JOC Note

Synthesis of 4-Deacetyl-1-dimethylsilyl-7-triethylsilylbaccatin III

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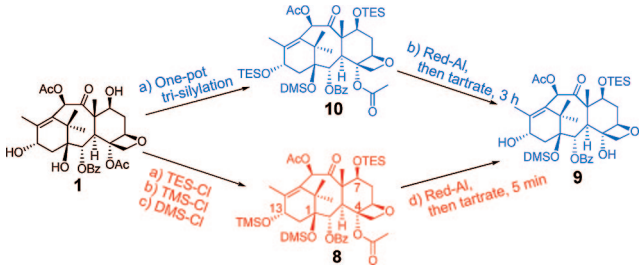
Received November 23, 2008



A one-pot trisilylation step to protect three hydroxyl groups of baccatin III (**1**), followed by hydride ester cleavage and base hydrolysis of a triethylsilyl ether at C13, provides efficient access to a key intermediate **9** (top path). This route removes two steps from a previously established reaction sequence to **9** (bottom path). In principle, inclusion of the truncated reaction sequence into widely utilized semisynthetic routes to next generation Taxol (paclitaxel) compounds could conceivably shorten the overall process.

Structure−activity studies have shown that the various ester and amide groups of the antineoplastic drug paclitaxel (Taxol)[1] (Figure 1) define the pharmacophore.[2−6] Strategic exchange of the acyl groups on the paclitaxel structure by synthetic methods has improved drug pharmacokinetics.[7−9]

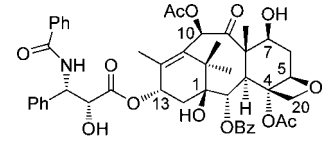


FIGURE 1. Paclitaxel (Taxol).

The various next generation analogs are usually derived from the natural product, baccatin III (**1**). Silyl ethers are routinely employed to protect the hydroxyl groups during the semisynthesis of modified taxanes; removal of these silyl groups typically requires reaction with acids, bases, or fluorides.[8,10−13] Unfortunately, these reagents generally lack regiospecificity when multiple silyl ethers are present, and accordingly, production yields of the target compound are reduced. Therefore, regioselective acylation of taxoids largely necessitates calculated and often redundant silylation chemistry.[8,10−14] By implementing a one-pot process along with a regiospecific desilylation step, we demonstrate a more efficient synthetic route to make the key precursor 4-deacetyl-1-dimethylsilyl-7-triethylsilylbaccatin III (**9**), which potentially could be used to construct new generation paclitaxel compounds.

The basis of the synthetic procedure described herein was encouraged from our several attempts to convert **1** to 13-acetyl-4-deacetylbaccatin III (**6**) (used as a product standard in our previous study).[15] The conversion of **1** to **4** was successful, following a described procedure;[16] however, our attempts to deacetylate compound **4** at C4 with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) reagent to acquire intermediate **5** (Scheme 1) were confounded by migration of the silyl group at C1.[17] Alternatively, a previously described synthesis in which the 4-acetyl and trimethylsilyl (TMS) groups were removed from **8** to produce **9** (Scheme 2)[18] was considered potentially suitable for the synthesis of **6**.

This latter four-step synthesis started from baccatin III (**1**), which was capped at the secondary hydroxyl of C7 by employing triethylsilyl chloride (TES-Cl) to make **2**, followed by separate TMS (trimethylsilyl) and DMS (dimethylsilyl) protection steps at the C13 and C1 hydroxyls to produce intermediates **7** and **8**, respectively. Following the hydride reduction of **8**, after a typical quench time (<5 min), the yield of **9** was recovered at 58%. This deacetylation mechanism is purportedly directed by coordination of the aluminum hydride

