New and Effective Synthesis of 7-Triethylsilylbaccatin III from 7*β*,13*α*-Bistriethylsiloxy-1*β*,2*α*,10*β*-trihydroxy-9-oxo-4(20),11-taxadiene

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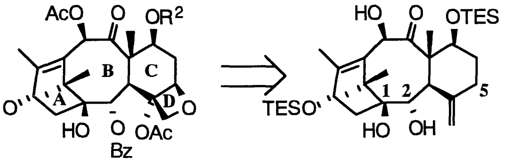
7β,13α-Bistriethylsiloxy-1β,2α,10β-trihydroxy-9-oxo-4(20), 11-taxadiene (**2**), derived from 10-deacetylbaccatin III *via* degradation of oxetane ring, was conveniently converted into 7-triethylsilylbaccatin III (**1**) by way of a new and effective method for constructing oxetane ring. Thus, the synthesis of a precursor of taxol from novel taxoid **2** was accomplished.

A new synthetic strategy of taxol and a stereoselective synthesis of optically active 8-membered ring enone that corresponds to B ring system of taxol were described in our previous communications.[1,2] *Via* allylation of a derivative of the above 8 membered ring compound and successive intramolecular aldol reaction, the synthesis of AB ring system of taxol was also achieved.[3,4] At the same time, retrosynthetic and synthetic studies on taxol and novel taxol derivatives using 10-deacetylbaccatin III were planned.[5] We would like to report herein a new and effective method for the synthesis of 7-triethylsilylbaccatin III (**1**),[6] a precursor of taxol, from 7β,13α-bistriethylsiloxy-1β,2α,10β-trihydroxy-9-oxo-4(20),11-taxadiene (**2**) which was derived from 10-deacetylbaccatin III *via* degradation of oxetane ring.

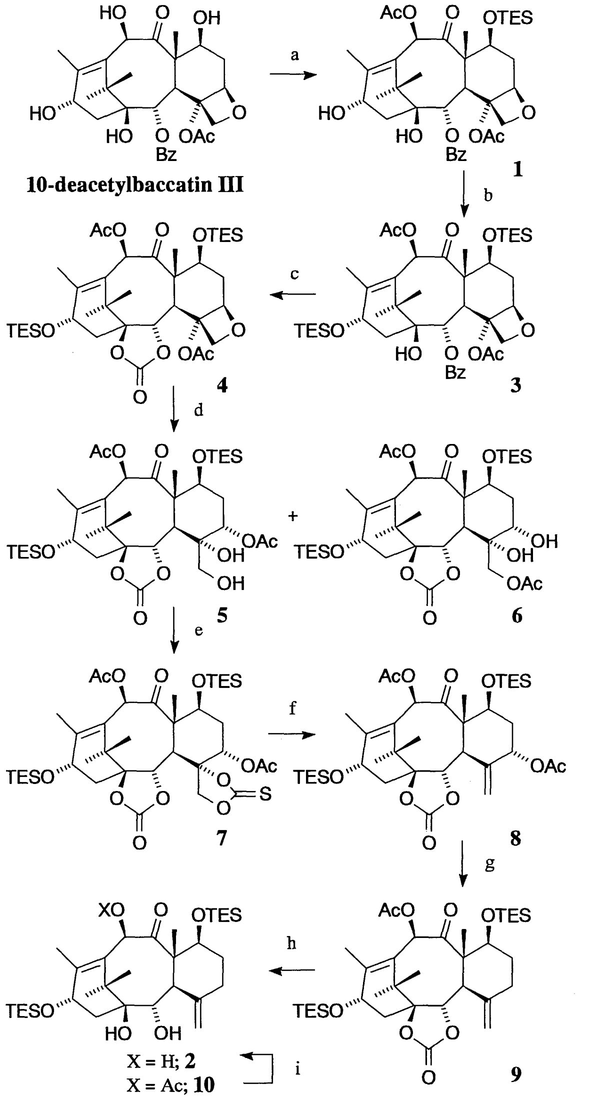


R^1 = PhCH(NHBz)CH(OH)CO, R^2 = H; **taxol** **2**
R^1 = H, R^2 = TES; **1**

Scheme 1.

Taxoids such as taxine and taxinine families, taxusin, brevifoliol, etc., have exo double bonds on their C rings and it is well known that, in biosynthesis, D rings of taxol and related compounds are formed by way of oxygenation of the exo olefins.[7] In order to develop a new method for the construction of oxetane rings onto the C rings,[8] the synthesis of new taxoid **2** from 10-deacetylbaccatin III was tried first (Scheme 2).

