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New Highly Active Taxoids from 9β-Dihydrobaccatin-9,10-acetals. Part 2

Takashi Ishiyama, Shin Iimura, Toshiharu Yoshino, Jun Chiba, Kouichi Uoto, Hirofumi Terasawa and Tsunehiko Soga*

Medicinal Chemistry Research Laboratory, Daiichi Pharmaceutical Co., Ltd., Tokyo R&D Center, 16-13 Kita-kasai 1-Chome Edogawa-ku, Tokyo 134-8630, Japan

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Abstract—To investigate structure–activity relationships of the 9,10-acetal-9β-dihydro taxoids, we modified the 7-hydroxyl groups of the 9,10-acetonide-3′-(4-pyridyl) analogue to deoxy, methoxy, α-F, and 7β,8β-methano group. As a result of this study, we found that the 7-deoxy analogue was the strongest among these analogues. In addition, we found that the 7-deoxy-3′-(4-pyridyl) and 7-deoxy-3′-(2-pyridyl) analogues showed stronger activity against cell lines expressing P-glycoprotein than the corresponding 3′-phenyl analogue.

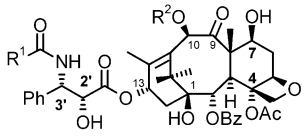
Introduction

Paclitaxel (**1**, Taxol®)[1] and docetaxel (**2**, Taxotere®)[2] are important drugs used in cancer chemotherapy (Fig. 1). In the previous paper, we reported on 9,10-acetal-9β-dihydro taxoids (**3**), which are much more potent than paclitaxel (**1**) and docetaxel (**2**) (Fig. 2).[3] To improve water solubility,[4] we synthesized the 3′-(4-pyridyl) analogue (**4**) and utilized it as a standard compound for investigation of structure activity relationships on 7-position moieties of the 9,10-acetal-9β-dihydro taxoids.

Chemical Synthesis

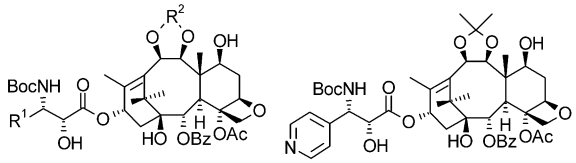
Synthesis of 9,10-acetonide-9β-dihydro-3′-4-pyridyl) taxoid (**4**) is described in Scheme 1. The 7-hydroxyl group was selectively protected by using TESOTf and 2,6-di-*tert*-butylpyridine in quantitative yield.[3] Introduction of the pyridylisoserine side chain to the 13-position of **6** using protected β-lactam (**7**)[5] in the presence of NaHMDS and deprotection of the silyl groups gave **4**[6] (Scheme 1).

Synthesis of 9,10-acetal-7-deoxy-9β-dihydro-3′-(4-pyridyl) taxoid (**14**) is described in Scheme 2. In the presence of DMAP, Tf_2O was reacted with **8** in DMF to introduce the formyl group selectively to 10-hydroxyl group.[7] Selective methylthiocarbonylation of the 7-hydroxyl group of **9**, radical hydrogenation of the resulting compound, and deprotection of the formyl group of **10** gave **11**. The following reduction of the



paclitaxel (**1**: R^1 = Ph, R^2 = Ac)
docetaxel (**2**: R^1 = *t*-BuO, R^2 = H)

Figure 1.



3
R^1 = phenyl, 2-furyl
R^2 = acetonide, propeniliden, 4-methoxybenzylidene

4

Figure 2.

