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

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Abstract—To synthesize new highly active taxoids, we designed and synthesized 9β-dihydro-9,10-acetal taxoids. In vitro study of these analogues clearly showed them to be more potent than docetaxel.

Introduction

Paclitaxel (**1**, Taxol®)[1] and docetaxel (**2**, Taxotere®)[2] are currently considered to be two of the most important drugs in cancer chemotherapy (Fig. 1). To synthesize new highly active analogues of these drugs, we designed 9,10-acetal taxoids. Ahond et al. reported the synthesis of 7-deoxy-9α-dihydro-9,10-isopropylidenedocetaxel (**3**) from a mixture of the natural products Taxine B and Isotaxine B, 9α-dihydro taxoids that were isolated from *Taxus canadenesis* (Fig. 2).[3] The cytotoxicity of **3**, however, was reported to be the same as that of docetaxel (**2**).

We hypothesized that the configuration of the 9-hydroxyl group is crucial and that there is a possibility to synthesize new highly active taxoids from the 9β-dihydrobaccatin skeleton reported by Holton et al.[4] Here we report 9β-dihydro-9,10-acetal taxoids, which showed activity stronger than that of docetaxel against several tumor cell lines.

Chemical Synthesis

10-Deacetylbaccatin III (**4**) was reduced by using *n*-Bu_4NBH_4 to give the key compound 10-deacetyl-9β-dihydrobaccatin III (**5**) (Scheme 1).[4] To synthesize 9,10-acetal taxoids, several aldehydes and ketones, whose structures are not shown, were reacted with **5** in the presence of an acid catalyst.[5] In this reaction, it was found that acetonide, 4-methoxybenzylidene, and propenylidene group could be obtained in satisfactory yields. To determine the structures of **6a**–**c**, the 7, 13-hydroxyl groups were acetylated, and ^{1}H NMR spectra of **7a**–**c** supported the structures.[6]

To introduce a phenylisoserine side chain to the 13-hydroxyl group of **6a**–**c**, β-lactams (**11**, **12**) were reacted with **6a**–**c** in the presence of NaHMDS. Contrary to our expectation, there was no selectivity between the 7-hydroxyl group and the 13-hydroxyl

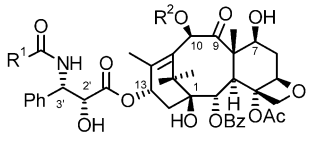

Figure 1.

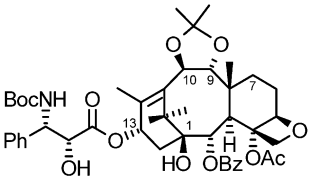

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Figure 2.

