (10 mL × 2), and brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified on a silica gel column using hexanes/EtOAc (2:1) as the eluent to give **13** as a white solid (113 mg, 99% yield): mp 183–184 °C; $[\alpha]_D^{22}$ −110 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.04 (m, 21H), 1.93 (td, J = 12.8, 4.0 Hz, 1H), 2.51 (dd, J = 12.8, 5.6 Hz, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.84 (dd, J = 12.8, 4.4 Hz, 1H), 4.09 (td, J = 10.8, 5.6 Hz, 1H), 4.64 (s, 1H), 4.74 (d, J = 12.8 Hz, 1H), 4.88 (dd, J = 10.8, 3.6, 1H), 5.18 (d, J = 12.8 Hz, 1H), 5.61 (d, J = 4.4 Hz, 1H), 7.28 (m, 2H), 8.04 (dd, J = 7.2, 2.0 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ −5.4, −5.1, 12.0, 17.9, 18.1, 25.6, 42.5, 55.2, 59.6, 66.2, 69.6, 73.8, 127.3, 128.3, 130.4, 132.7, 136.1, 139.9, 162.5. HRMS: *m*/*e* calcd for $C_{28}H_{49}NO_4Si_2H^+$: 520.3278, found: 520.3279 (Δ = 0.1 ppm).

6.1.14. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-9-(*tert*-butyldimethylsiloxymethyl)-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (14)

To a solution of **13** (60 mg, 0.115 mmol) and DMAP (4.8 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) was added triethylamine (0.13 mL, 0.92 mmol) and benzoyl chloride (0.1 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred overnight, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The organic layer was dried over anhydrous $MgSO_4$

and solvent was removed under reduced pressure to afford a liquid residue. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (6:1) as the eluent to afford **14** (73 mg, 100%) as colorless oil: $[\alpha]_D^{22}$ −110 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ −0.22 (s, 3H), 0.21 (s, 3H), 0.75 (s, 9H), 1.02 (m, 21H), 2.15 (m, 2H), 3.85 (m, 2H), 4.30 (td, *J* = 10.8, 6.0 Hz, 1H), 4.63 (s, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 4.76 (d, *J* = 14.0, 1H), 6.60 (d, *J* = 10.8 Hz, 1H), 7.48 (m, 3H), 7.64 (m, 2H), 8.13 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ −5.7, −5.8, 12.0, 17.9, 18.2, 25.7, 41.9, 55.1, 58.7, 63.2, 69.3, 73.2, 127.2, 128.3, 128.7, 129.2, 129.7, 129.8, 130.7, 133.7, 133.8, 138.9, 162.6, 165.5. HRMS: *m*/*e* calcd for $C_{35}H_{53}NO_5Si_2H^+$: 624.3541, found: 624.3516 (Δ = −3.9 ppm).

6.1.15. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (15)

To a solution of **14** (134 mg, 0.21 mmol) in ethanol (10 mL) was added 0.5 N HCl in ethanol (2 mL). The mixture was stirred at room temperature for 2.5 h. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (2:1) as the eluent to afford **15** as a white solid (102 mg, 95% yield): mp 95–98 °C; $[\alpha]_D^{22}$ −130 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (m, 21H), 2.17 (m, 2H), 2.68 (br s, 1H), 3.75 (d, *J* = 12.8 Hz, 1H), 3.88 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.30 (td, *J* = 10.8, 6.0 Hz, 1H), 4.55 (d, *J* = 13.6 Hz, 1H), 4.62 (d, *J* = 13.6, 1H), 4.66 (s, 1H), 6.53 (d, *J* = 10.8 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.61 (m, 2H), 7.86 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.2 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.9, 42.0, 55.1, 58.8, 63.1, 69.2, 73.0, 127.5, 128.4, 128.7, 129.1, 129.8, 132.1, 133.7, 134.1, 138.9, 162.7, 165.9. HRMS: *m*/*e* calcd for $C_{29}H_{39}NO_5SiH^+$: 510.2676, found: 510.2672 (Δ = −0.7 ppm).