*Corresponding author. Tel.: +81-3-3680-0151; fax: +81-3-5696-8344; e-mail: sogatf7t@daiichipharm.co.jp

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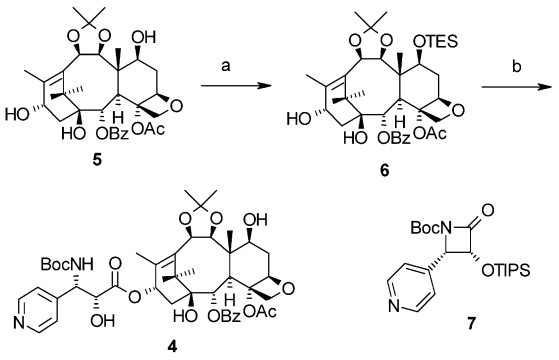
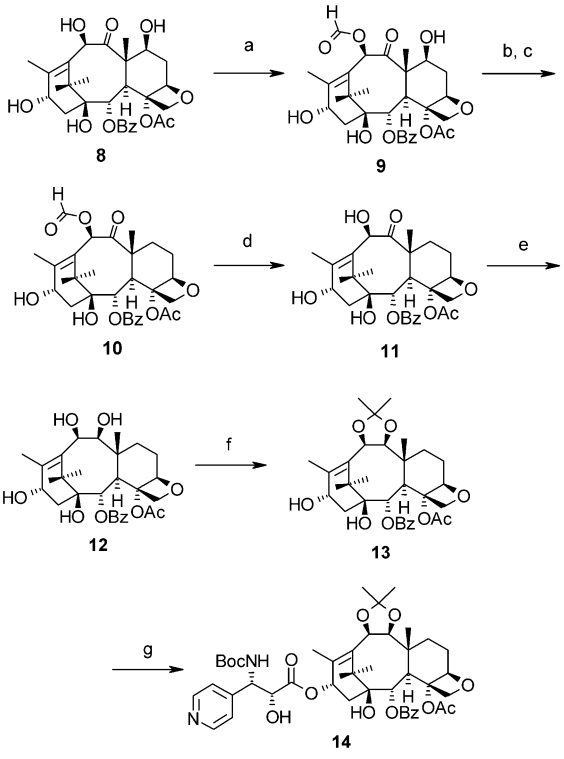


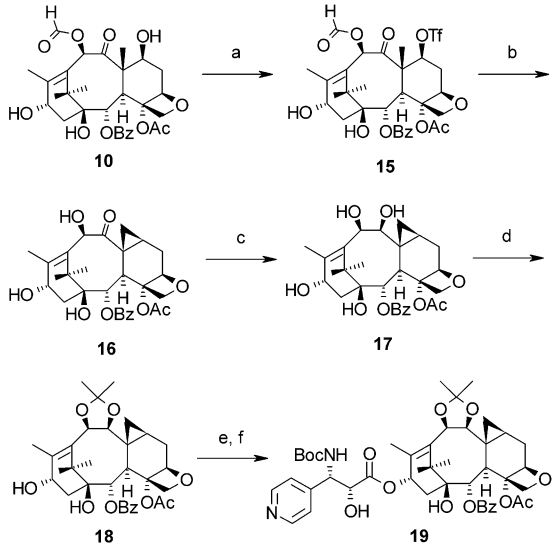
Scheme 1. Reagents and conditions: (a) TESOTf, THF/CH_2Cl_2, −78 °C (100%); (b) (1) **7**, NaHMDS, THF, −78 °C; (2) HF-pyridine, pyridine, rt (41% from **6**).



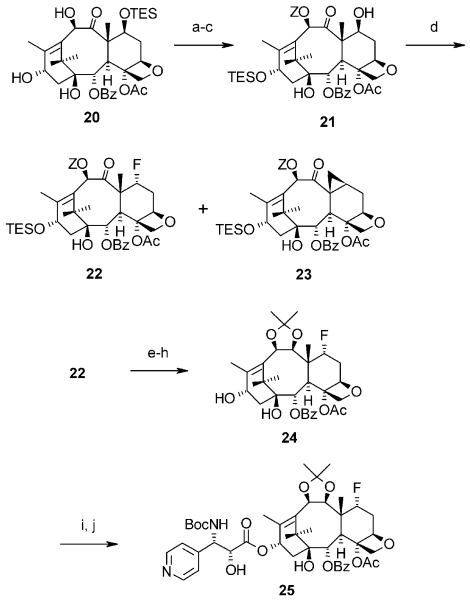
Scheme 2. Reagents and conditions: (a) Tf_2O, DMAP, DMF, 0 °C (95%); (b) thiocarbonyldiimidazole, DBU, THF, PhH, rt (75%); (c) *n*-Bu_3SnH, AIBN, dioxane, 80 °C (46%); (d) N_2H_4, EtOH, rt (61%); (e) BH_3-THF, THF, 0 °C (58%); (f) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt (87%); (g) (1) **7**, LiHMDS, THF, 0 °C, (2) HF-pyridine, pyridine, rt (64% from **13**).