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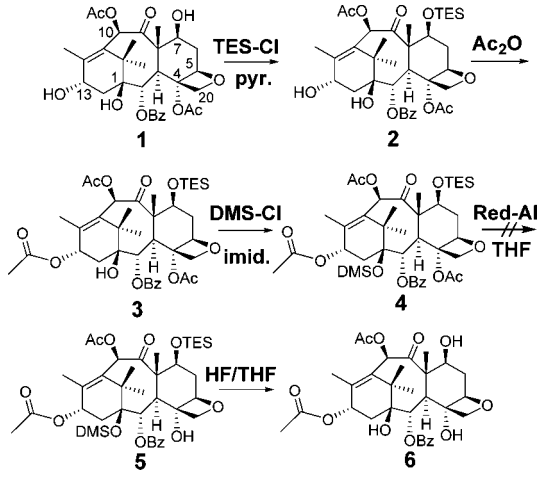
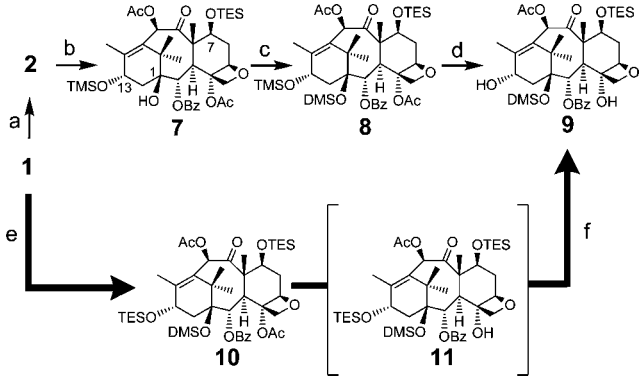
10.1021/jo802598m CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/29/2009

SCHEME 1. Attempted Synthesis of 6



SCHEME 2. Parallel Synthetic Routes to a Key Precursor of Next Generation Taxoids[a]



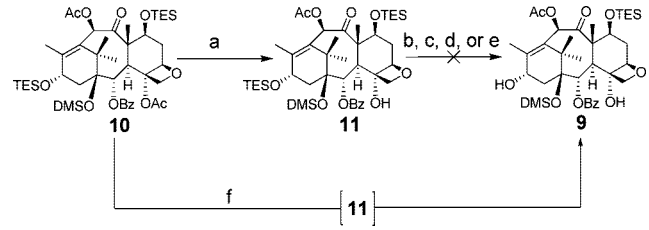
[a] (a) TES-Cl, pyradine, 61% yield; (b) TMS-Cl, imidazole, DMF; (c) DMS-Cl, imidazole, DMF, 87% yield after steps a and b; (d) Red-Al, THF, then sat. Na tartrate in water (pH 8.5) for 10 min, 58% yield; (e) TES-Cl, imidazole, then add DMS-Cl in one pot, 65% yield; (f) Red-Al, THF, then sat. Na tartrate in water (pH 8.5), 3 h, 70% yield (steps e and f not fully optimized).

with the proximate oxygen of the 4(5)-oxetane of **10** (or **8**) to promote regioselective ester cleavage.[19]

In the present study, we demonstrate a method to shorten this previously described 13-*O*-desilylation route to **9** from four to two steps. Our procedure advanced directly from **1** to **10** by adding DMS-Cl to the reaction mixture to protect the tertiary hydroxyl at C1. The latter reaction was performed in the same reaction pot in which the hydroxyls at C7 and C13 were first protected as TES ethers, using excess TES-Cl. The trisilylated product **10** was isolated and treated with aluminum hydride reagent to selectively remove the C4 acetate. Final quenching with the Na tartrate solution (<5 min) resulted in clean conversion of **10** to the transient intermediate 4-deacetyl-1-DMS-7,13-bis(TES)-baccatin III (**11**) (Scheme 2), but less than 2.5% conversion to **9** was evident by ESI-MS analysis. Surprisingly, by extending the tartrate reaction to >3 h, ~70% of this intermediate was converted to **9**. Notably, C13 deprotection was not observed prior to C4-deacetylation.