6.1.16. (2*S*,10*S*,10a*R*)-9-Acetoxymethyl-10-benzoyloxy-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (16a)

To a solution of **15** (32 mg, 0.06 mmol) and DMAP (1 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (0.08 mL, 0.24 mmol) and acetic anhydride (0.05 mL, 0.12 mmol) at 0 °C. The reaction mixture was stirred overnight, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (2:1) as the eluent to afford **16a** (35 mg, 100%) as a colorless oil: $[\alpha]_D^{22}$ −164 (*c* 14.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (m, 21H), 1.89 (s, 3H), 2.17 (m, 2H), 3.83 (td, *J* = 12.8, 3.6 Hz, 1H), 4.32 (dd, *J* = 16.4, 9.2 Hz, 1H), 4.63 (d, *J* = 2.0 Hz, 1H), 5.02 (d, *J* = 12.8, 1H), 5.20 (d, *J* = 12.4 Hz, 1H), 6.70 (d, *J* = 10.8 Hz, 1H), 7.48 (m, 4H), 7.64 (ddd, *J* = 8.8, 2.4, 1.2 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.20 (dd, *J* = 6.8, 2.4 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.9, 20.4, 41.9, 55.1, 58.8, 65.3, 69.3, 73.1, 128.5, 128.7, 129.0, 129.1, 129.7, 130.6, 133.0, 133.8, 134.3, 135.7, 162.2, 165.7, 170.3. HRMS: *m*/*e* calcd for $C_{31}H_{41}NO_6SiH^+$: 552.2781, found: 552.2781 (Δ = −0.1 ppm).

6.1.17. (2*S*,10*S*,10a*R*)-9-Acetoxymethyl-10-benzoyloxy-2-hydroxyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (17a)

To a solution of **16a** (31 mg, 0.056 mmol) in CH_3CN (0.6 mL) and pyridine (0.6 mL) was added HF-pyridine (70:30, 0.31 ml) and the mixture was stirred overnight. The reaction mixture was diluted with EtOAc (40 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL × 2), $CuSO_4$ solution (10 mL × 3), water (10 mL × 3) and brine (3 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by column chromatography using hexanes/EtOAc (1:4) as the eluent to afford **17a** as white solid (23 mg, 100% yield): mp 76–77 °C; $[\alpha]_D^{22}$ −239 (*c* 10.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.24 (m, 2H), 3.83 (dd, *J* = 11.2, 3.2 Hz, 2H), 4.32 (td, *J* = 8.4, 4.4 Hz, 1H), 4.64 (t, *J* = 3.2 Hz, 1H), 5.04 (d, *J* = 10.0, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 7.48 (m, 4H), 7.64 (t, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 6.0 Hz, 2H), 8.18 (dd, *J* = 6.0, 1.2 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.6, 41.2, 54.8, 58.9, 65.6, 68.8, 73.4, 128.8, 129.0, 129.1, 129.2, 130.0, 130.7, 133.4, 134.1, 134.6, 135.9, 162.6, 165.9, 170.6. HRMS: *m*/*e* calcd for $C_{22}H_{21}NO_6H^+$: 396.1447, found: 396.1436 (Δ = −2.8 ppm).

6.1.18. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-9-pent-4-enoyloxymethyl-2-triisopropylsiloxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (16b)

Colorless oil; 100% yield; $[\alpha]_D^{22}$ −158 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (m, 21H), 2.22 (m, 6H), 3.83 (m, 2H), 4.32 (dd, *J* = 18.0, 8.8 Hz, 1H), 4.63 (d, *J* = 2.0 Hz, 1H), 4.92 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.98 (t, *J* = 5.6 Hz, 1H), 5.06 (d, *J* = 12.8, 1H), 5.22 (d, *J* = 12.8 Hz, 1H), 5.72 (m, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 7.49 (m, 4H), 7.64 (t, *J* = 7.6 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.20 (dd, *J* = 7.2, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 11.9, 17.9, 28.5, 32.9, 41.9, 55.1, 58.9, 65.1, 69.3, 73.2, 115.4, 128.4, 128.7, 128.9, 129.0, 129.7, 130.6, 133.2, 133.8, 134.3, 135.7, 136.5, 162.2, 165.7, 172.3. HRMS: *m*/*e* calcd for $C_{34}H_{45}NO_6SiH^+$: 592.3094, found: 592.3077 (Δ = −2.9 ppm).

