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New Highly Active Taxoids from 9β-Dihydrobaccatin-9,10-acetals. Part 3

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Abstract—We synthesized novel water-soluble and orally active taxane analogues, 7-deoxy-9β-dihydro-9,10-*O*-acetal taxanes. Cytotoxicities of the synthetic compounds were greater than those of paclitaxel and docetaxel, especially against resistant cancer cell lines expressing P-glycoprotein. In addition, some compounds showed potent antitumor effects against B16 melanoma BL6 in vivo by both iv and po administration.

Introduction

Paclitaxel (**1**, Taxol®)[1] and docetaxel (**2**, Taxotere®)[2] are currently considered to be some of the most important drugs used in cancer chemotherapy. Although paclitaxel is currently the agent of choice for the treatment of ovarian, breast, and lung cancer, the lack of sufficient aqueous solubility (paclitaxel: 0.25 μg/mL, docetaxel: 6–7 μg/mL)[3] was one of the major problems associated with paclitaxel's formulation for clinical applications. To resolve this problem, we previously synthesized non-prodrug water-soluble docetaxel analogues possessing an amine moiety, exemplified by compound **3**.[4] Furthermore, we recently reported new taxane analogues, 7-deoxy-9β-9,10-*O*-acetal taxanes exemplified by compound **4**, which showed stronger activity against several tumor cell lines than that of paclitaxel and docetaxel.[5] As a combination of these two modifications, we designed a procedure to introduce the morpholine moiety to the acetal region. Herein, we report the synthesis and antitumor activity of these novel taxane analogues (Fig. 1).

Chemistry

The reaction of **5**[5] with acrolein diethyl acetal in the presence of CSA afforded 9,10-*O*-acetal **6**. The coupling of **6** with the β-lactam **7**[6] and the subsequent removal of the protecting group at C-2′ were carried out following procedures similar to those reported by Ojima et al.[7] to give compound **8**. Finally, oxidation of **8** with OsO_4 followed by cleavage with $NaIO_4$ gave the aldehyde, to which the morpholine moiety was introduced by reductive amination to afford the targeted compound **9** (Scheme 1).[8]

It was reported that the introduction of a methyl group into the C-2′ position of paclitaxel and docetaxel led to increased cytotoxicity.[9] Thus, we tried to apply this C-13 side chain to our new taxane analogues. According to a procedure similar to that described for the synthesis of compound **9**, the targeted compound **12**[10] was obtained by using β-lactam **10**[9] (Scheme 2).

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In our previous paper, we reported that the 3′-(2-pyridyl) analogue **4** showed more potent cytotoxicity than that of the corresponding 3′-phenyl analogue.[5] Compound **15**,[11] possessing a 2-pyridine ring at the C-13 side chain, was synthesized in a similar manner by using β-lactam **13**[12] (Scheme 3).

The synthesis of 3′-(2-pyridyl)-2′-methyl analogue (**20a**, **20b**) is described in Scheme 4. The key intermediate β-lactam **17** was synthesized via the ester enolate-imine cyclocondensation. The reaction of lithium ester enolate generated in situ from silyloxypropionate **16** with *N*-trimethylsilylaldimine[13] gave the racemic *cis*-β-lactam,