The cleavage of the C4 acetate of the 4-acetoxy-4(20),5-oxetane taxoids by reaction with Red-Al, described herein, is

SCHEME 3. Putative 13-*O*-Desilylation Reaction Conditions To Make Compound 9[a]



[a] (a) Red-Al, THF, 3 h, then aq Na tartrate (pH 8.5), 5 min; (b) aq Na tartrate (pH 8.5), 3 h; (c) Red-Al, THF, 3 h, then aq Na tartrate (pH 8.5), 5 min; (d) Red-Al, THF, 3 h, then water (pH 5.6), 3 h; (e) Red-Al, THF, 0°C, 3 h, then NaOH solution (pH 8.5), 3 h; (f) Red-Al, THF, 3 h, then aq Na tartrate (pH 8.5), 3 h.

broadly used to make 4-deacetyltaxanes.[11] However, hydride reduction has also been described for the cleavage of silyl ethers.[20] Knowledge of the correct reaction process aided our efforts to optimize the deprotection of **10** to make **9** via intermediate **11**. Therefore, we systematically assessed whether the silyl group at the C13 hydroxyl of **10** was analogously removed by hydride reduction upon treatment with Red-Al or by some other process. The mode of this desilylation has not been described in previous work and has only been generally explained as occurring during reaction workup.[18]

Several reaction conditions were tested to assess how the regioselective deprotection was promoted (Scheme 3). To obtain compound **11**, a solution of **10** in THF at 0 °C was added to Red-Al (5 equiv from a 3.5 M solution in toluene) and stirred for 3 h. The reaction was quenched with saturated Na tartrate solution (1 mL, pH 8.5) for 5−10 min, and compound **11** was then tested under various desilylation reaction conditions as follows. After treatment of **11** with Red-Al for 3 h, the reaction was quenched for 3 h with a NaOH solution (pH 8.5) or with acidic water (pH 5.6) instead of with the typical sodium tartrate solution. Neither of these alternative conditions converted **11** to the 13-desilylated product **9**, as assessed by ESI-MS analysis, suggesting that pH-buffering by the quench solvent was necessary. In brief, the only process suitable to regioselectively deprotect **11** was sequential treatment with Red-Al followed by long-term treatment with basic sodium tartrate solution. The tartrate buffer alone did not deprotect **11**, indicating that it was necessary to add Red-Al to the reaction pot in a prior step.

In conclusion, our modified method for the conversion of **1** to **9** (Scheme 2; steps e and f) removes two synthetic steps from the previously described reaction sequence (Scheme 2; steps a−d).[18] The condensed synthetic pathway employs a commonly used hydride-deacetylation step but more significantly invokes removal of a more recalcitrant triethylsilyl group (compared to a TMS group of **8**)[18] from the 13-hydroxyl of **10**.

Whereas the synthesis described herein is relatively straightforward, it nevertheless has not been described in methods within the compendium of literature pertaining to semisynthesizing taxane analogs. Foreseeably, the application of this one-pot trisilylation and reductive ester cleavage steps to acquire compound **9** can be extended toward synthesizing the plethora of paclitaxel analogs that bear alternative acyloxy moieties or alkylcarbonate groups at C4 and/or C13 and are currently deployed in bioactivity tests.[8,21,22] Consequently, the routes to these next generation taxanes would be effectively shortened,

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starting from **1**, by eliminating redundant silyl group manipulations, reducing the use of reagents, and minimizing the number of workup and purification steps. In addition, taxane compounds derived via **9** could also be used as substrates in the ongoing biosynthetic studies on paclitaxel in *Taxus* cell cultures.