6.1.19. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-2-hydroxy-9-pent-4-enoyloxymethyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (17b)

White solid; 97% yield; mp 50–52 °C; $[\alpha]_D^{22}$ −227 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (m, 6H), 3.85 (d, *J* = 2.4 Hz, 2H), 4.33 (td, *J* = 10.4, 5.6 Hz, 1H), 4.61 (t, *J* = 2.4 Hz, 1H), 4.92 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.95 (dd, *J* = 13.2, 1.6 Hz, 1H), 5.06 (d, *J* = 12.8 Hz, 1H), 5.21 (d, *J* = 12.8 Hz, 1H), 5.70 (m, 1H), 6.68 (d, *J* = 10.8 Hz, 1H), 7.48 (m, 4H), 7.63 (t, *J* = 7.3 Hz, 1H), 8.08 (d, *J* = 8.4, 1.2 Hz, 2H), 8.14 (dd, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.5, 32.9, 40.9, 54.5, 58.7, 65.1, 68.4, 73.1, 115.5, 128.5, 128.7, 128.8, 128.9, 129.8, 130.4, 133.3, 133.9, 134.3, 135.7, 136.5, 162.6, 165.6, 172.3. HRMS: *m*/*e* calcd for $C_{25}H_{25}NO_6H^+$: 436.1760, found: 436.1750 (Δ = −2.3 ppm).

6.1.20. (2*S*,11*R*,11a*R*)-11-Hydroxy-10-(methoxymethoxymethyl)-2-triisopropylsiloxy-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6H)-one (18)

To a solution of **11d** (260 mg, 0.51 mmol) in methanol (20 mL) and water (10 mL) was added potassium carbonate (180 mg, 1.02 mmol). The mixture was stirred at room temperature for 30 min. Then, the reaction mixture was quenched with ethyl acetate and the organic layer was washed with saturated aqueous NH_4Cl solution (20 mL), water (10 mL × 2) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (3:1) as the eluent to afford **18** as a white solid (189 mg, 81% yield): mp 104–105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (m, 21H), 2.20 (m, 1H), 2.54 (m, 1H), 3.35 (d, *J* = 14.0 Hz, 1H), 3.40 (s, 3H), 3.42 (d, *J* = 5.2 Hz, 1H), 3.64 (dd, *J* = 11.6, 3.6 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 4.42 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.71 (dd, *J* = 11.6, 6.4 Hz, 2H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.85 (s, 1H), 7.26 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 12.0, 17.9, 43.0, 43.7, 53.9, 55.8, 60.5, 68.5, 69.4, 73.1, 95.6, 128.2, 130.9, 131.9, 133.7, 136.9, 138.6, 172.2. HRMS: *m*/*e* calcd for $C_{25}H_{41}NO_5SiH^+$: 464.2832, found: 464.2837 (Δ = 1.1 ppm).

6.1.21. (2*S*,11*S*,11a*R*)-10-(Acetoxymethyl)-11-benzoyloxy-2-triisopropylsiloxy-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6H)-one (16c)

To a solution of **18** (125 mg, 0.27 mmol), benzoic acid (40 mg, 0.32 mmol) and triphenylphosphine (78 mg, 0.30 mmol) in THF (1 mL) was added diisopropyl azodicarboxylate (0.060 mL, 0.30 mmol). The mixture was stirred overnight and refluxed for 3 days. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexanes/EtOAc (5:1) to afford the corresponding Mitsunobu coupling product, (2*S*,11*R*,11a*R*)-11-benzoyloxy-10-(methoxy-methoxymethyl)-2-triisopropyl-siloxy-2,3,11,11a-tetra-hydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]-azepin-5(6H)-one (47 mg, conversion 36%) accompanied by impurity and the starting material **18** (80 mg).

To a solution of the Mitsunobu coupling product thus obtained and anisole (0.2 mL) in CH_2Cl_2 (2.0 mL) was added trifluoroacetic acid (2.0 mL) at 0 °C. The reaction mixture was stirred 2 h at room temperature and diluted with ethyl acetate (50 mL). The organic layer was washed by saturated $NaHCO_3$ solution (10 mL × 2) and NaCl (10 ml), dried over anhydrous $MgSO_4$, and solvent was removed under reduced pressure to afford a liquid residue. The residue was purified by column chromatography on silica gel using hexanes:EtOAc (2:1) as the eluent to afford **19** (32 mg, 63% yield in 2 steps) as colorless oil.

