A New Method to Modify the C-4 Position of 10-Deacetylbaccatin III

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We have developed a new method to modify the C-4 position of 10-deacetylbaccatin III (5) using the C-4 acetoxy anion of the 13-keto derivative (7) and various alkyl halides. The method developed herein shoud be very useful for the preparation of C-4 modified taxoid analogs.

Key words paclitaxel; taxoid; 10-deacetylbaccatin III; C-4 acetyl group; alkylation; anion

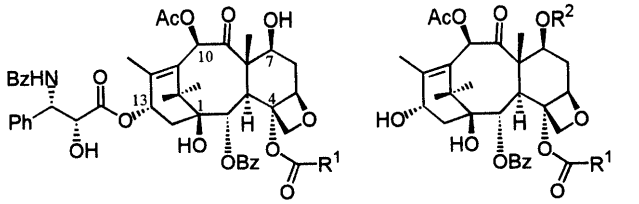
Paclitaxel (**1**, Taxol®),[1] a diterpene natural product isolated by Wani *et al.* from *Taxus brevifolia*, has shown exceptional efficacy in cancer chemotherapy and was approved by the Food and Drug Administration (FDA) for the treatment of advanced ovarian and breast cancer in December, 1992 and April, 1994, respectively. Paclitaxel possesses a unique mechanism of action as a promoter of tubulin assembly and inhibitor of microtubule disassembly.[2]

Recently, Chen's group has reported a regioselective method for the preparation of C-4 paclitaxel analogs (**2**).[3] The key intermediates (**4**) for the preparation of the analogs (**2**) were obtained from baccatin III (**3**) in six steps based on C-4 deacetylation and reacylation.[3a] Preliminary biological evaluation of **2** has shown that these compounds are more potent *in vitro* than paclitaxel. We have developed a new method to modify the C-4 position using 10-deacetylbaccatin III (10-DAB III, **5**) as the starting material.

Chart 1 outlines the route for the synthesis of 4-modified 7-triethylsilyl (TES)-baccatin III (**9a—d**). Selective protection of the C-7 hydroxy group on 10-DAB III (**5**) with a TES group according to Greene's method[4] gave compound **6**. We first attempted to obtain **9a** by formation of an anion at the C-4 acetyl group followed by alkylation using **6** and iodomethane, but this approach resulted in no reaction or a complex mixture. We next tried the same reaction using the 13-keto derivative (**7**),[5] which was synthesized from **6** by chemoselective oxidation at the C-13 position with activated MnO_2. Interestingly, the treatment of **7** with lithium bis(trimethylsilyl)amide (LiHMDS) or sodium bis(trimethysilyl)amide (NaHMDS) in dry tetrahydrofuran (THF) and successive reaction with various alkyl halides gave the 13-keto-4-modified-7-TES-baccatin III (**8a—d**).[6] These results are shown in Table 1.

The reaction of **7** with 10.6 eq of iodomethane in the presence of 5.3 eq of LiHMDS at −45° for 3 h gave the 4-propionyl derivative (**8a**) in 70% yield (run 1). The 4-(4-pentenoyl) derivative (**8d**) could be synthesized from allyl iodide using the same procedure (run 6). On the other hand, the reaction of iodoethane or 1-iodopropane gave the corresponding 4-acyl derivatives (**8b**, **8c**) in low yields, respectively, accompanied with the decomposition of the substrate (runs 2, 4).

However, when NaHMDS, a stronger base than LiHMDS, was used, the yield of **8b** and **8c** was remarkably increased (runs 3, 5). Finally, the C-13 keto group on



1: R^1 = Me (Paclitaxel)
2: R^1 = Et, *n*-Pr, etc.