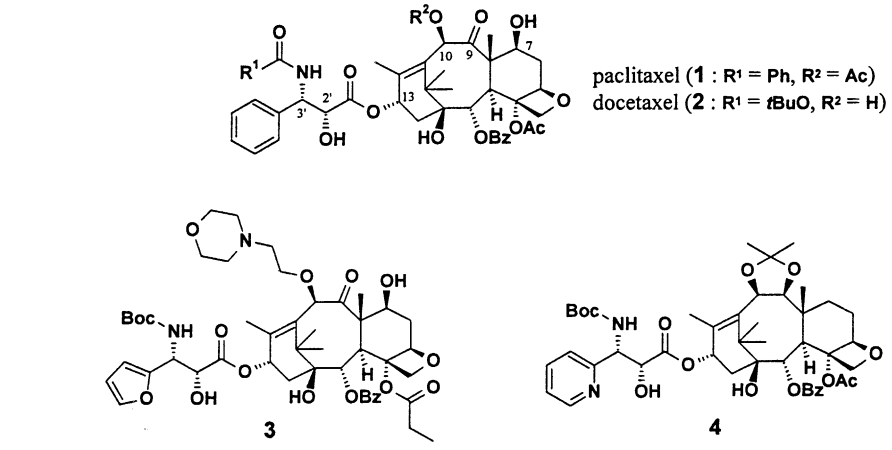
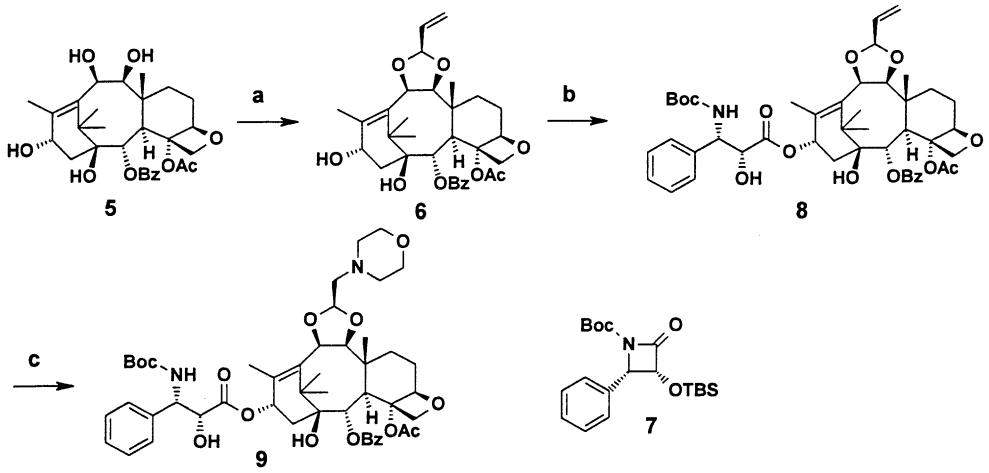
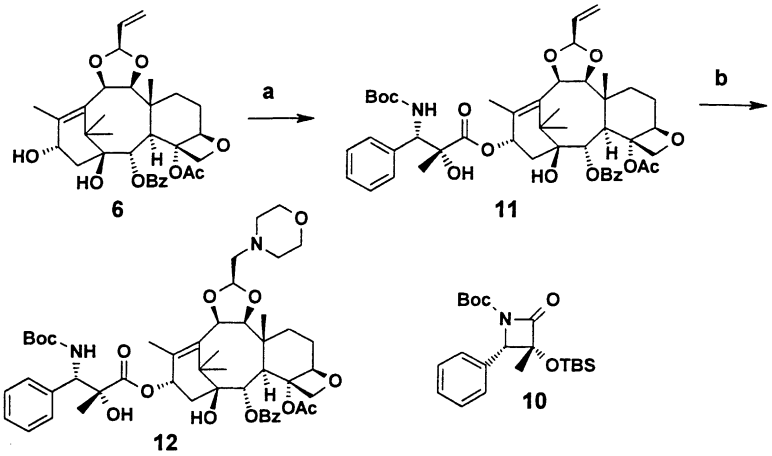


Figure 1. Structures of taxane analogues.



Scheme 1. Reagents and conditions: (a) acrolein diethyl acetal, CSA, THF (47%); (b) (i) **7**, NaHMDS, THF; (ii) HF-pyridine, pyridine (34%); (c) (i) OsO_4, NMO, THF, acetone, H_2O; (ii) $NaIO_4$, THF, MeOH, H_2O; (iii) morpholine, AcOH, $NaBH_3CN$, EtOH (61%).