9-carbonyl group of **11** and acetalization of the 9,10-hydroxyl groups of **12** gave **13**. Compound **13** was converted to **14**[8] by reactions similar to those used for preparation of **4**. Configuration of the 9-hydroxyl group of **13** was identified by comparison of the proton NMR data between **13** and that of the 9á-hydroxyltaxoids (**40**) from *Taxus canadenesis*.[9]

Synthesis of 9,10-acetal-7-deoxy-9β-dihydro-7β,8β-methano-3′-(4-pyridyl)taxoid (**19**) is described in Scheme 3. The key intermediate (**18**) was synthesized from **10** in satisfactory yield.[9,10] Compound **18** was converted to **19**.[11]



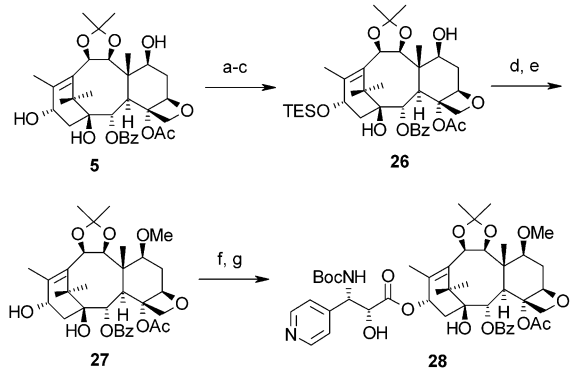
Scheme 3. Reagents and conditions: (a) Tf_2O (1.5 equiv), pyridine, CH_2Cl_2, 0 °C (88%); (b) (1) SiO_2, 1,2-dichloroethane, 60 °C; (2) N_2H_4, EtOH, rt (79% from **15**); (c) BH_3–THF, THF, 0 °C (58%); (d) 2,2-dimethoxypropane, TsOH, acetone, rt (86%); (e) **7**, LiHMDS, THF, 0 °C (55%); (f) HF-Py, pyridine, rt (93%).



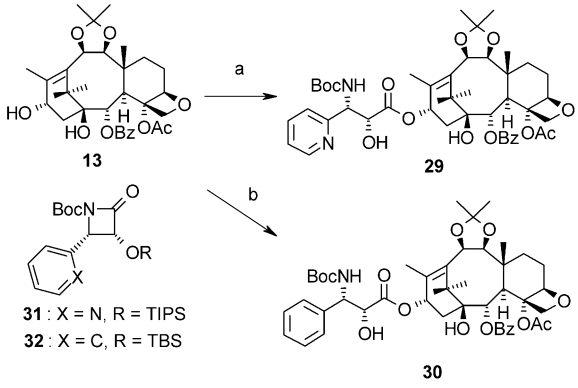
Scheme 4. Reagents and conditions: (a) *n*-BuLi, ZCl, THF, −40 °C (95%); (b) TESCl, imidazole, DMF, rt (76%); (c) TsOH, MeOH, rt (85%); (d) (diethylamino)sulfur trifluoride, CH_2Cl_2, −78 °C to rt (42% for **22**, 24% for **23**); (e) 10% Pd/C, H_2, EtOH, rt (89%); (f) BH_3–THF, THF, 0 °C (88%); (g) 2,2-dimethoxypropane, TsOH, acetone, rt (91%); (h) HF-Py, pyridine, rt (97%); (i) **7**, LiHMDS, THF, 0 °C (60%); (j) HF-Py, pyridine, rt (95%).