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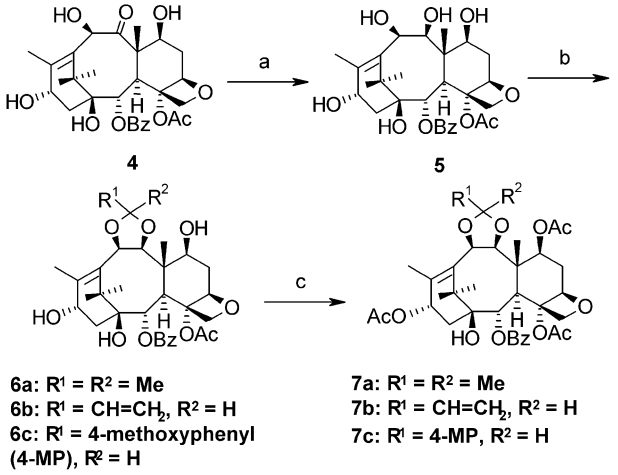
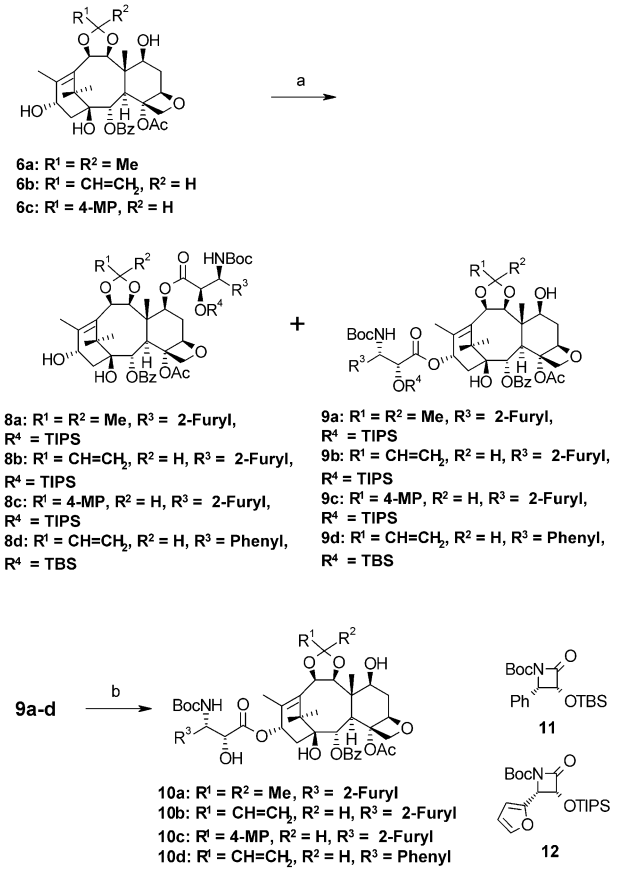
group. The desired **9a**–**d** were obtained in low yields. Deprotection of **9a**–**d** by the reported method gave **10a**–**d**[7] (Scheme 2).[8]

To improve synthetic yields of the 9,10-acetal taxoids, selective protection of the 7-hydroxyl group of **6b** by TES group was studied (Scheme 3). It was found that **13a** was synthesized by using TESOTf and 2,6-di-*tert*-butylpyridine in dichloromethane at −78 °C in fairly good yield (Table 1, entry 5). The following reaction gave **10d** in high yield (Scheme 4).

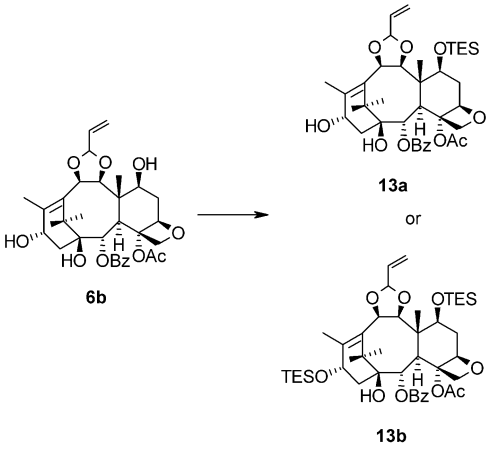
We synthesized 9β-dihydro-3′-furyldocetaxel (**16**) for comparison. Although **16** was not obtained from **10a** by acidic deprotection of the acetal group, we synthesized **16** from **5** via 10-deacetyl-7,10-bis TES-9β-dihydrobaccatin III (**14**) (Scheme 5).[9]



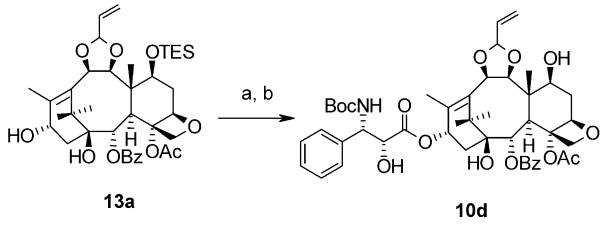
Scheme 1. Reagents and conditions: (a) *n*-Bu_4NBH_4, 1:1 dioxane–CH_2Cl_2, rt, 19 h (68%); (b) 2,2-dimethoxypropane or acrolein diethylacetal or 4-methoxybenzaldehyde dimethylacetal, CSA, CH_2Cl_2, dioxane, rt, 1 h, (57% for **6a**, 45% for **6b**, 25% for **6c**); (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (70% for **7a**, 88% for **7b**, 72% for **7c**).