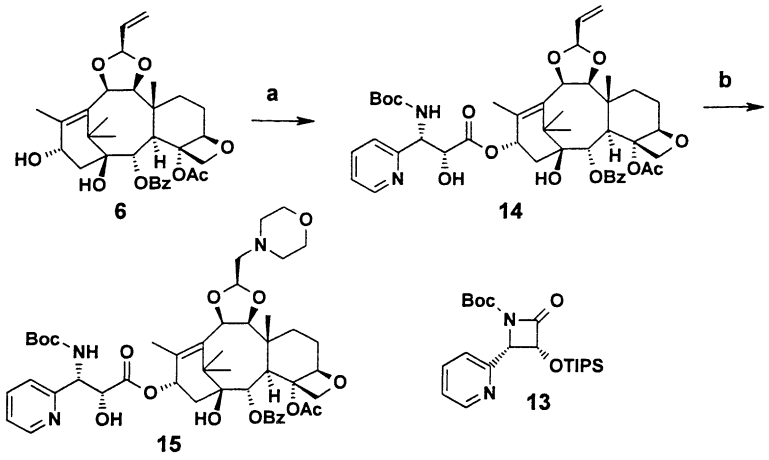
Scheme 2. Reagents and conditions: (a) (i) **10**, LiHMDS, THF; (ii) TBAF, THF (48%); (b) (i) OsO_4, NMO, THF, acetone, H_2O; (ii) $NaIO_4$, THF, MeOH, H_2O; (iii) morpholine, AcOH, $NaBH_3CN$, EtOH (69%).

which was resolved by using a chiral HPLC column to afford the optically pure *cis*-β-lactam **17**. Acylation of **17** was accomplished with di-*tert*-butyl dicarbonate or benzoyl chloride to afford the desired β-lactams (**18a**, **18b**) in good yield. Finally, the reaction of **6** with **18a** and **18b** was followed by deprotection to afford the intermediates **19a** and **19b**, which were converted to the targeted compounds **20a** and **20b**, respectively.[14]

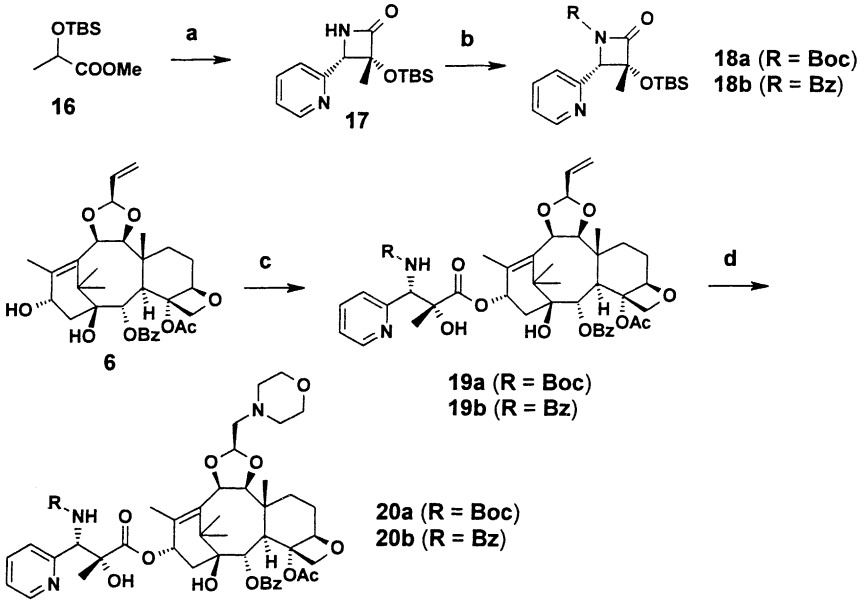
The absolute configuration of the acetal moiety was determined to be *S* configuration by X-ray analysis of compound **15**, as shown in Figure 2.[15] As for C-9 configuration, we had identified it to be *S* by proton NMR analysis;[5] it was confirmed to be correct by X-ray analysis.

Results and Discussion

Activities of the compounds (**9**, **12**, **15**, **20a**, and **20b**) were evaluated in cytotoxicity assays against five cell lines (P388, PC-6, PC-12, PC-6/VCR29-9, and PC-6/VP1-1), and activities were compared with those of paclitaxel (**1**) and docetaxel (**2**). The activities of all the synthetic compounds were greater than those of paclitaxel and docetaxel, especially against the resistant cancer cell lines expressing P-glycoprotein (PC-12, PC-6/VCR29-9, and PC-6/VP1-1). Modifications of the region between C-7 and C-10 might disrupt the specific binding of the molecules to P-glycoprotein, resulting in reduced P-glycoprotein-mediated efflux and increased activity against resistant cancer cell lines. Among these



Scheme 3. Reagents and conditions: (a) (i) **13**, LiHMDS, THF; (ii) TBAF, THF (85%); (b) (i) OsO_4, NMO, THF, acetone, H_2O; (ii) $NaIO_4$, THF, MeOH, H_2O; (iii) morpholine, AcOH, $NaBH_3CN$, EtOH (82%).