Experimental Section

Synthesis of 9. To a solution of 1-DMS-7,13-bis(TES)baccatin III (48 mg, 0.082 mmol) in THF (2 mL) was added Red-Al (80 μL, 3.5 μM solution in toluene) dropwise over 5 min at 0 °C. The reaction was stirred for 40 min and quenched with 1 mL of saturated Na tartrate solution (pH 8.5), and the reaction mixture was stirred for 3 h. The solution containing crude product was diluted with EtOAc (20 mL), washed with an equal amount of water, and dried (Na_2SO_4). The organic layer was removed under vacuum, and the crude product was purified by PTLC (20:80 (v/v) EtOAc in hexane) to give 4-deacetyl-1-DMS-7-TES-baccatin III (**9**) (70% yield, >99% pure by ^{1}H NMR). The product was characterized by ESI-MS (positive ion mode), *m*/*z* 717.3 ($M + H^+$), 739.3 ($M + Na^+$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.4 (d, J = 3 Hz, C*H*$_3$Si(H)CH$_3$), 0.0 (d, J = 3 Hz, CH$_3$Si(H)C*H*$_3$), 0.5 (m, C*H*$_3$CH$_2$Si−O), 0.9 (m, CH$_3$C*H*$_2$Si−O), 1.0 (s, CH$_3$-16), 1.2 (s, CH$_3$-17), 1.6 (s, CH$_3$-19), 2.08 (s, CH$_3$-18), 2.13 (s, OC(O)CH$_3$ at 10β), 2.2 (s, OC(O)CH$_3$ at 4α), 2.3 (m, 6α, β), 2.6 (m, 14α, β), 3.3 (d, J = 6 Hz, 3α), 4.0 (dd, J = 6 Hz, J = 6 Hz, 7α), 4.2 (dd, J = 9 Hz, J = 9 Hz, 20α, 20β), 4.6 (m, *H*-Si(CH$_3$)$_2$), 4.7 (dd, J = 3 Hz, J = 3 Hz, 5α), 4.9 (m, 13α), 5.6 (d, J = 6 Hz, 2β), 6.38 (s, 10α), 7.4 (t, J = 6 Hz), 7.5 (t, J = 6 Hz), 8.0 (d, J = 6 Hz) [*m*-H, *p*-H, *o*-H of OBz, respectively].

Synthesis of 10. To a solution of baccatin III (**1**) (50 mg, 0.085 mmol) in DMF (3 mL) was added imidazole (70 mg, 1.02 mmol) and TES-Cl (285 μL, 1.7 mmol), and the reaction mixture was stirred at 45 °C. After 3 h the reaction was judged to be complete by TLC monitoring. The reaction flask was cooled to 0 °C, after which DMS-Cl (190 μL, 1.7 mmol) was added, and the reaction was stirred at 0 °C for 2 h. The reaction was warmed to room temperature over 2 h, quenched by adding water (20 mL), and diluted with EtOAc (50 mL). The organic fraction was washed with saturated brine and water (20 mL × 3 each), dried over Na_2SO_4, and purified by PTLC (20% EtOAc in hexanes) to obtain 48 mg of 1-DMS-7,13-bis(TES)baccatin III (**10**) (∼70% isolated yield and >99% by ^{1}H NMR). The identity of the compound was verified by ESI-MS (positive ion mode), *m*/*z* 873.3 ($M + H^+$), 895.3 ($M + Na^+$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.3 (d, J = 3 Hz, C*H*$_3$Si(H)CH$_3$), 0.0 (d, J = 3 Hz, CH$_3$Si(H)C*H*$_3$), 0.5 (m, CH$_3$C*H*$_2$Si−O), 0.6 (m, CH$_3$C*H*$_2$Si−O), 0.9 (m, C*H*$_3$CH$_2$Si−O), 0.98 (m, C*H*$_3$CH$_2$Si−O) 1.01 (s, CH$_3$−16), 1.1 (s, CH$_3$−17), 1.6 (s, CH$_3$−19), 2.0 (s, CH$_3$−18), 2.1 (s, OC(O)CH$_3$ at 10β), 2.2 (s, OC(O)CH$_3$ at 4α), 2.3 (m, 6α, β), 2.4 (m, 14α, β), 3.8 (d, J = 6 Hz, 3α), 4.2 (dd, J = 9 Hz, J = 9 Hz, 20α, 20β), 4.4 (dd, J = 6 Hz, J = 6 Hz, 5α), 4.5 (m, *H*-Si(CH$_3$)$_2$), 4.9 (m, 7α, 13α), 5.7 (d, J = 6 Hz, 2β), 6.4 (s, 10α), 7.4 (t, J = 6 Hz), 7.5 (t, J = 6 Hz), 8.0 (d, J = 6 Hz) [*m*-H, *p*-H, *o*-H of OBz, respectively].