3: R^1 = Me, R^2 = H (Baccatin III)
4: R^1 = Et, *n*-Pr, etc., R^2 = TES

Fig. 1

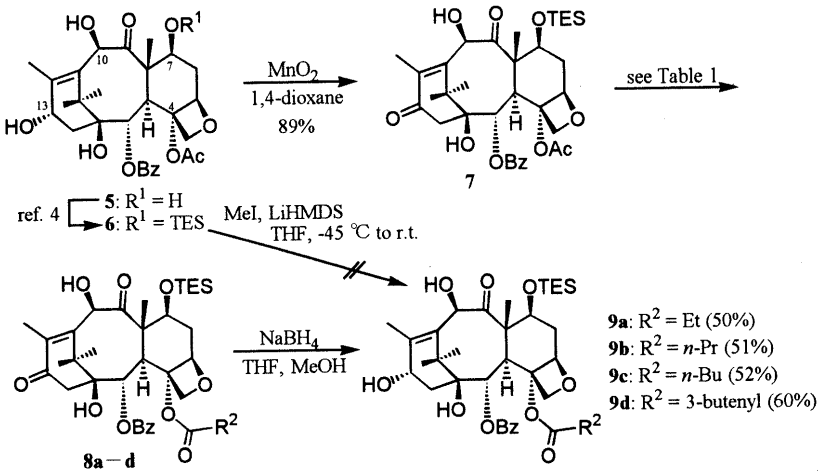


Chart 1

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Table 1. Synthesis of 13-Keto-4-modified-7-TES-baccatin III (**8a—d**)[a]

Run	Product	R^2	Base (eq)	Alkyl halide (eq)	Temp (°C)	Reaction Time (h)	Isolated yield (%)	Conversion yield (%)
1	**8a**	Et	LiHMDS (5.3)	MeI (10.6)	−45	3	70	87
2	**8b**	*n*-Pr	LiHMDS (5.3)	EtI (6.5)	−45 to r.t.	18	11[b]	15[b]
3	**8b**	*n*-Pr	NaHMDS (5.3)	EtI (6.5)	−45	3	63	78
4	**8c**	*n*-Bu	LiHMDS (5.3)	*n*-PrI (6.5)	−45 to r.t.	18	8[b]	10[b]
5	**8c**	*n*-Bu	NaHMDS (5.3)	*n*-PrI (6.5)	−35	4	45	72
6	**8d**	3-butenyl	LiHMDS (5.0)	Allyl-I (1.0)	−45	1	55	73

a) THF was used as the solvent. *b*) Due to severe decomposition.

8a—d was reduced with $NaBH_4$ according to Nicolaou's method[5a] to give the desired 4-modified 7-TES-baccatins III (**9a—d**). Compounds **9a—d** can be converted to 4-modified baccatin III (**4**) by C-10 acetylation[4] or 10-modified intermediates for the preparation of various taxoid derivatives.[7] This method should be very useful for the preparation of novel C-10 water-soluble taxoid analogs modified at the C-4 position.[8]

In summary, we have developed a new method to modify the C-4 position of 10-DAB III (**5**) using the C-4 acetoxy anion of the 13-keto derivative (**7**) and various alkyl halides.

Experimental

All melting points were determined using a Yanaco MP-S3 or MP-500D apparatus and are uncorrected. IR spectra were obtained using a Hitachi 270-300 IR spectrophotometer. Mass spectra were recorded on a JEOL JMS-HX-100, a JEOL AX505W, or a JMS-D300 spectrometer. ^{1}H-NMR spectra were taken at 400 MHz with a JEOL JNM-EX400 spectrometer and all values are reported in ppm (δ) downfield from $(CH_3)_4Si$. Elemental analyses were obtained on a Heraeus CHN-*O*-Rapid or a Perkin-Elmer 2400CHN instrument. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Merck Silica gel (230—400 mesh) was used for column chromatography.