Scheme 4. Reagents and conditions: (a) (i) 2-pyridinecarboxaldehyde, LiHMDS, TMS, THF; (ii) **16**, LDA, THF; (iii) Chiralcel OD (31%); (b) $(Boc)_2O$, DMAP, THF or BzCl, Et_3N, DMAP, CH_2Cl_2 (98% for **18a**, 98% for **18b**); (c) (i) **18a**, NaHMDS, THF or **18b**, LiHMDS, THF; (ii) TBAF, THF (25% for **19a**, 50% for **19b**); (d) (i) OsO_4, NMO, THF, acetone, H_2O; (ii) $NaIO_4$, THF, MeOH, H_2O; (iii) morpholine, AcOH, AcOH, $NaBH_3CN$, EtOH (83% for **20a**, 77% for **20b**).

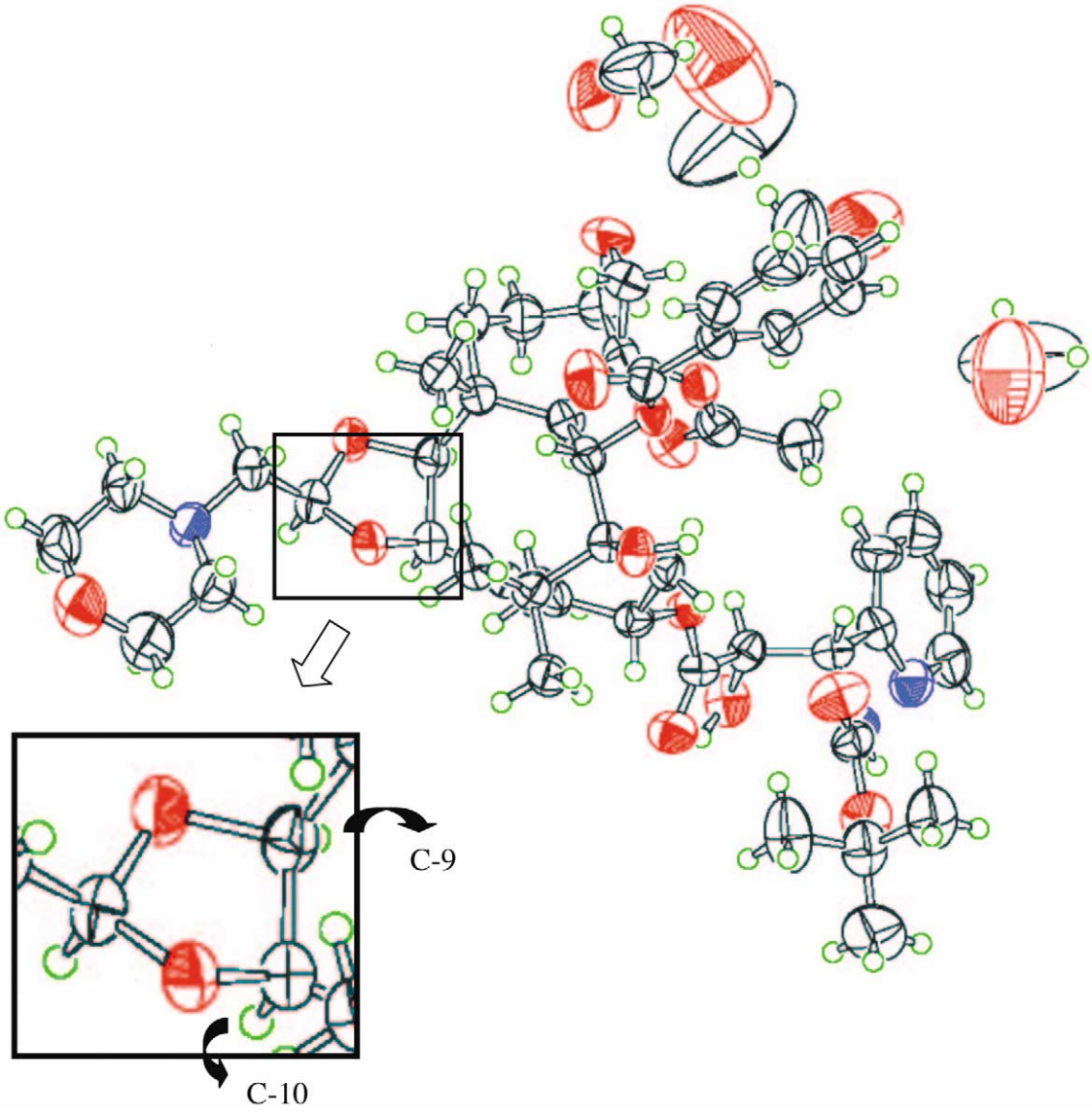


Figure 2. ORTEP representation of **15** with four MeOH molecules.

analogues, the compounds possessing a phenyl ring at the C-13 side chain (**9** and **12**) showed stronger cytotoxicity against P388 compared with the compounds possessing a pyridine ring (**15**, **20a** and **20b**). Replacement of the *N*-*tert*-butoxycarbonyl moiety of **20a** by the benzoyl moiety (**20b**) led to decreased cytotoxicity (Table 1).

We selected compounds **15**, **20a**, and **20b** for further in vivo investigation, because their possession of a pyridine ring in addition to a morpholine moiety made them more soluble in water (Table 2).

To evaluate the antitumor effects in vivo, we implanted B16 melanoma BL6 subcutaneously into mice and compared the activities of the selected compounds with that of docetaxel when administered intravenously (iv) and orally (po). Compound **20a**, which showed the most potent cytotoxicity among these three compounds, exhibited potent antitumor effects by both iv and po administration; however, the range of its effective dose by po administration was narrow. Only at a dose of 12.0 mg/kg, compound **20a** showed potent antitumor activity with an IR value of 92.2% and no body weight loss. The higher dosage (18.0 mg/kg) resulted in death, and the lower dosage (8.0 mg/kg) did not exhibit the high