Synthesis of 9,10-acetal-7-deoxy-9β-dihydro-7α-fluoro-3′-(4-pyridyl)taxoid (**25**) is described in Scheme 4. The key intermediate (**24**) was synthesized from **20**.[9,12] Compound **24** was converted to **25**.[13]

Synthesis of 9,10-acetal-9β-dihydro-7-*O*-methyl-3′-(4-pyridyl) taxoid (**28**) is described in Scheme 5. Selective protection of the 7-hydroxyl group of **5** by Troc, introduction of TES to the 13-hydroxyl group and deprotection of 7-Troc gave **26** in moderate yield. We



Scheme 5. Reagents and conditions: (a) TrocCl, pyridine, 0 °C (47%); (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (54%); (c) Zn, AcOH–MeOH–dioxane 1:1:1, rt (80%); (d) MeOTf, 2, 6-di-*tert*-BuPy, rt (12%); (e) HF-Py, pyridine, rt (85%); (f) **7**, NaHMDS, THF, −55 °C (56%); (g) HF-Py, pyridine, rt (76%).



Scheme 6. Reagents and conditions: (a) (1) **31**,[5] NaHMDS, THF, −55 °C (75%); (2) HF-Py, pyridine, rt (75%); (b) (1) **32**, NaHMDS, THF, −55 °C (72%); (2) HF-Py, pyridine, rt (83%).

reported 7-*O*-methylation of taxoid by using methylthiomethylation and following desulfurylation.[14] However, oxidation of the 7-hydroxyl group to ketone was mainly observed in the methylthiomethylation step by DMSO and Ac_2O. We tried several conditions and found that the 7-methylated intermediate is derived by using 2,6-di-*tert*-butylpyridine and methyltriflate. Deprotection of 13-TES of the derived intermediate gave **27**. Compound **27** was converted to **28**.[15]

As a result of in vitro studies, the 7-deoxy analogue showed the strongest activity against cancer cell lines. To investigate the structure–activity relationship on the 3′-aryl group, we synthesized a 2-pyridyl analogue (**29**) and a phenyl analogue (**30**)[5,16] (Scheme 6). β-Configuration of the 9-position was confirmed by comparison of the ^1H NMR of **30** with the α-isomer of that synthesized from the 9-α taxoid extracted from *T. canadenesis*.[9]

Results (Biological Activity) and Discussion

Antitumor activities of the 9-β-dihydro-9,10-acetal taxoids (**4**, **14**, **19**, **25**, **28**, **29**, **30**) were evaluated in vitro against three cell lines (PC-6, PC-12, and PC-6/VCR). Among the 7-position modified 3′-(4-pyridyl) analogues (**14, 19, 25, 28**), deoxy type (**14**) showed the strongest activity against two cell lines expressing P-glycoprotein, PC-12 and PC-6/VCR. 7-*O*-Methyl and 7-α-fluoro analogues also showed strong activity; however, methano analogue (**19**) was less potent than docetaxel. This structure activity relationship on the 7-position is almost the same as that of the 10-*C*-alkyl docetaxel analogue,[14] except for the methano analogue (**19**). The 7-Deoxy-3′-(4-pyridyl) analogue (**14**) was more potent than the corresponding 3′-phenyl analogue (**30**) against PC-12, and the 3′-(2-pyridyl) analogue (**29**) was more potent than **30** against PC-6/VCR. We think that the 7-deoxy-3′-pyridyl analogues are useful for increasing water solubility and activity against cell lines expressing P-glycoprotein (Table 1).

Table 1. Cytotoxicity of 9-β-dihydro-9,10-acetal taxoids[a]

	3′	7	Cytotoxic activity GI_{50} (ng/mL) [b]		
			PC-6	PC-12	PC-6/VCR
2	Docetaxel		1.48	42.2	135
4	4-Py	OH	0.380	0.655	13.5
14	4-Py	Deoxy	0.386	0.038	3.84
19	4-Py	Methano	7.03	33.7	>100
25	4-Py	α-F	0.266	0.130	3.87
28	4-Py	OMe	0.229	2.26	38.1
29	2-Py	Deoxy	0.145	0.116	0.538
30	Phenyl	Deoxy	0.332	0.151	2.91

[a]The in vitro experiments were performed with three different cell lines: PC-6, a human small cell lung cancer,[17] its variant, PC-6/VCR29–9, a vincristine-resistant cell line expressing P-glycoprotein,[18] PC-12, a human non-small cell lung cancer cell line.[17] Determination of GI_{50} was performed by using the MTT assay.[19] The cells were exposed continuously to the test compounds for 72 h.
[b]Growth inhibition of 50%: the concentration required to obtain half of the maximal inhibition for cell growth.