10-Deacetyl-13-deoxy-13-oxo-7-*O*-triethylsilylbaccatin III (7) Activated MnO_2 (2.50 g) was added to a solution of 10-deacetyl-7-*O*-triethylsilylbaccatin III (**6**) (2.50 g, 3.79 mmol) in 1,4-dioxane (62.5 ml) at room temperature. After 20 h, the mixture was filtered to remove any insoluble material. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (20% AcOEt/*n*-hexane) to give **7** (2.22 g, 89%), which was recrystallized from diethyl ether. **7**: Colorless crystalline solid. mp 245—250 °C. MS (FAB) *m/z* 657 (MH^+). $[\alpha]_D^{26}$ +20.0° (*c*=1.1, $CHCl_3$). *Anal.* Calcd for $C_{35}H_{48}O_{10}Si$: C, 64.00; H, 7.36. Found: C, 63.89; H, 7.25. IR (KBr) 3472, 2960, 2884, 1728, 1712, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.47—0.63 (m, 6H), 0.93 (t, 9H, *J*=8 Hz), 1.16 (s, 3H), 1.23 (s, 3H), 1.73 (s, 3H), 1.86—1.93 (m, 1H), 2.10 (s, 3H), 2.19 (s, 3H), 2.44—2.52 (m, 1H), 2.64 (d, 1 H, *J*=20 Hz), 2.94 (d, 1H, *J*=20 Hz), 3.96 (d, 1H, *J*=7 Hz), 4.13 (d, 1H, *J*=8 Hz), 4.35 (d, 1H, *J*=8 Hz), 4.40 (dd, 1H, *J*=10, 7 Hz), 4.91 (d, 1H, *J*=8 Hz), 5.32 (s, 1H), 5.65 (d, 1H, *J*=7 Hz), 7.49 (t, 2H, *J*=8 Hz), 7.63 (t, 1H, *J*=8 Hz), 8.06 (d, 2H, *J*=8 Hz).

13-Deoxy-4,10-dideacetyl-13-oxo-4-*O*-propionyl-7-*O*-triethylsilylbaccatin III (8a) (General Procedure) A 1 M THF solution of LiHMDS (2.65 ml) was added dropwise to a solution of **7** (329 mg, 0.50 mmol) in THF (1.65 ml) at −45 °C under a nitrogen atmosphere. After 10 min, a solution of iodomethane (0.16 ml, 2.7 mmol) in THF (1.65 ml) was added, and stirring was continued for 3 h at −45 °C. The reaction mixture was poured into cold aqueous NH_4Cl solution, and extracted with AcOEt. The extract was washed with brine, and dried over anhydrous Na_2SO_4, then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% AcOEt/*n*-hexane) to give **8a** (234 mg, 70%), which was recrystallized from MeOH–H_2O. **8a**: Colorless crystalline solid. mp 181—184 °C. MS (FAB) *m/z* 671 (MH^+). $[\alpha]_D^{25}$ +15.5° (*c*=1.1, $CHCl_3$). *Anal.* Calcd for $C_{36}H_{50}O_{10}Si$: C, 64.45; H, 7.51. Found: C, 64.64; H, 7.64. IR (KBr) 3464, 2964, 1730, 1676 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.93 (t, 9H, *J*=8 Hz), 1.16 (s, 3H), 1.21 (s, 3H), 1.22 (t, 3H, *J*=7 Hz), 1.73 (s, 3H), 1.86—1.93 (m, 1H), 2.10 (s, 3H), 2.38—2.54 (m, 3H), 2.62 (d, 1H, *J*=20 Hz), 2.93 (d, 1H, *J*=20 Hz), 3.96 (d, 1H, *J*=7 Hz), 4.14 (d, 1H, *J*=8 Hz), 4.32 (d, 1H, *J*=8 Hz), 4.41 (dd, 1H, *J*=10, 7 Hz), 4.88 (d, 1H, *J*=8 Hz), 5.32 (s, 1H), 5.65 (d, 1H, *J*=7 Hz), 7.48 (t, 2H, *J*=8 Hz), 7.62 (t, 1H, *J*=8 Hz), 8.08 (d, 2H, *J*=8 Hz).