Table 1. Cytotoxicity of 7-deoxy-9,10-*O*-acetal taxane analogues

Compd	Cytotoxicity GI_{50} (ng/mL)[a]				
	P388	PC-6	PC-12	PC-6/VCR29-9	PC-6/VP1-1
Paclitaxel (**1**)	2.93	1.27	539	455	1000
Docetaxel (**2**)	0.78	0.41	14.9	104	958
9	0.02	0.38	0.02	3.35	14.7
12	0.02	0.47	0.07	3.37	7.16
15	0.18	0.39	0.21	1.87	24.8
20a	0.12	0.11	0.06	1.30	6.55
20b	0.19	0.45	0.57	2.54	30.4

[a]Concentration that inhibited the growth of cells by 50% upon 72 h continuous exposure for the five cell lines [mouse leukemia (P388), human lung cancer cell lines (PC-6 and PC-12), and resistant cancer cell lines (PC-6/VCR29-9 and PC-6/VP1-1)].[16]

Table 2. Estimated water solubility

Compd	Solubility (μg/mL)[a]		
	Water	JP1 (pH 1.2)	JP2 (pH 6.8)
Docetaxel (**2**)	<4	<4	<4
9	<4	1200	<4
12	<4	350	<4
15	14.0	1700	11
20a	6.0	1800	5
20b	<4	>1800	<4

[a]The solubility of each compound was determined by using the UV assay.

antitumor effect. On the other hand, compounds **15** and **20b** showed potent antitumor effects over a wide dosage range by both iv and po administration. Furthermore, both compounds could be assumed to have good oral bioavailabilities. Since **15** or **20b** administered orally gave nearly the same antitumor effects and body weight losses as 2–3-fold amount of those administered intravenously. In contrast, docetaxel administered orally exhibited no antitumor effect and no body weight loss at a dose of 600 mg/kg, which indicates that docetaxel has very poor oral bioavailability (Table 3).