To a solution of **19** (22 mg, 0.042 mmol) and DMAP (1 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (0.04 mL, 0.12 mmol) and acetic anhydride (0.03 mL, 0.08 mmol) at 0 °C. The reaction mixture was stirred overnight, quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure to afford a liquid residue. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (2:1) as the eluent to afford **16c** (21 mg, 80% yield) as colorless oil: $[\alpha]_D^{22}$ +5.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (m, 21H), 1.95 (s, 3H), 2.18 (m, 2H), 3.55 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 17.8 Hz, 1H), 4.04 (d, *J* = 13.2, 5.4 Hz, 1H), 4.35 (dd, *J* = 10.2, 6.0 Hz, 1H), 4.39 (d, *J* = 18.0 Hz, 1H), 4.46 (s, 1H), 4.25 (d, *J* = 12.6 Hz, 1H), 5.57 (d, *J* = 12.0 Hz, 1H), 5.59 (s, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 12.1, 18.1, 29.9, 41.1, 44.3, 57.8, 60.0, 64.8, 67.9, 69.9, 128.9, 129.3, 129.5, 130.0, 130.5, 132.2, 133.9, 134.7, 134.8, 135.5, 165.8, 167.9, 170.5. HRMS: *m*/*e* calcd for $C_{32}H_{43}NO_6SiH^+$: 566.2938, found: 566.2955 (Δ = 3.0 ppm).

6.1.22. (2*S*,11*S*,11a*R*)-10-(Acetoxymethyl)-11-benzoyloxy-2-hydroxy-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]-azepin-5(6H)-one (17c)

White solid; 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.20 (m, 2H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.93 (d, *J* = 17.5 Hz, 1H), 3.98 (m, 1H), 4.40 (m, 2H), 4.48 (s, 1H), 5.26 (d, *J* = 12.5, 1H), 5.58 (d, *J* = 12.5 Hz, 1H), 6.61 (s, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 20.8, 39.8, 44.0, 57.1, 59.5, 64.5, 67.0, 69.5, 128.7, 129.1, 129.3, 129.7, 129.8, 130.0, 131.8, 133.7, 134.3, 134.5, 135.2, 165.6, 167.9, 170.3. HRMS: *m*/*e* calcd for $C_{23}H_{23}NO_6H^+$: 410.1604, found: 410.1594 (Δ = −2.4 ppm).

6.1.23. (*4S*,*5R*)-2-(4-Methoxyphenyl)-3-benzoyl-4-phenyloxazolidine-5-carboxylic acid (20a)

White solid; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.41 (s, 1H), 4.90 (s, 1H), 5.48 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.90 (m, 1H), 7.21–7.39 (m, 11H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 55.0, 55.6, 72.5, 114.3, 127.0, 127.1, 127.3, 128.1, 128.3, 128.3, 128.7, 128.8, 130.0, 132.0, 132.3, 133.2, 138.1, 164.6, 174.0, 190.9. HRMS: *m*/*e* calcd for $C_{24}H_{22}NO_5H^+$: 404.1498, found: 404.1495 (Δ = −0.7 ppm).

6.1.24. (*4S*,*5R*)-4-(2-Allyloxyphenyl)-3-benzoyl-2-(4-methoxyphenyl)oxazolidine-5-carboxylic acid (20b)

White solid; 88% yield; mp 47–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.47 (dd, *J* = 12.8, 3.6 Hz, 1H), 4.55 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.91 (s, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.59 (s, 1H), 5.92 (m, 1H), 6.88 (m, 4H), 7.03 (m, 1H), 7.20 (m, 3H), 7.28 (m, 4H), 7.59 (s, 2H), 8.71 (br s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 55.2, 60.5, 68.9, 81.4, 90.7, 111.6, 113.3, 117.7, 120.4, 127.0, 128.2, 128.6, 129.0, 129.2, 129.9, 130.7, 132.7, 135.5, 154.9, 159.9, 170.4. HRMS: *m*/*e* calcd for $C_{27}H_{25}NO_6H^+$: 460.1760, found: 460.1754 (Δ = −1.3 ppm).