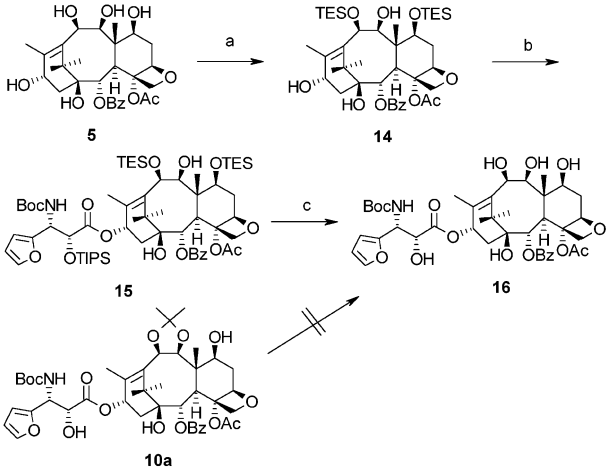
Scheme 2. Reagents and conditions: (a) (1) **11** or **12**, NaHMDS, THF, −55 °C, 0.5 h (15% for **8a**, 19% for **9a**, 19% for **8b**, 19% for **9b**, 8.8% for **8c**, 13% for **9c**, 31% for **8d**, 9.8% for **9d**); (b) HF-pyridine, pyridine, rt (88% for **10a**, 87% for **10b**, 68% for **10c**, 70% for **10d**).



Scheme 3.



Scheme 4. Reagents and conditions: (a) **11**, NaHMDS, THF, −55 °C, 0.5 h (71%); (b) HF-pyridine, pyridine, rt (78%).

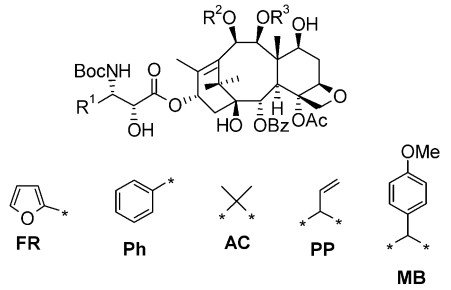


Scheme 5. Reagents and conditions: (a) TESCl, Et_3N, DMF, rt (9%); (b) **12**, NaHMDS, THF, −55 °C, 0.5 h (59%); (c) HF-pyridine, pyridine, rt (59%).

Table 1. 7-*O* selective silylation of **6b**

Entry	Conditions	**13a** (%)	**13b** (%)
1	TESCl (1.5 equiv), imidazole (1.8 equiv), DMF, rt	25	50
2	TESCl (15 equiv), imidazole (18 equiv), DMF, 65 °C	0	63
3	TESCl (1.2 equiv), pyridine, rt	27	30
4	TESOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, −78 °C	24	20
5	TESOTf (1.3 equiv), 2,6-di-*tert*-butylpyridine (1.5 equiv), CH_2Cl_2, −78 °C	80	0

Table 2. Cytotoxicity of 9-β-dihydro taxoids[a]



	R^1	R^2, R^3	Cytotoxic activity GI_{50} (ng/mL)[b]		
			PC-6	PC-12	PC-6/VCR
2	Ph		0.408–2.55	11.7–72.7	39.6–230
10a	FR	AC	0.331	0.235	1.88
10b	FR	PP	0.743	1.30	1.27
10c	FR	MB	6.26	0.605	9.25
10d	Ph	PP	0.365	0.328	4.64
16	FR	H, H	21.0	37.3	422

[a]The in vitro experiments were performed with three different cell lines: PC-6, a human small cell lung cancer,[10] its variant, PC-6/VCR29–9, a vincristine-resistant cell line expressing P-glycoprotein,[11] and PC-12, a human non-small cell lung cancer cell line.[10] Determination of GI50 was performed by using the MTT assay.[12] 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.