Table 3. Antitumor activity against B16 melanoma BL6[a]

Compd	Route	Dose (mg/kg)	IR (%)[b]	BWL_{max} (%)[c]	Mortality
2	po	600.0	6.2	<0	0/6
	iv	100.0	95.1	<0	0/6
20a	po	18.0	98.0	18.1	2/6
		12.0	92.2	<0	0/6
		8.0	42.2	<0	0/6
	iv	18.0	—	—	6/6
		12.0	96.4	13.5	0/6
20b	po	40.5	96.9	4.1	0/6
		27.0	91.3	<0	0/6
		18.0	59.7	<0	0/6
		12.0	23.4	<0	0/6
	iv	27.0	95.8	2.4	0/6
		18.0	89.8	<0	0/6
		12.0	75.4	<0	0/6
		8.0	61.3	<0	0/6
15	po	27.0	97.3	4.5	0/6
		18.0	93.3	0.3	0/6
		12.0	84.9	<0	0/6
		8.0	27.2	<0	0/6
	iv	18.0	95.6	3.7	0/6
		12.0	94.4	<0	0/6
		8.0	87.2	<0	0/6
		5.3	62.4	<0	0/6

[a]Cultured B16 melanoma BL6 was kindly provided by Dr. Tsuruo (Institute of Molecular and Cellular Biosciences, University of Tokyo) by courtesy of Dr. Fidler (The University of Texas M. D. Andersen Cancer Center).[17] B16 melanoma BL6 cells were subcutaneously inoculated into C57BL/6 mice (six mice per group) on day 0. Compounds were administered intravenously or orally on day 4 (single administration). Tumor masses were weighed on day 15.
[b]IR (%) = (1−TWt/TWc)×100. TWt, the mean tumor weight of the treated group. TWc, the mean tumor weight of the control group.
[c]BWL_{max} (%), Maximum rate of body weight loss (<0 indicates no body weight loss).

From the considerations of the cytotoxicity, the antitumor effect, and water-solubility, we estimated that compound **15** is the most promising candidate for further development. Extensive studies to explore the biological properties of **15** are in progress and will be reported in due course.

Acknowledgements

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8. Spectral data of **9** are as follows: mp: 146–149 °C; ^{1}H NMR ($CDCl_3$) δ: 1.24 (3H, s), 1.40 (9H, s), 1.46 (3H, s), 1.59 (3H, s), 1.63 (3H, s), 1.60–2.15 (5H, m), 2.27 (3H, s), 2.30–2.45 (1H, m), 2.58–2.94 (6H, m), 2.90 (1H, d, J = 4.4 Hz), 3.74 (4H, t, J = 4.8 Hz), 4.09 (1H, d, J = 7.4 Hz), 4.23 (1H, d, J = 8.8 Hz), 4.31 (1H, d, J = 8.8 Hz), 4.50 (1H, br s), 4.62 (1H, s), 4.91 (1H, s), 5.04 (1H, t, J = 3.9 Hz), 5.22 (1H, d, J = 7.4 Hz), 5.31 (1H, d, J = 9.3 Hz), 5.70 (1H, d, J = 9.3 Hz), 6.05 (1H, d, J = 4.4 Hz), 6.05–6.18 (1H, m), 7.20–7.48 (7H, m), 7.60 (1H, t, J = 7.3 Hz), 8.11 (2H, d, J = 7.3 Hz); FAB-MS (m/z): 905 $(M+H)^+$. Anal. calcd for $C_{49}H_{64}N_2O_{14}H_2O$: C, 63.76; H, 7.21; N, 3.09; Found: C, 63.74; H, 7.22; N, 3.09; IR (KBr): 3423, 2950, 1712, 1602, 1492, 1452 cm^{-1}; $[\alpha]_D^{25}$ −14.8° (c 0.05, $CHCl_3$).
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10. Spectral data of **12** are as follows: mp: 160–161 °C; ^{1}H NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.35 (9H, s), 1.47 (3H, s), 1.58 (3H, s), 1.61 (3H, s), 1.63 (3H, s), 1.80–2.15 (5H, m), 2.27 (1H, dd, J = 9.8, 15.1 Hz), 2.44 (3H, s), 2.46–2.83 (6H, m), 2.92 (1H, d, J = 4.8 Hz), 3.61–3.80 (4H, m), 4.10 (1H, d, J = 7.3 Hz), 4.25 (1H, d, J = 8.3 Hz), 4.32 (1H, d, J = 8.3 Hz), 4.92 (1H, s), 4.95–5.10 (2H, m), 5.20 (1H, d, J = 6.4 Hz), 5.70 (1H, d, J = 10.3 Hz), 5.98 (1H, d, J = 4.8 Hz), 6.20 (1H, t, J = 6.8 Hz), 7.20–7.55 (7H, m), 7.60 (1H, t, J = 7.3 Hz), 8.12 (2H, d, J = 7.3 Hz); FAB-MS (m/z): 919 $(M+H)^+$. Anal. calcd for $C_{50}H_{66}N_2O_{14}\cdot 0.75H_2O$:

C, 64.40; H, 7.30; N, 3.00; Found: C, 64.40; H, 7.32; N, 2.86; IR (KBr): 3430, 2969, 1716, 1602, 1492, 1452, 1367 cm^{-1}; $[\alpha]_D^{24}$ −13.3° (*c* 0.2, $CHCl_3$).

11. Spectral data of **15** are as follows: mp: 160–162 °C; ^1H NMR ($CDCl_3$) δ: 1.27 (3H, s), 1.30–2.15 (6H, m), 1.43 (9H, s), 1.48 (3H, s), 1.60 (3H, s), 1.73 (3H, s), 2.27–2.38 (1H, m), 2.37 (3H, s), 2.55–2.68 (4H, m), 2.72 (1H, dd, *J* = 5.1, 13.6 Hz), 2.79 (1H, dd, *J* = 3.9, 13.6 Hz), 2.93 (1H, d, *J* = 4.9 Hz), 3.74 (4H, t, *J* = 4.6 Hz), 4.12 (1H, d, *J* = 7.1 Hz), 4.22 (1H, d, *J* = 8.3 Hz), 4.33 (1H, d, *J* = 8.3 Hz), 4.85 (1H, br s), 4.88–4.95 (2H, m), 5.14 (1H, t, *J* = 4.4 Hz), 5.23 (1H, d, *J* = 7.1 Hz), 5.35 (1H, br d, *J* = 9.4 Hz), 5.97 (1H, br d, *J* = 9.4 Hz), 5.98 (1H, d, *J* = 4.9 Hz), 6.09 (1H, br t, *J* = 8.3 Hz), 7.23 (1H, dd, *J* = 5.2, 7.1 Hz), 7.42 (1H, d, *J* = 7.8 Hz), 7.47 (2H, t, *J* = 7.8 Hz), 7.60 (1H, t, *J* = 7.8 Hz), 7.72 (1H, dt, *J* = 1.5, 7.8 Hz), 8.12 (2H, d, *J* = 7.8 Hz), 8.53 (1H, br d, *J* = 5.2 Hz); FAB-MS (*m*/*z*): 906 $(M+H)^+$. Anal. calcd for $C_{48}H_{63}N_3O_{14}$: C, 63.63; H, 7.01; N, 4.64; Found: C, 63.62; H, 7.03; N, 4.47; IR (KBr): 2950, 1722, 1689, 1592, 502, 1434, 1365 cm^{-1}; $[\alpha]_D^{23}$ −5.6° (*c* 1.06, $CHCl_3$).