4-*O*-Butyryl-13-deoxy-4,10-dideacetyl-13-oxo-7-*O*-triethylsilylbaccatin III (**8b**): Colorless crystalline solid, mp 192—195 °C. MS (FAB) *m/z* 685 (MH^+). $[\alpha]_D^{25}$ +5.4° (*c*=0.5, $CHCl_3$). *Anal.* Calcd for $C_{37}H_{52}O_{10}Si \cdot 1/2H_2O$: C, 64.04; H, 7.70. Found: C, 63.95; H, 7.57. IR (KBr) 3452, 2964, 2884, 1724, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.64 (m, 6H), 0.93 (t, 9H, *J*=8 Hz), 1.08 (t, 3H, *J*=7 Hz), 1.16 (s, 3H), 1.21 (s, 3H), 1.66—1.83 (m, 2H), 1.72 (s, 3H), 1.85—1.93 (m, 1H), 2.09 (s, 3H), 2.31—2.55 (m, 3H), 2.61 (d, 1H, *J*=20 Hz), 2.92 (d, 1H, *J*=20 Hz), 3.96 (d, 1H, *J*=7 Hz), 4.13 (d, 1H, *J*=8 Hz), 4.33 (d, 1H, *J*=8 Hz), 4.40 (dd, 1H, *J*=10, 7 Hz), 4.89 (d, 1H, *J*=8 Hz), 5.32 (s, 1H), 5.65 (d, 1H, *J*=7 Hz), 7.49 (t, 2H, *J*=8 Hz), 7.62 (t, 1H, *J*=8 Hz), 8.09 (d, 2H, *J*=8 Hz).

13-Deoxy-4,10-dideacetyl-13-oxo-4-*O*-pentanoyl-7-*O*-triethylsilylbaccatin III (**8c**): Colorless crystalline solid, mp 188—191 °C. MS (FAB) *m/z* 699 (MH^+). $[\alpha]_D^{25}$ +9.8° (*c*=0.5, $CHCl_3$). *Anal.* Calcd for $C_{38}H_{54}O_{10}Si \cdot 1/2H_2O$: C, 64.47; H, 7.69. Found: C, 64.66; H, 7.78. IR (KBr) 3560, 3436, 2960, 2884, 1730, 1710, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.93 (t, 9H, *J*=8 Hz), 1.02 (t, 3H, *J*=7 Hz), 1.16 (s, 3H), 1.21 (s, 3H), 1.41—1.51 (m, 2H), 1.61—1.72 (m, 2H), 1.73 (s, 3H), 1.86—1.93 (m, 1H), 2.09 (s, 3H), 2.34—2.53 (m, 3H), 2.62 (d, 1H, *J*=19.5 Hz), 2.92 (d, 1H, *J*=19.5 Hz), 3.96 (d, 1H, *J*=7 Hz), 4.13 (d, 1H, *J*=8 Hz), 4.33 (d, 1H, *J*=8 Hz), 4.41 (dd, 1H, *J*=10, 7 Hz), 4.87 (d, 1H, *J*=8 Hz), 5.32 (s, 1H), 5.64 (d, 1H, *J*=7 Hz), 7.48 (t, 2H, *J*=8 Hz), 7.63 (t, 1H, *J*=8 Hz), 8.08 (d, 2H, *J*=8 Hz).