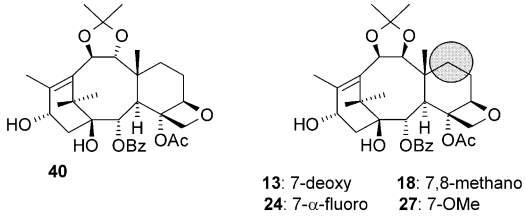


Figure 3.

In conclusion, we synthesized the 7-position- and 3′-position-modified 9,10-acetal-9β-dihydro taxoids and found that the 7-deoxy-3′-pyridyl analogues showed potent activities. We believe that we can report synthesis of the optimized lead compound in the near future.

Table 2. Solubility of taxanes

	Solubility (μg/mL)	
	JP1 (pH 1.2)	JP2 (pH 6.8)
Taxol	<4	<4
Taxotere	<4	<4
4	333	57

Table 3. NMR data of 9-α and 9-β taxoids

		9-H (ppm)	10-H (ppm)	*J* (Hz)
9α:	**40**	4.39	4.72	9.5
9β	**13**	4.18	5.62	7.3
	18	4.49	5.49	7.8
	24	4.61	5.59	8.8
	27	4.57	5.53	7.8

Acknowledgements

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4. Analogue **4** showed the better water solubility than Taxol and Taxotere (Table 2).
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6. Analytical data of **4** are as follows: **4**: mp 160–163 °C; FAB-MS *m*/*z* 851 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29, 1.40, 1.59, 1.63, 1.68, and 1.81 (each s, each 3H, Me×6), 1.40 (s, 9H, *tert*-Bu), 1.92 (broad s, 1H, OH), 2.05–2.42 (m, 4H), 2.19 (s, 3H, Ac), 2.93 (d, 1H, *J* = 4.9 Hz, H-3), 3.83 (d, *J* = 7.3 Hz, 1H, H-9), 4.03–4.13 (m, 1H, H-7), 4.32 and 4.39 (ABq, *J* = 8.3 Hz, each 1H, H-20, H-20′), 4.51 (broad s, 1H), 4.73 (d, *J* = 7.3 Hz, 1H), 5.18 (s, 1H), 5.30 (broad d, *J* = 8.4 Hz, 1H), 5.46–5.61 (m, 2H), 6.06 (d, *J* = 4.9 Hz, 1H, H-2), 6.23 (m, 1H, H-13), 7.42 (d, *J* = 6.8 Hz, 2H, Py), 7.46 (t, *J* = 7.6 Hz, 2H, Bz), 7.60 (t, *J* = 7.6 Hz, 1H, Bz), 8.10 (d, *J* = 7.6 Hz, 2H, Bz), 8.62 (d, *J* = 6.8 Hz, 2H, Py).
7. Selective 10-acetylation of 10-deacetylbaccatin III was reported in the following article: Damen, E. W. P.; Braamer, L.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 6081.
8. Analytical data of **14** are as follows: mp 163–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H, Me), 1.43 (s, 9H, *tert*-Bu), 1.51 (s, 3H, Me), 1.55 (s, 3H, Me), 1.57 (s, 3H, Me), 1.61 (s, 3H, Me), 1.71 (s, 3H, Me), 1.60–2.10 (m, 5H, 6-H×2, 7-H×2 and 14-H), 1.97 (broad s, 1H, OH), 2.28 (s, 3H, Ac), 2.34 (dd, *J* = 10.2, 15.2 Hz, 1H, 14-H), 2.91 (d, *J* = 4.9 Hz, 1H, 3-H), 4.12 (d, *J* = 7.1 Hz, 1H, 9-H), 4.27 (d, *J* = 8.3 Hz, 1H, 20-H), 4.32 (d, *J* = 8.3 Hz, 1H, 20-H), 4.63 (broad s, 1H, 2′-H), 4.82 (broad s, 1H, OH), 4.93 (broad s, 1H, 5-H), 5.30 (d, *J* = 9.1 Hz, 1H, 3′-H), 5.56 (d, *J* = 7.1 Hz, 1H, 10-H), 5.81 (d, *J* = 9.3 Hz, 1H, NH), 6.00 (d, *J* = 4.9 Hz, 1H, 2-H), 6.09 (broad t, *J* = 7.8 Hz, 1H, 13-H), 7.36 (d, *J* = 5.9 Hz, 2H, Py), 7.47 (t, *J* = 7.3 Hz, 2H, Bz), 7.60 (t, *J* = 7.3 Hz, 1H, Bz), 8.12 (d, *J* = 7.3 Hz, 2H, Bz), 8.59 (d, *J* = 5.9 Hz, 2H, Py).