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14. Spectral data of **20a** and **20b** are as follows; **20a**: mp: 150–152 °C; ^1H NMR ($CDCl_3$) δ: 1.29 (3H, s), 1.42 (9H, s), 1.48 (3H, s), 1.53 (3H, s), 1.56 (3H, s), 1.59 (3H, s), 1.60–1.80 (1H, m), 1.83–2.50 (5H, m), 2.51 (3H, s), 2.50–2.84 (6H, m), 2.92 (1H, d, *J* = 5.4 Hz), 3.74 (4H, t, *J* = 4.4 Hz), 4.11 (1H, d, *J* = 6.8 Hz), 4.20 (1H, d, *J* = 8.3 Hz), 4.34 (1H, d, *J* = 8.3 Hz), 4.93 (1H, s), 5.01 (1H, t, *J* = 4.4 Hz), 5.16 (1H, d, *J* = 6.8 Hz), 5.95 (1H, d, *J* = 5.4 Hz), 6.04 (1H, d, *J* = 10.2 Hz), 6.16 (1H, br t, *J* = 8.8 Hz), 7.20–7.35 (1H, m), 7.40–7.60 (3H, m), 7.60 (1H, t, *J* = 7.3 Hz), 7.72 (1H, t, *J* = 7.4 Hz), 8.15 (2H, d, *J* = 7.3 Hz), 8.49 (1H, d, *J* = 4.4 Hz); FAB-MS (*m*/*z*): 920 $(M+H)^+$. Anal. calcd for $C_{49}H_{65}N_3O_{14}\cdot 1.25H_2O$: C, 62.44; H, 7.22; N, 4.46; Found: C, 62.48; H, 7.19; N, 4.45; IR (KBr): 3440, 2973, 1716, 1592, 1490, 1452 cm^{-1}; $[\alpha]_D^{25}$ −8.7° (*c* 0.48, $CHCl_3$). **20b**: mp: 160–165 °C; ^1H NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.40–2.05 (5H, m), 1.48 (3H, s), 1.51 (3H, s), 1.59 (3H, s), 1.61 (3H, s), 2.13–2.22 (2H, m), 2.52 (3H, s), 2.53–2.70 (4H, m), 2.71 (1H, dd, *J* = 5.1, 13.2 Hz), 2.77 (1H, dd, *J* = 3.9, 13.2 Hz), 2.93 (1H, d, *J* = 5.4 Hz), 3.73 (4H, t, *J* = 4.4 Hz), 4.08 (1H, d, *J* = 7.3 Hz), 4.20 (1H, d, *J* = 8.3 Hz), 4.35 (1H, d, *J* = 8.3 Hz), 4.93 (1H, s), 5.00 (1H, t, *J* = 4.4 Hz), 5.12 (1H, d, *J* = 7.3 Hz), 5.69 (1H, d, *J* = 9.5 Hz), 5.96 (1H, d, *J* = 5.4 Hz), 5.98 (1H, br s), 6.21 (1H, br t, *J* = 8.8 Hz), 7.25–7.35 (1H, m), 7.42–7.55 (5H, m), 7.61 (1H, t, *J* = 7.5 Hz), 7.72 (1H, dt, *J* = 1.5, 7.5 Hz), 7.87 (2H, d, *J* = 7.8 Hz), 7.91 (1H, d, *J* = 7.5 Hz), 8.15 (2H, d, *J* = 7.5 Hz), 8.52 (1H, d, *J* = 4.4 Hz); FAB-MS (*m*/*z*): 924 $(M+H)^+$. Anal. calcd for $C_{51}H_{61}N_3O_{13}\cdot 1.25H_2O$: C, 64.71; H, 6.76; N, 4.44; Found: C, 64.71; H, 6.78; N, 4.37; IR (KBr): 3421, 2950, 1720, 1664, 1592, 1511, 1482, 1436 cm^{-1}; $[\alpha]_D^{25}$ −10.4° (*c* 0.42, $CHCl_3$).

15. A colorless, prismatic crystal of $C_{52}H_{79}N_3O_{18}$ having approximate dimensions of 0.30×0.20×0.10 mm was grown from MeOH–MeCN and mounted in a glass capillary. The lattice parameters and intensities were measured on a RIGAKU AFC7R diffractometer with monochromated CuK_α radiation by using the ω-2θ scan technique. The compound crystallized in orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 17.1295$ Å, $b = 30.1980$ Å, $c = 10.3530$ Å, $V = 5335.4$ $Å^3$. The structure was solved by the direct method with the program *SIR92*. After several cycles of refinement, eight extra peaks of electron density are observed. They were assigned as four MeOH molecules. For $Z = 4$ and F.W. = 1034.21, the calculated density was 1.28 g/cm^3. The final *R* value was 0.061.

16. PC-6/VCR29-9: PC-6 cell line, which is resistant to Vincristine®. PC-6/VP1-1: PC-6 cell line, which is resistant to VP-16 (Etoposide®).

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