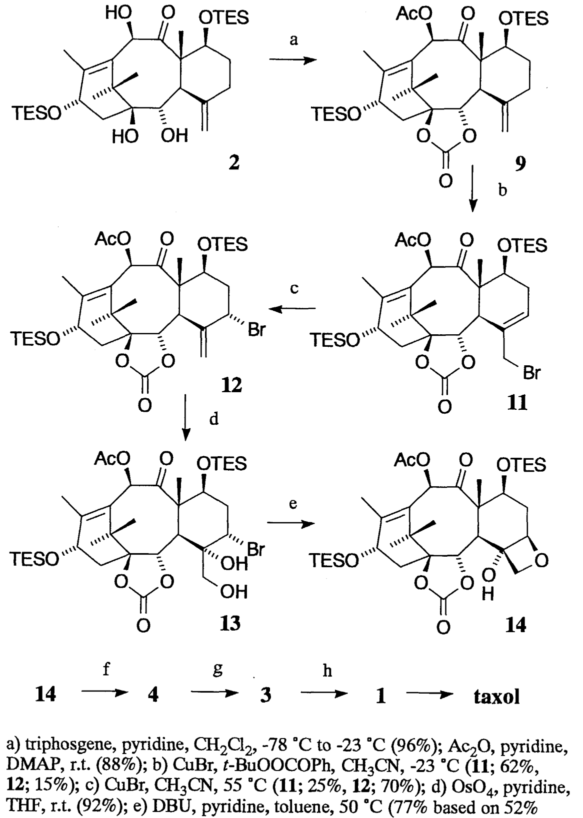
7,13-Bistriethylsilylbaccatin III (**3**) was prepared from 10-deacetylbaccatin III according to literature procedures.[6a)] A C1-C2 carbonate **4** was synthesized from **3** by reductive cleavage of C-2 benzoate with Red-Al,[9] followed by carbonylation using triphosgene.[10] When **4** was treated with $SnCl_4$ in CH_2Cl_2 at 0 °C, the oxetane-opening reaction took place to give desired kinetic product **5** as well as undesired thermodynamic product **6** in a ratio of 4 / 6.[11] After screening several acidic reaction conditions, the diols were obtained in quantitative yields with good selectivity (**5** / **6** = 8 / 2) when the reaction was carried out in CH_2Cl_2 at 0 °C using $TiCl_4$. Protection of the diol **5** with thiocarbonyl-diimidazole afforded the corresponding cyclic thionocarbonate **7** in excellent yield. Successive Corey-Winter deoxygenation of the thionocarbonate **7** with trimethylphosphite afforded **8** with exo double bond in nearly quantitative yield.[12] Selective deoxygenation at C-5 position of the allylic acetate **8** with formic acid-triethylamine and $Pd_2(dba)_3 \cdot CHCl_3$ proceeded smoothly to produce **9** in 85% yield.[13] Finally, saponification of the acetyl carbonate **9** with aqueous NaOH afforded triol **2** and diol **10** in 63% and 30% yields, respectively. Thus, the novel taxoid **2** was synthesized from 10-deacetylbaccatin III in *ca.* 35% overall yield *via* degradation of the oxetane ring.



a) TESCl, pyridine, r.t. (98%); AcCl, pyridine, -10 °C (83%);
b) TESCl, imidazole, DMF, r.t. (85%); c) Red-Al, THF, 0 °C (100%); triphosgene, pyridine, CH_2Cl_2, -78 °C to 0 °C (87%); d) $TiCl_4$, CH_2Cl_2, 0 °C (**5**; 80%, **6**; 20%); e) thiocarbonyldiimidazole, toluene, reflux (98%); f) $(MeO)_3P$, 130 °C (97%); g) HCOOH, Et_3N, $Pd_2(dba)_3 \cdot CHCl_3$, *n*-Bu_3P, THF, 75 °C (85%); h) NaOH, H_2O, MeOH, r.t. (**2**; 63%, **10**; 30%);
i) NaOH, H_2O, MeOH, 0 °C to r.t. (**2**; 54%, **10**; 21%).

Scheme 2.

Next, a new and effective method was developed for constructing oxetane ring on the above novel taxoid **2** (Scheme 3). Successive treatment of the triol **2** with triphosgene and acetic anhydride gave acetyl carbonate **9** in high yield. However, allylic oxygenation at C-5 position of **9** using SeO_2 with or without TBHP did not take place at all while PCC oxidation gave a mixture of undesired oxygenated products. On the other hand, allylic bromides **11** and **12** were unexpectedly produced in 62% and 15% yields, respectively, when the oxygenation of **9** was carried out with exccess amounts of CuBr and t-BuOOCOPh under the condition of allylic oxyacylation of olefins.[14] Further, on treating the allylic bromide **11** with CuBr at 55 °C in CH_3CN, a mixture of **11** and **12** was obtained in 95% yield (**11**; 25%, **12**; 70%). Osmylation of thus formed allylic bromide **12** with pyridine gave dihydroxy bromide **13** in 92% yield as a single stereoisomer. The desired oxetanol **14** was obtained in good yield when the dihydroxy bromide **13** was treated with DBU at 50 °C in toluene.[15] Acetylation of the tertiary alcohol **14** using acetic anhydride in pyridine gave the corresponding acetate **4**. The above experiments supported that the relative stereochemistries of **12**-**14** are as described in scheme 3. 7,13-Bistriethylsilylbaccatin III (**3**) was synthesized in high yield by benzoylation at C-2 position of C1-C2 carbonate **4**.[5),6d),6e),6f)] Desilylation of **3** and successive monosilylation of the triol afforded 7-triethylsilylbaccatin III (**1**) in good yield. It is noted that the synthesis of precursor of taxol was successfully accomplished from the novel taxoid **2** in *ca.* 25% overall yield by way of a new and effective method of constructing oxetane ring.



a) triphosgene, pyridine, CH_2Cl_2, -78 °C to -23 °C (96%); Ac_2O, pyridine, DMAP, r.t. (88%); b) CuBr, *t*-BuOOCOPh, CH_3CN, -23 °C (**11**; 62%, **12**; 15%); c) CuBr, CH_3CN, 55 °C (**11**; 25%, **12**; 70%); d) OsO_4, pyridine, THF, r.t. (92%); e) DBU, pyridine, toluene, 50 °C (77% based on 52% conversion); f) Ac_2O, pyridine, DMAP, r.t. (91%); g) PhLi, THF, -78 °C (94%); h) TBAF, THF, r.t. (81%); TESCl, imidazole, DMF, r.t. (87%).

Scheme 3.

Thus, chemical pathways of converting 10-deacetylbaccatin III to a variety of novel taxoids, useful synthetic intermediates of taxol, were established.

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