9. Proton NMR data of 9α-10β-taxoids (**40**) and 9β-10β-taxoids (**13**, **18**, **24**, **27**, Fig. 3) were compared as follows (Table 3), and these data seemed to support the 9-β configuration. Proton NMR data of the 9α-10β-taxoid were obtained from the article: Poujol, H.; Mourabit, A. A., Ahond, A., Poupat, C. and Potier, P. *Tetrahedron* **1997**, *53*, 12575.
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11. Analytical data of **19** is as follows: mp 152–157 °C; FAB-MS *m*/*z* 833 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (broad s, 1H), 1.15–1.45 (m, 2H), 1.22 (s, 3H), 1.35 (s, 12H), 1.49 (s, 3H), 1.57 (s, 3H), 1.70–1.80 (m, 1H), 1.70 (s, 3H), 1.85 (s, 1H), 2.26 (s, 3H), 2.29 (dd, *J* = 8.3, 15.6 Hz, 1H), 2.57 (dd, *J* = 9.0, 15.6 Hz, 1H), 2.65–2.77 (m, 1H), 3.17 (d, *J* = 7.8 Hz, 1H), 3.83 (broad s, 1H), 4.18 (d, *J* = 7.8 Hz, 9-H, 1H), 4.38 (d, *J* = 8.3 Hz, 1H), 4.48 (d, *J* = 7.5 Hz, 1H), 4.55 (broad t, *J* = 8.8 Hz, 1H), 4.64 (broad, s 1H), 5.31 (broad t, *J* = 9.3 Hz, 1H), 5.44 (d, *J* = 7.5 Hz, 10-H, 1H), 5.54 (d, *J* = 8.3 Hz, 1H), 5.58 (d, *J* = 9.3 Hz, 1H), 6.24 (broad t, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 6.1 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 2H), 8.59 (d, *J* = 6.1 Hz, 2H).
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13. Analytical data of **25** are as follows: mp 154–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H, Me), 1.41 (s, 9H, *tert*-Bu), 1.42 (s, 3H, Me), 1.56 (s, 3H, Me), 1.61 (s, 3H, Me), 1.62 (s, 3H, Me), 1.63 (s, 3H, Me), 1.87 (s, 1H, OH), 2.32 (s, 3H, acetyl), 2.08–2.47 (m, 4H, 6-H, 14-H), 3.46 (d, *J* = 5.4 Hz, 1H, 3-H), 4.28–4.40 (br, 1H), 4.31 (d, *J* = 8.5 Hz, 1H, 20-H), 4.36 (d, *J* = 8.5 Hz, 1H, 20-H), 4.59 (d, *J* = 8.6 Hz, 1H, 9-H), 4.63 (br, 1H, 2′-H), 4.87 (ddd, *J* = 3.9, 7.8, 45.9 Hz, 1H, 7-H), 4.93–4.97 (m, 1H, 5-H), 5.31 (broad d, *J* = 9.6 Hz, 1H, 3′-H), 5.52 (d, *J* = 8.6 Hz, 1H, 10-H), 5.69 (broad d, *J* = 9.6 Hz, 1H, NH), 5.92 (d, *J* = 5.4 Hz, 1H, 2-H), 6.12 (broad t, *J* = 8.3 Hz, 1H, 13-H), 7.35 (d, *J* = 6.2 Hz, 2H, pyridine), 7.48 (t, *J* = 7.6 Hz, 2H, Bz), 7.62 (t, *J* = 7.6 Hz, 1H, Bz), 8.10 (d, *J* = 7.6 Hz, 2H, Bz), 8.60 (d, *J* = 6.2 Hz, 2H, pyridine).