6.1.25. (2*S*,10*S*,10a*R*)-9-Acetoxymethyl-10-benzoyloxy-5-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (4′*S*,5′*R*)-3′-benzoyl-2′-(4-methoxy-phenyl)-4′-phenyloxazolidine-5′-carboxylate (21a)

To a solution of **17a** (20 mg, 0.053 mmol), **20a** (21 mg, 0.053 mmol) and DMAP (3.5 mg, 0.026 mmol) in CH_2Cl_2 (0.5 mL) was added EDC (22 mg, 0.11 mmol) and the reaction mixture was stirred overnight. The mixture was then quenched with EtOAc (50 mL) and washed with water (10 mL × 2) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (1:2) as the eluent to afford **21a** as a white solid (27 mg, 82% yield based on 85% conversion): mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.32 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.42 (td, *J* = 10.8, 4.4 Hz, 1H), 3.80 (s, 3H), 3.89 (d, *J* = 14.8 Hz, 1H), 4.05 (d, *J* = 14.4, 4.8, 1H), 4.17 (td, *J* = 10.8, 5.6 Hz, 1H), 4.81 (d, *J* = 2.0 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 5.22 (d, *J* = 12.8 Hz, 1H), 5.36 (br s, 1H), 5.55 (t, *J* = 4.0 Hz, 1H), 6.71 (d, *J* = 10.8 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.25 (m, 11H), 7.47 (m, 4), 7.63 (t, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 2H), 8.21 (dd, *J* = 7.2, 2.0 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.4, 38.3, 51.8, 55.3, 58.8, 65.4, 72.9, 73.0, 113.5, 127.0, 127.1, 128.1, 128.2, 128.6, 128.7, 128.7, 128.8, 129.0, 129.8, 129.8, 130.2, 130.7, 133.3, 134.0, 134.6, 135.2, 135.4, 159.9, 162.1, 165.6, 169.3, 170.2. HRMS: *m*/*e* calcd for $C_{46}H_{40}N_2O_{10}H^+$: 781.2761, found: 781.2789 (Δ = 3.6 ppm).

6.1.26. (2*S*,10*S*,10a*R*)-9-Acetoxymethyl-10-benzoyloxy-5-oxo-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-phenylpropanoate (1)

To a solution of **21a** (26 mg, 0.03 mmol) in methanol (0.5 mL) was added *p*-toluenesulfonic acid (1.5 mg, 0.006 mmol). After stirring the mixture overnight, the solvent was removed and the residue purified by column chromatography on silica gel using hexanes/EtOAc = 1:2 as the eluent to afford **1** as a white solid (16 mg, 75% yield): mp 116–118 °C; $[\alpha]_D^{22}$ −135 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.37 (td, *J* = 8.8, 3.2 Hz, 1H), 2.48 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.18 (d, *J* = 2.8 Hz, 1H), 3.99 (dd, *J* = 11.2, 3.6 Hz, 1H), 4.03 (d, *J* = 12.0 Hz, 1H), 4.44 (td, *J* = 8.8, 4.4 Hz, 1H), 4.62 (s, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 5.59 (t, *J* = 3.2 Hz, 1H), 5.69 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 9.2 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 6.0 Hz, 1H), 7.41 (m, 11H), 7.61 (t, *J* = 6.0 Hz, 1H), 8.13 (d, *J* = 6.0 Hz, 2H), 8.20 (dd, *J* = 5.6, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.3, 38.1, 51.5, 54.4, 58.7, 65.5, 73.2, 73.6, 126.8, 126.9, 128.0, 128.4, 128.5, 128.7, 128.7, 128.9, 128.9, 130.0, 130.3, 131.5, 133.2, 133.6, 133.7, 134.5, 136.0, 138.4, 162.5, 165.7, 166.7, 170.2, 172.2. HRMS: *m*/*e* calcd for $C_{38}H_{34}N_2O_9H^+$: 663.2343, found: 663.2361 (Δ = 2.8 ppm).

6.1.27. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-5-oxo-9-pent-4-enoyloxymethyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (4′*S*,5′*R*)-4′-(2-allyloxyphenyl)-3′-benzoyl-2′-(4-methoxyphenyl)oxazolidine-5-carboxylate (21b)