Synthesis of 11. The synthesis of **11** was identical to that of **9**, except that during the quenching step with Na tartrate solution (pH 8.5) the mixture was stirred for 5 min instead of 3 h. The crude product mixture containing **11** was worked up and purified by PTLC (20:80 (v/v) EtOAc in hexane) similarly to the procedure described for **9** to give 4-deacetyl-1-DMS-7,13-bis(TES)-baccatin III (**11**) (53% yield, >97% pure by ^{1}H NMR), *m*/*z* 831.3 ($M + H^+$), 853.3 ($M + Na^+$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: −0.3 (d, J = 3 Hz, C*H*$_3$Si(H)CH$_3$), 0.0 (d, J = 3 Hz, CH$_3$Si(H)C*H*$_3$), 0.5 (m, CH$_3$C*H*$_2$Si−O), 0.6 (m, CH$_3$C*H*$_2$Si−O), 0.8 (m, C*H*$_3$CH$_2$Si−O), 0.9 (m, C*H*$_3$CH$_2$Si−O) 1.1 (s, CH$_3$−16), 1.2 (s, CH$_3$−17), 1.5 (s, CH$_3$−19), 2.0 (m, 6β), 2.1 (s, CH$_3$−18), 2.2 (s, OC(O)CH$_3$ at 10β), 2.3 (m, 6α), 2.4−2.8 (m, 14α, β), 3.5 (d, J = 6 Hz, 3α), 3.6 (bs, OH-4α), 4.1 (m, 7α), 4.2 (dd, J = 9 Hz, J = 9 Hz, 20α, 20β), 4.6 (m, *H*-Si(CH$_3$)$_2$), 4.6−4.7 (m, 5α, 13α), 5.6 (d, J = 6 Hz, 2β), 6.4 (s, 10α), 7.4 (t, J = 6 Hz), 7.5 (t, J = 6 Hz), 8.0 (d, J = 6 Hz) [*m*-H, *p*-H, *o*-H of OBz, respectively].

Rate of TES Ether Hydrolysis of 11 at C13. To a solution of 1-DMS-7,13-bis(TES)-baccatin III (**10**) (160 mg, 0.183 mmol) in THF (3 mL) at 0 °C was added Red-Al (250 μL, 1.26 mmol) dropwise within 1 min. After 2 h, 2 mL of saturated Na tartrate (2 mL, pH 8.5) was added slowly within 1 min; the reaction mixture was stirred at 0 °C for another 3 h, during which time 250-μL aliquots were removed from the reaction mixture every 15 min within the first hour and then every 30 min. Each sample was immediately quenched for 5 min with Na tartrate (pH 8.5), and the products in each aliquot were separately extracted into 500 μL of EtOAc. A 50-μL aliquot of the organic extract was diluted with 250 μL of acetonitrile and analyzed by ESI-MS.

Assessment of the Conditions that Promote Regioselective 13-O-Desilylation of 14. For each of the following experiments 20 mg (0.024 mmol) of 4-deacetyl-1-DMS-7,13-bis(TES)-baccatin III (**11**) was used. Scheme 3, step b: to a solution of **11** in THF (2 mL) at 0 °C was added saturated Na tartrate (1 mL) dropwise for 5 min. The reaction was monitored by drawing 250-μL aliquots every 30 min for 3 h. Scheme 3, step c: to a solution of **11** in THF (2 mL) at 0 °C was added Red-Al (5 μL, 0.025 mmol), and 250-μL aliquots were removed from the reaction every 30 min for 3 h. Saturated Na tartrate (pH 8.5) was added dropwise within 5 min, and EtOAc (2 mL) was added immediately to extract the products, which were analyzed by ESI-MS as described. Scheme 3, step d: to a solution of **11** in THF (2 mL) at 0 °C was added Red-Al (5 μL, 0.025 mmol), and 250-μL aliquots were withdrawn every 30 min for 3 h, after which, water (2 mL, pH 5.6) was added slowly within 1 min, and 250-μL aliquots were removed from the reaction vessel every 30 min for 3 h. Scheme 3, step e: to a solution of **11** in THF (2 mL) was added Red-Al (5 μL, 0.025 mmol) at 0 °C, and aliquots were withdrawn every 30 min for 3 h, after which NaOH (1 mL, pH 8.6) was added, and again aliquots were withdrawn every 30 min for 3 h.

Acknowledgment. This work was supported by the MSU College of Natural Science and by the Michigan Agricultural Experiment Station. We thank Irosha Nawarathne for her generous technical assistance.

Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802598M

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