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15. Analytical data of **28** are as follows: mp 155–158 °C; FAB-MS *m*/*z* 865 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.40 (s, 3H), 1.41 (s, 9H), 1.51 (s, 3H), 1.57 (s, 3H), 1.59 (s, 6H), 1.80–2.40 (m, 5H), 2.31 (s, 3H), 3.00 (d, *J* = 4.9 Hz, 1H), 3.33 (s, 3H), 3.40 (d, *J* = 4.0 Hz, 1H), 4.08 (d, *J* = 7.8 Hz, 1H), 4.19 (d, *J* = 7.8 Hz, 1H, 9-H), 4.55 (d, *J* = 7.8 Hz, 1H), 4.63 (s, 1H), 4.86 (s, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 5.47 (d, *J* = 7.8 Hz, 1H, 10-H), 5.73 (d, *J* = 9.3 Hz, 1H), 5.94 (d, *J* = 4.9 Hz, 1H), 6.13 (t, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 5.9 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 8.10 (d, *J* = 7.3 Hz, 1H), 8.58 (d, *J* = 5.9 Hz, 2H).
16. Analytical data of **29** and **30** are as follows. **29**: mp 145–148 °C; FAB-MS *m*/*z* 835 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.43 (s, 3H), 1.44 (s, 9H), 1.52 (s, 3H), 1.56 (s, 3H), 1.61 (s, 3H), 1.71 (s, 3H), 1.80–2.20 (m, 4H), 2.22–2.31 (m, 2H), 2.35 (s, 3H), 2.94 (d, *J* = 4.9 Hz, 1H), 4.17 (d, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 8.3 Hz, 1H), 4.32 (d, *J* = 8.3 Hz, 1H), 4.88 (d, *J* = 2.5 Hz, 1H), 4.92 (s, 1H), 5.34 (d, *J* = 9.3 Hz, 1H), 5.56 (d, *J* = 7.3 Hz, 1H), 5.94 (d, *J* = 9.4 Hz, 1H), 5.96 (d, *J* = 4.9 Hz, 1H), 6.09 (t, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 7.3 Hz, 4.9 Hz, 1H), 7.38–7.50 (m, 3H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.3 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.54 (d, *J* = 4.4 Hz, 1H). **30**: mp 145–148 C; FAB-MS *m*/*z* 834 $(M+1)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (s, 3H), 1.42 (s, 9H), 1.45 (s, 3H), 1.50 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.80–2.10 (m, 4H), 2.30 (s, 3H, Ac), 2.48 (dd, *J* = 10.0 Hz, 15.0 Hz, 1H), 2.91 (d, *J* = 4.8 Hz, 1H), 4.14 (d, *J* = 7.3 Hz, 1H, 9-H), 4.25 (d, *J* = 8.3 Hz, 1H), 4.30 (d, *J* = 8.3 Hz, 1H), 4.39 (brs, 1H), 4.61 (brs, 1H), 4.91 (s, 1H), 5.30 (d, *J* = 9.0 Hz, 1H), 5.56 (d, *J* = 7.3 Hz, 1H, 10-H), 5.70 (d, *J* = 9.0 Hz, 1H), 6.00 (d, *J* = 4.9 Hz, 1H), 6.07 (m, 1H), 7.27–7.37 (m, 5H), 7.40–7.46 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 2H).

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