Results (Biological Activity) and Discussion

The antitumor activities of the 9β-dihydrotaxoids (**10a–d**, **16**) were evaluated in vitro against three cell lines, PC-6, PC-12, and PC-6/VCR. The PC-12 and PC-6/VCR cell lines are expressing P-glycoprotein. 9β-Dihydro-9,10-acetal taxoids (**10a–d**) showed strong activities against these cell lines (Table 2). On the contrary, the activity of 9β-dihydrodocetaxel (**16**) was less potent than docetaxel. These data clearly showed the effectiveness of acetal groups in the 9,10-position of the taxane skeleton and suggested the importance of the β-configuration of the 9-OH group.

In conclusion, we synthesized several 9β-dihydro-9,10-acetal taxoids and found that analogues based on the 9,10-acetal taxane skeleton are more potent than docetaxel. It appears that the 9β-configuration is important for increasing the potency. Further investigation of these highly active 9β-9,10-acetal taxoids will be reported in the near future.

References and Notes

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4. (a) Holton R. A. WO patent 15599, 1995. (b) Holton R. A. WO Patent 20485, 1995. In this reaction, the 9-α-isomer was not obtained.
5. There were no differences among CSA, TsOH and PPTS in this reaction.
6. Comparison of 7-, 9-, 10-, and 13-protons of **6a–c** and **7a–c** supported the structures (Table 3).

Table 3. Chemical shifts of 7-, 9-, 10-, and 13-protons (ppm)

	7	9	10	13
6a	4.04	3.85	5.58	4.80
7a	5.14	4.01	5.50	6.13
6b	4.16	3.89	5.30	4.82
7b	5.20	3.96	5.31	6.15
6c	4.15	3.98	5.47	4.84
7c	5.22	4.09	5.46	6.16

7. Analytical data of **10a–d** are as follows. **10a**: mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 and 1.28 (each 3H, each s, Me×2), 1.41 (9H, s, *tert*-Bu), 1.58, 1.65, 1.67, and 1.70 (each 3H, each s, Me×4), 1.83–1.94 (1H, m), 2.07–2.27 (2H, m), 2.36 (3H, s, Ac), 2.29–2.47 (1H, m), 2.94 (1H, d, H-3, J = 4.9 Hz), 3.83 (1H, d, H-9, J = 7.3 Hz), 4.32 and 4.39 (each 1H, ABq, H-20, H-20′, J = 8.7 Hz), 4.65–4.76 (2H, m), 5.10 (1H, s), 5.30–5.42 (2H, m), 5.54 (1H, d, H-10, J = 7.3 Hz), 6.05 (1H, d, H-2, J = 4.9 Hz), 6.11 (1H, d, furan, J = 3.5 Hz), 6.36 (1H, dd, furan, J = 3.5, J = 1.4 Hz), 7.39 (1H, d, furan, J = 1.4 Hz), 7.48 (2H, t, Bz, J = 7.3 Hz), 7.60 (1H, t, Bz, J = 7.3 Hz), 8.11 (2H, d, Bz, J = 7.3 Hz). **10b**: mp 147–150 °C; FAB-MS m/z 838 $(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ 1.28, 1.62, 1.69, and 1.71 (each 3H, each s, Me×4), 1.41 (9H, s, *tert*-Bu), 2.05–2.26 (3H, m), 2.29–2.44 (1H, m), 2.35 (3H, s, Ac), 2.93 (1H, d, H-3, J = 4.9 Hz), 3.89 (1H, d, H-9, J = 6.8 Hz), 4.04–4.16 (1H, m, H-7), 4.32 and 4.39 (each 1H, ABq, H-20, H-20′, J = 8.3 Hz), 4.71 (1H, s like), 5.10 (1H, s like), 5.22 (1H, d, acetal, J = 5.9 Hz), 5.27 (1H, d, H-10, J = 6.8 Hz), 5.32–5.46 (2H, m), 5.46 (H, d, CH=CH_2, J = 10.8 Hz), 5.57 (1H, d, CH=CH_2, J = 17.6 Hz), 5.97–6.19 (2H, m, H-13, CH=CH_2), 6.08 (1H, d, H-2, J = 4.9 Hz), 6.32 (1H, d, furan, J = 1.9 Hz), 6.36 (1H, dd, furan, J = 3.0, J = 1.9 Hz), 7.39 (1H, d, furan, J = 3.0 Hz), 7.48 (2H, t, Bz, J = 7.8 Hz), 7.60 (1H, t, Bz, J = 7.8 Hz), 8.10 (2H, d, Bz, J = 7.8 Hz). **10c**: mp 148–151 °C; FAB-MS m/z 918 $(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, s, Mde), 1.42 (9H, s, *tert*-Bu), 1.56 (3H, s, Me), 1.76 (6H, s, Me×2), 2.10–2.26 (3H, m), 2.36 (3H, s, Ac), 2.31–2.48 (1H, m), 2.99 (1H, d, H-3, J = 4.9 Hz),