White solid; 96% yield; mp 73-75 °C; $[\alpha]_D^{22}$ -145 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (m, 5H), 2.42 (m, 1H), 3.81 (s, 3H), 3.86 (d, *J* = 14.4 Hz, 1H), 4.05 (dd, *J* = 14.4, 4.8, 1H), 4.25 (td, *J* = 10.8, 5.6, Hz, 1H), 4.39 (m, 2H), 4.80 (s, 1H), 4.93 (dd, *J* = 10.0, 0.8 Hz, 1H), 4.96 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 5.08 (s, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 5.24 (d, *J* = 12.8 Hz, 1 H0, 5.43 (s, 1H), 5.55 (t, *J* = 4.8 Hz, 1H), 5.74 (m, 2H), 6.71 (d, *J* = 10.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.81 (m, 3H), 6.94 (s, 1H), 7.08 (m, 3H), 7.19 (m, 5H), 7.50 (m, 6H), 7.64 (t, *J* = 7.2 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 2H), 8.22 (dd, *J* = 7.6, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.5, 32.9, 38.4, 51.9, 55.2, 58.8, 65.2, 68.8, 72.4, 73.0, 111.5, 113.3, 115.5, 117.7, 120.5, 126.9, 128.2, 128.7, 128.7, 128.8, 128.8, 128.9, 129.2, 129.9, 130.2, 132.5, 133.4, 133.9, 134.6, 135.3, 136.5, 154.7, 159.8, 162.0, 165.5, 169.3, 172.3. HRMS: *m*/*e* calcd for $C_{52}H_{48}N_2O_{11}H^+$: 877.3336, found: 877.3322 (Δ = −1.6 ppm).

6.1.28. (2*S*,10*S*,10a*R*)-10-Benzoyloxy-5-oxo-9-pent-4-enoyloxymethyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-2-yl (2′*S*,3′*R*)-3′-(2-allyloxyphenyl)-3′-benzoylamino-2′-hydroxypropanoate] (22)

White solid; 82% yield; mp 110–112 °C; $[\alpha]_D^{22}$ −139 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (m, 6H), 3.34 (br s, 1H), 3.95 (m, 2H), 4.29 (d, *J* = 8.0 Hz, 1H), 4.33 (d, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 4.8 Hz, 2H), 4.65 (d, *J* = 3.2 Hz, 1H), 4.92 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.96 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.09 (d, *J* = 12.8 Hz, 1H), 5.21 (dd, *J* = 12.0, 1.2 Hz, 1H), 5.23 (dd, *J* = 19.6, 12.8 Hz, 1H), 5.48 (dd, *J* = 25.2, 1.6 Hz, 1H), 5.66 (d, *J* = 6.0 Hz, 1H), 5.73 (m 1H), 5.98 (m, 2H), 6.67 (d, *J* = 10.8 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 7.19 (m, 5H), 7.38 (t, *J* = 11.6 Hz, 1H), 7.45 (m, 6H), 7.62 (t, *J* = 7.2 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 2H), 8.18 (dd, *J* = 7.6, 1.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.5, 32.9, 38.2, 51.6, 52.0, 58.8, 65.3, 68.7, 72.9, 73.2, 111.8, 115.5, 117.7, 120.9, 126.1, 126.8, 127.8, 128.4, 128.5, 128.7, 128.8, 128.9, 129.2, 130.0, 130.3, 131.4, 132.5, 133.3, 133.7, 133.9, 134.5, 135.9, 136.5, 155.5, 162.3, 165.6, 166.7, 172.1, 172.2. HRMS: *m*/*e* calcd for $C_{44}H_{42}N_2O_{10}H^+$: 759.2918, found: 759.2893 (Δ = −3.3 ppm).

6.1.29. (2*S*,11*S*,11a*R*)-10-(Acetoxymethyl)-11-benzoyloxy-2-hydroxy-2,3,11,11a-tetrahydro-1*H*-benzo[*d*]-pyrrolo-5(6H)-oxo-[1,2-*a*]azepin-2-yl (2′*S*,3′*R*)-3′-benzoylamino-2′-hydroxy-3′-phenylpropanoate (2)

To a solution of **17c** (11 mg, 0.027 mmol), **20a** (12 mg, 0.03 mmol) and DMAP (3.2 mg, 0.027 mmol) in CH_2Cl_2 (0.5 mL) was added EDC (22 mg, 0.11 mmol) and the mixture was stirred for 1 day. The reaction mixture was then quenched with EtOAc (50 mL) and washed with water (10 mL × 2) and brine (10 mL). The organic layer was dried over anhydrous MgSO4, filtered, and then solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc (1:1) as the eluent to afford the coupling product **21c** as a white solid (11 mg, 92% based on 50% conversion).