13-Deoxy-4,10-dideacetyl-13-oxo-4-*O*-(4-pentenoyl)-7-*O*-triethylsilylbaccatin III (**8d**): Colorless crystalline solid, mp 202—206 °C. MS (FAB) *m/z* 697 (MH^+). $[\alpha]_D^{25}$ +7.0° (*c*=0.5, $CHCl_3$). *Anal.* Calcd for $C_{38}H_{52}O_{10}Si$: C, 65.49; H, 7.52. Found: C, 65.20; H, 7.55. IR (KBr) 3564, 3444, 2964, 2888, 1730, 1712, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.93 (t, 9H, *J*=8 Hz), 1.16 (s, 3H), 1.22 (s, 3H), 1.73 (s, 3H), 1.85—1.92 (m, 1H), 2.09 (s, 3H), 2.45—2.58 (m, 5H), 2.63 (d, 1H, *J*=20 Hz), 2.93 (d, 1H, *J*=20 Hz), 3.96 (d, 1H, *J*=7 Hz), 4.14 (d, 1H, *J*=9 Hz), 4.32 (d, 1H, *J*=9 Hz), 4.38 (dd, 1H, *J*=10, 7 Hz), 4.87 (d, 1H, *J*=8 Hz), 5.10 (dd, 1H, *J*=10, 1.5 Hz), 5.18 (dd, 1H, *J*=17, 1.5 Hz), 5.32 (s, 1H), 5.65 (d, 1H, *J*=7 Hz), 5.88—5.96 (m, 1H), 7.49 (t, 2H, *J*=8 Hz), 7.63 (t, 1H, *J*=8 Hz), 8.06—8.08 (m, 2H).

4,10-Dideacetyl-4-*O*-propionyl-7-*O*-triethylsilylbaccatin III (9a) (General Procedure) Sodium borohydride (100 mg, 2.64 mmol) was added in limited amounts to a solution of **8a** (500 mg, 0.745 mmol) in THF (30 ml) and MeOH (1.5 ml) at room temperature. The reaction mixture was then stirred for 3 h at room temperature, and neutralized with saturated aqueous NH_4Cl under ice cooling. The mixture was extracted with AcOEt, and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (25% AcOEt/*n*-hexane) to give **9a** (251 mg, 50%), which was recrystallized from MeOH–H_2O. **9a**: Colorless crystalline solid. mp 202—204 °C. MS (FAB) *m/z* 673 (MH^+). $[\alpha]_D^{25}$ −55.6° (*c*=0.6, $CHCl_3$). *Anal.* Calcd for $C_{36}H_{52}O_{10}Si$: C, 64.25; H, 7.79. Found: C, 63.96; H, 7.80. IR (KBr) 3476, 2960, 2888, 1728, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.94 (t, 9H, *J*=8 Hz), 1.07 (s, 3H), 1.24 (t, 3H, *J*=7 Hz), 1.26 (s, 3H), 1.73 (s, 3H), 1.86—1.93 (m, 1H), 2.07 (s, 3H), 2.22—2.28 (m, 2H), 2.45—2.51 (m, 1H), 2.52—2.67 (m, 2H), 3.94 (d, 1H, *J*=7 Hz), 4.16 (d, 1H, *J*=8 Hz), 4.31 (d, 1H, *J*=8 Hz), 4.42 (dd, 1H, *J*=10, 7 Hz), 4.84 (t, 1H, *J*=8 Hz), 4.91 (d, 1H, *J*=8 Hz), 5.18 (s, 1H), 5.59 (d, 1H, *J*=7 Hz), 7.46 (t, 2H,

$J=8$ Hz), 7.60 (t, 1H, $J=8$ Hz), 8.10—8.12 (m, 2H).

4-*O*-Butyryl-4,10-dideacetyl-7-*O*-triethylsilylbaccatin III (**9b**): Colorless crystalline solid, mp 160—163 °C. MS (FAB) *m/z* 687 (MH^+). $[\alpha]_D^{25}$ −67.5° ($c=0.6$, $CHCl_3$). *Anal.* Calcd for $C_{37}H_{54}O_{10}Si$: C, 64.96; H, 7.92. Found: C, 64.93; H, 8.12. IR (KBr) 3484, 2968, 2888, 1714 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.64 (m, 6H), 0.94 (t, 9H, $J=8$ Hz), 0.98 (t, 3H, $J=7$ Hz), 1.08 (s, 6H), 1.73 (s, 3H), 1.85—1.92 (m, 1H), 2.08 (s, 3H), 2.25 (d, 2H, $J=8$ Hz), 2.43—2.51 (m, 1H), 2.56 (t, 2H, $J=7$ Hz), 3.95 (d, 1H, $J=7$ Hz), 4.17 (d, 1H, $J=8$ Hz), 4.31 (d, 1H, $J=8$ Hz), 4.42 (dd, 1H, $J=11$, 7 Hz), 4.86 (t, 1H, $J=8$ Hz), 4.92 (dd, 1H, $J=9$, 2 Hz), 5.17 (s, 1H), 5.60 (d, 1H, $J=7$ Hz), 7.47 (t, 2H, $J=8$ Hz), 7.60 (t, 1H, $J=8$ Hz), 8.12 (d, 2H, $J=8$ Hz).