3.84 (3H, s, OMe), 3.98 (1H, d, H-9, $J=7.4$ Hz), 4.05–4.17 (1H, m, H-7), 4.30 and 4.38 (each 1H, ABq, H-20, H-20′, $J=8.3$ Hz), 4.57 (1H, d, $J=8.3$ Hz), 4.72 (1H, d, $J=3.9$ Hz), 5.11 (1H, s like), 5.38 (2H, broad s), 5.43 (1H, d, $J=7.4$ Hz), 5.80 (1H, s, acetal), 6.07 (1H, d, H-2, $J=4.9$ Hz), 6.15 (1H, broad t, H-13, $J=8.0$ Hz), 6.32 (1H, d, furan, $J=3.8$ Hz), 6.36 (1H, dd, furan, $J=3.8$ Hz, $J=2.0$ Hz), 6.93 (2H, d like aromatic protons of MP, $J=8.8$ Hz), 7.40 (1H, d, furan, $J=2.0$ Hz), 7.43–7.53 (4H, m), 7.60 (1H, t, Bz, $J=7.3$ Hz), 8.11 (2H, d, Bz, $J=7.3$ Hz). **10d**: mp 145–150 °C; FAB-MS *m*/*z* 848 $(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, s, Me), 1.40 (9H, s, *tert*-Bu), 1.61 (6H, s, Me×2), 1.68 (3H, s, Me), 1.91 (1H, s, OH), 2.00–2.36 (3H, m), 2.30 (3H, s, Ac), 2.39 (1H, dd, $J=9.8$, 15.2 Hz), 2.90 (1H, d, H-3, $J=4.9$ Hz), 3.85 (1H, d, H-9, $J=5.8$ Hz), 4.05–4.15 (1H, m, H-7), 4.16 (1H, broad s), 4.32 and 4.38 (each 1H, ABq, H-20, H-20′, $J=8.8$ Hz), 4.57 (1H, d, H-5, $J=8.3$ Hz), 4.62 (1H, broad s), 5.10 (1H, s), 5.22 (1H, d, acetal, $J=6.3$ Hz), 5.26 (1H, d, H-10, $J=6.8$ Hz), 5.30 (1H, broad d, $J=9.7$ Hz), 5.97–6.13 (2H, m, H-13, $CH=CH_2$), 6.07 (1H, d, H-2, $J=4.3$ Hz), 7.20–7.45 (5H, m, aromatic protons), 7.47 (2H, t, Bz, $J=7.4$ Hz), 7.60 (1H, t, Bz, $J=7.4$ Hz), 8.10 (2H, d, Bz, $J=7.4$ Hz).

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9. In step a, there was no selectivity among the 7-, 10-, and 13-hydroxyl groups of **5**.
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