To a solution of **21c** (11 mg, 0.014 mmol) in methanol (0.5 mL) was added *p*-TSA (0.5 mg, 0.003 mmol). After stirring overnight, the solvent was removed and the residue purified by column chromatography on silica gel using hexanes/EtOAc (1:2) as the eluent to afford **2** as a white solid (7 mg, 74% yield for 2 steps): mp 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (s, 1H), 2.27 (td, *J* = 11.0, 5.0 Hz, 1H), 2.40 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.27 (d, *J* = 4.0 Hz, 1H), 3.79 (d, *J* = 14.0 Hz, 1H), 4.02 (d, *J* = 17.0, 1H), 4.04 (dd, *J* = 14.5, 5.0 Hz, 1H), 4.40 (dd, *J* = 17.0 Hz, 1H), 4.50 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.65 (dd, *J* = 4.2, 1.2 Hz, 1H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.41 (d, *J* = 12.5 Hz, 1H), 5.49 (d, *J* = 12.5 Hz, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 6.64 (s, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.26 (m, 4H), 7.43 (m, 6H), 7.55 (m, 3H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 22.6, 36.8, 44.0, 53.7, 54.4, 59.6, 64.2, 69.1, 72.6, 73.1, 126.8, 127.0, 128.0, 128.7, 128.8, 129.0, 129.4, 129.7, 129.8, 131.7, 131.9, 133.7, 133.8, 134.2, 134.5, 135.0, 138.2, 165.4, 166.9, 168.1, 170.5, 172.4. HRMS: *m*/*e* calcd for $C_{39}H_{36}N_2O_9H^+$: 677.2499, found: 677.2502 (Δ = 0.4 ppm).

6.1.30. Macrocyclic paclitaxel mimic 3

To a solution of **22** (17 mg, 0.02 mmol) in CH_2Cl_2 (12 mL) was added $Cl_2Ru(=CHPh)(PCy_3)_2$ (3 mg, 0.004 mmol) in CH_2Cl_2 (0.2 mL). The mixture was stirred at room temperature for 3 days and reflux for 2 days. The solvent was removed under reduced pressure. The residue was passed through a short silica gel column (hexanes/EtOAc = 1:1.5) to remove the catalyst and then afford **3** (8 mg, 66% yield based on 71% conversion) as a white solid, as well as the starting material (5 mg).

Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (m, 5H), 2.78 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.32 (d, *J* = 2.8 Hz, 1H), 3.82 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.96 (m, 2H), 4.36 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.52 (s, 1H), 4.59 (m, 1H), 4.77 (d, *J* = 9.2 Hz, 1H), 5.44 (d, *J* = 9.2 Hz, 1H), 5.56 (s, 2H), 6.14 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 9.6 Hz, 1H), 6.78 (d, *J* = 6.4 Hz, 1H), 6.96 (t, *J* = 6.4 Hz, 1H), 7.24 (m, 1H), 7.42 (m, 3H), 7.46 (m, 4H), 7.59 (m, 3H), 7.74 (dd, *J* = 6.0, 1.2 Hz, 1H), 8.21 (dd, *J* = 6.4, 1.2 Hz, 1H), 8.36 (dd, *J* = 6.0, 0.4 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.2, 33.6, 36.9, 49.2, 51.9, 59.1, 64.1, 68.4, 72.9, 73.0, 73.3, 112.4, 121.0, 125.8, 127.0, 127.5, 128.1, 128.4, 128.5, 128.6, 128.6, 129.2, 129.2, 129.6, 130.5, 130.6, 130.7, 131.6, 131.8, 133.8, 134.0, 137.0, 138.8, 154.8, 162.2, 166.7, 171.8, 172.6. HRMS: *m*/*e* calcd for $C_{42}H_{38}N_2O_{10}H^+$: 731.2605, found: 731.2597 (Δ = −1.1 ppm).

6.1.31. (2*S*,8*S*,8a*R*)-8-(3-Methoxybenzoyloxy-6,7-di-dehydroindolizidin-5-one-2-yl (2′*R*,3′*S*)-2′-hydroxy-3′-phenyl-3′-benzylaminopropionate (24)