4,10-Dideacetyl-4-*O*-pentanoyl-7-*O*-triethylsilylbaccatin III (**9c**): Colorless crystalline solid, mp 142—146 °C. MS (FAB) *m/z* 701 (MH^+). $[\alpha]_D^{25}$ −50.6° ($c=0.3$, $CHCl_3$). *Anal.* Calcd for $C_{38}H_{56}O_{10}Si \cdot 2/3H_2O$: C, 64.02; H, 8.10. Found: C, 63.77; H, 7.90. IR (KBr) 3480, 2960, 2884, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.94 (t, 9H, $J=8$ Hz), 1.00 (t, 3H, $J=7$ Hz), 1.08 (s, 6H), 1.40—1.48 (m, 2H), 1.66—1.72 (m, 2H), 1.73 (s, 3H), 1.86—1.90 (m, 1H), 2.08 (s, 3H), 2.25 (d, 2H, $J=8$ Hz), 2.45—2.53 (m, 1H), 2.58 (t, 2H, $J=7$ Hz), 3.94 (d, 1H, $J=7$ Hz), 4.16 (d, 1H, $J=8$ Hz), 4.31 (d, 1H, $J=8$ Hz), 4.43 (dd, 1H, $J=11$, 7 Hz), 4.85 (br, 1H), 4.91 (d, 1H, $J=8$ Hz), 5.17 (s, 1H), 5.60 (d, 1H, $J=7$ Hz), 7.47 (t, 2H, $J=8$ Hz), 7.60 (t, 1H, $J=8$ Hz), 8.12 (d, 2H, $J=8$ Hz).

4,10-Dideacetyl-4-*O*-(4-pentenoyl)-7-*O*-triethylsilylbaccatin III (**9d**): Colorless crystalline solid, mp 151—153 °C. MS (FAB) *m/z* 699 (MH^+). $[\alpha]_D^{25}$ −53.9° ($c=0.2$, $CHCl_3$). *Anal.* Calcd for $C_{38}H_{54}O_{10}Si \cdot 1/2H_2O$: C, 64.47; H, 7.93. Found: C, 64.44; H, 7.69. IR (KBr) 3476, 2956, 2884, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.48—0.63 (m, 6H), 0.94 (t, 9H), 1.08 (s, 6H), 1.73 (s, 3H), 1.86—1.92 (m, 1H), 2.07 (s, 3H), 2.24—2.28 (m, 2H), 2.46—2.52 (m, 3H), 2.69 (t, 2H, $J=7$ Hz), 3.95 (d, 1H, $J=7$ Hz), 4.16 (d, 1H, $J=8$ Hz), 4.31 (d, 1H, $J=8$ Hz), 4.41 (dd, 1H, $J=10$, 7 Hz), 4.85 (m, 1H), 4.91 (d, 1H, $J=8$ Hz), 5.07 (dd, 1H, $J=10$, 1 Hz), 5.12 (dd, 1H, $J=17$, 1 Hz), 5.16 (s, 1H), 5.59 (d, 1H, $J=7$ Hz), 5.86—5.96 (m, 1H), 7.47 (t, 2H, $J=8$ Hz), 7.60 (t, 1H, $J=8$ Hz), 8.11 (d, 2H, $J=8$ Hz).

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