White solid; 76% yield for 2 steps; mp 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (td, *J* = 10.8, 4.4 Hz, 1H), 2.47 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.54 (br s, 1H), 3.82 (s, 3H), 3.83 (m, 2H), 4.33 (td, *J* = 11.2, 5.3, Hz, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 5.11 (d, *J* = 3.6 Hz, 1H), 5.75 (m, 2H), 6.01 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.53 (dd, *J* = 10.0, 1.6 Hz, 1H), 7.13 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.19-7.41 (m, 6H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 31.5, 38.2, 50.8, 54.5, 55.4, 55.4, 58.3, 73.0, 114.4, 120.2, 122.5, 125.7, 126.9, 126.9, 128.0, 128.5, 128.8, 129.6, 130.3, 131.6, 133.8, 140.6, 159.6, 162.4, 165.7, 166.8, 172.2. HRMS: *m*/*e* calcd for $C_{32}H_{30}N_2O_8Na^+$: 593.1900, found: 593.1893 (Δ = −1.2 ppm).

6.2. In vitro cell growth inhibition assay

Tumor cell growth inhibition was determined according to the method established by Skehan et al.[34] Human cancer cell lines, LCC6-WT (Pgp−), MCF-7 (Pgp−), LCC6-MDR (Pgp+), NCI/ADR (Pgp+), A2780 (Pgp−) and HT-29 (Pgp−) were plated at a density of 400–2000 cells/well in 96-well plates and allowed to attach overnight. These cell lines were maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum and 5% Nu serum (Collaborative Biomedical Product, MA). Paclitaxel mimics were dissolved in DMSO and further diluted with RPMI-1640 medium. Triplicate wells were exposed to various treatments. After 72 h incubation, 100 μL of ice-cold 50% trichloroacetic acid (TCA) was added to each well, and the samples were incubated for 1 h at 4 °C. Plates were then washed five times with water to remove

TCA and serum proteins, and 50 μL of 0.4% sulforhodamine B (SRB) was added to each well. Following a 5 min incubation, plates were rinsed five times with 0.1% acetic acid and air-dried. The dye was then solubilized with 10 mM Tris base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm. The IC_{50} values were then calculated by fitting the concentration-effect curve data with the sigmoid-E_{max} model using nonlinear regression, weighted by the reciprocal of the square of the predicted effect.[35]

6.3. Computational methods

6.3.1. Construction of molecular complexes

Paclitaxel mimics **1** and **2** were manually docked into the paclitaxel binding site of the REDOR-Taxol-1JFF structure[18,19] using the InsightII 2000 program (CVFF force field) by overlaying three hydroxyl groups of each mimic with those of the paclitaxel molecule (C13, C2, and C4 hydroxyl groups) with the REDOR-Taxol-ITUB[13,18] conformation. The resulting molecular complex was energy-minimized in 5000 steps or until the maximum derivative became <0.001 kcal/Å by means of the conjugate gradients method using the CVFF force field and the distance-dependent dielectric. The backbone of the protein was fixed during the energy minimization. In the same manner, the molecular complex of paclitaxel mimic **3** was obtained. The overlays of mimics **1**, **2** and **3** with REDOR-Taxol-1TUB are shown in Figure 3.

The molecular complexes of **1** and **2** in the 1JFF tubulin[32] were constructed using the same protocol as that described above except for employing REDOR-Taxol-1JFF[18,19] in place of REDOR-Taxol-1TUB. Since there are differences in the protein structure between 1TUB and 1JFF, the mimics' structures underwent small changes, but the critical H-bond between the C2′-OH and His^{229} was very stable during the energy minimization. After the energy minimization, the snapshots were overlaid by superimposing the backbones of the proteins. The overlays are shown in Figure 5. The mimics **1** and **2** showed very good overlays with REDOR-Taxol-1JFF.

6.3.2. MD simulations of mimics 1 and 2 in 1JFF

To examine the stability of the structures of mimics **1** and **2**, molecular dynamics (MD) simulation was performed using the Macromodel program (MMFF94 force field).[33] The molecular complexes, after 1000-step energy minimization (MMFF94), were used for the MD simulations with a 10 Å sphere around the binding site at 300 K with the time step of 0.5 fs for 50 ps in a generalized Born with surface area term (GBSA) continuum solvent description of water solvation.[36] Within the 10 Å sphere of the binding site, the ligand and the protein were allowed to move, while all atoms outside the sphere were frozen in order to maintain the overall integrity of the protein. The structures were sampled every 0.25 ps and overlaid by the backbones of the protein. The overlays of 200 snapshots for each of the mimics **1** and **2** are shown in Figure 5 in comparison with those of REROR-Taxol-1JFF.

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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.2010.07.069.

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